Model-based Computer-aided Framework for Design of Process Monitoring and Analysis Systems

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Model-based Computer-aided Framework for Design of Process Monitoring and Analysis Systems

Ph. D. Thesis

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Preface

This thesis is submitted as partial fulfillment of the requirements for the Ph. D. degree at Denmark Tekniske Universitet (Technical University of Denmark). The work has been carried out at Institut for Kemiteknik (Department of Chemical Engineering) from September 2006 to August 2009 under the supervision of Professor Rafiqul Gani and Associate Professor Krist V. Gernaey. Financial support of the Technical University of Denmark for this project is highly appreciated.

This work was supported, encouraged and inspired by a number of people. It is my great pleasure to reach the point in which I can look back in time and express my gratitude to them. First of all, I would like to thank my supervisors Professor Rafiqul Gani and Associate Prof. Krist V. Gernaey for introducing me to a very challenging and rewarding research topic and for their guidance, supports and motivation throughout this project. A special thanks to my main supervisor Prof. Rafiqul Gani to integrate me in a very international and dynamic group CAPEC and for providing numerous travels through conferences which gave me an insight to the international research.

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Lyngby, August 2009

Ravendra Singh

Abstract

In chemicals based product manufacturing, as in pharmaceutical, food and agrochemical industries, a well-designed process monitoring and analysis system (PAT system) plays a very important role. These PAT systems ensure that the chemicals based product is manufactured with the specified end-product qualities. Systematic computer-aided methods and tools provide the means to design the necessary process monitoring and analysis system and/or to validate any existing process monitoring and analysis system. In this work a generic model and data (knowledge) based computer-aided framework for including the methods and tools through which a process monitoring and analysis system for product quality control can be designed, analyzed and/or validated, has been developed. Corresponding software has been developed as well.

Two important supporting tools developed as part of the framework are a knowledge base and a model library. The knowledge base provides the necessary information/data during the design of the process monitoring and analysis system while the model library generates additional or missing data needed for design and analysis. The developed design methodology consists of nine hierarchical steps for design of a process monitoring and analysis system. These steps cover problem definition, analysis (process, sensitivity, interdependency), design and verification of the PAT system. The developed framework and methodology has been implemented into a software (ICAS-PAT) that has made the use of the PAT design procedure easy, consistent and fast. Some additional features have also been added to the ICAS-PAT software that has made it more useful and user-friendly. For example, the options to open and analyze stored solved examples, to find the different applications of any monitoring tools, to search the knowledge/data stored in the knowledge base, to draw the open and closed-loop process flow diagrams and to build reports in MS word for documenting the design of a process monitoring and analysis system. To demonstrate the wide applicability of the developed framework, methodology and corresponding software (ICAS-PAT) in pharmaceutical, biochemical and food production processes three case studies involving a tablet manufacturing process, a fermentation process and a cheese manufacturing process have been developed.

Resume på Dansk

I kemikaliebaseret produktfremstilling, såsom farmaceutiske, fødevare- og agrokemiske insustrier, er veldesignede procesovervågnings- og analysesystemer (PAT-systemer; *process analytical technology*) vigtige elementer. Disse PAT-systemer sikrer, at det kemikaliebaserede produkt er fremstillet med de ønskede produktkvaliteter. Systematiske computer-assisterede metoder og værktøjer leverer ressourcerne til design af nødvendige procesovervågnings- og analysesystemer, samt validere evt. eksisterende systemer. I denne afhandling er en generisk model- og databaseret computer-assisteret struktur til inklusion af de metoder og værktøjer – gennem hvilke et procesovervågnings- og analysesystem for produktkvalitetskontrol kan designes, analyseres og/eller valideres – blevet udviklet. Tilsvarende programmel er ligeledes udviklet.

To vigtige værktøjer, udviklet som del af strukturen, er en vidensbase og modelbibliotek. Vidensbasen leverer nødvendig information/data under designet af procesovervågnings- og analysesystemet, mens modelbiblioteket genererer yderligere, eller manglende, data nødvendig for design og analyse. Den udviklede metodik består af ni hierarkiske trin til design af et procesovervågnings- og analysesystem. Disse skridt dækker problemformulering, analyse (proces, sensitivitet, gensidig afhængighed), design og verificering af PAT-systemet. Den udviklede struktur og metodik er implementeret som programmel (ICAS-PAT), der nemt, konsistent og hurtigt gør brug af PAT-design-proceduren. Nogle yderligere funktioner er ligeledes implementeret i ICAS-PAT programmellet, for større anvendelighed og brugervenlighed. Heriblandt mulighederne for at åbne og analysere gemte eksempler, for at finde forskellige anvendelser af overvågningsværktøjer, for at søge viden/data gemt i vidensbasen, for at tegne den åbne, såvel som lukkede, processløjfe og for at generere rapporter i MS Word som dokumentation for designet af et procesovervågnings- og analysesystem. For at illustrere den brede anvendelse af den udviklede struktur, metodik og tilsvarende programmel i farmaceutiske, biokemiske og fødevareproduktionsprocesser, er tre eksempler gennemarbejdet. Disse involverer en tablet produktionsproces, en fermenteringsproces samt ostefremstilling.

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1. Introduction

Today a significant opportunity exists to improve product quality and to optimize the production process through the implementation of innovative solutions for on-line monitoring, analysis and system control. The U.S. food and drug administration have taken an initiative (FDA/CDER, 2005) for application of process analytical technology (PAT) in the manufacturing industries. Application of PAT systems (FDA/CDER, 2005) – also called process monitoring and analysis systems – in manufacturing paves the way for continuous process and product improvements through improved process supervision based on knowledge-based data analysis, 'Quality by design' concepts, and through feedback control (Gnoth et al., 2007). The primary goal of PAT is to better understand the manufacturing process, and to use that knowledge on-line to achieve better control of the process, and as a consequence of applying control, also achieve a more consistent product quality. PAT is therefore defined as a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (FDA, 2004; FDA/CDER, 2005).

The production methods for most industries, for instance, the pharmaceutical industry have changed considerably during the past years. Growing emphasis has been given to real-time adjustment of process operations in order to consistently produce products with predefined quality attributes. Extensive off-line laboratory testing of product quality should, for example, be reduced considerably when introducing PAT by the implementation of the real-time release concept, where product quality is assessed in real-time based on on-line measurement of critical process variables. It can thus be concluded that significant opportunities exist nowadays for improving the efficiency of manufacturing processes and quality assurance systems in the chemical, biochemical and pharmaceutical industries through introduction of novel and innovative techniques for product and process development, process control, and process analytical chemistry.

Originally, the application of PAT was mainly focused towards the pharmaceutical industry. However, PAT applications are rapidly spreading towards other regulated industries also, for example, the food industry. The introduction of PAT can generally be

considered as a landmark in the acceptance of process systems engineering tools in modern pharmaceutical manufacturing and quality assurance of food and drug production processes. In terms of process monitoring, the use of PAT represents a paradigm shift in the sense that sophisticated quality control moves from laboratory-based to process-based (i.e., in-process) approaches (Lopes et al., 2004). The availability of real time monitoring tools and its efficient utilization are two prerequisites to shift from the traditional lab-centric production approach to the PAT inspired approach. In the last decade, emphasis has been given towards the development of efficient innovative on-line monitoring tools. However, less attention has been paid towards the development of systematic methods and tools for efficient utilization of the existing measurement methods and accompanying control systems to improve the production process such that the end product quality can be achieved consistently with minimum complexity and optimum cost.

There is general agreement (FDA, 2004; Lawrence et al., 2004; FDA/CDER, 2005; Smith & Crofts, 2006; Gnoth et al., 2007; Chen et al., 2008; Kano & Nakagawa, 2008; Singh et al., 2009a) about the necessity of the design of a suitable process monitoring and analysis system (PAT system) for systematic product quality monitoring and control. As reported by Singh et al. (2009a), the design of a process monitoring and analysis system involves the identification of the critical quality parameters, selection of economical and reliable on-line measurement tools and integration of these on-line sensors with the control system. The need for systematic methods and tools for PAT system design and therefore for product quality control is illustrated in Figure 1.1. The figure shows two manufacturing approaches, the ‘fixed manufacturing process’ and the ‘robust, adjustable, PAT based process’. The fixed manufacturing process does not have a proper process monitoring and control system implemented. Therefore, it is difficult to identify and overcome the process disturbances in this kind of manufacturing practice and the process disturbances propagate to the process outputs. Predefined consistent end product quality can not be achieved for this kind of manufacturing process. To assure a consistent end product quality, the fixed process needs to be replaced by a robust and adjustable manufacturing process through the proper design and implementation of a PAT system. Therefore, systematic methods and tools are needed to design the PAT system. The design of a PAT system needs knowledge/data that can be available from open sources or

can be generated through simulations/experiments. Therefore a knowledge base and a model library are also needed to supply the necessary knowledge/data during PAT system design.

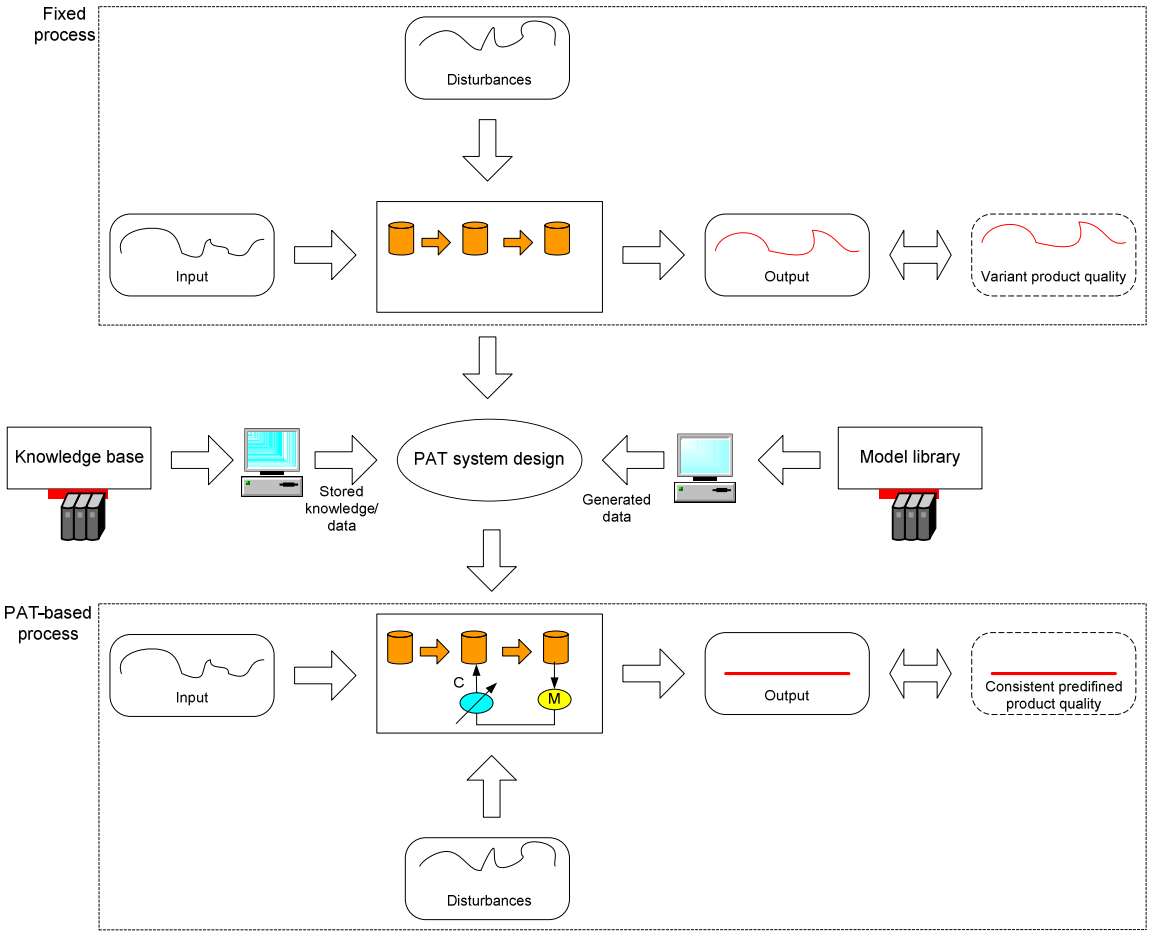

Figure 1.1: Fixed process versus PAT based process

In this introductory chapter a concise literature review, objective of the PhD project, summary of the work done and an overview of the structure of the thesis is given.

1.1. Literature review

A substantial number of papers related to the application of PAT in the manufacturing industries – mainly the pharmaceutical industry – have been published since 2000. In these papers, emphasis has been given mainly to the development of cutting edge on-line measurement and monitoring tools. Several spectroscopic techniques have, for example, been successfully implemented in pharmaceutical manufacturing processes (Fountain et

al., 2003; Roggo et al., 2007; De Beer et al., 2008; Eliasson et al., 2008; Rodionova et al., 2008), and in food processes (Scotter, 1990; Wählby & Skjöldebrand, 2001; Vlachos et al., 2006; Huang et al., 2008). In this review, some of the issues related to PAT system design, such as sensor network design, sensor selection, knowledge base, process understanding, modeling and simulation tools are highlighted.

1.1.1. Sensor network design (SND)

Currently, one of the main difficulties in implementing PAT systems on an existing manufacturing process is the unavailability of methods and tools through which a PAT system can be designed and/or evaluated. Methods for sensor network design (SND) – one of the important issues for achieving product quality control – can be considered as attempts to provide a systematic approach, and have been extensively researched. Sen et al. (1998) proposed a method for SND based on genetic algorithms combined with a graphical approach. The use of a coarse grain decomposition based genetic algorithm has been proposed (Carballido et al., 2007) to provide the initial sensor network for observability and redundancy analysis. The design of sensor networks in perspective of observability and reliability has also been discussed in the literature for simple systems (Václavel & Loucka, 1976) as well as for complex systems (Chamseddine et al., 2007). To achieve the dual objective (requirement of reliability as well as precision) the sensor reliability requirement has been successfully integrated with the precision in the design of sensor networks (Kotecha et al., 2008). Narasimhan and Rengaswamy (2007) have also considered the safety issue and proposed a fault diagnosis approach for sensor network design. Gerkens and Heyen (2005) have proposed a design algorithm supported by process models and a knowledge base but mainly focusing on solving the problem of excessive computational time needed to achieve SND. Orantes et al. (2007) proposed a new methodology based on coupling of the classification techniques with the entropy criteria for selection of the sensor. However, they mainly address the problem of sensor location for fault identification. Chakraborty & Deglon (2008) have developed a heuristic methodology for design of precise sensor networks for linear material flow. Their method is based on the general principle of variance reduction through data reconciliation. Subrahmanya et al. (2009) converted the sensor selection problem to the problem of

selecting an optimal set of groups of features during model selection and proposed an algorithm based on the use of a Bayesian framework for the purpose of selecting groups of features during regression and classification. However, they mainly focused on the problem of fault diagnosis.

1.1.2. Selection of sensors

The selection of a proper monitoring and analysis tool is a prerequisite to successful implementation of control systems and/or to achieve "quality by design". The availability of a large number of different process monitoring and analysis tools has made the selection process a difficult and challenging task. Therefore an efficient and systematic knowledge base and inference system are needed to support the selection of the optimum process monitoring and analysis tools, satisfying the process and user constraints. However, only few attempts have been made, to develop systematic methods and tools for selection of suitable sensors. Shieh et al. (2001) proposed a graphical approach for selection of sensors. They attempted to locate the sensors in the graph on the basis of their specifications. A pair of sensor specifications – for example sensing range and resolution – was considered to plot a 2-dimensional graph. However, in most selection procedures, more than two sensor specifications need to be compared in order to take the final decision on which sensor should be selected, which is clearly a limitation of this graphical approach. Ong et al. (1992) proposed a knowledge based system (KBS) for sensor selection based on a group technology coding scheme. The proposed KBS can provide a set of alternatives for sensors that satisfy the operational requirements. The selection of the final sensor is, however, manual. Barua et al. (1993) also attempted to develop a knowledge based expert system for transducers selection but only for measurements of temperatures, flows and pressures. The interferences due to the presence of other components in the medium also affect the measurements related to the component of interest. The interferences (cross-sensitivities) affect the selectivity and the sensitivity of the sensors. Brudzewski & Dolecka (1995) took the effect of these interferences (cross-sensitivities) into account for selection of sensors for gas measurements.

1.1.3. Knowledge based system

A substantial number of papers related to knowledge based systems (KBS) have been published since the early 1990s (Kandil et al., 1992; Paton et al., 2000; Lai, 2007; Wen et al., 2008; Qian et al., 2009; Choi, 2009; Gebus & Leiviska, 2009; Pirró et al., 2009). In these papers, emphasis has been given mainly to the collection, management and application of the knowledge using information technology. The knowledge base needs to be well structured and organized, so that it can be accessed straightforwardly through a computer and therefore a robust and efficient inference system can be designed. Ontologies have been used extensively by information technologists to systematically represent the knowledge in a domain. Basically the term 'ontology' has been borrowed from philosophy. Philosophers like Plato and Aristotle dealt with this branch (ontology), trying to find the fundamental categories of being and to determine whether items in these categories belonged to 'be'. The idea of having a means to represent fundamental categories of a particular domain to establish a common understanding between interaction partners is also interesting to computer scientists. So the ontology concept has become popular in Artificial Intelligence (AI) and knowledge representation (Yildiz, 2007). However, very few attempts have been made to design an ontology related to process monitoring and analysis systems. Eid et al. (2006) have proposed an ontology for sensor network data. Basically each ontology defines a set of classes, relations, functions, and object constants for some domain of discourse, and includes an axiomatization to constrain the interpretation (Gruber, 1995). An ontology, together with a set of instances of its classes, constitutes a knowledge base. Methodologies for design of an ontology is available in the literature, for example, Natalya & McGuinness (2007), and it is this methodology which has been applied for design of the ontological structure of the developed knowledge base for selection of process monitoring and analysis system (see chapter 3) in this thesis. The category, 'Processes' is the route of the evolved ontological structure while the specifications of monitoring tools, such as accuracy (Haby, 2008), precision (Haby, 2008), operating range (Carr & Brown, 2008), response time (Sutherland, 2004), resolution (Sutherland, 2004), sensitivity (Sutherland, 2004), drift (Capgo, 2007), operating temperature range (Kionix, 2004), cost etc. are the leaves. The theoretical background and detailed literature survey regarding the knowledge base is

presented in chapter 3, together with the description of the structure of the knowledge. Note that, the knowledge base has been developed based on an intensive literature and industrial survey that involved more than 240 references. This reference list is not included in the thesis (it can be provided, if requested).

1.1.4. Process understanding, modeling and simulation issues

Process understanding is a primary step towards designing an efficient PAT system. A process is generally considered well understood when all critical sources of variability are identified and explained, variability is managed by the process and product quality attributes can be accurately and reliably predicted (FDA, 2004). Experiments or simulations with process models provide a means to understand the process better. Experiments are usually expensive and time consuming, and therefore, process models play an important role for the generation of process data required for design and/or validation of PAT systems, and thus to reduce experimental efforts needed to design a PAT system. In the last decade, most emphasis has been given to the development of reliable process models, based on a first principles approach as well as a data driven approach (empirical correlations). For example, specific models for chemical and biochemical processes (Potocnik & Grabec, 1999; Soejima et al., 2008; Singh et al., 2009a; Charalampopoulos et al., 2009), pharmaceutical processes (Westerhuis et al., 1997; Wu et al., 2005: Zhou et al., 2005; Jia & Williams, 2007; Singh et al., 2009b), and food processes (Zwietering & Hasting, 1997; Otero & Sanz, 2003, Mittal, 2007; González-Sáiz et al., 2009) have been developed successfully. Process models are extensively used for different applications, for instance, in process optimization and control (Fu & Barford, 1993; Sen & Srinivasa Babu, 2005; Kawohl et al., 2007; Nagy, 2007; Pintaric & Kravanja, 2008; Ashoori et al., 2009; Papadopoulos & Seferlis, 2009). Much less attention, however, has been paid to application of process models for design and/or validation of process monitoring and analysis systems (PAT systems) and thus for assurance of end product quality (Singh et al., 2008, 2009a, 2009b). A substantial number of simulation tools are commercially available (gPROMS (PSE, 1997), MATLAB (Mathworks, 1970) etc.) or available only to consortium members (ICAS-MoT (Sales-

Cruz & Gani, 2003)) that can be used to generate the necessary process data, required for design of process monitoring and analysis systems.

1.2. Gaps in the current state of the art

The review of previous work done in the area of process monitoring and analysis (PAT) (see section 1.1) clearly shows some gaps in the current state of the art, when already existing approaches are confronted with the problem of designing a PAT system. These gaps need to be filled, and are summarized as follows:

- Most of the available literatures regarding SND mainly focus on the minimization of the number of sensors in the process under constraints such as high reliability, precision, redundancy and low cost and variability of process operational conditions and product quality. The minimum number of sensors was achieved by assuming that the remaining variables can be predicted accurately by process models. However, the process models are often not sufficiently reliable for prediction. Much less attention has been given to the problem of sensor network design for placement of appropriate sensors at appropriate production steps for monitoring and control of critical process variables and thereby assuring end-product quality. Certainly, the monitoring and analysis system (PAT system) of any process need to be designed carefully to obtain the end product quality consistently. However, the complexity involved in the design and maintenance of PAT systems make its implementation a difficult, time consuming and expensive task. Therefore, there is an obvious need for systematic computer-aided methods and tools through which a PAT system can be designed and implemented easily, faster and economically.
- Proper selection of measurement methods and tools (sensors) is one of the important aspects for design and implementation of PAT systems. Attempts that have been made for sensor selection have a clear focus on the selection of sensors based on sensor specifications. Process knowledge needed to integrate the sensor selection within the design of the process monitoring and analysis system, however, is typically not taken into consideration. Therefore, a well-designed knowledge based system (KBS) consisting of the process knowledge as well as knowledge on measurement methods

and tools is needed to support the selection of the appropriate process monitoring and analysis techniques/tools.

- One of the key issues in handling data/knowledge is how to develop and represent the knowledge base so that it can be used efficiently to provide the problem solutions. Ontologies have been considered to provide the means for systematic representation of the knowledge base. Knowledge based systems have been used extensively to solve general complex problems. Much less attention, however, has been paid to the design and development of a knowledge based system that can be applied systematically for selection of appropriate process monitoring and analysis techniques/tools. The development of such a knowledge system was one of the objectives of this work. An extensive literature and industrial survey is necessary to build the required knowledge base.
- One of the challenges for design of PAT systems is to generate the necessary data. Simulation with appropriate process operational models provides the means to generate the required data. However, much less attention has been paid to development of a systematic model library integrated with a simulation tool through which the required data for PAT system design can be generated. A generic and flexible model library consisting of the mathematical models for different types of unit processes, sensors and controllers is therefore needed, to utilize the developed models systematically and efficiently for design of process monitoring and analysis systems. A suitable simulation tool also needs to be integrated with the model library to solve the mathematical models. A number of models found in open literature have been reviewed to develop such a model library. Some of these references are provided in the description of the process models (given in Appendix A and B).

1.3. Objective of the project

The objective of this PhD project is to develop a systematic model-based computer-aided framework for design of process monitoring and analysis systems. The *design of a process monitoring and analysis system* requires a hierarchical step-wise procedure involving the selection of critical process variables, followed by the selection and placement of suitable monitoring and analysis equipments, and finally, the coupling of

the monitoring and analysis tools to a control system to ensure that the selected critical process variables can be controlled adequately.

1.4. Work done

In this work a model-based computer-aided framework is developed together with the methods and tools through which the design of monitoring and analysis systems for product quality control can be generated, analyzed and/or validated. The developed framework and methodology are generic: its systematic approach to the design of a PAT system is complimentary to traditional process design, and should thus have a broad application range in chemical, biological, food and pharmaceutical processes.

The first main result described in the thesis is the systematic framework and methodology for design of process monitoring and analysis systems. The design methodology consists of nine hierarchical steps. The first step (product property specifications) is concerned with specifying the product properties that are desired (to be achieved) in the considered production process. The necessary process related information, such as, the raw materials, their composition and the equipments used in the production process are provided through step 2 (process specifications). The information provided through these two steps of the design methodology act as input data for the design problem. On the basis of the input data and with the consultation of the knowledge base, step 3 (process analysis) of the methodology generates a list of process points (in general, process equipments are considered as the process points) and a list of the corresponding process variables. The outcome of this step becomes the basis for subsequent analysis steps. The critical process points where monitoring and analysis equipments need to be placed and the corresponding critical process variables that need to be monitored and controlled in order to achieve the desired end product quality are then identified through step 4 (sensitivity analysis). The identification of the appropriate actuators and the selection of suitable on-line monitoring techniques and tools are necessary to successfully implement the control system in order to control the critical process variables obtained in step 4. The appropriate actuators for each selected critical process variable are identified through step 5 (interdependency analysis) while step 6 (performance analysis of monitoring tools) generates the list of the feasible measurement methods and tools for selected critical

process variables. On the basis of the outcomes of steps 4 - 6, a process monitoring and analysis system is suggested in step 7. The proposed monitoring and analysis system consists of a list of critical process points, corresponding critical process variables, actuators, monitoring techniques and monitoring tools. The proposed process monitoring and analysis system is validated in step 8 and finally step 9 identifies a final process monitoring and analysis system.

The second main result to be reported in the thesis are two important supporting tools developed as part of the design framework: a knowledge base and a model library. The knowledge base provides the necessary information/data during the design of the process monitoring and analysis system while the model library generates additional or missing data needed for design and analysis. The knowledge base consists of two sections. The first section stores the necessary process knowledge (type of processes, corresponding process points, process variables and actuators) while the second section stores the knowledge/data on measurement methods and tools (type of variables, available monitoring techniques and tools with specifications such as accuracy, precision, operating range, response time, resolution, cost etc.). The model library contains a set of mathematical models for different types of unit processes, sensors and controllers.

The third main result of the thesis is the framework and methodology that has been implemented in a software (ICAS-PAT) to make the use of the PAT design procedure easier, consistent and faster. The supporting tools, knowledge base and model library, together with the simulation tool, ICAS-MoT are integrated with the user interface of ICAS-PAT to provide the data required for design of PAT systems. The supporting tools have been provided with sufficient data/models to make them generic and applicable for a wide range of industrial processes. Also, the structure of both the knowledge base and the model library is generic, and can be extended easily to widen its range of applications. Another useful feature in ICAS-PAT is that it allows the replacement of built-in supporting tools (general knowledge base and model library) with user provided supporting tools, if required. Other features provide the options to open and analyze previously stored solved examples, to find applications of specific monitoring tools, to search the knowledge/data stored in the knowledge base, to draw the open as well as closed-loop process flow diagrams and finally to build a report in MS-word documenting

the steps and results from the 'design of a process monitoring and analysis system' through ICAS-PAT.

The forth main results of the thesis are the case studies that have been developed to demonstrate the application of the developed framework, methodology and the corresponding software. Three case studies, a pharmaceutical tablet manufacturing process, a fermentation process and a cheese manufacturing process have been prepared and included in the thesis

1.5. Overview of thesis

The PhD-thesis is organized into six chapters including this chapter (Introduction). Chapter 2 provides a detailed description of the developed framework and methodology for design of process monitoring and analysis systems. The application of the developed framework and methodology is demonstrated through a "conceptual" fermentation process case study at the end of the chapter. The case study demonstrates how the design algorithm can be applied for design of process monitoring and analysis systems. Process operational models are used to generate the process data needed for the design of a monitoring and analysis system. Therefore, a brief analysis of these process models is also given in this chapter while the detailed description of the models is given in Appendix A. In appendix B the values of known variables and parameters required to solve the process models are given.

Based on the developed framework and methodology, a software (ICAS-PAT) has been developed. The software development issues are discussed in chapter 3. This chapter is mainly focusing on the supporting tools needed to develop the software (ICAS-PAT). A knowledge base and a model library have been developed to provide the necessary knowledge/data during the design of process monitoring and analysis systems. The chapter also discusses procedures related to the development and further extension of the knowledge base and model library. To enable an efficient inference system, the structure of the knowledge base needs to be well-designed. Therefore, a significant part of the chapter is dedicated to describing the design of the ontological structure of the developed knowledge base. The issues related to solving the process operational models stored in the model library are also highlighted at the end of the chapter.

The ICAS-PAT software is described in detail in chapter 4 together with the software architecture necessary to implement the design algorithm. The main challenges were the design of the user interface through which the input information/data can be provided by the user and a data flow structure through which the generated output information/data can be accessed by different tools at various steps of the design procedure. To process the input/output information/data, command buttons within the user interface also had to be designed carefully. The input information/data can be provided either from the user or from the supporting tools (knowledge base and model library) as per requirements. Therefore, the integration of the knowledge base, the model library and the simulation tool within the user interface is important. The work-flow and data-flow corresponding to the execution of each design step of ICAS-PAT is described through activity diagrams. The main task of the ICAS-PAT software is the design of PAT systems through the 9-step methodology. Each step has been implemented in a separate window, through which the input information/data are provided and the output information/data are accessed. Additional features to make the software more user-friendly are also described at the end of this chapter.

The case studies, demonstrating the application of the methodology through the ICAS-PAT software are presented in chapter 5. This chapter also provides the analysis of process models of the unit operations involved in the case studies. Emphasis has been given to clearly outline the application issues of the ICAS-PAT software, so that the reader can easily understand the functionality and the needs for each option within the software. The objective in chapter 5 has been to also provide the readers of the thesis with sufficient information so that they can easily use the methodology (with or without the software) for design of PAT systems. Two case studies involving a tablet manufacturing process and a cheese manufacturing process have been included in this chapter, supplementing the fermentation process case study included in chapter 2. In principle, the software ICAS-PAT can be used in any chemical, biochemical, food and pharmaceutical processes for design of process monitoring and analysis systems because of the generic nature of its supporting tools. All the models related to the considered case studies are given in Appendix A and the values of the known variables and parameters of these models are given in Appendix B.

In chapter 6, the conclusions of this work and directions for future developments are given.

2. Generic framework for design of process monitoring and analysis systems

2.1. Design framework overview

The *design of a process monitoring and analysis system* requires a step-wise procedure involving the selection of critical process variables, followed by the selection and placement of suitable monitoring and analysis equipments, and finally, the coupling of the monitoring and analysis tools to a control system to ensure that the selected critical process variables can be controlled adequately, such that the process is kept within its design space (FDA, 2007, Gani et al., 2006b). The design decisions need to be made in an integrated manner taking into account the interaction between product quality specifications, process operational constraints, cost of the PAT system and the time needed for analysis.

The overview of the proposed framework for design of process monitoring and analysis systems is shown in Figure 2.1. The starting point for the design methodology is the problem definition in terms of process specifications and product quality specifications that can be provided by the manufacturer or PAT system designer. These specifications will be used as the input to the developed system for design of process monitoring and analysis systems. A model library and a knowledge base act as supporting tools for the design of the process monitoring and analysis systems. The modeling tool, such as, ICAS-MoT (Sales-Cruz, 2006), is necessary for simulation of process models to be included in the model library. As shown in Figure 2.1, the developed design algorithm relates the product and process specifications to the available supporting tools, and subsequently generates a design proposal for the monitoring and analysis system. If the obtained PAT system satisfies the requirements then it is selected as the designed monitoring and analysis system. A well-designed monitoring and analysis system can subsequently be implemented and used to obtain the predefined product quality consistently and viably. The design methodology, a knowledge base and a model library are three important parts of the design framework. The design methodology is described

in the following section while the knowledge base and model library (supporting tools) are described in the next chapter.

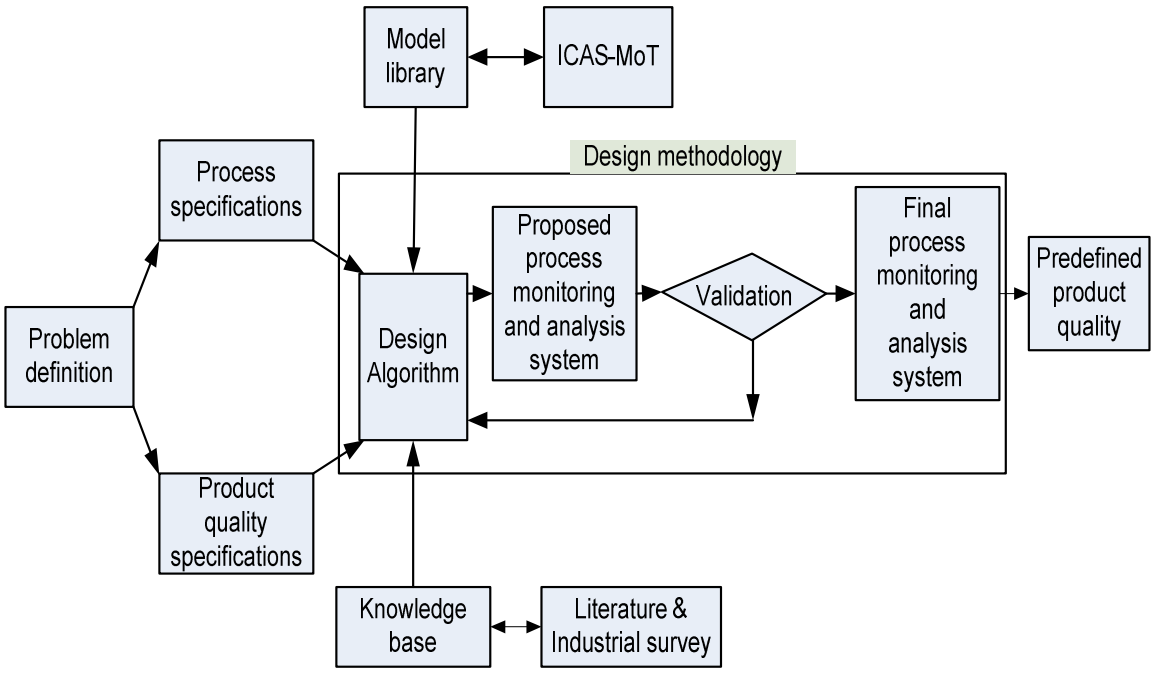

Figure 2.1: Schematic representation of the design framework

2.2. Design methodology

The methodology for design of a process monitoring and analysis system is shown in Figure 2.2. There are nine hierarchical steps through which the monitoring and analysis system is designed. Figure 2.2 also shows where the supporting tools (knowledge base and model library) are necessary, for example, in steps 3-6 (for process, sensitivity, interdependency and performance analysis). Moreover, the corresponding results of each analysis step are also highlighted. The detailed description of each step is given in subsequent subsections of this chapter.

Two types of notations are used in the description of the design methodology, point variables and vectors. Each vector consists of a set of selected point variables.

Table 2.1 summarizes the relation between point variables and vectors. The point variables are first identified, and the corresponding vectors are then obtained by grouping those point variables. For example, $\overline{PP_i}$ is a vector consisting of the process points of the i^{th} process while $PP_{j,i}$ is a point variable representing the j^{th} process point of the i^{th} process. In general, the process equipments are considered as the process points.

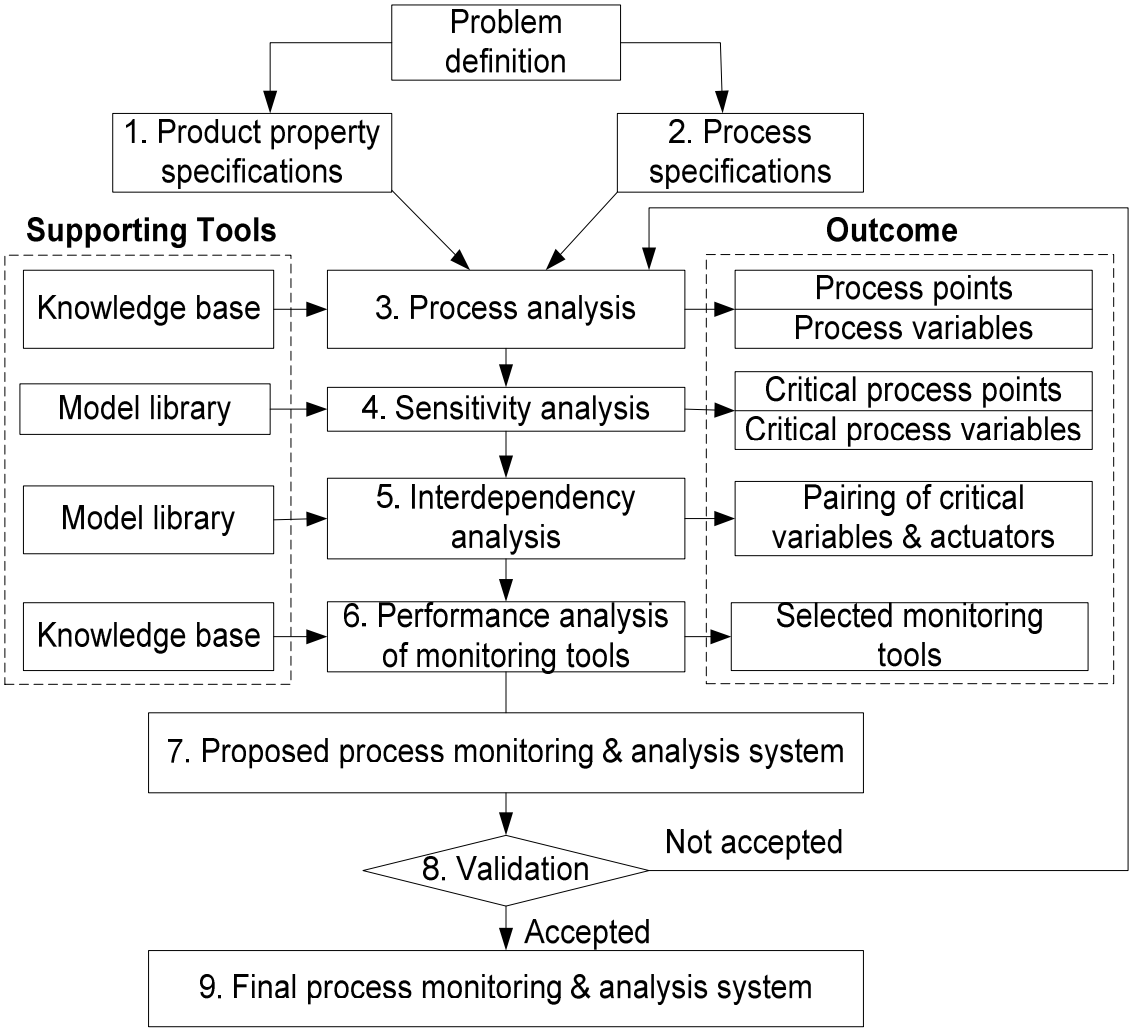

Figure 2.2: Overview of the design methodology, including the use of the supporting tools and the outcome of the individual analysis steps

Table 2.1: Vectors and point variables used in the design methodology

Vector	Relation with point variable	No. of objects
Process points ($\overline{PP_i}$)	$\overline{PP_i}=\left[PP_{1,i}\ .....\ PP_{j,i}\ .....PP_{n_i,i}\right]$	n_i
Process variables ($\overline{V_i}$)	$\overline{V}_i=\left[\overline{V}_{1,i}\ .....\ \overline{V}_{j,i}\ .....\ \overline{V}_{n_i,i}\right]$; $\overline{V}_{j,i}=\left[V_{1,j,i}\ .....\ V_{k,j,i}\ .....\ V_{q_{j,i},j,i}\right]$	$\sum_{j=1}^{n_i} q_{j,i}$ $q_{j,i}$
Critical process points ($\overline{PP_i^c}$)	$\overline{PP_i^c}=\left[PP_{1,i}^c\ .....\ PP_{j,i}^c\ .....PP_{n_i^c,i}^c\right]$	n_i^c
Critical process variables ($\overline{V_i^c}$)	$\overline{V_i^c}=\left[\overline{V_{1,i}^c}\ .....\ \overline{V_{j,i}^c}\ .....\ \overline{V_{n_i^c,i}^c}\right]$; $\overline{V_{j,i}^c}=\left[V_{1,j,i}^c\ .....\ V_{k,j,i}^c\ .....\ V_{q_{j,i}^c,j,i}^c\right]$	$\sum_{j=1}^{n_i^c} q_{j,i}^c$ $q_{j,i}^c$
Actuators ($\overline{u_i}$)	$\overline{u}_i=\left[\overline{u}_{1,i}.....\overline{u}_{j,i}.....\overline{u}_{n_i,i}\right]$; $\overline{u}_{j,i}=\left[u_{1,j,i}\ .....\ u_{k,j,i}\ .....\ u_{q_{j,i},j,i}\right]$	$\sum_{j=1}^{n_i^c} q_{j,i}^c$ $q_{j,i}^c$
Monitoring techniques ($\overline{MTE_i}$)	$\overline{MTE_i}=\left[\overline{MTE}_{1,i}\ .....\ \overline{MTE}_{j,i}\ .....\ \overline{MTE}_{n_i^c,i}\right]$ $\overline{MTE}_{j,i}=\left[MTE_{1,j,i}\ .....\ MTE_{k,j,i}\ .....\ MTE_{q_{j,i}^c,j,i}\right]$	$\sum_{j=1}^{n_i^c} q_{j,i}^c$ $q_{j,i}^c$
Monitoring tools ($\overline{MT_i}$)	$\overline{MT_i}=\left[\overline{MT}_{1,i}\ .....\ \overline{MT}_{j,i}\ .....\ \overline{MT}_{n_i^c,i}\right]$; $\overline{MT_{j,i}}=\left[MT_{1,j,i}\ .....\ MT_{k,j,i}\ .....\ MT_{q_{j,i}^c,j,i}\right]$;	$\sum_{j=1}^{n_i^c} q_{j,i}^c$ $q_{j,i}^c$
Specifications ($\overline{SP}_{k,j,i}$)	$\overline{SP}_{k,j,i}=\left[\begin{array}{l}\text{accuracy, precision, operating range, response}\\ \text{time, sensitivity, drift, resolution, otr, cost, ...}\end{array}\right]$	NSP

2.2.1. Product property specifications (step 1)

Product property specifications include the target properties of the final product that have to be achieved, as well as the known properties of the intermediate products if any intermediate product quality standard is also required to be achieved.

2.2.2. Process specifications (step 2)

The available information regarding the process which can be useful to increase process understanding, and will provide the basis for subsequent analysis, has to be included in the process specifications. For example, the list of raw materials required and the list of equipments used in the process are both part of the process specifications. These specifications can be obtained directly from the process flowsheet, if available. Otherwise, they have to be provided by the PAT system designer.

2.2.3. Process analysis (step 3)

This step is concerned with the listing of process points where monitoring might be required and corresponding relevant variables involved in the process. In general, all the process equipments in the flowsheet are considered as the process points. The systematic procedure for process analysis is highlighted through the flow-diagram in Figure 2.3.

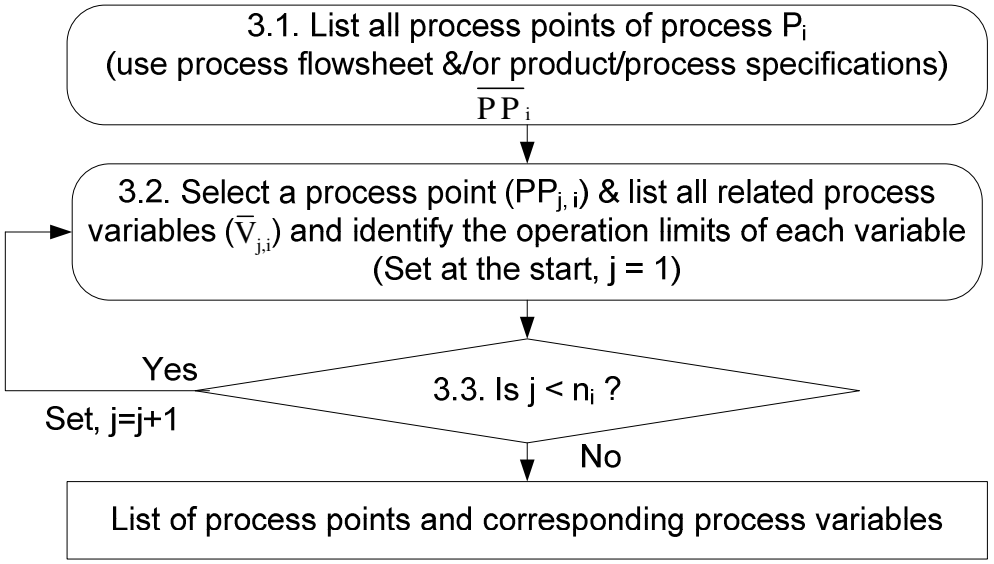

Figure 2.3: Systematic procedure for process analysis (step 3)
(n_i: number of process points in the considered i^{th} process)

The detailed steps of the algorithm corresponding to Figure 2.3 are given below:

Step 3.1: Use the process flowsheet and/or product/process specifications (for a new process) and list all the process points ($\overline{PP}_i$). These are the points where monitoring might be required.

Step 3.2: Select a process point ($PP_{j,i}$) from the list obtained in step 3.1 ($\overline{PP_i}$) and list the entire set of process variables involved with that point ($\overline{V}_{j,i}$). Identify the operational limits of each process variable. A knowledge base is used to generate the necessary data.

Step 3.3: Repeat step 3.2 until all process points and their corresponding variables ($\overline{V}_i$) have been obtained.

The results of process analysis (step 3) provide the basis for subsequent analysis steps, as illustrated in Figure 2.4. The process analysis (step 3) provides an extended set of relevant process variables among which the critical process variables and the corresponding actuators have to be selected in subsequent analysis steps. In Figure 2.4, this large set of variables – or variable space – is represented by the large area at the top of the figure. Through a subsequent screening process (step 4), the number of candidate critical process variables is reduced, until the final selected set of critical process variables is obtained (Figure 2.4, middle). The set of actuators corresponding to the selected set of critical process variables are obtained in step 5 (Figure 2.4, bottom).

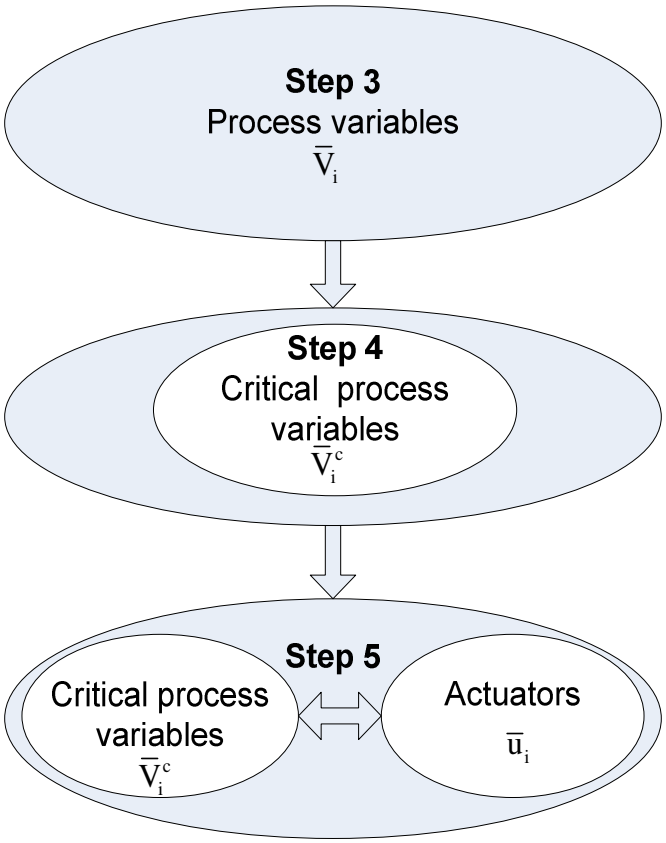

Figure 2.4: Illustration of the variable selection procedure

2.2.4. Sensitivity analysis (step 4)

The critical process variables that need to be monitored and controlled are identified through this step. The model library or process data (if available) are used for this analysis. To perform the sensitivity analysis, simulation with the appropriate process operational model (in open-loop) is necessary. The main idea for this step is to check whether the operational objective of the process point is achieved or not. If the operational objective is not achieved then the process variables (involved with that process point) are identified that are violating the operational limits and therefore need to be monitored and controlled. The systematic procedure for sensitivity analysis is highlighted through the flow-diagram in Figure 2.5.

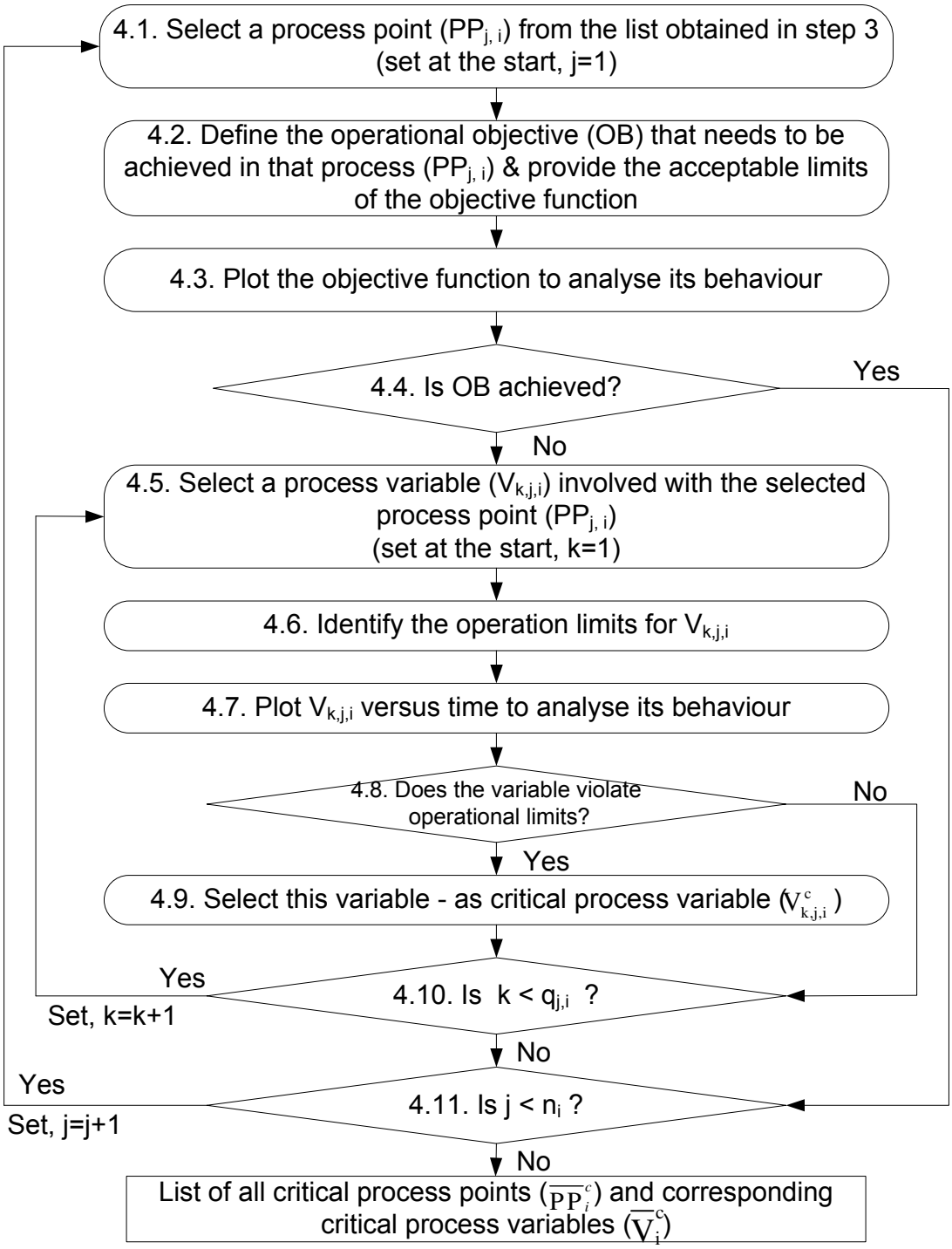

Figure 2.5: Systematic procedure for sensitivity analysis (step 4)
($q_{j,i:}$ number of variables involved with the j^{th} process point of the i^{th} process; n_i: number of process points in i^{th} process)

The detailed steps of the algorithm corresponding to Figure 2.5 are given below:

Step 4.1: Select a process point ($PP_{j,i}$) from the list obtained in step 3

Step 4.2: Define an operational objective (OB) that needs to be achieved in that process ($PP_{j,i}$). Provide the lower and upper acceptable values of the objective function (use knowledge base).

Step 4.3: Plot the objective function versus time to check whether the operational objective (OB) is achieved or not. Use the model library to generate the necessary data to be plotted

Step 4.4: If OB is achieved then go back to step 4.1 and select the next process point until all process points are covered. Otherwise, go to the next step.

Step 4.5: Select a variable ($V_{k,j,i}$) (from the list obtained in step 3) involved with the process point ($PP_{j,i}$) that is under investigated

Step 4.6: Identify the operational limits for selected variable ($V_{k,j,i}$) (obtained from knowledge base in step 3)

Step 4.7: Plot the selected process variable versus time together with the operational limits. Use the model library to generate the necessary data

Step 4.8: If the variable ($V_{k,j,i}$) is within the operational limit then go back to step 4.5 and select the next process variable until all process variables of the selected process point are covered. Follow the next step, if this variable violates the operational limits

Step 4.9: Select the variable ($V_{k,j,i}$) as critical process variable[1] ($V_{k,j,i}^{c}$) and consider the corresponding process point as a critical process point ($P_{j,i}^{c}$)

Step 4.10: Repeat steps 4.5 – 4.9 for each variable involved in the selected process point and collect the critical process variables ($\overline{V}_{j,i}^{c}$)

Step 4.11: Repeat steps 4.1 – 4.10 for each process point and collect the critical process variables ($\overline{V}_{i}^{c}$) and critical process points ($\overline{PP}_{i}^{c}$).

It should be noted that the operational objective of each process point should be achieved by controlling the corresponding critical process variables. These operational objectives

[1] **Critical process variable:** If the considered process variable is not within the operational limits that means it needs to be maintained within the operational limits by employing a suitable controller and therefore it is selected as a critical process variable that need to be monitored and controlled

could not be verified in this step because of the unavailability of control systems (control systems are implemented through next steps). However, these operational objectives need to be verified in validation step (see section 2.2.8, step 8.3.9) before selecting the final set of the controlled variables. Furthermore, the sensitivity of the obtained controlled variables for operational objective also need to be verified (see section 2.2.8, step 8.4) and the variables which are relatively less sensitive or not sensitive for the operational objective can be ignore to reduce the operational cost.

For those variables that can not be modeled, the procedure for sensitivity analysis is similar to the procedure given above (steps 4.1-4.11), except that the process data are generated through experiments instead of a model library in steps 4.3 and 4.6. For example, in a chemical reaction, the objective could be to maximize the product yield while temperature, pressure and reactant concentration can be some of the process variables. The objective here is to identify the critical process variables that need to be monitored and controlled in order to achieve the desired product yield. One would typically investigate this in the lab by performing experiments to generate the dynamic data for product yield (needed in step 4.3) and for process variables (needed in step 4.6). Interpretation of these data would then allow one to determine which process variables are critical. In principle, according to this approach all critical process variables need to be monitored and controlled. However, for critical variables that can not be measured in real time, some other variables have to be measured that are correlated to the critical variable.

2.2.5. Interdependency analysis (step 5)

The interdependency analysis is performed to select the appropriate actuators for each selected critical process variable. In this analysis the effects of process parameters on the individual selected critical process variable are compared. Note that only SISO control is considered in the design methodology. The model library and knowledge base are used to generate the necessary data for this analysis. The systematic procedure for interdependency analysis is highlighted through the flow-diagram in Figure 2.6.

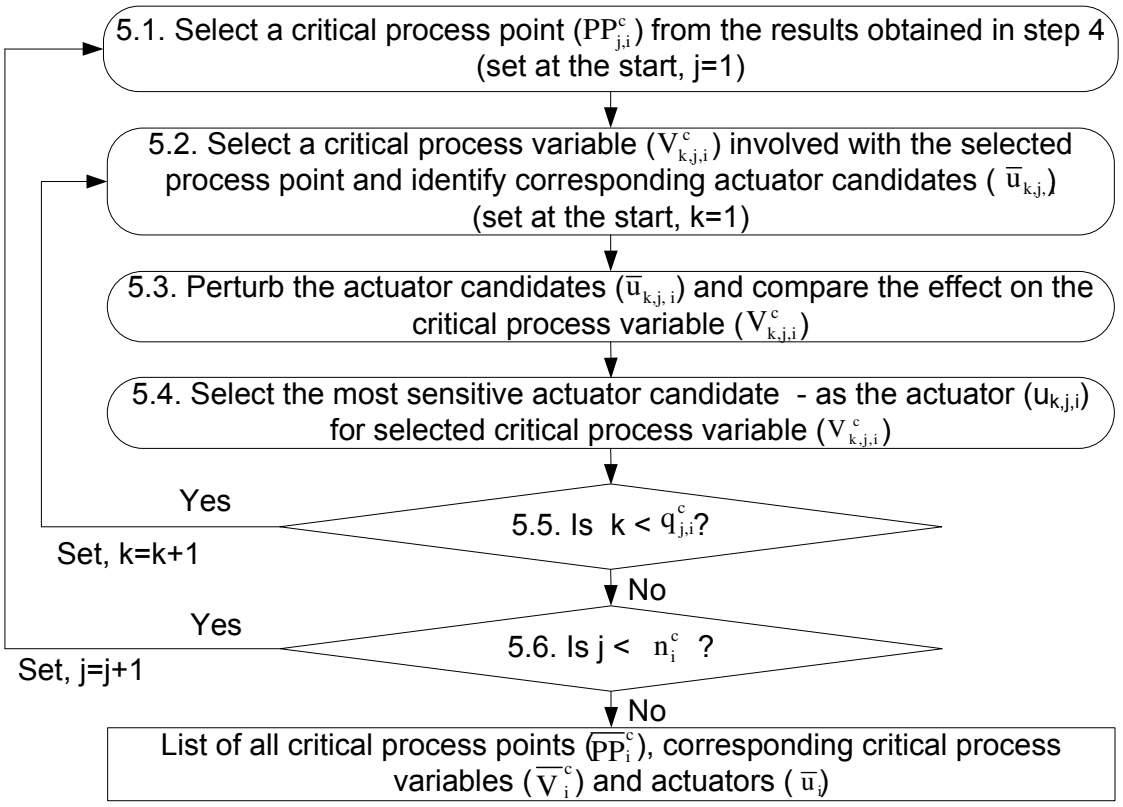

Figure 2.6: Systematic procedure for interdependency analysis (step 5)
($q^c_{j,i}$: number of critical process variables involved with the j^{th} process point of the i^{th} process; n^c_i : number of critical process points in i^{th} process)

The detailed steps of the algorithm corresponding to Figure 2.6 are given below:

Step 5.1: Select a critical process point ($PP_{j,i}^c$) from the results obtained in step 4

Step 5.2: Select a critical process variable ($V_{k,j,i}^c$) involved with the selected process point ($PP_{j,i}^c$) from the results obtained in step 4 and list all the actuator candidates ($\overline{u}_{k,j,i}$) for the selected critical process variable. A knowledge base is used to generate the actuator candidates.

Step 5.3: Perturb the actuator candidates (sensitivity parameters)[2] and compare the effect on the critical process variable (response variable)[3] using an appropriate process model

Step 5.4: Select the actuator candidate that has the largest effect on the critical process variable as actuator ($u_{k,j,i}$) for the critical process variable ($V_{k,j,i}^c$) selected in step 5.2.

[2] Actuator candidates (sensitivity parameter): known variables (= model inputs) of the model can be specified as the sensitivity parameter for interdependency analysis

[3] Critical process variable (response variable): unknown variables of the model (= model outputs) can be specified as the response variable for interdependency analysis

Step 5.5: Repeat steps 5.2-5.4 for each critical process variable involved with the selected critical process point ($P_{j,i}^{c}$) to select the corresponding actuators ($\overline{u}_{j,i}$)

Step 5.6: Repeat steps 5.1-5.5 for each critical process point to obtain the final list of controlled (critical process) variables ($\overline{V}_i^c$) and their corresponding actuators ($\overline{u}_i$).

The procedure for interdependency analysis given above is also applied to variables that can not be modeled, with the only difference that instead of using the model library, the process data (needed in step 5.3) generated through experiments have to be interpreted. As an example, consider again (as discussed in step 4) a batch reactor with temperature as a critical process variable. The objective now is to determine the most appropriate actuator for reactor temperature control. The flow rate of cooling/heating fluid and the inlet temperature of cooling/heating fluid are two actuator candidates. The effect of both actuators could be investigated in the lab by performing a series of batch experiments under identical reaction conditions, except for the cooling/heating fluid flow rate and the inlet temperature of the cooling/heating fluid which are varied. Based on the data generated from the experiments, the effect of flow rate and inlet temperature of cooling/heating fluid on reactor temperature are compared, and the actuator with the most control authority (controlled variable is most sensitive to this actuator) is selected as the most suitable actuator for controlling the temperature.

2.2.6. Performance analysis of monitoring tools (step 6)

The performance analysis of the process monitoring tools aims at selecting the appropriate monitoring tools for each measurable critical process variable. The equipment for each measured critical process variable is selected from the knowledge base, where one is able to list all the available sensors (monitoring tools) included in the knowledge base for that specific variable. The systematic procedure for selection of monitoring tools is highlighted through the flow-diagram in Figure 2.7.

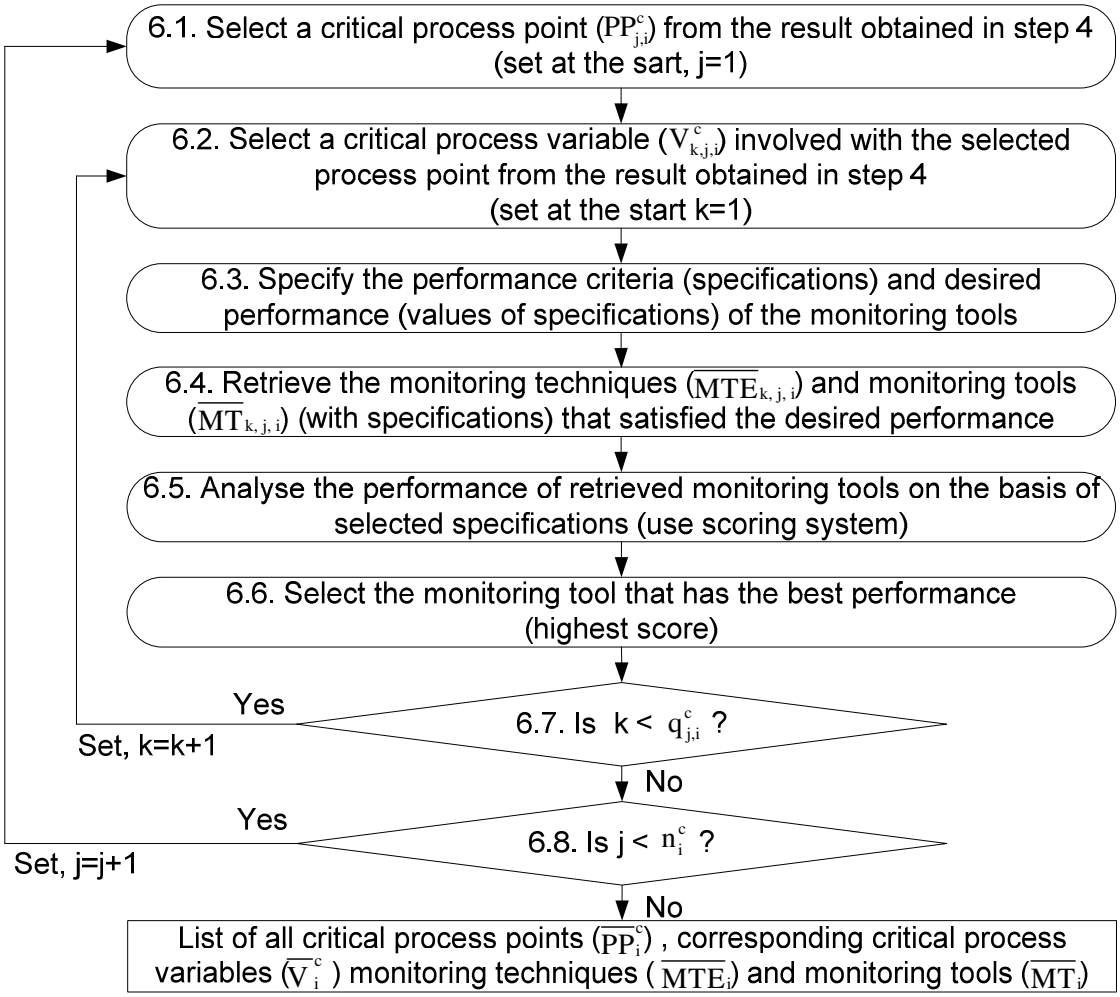

Figure 2.7: Systematic procedure for performance analysis of monitoring tools (step 6)

The detailed steps of the algorithm corresponding to Figure 2.7 are given below:

Step 6.1: Select a critical process point ($PP_{j,i}^c$) from the result obtained in step 4

Step 6.2: Select a critical process variable ($V_{k,j,i}^c$) involved with the selected process point ($PP_{j,i}^c$), from the result obtained in step 4

Step 6.3: Specify the performance criteria (specifications of monitoring tools) and desired performance (desired value of each selected specification) of monitoring tools. The selection of performance criteria is application and user specific

Step 6.4: Retrieve the monitoring techniques ($\overline{MTE}_{k,j,i}$) and corresponding monitoring tools ($\overline{MT}_{k,j,i}$) (with selected specifications) that satisfied the desired performance from the knowledge base.

Step 6.5: Analyze the performance of the retrieved monitoring tools on the basis of one or more of the following performance criteria ($\overline{SP}_{k,j,i}$):

- Accuracy (higher accuracy means a better score)
- Precision (higher precision means a better score)
- Response time (shorter response time means a better score)
- Drift (lower drift means a better score)
- Sensitivity (higher sensitivity means a better score)
- Resolution (higher resolution means a better score)
- Operating range (wider operating range means a better score)
- Operating temperature range (wider operating temperature range means a better score)
- Cost (lower cost means a better score)

The performances of the monitoring tools are compared directly on the basis of either a single criterion (e.g. accuracy) or several criteria in order to select the final monitoring and analysis tools. Therefore a scoring system has been developed to compare the performance of the monitoring tools during this phase. The systematic procedure used for assigning the score to the monitoring tools is highlighted through the flow-diagram in Figure 2.8.

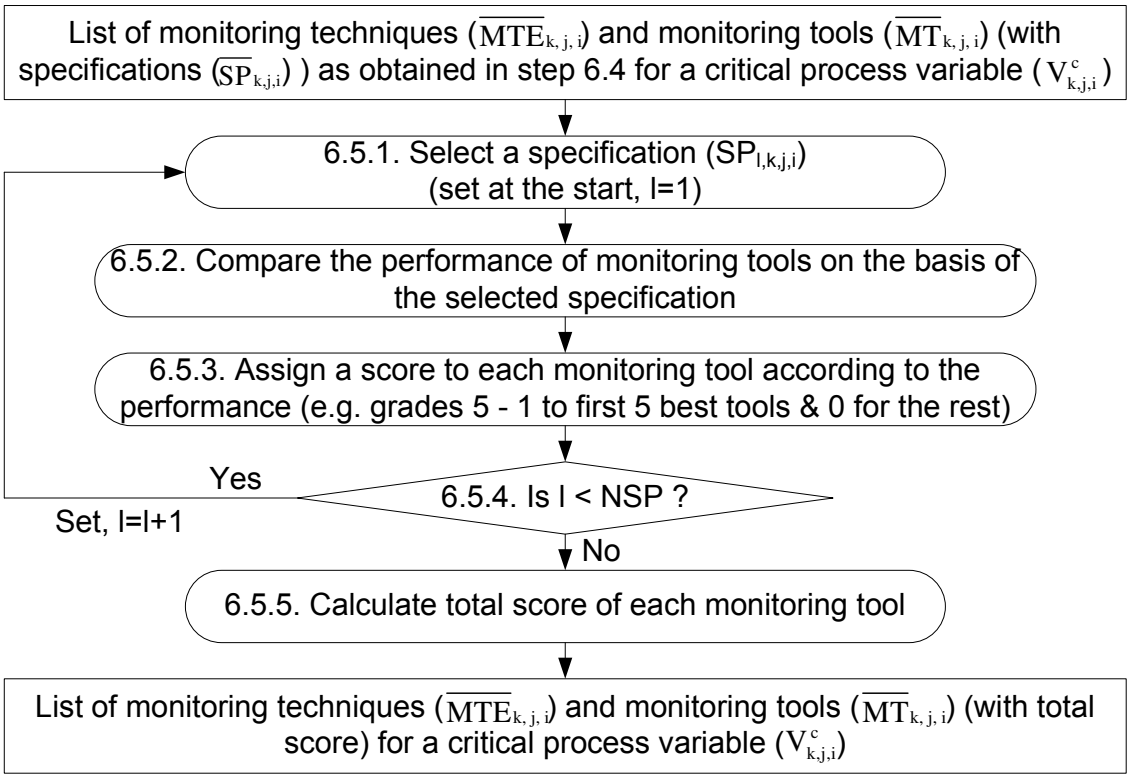

Figure 2.8: Systematic procedure for assigning the score to monitoring tools (NSP: number of specifications)

The procedure (steps 6.5.1-6.5.5) used for assigning scores to the monitoring tools is described as follows:

Step 6.5.1: Select a specification ($SP_{l,k,j,i}$) as obtained in step 6.4

Step 6.5.2: Compare the performance of monitoring tools ($\overline{MT}_{k,j,i}$) obtained in step 6.4, on the basis of the selected specification

Step 6.5.3: Assign a score to each monitoring tool according to its performance. For example score values 5 to 1 can be assigned to the best five monitoring tools and zero is given to the remaining monitoring tools

Step 6.5.4: Repeat steps 6.5.1-6.5.3 until all specifications have been considered

Step 6.5.5: Calculate the total score (summation of individual scores obtained for each specification) obtained by each monitoring tool

Step 6.6: Select the monitoring tool ($MT_{k,j,i}$) that has the best performance (highest total score) for the selected performance criteria, compared to the other available monitoring tools and select the corresponding monitoring technique ($MTE_{k,j,i}$)

Step 6.7: Repeat steps 6.2 – 6.6 for each critical process variable involved with that critical process point ($PP_{j,i}^{c}$).

Step 6.8: Repeat steps 6.1 – 6.7 for each critical process point and select the monitoring tools ($\overline{MT_i}$) and techniques ($\overline{MTE_i}$)

2.2.7. Proposed process monitoring and analysis system (step 7)

On the basis of the above analysis (3.2.1 – 3.2.6) a process monitoring and analysis system can be proposed. Critical process variables were identified in step 4 while the corresponding actuators and monitoring techniques/tools were identified in steps 5 and 6, respectively.

2.2.8. Validation (step 8)

The validation of the designed monitoring and analysis system is achieved by comparing the simulated process performance with known (desired) product/process specifications. If the process performance does not comply with the (desired) product/process specifications then the corresponding design steps are repeated iteratively until a satisfactory design is obtained. A model-based system has been developed to validate a (designed or existing) process monitoring and analysis system.

A closed-loop simulation is used for control-monitor performance verification, for verification of the sensitivity of critical process variables and for product properties verification. First each selected pair consisting of a critical process variable and the corresponding actuator is validated by verifying that the selected critical process variable can be controlled by manipulating the selected actuator. Then it is verified that the selected critical process variables are critical to achieve the operational objective and finally, it is verified that the specified end product properties are achieved. It should be noted that the proposed process monitoring techniques and tools already satisfied the user (performance) specification as this type of criteria formed the basis for selection of monitoring techniques and tools in step 6. Therefore, further verification of the performance of proposed monitoring techniques and tools is not considered here. The systematic procedure for validation of a designed process monitoring and analysis system is highlighted through the flow-diagram in Figure 2.9

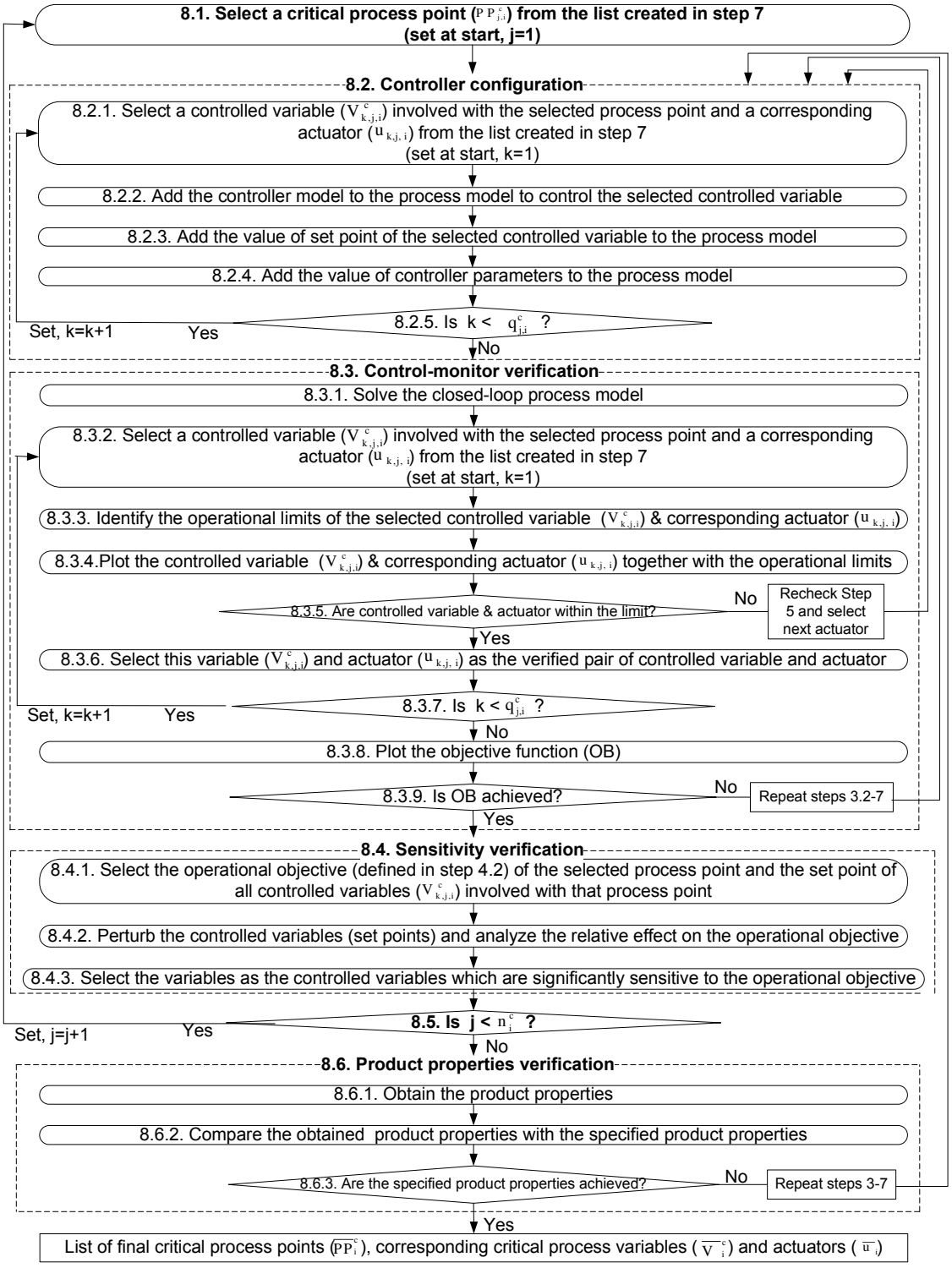

Figure 2.9: Systematic procedure for validation (step 8)

The detailed steps of the algorithm corresponding to Figure 2.9 are given below:

Step 8.1: Select a critical process point ($PP_{j,i}^{c}$) from the list created in step 7

Step 8.2: Controller configuration: Follow the following sub-steps to configure the control system:

Step 8.2.1: Select a controlled variable ($V_{k,j,i}^{c}$) (critical process variable) involved with the selected process point and corresponding actuator ($u_{k,j,i}$) from the list created in step 7

Step 8.2.2: Add the controller model (e.g. for PI or PID controller) to the process model, to control the selected controlled variable. Use the model library to obtain the necessary process operational model.

Step 8.2.3: Add the value of the set point of the controlled variable to the process model. The set point needs to be within the operational limits (obtained in step 3)

Step 8.2.4: Add the value of the controller parameters to the process model. The controller parameters need to be tuned.

Step 8.2.5: Repeat steps 8.2.1-8.2.4 for the next controlled variable until all controller models to control the critical process variables of the selected process point have been added to the process model

Step 8.3: Control-monitor verification: Follow the following sub-steps to verify that the selected controlled variables can be controlled by manipulating the corresponding selected actuators:

Step 8.3.1: Solve the closed-loop process model, using the appropriate simulation tool

Step 8.3.2: Select a controlled variable ($V_{k,j,i}^{c}$) involved with the selected process point and corresponding actuator ($u_{k,j,i}$) from the list created in step 7

Step 8.3.3: Identify the operational limits of the selected controlled variable ($V_{k,j,i}^{c}$) and corresponding actuator ($u_{k,j,i}$). Operational limits of all process variables are obtained in step 3

Step 8.3.4: Plot the selected controlled variable ($V_{k,j,i}^{c}$) and corresponding actuator ($u_{k,j,i}$) together with their operational limits to analyze their behavior.

Step 8.3.5: If the controlled variable and/or corresponding actuator violates the operational limits then return to step 5 (interdependency analysis) and select the next sensitive actuator candidate as the actuator and repeat steps 8.2-8.3.4. Proceed to the next step, if controlled variable and actuator both are within the operational limits.

Step 8.3.6: Select this variable ($V_{k,j,i}^{c}$) and actuator ($u_{k,j,i}$) as the verified pair of controlled variable and actuator

Step 8.3.7: Repeat steps 8.3.1 – 8.3.6 for the next controlled variable involved in the selected process point until all controlled variables and actuators are verified.

Step 8.3.8: Plot the objective function to check whether the operational objective (OB) of the selected process point is achieved or not (similar to step 4.3)

Step 8.3.9: Follow the next step, if this OB is achieved; otherwise repeat the steps 3.2-8.3.8 for the selected process point ($PP_{j,i}^{c}$) until this OB is achieved. One check point in the procedure is step 3.2 where operational limits of process variables ($\overline{V}_{j,i}$) involved with the selected process point ($PP_{j,i}^{c}$) can be rechecked.

Step 8.4: Sensitivity verification: Follow the following sub-steps to verify the sensitivity of the critical process variables

Step 8.4.1: Select the operational objective (defined in step 4.2) of the selected process point and select the set points of all controlled variables (critical process variables) ($V_{k,j,i}^{c}$) involved with that process point

Step 8.4.2: Perturb the controlled variables (set points) and analyze the relative effect on the operational objective.

Step 8.4.3: The variables which are relatively more sensitive for the operational objective should be monitored and controlled while the variables which are relatively less sensitive or not sensitive for the operational objective can be ignored to reduce the operational cost

Step 8.5: Repeat steps 8.1-8.4 for each critical process point.

Step 8.6: Product property verification: Follow the following sub-steps to verify the product properties:

Step 8.6.1: Obtain the product properties. To obtain the product properties, solve the closed-loop model of each unit process according to the order specified in the flowsheet with the constraints that the output of an individual unit process needs to be the input of the next adjacent unit process.

Step 8.6.2: Compare the obtained product properties with the specified product properties.

Step 8.6.3: Collect the final critical process points, the corresponding critical process variables and actuators if the specified product properties are achieved, otherwise repeat steps 3-8.6.2 until the specified product properties are achieved.

2.2.9. Final process monitoring and analysis system (step 9)

Successful completion of step 8 means that the proposed process monitoring and analysis system has been validated and can be considered as the final design. The final process monitoring and analysis system consists of a list of critical process points, corresponding critical process variables, actuators, monitoring techniques and monitoring tools.

2.3. Case study: Fermentation process

To demonstrate the application of the developed framework and methodology for the design of process monitoring and analysis systems, a fermentation process has been selected as a case study.

2.3.1. Process description

The fermentation process shown in Figure 2.10 (adopted from Petrides et al., 1995) is considered here. Fermentation medium is prepared in a mixing tank and sterilized in a continuous heat sterilizer. The axial compressor and the absolute filter provide sterile air and ammonia to the fermentor. A jacketed fermentor is used to carry out an aerobic batch fermentation with *E. coli* cells. These cells are used to produce the Trp-LE'-MET-pro-insulin precursor of insulin, which is not excreted in the fermentation broth but retained in the cellular biomass. The fermentation time in the production fermentor is about 18 hours per batch, and the fermentation temperature is 32 ^{o}C. Water is used as a coolant to maintain the fermentor temperature. The final concentration of *E. coli* cells in the production fermentor is about 50 g/l (30 g/liter dry cell weight). The chimeric protein Trp-LE'-MET-pro-insulin accumulates intracellularly as insoluble aggregates (inclusion bodies) and this decreases the rate at which the protein is degraded by proteolytic enzymes. In the base case, it was assumed that the inclusion bodies (IB's) constitute 20% of total dry cell mass, similar to Petrides et al. (1995). At the end of the fermentation, the broth is cooled down to 10 ^{o}C to minimize cell lysis.

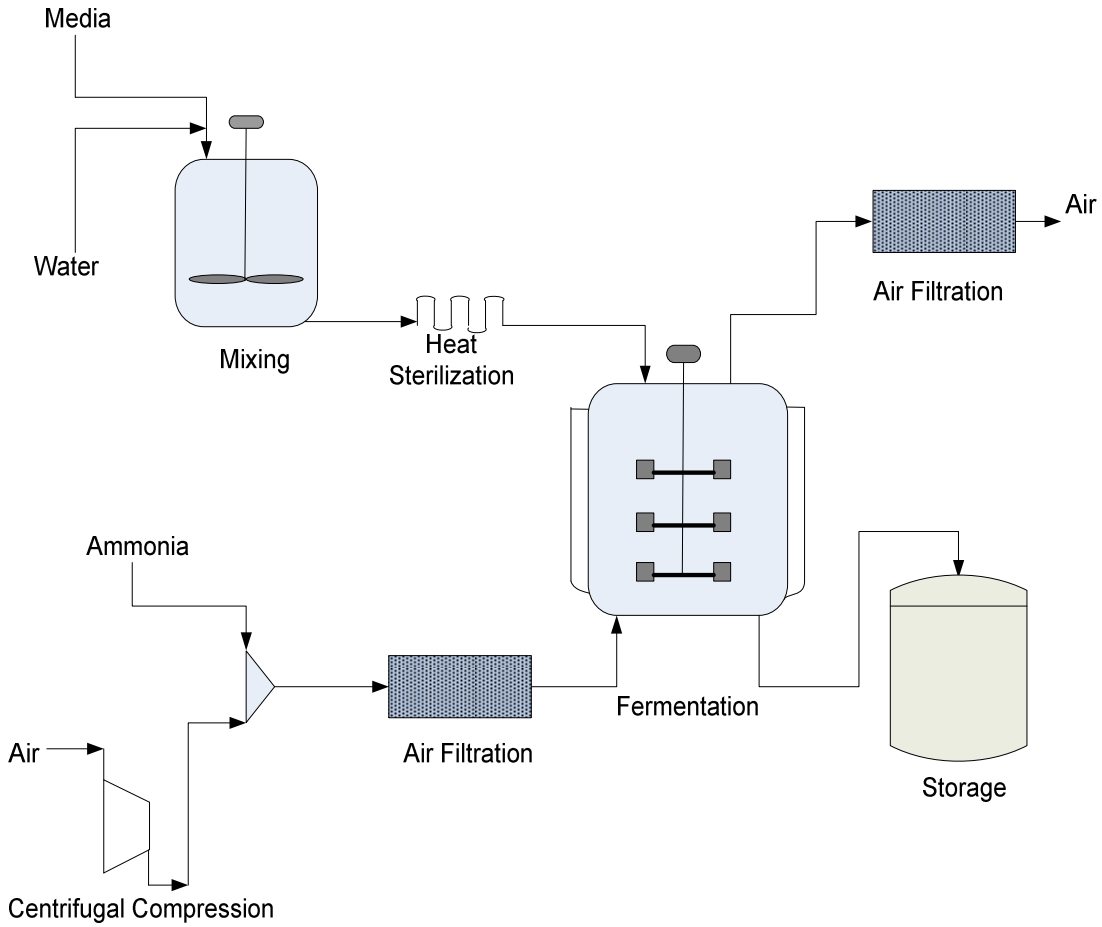

Figure 2.10: Process flowsheet for the fermentation process
(adopted from Petrides et al., 1995)

2.3.2. Process models

The considered case study (see Figure 2.10) involves three process points (mixing tank, heat sterilizer and fermentor). The corresponding process models are described in the following sections.

2.3.2.1. Mixing process model

The list of model equations is given in Appendix A1.1. The total number of equations in this case is 2 (algebraic). The total number of variables involved in the model is 10 (see Table 2.2). The degree of freedom is calculated to be 8. The detailed classification of the variables is given in Table 2.2. The model equations are solved sequentially (eq. 2 followed by eq. 1).

Table 2.2: Classification of variables of the mixing process model

Variable types		Variables	No. of variables	Total no
To be specified	Constant for process	α, β, K	3	8
	Fixed by problem	n, t_0	2	
	Fixed by mixing equipment	d_{str}, d_{tank}, T_L,	3	
To be predicted	Explicit	HO, λ	2	2
Total number of variables involved in the model				10
Total number of algebraic equations (explicit)				2

2.3.2.2. Sterilization process model

The list of model equations is given in Appendix A1.2. The total number of equations in this case is 31. The total number of variables involved in the model is 58 (see Table 2.3) Based on the total number of variables and the total number of equations the degree of freedom is calculated to be 27. The detailed classification of the variables is given in Table 2.3. Based on the classification of variables an incidence matrix between the number of equations and the number of unknown variables is prepared as shown in Table 2.4. Equations 1.2.5, 1.2.6, 1.2.12, 1.2.13, 1.2.23 and 1.2.24 are implicit (see shaded equations in incidence matrix), and therefore these equations need to be solved iteratively. Section 3.3.1 describes the construction and use of incidence matrices

Table 2.3: Classification of variables of the sterilization process model

Variable types		Variable	No. of variables	Total no
To be specified	Constant	π, R , Cpw, ρ_w	4	27
	Fixed by problem	K_{do}, E_d, N_0, T_0, ρ_m, C_{p_m}, f, f_{hw} , f_{cw}, T_{hw_in}, T_{cw_in}, U_{pre}, U_h, U_c	14	
	Fixed by system	l_{pre}, l_h, l_{hold}, l_c, r_{pre}, r_h, r_{hold}, r_{c1}, r_c	9	
To be predicted	Explicit	A_{pre}, t_{pre}, A_h, t_h, A_{hold}, t_{hold}, A_{c1}, t_{c1}, A_c, t_c, b_{pre}, a_h, b_h, β_h, c_h, a_c, b_c, β_c, c_c, T, K_d, N, T_{pre}, T_h, T_c	25	31
	Implicit	T_{pre_f}, T_1, T_p, T_{hw_out}, T_f, T_{cw_out}	6	
Total number of variables involved in the model				58
Total number of algebraic equations (explicit: 25, implicit: 6)				31

Table 2.4: Incidence matrix of sterilization process model

Eq. No.	A_{pre}	t_{pre}	A_h	t_h	A_{hold}	t_{hold}	A_{c1}	t_{c1}	A_c	t_c	b_{pre}	a_h	b_h	β_h	c_h	a_c	b_c	β_c	c_c	T_{pre_f}	T_f	T_p	T_{hw_out}	T_f	T_{cw_out}	T_{pre}	T_h	T_c	T	K_d	N
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2.3.2.3. Fermentation process model

The detailed description of the process model is given in Appendix A1.3. There are 20 differential and 25 algebraic equations (see Appendix A1.3) in the fermentation process operation model. The total number of variables involved in the model is found to be 104 (see Table 2.5). The degree of freedom is calculated to be 59. The detailed classification of the variables is given in Table 2.5. The incidence matrix of this model has also shown a lower triangular form (see Table 2.5, 25 by 25 square matrix forming the top right part of the table), and therefore all the equations can be solved sequentially.

Table 2.5: Classification of variables of the fermentation process model

Variable	Status	Symbol	Number	Total
To be specified	Constant	C_{p_w}, $\rho_{w,}$ α, β, K	5	59
	Fixed by problem	$C^*_{CO_2}$, $C^*_{NH_3}$, C_{p_b}, V_w, U_1, U_2, $\rho_{b,}$ $T_{w_{in}}$, T_{surr}, H_{gr}, H_{ag}, H_{surr}, H_{evp}, H_{sen}, n, u_{O_2}, u_{NH_3}, $F_{w_{in}}$, P_n, μ_{max}, ms_1, bx_1, Y_{XO_2}, Y_{XCO_2}, Y_{XS}, $Y_{XH_3PO_4}$, Y_{XNH_3}, $Y_{XH_2SO_4}$, k_s, k_{O_2}, k_{NH_3}, $k_{H_3PO_4}$, kf_{CO_2}, K_{CO_2}, $kf_{H_2CO_3}$, $K_{H_2CO_3}$, $kf_{HCO_3^-}$, $K_{HCO_3^-}$, $kf_{H_3PO_4}$, $K_{H_3PO_4}$, $kf_{H2PO_4^-}$, $K_{H_2PO_4^-}$, $kf_{NH_4^+}$, $K_{NH_4^+}$, $kf_{H_2SO_4}$, $K_{H_2SO_4}$, $kf_{HSO_4^-}$, $K_{HSO_4^-}$	48	
	Fixed by system	V, A_1, A_2, d_i, d_{tank}, T_L,	6	
To be predicted	Algebraic (explicit)	Pow, kla_{O_2}, kla_{CO_2}, kla_{NH_3}, ms, bx, $C^*_{O_2}$, q_{O_2}, Q_{O_2}, q_{CO_2}, Q_{CO_2}, pH, r_{CO_2}, $r_{H_2CO_3}$, $r_{HCO_3^-}$, $r_{H_3PO_4}$, $r_{H2PO_4^-}$, $r_{HPO_4^{--}}$, r_{NH_3}, $r_{H_2SO_4}$, $r_{HSO_4^-}$, r_{H_2O}, μ, λ, HO	25	45
	Differential	C_{O_2}, C_{CO_2}, C_S, C_{NH_3}, $C_{H_3PO_4}$, C_X, $C_{H_2CO_3}$, $C_{HCO_3^-}$, C_{H^+}, $C_{CO_3^{--}}$, $C_{H_2PO_4^-}$, $C_{HPO_4^{--}}$, $C_{PO_4^{---}}$, $C_{NH_4^+}$, $C_{H_2SO_4}$, C_{HSO_4}, $C_{SO_4^{--}}$, C_{OH^-}, T_b, T_w,	20	
Total number of variables involved in the model				104
Total number of differential equations				20
Total number of algebraic equations (explicit)				25

Table 2.6: Incidence matrix of fermentation process model

		Differential Variables																																												
	Eq. No.	$C_{H_2CO_3}$	$C_{HCO_3^-}$	$C_{CO_3^{--}}$	$C_{H_2PO_4^-}$	$C_{HPO_4^{--}}$	$C_{PO_4^{--}}$	$C_{HSO_4^-}$	$C_{SO_4^{--}}$	$C_{NH_4^+}$	C_X	C_S	C_{O_2}	C_{CO_2}	$C_{H_3PO_4}$	C_{NH_3}	$C_{H_2SO_4}$	C_{OH^-}	C_{H^+}	T_b	T_w	Pow	λ	HO	kla_{O_2}	kla_{CO_2}	kla_{NH_3}	μ	ms	bx	$C^*_{O_2}$	q_{O_2}	Q_{O_2}	q_{CO_2}	Q_{CO_2}	pH	r_{co2}	$r_{H_2CO_3}$	$r_{HCO_3^-}$	$r_{H_3PO_4}$	$r_{H_2PO_4^-}$	$r_{HPO_4^{--}}$	r_{NH_3}	$r_{H_2SO_4}$	$r_{HSO_4^-}$	r_{H_2O}
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2.3.3. Design of the process monitoring and analysis system

The process monitoring and analysis system for the fermentation process (P_1) is then designed as follows by applying the design methodology:

2.3.3.1. Product property specifications (step 1)

The desired product from the fermentation process (P_1) is *E. coli* cells, and is produced in an aerobic batch fermentation. At the end of the fermentation process, the assumed *E. coli* cell concentration is 50 g/liter (30 g/l dry cell weight) in which the protein content is assumed to be 20% of the dry cell mass (Petrides et al., 1995). The composition (mass basis) of the outlet stream from the fermentor comprises 2.95% biomass, 4.00% glucose, 0.58% salts, and 92.46% water.

2.3.3.2. Process specifications (step 2)

The basic raw materials required include: starter culture for inoculation of the fermentor (*E. coli* cells), nutrients (glucose and salts), tryptophan, water, ammonia and air. The process equipments include: a fermentor to carry out the fermentation process, a mixing tank to prepare the homogeneous mixture of nutrients, a continuous heat sterilizer to sterilize the glucose and salt solution, a centrifugal compressor to pump the air, an air filter to remove the solid impurities such that sterile air reaches the fermentation tank, and a storage tank to collect the final product.

2.3.3.3. Process analysis (step 3)

The process points and process variables are identified through the following steps:

Step 3.1: The considered process flowsheet (see Figure 2.10) involved 3 process points ($\overline{PP_i}$): fermentor, heat sterilizer and mixing tank

Step 3.2: The process point fermentor ($PP_{1,1}$) is selected for further analysis. The variables involved with the fermentor ($\overline{V}_{1,1}$), are obtained from the knowledge base and listed in Table 2.7. The operational limits of the retrieved variables are also identified and included in the Table 2.7.

Step 3.3: Repeating step 3.2 for other process points (heat sterilizer and mixing tank) yields the variables involved with these process points. These variables are also listed in Table 2.7.

Table 2.7: List of process points and process variables (with operational limits) of fermentation process

Process points ($\overline{PP_1}$)	Process variables ($\overline{V_1}$)	Symbols	Lower limits	Upper limits	Units
Fermentor	Dissolved oxygen (DO) concentration	C_{O_2}	0.00067	0.007	kg/m^3
	pH	pH	6	7	pH
	Temperature	T_b	293	310	K
	Pressure	P	1	2	atm
	Dissolved CO_2 concentration	C_{CO_2}	0.0005	0.004	kg/m^3
	Dissolved NH_3 concentration	C_{NH_3}	0.00001	0.004	kg/m^3
	Inlet flow rate of air	$u_{O_2\_in}$	0	0.65	m/s
	Outlet flow rate of air	$u_{O_2\_out}$	0	0.65	m/s
	Inlet flow rate of NH_3	$u_{NH_3\_in}$	0	0.65	m/s
	Outlet flow rate of NH_3	$u_{NH_3\_out}$	0	0.65	m/s
	Coolant flow rate	$F_{w_{in}}$	0	2300	m^3/hr
	Coolant temperature	$T_{w_{in}}$	0	20	^{o}C
	Substrate concentration	C_S	1	180	kg/m^3
	Biomass concentration	C_X	1	30	kg/m^3
	Cell mass	M_X	30	900	kg
	Foaming level	FL	0	0.01	m
	Stirrer speed	n	0	10	rps
	Cell growth rate	μ	0.1	0.15	hr^{-1}
	Phosphate concentration	$C_{H_3PO_4}$	2	15	kg/m^3
	Sulfate concentration	$C_{H_2SO_4}$	1	5	kg/m^3
	Homogeneity	HO_F	0.90	1	fractional
Heat sterilizer	Sterilization temperature	T_{ster}	120	150	^{o}C
	Heating fluid temperature	T_{hw}	120	200	^{o}C
	Heating fluid flow rate	F_{hw}	300	700	kg/hr
	Main stream flow rate	F	300	700	kg/hr
	Sterilization duration	t_h	0.5	7	hr
Mixing tank	Homogeneity	HO_{MT}	0.90	1.00	fractional
	Stirrer speed	n	0	10	rps
	Mixing time	t_0	0	3	hr

2.3.3.4. Sensitivity analysis (step 4)

Open-loop simulation of an aerobic batch fermentation process is performed with constant and limited supply of air and ammonia during the fermentation process. The stirrer speed is assumed to be constant at 480 rpm. The values of known variables and parameters are taken from the available literature (see Appendix B). Sensitivity analysis is performed through the following steps:

Step 4.1: The process point, fermentor, is selected from Table 2.7 for further analysis.

Step 4.2: The operational objective for the fermentation step is to maximize the specific growth rate. The desired specific growth rate in the fermentation step should be within 0.1 – 0.15 per hour (66.67 – 100 % of maximum specific growth rate) (obtained from data stored in knowledge base)

Step 4.3: The profile of the objective function (specific growth rate) is shown in Figure 2.11. This figure shows that the value of the specific growth rate (μ) is considerably lower than the maximum specific growth rate (μ_{max}) throughout the batch fermentation.

Step 4.4: The operational objective (OB) of the fermentation step is not achieved (see Figure 2.11), and therefore the following steps have been followed:

Step 4.5: The process variable, dissolved oxygen concentration (DO) involved in the fermentor is selected from Table 2.7 for analysis.

Step 4.6: The operational limits of DO are identified (from stored data in the knowledge base), where the DO should be maintained above a minimum limiting value (D_{min} > 0.00067 kg/m^3) (Doran, 2006).

Step 4.7: The simulated behavior of the DO concentration in open-loop is shown in Figure 2.12.

Step 4.8: The DO violates the lower limit (see Figure 2.12) required to avoid the inhibition of the cell growth rate due to lack of oxygen, indicating thereby that this variable needs to be monitored and controlled throughout the fermentation process.

Step 4.9: This variable (DO) is therefore selected as a critical process variable, and the corresponding process point (fermentor) is considered as a critical process point where monitoring is required

Step 4.10: Repeating steps 4.5 - 4.9 for next process variable as follows:

- **Step 4.5:** pH is selected for analysis.

- **Step 4.6:** The operational limits of pH are identified (from the knowledge base)**:** It was assumed that the pH should be maintained between 6 and 7. Note that these pH limits can be adjusted depending on the optimal pH range of the process that is studied. The pH values used here are only for illustrative purposes.
- **Step 4.7:** The behavior of pH is shown in Figure 2.13.
- **Step 4.8:** pH violates the lower and upper limits of the optimal pH range (see Figure 2.13), indicating thereby that this variable needs to be monitored and controlled throughout the fermentation process.
- **Step 4.9:** pH is therefore selected as a critical process variable
- **Step 4.10:** Repeating the procedure (steps 4.5-4.9) for all other process variables of the selected process point (fermentor) identifies all the critical process variables in the fermentor, which are listed in Table 2.8.

Step 4.11: Repeating this procedure (steps 4.1-4.10) for the remaining process points (heat sterilizer and mixing tank) identifies all the corresponding critical process variables which are also added in Table 2.8. Since the fermentor, heat sterilizer and mixing tank all contain critical process variables, therefore these points are considered as the critical process points where monitoring is required

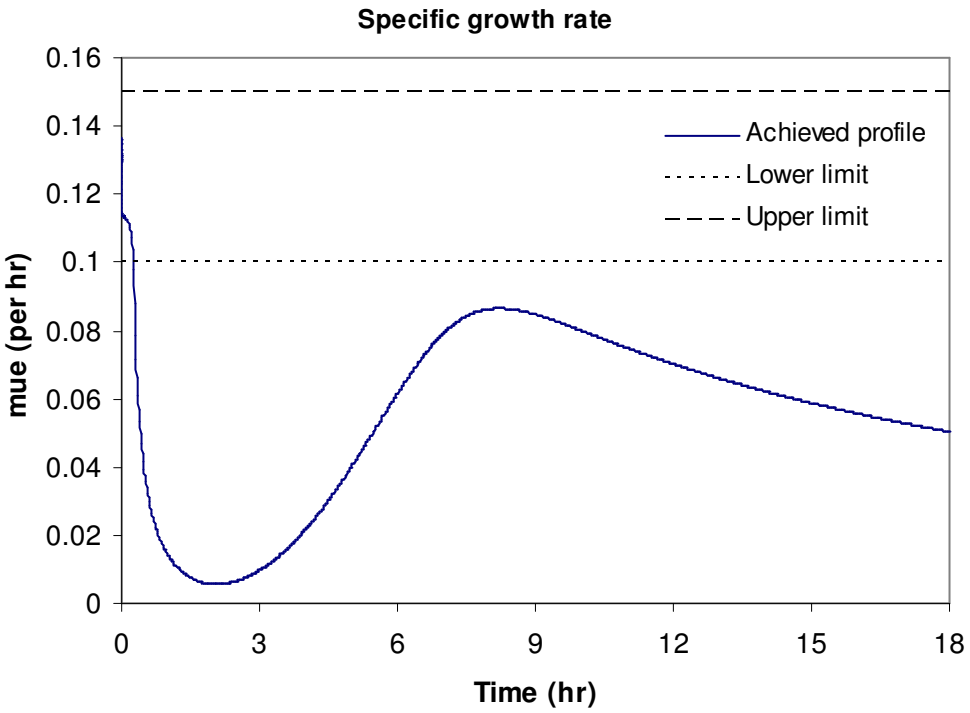


Figure 2.11: Profile of operational objective in fermentor (open-loop simulation)

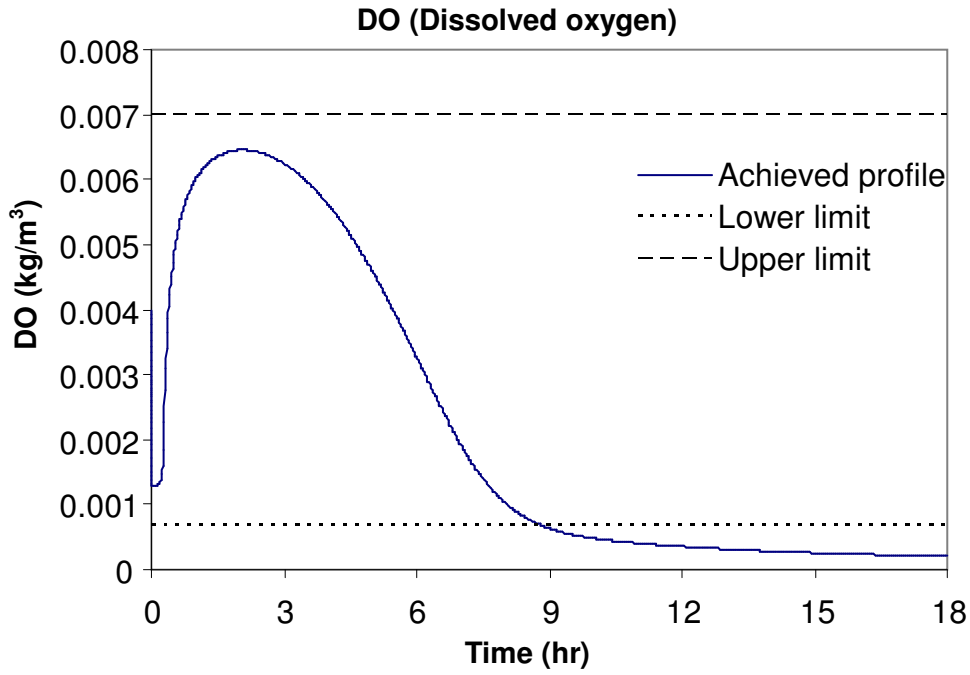


Figure 2.12: Simulated dissolved oxygen concentration in open-loop

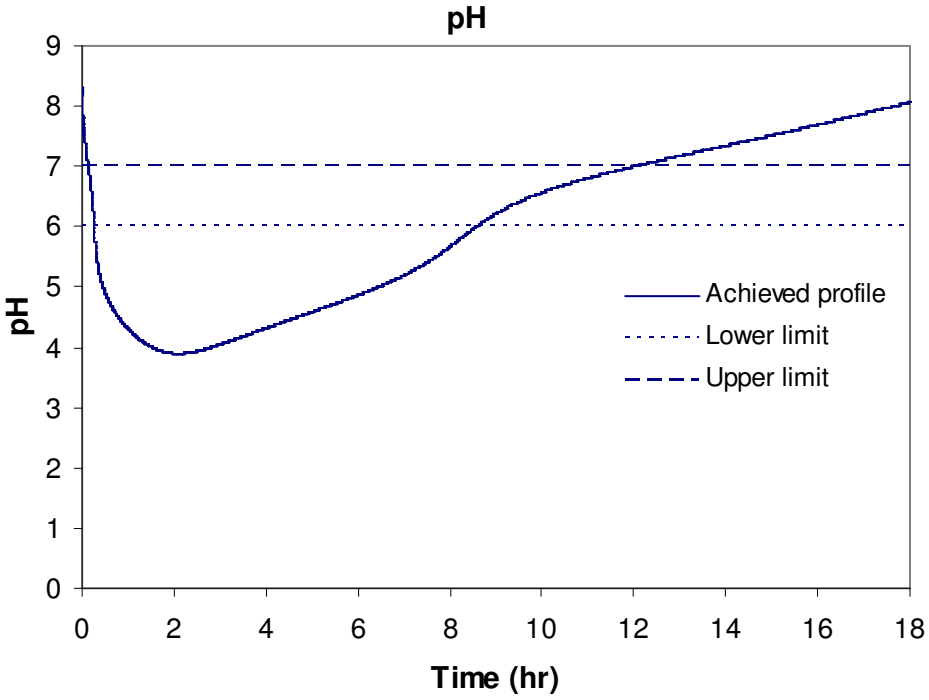


Figure 2.13: Simulated pH profile in open-loop

Table 2.8: List of critical process points and critical process variables of fermentation process

Critical process points ($\overline{PP}_l^c$)	Critical process variables ($\overline{V}_l^c$)
Fermentor	Dissolved oxygen concentration
	pH
	Temperature
	Dissolved CO_2 concentration
	Homogeneity
Heat sterilizer	Sterilization temperature
Mixing tank	Homogeneity

2.3.3.5. Interdependency analysis (step 5)

The interdependency analysis is performed to find the appropriate actuators for each critical process variable. The process parameters (possible actuators ($\overline{u}_{k,j,i}$)) that can influence the particular critical process variable ($V_{k,j,i}^c$) have been selected first by searching the knowledge base. The effect of these parameters on the particular critical

process variable has then been compared through the interdependency analysis. The interdependency analysis is performed as given below:

Step 5.1: The fermentor is selected for further analysis (from Table 2.8)

Step 5.2: DO is selected as a response variable (controlled variable) while air flow rate and stirrer speed[4] are selected as the sensitivity parameters (actuator candidates). The later information is obtained from the knowledge base. A fermentation process expert could have provided similar information.

Step 5.3: The simulated effect of air flow rate and stirrer speed on the DO is shown in Figure 2.14

Step 5.4: The air flow rate is selected as an actuator to control the DO in the fermentor, since the DO concentration is more sensitive to the air flow rate in comparison with the stirrer speed (see Figure 2.14)

Step 5.5: Repeating steps 5.1-5.4 for each critical process variable involved with the fermentor yields the corresponding actuators, which are given in Table 2.9

Step 5.5: Repeating this procedure (steps 5.1-5.5) for the remaining critical process points yields the corresponding actuators, which are also given in Table 2.9

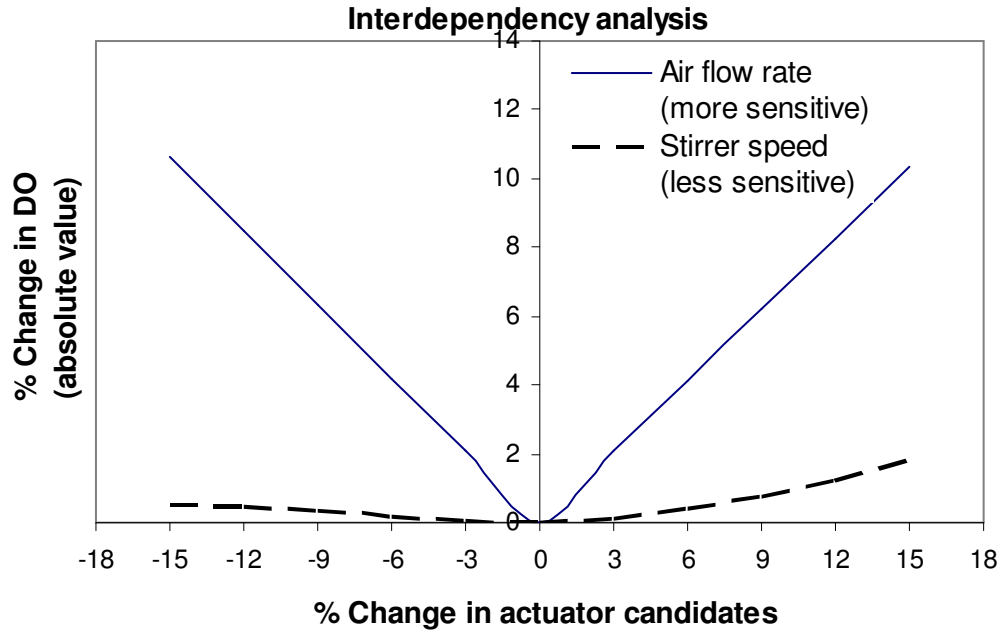


Figure 2.14: Actuator selection for dissolved oxygen concentration

[4] Stirring duration and stirrer speed are known variables in the model (see Table 2.5)

Table 2.9: List of critical process variables and corresponding actuators for fermentation process

Critical process points ($\overline{PP}_1^c$)	Critical process variables ($\overline{V}_1^c$)	Actuators ($\overline{u}_1$)
Fermentor	Dissolved oxygen concentration	Air flow rate
	pH	Ammonia flow rate
	Temperature	Coolant flow rate
	Dissolved CO_2 concentration	Air flow rate
	Homogeneity	Stirrer speed
Heat sterilizer	Sterilization temperature	Heating fluid flow rate
Mixing tank	Homogeneity	Mixing time

2.3.3.6. Performance analysis of monitoring tools (step 6)

The performance analysis of the monitoring tools has been carried out by using the knowledge base to select the monitoring tool for each critical process variable. The following steps were used for this analysis:

Step 6.1: The fermentor is selected as the critical process point for further analysis from Table 2.8

Step 6.2: In the fermentor, the DO concentration is selected for further analysis (from Table 2.8)

Step 6.3: The specified performance criteria (specifications of monitoring tools) and their desired performances (desired values of specifications) are given in Table 2.10. This information is provided by the user

Table 2.10: Selected specifications of monitoring tools and their desired values (user specific)

Specifications (performance criteria)	Desired value of specifications (desired performance)
Accuracy (Ac)	Ac ≤ 5 % of reading
Precision (Pr)	Pr ≤ 5 % of reading
Lower operating limit (LOL)	LOL ≤ 0.001 mg/l
Upper operating limit (UOL)	UOL ≥0 .15 mg/l
Response time (RT)	RT (T90) ≤ 100 seconds
Resolution (R)	R ≤ 0.2 mg/l
Drift (D)	D ≤ 2 % of reading per week
Lower operating temperature (LOT)	LOT ≤ 0 ^{o}C
Upper operating temperature (UOT)	UOT ≥ 40 ^{o}C

Step 6.4: The available monitoring techniques and corresponding monitoring tools for DO measurement that satisfied the desired performance are obtained from the knowledge base and given in Table 2.11.

Step 6.5: The performance of the monitoring tools (listed in Table 2.11) is compared on the basis of the specified performance criterion (specifications) given in Table 2.10. The scoring system is used to compare the monitoring tools, as described below:

Step 6.5.1: Accuracy is selected as performance criterion for further analysis from Table 2.11

Step 6.5.2: The performance of all the monitoring tools listed in Table 2.11 (for DO monitoring) is compared based on accuracy. For example, the comparison shows that the 'FOXY sensor system (based on optical technique)' is most accurate among the monitoring tools listed in Table 2.11

Step 6.5.3: Each monitoring tool is assigned a score based on its accuracy as given in Table 2.12 (see 3rd column of this table). For example, the highest score (5) is assigned to the 'FOXY sensor system (based on optical technique)'.

Step 6.5.4: Steps 6.5.1-6.5.3 are repeated for other specifications, and the obtained corresponding scores are added in Table 2.12

Step 6.5.5: The total score obtained by each monitoring tool is calculated and added to Table 2.12 (see last column of this table).

Step 6.6: The 'FOXY sensor system (based on optical technique)' obtained the highest total score (see Table 2.12, last column), and therefore this monitoring tool is selected for DO monitoring. The selected monitoring tool is based on an optical technique.

Step 6.7: Repeating the procedure (steps 6.2-6.6) for the other critical process variables for the fermentor yields the monitoring tools and techniques as listed in Table 2.13

Step 6.6: Repeating the procedure (steps 6.1-6.5) for the other critical process points (Heat sterilizer and mixing tank) yields the monitoring tools ($\overline{MT_l}$) and techniques ($\overline{MTE_l}$) as listed in Table 2.13.

Table 2.11: Monitoring tools for dissolved oxygen concentration with specifications (obtained from the knowledge base)
(Ac: Accuracy; Pr: Precision; LOL: Lower operating limit; UOL: Upper operating limit; RT: response time; R: Resolution; D: Drift; LOT: Lower operating temperature; UOT: Upper operating temperature; [ ]: indicates the reference number in the knowledge base)

Monitoring techniques	**Monitoring tools**	**Ac**	**Pr**	**LOL**	**UOL**	**RT (T90)**	**R**	**D**	**LOT**	**UOT**
Optical sensor	RDO [185]	1.0 % of reading [50]	0.11 % of reading [77]	0.0 mg/l [50]	20.0 mg/l [50]	30.0 s [185]	0.001 mg/l [96]	0.019 % of reading per week [77]	0.0 °C [106]	50.0 °C [106]
	FOXY Sensor System [182]	0.1 % of reading	0.1 % of reading	0.0 mg/l	40.7 mg/l [50]	1.0 s	0.001 mg/l [96]	0.019 % of reading per week[77]	-44.0 °C	80.0 °C
	ROX optical dissolved oxygen sensor [186]	1.0 % of reading	1.0 % of reading	0.0 mg/l [50]	50.0 mg/l	N/A	0.010 mg/l	0.019 % of reading per week[77]	0.0 °C [106]	80.0 °C [106]
Electrochemical polarographic sensor	DirectLine® Series DL5000 [179]	5.0 % of reading	5.0 % of reading	0.0 mg/l	N/A	60.0 s	0.01 mg/l [109]	1.000 % of reading per week [77]	2.0 °C	60.0 °C
	Universal Dual Analyzer UDA2182 [180]	0.5 % of reading	0.05 % of reading	0.0 mg/l	200.0 mg/l	N/A	0.01 mg/l [109]	1.000 % of reading per week [110]	0.0 °C	60.0 °C
	770MAX 368-210 [181]	2.0 % of reading	2.0 % of reading	0.0 mg/l	5.0 mg/l	60.0 s	0.01 mg/l [109]	1.000 % of reading per week [110]	5.0 °C	50.0 °C [106]
	770MAX High Performance DO Sensor -- 357-210 [181]	1.0 % of reading	1.0 % of reading	0.0 mg/l	10.0 mg/l	90.0 s	0.01 mg/l [109]	1.000 % of reading per week [110]	0.0 °C	60.0 °C
	770MAX Long-Life DO Sensor -- 357-110 [181]	2.0 % of reading	2.0 % of reading	0.0 mg/l	10.0 mg/l	20.0 s	0.01 mg/l [109]	1.000 % of reading per week [110]	5.0 °C	50.0 °C [106]
	M300 High Performance DO Sensor -- 58-037-204 [181]	1.0 % of reading	1.0 % of reading	0.0 mg/l	10.0 mg/l	90.0 s	0.01 mg/l [109]	1.000 % of reading per week [110]	0.0 °C	60.0 °C
	M300 High Performance DO Sensor -- 58-037-205 [181]	1.0 % of reading	1.0 % of reading	0.0 mg/l	10.0 mg/l	90.0 s	0.01 mg/l [109]	1.000 % of reading per week [110]	0.0 °C	60.0 °C
	M300 High Performance DO Sensor -- 58-037-206 [181]	1.0 % of reading	1.0 % of reading	0.0 mg/l	10.0 mg/l	90.0 s	0.01 mg/l [109]	1.000 % of reading per week [110]	0.0 °C	60.0 °C

Table 2.11 (continued)

Monitoring techniques	Monitoring tools	Ac	Pr	LOL	UOL	RT (T90)	R	D	LOT	UOT
Electrochemical polarographic sensor (continued)	M300 High Performance DO Sensor -- 58-037-207 [181]	1.0% of reading	1.0 % of reading	0.0 mg/l	10.0 mg/l	90.0 s	0.01 mg/l [109]	1.000 % of reading per week [110]	0.0 °C	60.0 °C
	M300 Long-Life DO Sensor -- 58-037-221 [181]	2.0 % of reading	2.0 % of reading	0.0 mg/l	10.0 mg/l	20.0 s	0.01 mg/l [109]	1.000 % of reading per week [110]	5.0 °C	50.0 °C [106]
	Polarographic Dissolved Oxygen Probe -- D701 [183]	1.0 % of reading	1.0 % of reading	0.0 mg/l	10.0 mg/l	50.0 s	0.01 mg/l [109]	1.000 % of reading per week [110]	20.0 °C	50.0 °C [106]
	Orion Dissolved Oxygen/BOD Probe – 970800 [184]	2.0 % of reading	2.0 % of reading	0.0 mg/l	14.0 mg/l	30.0 s	0.01 mg/l [109]	1.000 % of reading per week [110]	0.0 °C	45.0 °C
Electrochemical galvanic sensor	Dissolved Oxygen Probe -- Model 760DOP [174]	0.15 % of reading [1]	0.18 % of reading [7]	0.0 mg/l	20.0 mg/l	9.0 s [102]	0.10 mg/l	0.110 % of reading per week [102]	0.0 °C	50.0 °C [106]
	Heavy Duty Dissolved Oxygen Meter [175]	2.0 % of reading	2.0 % of reading	0.0 mg/l	20.0 mg/l	8.0 s	N/A	0.110 % of reading per week [102]	0.0 °C	50.0 °C [106]
	Waterproof ExStik® II Dissolved Oxygen Meter/Kit [176]	2.0 % of reading	2.0 % of reading	0.0 mg/l	20.0 mg/l	N/A	0.010 mg/l	0.110 % of reading per week [102]	0.0 °C	55.0 °C
	CS511-L [187]	2.0 % of reading	2.0 % of reading	0.0 mg/l	20.0 mg/l	N/A	N/A	0.110 % of reading per week [102]	0.0 °C	50.0 °C [106]
	DO 100 [177]	3.0 % of reading	3 .0 % of reading	0.0 mg/l	20.0 mg/l	2400.0 s	N/A	0.110 % of reading per week [102]	0.0 °C	55.0 °C
	DirectLine® Series -- DL424 [178]	1.0 % of reading	1.0 % of reading	0.0 mg/l	20.0 mg/l	60.0 s	0.010 mg/l	0.110 % of reading per week [102]	-20.0 °C	60.0 °C
	DirectLine® Series -- DL425	5.0 % of reading	5.0 % of reading	0.0 mg/l	0.2 mg/l	60.0 s	0.001 mg/l	0.110 % of reading per week	0.0 °C	50.0 °C

Table 2.12: Monitoring tools for dissolved oxygen concentration with grades

Monitoring techniques	Monitoring tools	Ac	Pr	LOL	UOL	RT	R	D	LOT	UOT	Total scores
Optical sensor	RDO	2	3	5	2	1	5	5	3	2	28
	FOXY Sensor System	5	4	5	3	5	5	5	5	5	**42**
	ROX optical dissolved oxygen sensor	2	1	5	4	0	4	5	3	5	29
Electrochemical polarographic sensor	DirectLine® Series DL5000	0	0	5	0	0	4	3	2	4	18
	Universal Dual Analyzer UDA2182	3	5	5	5	0	4	3	3	4	32
	770MAX 368-210	1	0	5	0	0	4	3	1	3	17
	770MAX High Performance DO Sensor -- 357-210	2	1	5	0	0	4	3	3	4	22
	770MAX Long-Life DO Sensor -- 357-110	1	0	5	0	2	4	3	1	3	19
	M300 High Performance DO Sensor -- 58-037-204	2	1	5	0	0	4	3	3	4	22
	M300 High Performance DO Sensor -- 58-037-205	2	1	5	0	0	4	3	3	4	22
	M300 High Performance DO Sensor -- 58-037-206	2	1	5	0	0	4	3	3	4	22
	M300 High Performance DO Sensor -- 58-037-207	2	1	5	0	0	4	3	3	4	22
	M300 Long-Life DO Sensor -- 58-037-221	1	0	5	0	2	4	3	1	2	18
	Polarographic Dissolved Oxygen Probe -- D701	2	1	5	0	0	4	3	0	2	17
	Orion Dissolved Oxygen/BOD Probe -- 970800	1	0	5	1	1	4	3	3	1	19
Electrochemical galvanic sensor	Dissolved Oxygen Probe -- Model 760DOP [174]	4	2	5	2	3	3	4	3	2	28
	Heavy Duty Dissolved Oxygen Meter	1	0	5	2	4	0	4	3	2	21
	Waterproof ExStik® II Dissolved Oxygen Meter/Kit	1	0	5	2	0	4	4	3	3	22
	CS511-L	1	0	5	2	0	0	4	3	2	17
	DO 100	0	0	5	2	0	0	4	3	3	17
	DirectLine® Series -- DL424	2	1	5	2	0	4	4	4	4	26
	DirectLine® Series -- DL425	0	0	5	0	0	5	4	3	2	19

Table 2.13: Critical controlled variables and selected monitoring techniques and tools for the fermentation process

Critical process points ($\overline{PP_1^c}$)	Critical process variables ($\overline{V_1^c}$)	Monitoring techniques ($\overline{MTE_1}$)	Monitoring tools ($\overline{MT_1}$)
Fermentor	Dissolved oxygen concentration (DO)	Optical sensor	FOXY Sensor System
	pH	Electrochemical sensor	pH Meter -- Model 2410
	Temperature	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
	Dissolved CO_2 concentration	Optical sensor	FOXY Sensor System
	Homogeneity	NIR	EPP 2000 Fiber Optic Spectrometer-NIR2
Heat sterilizer	Temperature	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
Mixing tank	Homogeneity	NIR	EPP 2000 Fiber Optic Spectrometer-NIR2

2.3.3.7. Proposed process monitoring and analysis system (step 7)

Following the application of the above-mentioned stepwise procedure, a monitoring and analysis system for the fermentation process is now suggested (see Table 2.14).

Table 2.14: Suggested monitoring and analysis system for the fermentation process

Critical process points ($\overline{PP_1^c}$)	Critical process variables ($\overline{V_1^c}$)	Actuators ($\overline{u_1}$)	Monitoring techniques ($\overline{MTE_1}$)	Monitoring tools ($\overline{MT_1}$)
Fermentor	Dissolved oxygen concentration	Air flow rate	Optical sensor	FOXY Sensor System
	pH	Ammonia flow rate	Electrochemical sensor	pH Meter -- Model 2410
	Temperature	Coolant flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
	Dissolved CO_2	Air flow rate	Optical sensor	FOXY Sensor System
	Homogeneity	Stirrer speed	NIR	EPP 2000 Fiber Optic Spectrometer-NIR2
Heat sterilizer	Temperature	Heating fluid flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
Mixing tank	Homogeneity	Mixing time	NIR	EPP 2000 Fiber Optic Spectrometer-NIR2

2.3.3.8. Model-based validation (step 8)

Closed-loop simulation has been performed to validate the obtained process monitoring and analysis system. The same simulation scenario as used in open-loop simulation has been used in this case also. The following steps were used for validation:

Step 8.1: The fermentor is selected as critical process point for further analysis (from Table 2.14)

Step 8.2: Controller configuration: The control systems involved in the fermentor are configured as follows:

Step 8.2.1: A controlled variable DO and corresponding actuator 'air flow rate' is selected from Table 2.14.

Step 8.2.2: A PI (proportional integral) controller is added to the process model to control the DO (see Appendix A1.3.3)

Step 8.2.3: Set point of DO is specified to the process model (see Appendix B3)

Step 8.2.4: Proportional and integral constants of the selected PI controller for DO control are specified to the process model (see Appendix B3)

Step 8.2.5: Steps 8.2.1 - 8.2.4 are repeated for each critical process variable (pH, temperature, Homogeneity) involved in the fermentation process; corresponding controller models and data (set points and tuning constants) are given in Appendix A1.3.3 and B3 respectively. It should be noted that DO and DCO_2 have the same actuator. Therefore only one variable need to be controlled independently (DO is considered in this case)

Step 8.3: Control-monitor verification: Through the following steps, it is verified that the selected controlled variables can be controlled by manipulating the corresponding selected actuators:

Step 8.3.1: The closed-loop model of the fermentation process (model is given in Appendix A1.3) is solved, using the simulation tool, ICAS-MoT

Step 8.3.2: A controlled variable, DO and corresponding actuator, air flow rate is selected from Table 2.14 for analysis

Step 8.3.3: Operational limits of DO (same as used in step 4.6: 0.00067 - 0.007 kg/m^3) and air flow rate (0 – 0.65 m/s) are obtained from Table 2.7

Step 8.3.4: The behavior of DO (controlled variable) and air flow rate (actuator) are shown in Figure 2.15 and Figure 2.16 respectively

Step 8.3.5: As shown in Figure 2.15. The set point of dissolved oxygen concentration (DO) is tracked successfully by manipulation of the air flow rate. Figure 2.16 shows the simulated dynamic profile of the manipulated variable during the batch fermentation. Controlled variable responses and actuator actions are within the specified limits. Therefore, it is concluded that the DO can be controlled by manipulating the air flow rate.

Step 8.3.6: DO and air flow rate are selected as the verified pair of controlled variable and actuator.

Step 8.3.7: Steps 8.3.1 - 8.3.6 are repeated for other controlled variables (pH, temperature, Homogeneity) involved in the fermentation process. The profiles of pH and its corresponding actuator are shown in Figure 2.17 and Figure 2.18 respectively. Similarly, Figure 2.19 and Figure 2.20 show the temperature profile and their corresponding actuators, respectively. A good agreement between the set points and the achieved profiles can be observed. These controlled variables and actuators are also within the operational limits. Figure 2.21 shows that a complete homogeneity is achieved

in the fermentor within a reasonable time interval. The actuator (stirrer speed) is also found to be within the operational limits. Therefore it is not necessary to control the homogeneity explicitly. This analysis concludes that the performance of control loops for controlling the DO, pH and temperature are satisfactory.

Step 8.3.8: The dynamic profile of the operational objective (specific cell growth rate) is shown in Figure 2.22.

Step 8.3.9: Figure 2.22 shows that the achieved profile of specific growth rate (OB) is within the specified limit values, meaning that the operational objective is achieved. Note that, an overshoot is observed in the profile of dissolved oxygen concentration (see Figure 2.15) and pH (Figure 2.17) at the beginning of the fermentation process that leads to a sudden decrease of specific growth rate also at that point. This sudden decrease of specific growth rate is, however observed only for a very short time interval, and therefore it can be neglected.

Step 8.4: Sensitivity verification: In order to verify to what extent a selected critical process variable influences the operational objective, a number of closed-loop simulations have been performed for different values of that particular critical process variable while keeping the other process variables constant during these simulations. The following steps are used for sensitivity verification of the critical process variables:

Step 8.4.1: The operational objective (specific growth rate) and the set points of controlled variables (DO, pH, and temperature) are considered in the fermentation process for analysis.

Step 8.4.2: Controlled variables set points of DO, pH and temperature are perturbed and the effects on the operational objective (specific growth rate) is recorded and plotted as shown in Figure 2.23.

Step 8.4.3: Figure 2.23 shows that the DO is the most critical process variable in the fermentation process followed by pH and temperature. It is also concluded that DO, pH, and temperature are quite sensitive for cell growth rate and therefore need to be monitored and controlled during the fermentation process. It should be noted that the plot in Figure 2.23 is based on the final value of the objective function obtained after each perturbation. However in order to analyze the effect of critical controlled variables on the objective function during the batch run the dynamic simulated data are also plotted as

shown in Figure 2.24 and Figure 2.25. For example, Figure 2.24 shows that the dissolved oxygen concentration – one of the selected critical process variables – influences the specific cell growth rate positively during the batch run and hence the final biomass concentration. Similarly from Figure 2.25 it can be seen that a change in pH also affects the cell growth rate (cell growth rate increases significantly, on increasing the pH up to 7 but beyond this value no significant change in cell growth is observed). Similarly the dynamic behavior of other selected critical process variables can be analyzed.

Step 8.5: Steps 8.1-8.4 are repeated for other critical process points (heat sterilizer and mixing tank).

Step 8.6: Product property verification: The product properties as specified in step 1 are verified as follows:

Step 8.6.1: The profile of achieved cell concentration during the fermentation process is shown in Figure 2.26. This figure shows that the obtained cell concentration at the end of the fermentation process is 52 kg/m^3. The desired (specified) cell concentration at the end of the fermentation process is 50 kg/m^3.

Step 8.6.2: The difference between the achieved cell concentration and the specified cell concentration is found to be 4%. That can be accepted.

Step 8.6.3: The specified product property (cell concentration) is achieved. The final verified critical process points, corresponding critical process variables and actuators are given in Table 2.15.

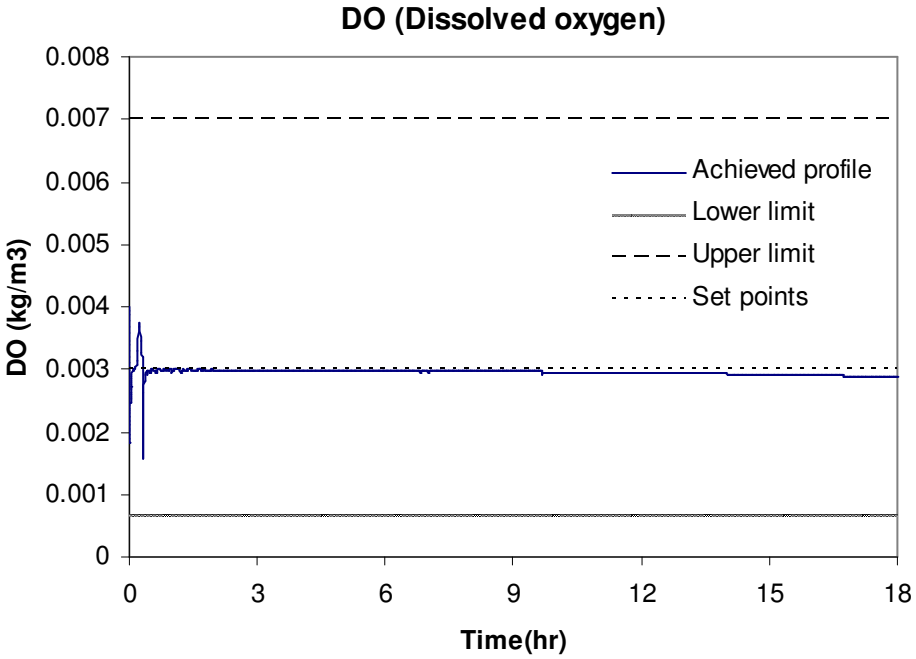


Figure 2.15: Dissolved oxygen concentration control

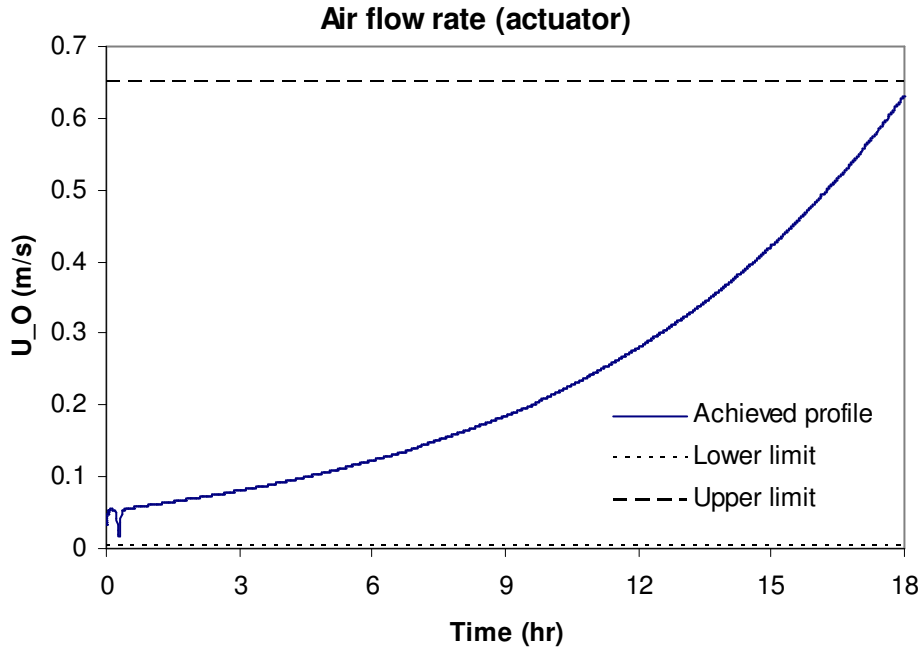


Figure 2.16: Superficial velocity of air (actuator for DO control)

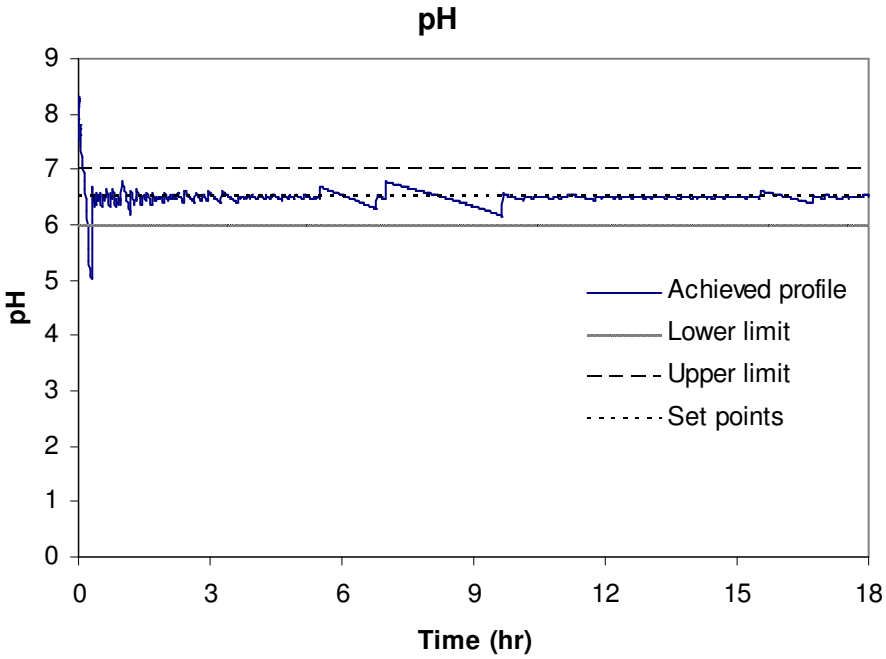


Figure 2.17: pH control

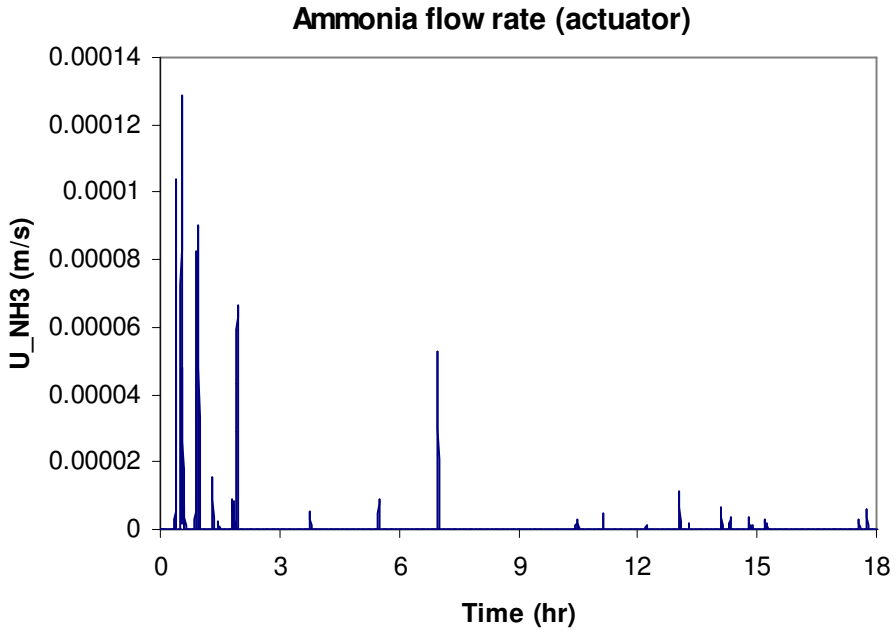


Figure 2.18: Superficial velocity of ammonia (actuator for pH control)
(Lower limit=0, upper limit=0.65; ammonia flow rate is considerably lower than the upper limit)

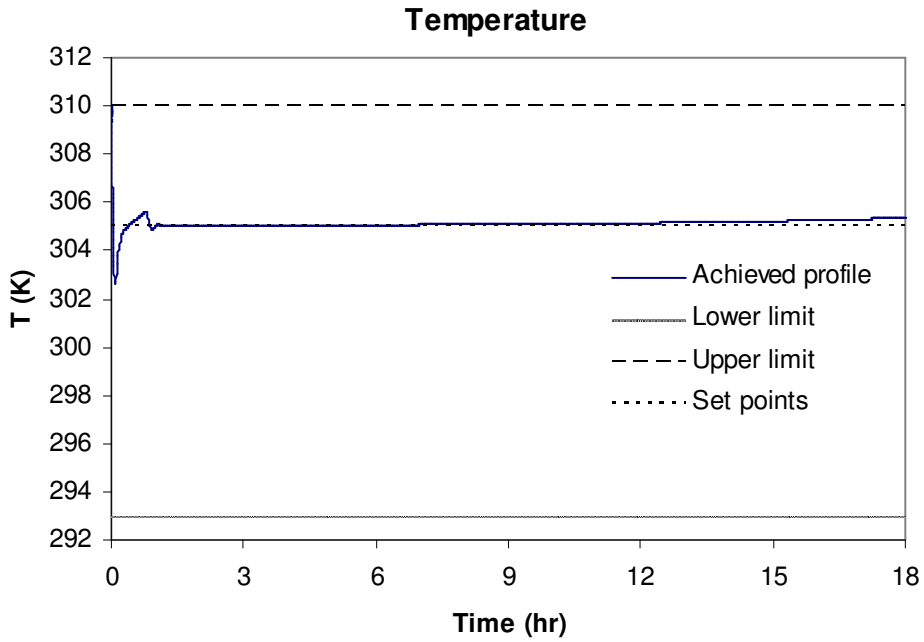


Figure 2.19: Temperature control

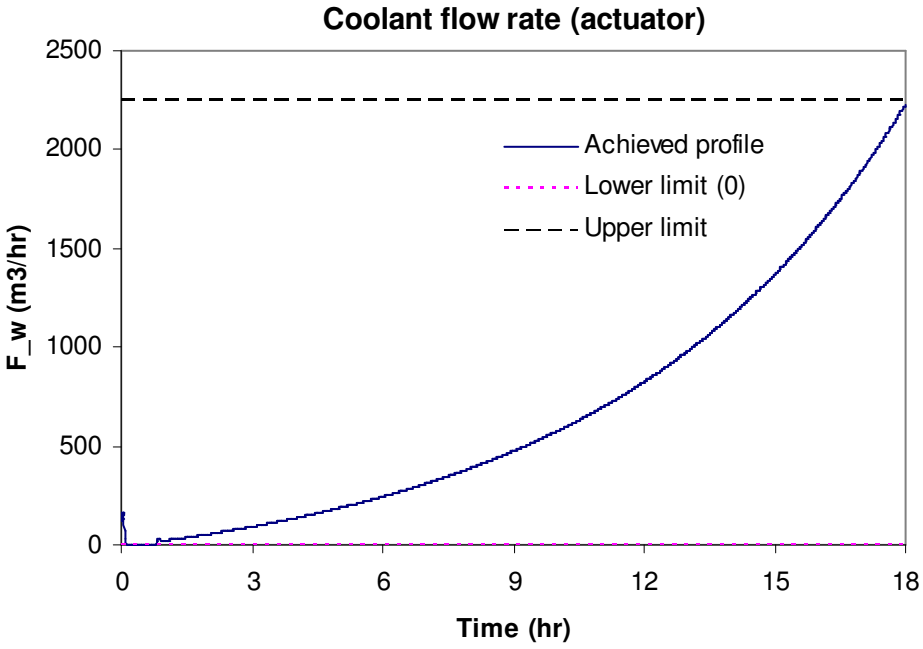


Figure 2.20: Coolant flow rate (actuator for temperature control)

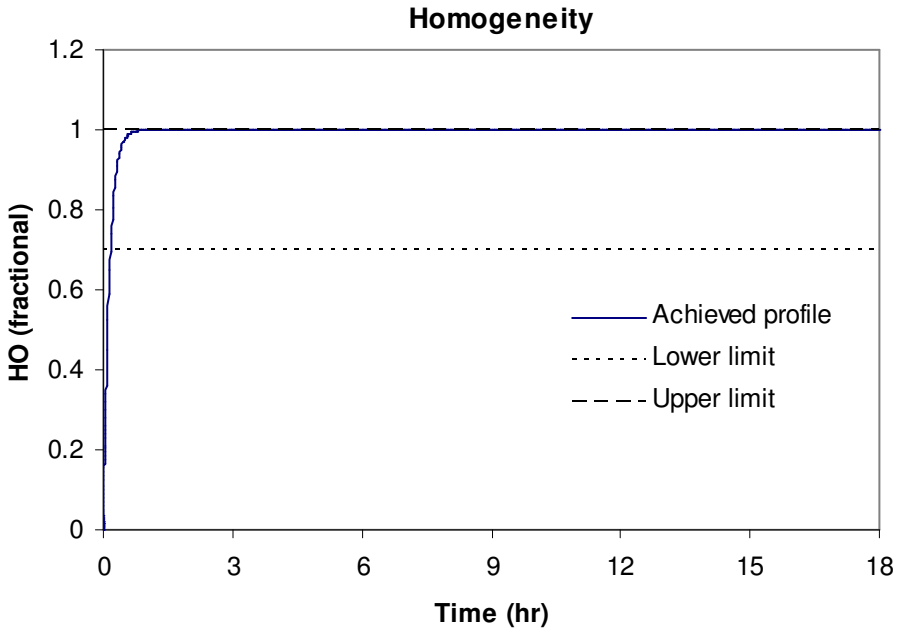


Figure 2.21: Homogeneity

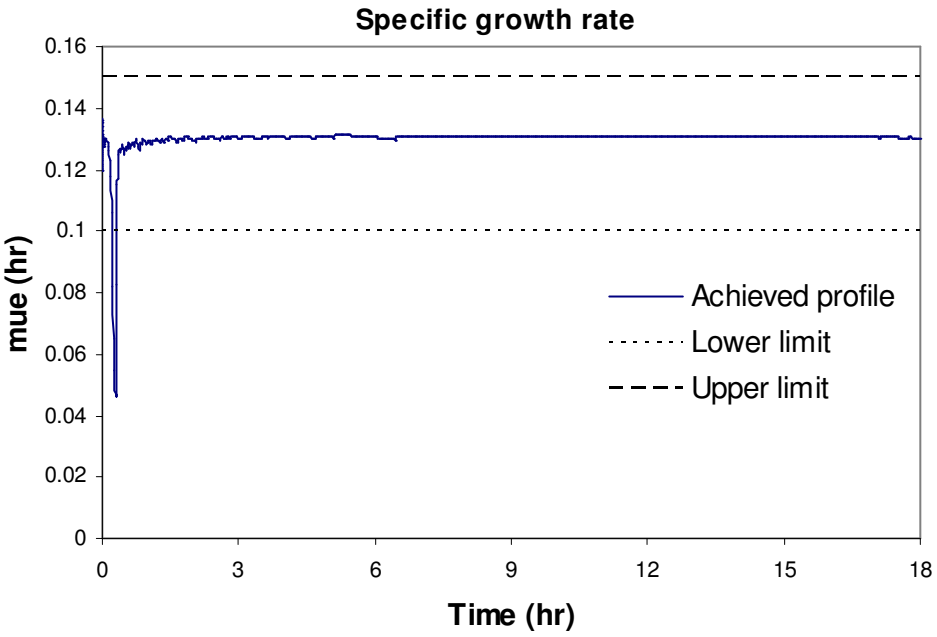


Figure 2.22: Profile of operational objective in fermentor (closed-loop simulation)

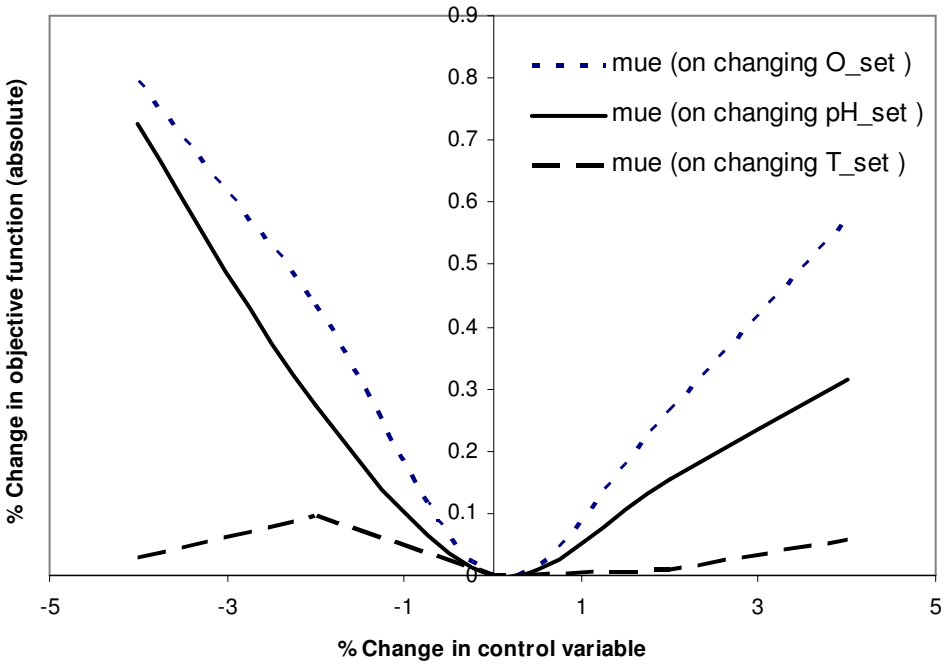


Figure 2.23: Sensitivity verification

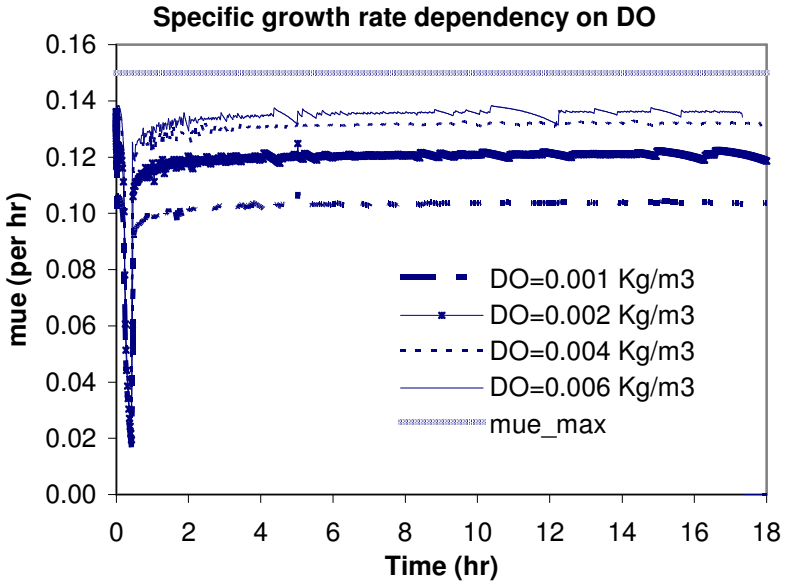


Figure 2.24: Effect of dissolved oxygen concentration on cell growth rate (pH=6, T_b =37 ^oC, N=480 rpm)

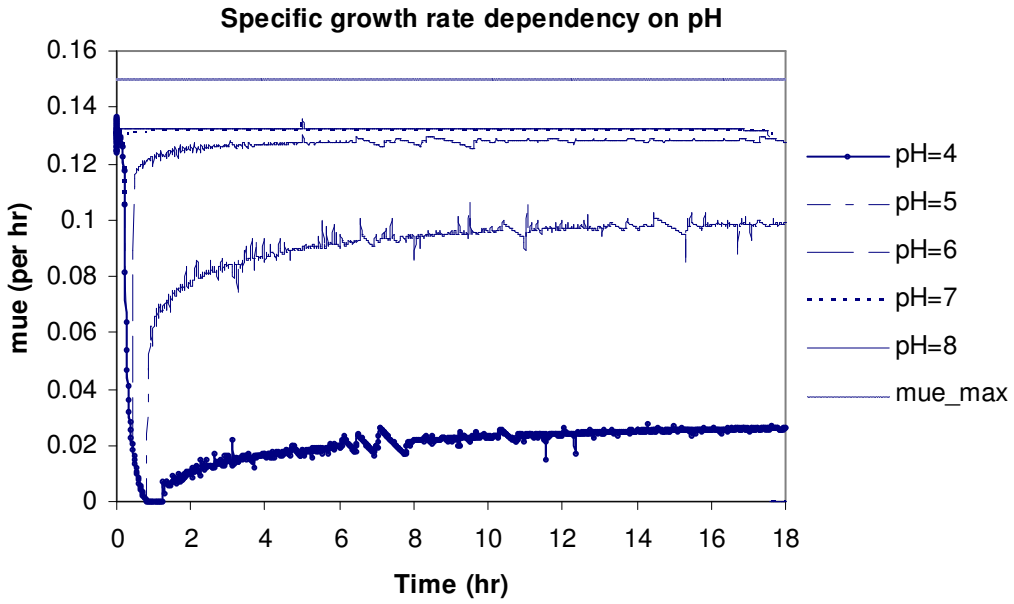


Figure 2.25: Effect of pH on cell growth rate (DO=0.003 kg/m^3, T_b=37 ^oC, N=480 rpm)

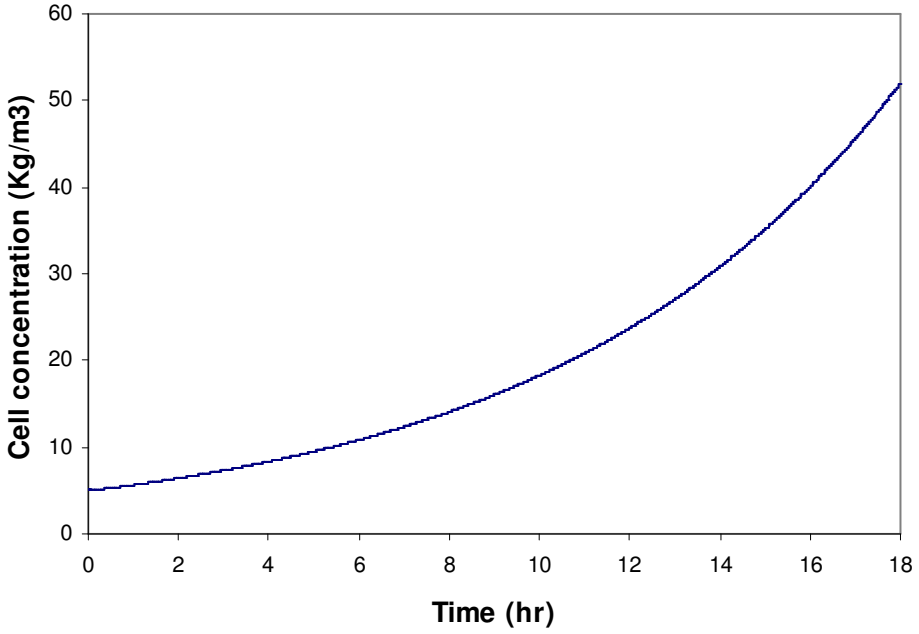


Figure 2.26: Cell concentration during the fermentation process (obtained product property profile in closed-loop simulation)

2.3.3.9. Final process monitoring and analysis system (step 9)

The final list of critical process points, corresponding critical process variables, actuators, monitoring techniques and tools are listed in Table 2.15. A feasible alternative of the process monitoring and analysis system is also shown in Figure 2.27. Within the fermentor, the DO concentration, pH and temperature need to be monitored and controlled. The temperature in the heat sterilizer and the homogeneity in the mixing tank also need monitoring and control. The dissolved oxygen concentration can be monitored by an optical sensor and it can be controlled by manipulating the air flow rate. The aeration intensity used for DO control has a significant influence on the dissolved CO_2 concentration as well, and as a consequence, it is not needed to control this variable explicitly. pH can be monitored by an electrochemical sensor and it can be controlled by manipulating the ammonia flow rate. The homogeneity in the fermentor can be monitored by near infrared spectroscopy and it can also be controlled by manipulating the stirrer speed. The viscosity of the fermentation broth in the case of unicellular organisms like *E.coli* is typically not too high. The broth can therefore be considered homogeneous, and

in order to reduce the process monitoring cost (a NIR sensor is expensive), the monitoring of the homogeneity in the fermentor could be ignored. The fermentation process is exothermic. If not controlled properly, biomass growth can cause a temperature rise in the fermentor, thus resulting in conditions that are sub-optimal for reaching the maximum productivity. A thermocouple can be used for temperature measurement, and the temperature can be controlled by manipulating the coolant flow rate. The sterilization temperature can be controlled by manipulating the heating fluid flow rate. To achieve a homogeneous mixture, the homogeneity needs to be monitored in the mixing tank and the mixing time has to be adjusted based on the desired level of homogeneity. The response time of the selected monitoring tools is also shown in Figure 2.27, and indicates that the selected monitoring tools are fast enough to allow for successful implementation of the control system.

Table 2.15: Monitoring and analysis system for the fermentation process

Critical process points ($\overline{PP}_i^c$)	Critical process variables ($\overline{V}_i^c$)	Actuators ($\overline{u}_i$)	Monitoring techniques ($\overline{MTE}_i$)	Monitoring tools ($\overline{MT}_i$)
Fermentor	Dissolved oxygen	Air flow rate	Optical sensor	FOXY Sensor System
	pH	Ammonia flow rate	Electrochemical sensor	pH Meter -- Model 2410
	Temperature	Coolant flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
Heat sterilizer	Temperature	Heating fluid flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
Mixing tank	Homogeneity	Mixing time	NIR	EPP 2000 Fiber Optic Spectrometer-NIR2

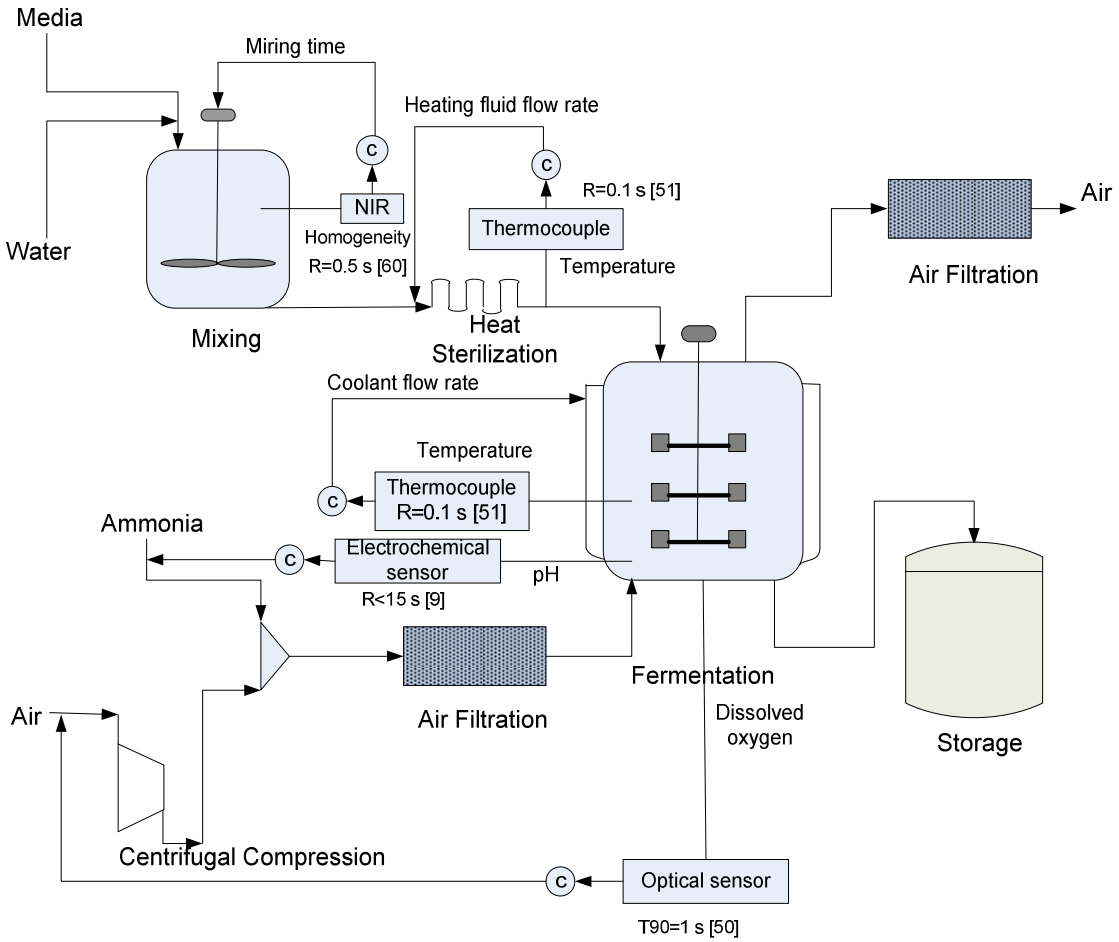


Figure 2.27: Process monitoring and analysis system (one feasible alternative) for the fermentation process

3. Methodology implementation issues

3.1. Introduction

The main issue in the implementation of the design methodology into a software is the availability of sufficient knowledge/data sources to provide the necessary information/data during the design of PAT systems. A knowledge base and a model library are two main sources of information/data needed for design of process monitoring and analysis systems. The knowledge base has been built through an extensive literature and industrial survey. It provides the necessary information/data during the design of the PAT system. The model library contains a set of mathematical models for different types of unit processes, sensors and controllers. These models are used to generate data (e.g., when sufficient measured data are not available) as well as for verification of the performance of the closed-loop controlled process. The knowledge base and model library cover a wide range of industrial processes such as tablet manufacturing, fermentation, downstream separation, crystallization and cheese manufacturing. These sources of information/data (knowledge base and model library) are considered as the main supporting tools for design of process monitoring and analysis systems. A simulation tool is also needed to solve the models available in the model library.

3.2. General knowledge base

The useful knowledge/data needed for design of process monitoring and analysis systems is stored in the general knowledge base. The knowledge acquisition and knowledge management are visually illustrated in Figure 3.1. Literature survey, an industrial survey and process experience are the primary sources of knowledge. The knowledge obtained from these sources has been organized in a well defined structure so that it can be used by an inference system and can contribute to the solution of specific problems.

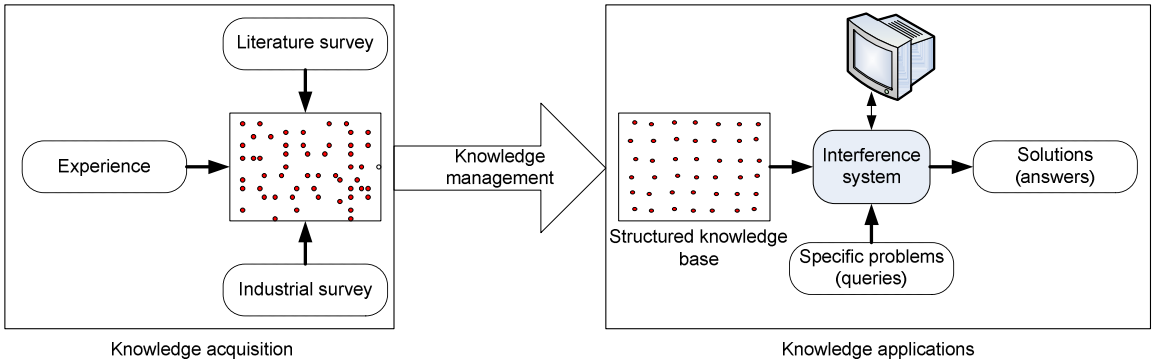


Figure 3.1: Knowledge acquisition and reuse

3.2.1. Systematic representation of the knowledge base

Ontology has been used to systematically represent the knowledge on process monitoring and analysis systems. The literature contains many, partly contradicting definitions of an ontology. Guarina (1997) presented some of the definitions of ontology available in the literature and discussed the importance and the major limitations of the definitions. However, the definition given by Gruber is widely accepted, which is given as follows (Gruber, 1995): "an ontology is an explicit specification of a conceptualization". Gruber has also proposed the design criteria for ontologies. An ontology should have clarity in defined terms and relations. It should be coherent: that is, it should sanction inferences that are not consistent with the definitions. The ontology should be extendible to increase the range of applications. The encoding bias and the ontological commitment[5] should be minimal to make it more generic (Gruber, 1995).

Basically each ontology defines a set of classes, relations, functions, and objects for some domain of discourse, and includes an axiomatization to constrain the interpretation (Gruber, 1995). A knowledge base may use an ontology to specify its structure (entity types and relationships) and classification scheme. An ontology, together with a set of instances of its classes, constitutes a knowledge base. The general terms commonly used in the ontology are described in Table 3.1.

[5]Ontological commitments is to describe some of the demands that the sentence's truth imposes on the world—those demands that concern ontology (Rayo, 2007)

Table 3.1: Definition of the general terms commonly used in the ontology (Knowledge Systems Laboratory, 1997)

General terms	Definitions
Class	A class is a representation for a conceptual grouping of similar terms. Classes are the focus of most ontologies. A class describes concepts in the domain. A class can have subclasses that represent concepts that are more specific than the super class.
Slot	A slot is used to describe a relationship between two terms. The first term must be an instance of the class that is the Domain of the slot and the second must be an instance of the class that is the Range of the slot. For example, brother could be represented as a slot such that its Domain was Animal and its Range was Male-Animal.
Domain of the slot	The domain of a slot is a class that restricts the terms on which the slot can be added. A slot can only be added to terms which are an instance of its domain. An object is an instance of a class if it is a member of the set denoted by that class
Range of the slot	The range of a slot is a class that restricts the values which the relation can have
Facets	Facets are used to represent information about a slot on an object. Usually facets represent some constraint on an instance slot .
Relation and function	A relation is used to describe a relationship among two or more terms. If a relation represents a relationship between only two terms, it is called a slot or a binary relation. If the relation describes a relationship among n terms such that there is a unique n^{th} term corresponding to any set of the first n-1 terms, then the relation is called a function.
Instances	All of the terms in an ontology that have an associated definition (i.e., classes, slots, relations, functions, and facets) are an instance of some class. Classes are instances of class, functions are instances of function, etc. An instance should not be confused with an Individual because an instance may be a class whereas an Individual cannot be a class.
Axiom	An axiom is a sentence in first order logic that is assumed to be true without proof. In practice, we use axioms to refer to the sentences that cannot be represented using only slots and values on a frame.

3.2.1.1. Design of ontology

The methodology for design of an ontology is shown in Figure 3.2 (adopted from Natalya & McGuinness (2007)).

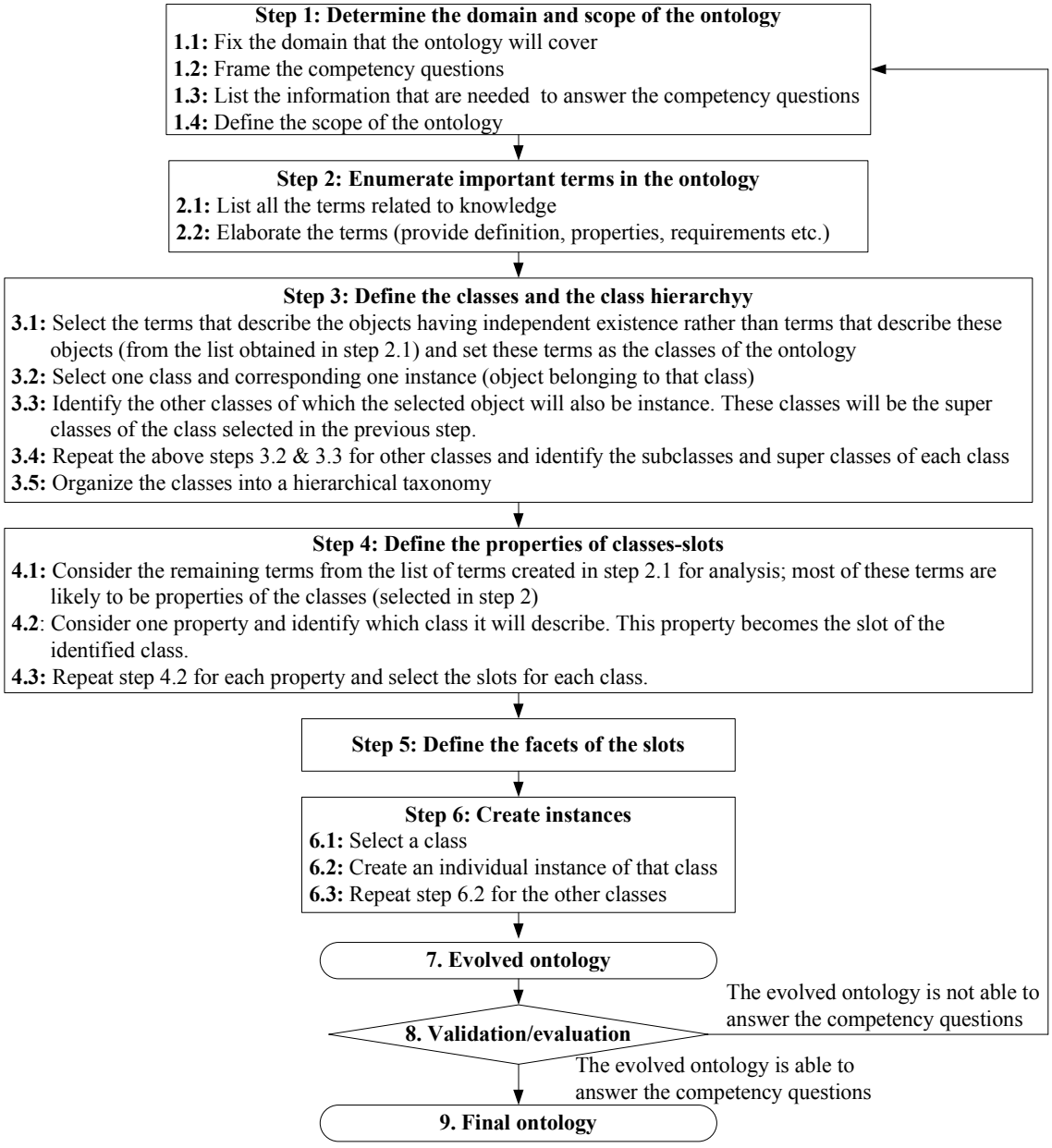


Figure 3.2: Methodology for design of ontology
(adopted from Natalya & McGuinness, 2007)

Following the methodology proposed by Natalya and McGuinness (2007) (shown in Figure 3.2), the ontology for process monitoring and analysis systems is developed as follows:

Step 1: Domain and scope of the ontology

- ***Domain (step 1.1):*** First the domain of the ontology has been identified. The representation of process monitoring and analysis systems is the domain of the ontology.
- ***Competency questions (step 1.2):*** Natalya and McGuinness (2007) have suggested to frame competency questions to determine the scope of the ontology. In the process monitoring and analysis domain, the following are the possible competency questions:

a. What is the process points where monitoring might be needed?
b. Which process variables should be considered for monitoring?
c. Which monitoring techniques are available for monitoring of a particular process variable?
d. Which monitoring tools are available for monitoring of a particular process variable?
e. Which monitoring tools satisfied the user specifications and constraints for monitoring a particular variable?
f. What is the cost of a particular monitoring tool?
g. Who are the suppliers of a particular monitoring tool?
h. What are the actuator candidates for a particular controlled variable?

- ***List of information needed to answer the competency questions (step 1.3):*** To answer the above mentioned competency questions, the knowledge base should have information about the contents: process, process points, process variables, monitoring techniques, monitoring tools, monitoring tools specifications, cost, supplier, actuator candidates.
- ***Scope (step 1.4):*** This ontology has to be used for the design of process monitoring and analysis systems.

Step 2: Enumeration of important terms in the ontology

- ***List of important terms (step 2.1)***

The important terms related to process monitoring and analysis systems are listed in Table 3.2

Table 3.2: List of the important terms

Processes, process points, process variables, actuator candidates, variable types, monitoring techniques, monitoring tools, supplier, specifications, accuracy, precision, operating range, response time, resolution, sensitivity, drift, operating temperature range, cost, process points of a process, process variables related to a process point, process variables of a process, actuator candidates of a variable, type of a process variable, monitoring techniques for a variable type, monitoring tools based on a monitoring technique, monitoring tools of a variable type, supplier of a monitoring tool, specifications of a monitoring tool, accuracy of a monitoring tool, precision of a monitoring tool, operating range of a monitoring tool, response time of a monitoring tool, resolution of a monitoring tool, sensitivity of a monitoring tool, drift of a monitoring tool, cost of a monitoring tool

- ***Elaboration of the important terms (step 2.2):***

Process: It consists of any chemical or biological process e.g. fermentation process, tablet manufacturing process, crystallization process etc.

Process points: In general the process equipments are considered as the process points. Note that each considered process point can have more than one process operation (e.g. the fermentor has more than one operation: charging, fermentation, discharging)

Process variables: Each process operation is defined by the set of variables. The variables defining each operation related to the considered process points come under this category.

Variable types: Sometimes it happens that a group of process variables can be monitored by the same monitoring tools. So this set of variables can be represented by a single variable type. For instance the three variables, inlet temperature, outlet temperature and process temperature can be placed in the category of the variable temperature because the monitoring tools are the same for these variables.

Actuator candidates: In this category those variables have to be listed which can be the actuator of the considered variable. This list provides the alternatives available for the manipulated variables.

Monitoring techniques: The available monitoring techniques/methods for each variable have to be listed in this category.

Monitoring tools: Each monitoring technique/method comprises a set of monitoring tools.

Monitoring tools specifications: Each monitoring tool has some characteristics which reflect its performance. Some of them are described here:

Accuracy: The accuracy is defined as, "The ability of a measurement to match the actual value of the quantity being measured" (Haby, 2008). Accuracy of a displayed value is characterized as an uncertainty of a measurement display representing the actual value being measured. It is expressed in terms of how far off any given reading could be from the true value, given in terms of a fixed value (e.g., +/-0.5 deg. F), a percent of reading (e.g., 0.2% of reading), a fixed value plus a percent of reading or a percent of the instrument's full scale value. The accuracy of the sensors varies with the type, purpose and manufacturer (Stum, 2006).

Precision: Precision is defined as, "The ability of a measurement to be consistently reproduced", i.e. it is the ability of repeatability (Haby, 2008). In other words the precision is how close the measured values are to each other. There are several ways to report the precision of results. The simplest is the range (the difference between the highest and lowest results) often reported as a ± deviation from the average. A better way, but one that requires statistical analysis, would be to report the standard deviation. Note that, it is possible for an instrument to have good accuracy and good precision, good accuracy but bad precision, bad accuracy but good precision and bad accuracy and bad precision.

Operating range: The operating range of a monitoring tool is defined as the minimum and maximum limiting value that it can measure. For example, a given pressure sensor may have a range of 0 to + 400 mm Hg (Carr & Brown, 2008).

Response time: Sensors do not change output state immediately when an input parameter change occurs. Rather, the sensor output will evolve over a period of time before truly reflecting the new state. The response time can be defined as the time required for a sensor output to change from its previous state to a final settled value (when subjected to a step input change) within a tolerance band of the correct new value (Carr & Brown, 2008; Sutherland, 2004). For example, T90 means time required for a sensor output to reach 90% of the final value, when subjected to a step input change.

Sensitivity: The sensitivity of the sensor is defined as the change in sensor output per unit change in measured quantity (Sutherland, 2004). Sensors that measure very small changes must have very high sensitivities.

Resolution: The resolution of the sensor is defined as the smallest change in measurable quantity, that the sensor can detect (Sutherland, 2004). In other words, the smallest detectable incremental change of the input variable that can be detected in the output signal. Resolution can be expressed either as a proportion of the reading (or the full-scale reading) or in absolute terms (Carr & Brown, 2008).

Drift: Drift is defined as the gradual change in any quantitative characteristic that is supposed to remain constant. It is an undesired change in output over a period of time that is unrelated to the input. It can be due to aging, temperature effects, sensor contamination etc. (Capgo, 2007)

Operating temperature range: It is defined as the temperature range within which the monitoring tools can be used i.e. the temperature range in which the device will meet performance specifications (Kionix, 2004).

Cost: It is the price of the monitoring tool. The cost of a specific monitoring tool depends on the supplier and the location of the manufacturing company.

Supplier: It is important to know the manufacturer of the monitoring tools. It should be noted that the same manufacturing companies can produce different monitoring tools (depending on the specifications) for measurement of one variable.

Selection of monitoring tools: The process of finding out the best monitoring tool for a particular application

Step 3: Defining the classes and the class hierarchy

- The classes of the ontology have been identified and listed in Table 3.3 (step 3.1).

Table 3.3: List of the classes

Processes, process points, process variables, actuator candidates, variable types, monitoring techniques, monitoring tools, supplier, specifications, accuracy, precision, operating range, response time, resolution, sensitivity, drift, operating temperature range, cost

- A class 'process points' and one object belonging to this class 'fermentor' is considered for analysis (step 3.2).
- The selected object 'fermentor' is not the instance of any other classes (step 3.3).
- Steps 3.2 and 3.3 have been repeated for other terms (step 3.4)
- The classes have been organized as the hierarchical taxonomy shown in Figure 3.3 (step 3.5).

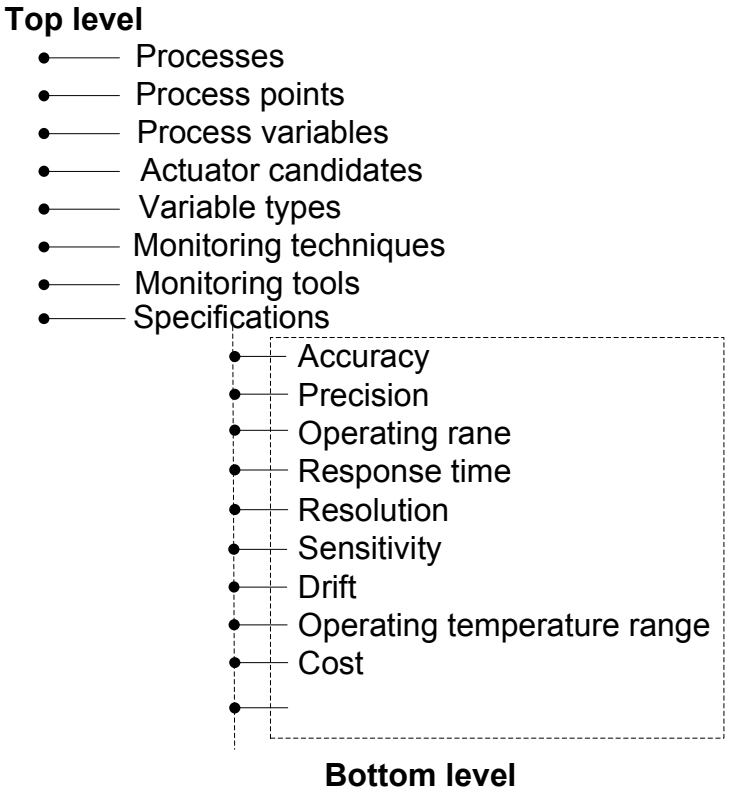


Figure 3.3: Hierarchical taxonomy of the classes

Step 4: Define the properties of classes-slots

- The remaining terms of the Table 3.2 are: process points of a process, process variables related to a process point, process variables of a process, actuator candidates of a variable, type of a process variable, monitoring techniques for a variable type, monitoring tools based on a monitoring technique, monitoring tools for a variable type, supplier of a monitoring tool, specifications of a monitoring tool, accuracy of a monitoring tool, precision of a monitoring tool, operating range of a monitoring tool,

response time of a monitoring tool, resolution of a monitoring tool, sensitivity of a monitoring tool, drift of a monitoring tool, cost of a monitoring tool (step 4.1)

- The property, 'process points of a process' is considered as a slot which relates the instances of the class 'processes' (domain of the slot) with the instances of the class (process points) (range of the slot) (step 4.2)
- Step 4.2 has been repeated for other properties, and slots for each class have been identified (step 4.3)

Step 5: Define the facet of the slots

Two types of values can fill in the slot, character strings and numerical values. For instance the slot, 'process points of a process' is filled with the names of process points while the slot, 'accuracy of a monitoring tool' is a value type.

Step 6: Create instances

- Class 'processes' is selected for consideration (step 6.1)
- Different processes such as fermentation process, tablet manufacturing process etc. are the instances of this class (step 6.2)
- Step 6.2 is repeated for the other classes (process points, process variables, actuator candidates etc.) and instances of all classes have been created (step 6.3)

Step 7: Evolved ontology

The obtained structure of the knowledge base is shown in Figure 3.4 and Figure 3.5. The detailed description of the knowledge base is given in section 3.2.2. The contents of the knowledge base have been arranged in 2 sections. Section 1 contains the process knowledge (Figure 3.4) while the section 2 contains the knowledge on monitoring techniques and tools (Figure 3.5).

Step 8: Validation/evaluation

The evolved ontology is found to be able to provide the answer to the competency questions (as framed in step 1.2). The application of the knowledge base has been demonstrated for design of the process monitoring and analysis system of a fermentation process (see section 2.3), a tablet manufacturing process (see section 5.1) and a cheese manufacturing process (see section 5.2)

Step 9: Final ontology

The final structure of the knowledge base is shown in Figure 3.4 and Figure 3.5. It is described in detail in the section 3.2.2

3.2.2. Knowledge base structure

The knowledge base involves two sections. The first section of the knowledge base consists of the information related to the process while the second section of the knowledge base consists of information related to measurement methods and tools. The structure of the first section of the knowledge base (process knowledge) is shown in Figure 3.4, while Figure 3.5 illustrates the structure of the second section of the knowledge base (measurement methods and tools).

3.2.2.1. First section of the knowledge base

The type of processes, process points, process variables and the actuator candidates are the main process knowledge categories included, and they are classified hierarchically (see Figure 3.4). The first process knowledge level consists of the list of processes. The set of independent processes (e. g. fermentation process, tablet manufacturing process etc.) form the objects of this class. The second level of the knowledge base consists of the list of process points. The objects under this category (process points) are placed in a set of groups, and each group is linked to the corresponding process listed on the first level. The process points, corresponding to the process equipments of the existing processes, are identified directly from the process flow-sheet. The third category, process variables, contains the variables involved in different processes. The objects under this category (process variables) are placed in a set of groups, and each group is linked to the corresponding process point on the second level. The variables are further grouped on the basis of monitoring tools needed to monitor those variables. The latter groups are named the variable types. The elements of a variable types group are the variables which can be monitored with the same monitoring tools. The objects of these groups are on the one hand linked with the process variables (see Figure 3.4) and are on the other hand linked with the monitoring techniques (see Figure 3.5). These objects are therefore crucial in the knowledge base, since they act as the necessary link between the process knowledge section and the section containing the knowledge on the monitoring tools. Ensuring a

consistent predefined product quality in the process also depends on the successful implementation of the control system. The availability of on-line monitoring tools and the identification of the proper actuators are two important prerequisites for successful implementation of the control system. A category named actuator candidates is therefore also created in the knowledge base. The objects of this category are the potential actuator candidates (manipulated variables) of the considered process variables.

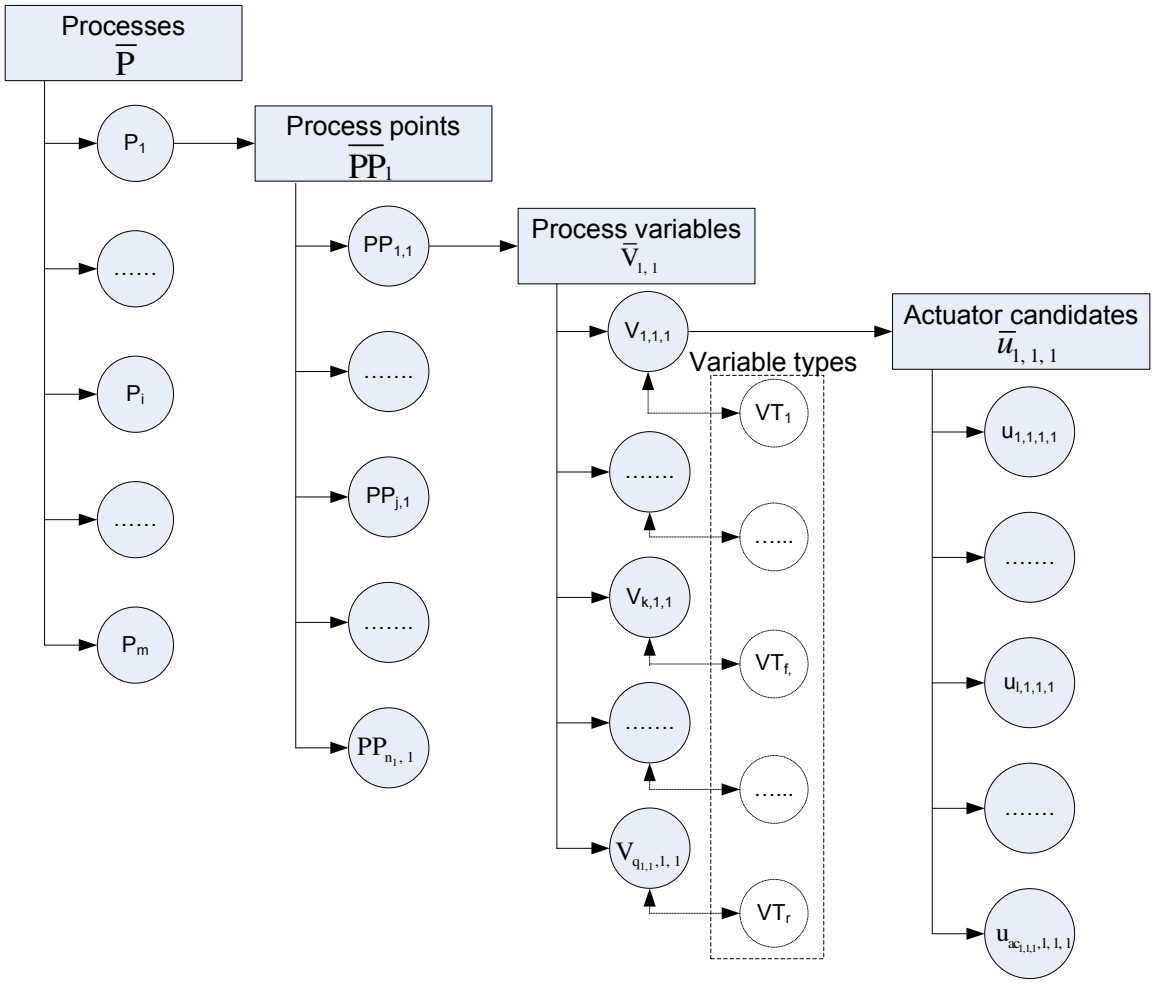


Figure 3.4: Structure of knowledge base (section 1)

3.2.2.2. Second section of the knowledge base

The variable types, monitoring techniques, monitoring tools, specifications and suppliers (of monitoring tools) are the main categories in the second section of the knowledge base. The first category, variable types, contains the independent set of variables that need

different monitoring techniques. The next level, monitoring techniques, contains the list of monitoring techniques available for each variable type. These monitoring techniques have been placed in different groups on the basis of the potential applications of each monitoring technique, and each group has been linked with the corresponding measurement. One of the main difficulties in product quality control is to identify the monitoring tools that are most suitable for measurement of the process variables in such a way that they can satisfy the user and process constraints (e.g. economical and controllability constraints). Therefore a category named monitoring tools has been created in the knowledge base. For a specific measured variable that is measured by a specific technique, many monitoring tools can be available. Taking measurement of the gas flow rate as an example, some of the available monitoring tools that are based on the 'variable area flow technology' are as follows: Rotameter -- T11T1-TA0A-032-06-SA (Aalborg instrumentation); Acrylic VA Flow meter -- FP2000 Series (ABB instrumentation), Acrylic Flow meter -- KFR-2100 (Kobold Instruments); Acrylic Variable Area Flow meters -- FR2000, 4000, 4500 Series (Clark solutions) etc. Therefore all the monitoring tools available for measurement of a specific variable are placed in several groups based on the specific techniques used in the monitoring tools, and each group is linked with the corresponding monitoring techniques. Each monitoring tool is also linked with the corresponding supplier. It should be noted that one of the most important applications of the knowledge base is the selection of the monitoring tools for a specific application. As a consequence, a number of criteria are needed on the basis of which the monitoring tools can be selected. Therefore the most important specifications of the monitoring tools are also included in the knowledge base. Examples of these specifications are the accuracy, precision, operating range, response time, sensitivity, resolution, drift, operating temperature range, cost etc. These specifications have a numerical value and can be considered as the leaves of the knowledge base. Representation of this information is complicated by the fact that each specification of the monitoring tools can be represented in different ways. For instance, the accuracy can be represented as a fixed value deviation, as a percent value of reading and as a percent value of full span. One of the objectives of structuring the knowledge base is to enable efficient retrieval of information, as well as application of an automatic monitoring tools

comparison procedure. Therefore, the specifications of all the monitoring tools in the knowledge base for a particular variable need to be represented in a consistent way to allow comparison. It should be noted that the consistency is mandatory only within a group of monitoring tools (represented by $\overline{MT_f}$ in Table 3.4) that can be used for monitoring a particular variable; inconsistency can be allowed between such groups (e.g. $\overline{MT_f}$ & $\overline{MT_{f\text{-}1}}$). For example, when considering temperature and pressure monitoring tools, the accuracy of the pressure monitoring tools can be in percentage of a reference value, while the accuracy of the temperature monitoring tools can be in fixed temperature value.

In the knowledge base the specifications of the monitoring tools have been represented as shown in Figure 3.6. Each specification has a numerical value, corresponding unit and explanation on the source of the data (reference). All the references have been listed in a separate file with a unique reference number. The knowledge base contains these reference numbers and they have been linked with the original references. As shown in Figure 3.6 some specifications (operating range and the operating temperature range) have on purpose been divided in two parts such that the numerical data can be compared easily.

The main contents of the knowledge base are summarized in Table 3.4. The type of knowledge (main process/monitoring tool category) that the knowledge base contains is listed in the first row of the table. The second row of the table relates these categories with the corresponding objects that these categories contain. For instance, the main category types 'processes' contains a list of process attributes (P_1 to P_m) where P_i is the i^{th} process. A list of attributes for different categories is given in Table 3.5. Table 3.4 also shows how the objects of one category are linked to objects of other categories. For instance $\overline{PP_i}$ is the i^{th} attribute of the vector of process points $\overline{PP}$, corresponding to the process points of process P_i. Similarly, $\overline{V}_{j,i}$ is the j^{th} attribute of the vector of variables $\overline{V}_i$ corresponding to the i^{th} process.

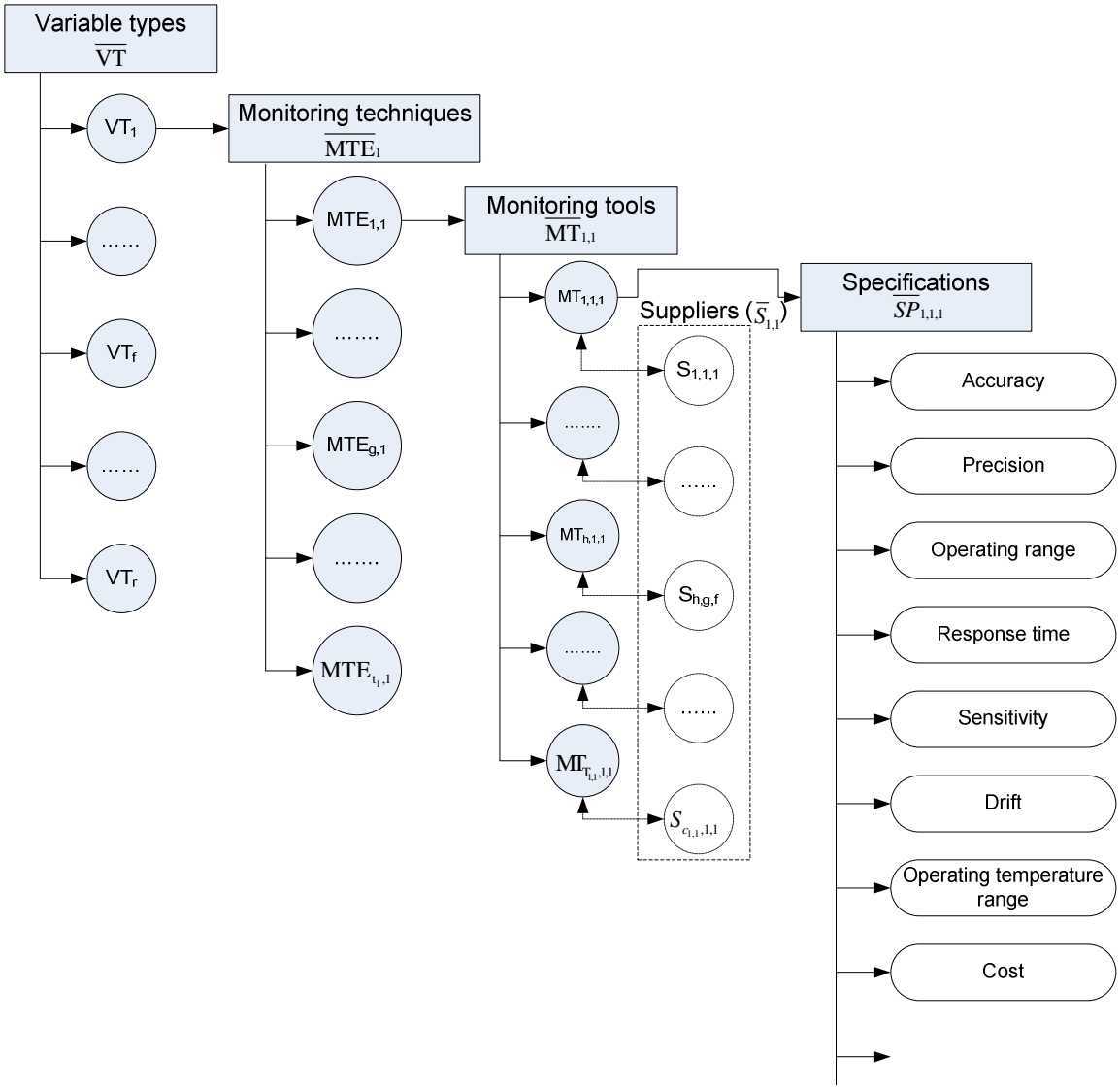


Figure 3.5: Structure of knowledge base (section 2)

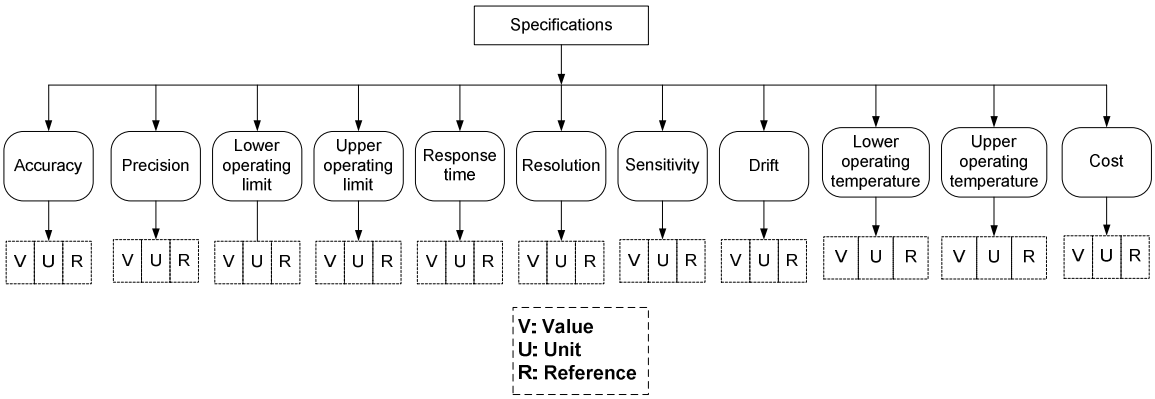


Figure 3.6: Systematic representation of the specifications of the monitoring tools

Table 3.4: Main categories of the knowledge base and corresponding objects

Main category	Relation with objects
Processes ($\overline{P}$)	$\overline{P}=[P_1 \ldots P_i \ldots P_m]$
Process points ($\overline{PP}$)	$\overline{PP}=[\overline{PP_1} \ldots \overline{PP_i} \ldots \overline{PP_m}]$; $\overline{PP_i}=[PP_{1,i} \ldots PP_{j,i} \ldots PP_{n_i,i}]$
Process variables ($\overline{V}$)	$\overline{V}=[\overline{V}_1 \ldots \overline{V}_i \ldots \overline{V}_m]$; $\overline{V}_i=[\overline{V}_{1,i} \ldots \overline{V}_{j,i} \ldots \overline{V}_{n_i,i}]$
	$\overline{V}_{j,i}=[V_{1,j,i} \ldots V_{k,j,i} \ldots V_{q_{j,i},j,i}]$
Actuator candidates ($\overline{u}$)	$\overline{u}=[\overline{u}_1 \ldots \overline{u}_i \ldots \overline{u}_m]$; $\overline{u}_i=[\overline{u}_{1,i} \ldots \overline{u}_{j,i} \ldots \overline{u}_{n_i,i}]$;
	$\overline{u}_{j,i}=[\overline{u}_{1,j,i} \ldots \overline{u}_{k,j,i} \ldots \overline{u}_{q_{j,i},j,i}]$
	$\overline{u}_{k,j,i}=[u_{1,k,j,i} \ldots u_{l,k,j,i} \ldots u_{ac_{k,j,i},k,j,i}]$
Variable types ($\overline{VT}$)	$\overline{VT}=[VT_1 \ldots VT_f \ldots VT_r]$
Monitoring techniques ($\overline{MTE}$)	$\overline{MTE}=[\overline{MTE_1} \ldots \overline{MTE_f} \ldots \overline{MTE_r}]$
	$\overline{MTE_f}=[MTE_{1,f} \ldots MTE_{g,f} \ldots MTE_{t_f,f}]$
Monitoring tools ($\overline{MT}$)	$\overline{MT}=[\overline{MT_1} \ldots \overline{MT_f} \ldots \overline{MT_r}]$;
	$\overline{MT_f}=[\overline{MT}_{1,f} \ldots \overline{MT}_{g,f} \ldots \overline{MT}_{t_f,f}]$;
	$\overline{MT}_{g,f}=[MT_{1,g,f} \ldots MT_{h,g,f} \ldots MT_{T_{g,f},g,f}]$
Suppliers ($\overline{S}$)	$\overline{S}=[\overline{S}_1 \ldots \overline{S}_f \ldots \overline{S}_r]$; $\overline{S}_f=[\overline{S}_{1,f} \ldots \overline{S}_{g,f} \ldots \overline{S}_{t_f,f}]$;
	$\overline{S}_{g,f}=[S_{1,g,f} \ldots S_{h,g,f} \ldots S_{c_{g,f},g,f}]$;
Specifications ($\overline{SP}$)	$\overline{SP}=[\overline{SP_1} \ldots \overline{SP_f} \ldots \overline{SP_r}]$; $\overline{SP_f}=[\overline{SP}_{1,f} \ldots \overline{SP}_{g,f} \ldots \overline{SP}_{t_f,f}]$;
	$\overline{SP}_{g,k}=[\overline{SP}_{1,g,f} \ldots \overline{SP}_{h,g,f} \ldots \overline{SP}_{T_{g,f},g,f}]$;
	$\overline{SP}_{h,g,f}=[$accuracy, precision, operating range, response time, sensitivity, drift, resolution, otr, cost, ...$]$

Table 3.5: Description of the general terms

Object	Description
P_i	i^{th} process in the knowledge base
$PP_{j,i}$	j^{th} process point of the i^{th} process in the knowledge base
$V_{k,j,i}$	variable k related to the j^{th} process point of the i^{th} process
$u_{l,k,j,i}$	actuator candidate l of the variable k related to the j^{th} process point of the i^{th} process
VT_f	variable type f
$MTE_{g,f}$	monitoring technique g available for the variable type f
$MT_{h,g,f}$	monitoring tool h for monitoring technique g for the variable type f
$S_{h,g,f}$	Supplier of monitoring tool h for monitoring technique g for the variable type f

3.2.3. Extension of the knowledge base

The structure of the knowledge base is generic and can be easily extended to increase the range of applications and/or to accommodate newly developed process monitoring and analysis tools. The range of applications of the knowledge base can be increased by vertical extension, while it can be made more predictable (can provide more information) through horizontal extension. Horizontal extension (adding more columns of data) means simply addition of more categories in the knowledge base while the vertical extension (adding more rows of data) means addition of more objects to the existing categories. Addition of new specifications for a monitoring tool is an example of horizontal extension while the addition of new processes in the knowledge base is an example of the vertical extension of the knowledge base.

The procedure for vertical extension of the knowledge base is shown in Figure 3.7. The vertical extension of section 1 of the knowledge base (process knowledge) needs the addition of new processes and corresponding process points and process variables in the knowledge base (section 1) and the vertical extension of section 2 of the knowledge base (knowledge of process monitoring and analysis tools) needs the addition of a new variable type, corresponding monitoring techniques, tools, specifications and suppliers.

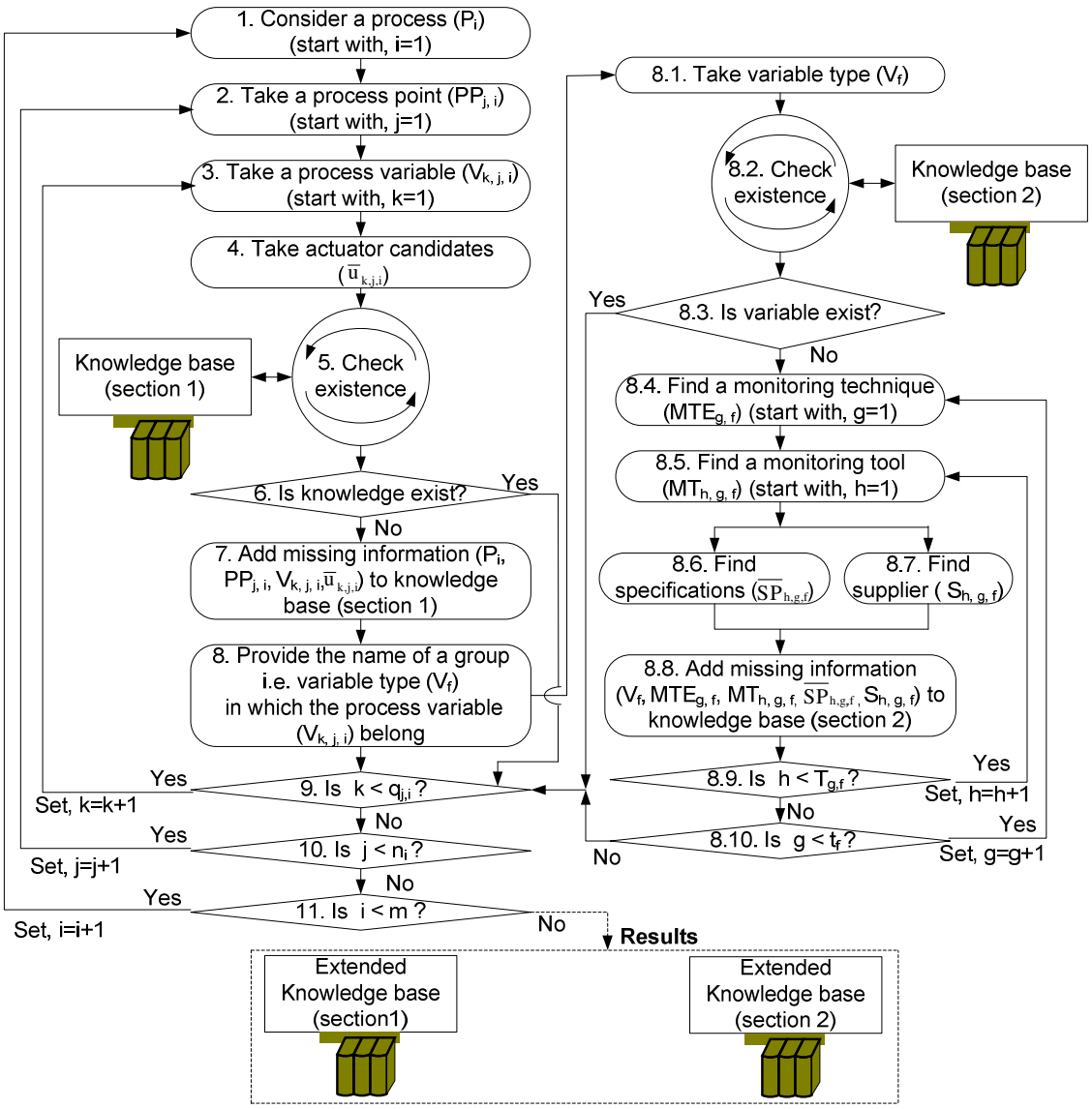


Figure 3.7: Procedure for extension of the knowledge base

(m: no. of processes added to the knowledge base; n_i: no. of process ponts of i^{th} process; $q_{j,i}$: no. of process variables involed in j^{th} process point of ith process; t_f: no. of monitoring techniques available for f^{th} variable type; $T_{g,f}$: no. of monitoring tools based on g^{th} techniques for f^{th} variable type)

3.2.4. Statistics of the knowledge base

Often statistics of the knowledge base are needed to determine the range of applications and the capability of the knowledge base. A general rule is that the more objects in the knowledge base, the more it will be useful. Table 3.6 summarizes the calculation procedure of the various objects of the knowledge base. For instance the maximum total number of monitoring tools (T) stored in the knowledge base can be estimated by

summing of all monitoring tools available for each technique for each variable (see Table 3.6).

The statistics as calculated in Table 3.6 give the maximum number of objects in the knowledge base corresponding to the considered category. However the repetition of the objects in the knowledge base can also be possible. Figure 3.8 illustrates the repetition of the objects in the process knowledge while Figure 3.9 shows the repetition of the objects in the knowledge of monitoring tools. As shown in Figure 3.8, some of the process points corresponding to any process can be the process points of other processes also. Similarly, some of the process variables related to any process points of any process can be the variables of other process points of the same process or any other processes. Any actuator candidate of any variable can be the actuator candidate of other variables of the same process point of the same process or any other process points of the same process or of the variables of any other processes. Note that if some variable of a process point have the same actuator, it means that these variables can not be controlled independently by manipulating the selected actuator. As shown in Figure 3.8, $\overline{PP}_{i-1}$, $\overline{PP}_i$ and $\overline{PP}_{i+1}$ are the groups of process points related to the processes P_{i-1}, P_i and P_{i+1}. The intersection of the circles shows the sharing of the objects. If the two objects are exactly identical only then they have to be considered as repeated objects. Care should be taken to identify the repeated objects. For example, if two processes have some common equipment but the equipment contents or operations are different then they can not be considered as repeated process points.

As shown in Figure 3.9, there is no repetition of the objects under the category, 'variable types', but it has been seen often that the same monitoring techniques can be applied to monitor several variables, i.e., the objects under the category of 'monitoring techniques' can be repeated. However, the repetition of monitoring tools is not common. If some monitoring tool based on some technique has been designed to monitor any specific variable then it can not be suitable to monitor other variables. Note that some monitoring tools are available on the market that can monitor more than one variable simultaneously (e.g. temperature and pH) but, these tools are using separate techniques to monitor different variables. Therefore this kind of monitoring tools should not be considered as repeated objects. In general each monitoring tool has distinct specifications. Some of the

monitoring tools can have the same numerical values of some of the specifications but the repetition of all the characteristics of two different monitoring tools is rare. For instance, two monitoring tools can have same accuracy but other characteristics like response time, sensitivity etc. can be different. Also, same companies often have been engage in the manufacturing of several types of monitoring tools, and therefore, the objects under the 'supplier' category can be repeated. For instance, the same supplier can provide temperature sensors as well as pH sensors.

Table 3.6: Knowledge base statistics

Number of elements	**Calculation**
Total number of processes (m)	m
Total number of process points (n)	$n = \sum_{1}^{m} n_i$
Total number of process variables (q)	$q = \sum_{i=1}^{m} q_i = \sum_{i=1}^{m} \sum_{j=1}^{n_i} q_{j,i}$
Total number of actuator candidates (ac)	$ac = \sum_{i=1}^{m} \sum_{j=1}^{n_i} \sum_{k=1}^{q_{j,i}} ac_{k,j,i}$
Total number of variable types (r)	r
Total number of monitoring techniques (t)	$t = \sum_{f=1}^{r} t_f$
Total number of monitoring tools (T)	$T = \sum_{f=1}^{r} \sum_{g=1}^{t_f} T_{g,f}$
Total number of suppliers (c)	$c = \sum_{f=1}^{r} \sum_{g=1}^{t_f} c_{g,f}$

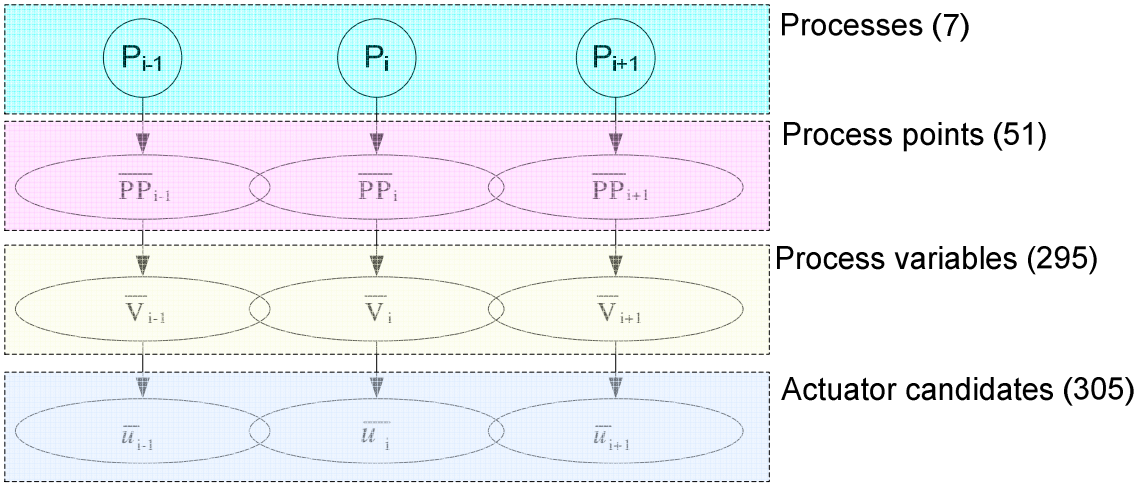


Figure 3.8: Repetition of the objects in process knowledge (section 1)

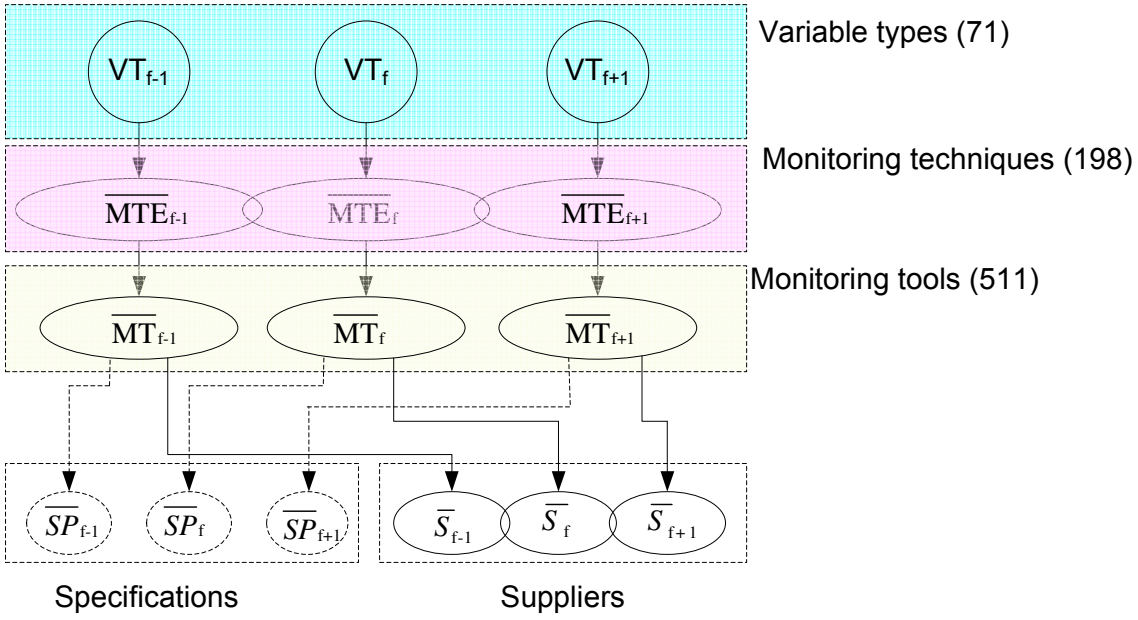


Figure 3.9: Repetition of the objects in the knowledge of monitoring tools (section 2)

The current knowledge base statistics are shown in Figure 3.8 and Figure 3.9 (see the numbers in the brackets). The first section of the knowledge base includes seven processes (a fermentation process, a pharmaceutical tablet manufacturing process, a crystallization process, an insulin production process, chemical reactions, cheese manufacturing process and butter manufacturing process). These processes consist of 51 process points and 295 process variables and 305 actuator candidates. The second section of the knowledge base includes 71 independent variable types. For the monitoring of

these variables, 198 monitoring techniques and 511 monitoring tools are added to the knowledge base. Each monitoring tools consist of 11 specifications. These information has been collected based on intensive literature and industrial survey that involves more than 240 references

3.3. General model library

The developed model library provides the process operational models. These models are important for predicting the product quality for new production processes as well as for the improvement of the product quality in existing production lines. The process models in the developed model library include first principles models as well as empirical models in the form of correlations between variables which can be exploited to estimate the product quality as a function of operating conditions, and thus are helpful in the selection of suitable operating conditions. These models support process analysis and help to generate additional or missing data needed to obtain the design of a process monitoring and analysis system. For example, the models can be applied for the prediction of the values of process variables which are not directly measurable but required for the final design (e.g. the cell growth rate in a fermentation process). Also, model-based sensitivity analysis may be performed to analyze the effect of changes in model inputs (model parameters) on the final product properties and based on this, to identify the critical process variables. The simulation models also provide input for the interdependency analysis, the analysis step through which the appropriate actuators for each controlled variable can be selected (see section 2.2.5). Moreover, through closed-loop simulation the effectiveness of the selected pairs of critical controlled variables and actuators can be analyzed. Thus the process models play a significant role in the design of the process monitoring and analysis system, and therefore also in the achievement of the desired product quality.

3.3.1. Model library development and extension

The systematic procedure shown in Figure 3.10 is used to build and extend the model library.

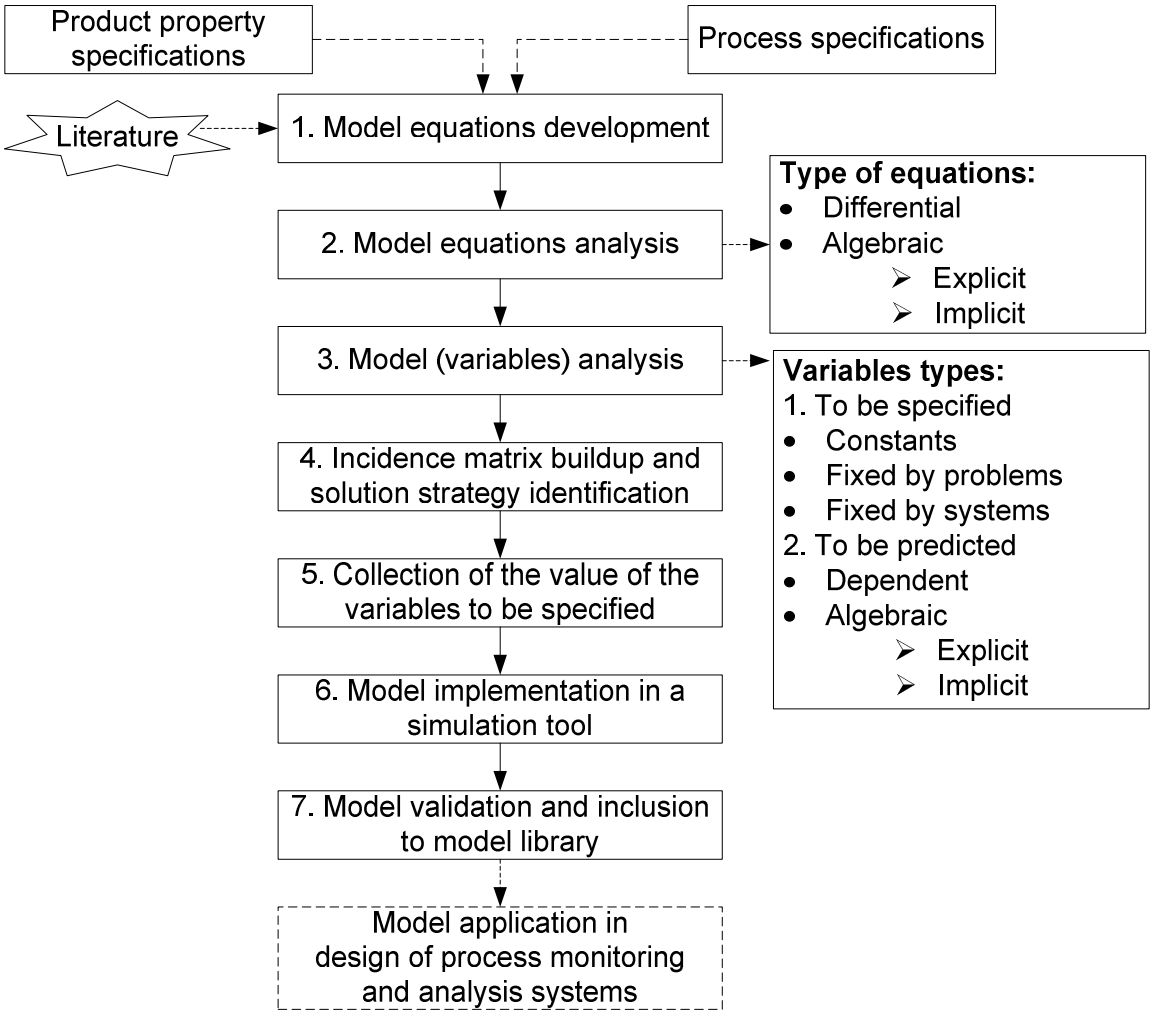


Figure 3.10: Procedure for buildup and extension of the model library

Step 1: Model equations development
For each set of unit processes, the model equations are developed based on process and product quality specifications and with the help of relevant literature references.

Step 2: Model equations analysis
The developed model equations are analyzed to characterize the equations (differential, explicit algebraic, implicit algebraic)

Step 3: Model (variables) analysis
Model variables are analyzed to identify the variables that need to be specified (constant, fixed by problem, fixed by system) and the variables that need to be predicted (differential variables, explicit algebraic variables and implicit algebraic variables). The systematic procedure proposed by Gani et al. (2006a) is used for this analysis.

Step 4: Incidence matrix buildup and solution strategy identification

On the basis of characterization of model equations and variables an incidence matrix for each process model is prepared. The incidence matrix shows the relationship between two classes of objects, in this case the model equations and the unknown model variables. The model equations are listed in the first row and the unknown model variables are listed in the first column. If possible, the model equations are ordered to obtain the lower triangular form. In case the incidence matrix shows a lower triangular form that indicates that all the equations can be solved sequentially (one unknown for each equation) in the order giving the lower triangular form. If there are elements in the upper triangular portion of the matrix, equations will need to be solved simultaneously and/or iteratively (Gani et al., 2006a).

For illustration of the incidence matrix, a hypothetical process model is assumed which consists of 20 algebraic (AE 1-AE 20) and 5 ordinary differential equations (ODE 1-ODE 5). There are 25 unknown variables (V1-V25) in the model. The incidence matrix of this model is shown in Table 3.7. The shaded portion of the matrix represents differential variables and differential equations. After ignoring the shaded portion, the incidence matrix (see Table 3.7, the unshaded part of the matrix) shows a lower triangular form, which means that all the equations can be solved explicitly and also sequentially (one unknown for each equation) without requiring any iterative solution technique. Following this procedure, the incidence matrix of each process model included in the model library is prepared to identify the solution strategy

Table 3.7: General incidence matrix, demonstrating the incidence matrix concept

	V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8	V_9	V_{10}	V_{11}	V_{12}	V_{13}	V_{14}	V_{15}	V_{16}	V_{17}	V_{18}	V_{19}	V_{20}	V_{21}	V_{22}	V_{23}	V_{24}	V_{25}
AE 1	*			*		*																			
AE 2				*		*	*																		
AE 3						*	*	*																	
AE 4						*			*																
AE 5	*	*								*															
AE 6					*					*	*														
AE 7		*					*		*			*													
AE 8					*	*				*			*												
AE 9	*	*									*			*											
AE 10				*							*				*										
AE 11					*						*		*			*									
AE 12						*					*	*					*								
AE 13								*			*				*	*		*							
AE 14		*				*				*			*						*						
AE 15												*							*	*					
AE 16							*		*							*		*		*	*				
AE 17								*													*	*			
AE 18	*									*			*										*		
AE 19																*			*				*	*	
AE 20								*		*			*											*	*
ODE 1	*													*		*									*
ODE 2		*							*										*			*			
ODE 3			*									*	*												*
ODE 4				*								*	*								*				
ODE 5					*									*	*	*	*								*

Step 5: Collection of the values of the variables to be specified

The values of known variables and parameters are collected through an extensive literature search combined with an industrial survey, and are listed in a separate table.

Step 6: Model implementation in a simulation tool

Based on the information obtained from the above steps, the model can now be simulated in a modeling tool. All process operational models included in the model library have been simulated in the modeling tool ICAS-MoT. The implementation procedure of model equations in ICAS-MoT, the operations which can be performed within ICAS-MoT and the supporting tools are shown in Figure 3.11. The mathematical equations can be exported directly from paper (manuscript, report, document etc.) and subsequently implemented in ICAS-MoT. Some operations such as model translation, model analysis and model verification can be performed within ICAS-MoT. The database and solvers used by ICAS-MoT are also shown in Figure 3.11. The detailed description of the ICAS-MoT modeling tool can be found in Sales-Cruz (2006).

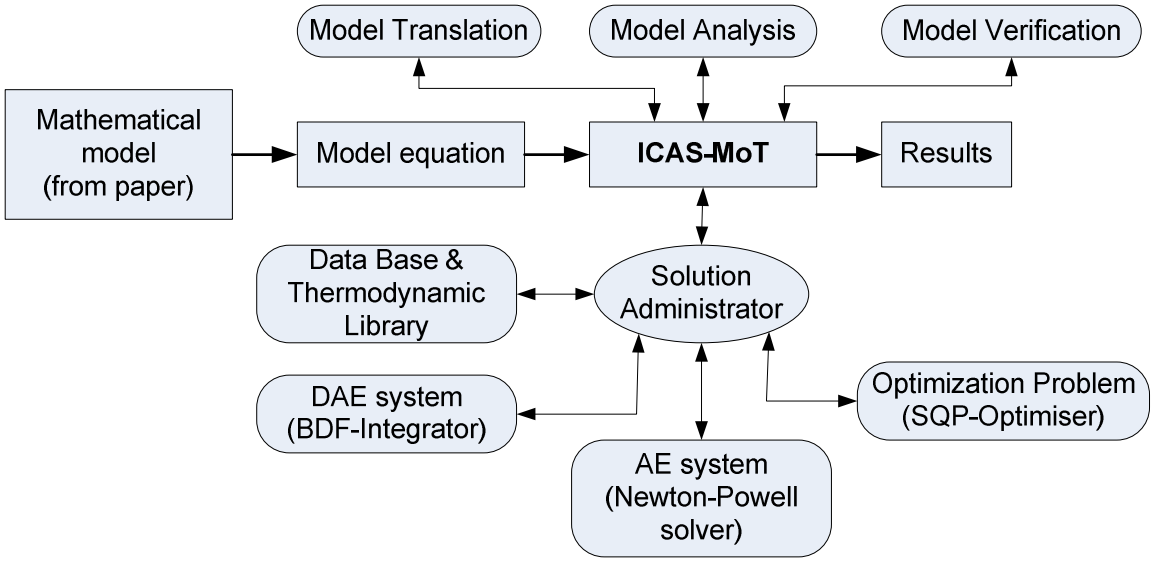


Figure 3.11: Modeling tool (ICAS-MoT) description (Sales-Cruz, 2006)

Step 7: Model validation and inclusion to model library

Finally models can be validated and included to the model library. The models stored in the model library can subsequently be used for design of process monitoring and analysis systems.

3.3.2. Model library and simulation tool integration with the software

The model library and the simulation tool (ICAS-MoT) are integrated with the user interface of ICAS-PAT (see chapter 4) as illustrated in Figure 3.12. Through the user interface, a MoT Model interface can be generated which is integrated with the MoT solver (by using a COM object) as well as connected with the model library. The MoT model interface is shown in Figure 3.13, where the access of a relevant process model and its upload to the interface (model details of a mixing process are shown in the table, see Figure 3.13, bottom) are highlighted through a mixing process[6] example. The interface also provides the options to edit the uploaded process model as well as the value of known variables and parameters. The uploaded model is then solved and the simulation data uploaded to the user interface and subsequently used for design of PAT

[6] Mixing process model is described in Appendix A1.1 and the values of known variables and parameters of the model are given in Appendix B1.1. Model analysis is given in section 2.3.2.1

systems. Note that only the final values of the variables are shown in the figure and the entire dynamic simulated data are stored in a different file.

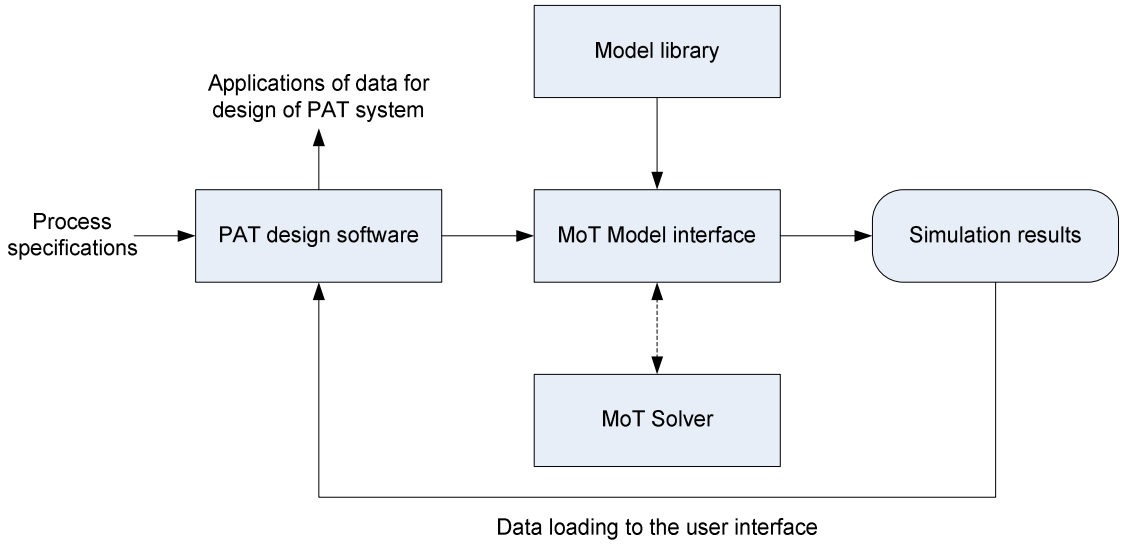
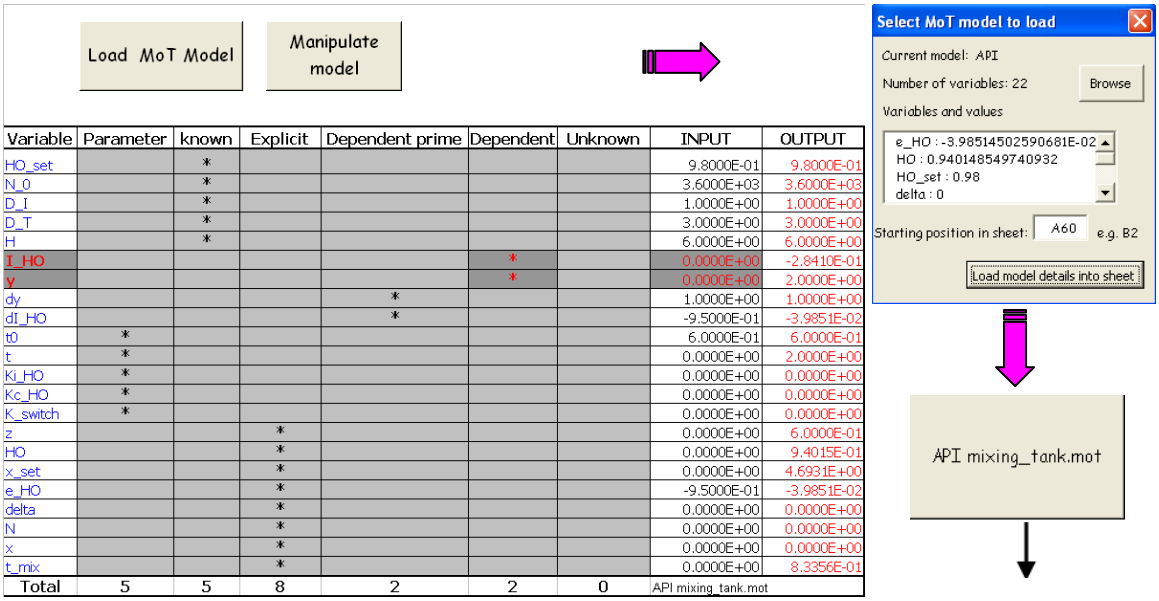


Figure 3.12: Integration of model library with the user interface



Variable	Parameter	known	Explicit	Dependent prime	Dependent	Unknown	INPUT	OUTPUT
HO_set		*					9.8000E-01	9.8000E-01
N_0		*					3.6000E+03	3.6000E+03
D_I		*					1.0000E+00	1.0000E+00
D_T		*					3.0000E+00	3.0000E+00
H		*					6.0000E+00	6.0000E+00
I_HO					*		0.0000E+00	-2.8410E-01
y					*		0.0000E+00	2.0000E+00
dy				*			1.0000E+00	1.0000E+00
dI_HO				*			-9.5000E-01	-3.9851E-02
t0	*						6.0000E-01	6.0000E-01
t	*						0.0000E+00	2.0000E+00
Ki_HO	*						0.0000E+00	0.0000E+00
Kc_HO	*						0.0000E+00	0.0000E+00
K_switch	*						0.0000E+00	0.0000E+00
z			*				0.0000E+00	6.0000E-01
HO			*				0.0000E+00	9.4015E-01
x_set			*				0.0000E+00	4.6931E+00
e_HO			*				-9.5000E-01	-3.9851E-02
delta			*				0.0000E+00	0.0000E+00
N			*				0.0000E+00	0.0000E+00
x			*				0.0000E+00	0.0000E+00
t_mix			*				0.0000E+00	8.3356E-01
Total	5	5	8	2	2	0	API mixing_tank.mot	

Figure 3.13: MoT Model interface

4. ICAS-PAT software

4.1. Implementation of framework in a software

The developed framework and methodology for design of process monitoring and analysis systems (PAT systems) has been implemented in a software (ICAS-PAT) as illustrated in Figure 4.1. As shown in the figure the general supporting tools (protected general knowledge base and model library) as well as the user specific supporting tools (specific knowledge base and model library developed by the user) are integrated within a general user interface. The system has built-in flexibility to either use the general supporting tools or the user specific supporting tools. The user specific supporting tools can be developed, extended and managed according to the user's needs while administrator rights are needed to edit/replace the general supporting tools. In either case a problem specific supporting tool (consisting of the problem specific knowledge and models) is generated and used for design of a specific PAT system. The use of problem specific knowledge/data and models reduces the data retrieval time since only a limited part of the knowledge base needs to be searched, and therefore the final PAT system is designed faster. As shown in Figure 4.1, the starting point for new problems is to provide the problem specifications, followed by the creation of problem specific supporting tools and then to design the PAT system according to the developed methodology (described in chapter 3). For already existing case specific problems (saved earlier) the design methodology is used directly to generate new solutions, or, earlier solved case studies may be opened and consulted.

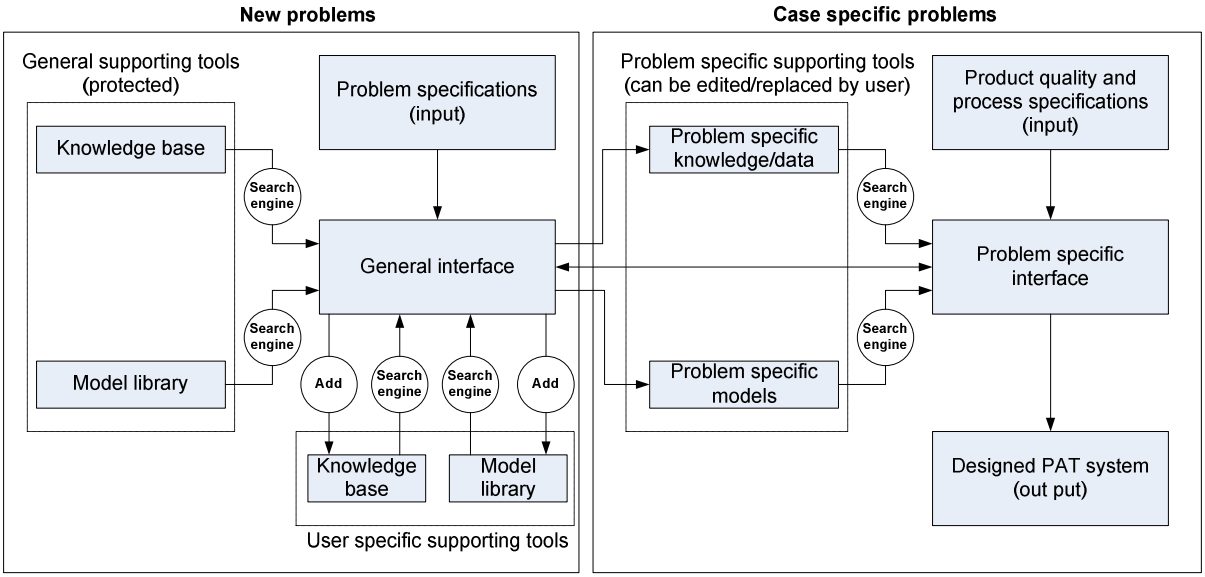


Figure 4.1: Implementation of the framework in a software

4.1.1. General supporting tools

The general supporting tools (general knowledge base and general model library) are integrated with the ICAS-PAT interface to provide the necessary data/knowledge during design of process monitoring and analysis systems. The general supporting tools are protected and administrator rights are needed to edit/replace the contents of the general supporting tools. The general supporting tools are described in chapter 3.

4.1.2. User specific supporting tools

Users can build their own supporting tools (knowledge base and model library). The organization of the user specific supporting tools needs to have the same structure as the general supporting tools so that they can be integrated. One of the advantages of creating the user specific supporting tools is that the users can store and manage their own knowledge/data and models depending on the current process requirements. If, for, example the user is not satisfied with a model in the user specific model library, a more complex model can be added by the user, or process data can be included instead. For industry, the potential to develop user specific supporting tools also means that confidential data can be kept in-house.

4.1.3. Problem specific supporting tools

4.1.3.1. Problem specific knowledge base

All data/knowledge is stored in two sections (two different files) in the general knowledge base (see Figure 3.4 and Figure 3.5). Figure 3.4 represents the structure of the 'process knowledge' and Figure 3.5 represents the structure of the 'knowledge on measurement methods and tools'. Using these two files, a single file containing all the useful information (process knowledge as well as knowledge on measurement methods and tools) needed for design of the PAT system for a specific process is created by combining the process knowledge on that specific process (Figure 3.4) with the knowledge on measurement methods and tools relevant for the specific process (Figure 3.5). The generated output file is termed as the problem specific knowledge base that provides the basis for the design of a specific PAT system. The advantage of creating a specific knowledge base is that it provides the flexibility to modify the solution for an existing process or to create a new problem definition with the corresponding knowledge base. The structure of the problem specific knowledge base is shown in Figure 4.2. It should be clarified that the process knowledge (shown in Figure 3.4) is linked with the knowledge on measurement methods and tools (shown in Figure 3.5) through a common term, 'Variable type'. However this common term does not appear in the problem specific knowledge base (shown in Figure 4.2). In Figure 4.2, process variables are directly linked with monitoring techniques in the problem specific knowledge base.

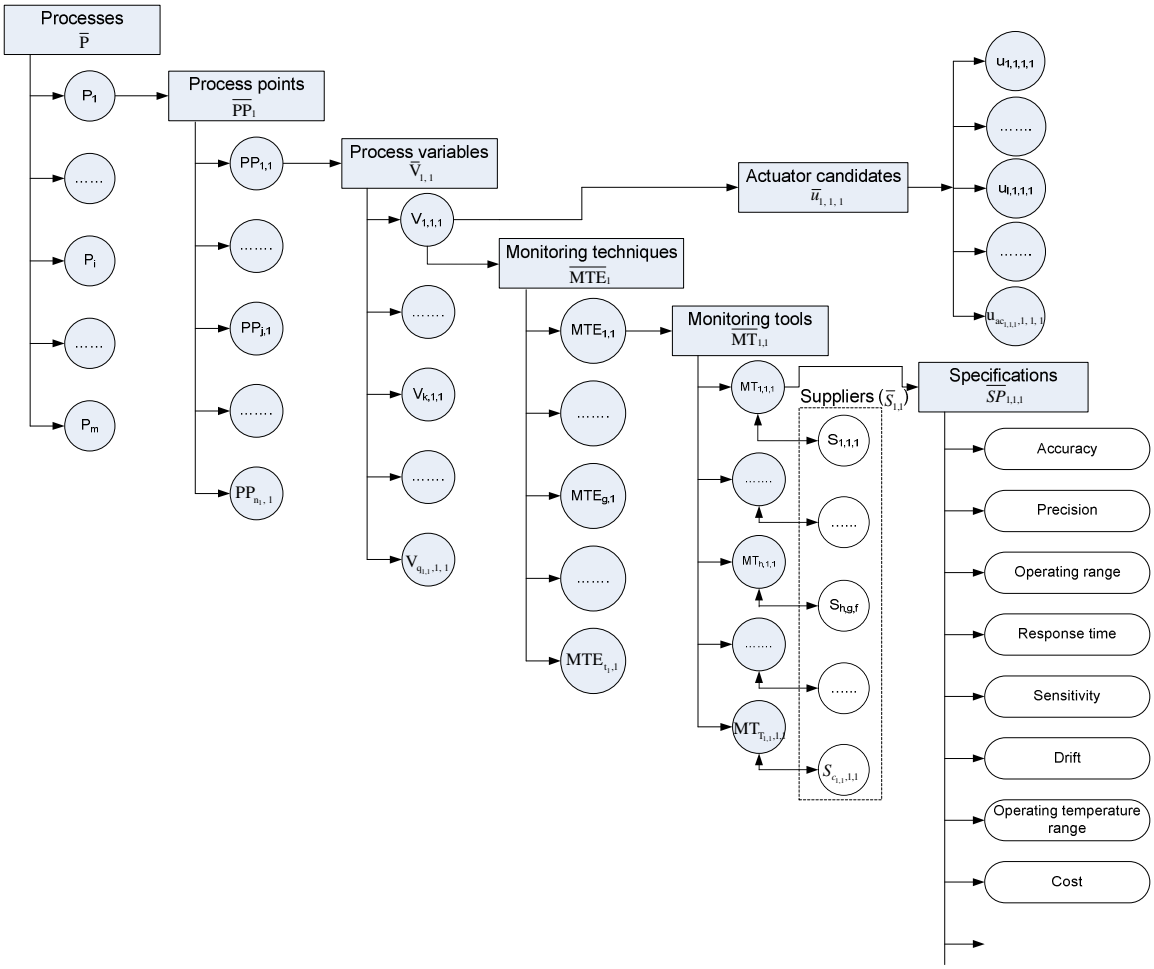


Figure 4.2: Structure of the problem specific knowledge base

4.1.3.2. Problem specific model library

All the process operational models as implemented in ICAS-MoT are stored in the general model library through which a problem specific model library can be generated. The problem specific model library contains only the models related to a specific PAT system design problem. One of the advantages of creating the problem specific model library is that it can be modified according to the requirements of the current process-product conditions

4.2. Software overview

An overview of the ICAS-PAT software is shown in Figure 4.3. The main interface consists of options for creating problem specific supporting tools (knowledge base and

model library) (see Figure 4.3, left) and the generation of a problem specific interface (see Figure 4.3, bottom right) through which the PAT system can be designed.

As shown in Figure 4.3, the starting point for creating the problem specific knowledge base is the selection of the process followed by the selection of the process points. Then the program reads the process knowledge (process, process points, process variables) from section 1 of the general knowledge base and searches for the appropriate measurement methods and tools including the specifications and the suppliers from section 2 of the general knowledge base. Finally, the software generates an output file containing the process knowledge as well as the knowledge of measurement methods and tools combined with the specifications and suppliers of the monitoring tools. Similarly, the problem specific model library is also created (see Figure 4.3, bottom left). The models related to a specific process are selected from the general model library and a copy of the selected models is stored in the problem specific model library. It should be noted that, the creation of problem specific supporting tools is needed only for new problems while the problem specific interface can be accessed directly for the existing (already solved) PAT design problems. The ICAS-PAT interface is user-friendly (guides the user through instructions/provides help with each step) and allows easy extension of supporting tools, knowledge base and model library.

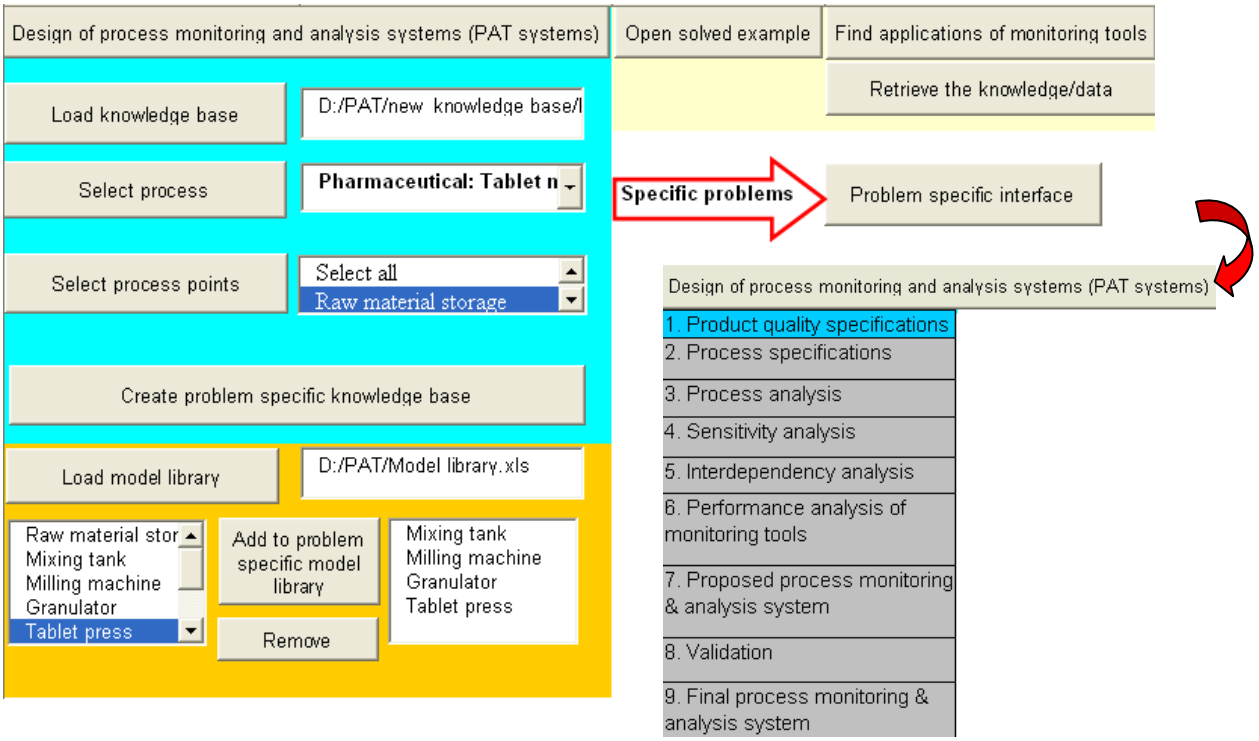


Figure 4.3: ICAS-PAT Software overview

The VBA (visual basic for applications) programming language with excel interface is used in ICAS-PAT. The architecture of the ICAS-PAT software is illustrated in Figure 4.4. The figure shows the work-flow (shown with solid lines) and data-flow (shown with dashed lines) through an "activity" diagram. The supporting tools needed in each design step are also shown in Figure 4.4 (shown with arrow shaped text box). The detailed description of the procedure to build a new architecture for development of any software is available in the literature (Bayer et al., 2002). As shown in Figure 4.4, step 1 and step 2 of the ICAS-PAT design procedure are to provide the product properties and process specifications, respectively. Both steps are necessary to provide inputs to the system. Process knowledge/data forms the additional input and is acquired through step 3, where a list of process points and corresponding process variables is generated. The knowledge base (KB) is used as the supporting tool for this step. Process models/experimental data together with the results of step 3 are the input for step 4, which generates the list of critical process points and their corresponding critical process variables as the output. Output of step 4 acts as the input for steps 5, 6 and 7, with the help of two supporting tools (Model library, MoT). Step 5 has three input data streams (process

models/experimental data, results of step 4, actuator candidates) and three supporting tools, and generates a list of manipulated variables. Step 6 has two inputs and one supporting tool, and provides the monitoring techniques and tools as a result. The results of step 4, 5 and 6 act as the input for step 7, where a PAT system is configured. The results of step 7 together with the product properties specification and the process models/experimental data are used in the validation (step 8). When the validation demonstrates that the design target is achieved, the PAT system with all the details is generated in step 9.

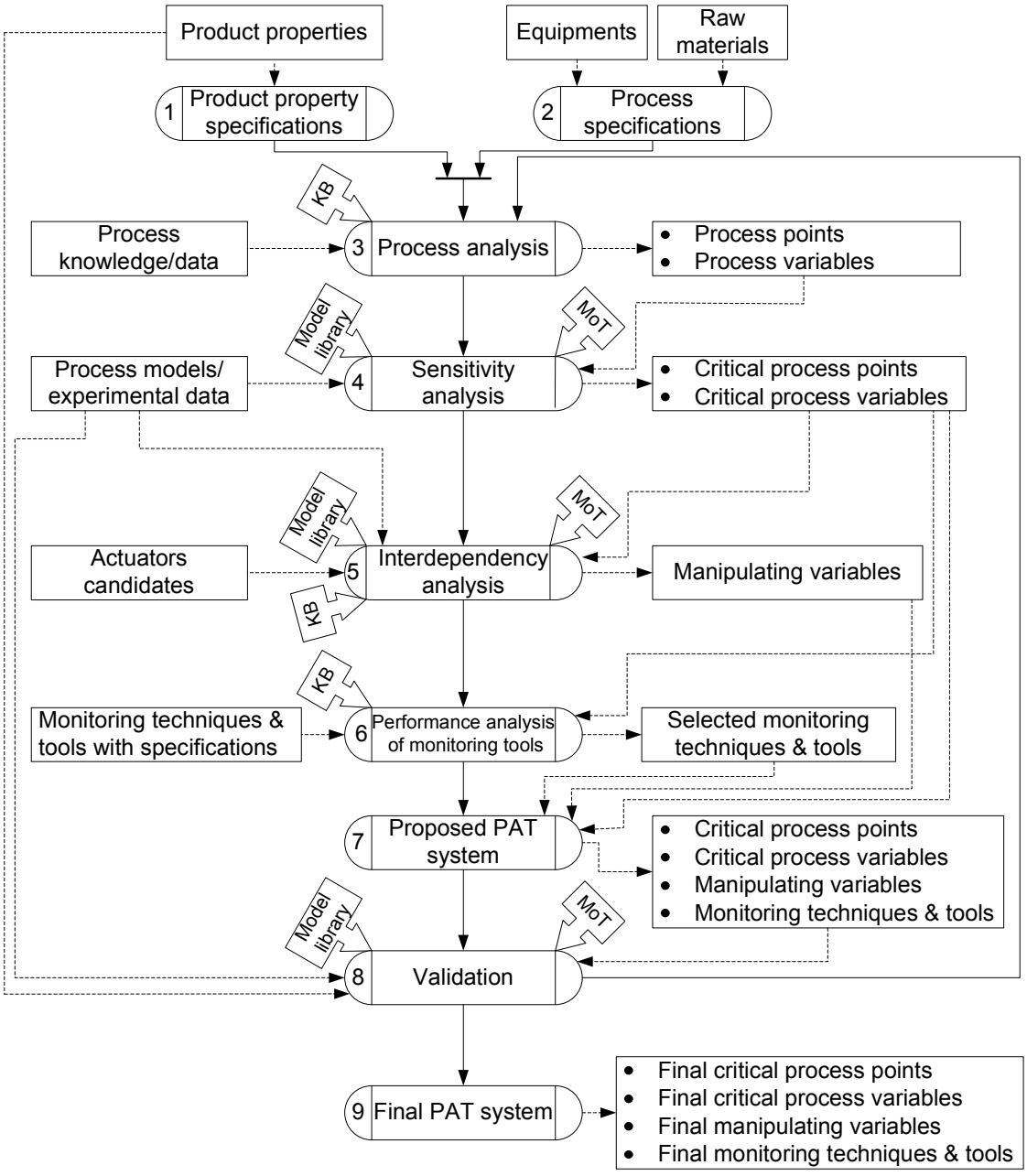


Figure 4.4: Activity diagram
(KB = knowledge base; MoT=ICAS-MoT (simulation tool))

4.2.1. Design of PAT systems – problem specific interface

Through the general ICAS-PAT interface, the user can move to the problem specific interface (see Figure 4.3, bottom right) for design of PAT systems. The design procedure

consists of 9 hierarchical steps (see Figure 4.3, right). Each design step consists of a specific interface (window) through which the required input can be provided, and the results can be accessed and analyzed. The implementation of each design step in the ICAS-PAT software together with the established work-flow and data-flow are described in the following subsections:

4.2.1.1. Product property specifications (step 1)

This step is concerned with providing the product quality specifications that have to be achieved by the production process. This information acts as the input to the system. The work-flow (shown with solid lines) and data-flow (shown with dashed lines) for this design step of ICAS-PAT is shown in Figure 4.5. As shown in the figure, the first step is to provide the desired product name (or product names, if quality standards need to be achieved for some side-product as well). The output of this step (desired product names) is the input of the next step which is concerned with providing the corresponding desired product specifications. The product names and corresponding specifications are provided by the user. The final output of this step is a list of desired products and corresponding desired specifications with values and units. It should be noted that the "measurement units" of specifications need to be consistent.

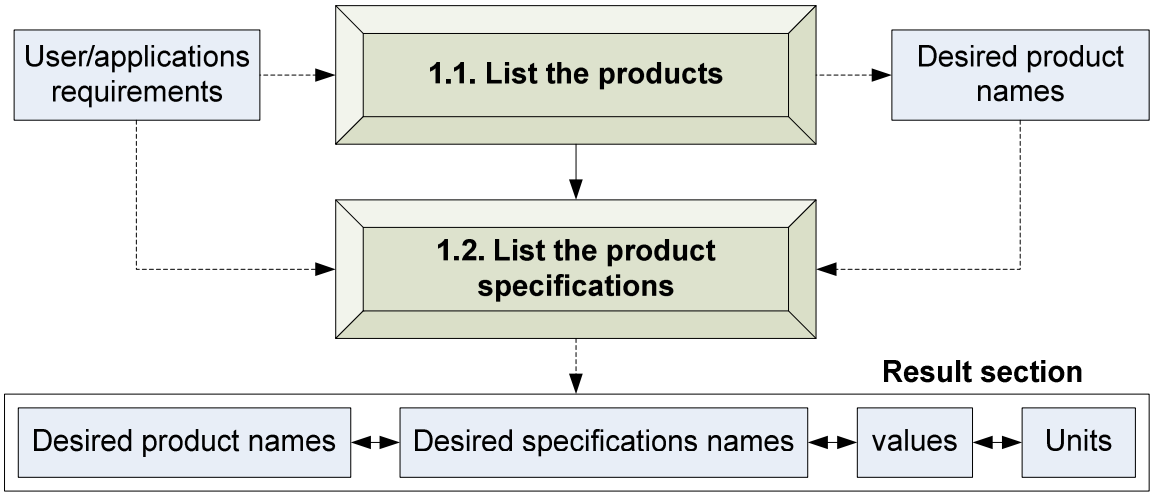


Figure 4.5: Activity diagram for product property specifications (step 1)

4.2.1.2. Process specifications (step 2)

Through this step, the process related information is provided. The work-flow (shown with solid lines) and data-flow (shown with dashed lines) for this design step of ICAS-PAT is shown in Figure 4.6. As shown in the figure, the knowledge base is first connected with the interface, and then the appropriate process which produces the desired product is selected from the list generated from the knowledge base. The generated list contains the list of all processes available in the knowledge base together with two additional options: 'Not found' and 'Unknown'. If the required process is not found in the list or any existing process does not exactly satisfy the user needs (e. g. for new or modified processes), then the possibility exists to proceed further by selecting the additional options as needed for the specific problem. In the next step the equipments used in the process are selected from the list generated from the knowledge base. The equipments available in the generated list depend on the selected process. The process flowsheet can be consulted to figure out the type of equipments used in the process. A list of raw materials used for the production is provided afterwards. The next step is concerned with providing the detailed input/output information of the production process. This information is then used to generate a simplified process flowsheet (open-loop) of the considered process. The process monitoring and analysis system will be designed and added to the generated process flowsheet through the next steps (steps 3 - 9).

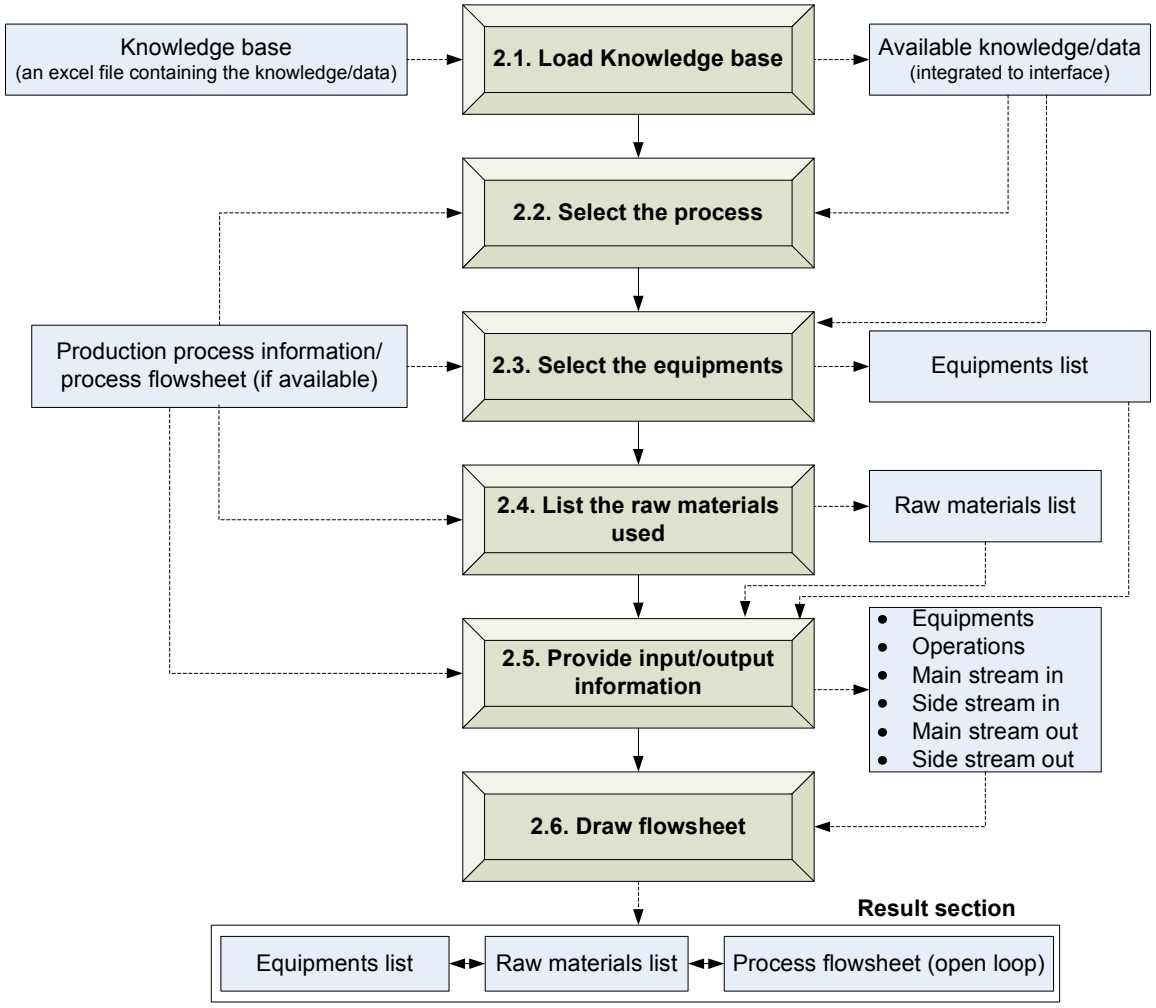


Figure 4.6: Activity diagram for process specifications (step 2)

4.2.1.3. Process analysis (step 3)

This step provides the list of process points and corresponding process variables. The work-flow (shown with solid lines) and data-flow (shown with dashed lines) of this design step of ICAS-PAT is shown in Figure 4.7. First the process points are listed based on the information provided in step 2, then the process variables related to each process point are retrieved from the knowledge base (see Figure 4.7). Note that the retrieved list of process variables provides the basis to start the design of the PAT system. The obtained list can be edited, replaced or extended as needed for the specific problem. In general, the process equipments are considered as the process points. The operational limits of the retrieved process variables should also be provided. They can be accessed

through the stored data (these data are collected based on literature and industrial survey and stored in a file named Data_sheet.xls). The data/information provided through this step is linked with the next steps and will be accessed when required. A list containing the process points, corresponding process variables together with the operational process limits forms the output of this step. Note that the knowledge/data as stored in the result section of this step are linked with the next steps of the design procedure, and will act as input to these steps.

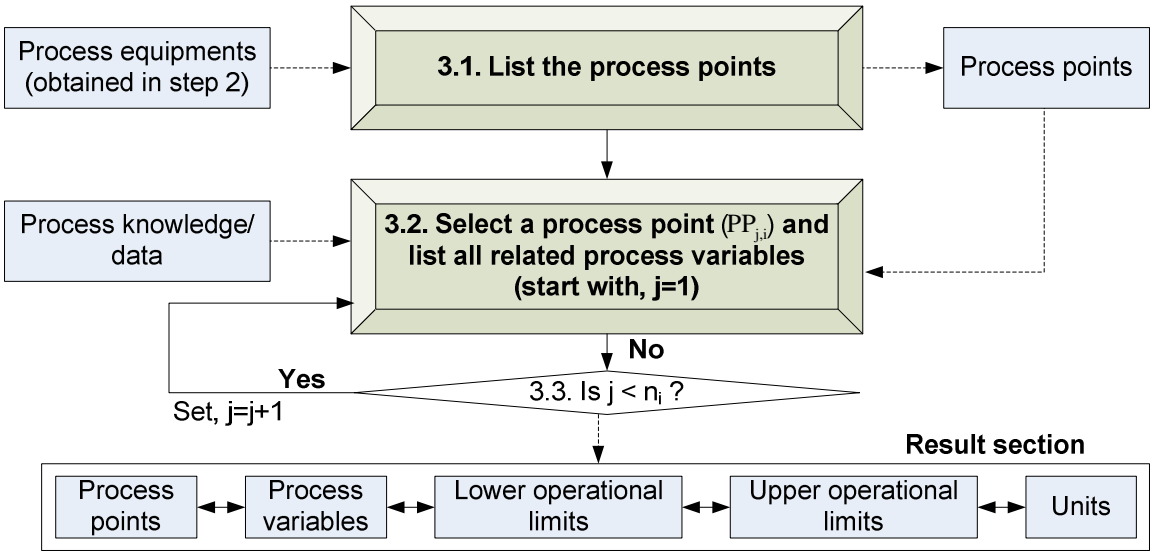


Figure 4.7: Activity diagram for process analysis (step 3)

4.2.1.4. Sensitivity analysis (step 4)

This step is concerned with the identification of the critical process variables (controlled variables). The implementation of the sensitivity analysis procedure (described in section 2.2.4) into the ICAS-PAT software is shown in Figure 4.8. The work-flow during the sensitivity analysis is represented with solid lines and the corresponding data-flow (necessary input information/data that is needed to execute the command buttons and generated output information/data) is represented with dashed lines in the Figure. As shown in Figure 4.8, the starting step is to select a process point. The result of step 3 acts as the input to this step. The selected process point and the pre-defined objective function are the input for next step (step 4.2) through which an objective function is selected/defined. The operational objectives of some known processes are pre-defined and can be accessed through the user interface. Through the next option (step 3) the

model of selected process point is solved, the corresponding simulation results are uploaded to the interface and the objective function is plotted (OB versus Time). Note that the process models are stored in the model library which is integrated with the user interface. Now the user intervention is needed to decide whether the objective function is achieved or not. If the objective function is achieved then the next process point is selected through step 4.1 to repeat the procedure and if the objective function is not achieved then a process variable is selected through step 4.5. The model variables and the selected process points are the input for this step. The next step is concerned with providing the operational limits of the selected process variable (by using the input data obtained in step 3). Step 4.7 provides the option to plot the selected variable together with specified operational limits. Generated simulation data, selected variable (name and symbol) and operational limits are the input stream for step 4.7. The plotted process variable (open-loop) is then analyzed to check whether it is violating the operational limits or not (through step 4.8). If the considered process variable is not within the operational limits that means it needs to be maintained within the operational limits by employing a suitable controller. Hence, a process variable is considered as critical if it is violating the operational limit. Finally the selected process variable is transferred to the result section (see Figure 4.8, bottom) if it is found to be critical. Note that the critical process points and critical process variables as stored in the result section are linked with the next steps of the design procedure, and will act as input to these steps. There are also options for data management which allow saving of the simulated data for future use. Already available data (simulated or experimental) may also be loaded to the interface and can be used directly to save time. The software also provides the option to use experimental data for sensitivity analysis, in case of unavailability of a process model. The procedure for generating the experimental data and its application for sensitivity analysis is described in section 2.3.3.4 of this thesis.

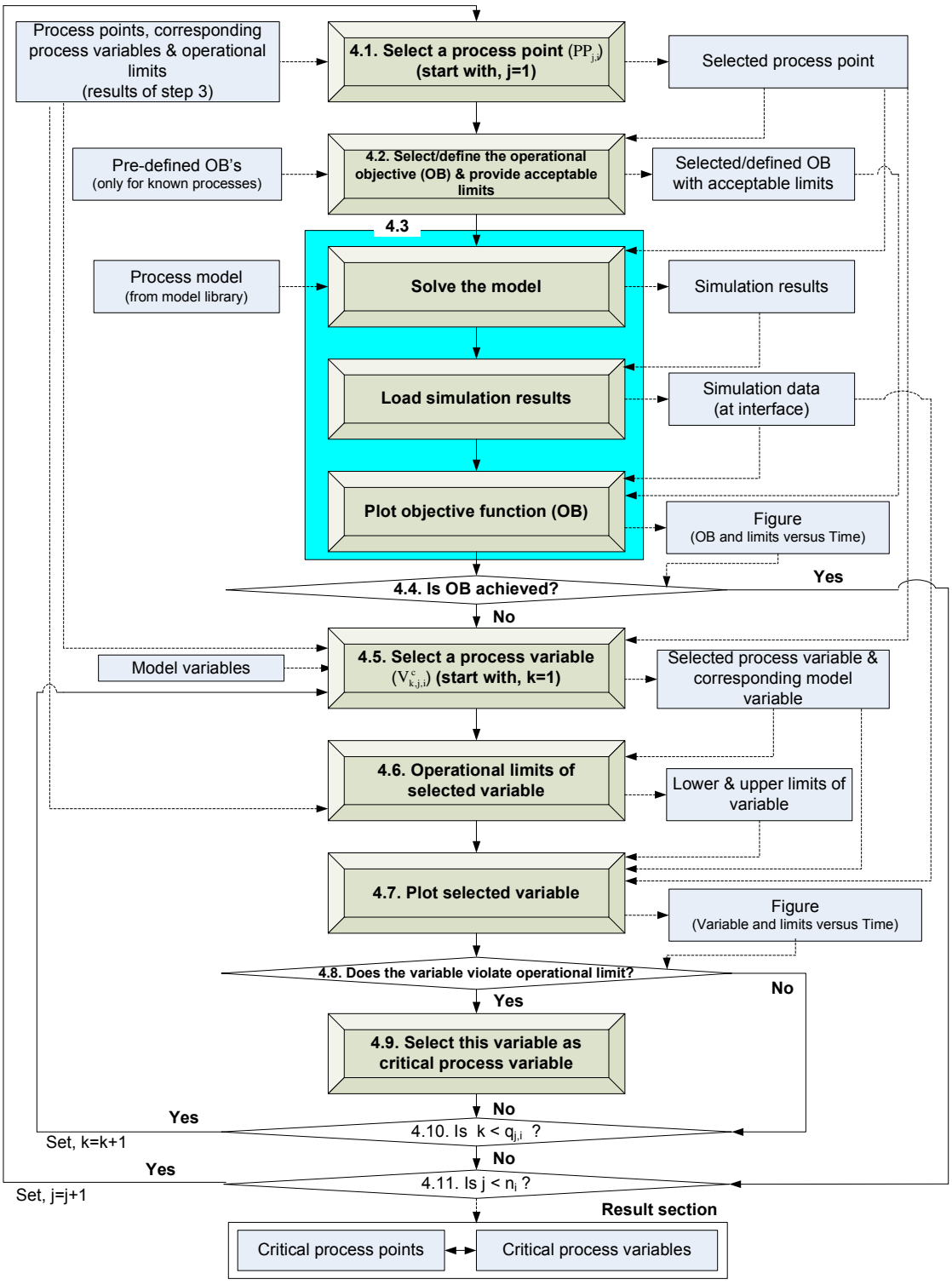


Figure 4.8: Activity diagram for sensitivity analysis (step 4)

4.2.1.5. Interdependency analysis (step 5)

This step relies on selecting an actuator for each critical process variable. The work-flow and data-flow for this step is shown in Figure 4.9 through an activity diagram. As shown in the figure, the starting step is to select a process point (result of step 4 is the input for this step). The selected process point together with the results of step 4 is the input to the next step through which a critical process variable is selected. The actuator candidates for the selected process variable are then retrieved from the knowledge base. Note that there is an option to retrieve the actuator candidates for all critical process variables in a single run to save the data retrieval time. The retrieved actuator candidates are only listed to provide the available alternatives. However, the final manipulated variable is selected through the interdependency analysis. The retrieved actuator candidates can be edited or extended (i.e. a new candidate can be added in the list) as needed for the specific problem, with the limitation that the included new actuator candidates must be known variables or parameters of the considered process model, to be able to perform the interdependency analysis. The basic idea of interdependency analysis is to perturb the actuator candidates and compare the effects of the perturbations on the critical process variable. The actuator candidate which has the largest effect on the critical process variable is selected as the most suitable actuator. It should be noted that poor performance of the control loop might result if the selected actuator has a large dead time. Therefore the performance of the control loop needs to be verified (see step 8) before confirming the selection of the final actuator.

The model library is used to generate the data for interdependency analysis, and therefore the critical process variables and corresponding actuator candidates are linked with the process model variables. The considered critical process variable (controlled variable) should be selected from the unknown variables of the model while the corresponding actuator candidates should be selected from the known variables/parameters of the model (see step 5.3 in Figure 4.9). Finally, depending on the specified perturbation setup, the data are generated, uploaded to the interface, plotted and analyzed to identify the proper actuator. Similar to the sensitivity analysis (section 4.3.4), this step of the procedure also has the option for data management and utilization of experimental data in case of unavailability of a process model. The knowledge/data as stored in the result section of

this step are linked with the next steps of the design procedure, and will act as input to these steps.

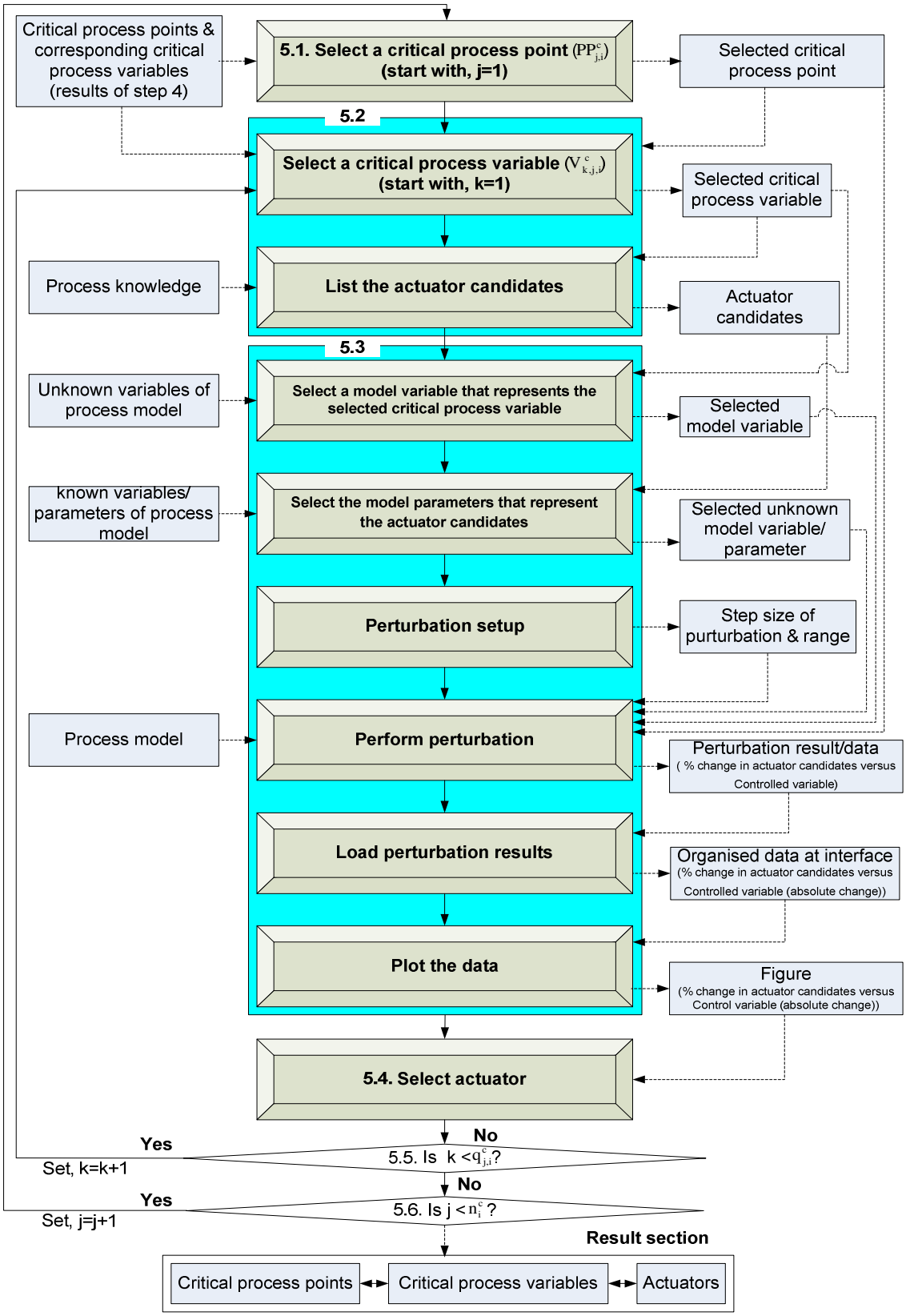


Figure 4.9: Activity diagram for interdependency analysis (step 5)

4.2.1.6. Performance analysis of monitoring tools (step 6)

Through this step, the suitable measurement methods and tools for each critical process variable is identified. The work-flow and data-flow for this step is shown in Figure 4.10 through an activity diagram. As shown in the figure, a process point is first selected through step 6.1 (results of step 4 are the input for this step). A corresponding critical process variable is selected through step 6.2 for which the selected process point and the results of the step 4 act as the inputs. Selected critical process variable is the input to step 6.3 through which the required specifications of the monitoring tools are selected and their desired values are provided that will be considered as criteria to be used in the selection of the monitoring tools. The selected specifications, their desired values together with the selected critical process point and critical process variable are the input to step 6.4 through which the monitoring techniques and tools (with specifications) that satisfied the specified criteria are retrieved from the knowledge base. Note that there is an option to retrieve the monitoring techniques and tools for all the critical process variables through a single run to save the data retrieval time. The results of step 6.4 are the input for step 6.5 through which the performance of the monitoring tools is compared. Based on the algorithm described in section 2.2.6 (see Figure 2.8), a scoring system has been developed to compare the performance of the monitoring tools. First the monitoring tools are assigned scores according to their specifications and then the total score obtained by each monitoring tool is obtained. Finally, through step 6.6, the monitoring tools with the highest score are selected. The knowledge/data as stored in the result section of this step are linked with the next steps of the design procedure, and will act as input to these steps.

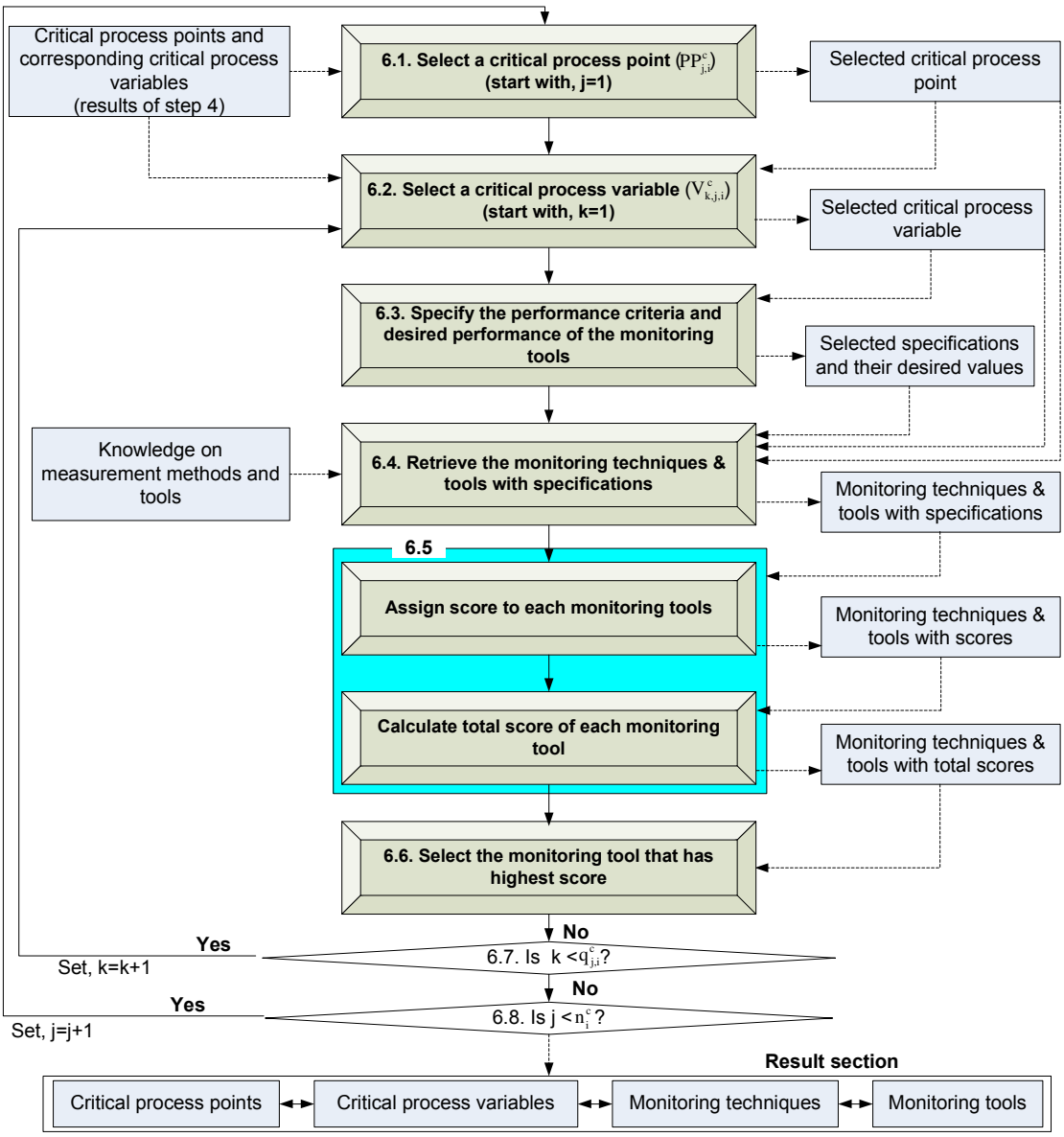


Figure 4.10: Activity diagram for performance analysis of monitoring tools (step 6)

4.2.1.7. Proposed process monitoring and analysis system (step 7)

Based on the outcomes of steps 1 - 6, a process monitoring and analysis system (PAT system) is proposed as shown in Figure 4.11. The proposed process monitoring and analysis system consist of a list of process points, corresponding critical process variables, actuators, monitoring techniques and tools.

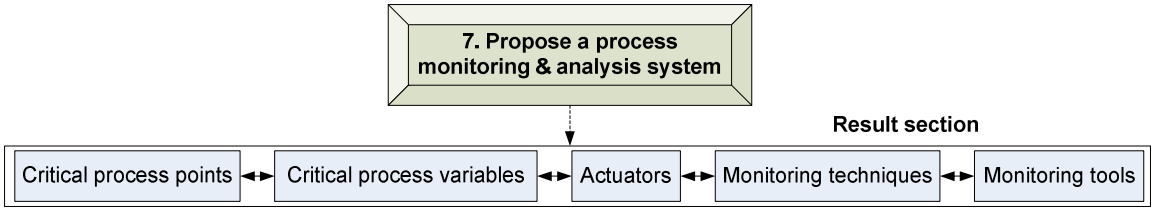


Figure 4.11: Activity diagram for proposed process monitoring and analysis system (step 7)

4.2.1.8. Model-based validation (step 8)

Through this step, the performance of the proposed process monitoring and analysis system is verified. Similar to the sensitivity analysis (see section 4.2.1.4), this step also has the option for data management (storage and access of simulated or experimental data). The activity diagram, showing the work-flow and data-flow in the validation step of ICAS-PAT is shown in Figure 4.12. The validation is achieved through the following four stages:

Controller configuration: As shown in Figure 4.12, a process point is first selected, and then controllers are configured for selected process point. To configure the controller, first a controlled variable and corresponding actuator are selected from the results obtained in step 7 then the controller is decided and the corresponding controller parameters are selected. The software has the option for selecting a P, PI, PID or On-off controller. The controller parameters (for P, PI, PID) can be either accessed from the database (pre-tuned set of controller parameters for each control loop are stored in the database) or can be given by the user–in case the user wants to try a different set of controller parameters. For the on-off controller, a parameter (K_switch) has been defined as a switch (K_switch = 0 for open-loop and 1 for closed-loop). After selecting the control loop, the type of controller and parameter values, the control loop is activated (there is also an option to deactivate the control loop if needed). Activation of control loop adds the selected controller and the corresponding parameters to the open-loop process model. Similarly the other control loops of the selected process points are activated

Control-monitor verification: When the controller configuration is finished, the closed-loop model is solved and subsequently the simulation data are loaded to the interface. Finally, the controlled variables, together with the set points and the operational limits are

plotted and analyzed. Similarly the corresponding manipulated variables together with minimum and maximum bounds, if any, are plotted and analyzed. If the considered controlled variable is within the operational limit and approaching the set point and the corresponding manipulated variable is also within the feasible bounds then the considered pair of controlled variable and actuator is considered as the verified pair of controlled variable and actuator. After verifying all pairs of controlled variables and corresponding actuators of the considered process point, the operational objective is analyzed to verify whether it is achieved or not.

Sensitivity verification: When control-monitor verification is done, the sensitivities of proposed controlled variables are verified. In this part of the verification, the controlled variables (set points) are perturbed and the relative effect on the objective function is analyzed. As shown in Figure 4.12, the objective function is first selected from the unknown variables of the process model, and then the set points of the controlled variables are selected. After setting up the perturbation test, the required data for sensitivity verification are generated through a number of closed-loop simulations. The generated data are subsequently loaded to the interface to plot the objective function against the controlled variables. The relative sensitivity of the controlled variables can be seen in the plot.

Product properties verification: After implementation of all control loops in the production process model, the product properties are verified. First the product properties are obtained through closed-loop simulation. Then the obtained product properties are compared with the specified product properties. If the specified product properties are achieved then the designed process monitoring and analysis system is considered as the final process monitoring and analysis system.

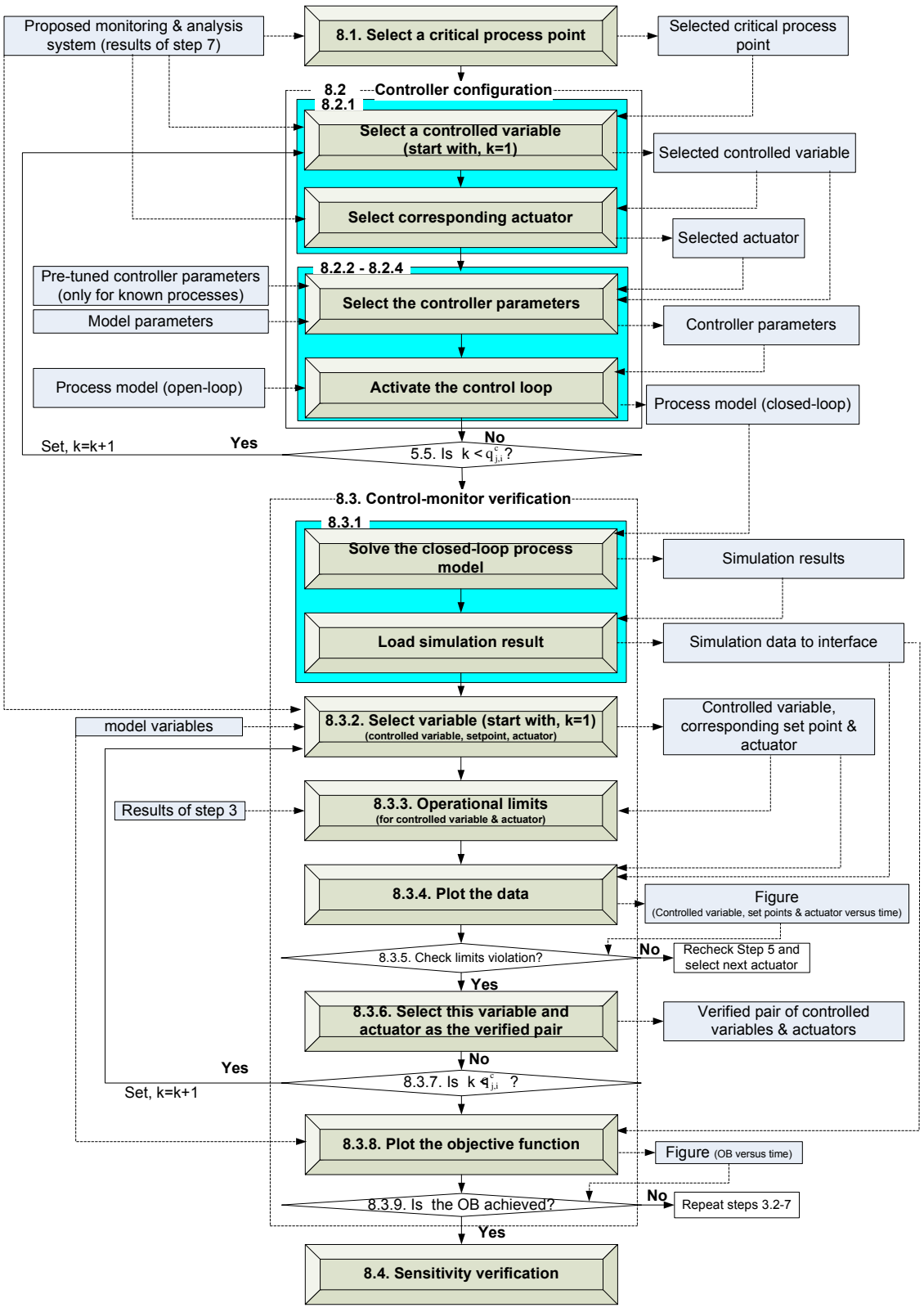


Figure 4.12: Activity diagram for validation of the proposed PAT system (step 8)

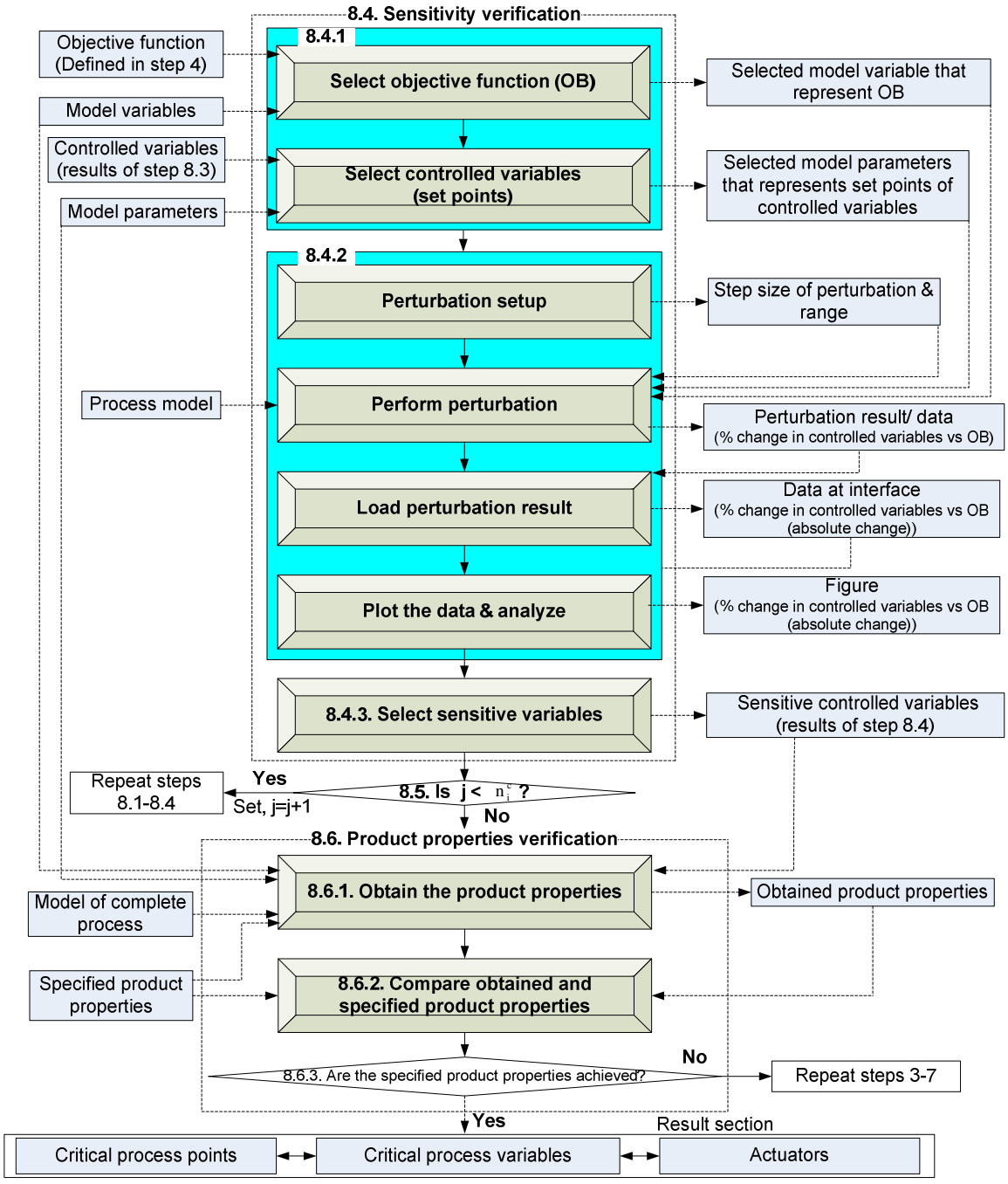


Figure 8.12: (continued)

4.2.1.9. Final process monitoring and analysis system (step 9)

The final process monitoring and analysis system is obtained through this step. The work-flow and the data-flow for this step are shown in Figure 4.13. As shown in the figure final process monitoring and analysis system, consist of the final list of process points, the

corresponding critical process variables, actuators, monitoring techniques and tools. There is also an option that allows the user to draw the closed-loop process flowsheet. Through this option, the result reported in tabulated form, can be seen in the form of a flowsheet. The drawn flowsheet contains the information regarding the controlled variables, corresponding actuators, monitoring techniques and tools with selected specifications. Finally the software has the option to create a report in MS Word (see Figure 4.13, bottom). The generated report contains the result of each design step with explanation and details of the methodology.

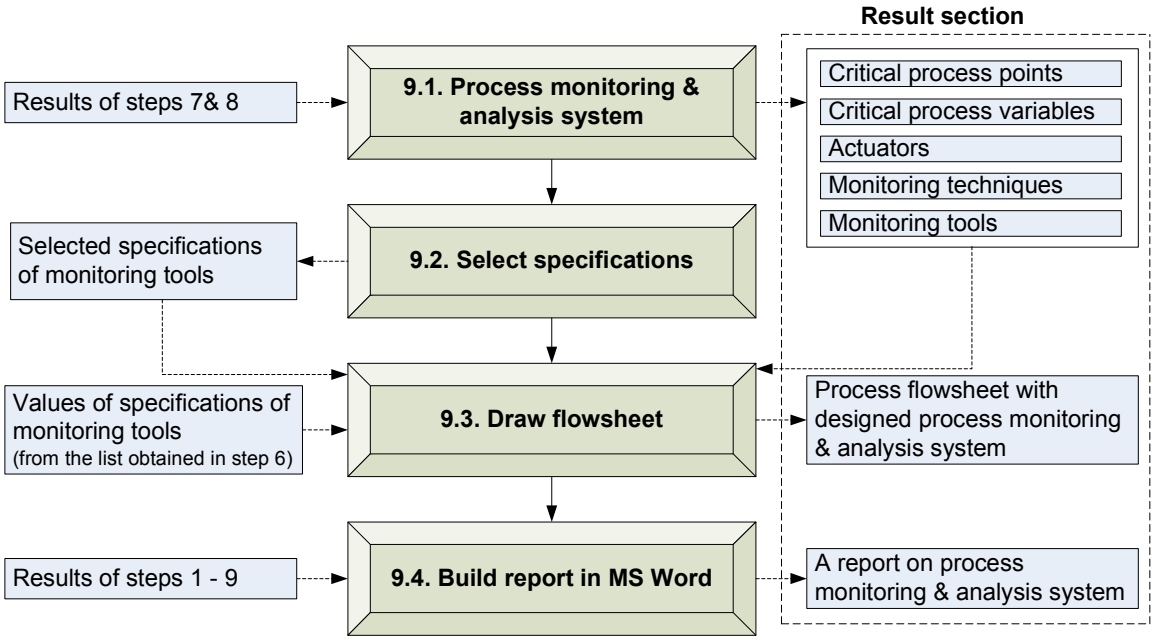


Figure 4.13: Activity diagram for final process monitoring and analysis system (step 9)

4.2.2. Additional features of the software

Some additional features have also been added to the ICAS-PAT software that has made it more useful and user-friendly. These additional features are described in the following sections:

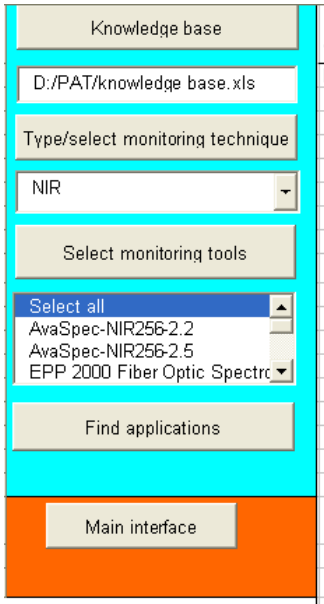
4.2.2.1. Open solved example

The solved problems (with designed process monitoring and analysis systems) are stored in the exercise section of the software for future access/applications. Through this option

(see Figure 4.3, top), stored/solved case studies can be accessed and/or modified and can be used directly if a case study satisfies current user requirements.

4.2.2.2. Find applications of monitoring tools

This option is created to allow data retrieval from the knowledge base on monitoring tools (see Figure 4.3, right, top) using a "reverse" search procedure. Through this option the potential application range of a specific monitoring technique/tool can be identified (e.g. to find out the potential applications of the NIR/NIR based tools for monitoring of the different variables in different processes). The user interface for this additional feature of the software is shown in Figure 4.14 (left); the right portion of the figure shows the results of the "reverse" search. As shown in the figure, the general knowledge base is integrated with the interface. The monitoring technique for which the applications have to be found, are selected from the drop-down list which contains all the monitoring techniques available in the knowledge base. All the available monitoring tools based on the selected monitoring technique are then listed (see Figure 4.14, under "Select monitoring tools"). The monitoring tools for which the applications have to be retrieved are then selected from the list. Furthermore, based on this software feature the system can predict exactly for which process and – especially within the process – for which process point a certain monitoring tool can be used. For instance, some potential applications of some of the NIR based tools are listed in the results section of Figure 4.14 (only a part of the results is shown for illustration purposes).

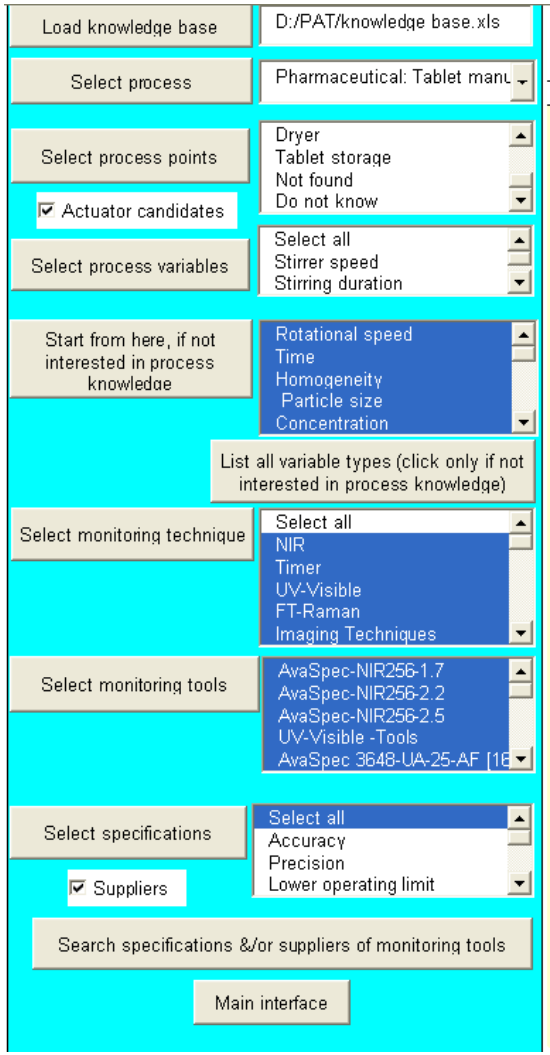


Monitoring techniques	Monitoring tools	Monitoring variables	Process points	Processes
NIR	AvaSpec-NIR256-1.7	Content uniformity	Tablet storage	Pharmaceutical: Tablet manufacturing
		Homogeneity	Fermentor	Fermentation
		Homogeneity	Mixing tank	Fermentation
		Homogeneity	Mixing tank	Pharmaceutical: Tablet manufacturing
		Homogeneity	Crystallizer	Crystallization
		Homogeneity	Mixing tank	Insulin production
		Homogeneity	Fermentor	Insulin production
		Homogeneity	Blender	Insulin production
		Homogeneity	Crystallizer	Insulin production
	AvaSpec-NIR256-2.2	Content uniformity	Tablet storage	Pharmaceutical: Tablet manufacturing
		Homogeneity	Fermentor	Fermentation
		Homogeneity	Mixing tank	Fermentation
		Homogeneity	Mixing tank	Pharmaceutical: Tablet manufacturing
		Homogeneity	Crystallizer	Crystallization
		Homogeneity	Mixing tank	Insulin production
		Homogeneity	Fermentor	Insulin production
		Homogeneity	Blender	Insulin production
		Homogeneity	Crystallizer	Insulin production
	KJT270 Desktop Composition Analyzer	Identifying and qualifying the raw materials (Compositions)	Raw material storage	Pharmaceutical: Tablet manufacturing
		Centrate composition (liquid waste)	Centrifuge	Insulin production
		Sludge solid composition (centrifuge end product)	Centrifuge	Insulin production
		Centrate composition (liquid waste)	Centrifuge	Cheese & butter manufacturing
		Sludge solid composition (centrifuge end product)	Centrifuge	Cheese & butter manufacturing
	KJT550 NIR Online Composition Analyzer	Identifying and qualifying the raw materials (Compositions)	Raw material storage	Pharmaceutical: Tablet manufacturing
		Centrate composition (liquid waste)	Centrifuge	Insulin production
		Sludge solid composition (centrifuge end product)	Centrifuge	Insulin production
		Centrate composition (liquid waste)	Centrifuge	Cheese & butter manufacturing
		Sludge solid composition (centrifuge end product)	Centrifuge	Cheese & butter manufacturing
	uniSPEC-4000	Casein protein	Milk storage tank	Cheese & butter manufacturing
		Casein protein	Pasteurizer & cooling	Cheese & butter manufacturing
		Casein protein	Cheese vat	Cheese & butter manufacturing
		Fat	Milk storage tank	Cheese & butter manufacturing
		Fat content in whey	Whey separator	Cheese & butter manufacturing
	EPP 2000 Fiber Optic	Homogeneity	Fermentor	Fermentation
		Homogeneity	Mixing tank	Fermentation
		Homogeneity	Mixing tank	Pharmaceutical: Tablet manufacturing
		Homogeneity	Crystallizer	Crystallization

Figure 4.14: Find applications of monitoring tools, user interface (left) with example of a result (right)

4.2.2.3. Retrieve the knowledge/data

This option is based on the forward search procedure (see Figure 4.3, right, top). It provides direct access to the knowledge/data stored in the knowledge base, and it is especially designed for the cases where the user would like to explore the available alternatives of process monitoring and analysis systems (e.g. to find out the available monitoring tools and their specifications for a particular process variable). The user interface for this additional feature of the software is shown in Figure 4.15. It has two sections, the input section (query sheet) and the results section. As shown in the figure, the general knowledge base is integrated with the interface. Some information related to the process and measurement methods and tools are provided as input to the system (through the query sheet) and the search engine then provides the retrieved data through the access of the knowledge base. The query sheet has two parts: the first part of the query sheet can be used separately to retrieve the process knowledge while the second part can be used to retrieve the knowledge on measurement methods and tools.



RESULTS

Process	Process points	Process variables	Variable types	Actuator candidates
Pharmaceutical: Tablet manufacturing	Mixing tank	Stirrer speed	Rotational speed	
Pharmaceutical: Tablet manufacturing	Mixing tank	Stirring duration	Time	
Pharmaceutical: Tablet manufacturing	Mixing tank	Homogeneity	Homogeneity	Stirrer speed
Pharmaceutical: Tablet manufacturing	Milling machine	Particle size	Particle size	Mill speed
Pharmaceutical: Tablet manufacturing	Milling machine	Milling duration	Time	
Pharmaceutical: Tablet manufacturing	Milling machine	Rotational speed	Rotational speed	
Pharmaceutical: Tablet manufacturing	Milling machine	Solute concentration	Concentration	
Pharmaceutical: Tablet manufacturing	Milling machine	Feed weight	Weight	
Pharmaceutical: Tablet manufacturing	Granulator	Granule size	Granule size	Rotational speed
Pharmaceutical: Tablet manufacturing	Granulator	Moisture content	Moisture content	Flow rate of hot air
Pharmaceutical: Tablet manufacturing	Granulator	Dissolution	Dissolution	Binder flow rate
Pharmaceutical: Tablet manufacturing	Granulator	Fluidisation air flow rate	Gas flow rate	Valve pressure
Pharmaceutical: Tablet manufacturing	Granulator	Fluidisation air temperature	Gas temperature	Steam flow rate
Pharmaceutical: Tablet manufacturing	Granulator	Binder flow rate	Liquid flow rate	Valve pressure
Pharmaceutical: Tablet manufacturing	Granulator	Atomizing air flow rate	Gas flow rate	Valve pressure
Pharmaceutical: Tablet manufacturing	Granulator	True density	True density	
Pharmaceutical: Tablet manufacturing	Granulator	Bulk density	Bulk density	
Pharmaceutical: Tablet manufacturing	Granulator	Tap density	Tap density	
Pharmaceutical: Tablet manufacturing	Granulator	Bed temperature	Gas temperature	Steam flow rate
Pharmaceutical: Tablet manufacturing	Granulator	Porosity	Porosity	Moisture content
Pharmaceutical: Tablet manufacturing	Tablet press	Weight	Weight	Pre compression force
Pharmaceutical: Tablet manufacturing	Tablet press	Thickness	Thickness	Main compression force
Pharmaceutical: Tablet manufacturing	Tablet press	Shape	Shape	Main compression force
Pharmaceutical: Tablet manufacturing	Tablet press	Hardness	Hardness	Main compression force
Pharmaceutical: Tablet manufacturing	Tablet press	Pre-compression force	Force	Feed volume
Pharmaceutical: Tablet manufacturing	Tablet press	Main compression force	Force	Feed volume
Pharmaceutical: Tablet manufacturing	Tablet press	Press speed	Press speed	
Pharmaceutical: Tablet manufacturing	Tablet press	Dwell time	Time	
Pharmaceutical: Tablet manufacturing	Tablet press	Punch position	Punch position	
Pharmaceutical: Tablet manufacturing	Tablet press	Crushing strength of tablet	Crushing strength of tablet	
Pharmaceutical: Tablet manufacturing	Tablet press	Disintegration time	Disintegration time	
Pharmaceutical: Tablet manufacturing	Tablet press	Friability	Friability	
Pharmaceutical: Tablet manufacturing	Tablet coater	Film thickness (coating)	Film thickness (coa	Inflow rate of coating materials
Pharmaceutical: Tablet manufacturing	Tablet coater	Inlet air flow rate	Gas flow rate	Valve pressure
Pharmaceutical: Tablet manufacturing	Tablet coater	Inlet air temperature	Gas temperature	Coolant flow rate
Pharmaceutical: Tablet manufacturing	Tablet coater	Inlet air humidity	Humidity	
Pharmaceutical: Tablet manufacturing	Tablet coater	Outlet air flow rate	Gas flow rate	Valve pressure
Pharmaceutical: Tablet manufacturing	Tablet coater	Outlet air temperature	Gas temperature	Coolant flow rate
Pharmaceutical: Tablet manufacturing	Tablet coater	Outlet air humidity	Humidity	

Figure 4.15: Knowledge/data retrieval system, user interface (left) with example of a result on the right (only process knowledge is shown)

4.2.2.4. Draw process flowsheet (open and closed-loop)

ICAS-PAT provides the options to draw the open-loop (without the process monitoring and analysis system) and closed-loop (with the process monitoring and analysis system) flowsheets. This option is created to represent the input (process specifications)/output (designed PAT system) information of ICAS-PAT in the form of a flowsheet.

Open-loop process flowsheet

The user interface for drawing the open-loop process flowsheet is shown in Figure 4.16. The process specifications that need to be provided to draw the flowsheet are also shown in the figure (see Figure 4.16, right). The type of equipments (process points), corresponding operations and inlet/outlet streams are the necessary process information that needs to be provided. The application of this feature of ICAS-PAT is demonstrated through a fermentation process example (described in section 2.3). If some equipment does not have some input/output streams then the corresponding space should be left blank. For instance, there is no side stream out from the equipment 'Mixing tank', therefore the corresponding cell in the table (see Figure 4.16, right) is left blank. The generated flowsheet of the fermentation process is shown in Figure 4.17 as an example.

Provide input/output information

Draw flowsheet

Equipments	Operations	Main stream in	Side stream in	Main stream out	Side stream out
Mixing tank	Mixing	Mixed media	Water	Mixed media	
			Media		
Heat sterilizer	Heat sterilization	Sterilized media			
Fermentor	Fermentation		Ammonia	Biomass	Air
			Air		

Figure 4.16: User interface for drawing the open-loop process flowsheet

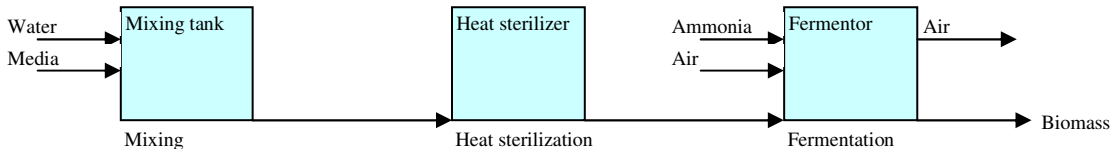


Figure 4.17: Open-loop process flowsheet generated through ICAS-PAT

Closed-loop process flowsheet

This feature provides the option to draw the process flowsheet with the designed process monitoring and analysis system. Through this option, all the control loops including the controlled variables, monitoring techniques/tools, specifications of the monitoring tools, controllers and actuators can be seen in a process flowsheet. The fermentation process is again considered to demonstrate the application of this feature of ICAS-PAT. The user interface and generated closed-loop process flowsheet are shown in Figure 4.18. The designed process monitoring and analysis system (see table at the top of Figure 4.18) as generated through ICAS-PAT is used as the input to generate the closed-loop process flowsheet. The user has to select the specifications of the monitoring tools if it is desired that they appear in the flowsheet (see Figure 4.18, top, right). Finally, a closed-loop process flowsheet, as shown in Figure 4.18 is generated. The generated process flowsheet includes the controlled variables, corresponding actuators, monitoring techniques and selected specifications of monitoring tools. The generated closed-loop process flowsheet can be considered as the output of ICAS-PAT.

4.2.2.5. Build report in MS Word

This feature of ICAS-PAT provides the option to build the report of a PAT system design case study in MS Word. The report includes the result of each step of the PAT system design and can be printed or saved for documentation purposes. It is important to generate the report after each PAT system design to keep it as a record for future consultation.

Critical process points	Critical process variables	Actuators	Monitoring techniques	Monitoring tools
Mixing tank	Homogeneity	Mixing time	NIR	EPP 2000 Fiber Optic Spectrometer-NIR2
Sterilizer	Main stream temperature	Heating fluid flow rate	Thermocouple	WZ-08541-28 (E 20-gauge thermocouple)
Fermentor	DO (Dissolved oxygen)	Air flow rate	Optical sensor	FOXY Sensor System
Fermentor	pH	Flow rate of NH3	Electrochemical sensor	Electrochemical sensor
Fermentor	Temperature	Coolant flow rate	Thermocouple	WZ-08541-28 (E 20-gauge thermocouple)

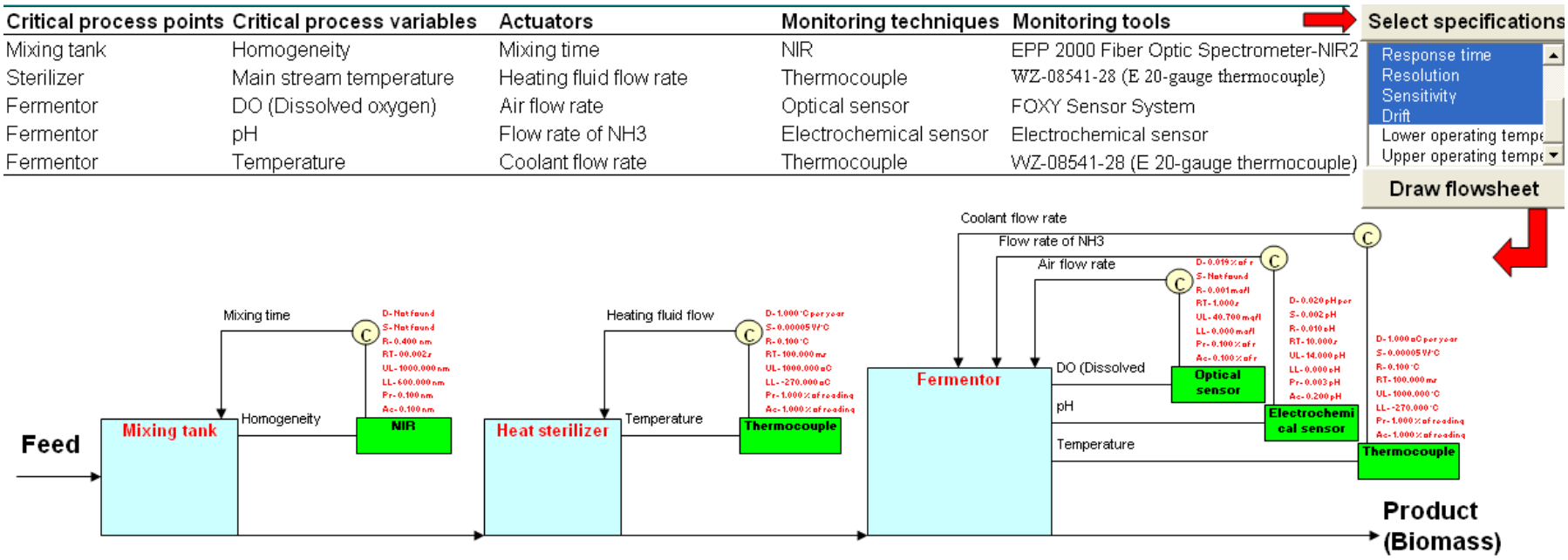


Figure 4.18: Closed-loop process flowsheet generation through ICAS-PAT

5. Case studies

In this chapter the applications of developed framework, methodology and corresponding software (ICAS-PAT) for design of process monitoring and analysis systems (PAT systems) are demonstrated through two case studies. The first case study (tablet manufacturing process) demonstrates their applications in the pharmaceutical processes while the second case study (cheese manufacturing processes) demonstrates their applications in food processes. Full details of the considered manufacturing processes including the process models (see appendix A and appendix B) is provided to allow the interested reader to independently verify the results.

5.1. Tablet manufacturing process

A pharmaceutical tablet manufacturing process has been selected as an illustrative case study. The process operational models of the tablet manufacturing process are given in Appendix A2 while the value of known variables and parameters needed to solve the models are given in Appendix B2. These process models are used by ICAS-PAT to generate the data needed for design of a process monitoring and analysis system for the tablet manufacturing process.

5.1.1. Process description

The tablet manufacturing process shown in Figure 5.1 (adopted from Papavasileiou et al., 2007) is considered here. A batch run begins by charging 705 L of USP-Water into a 1500 L mixing tank, then adding 200 kg of sucrose and 400 kg of API. The suspension is agitated thoroughly for 8 h. The suspension is then transferred into another 1500 L tank that feeds the nano-mill. The role of the nano-mill is to homogenize the suspension thoroughly and to reduce the API particles to nanometer scale. This step is required because this specific API is insoluble in water. The suspension is pumped twice through the nano-mill over a period of 22 h. After the completion of the homogenization, the material is transferred into a 2000 L tank where 70 kg of an excipient and 50 kg of a flavoring agent are added along with 100 L of USP water. The material is agitated thoroughly for 5 h. The material is afterwards transferred into another 2000 L tank that feeds the granulator. A stabilizer solution is prepared in a 500 L tank by dissolving 80 kg

of the stabilizer into 180 L of USP water. The stabilizer solution is combined with the homogenized solution in the mixing tank.

In preparation for the granulation/drying step, mannitol is added into the bowl of the granulator. The suspension is subsequently sprayed into the chamber of the granulator at a rate of 120 kg/h. Almost all of the water is removed (final water content 0.005% w/w). The granulated/dried material is removed from the granulator and stored into multiple 50 L mobile containers. The granulator handles a batch of homogenized material resulting from the previous unit operation in two cycles because of its limited bowl volume that can hold up to around 1350 L (or 600 kg) of bulk solids.

The mobile tanks are moved into the tablet press room. The tablet press makes 0.5 g tablets at a rate of 250,000 tablets per hour. The processing of a batch is completed in approximately 9.6 h. The tablets are collected in a storage bin. A tablet coater is afterwards used to coat the tablets with a material that gives them a sweet taste and a white color. A batch is processed in four cycles because the coater can handle up to around 300 kg of tablets per batch. The coating solution is prepared ahead of time in a 150 L mixing tank. A coating cycle takes around 6 h. Warm air is pumped through the drum of the coater during the coating process to vaporize the water of the coating solution. The coated tablets are stored in drums (not shown in the flow-sheet) and taken to the packaging area.

All the unit processes up to the granulator require a sanitization operation prior to the main processing activities and a CIP (cleaning in place) operation after the main processing activities.

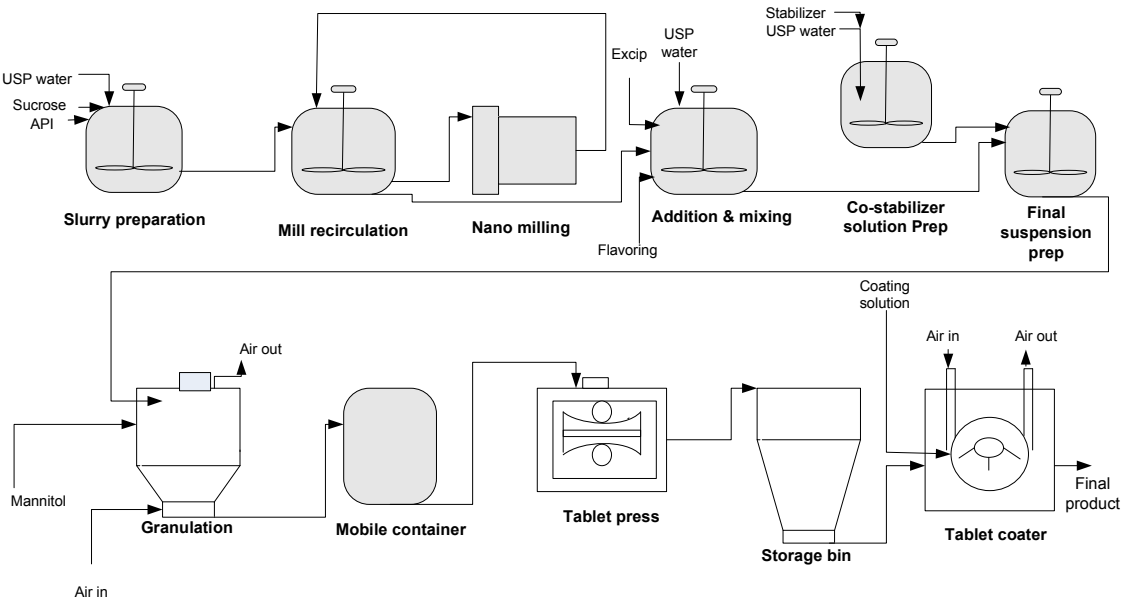


Figure 5.1: Process flowsheet for the tablet manufacturing process (adopted from Papavasileiou *et al.*, 2007)

5.1.2. Process models

The model library consists of operational models of different unit processes (mixing, milling, granulation, tablet storage, tablet pressing, tablet coating) involved in the tablet manufacturing process that can be accessed through the user interface and can be used for design of the PAT system. The detailed description of the process models is given in Appendix A2 while Appendix B2 contains the values of the known variables and parameters of the models. It is important to emphasize here that we have on purpose chosen to provide all the details on the models used for the tablet manufacturing case study such that the reader can implement the models and repeat our simulations if that is desired. Also, by providing the model details it is hoped that the tablet manufacturing process will become a simulation benchmark case study for the comparison of suitable control strategies. Each process model has been developed and solved individually, however the developed models of unit processes can be arranged as the given flowsheet and can be integrated with the constraints that the output of an individual unit process needs to be the input of the next adjacent unit process according to the connectivity specified in the flowsheet.

As mentioned in section 3.3.1, each process model has been built, analyzed and then implemented to the simulation tool of ICAS-MoT. For each process model, based on the total number of variables and the total number of equations the degree of freedom is calculated. The degree of freedom represents the number of variables which have to be specified to solve the model. Based on the calculated degree of freedom, the variables which have to be specified and which have to be predicted by the model are identified. Based on the classification of variables an incidence matrix between number of equations and the number of unknown variables is prepared. The solution strategy is identified, based on the characteristics of the incidence matrix. If the incidence matrix shows the lower triangular form then all the model equations can be solved sequentially, otherwise some of the equations need to be solved iteratively (Gani et al., 2006a). This also means that all the DAE (differential and algebraic equations) based models are of type Index = 1 (Gani and Cameron, 1992)

5.1.2.1. Mixing process model

The list of model equations is given in Appendix A1.1. The model is described in section 2.3.2.1 of chapter 2

5.1.2.2. Milling process model

The total number of equations in this case (for z size intervals) is [z (z-1)/2+5z+6] (see appendix A2. 2). The total number of variables involved in the model is found to be [z (z-1)/2+6z+22] (see Table 5.1). The degree of freedom is calculated to be (z+16). The detailed classification of the variables is given in Table 5.1. The incidence matrix of this model has shown a lower triangular form (see Table 5.2), meaning that the equations of this model can be solved sequentially.

Table 5.1: Classification of milling process model variables
(z is the number of size interval considered for the particle size distribution)

Variable types		Variables	No. of variables	Total no
To be specified	Constant	π, g	2	z+16
	Fixed by problem	M, n, x_m, x_c, X_s	5	
		$\underline{x} = [x_1 ... x_i .... x_z]$	z	
	Fixed by system	ρ, K_v, α, β, γ, k, S, R, r	9	
To be predicted	Algebraic (explicit)	a, Φ_{cr}, N_{cr}, M_s, N_{p_total}, L_{avg}	6	z(z-1)/2+5z+6
		$\underline{b_{ij}} = [b_{11} ... b_{ij} .... b_{zz}]$	z(z-1)/2	
		$\underline{S} = [S_1 ... S_i .... S_z]$	z	
		$\underline{M} = [M_1 .... M_i .... M_z]$	z	
		$\underline{M_p} = [M_{p_1} .... M_{p_i} .... M_{p_z}]$	z	
		$\underline{N_p} = [N_{p_1} .... N_{p_i} .... N_{p_z}]$	z	
	Differential	$\underline{X} = [X_1 ... X_i .... X_z]$	z	
Total number of variables involved in the model				z(z-1)/2+6z+22
Total number of differential equations				z
Total number of algebraic equations				z(z-1)/2+4z+6

Table 5.2: Incidence matrix of the milling process model

Eq. No.	$\underline{x}$	$\underline{M_p}$	M_s	$\underline{M}$	$\underline{N_p}$	N_{p_total}	L_{avg}	$\underline{b}$	N_c	Φ_{cr}	a	$\underline{S}$
2.2.1		*										
2. 2.2			*									
2. 2.3	*		*	*								
2. 2.4		*		*	*							
2. 2.5					*	*						
2. 2.6					*	*	*					
2. 2.7								*				
2. 2.8									*			
2. 2.9									*	*		
2. 2.1										*	*	
2. 2.11											*	*
2. 2.12	*							*				*

5.1.2.3. Granulation process model

The total number of equations in this case is 29 (see Appendix A2.3). The total number of variables involved in the model is found to be 62 (see Table 5.3). The degree of freedom is calculated to be 33. The detailed classification of the variables is given in Table 5.3. The incidence matrix of this model has also shown a lower triangular form (see Table 5.4) meaning that the model equations can be solved sequentially.

Table 5.3: Classification of granulation process model variables

Variable types		Variables	No. of variables	Total no
To be specified	Constant	π, ρ_w, ΔH_v, $\tilde{M}_w$	4	33
	Fixed by problem	M_0, d_0, ρ_s, K, ρ_g, β_{pg}, X_{bw}, F_b, ρ_b, P, $\dot{\nu}$, f_{a_in}, f_{a_out}, ρ_{g_ex}, T_{a_in}, T_{a_out}, T_b, Y_{w_in}, $\tilde{M}_g$	19	
	Fixed by system	U, A_S, T_S, B_1, B_2, B_3, C_{PT}, C_{Pa_in}, C_{Pa_out}, C_{pb}	10	
To be predicted	Explicit	N, N_0, τ, F_{bw}, A_{bed}, Y_{eq}, d_p, V_P, M_T, ρ_p, X_w, X_b, P_{eq}, P_{sat}, T, F_{a_in}, F_{a_out}, h_{a_in}, h_{a_out}, h_b, Q_{en}, Y_s, F_{ev}	23	29
	Implicit	Φ	1	
	Differential	M_b, M_w, M_g, M_{gw}, h	5	
Total number of variables involved in the model				62
Total number of differential equations				5
Total number of algebraic equations				24

Table 5.4: Incidence matrix of granulation process model

Eq. No.	M_b	M_w	M_g	M_{wg}	h	N_θ	τ	$\mathcal{N}$	F_{bw}	M_T	T	F_{a_in}	F_{a_out}	Q_S	h_b	h_{a_out}	h_{a_in}	P_{sat}	X_w	Φ	P_{eq}	Y_{eq}	X_b	ρ_p	V_p	d_p	A_{bed}	Y_s	F_{ev}
2.3.1						*																							
2.3.2						*	*																						
2.3.3						*	*	*																					
2.3.4									*																				
2.3.5	*	*								*																			
2.3.6					*					*	*																		
2.3.7												*																	
2.3.8													*																
2.3.9											*			*															
2.3.10											*				*														
2.3.11											*		*			*													
2.3.12											*	*					*												
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2.3.15																			*	*									
2.3.16																		*		*	*								
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2.3.18	*									*													*						
2.3.19																			*				*	*					
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2.3.22								*																		*	*		
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2.3.27			*									*	*																*
2.3.28				*								*	*															*	*
2.3.29					*									*	*	*	*												*

5.1.2.4. Storage tank model

The total number of equations is 11 in this case (see Appendix A2.4). The total number of variables involved in the model is 30 (see Table 5.5). The degree of freedom is calculated to be 19. The detailed classification of the variables is provided in Table 5.5. The incidence matrix of this model has also shown a lower triangular form (see Table 5.6) and therefore the model equations can be solved sequentially.

Table 5.5: Classification of storage tank process model variables

Variable types		Variables	No. of variables	Total no
To be specified	Constant	π	1	19
	Fixed by problem	$T_{in}, F_{in}, F_{out}, T_C, T_S, U_S, V_c, F_c, Tc_{in}$	9	
	Fixed by system	$d, \rho, \rho_{in}, C_P, d_0, \rho_c, Cp_c, U_1, U_2$	9	
To be predicted	Algebraic (explicit)	$Q_{in}, Q_s, A, M, L, M_w, A_1, A_2$	8	11
	Differential	V, T, T_C	3	
Total number of variables involved in the model				30
Total number of differential equations				3
Total number of algebraic equations				8

Table 5.6: Incidence matrix of the storage tank model

Eq. No.	V	T	T_c	M	M_w	A	L	A_1	A_2	Q_{in}	Q_s
2.4.1	*			*							
2.4.2				*	*						
2.4.3						*					
2.4.4	*					*	*				
2.4.5							*	*			
2.4.6							*		*		
2.4.7		*								*	
2.4.8		*				*					*
2.4.9	*										
2.4.10	*	*	*					*		*	*
2.4.11		*	*					*	*		

5.1.2.5. Tablet press process model

The total number of equations in this case is 23 (see Appendix A2.5). The total number of variables involved in the model is found to be 35 (see Table 5.7). The degree of freedom is calculated to be 12. The detailed classification of the variables is given in Table 5.7. The incidence matrix has shown a lower triangular form (see Table 5.8), so the model equations can be solved sequentially.

Table 5.7: Classification of tablet pressing process model variables

Variable types		Variables	No. of variables	Total no
To be specified	Constant	B	1	12
	Fixed by problem	ε_0, H_{max}, L, L_{Pre}, r_{Tab}, t, u, V_m, ρ, ρ_{rcr}	10	
	Fixed by system	D	1	
To be predicted	Algebraic (explicit)	ε_0, ε_{main}, A, C_F_{main}, C_F_{Pre}, H, L_{depth}, L_{depth_displ}, M, n_t_{ε}, n_t_F, C_P_{Pre}, C_P_{main}, t_{dwell}, V, V_0, V_{Pre}, V_s, λ_H, λ_{pre}, λ_{main}, ρ_r,	22	23
	Differential	N_{Tab}	1	
Total number of variables involved in the model				35
Total number of differential equations				1
Total number of algebraic equations				22

Table 5.8: Incidence matrix of tablet compression process model

Eq. No.	N_{Tab}	A	V	V_{Pre}	n_t_{ε}	ε	n_t_F	V_0	M	L_{depth}	L_{punch}	t_{dwell}	λ_{pre}	C_P_{pre}	C_F_{pre}	ε_{main}	λ_{main}	C_P_{main}	C_F_{main}	V_s	ρ_r	λ_H	H
2.5.1		*																					
2.5.2		*	*																				
2.5.3		*		*																			
2.5.4					*																		
2.5.5					*	*																	
2.5.6							*																
2.5.7							*	*															
2.5.8						*		*	*														
2.5.9		*						*		*													
2.5.10										*	*												
2.5.11											*	*											
2.5.12				*		*		*					*										
2.5.13				*				*					*	*									
2.5.14		*												*	*								
2.5.15				*		*		*								*							
2.5.16			*	*		*											*						
2.5.17			*	*													*	*					
2.5.18		*																*	*				
2.5.19						*		*												*			
2.5.20			*																	*	*		
2.5.21																					*	*	
2.5.22																					*	*	*
2.5.23	*																						

5.1.2.6. Tablet coating process model

The total number of equations in this case is 31 (see Appendix A2.6). The total number of variables involved in the model is 63 (see Table 5.9). The degree of freedom is 32. The detailed classification of the variables is given in Table 5.9. The incidence matrix has shown a lower triangular form (see Table 5.10), so the model equations can be solved sequentially

Table 5.9: Classification of tablet coating process model variables

Variable types		Variables	No. of variables	Total no
To be specified	Constant	π, ρ_w, ΔH_v, $\tilde{M}_w$	4	32
	Fixed by problem	M_{p0}, d_0, ρ_{cs}, ρ_g, β_{pg}, X_{sw}, F_s, P, $\dot{v}$, f_{a_in}, f_{a_out}, ρ_{g_ex}, T_{a_in}, T_{a_out}, T_s, Y_{w_in}, $\tilde{M}_g$, N	18	
	Fixed by system	U, A_{en}, T_{en}, B_1, B_2, B_3, C_{PT}, C_{Pa_in}, C_{Pa_out}, C_{pb},	10	
To be predicted	Explicit	F_{sw}, A_{Total}, Y_{eq}, d_p, M_T, X_w, X_{co}, P_{eq}, P_{sat}, T, F_{a_in}, F_{a_out}, h_{a_in}, h_{a_out}, h_s, Q_{en}, Y_s, F_{ev}, A_o, M_p, ΔM_p, δ, d_p, L_p, A_p	25	31
	Implicit	Φ	1	
	Differential	M_s, M_w, M_g, M_{gw}, h	5	
Total number of variables involved in the model				63
Total number of differential equations				5
Total number of algebraic equations				26

Table 5.10: Incidence matrix of tablet coating process model

Eq. No.	M_{co}	M_w	M_g	M_{gw}	h	F_{csw}	A_o	M_T	X_w	X_{co}	ρ_α	M_p	ΔM_y	δ	d_p	L_p	A_p	A_{Total}	Y_s	Φ	T	P_{sat}	P_{eq}	Y_{eq}	F_{ev}	F_{a_in}	F_{a_out}	h_{a_in}	h_{a_out}	h_s	Q_S
2.6.1						*																									
2.6.2							*																								
2.6.3	*	*						*																							
2.6.4		*						*	*																						
2.6.5	*							*		*																					
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2.6.30				*															*						*	*	*				
2.6.31					*																				*			*	*	*	*

5.1.3. Design of the process monitoring and analysis system

The process monitoring and analysis system for the tablet manufacturing process was then designed as follows, using the developed software (ICAS-PAT):

5.1.3.1. Product property specifications (step 1)

The interface for providing the product quality specifications is shown in Figure 5.2. In the considered case study, the desired final product is the pharmaceutical tablet. The specifications of the desired product are shown in Figure 5.2. It should be noted that the "measurement units" of quantitative specifications are consistent. The qualitative specifications are only for documentation purposes and are optional but recommended.

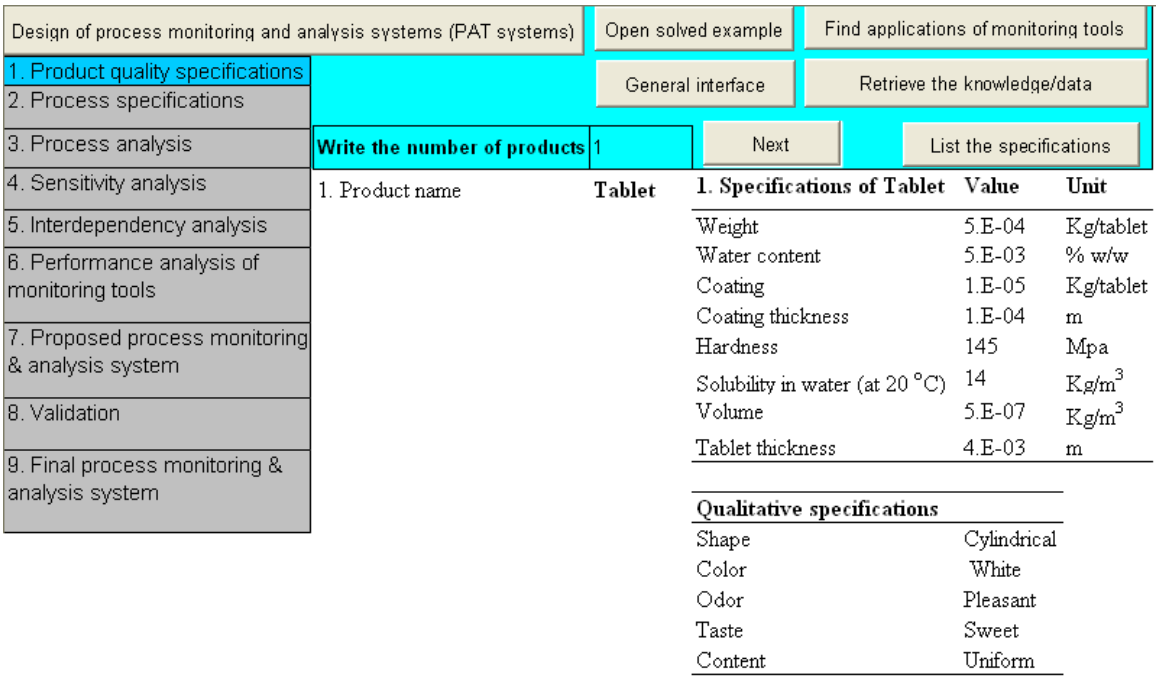


Figure 5.2: Product property specifications (step 1)

5.1.3.2. Process specifications (step 2)

The specifications of the tablet manufacturing process are provided through this step. The interface for this step is shown in Figure 5.3. As shown in the figure, first the full directory (e.g. D:/PAT/knowledge base.xls) of the knowledge base is provided and then the knowledge base is connected with the interface through the command button, 'Load knowledge base'. The command button, 'select the process' generates a list of processes available in the knowledge base. The appropriate process (Pharmaceutical: Tablet manufacturing process) which produces the desired product (Tablet) is then selected from the drop-down list. The drop-down list also contains two additional options, 'Not found' and 'Unknown', to proceed further in case the required process is not found in the list or any existing process does not exactly satisfy the user needs. The command button, 'Next' is directed to the appropriate place where the number of equipments and the number of raw materials used in the production process are required to be typed. The next command button, 'Select the equipments' generates a list of available equipments related to the selected process from which the relevant equipments are selected based on the consultation of the process flowsheet. A list of raw materials used for the production is

provided in the next step. The equipment list and the used raw material list are shown in Figure 5.3.

The user interface to draw the open-loop process flowsheet is shown in Figure 5.4 (left). The command button, 'Provide input/output information', generates a table (only with heading) in which the corresponding input/output information is provided. The input/output information of the tablet manufacturing process is shown in Figure 5.4 (see right). The command button, 'Draw flowsheet', creates a flowsheet based on provided input/output information. The generated simplified flowsheet of the tablet manufacturing process is shown in Figure 5.5

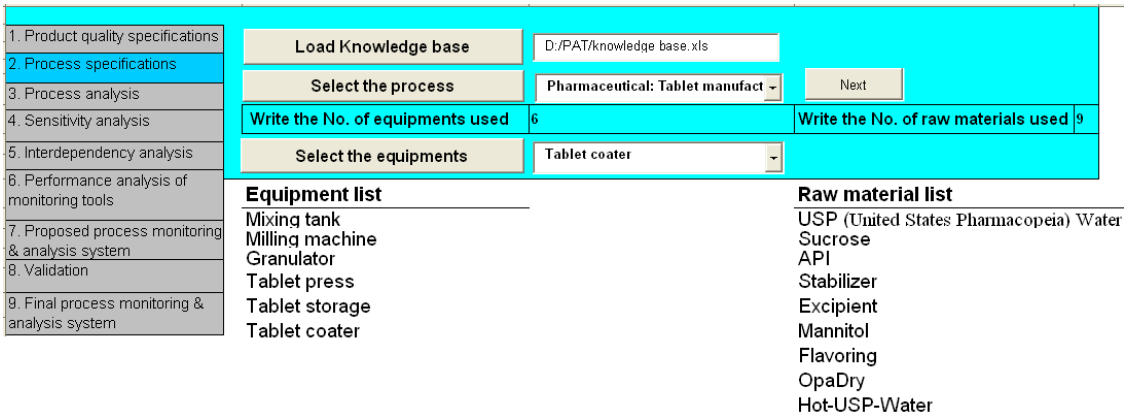


Figure 5.3: Process specifications (step 2)

Provide input/output information

Draw flowsheet

Equipments	Operations	Main stream in	Side stream in	Main stream out	Side stream out
Mixing tank	Slurry preparation		USP water	Slurry	
			Sucrose		
			API		
Mixing tank	Mill recirculation	Slurry	Mill product	Powder	Mill feed
Milling machine	Milling	Mill feed		Mill product	Mill product
Mixing tank	Addition & mixing	Powder	USP water	Mixed excipients	
			Excipient		
			Flavoring		
Mixing tank	Co-stablizer solution preparation		Stablizer	Stabilizer	
			USP water		
Mixing tank	Final suspension pre	Mixed excipients	Stabilizer		
Granulator	Granulation	Final suspension	Air in	Granules	Air out
			Manitol		
Storage tank	Granule storage	Granules		Granules	
Tablet press	Tablet pressing	Granules		Tablet	
Storage tank	Tablet storage	Tablet		Tablet	
Tablet coater	Tablet coating	Tablet	Air in	Coated tablet	Air out
			Coating solution		

Figure 5.4: User interface to draw the open-loop process flowsheet

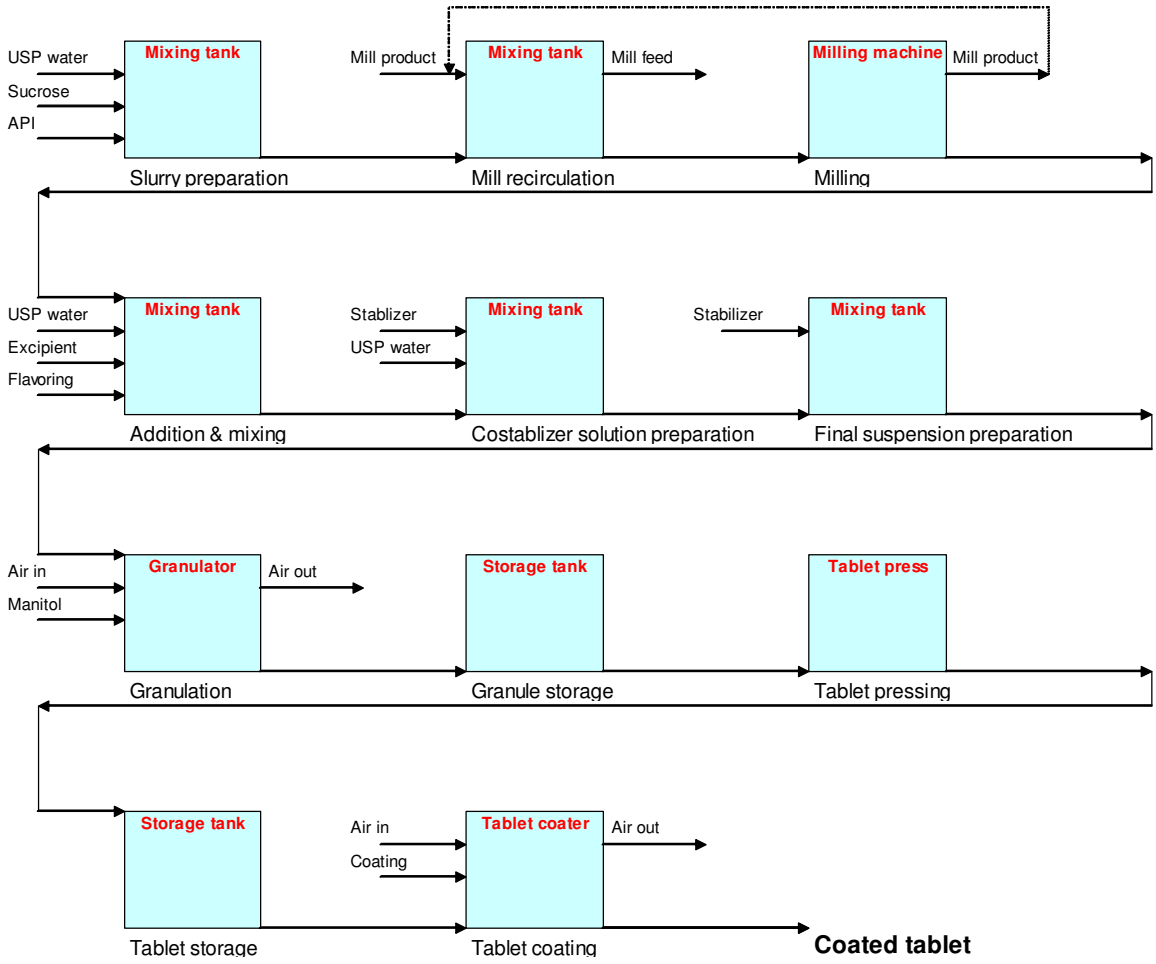


Figure 5.5: Tablet manufacturing process flowsheet as generated through ICAS-PAT

5.1.3.3. Process analysis (step 3)

The process points and corresponding process variables of the tablet manufacturing process are listed through this step. The interface for this step is shown in Figure 5.6. As shown in the figure, the command button, 'List the process points', generates a list of process points based on the information provided in step 2. The process variables related to each process point are then retrieved from the knowledge base through the command button 'List the variables related to each process point' (see Figure 5.6). The operational limits of the retrieved process variables are accessed from the stored data file (Data_sheet.xls). The total number of process variables found in the knowledge base is also mentioned at the end of each list. The process points, the corresponding process

variables together with the operational process limits are shown in Figure 5.6 for the considered tablet manufacturing process. The output of this step will be used in subsequent design steps.

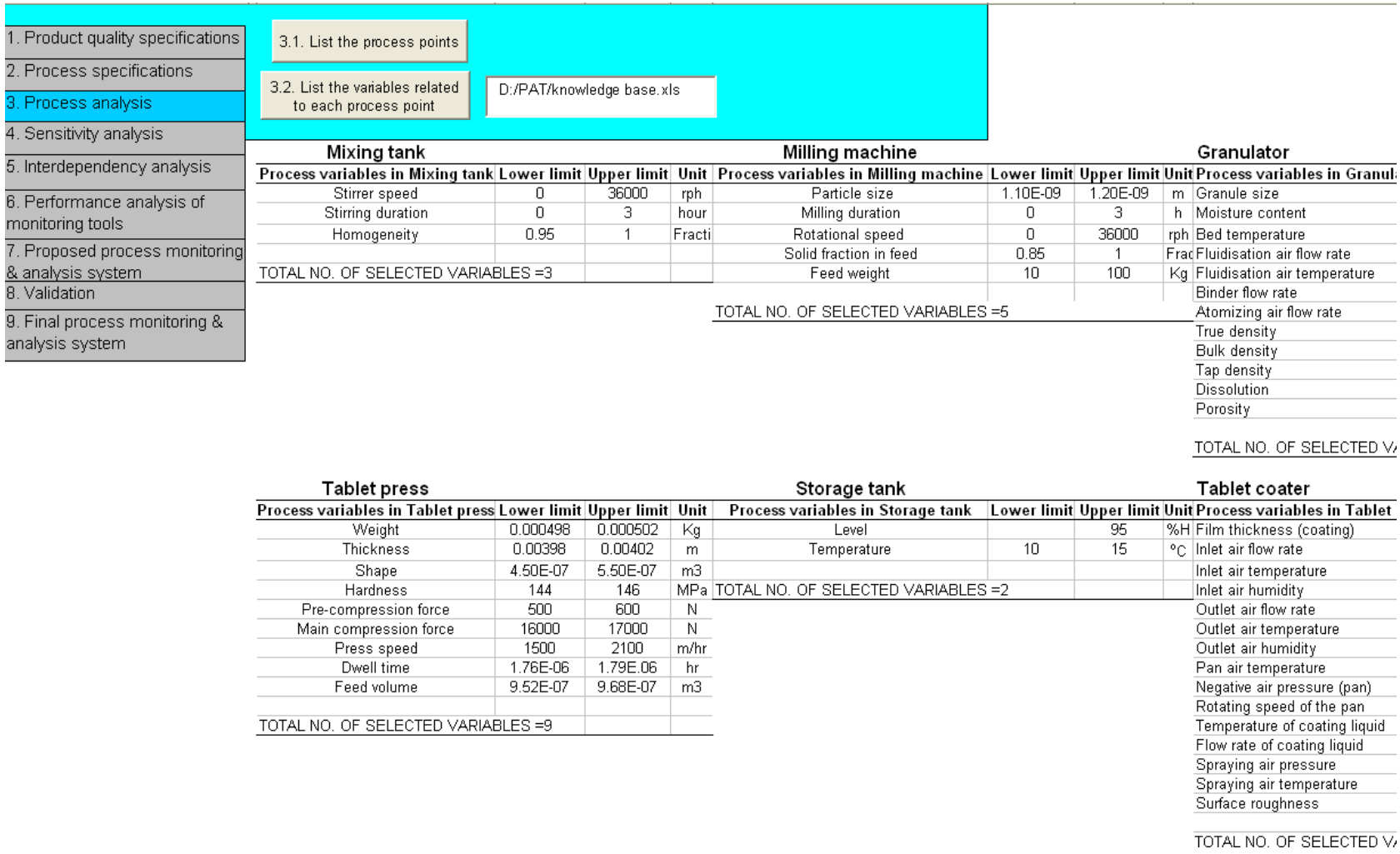


Figure 5.6: Process analysis (step 3)

5.1.3.4. Sensitivity analysis (step 4)

The critical process variables (controlled variables) involved in the tablet manufacturing process are identified through this step. The user interface for this step is shown in Figure 5.7. As shown in the figure, first the process point is selected from the drop-down list, and then the operational objective in that process point is fixed. The command button, 'Select the operational objective' provides a list of pre-defined process operational objectives from which one can be selected or a new operational objective can be defined. The model library and the simulation tool are integrated with the ICAS-PAT interface through a connecting program (MoT Model interface) as shown in Figure 5.7. The integration of model library and the simulation tool to the ICAS-PAT interface is described in section 3.3.2. Through the command button, 'Solve the model', the process model is solved to generate the dynamic data. The command button, 'Load simulation result' imports the simulated data to the interface. Through the next command button ('Select variable') a process variable (it can be the objective function also) associated with the considered process point is selected. Note that, both, the name of the variable and corresponding symbol should be selected from the corresponding list boxes (see Figure 5.7). The operational limits of the selected process variable are then provided through the command button, 'Operational limits of selected variable'. The selected process variable together with specified operational limits is plotted by using the 'plot' command button. Finally the plotted process variable (open-loop) is analyzed to check whether it is critical or not. As mentioned in section 4.2.1.4, the operational objective is analyzed first, and then the process variables are analyzed. The identified critical process variables are then transferred to the results section (see Figure 5.7, right). There are also options for data management (see Figure 5.7, bottom left) which allow saving of the simulated data for future use. Already available data (simulated or experimental) may also be loaded to the interface and can be used directly to save time.

Figure 5.7, illustrates one example from the tablet manufacturing process for the mixing tank as the process point. The operational objective in the mixing process is to obtain a homogeneous mixture. The homogeneity (also the objective function in this specific case) is considered for analysis. As shown in the figure, the homogeneity in the mixing tank

violates the lower operational limit (see Figure 5.7, bottom) and therefore is considered as a critical process variable which needs to be monitored and controlled. Similarly the critical process variables related to each process point have been identified as listed in the results section.

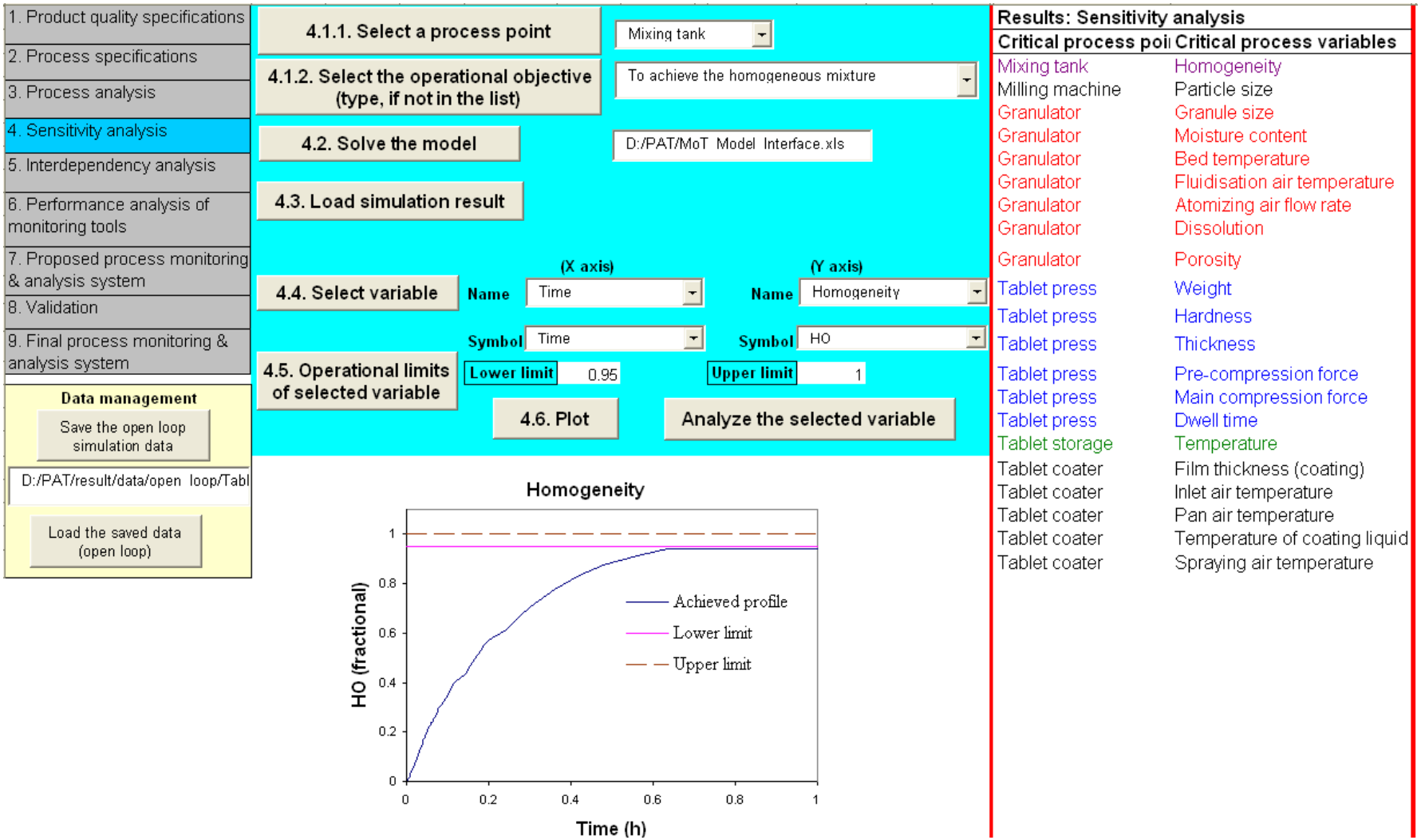


Figure 5.7: Sensitivity analysis (step 4)

5.1.3.5. Interdependency analysis (step 5)

The actuators for each selected critical process variable (controlled variables) of the tablet manufacturing process are identified through this step. The user interface to perform the interdependency analysis is shown in Figure 5.8. As shown in the figure, first a process point is selected from the drop-down list. This list is obtained from the result section of step 4. Then a critical process variable, related to the selected process point is selected from the next drop-down list. This list contained all critical process variables related to the selected process point together with an additional option, 'Select all', to select all critical process variables at once. The actuator candidates for the selected process variables are then retrieved from the knowledge base, through the command button, 'List the actuator candidates'. The critical process variables and corresponding actuator candidates are linked with the process model as shown in Figure 5.8 (see the list boxes at the top of the figure). Then the lower limit, upper limit and the step change for perturbations are specified as shown in the figure. Finally, depending on the specified perturbation setup, the data are generated. The generated data contains the values of the controlled variable obtained by changing the actuator candidates (i.e. % change in actuator candidates versus controlled variable response) and are stored in a separate file. From these data, the absolute change in controlled variable is calculated and imported to the interface through the command button 'Result'. These data are then plotted by using the 'Plot' option and the appropriate actuator is selected. Similar to the sensitivity analysis (step 4), this step of the procedure also has the option for data management and utilization of experimental data in case of unavailability of a process model (see Figure 5.8, bottom left).

Figure 5.8 illustrates the actuator selection procedure for the tablet manufacturing process. The actuator candidates as retrieved from the knowledge base are listed at the bottom of the figure for each critical process variable. In order to come up with a final proposal for the actuator, the interdependency analysis needs to be performed for each critical process variable. The mixing time and the stirrer speed are two examples of actuator candidates for homogeneity in the mixing tank. The considered critical process variable (homogeneity) and actuator candidates (mixing time and stirrer speed) are linked

with the corresponding process variables in the process model (indicated with arrows), as shown in Figure 5.8. Then the mixing time and stirrer speed are perturbed according to the specified perturbation setup and the effect on the homogeneity is analyzed. The analysis shows that both actuator candidates have equal control authority (sensitivity) for homogeneity (see Figure 5.8, bottom right), so any of them can be selected. However, the final selection depends on the type of control system available. Figure 5.9 shows an example of interdependency analysis (critical process variable is the moisture content of the granules and actuator candidates are binder flow rate, fluidization air flow rate and fluidization air temperature), where the actuator candidates have a different control authority. As shown in the figure the binder flow rate has a comparatively larger effect on the moisture content of the granules, and therefore it is selected as the final manipulated variable. The manipulated variables for each critical process variable are identified in a similar way as listed in the results section (see Figure 5.9, right).

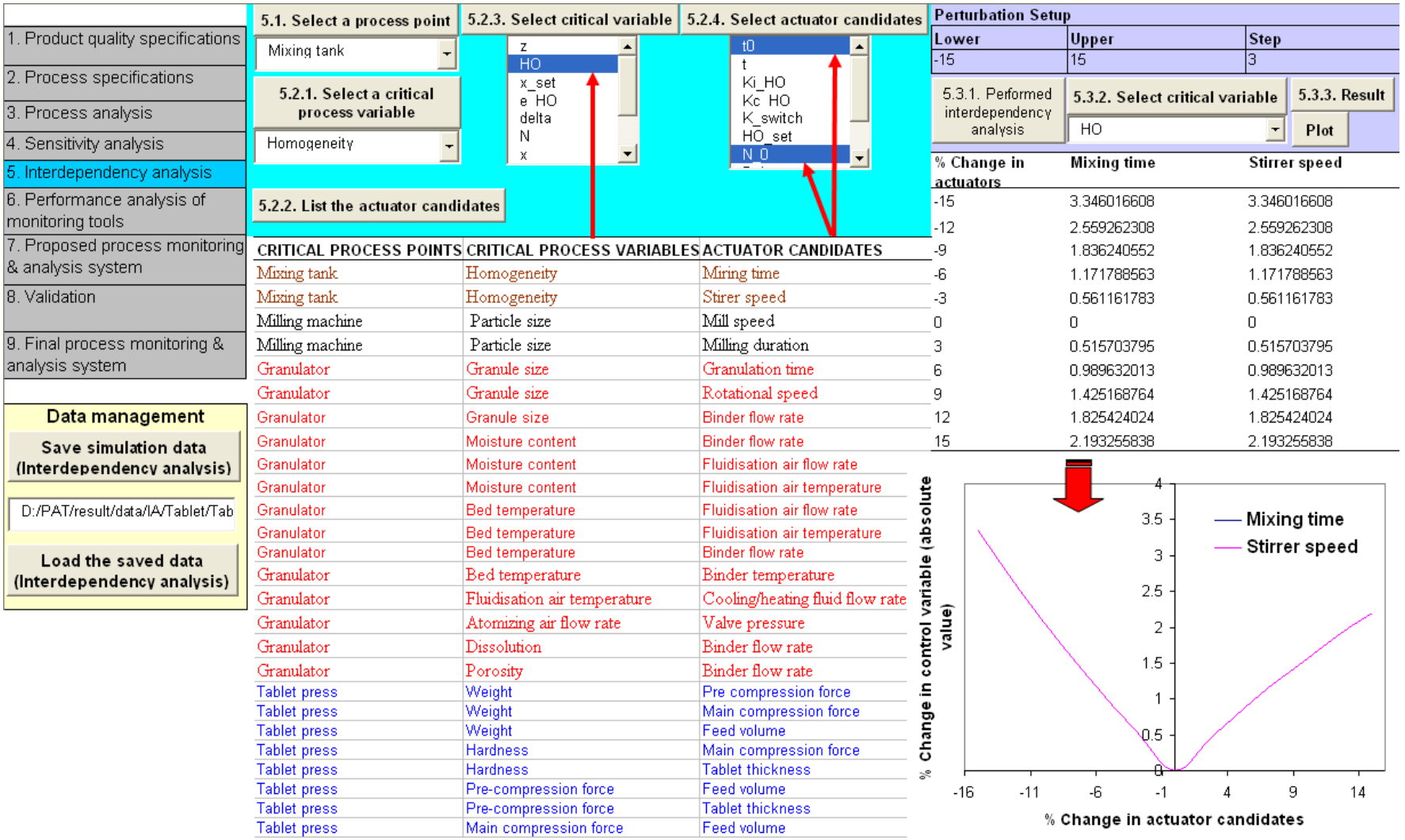


Figure 5.8: Interdependency analysis (step 5)

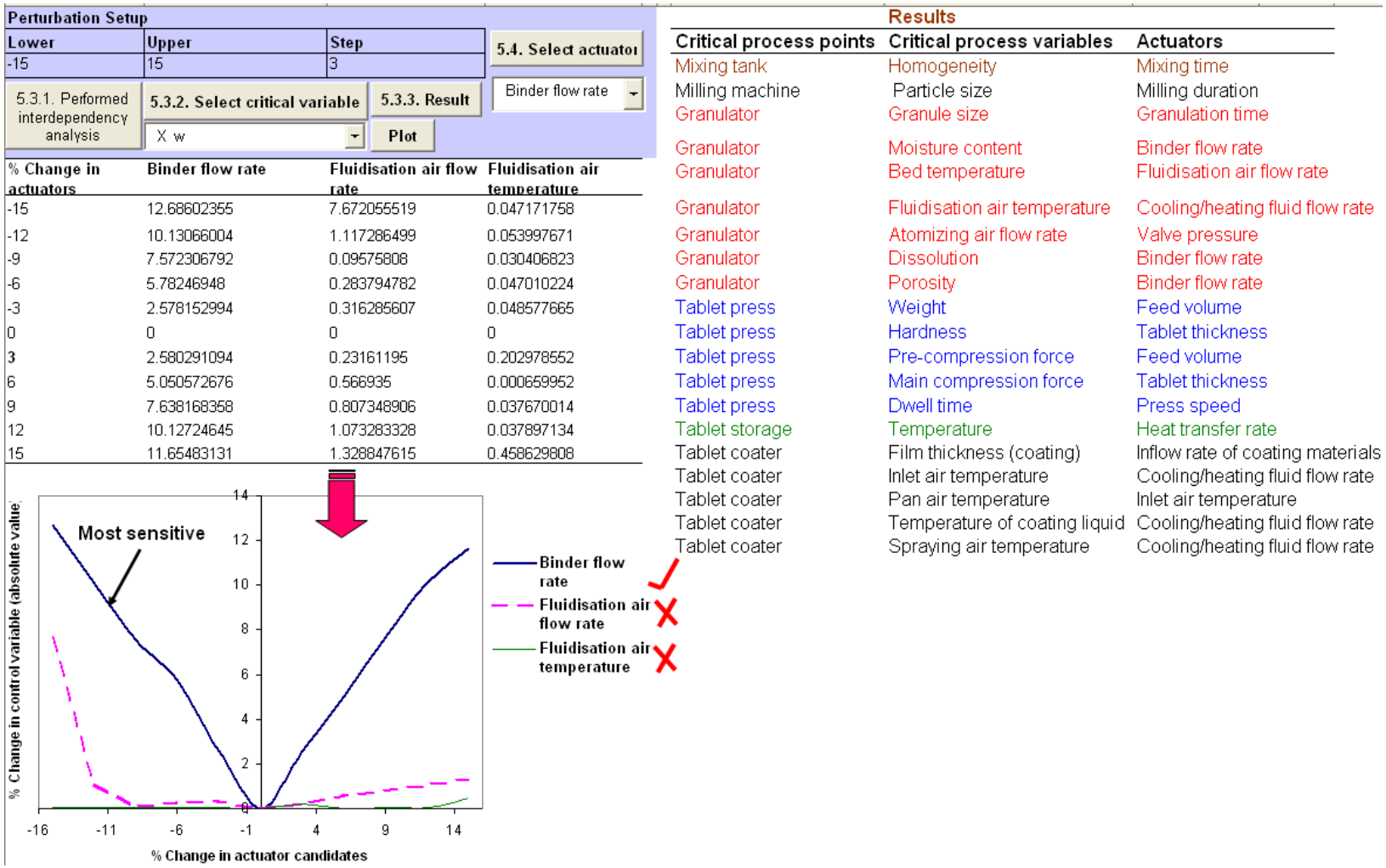
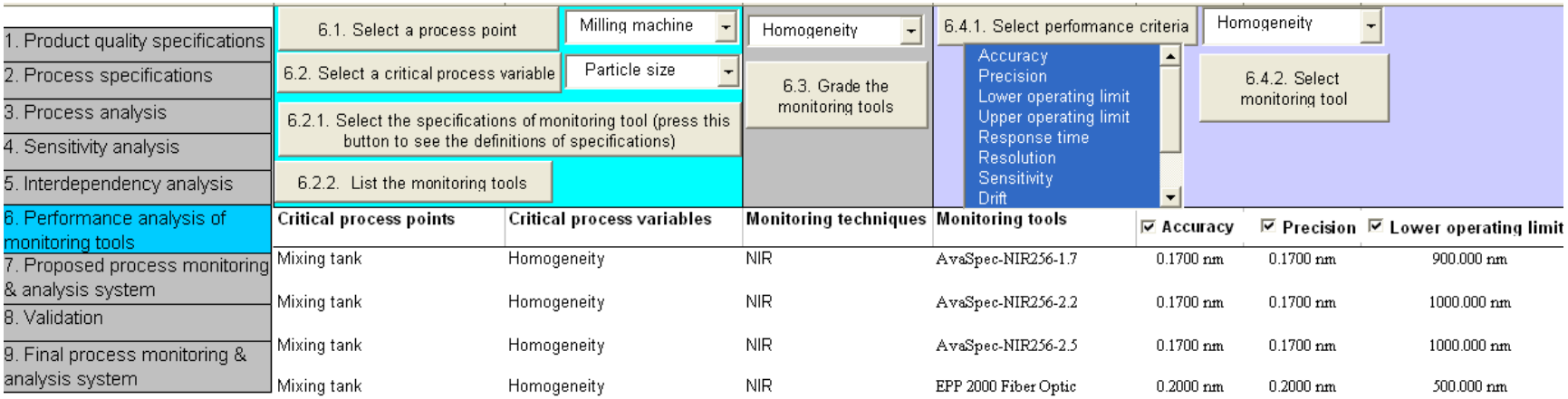


Figure 5.9: Interdependency analysis example

5.1.3.6. Performance analysis of monitoring tools (step 6)

Suitable measurement methods and tools for each critical process variable of the tablet manufacturing process are identified in this step. The user interface for this step is shown in Figure 5.10. As shown in the figure, first a process point is selected and then a critical process variable from the corresponding drop-down list is selected. Then the specifications that need to be retrieved from the knowledge base are selected (see the option in Figure 5.10). Only few specifications are shown in the figure for demonstration purposes. Through the command button, 'List the monitoring tools', the monitoring techniques and tools together with the selected specifications for the considered critical process variable are retrieved from the knowledge base. The command button, 'Grade the monitoring tools', assigns the scores to each monitoring tool based on the specifications. The specifications on the basis of which the final monitoring tools will be selected, are then chosen (see Figure 5.10, top right). Finally, through the command button, 'Select monitoring tool', the total scores of each monitoring tool are obtained and the monitoring tools with the highest score are selected.

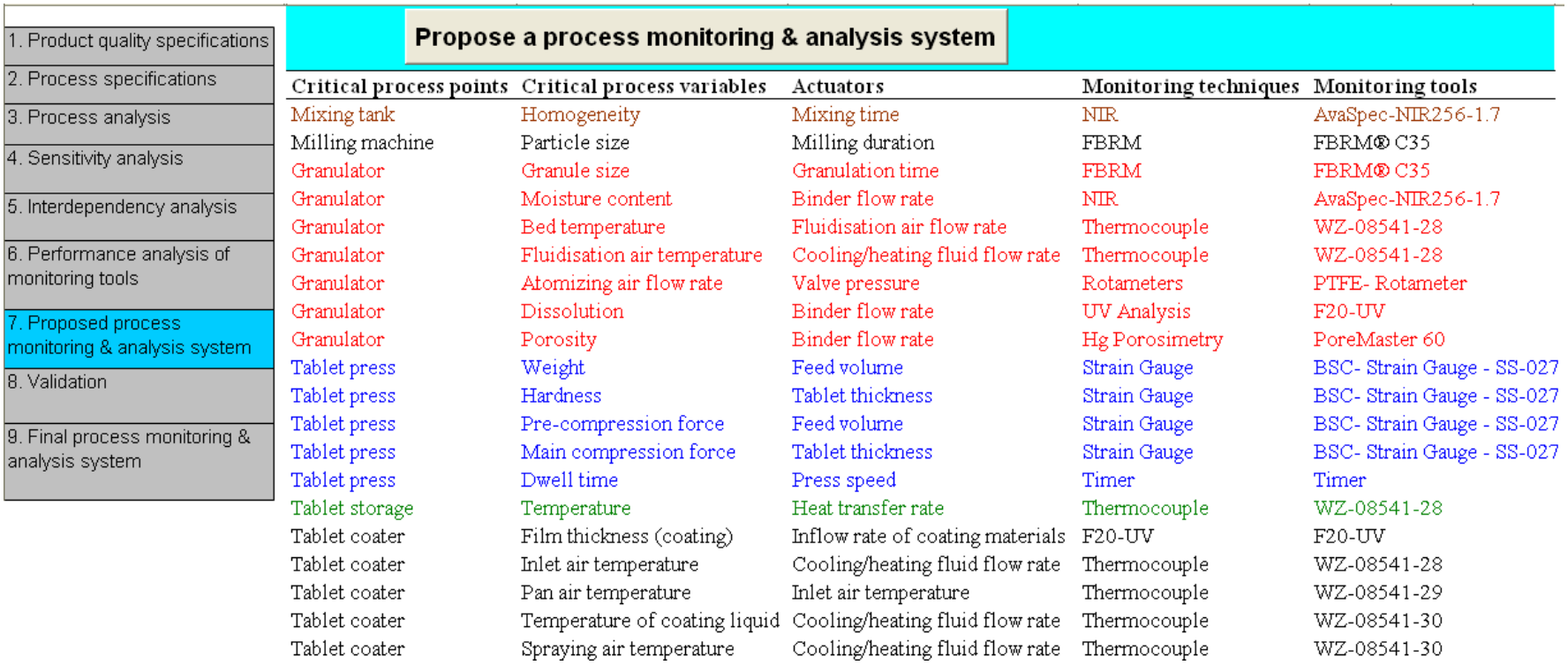


Critical process points	Critical process variables	Monitoring techniques	Monitoring tools	Accuracy	Precision	Lower operating limit
Mixing tank	Homogeneity	NIR	AvaSpec-NIR256-1.7	0.1700 nm	0.1700 nm	900.000 nm
Mixing tank	Homogeneity	NIR	AvaSpec-NIR256-2.2	0.1700 nm	0.1700 nm	1000.000 nm
Mixing tank	Homogeneity	NIR	AvaSpec-NIR256-2.5	0.1700 nm	0.1700 nm	1000.000 nm
Mixing tank	Homogeneity	NIR	EPP 2000 Fiber Optic Spectrometer-NIR	0.2000 nm	0.2000 nm	500.000 nm
Mixing tank	Homogeneity	NIR	EPP 2000 Fiber Optic Spectrometer-NIR2	0.1000 nm	0.1000 nm	600.000 nm
Mixing tank	Homogeneity	NIR	EPP 2000 Fiber Optic Spectrometer-NIR2b	0.1000 nm	0.1000 nm	785.000 nm
Mixing tank	Homogeneity	NIR	Antaris target blend analyzer			1350.000 nm
Mixing tank	Homogeneity	UV-Visible	AvaSpec 3648-UA-25-AF	0.1400 nm	0.1400 nm%	200.000 nm
Mixing tank	Homogeneity	UV-Visible	AvaSpec 2048-UA-50-AF	2.4000 nm	2.4000 nm	200.000 nm
Mixing tank	Homogeneity	UV-Visible	AvaSpec 2048-UA-200-AF	8.0000 nm	8.0000 nm	360.000 nm
Mixing tank	Homogeneity	UV-Visible	Oriel 78345	0.5000 nm	0.1000 nm	195.000 nm
Mixing tank	Homogeneity	UV-Visible	V 7000	0.0800 nm	0.0800 nm	175.000 nm
Mixing tank	Homogeneity	UV-Visible	DR 2800™ Portable Spectrophotometer	1.5000 nm	1.5000 nm	340.000 nm
Mixing tank	Homogeneity	FT-Raman	AvaRaman-532 [170]			535.000 nm
Milling machine	Particle size	FBRM	FBRM® C35 [171]	0.01%	0.01%	3.000 µm
Milling machine	Particle size	PVM	Lasentec® V819 with PVM® technology [172]	0.01%	0.01%	2.000 µm
Milling machine	Particle size	NIR	Diffuse reflectance probe	5.00%	5.00%	0.010 µm [59]

Figure 5.10: Performance analysis of monitoring tools (step 6)

5.1.3.7. Proposed process monitoring and analysis system (step 7)

A process monitoring and analysis system of the tablet manufacturing process is suggested in this step. The user interface for this step is shown in Figure 5.11. Through the command button, 'Propose a process monitoring and analysis system', a table summarizing the process monitoring and analysis system (PAT system) is generated as shown in the figure. The proposed process monitoring and analysis system of the tablet manufacturing process consists of a list of process points, corresponding critical process variables, actuators, monitoring techniques and tools.



Critical process points	Critical process variables	Actuators	Monitoring techniques	Monitoring tools
Mixing tank	Homogeneity	Mixing time	NIR	AvaSpec-NIR256-1.7
Milling machine	Particle size	Milling duration	FBRM	FBRM® C35
Granulator	Granule size	Granulation time	FBRM	FBRM® C35
Granulator	Moisture content	Binder flow rate	NIR	AvaSpec-NIR256-1.7
Granulator	Bed temperature	Fluidisation air flow rate	Thermocouple	WZ-08541-28
Granulator	Fluidisation air temperature	Cooling/heating fluid flow rate	Thermocouple	WZ-08541-28
Granulator	Atomizing air flow rate	Valve pressure	Rotameters	PTFE- Rotameter
Granulator	Dissolution	Binder flow rate	UV Analysis	F20-UV
Granulator	Porosity	Binder flow rate	Hg Porosimetry	PoreMaster 60
Tablet press	Weight	Feed volume	Strain Gauge	BSC- Strain Gauge - SS-027
Tablet press	Hardness	Tablet thickness	Strain Gauge	BSC- Strain Gauge - SS-027
Tablet press	Pre-compression force	Feed volume	Strain Gauge	BSC- Strain Gauge - SS-027
Tablet press	Main compression force	Tablet thickness	Strain Gauge	BSC- Strain Gauge - SS-027
Tablet press	Dwell time	Press speed	Timer	Timer
Tablet storage	Temperature	Heat transfer rate	Thermocouple	WZ-08541-28
Tablet coater	Film thickness (coating)	Inflow rate of coating materials	F20-UV	F20-UV
Tablet coater	Inlet air temperature	Cooling/heating fluid flow rate	Thermocouple	WZ-08541-28
Tablet coater	Pan air temperature	Inlet air temperature	Thermocouple	WZ-08541-29
Tablet coater	Temperature of coating liquid	Cooling/heating fluid flow rate	Thermocouple	WZ-08541-30
Tablet coater	Spraying air temperature	Cooling/heating fluid flow rate	Thermocouple	WZ-08541-30

Figure 5.11: Proposed process monitoring and analysis system (step 7)

5.1.3.8. Model-based validation (step 8)

The proposed monitoring and analysis system of the tablet manufacturing process is verified in this step. The user interface for this step is shown in Figure 5.12. Similar to the sensitivity analysis (step 4), this step also has the option for data management (storage and access of simulated or experimental data), as shown in the figure (see Figure 5.12, left bottom). The obtained monitoring and analysis system in step 7 is validated as follows:

Controller configuration: As shown in the Figure 5.12, first a process point (mixing tank) of the tablet manufacturing process is selected and then one control loop (controlled variable: homogeneity and actuator: mixing time) related to that process point is considered. The command button, 'Select the controller parameters', provides a list of parameters from which the appropriate controller parameters, depending on the type of controller used (P, PI, PID, On-off) are selected and the corresponding values of the controller parameters are provided in the boxes available below the selected parameters. Note that a message will appear on selection of the controller parameters, asking whether the user wants to use the stored values of parameters or not. An on-off controller is used to control the homogeneity in the mixing tank. The selected control parameter and its corresponding value (K_{switch}=1) are shown in the figure. Then, through the command button, 'Activate the loop' this control loop is added to the process model. Similarly, all the control loops involved with the selected process point need to be activated before starting the control-monitor verification. If any added loop needs to be removed from the process model, then the command button, 'Deactivate the loop' can be used. Note that in this process point (mixing tank) only a single control loop is involved.

Control-monitor verification: After activating the control loop in the selected process point (mixing tank), the closed-loop model is solved through the command button, 'Solve the closed-loop model' and subsequently, the simulated data are loaded to the interface through the command button, 'Load simulation result. The command button, 'Select variable', provides a list of controlled variables, corresponding set points and actuators from which a controlled variable, corresponding set point and actuator are selected for analysis. Note that, on selection of a variable name, the corresponding symbol used in

process model will appear automatically in the box provided below the variable name. The command button, 'Operational limits of selected variable' is for providing the operational limits of the selected controlled variable and corresponding actuator. Then this controlled variable and actuator together with the operational limits are plotted by using the 'Plot', command button. Finally, the plotted controlled variable and actuator are analyzed to check whether this pair of controlled variable and actuator is validated or not. The verification of the performance of one control loop (controlled variable: homogeneity in mixing tank; actuator: mixing time; controller: on-off) is demonstrated in Figure 5.12. The closed-loop response shows that the desired homogeneity is achieved (within the operational limits) within the feasible mixing time (see Figure 5.12, bottom left). Therefore this controlled variable (homogeneity) and actuator (mixing time) is selected as the verified pair of controlled variable and actuator. Note that, homogeneity is also the objective function in this specific case.

It should be emphasized here that dead times (process dead time, actuator dead time, sensor dead time) can also affect the performance of control loops. Sensor dead times have been taken into account in the selection of the monitoring tools (through step 6, the sensor with the shortest response time can be selected). The process dead time has been considered in the process model. The actuator dead time has not been considered for this particular case study. However, if the actuator dead time is included in the process model then its effect can be analyzed in the validation step and the most suitable actuators (more sensitive and having less dead time) for each controlled variable can be selected. If some controlled variables have a common actuator then only one variable can be controlled independently with that actuator. For instance, three variables of the granulation process (moisture content, dissolution, porosity) have a common actuator (binder flow rate). However, only one variable (moisture content in this case) can be controlled independently.

Sensitivity verification: The controlled variable (homogeneity) is also the objective function in this specific case, therefore the sensitivity verification is not needed explicitly at this process point (mixing tank). However, the option to perform the sensitivity verification is shown in Figure 5.12. As shown in the figure, the command button, 'Select objective function' provides a list of model variables from which the objective function is

selected (see Figure 5.12, bottom). Similarly, the command button, 'Select controlled variable (set point)', provides a list of model parameters from which the set points of the controlled variables are selected. Then the perturbation is set up and through the command button, 'Sensitivity verification', the required data are generated and loaded to the interface (by using the command button, 'Result'). Finally the data are plotted and analyzed.

Product properties verification: After implementation of all control loops in all process points, the process models are solved in the order of connectivity specified in the flowsheet. Then the product properties are plotted and verified by using the plotting feature of this validation step. The obtained weight of the tablets through the closed-loop simulation is shown in Figure 5.13. The desired weight of the tablet is 0.0005 kg (as specified by the user in step 1). The figure shows that, the obtained weight of the tablet is within the acceptable limit. Figure 5.14, shows the obtained profile of the tablet hardness. The tablet hardness is also within the acceptable limits. The thickness of the tablet is shown in Figure 5.15. The figure shows that the tablet thickness is also within the acceptable limits. Similarly the other properties of the tablet are verified.

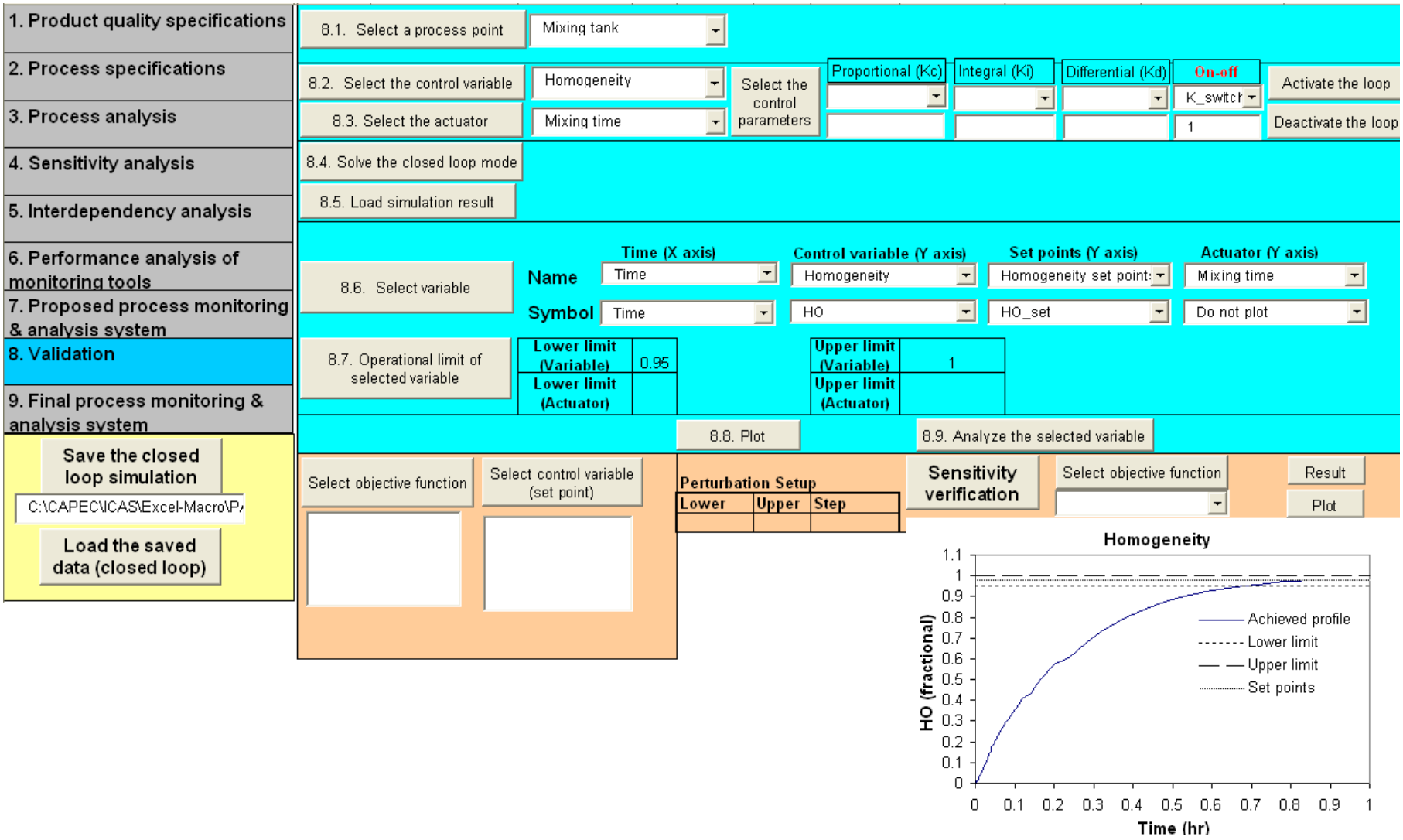


Figure 5.12: Validation of proposed PAT system (step 8)

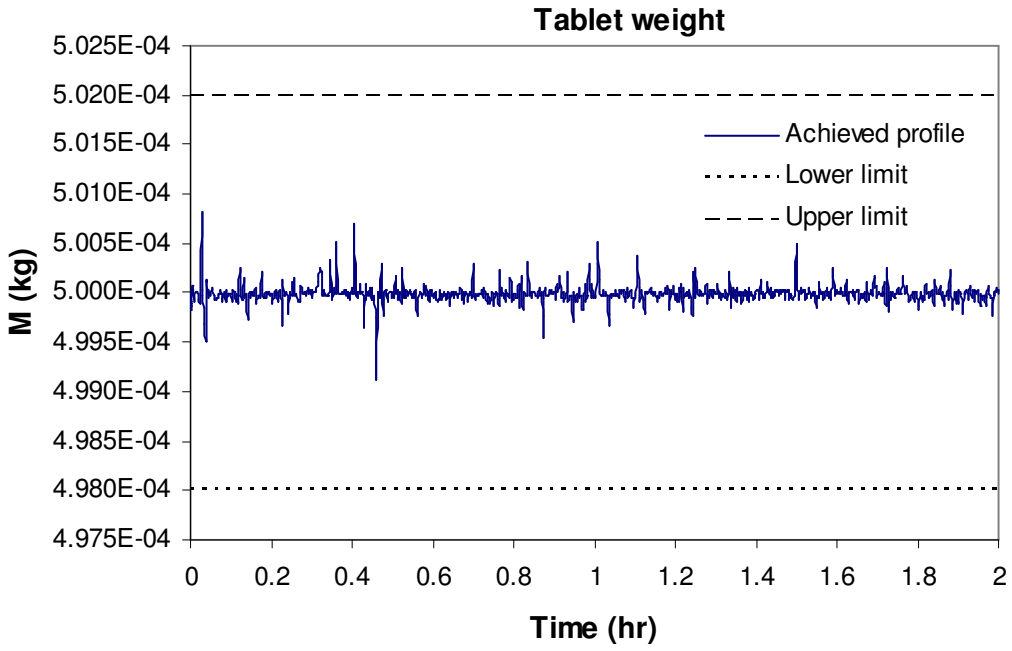


Figure 5.13: Tablet weight (obtained product property profile)

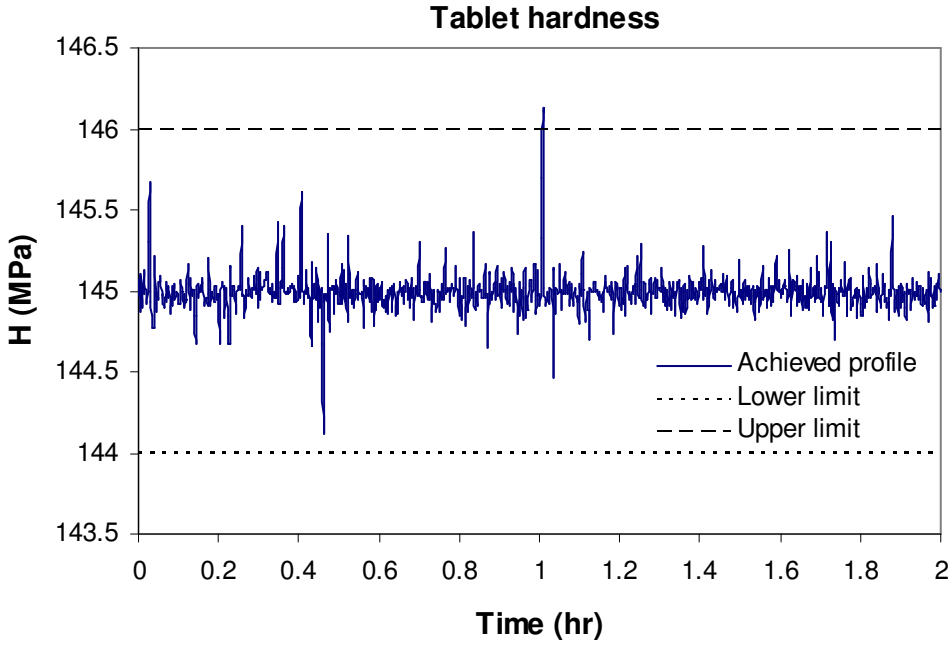


Figure 5.14: Tablet hardness (obtained product property profile)

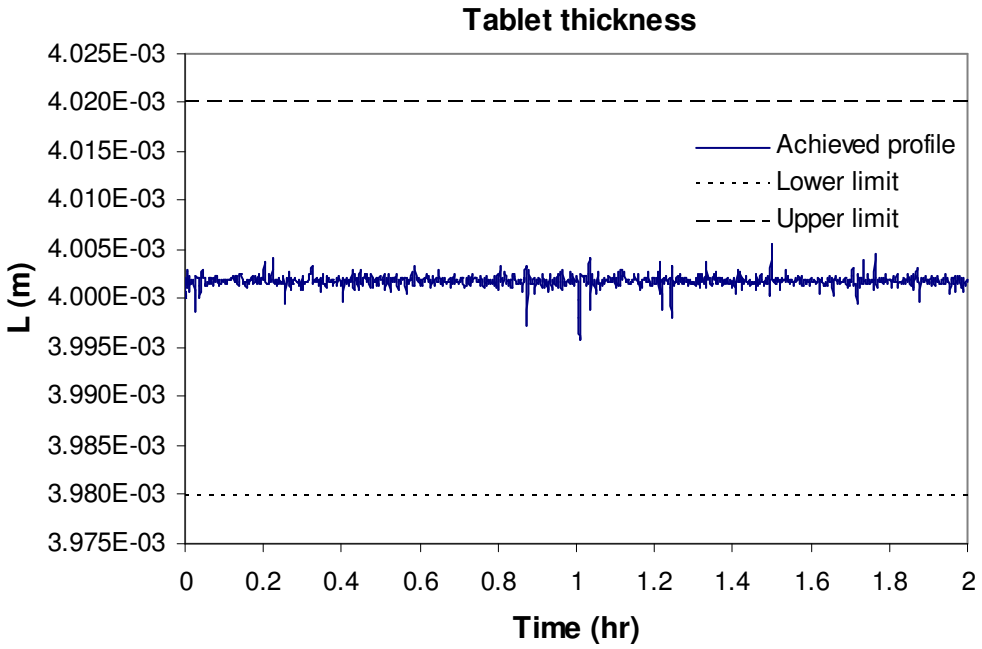
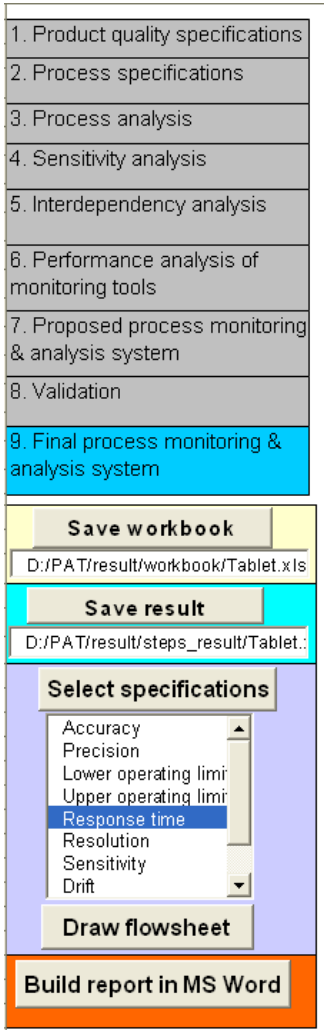


Figure 5.15: Tablet thickness (obtained product property profile)

5.1.3.9. Final process monitoring and analysis system (step 9)

The final process monitoring and analysis system as shown in Figure 5.16, consist of the final list of process points, the corresponding critical process variables, actuators, monitoring techniques and tools for the tablet manufacturing process. The options to save the results are also available (see Figure 5.16, left). The solved case study (with the designed PAT system) can be saved in the exercise section of the software for future access and the results of each design step can also be saved in separate files for documentation purposes. There is also an option that allows the user to draw the closed-loop process flowsheet (see Figure 5.16, left). Through this option, the result reported in Figure 5.16, can be seen in the form of a flowsheet. The drawn flowsheet contains the information regarding the controlled variables, corresponding actuators, monitoring techniques and tools with selected specifications. The user has to select the specifications of the monitoring tools if it is desired that they appear in the flowsheet. A modified version of the flowsheet of the tablet manufacturing process generated by the software (more compact to fit on a page) is shown in Figure 5.17. Finally the software has the option to create a report in MS Word (see Figure 5.16, bottom left). The generated report contains the result of each design step with explanation and details of the methodology.



Process monitoring & analysis system

Critical process points	Critical process variables	Actuators	Monitoring techniques	Monitoring tools
Mixing tank	Homogeneity	Mixing time	NIR	AvaSpec-NIR256-1.7
Milling machine	Particle size	Milling duration	FBRM	FBRM® C35
Granulator	Granule size	Granulation time	FBRM	FBRM® C35
Granulator	Moisture content	Binder flow rate	NIR	AvaSpec-NIR256-1.7
Granulator	Bed temperature	Fluidisation air flow rate	Thermocouple	WZ-08541-28
Granulator	Fluidisation air temperature	Cooling/heating fluid flow rate	Thermocouple	WZ-08541-28
Tablet press	Weight	Feed volume	Strain Gauge [147]	BSC- Strain Gauge - SS-027
Tablet press	Hardness	Tablet thickness	Strain Gauge [147]	BSC- Strain Gauge - SS-027
Tablet storage	Temperature	Cooling/heating fluid flow rate	Thermocouple	WZ-08541-28
Tablet coater	Film thickness (coating)	Inflow rate of coating materials	F20-UV	F20-UV
Tablet coater	Pan air temperature	Inlet air temperature	Thermocouple	WZ-08541-29
Tablet coater	Temperature of coating liquid	Cooling/heating fluid flow rate	Thermocouple	WZ-08541-30
Tablet coater	Spraying air temperature	Cooling/heating fluid flow rate	Thermocouple	WZ-08541-30

Figure 5.16: Final process monitoring and analysis system (step 9)

Figure 5.17 (modified version of the flowsheet generated by the software i.e. more compact to fit on a page) shows one feasible alternative of the process monitoring and analysis system for the tablet manufacturing process. The critical process variables, corresponding actuators and monitoring techniques are shown at each critical process point. Note that because of space limitations, monitoring tools are not included in the flowsheet. However the details of specific selected monitoring tools corresponding to each monitoring technique can be found in Figure 5.16.

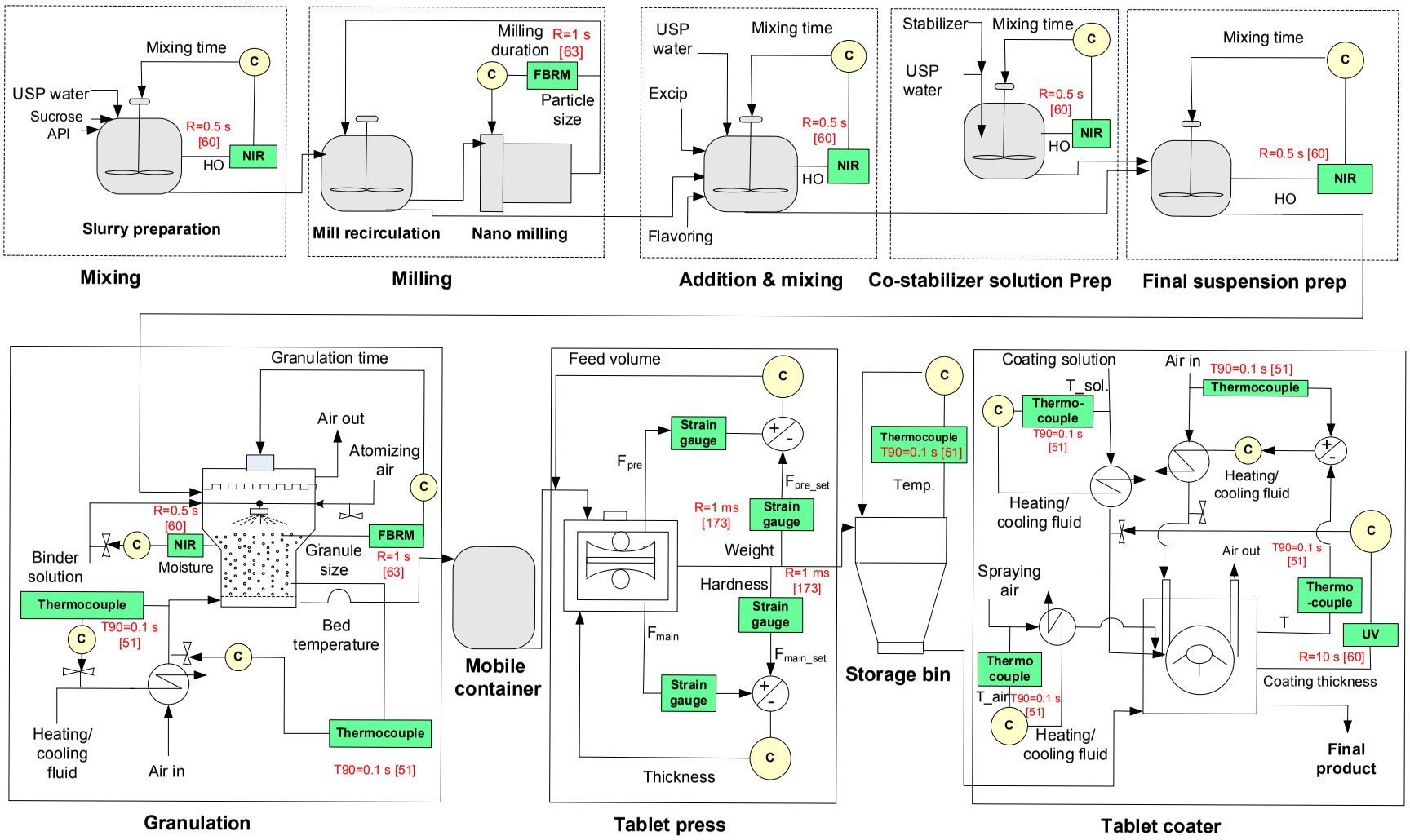


Figure 5.17: Process monitoring and analysis system for the tablet manufacturing process.
c: controller, R: response time, T90: time for 90% response, HO: homogeneity

5.2. Cheese manufacturing process

A cheese manufacturing process has been selected as a second illustrative case study. The process operational models of this process are given in Appendix A3 while the values of known variables and parameters needed to solve the models are given in Appendix B3. These process models are used by ICAS-PAT to generate the data needed for design of a process monitoring and analysis system for the cheese manufacturing process.

5.2.1. Process description

The process flowsheet is shown in Figure 5.18 (Adopted from Zaror & Pyle, 1997). The process flowsheet is implemented by the Golden Cheese Company of California. Milk is pumped from tankers into a storage tank. The temperature in the storage tank is maintained at around 4 ^{o}C. From the storage tank milk flows through a pasteurizer, which is a heat exchanger operating at around 70 ^{o}C. The milk then flows through a cooler to reduce its temperature at the inlet to the cheese vats to 30 ^{o}C. Lactic-acid starter culture and rennin are added in small proportions to the contents of the vats. Next, the curd is solidified for two hours in the Cheddar Tower. The aqueous whey stream is removed. The whey stream is composed of unconsumed proteins, fat, lactose, mineral salts, and water. Next, salts are added to the stream and the cheese is formed into blocks. After block formation, the cheese is sealed, cooled and stored to mature.

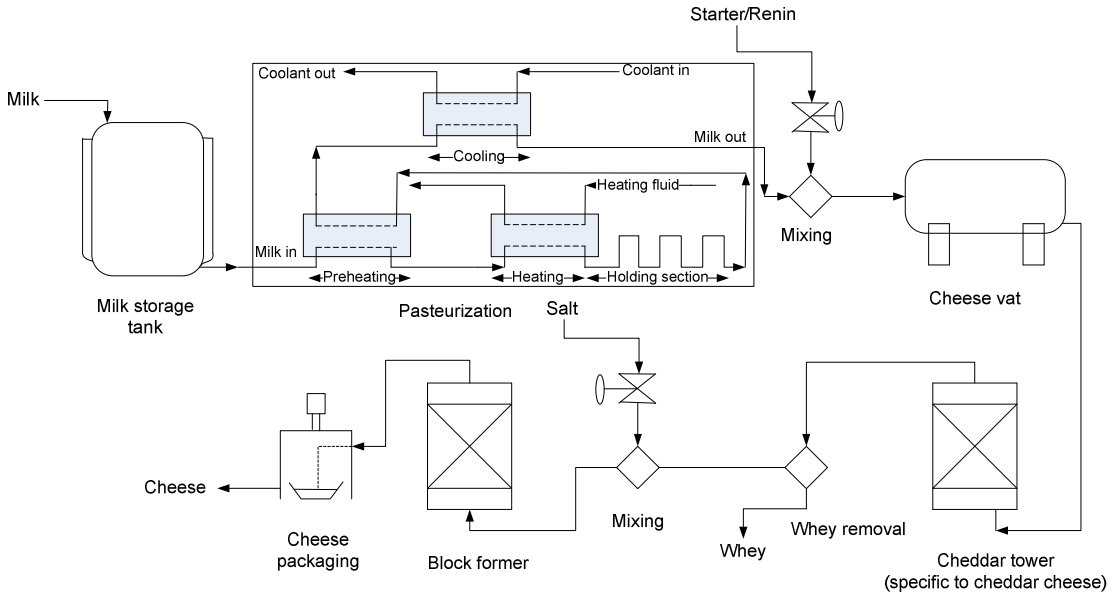


Figure 5.18: Process flowsheet for the cheese manufacturing process (Adopted from Zaror & Pyle, 1997)

5.2.2. Process models

5.2.2.1. Milk storage tank

The total number of equations is 18 in this case (see Appendix A3.1). The total number of variables involved in the model is 43 (see Table 5.11). The degree of freedom is calculated to be 25. The detailed classification of the variables is provided in Table 5.11. The incidence matrix of this model has shown a lower triangular form (see Table 5.12) and therefore all the equations can be solved sequentially.

Table 5.11: Classification of milk storage tank process model variables

Variable types		Variables	No. of variables	Total no
To be specified	Constant	π	1	25
	Fixed by problem	X_{fat}, X_{case_p}, X_{whey_p}, $X_{minerals}$, $X_{organism}$, T_{in}, T_{out}, f_{in}, f_{out}, T_S, U_S, V_c, f_c, Tc_{in}	14	
	Fixed by system	d, ρ, ρ_{in}, ρ_{out}, C_P, d_0, ρ_c, Cp_c, U_1, U_2	10	
To be predicted	Algebraic (explicit)	$M_{organism}$, $M_{minerals}$ M_{whey_p}, M_{case_p}, M_{fat}, Q_{in}, Q_{out}, Q_s, A , M, L, M_w, X_w, A_1, A_2	15	18
	Differential	V, T, T_C	3	
Total number of variables involved in the model				43
Total number of differential equations				3
Total number of algebraic equations (explicit)				15

Table 5.12: Incidence matrix of the milk storage tank model

Eq. No.	V	T	T_c	M	$M_{organism}$	$M_{minerals}$	M_{whey_p}	M_{case_p}	M_{fat}	X_w	M_w	A	L	A_2	A_1	Q_s	Q_{out}	Q_{in}
3.1.1	*			*														
3.1.2				*	*													
3.1.3				*		*												
3.1.4				*			*											
3.1.5				*				*										
3.1.6				*					*									
3.1.7										*								
3.1.8											*							
3.1.9												*						
3.1.10	*												*					
3.1.11													*	*				
3.1.12													*		*			
3.1.13		*										*				*		
3.1.14		*															*	
3.1.15		*																*
3.1.16	*																	
3.1.17	*	*	*											*	*	*	*	*
3.1.18		*	*											*	*			

5.2.2.2. Pasteurization of milk

The list of model equations is given in Appendix A3.2. The total number of equations in this case is 41. The total number of variables involved in the model is 74 (see Table 5.13). Based on the total number of variables and the total number of equations the degree of freedom is calculated to be 33. The detailed classification of the variables is given in Table 5.13. Based on the classification of variables an incidence matrix between the number of equations and the number of unknown variables is prepared as shown in Table 5.14. Equations 3.2.15, 3.2.16, 3.2.22, 3.2.23, 3.2.33 and 3.2.34 are implicit because there are crosses on the upper triangular (see shaded equations in incidence matrix), and therefore these equations need to be solved iteratively.

Table 5.13: Classification of variables of the pasteurization process model

Variable types		Variables	No. of variables	Total no
To be specified	Constant	π, R , Cpw, ρ_w	4	33
	Fixed by problem	K_{do}, E_d, N_0, T_0, ρ_{milk}, $C_{p_{milk}}$, f, f_{hw}, f_{cw}, T_{hw_in}, T_{cw_in}, U_{pre}, U_h, U_c, $M_{0\_organism}$, $X_{minerals}$, X_{whey_p}, X_{case_p}, X_{fat}, $X_{lactose}$,	20	
	Fixed by system	l_{pre}, l_h, l_{hold}, l_c, r_{pre}, r_h, r_{hold}, r_{c1}, r_c	9	
To be predicted	Explicit	A_{pre}, t_{pre}, A_h, t_h, A_{hold}, t_{hold}, A_{c1}, t_{c1}, A_c, t_c, b_{pre}, a_h, b_h, β_h, c_h, a_c, b_c, β_c, c_c, T, K_d, N, T_{pre}, T_h, T_c, F, $X_{organism}$, $F_{organism}$, $F_{minerals}$, F_{whey_p}, F_{case_p}, F_{fat}, $F_{lactose}$, F_w, X_w	35	41
	Implicit	T_{pre_f}, T_1, T_p, T_{hw_out}, T_f, T_{cw_out}	6	
Total number of variables involved in the model				74
Total number of algebraic equations (explicit: 35, implicit: 6)				41

Table 5.14: Incidence matrix of pasteurization process model

Eq. No	A_{pre}	t_{pre}	A_h	t_h	A_{hold}	t_{hold}	A_{c1}	t_{c1}	A_c	t_c	b_{pre}	a_h	b_h	β_h	c_h	a_c	b_c	β_c	c_c	$T_{pre\ f}$	T_1	T_p	$T_{hw\ out}$	T_f	$T_{cw\ out}$	T_{pre}	T_h	T_c	T	K_d	N	F	$X_{organism}$	$F_{organism}$	$F_{minerals}$	$F_{whey\ p}$	$F_{case\ p}$	F_{fat}	$F_{lactose}$	X_w	F_w
3.2.18	*																																								
3.2.17	*	*																																							
3.2.27			*																																						
3.2.26			*	*																																					
3.2.29					*																																				
3.2.28					*	*																																			
3.2.41							*																																		
3.2.40							*	*																																	
3.2.38									*																																
3.2.37									*	*																															
3.2.14											*																														
3.2.20												*																													
3.2.21													*																												
3.2.25												*	*	*																											
3.2.24												*		*	*																										
3.2.31																*																									
3.2.32																	*																								
3.2.36																*	*	*																								
3.2.35																*		*	*																							
3.2.15											*									*	*																					
3.2.16																				*	*	*																				
3.2.22												*		*								*	*																			
3.2.23															*					*			*																			
3.2.33																*		*			*			*	*																	
3.2.34																			*		*				*																	
3.2.13											*										*					*																
3.2.19												*	*							*			*				*															
3.2.30																*	*				*				*			*														
3.2.39		*		*		*		*		*												*		*		*	*	*	*												
3.2.1																													*	*												
3.2.2																														*	*											
3.2.3																																*										
3.2.4																															*		*									
3.2.5																																*	*	*								
3.2.6																																*			*							
3.2.7																																*				*						
3.2.8																																*					*					
3.2.9																																*						*				
3.2.10																																*							*			
3.2.11																																								*		
3.2.12																																*								*	*	

5.2.2.3. Starter/rennin mixer

The list of model equations is given in Appendix A3.3. The total number of equations in this case is 11. The total number of variables involved in the model is 19 (see Table 5.15). Based on the total number of variables and the total number of equations the degree of freedom is calculated to be 8. The detailed classification of the variables is given in Table 5.15. Based on the classification of variables an incidence matrix between the number of equations and the number of unknown variables is prepared as shown in Table 5.16. The incidence matrix of this model has also shown a lower triangular form and therefore all the equations can be solved sequentially.

Table 5.15: Classification of variables of the starter/rennin mixing process model

Variable types		Variables	No. of variables
To be specified	Fixed by problem	F_{in_o}, $F_{starter}$, F_{rennin} $F_{minerals}$, F_{whey_p}, F_{case_p}, F_{fat}, $F_{lactose}$	8
To be predicted	Explicit	$n\_t_{F_{in}}$, F_{in}, F_{out}, $X_{starter}$, X_{rennin}, $X_{minerals}$, X_{whey_p}, X_{case_p}, X_{fat}, $X_{lactose}$, X_w	11
Total number of variables involved in the model			19
Total number of algebraic equations (explicit)			11

Table 5.16: Incidence matrix of starter/rennin mixing process model

Eq. No.	$n\_t_{F_{in}}$	F_{in}	F_{out}	$X_{starter}$	X_{renin}	$X_{mineral}$	X_{whey_p}	X_{case_p}	X_{fat}	$X_{lactose}$	X_w
3.3.1	*										
3.3.2	*	*									
3.3.3		*	*								
3.3.4			*	*							
3.3.5			*		*						
3.3.6			*			*					
3.3.7			*				*				
3.3.8			*					*			
3.3.9			*						*		
3.3.10			*							*	
3.3.11				*	*	*	*	*	*	*	*

5.2.2.4. Cheese vat

The list of model equations is given in Appendix A3.4. The total number of equations in this case is 13. The total number of variables involved in the model is 37 (see Table 5.17). Based on the total number of variables and the total number of equations the degree of freedom is calculated to be 24. The detailed classification of the variables is given in Table 5.17. Based on the classification of variables an incidence matrix between the number of equations and the number of unknown variables is prepared as shown in Table 5.18. The incidence matrix of this model has also shown a lower triangular form and therefore all the equations can be solved sequentially.

Table 5.17: Classification of variables of the curd formation process model

Variable types		Variable	No. of variables	Total no
To be specified	Constant	Cpw, ρ_w	2	24
	Fixed by problem	μ_{max}, K_S, ms_1, kf_{lactic}, K_{lactic}, kf_w, K_w, ρ_b, C_{pb}, U_1, U_2, H_{gr}, H_{surr}, V_w, $F_{w_{in}}$, $T_{w_{in}}$, T_{surr}, Y_{XS}, $Y_{Xlactic}$	19	
	Fixed by system	V, A_1, A_2	3	
To be predicted	Algebraic (explicit)	μ, ms, r_{lactic}, r_{H2O}, pH	5	13
	Differential	C_x, C_s, C_{lactic}, $C_{lactate}$, C_{OH^-}, C_{H^+}, T_b, T_w	8	
Total number of variables involved in the model				37
Total number of differential equations				8
Total number of algebraic equations (explicit)				5

Table 5.18: Incidence matrix of curd formation process model

Eq. No.	C_x	C_s	C_{lactic}	$C_{lactate}$	C_{OH^-}	C_{H^+}	T_b	T_w	μ	ms	r_{lactic}	r_{H2O}	pH
3.4.1		*							*				
3.4.2		*								*			
3.4.3			*	*		*					*		
3.4.4					*	*						*	
3.4.5						*							*
3.4.6	*								*				
3.4.7	*	*							*	*			
3.4.8	*		*						*		*		
3.4.9				*							*		
3.4.10					*							*	
3.4.11						*					*	*	
3.4.12							*	*					
3.4.13							*	*					

5.2.2.5. Whey separator

The list of model equations is given in Appendix A3.6. The total number of equations in this case is 8. The total number of variables involved in the model is 18 (see Table 5.19). Based on the total number of variables and the total number of equations the degree of freedom is calculated to be 10. The detailed classification of the variables is given in Table 5.19 .The model equations are solved sequentially (eq. 3.6.1 to 3.6.8, in sequential order)

Table 5.19: Classification of variables of the whey separation process model

Variable types		Variables	Total no
To be specified	Fixed by problem	F_{in_o}, F_{whey}, X_{fat_in}, X_{fat_whey}, $X_{case\_p\_in}$, $X_{case\_p\_whey}$, $X_{minerals\_in}$, $X_{minerals\_whey}$, $X_{lactose\_in}$, $X_{lactose\_whey}$	10
To be predicted	Algebraic (explicit)	$n\_t_{F_{in}}$, F_{in}, F_{out}, X_{fat_out}, $X_{case\_p\_out}$, $X_{minerals\_out}$, $X_{lactose\_out}$, X_{w_out}	8
Total number of variables involved in the model			18
Total number of equations (algebraic, explicit)			8

5.2.2.6. Salt mixer

The list of model equations is given in Appendix A3.7. The total number of equations in this case is 9. The total number of variables involved in the model is 15 (see Table 5.20). Based on the total number of variables and the total number of equations the degree of freedom is calculated to be 6. The detailed classification of the variables is given in Table 5.20. The model equations are solved sequentially (eq. 3.7.1 to 3.7.9, in sequential order)

Table 5.20: Classification of variables of the salt mixing process model

Variable types		Variables	Total no
To be specified	Fixed by problem	F_{in_o}, F_{salt}, X_{fat_in}, $X_{case\_p\_in}$, $X_{minerals\_in}$, $X_{lactose\_in}$	6
To be predicted	Algebraic (explicit)	$n\_t_{F_{in}}$, F_{in}, F, X_{fat}, X_{case_p}, $X_{minerals}$, $X_{lactose}$, X_{salt}, X_w	9
Total number of variables involved in the model			15
Total number of equations (algebraic, explicit)			9

5.2.3. Design of the process monitoring and analysis system

A process monitoring and analysis system of the cheese manufacturing process has been designed by using the developed design methodology in the ICAS-PAT software as follows:

5.2.3.1. Product property specifications (step 1)

The desired final product is cheese. The desired specifications of the final product are given in Table 5.21

Table 5.21: Desired properties of cheese

Specifications of cheese		Values	Units
Composition	Fat	32.42	% (w/w)
	Casein (protein)	23.70	% (w/w)
	Minerals	0.31	% (w/w)
	Salt	1.99	% (w/w)
	Moisture	39.17	% (w/w)
	Lactose	2.17	% (w/w)
	Whey	0.22	% (w/w)
Acidity		5	pH
Weight		1	kg

5.2.3.2. Process specifications (step 2)

The basic raw materials required include: milk, starter culture, rennin and salt. The process equipments include: a milk storage tank to store the milk, a pasteurizer to reduce the number of living organisms (micro-organisms), a mixer to add starter/rennin, a cheese vat to convert the milk in the form of curd, a cheddar tower to solidify the curd, a separator to remove the whey from the curd, a salt mixer to add the salt to the cheese curd, a block former/cheese press to compress the cheese in the form of a block and a packaging system to pack the cheese.

5.2.3.3. Process analysis (step 3)

The process analysis has been performed to list the process points and corresponding process variables. The obtained process points and corresponding process variables involved in the cheese manufacturing process are given in Table 5.22 (retrieved from the knowledge base)

Table 5.22: List of process points and process variables of the cheese manufacturing process

Process points	Process variables	Lower limits	Upper limits	Units
Milk storage tank	Temperature	3.5	4.5	^{o}C
	Pressure	0.9	1.1	atm
	Level	2.7	2.9	m
	pH	6.5	6.7	pH
	Fat	0.035	0.045	Mass fraction
	Casein protein	0.024	0.028	Mass fraction
	Whey protein	0.006	0.007	Mass fraction
	Minerals	0.006	0.007	Mass fraction
	Lactose	0.045	0.05	Mass fraction
	Water	0.85	0.89	Mass fraction
	Living organism	1E08	1E10	no./m^3
Pasteurizer	Main stream (milk) temperature (inlet)	3.5	4.5	^{o}C
	Main stream (milk) temperature (holding section)	68	72	^{o}C
	Main stream (milk) temperature (outlet)	28	32	^{o}C
	Heating fluid temperature	68	80	^{o}C
	Heating fluid flow rate	0	10	m^3/hr
	Casein protein	0.024	0.028	Mass fraction
	Whey protein	0.006	0.007	Mass fraction
	Pasteurization time	0.004	0.2	hr
	Bacteria counts	0	1000	no./m^3
	Coolant temperature	15	22	^{o}C
	Main stream (milk) flow rate	2	12	m^3/hr
	Coolant flow rate	2	10	m^3/hr
Starter/renn in mixer	Starter concentration in milk stream	1.25	2	% V/V
	Rennin concentration in milk stream	0.023	0.027	% V/V
	Starter flow rate	0	6	kg/hr
	Rennin flow rate	0	2	kg/hr
Cheese vat	Temperature	28	32	^{o}C
	pH	3	6.7	pH
	Starter concentration	1.25	2	% V/V
	Rennin concentration	0.023	0.027	% V/V
	Lactic acid concentration	0	70	kg/m^3
	Coagulum concentration			
	Casein protein	0.024	0.028	Mass fraction
	Whey protein	0.006	0.007	Mass fraction
	Lactose	0	0.05	Mass fraction
	Stirrer speed	0	10	rps
	Stirring duration	0	2	hr
	Coagulation time	0.45	2	hr
Cheddar tower	Lactic acid concentration	0	60	kg/m^3
	Curd moisture content	0	0.70	Mass fraction
	Solidification time	0	2	hr

Table 5.22: (continued)

Process points	Process variables	Lower limits	Upper limits	Units
Whey separator	Curd moisture content	0.38	0.42	Mass fraction
	Fat content in whey	0	0.001	Mass fraction
	Whey flow rate	0	100	kg/hr
	Flow rate of separated cheese curd	0	100	kg/hr
Salt mixing equipment	Salt flow rate	0	1	kg/hr
	Salt	0.01	0.03	Mass fraction
Block former/	Hardness	50	55	MPa
	Weight	0.99	1.1	kg
Cheese press	Moisture content	0.38	0.42	Mass fraction
	Compression pressure	0	100	MPa
	Cheese thickness	0.05	0.055	m
	Cheese pressing duration	0	5	hr
Cheese packaging	Shape	-	-	Rectangular

5.2.3.4. Sensitivity analysis (step 4)

The critical process variables (among the variables listed in Table 5.22) that need to be monitored and controlled during the cheese manufacturing process are identified through this step. The open-loop simulation has been performed for each unit process involved in the cheese manufacturing process to identify the critical process variables. As mentioned before (see section 2.2.4 and 4.2.1.4), first the operational objective of each process point is analyzed and if the operational objective is not achieved then the corresponding process variables are analyzed to identify the variables which are violating the operational limits and therefore need to be monitored and controlled. For illustration purposes, one process point – pasteurization - is considered here. The operational objective for the pasteurization step is to pasteurize the milk (reduce the number of micro-organisms in the milk). The sterility ratio[7] (objective function in pasteurization) is desired to maintain above 4 (minimum limit). The profile of the objective function (sterility ratio) is shown in Figure 5.19. This figure shows that the obtained value of the sterility ratio (r) is considerably lower than the minimum limit. It means that the

[7] Sterility ratio: logarithm of the ratio of the initial number of living organisms (raw milk) to the final number of the living organisms (heat-treated milk) $\left(\log\left(\frac{N_0}{N}\right)\right)$

operational objective (OB) of the pasteurization step is not achieved (see Figure 5.19), and therefore the variables involved in the pasteurization process need to be analyzed to identify the critical controlled variables. The process variable, "main stream (milk) temperature of pasteurization" is selected from Table 5.22 for analysis. The operational limits of the main stream (milk) temperature are identified (from stored data in the knowledge base), where the main stream (milk) temperature in the holding section (pasteurization temperature) should be maintained between 68-72 ^{o}C for 0.004 to 0.2 hour (depending on the actual temperature) and also the outlet milk stream need to be cooled to around 30 ^{o}C (Bylund, 2003). The simulated behavior of the main stream temperature in open-loop is shown in Figure 5.20. The pasteurization temperature (main stream temperature in holding section) violates the lower limit (see Figure 5.20), required to reduce the number of micro-organisms. The outlet temperature of the milk stream is also not within the acceptable limit, suitable for further acidification and coagnition of the milk. Therefore the pasteurization temperature and the outlet milk temperature are selected as the critical process variables, and the corresponding process point (pasteurizer) is considered as a critical process point where monitoring is required. Similarly, the other critical process points and corresponding critical process variables are identified as listed in Table 5.23.

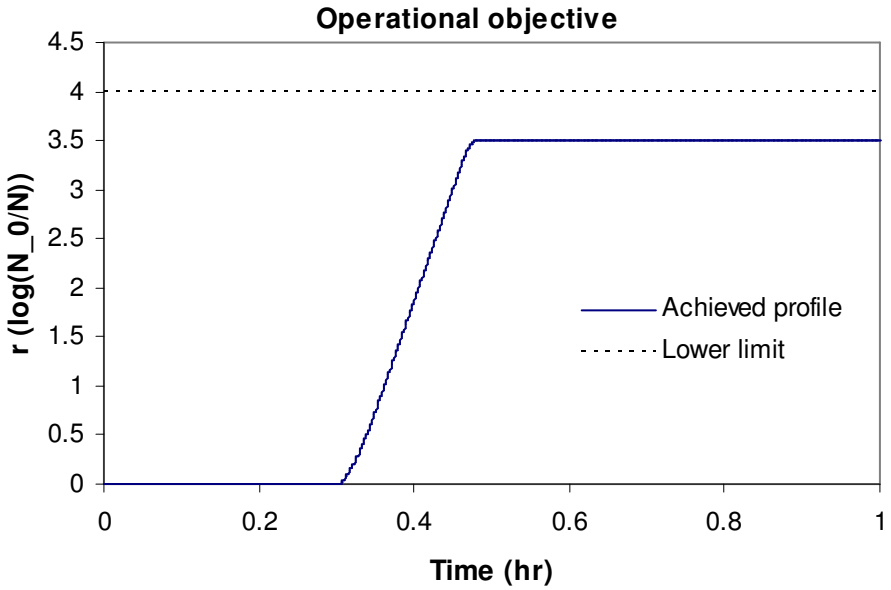


Figure 5.19: Profile of operational objective (sterility ratio) in pasteurizer (open-loop simulation)

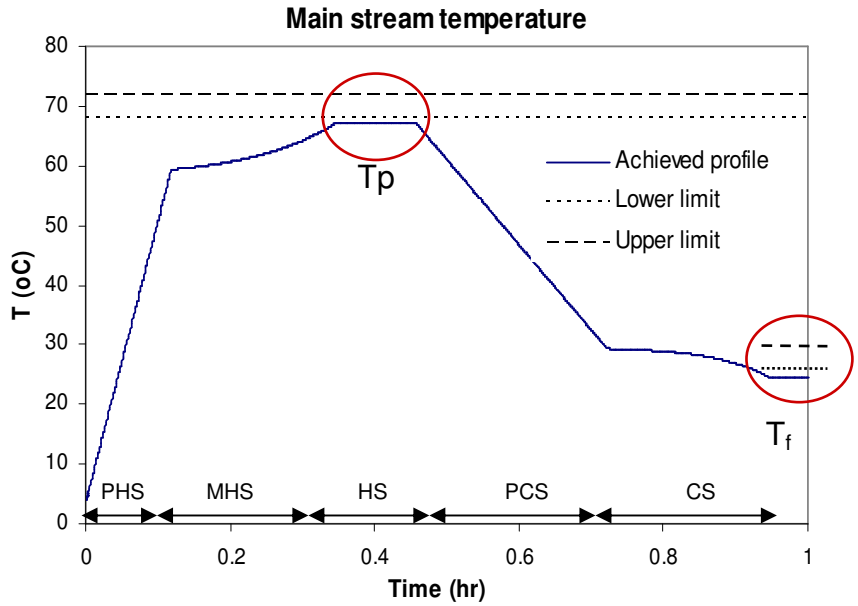


Figure 5.20: Simulated main stream (milk) temperature in open-loop
(PHS=Preheating section, MHS=Main heating section, HS=Holding section, PCS=Pre-cooling section, CS=Cooling section)

Table 5.23: List of critical process points and corresponding critical process variables for the cheese manufacturing process

Critical process points	Critical process variables
Milk storage tank	Temperature
	Fat
	Casein protein
	Whey protein
	Lactose
Pasteurizer	Pasteurization temperature
	Outlet milk temperature
Starter/rennin mixer	Starter concentration in milk stream
	Rennin concentration in milk stream
Cheese vat	Temperature
	pH
	Lactic acid concentration
	Coagulum concentration
Cheddar tower	Lactic acid concentration
	Curd moisture content
Whey separator	Curd moisture content
Salt mixing equipment	Salt concentration
Block former/ Cheese press	Hardness
	Weight
	Moisture content

5.2.3.5. Interdependency analysis (step 5)

The interdependency analysis has been performed to find the appropriate actuators for each critical variable of the cheese manufacturing process. As described before (see section 2.2.5 section 4.2.1.5), in this step the effects of actuator candidates on the controlled variables (critical variables) are compared to identify the suitable manipulated variables for each controlled variable. For example, a process point pasteurizer and a corresponding critical process variable ‘pasteurization temperature’ are considered for further analysis. Milk flow rate, heating fluid temperature and heating fluid flow rate are three actuator candidates (retrieved from the knowledge base) for pasteurization temperature. The simulated effect of actuator candidates on the controlled variable is shown in Figure 5.21, which shows that, the ‘heating fluid temperature’ is most sensitive actuator candidate but is also the most difficult to manipulate (necessitates an additional heat exchanger). The next sensitive actuator candidate ‘milk flow rate’ can not be manipulated because it will affect the operation time. The heating fluid flow rate is the

least sensitive actuator candidate but it is easier to manipulate, and therefore the heating fluid flow rate is selected as the actuator for controlling the pasteurization temperature. Similarly, the manipulated variables of other controlled variables are identified as summarized in Table 5.24

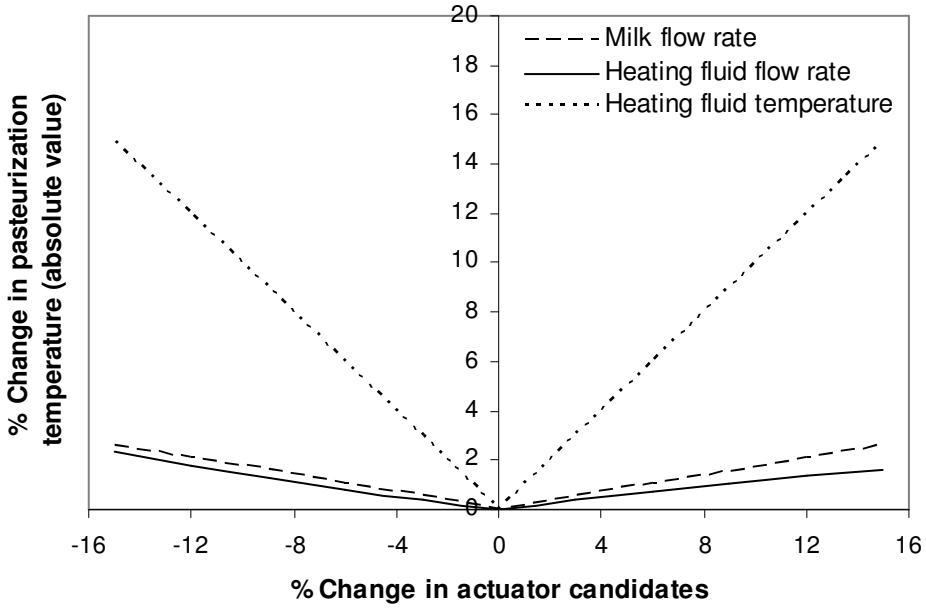


Figure 5.21: Actuator selection for pasteurization temperature

Table 5.24: Critical process variables and selected actuators

Critical process points	Critical process variables	Actuators
Milk storage tank	Temperature	Cooling/heating fluid flow rate
	Fat	Addition/removal rate of fat
	Casein protein	Addition/removal rate of casein protein
	Whey protein	Addition/removal rate of whey protein
	Lactose	Addition/removal rate of lactose
Pasteurizer	Pasteurization temperature	Heating fluid flow rate
	Outlet milk temperature	Cooling fluid flow rate
Starter/rennin mixer	Starter concentration in milk stream	Starter flow rate
	Rennin concentration in milk stream	Rennin flow rate
Cheese vat	Temperature	Heating/Cooling fluid flow rate
	pH	Fermentation time
	Lactic acid concentration	Fermentation time
	Coagulum concentration	Rennin flow rate
Cheddar tower	Lactic acid concentration	Cheddaring time
	Curd moisture content	Cheddaring time
Whey separator	Curd moisture content	Separation force
Salt mixing equipment	Salt concentration	Salt flow rate
Block former/ Cheese press	Hardness	Compression pressure
	Weight	Cheese curd flow rate
	Moisture content	Compression pressure

5.2.3.6. Performance analysis of monitoring tools (step 6)

The suitable monitoring techniques and tools for each critical variable of the cheese manufacturing process are identified through this step following the procedure described in section 4.2.6. First the available monitoring techniques and tools that satisfied the user constraints for each critical process variable are retrieved from the knowledge base, and then the performance of these monitoring tools is compared to select the final monitoring tools. The pasteurization temperature is considered here for the illustration of monitoring tool selection. The specified performance criterion (specifications of temperature monitoring tools) and their desired performances (desired values of specifications) are given in Table 5.25. This information is provided by the user. The available monitoring techniques and corresponding monitoring tools for temperature measurement that satisfied the desired performance are retrieved from the knowledge base and given in

Table 5.26. The performance of the monitoring tools (listed in Table 5.26) is compared on the basis of the specified performance criteria (specifications) given in Table 5.25. The scoring system is used to compare the monitoring tools. The score obtained by each monitoring tool is calculated as given in Table 5.27. The 'T Series Standard Temperature Sensor -- T4267-K20FGEJ (thermocouple)' obtained the highest total score (see Table 5.27, last column), and therefore this monitoring tool is selected for temperature monitoring. The selected monitoring tool is a thermocouple. Similarly the monitoring techniques and monitoring tools for other critical process variables are identified as given in Table 5.28

Table 5.25: Selected specifications of monitoring tools and their desired values (user specific)

Specifications (performance criterion)	Desired value of specifications (desired performance)
Accuracy (Ac)	Ac $\leq$ 1 % of reading
Precision (Pr)	Pr $\leq$ 0.02 ^{o}C
Lower operating limit (LOL)	LOL $\leq$ 0 ^{o}C
Upper operating limit (UOL)	UOL $\geq$ 100 ^{o}C
Response time (RT)	RT (T90) $\leq$ 30 seconds
Resolution (R)	R $\leq$ 0.1 ^{o}C
Sensitivity (S)	S $\geq$ 5E-5 sensor output/ ^{o}C
Drift (D)	D $\leq$ 1 ^{o}C per year
Lower operating temperature (LOT)	LOT $\leq$ 0 ^{o}C
Upper operating temperature (UOT)	UOT $\geq$ 80 ^{o}C

Table 5.26: Monitoring tools for pasteurization temperature measurement with specifications. Results obtained from the knowledge base (Ac: Accuracy; Pr: Precision; LOL: Lower operating limit; UOL: Upper operating limit; RT: response time; R: Resolution; S: Sensitivity; D: Drift; LOT: Lower operating temperature; UOT: Upper operating temperature; [ ]: indicates the reference number in the knowledge base)

Monitoring techniques	Monitoring tools	Ac	Pr	LOL	UOL	RT (T90)	R	S	D	LOT	UOT
Thermocouple	Base Metal Thermocouple Element -- TEAB	0.75 % of reading [119]	0.02 °C [126]	-270.0 °C	1000.0 °C	100.0 ms [107]	0.1 °C [121]	0.00005 V/°C [123]	1.0 °C per year [119]	-200.0 °C [117]	1750.0 °C [117]
	Base Metal Thermocouple Element -- TEBA	0.75% of reading [119]	0.02 °C [126]	-270.0 °C	1000.0 °C	100.0 ms [107]	0.1 °C [121]	0.00005 V/°C [123]	1.0 °C per year [119]	-200.0 °C [117]	1750.0 °C [117]
	Base Metal Thermocouple Element -- TEBD	0.75 % of reading [119]	0.02 °C [126]	-270.0 °C	1000.0 °C	100.0 ms [107]	0.1 °C [121]	0.00005 V/°C [123]	1.0 °C per year [119]	-200.0 °C [117]	1750.0 °C [117]
	T Series Standard Temperature Sensor -- T4266-J12	0.75 % of reading [119]	0.02 °C [126]	-210.0 °C	1200.0 °C	100.0 ms [107]	0.1 °C [121]	0.00005 V/°C [123]	1.0 °C per year [119]	-200.0 °C [117]	1750.0 °C [117]
	WZ-08541-28 (E 20-gauge thermocouple)	1.0 % of reading	0.02 °C [126]	-270.0 °C	1000.0 °C	100.0 ms [107]	0.1 °C [121]	0.00005 V/°C [123]	1.0 °C per year [119]	-28.0 °C	105.000 000 °C
	T Series Standard Temperature Sensor -- T4267-K20FGEJ	0.75 % of reading [119]	0.02 °C [126]	-270.0 °C	1372.0 °C	100.0ms [107]	0.1 °C [121]	0.00005 V/°C [123]	1.0 °C per year [119]	-200.0 °C [117]	1750.0 °C [117]
Resistance thermometers (RTD)	Thin Film Platinum RTD -- PPG101A1	0.06 % of reading	0.001 °C [115]	-50.0 °C	500.0 °C	15000 ms	0.001 °C [118]	0.39200 Ω/°C [118]	0.05 °C per year [119]	-50.0 °C	500.0 °C
Thermistor	DO-35 Interchangeable Thermistor -- 103JL1A	0.40 % of reading [11]	0.003 °C [125]	-55.0 °C	300.0 °C	150.0 ms [123]	0.0 °C [127]	3.92000 Ω/°C [124]	0.027 °C per year [122]	-55.0 °C	80.0 °C
	DO-35 Standard Thermistor -- 103JG1J	0.40 % of reading [11]	0.003 °C [125]	-55.0 °C	300.0 °C	150.0 ms [123]	0.0001 °C [127]	3.92000 Ω/°C [124]	0.027 °C per year [122]	-55.0 °C	80.0 °C
	CWF Series -- CWF 3100	1.0 % of reading	0.003 °C [125]	-55.0 °C	125.0 °C	15000 ms	0.0001°C [127]	3.92000 Ω/°C [124]	0.027 °C per year [122]	-55.0 °C	125.0 °C
	MF11 Series -- MF11 150	0.4 % of reading [11	0.003 °C [125]	-55.0 °C	125.0 °C	30000 ms	0.0001°C [127]	3.92000 Ω/°C [124]	0.027 °C per year [122]	-55.0 °C	125.0 °C
	T101 NTC Thermistor -- T101D102.CA	0.4 % of reading [11]	0.003 °C [125]	-40.0 °C	105.0 °C	150.0 ms [123]	0.0001 °C [127]	3.92000 Ω/°C [124]	0.027 °C per year [122]	-60.0 °C	300.0 °C
	111-102CAJ-H01	0.4 % of reading [11]	0.003 °C [125]	-60.0 °C	300.0 °C	150.0 ms [123	0.0001°C [127]	3.92000 Ω/°C [124]	0.027 °C per year [122]	N/A	N/A
	FT Series -- FT003-103	0.4 % of reading [11]	0.003 °C [125]	-40.0 °C	120.0 °C	150.0ms [123]	0.0001 °C [127]	3.92000 Ω/°C [124]	0.027 °C per year [122]	N/A	N/A

Table 5.27: Monitoring tools for pasteurization temperature measurement with scores

Monitoring techniques	Monitoring tools	Ac	Pr	LOL	UOL	RT (T90)	R	S	D	LOT	UOT	Total scores
Thermocouple	Base Metal Thermocouple Element -- TEAB	3	3	5	3	5	3	3	3	5	5	38
	Base Metal Thermocouple Element -- TEBA	3	3	5	3	5	3	3	3	5	5	38
	Base Metal Thermocouple Element -- TEBD	3	3	5	3	5	3	3	3	5	5	38
	T Series Standard Temperature Sensor -- T4266-J12	3	3	4	4	5	3	3	3	5	5	38
	WZ-08541-28 (E 20-gauge thermocouple)	2	3	5	3	5	3	3	3	1	1	28
	T Series Standard Temperature Sensor -- T4267-K20FGEJ	3	3	5	5	5	3	3	3	5	5	**40**
Resistance thermometers (RTD)	Thin Film Platinum RTD -- PPG101A1	5	5	1	2	3	4	4	4	2	4	34
Thermistor	DO-35 Interchangeable Thermistor -- 103JL1A	4	4	2	1	4	5	5	5	3	0	33
	DO-35 Standard Thermistor -- 103JG1J	4	4	2	1	4	5	5	5	3	0	33
	CWF Series -- CWF 3100	2	4	2	0	3	5	5	5	3	2	31
	MF11 Series -- MF11 150	4	4	2	0	2	5	5	5	3	2	32
	T101 NTC Thermistor -- T101D102.CA	4	4	0	0	4	5	5	5	4	3	34
	111-102CAJ-H01	4	4	3	1	4	5	5	5	0	0	31
	FT Series -- FT003-103	4	4	0	0	4	5	5	5	0	0	27

Table 5.28: Critical process variables and selected monitoring techniques and tools for the cheese manufacturing process

Critical process points	Critical process variables	Monitoring techniques	Monitoring tools
Milk storage tank	Temperature	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
	Fat	NIR	KJT550 NIR On-line Composition Analyzer
	Casein protein	NIR	KJT550 NIR On-line Composition Analyzer
	Whey protein	NIR	KJT550 NIR On-line Composition Analyzer
	Lactose	NIR	KJT550 NIR On-line Composition Analyzer
Pasteurizer	Pasteurization temperature	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
	Outlet milk temperature	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
Starter/rennin mixer	Starter concentration in milk stream	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
	Rennin concentration in milk stream	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
Cheese vat	Temperature	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
	pH	Electrochemical sensor	pH Meter -- Model 2410
	Lactic acid concentration	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
	Coagulum concentration	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
Cheddar tower	Lactic acid concentration	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
	Curd moisture content	NIR	AvaSpec-NIR256-1.7
Whey separator	Curd moisture content	NIR	AvaSpec-NIR256-1.7
Salt mixing equipment	Salt concentration	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
Block former/	Hardness	Strain Guage	BBC-Strain Gauge-SS-027
Cheese press	Weight	Strain Guage	BBC-Strain Gauge-SS-027
	Moisture content	NIR	AvaSpec-NIR256-1.7

5.2.3.7. Proposed process monitoring and analysis system (step 7)

On the basis of the results obtained in steps 4-6, a process monitoring and analysis system for the cheese manufacturing process is suggested as given in Table 5.29.

Table 5.29: Suggested monitoring and analysis system for the cheese manufacturing process

Critical process points	Critical process variables	Actuators	Monitoring techniques	Monitoring tools
Milk storage tank	Temperature	Cooling/heating fluid flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
	Fat	Addition/removal rate of fat	NIR	KJT550 NIR On-line Composition Analyzer
	Casein protein	Addition/removal rate of casein protein	NIR	KJT550 NIR On-line Composition Analyzer
	Whey protein	Addition/removal rate of whey protein	NIR	KJT550 NIR On-line Composition Analyzer
	Lactose	Addition/removal rate of lactose	NIR	KJT550 NIR On-line Composition Analyzer
Pasteurizer	Pasteurization temperature	Heating fluid flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
	Outlet milk temperature	Cooling fluid flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
Starter/rennin mixer	Starter concentration in milk stream	Starter flow rate	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
	Rennin concentration in milk stream	Rennin flow rate	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
Cheese vat	Temperature	Heating/Cooling fluid flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
	pH	Fermentation time	Electrochemical sensor	pH Meter -- Model 2410
	Lactic acid concentration	Fermentation time	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
	Coagulum concentration	Rennin flow rate	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
Cheddar tower	Lactic acid concentration	Cheddaring time	Refractometer	ATR W Series (Automatic Critical angle Refractometer)

	Curd moisture content	Cheddaring time	NIR	AvaSpec-NIR256-1.7
Whey separator	Curd moisture content	Separation force	NIR	AvaSpec-NIR256-1.7
Salt mixing equipment	Salt concentration	Salt flow rate	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
Block former/ Cheese press	Hardness	Compression pressure	Strain Guage	BBC-Strain Gauge-SS-027
	Weight	Cheese curd flow rate	Strain Guage	BBC-Strain Gauge-SS-027
	Moisture content	Compression pressure	NIR	AvaSpec-NIR256-1.7

5.2.3.8. Model-based validation (step 8)

The obtained process monitoring and analysis system has been validated in ICAS-PAT by following the procedure described in section 2.2.8. First the controllers are configured and then the closed-loop simulation has been performed for control-monitor verification. The sensitivity of each critical variable is verified afterwards. For instance, a controlled loop (controlled variable: pasteurization temperature, actuator: heating fluid flow rate, controller: PI) in the pasteurizer process point is considered as an example. The behavior of the main stream temperature is shown in Figure 5.22 which shows that the set point for the pasteurization temperature (main stream temperature in holding section) is tracked successfully by manipulation of the heating fluid flow rate. Figure 5.23 shows the simulated dynamic profile of the manipulated variable for control of pasteurization temperature. Both, controlled variables and the actuator are within the specified limits. Therefore it is concluded that the pasteurization temperature can be controlled by manipulating the heating fluid flow rate. The outlet temperature of milk from the pasteurization is also within the limits (see Figure 5.23), and therefore it is concluded that this variable does not need to be controlled explicitly. The dynamic profile of the operational objective (sterility ratio) in the pasteurization process is shown in Figure 5.24. The figure shows that the achieved profile of the sterility ratio (OB) is above the specified minimum value, meaning that the operational objective is achieved. In order to verify to what extent a selected critical process variable influences the operational objective, a number of closed-loop simulations have been performed for different values

of that particular critical process variable while the other process variables were kept constant during these simulations. For example, the objective function (sterility ratio) and the controlled variable (pasteurization temperature) are considered in the pasteurizer process point for analysis. The pasteurization temperature is perturbed and the effect on the sterility ratio is analyzed. Figure 5.25 shows that the sterility ratio is sensitive to the pasteurization temperature, meaning that this variable needs to be monitored and controlled to achieve the desired sterility ratio. Similarly, the control-monitor verification and the sensitivity verification for other control loops and critical process variables are achieved.

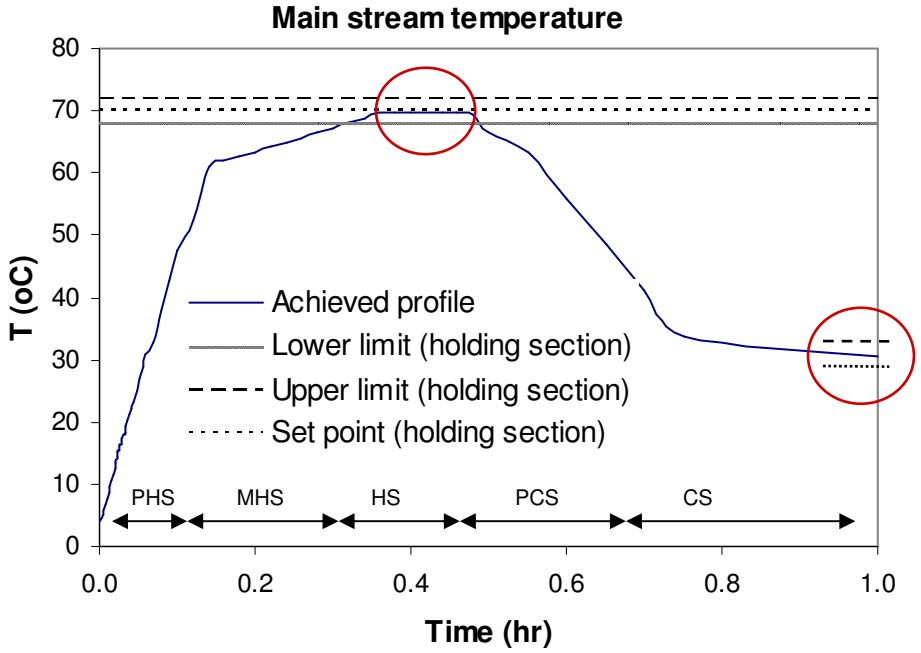


Figure 5.22: Pasteurization temperature (Main stream temperature in holding section) control

(PHS=Preheating section, MHS=Main heating section, HS=Holding section, PCS=Pre-cooling section, CS=Cooling section)

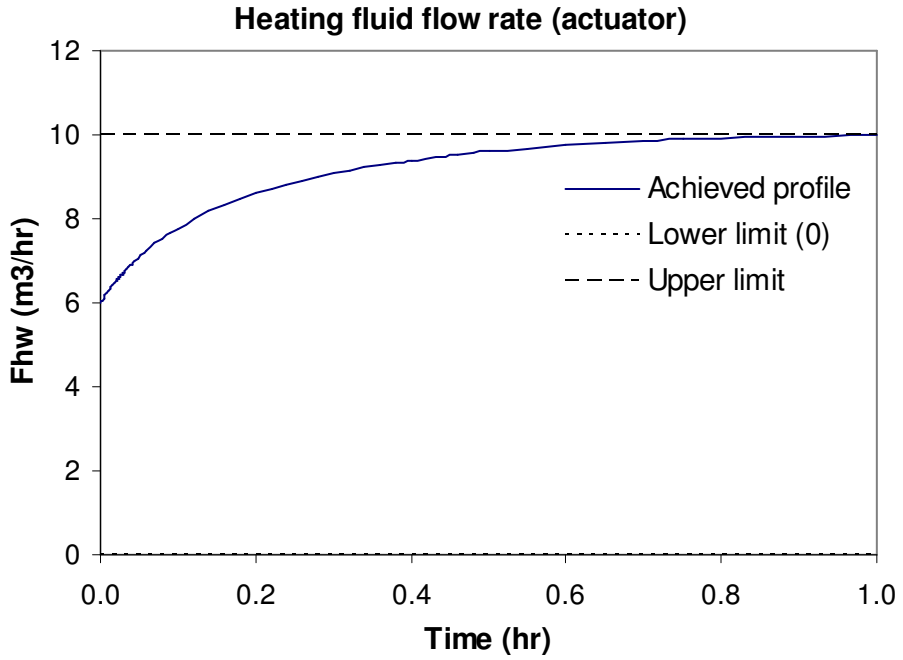


Figure 5.23: Heating fluid flow rate (actuator for pasteurization temperature control)

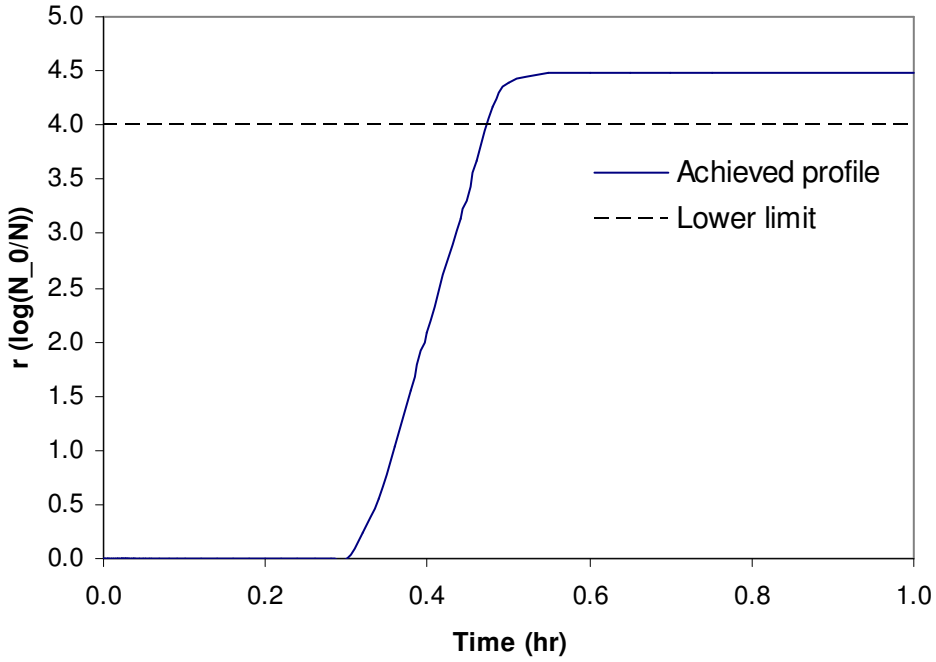


Figure 5.24: Profile of operational objective (sterility ratio) in pasteurization (closed-loop simulation)

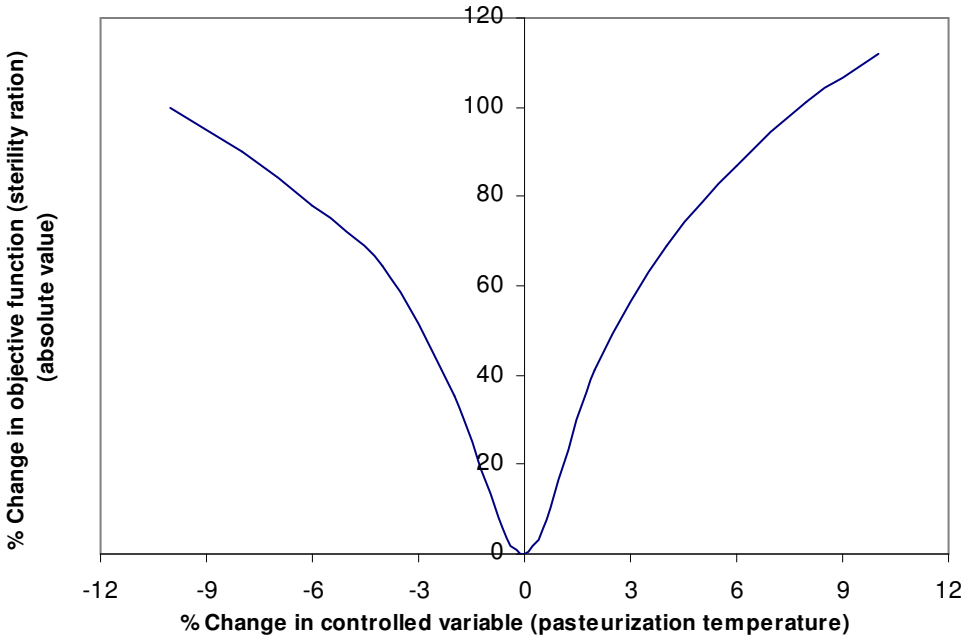


Figure 5.25: Sensitivity verification in pasteurization process

5.2.3.9. Final process monitoring and analysis system (step 9)

The final list of critical process points, corresponding critical process variables, actuators, monitoring techniques and tools are listed in Table 5.30. A feasible alternative of the process monitoring and analysis system is also shown in Figure 5.26. In the milk storage tank the temperature need to be monitored and controlled to keep the milk temperature at around 4 ^{o}C. In order to produce the cheese with consistent quality the milk composition need to be consistent. However, the milk composition can vary depending on the sources of milk, seasons, and changes in the feed that milk producing animal digest. Therefore the milk composition (fat, casein protein, whey protein, lactose) needs to be standardized by addition/removal of appropriate components of milk (Bylund, 2003). The pasteurization temperature also needs to be monitored and controlled to assure that the undesired micro-organisms in the milk are sufficiently reduced in number before starting the curd formation process. Note that the pasteurized milk needs to be cooled to around 30 ^{o}C to promote the milk acidification process (conversion of lactose to lactic acid). To assure the proper level of starter and rennin in the milk stream these variables need to be monitored and controlled during the starter/rennin mixing process. A proper level of

starter is needed to achieve the desired level of acidification while a proper level of rennin is needed to achieve the desired level of coagulation (Bylund, 2003). It should be noted that the control of starter and rennin concentration in the milk is practically difficult and still a challenging task. In the cheese vat (curd formation process) temperature, pH and coagulum concentration need to be monitored and controlled. In the cheddar tower the moisture content needs monitoring and the cheddaring time can be adjusted to achieve the desired moisture level. To assure that the undesired whey has been removed completely, the moisture content of the curd in the whey separation process also needs to be monitored and controlled. Monitoring and control of the salt concentration is needed to assure the desired level of salt in the cheese. In the cheese pressing process, hardness, weight and moisture content need to be monitored and controlled.

Table 5.30: Monitoring and analysis system for the cheese manufacturing process

Critical process points	Critical process variables	Actuators	Monitoring techniques	Monitoring tools
Milk storage tank	Temperature	Cooling/heating fluid flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
	Fat	Addition/removal rate of fat	NIR	KJT550 NIR On-line Composition Analyzer
	Casein protein	Addition/removal rate of casein protein	NIR	KJT550 NIR On-line Composition Analyzer
	Whey protein	Addition/removal rate of whey protein	NIR	KJT550 NIR On-line Composition Analyzer
	Lactose	Addition/removal rate of lactose	NIR	KJT550 NIR On-line Composition Analyzer
Pasteurizer	Pasteurization temperature	Heating fluid flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
Starter/rennin mixer	Starter concentration in milk stream	Starter flow rate	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
	Rennin concentration in milk stream	Rennin flow rate	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
Cheese vat	Temperature	Heating/Cooling fluid flow rate	Thermocouple	T Series Standard Temperature Sensor -- T4267-K20FGEJ
	pH	Fermentation time	Electrochemical sensor	pH Meter -- Model 2410
	Coagulum concentration	Rennin flow rate	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
Cheddar tower	Curd moisture content	Cheddaring time	NIR	AvaSpec-NIR256-1.7
Whey separator	Curd moisture content	Separation force	NIR	AvaSpec-NIR256-1.7
Salt mixing equipment	Salt concentration	Salt flow rate	Refractometer	ATR W Series (Automatic Critical angle Refractometer)
Block former/	Hardness	Compression pressure	Strain Guage	BBC-Strain Gauge-SS-027
Cheese press	Weight	Cheese curd flow rate	Strain Guage	BBC-Strain Gauge-SS-027

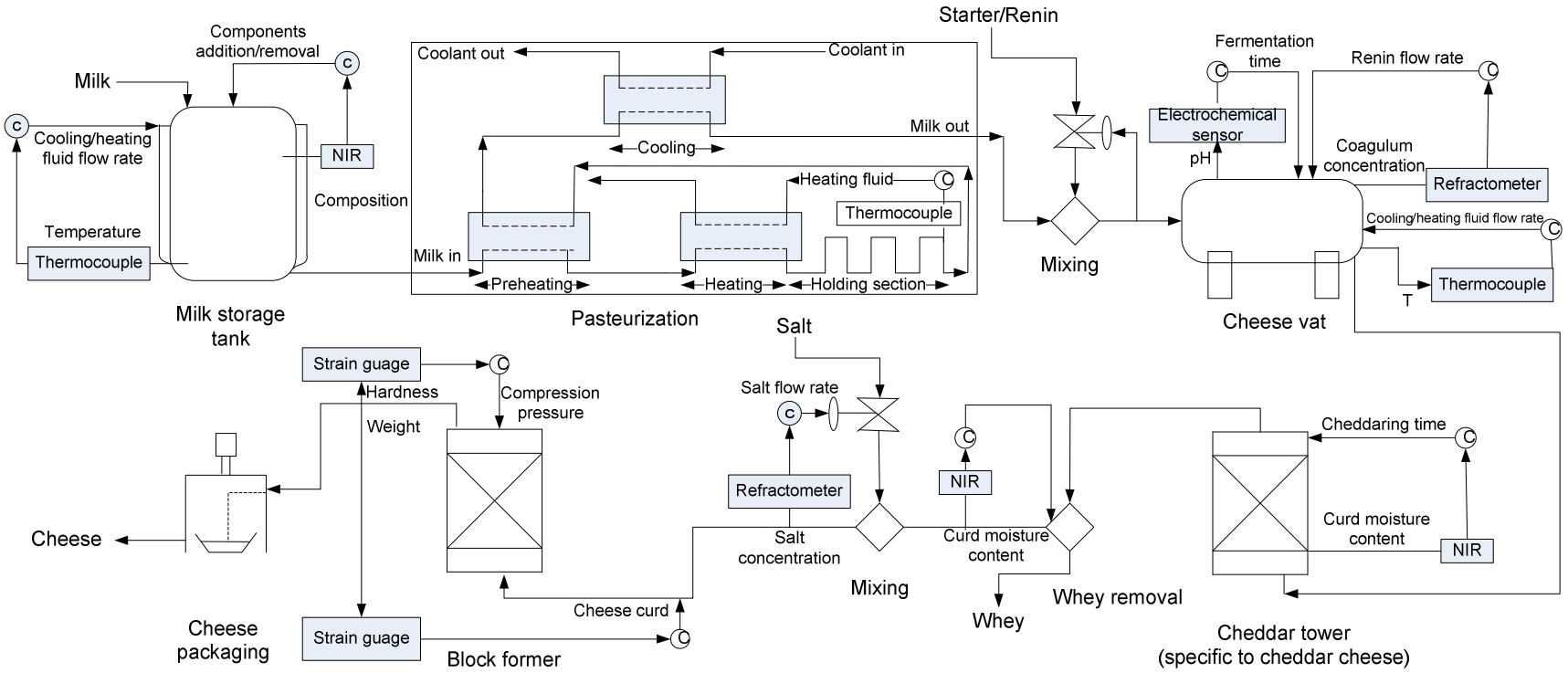


Figure 5.26: Processed monitoring and analysis system (one feasible alternative) for the cheese manufacturing process

6. Conclusions and future perspectives

6.1. Achievements

In this work a systematic model-based computer-aided framework has been developed together with the methods and tools through which the design of monitoring and analysis systems for product quality control can be generated, analyzed and/or validated. The major achievements of this PhD project are summarized below.

6.1.1. Design framework and methodology

The developed framework and the corresponding methodology are generic: its systematic approach to the design of a PAT system is complimentary to traditional process design, and should thus have a broad application range in chemical, biochemical, food production and pharmaceutical processes. The developed design methodology provides the means for successful implementation of a suitable process monitoring and control system that allows to achieve the end product quality consistently. The developed framework and methodology provide a clear opportunity to the manufacturing industry for moving from a lab-centric fixed type of process to a robust well-controlled and flexible PAT based process. This move is highly desirable in most of the regulated industries, for instance, the pharmaceutical industry, in an attempt to introduce more efficient production methods. The developed, systematic computer-aided methods and tools make the PAT system design procedure structured, simple, reliable and fast, that is, the design framework can *manage the complexity* of the PAT system design in a more efficient manner. The importance and applicability of the developed framework and methodology is proved through a "conceptual" fermentation process case study. Each step of the design methodology is quite clear in terms of calculations and generic in terms of application range. This makes the implementation of the methodology into a software quite easy.

6.1.2. Knowledge base and model library

A knowledge base and a model library have been developed to provide the necessary information/data during the design of process monitoring and analysis systems. The

knowledge base consists of the process knowledge as well as the knowledge on measurement methods and tools. The structure of the knowledge base has been designed such that it allows easy implementation of the inference engine. The developed knowledge base covers a wide range of industrial processes, such as, fermentation, pharmaceutical tablet manufacturing, insulin production, cheese manufacturing, butter manufacturing, chemical reaction and a crystallization process. The structure of the knowledge base is generic and can be easily extended to include new processes as well as to include new objects (e. g., to add a newly developed sensor) within the existing processes. Moreover, the structure of the knowledge base can be adopted to build similar knowledge based systems for other applications, for example, a knowledge base on reaction systems can be built to represent the type of processes, corresponding process points, reactions involved in each process points, favorable reactions conditions, available catalyst and corresponding catalyst properties. This kind of knowledge base can be employed to identify the appropriate catalyst and optimum operating conditions for any reaction. In particular, the developed knowledge base is by itself a useful tool because it provides the manufacturing industries an easily accessible and systematic option to compare the salient features of available sensors in order to select the best one that satisfies their requirements.

A model library has been developed to generate additional or missing data needed for the design of a process monitoring and analysis system. The model library contains a set of mathematical models for different types of unit processes, sensors and controllers. Similar to the knowledge base, the model library also covers a wide range of industrial processes. The structure of the model library is generic and can be easily extended to include new process models. A systematic and simple model development procedure has been suggested (see section 3.3.1) that when followed, leads easily to the development of new models for inclusion in the model library. Each process model is analyzed systematically to classify the equations (differential, explicit algebraic, implicit algebraic), to identify the variables that need to be solved (dependent, explicit, implicit) and the variables that need to be specified (constants, fixed by problem, fixed by system) and to build the incidence matrix (variable-equation relationships). This systematic procedure makes the application and solution of the model equations through a computer-

aided system quite simple and straightforward. Furthermore, this systematic representation of the model equations has made the process models generic and applicable to a wide range of problems and systems. Therefore, the model library is considered a useful tool by itself that can be easily employed to study the process behavior for simple as well as complex systems.

6.1.3. Software (ICAS-PAT)

The developed framework and methodology has been implemented into a user-friendly software (ICAS-PAT) that made the use of the PAT design procedure easy, consistent and fast. A knowledge base and a model library, together with the simulation tool (ICAS-MoT) have been integrated with the user interface of ICAS-PAT through which the data required for design of PAT systems are provided. ICAS-PAT also allows the replacement of built-in supporting tools (general knowledge base and model library) with user defined supporting tools. This feature makes the software more generic and applicable for those industries where the models and data are to be kept confidential. The objectives for developing the software have been to provide the user a means to quickly evaluate and/or design PAT systems and thereby, contribute to bringing a product to the market quickly, safely and at low cost. Some additional features have also been added to the ICAS-PAT software that has made the software more useful and user-friendly. These additional features of ICAS-PAT provide the options to open and analyze stored solved examples, to find the different applications of any monitoring tools, to search the knowledge/data stored in the knowledge base, to draw the open-loop as well as closed-loop process flow diagrams and to build reports in MS word documenting the design of a process monitoring and analysis system. Thus ICAS-PAT has a potentially wide range of applications in chemical, biochemical, food and pharmaceutical industries.

6.1.4. Case studies

Case studies have been developed to demonstrate the wide applicability of the developed framework, methodology and corresponding software (ICAS-PAT) in pharmaceutical, biochemical and food production processes. A successful application of the ICAS-PAT software for the design of a process monitoring and analysis system of a tablet manufacturing process demonstrates the use of the software in the pharmaceutical

industry. Also, applications to a fermentation and a cheese manufacturing process have been considered to highlight the applications of the design methodology and software in biochemical and food production processes, respectively.

6.1.5. Filled gaps in the current state of the art

The work done in this PhD project clearly shows that the stated gaps (see section 1.2) in the current state of the art are filled through this work as mentioned below:

- The developed systematic framework, methodology and corresponding software fulfill the requirements of systematic computer-aided methods and tools for design and implementation of process monitoring and analysis systems (PAT systems).
- The developed knowledge base and accompanying inference system fulfill the requirements of a systematic well-designed knowledge based system (KBS) consisting of the process knowledge as well as the knowledge on measurement methods and tools that can be employed for selection of appropriate process monitoring and analysis tools. The ontology of process monitoring and analysis systems is now available
- The developed model library fulfills the requirement of a systematic generic model library consisting of the mathematical models of different types of unit processes, sensors and controllers that can be employed to solve the general problems. Mathematical models of different unit processes involved in a tablet manufacturing process, a fermentation process, a cheese manufacturing process and a crystallization process are particularly important

6.2. Recommendations for future work

A systematic framework including the methods and tools needed for design of process monitoring and analysis systems (PAT systems) has been developed successfully in the course of this PhD project. However, there are still a lot of opportunities in this field for further developments. Some suggestions for future work are given below:

6.2.1. Extension of knowledge base and model library

To make the software more generic and applicable to an even wider range of industrial processes, the knowledge base and model library need to be further extended. Further extension of the knowledge base means simply adding new columns (horizontal

extension) and new rows (vertical extension) of additional data. Addition of new specifications for a monitoring tool is an example of horizontal extension while the addition of new processes in the knowledge base is an example of the vertical extension of the knowledge base. Similarly, extension of the model library means introduction of new models to the model library.

Presently, the main difficulty in the application of the models stored in the model library is that these models needs to be modified manually, according to the type of products, input, output materials and production process conditions. For example, a typical fermentation process model need to be modified according to the specific input/output materials (e.g., type of substrates and nutrients used), process conditions (e.g. aerobic or anaerobic), operation mode (e.g., batch or fed batch), type of product (e. g., insulin, curd). Therefore, a more generic model library consisting of more generic process models is needed, to make the software less dependent on user intervention. In the generic process model, the mathematical equations need to be written in a more general way, so that on imposing the different process conditions/assumptions, the required process model is created by the modeling tool.

6.2.2. New application examples

New case studies need to be developed to further demonstrate the application of the ICAS-PAT software for design of process monitoring and analysis systems. Inclusion of new case studies also assures that the relevant knowledge/data and models required for design of process monitoring and analysis system of those processes are included in the software.

6.2.3. Experimental/real process based validation

Presently process operational models are used to validate the designed process monitoring and analysis systems. However, the experimental/real process based validation of the monitoring and analysis systems designed through ICAS-PAT would be very interesting as well, and could be used as the final validation of the software.

6.2.4. Extension of ICAS-PAT to incorporate detailed control algorithms

Presently, the ICAS-PAT software is focused mostly on the process monitoring part rather than on achieving process control. A simple feedback control system has been implemented in the ICAS-PAT software to verify the closed-loop performance of the processes. However, the software can be extended to also incorporate a more extended control system design algorithm, needed to design/validate the product quality through implementation of more efficient and advanced control systems. In the control algorithm, options for steady state and dynamic analysis can be implemented. The steady state analysis can be developed in order to identify candidate operational scenarios and results could be analyzed using steady state sensitivity analysis. The results of this analysis can then be transferred to corresponding dynamic models to assess controllability performance using steady state and dynamic relative gain arrays and interaction between controlled and manipulated variables. Ideally, the extended version of ICAS-PAT should be capable of providing a product recipe that can be directly used on the manufacturing floor to produce the product with the desired quality.

6.2.5. Couple knowledge base with different sensor model classes

Information on monitoring tools (sensors) and their specifications are stored in the knowledge base that has been developed as part of this PhD project. The specifications (as provided by manufacturer) of the monitoring tools are considered as the basis for comparison and selection of monitoring tools for measurement of a specific variable. The monitoring tools are selected through a scoring system, which was also developed and implemented in the frame of this thesis. This method is robust and suitable for automatic selection of monitoring tools. However, the sensor performance could even be analyzed in more detail, by coupling the knowledge base with different sensor model classes implemented in the model library. Therefore, in the future a number of different sensor models could be developed and coupled with the knowledge base, such that the results obtained in the validation step reflect the real behavior of the sensor as well as possible.

6.2.6. Model-based computer-aided framework for identification of 'Design space'

The identification – and especially the documentation - of the design space[8] is mandatory in many of the regulated industries, for instance the pharmaceutical industry. Once the design space is defined, it is sufficient to verify that the operations are within the design space to guarantee the quality of the final product. Moving the process within the design space is not considered as a change while moving the process out of the design space is considered to be a process change which would normally initiate a regulatory post approval process change (FDA, 2007). Presently, these design spaces have been established based on experience and/or experimental approaches and their identification remains a challenging task in the PAT area. Therefore, a systematic model-based computer-aided framework could support the accurate and rapid identification of the design space of any operation, and could thereby contribute to achieving a shorter 'time to market' when developing pharmaceutical production processes

6.2.7. Virtual lab to develop and verify Quality by Design strategies

'Quality by Design (QbD)' is a systematic, scientific, risk-based, holistic and proactive approach to process and product development that begins with predefined objectives and emphasizes product and process understanding and process control (Lawrence, 2007). The QbD strategy is a systematic methodology which focuses on designing and developing formulation and manufacturing processes to ensure the predefined product quality.

Basically, the concept of PAT is a subset of the larger concept of 'Quality by Design'. The availability of on-line monitoring tools, efficient control systems, product and process design and optimization tools are some of the prerequisites for successful implementation of the Quality by Design strategies. However, the developed system typically covers a subset of the QbD strategy. An integrated computer-aided system, comprising of product and process design, on-line monitoring system design, control

[8] Design space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality (FDA, 2007)

system design and a dynamic optimization software is needed to implement the QbD strategy in an efficient way. Such an integrated system (virtual QbD lab) could be developed in the future.

The framework for the proposed virtual **'Quality by Design'** lab is shown in Figure 6.1. A **QbD Toolbox**, a **knowledge base** and a **model library** form the foundation for the proposed virtual QbD lab (see Figure 6.1, top). The starting point of a QbD strategy is to define the target product profile. The target product profile is a prospective and dynamic summary of the quality characteristics of a product (drug) that ideally will be achieved to ensure that the desired quality, and hence the safety and efficacy, of the product is realized (FDA, 2007). The relation between the properties of chemical species involved in the production and the target product profile need to be reconciled for efficient product development. The next step is rapid design of the process to manufacture the product. Conceptual process design is the initial stage of process development where an outline of the final manufacturing process can be quickly identified. Following product and process design, the critical quality attributes of product, raw materials and intermediates are identified together with the key process parameters. The critical quality attributes are a collection of physical, chemical, biological, or microbiological properties or characteristics that should be within specific limits or distributions to ensure the desired product quality (FDA, 2007). The relations among the process inputs, critical quality attributes and the target product profile lead to the establishment of a design space within which critical control (process) variables have influence. Finally, on-line monitoring tools for each control variable are selected and implemented within suitable control systems to complete the application of a QbD strategy. Additionally, the virtual QbD lab will provide product operational recipes that will allow in an efficient way to produce the product having the desired qualities with a minimum of difficulties. Using the methods and tools developed in this PhD-thesis as the starting point, the virtual lab for QbD would certainly be feasible.

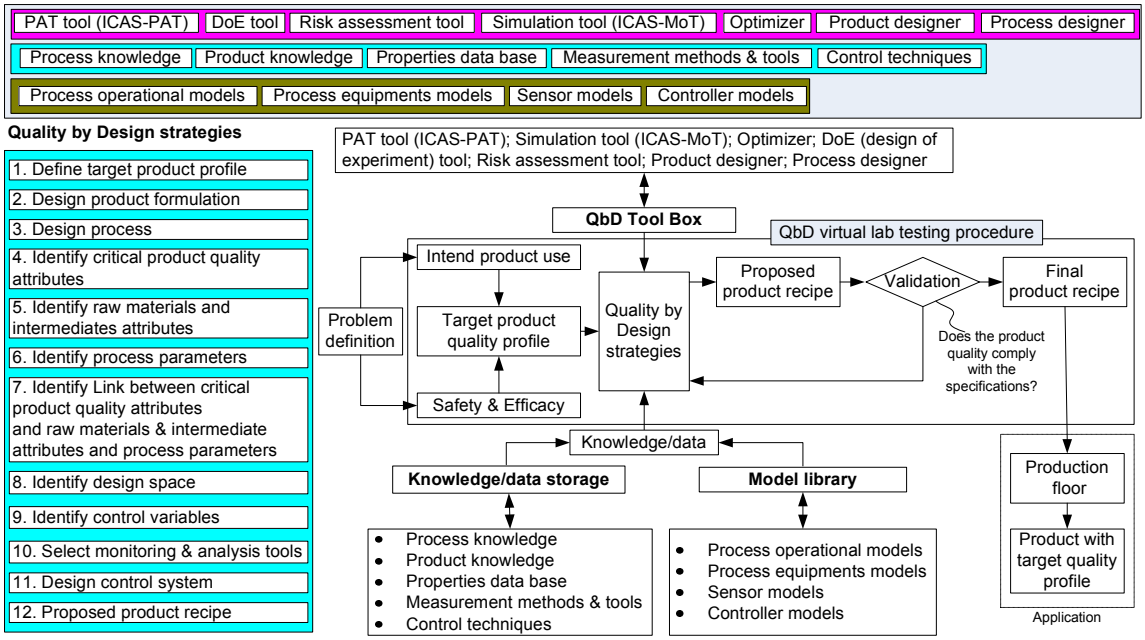


Figure 6.1 Overview of the 'Quality by Design' virtual laboratory

7.Appendix A: Process models

The process models required for design of process monitoring and analysis systems of considered processes are described in following sections.

Appendix A1: Fermentation process model

The fermentation process flowsheet is shown in Figure 2.10. Mixing tank, sterilizer and the fermentor are three major equipments (process points) involved in the process. The models for mixing, sterilization and the fermentation are described in the following sections:

A1. 1. Mixing process

Process description

The mixing process is shown in Figure 7.1. The ingredients that have to be mixed are added in a mixing tank equipped with a stirrer. After mixing, a homogeneous mixture is obtained.

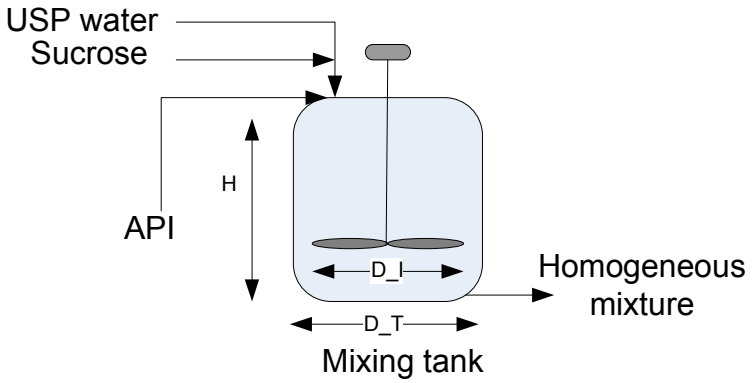


Figure 7.1: Mixing process

Assumptions

- Spatial distribution of homogeneity in the tank is neglected

- The effect of feed properties (concentration, density etc.) on the homogeneity is not considered

A1. 1. 1. Algebraic equations (explicit)

The homogeneity in the tank is calculated as follows (Ochieng & Onyango, 2008):

$$HO = \begin{cases} 1-\exp(-\lambda t); & t \le t_0 \\ 1-\exp(-\lambda t_0); & t > t_0 \end{cases} \quad (1.1.1)$$

The value of the parameter λ depends on the tank dimensions as given below:

$$\lambda = K.n\left(\frac{d_{str}}{d_{tank}}\right)^{\alpha}\left(\frac{d_{tank}}{T\_L}\right)^{\beta} \quad (1.1.2)$$

A1. 1. 2. Controller model

Homogeneity in the mixing tank (On-off controller)

The mixing time to achieve the required pre-specified homogeneity is calculated as follows:

$$t_{mix} = \frac{-\ln\left(1-HO_{set}\right)}{\lambda} \quad (1.1.3)$$

The control parameter (K_{switch}) is defined as follows (K_{switch}=0 for open-loop; K_{switch}=1 for closed-loop):

$$Z = t_{mix}K_{switch} + t_0\left(1-K_{switch}\right) \quad (1.1.4)$$

Based on the calculated mixing time the mixing process needs to be stopped when t > Z (i. e., n = 0).

$$n = \begin{cases} n_0; & t \le Z \\ 0 \ ; & t > Z \end{cases} \quad (1.1.5)$$

A1. 2. Sterilization process

Process description

The schematic diagram of a continuous sterilization system is shown in Figure 7.2 (adopted from Armenante & Leskowicz, 1990). The whole process can be divided into

sections: preheating section, heating section, holding section and cooling section. In the preheating section the heat content in the hot fermentation medium is utilized to heat the cold fermentation medium and then the preheated medium is heated up to its sterilization temperature in the heating section and kept at this temperature as it flows in the holding section where sterilization takes place. The sterilized medium is then passed through the pre-heater, and is afterwards cooled to its final temperature in a cooler and then fed to the fermentor.

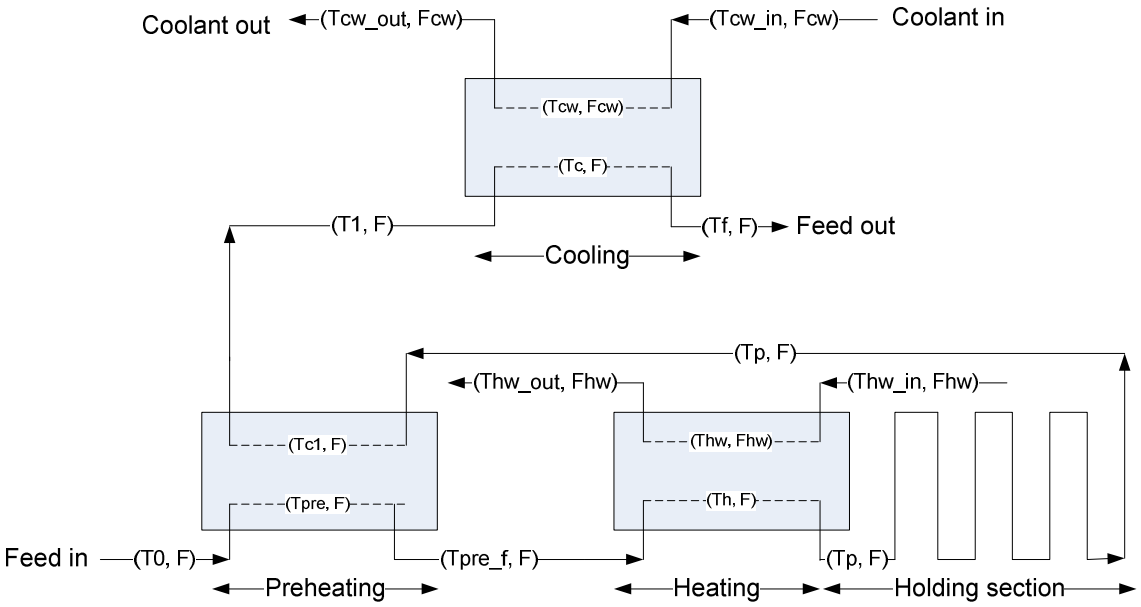


Figure 7.2: Schematic diagram of a continuous sterilization system (adopted from Armenante & Leskowicz, 1990)

Assumptions

- Heat capacity and density of fermentation medium is constant (independent of temperature)
- No loss of heat to the surroundings
- No accumulation of fermentation medium in the heating, holding and cooling sections
- Counter current double pipe heat exchangers are used

A1.2.1. Algebraic equations

The rate of thermal death for the contaminating organisms is assumed to follow first-order kinetics where the specific reaction kinetic rate, K_d, is a function of the Arrhenius constant K_{dO}, the activation energy E_d, and the sterilization temperature T, according to the following equation (Armenante & Leskowicz, 1990):

$$K_d = K_{do} \exp\left(-\frac{E_d}{R*T}\right) \tag{1.2.1}$$

For a generic sterilization process, a balance for the final number of surviving microorganisms per unit volume of fluid, N, can be written as:

$$\ln\left(\frac{N}{N_0}\right) = -\int_0^t K_d dt \tag{1.2.2}$$

Preheating section

The temperature of the fermentation medium in the pre-heater is given as follows:

$$T_{pre} = T_0 + b_{pre}\left(T_1 - T_0\right)t \tag{1.2.3}$$

b_{pre} is a function of the system. The time, t is counted from the instant the fluid element enters the heat exchanger (Armenante & Leskowicz, 1990).

$$b_{pre} = \frac{A_{pre}U_{pre}}{S_{pre}\rho_m C_{p_{mi}} l_{pre}}$$

For a double-pipe countercurrent heat exchanger b_{pre} becomes:

$$b_{pre} = \frac{2U_{pre}}{\rho_m r_{pre} C_{p_{mi}}} \tag{1.2.4}$$

The outlet temperature of the medium from the pre-heater is calculated as follows:

$$T_{pre\_f} = T_0 + b_{pre}\left(T_1 - T_0\right)t_{pre} \tag{1.2.5}$$

The outlet temperature of the hot medium is given as follows:

$$T_1 = T_p - \left(T_{pre\_f} - T_0\right) \tag{1.2.6}$$

The holding time in the pre-heater is calculated as follows:

$$t_{pre} = \frac{A_{pre}l_{pre}}{f} \tag{1.2.7}$$

The flow area in pre-heater is defined as follows:

$$A_{pre} = \pi r_{pre}^2 \tag{1.2.8}$$

Heating section

The temperature of the medium in the heat exchanger is given as follows:

$$T_h = T_{pre\_f} + \left(\frac{T_{pre\_f} - T_{hw\_out}}{a_h - 1} \right) \left[1 - \exp\left((a_h - 1) b_h t \right) \right] \tag{1.2.9}$$

Parameter a_h is defined as follows:

$$a_h = \frac{f \rho_m C_{p_m}}{f_{hw} \rho_w C_{p_w}} \tag{1.2.10}$$

b_h is the function of the system. The time, t is counted from the instant the fluid element enters the heat exchanger (Armenante & Leskowicz, 1990).

$$b_h = \frac{A_h U_h}{S_h \rho_m C_{p_{mi}} l_h}$$

For a double-pipe countercurrent heat exchanger b_h becomes:

$$b_h = \frac{2U_h}{\rho_m r_h C_{p_m}} \tag{1.2.11}$$

The outlet temperature of the fermentation media from the heating section is calculated as follows:

$$T_p = T_{pre\_f} + \left(\frac{T_{pre\_f} - T_{hw\_out}}{a_h - 1} \right) \beta_h \tag{1.2.12}$$

The outlet temperature of the heating fluid is calculated as follows

$$T_{hw\_out} = \frac{c_h T_{pre\_f} - T_{hw\_in}}{c_h - 1} \tag{1.2.13}$$

Where c is defined as follows:

$$c_h = \frac{a_h \beta_h}{a_h - 1} \tag{1.2.14}$$

$$\beta_h = 1 - \exp\left((a_h - 1) b_h t_h \right) \tag{1.2.15}$$

The residence time (t_h) of fermentation media in the heater is defined as follows:

$$t_h = \frac{A_h l_h}{f} \tag{1.2.16}$$

The flow area in heater is defined as follows:

$$A_h = \pi r_h^2 \tag{1.2.17}$$

Holding section

The temperature of fermentation media in the holding section is assumed to be constant and it will be equal to the outlet temperature from the heater. The holding time is calculated as follows:

$$t_{hold} = \frac{A_{hold} l_{hold}}{f} \tag{1.2.18}$$

The flow area of the pipe in the holding section is defined as follows:

$$A_{hold} = \pi r_{hold}^2 \tag{1.2.19}$$

Cooling section

The temperature of the fermentation media in the heat exchanger is given as follows:

$$T_c = T_1 + \left(\frac{T_1 - T_{cw\_out}}{a_c - 1} \right) \left[1 - \exp\left((a_c - 1) b_c t \right) \right] \tag{1.2.20}$$

The parameter a_c is defined as follows:

$$a_c = \frac{f \rho_m C_{p_m}}{f_{cw} \rho_w C_{p_w}} \tag{1.2.21}$$

b_c is the function of the system. The time, t is counted from the instant the fluid element enters the heat exchanger (Armenante & Leskowicz, 1990).

$$b_c = \frac{A_c U_c}{S_c \rho_m C_{p_m} l_c}$$

For a double-pipe countercurrent heat exchanger b_c becomes:

$$b_c = \frac{2U_c}{\rho_m r_c C_{p_m}} \tag{1.2.22}$$

The outlet temperature of the media from the cooler is calculated as follows:

$$T_f = T_1 + \left(\frac{T_1 - T_{cw\_out}}{a_c - 1} \right) \beta_c \tag{1.2.23}$$

The outlet temperature of the cooling liquid is calculated as follows

$$T_{cw\_out} = \frac{c_c T_1 - T_{cw\_in}}{c_c - 1} \tag{1.2.24}$$

Where c_c is defined as follows:

$$c_c = \frac{a_c \beta_c}{a_c - 1} \tag{1.2.25}$$

$$\beta_c = 1 - \exp\left((a_c - 1) b_c t_c\right) \tag{1.2.26}$$

The residence time (t_c) of fermentation media in the cooler is defined as follows:

$$t_c = \frac{A_c l_c}{f} \tag{1.2.27}$$

The flow area in cooler is defined as follows:

$$A_c = \pi r_c^2 \tag{1.2.28}$$

The temperature of the fermentation media throughout the process is defined as follows:

$$T = \begin{cases} T_{pre}; \text{ if } t \le t_{pre} \\ T_h; \text{ if } t_{pre} < t \le \left(t_{pre} + t_h\right) \\ T_p; \text{ if } \left(t_{pre} + t_h\right) < t \le \left(t_{pre} + t_h + t_{hold}\right) \\ T_{c1}; \text{ if } \left(t_{pre} + t_h + t_{hold}\right) < t \le \left(t_{pre} + t_h + t_{hold} + t_{c1}\right) \\ T_c; \text{ if } \left(t_{pre} + t_h + t_{hold} + t_{c1}\right) < t \le \left(t_{pre} + t_h + t_{hold} + t_{c1} + t_c\right) \\ T_f; \text{ if } t > \left(t_{pre} + t_h + t_{hold} + t_{c1} + t_c\right) \end{cases} \tag{1.2.29}$$

The holding time of hot fluid in the pre-heater is defined as follows:

$$t_{c1} = \frac{A_{c1} l_{pre}}{f} \tag{1.2.30}$$

The flow area is defined as follows:

$$A_{c1} = \pi\left(r_{c1}^2 - r_{pre}^2\right) \tag{1.2.31}$$

A1.2.2. Controller model

Main stream temperature in holding section (PI controller)

The deviation of measured temperature from the set point is calculated as follows:

$$error_{T_p} = T_{p\_set} - T_p \tag{1.2.32}$$

The heating/cooling fluid flow rate (manipulated variable) is calculated as follows:

$$fhw - fhw\_0 = K_C^{T_p} error_{T_p} + K_I^{T_p} \int_0^t error_{T_p} dt \tag{1.2.33}$$

Final main stream temperature (outlet from cooling section) (PI controller)

The deviation of measured temperature from the set point is calculated as follows:

$$error_{T_f} = T_{f\_set} - T_f \tag{1.2.34}$$

The heating/cooling fluid flow rate (manipulated variable) is calculated as follows:

$$fcw - fcw\_0 = K_C^{T_f} error_{T_f} + K_I^{T_f} \int_0^t error_{T_f} dt \tag{1.2.35}$$

A1. 3. Fermentation process

Process description

The process flowsheet is shown in Figure 7.3. The sterilized medium is added to the fermentor. There is continuous supply of air and ammonia. Biomass is obtained after fermentation.

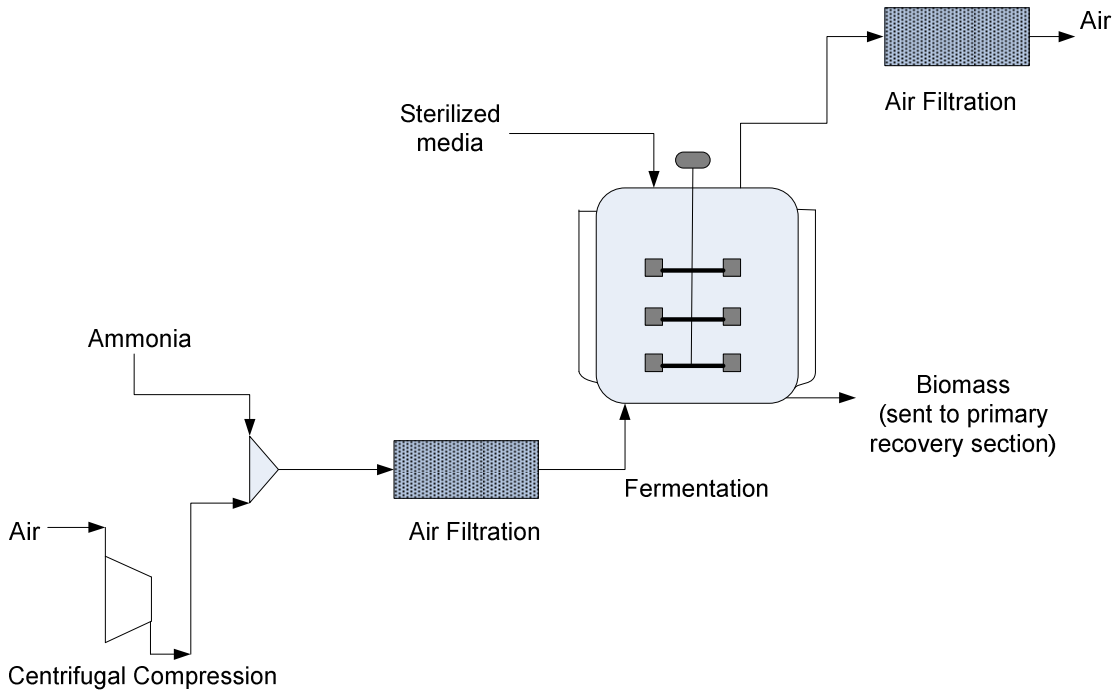


Figure 7.3: Fermentor

Assumptions

- Death rate of cells is negligible
- Spatial distribution of concentrations in the fermentor is not considered

- Spatial distribution of temperature in the fermentor is not considered
- Coolant temperature is uniform in the cooling jacket

A1. 3. 1. Algebraic equations (explicit)

Power dissipation

Power dissipation due to agitation can be expressed as a function of power number (P_n), impeller speed (n), impeller diameter (d_i) and fluid density (ρ_b) as follows (Angst and Kraume, 2006):

$$Pow = P_n n^3 d_i^5 \rho_b \tag{1.3.1}$$

Homogeneity

An intermediate parameter (λ) relating homogeneity with the fermentor dimensions is given as below:

$$\lambda = K.n\left(\frac{d_i}{d_{tank}}\right)^{\alpha}\left(\frac{d_{tank}}{T\_L}\right)^{\beta} \tag{1.3.2}$$

The homogeneity in the fermentor is calculated as follows (Ochieng & Onyango, 2008):

$$HO = 1-\exp(-\lambda t) \tag{1.3.3}$$

Gas liquid mass transfer coefficient

The gas liquid mass transfer coefficient for oxygen can be correlated with the power density (Pow/V) and the superficial gas velocity (u_{O_2}) as follows (Linek et al., 1987):

$$kla_{O_2} = 0.00495\left(\frac{Pow}{V}\right)^{0.593} u_{o_2}^{0.4} \tag{1.3.4}$$

The gas liquid mass transfer coefficient for CO_2 depends on the gas liquid mass transfer coefficient of oxygen:

$$kla_{CO_2} = kla_{O_2}\left(\frac{C_{CO_2}}{C_{O_2}}\right)^{0.5} \tag{1.3.5}$$

Similar to the gas liquid mass transfer coefficient of oxygen, the gas liquid mass transfer coefficient for ammonia is also correlated with the power density (Pow/V) and the superficial velocity (u_{NH_3}) (Linek et al., 1987):

$$kla_{NH_3} = 0.00495\left(\frac{Pow}{V}\right)^{0.593} u_{NH_3}^{0.4} \quad (1.3.6)$$

Specific cell growth rate

The dependency of the specific cell growth rate (μ) on the dissolved oxygen concentration (C_{O_2}) and the nutrient concentrations (glucose (C_S), ammonia (C_{NH_3}) and phosphoric acid ($C_{H_3PO_4}$)) was incorporated in the model as follows:

$$\mu = \mu_{max}\frac{C_S}{(k_s + C_S)}\frac{C_{O_2}}{(k_{O_2} + C_{O_2})}\frac{C_{NH_3}}{(k_{NH_3} + C_{NH_3})}\frac{C_{H_3PO_4}}{(k_{H_3PO_4} + C_{H_3PO_4})} \quad (1.3.7)$$

Maintenance coefficient

A fraction of the substrate and dissolved oxygen which are taken up by the *E. coli* cells is assumed to be consumed for cell maintenance. The dependency of the maintenance coefficient on the substrate (C_S) and dissolved oxygen (C_{O_2}) concentration can be expressed as follows:

$$m_s = \frac{m_{s_1} C_S C_{O_2}}{(k_s + C_S)(k_{O_2} + C_{O_2})} \quad (1.3.8)$$

Biomass decay

The specific biomass decay can be expressed as a function of the dissolved oxygen concentration (C_{O_2}), as follows:

$$b_x = b_{x_1}\frac{C_{O_2}}{k_{O_2} + C_{O_2}} \quad (1.3.9)$$

Oxygen saturation concentration

The temperature is inversely related to the solubility of dissolved oxygen. As a consequence, the driving force for mass transfer ($C^*_{O_2} - C_{O_2}$) is reduced with increasing temperature. Oxygen solubility in pure water as a function of temperature has been included in the model by the following equation (Truesdale et al., 1955):

$$C^*_{O_2} = 14.161 - 0.3943T_b + 0.007714T_b^2 - 0.0000646T_b^3 \quad (1.3.10)$$

Specific oxygen uptake rate

The specific oxygen uptake rate (oxygen uptake rate per unit biomass concentration) depends on the specific cell growth rate (μ) and the yield coefficient for oxygen (Y_{XO_2}) as given below:

$$q_{O_2} = \frac{\mu}{Y_{XO_2}} \tag{1.3.11}$$

Rate of oxygen consumption for cell growth rate

The oxygen uptake rate per unit volume of broth can be expressed as follows:

$$Q_{O_2} = q_{O_2} C_X \tag{1.3.12}$$

Specific CO_2 production rate

The specific CO_2 production rate (rate of production per unit biomass concentration) can be expressed as a function of the specific cell growth rate and the yield coefficient of CO_2 as follows:

$$q_{CO_2} = \frac{\mu}{Y_{XCO_2}} \tag{1.3.13}$$

Rate of CO_2 production by cells

The rate of carbon dioxide production due to the fermentation process can be expressed as a function of the biomass concentration as follows:

$$Q_{CO_2} = q_{CO_2} C_X \tag{1.3.14}$$

pH

pH and all relevant chemical equilibrium were modeled as described in Sin et al. (2008). pH can be expressed as a function of the hydrogen ion concentration present in the broth:

$$pH = -\log\left(C_H^+\right) \tag{1.3.15}$$

Carbon dioxide and bicarbonate equilibrium

The dissolved CO_2 can react with the water to form H_2CO_3 (carbonic acid). The carbonic acid can dissociate into a proton and a bicarbonate ion, and the bicarbonate ion can subsequently dissociate into a proton and a carbonate ion by subsequent equilibrium reactions (Descoins et al., 2006).

The rate of CO_2 dissociation into bicarbonate can be expressed as follows:

$$r_{CO_2} = kf_{CO_2}\left(C_{CO_2} - \frac{C_{H_2CO_3}}{K_{CO_2}}\right) \quad (1.3.16)$$

Equilibrium between the carbonate and bicarbonate ions is assumed (Descoins et al., 2006), and the rate of carbonic acid dissociation into the bicarbonate ion can be expressed as follows:

$$r_{H_2CO_3} = kf_{H_2CO_3}\left(C_{H_2CO_3} - \frac{C_{HCO_3^-}C_{H^+}}{K_{H_2CO_3}}\right) \quad (1.3.17)$$

Equilibrium between bicarbonate ion and carbonate ion is also assumed and the rate of bicarbonate ion dissociation can be expressed as follows:

$$r_{HCO_3^-} = kf_{HCO_3^-}\left(C_{HCO3^-} - \frac{C_{CO_3^{--}}C_{H^+}}{K_{HCO_3^-}}\right) \quad (1.3.18)$$

Phosphate dissociation

Phosphoric acid (H_3PO_4) is used as one of the nutrients for the fermentation process. It is assumed that phosphoric acid can dissociate and form phosphate ions through the following set of equilibrium reactions (Musvoto et al., 2000):

$H_3PO_4 \Leftrightarrow H_2PO_4^- + H^+$ $\quad K_{P1}$

$H_2PO_4^- \Leftrightarrow HPO_4^{--} + H^+$ $\quad K_{P2}$

$HPO_4^{--} \Leftrightarrow PO_4^{3-} + H^+$ $\quad K_{P3}$

The rate of phosphoric acid dissociation can be expressed as follows:

$$r_{H_3PO_4} = kf_{H_3PO_4}\left(C_{H_3PO_4} - \frac{C_{H_2PO_4^-}C_{H^+}}{K_{H_3PO_4}}\right) \quad (1.3.19)$$

The rate of dihydrogen phosphate and hydrogen phosphate dissociation can be expressed as follows:

$$r_{H_2PO_4^-} = kf_{H_2PO_4^-}\left(C_{H_2PO_4^-} - \frac{C_{HPO_4^{--}}C_{H^+}}{K_{H_2PO_4^-}}\right) \quad (1.3.20)$$

$$r_{HPO_4^{--}} = kf_{HPO_4^{--}} \left(C_{HPO_4^{--}} - \frac{C_{PO_4^{---}} C_{H^+}}{K_{HPO_4^{--}}} \right) \quad (1.3.21)$$

Ammonia dissociation

A chemical reaction also occurs when ammonia dissolves in water. In aqueous solution, ammonia acts as a base, acquiring hydrogen ions from H_2O to yield ammonium and hydroxide ions (Shakhashiri, 2007). Equilibrium between ammonia and the ammonium ion is assumed (Musvoto et al., 2000). The rate of ammonia dissociation is equal to the rate of ammonium ion formation, which can be expressed as follows:

$$r_{NH_3} = -kf_{NH_4^+} \left(C_{NH_4^+} - \frac{C_{NH_3} C_{H^+}}{K_{NH_4^+}} \right) \quad (1.3.22)$$

Sulfate dissociation

Equilibrium between sulfuric acid (a strong acid), hydrogen sulfate ions and sulfate ions is assumed. The rate of dissociation of sulfuric acid can be expressed as follows:

$$r_{H_2SO_4} = kf_{H_2SO_4} \left(C_{H_2SO_4} - \frac{C_{HSO_4^-} C_{H^+}}{K_{H_2SO_4}} \right) \quad (1.3.23)$$

The rate of hydrogen sulfate ion dissociation can be expressed as follows:

$$r_{HSO_4^-} = kf_{HSO_4^-} \left(C_{HSO_4^-} - \frac{C_{SO_4^{--}} C_{H^+}}{K_{HSO_4^-}} \right) \quad (1.3.24)$$

Water dissociation

The rate of water dissociation can be expressed as follows:

$$r_{H_2O} = kf_w \left(1 - \frac{C_{H^+} C_{OH^-}}{K_w} \right) \quad (1.3.25)$$

A1. 3.2. Differential equations

Accumulation of carbonic acid

The difference between the formation and the dissociation rate of carbonic acid gives the rate of change of the carbonic acid concentration during the fermentation process:

$$\frac{dC_{H_2CO_3}}{dt} = r_{CO_2} - r_{H_2CO_3} \quad (1.3.26)$$

Accumulation of bicarbonate ion

The rate of change of the bicarbonate ion concentration can be obtained by subtracting the bicarbonate ion dissociation rate from the carbonic acid dissociation rate. The rate of change of the carbonate ion concentration is equal to the bicarbonate dissociation rate.

$$\frac{dC_{HCO_3^-}}{dt} = r_{H_2CO_3} - r_{HCO_3^-} \tag{1.3.27}$$

$$\frac{dC_{CO_3^{--}}}{dt} = r_{HCO_3^-} \tag{1.3.28}$$

Accumulation of phosphate ions concentration

The difference of the dissociation rates of phosphoric acid and the dihydrogen phosphate ion gives the accumulation rate of the dihydrogen phosphate ion as follows:

$$\frac{dC_{H_2PO_4^-}}{dt} = r_{H_3PO_4} - r_{H_2PO_4^-} \tag{1.3.29}$$

The rate of accumulation of the hydrogen phosphate ion is obtained by subtracting the rate of dissociation of the hydrogen phosphate ion from the dissociation rate of the dihydrogen phosphate ion as given follows:

$$\frac{dC_{HPO_4^{--}}}{dt} = r_{H_2PO_4^-} - r_{HPO_4^{--}} \tag{1.3.30}$$

The rate of phosphate ion accumulation is the same as the rate of the hydrogen phosphate ion dissociation, as follows:

$$\frac{dC_{PO_4^{---}}}{dt} = r_{HPO_4^{--}} \tag{1.3.31}$$

Accumulation of ammonium ion concentration

The rate of ammonium ion accumulation is equal to the rate of dissociation of the ammonia as follows:

$$\frac{dC_{NH_4^+}}{dt} = r_{NH_3} \tag{1.3.32}$$

Accumulation of sulfate ion concentration

The rate of accumulation of the hydrogen sulfate ion is obtained by subtracting the dissociation rate of the hydrogen sulfate ion from the dissociation rate of sulfuric acid as follows:

$$\frac{dC_{HSO_4^-}}{dt} = r_{H_2SO_4} - r_{HSO_4^-} \tag{1.3.33}$$

The rate of accumulation of the sulfate ion is equal to the rate of dissociation of the hydrogen sulfate ion, which can be given as follows:

$$\frac{dC_{SO_4^{--}}}{dt} = r_{HSO_4^-} \tag{1.3.34}$$

Rate of change of biomass concentration

The change in the biomass concentration during the fermentation process is governed by the following equation (Doran, 2006):

$$\frac{dC_x}{dt} = \mu C_X \tag{1.3.35}$$

Rate of change of substrate concentration

The substrate is mainly consumed for biomass production but some amount of it is also used for maintenance. The consumption rate of substrate can be expressed as follows (Doran, 2006):

$$\frac{dC_s}{dt} = -\left(\frac{\mu}{Y_{XS}} + m_S\right) C_X \tag{1.3.36}$$

Rate of change of dissolved oxygen concentration

The oxygen in gaseous form is supplied to the fermentor. The gaseous oxygen then dissolved to the liquid (rate of dissolution= $kla_{O_2}(C^*_{o_2} - C_{o_2})$). Some quantity of dissolved oxygen ($q_{O_2}C_X$) is assumed to be used for cell growth, some quantity for maintenance (m_sC_X) and some quantity (b_xC_X) for biomass decay. The rate of accumulation of dissolved oxygen can be expressed as follows:

$$\frac{dC_{O_2}}{dt} = kla_{O_2}\left(C^*_{O_2} - C_{O_2}\right) - q_{O_2}C_X - m_sC_X - b_xC_X \tag{1.3.37}$$

Rate of change of dissolved CO_2 concentration

CO_2 is produced through biomass production, maintenance and biomass decay. A fraction of it can be converted into carbonic acid, and another fraction can be removed by aeration. The rate of accumulation of dissolved CO_2 can be expressed as follows:

$$\frac{dC_{CO_2}}{dt} = q_{CO_2}C_X + m_s C_X + b_x C_X + kla_{CO_2}\left(C^*_{CO_2} - C_{CO_2}\right) - r_{CO_2} \tag{1.3.38}$$

Rate of change of phosphoric acid concentration

Phosphoric acid is used as a nutrient for the biomass production. Some phosphoric acid is assumed to be regenerated by biomass decay. The rate of accumulation of phosphoric acid can be expressed as follows:

$$\frac{dC_{H_3PO_4}}{dt} = \frac{(bx-\mu)}{Y_{XH_3PO_4}}C_X - r_{H_3PO_4} \tag{1.3.39}$$

Rate of change of ammonia concentration

Ammonia is used as a nutrient for the biomass production. Some ammonia is assumed to be regenerated as a consequence of biomass decay, and a considerable amount of ammonia can be present in the form of ammonium ions. An external supply of ammonia is assumed for pH control, where the supplied gaseous form of ammonia is converted to the liquid form. The rate of accumulation of ammonia can be expressed as follows:

$$\frac{dC_{NH_3}}{dt} = \frac{(bx-\mu)}{Y_{XNH_3}}C_X + kla_{NH_3}\left(C^*_{NH_3} - C_{NH_3}\right) - r_{NH_3} \tag{1.3.40}$$

Rate of change of sulfuric acid concentration

Sulfate is consumed as an essential nutrient during biomass production. A fraction of it can be released again as a consequence of biomass decay. The equilibrium between sulfuric acid, hydrogen sulfate and sulfate ions is assumed. The rate of accumulation of sulfate can be expressed as follows:

$$\frac{dC_{H_2SO_4}}{dt} = \frac{(bx-\mu)}{Y_{XH_2SO_4}}C_X - r_{H_2SO_4} \tag{1.3.41}$$

Rate of change of hydroxyl ion concentration

The dissociation of water in hydroxyl and hydrogen ions is assumed. The rate of change of the hydroxyl ion concentration is given as follows:

$$\frac{dC_{OH^-}}{dt} = r_{H_2O} \qquad (1.3.42)$$

Rate of change of hydrogen ion (proton) concentration

Protons are formed in the medium, due to the dissociation of salts, salt ions and water. Some fraction of these protons can be combined with ammonia to form the ammonium ion. The rate of change of the hydrogen ion concentration can be expressed as follows:

$$\frac{dC_{H^+}}{dt} = \left(r_{H_3PO_4} + r_{H_2PO_4^-} + r_{HPO_4^{--}}\right) + \left(r_{H_2SO_4} + r_{HSO_4^-}\right) + \left(r_{H_2CO_3} + r_{HCO_3^-}\right) + r_{H_2O} - r_{NH_3} \qquad (1.3.43)$$

Fermentor temperature

In the fermentation process heat is generated due to the fermentation process itself and due to agitation. Some heat is lost directly to the surroundings through the fermentor walls, some is lost due to evaporation of water into the air stream and some heat is also lost as a sensible heat loss to the air stream (Cooney et al., 1968). Water is used as a coolant to maintain the fermentor temperature. The rate of change of fermentor temperature can be expressed as follows:

$$\rho_b V C_{p_b} \frac{dT_b}{dt} = -U_1 A_1 \left(T_b - T_w\right) + V\left(H_{gr} + H_{ag} - H_{surr} - H_{evp} - H_{sen}\right) \qquad (1.3.44)$$

Coolant temperature

The coolant is circulated in e.g. a coil, and exchanges the heat with the fermentation broth. Finally, some heat is lost to the surroundings. A simplified expression for heat exchange between coolant and vessel contents in the jacketed vessel has been adopted from the literature (Quintana-Hernàndez et al., 2004). The rate of change of coolant temperature can be expressed as follows:

$$\rho_w C_{p_w} V_w \frac{dT_w}{dt} = \rho_w f_{w_{in}} C_{p_w} \left(T_{w_{in}} - T_w\right) + U_1 A_1 \left(T_b - T_w\right) + U_2 A_2 \left(T_{surr} - T_w\right) \qquad (1.3.45)$$

A1. 3. 3. Controller model

Dissolved oxygen concentration (PI controller)

The deviation of the measured DO concentration from the set point is calculated as follows:

$$error_{O_2} = C_{O_2\_set} - C_{O_2} \tag{1.3.46}$$

The setting of the air flow rate (manipulated variable) is calculated as follows:

$$u_{O_2} - u_{O_2\_0} = 3600\left(K_C^{O_2} error_{O_2} + K_I^{O_2} \int_0^t error_{O_2} dt \right) \tag{1.3.47}$$

The right hand side of the above equation is multiplied by 3600 to adjust it to the units of the air velocity (m/s).

pH (PI controller)

The deviation of the measured pH from the set point is calculated as follows:

$$error_{pH} = pH_{set} - pH \tag{1.3.48}$$

The setting of the ammonia flow rate (manipulated variable) is calculated as follows:

$$u_{NH_3} - u_{NH_3\_0} = 3600\left(K_C^{pH} error_{pH} + K_I^{pH} \int_0^t error_{pH} dt \right) \tag{1.3.49}$$

The right hand side of the above equation is multiplied by 3600 to adjust it to the units of the ammonia flow rate (m/s).

Temperature (PI controller)

The deviation of measured temperature from the set point is calculated as follows:

$$error_{T_b} = T_{b\_set} - T_b \tag{1.3.50}$$

The coolant flow rate (manipulated variable) is calculated as follows:

$$f_{w_{in}} - f_{w_{in}\_0} = K_C^{T_b} error_{T_b} + K_I^{T_b} \int_0^t error_{T_b} dt \tag{1.3.51}$$

Homogeneity (PI controller)

The deviation of measured homogeneity from the set point is calculated as follows:

$$error_{HO} = HO_{set} - HO \tag{1.3.52}$$

The stirrer speed (manipulated variable) is calculated as follows:

$$n - n_0 = K_C^{HO} error_{HO} + K_I^{HO} \int_0^t error_{HO} dt \tag{1.3.53}$$

Appendix A2. Tablet manufacturing process model

The software used the following model to generate the data needed for the design of a PAT system for the tablet manufacturing process:

A2. 1. Mixing process

The mixing process model is described in appendix A1 (section A.1.1)

A2. 2. Milling process

Process description

A batch wet milling machine is shown in Figure 7.4. The feed is introduced batchwise in the machine and after the milling time the size of the particles is reduced to nano scale.

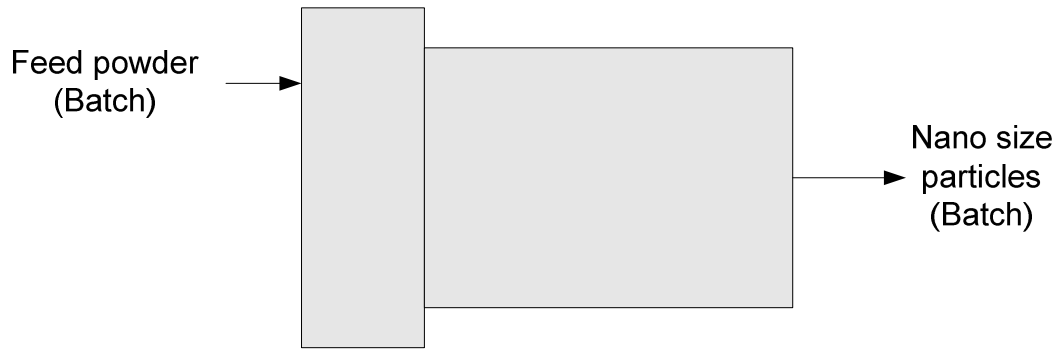


Figure 7.4: Milling process

Assumptions

- The particle size reduction due to attrition is negligible
- The spatial distribution of particle size is neglected

A2. 2. 1. Algebraic equations (explicit)

Mass of one particle in the size interval i is given as follows (Hogg, 1999):

$$M_{p\_i} = \rho K_v x_i^3 \qquad (2.2.1)$$

The mass of solids in the feed is calculated as follows:

$$M_{s\_F} = X_s M_F \tag{2.2.2}$$

The total mass of the particles in the size interval i is given as follows:

$$M_i = X_i M_{s\_F} \tag{2.2.3}$$

The number of particles in the size interval i is calculated as follows:

$$N_{p\_i} = \frac{M_i}{M_{p\_i}} \tag{2.2.4}$$

The total number of particles in the milling machine is given as follows:

$$N_{p\_total} = \sum_{i=1}^{z} N_{P\_i} \tag{2.2.5}$$

The average size of the particles in the milling machine is calculated as follows:

$$L_{avg} = \frac{\sum_{i=1}^{z} N_{P\_i} x_i}{N_{P\_total}} \tag{2.2.6}$$

The breakage parameter b_{ij} (primary breakage distribution), is defined as below (Hogg, 1999):

$$b_{ij} = 1 - \exp\left[-\left\{ \frac{x_i}{x_{cr}} \left(\frac{x_j - x_{cr}}{x_j - x_i} \right)^{\gamma} \right\} \right] \tag{2.2.7}$$

The critical rotational speed is given as follows (McCabe et al., 2005):

$$n_{cr} = \frac{1}{2\pi} \sqrt{\frac{g}{R-r}} \tag{2.2.8}$$

The ratio between the operational speed of the mill and the critical speed of the mill (Φ_{cr}) is given as below:

$$\Phi_{cr} = \frac{n}{n_{cr}} \tag{2.2.9}$$

The parameter a depends on the rotational speed of the mill as follows (Austin & Brame, 1983):

$$a = \begin{cases} \dfrac{k\left(\Phi_{cr} - 0.1\right)}{1 + \exp\left[15.7\left(\Phi_{cr} - 0.95\right)\right]} \; ; & \Phi_{cr} > 0.1 \\ 0 \; ; & \Phi_{cr} \le 0.1 \end{cases} \tag{2.2.10}$$

The specific rate of breakage is calculated as (Austin & Brame, 1983; Hogg, 1999):

$$S_i = a\left(\frac{S\left(\frac{x_i}{x_1}\right)^{\alpha}}{1+\left(\frac{x_i}{x_m}\right)^{\beta}}\right) \tag{2.2.11}$$

A2. 2. 2. Differential equations

By performing a rate–mass balance on material in each size interval i present at time t in a mill, the mass fraction of particles of size x_i is given as follows (Tangsathitkulchai, 2002):

$$\frac{dw_i}{dt} = -S_i w_i + \sum_{j=1}^{i-1} b_{ij} S_j w_j; \quad \text{n} \geq \text{i} \geq \text{j} \tag{2.2.12}$$

A2. 2. 3. Controller model

Particle size (On-off controller)

The deviation from the set point is calculated as follows:

$$error_L = L_{avg\_set} - L_{avg} \tag{2.2.13}$$

The control parameter (K_{switch}) is defined as follows (K_{switch}=0 for open-loop and 1 for closed-loop):

$$Z = (1 - K_{switch})\, n_0 \tag{2.2.14}$$

Based on the calculated deviation from the set point, a decision is taken on whether or not to stop the milling process (i. e. stop means n = 0).

$$n = \begin{cases} n_0; & \text{error}_\text{L} > 0 \\ \text{Z} \;\; ; & \text{error}_\text{L} \leq 0 \end{cases} \tag{2.2.15}$$

A2. 3. Granulation process

Process description

The fluidized bed granulator is shown in Figure 7.5 (adopted from de Jong (1991)). As shown in this figure, the heated air is used as the fluidization medium. Above the powder bed, there is a nozzle by which the binder solution is atomized by adding air. A shaking filter is used to prevent the entrainment of the fine particles.

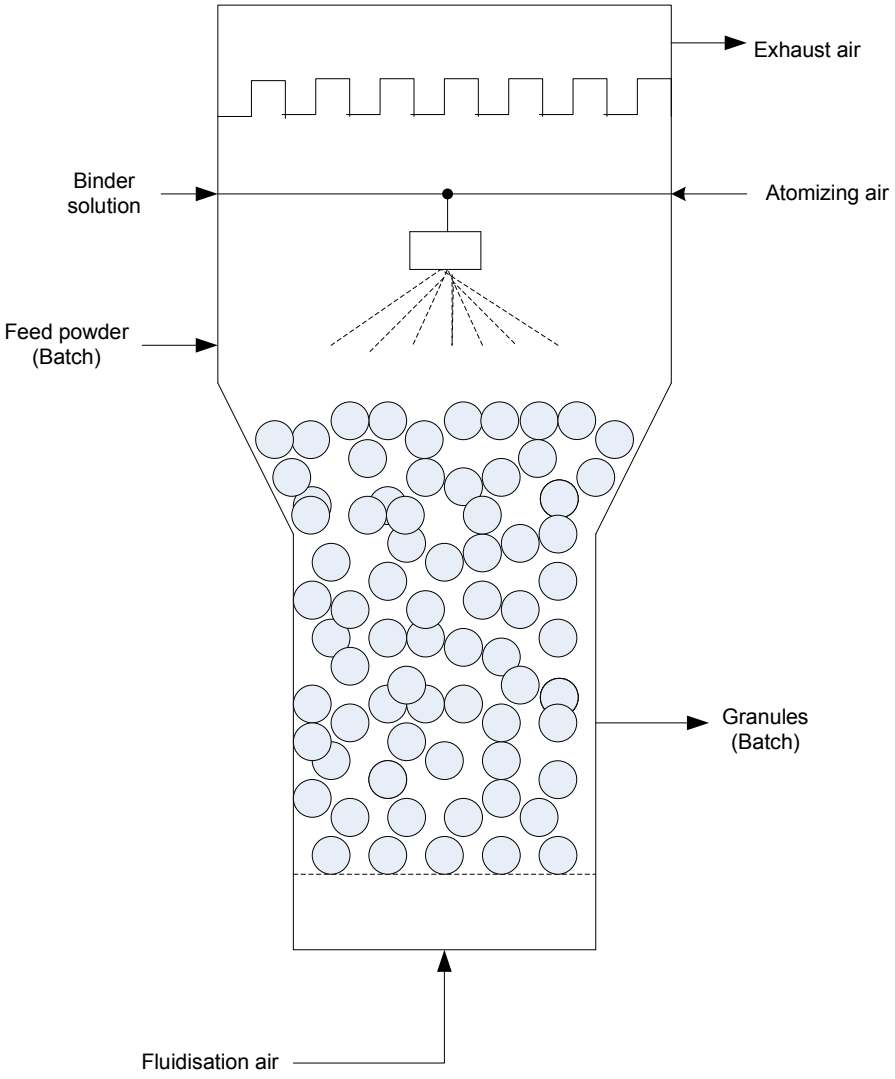


Figure 7.5: Fluidized bed granulation process
(adopted from de Jong (1991))

Assumptions

- Collision frequency and collision efficiency factors are constant (independent of agglomerate size i.e. of the extent of agglomeration)
- Uniform particle size of the feed powder
- Uniform size of granules in the granulator (size distribution is not considered)
- Powder particles and granules are spherical in shape
- Temperature is uniform in the granulator
- Constant growth rate of granules

A2. 3. 1. Algebraic equations (explicit)

The total number of initial particles in the powder is calculated as follows:

$$N_0 = \frac{6M_0}{\pi d_0^3 \rho_s} \tag{2.3.1}$$

The coagulation half-time is given as follows (Hogg, 1992):

$$\tau = \frac{2}{KN_0} \tag{2.3.2}$$

The number of granules after time t is given by (Hogg, 1992):

$$N = \frac{N_0}{1 + t/\tau} \tag{2.3.3}$$

The water fraction in the binder solution is calculated as:

$$F_{bw} = X_{bw} F_b \tag{2.3.4}$$

The total mass of liquid in the granulator is given by:

$$M_T = M_b + M_w + M_0 \tag{2.3.5}$$

The temperature in the fluidized bed is defined as:

$$T = \frac{h}{M_T C_{PT}} \tag{2.3.6}$$

The mass flow rate of air is related to the volumetric air flow rate:

$$F_{a\_in} = f_{a\_in} \rho_g \tag{2.3.7}$$

The mass flow rate of exhaust air is related to the volumetric air flow rate:

$$F_{a\_out} = f_{a\_out} \rho_{g\_ex} \tag{2.3.8}$$

The rate of heat loss to the surroundings through the granulator wall is given by:

$$Q_S = UA_S \left(T - T_S\right) \tag{2.3.9}$$

The enthalpy flow associated with the binder flow is obtained as:

$$h_b = F_b C_{Pb} \left(T_b - T\right) \tag{2.3.10}$$

The enthalpy flow associated with the outlet air is given by:

$$h_{a\_out} = F_{a\_out} C_{Pa\_out} \left(T_{a\_out} - T\right) \tag{2.3.11}$$

The enthalpy flow due to the inlet air is calculated as follows:

$$h_{a\_in} = F_{a\_in} C_{Pa\_in} \left(T_{a\_in} - T\right) \tag{2.3.12}$$

The saturation pressure is calculated by means of the Antoine equation:

$$P_{sat} = B_1 - \frac{B_2}{T + B_3} \tag{2.3.13}$$

The mass fraction of moisture in a granule is calculated as follows:

$$X_w = \frac{M_w}{M_T} \tag{2.3.14}$$

The relation between the relative humidity and the moisture content is calculated (Peglow et al., 2007):

$$X_w = X_1 \left(\frac{\Phi c}{1-\Phi} \right) \left(\frac{1-\left(N_l+1\right)\Phi^{N_l} + N\Phi^{N_l+1}}{1+\left(c-1\right)\Phi - c\Phi^{N_l+1}} \right)$$

Assuming N_l=8, c=10, X_1=0.04 the above equation can be reduced to a more simple form:

$$X_w = 0.04 \left(\frac{10\Phi}{1-\Phi} \right) \left(\frac{1-9\Phi^8+8\Phi^9}{1+9\Phi-10\Phi^9} \right) \tag{2.3.15}$$

The equilibrium pressure is given as below:

$$P_{eq} = P_{sat}\Phi \tag{2.3.16}$$

The equilibrium moisture content can be calculated as follows (Peglow et al., 2007):

$$Y_{eq} = \frac{\tilde{M}_w}{\tilde{M}_g} \left(\frac{P_{eq}}{P - P_{eq}} \right) \tag{2.3.17}$$

The mass fraction of binder in a granule is calculated as follows:

$$X_b = \frac{M_b}{M_T} \tag{2.3.18}$$

The average density of a granule is calculated as follows:

$$\rho_p = \frac{\rho_s \rho_b \rho_w}{\rho_b \rho_w \left(1 - X_w - X_b\right) + \rho_s \rho_w X_b + \rho_s \rho_b X_w} \tag{2.3.19}$$

The volume of a granule is calculated as follows

$$V_P = \frac{M_T}{N\rho_p} \tag{2.3.20}$$

The diameter of a granule is obtained as follows

$$d_p = \frac{6\left(V_P\right)^{1/3}}{\pi} \tag{2.3.21}$$

The total surface area of all granules can then be calculated:

$$A_{bed} = \pi d_p^2 N \tag{2.3.22}$$

The moisture content in the gas phase is calculated as:

$$Y_s = \frac{M_{gw}}{M_g} \tag{2.3.23}$$

The rate of evaporation from the granule surface is defined as (Peglow et al., 2007):

$$F_{ev} = \rho_g \beta_{pg} A_{bed} \left(Y_{eq} - Y_s\right)\dot{v} \tag{2.3.24}$$

A2. 3. 2. Differential equations

The rate of change of mass of binder spread is given by:

$$\frac{dM_b}{dt} = \left(1 - X_{bw}\right) F_b \tag{2.3.25}$$

The rate of change of liquid mass in the granulator is given by:

$$\frac{dM_w}{dt} = F_{bw} - F_{ev} \tag{2.3.26}$$

The rate of change of the total mass of the gas phase is given by:

$$\frac{dM_g}{dt} = F_{a\_in} - F_{a\_out} + F_{ev} \tag{2.3.27}$$

The rate of change of the moisture content in the gas phase can be obtained as:

$$\frac{\mathrm{dM_{gw}}}{\mathrm{dt}} = \mathrm{F_{ev}} - \mathrm{F_{a\_out}}\,\mathrm{Y_s} + \mathrm{F_{a\_in}}\,\mathrm{Y_{w\_in}} \tag{2.3.28}$$

The rate of change of enthalpy in the granulator is calculated as follows:

$$\frac{dh}{dt} = h_{a\_in} - h_{a\_out} + h_b + F_{ev}\Delta H_v - Q_{en} \tag{2.3.29}$$

A2. 3. 3. Controller model

Moisture contents of granules (PI controller)

The deviation from the set point is calculated:

$$error_{X_w} = X_{w\_set} - X_w \tag{2.3.30}$$

The actuator setting is calculated on the basis of the deviation from the set point, using a PI control law:

$$F_b - F_{b0} = K_C^{X_w} error_{X_w} + K_I^{X_w} \int_0^t error_{X_w} dt \tag{2.3.31}$$

Bed temperature (PI controller)

The deviation from the set point is calculated:

$$error_T = T_{set} - T \tag{2.3.32}$$

The actuator setting is calculated, using a PI control law:

$$f_{a\_in} - f_{a\_in\_0} = K_C^T error_T + K_I^T \int_0^t error_T dt \tag{2.3.33}$$

Granules size (On-off controller)

The deviation from the set point is calculated:

$$error_{d_p} = d_{p\_set} - d_p \tag{2.3.34}$$

Based on the calculated deviation from the set point, a decision is taken on whether the granulation process needs to be stopped (K_{switch}=0 for open-loop and 1 for closed-loop):

$$F_b = \begin{cases} F_{b0}; \ \text{error}_{d_p} < 0 \\ F_{b0}\left(1\text{-}K_{switch}\right) \ ; \ \text{error}_{d_p} \geq 0 \end{cases} \tag{2.3.35}$$

A2. 4. Storage tank

Process description

The storage tank is shown in Figure 7.6. Powder granules come from the granulation process into the storage tank. The stored granules are then sent to the tablet pressing process to make the tablet.

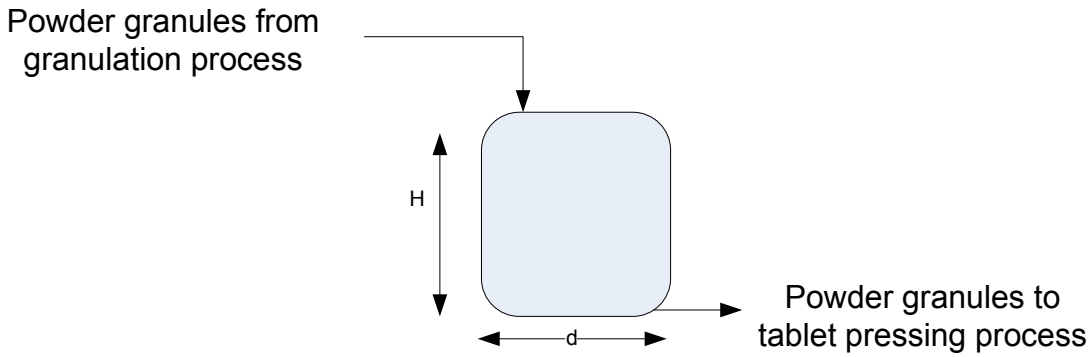


Figure 7.6: Storage tank

Assumptions

- Contents of the tank is uniformly mixed
- No reaction in the tank
- Cylindrical shape of the tank
- No heat loss through the lid of the tank

A2. 4. 1. Algebraic equations (explicit)

The mass of the tank contents (granules) can be calculated as follows:

$$M = \rho V \tag{2.4.1}$$

The mass of water is obtained as:

$$M_w = MX_w \tag{2.4.2}$$

The base area of tank is given by:

$$A = \frac{\pi d^2}{4} \tag{2.4.3}$$

The level of the tank is given by:

$$L = \frac{V}{A} \tag{2.4.4}$$

The heat transfer areas are defined as follows:

$$A_1 = \pi dL \tag{2.4.5}$$

$$A_2 = \pi d_0 L \tag{2.4.6}$$

The rate of heat entering the storage tank with the feed is calculated as follows:

$$Q_{in} = f_{in}\rho_{in}C_P\left(T_{in} - T\right) \tag{2.4.7}$$

The rate of heat loss to the surroundings through the tank wall is given as follows:

$$Q_S = U_S A_2\left(T_S - T\right) \tag{2.4.8}$$

A2. 4. 2. Differential equations

The rate of change of the mass of the granules in the tank is given by:

$$\frac{\rho dV}{dt} = f_{in}\rho_{in} - f_{out}\rho \tag{2.4.9}$$

The rate of change in temperature in the tank is given by:

$$\rho V C_P \frac{dT}{dt} = -U_1 A_1\left(T - T_c\right) + Q_{in} + Q_s \tag{2.4.10}$$

For a jacketed tank, the change of coolant temperature is given as follows (Quintana-Hernàndez et al., 2004)

$$\rho_c \mathrm{Cp_c V_c}\frac{\mathrm{dT_c}}{\mathrm{dt}} = \rho_c f_c \mathrm{Cp_c}\left(\mathrm{T_{c_{in}} - T_c}\right) + \mathrm{U_1 A_1}\left(\mathrm{T - T_c}\right) + \mathrm{U_2 A_2}\left(\mathrm{T_s - T_c}\right) \tag{2.4.11}$$

A2. 4. 3. Controller model

Temperature (PI controller)

The deviation from the set point is calculated:

$$error_T = T_{set} - T \tag{2.4.12}$$

The actuator setting is calculated using a PI control law:

$$f_c - f_{c0} = K_C^T error_T + K_I^T \int_0^t error_T dt \tag{2.4.13}$$

A2. 5. Tablet pressing process

Process description

The schematic diagram of a cross sectional view of a tablet press is shown in Figure 7.7 (Venkataram et al., 1996). The powder granules are filled in the die and then appropriate pressure is applied to compress the granules and therefore to make the tablet. The formed tablet is then sent to the tablet coater for the coating.

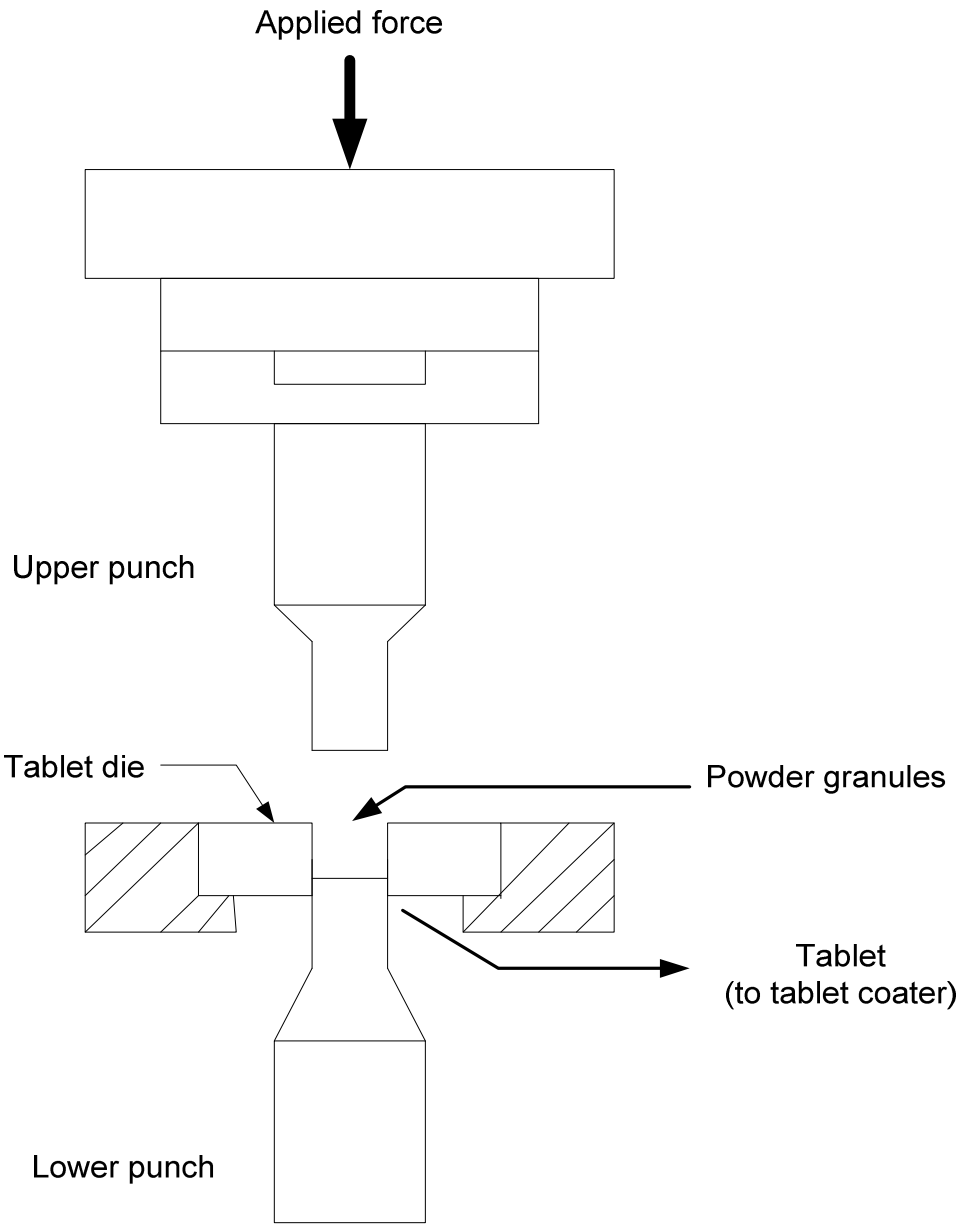


Figure 7.7: Tablet pressing process
(adopted from Venkataram et al. (1996))

Assumptions

- Tablet shape is cylindrical
- Loss of granules in the tablet pressing process is negligible
- Temperature variation in the compression process is neglected
- Powder density is constant

A2. 5. 1. Algebraic equations (explicit)

The base area of a tablet is calculated as follows, assuming that the tablet has a cylindrical shape:

$$A = \frac{3.14 d^2}{4} \tag{2.5.1}$$

The volume of a tablet is calculated as follows:

$$V = AL \tag{2.5.2}$$

The pre-compression volume is given by:

$$V_{\mathrm{Pr}e} = AL_{pre} \tag{2.5.3}$$

A noise term is assumed to take into account the variation in porosity, and is implemented as given below:

$$n\_t_{\varepsilon} = 0.009\left(t + t^2 - 2.5t^3 + t^4 - Sin(10t)\right) \tag{2.5.4}$$

The porosity of powder with added noise is then obtained as:

$$\varepsilon = \varepsilon_0 + \mathrm{n\_t}_{\varepsilon} \tag{2.5.5}$$

A noise term is assumed to show the variation in feed volume, as given below:

$$n\_t_F = 3*10^{-9}\left(t - t^2 + 2t^3 - t^4 - Sin(10t)\right) \tag{2.5.6}$$

The feed volume with added noise is then:

$$V_0 = V_m + n\_t_F \tag{2.5.7}$$

The weight of a tablet is calculated:

$$M = (1 - \varepsilon) V_0 \rho \tag{2.5.8}$$

The height of the powder in the die is calculated as follows:

$$\mathrm{L_{depth}} = \frac{\mathrm{V_0}}{\mathrm{A}} \tag{2.5.9}$$

The displacement of the upper punch in the compression process is calculated as follows:

$$L_{punch\_displ} = L_{depth} - L \tag{2.5.10}$$

The dwell time is calculated as follows:

$$t_{dwell} = \frac{L_{punch\_displ}}{u} \tag{2.5.11}$$

All the expressions for compression pressure (eq. 5.13, 5.17, 5.26) are derived from the Kawakita compression equation (Kawakita & Lüdde, 1971). An intermediate term used for calculation of pre-compression pressure is first computed:

$$\lambda_{pre} = b\left(V_0\left(\varepsilon - 1\right) + V_{pre}\right) \tag{2.5.12}$$

The pre-compression pressure is given by:

$$C\_P_{pre} = \frac{b\left(V_0 - V_{pre}\right)}{\lambda_{pre}} \tag{2.5.13}$$

The pre-compression force is given by:

$$C\_F_{pre} = 10^6 C\_P_{pre} A \tag{2.5.14}$$

The right hand side of the above equation is multiplied by 10^6 to adjust the unit of force. The porosity of the powder after the pre-compression is then calculated:

$$\varepsilon_{main} = 1 - \frac{\left(1 - \varepsilon\right)V_0}{V_{pre}} \tag{2.5.15}$$

The intermediate term used for calculation of the main compression pressure is given by:

$$\lambda_{main} = b\left(V_{pre}\left(\varepsilon_{main} - 1\right) + V\right) \tag{2.5.16}$$

The main compression pressure is given by:

$$C\_P_{main} = \frac{b\left(V_{pre} - V\right)}{\lambda_{main}} \tag{2.5.17}$$

The main compression force is obtained as:

$$C\_F_{main} = 10^6 C\_P_{main} A \tag{2.5.18}$$

The solid volume of powder is given by:

$$V_s = \left(1 - \varepsilon\right)V_0 \tag{2.5.19}$$

The relative density is defined as follows:

$$\rho_r = \frac{V_s}{V} \tag{2.5.20}$$

An intermediate term used for hardness calculation is then introduced:

$$\lambda_H = \ln\left(\frac{1 - \rho_r}{1 - \rho_{r_c}}\right) \tag{2.5.21}$$

The hardness of a tablet is calculated as (Kuentz & Leuenberger, 2000):

$$H = H_{\max}\left(1-\exp\left(\rho_r - \rho_{r_{cr}} + \lambda_H\right)\right) \tag{2.5.22}$$

A2. 5. 2. Differential equations

The tablet production rate is given by:

$$\frac{d\left(N_{Tab}\right)}{dt} = r_{Tab} \tag{2.5.23}$$

A2. 5. 3. Controller model

Tablet weight (PI controller)

A cascade control system is used to control the tablet weight. Based on the given weight set point, the outer control loop is calculating the set point for pre-compression force and then the inner control loop is designed to track the set point of pre-compression force. The set point for pre-compression force is calculated as follows:

$$V_{0\_set} = \frac{M_{set}}{(1-\varepsilon)\rho} \tag{2.5.24}$$

$$\lambda_{pre\_set} = b\left(V_{0\_set}\left(\varepsilon-1\right)+V_{pre}\right) \tag{2.5.25}$$

$$C\_P_{pre\_set} = \frac{b\left(V_{0\_set}-V_{pre}\right)}{\lambda_{pre\_set}} \tag{2.5.26}$$

$$C\_F_{pre\_set} = 10^6 C\_P_{pre\_set} A \tag{2.5.27}$$

The deviation from the set point is calculated:

$$error_{pre} = C\_P_{pre\_set} - C\_P_{pre} \tag{2.5.28}$$

The setting for the actuator is adjusted based on the error term of eq. 2.5.28:

$$V_m - V_{m_0} = K_C^M error_{pre} + K_I^M \int_0^t error_{pre} dt \tag{2.5.29}$$

Tablet hardness (PI controller)

The set point for main compression pressure is calculated as follows:

$$\rho_{r\_set} + \ln\left(1-\rho_{r\_set}\right) = \ln\left(1-\frac{H_{set}}{H_{\max}}\right) + \rho_{r_{cr}} + \ln\left(1-\rho_{r_{cr}}\right) \tag{2.5.30}$$

$$V_{set} = \frac{V_s}{\rho_{r\_set}} \tag{2.5.31}$$

$$\lambda_{main\_set} = b\left(V_{pre}\left(\varepsilon_{main} - 1\right) + V_{set}\right) \tag{2.5.32}$$

$$C\_P_{main\_set} = \frac{b\left(V_{pre} - V_{set}\right)}{\lambda_{main\_set}} \tag{2.5.33}$$

The deviation from the set point is calculated:

$$error_{main} = C\_P_{main\_set} - C\_P_{main} \tag{2.5.34}$$

The actuator setting is then calculated as follows:

$$L - L_0 = K_C^H error_{main} + K_I^H \int_0^t error_{main} dt \tag{2.5.35}$$

A2. 6. Tablet coating process

Assumptions

- Coating thickness is uniform
- Cylindrical shape of the coated tablet
- Physiochemical properties of the coating material is constant

A2. 6. 1. Algebraic equations (explicit)

The water fraction in the coating solution can be calculated as follows:

$$F_{csw} = X_{csw} F_{cs} \tag{2.6.1}$$

The surface area of an uncoated tablet is given by:

$$A_0 = \frac{\pi d_0^2}{2} + \pi d_0 L_0 \tag{2.6.2}$$

The total mass of tablets in the coating pan is calculated as follows:

$$M_T = M_{co} + M_w + NM_{p0} \tag{2.6.3}$$

The mass fraction of moisture in a tablet is obtained as:

$$X_w = \frac{M_w}{M_T} \tag{2.6.4}$$

The mass fraction of coating in a tablet is obtained as:

$$X_{co} = \frac{M_{co}}{M_T} \tag{2.6.5}$$

The average density of the tablet coating is calculated:

$$\rho_{cs} = \frac{\rho_{co}\rho_w}{\rho_{co}X_w + \rho_w(1-X_w)} \tag{2.6.6}$$

The mass of one tablet is calculated:

$$M_p = \frac{M_T}{N} \tag{2.6.7}$$

The mass of coating material surrounding a single tablet can now be calculated:

$$\Delta M_p = M_p - M_{p0} \tag{2.6.8}$$

The coating thickness is given by:

$$\delta = \frac{\Delta M_p}{\rho_{cs}A_0} \tag{2.6.9}$$

The characteristic dimensions of the tablet (diameter, thickness, surface area) are now calculated:

$$d_p = d_0 + 2\delta \tag{2.6.10}$$

$$L_p = L_0 + 2\delta \tag{2.6.11}$$

$$A_P = \frac{\pi d_p^2}{2} + \pi d_p L_p \tag{2.6.12}$$

The total surface area of all tablets is then obtained as:

$$A_{Total} = A_p N \tag{2.6.13}$$

The moisture content in the gas phase is given by:

$$Y_s = \frac{M_{gw}}{M_g} \tag{2.6.14}$$

The relation between the relative humidity and the moisture content is given by (Peglow et al., 2007):

$$X_w = 0.04\left(\frac{10\Phi}{1-\Phi}\right)\left(\frac{1-9\Phi^8+8\Phi^9}{1+9\Phi-10\Phi^9}\right) \tag{2.6.15}$$

The temperature in the coater can be defined as:

$$T = \frac{h}{M_T C_{PT}} \tag{2.6.16}$$

The saturation pressure is calculated by means of the Antoine equation:

$$P_{sat} = B_1 - \frac{B_2}{T + B_3} \tag{2.6.17}$$

The equilibrium pressure is given as below:

$$P_{eq} = P_{sat}\Phi \tag{2.6.18}$$

The equilibrium moisture content can be calculated as follows (Peglow et al., 2007):

$$Y_{eq} = \frac{\tilde{M}_w}{\tilde{M}_g}\left(\frac{P_{eq}}{P - P_{eq}}\right) \tag{2.6.19}$$

The rate of evaporation from the coating surface is defined as (Peglow et al., 2007):

$$F_{ev} = \rho_g \beta_{pg} A_{Total}\left(Y_{eq} - Y_s\right)\dot{v} \tag{2.6.20}$$

The mass flow rate of air is related to the volumetric flow rate according to the following expression:

$$F_{a\_in} = f_{a\_in}\rho_g \tag{2.6.21}$$

The mass flow rate of exhaust air is related to the volumetric flow rate:

$$F_{a\_out} = f_{a\_out}\rho_{g\_ex} \tag{2.6.22}$$

The enthalpy flow due to the inlet air is given by:

$$h_{a\_in} = F_{a\_in}C_{Pa\_in}\left(T_{a\_in} - T\right) \tag{2.6.23}$$

The enthalpy flow associated with the outlet air is given by:

$$h_{a\_out} = F_{a\_out}C_{Pa\_out}\left(T_{a\_out} - T\right) \tag{2.6.24}$$

The enthalpy flow associated with the coating flow is given by:

$$h_{cs} = F_{cs}C_{P_{cs}}\left(T_{cs} - T\right) \tag{2.6.25}$$

The rate of heat loss to the surroundings through the coating pan wall is given by:

$$Q_S = UA_S\left(T - T_S\right) \tag{2.6.26}$$

A2. 6. 2. Differential equations

The rate of change of the total mass of coating material spread is obtained as:

$$\frac{dM_{co}}{dt} = \left(1 - X_{csw}\right)F_{cs} \tag{2.6.27}$$

$$\frac{dM_w}{dt} = F_{csw} - F_{ev} \tag{2.6.28}$$

The rate of change of the total mass of the gas phase is calculated as:

$$\frac{dM_g}{dt} = F_{a\_in} - F_{a\_out} + F_{ev} \tag{2.6.29}$$

The rate of change of the moisture content in the gas phase is:

$$\frac{\mathrm{dM_{gw}}}{\mathrm{dt}} = \mathrm{F_{ev}} - \mathrm{F_{a\_out}}\,\mathrm{Y_s} + \mathrm{F_{a\_in}}\,\mathrm{Y_{w\_in}} \tag{2.6.30}$$

The rate of change of enthalpy in the coater is:

$$\frac{dh}{dt} = h_{a\_in} - h_{a\_out} + h_s + F_{ev}\Delta H_v - Q_S \tag{2.6.31}$$

A2. 6. 3. Controller model

Coating pan temperature (PI controller)

The deviation from the set point is calculated:

$$error_T = T_{set} - T \tag{2.6.32}$$

The actuator setting is then obtained on the basis of the error, using a PI control law:

$$f_{a\_in} - f_{a\_in\_0} = K_C^T error_T + K_I^T \int_0^t error_T dt \tag{2.6.33}$$

Coating thickness (On-off controller)

The deviation from the set point is calculated:

$$error_\delta = \delta_{set} - \delta \tag{2.6.34}$$

Based on the calculated deviation from the set point, the coating process needs to be stopped according to the following criterion (K_{switch}=0 for open-loop and 1 for closed-loop):

$$F_{cs} = \begin{cases} F_{cs0}; & \mathrm{error}_\delta < 0 \\ F_{cs0}\left(1\text{-}\mathrm{K_{switch}}\right) & ;\ \mathrm{error}_\delta \geq 0 \end{cases} \tag{2.6.35}$$

Appendix A3. Cheese manufacturing process model

The process models of different unit operations involved in the cheese manufacturing process are described as follows:

A3. 1. Milk storage tank

Process description

The milk storage tank is shown in Figure 7.8. Milk is pumped from the tankers into the storage tank. Milk from the storage tank flows to the pasteurizer.

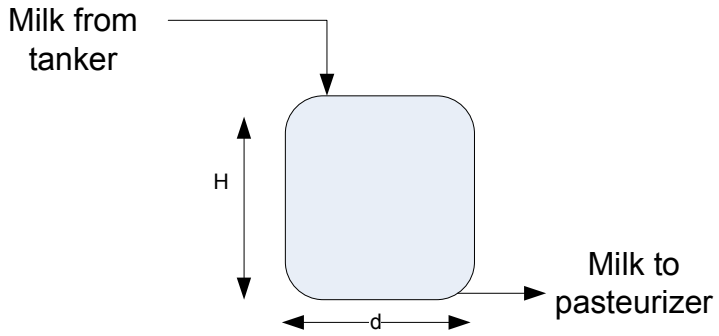


Figure 7.8: Milk storage tank

Assumptions

- Milk is uniformly mixed in the tank
- No reaction in the tank
- Cylindrical shape of the tank
- No heat loss through the lid of the tank
- Heat capacity and density of milk is constant (independent of temperature)

A3. 1. 1. Algebraic equations (explicit)

The mass of milk is given as follows:

$$M = V\rho \qquad (3.1.1)$$

The total mass of living micro-organisms is calculated as follows:

$$M_{organism} = MX_{organism} \tag{3.1.2}$$

The total mass of minerals is calculated as follows:

$$M_{\min erals} = MX_{\min erals} \tag{3.1.3}$$

The mass of whey protein is calculated as follows:

$$M_{whey\_p} = MX_{whey\_p} \tag{3.1.4}$$

The mass of casein protein is calculated as follows:

$$M_{case\_p} = MX_{case\_p} \tag{3.1.5}$$

The mass of fat is calculated as follows:

$$M_{fat} = MX_{fat} \tag{3.1.6}$$

The mass of lactose is calculated as follows:

$$M_{lactose} = MX_{lactose} \tag{3.1.7}$$

The weight fraction of water is calculated as follows:

$$X_w = 1 - X_{fat} - X_{case\_p} - X_{whey\_p} - X_{\min erals} - X_{organism} - X_{lactose} \tag{3.1.8}$$

The mass of water is calculated as follows:

$$M_w = MX_w \tag{3.1.9}$$

The base area is calculated as follows:

$$A = \frac{\pi d^2}{4} \tag{3.1.10}$$

The height of milk in the tank is given as follows:

$$L = \frac{V}{A} \tag{3.1.11}$$

The heat transfer areas are defined as follows:

$$A_2 = \pi d_0 L \tag{3.1.12}$$

$$A_1 = \pi d L \tag{3.1.13}$$

The rate of heat loss to the surrounding through the tank wall is given as follows:

$$Q_S = U_S A_2 \left(T_S - T\right) \tag{3.1.14}$$

The rate of heat out due to the outlet stream is calculated as follows:

$$Q_{out} = f_{out}\rho_{out}C_P\left(T_{out} - T\right) \tag{3.1.15}$$

The rate of heat entering with the feed is calculated as follows:

$$Q_{in} = f_{in}\rho_{in}C_P\left(T_{in} - T\right) \tag{3.1.16}$$

A3.1. 2. Differential equations

The rate of change of the mass of the milk in the tank is given as follows:

$$\frac{d\left(\rho V\right)}{dt} = f_{in}\rho_{in} - f_{out}\rho_{out}$$

If density is assumed constant then the above equation is simplified as follows:

$$\frac{\rho dV}{dt} = f_{in}\rho_{in} - f_{out}\rho_{out} \tag{3.1.17}$$

The temperature in the tank depends on the inlet and outlet stream temperatures, the surrounding temperature and the extent of cooling. The change in temperature in the tank is given as follows:

$$\rho V C_P \frac{dT}{dt} = -U_1 A_1\left(T - T_c\right) + Q_{in} - Q_{out} + Q_s \tag{3.1.18}$$

For a jacketed storage tank, the change of coolant temperature is given as follows (Quintana-Hernàndez et al., 2004):

$$\rho_c Cp_c V_c \frac{dT_c}{dt} = \rho_c f_c Cp_c\left(T_{c_{in}} - T_c\right) + U_1 A_1\left(T - T_c\right) + U_2 A_2\left(T_s - T_c\right) \tag{3.1.19}$$

A3. 1. 3. Controller model

Temperature (PI controller)

The deviation from the set point is calculated:

$$error_T = T_{set} - T \tag{3.1.20}$$

The actuator setting is calculated using a PI control law:

$$f_c - f_{c0} = K_C^T error_T + K_I^T \int_0^t error_T dt \tag{3.1.21}$$

A3. 2. Pasteurization process

Process description

The schematic diagram of a continuous pasteurization and cooling system is shown in Figure 7.9 (adopted from Armenante & Leskowicz, 1990). The whole process can be divided in 4 sections, preheating section, heating section, holding section and cooling section. In the preheating section the heat content in the hot milk is utilized to heat the cold milk. The preheated milk is then heated up to its pasteurization temperature in the heating section and is kept at this temperature as it flows in the holding section where pasteurization takes place. The pasteurized milk is then passed through the pre-heater and then cooled to its final temperature in a cooler. This milk is then fed to the cheese vat.

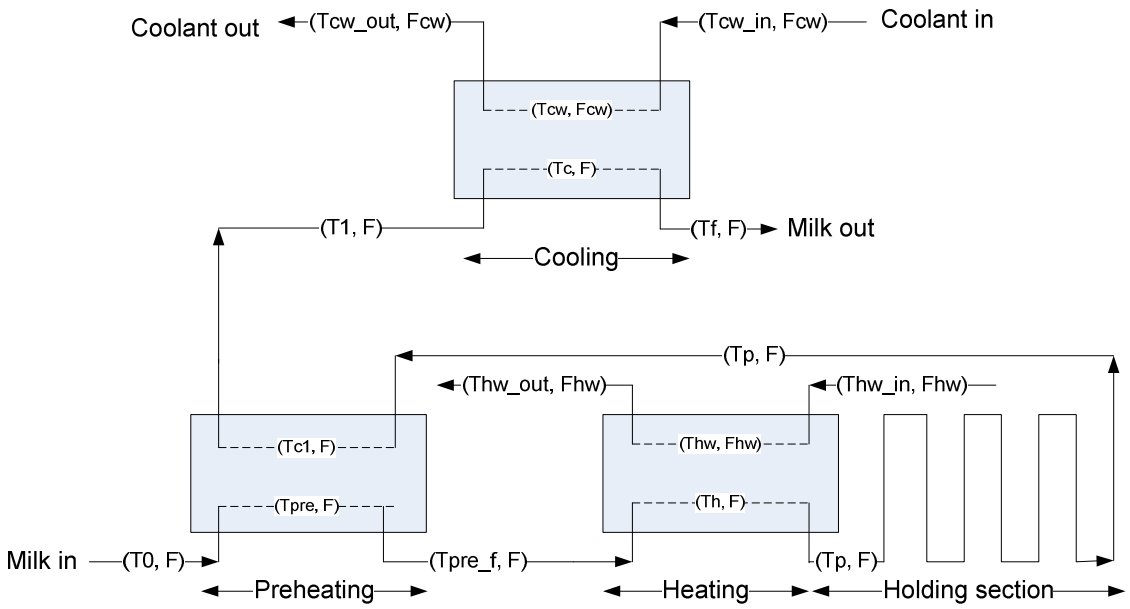


Figure 7.9: Schematic diagram of a continuous pasteurization system (adopted from Armenante & Leskowicz, 1990)

Note that the pasteurization process equipment is similar to the sterilization process equipment as discussed in section A1.2. However, the process operational conditions and the inlet/outlet stream are different. In case of the pasteurization process the main stream is the milk that needs to be pasteurized while in the sterilization process as discussed in section A1.2, the main stream was the fermentation medium

Assumptions

- Heat capacity and density of milk are constant (independent of temperature)
- No loss of heat to the surroundings
- No accumulation of milk in the heating, holding and cooling sections
- Counter current double pipe heat exchangers

A3.2.1. Algebraic equations

The rate of thermal death for the contaminating organisms is assumed to follow first-order kinetics where the specific reaction kinetic rate, K_d, is a function of the Arrhenius constant K_{dO}, the activation energy E_d, and the pasteurization temperature T, according to the following equation (Armenante & Leskowicz, 1990):

$$K_d = K_{do} \exp\left(-\frac{E_d}{R*T}\right) \tag{3.2.1}$$

For a generic pasteurization process, a balance for the final number of surviving microorganisms per unit volume of fluid, N, can be written as:

$$\ln\left(\frac{N}{N_0}\right) = -\int_0^t K_d dt \tag{3.2.2}$$

The mass flow rate of milk to the pasteurizer is calculated as follows:

$$F = \rho_{milk} f \tag{3.2.3}$$

The mass fraction of living micro-organisms in the milk is calculated as follows:

$$X_{organism} = \frac{NM_{0\_organism}}{\rho_{milk}} \tag{3.2.4}$$

The mass of living micro-organisms in the milk is calculated as follows:

$$F_{organism} = FX_{organism} \tag{3.2.5}$$

The mass of minerals in the milk is calculated as follows:

$$F_{\min erals} = FX_{\min erals} \tag{3.2.6}$$

The mass of whey protein in the milk is calculated as follows:

$$F_{whey\_p} = FX_{whey\_p} \tag{3.2.7}$$

The mass of casein protein in the milk is calculated as follows:

$$F_{case\_p} = FX_{case\_p} \tag{3.2.8}$$

The mass of fat in the milk is calculated as follows:

$$F_{fat} = FX_{fat} \tag{3.2.9}$$

The mass of lactose in the milk is calculated as follows:

$$F_{lactose} = FX_{lactose} \tag{3.2.10}$$

The mass fraction of water in the milk is calculated as follows:

$$X_w = 1 - X_{fat} - X_{case\_p} - X_{whey\_p} - X_{\min erals} - X_{organism} - X_{lactose} \tag{3.2.11}$$

The mass of water in the milk is calculated as follows:

$$F_w = FX_w \tag{3.2.12}$$

Preheating section

The temperature of the milk in the pre-heater is given as follows:

$$T_{pre} = T_0 + b_{pre}\left(T_1 - T_0\right)t \tag{3.2.13}$$

The expression for the parameter b_{pre} is a function of the system that is studied. The time, t is counted from the instant the fluid element enters the heat exchanger (Armenante & Leskowicz, 1990):

$$b_{pre} = \frac{A_{pre}U_{pre}}{S_{pre}\rho_{milk}C_{p_{milk}}l_{pre}}$$

For a double-pipe countercurrent heat exchanger b_{pre} becomes:

$$b_{pre} = \frac{2U_{pre}}{\rho_{milk}r_{pre}C_{p_{milk}}} \tag{3.2.14}$$

The outlet temperature of the milk from the pre-heater is calculated as follows:

$$T_{pre\_f} = T_0 + b_{pre}\left(T_1 - T_0\right)t_{pre} \tag{3.2.15}$$

The outlet temperature of the hot milk is given as follows:

$$T_1 = T_p - \left(T_{pre\_f} - T_0\right) \tag{3.2.16}$$

The holding time in the pre-heater is calculated as follows:

$$t_{pre} = \frac{A_{pre}l_{pre}}{f} \tag{3.2.17}$$

The flow area in the pre-heater is defined as follows:

$$A_{pre} = \pi r_{pre}^2 \tag{3.2.18}$$

Heating section

The temperature of the milk in the heat exchanger is given as follows:

$$T_h = T_{pre\_f} + \left(\frac{T_{pre\_f} - T_{hw\_out}}{a_h - 1} \right) \left[1 - \exp\left((a_h - 1) b_h t \right) \right] \tag{3.2.19}$$

The parameter a_h is defined as follows:

$$a_h = \frac{f \rho_{milk} C_{p_{milk}}}{f_{hw} \rho_w C_{p_w}} \tag{3.2.20}$$

The expression for the parameter b_h is a function of the specific heat exchanger system that is studied. The time, t is counted from the instant the fluid element enters the heat exchanger (Armenante & Leskowicz, 1990):

$$b_h = \frac{A_h U_h}{S_h \rho_{milk} C_{p_{milk}} l_h}$$

For a double-pipe countercurrent heat exchanger bh becomes:

$$b_h = \frac{2U_h}{\rho_{milk} r_h C_{p_{milk}}} \tag{3.2.21}$$

The outlet temperature of the milk from the heating section is calculated as follows:

$$T_p = T_{pre\_f} + \left(\frac{T_{pre\_f} - T_{hw\_out}}{a_h - 1} \right) \beta_h \tag{3.2.22}$$

The outlet temperature of the heating fluid is calculated as follows

$$T_{hw\_out} = \frac{c_h T_{pre\_f} - T_{hw\_in}}{c_h - 1} \tag{3.2.23}$$

Where c_h is defined as follows:

$$c_h = \frac{a_h \beta_h}{a_h - 1} \tag{3.2.24}$$

$$\beta_h = 1 - \exp\left((a_h - 1) b_h t_h \right) \tag{3.2.25}$$

The residence time (t_h) of milk in the heater is defined as follows:

$$t_h = \frac{A_h l_h}{f} \tag{3.2.26}$$

The flow area in the heater is defined as follows:

$$A_h = \pi r_h^2 \tag{3.2.27}$$

Holding section

The temperature of milk in the holding section is assumed to be constant and it will be equal to the outlet temperature from the heater. The holding time is calculated as follows:

$$t_{hold} = \frac{A_{hold} l_{hold}}{f} \tag{3.2.28}$$

The flow area of the pipe in the holding section is defined as follows:

$$A_{hold} = \pi r_{hold}^2 \tag{3.2.29}$$

Cooling section

The temperature of the milk in the heat exchanger is given as follows:

$$T_c = T_1 + \left(\frac{T_1 - T_{cw\_out}}{a_c - 1} \right) \left[1 - \exp\left((a_c - 1) b_c t \right) \right] \tag{3.2.30}$$

The parameter a_c is defined as follows:

$$a_c = \frac{f \rho_{milk} C_{p_{milk}}}{f_{cw} \rho_w C_{p_w}} \tag{3.2.31}$$

b_c is the function of the system. The time, t is counted from the instant the fluid element enters the heat exchanger (Armenante & Leskowicz, 1990):

$$b_c = \frac{A_c U_c}{S_c \rho_{milk} C_{p_{milk}} l_c}$$

For a double-pipe countercurrent heat exchanger b_c becomes:

$$b_c = \frac{2U_c}{\rho_{milk} r_c C_{p_{milk}}} \tag{3.2.32}$$

The outlet temperature of the milk from the cooler is calculated as follows:

$$T_f = T_1 + \left(\frac{T_1 - T_{cw\_out}}{a_c - 1} \right) \beta_c \tag{3.2.33}$$

The outlet temperature of the cooling liquid is calculated as follows

$$T_{cw\_out} = \frac{c_c T_1 - T_{cw\_in}}{c_c - 1} \tag{3.2.34}$$

Where c_c is defined as follows:

$$c_c = \frac{a_c \beta_c}{a_c - 1} \tag{3.2.35}$$

$$\beta_c = 1 - \exp\left((a_c - 1) b_c t_c\right) \tag{3.2.36}$$

The residence time (t_c) of milk in the cooler is defined as follows:

$$t_c = \frac{A_c l_c}{f} \tag{3.2.37}$$

The flow area in the cooler is defined as follows:

$$A_c = \pi r_c^2 \tag{3.2.38}$$

The temperature of the milk through out the different stages of the process is defined as follows:

$$T = \begin{cases} T_{pre}; \text{ if } t \le t_{pre} \\ T_h; \text{ if } t_{pre} < t \le \left(t_{pre} + t_h\right) \\ T_p; \text{ if } \left(t_{pre} + t_h\right) < t \le \left(t_{pre} + t_h + t_{hold}\right) \\ T_{c1}; \text{ if } \left(t_{pre} + t_h + t_{hold}\right) < t \le \left(t_{pre} + t_h + t_{hold} + t_{c1}\right) \\ T_c; \text{ if } \left(t_{pre} + t_h + t_{hold} + t_{c1}\right) < t \le \left(t_{pre} + t_h + t_{hold} + t_{c1} + t_c\right) \\ T_f; \text{ if } t > \left(t_{pre} + t_h + t_{hold} + t_{c1} + t_c\right) \end{cases} \tag{3.2.39}$$

The holding time of hot fluid in the pre-heater is defined as follows:

$$t_{c1} = \frac{A_{c1} l_{pre}}{f} \tag{3.2.40}$$

The flow area is defined as follows:

$$A_{c1} = \pi\left(r_{c1}^2 - r_{pre}^2\right) \tag{3.2.41}$$

A3.2.2. Controller model

Main stream temperature in holding section (PI controller)

The deviation of measured temperature from the set point is calculated as follows:

$$error_{T_p} = T_{p\_set} - T_p \tag{3.2.42}$$

The heating/cooling fluid flow rate (manipulated variable) is calculated as follows:

$$fhw - fhw\_0 = K_C^{T_p} error_{T_p} + K_I^{T_p} \int_0^t error_{T_p} dt \tag{3.2.43}$$

Final main stream temperature (outlet from cooling section) (PI controller)

The deviation of measured temperature from the set point is calculated as follows:

$$error_{T_f} = T_{f\_set} - T_f \tag{3.2.44}$$

The heating/cooling fluid flow rate (manipulated variable) is calculated as follows:

$$fcw - fcw\_0 = K_C^{T_f} error_{T_f} + K_I^{T_f} \int_0^t error_{T_f} dt \tag{3.2.45}$$

A3. 3. Starter/rennin mixing

Process description

The starter/rennin mixing process is shown in Figure 7.10. As shown in the figure, starter culture and rennin are mixed to the milk stream coming from the pasteurization and cooling process. The outlet milk stream obtained from the mixing section is then sent to the cheese vat

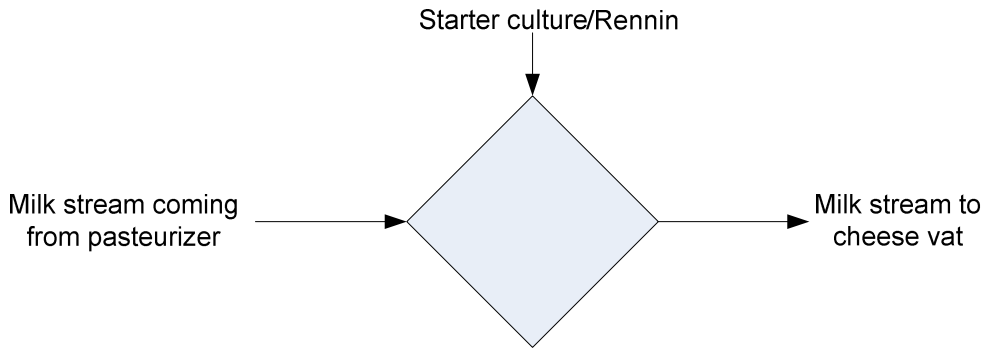


Figure 7.10: Starter/rennin mixing process

Assumptions

- Mixing heat is negligible
- No accumulation/loss of materials in the mixing process

A3.3.1. Algebraic equations

The inlet flow rate of milk stream can vary depending upon the process conditions in the pasteurization process. A noise term is assumed to take into account the variation in milk flow rate, and is implemented as given below:

$$n\_t_{F_{in}} = Sin(10t) \tag{3.3.1}$$

The milk flow rate with added noise is then obtained as:

$$F_{in} = F_{in\_o} + n\_t_{F_{in}} \tag{3.3.2}$$

The mass flow rate of the milk stream after mixing the starter and rennin is given as follows:

$$F_{out} = F_{in} + F_{starter} + F_{rennin} \tag{3.3.3}$$

The mass fraction of starter in the outlet milk stream is calculated as follows:

$$X_{starter} = \frac{F_{starter}}{F_{out}} \tag{3.3.4}$$

The mass fraction of rennin in the outlet milk stream is calculated as follows:

$$X_{renin} = \frac{F_{rennin}}{F_{out}} \tag{3.3.5}$$

The mass fraction of minerals in the outlet milk stream is calculated as follows:

$$X_{\min eral} = \frac{F_{\min erals}}{F_{out}} \tag{3.3.6}$$

The mass fraction of whey protein in the outlet milk stream is calculated as follows:

$$X_{whey\_p} = \frac{F_{whey\_p}}{F_{out}} \tag{3.3.7}$$

The mass fraction of casein protein in the outlet milk stream is calculated as follows:

$$X_{case\_p} = \frac{F_{case\_p}}{F} \tag{3.3.8}$$

The mass fraction of fat in the outlet milk stream is calculated as follows:

$$X_{fat} = \frac{F_{fat}}{F_{out}} \tag{3.3.9}$$

The mass fraction of lactose in the outlet milk stream is calculated as follows:

$$X_{lactose} = \frac{F_{lactose}}{F_{out}} \tag{3.3.10}$$

The mass fraction of water in the outlet milk stream is calculated as follows:

$$X_w = 1 - X_{fat} - X_{case\_p} - X_{whey\_p} - X_{\min erals} - X_{lactose} - X_{starter} - X_{rennin} \tag{3.3.11}$$

A3.3.2. Controller model

Following controller models for controlling the starter and rennin concentration in the milk stream is proposed. It should be noted that the monitoring and control of these variables are practicaly difficult and still a challenging task.

Starter culture (lactic acid) (PI controller)

The deviation of measured starter culture from the set point is calculated as follows:

$$error_{X_{starter}} = X_{starter\_set} - X_{starter} \tag{3.3.12}$$

The starter culture dosage flow rate is calculated as follows:

$$F_{starter} - F_{starter\_0} = K_C^{X_{starter}} error_{X_{starter}} + K_I^{X_{starter}} \int_0^t error_{X_{starter}} dt \tag{3.3.13}$$

Rennin (PI controller)

The deviation of the measured rennin concentration from the set point is calculated as follows:

$$error_{X_{renin}} = X_{renin\_set} - X_{renin} \tag{3.3.14}$$

The starter flow rate is calculated as follows:

$$F_{renin} - F_{renin\_0} = K_C^{X_{renin}} error_{X_{renin}} + K_I^{X_{renin}} \int_0^t error_{X_{renin}} dt \tag{3.3.15}$$

A3. 4. Cheese vat

Process description

The curd formation process is schematically illustrated in Figure 7.11. The pasteurized milk is transferred to the cheese vat and is then converted to cheese curd. The main

operations involved in this process are: acidification, coagulation and dehydration. Acidification is usually achieved through the in situ production of lactic acid through the fermentation of the milk sugar lactose by lactic acid bacteria (LAB). Lactic acid bacteria grow anaerobically (Toder, 2009). Then the coagulation of the casein protein of the milk forms a gel that entraps the fat. Renet is normally used to achieve the coagulation (Fox et al., 2000). Basically, proteins normally exist as negatively charged groups that repel each other, and are thus distributed evenly throughout the milk. When the acidity increases (pH decreases) in the milk, the groups of casein proteins lose their negative charges. They also lose their ability to repel each other, and then bond with each other causing coagulation, or curdling of the milk. Finally, water is removed from the curd through dehydration.

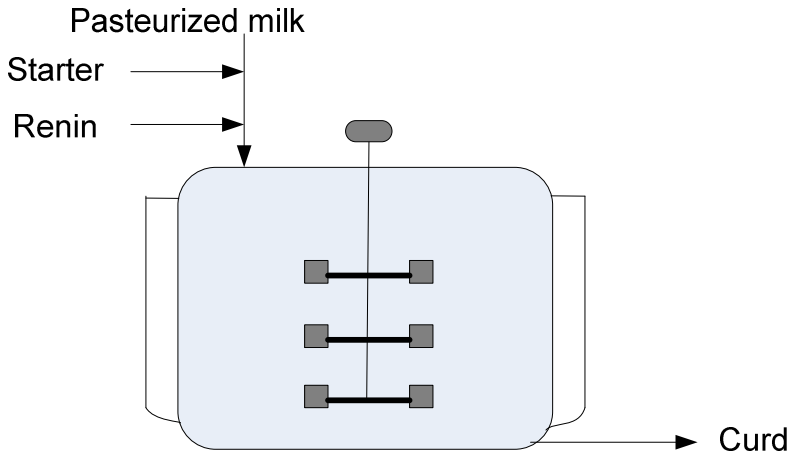


Figure 7.11: Cheese vat

Assumptions

- The fermentation process is anaerobic
- The death rate of cells is negligible
- Spatial distribution of concentrations in the cheese vat is not considered
- Spatial distribution of temperature in the cheese vat is not considered
- Coolant temperature is uniform in the cooling jacket

A3.4.1. Algebraic equations (explicit)

Specific cell growth rate

The lactose is converted to lactic acid according to the following stoichiometry (Fu & Mathews, 1999):

$$C_{12}H_{22}O_{11}(Lactose) + Starter(Biomass) \rightarrow CH_3CH(OH)COOH(Lacticacid) + Biomass$$

The specific cell growth rate is assumed to follow the Monod equation and is defined as (Fu & Mathews, 1999):

$$\mu = \frac{\mu_{\max} C_S}{K_S + C_S} \tag{3.4.1}$$

Maintenance coefficient

A fraction of the substrate which is taken up by the cells is assumed to be consumed for cell maintenance. The dependency of the maintenance coefficient on the substrate concentration (C_S) can be expressed as follows:

$$m_s = \frac{m_{s_1} C_S}{(k_s + C_S)} \tag{3.4.2}$$

Lactic acid dissociation

Lactic acid dissociates to form the lactate ion as follows:

$$CH_3CH(OH)COOH \rightleftharpoons CH_3CH(OH)COO^- + H^+$$

The rate of dissociation of lactic acid is given as follows:

$$r_{lactic} = kf_{lactic}\left(C_{lactic} - \frac{C_{lactate} C_{H^+}}{K_{lactic}}\right) \tag{3.4.3}$$

Water dissociation

The rate of water dissociation can be expressed as follows:

$$r_{H_2O} = kf_w\left(1 - \frac{C_{H^+} C_{OH^-}}{K_w}\right) \tag{3.4.4}$$

pH

pH can be expressed as a function of the hydrogen ion concentration present in the cheese vat:

$$pH = -\log\left(C_H^+\right) \tag{3.4.5}$$

A3.4.2. Differential equations

Rate of change of biomass concentration

The rate of change of the biomass concentration (LAB) is given as follows (Fu & Mathews, 1999):

$$\frac{dC_x}{dt} = \mu C_x \tag{3.4.6}$$

Rate of change of lactose (substrate) concentration

The substrate is mainly consumed for biomass production but some amount of it is also used for maintenance. The consumption rate of substrate can be expressed as follows (Doran, 2006):

$$\frac{dC_S}{dt} = -\left(\frac{\mu}{Y_{XS}} + m_S\right) C_X \tag{3.4.7}$$

Rate of change of lactic acid concentration

Lactic acid is the main product of the fermentation process. The rate of change of the lactic acid concentration is given as follows:

$$\frac{dC_{lactic}}{dt} = \frac{\mu}{Y_{Xlactic}} C_X - r_{lactic} \tag{3.4.8}$$

Lactate concentration is given as follows:

$$\frac{dC_{lactate}}{dt} = r_{lactic} \tag{3.4.9}$$

Rate of change of hydroxyl ion concentration

The dissociation of water in hydroxyl and hydrogen ions is assumed. The rate of change of the hydroxyl ion concentration is given as follows:

$$\frac{dC_{OH^-}}{dt} = r_{H_2O} \tag{3.4.10}$$

Rate of change of hydrogen ion (proton) concentration

Protons are formed in the medium, due to the dissociation of lactic acid and water. The rate of change of the hydrogen ion concentration can be expressed as follows:

$$\frac{dC_{H^+}}{dt} = r_{lactic} + r_{H_2O} \tag{3.4.11}$$

Cheese vat temperature

In the cheese vat heat is generated due to the fermentation process and some heat is lost directly to the surroundings through the cheese vat walls (Cooney et al., 1968). Water is used as a coolant to maintain the cheese vat temperature. The rate of change of cheese vat temperature can be expressed as follows:

$$\rho_b V C_{p_b} \frac{dT_b}{dt} = -U_1 A_1 \left(T_b - T_w\right) + V\left(H_{gr} - H_{surr} - H_{ev} - H_{sen}\right) \tag{3.4.12}$$

Coolant temperature

The coolant is circulated in e.g. a coil, and exchanges the heat with the fermentation broth. Finally, some heat is lost to the surroundings. A simplified expression for heat exchange between coolant and vessel contents in the jacketed vessel has been adopted from the literature (Quintana-Hernàndez et al., 2004). The rate of change of coolant temperature can be expressed as follows:

$$\rho_w C_{p_w} V_w \frac{dT_w}{dt} = \rho_w f_{w_{in}} C_{p_w}\left(T_{w_{in}} - T_w\right) + U_1 A_1\left(T_b - T_w\right) + U_2 A_2\left(T_{surr} - T_w\right) \tag{3.4.13}$$

A3.4.3. Controller model

Temperature (PI controller)

The deviation of measured temperature from the set point is calculated as follows:

$$error_{T_b} = T_{b\_set} - T_b \tag{3.4.14}$$

The coolant flow rate (manipulated variable) is calculated as follows:

$$F_{w_{in}} - F_{w_{in}\_0} = K_C^{T_b} error_{T_b} + K_I^{T_b} \int_0^t error_{T_b}\, dt \tag{3.4.15}$$

pH (PI controller)

The deviation of the measured pH from the set point is calculated as follows:

$$error_{pH} = pH_{set} - pH \tag{3.4.16}$$

Based on the calculated deviation from the set point, a decision is taken on whether the fermentation process needs to be stopped (K_{switch}=0 for open-loop and 1 for closed-loop). To stop the fermentation process, the temperature in the fermentation broth is reduced:

$$T_{b\_set} = \begin{cases} T_{b\_set\_0}; & \text{error}_{pH} < 0 \\ T_{b\_set\_0}\left(1\text{-}K_{switch}\right) & ; \ \text{error}_{pH} \geq 0 \end{cases} \tag{3.4.17}$$

A3. 5. Cheddar tower

Process description

The purpose of cheddaring is to control moisture content and to allow the curd to obtain the right consistency. The curd is cut repeatedly and piled in overlapping blocks to allow maximum whey drainage. The desired texture is achieved after approximately 2 hours. The cheddar tower is used only for manufacturing of cheddar cheese. As shown in the Figure 7.12, the curd from the cheese vat is transferred to the cheddar tower for further solidification. This step also assures that all the lactose is fermented and the complete coagulation is achieved. The model describing the further conversion of lactose and the lactic acid dissociation as described in section A3.4 is also applicable in this process and therefore not presented here explicitly.

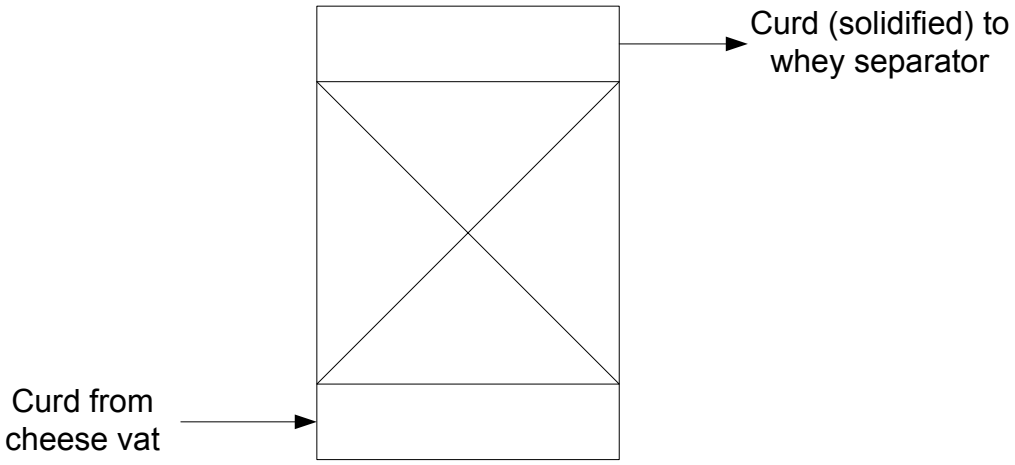


Figure 7.12: Cheddaring tower

A3. 6. Whey separator

Process description

As shown in the Figure 7.13, the aqueous whey stream is removed in this operation. The whey stream is composed of unconsumed proteins, fat, lactose, mineral salts, and water. Flat screen and draining belt are normally used for separation of curd and whey.

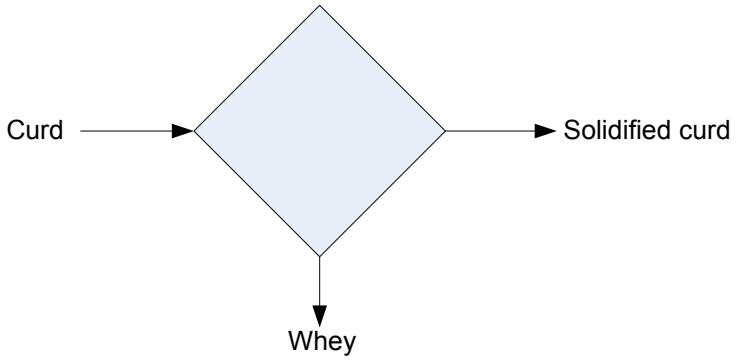


Figure 7.13: Whey separator

Assumptions

- No accumulation/loss of materials in the separation process
- Mass fraction of the living micro-organisms is neglected
- Whey protein is completely removed with the whey

Process model (Algebraic explicit equations)

The main fluctuation can be in the feed flow rate of whey separator. A noise term is assumed to take into account the variation in feed flow rate, and is implemented as given below:

$$n\_t_{F_{in}} = Sin(10t) \tag{3.6.1}$$

The feed flow rate with added noise is then obtained as:

$$F_{in} = F_{in\_o} + n\_t_{F_{in}} \tag{3.6.2}$$

The rate of separation of curd from whey is given as follows:

$$F_{out} = F_{in} - F_{whey} \tag{3.6.3}$$

Composition of solidified curd

It is assumed that whey protein is removed completely to the whey. The mass fraction of fat in the cheese curd is calculated as follows:

$$X_{fat\_out} = \frac{X_{fat\_in}F_{in} - X_{fat\_whey}F_{whey}}{F_{out}} \quad (3.6.4)$$

The mass fraction of casein protein in the cheese curd is calculated as follows:

$$X_{case\_p\_out} = \frac{X_{case\_p\_in}F_{in} - X_{case\_p\_whey}F_{whey}}{F_{out}} \quad (3.6.5)$$

The mass fraction of minerals in the cheese curd is calculated as follows:

$$X_{\min erals\_out} = \frac{X_{\min erals\_in}F_{in} - X_{\min erals\_whey}F_{whey}}{F_{out}} \quad (3.6.6)$$

The mass fraction of lactose in the cheese curd is calculated as follows:

$$X_{lactose\_out} = \frac{X_{lactose\_in}F_{in} - X_{lactose\_whey}F_{whey}}{F_{out}} \quad (3.6.7)$$

The mass fraction of the living micro-organisms is assumed to be negligible. The mass fraction of water in the cheese curd is calculated as follows:

$$X_{w\_out} = 1 - X_{fat\_out} - X_{case\_p\_out} - X_{\min erals\_out} - X_{lactose\_out} \quad (3.6.8)$$

Note that only material balance is considered in the whey separation process model. However, in order to implement the controller, more detailed separation process model is required

A3. 7. Salt mixing

Process description

In this step salt is added to the cheese curd obtained from the whey separator.

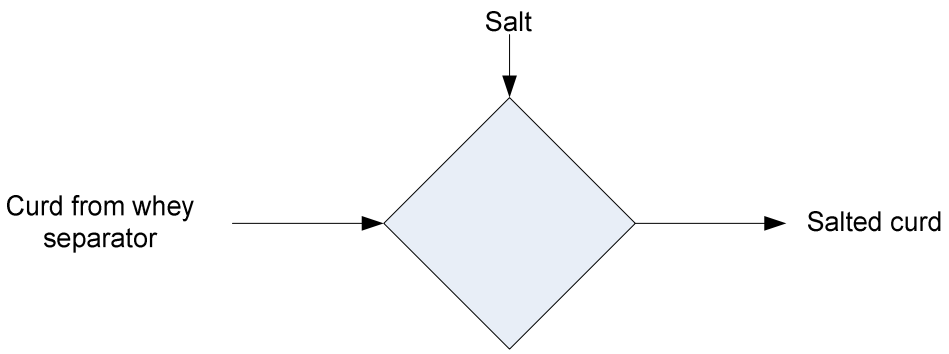


Figure 7.14: Salt mixing process

Assumptions

- Mixing heat is neglected (energy balance is not considered)
- Water content in the salt is negligible
- Chemical reactions are not considered

A3.7.1. Algebraic equations (explicit)

The main fluctuation can be in the feed flow rate of salt mixing process. A noise term is assumed to take into account the variation in feed flow rate, and is implemented as given below:

$$n\_t_{F_{in}} = 0.9\left(t + t^2 - 2.5t^3 + t^4 - Sin(10t)\right) \quad (3.7.1)$$

The feed flow rate with added noise is then obtained as:

$$F_{in} = F_{in\_o} + n\_t_{F_{in}} \quad (3.7.2)$$

The flow rate of salted cheese curd is calculated as follows:

$$F = F_{in} + F_{salt} \quad (3.7.3)$$

Composition of salted cheese curd

The mass fraction of fat in the salted cheese curd is calculated as follows:

$$X_{fat} = \frac{X_{fat\_in} F_{in}}{F_{in} + F_{salt}} \quad (3.7.4)$$

The mass fraction of casein protein in the salted cheese curd is calculated as follows:

$$X_{case\_p} = \frac{X_{case\_p\_in} F_{in}}{F_{in} + F_{salt}} \tag{3.7.5}$$

The mass fraction of minerals in the salted cheese curd is calculated as follows:

$$X_{\min erals} = \frac{X_{\min erals\_in} F_{in}}{F_{in} + F_{salt}} \tag{3.7.6}$$

The mass fraction of lactose in the salted cheese curd is calculated as follows:

$$X_{lactose} = \frac{X_{lactose\_out} F_{in}}{F_{in} + F_{salt}} \tag{3.7.7}$$

The mass fraction of salt in the salted cheese curd is calculated as follows:

$$X_{salt} = \frac{F_{salt}}{F_{in} + F_{salt}} \tag{3.7.8}$$

The mass fraction of water in the salted cheese curd is calculated as follows:

$$X_w = 1 - X_{fat} - X_{case\_p} - X_{\min erals} - X_{lactose} - X_{salt} \tag{3.7.9}$$

A3.4.3. Controller model

Salt fraction in cheese (PI controller)

The deviation of measured salt from the set point is calculated as follows:

$$error_{X_{salt}} = X_{salt\_set} - X_{salt} \tag{3.7.10}$$

The salt flow rate (manipulated variable) is calculated as follows:

$$F_{salt} - F_{salt\_0} = K_C^{X_{salt}} error_{X_{salt}} + K_I^{X_{salt}} \int_0^t error_{X_{salt}} dt \tag{3.7.11}$$

8.Appendix B: Value of known variables and parameters

For each process model described in Appendix A, the initial value of the differential variables and the values of known variables and parameters used for solving the model are given in the following tables:

Appendix B1: Fermentation process

B1. 1. Mixing process

Known variables	**Symbol**	**Value**
Tank level (m)	T_L	6
Stirrer speed (rph)	n	3600
Mixing time (hr)	t	3
Parameters	**Symbol**	**Value**
Stirrer diameter (m)	d_{str}	1
Tank diameter (m)	d_{tank}	2.6
Coefficient	K	1.06
Coefficient	α	2.17
Coefficient	β	0.5
Controller parameters	**Symbol**	**Value**
Switching parameter (for homogeneity control)	K_{switch}	1

B1. 2. Sterilization process

Known variables	**Symbol**	**Value**
Length of heat exchanger in preheating section (m)	l_{pre}	2
Length of heat exchanger in cooling section (m)	l_c	2
Length of heat exchanger in heating section (m)	l_h	2
Length of holding pipe (m)	l_{hold}	1
Radius of inner pipe of heat exchanger in preheating section (m)	r_{pre}	0.6
Radius of outer pipe of heat exchanger in preheating section (m)	r_{c1}	1

Radius of inner pipe of heat exchanger in cooling section (m)	r_c	0.6
Radius of inner pipe of heat exchanger in heating section (m)	r_h	0.6
Radius of holding pipe (m)	r_{hold}	0.6
Heat capacity of fermentation media (J/kg.K)	C_{p_m}	3770
Activation energy (J/mol)	Ed	278924
Fermentation media flow rate (m^3/hr)	f	10
Hot water flow rate (m^3/hr)	fhw	12
Coolant flow rate (m^3/hr)	fcw	11
Arrhenius type constant	K_{d0}	1E44
Initial number of microorganism (no./m^3)	N_0	1E10
Fermentation media temperature in feed (^oC)	T_0	4
Hot water inlet temperature (^oC)	T_{hw_in}	70
Cold water inlet temperature (^oC)	T_{cw_in}	10
Overall heat transfer coefficient in cooler (J/hr.m^2.K)	U_c	1.8E07
Overall heat transfer coefficient in heater (J/hr.m^2.K)	U_h	1.8E07
Overall heat transfer coefficient in pre-heater (J/hr.m^2.K)	U_{pre}	1.8E07
Density of fermentation media (kg/m^3)	ρ_m	1030
Parameters	**Symbol**	**Value**
Pi	π	3.14
Heat capacity of water (J/kg.K)	C_{pw}	4186
Universal gas constant (J/mol.K)	R	8.314
Density of water (kg/m^3)	ρ_w	1000
Controller parameters	**Symbol**	**Value**
Proportional constant for sterilization temperature control (m^3/(hr .K))	$K_C^{T_p}$	10
Integral constant for sterilization temperature control (m^3/(hr^2 .K))	$K_I^{T_p}$	1000
Proportional constant for outlet temperature control (m^3/(hr .K))	$K_C^{T_f}$	10
Integral constant for final temperature control (m^3/(hr^2 .K))	$K_I^{T_f}$	1000

B1. 3. Fermentation process

Differential Variables	**Symbol**	**Initial value**
Dissolved oxygen concentration (kg/m^3)	C_{O_2}	0.004
Dissolved CO_2 concentration (kg/m^3)	C_{CO_2}	1.000

Substrate concentration (kg/m^3)	C_S	150.000
Dissolved NH_3 concentration (kg/m^3)	C_{NH_3}	2.000
Phosphate concentration (kg/m^3)	$C_{H_3PO_4}$	14.000
Biomass concentration (kg/m^3)	C_X	5.000
Bicarbonate concentration (kg/m^3)	$C_{H_2CO_3}$	1.000
HCO_3^- concentration (kg/m^3)	$C_{HCO_3^-}$	0.100
Hydrogen ion concentration (kg/m^3)	C_{H^+}	1.00E-07
CO_3^- concentration (kg/m^3)	$C_{CO_3^-}$	0.001
$H_2PO_4^-$ concentration (kg/m^3)	$C_{H_2PO_4^-}$	2.000
HPO_4^{--} concentration (kg/m^3)	$C_{HPO_4^{--}}$	1.000
PO_4^{---} concentration (kg/m^3)	$C_{PO_4^{---}}$	0.100
NH_4^+ concentration (kg/m^3)	$C_{NH_4^+}$	1.000
Sulfate concentration (kg/m^3)	$C_{H_2SO_4}$	5.000
HSO_4^- concentration (kg/m^3)	$C_{HSO_4^-}$	1.000
SO_4^{--} concentration (kg/m^3)	$C_{SO_4^{--}}$	1.000
OH^- concentration (kg/m^3)	C_{OH^-}	1.00E-07
Fermentation temperature (K)	T_b	310.000
Coolant temperature (K)	T_w	283.000
Known variables	**Symbol**	**Value**
Saturation concentration of CO_2 (kg/m^3)	$C^*_{CO_2}$	1.450
Saturation concentration of NH_3 (kg/m^3)	$C^*_{NH_3}$	500.000
Heat capacity of broth (kJ / (kg. K))	C_{p_b}	4.200
Heat capacity of water (kJ / (kg. K))	C_{p_w}	4.200
Volume of cooling jacket (m^3)	V_w	4.000
Over all Heat transfer coefficient (broth-coolant) (W/m^2.K)	U_1	370.000
Over all Heat transfer coefficient (coolant-air) (W/m^2.K)	U_2	11.300

Broth density (kg/m^3)	ρ_b	1200.000
Water density (kg/m^3)	ρ_w	1000.000
Inlet temperature of coolant (K)	$T_{w_{in}}$	278.000
Surrounding temperature (K)	T_{surr}	298.000
Heat of fermentation (kJ/m^3.hr)	H_{gr}	4704.000
Heat of agitation (kJ/m^3.hr)	H_{ag}	13944.000
Heat lost to surroundings (kJ/m^3.hr)	H_{surr}	2562.000
Heat of evaporation (kJ/m^3.hr)	H_{evp}	96.000
Sensible heat lost (kJ/m^3.hr)	H_{sen}	21.000
Stirrer speed (rps)	n	8.000
Superficial velocity of air (m/s)	u_{O_2}	0.100
Superficial velocity of ammonia (m/s)	u_{NH_3}	1.000E-005
Coolant flow rate (m^3/hr)	$F_{w_{in}}$	71.000
Power number	P_n	2.000
Parameters	**Symbol**	**Value**
Maximum specific cell growth rate (hr^{-1})	μ_{max}	0.150
Maintenance coefficient (hr^{-1})	ms_1	0.020
Decay coefficient (hr^{-1})	bx_1	0.005
Yield coefficient(oxygen)	Y_{XO_2}	0.482
Yield coefficient(CO_2)	Y_{XCO_2}	0.470
Yield coefficient(substrate)	Y_{XS}	0.320
Yield coefficient(phosphate)	$Y_{XH_3PO_4}$	54.348
Yield coefficient(ammonia)	Y_{XNH_3}	5.988
Yield coefficient(sulfate)	$Y_{XH_2SO_4}$	312.500
Monod constant for substrate (kg/m^3)	k_s	0.004
Monod constant for oxygen (kg/m^3)	k_{O_2}	0.0004
Monod constant for ammonia (kg/m^3)	k_{NH_3}	0.0004
Monod constant for phosphate (kg/m^3)	$k_{H_3PO_4}$	0.0004

Forward rate constant (CO_2)	kf_{CO_2}	4.000
Equilibrium constant (CO_2 - H_2CO_3)	K_{CO_2}	0.0016
Forward rate constant (H_2CO_3)	$kf_{H_2CO_3}$	4.444
Equilibrium constant (H_2CO_3 - HCO_3^-)	$K_{H_2CO_3}$	4.440E-07
Forward rate constant (HCO_3^-)	$kf_{HCO_3^-}$	0.468
Equilibrium constant (HCO_3^- - CO_3^{--})	$k_{HCO_3^-}$	4.680E-11
Forward rate constant (H_3PO_4)	$kf_{H_3PO_4}$	7.089E5
Equilibrium constant (H_3PO_4 – H_2PO_4-)	$K_{H_3PO_4}$	7.089E-3
Forward rate constant (H_2PO_4-)	$kf_{H_2PO_4^-}$	6.303E4
Equilibrium constant (H_2PO_4- - HPO_4--)	$K_{H_2PO_4^-}$	6.300E-08
Forward rate constant (NH_4^+)	$kf_{NH_4^+}$	5.678E2
Equilibrium constant (NH_4^+ - NH_3)	$K_{NH_4^+}$	5.680E-10
Forward rate constant (H_2SO_4)	$kf_{H_2SO_4}$	1.000
Equilibrium constant (H_2SO_4- - HSO_4-)	$K_{H_2SO_4}$	1000.00
Forward rate constant (HSO_4-)	$kf_{HSO_4^-}$	20.000
Equilibrium constant (HSO_4- - SO_4--)	$K_{HSO_4^-}$	1.200e-002
Fermentor volume (m^3)	V	30.000
Heat exchange area (fermentor-cooling jacket) (m^2)	A_1	50.000
Heat exchange area (cooling jacket-environment) (m^2)	A_2	55.000
Impeller diameter (m)	d_i	0.830
Controller parameters	**Symbol**	**Value**
Proportional constant for DO control (m^4/(kg . hr)	$K_C^{O_2}$	-2.778E-03
Integral constant for DO control (m^4/(kg . hr^2)	$K_I^{O_2}$	-2.778E03
Proportional constant for pH control (m/hr)	K_C^{pH}	-2.778E-03
Integral constant for pH control (m/hr^2)	K_I^{pH}	-2.778

Proportional constant for temperature control ($m^3/(hr\ .K)$)	$K_C^{T_b}$	10
Integral constant for temperature control ($m^3/(hr^2\ .K)$)	$K_I^{T_b}$	1000
Proportional constant for homogeneity control (rph)	K_C^{HO}	1
Integral constant for homogeneity control (rph/hr)	K_I^{HO}	10

Appendix B2: Tablet manufacturing process

B2. 1. Mixing process

Known variables	**Symbol**	**Value**
Tank level (m)	T_L	6
Stirrer speed (rph)	n	3600
Mixing time (hr)	t	3
Parameters	**Symbol**	**Value**
Stirrer diameter (m)	d_{str}	1
Tank diameter (m)	d_{tank}	2.6
Coefficient	K	1.06
Coefficient	α	2.17
Coefficient	β	0.5
Controller parameters	**Symbol**	**Value**
Switching parameter (for homogeneity control)	K_{switch}	1

B2. 2. Milling process

Differential variables	**Symbol**	**Initial value**
Mass fraction of particles of size x_1	X_1	1
Mass fraction of particles of size x_i; i >1	X_i	0
Known variables	**Symbol**	**Value**
Weight of feed (kg)	M_F	100
Mill rotational speed (rph)	n	300
Characteristic size (m)	x_m	1E-04
Critical size of particle (m)	x_{cr}	1E-05
Weight fraction of solid in feed	X_s	0.9
Particle density (kg/m^3)	ρ	2650
Parameters	**Symbol**	**Value**
Acceleration due to gravity (m/s^2)	g	9.18
Volume shape factor	K_v	0.5
Coefficient	α	0.5
Coefficient	β	0.5
Coefficient	γ	0.3

Coefficient	k	1
Controller parameters	**Symbol**	**Value**
Switching parameter (for particles size control)	K_{switch}	1

B2. 3. Granulation process

Differential variables	**Symbol**	**Initial value**
Mass of binder in granulator (kg)	M_b	0
Water contents in solid phase (kg)	M_w	2
Total mass of gas phase (kg)	M_g	5
Water contents in gas phase (kg)	M_{gw}	1E-10
Enthalpy (J)	h	83740000
Known variables	**Symbol**	**Value**
Weight of feed powder (kg)	M_0	1000
Size of powder particles (m)	d_0	1E-09
True density of the powder particles (kg/m^3)	ρ_s	2650
Air density (kg/m^3)	ρ_g	1.2
Mass fraction of water in binder	X_{bw}	0.3
Binder flow rate (kg/hr)	F_b	5
Binder density (kg/m^3)	ρ_b	1500
Pressure (atm)	P	1
Inlet air flow rate (m^3/hr)	f_{a_in}	10
Outlet air flow rate (m^3/hr)	f_{a_out}	9.5
Exhaust air density (kg/m^3)	ρ_{g_ex}	1.2
Inlet air temperature (^{o}C)	T_{a_in}	40
Outlet air temperature (^{o}C)	T_{a_out}	20
Binder temperature (^{o}C)	T_b	18
Mass fraction of water in inlet air	Y_{w_in}	0
Over all heat transfer coefficient (J/ (hr. m^2. K))	U	90000
Heat transfer area between granulator wall and surrounding (m)	A_S	25
Surrounding temperature (^{o}C)	T_S	21.3
Parameters	**Symbol**	**Value**
Effective coagulation rate constant (hr^{-1})	K	1E-26
Heat capacity of bed contents (J/ (kg. K))	C_{PT}	5000
Heat capacity of binder (J/ (kg. K))	C_{pb}	4200
Heat capacity of inlet air (J/ (kg. K))	C_{Pa_in}	1003.5

Heat capacity of outlet air (J/ (kg. K))	C_{Pa_out}	1003.5
Antoine equation constant (atm)	B_1	11.67
Antoine equation constant (atm. K)	B_2	3816.44
Antoine equation constant (K)	B_3	-46.13
Water density (kg/m^3)	ρ_w	1000
Mass transfer coefficient (m/s)	β_{pg}	0.1
Normalized drying rate	$\dot{\nu}$	1
Heat of vaporization (J/kg)	ΔH_v	2500000
Molecular weight of water	$\tilde{M}_w$	18
Molecular weight of air	$\tilde{M}_g$	29
Controller parameters	**Symbol**	**Value**
Proportional constant for moisture control (kg / hr)	$K_C^{X_W}$	1E05
Integral constant for moisture control (kg / hr^2)	$K_I^{X_w}$	1E05
Proportional constant for bed temperature control (m^3/(K. hr))	K_C^T	1E02
Integral constant for bed temperature control (m^3/(K. hr^2)	K_I^T	1E04
Switching parameter (for granules size control)	K_{switch}	1

B2. 4. Storage tank

Differential variables	**Symbol**	**Initial value**
Volume of contents in the tank (m^3)	V	0
Tank temperature (K)	T	283.15
Coolant temperature (K)	T_C	278.15
Known variables	**Symbol**	**Value**
Inlet stream temperature (K)	T_{in}	298.15
Inlet stream flow rate (during discharge of a granulator) (kg/hr)	F_{in}	500
Outlet stream flow rate (to tablet press) (kg/hr)	F_{out}	125
Surrounding temperature (K)	T_S	293.15
Over all heat transfer coefficient (coolant-surrounding) (J/ (hr. m^2. K))	U_S	30000
Coolant volume (m^3)	V_c	10
Coolant flow rate (m^3/hr)	F_c	6
Coolant inlet temperature (K)	Tc_{in}	278.15
Bulk density of granules (in tank) (kg/m^3)	ρ	1.2

Bulk density of granules (inlet) (kg/m^3)	ρ_{in}	1.2
Heat capacity of granules (J/(kg. K))	C_P	500
Tank inner diameter (m)	d	0.5
Tank outer diameter (m)	d_0	0.54
Parameters	**Symbol**	**Value**
Coolant density (kg/m^3)	ρ_c	1000
Coolant heat capacity (J/(kg. K))	Cp_c	4120
Over all heat transfer coefficient (tank contents - coolant) (J/ (hr. m^2. K))	U_1	1668000
Over all heat transfer coefficient (coolant - surrounding) (J/ (hr. m^2. K))	U_2	3000
Controller parameters	**Symbol**	**Value**
Proportional constant for tank temperature control (m^3/(K. hr))	K_C^T	-2.778E-03
Integral constant for tank temperature control (m^3/(K. hr^2)	K_I^T	-2.778

B2. 5. Tablet pressing process

Differential variables	**Symbol**	**Initial value**
Rate of production of tablet (no./hr)	N_{Tab}	0
Known variables	**Symbol**	**Value**
Powder porosity	ε_0	0.55
Tablet diameter (m)	d	0.012
Maximum tablet hardness (MPa)	H_{max}	236
Thickness of tablet (m)	L	0.004
Pre-compression thickness (m)	L_{pre}	0.007
Punch speed (m/hr)	u	2019.6
Feed volume(m^3)	V_m	9.6E-007
Powder solid density (kg/m^3)	ρ	1157
Critical relative density (kg/m^3)	$\rho_{r_{cr}}$	0.4
Parameters	**Symbol**	**Value**
Kawakita constant (MPa)	b	0.04
Controller parameters	**Symbol**	**Value**
Proportional constant for tablet weight control (m^3/MPa)	K_C^M	1E-012
Integral constant for tablet weight control (m^3/hr. MPa)	K_I^M	-2.7E-005

Proportional constant for tablet hardness control (m/MPa)	K_C^H	1E-012
Integral constant for tablet hardness control (m/hr.MPa)	K_I^H	2.7E-02

B2. 6. Tablet coating process

Differential variables	**Symbol**	**Initial value**
Coating material in solid phase	M_{co}	1E-10
Water contents in solid phase (kg)	M_w	1E-10
Mass in gas phase (kg)	M_g	5
Water contents in gas phase (kg)	M_{gw}	1E-10
Enthalpy (J)	h	56524500
Known variables	**Symbol**	**Value**
Weight of uncoated tablet (kg)	M_{p0}	0.5E-03
Diameter of uncoated tablet (m)	d_0	1.2E-02
Density of coating solution (kg/m^3)	ρ_s	1157
Air density (kg/m^3)	ρ_g	1.2
Mass fraction of water in coating solution	X_{csw}	0.8
Coating solution flow rate (kg/hr)	F_{cs}	5
Pressure (atm)	P	1
Inlet air flow rate (m^3/hr)	f_{a_in}	51
Outlet air flow rate (m^3/hr)	f_{a_out}	50
Exhaust air density (kg/m^3)	ρ_{g_ex}	1.2
Inlet air temperature (^{o}C)	T_{a_in}	70
Outlet air temperature (^{o}C)	T_{a_out}	40
Coating solution temperature (^{o}C)	T_{cs}	60
Mass fraction of water in inlet air	Y_{w_in}	0.001
Over all heat transfer coefficient (J/ (hr. m^2. K))	U	90000
Heat transfer area between coating equipment wall and surrounding (m)	A_S	5
Surrounding temperature (^{o}C)	T_S	22
Number of tablets in one batch	N	600000
Parameters	**Symbol**	**Value**
Heat capacity of coating equipment contents (J/(kg. K))	C_{PT}	4200
Heat capacity of coating solution (J/(kg. K))	C_{pcs}	4187
Heat capacity of inlet air (J/(kg. K))	C_{Pa_in}	1003.5
Heat capacity of outlet air (J/(kg. K))	C_{Pa_out}	1003.5

Antoine equation constant (atm)	B_1	11.67
Antoine equation constant (atm. K)	B_2	3816.44
Antoine equation constant (K)	B_3	-46.13
Water density (kg/m^3)	ρ_w	1000
Mass transfer coefficient (m/s)	β_{pg}	0.1
Normalized drying rate	$\dot{\nu}$	1
Heat of vaporization (J/kg)	ΔH_v	2500000
Molecular weight of water	$\tilde{M}_w$	18
Molecular weight of air	$\tilde{M}_g$	29
Controller parameters	**Symbol**	**Value**
Proportional constant for temperature control (m^3 / (hr. ^{o}C))	K_C^T	-10
Integral constant for temperature control (m^3 / (hr^2. ^{o}C))	K_I^T	-10000
Switching parameter (for coating thickness control)	K_{switch}	1

Appendix B3: Cheese manufacturing process

B3. 1. Milk storage tank

Differential variables	**Symbol**	**Initial value**
Volume of milk in the tank (m^3)	V	0
Tank temperature (K)	T	288.15
Coolant temperature (K)	T_C	278.15
Known variables	**Symbol**	**Value**
Inlet stream temperature (K)	T_{in}	288.15
Inlet stream flow rate (m^3/hr)	F_{in}	5
Outlet stream flow rate (to pasteurizer) (m^3/hr)	F_{out}	0
Surrounding temperature (K)	T_S	20
Over all heat transfer coefficient (coolant-surrounding) (J/ (hr. m^2. K))	U_S	3E04
Coolant volume (m^3)	V_c	10
Coolant flow rate (m^3/hr)	F_c	4
Coolant inlet temperature (K)	Tc_{in}	275.15
Milk density (in tank) (kg/m^3)	ρ	1030
Milk density (inlet) (kg/m^3)	ρ_{in}	1030
Milk density (outlet) (kg/m^3)	ρ_{out}	1030
Heat capacity of milk (J/(kg. K))	C_P	3770
Tank inner diameter (m)	d	2
Tank outer diameter (m)	d_0	2.5
Mass fraction of fat in milk (-)	X_{fat}	0.039
Mass fraction of casein protein in milk (-)	X_{case_p}	0.026
Mass fraction of whey protein in milk (-)	X_{whey_p}	0.0065
Mass fraction of minerals in milk (-)	$X_{minerals}$	0.0065
Mass fraction of micro-organisms in milk (-)	$X_{organism}$	0.0032
Mass fraction of lactose in milk (-)	$X_{Lactose}$	0.049
Parameters	**Symbol**	**Value**
Coolant density (kg/m^3)	ρ_c	1000
Coolant heat capacity (J/(kg. K))	Cp_c	4120

Over all heat transfer coefficient (tank contents - coolant) (J/ (hr. m^2. K))	U_1	9E05
Over all heat transfer coefficient (coolant - surrounding) (J/ (hr. m^2. K))	U_2	3E04
Controller parameters	**Symbol**	**Value**
Proportional constant for tank temperature control (m^3/(K. hr))	K_C^T	-10
Integral constant for tank temperature control (m^3/(K. hr^2)	K_I^T	-10000

B3. 2. Pasteurization

Known variables	**Symbol**	**Value**
Length of heat exchanger in preheating section (m)	L_{pre}	2
Length of heat exchanger in cooling section (m)	l_c	2
Length of heat exchanger in heating section (m)	l_h	2
Length of holding pipe (m)	l_{hold}	1
Radius of inner pipe of heat exchanger in preheating section (m)	r_{pre}	0.6
Radius of outer pipe of heat exchanger in preheating section (m)	r_{c1}	1
Radius of inner pipe of heat exchanger in cooling section (m)	r_c	0.6
Radius of inner pipe of heat exchanger in heating section (m)	r_h	0.6
Radius of holding pipe (m)	r_{hold}	0.6
Heat capacity of milk (J/kg.K)	$C_{p_{milk}}$	3770
Activation energy (J/mol)	Ed	278924
Milk flow rate (m^3/hr)	f	10
Hot water flow rate (m^3/hr)	f_{hw}	12
Coolant flow rate (m^3/hr)	f_{cw}	11
Arrhenius type constant	K_{d0}	1E44
Initial number of microorganism (no./m^3)	N_0	1E10
Milk temperature in feed (^oC)	T_0	4
Hot water inlet temperature (^oC)	T_{hw_in}	70
Cold water inlet temperature (^oC)	T_{cw_in}	10
Overall heat transfer coefficient in cooler (J/hr.m^2.K)	U_c	1.8E07
Overall heat transfer coefficient in cooler (J/hr.m^2.K)	U_h	1.8E07
Overall heat transfer coefficient in cooler (J/hr.m^2.K)	U_{pre}	1.8E07
Density of milk (kg/m^3)	ρ_{milk}	1030
Parameters	**Symbol**	**Value**
Pi	π	3.14

Heat capacity of water (J/kg. K)	C_{pw}	4186
Universal gas constant (J/mol. K)	R	8.314
Density of water (kg/m^3)	ρ_w	1000
Controller parameters	**Symbol**	**Value**
Proportional constant for holding section temperature control (m^3/(K. hr))	$K_C^{T_p}$	0.001
Integral constant for holding section temperature control (m^3/(K. hr^2)	$K_I^{T_p}$	10
Proportional constant for control of outlet temperature from cooling section (m^3/(K. hr))	$K_C^{T_f}$	0.0001
Integral constant for control of outlet temperature from cooling section (m^3/(K. hr^2)	$K_I^{T_f}$	12

B3. 3. Starter/rennin mixing

Known variables	**Symbol**	**Value**
Milk flow rate (inlet to mixer) (kg/hr)	F_{in}	10300
Starter flow rate (kg/hr)	$F_{starter}$	10
Rennin flow rate (kg/hr)	F_{rennin}	1
Minerals in milk (kg/hr)	$F_{minerals}$	66.95
Whey protein in milk (kg/hr)	F_{whey_p}	66.95
Casein proteins in milk (kg/hr)	F_{case_p}	267.8
Fat in milk (kg/hr)	F_{fat}	401.7
Lactose in milk (kg/hr)	$F_{lactose}$	412
Controller parameters	**Symbol**	**Value**
Proportional constant for starter control (kg/(hr))	$K_C^{X_{starter}}$	100
Integral constant for starter control (kg/(hr^2)	$K_I^{X_{starter}}$	1E5
Proportional constant for rennin control (kg/(hr))	$K_C^{X_{renin}}$	10
Integral constant for rennin control (kg/(hr^2)	$K_I^{X_{renin}}$	1E5

B3. 4. Cheese vat

Differential Variables	**Symbol**	**Initial value**
Biomass concentration (kg/m^3)	C_X	9.800

Substrate concentration (kg/m^3)	C_S	48.000
Lactic acid concentration (kg/m^3)	C_{lactic}	0
OH^- concentration (kg/m^3)	C_{OH^-}	1.00E-07
Hydrogen ion concentration (kg/m^3)	C_{H^+}	1.00E-07
Cheese vat temperature (K)	T_b	303.000
Coolant temperature (K)	T_w	283.000
Known variables	**Symbol**	**Value**
Broth density (kg/m^3)	ρ_b	1200.000
Heat capacity of broth (kJ /(kg. K))	C_{p_b}	4.200
Over all Heat transfer coefficient (broth-coolant) (W/m^2.K)	U_1	370.000
Over all Heat transfer coefficient (coolant-air) (W/m^2.K)	U_2	11.300
Heat of fermentation (kJ/m^3.hr)	H_{gr}	4704.000
Heat lost to surroundings (kJ/m^3.hr)	H_{surr}	2562.000
Volume of cooling jacket (m^3)	V_w	4.000
Coolant flow rate (m^3/hr)	$F_{w_{in}}$	71.000
Inlet temperature of coolant (K)	$T_{w_{in}}$	278.000
Surrounding temperature (K)	T_{surr}	298.000
Volume of cheese vat (m^3)	V	30.000
Heat exchange area (fermentor-cooling jacket) (m^2)	A_1	50.000
Heat exchange area (cooling jacket-environment) (m^2)	A_2	55.000
Parameters	**Symbol**	**Value**
Heat capacity of water (kJ /(kg. K))	C_{p_w}	4.200
Water density (kg/m^3)	ρ_w	1000.000
Maximum specific cell growth rate (hr^{-1})	μ_{max}	0.382
Monod constant for substrate (kg/m^3)	K_s	0.004
Maintenance coefficient (hr^{-1})	ms_1	0.020
Forward rate constant (lactic acid-lactate)	kf_{lactic}	1.6
Lactic acid dissociation constant	K_{lactic}	1.38E-04

Yield coefficient(substrate)	Y_{XS}	0.45
Yield coefficient(lactic acid)	$Y_{Xlactic}$	0.46
Control parameters	**Symbol**	**Value**
Proportional constant for temperature control (m^3/(hr .K))	$K_C^{T_b}$	10
Integral constant for temperature control (m^3/(hr^2 .K))	$K_I^{T_b}$	1000

B3. 5. Whey separator

Known variables	**Symbol**	**Value**
Inlet stream flow rate(kg/hr)	F_{in}	1000
Separated stream flow rate (kg/hr)	F_{whey}	600
Composition of fat in inlet stream	X_{fat_in}	0.0386
Composition of casein protein in inlet stream	$X_{case\_p\_in}$	0.0267
Composition of minerals in inlet stream	$X_{minerals\_in}$	0.0022
Composition of lactose in inlet stream	$X_{lactose\_in}$	0.0485
Composition of fat in whey	X_{fat_whey}	0.0047
Composition of casein protein in whey	$X_{case\_p\_whey}$	0.0019
Composition of minerals in whey	$X_{minerals\_whey}$	0.0015
Composition of lactose in whey	$X_{lactose\_whey}$	0.0515

B3. 6. Salt mixing

Known variables	**Symbol**	**Value**
Flow rate of stream coming from whey separator (kg/hr)	F_{out}	90
Rate of salt addition (kg/hr)	F_{salt}	1.78
Composition of fat in curd before salt mixing	X_{fat_out}	0.3242
Composition of casein protein in curd before salt mixing	$X_{case\_p\_out}$	0.2370
Composition of minerals in curd before salt mixing	$X_{minerals\_out}$	0.0031
Composition of lactose in curd before salt mixing	$X_{lactose\_out}$	0.0217
Control parameters	**Symbol**	**Value**
Proportional constant for salt control (kg/(hr))	$K_C^{X_{salt}}$	10
Integral constant for salt control (kg/(hr^2)	$K_I^{X_{salt}}$	1E5

9.Nomenclature

a	Milling speed correction parameter
A	Area (m^2)
b	Kawakita constant (MPa)
B	Antoine equation constant (atm. K)
bx	Specific biomass decay (hr^{-1})
bx_1	Decay constant (hr^{-1})
C	Concentration (Kg/m^3)
C_F	Compression force (N)
C_P	Heat capacity (J/(kg. K))
C_P	Compression pressure (MPa)
d	Diameter (m)
error	deviation from set point
f	Volumetric flow rate (m^3/hr)
F	Mass flow rate (kg/hr)
g	Acceleration due to gravity (m/s^2)
h	Enthalpy (J)
H	Tablet hardness (MPa)
HO	Homogeneity (fractional)
ΔH_v	Heat of vaporization (J/kg)
K	Coefficient (-)
K_C	Proportional gain (PI controller)
kf	Forward rate constant
K_I	Integral time (PI controller)
kla	Mass transfer coefficient (m/s)
K_v	Volume shape factor
L	Width (m)
M	Mass (kg)
$\tilde{M}$	Molecular weight
ms	Specific maintenance coefficient (hr^{-1})
ms_1	Maintenance constant (hr^{-1})
n	Rotational speed (rph)
N	Number (-)
n_t	Noise term (-)
P	Pressure (atm)

Q	Rate of heat exchange (J/hr)
P_n	Power number
Pow	Power dissipation through agitation (W)
q_{CO2}	Specific CO_2 production rate (hr^{-1})
Q_{CO2}	CO_2 production rate ($Kg/m^3.hr$)
q_{O2}	Specific oxygen uptake rate (hr^{-1})
Q_{O2}	Oxygen uptake rate ($Kg/ (m^3.hr)$)
r	Radius (m)
r_{Tab}	Rate of production of tablets (no./hr)
t	Time (hr)
T	Temperature (^oC)
T_L	Tank level (m)
ts	Stirring duration (s)
u	Punch speed (m/hr)
U	Over all heat transfer coefficient ($J/(hr. m^2. K)$)
V	Volume (m^3)
x	Size (m)
X	Mass fraction (-)
Y	Moisture in gas phase (fractional)
Y_{XZ}	Yield coefficient for compound Z on compound X
z	Number of size intervals (-)
Greek letters	
α, β, γ	Coefficient (-)
Φ	Velocity fraction (-)
ρ	Density (kg/m^3)
π	Pi
τ	Coagulation half-time (hr)
β_{pg}	Mass transfer coefficient (m/s)
$\dot{\nu}$	Normalized drying rate (-)
ε	Powder porosity (-)
μ	Specific growth rate (hr-1)
Vectors	
$\underline{b}$	Primary breakage distributions
$\underline{M}$	Mass of particles of a specific size range (kg)
$\underline{M_p}$	Mass of one particle in a specific size range (kg)

$\underline{N_p}$	Number of particles in a specific size range (-)
$\underline{S}$	Specific rate of breakage (per hr)
$\underline{X}$	Weight fraction of solid in a specific size range

Subscripts

ag	Agitation
a_in	Air in
a_out	Air out
avg	Average
b	Binder
bw	Water in binder
c	Coolant
C	Controller
co	Coating
CO_2	Carbon dioxide
CO_3^{--}	Carbonate ion
cr	Critical
cs	Coating solution
csw	Water in coating solution
depth	Die depth
dwell	Dwell time
en	Environment
eq	Equilibrium
evp	Evaporation
F	Feed
Fv	Feed volume
g	Gas
gr	Generation
gw	Moisture in gas
g_ex	Exhaust gas
H^+	Hydrogen ion
H_3PO_4	Phosphoric acid
$H_2PO_4^-$	Dihydrogen phosphate ion
HPO_4^{--}	Hydrogen phosphate ion
H_2CO_3	Carbonic acid
HCO_3^-	Bicarbonate ion
H_2O	Water

H_2SO_4	Sulfuric acid
HSO_4^-	Hydrogen sulfate ion
H_2CO_3	Carbonic acid
i	Size interval
I	Integral
in	Inlet
mix	Mixing
max	Maximum
MT	Mixing tank
NH_3	Ammonia
NH_4^+	Ammonium ion
0	Initial
out	Outlet
O_2	Oxygen
OH^-	Hydroxyl ion
PO_4^{---}	Phosphate ion
P_i	Particle in the i^{th} size interval
p_total	Total particles
r	Relative
s	Solid
S	Substrate
S_F	Solid in feed
sat	Saturation
sen	Sensible
SO_4^{--}	Sulfate ion
ster	Sterilizer
str	Stirrer
surr	Surrounding
tab	Tablet
T	Total
w	Water
X	Biomass

Superscripts

*	Saturation
0	Steady state value
H	Hardness
M	Weight

X_w	Moisture content (fractional)
T	Temperature

Abbreviations

DO	Dissolved oxygen
DOF	Degree of freedom
FDA	U. S. Food and Drug Administration
ICAS	Integrated computer-aided system
MoT	Modeling testbed
PAT	Process analytical technology
PI	Proportional integral
rpm	Revolutions per minute
SISO	Single input single output

10. References

Aalborg flow instrumentation, PTEE-single glass flow meters, http://www.aalborg.com/images/file_to_download/en_Aalborg_EM200710_T_TX_Meters.pdf

ABB Instrumentation, Inc. http://library.abb.com/GLOBAL/SCOT/SCOT212.nsf/VerityDisplay/554E7430763349D585256E270072B6DD/$File/D-FV-FP_2.pdf

Angst, R., & Kraume, M. (2006). Experimental investigations of stirred solid/liquid systems in three different scales: Particle distribution and power consumption. Chemical Engineering Science, 61, 2864-2870.

Armenante, P. M., & Leskowicz, M. A. (1990). Design of Continuous Sterilization Systems for Fermentation Media Containing Suspended Solids. Biotechnol. Prog., 6, 292-306

Ashoori, A., Moshiri, B., Khaki-Sedigh, A., & Bakhtiari, M. R. (2009). Optimal control of a nonlinear fed-batch fermentation process using model predictive approach. Journal of Process Control, 19, 1162–1173

Austin, L. G., & Brame, K. (1983). A comparison of the Bond method for sizing wet tumbling ball mills with a size-mass balance simulation model. Powder Technology, 34, 261-274.

Barua, A., Ray, S., & Sinha, S. (1993). Transelex: A knowledge-based approach for the selection of transducers using a dynamic database. Engineering Applications of Artificial Intelligence, 6(1), 73-75.

Bayer, B., Eggersmann, M., Gani, R., & Schneider, R. (2002). Software architectures and tools for computer-aided process engineering. Computer-aided chemical engineering, 11, Elsevier, editors: B. Braunschweig & R. Gani, 591-634

Bylund, G. (2003). Dairy processing handbook. Tetra Pack Processing Systems AB, SE-221 86 Lund, Sweden. 2nd Edition, ISBN 91-631-3427-6

Blanco, M., & Alcalá, M. (2006). Content uniformity and tablet hardness testing of intact pharmaceutical tablets by near infrared spectroscopy: a contribution to process analytical technologies. Analytica Chimica Acta, 557, 353-359.

Brudzewski, K., & Dolecka, U. (1995). Optimal selection of sensors based on the catalogue data: a vector-space approach to cross-sensitivity effects. Sensors and actuators, B, 23, 71-73.

CAPGO (2007). Sensor Glossary, http://www.capgo.com/Resources/Sensors/SensorGlossary.html

Carr, J. J., & Brown, J. M. (2008). Sensor terminology, 3rd Edition. National instruments, http://zone.ni.com/devzone/cda/ph/p/id/227

Carballido, J. A., Ponzoni, I., & Brignole, N. B. (2007). CGD-GA: A graph-based genetic algorithm for sensor network design. Information Sciences, 177, 5091-5102.

References

Chakraborty, A., & Deglon, D. (2008). Development of a heuristic methodology for precise sensor network design. Computers and Chemical Engineering 32, 382-395

Chamseddine, A., Noura, H., & Raharijaona, T. (2007). Optimal sensor network design for observability of complex systems. Proceedings of the American control conference, New York City, USA, July 11-13,

Charalampopoulos, D., Vázquez, J. A., & Pandiella, S. S. (2009). Modelling and validation of Lactobacillus plantarum fermentations in cereal-based media with different sugar concentrations and buffering capacities. Biochemical Engineering Journal, 44, 96–105

Chen, Z. P., Lovett, D., & Morris, J. (2008). Process Analytical Technologies (PAT)—the impact for Process Systems Engineering. Computer Aided Chemical Engineering, Volume 25, 967-972

Choi, J. W. (2009). Architecture of a knowledge based engineering system for weight and cost estimation for a composite airplane structures. Expert Systems with Applications, 36, 10828–10836

Clark solutions. http://www.clarksol.com/PDF/FR200040004500.pdf

Cooney, C. L., Wang, D. I. C., & Mateles, R. I. (1968). Measurement of heat evolution and Correlation with oxygen consumption during microbial growth. Biotechnology and Bioengineering, 11, 269-281.

De Beer, T. R. M., Bodson, C., Dejaegher, B., Walczak, B., Vercruysse, P., Burggraeve, A., et al. (2008). Raman spectroscopy as a process analytical technology (PAT) tool for the in-line monitoring and understanding of a powder blending process. Journal of Pharmaceutical and Biomedical Analysis, 48, 772–777.

Descoins, C., Mathlouthi, M., Le Moual, M., & Hennequin, J. (2006). Carbonation monitoring of beverage in a laboratory scale unit with on-line measurement of dissolved CO_2. Food Chemistry, 95, 541-553.

De Jong, J. A. H. (1991). Tablet properties as a function of the properties of granules made in a fluidized bed process. Powder Technology, 65, 293-303

Doran, P. M. (2006 a). Bioprocess engineering principles. New York: Academic Press.

Eid, M., Liscano, R., & Saddik, A. E. (2006). A novel ontology for sensor networks data. International conference on computational intelligence for measurement systems and applications, La Coruna-Spain.

Eilertsen, J., Rytter, E., & Ystenes, M. (2000). In situ FTIR spectroscopy during addition of trimethylaluminium (TMA) to methylaluminoxane (MAO) shows no formation of MAO-TMA compounds. Vibrational Spectroscopy, 24, 257-264.

Eliasson, C., Macleod, N. A., Jayes, L. C., Clarke, F. C., Hammond, S. V., Smith, M. R., et al. (2008). Non-invasive quantitative assessment of the content of pharmaceutical capsules using transmission Raman spectroscopy. Journal of Pharmaceutical and Biomedical Analysis, 47, 221–229.

FDA (2004). PAT - A framework for innovative pharmaceutical development, manufacturing, and quality assurance. http://www.fda.gov/cder/guidance/6419fnl.pdf

References

FDA (2007). Guidance for industry, Q8 (R1) pharmaceutical development revision 1. http://www.fda.gov/Cder/guidance/8084dft.pdf

FDA/CDER (2005). PAT, Process Analytical Technology (PAT) Initiative, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, http://www.fda.gov/Cder/OPS/PAT.htm

Fountain, W., Dumstorf, K., Lowell, A. E., Lodder, R. A., Mumper, R. J., (2003). Near-infrared spectroscopy for the determination of testosterone in thin-film composites. Journal of Pharmaceutical and Biomedical Analysis, 33, 181–189.

Fox, P. F., Cogan, T. M., & Guinee, T. P. (2000). Fundamentals of cheese science. Aspen Publishers, Inc., Gaithersburg

Fu, P.-C., & Barford, J. P. (1993). Non-singular optimal control for fed-batch fermentation processes with a differential-algebraic system model. J. Proc. Cont., Volume 3, Number 4

Gani, R., & Cameron, I. T. (1992). Modelling for dynamic simulation of chemical process: The INDEX problem. Chemical Engineering Science, 47, 1131-1135.

Gani, R., Muro-Suñé, N., Sales-Cruz, M., Leibovici, C., & Connell, J. P. O. (2006a). Mathematical and numerical analysis of classes of property models. Fluid phase Equilibria, 250, 1-32.

Gani, R., Jiménez-González, C., Kate, A. T., Peter A. (2006b). A modern approach to solvent selection. Chemical Engineering, 113(3), 30–43.

Gebus, S., & Leiviska, K. (2009). Knowledge acquisition for decision support systems on an electronic assembly line. Expert Systems with Applications 36, 93–101

Gerkens, C., & Heyen, G. (2005). Use of parallel computers in rational design of redundant sensor networks. Computers and Chemical Engineering, 29, 1379-1387.

Gnoth, S., Jenzsch, M., Simutis, R., & Lübbert, A. (2007). Process Analytical Technology (PAT): Batch-to-batch reproducibility of fermentation processes by robust process operational design and control. Journal of Biotechnology, 132 (2), 180-186.

González-Sáiz, J., Garrido-Vidal, D., & Pizarro, C. (2009). Modelling the industrial production of vinegar in aerated-stirred fermentors in terms of process variables. Journal of Food Engineering, 91 183–196

Gruber, T. R. (1995). Toward principles for the design of ontologies used for knowledge sharing. International Journal of Human-Computer Studies, 43, 907-928

Guarina, N. (1997). Understanding, building and using ontologies. International Journal of Human-Computer Studies, 46, 293-310

Hausman, D., Cambron, R., & Sakr, A. (2005). Application of Raman spectroscopy for on-line monitoring of low dose blend uniformity. International Journal of Pharmaceutics, 298, 80-90.

Heredia , J. A., Fan , I. , Romer, F., & Rosado, P. (1996). A Framework for an Integrated Quality System. Journal of Materials Processing Technology 61, 195-200

Hogg, R. (1992). Agglomeration models for process design and control. Powder Technology, 69, 69-76.

Hogg, R. (1999). Breakage mechanisms and mill performance in ultrafine grinding. Powder Technology 105, 135-140.

References

Huang, H., Yu, H., Xu, H., Ying, Y., (2008). Near infrared spectroscopy for on/in-line monitoring of quality in foods and beverages: A review. Journal of Food Engineering, 87, 303–313.

Jia, X., & Williams, R. A. (2007). A hybrid mesoscale modelling approach to dissolution of granules and tablets. Chemical Engineering Research and Design, Trans IChemE, Part A, Vol 85 (A7), 1027–1038

Kandil, M. S., Farghal, S. A., & Abdel-Aziz, M. R. (1992). Knowledge base of an expert system for generation expansion planning. Electric Power Systems Research, 23, 59-70

Kano, M., & Nakagawa, Y. (2008). Data-based process monitoring, process control and quality improvement: Recent developments and applications in steel industry. Computers and Chemical Engineering 32, 12–24

Stum, K. (2006). Sensor Accuracy and Calibration Theory and Practical Application. National Conference on Building Commissioning, April 19-21

Kawakita, K., & Lüdde, K. H. (1971). Some considerations on powder compression equations, Powder Technology 4, 61-68

Kawohl, M., Heine, T., & King, R. (2007). Model based estimation and optimal control of fed-batch fermentation processes for the production of antibiotics. Chemical Engineering and Processing 46, 1223–1241

Key instruments. http://www.keyinstruments.com/pdf/fr.pdf

Kionix (2004). MEMS Sensor Terminology Accelerometers/Inclinometers, http://www.kionix.com/Adobe-Documents/MEMS%20Sensor%20Terminology.pdf

Kuentz, M., & Leuenberger, H. (2000). A new model for the hardness of a compacted particle system, applied to tablets of pharmaceutical polymers, Powder Technology, 111, 145-143.

Kobold Instruments, Inc. http://www.koboldusa.com/product_files/KFR_datasheet.pdf

Kotecha, P. R., Bhushan, M., Gudi, R. D., & Keshari, M. K. (2008). A duality based framework for integrating reliability and precision for sensor network design. Journal of process control, 18, 189–201.

Knowledge Systems Laboratory (1997). Report, A Glossary of Ontology Terminology. Stanford University., USA, http://www-ksl-svc.stanford.edu:5915/doc/frame-editor/glossary-of-terms.html

Lai, L. F. (2007). A knowledge engineering approach to knowledge management. Information Sciences 177, 4072-4094.

Lawrence X. Y., Lionberger, R. A., Raw, A. S., D'Costa, R., Wu, H., Hussain, A. S. (2004). Applications of process analytical technology to crystallization processes. Advanced Drug Delivery Reviews 56, 349– 369

Lawrence X. Y (2007). Pharmaceutical Quality by Design Product and Process Development, Understanding, and Control. Pharmaceutical Research, Vol. 25, No. 4, 788-791

References

Linek, V., Vacek , V., & Benes, P. (1987). A Critical Review and Experimental Verification of the Correct Use of the Dynamic Method for the Determination of Oxygen Transfer in Aerated Agitated Vessels to Water, Electrolyte Solutions and Viscous Liquids. The Chemical Engineering Journal, 34, 11-34.

Lopes, J. A., Costa, P. F., Alves, T. P., & Menezes, J. C. (2004). Chemometrics in bioprocess engineering: process analytical technology (PAT) applications. Chemometrics and Intelligent Laboratory Systems, 74, 269-275.

Mathworks, 1970. http://www.mathworks.com/products/matlab/

McCabe, W. L., Smith, J. C., & Harriott, P. (2005). Unit operations of Chemical Engineering, 7th edition, McGraw Hill.

Mittal, G. S. (2007). Food Process Modeling, Simulation and Optimization. Handbook of Farm, Dairy, and Food Machinery, 2007, Pages 449-484

Musvoto, E. V., Wentzel, M. C., Loewenthal, R. E., & Ekama, G. A. (2000). Integrated chemical physical processes modeling-1. Development of a kinetic-based model for mixed weak acid/base systems. Water Research, 34 (6), 1857-1867.

Nagy, Z. K. (2007). Model based control of a yeast fermentation bioreactor using optimally designed artificial neural networks. Chemical Engineering Journal 127, 95–109

Narasimhan, S., & Rengaswamy, R. (2007). Quantification of performance of sensor networks for fault diagnosis. AIChE Journal, 53 (4), 902-917

Natalya, F. N., & McGuinness, D. L. (2007). Ontology development 101: a guide to creating your first ontology. Stanford university, Stanford, CA, 94305. http://protege.stanford.edu/publications/ontology_development/ontology101-noy-mcguinness.html

Ochieng, A., & Onyango, M.S. (2008). Homogenization energy in a stirred tank, Chemical Engineering and Processing, 47, 1853–1860

Ong, J. B., Masud, A. S. M., & Eyada, O. K. (1992). Senses: A knowledge-based sensor selection system. Computers & Industrial Engineering, Vol. 22, No. 1, 1-8

Orantes, A., Kempowsky, T., Le Lann, M. V., Prat, L., Elgue, S., Gourdon, C., & Cabassud, M. (2007). Selection of sensors by a new methodology coupling a classification technique and entropy criteria. Trans IChemE, Part A, Vol. 85 (A6), 825–838

Otero, L., & Sanz, P. D. (2003). Modelling heat transfer in high pressure food processing: a review. Innovative Food Science and Emerging Technologies, 4, 121–134

Papadopoulos, A. I., & Seferlis, P. (2009). Generic modelling, design and optimization of industrial phosphoric acid production processes. Chemical Engineering and Processing, 48, 493–506

Papavasileiou, V., Koulouris, A., Siletti, C., & Petrides, D. (2007). Optimize manufacturing of pharmaceutical products with process simulation and production scheduling tools. Trans IChemE, Part A, Chemical Engineering Research and Design, 85 (A7), 1086-1097

Paton, N. W., Goble, C. A., & Bechhofer, S. (200). Knowledge based information integration systems. Information and software technology 42, 299-312.

References

Peglow, M., Kumar, J., Heinrich, S., Warnecke, G., Tsotsas, E., Mörl, L., et al., (2007). A generic population balance model for simultaneous agglomeration and drying in fluidized beds. Chemical Engineering Science, 62, 513–532.

Petrides, D., Sapidou, E., & Calandranis, J. (1995). Computer-aided process analysis and economic evaluation for biosynthetic human insulin production - a case study. Biotechnology and Bioengineering, 48 (5), 529-541.

Pintaric, Z. N., & Kravanja, z. (2008). Identification of critical points for the design and synthesis of flexible processes. Computers and Chemical Engineering, 32, 1603–1624

Pirró, G., Mastroianni, C., & Talia, D. (2009). A framework for distributed knowledge management: Design and implementation. Future Generation Computer Systems, doi:10.1016/j.future.2009.06.004

Potocnik, P., & Grabec, I. (1999). Empirical modeling of antibiotic fermentation process using neural networks and genetic algorithms. Mathematics and Computers in Simulation, 49, 363-379

PSE, 1997. Process Systems Enterprise, London. http://www.psenterprise.com/gproms/index.html

Qian, Y., Liang, J., & Dang, C. (2009). Knowledge structure, knowledge granulation and knowledge distance in a knowledge base. International Journal of Approximate Reasoning, 50, 174–188

Quintana-Hernàndez, P., Bolanos-Reynoso, E., Miranda-Castro, B., & Salcedo-Estrada, L. (2004). Mathematical modeling and kinetic parameter estimation in batch crystallization. AIChE Journal, 50(7), 1407-1417.

Rayo, A. (2007). Ontological Commitment. http://web.mit.edu/arayo/www/ontcom.pdf

Rodionova, O. Ye., Sokovikov, Ya. V., & Pomerantsev, A. L. (2009). Quality control of packed raw materials in pharmaceutical industry. Analytica Chimica Acta, 642, 222-227

Roggo, Y., Jent, N., Edmond, A., Chalus, P., & Ulmschneider, M. (2005). Characterizing process effects on pharmaceutical solid forms using near-infrared spectroscopy and infrared imaging. European Journal of Pharmaceutics and Biopharmaceutics, 61, 100-110.

Roggo, Y., Chalus, P., Maurer, L., Lema-Martinez, C., Edmond, A., Jent, N., (2007). A review of near infrared spectroscopy and chemometrics in pharmaceutical technologies. Journal of Pharmaceutical and Biomedical Analysis, 44, 683–700.

Sales-Cruz, M., & Gani, R. (2003). A modelling tool for different stages of the process life Computer Aided Chemical Engineering, 16, 209-249

Sales-Cruz, M. (2006). Development of a Computer Aided Modeling System for Bio and Chemical Process and Product Design. PhD. Thesis, CAPEC, Department of Chemical Engineering, Technical University of Denmark.

Sales-Cruz, M., & Gani, R. (2006). Computer-Aided modeling of short-path evaporation for chemical product purification, Analysis and design. Chemical Engineering research and design, 84 (A7), 583-594.

Scotter, C. (1990). Use of near infrared spectroscopy in the food industry with particular reference to its applications to on/in-line food processes. Food Control, 1(3), 142-149.

Sen, R., & Srinivasa Babu, K. (2005). Modeling and optimization of the process conditions for biomass production and sporulation of a probiotic culture. Process Biochemistry, 40, 2531–2538

Sen, S., Narasimhan, S., & Deb, K. (1998). Sensor network design of linear processes using genetic algorithms. Computers & Chemical Engineering, 22 (3), 385-390.

Shakhashiri, B. Z. (2007). Chemical of the week: Ammonia. Science is fun, in the lab of Shakhashiri. University of Wisconsin-Madison. http://scifun.chem.wisc.edu/CHEMWEEK/Ammonia/AMMONIA.html

Shieh, J., Huber, J. E., Fleck, N. A., & Ashby, M. F. (2001). The selection of sensors. Progress in Material Science 46, 461-504.

Sin, G., Ödman, P., Petersen, L., Lantz, A. E., & Gernaey, K. V. (2008). Matrix notation for efficient development of first-principles models within PAT applications: Integrated modeling of antibiotic production with Streptomyces coelicolor. Biotechnology and Bioengineering, 101, 153–171.

Singh, R., Gernaey, K.V., & Gani, R. (2008). Off-line design of PAT systems for on-line applications. Computer Aided Chemical Engineering, Volume 25, 423-428

Singh, R., Gernaey, K.V., & Gani, R. (2009a). Model-based computer-aided framework for design of process monitoring and analysis systems. Computers & Chemical Engineering, 33, 22-42.

Singh, R., Gernaey, K. V., & Gani, R. (2009b). ICAS-PAT: A software for design, analysis and validation of PAT systems. Computers and Chemical Engineering, doi:10.1016/j.compchemeng.2009.06.021

Smith, K. & Crofts, M. (2006). Real-time monitoring of an industrial batch process. Computers and Chemical Engineering 30, 1476–1481

Soejima, K., Matsumoto, S., Ohgushi, S., Naraki, K., Terada, A., Tsuneda, S., et al. (2008). Modeling and experimental study on the anaerobic/aerobic/anoxic process for simultaneous nitrogen and phosphorus removal: The effect of acetate addition. Process Biochemistry, 43, 605–614

Subrahmanya, N., Shin, Y. C., & Meckl, P. H. (2009). A Bayesian machine learning method for sensor selection and fusion with application to on-board fault diagnostics, Mechanical Systems and Signal, doi:10.1016/j.ymssp.2009.06.010

Sutherland, J. W. (2004). Sensor Fundamentals, http://www.mfg.mtu.edu/cyberman/machtool/machtool/sensors/fundamental.html

Tangsathitkulchai, C. (2002). Acceleration of particle breakage rates in wet batch ball milling. Powder Technology, 124, 67-75.

Todar, K. (2009). Lactic Acid Bacteria. Online textbook of bacteriology. Department of Bacteriology, University of Wisconsin. http://textbookofbacteriology.net/lactics.html

Truesdale, G. A., Downing, A. L., & Lowden, G. F. (1955). The solubility of oxygen in pure water and sea water. Journal of Applied Chemistry, 5, 53-62.

References

Václavel, V., & Loucka, M. (1976). Selection of measurements necessary to achieve multicomponent mass balance in chemical plant. Chemical Engineering Science, 31, 1199-1205.

Venkataram, S., Khohlokwane, M., Balakrishnan, S. , Litke, A., & Lepp, H. (1996). Tablet compression force measurement using strain gauges, Pharmaceutics Acta Helvetiae, 71, 329-334

Vlachos, N., Skopelitis, Y., Psaroudaki, M., Konstantinidou, V., Chatzilazarou, A., Tegou, E., (2006). Applications of Fourier transform-infrared spectroscopy to edible oils. Analytica Chimica Acta, 573–574, 459–465.

Wählby, U., & Skjöldebrand, C. (2001). NIR-measurements of moisture changes in foods. Journal of Food Engineering, 47, 303-312.

Haby, J. (2008). What is the difference between accuracy and precision,. Mississippi State University, USA. Weather prediction website. http://www.theweatherprediction.com/habyhints/246/

Wen, W., Chen, Y.H., & Chen, I.C. (2008). A knowledge-based decision support system for measuring enterprise performance. Knowledge-Based Systems 21, 148–163

Fu, W., & Methews, A. P. (1999). Lactic acid production from lactose by *Lactobacillus plantarum*: kinetic model and effects of pH, substate, and oxygen. Biochemical Engineering Journal 3, 163-170

Westerhuis, J. A., Coenegracht, P. M. J., & Lerk, C. F. (1997). Multivariate modelling of the tablet manufacturing process with wet granulation for tablet optimization and in-process control. International journal of Pharmaceutics, 156, 109-117

Wu, C. Y., Ruddy, O.M., Bentham, A.C., Hancock, B.C., Best, S.M., Elliott, J.A. (2005). Modelling the mechanical behaviour of pharmaceutical powders during compaction. Powder Technology, 152, 107– 117

Yildiz, B. (2007). Ontology-driven information extraction. Ph.D. Thesis, Vienna University of Technology, 7-8.

Zaror, C. A., & Pyle, D. L. (1997). Process design: an exercise and simulation examples, in Chemical Engineering for the Food Industry. Published in 1997 by Blackie A & P, an imprint of Chapman & Hall, London, ISBN 0 412 49500 7.

Zhou, Y., Chu, J. S., Zhou, T., & Wu, X. Y. (2005). Modeling of dispersed-drug release from two-dimensional matrix tablets. Biomaterials, 26, 945–952

Zwietering, M. H., & Hasting, A. P. M. (1997). Modelling the hygienic processing of foods- a global process overview. Food and Bioproducts Processing, Volume 75, Issue 3, 159-167

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