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Resource Consumption Models for Different Manufacturing System Configurations

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RESOURCE CONSUMPTION MODELS FOR DIFFERENT MANUFACTURING SYSTEM CONFIGURATIONS

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ABSTRACT

This thesis will focus on resource consumption models of productivity, cost of quality, and cycle time, to describe and select preferred configurations as a function of the system and operating parameters. Consider a production system which consists of workstations or machines that can be arranged in different configurations, where each configuration can affect the performance of the system. This thesis will model and analyze four main configurations, namely serial, parallel, and serial-parallel with and without crossover.

In a production system, parts are processed at each workstation or machine, where a value is added to the part. Inspection is performed to classify a quality characteristic of a part at each workstation or machine to be accepted, reworked, or scrapped. The short term probability of accept, rework, and scrap are utilized to model the long term probabilities using an absorption Markov Chain methodology. Each configuration will result in unique long term probabilities depending on the number of processes, order and location of each process. The long term probabilities and process flow are used to develop the resource consumption models for each alternative. At first, a two process production system is analyzed using pure serial and parallel configurations, and their performance is evaluated using sensitivity analysis. Then, a four process production system is analyzed using the four configurations, and the performance of each alternative is evaluated using a numerical example. Finally, general models for the resource consumption of an n-process production system

are developed for the serial, parallel, and serial-parallel without crossover. Mathematica® is utilized to develop the matrix calculations and equations for the n-process models. A case study of a biopharmaceutical company is used to apply the proposed models. All required data for three production systems are collected then analyzed to be used in identifying the productivity, quality cost, and cycle time for different configurations.

It is shown that there is a relationship between system configuration and its performance measured by productivity, quality cost, and cycle time. The proposed methodology in this thesis can be used to select the preferred configuration, where production systems with different parameters can result in different conclusions. The selection of the best configuration can be done by evaluating the resource consumption models for each possible alternative considering the different operating constrains, where the models in this thesis allow the manufacturer to select the best alternative based on specific performance targets. The developed models can also be used in discrete and continuous manufacturing systems, such as the biopharmaceutical industry case study.

Acknowledgments

I would like to thank my advisor Dr. Valerie Maier-Speredelozzi for her help and support. I also would like to thank all who supported this research from XY Biopharmaceutical Company by providing me with all the tools and access to their production plant and data.

Dedication

This thesis is dedicated to my mother and my husband, who their love, support, and belief in me inspired me to achieve this thesis. Also, I dedicate this thesis to my father and all of my siblings for their encouragement since the beginning of my graduate study.

TABLE OF CONTENTS

CHAPTER THREE

METHODOLOGY: MODEL FOR TWO PROCESS PRODUCTION SYSTEM

CHAPTER SEVEN

DISCUSSION AND CONCLUSIONS

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE

INTRODUCTION

1.1 Overview

Many studies have focused on efficiently designing the production system which has fluctuations in demand in an ever-changing global market. These studies also focused on the continuous need for improving the production system to meet customer expectations. Many models have been developed to improve the overall performance of the production system. These models have been concerned with production planning, facility layout, line balancing, and material handling, to name a few. The question then becomes, does the system configuration of equipment play a significant role in the overall system performance? If yes, then what are the performance measures?

The ability to cope with continuous changes in demand has become one of the fundamental challenges that modern manufacturers currently face. Recently there are some research projects that focus on diagnosing the relationship between the system configuration or layout and the performance. Many metrics have been used to evaluate the performance of each configuration.

This chapter will include a brief discussion about system configuration, the problem statement, the justification and significance of the study, a discussion of scrap and rework in production systems, a review of the biopharmaceutical industry, and a description of the thesis organization.

1.2 System Configuration and Challenges

Koren *et al.* (1999) defined the system configuration as the machine or workstation arrangement and connections. The machine arrangement means how the processes flow through the line, but not necessarily the physical layout of the machines. The serial layout is the traditional system configuration by which the material flows from one stage to another where each stage adds value to final product, there is only one path for the product flow, and the line is dedicated for one product or product family. This configuration was traditionally used in the automotive industry where the high volume and low product mix were required. Another configuration is the pure parallel by which each workstation is arranged parallel to the other and each one can perform all required tasks to complete the final product. In this configuration machines should be flexible and multi-task which means a high investment cost. Other than these two extreme configurations (pure serial and pure parallel), there are the parallel-serial and hybrid configurations. The parallel-serial includes two or more identical serial lines arranged in parallel, with or without crossover. Without crossover, the number of production flows equals the number of serial lines. The number of paths is larger when crossover is included, because of the flexibility in transferring products between lines. In contrast to the serial line, one benefit of the parallel-serial configuration is the ability to keep the system producing products even when one or more machines fail. It also facilitates the ability of the system to not be completely idle during the conversion from one product to another. In hybrid configurations, the number of identical machines at each stage is not equal as it is in the parallel-serial configuration, and crossover does not necessarily exist after each stage.

A number of performance metrics have been proposed in the literature to assess the performance of each of the above described configurations. Most of the studies in this area considered the following performance measures: productivity and reliability, quality, convertibility, number of product types, scalability, and cost. How the different types of configuration impact these measures has been the core concern of many studies. Diverse models have been pursued in analyzing the effect of configuration on performance measures separately, where an integrated model that combines all measures might be one option in finding the preferred system configuration that will satisfy all performance measures.

1.3 Problem Statement

There should be useful methods and principles for designing the manufacturing system and facilitating the selection among configuration alternatives. The effect of scrap and rework should be considered in modeling production systems, since it will reflect more accurate calculations for resource utilization. This could generate a strong baseline for selecting the preferred configuration.

Biopharmaceutical companies have been challenged to reduce their production costs to be able to deliver their products to the market at a reasonable price, and to remain competitive, maintaining the quality level that is required to provide customers with reliable products. Recognizing the effect of system configuration on performance, in addition to understanding biopharmaceutical processes, regulations, and limitations, will contribute significantly to improving the manufacturing system and decreasing high production costs that most biopharmaceutical companies currently face.

Different manufacturing system configurations result in different performance which is measured by many metrics. When the demand and product type or lifetime change, the efficiency of the production line deteriorates, unless the equipment layout is flexible and optimized to compensate for that change. Equipment configuration should be analyzed to improve the manufacturing line efficiency. Configuration selection requires proposing potential configurations, analyzing the model of each configuration and then identifying the preferred one.

Not all materials which enter the production line make it to the end as finished products, because there is material that leaves the line as scrap, which could be generated from processes or rework stations after parts fail to meet specifications. Rework and scrap rates strongly affect the production cost because they increase labor, material, quality and other costs, and hence reducing the rework and scrap rates improves the line efficiency and profitability.

Consider a production line with many equipment workstations where there is a need to improve the system output. Capturing how the configuration selection contributes to achieving this target is a large challenge. Different configurations such as: serial, parallel, serial-parallel with and without crossover, and hybrid configurations could be proposed and analyzed. The way of analyzing these alternatives and then finding the best one is another challenge that exists. In this thesis, the production flow through all stages is modeled, which includes: raw material, main processes, rework stations, scrap bins, and finished product. The probability of transition between stages is considered in building the model, where these probabilities are combined with the resource utilization at each stage. A Markov chain is a stochastic model that is applicable in this instance. After creating the model and depending on the type of resources that need to be considered, the model is analyzed to find system resource utilization for each configuration alternative and then the configuration that provides the best performance can be identified. The preferred system configuration will have higher productivity, lower cycle time, or lower quality cost. A case study in the biopharmaceutical industry will be applied to validate the model and verify the approach.

1.4 Justifications and Significance of the Study

The problem of finding the preferred system configuration is relatively new and it was addressed based on the objective of finding configurations other than the traditional serial line due to the continuous change in the demand and lifetime of products. Several studies have provided methodologies, guidelines, and principles to increase the system responsiveness to the short life cycle of products. Recent studies have proposed various models and methodologies for analyzing the effect of the system configuration by including different measures of performance.

In 1999, Koren *et al.* represented the Reconfigurable Manufacturing System (RMS) as a sufficient solution to increase the ability to adapt for dynamic changes in demands which in turn increases system responsiveness. They compared three types of manufacturing system: Dedicated Manufacturing Lines (DML), Flexible Manufacturing Systems (FMS), and Reconfigurable Manufacturing System (RMS) in terms of objectives and limitations. Zhong *et al.* (2000) built models used to measure productivity and quality of different system configurations. They emphasized the importance of the convertibility metric in measuring the system performance, especially for RMS, and pointed out that finding an integrated model that reflects the impact of configuration on all performance measures is very important in selecting the right configuration. Spicer *et al.* (2002) illustrated many principles that help in designing the system configuration. They compared the effect of different configurations on throughput, line balancing, and scalability. Freiheit *et al.* (2003) proposed a model to determine the productivity for mixed serial-parallel configurations, and showed how this non-traditional configuration is equivalent, in the ability of improving productivity, to the buffered serial configuration. Colledani *et al.* (2005) provided a decomposition method for evaluating the performance of configuration or reconfiguration of the production system. Shabaka *et al.* (2007) mentioned two levels of reconfiguration: system and machine. They explained how the ability of re-assigning the resources at these two levels leads to increases in the flexibility of the production system which becomes more able to cope with changes in product demands. The authors demonstrated how different configurations of machine axes of motion cause different capabilities for the machine.

Bohn and Terwiesch (1999) mentioned that in most production systems not all raw materials entering the line to be processed make it to the end and turn into a good quality final product. They explained that at the checking point components are tested and classified either as good or as defective items. They explained the high impact of scrap and rework on the system capacity utilization especially if defects are detected at bottleneck machines. The authors studied the effect of yield losses, caused by reworked and scrapped items, in yield-driven production processes. They demonstrated the importance of improving the yield in increasing the productivity. They summarized the rework and scrap effects on material, labor, capacity, and variability related costs.

Bowling *et al.* (2004) presented a model to determine the expected profit from n-stage serial production systems by considering the cost of processing, scrap, and rework. The authors used absorbing Markov chains to identify the long term probabilities of the three states of the product during the production processes: rework, scrap, and accepted.

Pillai *et al.* (2008) showed that Markov chain models can be used to represent the production system under uncertainties due to reworking and scrapping. The authors modeled material flow through a serial production system with rework and scrap by using the absorbing Markov chain. By using the model they adopted, system design and also production and inventory control could be efficiently improved. Using an absorbing Markov chain model enables the authors to build equations to determine the following: material requirements, number of machines, production cost, and manufacturing lead time.

As can be seen from the above, many studies focused on building models to study the impact of system configuration on productivity, quality, scalability, and convertibility, but they do not typically consider resource consumption which is strongly related to the production cost or profit. On the other hand, some studies focused on the effect of scrap and rework on the production system performance, but they only focused on the serial configuration and did not consider other types of system configurations. This thesis will use the Markovian approach to model the production flow of four different system configurations: serial, parallel, serial-parallel without crossover, and serial-parallel with crossover. Scrap and rework probabilities will be considered, and different system resources such as money and time will be built into the model. After that, the proposed model will be used to evaluate many configuration alternatives and select the best one. Scrapping and reworking make deterministic modeling unreasonable, so instead stochastic modeling is required which could be achieved by using Markov chains, as will be adopted in this thesis. Moreover, although most of the studies of the effect of configuration on system performance have been applied in machinery or similar production systems, in this thesis a case study will be applied at a biopharmaceutical company to validate the model. All of the above make this research unique with significant contributions to the literature.

1.5 Scrap and Rework States in Production Systems

The production system consists of stages where items are being processed, inspected, and forwarded to consecutive stages, such as reworked, scrapped, or finished products. Scrap and Rework are two states in the production system that affect the quality, cost, and cycle time, and if their probabilities are known, then the production system characteristics will be better understood which in turn will improve the process of achieving the production target.

In production, parts could conform to quality specifications or be defective. Parts that conform to the quality specifications continue through subsequent production processes, where the defective parts, which are items that do not confirm to predetermined specification limits and attribute requirements, could be then either reworked or scrapped. Parts that could not be repaired by the rework process have to be scrapped, but this is not the only criteria to classify items as scrapped or reworked; sometimes the items are scrapped because it is more economically feasible than repair. In specific types of production, such as machining, items are scrapped or reworked if the quality characteristic fall outside the specification limits.

Raw materials, unfinished products, rework, scrap or finished goods represent all possible states that material could transfer through when raw material enters the production line. Building a stochastic model that combines all of these states will be one of the challenges in this thesis.

1.6 Biopharmaceutical Industry

A Biopharmaceutical can be identified as: "A therapeutic product created through the genetic manipulation of living things, including (but not limited to) proteins and monoclonal antibodies, peptides, and other molecules that are not chemically synthesized, along with gene therapies, cell therapies and engineered tissues" (Odum, 2002).

Newcombe *et al.* (2008) mentioned that "more than a third of all drugs under development by pharmaceutical and biotechnology companies are biopharmaceuticals". They said that in 2005 there were nearly 300 licensed biopharmaceuticals on the worldwide market and the number is growing annually by 20%. They also said that the revenue for these biopharmaceuticals is approximately $85 billion.

Biopharmaceutical companies have been challenged to reduce their production costs to be able to deliver their products to the market at a reasonable price, and to remain competitive, maintaining the quality level that is required to provide customers with reliable products. There are many regulations that biopharmaceutical production processes have to meet before products exist in the market, which also increase the challenges. In addition, there are limitations that affect the ability of the companies to upgrade their production systems. For example, when a company changes from producing one product to producing multiple products it increases the risk of cross contamination which makes it more difficult to ensure the quality and safety of the products. Improving production and reducing operational costs in both continuous and discrete production environments is essential for the pharmaceutical and biopharmaceutical industries.

Recognizing the effect of machine configuration on system performance, in addition to gaining a better understanding of the biopharmaceutical processes, regulations, and limitations will contribute significantly in improving the manufacturing system and decreasing high production costs that most biopharmaceutical companies currently face.

1.7 Thesis Organization

This thesis is organized as follows: the introduction has been presented in Chapter 1. The literature review is addressed in Chapter 2. The research theory and development of models for a multi-stage production system with two, four, and n processes is provided in Chapters 3, 4, and 5 respectively. After that, a case study at a biopharmaceutical company is applied in chapter 6. The discussion and conclusions are included in chapter 7.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

As the ever-changing global market and the growth of competitiveness increases the pressure that modern manufacturing systems face, the production layout problem has attracted the interest of many scholars, with new models developed to address the complexity of today's production system design. Coping with the continuous demand changes has been considered as a fundamental challenge in designing the production layout. While much of the research in the field of manufacturing systems has been concerned with physical machine arrangement, others focus on the way that products flow through the workstations. Finding the relationship between system configuration and system performance is relatively new in literature. Some scholars have developed models for analyzing the system performance that is measured by one or more me trics such as: productivity, quality, scalability, convertibility, or cost. They have used the proposed models to analyze different configuration alternatives and find the best one. In this thesis a new model is developed to assess the performance for different configurations by also considering the scrap and rework rates which are in turn associated with resource utilization. Many scholars have studied and analyzed the effect of scrap and rework and used them in modeling the production system, but they have focused on serial configurations more than on other types of configurations. Moreover, many research projects for improving production layout have included case studies that have been applied in different types of production systems like automotive and machining, but not many studies have been implemented in biotech or pharmaceutical industries. However, some studies using Industrial Engineering principles and tools have been published in these industries.

This chapter presents som e literature that focuses on several relevant topics, which are:

1. Changing demands and needs for non-traditional system configuration.
2. Layout design problems and challenges.
3. The relationship between different configurations and system performance.
4. Scrap and rework effects and considering them in modeling the production system.
5. Challenges in the biopharmaceutical and pharmaceutical industries.
6. Studies that apply industrial engineering concepts or tools in system design at biopharmaceutical and pharmaceutical industries.

2.2 Changing Demands and Needs for Non-Traditional System Configuration

Continuous changes in customer demands and short product life cycles mean that manufacturers need to be more flexible when producing a large range of products. The challenge is to construct system configurations that have the ability to rapidly react to these changes at the lowest cost. Recently, research in this area has been increasing and generally focuses on proposing different configurations other than the traditional serial line.

Kochhar and Heragu (1999) proposed a methodology for layout design in a dynamic facility where the product mix and volume are not constant. The authors demonstrated that there is a continuous change in the product range and volume, and getting an accurate forecast becomes not possible any more. Based on that, they emphasized the importance of designing a dynamic layout that has the ability to be highly responsive to continuous changes.

Suh *et al.* (1998) demonstrated that there is a strong relationship between manufacturing system design and productivity. They illustrated that the different functional requirements and constraints which need to be satisfied generate different manufacturing system designs. They introduced the principles and methods for the axiomatic design of manufacturing systems which is based on the chosen functional requirements. The authors introduced the challenges that industry faces to produce a mix of products, and asserted the importance of using scientific principles and approaches rather than empirical knowledge when designing the manufacturing systems. The authors explained that constraints related to the available technology, cost, and performance metrics sometimes may affect the functional requirements which need to be considered in the design which, in turn, leads to weakness in the manufacturing system design.

Koren *et al.* (1998) explained that the traditional serial line configuration is not useful in "low volume – high variety" production systems. Freiheit *et al.* (2003)

mentioned that increasing buffer size to improve the system capacity is not beneficial anymore due to the continuous changes in demand which requires efficient reaction to market changes by reducing work in process, detecting quality problems quickly, and avoiding the risk of overproduction. In terms of productivity, Freiheit *et al.* proposed a model to analyze how the nontraditional configurations, such as mixed serial and parallel configurations, or reserve capacity configurations, could be equal to traditional serial systems with buffers. They described the importance of having a reliable material handling system to achieve the productivity improvement in the proposed nontraditional configurations.

Spicer *et al.* (2002) illustrated many fundamentals that help in the design of the system configuration. They mentioned how the continuous change in customer demand generates the need to obtain new alternatives for system configuration other than the traditional serial layout. These alternatives could be facilitated by the reduction in the cost of Computer Numerically Controlled (CNC) machines, and the introduction of new technologies. They also mentioned that multi-axes CNC machining systems generate multi-task systems that have the ability to align with different possible system configurations. The authors differentiated between two configurations with and without crossover, and between the symmetric and asymmetric configurations. In contrast to the symmetric configurations, in the asymmetric configurations the parts are processed by various plans and on different numbers of machines. They mentioned that the system configuration is defined not only by the machine layout but also by the machine connections. They introduced the effect of setup arrangements on system configuration length, which is determined by the number of machines the part should be processed on. The configuration length can be adjusted either by operation division or setup combination. They introduced the system configuration width as a number of parallel machine sets. Besides determining the upper and lower bounds for the configuration length, they also determined these bounds for the configuration width.

2.3 Layout Design Problems and Challenges

There have been many articles developed to study, investigate, and build models for layout design. Many targets and constraints have been considered in the layout design and many challenges have faced the researchers through their studies. In some of the literature, models for block layout (or physical arrangement of departments and machines) were built, where other literature looked at the layout as how the product parts flow through the machines, regardless of the physical location.

Kochhar and Heragu (1999) proposed a methodology for block design of a multiple-floor facility to be more flexible in the ability of rearranging the departments, workstations or machines in future periods. The objective of their methodology, the Dynamic Heuristically Operated Placement Evolution (DHOPE), was minimizing the rearrangement costs and material flow costs by designing a dynamic facility over two consecutive periods. They pointed out that the infrastructure and the supportive tools should be designed to have the ability to facilitate the rearrangement actions.

Hassan (1994) studied the problems that relate to the machine arrangement in production floors for modern manufacturing, and he argued that block layout is not applied practically in actual production systems and hence, other methodologies are required. The author demonstrates the importance of machine layout and the factors that play roles in its development. He differentiated among three types of layout: single row, multiple rows, and the loop layout (fig.1). The author also explained different measures that affect choosing among these layouts.

Hassan (1994) differentiated between the machine layout and the block layout problems, and explained the need for considering the issues of backtracking and bypassing and not ignoring them, as in the block layout problem. The author also asserted the importance of the material handling consideration in machine layout design, and pointed out the importance of the flexible machine layout to cope with uncertainties in customer demand and product mix with minimum or no changes in the layout arrangement. He discussed different studies about the formulations of the machine layout problem in terms of objective, constraints, and layout type, and about the different suggested layout performance measures. He mentioned that Quadratic Assignment Problem (QAP) as one of the most common procedures for formulation of the machine layout problem. The author compared the different suggested procedures in the literature for layout construction or improvement.

The comparison was in terms of problem formulation, solution methodology, layout type (row, multiple rows, or loop layout), and problem size. Evaluation of the solutions and results were mentioned also for each methodology. He criticized many of these suggested layout procedures. For example, he argued that these procedures were not performed in real manufacturing plants.

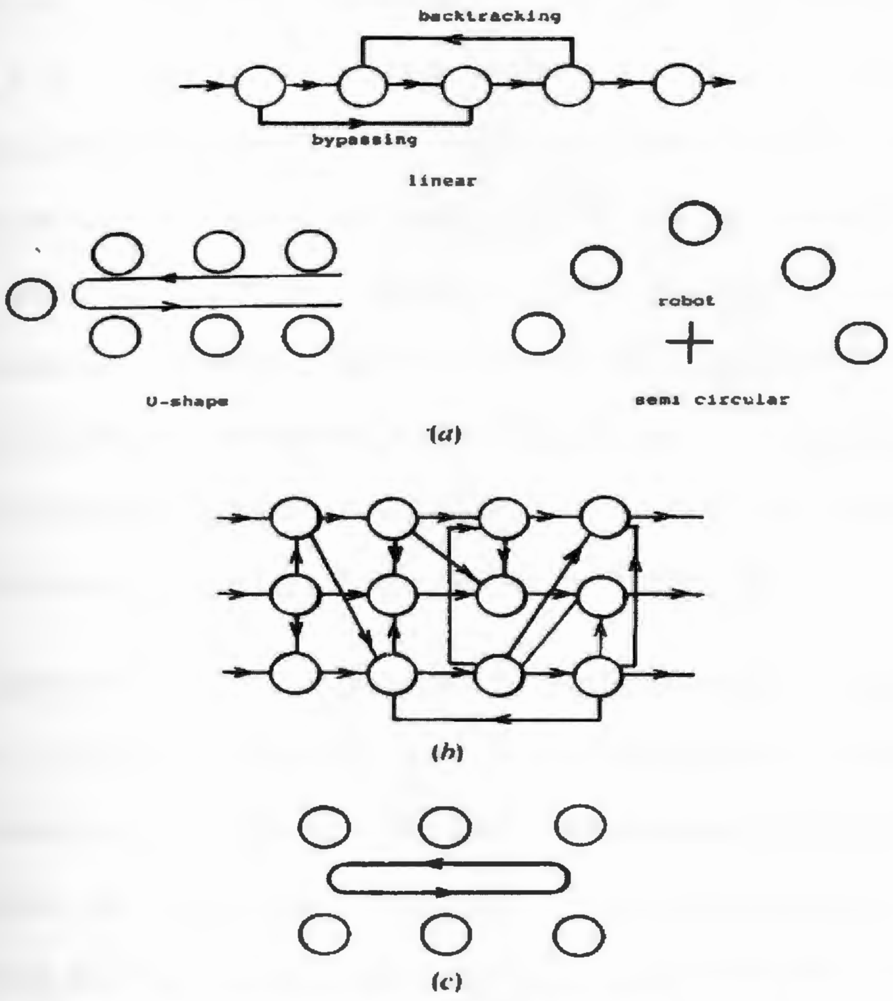


Fig. 2.1 Type of machine layout: (a) Single row layout; (b) multi-row layout; (c) loop layout (Hassan, 1994).

Klampfl *et al.* (2005) mentioned that although the mixed model assembly line responds quickly to variations in customer demand, many efforts are required to find the preferred production layouts. The authors proposed three formulations for optimizing the layout in automotive assembly lines. Their method was based on the lean system concept of decreasing the non value added time. They defined and used the e-Workcell tool, which is a tool that has been used by Ford to develop a 3D image of the workcell elements according to data from the production plant. They describe their optimization problem, and the objective of reducing the non-value added time which is affected by the arrangement of the workcell elements. The authors proposed several formulations (unconstrained, one-dimensional constrained, and two-dimensional constrained) to solve the objective function and optimize the layout. Their proposed methods for optimizing the layout efficiency enhance the objective of increasing the flexibility in the production system to respond efficiently to different product mix.

Kaebernick *et al.* (1996) presented an integrated model for designing the layout of a Cellular Manufacturing system. The authors pointed out that there are three phases of Cellular Manufacturing design: parts/machine grouping, the layout of machines within cells, and the layout of cells in the shop floor. They emphasized the importance of layout design as an essential element in achieving the desired benefits from Cellular Manufacturing. Their developed model is based on evaluating the integrated effects of the three phases of design on the overall system. It provides multiple alternatives which need to be assessed based on the predetermined criteria.

2.4 The Relationship between Different Configurations and System Performance

Some authors have started to recognize the strong relationship between the system configuration and its performance in their studies. The traditional serial configuration may be insufficient for adapting to dynamic customer demands, and hence, the need for new configuration designs is introduced with many associated challenges and problems which need to be considered. This section presents literature that has shown the impact of system configuration on its performance, and then presents some research that have focused on studying different performance measures.

Koren *et al.* (1998) discussed how different configurations of the manufacturing system lead to different performance. They described that choosing the preferred configuration is based on the following measures of performance: productivity, reliability, quality, capacity, and cost. They mentioned that there is a relationship between the number of machines in the system and the number of configurations that could exist. They analyzed the effect of system configuration on performance by proposing a methodology of comparing many configuration alternatives based on the above performance measures.

Spicer *et al.* (2002) demonstrated the relationship between the system configuration and its performance by comparing four symmetric configuration alternatives (pure serial, pure parallel and short serial lines in parallel with and without crossover) based on four metrics: throughput, line balancing, system investment cost, and capacity scalability.

Zhong *et al.* (2000) pointed out that there are different metrics for evaluating the performance of different configurations for the production line, where an integrated method that combines all measures is more efficient in selecting the best arrangement for machines. The authors proposed methodologies to determine three measures of performance: productivity, quality, and convertibility. As a case study, they compared four configurations of the machining system (serial, parallel, and two hybrid configurations) in terms of productivity, quality, and convertibility.

2.4.1 Productivity and System Reliability

System productivity is often the most important target that most manufacturers try to improve. There are many researchers who have used productivity as a basic objective in building their models for improving the system performance.

In terms of throughput, Spicer *et al.* (2002) explained examples of the effect of configuration on the gross throughput, on the expected throughput, and on the probability distribution function.

Zhong *et al.* (2000) used machine availability and complexity and processing rate as parameters for determining system productivity.

Sun *et al.* (2008) investigated the relationship between the machine configuration, machine-level reliability and the system-level reliability. They developed a methodology for analyzing the quality reliability at both the machine level and the system level. They analyzed the machine level quality reliability by considering the joining effect of product quality and tool degradation. Then they used the proposed integrated model for machine-level reliability to predict the system level reliability for serial-parallel hybrid manufacturing systems with various selected configurations

2.4.2 Quality and Stream of Variation Theory

Quality has been considered as a fundamental measure of system performance. Many studies have analyzed the effect of good quality on improving the production system.

Colledani and Tolio (2006) illustrated that configuration has an impact on both the productivity and quality control performance. They emphasized the fundamental importance of considering the quality and throughput measures together during the design phase of the production system. Colledani and Tolio proposed a method for evaluating the production system performance by considering both of these measures. They mentioned that there are many tools and techniques that have been developed to predict the production throughput and monitor the quality level, but only recently some literature has begun recognizing the importance of using an integrated method to deal with both of them. Zhong *et al.* (2000) used the mean and standard deviation as measures for the quality of the finished product.

Stream of variation

Recent works have analyzed the effect of the production and process system design on the quality of the finished parts. The stream of variation theory has been introduced to predict how the variability of products propagates through the workstations of a production system.

Hu and Koren (1997) suggested a model for the flow of dimensional errors when the product moves from one station to the next. The authors said that the assembly variation is larger than the variation in the component, since the dimensional variation is accumulated while the product is transformed through the assembly system. The developed model helps in solving the quality problem earlier, since it increases the ability to predict the variation evolution through the assembly line. They demonstrated that sheet metal parts in the automotive industry can be deformed through the assembly process, and that causes an increase in the dimensional changes. Hu and Koren (1997) explained the two elements of the Stream-of-Variation theory: 1) analyzing how the dimensional variation of the components is propagated through the assembly line so that the variation of the final product can be anticipated and 2) determining the variation causes and sources in the assembly line. He studied the relationship between the propagation of the assembly variation and the assembly configurations. He showed that variability and the diagnosability features of the serial and parallel assemblies are different. The author identified two causes of variation in the automotive body assembly: (1) by fixture and (2) by part or welding process deviation. He also developed a fault diagnosis strategy to reduce the variation.

Djurdjanovic and Ni (2006) demonstrated that the dimensional variations are transformed and accumulated from one operation to the next through a multi-station machining system. The authors introduced methods for measurement scheme analysis in multi-station machining systems to predict the root causes for the dimensional faults. In this methodology, the combinations of measurements are evaluated in terms of the goodness of information they provide about the machining process parameters. The best set of measurements is the one that is more informative in reflecting the root causes of the machining dimensional errors. The stream of variation model was the basis for their methodology.

2.4.3 System Responsiveness

Zhong *et al.* (2000) pointed out that the system responsiveness is measured by the convertibility and scalability of the system, where the convertibility reflects the system ability to produce different products, and the scalability reflects its ability to adjust the production volume depending on the demand, with less cost and less time. They asserted the importance of the convertibility measure in the Reconfigurable Manufacturing System (RMS). They proposed using the time required to convert the system as a measure for its convertibility.

Maier-Speredelozzi *et al.* (2003) discussed the significance of the production system responsiveness as a result of the continuing variation in customer demand. They introduced the meaning of convertibility which, together with capacity scalability, indicates the system responsiveness. The authors developed equations that reflect three metrics for the convertibility related to configuration, machines, and material handling. The authors showed that different layouts and different ways of connecting machines result in different alternatives of configuration which is associated with minimum conversion increment, number of routing connections, and the number of replicated machines. Regarding the machine convertibility measure, they explained how it depends on the machine's features. They also introduced many factors related to measuring the material handling convertibility. The authors analyzed two case studies as examples of using the convertibility metrics to compare alternatives.

In terms of capacity scalability, Spicer *et al.* (2002) suggested that different configurations cause different levels of scalability. Having more scalability, either through the ability to add new machines in parallel or by just adding a scalable tool to such a machine, increases th e ability to change the system capacity depending on customer demand. They proposed a multi-spindle scalable machine tool, which could help in improving the system scalability without adding new machines, reducing floor space and decreasing system investment cost.

2.4.4 Changeability and Reconfigurability of the Production System

The Reconfigurable Manufacturing System (RMS) concept has been developed to help manufacturers cope with continuous fluctuations in demand. Many research projects have been constructed to investigate and analyze the impact of the RMS.

Koren *et al.* (1999) showed that the reconfigurable system is required due to short pro duct lifetimes and continuous change in customer demand. They argued that there were studies and technologies created to develop the product design, but not that many efforts were invested to develop a method for designing the production system. They demonstrated that the reconfigurability of the system makes the system more adaptable to the changes in the capacity functionality, which will reduce the system design time. The authors compared three systems: Dedicated Manufacturing Lines (DML), Flexible Manufacturing Systems (FMS), and Reconfigurable Manufacturing Systems (RMS). DML produces high throughput but it is not scalable or flexible, and FMS is scalable but expensive and has general flexibility, while the RMS is scalable and has customized flexibility. They defined the RMS and its main aspects to be CNC machines, Re-configurable Machine Tools (or adjustable machine structure), and reconfigurable software and hardware. All of these enhance the quick response to the fluctuation in demand and product mix. The authors demonstrated five main characteristics for the reconfigurable system: modularity, integrability, customization, convertibility, and diagnosability. They also explained issues in RMS: system-level design, machine-level design, and system ramp up. They supported their discussion with examples about a reconfigurable machining system.

Azab and ElMaraghy (2007) proposed a mathematical model for Reconfigurable Process Planning and sequencing for the reason that the customer demand becomes unpredictable and requires an effective changeable or reconfigurable manufacturing system. They formulated the problem and set up the objectives and constraints, taking into account choosing the best location for the new required features.

Hon and Xu (2007) discussed the complexity that dynamic demand adds to the system design problem. The authors investigated the effect of the dynamic product life cycle on the timing and extent of reconfiguration. They asserted that companies should know when and how to perform a reconfiguration, where this decision depends on the individual circumstances and characteristics of each manufacturing system. The authors mentioned that there are three common methods for adding capacity to the system configuration, which are: using better tools or machine reconditioning, replacing the current machine, or adding a new machine. Th ey used the simulation method to analyze the multi-stage multi-product manufacturing system. The three steps in their simulation approach are: modeling the original configuration, optimizing the reconfigured system, and then optimizing the product portfolio.

Colledani *et al.* (2005) illustrated the meaning of changeability which reflects the ability of the company to respond to the unpredictable customer demand with minimum cost. They discussed the system reconfigurability which is one aspect of the system changeability. They proposed an approximate analytical method to assess the Reconfigurable Manufacturing System (RMS). They introduced a model based on two levels of decomposition: machine and buffer. Their suggested model was applied as a case study to evaluate different configurations as alternatives to increase the system capacity.

Shabaka *et al.* (2007) mentioned two levels of reconfiguration for RMS: system and machine. They explained how the ability of re-assigning the resources at these two levels leads to increases in the flexibility of the production system which becomes more able to cope with changes in product demand. The authors demonstrated how different configurations of machine axes of motion cause different capabilities for the machine. They proposed a methodology to construct the machine tool configuration based on part geometry and features, operations precedence constraints, tool approach directions (TAD), operation clusters, and the integration between the product features and machine capability.

2.5 Scrap and Rework in the Production System

Scrap and rework are two factors that have an impact on achieving the goal of improving the performance of a production system. Their effects could significantly increase cycle time and production cost, and decrease system efficiency. There are many scholars who have recognized that and hence, they have started to focus on studying and analyzing scrap and rework in the production system.

2.5.1 Scrap and Rework Definitions and Effects on Production System

Bowling *et al.* (2004) classified an item as scrap if the value of the quality characteristic of interest is less than the lower specification limit and as rework if the value is more than the specification limit. Bohn and Terwiesch (1999) mentioned that in most production systems not all raw materials entering the line to be processed make it to the end and turn into a good quality final product. In other words, the number of parts entering the process does not necessarily equal the number of parts coming out as finished products. They mentioned the possibility of having some scrapped items either directly from the main processes, or from the rework processes. They also explained that at the checking point components are tested and classified either as good or as defectives items. If the item is good then it proceeds to the next process, and if not, it could be reworked or scrapped. They explained the high impact of scrap and rework on the system capacity utilization especially if defects are detected at bottleneck machines. They described that more value is added to the items as they move forward through the production system, and hence, having more reworked or scrapped items at later processes means more losses. The authors studied the effect of yield losses, caused by reworked and scrapped items, in yield-driven production processes. They demonstrated the importance of improving the yield in increasing the productivity. Besides that, they analyzed the economics of multi-stage yield-driven production processes and showed the effect of consuming cost and time due to scrap and rework processes. They summarized the rework and scrap effects on material, labor, capacity, and variability related costs.

2.5.2 Scrap and Rework Considerations in Production System Modeling

Bowling *et al.* (2004) presented a model to determine the expected profit by considering the cost of processing, scrap, and rework. The authors used absorbing Markov chains to identify the long term probabilities of the three states of the product during the production process: rework, scrap, and accepted. The long term probabilities were used to build a profit model for one, two, and *n*-stage serial production systems to determine the optimal process target at each stage. They applied sensitivity analysis by varying the model parameters to study their impact on the output.

Pillai *et al.* (2008) showed that Markov chain models can be used to represent the production system under uncertainties due to rework and scrap. The authors modeled material flow through a serial production system with rework and scrap by using the absorbing Markov chain, where both the scrap and finished product states were considered as absorbing states. By using the model they adopted, system design and also production and inventory control could be efficiently improved. Using an absorbing Markov chain model enables the authors to build equations to determine the following: material requirements, number of machines, production cost, and manufacturing lead time.

Davis and Kennedy (1987) considered rework, work in process, inspection, and scrap in their modeling of a serial production system. They also took into account the tool wear and the scheduling impact of the tool wear rate utilizing a Markov chain model for the production system. They analyzed the serial production system under different scenarios using the Markov models to have outputs that assist in solving production planning problems.

2.6 Challenges in the Biopharmaceutical and Pharmaceutical Industries

Biopharmaceutical and pharmaceutical companies, like other industries, are facing the ever-increasing challenges of improving their production systems to produce high quality products with the lowest cost. Many production regulations in the biopharmaceutical and pharmaceutical industry increase the challenges and complexity in designing the production systems. Researchers have studied these challenges, analyzed data from these industries, and pointed out the issues that biopharmaceutical and pharmaceutical companies should start to consider for improving their outcomes.

Abboud and Hensley (2003) talked about how pharmaceutical companies and the FDA have begun recognizing the importance of focusing on improving the production system instead of focusing only on developing new drugs for the market. They mentioned that the increasing number of recalls and the high percentage of defects in pharmaceutical production were strong indications for the FDA (Food and Drug Administration) about the need to start improving and introducing new methods and techniques in the production process. The authors of this article mentioned that many production shortcomings in the pharmaceutical industry are due to the production system's insufficient tools and methodologies. They included results from the analysis of financial statements by Raymond Scherzer, 2001, in which he illustrated that the production cost for the top pharmaceutical companies are 36% of the total costs, which is two times the expenses for Research and Development (R&D). They also suggested that concentration on improving the manufacturing processes is the rational way to save money and increase the pharmaceutical companies' profits, since there are fewer chances to develop new drugs or to increase sales. The authors gave examples from some companies, like Pfizer, that start investing in their production systems by applying new technologies to improve production efficiency.

Basu *et al.* (2008) discussed a study aimed at analyzing the production cost for some pharmaceutical companies, which was divided into three categories: brand, generic, and biotech companies. They also studied the relationship between the material and production cost or Cost of Goods Sold (COGS), and the Research and Development (R&D) spending. They mentioned that some studies indicated that the cost for production was more than three times the expenditure for R&D. The authors illustrated that one of many factors causing the high production cost in the pharmaceutical industry are the FDA regulations that require the companies to abide by the "current Good Manufacturing Practices" (cGMP). By comparing the annual reports of the top pharmaceutical companies, the authors demonstrated that in 2005 the revenue of the brand name companies ($10 billion) was two times the revenue for the generic companies ($5 billion). On the other hand, they expected that the generic companies would have much higher revenue in 2008, due to the expectation that more than two thirds of prescriptions would be converted to generic substitutes instead of brand name drugs.

By comparing the data of pharmaceutical companies with the highest market share from the above three groups over a study period of twelve years (from 1994 to 2005), Basu *et al.* (2008) found the following:

- In terms of COGS% (COGS as a percentage of total sales), the generic companies have a higher average than that for brand name companies which are higher than the average of the biotech companies.
- In terms of R&D% (percentage of R&D spending divided by sales) and operating income, biotech companies have a higher average, and then the brand name has a lower average, while the generic companies have the lowest average.
- In terms of general expense, brand name companies have the higher average, then the biotech, followed by the generic companies.
- For the brand name companies there is a "strong negative correlation between the COGS% and R&D%".
- For the generic companies, there is "strong negative correlation between the COGS% and the operating income".
- The manufacturing costs for the generic and brand name companies are around 50% and 27% of the total sales revenue, respectively.

Basu *et al.* (2008) gave a hint that reducing the production cost by improving the efficiency of the production system will reduce the price of the drugs, increase the investment in R&D, and increase the pharmaceutical companies' profits. Odum (2005) pointed out that biopharmaceutical design engineers should reduce the production cost and capital expenditures, and improve the flexibility in the production system. Odum identified three attributes that influence the facility design. These are product, process, and facility attributes. He emphasized that there are fundamental principles that should be fully understood to improve design and operation in the biopharmaceutical industry. One of these principles is that the process and facility designs are connected to each other. The author addressed the implementation of closed process system, controlled processing capabilities, and manufacturing flexibility. He mentioned that there are companies starting to produce multiple products, and that there is new trend to apply concurrent manufacturing to help achieve multi-product facilities. He represented the need for building strong strategic planning for the manufacturing capability in order to cope with the dynamic markets of many biological products. He also explained the changes in equipment design principles due to the increasing trends to move to a multi-product manufacturing system which require the equipment design to be more flexible and cost effective.

2.7 Studies that Apply Industrial Engineering Concepts or Tools in System Design at Biopharmaceutical and Pharmaceutical Industries

Oh *et al.* (2004) proposed a method to improve the throughput and the capacity of the production lines of Monoclonal antibodies (Mabs). The authors demonstrated that the demand for Mabs products keeps increasing while the biomanufacturers are unable to increase their production capacity to meet this high demand. They suggested using a simulation tool from Superpro® software to determine the constraints or problems in such design, instead of using the traditional method of conducting pilot plant experiments, which is a more costly and time consuming approach. By demonstrating a case study, the authors gave an example of using Superpro to simulate the processes by entering the inputs from a simple laboratory experiment. Then the material flow steam was constructed, and then the batch process simulation model was obtained. After that, the software was used to produce the machine utilization chart, which was used to determine the bottleneck in the system. The authors suggested many scenarios to increase the system capacity and productivity. They economically analyzed one new design scenario by applying a cost and profit analysis of increasing the number of machines to study its impact on increasing the number of batches produced and profit.

Hamamoto *et al.* (1999) developed a model for designing the facility layout and implemented this model at two pharmaceutical companies producing solid dosage forms. They built their proposed model based on a genetic algorithm with an embedded simulation model. They pointed out that the previously developed heuristic algorithms are not flexible enough and are built based on only one objective, usually determined in advance, while their method is more flexible and allows for choosing objectives that are required for each specific layout. The authors asserted difficulties and constraints that affect the layout design due to the nature of the production of the pharmaceutical companies. Some of these constraints are: the contamination which could result from using different materials, the predetermined methods for transporting the materials, the high cost for making changes in the design, and also the FDA regulations. All of these constraints should be considered carefully in building the model, which should be designed in a perfect way from the beginning since it may stay and be used for a long time without the ability to be adjusted.

Hamamoto *et al.* (1999) used a genetic algorithm in their model as the search algorithm, and the growth and band layout methods as the decoding algorithms. Their model's objectives are improving the throughput and reducing the traveling time. They compared the layouts they generated, the actual layouts, and also the ones which resulted from existing layout algorithms such as: CORELAP (construction algorithm), CRAFT (improvement algorithm), and BLOCPLAN (hybrid algorithm).

Newcombe *et al.* (2008) pointed to many hidden sources of variability in the manufacturing process of biological products. Hence it is important, during the development stage, to propose manufacturing processes that will have the ability to meet predetermined specifications. They introduced the “design space” term, which indicates a range of process parameters that assure producing products with good quality if they fall within this range. They mentioned the increased trends in applying Design of Experiments (DOE) for modern biopharmaceutical development. They mentioned that DOE could be used to define the design space for the process. The authors also showed how the DOE approach is very useful in finding the critical process parameters and the quality attributes. The authors applied the DOE approach in case study to analyze the impact of some factors on stability of an antibody derived biotherapeutic.

2.8 Summary

Table 2.1 and table 2.2 are used to summarize most of the articles that are mentioned in the literature review chapter. Table 2.1 includes the articles in which authors are focused on studying the effect of system configuration on the following metrics: productivity, quality, scalability, convertibility, changeability. Table 2.2 includes the articles that are mentioned under each of the following subjects: layout design, relationship between system configuration and performance, Reconfigurable Manufacturing System, effects of scrap and rework on the production system, and biopharmaceutical industry.

Table 2.1: Literature summary (1)

Article	Productivity	Quality	Scalability	Convertibility	Changeability/RMS
Koren *et al.*,1998	√	√	√		
Koren *et al.*,1999					√
Zhong *et al.*, 2000	√	√		√	
Spicer *et al.*, 2002	√		√		
Speredelozzi *et al.*, 2003				√	
Freiheit et al., 2003	√				
Colledani et al. (2005)	√				√

Table 2.2: Literature summary (2)

Article	Layout Design	Configuration-Performance	RMS	Scrap and rework	Biotech and Pharm.
Abboud and Hensley, 2003					√
Azab and ElMaraghy, 2007			√		
Basu *et al.*, 2008					√
Bowling *et al.*, 2004				√	
Colledani *et al.*, 2005			√		
Davis and Kennedy, 1987				√	
Freiheit et al., 2003		√			
Hamamoto et al., 1999					√
Hassan,1994	√				
Hon and Xu, 2007			√		
Kaebernick *et al.* ,1996	√				
Klampfl et al., 2005	√				
Kochhar and Heragu,1999	√				
Koren *et al.*,1998		√			
Koren *et al.*,1999			√		
Maier-Speredelozzi *et al.*,2003		√			

Newcombe *et al.*,2008					√
Odum, 2005					√
Oh *et al.*, 2004					√
Pillai *et al.*, 2008				√	
Shabaka and Elmaraghy, 2007			√		
Spicer *et al.*, 2002		√			
Bohn and Terwiesch, 1999				√	
Zhong *et al.*, 2000		√			

CHAPTER THREE

METHODOLOGY: MODEL FOR TWO PROCESS PRODUCTION SYSTEM

3.1 Abstract

Davis and Kennedy (1987) used Markov models for a serial production system to assist in solving problems that related to production planning. Bowling *et al.* (2004) used the absorbing Markov chain to build a profit model for one, two, and *n*-stage serial production systems to determine the optimal process target at each stage. Pillai *et al.* (2008) also used the absorbing Markov chain to represent a serial production system, in order compute material requirements, number of machines, production cost, and manufacturing lead time. In this thesis, absorbing Markov chains are adopted to model four system configurations: serial, parallel, serial-parallel without crossover, and serial parallel with crossover, in order to develop models for cost of quality, productivity, and cycle time, that can be used in comparing the performance of the different configurations to find the preferred configuration. Chapters three, four, and five include develop the models for production systems with two, four, and n processes, respectively.

This chapter focuses on a two process production system, where two different configurations are applied: the serial (where products go through two stages) and parallel (where products go through one stage) configurations. A product is processed at any given stage and then moves to the next step if it

meets quality specifications, while it gets reworked or scrapped if it is defective. Three models for cost of quality, productivity, and cycle time are proposed to define the configurations that obtain the best output of each model. The results show that the different configurations have different values of quality cost, system productivity, and total cycle time.

A brief description of the Markov Chain tool is discussed first, since it is used as a starting point to develop the three models for each configuration. After building the models, simple numerical examples are used to apply these models, and then sensitivity analysis is provided.

3.2 Markov Chains

When a product goes through multiple states in a production line, the probability that describes the product at any specific state is a function of that process or state. As the product proceeds in the line, the probability at each state becomes related to the prior process, i.e. the probability of state i depends on that of state $i-1$, while it is not related to the probability at any states prior to state $i-1$. This process is described to follow a Markov Chain process. The independence of probability at state i from all previous states (except $i-1$) makes the Markov chain method widely applicable in industry to predict the long term and steady state probability distribution of any given state, since the probability at any state can be defined by only the state that is immediately before, and it is independent of all prior states and any history of prior states.

In a Markov Chain process, the transition probabilities are considered. A transition occurs when the system moves from one state to the next state during one period of time. A transition represents when the system changes its state from i to j at a probability of p_{ij}. For example, in a production line, when a product moves from process 1 to process 2, then the transition probability is defined to be the probability of moving a product from process 1 to process 2, which can be referred to as the acceptance probability between 1 and 2. There is a primary assumption related to Markov chains, which is the stationary assumption. It implies that the transition probability of any state i to another state j does not change over time and is always the same. A Markov Chain is usually represented as a matrix of transition probabilities between any two states.

One of the widely used applications of a Markov Chain is the Absorbing chain which includes absorbing states in addition to the transient states. An absorbing state is a state when the system or product enters permanently without any chance to leave to any other state, i.e. the probability of leaving an absorbing state is zero, and the probability that a product or the system stays in the same absorbing state is 1. An example of an absorbing state could be the finished product state, or scrap state. Absorbing Markov Chains are used to find the long term probabilities of states that the product of the system would eventually enter, like a finished product or scrap state.

3.3 Two Stage Serial System with Two Processes

Consider a two stage production line, where one process is in each stage. A product is processed at the first stage, and then needs to go through the second stage for another required processing step before it reaches the finished product status. This type of production can be referred to as a two stage production system with two processes. These two production stages do not necessarily have to be physically in series, as long as the product needs to go through process X_1 and then process X_2 before it can be called a finished product.

In a serial system raw material is released to enter the first production stage, stage 1, where process X_1 will occur. Stage 1 processes the raw material and adds value by performing certain set of operations, which will add new features to the raw material. At the end of stage 1, a quality characteristic needs to meet specific requirements defined by the customer (internal or external customer); hence, each product needs to be inspected against the pre-defined requirements, or the customer specifications. When a product is inspected at stage 1, there will be three outcomes that are assigned to that particular product.

- A product can proceed to the next stage (stage 2) if the quality characteristic at stage 1 falls within the acceptable range of the customer specifications.
- A product can be reworked by re-entering stage 1 if the quality characteristic at stage 1 falls within the rework range in the customer specifications. Each reworked product will go through the same exact

operations at stage 1 and will be then subjected to the inspection station at stage 1.

- A product is scrapped and will never be processed at any other stage if the quality characteristic falls within the scrap range in the customer specification.

Note that the rework and scrap ranges are not defined by the customer, but rather defined by the process capability, engineering assessment, nature of the product, ability to rework a product, etc... For example, consider a turning machine at stage 1, where the manufacturer cuts metallic shafts and produces to customer-defined specifications of 10+/- 0.5 mm in diameter, i.e. the acceptable range is 9.5 mm to 10.5 mm. If the shaft is produced at 9.3 mm, then it cannot be reworked, since the material has already been cut from the shaft, and it will be scrapped (material cannot be added to the shaft to bring the diameter up to the acceptable range). While if the shaft is produced at 10.7 mm, then it can be reworked by re-processing at stage 1 to reduce the diameter to within the acceptable range (9.5 mm – 10.5 mm).

A product that can be reworked will be sent back to the same stage, stage 1, to be processed again, while a scrapped product will be sent to scrap bin and never leave that bin. However, a good part at stage 1, which is a product that has a quality characteristic that falls within the acceptable range of the customer specifications, will be sent to the next stage, stage 2. Hence, only good parts from stage 1 can be transferred to stage 2.

At stage 2, other set of operations are performed on the incoming products from stage 1, where operations will attach a new quality characteristic (different from the quality characteristic at stage 1). At stage 2, each product will be inspected against the customer specifications defined for the new quality characteristic at stage 2, and each product can go through one of the three options defined above (rework, scrap, or accept). When the item is accepted at stage 2 (and it is also accepted at stage 1), then the part is considered as finished product, and it can be sold to a customer as finished goods.

Overall, we have two production stages, where each product is processed, and a unique quality characteristic is attached to the final product at each respective stage. There are two rework loops, the first rework loop takes items at stage 1 back to the same stage to re-process them until they are accepted or reworked. The second rework loop is defined at stage 2, where a rework-able item will be sent back to the same stage (stage 2) to be processed again. Similarly, there are two scrap states, where an item at stage 1 is sent to the scrap bin and will never leave if it is considered scrap-able, and also scrapped items at stage 2 will leave the production system and will be sent to the scrap bin is the quality characteristic at stage 2 is within the scrap range. Finally, we have two acceptance states, where good items at stage 1 are sent to stage 2, and all acceptable items at stage 2 will be sent to the finished product state.

The quality characteristic at each stage, stages 1 and 2 are unique and independent of each other; the acceptance of a product at stage 1 (implying the quality characteristic is within the accepted range) does not affect the acceptance of a product at stage 2, nor does it influence the quality characteristic at stage 2.

3.3.1 Model for Two Processes-Two Stages in Series

Figure (3.1) shows a flow diagram for the two stage production system in series.

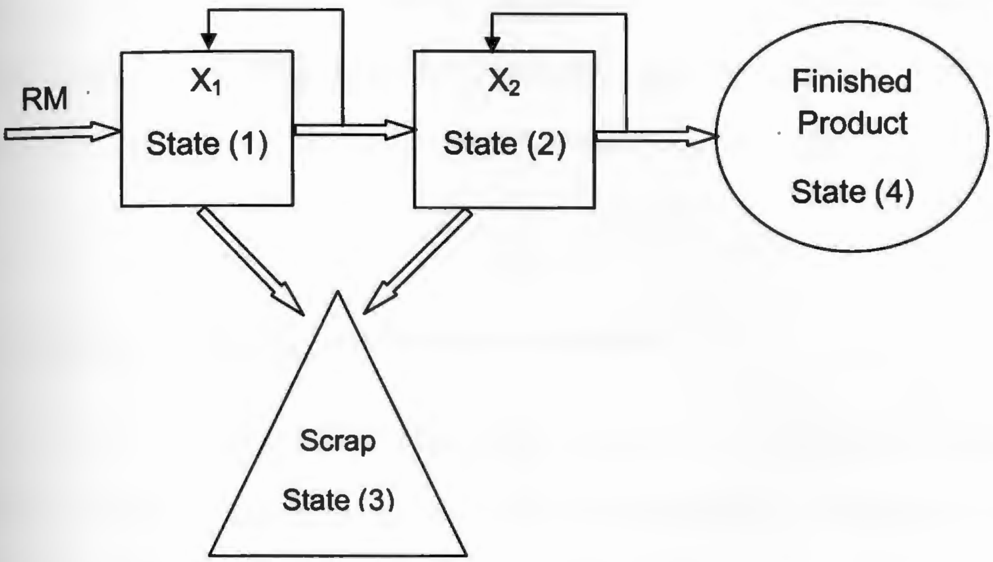


Fig. 3.1: Two processes production system in series

In this model, process X_1 (at stage 1) is considered as a transient state, state 1, whereas process X_2 (at stage 2) is considered a transient state 2. A transient state is any state that the system or the product enters and eventually leaves to another state. States 3 and 4 are considered to be absorbing states, since any product that enters states 3 or 4 (scrap or finished product respectively) stays and never leaves. For example, consider a production line where two chemicals are mixed at two different stages. One chemical is added at each stage and the two production stages for adding and mixing are considered to be transient states. When the product is finally mixed and meets all the specifications, it is sent to the finished product storage area and never returns to any other states. If the product fails to meet any of the specifications at either production stages, it will be scrapped (if it cannot be reworked), and sent to the scrap bin, where it stays and never leaves. In this example, the finished good storage, as well as the scrap bin are considered to be absorbing states, whereas all of the production processes are considered as transient states, since the part will eventually leave to another transient state (production process), or absorbing state (finished good or scrap).

3.3.2 Building Absorbing Markov Chain Matrices

In order to build an absorption chain matrix for any production system, we need to understand the material flow and the short term probabilities of moving from each state to the next. By collecting data about the considered quality characteristic at each production stage, we can understand the quality characteristic distributions of acceptance, rework, or scrap at each stage, and then the short term probabilities could be used to develop an absorbing Markov chain model. Using the states shown in figure 3.1, an absorbing Markov chain is built as shown in equation (3.1). First we start with the initial transition probability matrix (P):

$$P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{array}{c} \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \left[\begin{array}{cc:cc} P_{11} & P_{12} & P_{13} & 0 \\ 0 & P_{22} & P_{23} & P_{24} \\ \hdashline 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{array}\right] \end{array} \qquad (3.1)$$

P_{ij}: is the probability that an item at state i will go to state j, where i = 1, 2, 3, and 4 and j = 1, 2, 3, and 4. For example P_{12} is the short term probability that a part which starts at state 1 (process X_1) will go to state 2 (process X_2).

Matrix P is divided to four sub-matrices:

$$\left[\begin{array}{c:c} Q & R \\ \hdashline 0 & I \end{array}\right]$$

Where:

Q: is the matrix that contains the probabilities of moving from one transient state to another transient state.

R: is the matrix that contains the probabilities of moving from a transient state to an absorbing state.

0: is the zero matrix.

I: is the identity matrix.

The absorbing Markov chain that includes the long terms probabilities of moving from transient to absorbing states equals: $(I - Q)^{-1} R$, such that:

$$(I-Q)=\begin{bmatrix} 1-P_{11} & -P_{12} \\ 0 & 1-P_{22} \end{bmatrix}$$

$$A=(I-Q)^{-1}=\frac{1}{(1-P_{11})(1-P_{22})}\begin{bmatrix} 1-P_{22} & P_{12} \\ 0 & 1-P_{11} \end{bmatrix}$$

$$= \begin{array}{c} \\ 1 \\ 2 \end{array} \begin{array}{c} \begin{array}{cc} 1 & \qquad\qquad 2 \end{array} \\ \begin{bmatrix} \frac{1}{(1-P_{11})} & \frac{P_{12}}{(1-P_{11})(1-P_{22})} \\ 0 & \frac{1}{(1-P_{22})} \end{bmatrix} \end{array} \qquad (3.2)$$

Where:

a_{ij}: is the average number of times that an item from state i stay at state j.

Hence, the long term absorbing Markov chain matrix becomes:

$$B=(I-Q)^{-1}R=\begin{bmatrix} \frac{1}{(1-P_{11})} & \frac{P_{12}}{(1-P_{11})(1-P_{22})} \\ 0 & \frac{1}{1-P_{22}} \end{bmatrix}\cdot\begin{bmatrix} P_{13} & 0 \\ P_{23} & P_{24} \end{bmatrix}$$

$$= \begin{array}{c} \\ 1 \\ 2 \end{array} \begin{array}{c} \begin{array}{cc} 3 & \qquad\qquad 4 \end{array} \\ \begin{bmatrix} \frac{P_{13}(1-P_{22})+P_{12}P_{23}}{(1-P_{11})(1-P_{22})} & \frac{P_{12}P_{24}}{(1-P_{11})(1-P_{22})} \\ \frac{P_{23}}{1-P_{22}} & \frac{P_{24}}{1-P_{22}} \end{bmatrix} \end{array}. \qquad (3.3)$$

Where:

b_{ij}: is the long term probability that an item from state i ends up in state j.

For example, b_{13} is the long term probability that a part from state 1 (process X_1) ends up at state 3 (scrap pin), and b_{24} is the long term probability that a part from state 2 (process X_2) ends up at state 4 (finished good storage).

3.3.3 Resource Consumption Models

In any production system it is important to improve the cost of quality, productivity, and cycle time to stay competitive. There are four categories of cost of quality as determined by Juran *et. al* (1974): (1) internal failure costs, such as scrap and rework, (2) external failure costs, such as warranty charges, (3) appraisal costs, such as inspection and test, (4) prevention costs, such as quality planning. In this thesis, however, the cost of quality is considered to be a total of scrap and rework costs only. Scrapping a part means throwing away the unfinished product and losing all values that are added to that part such as raw material, labor hours, processing time, and overhead. Reworking a part means reprocessing that part again which consumes resources such as labor hours, processing time, and overhead. Reworking a part means reprocess the part again and that consumes resources such as labor hours, processing time, and overhead. Productivity is considered as a ratio between the system output and input. It is preferred to have higher productivity, but there are many factors affect that and reduce the productivity such as the existence of the scrap and rework, and hence not all the raw material (input) ends up as finished products (output). Cycle time is the total of the processing and reworking time from the point the part enters the system until it leaves as finished product. In this section three models are developed to identify the resource consumption per part. These resources could be quality cost defined by rework and scrap waste which will be translated into cost, material consumption measured by the productivity, and time consumption to produce one item measured by the cycle time. Equations (3.2) and (3.3) are used to develop the three models.

3.3.3.1 Cost of Quality Model

The cost of quality model is developed by recognizing that the expense of quality problems existing in the production system will be the sum of the total cost of reworking or scrapping an item. The quality cost is therefore:

Quality Cost = Rework Cost + Scrap Cost

$$QC = f(RC_1) + f(RC_2) + f(SC_1) + f(SC_2) \qquad (3.4)$$

Where:

QC: cost of quality per item

RC_i: the cost of reworking one item from stage (i)

$f(RC_i)$ = [Probability that an item enters stage (i)] x [Expected number of times an item is reworked at stage (i)] x [rework cost at stage (i) per item]

SC_i: the cost of scrapping one item from stage (i)

$f(SC_i)$ = [Probability that item enters stage (i)] x [probability an item from stage (i) is scrapped] x [Scrap cost per item from stage (i)]

Then:

$$QC = [(a_{11}-1)(RC_1)+(1-b_{13})(a_{22}-1)(RC_2)]+[(b_{13})(SC_1)+(1-b_{13})(b_{23})(SC_2)] \quad (3.5)$$

$$QC = \left[\left(\frac{1}{(1-P_{11})}-1\right)(RC1)+\left(1-\frac{P_{13}(1-P_{22})+P_{12}P_{23}}{(1-P_{11})(1-P_{22})}\right)\left(\frac{1}{1-P_{22}}-1\right)(RC_2)\right]+$$

$$\left[\left(\frac{P_{13}(1-P_{22})+P_{12}P_{23}}{(1-P_{11})(1-P_{22})}\right)(SC_1)+\left(1-\frac{P_{13}(1-P_{22})+P_{12}P_{23}}{(1-P_{11})(1-P_{22})}\right)\left(\frac{P_{23}}{1-P_{22}}\right)(SC_2)\right] \quad (3.6)$$

3.3.3.2 Productivity Model

Productivity is the ratio of the output from the production system to the input. The output is the total products accepted as finished goods. The input is the total raw material which enters to the system. Hence:

Productivity = (number of Finished Product) / (number of Raw Material)

= (N x probability an item is accepted at stage 1 and 2) / (N)

= Probability an item is accepted at stage 1 and 2

Where:

N is number of Raw Material (RM) parts which enters the first stage.

Therefore:

Productivity = (probability of accepting item at stage 1) x

(probability of accepting item at stage 2)

$$= (1-b_{13})(1-b_{23}) \tag{3.7}$$

$$= \left(1-\frac{P_{13}(1-P_{22})+P_{12}P_{23}}{(1-P_{11})(1-P_{22})}\right)\left(1-\frac{P_{23}}{1-P_{22}}\right) \tag{3.8}$$

3.3.3.3 Cycle Time Model

Cycle time is defined as the total time required to process product at stage 1, and then 2 so that it can be accepted as finished product. The cycle time is therefore:

$$\text{Total Cycle Time} = CT_1 + CT_2 \tag{3.9}$$

Where:

CT_i: cycle time at stage i, which includes processing time and reworking time at that stage.

CT_i = (processing time at stage i) + [(probability item is reworked at stage i) x (rework time per item at stage i)]

Therefore:

$$\text{Total Cycle Time} = (PT_1 + (a_{11} - 1)(RT_1)) + (PT_2 + (a_{22} - 1)(RT_2)) \quad (3.10)$$

$$= \left(PT_1 + \left(\frac{1}{1-P_{11}} - 1\right)(RT_1)\right) + \left(PT_2 + \left(\frac{1}{1-P_{22}} - 1\right)(RT_2)\right) \quad (3.11)$$

Where:

PT_i: processing time at stage i

RT_i: reworking time at stage i

3.3.4 Numerical Example (1)

Assume that we have two processing stages with two processes, A and B, and their quality characteristics follow the normal distribution. Table 3.1 shows all required parameters. The resource consumption models (quality cost, productivity, cycle time) are calculated based on the parameters shown in table 3.1.

Table 3.1: Numerical example (1) data

	Process A	Process B
Mean	8	22
StDev	1.1	2
Upper limit	10	26
Lower limit	6.5	19
P(rework), above USL	0.035	0.023
P(accept)	0.879	0.910
P(scrap), below LSL	0.086	0.067
RC ($/item)	0.2	0.5
SC ($/item)	1.2	2.2
PT (min/item)	3	5
RT (min/item)	1.5	2
Number of entered RM	2000	

From equation (3.6):

$$QC = \left[\left(\frac{1}{(1-0.035)}-1\right)(0.2)+\left(1-\frac{(0.086)(1-0.023)+(0.879)(0.067)}{(1-0.035)(1-0.023)}\right)\left(\frac{1}{1-0.023}-1\right)(0.5)\right]+$$

$$\left[\begin{array}{l}\left(\dfrac{(0.086)(1-0.023)+(0.879)(0.067)}{(1-.035)(1-0.023)}\right)(1.2)+\\ \left(1-\dfrac{(0.086)(1-0.023)+(0.879)(0.067)}{(1-.035)(1-0.023)}\right)\left(\dfrac{0.067}{1-0.023}\right)(2.2)\end{array}\right]$$

= $0.33 per item

So, on average each product will cost $0.33 as cost of quality problems.

From equation (3.8):

$$Productivity = \left(1-\frac{(0.086)(1-0.023)+(0.879)(0.067)}{(1-0.035)(1-0.023)}\right)\left(1-\frac{0.067}{(1-0.023)}\right) = 0.7903$$

So, the productivity for this production system is 79.03%.

From equation (3.11):

$$\text{Total cycle time}=\left(3+\left(\frac{1}{1-0.035}-1\right)\times 1.5\right)+\left(5+\left(\frac{1}{1-0.023}-1\right)\times 2\right)$$

= 8.10 min per item

That means that on average each item needs 8.10 minutes to be produced.

3.4 One Stage Parallel System with Two Processes

Consider a one stage production line consisting of two production processes in parallel, namely process $X`_1$ and process $X`_2$, both manufacturing the same product. Process $X`_1$ manufactures a product by adding value to meet pre-defined specifications required by the customer (internal or external). An item is pulled from the raw material store and process $X`_1$ performs certain operations on the item, where an inspection is being done to measure and evaluate a specific quality characteristic, and then a decision is made on either accepting the part and sending it to finished goods store, scrapping the item, or reworking it. If the quality characteristic falls within the acceptable range of customer specifications, then the part is considered as a good item, and it is sent to the finished goods storage ready to be sold for the customer. On the other hand, if the part falls within the rework range, then the part will be sent back to the same process (process $X`_1$) to be reworked, by performing more operations to bring the quality characteristic into the acceptable range, and the item will be inspected again. A part is scrapped if the quality characteristic falls in the scrap range, at which time an item is rejected, and sent to the scrap bin to never leave. Process $X`_2$ manufactures the same product, and each item that is pulled from the raw material store goes through the same set of operations, and similar decisions will be made: accepting the part, reworking, or scrapping the part.

Processes $X`_1$ and $X`_2$ run independently in parallel. Any item that is manufactured by process $X`_1$ will be reworked only on process $X`_1$, while any scrapped or accepted part will end up in the same scrap bin or finished goods storage. Rework loops are uniquely defined by each process; each process $X`_1$ and process $X`_2$ has a separate rework loop, and there is no crossover between processes at the rework loops (a reworked item at process $X`_1$ can not be reworked at process $X`_2$, and vice versa).

3.4.1 Model for Two Processes-One Stage in Parallel

Figure 3.2 shows the flow diagram for a one stage system which consists of two processes: $X`_1$ and $X`_2$. In this model, process $X`_1$ and $X`_2$ are considered to be transient states: (1) and (2) respectively. When the product enters any of them then it eventually leaves to another state. Scrap and finished product are absorbing states, (3) and (4) respectively, where any product which enters stays and never leaves.

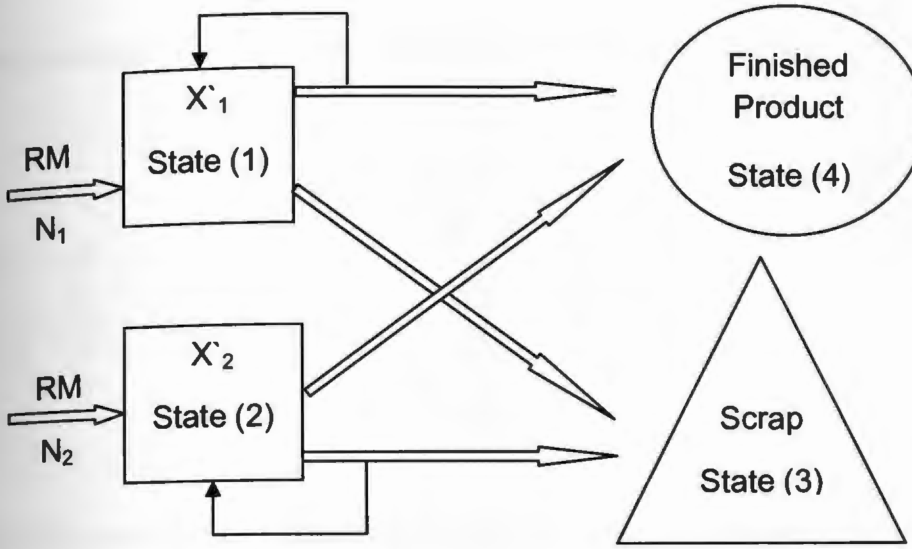


Fig. 3.2: Two processes production system in parallel

Process $X`_1$ and process $X`_2$ perform the same tasks, where the assumption is that both processes $X`_1$ and $X`_2$ could perform the same processes that both processes X_1 and X_2 can perform in the serial configuration model. Returning back to the example of adding two chemicals (described in section 3.3.1) in a parallel configuration each process has the ability of adding and mixing the two chemicals. This could require the two machines at process $X`_1$ and $X`_2$ to be more flexible and probably more expensive than X_1 and X_2 in the serial configuration. In this example, there are no transitions which occur between $X`_1$ and $X`_2$. In other words, P_{12} and P_{21} are equal to zero. The transition only occurs from $X`_1$ or $X`_2$ to either scrap or finished good storage which are the absorbing states.

3.4.2 Building Absorbing Markov Chain Matrices

Referring to figure 3.2, the initial transition probability matrix (P) is:

$$P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{array}{c} \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \left[\begin{array}{cc:cc} P_{11} & 0 & P_{13} & P_{14} \\ 0 & P_{22} & P_{23} & P_{24} \\ \hdashline 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{array}\right] \end{array} \tag{3.12}$$

As previously mentioned, the P matrix contains four sub-matrices: Q, R, 0, and I

$$\left[\begin{array}{c:c} Q & R \\ \hdashline 0 & I \end{array}\right]$$

To find the long term probabilities we need to find $(I\text{-}Q)^{-1}R$:

$$(I - Q) = \begin{bmatrix} 1 - P_{11} & 0 \\ 0 & 1 - P_{22} \end{bmatrix}$$

$$(I - Q)^{-1} = \frac{1}{(1 - P_{11})(1 - P_{22})} \begin{bmatrix} 1 - P_{22} & 0 \\ 0 & 1 - P_{11} \end{bmatrix}$$

$$A = (I - Q)^{-1} = \begin{array}{c} \\ 1 \\ 2 \end{array} \begin{array}{c} \begin{array}{cc} 1 & 2 \end{array} \\ \begin{bmatrix} \frac{1}{(1 - P_{11})} & 0 \\ 0 & \frac{1}{1 - P_{22}} \end{bmatrix} \end{array} \tag{3.13}$$

Where:

a_{ij}: is average number of times that an item from state i stays at state j.

$$(I-Q)^{-1}R=\begin{bmatrix}\frac{1}{(1-P_{11})} & 0\\ 0 & \frac{1}{1-P_{22}}\end{bmatrix}\cdot\begin{bmatrix}P_{13} & P_{14}\\ P_{23} & P_{24}\end{bmatrix}$$

$$B=(I-Q)^{-1}R=\begin{matrix} \\ 1\\ 2\end{matrix}\begin{matrix}\begin{matrix}3 & \quad\quad 4\end{matrix}\\ \begin{bmatrix}\frac{P_{13}}{(1-P_{11})} & \frac{P_{14}}{(1-P_{11})}\\ \frac{P_{23}}{1-P_{22}} & \frac{P_{24}}{1-P_{22}}\end{bmatrix}\end{matrix}. \qquad (3.14)$$

Where:

b_{ij}: is the long term probability item from state i ends up in state j.

3.4.3 Resource Consumption Models

Equations (3.13) and (3.14) are used to build the models for cost of quality, productivity, and cycle time for the parallel configuration system.

3.4.3.1 Cost of Quality Model

Using the same procedure that is used in developing equation (3.6), quality cost for the parallel configuration system is:

Quality Cost = Rework Cost + Scrap Cost

$$QC = (N_1)\, f(RC_1) + (N_2)\, f(RC_2) + (N_1)\, f(SC_1) + (N_2)\, f(SC_1) / (N_1 + N_2) \qquad (3.15)$$

Where;

QC: cost of quality per item.

RC_i: the cost of reworking one item from process ($X`_i$).

SC_i: the cost of scrapping one item from process ($X`_i$).

N_i: total number of raw material parts that enter process ($X`_i$).

Therefore:

$$QC = \frac{\text{[redacted]}(a_{11}-1)(RC_1)+N_2(a_{22}-1)(RC_2)]+[N_1(b_{13})(SC_1)+N_2(b_{23})(SC_2)])}{(N_1+N_2)} \qquad (3.16)$$

$$QC = \frac{\left[N_1\left(\frac{1}{1-P_{11}}-1\right)(RC1)+N_2\left(\frac{1}{1-P_{22}}-1\right)(RC_2)\right]+\left[N_1\left(\frac{P_{13}}{1-P_{11}}\right)(SC_1)+N_2\left(\frac{P_{23}}{1-P_{22}}\right)(SC_2)\right]}{(N_1+N_2)}$$

(3.17)

3.4.3.2 Productivity Model

Productivity is the percentage of the production system total output to the production system total input. The output is the total products accepted as finished goods from both process X`₁ and process X`₂. The input is the total raw material which enters to both processes. Hence:

Productivity = [(N_1 x probability an item from process $X`_1$ is accepted) +

(N_2 x probability an item from process $X`_2$ is accepted)] / (N_1 + N_2)

Therefore:

$$\text{Productivity} = \frac{[(N_1)(1-b_{13})+(N_2)(1-b_{23})]}{(N_1+N_2)} \qquad (3.18)$$

$$= \frac{\left[(N_1)\left(1-\frac{P_{13}}{1-P_{11}}\right)+(N_2)\left(1-\frac{P_{23}}{1-P_{22}}\right)\right]}{(N_1+N_2)} \qquad (3.19)$$

3.4.3.3 Cycle Time Model

The expected cycle time for the two process production system that is shown in figure 3.2 is:

Cycle Time = [(N_1)(CT_1) +(N_2)(CT_2)] / (N_1 + N_2) (3.20)

$$\text{Cycle Time} = \frac{[N_1((PT_1)+(a_{11}-1)(RT_1))]+[N_2((PT_2)+(a_{22}-1)(RT_2))]}{(N_1+N_2)} \qquad (3.21)$$

$$= \frac{N_1\left((PT_1)+\left(\frac{1}{1-P_{11}}-1\right)(RT_1)\right)+N_2\left((PT_2)+\left(\frac{1}{1-P_{22}}-1\right)(RT_2)\right)}{(N_1+N_2)} \qquad (3.22)$$

Where:

CT_i: cycle time at state i, which includes processing time and reworking time at process $X`_i$.

PT_i: processing time at process $X`_i$

RT_i: reworking time at process $X`_i$

3.4.4 Numerical Example (2)

Considering the same example of adding and mixing two chemicals, the assumptions are:

1- A\` and B\` have the same mean, standard deviation, specification limits, processing and rework times, and rework and scrap costs.

2- The considered quality characteristic at A\` and B\` is the same as in process B in the serial configuration system (the specification limits equal to that for process B).

3- The considered quality characteristic at A\` or B\` has the same mean and standard deviation for process B only.

4- The process time at each of processes A\` and B\` equals the summation of process times at processes A and B in the serial configuration system.

5- The rework time at each of processes A` and B` equals the summation of rework times at processes A and B.

6- The rework cost at each of processes A` and B` equals the summation of rework costs at processes A and B.

7- The scrap cost at each of processes A` and B` equals the summation of scrap costs at processes A and B.

Based on the above assumptions, the parameters required for calculating quality cost, productivity, and cycle time for the parallel production system are summarized in table 3.2.

Table 3.2: Numerical example (2) data

	Process A`	Process B`
Mean`	22	22
StDev`	2	2
Upper limit	26	26
Lower limit	19	19
P(rework), above USL	0.023	0.023
P(accept)	0.91	0.910
P(scrap), below LSL	0.067	0.067
RC` ($/item)	0.7	0.7
SC` ($/item)	3.4	3.4
PT` (min/item)	8	8
RT` (min/item)	3.5	3.5
Number of entered RM	1000	1000

Using equations (3.17), (3.19), and (3.22), the cost of quality, productivity, and expected cycle time can be found:

QC = $0.25 per item

Productivity = 93.16 %

Cycle time = 8.13 minutes per item

3.5 Sensitivity Analysis

In this section assumptions and values from example (1) and (2) are used for building sensitivity analysis for the three models to find the effect of main factors on each model and to compare the serial and parallel system configurations.

3.5.1 Sensitivity Analysis for Cost of Quality Model

This model has four main factors: RC_1, RC_2, SC_1, and SC_2. The cost of quality is plotted versus each one of these factors (one at a time). In each plot the considered factor has different values while the other factors stay constant.

Figure (3.3) shows the effect of RC_1 on the cost of quality while RC_2= 0.5, SC_1= 1.2, and SC_2= 2.2 stay constant. The plot indicates that for both serial and parallel configurations, quality cost increases as RC_1 increases. It also shows that the parallel configuration always has lower quality cost than the serial configuration. Figure (3.4) shows the effect of RC_2 on the cost of quality while RC_1= 0.2, SC_1= 1.2, and SC_2= 2.2 stay constant. It indicates that by increasing the RC_2 the quality cost increases for both configurations. For all values of RC_2, the parallel configuration gives lower quality cost than the serial.

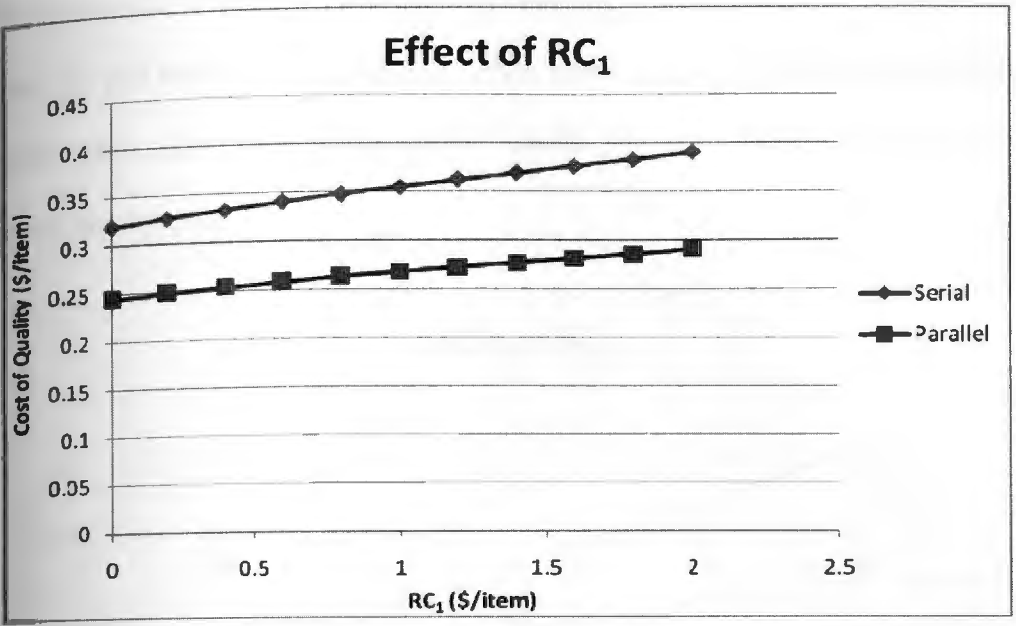


Fig. 3.3: Effect of RC_1 on quality cost

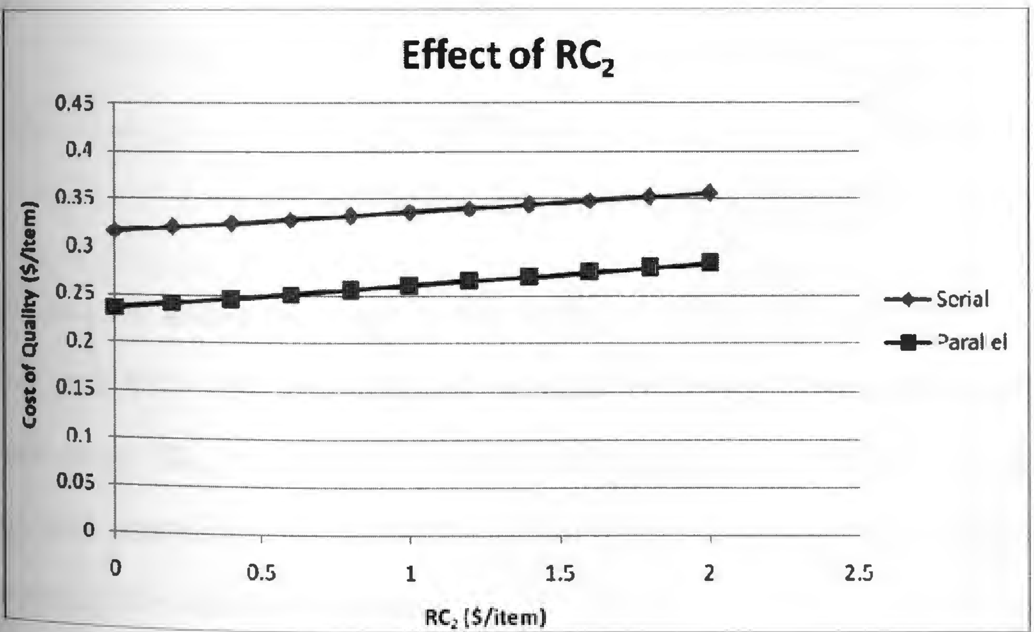


Fig. 3.4: Effect of RC_2 on quality cost

Figure (3.5) shows the effect of SC_1 on the cost of quality while RC_1= 0.2, RC_2= 0.5, and SC_2= 2.2 stay constant. It indicates that the quality cost for both configurations increases as SC_1 increases. It also shows that when SC_1 is less than $0.264 the serial configuration has lower quality cost than the parallel. On the other hand when the SC_1 is more than $0.264 the parallel configuration has the lower quality cost.

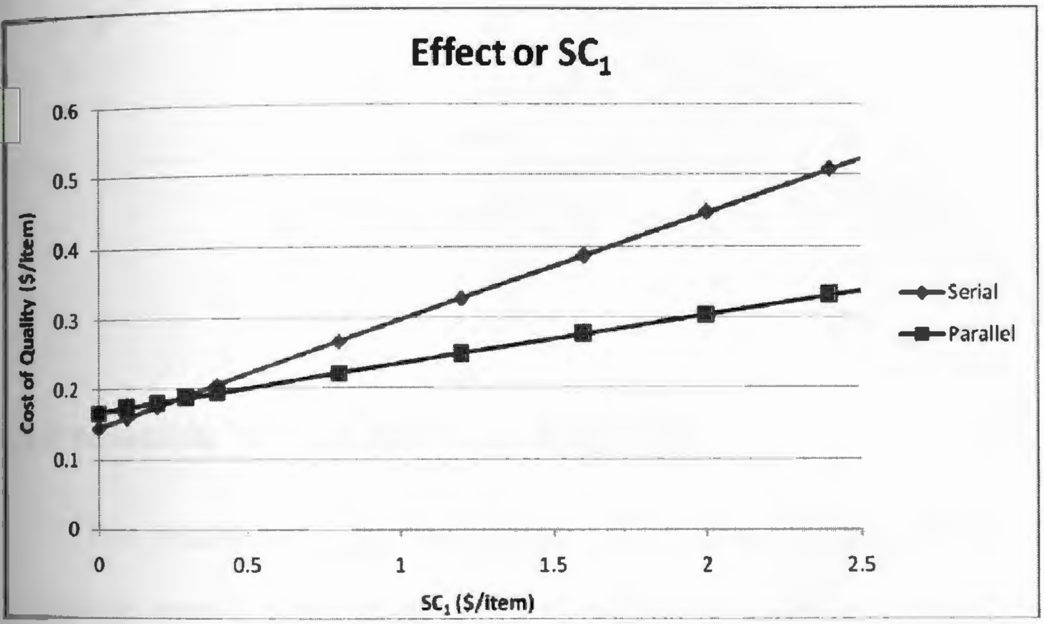


Fig. 3.5: Effect of SC_1 on quality cost

Figure (3.6) shows the effect of SC_2 on the cost of quality while RC_1= 0.2, RC_2= 0.5, and SC_1= 1.2 stay constant. It indicates that quality cost increases with increasing SC_2, and there is also a breakeven point. Below SC_2 = $9.8, the parallel configuration has the lower value, while above this point the serial configuration has the lower value.

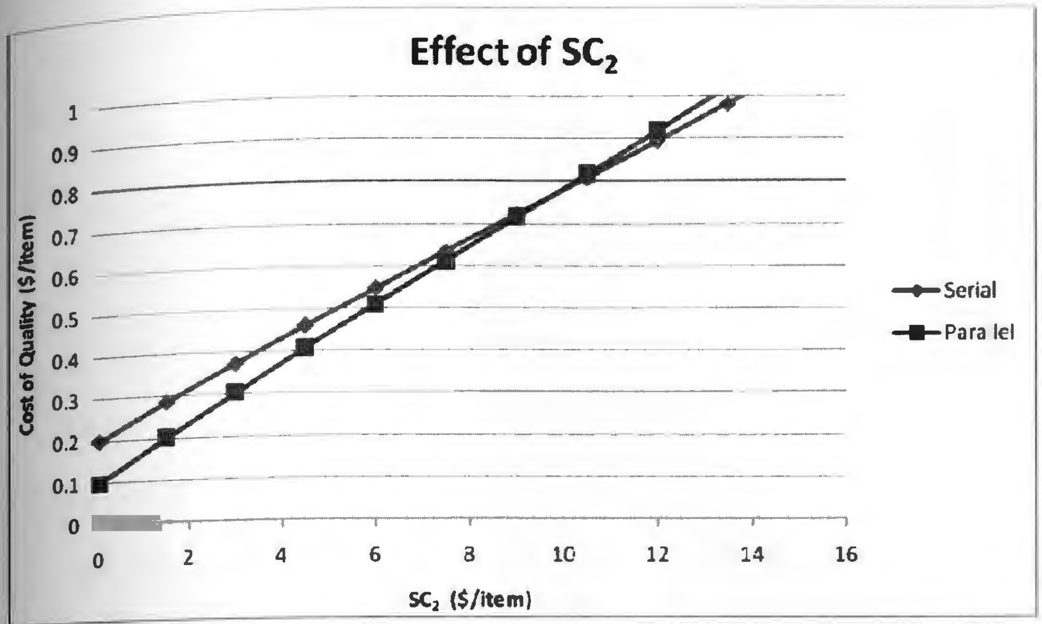


Fig. 3.6: Effect of SC_2 on quality cost

3.5.2 Sensitivity Analysis for Productivity Model

This model has two main factors: mean and standard deviation of the considered quality characteristics. The productivity is plotted versus these two factors (one at a time). In each plot, the considered factor has different values while the other factors stay constant. Figure (3.7) shows the effect of $mean_1$ on system productivity while $mean_2$= 22, $StDev_1$= 1.1, and $StDev_2$= 2 stay constant. It indicates that the system productivity of the parallel configuration almost stays constant as $mean_1$ increases. For the serial configuration, the system productivity increases and then become constant. This figure shows that the parallel configuration has higher productivity than the serial.

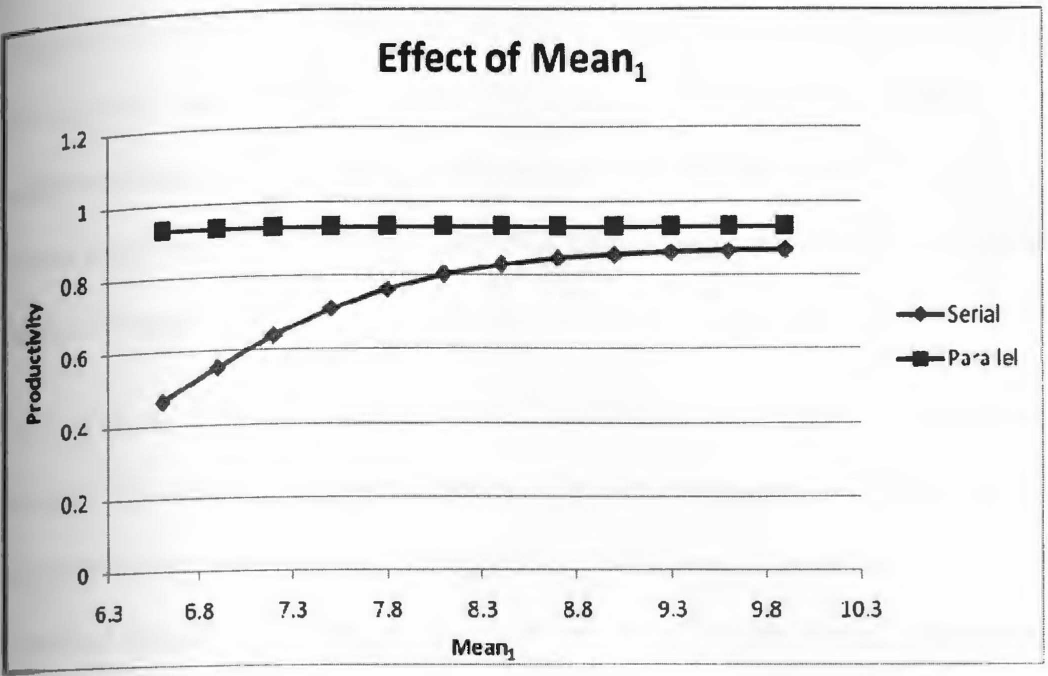


Fig. 3.7: Effect of $mean_1$ on productivity

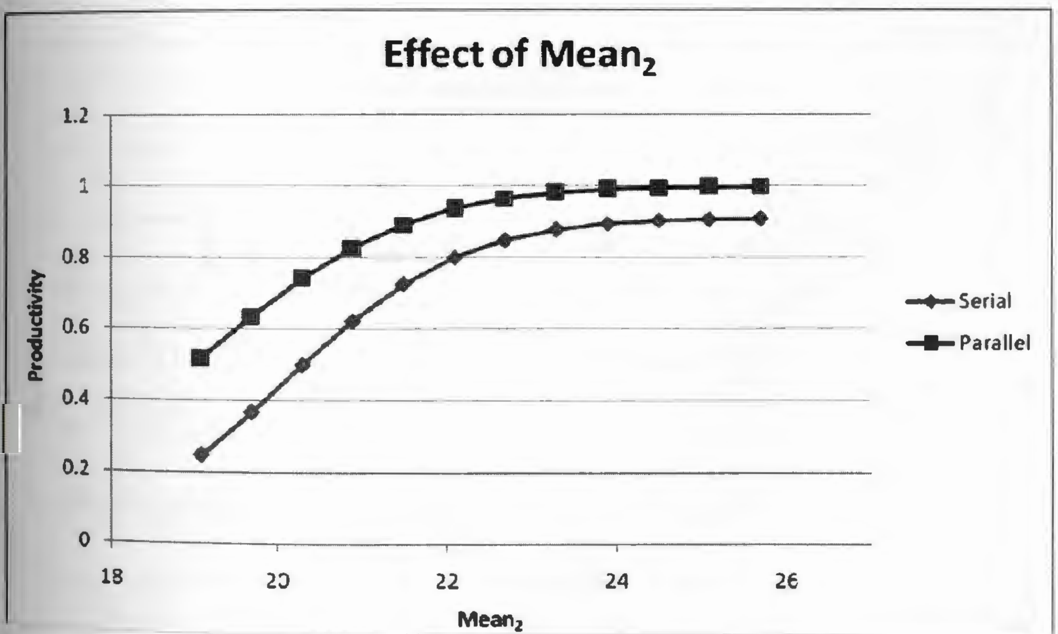


Fig. 3.8: Effect of $mean_2$ on productivity

Figure (3.8) shows the effect of $mean_2$ on system productivity while $mean_1$= 8, $StDev_1$= 1.1, and $StDev_2$= 2 stay constant. It indicates that for both serial and parallel configurations, system productivity increases as mean 2 increases. It also shows that the parallel configuration has higher productivity than the serial for all values of mean 2.

Figure (3.9) shows the effect of $StDev_1$ on system productivity while $mean_1$= 8, $mean_2$= 22, and $StDev_2$= 2 stay constant. It indicates that the productivity of the parallel configuration is almost constant for all values of Standard $Deviation_1$ ($StDev_1$). On the other hand, for the serial configuration, the system productivity decreases as StDev1 decreases. The productivity for the parallel configuration is higher than that for the serial.

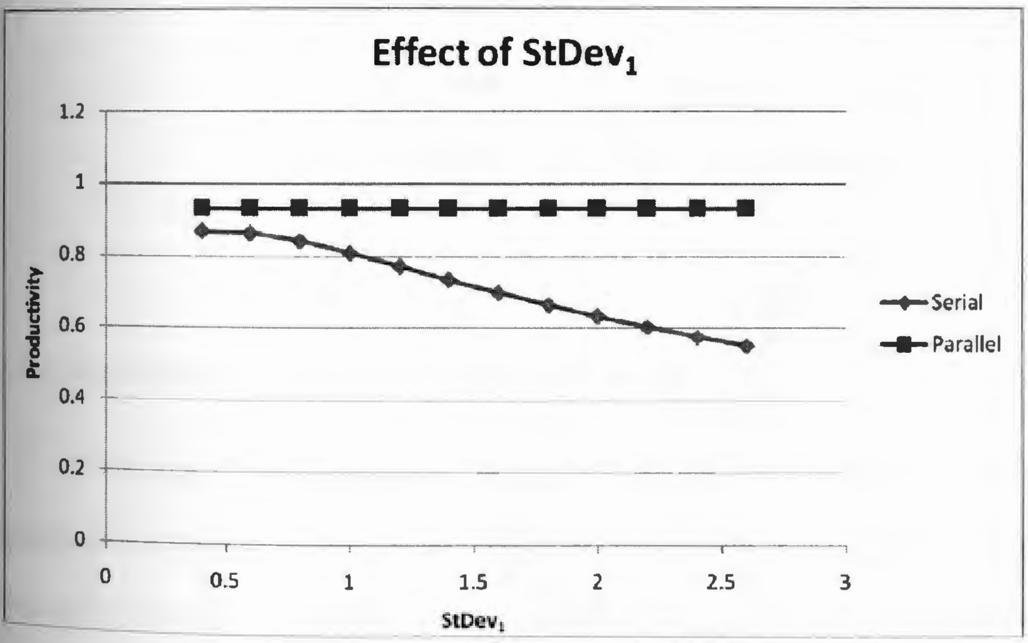


Fig. 3.9: Effect of $StDev_1$ on productivity

Figure (3.10) shows the effect of $StDev_2$ on system productivity while $mean_1$= 8, $mean_2$= 22, and $StDev_1$= 1.1 stay constant. It indicates that the productivity of both the parallel and serial configurations decreases as $StDev_2$ increases, but the parallel configuration has higher productivity than the serial.

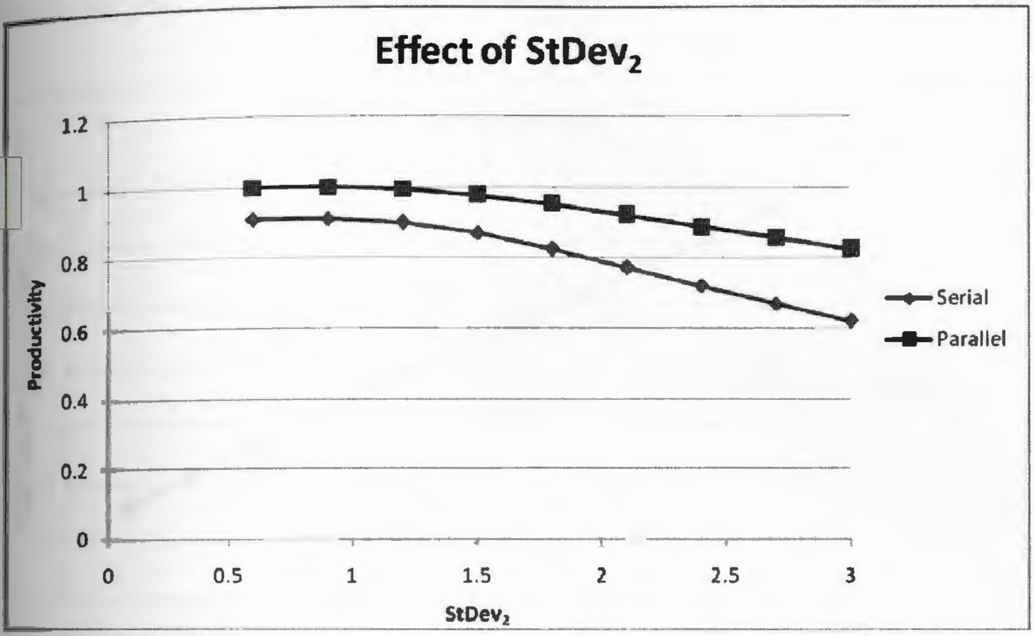


Fig. 3.10: Effect of $StDev_2$ on productivity

3.5.3 Sensitivity Analysis for Cycle Time Model

This model has four main factors: PT_1, PT_2, RT_1, and RT_2. As for cost of quality and productivity, the cycle time is plotted versus each one of these factors. For each plot the considered factor has different values while the other factors stay constant.

Figure (3.11) shows the effect of PT_1 on total cycle time while PT_2= 5, RT_1= 1.5, and RT_2= 2 stay constant. It indicates that by increasing the PT_1 the cycle time increases for both configurations. For all values of PT_1, the serial configuration gives slightly lower cycle time than the parallel (due to the very small difference, this not clearly shown in the graph).

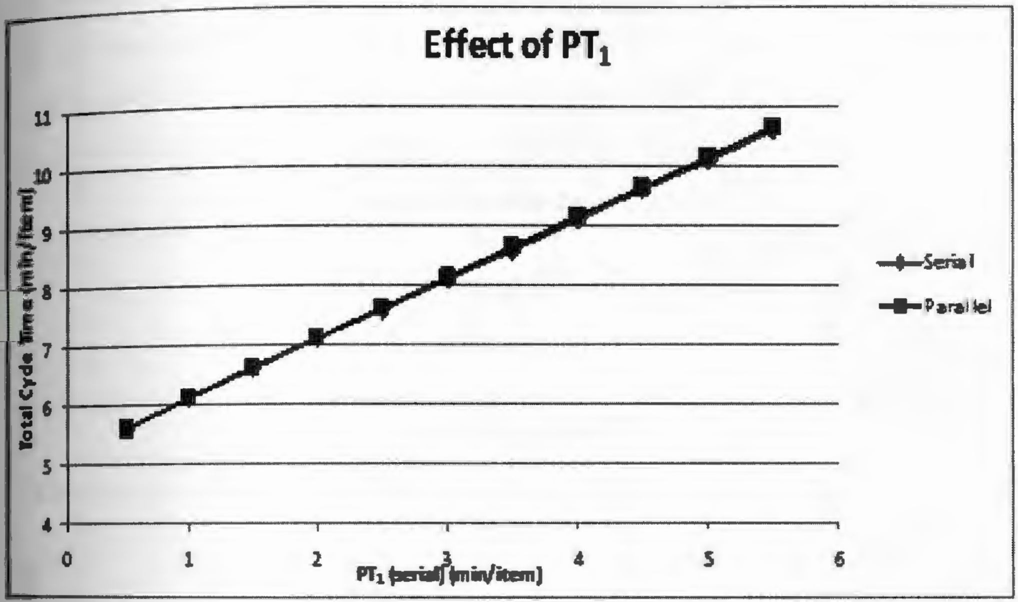


Fig. 3.11: Effect of PT_1 on cycle time

Figure (3.12) shows the effect of PT_2 on the total cycle time while PT_1= 3, RT_1= 1.5, and RT_2= 2 stay constant. It indicates that for both configurations, cycle time increases as PT_2 increases, and for all values of PT_2, the serial configuration gives slightly lower cycle time than the parallel (due to the very small difference, this not clearly shown in the graph).

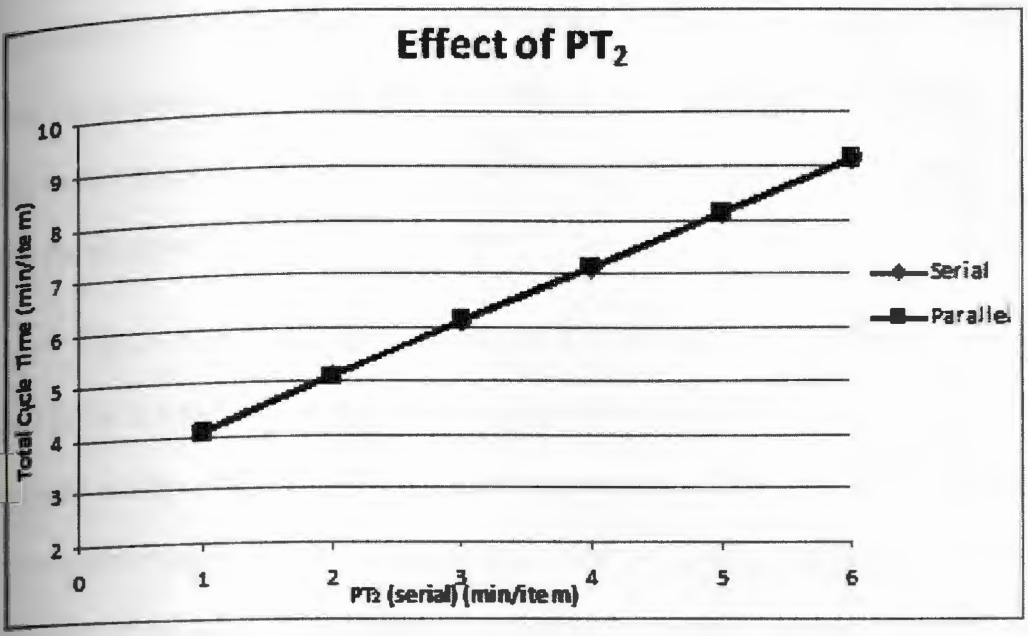


Fig. 3.12: Effect of PT_2 on cycle time

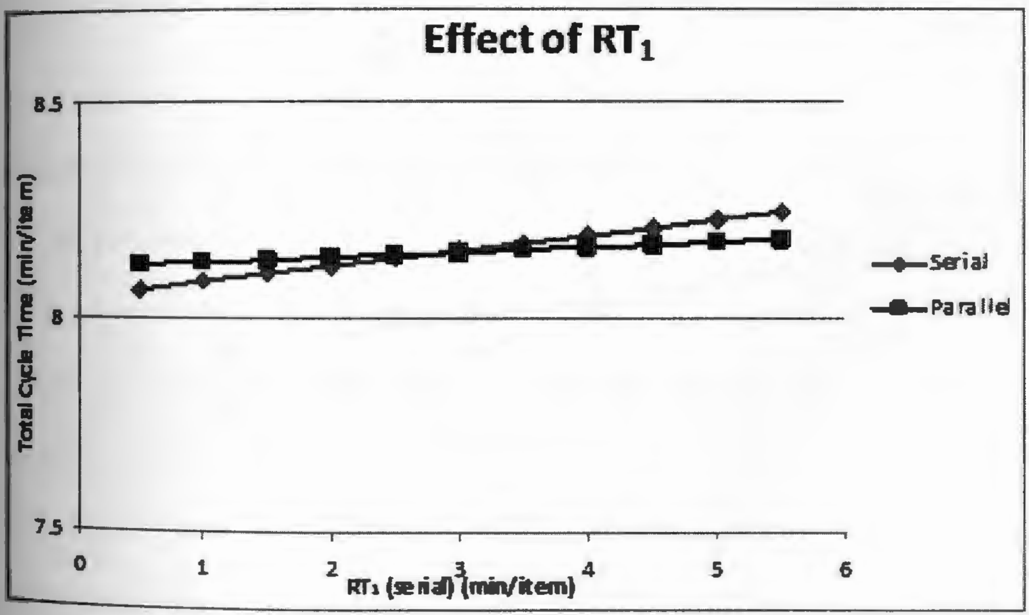


Fig. 3.13: Effect of RT_1 on cycle time

Figure (3.13) shows the effect of RT_1 on total cycle time while PT_1= 3, PT_2= 5, and RT_2= 2 stay constant. It indicates that by increasing the RT_1 the cycle time increases for both the serial and parallel configurations. The graph shows that there is a breakeven point, RT_1 = 3. Below this point the serial configuration has the lower value of cycle time, while above this point the parallel configuration has the lower value.

Figure (3.14) shows the effect of RT_2 on cycle time while PT_1= 3, PT_2= 5, and RT_1= 1.5 stay constant. It indicates that the cycle time for both the serial and parallel configurations increases as RT_2 increases. The graph shows that there is a breakeven point, RT_2 = 5. Below this point the serial configuration has the lower value of cycle time, while above this point the parallel configuration has the lower value.

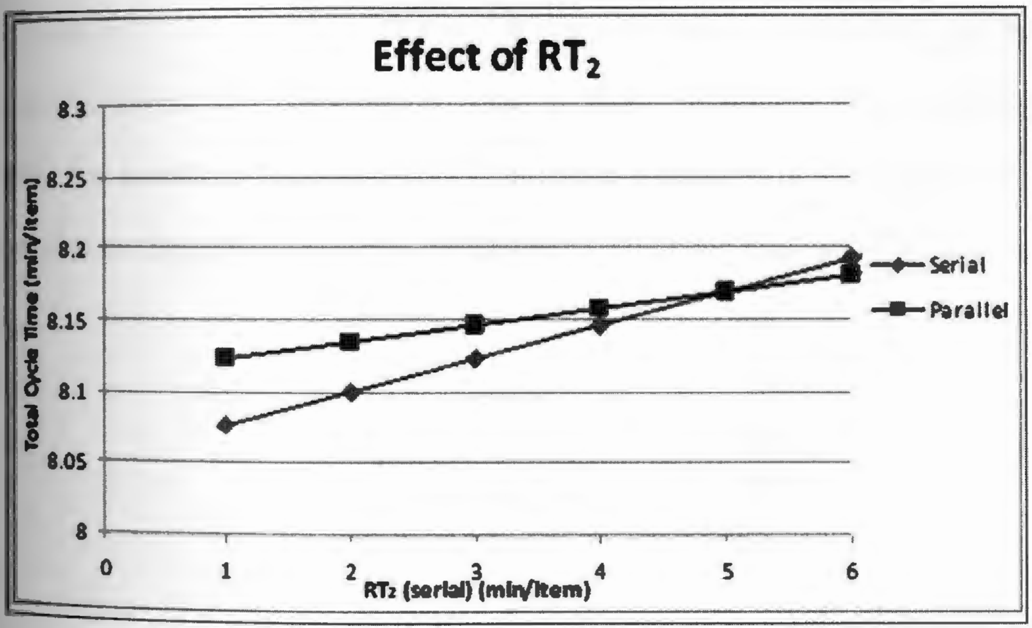


Fig. 3.14: Effect of RT_2 on cycle time

3.5.4 Summary for the Sensitivity Analysis Results:

At first it should be asserted that the result shown in figure 3.3 to figure 3.14 are based on the data from examples 1 and 2 (in sections 3.3.4 and 3.4.3 respectively). Different examples or cases could give different results.

In terms of quality cost, figures 3.3 – 3.6 show that within the specified range of each factor, parallel configuration performs better than the serial at different rework cost, while at different scrap cost the parallel or serial configuration could perform better. In terms of productivity, all of the figures 3.7 - 3.10 show that system productivity for parallel configuration is higher than that for the serial (within the specified range of each factor). In terms of total cycle time, figures 3.11 – 3.14 show that at different processing time both configurations perform almost the same since there is slight difference, while at lower rework time the serial configuration performs better, however at higher rework time the parallel configuration performs better (within the specified range of each factor).

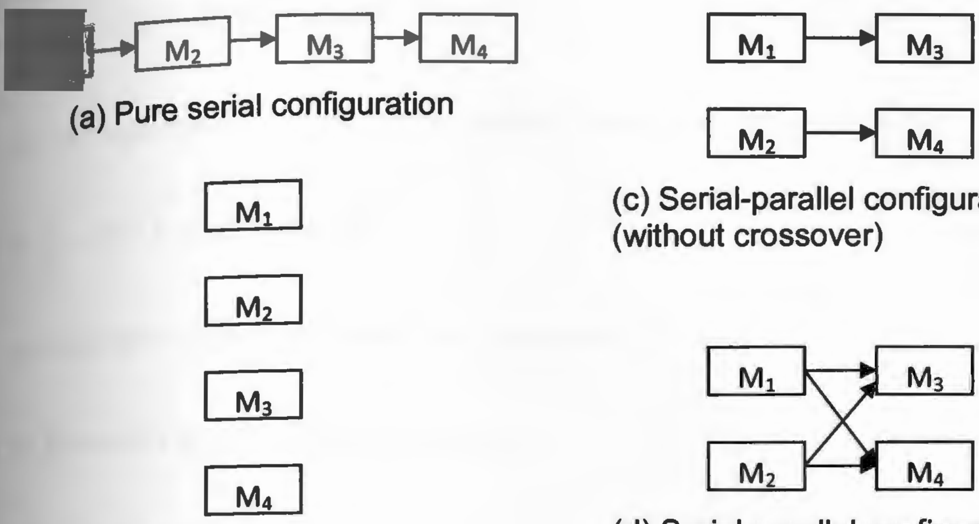
CHAPTER FOUR

METHODOLOGY: MODEL FOR FOUR PROCESS PRODUCTION SYSTEM

4.1 Abstract

In this chapter, four processes are considered in serial, parallel, and mixed serial-parallel configurations. Three resource consumption models are evaluated for each configuration to select the one that results in a better objective. Similar to previous analysis, a Markov chain is used to build the resource consumption models (cost of quality, productivity, and total cycle time), which represent the long term probabilities of good, rework, and scrap parts at each process.

Four machines can be arranged in different patterns giving different configurations. As shown in figure 4.1, four machines could be arranged one after each other obtaining a pure serial configuration; all of them could be arranged in pure parallel, or two serial machines could be parallel to another two serial machines. The mixed parallel and serial configuration may or may not allow crossover between production system stages. Each configuration is studied and modeled, and resource consumption models are developed, in order to analyze the performance of each configuration in terms of the output of each model. Simple numerical examples are used to apply these models.



(a) Pure serial configuration

(b) Pure parallel configuration

(c) Serial-parallel configuration (without crossover)

(d) Serial-parallel configuration (with crossover)

Fig. 4.1 Four different configurations of production system with four machines

4.2 Notation

In this chapter, notations similar to that in chapter three are used. All notations that are used in chapter four's sections are listed below.

- P_{ij}: the probability that an item at state i will go to state j.
- Q: matrix that contains the probabilities of moving from one transient state to another transient state.
- R: matrix that contains the probabilities of moving from a transient state to an absorbing state.
- 0: zero matrix.
- I: identity matrix.

- A: is $(I-Q)^{-1}$ matrix, where:

a_{ij}: average number of times that an item from state i stays at state j.

- B: $(I-Q)^{-1}R$ matrix, where:

b_{ij}: long term probability item from state i ends up in state j.

- X_i: process i in the production system.
- QC: quality cost per item.
- RC_i: rework cost per item from process (X_i).
- f(RC_i): function of RC at process (X_i), where:

f(RC_i) = [Probability that an item enters process (X_i)] x [Expected number of times an item is reworked at process (X_i)] x (RC_i).

- SC_i: scrap cost per item from process (X_i).
- f(SC_i): function of SC at process (X_i), where:

f(SC_i) = [Probability that item enters process (X_i)] x [probability an item from process (X_i) is scrapped] x (SC_i).

- N_i: total number of raw material parts that enter process (X_i).
- CT_i: cycle time at process (X_i), which includes processing time and reworking time, where:

CT_i = (processing time at process (X_i)) + [(probability an item is reworked at process (X_i)) x (rework time per item at process (X_i))]

- PT_i: processing time per item at process (X_i).
- RT_i: reworking time per item at process (X_i).
- w_{ij}: the percentage of accepted parts from process $\hat{X}_i$ that go to process $\hat{X}_j$.

4.3 Four Stage Serial System with Four Processes

Consider four processes in series, where raw material enters the first process and a product is processed and it moves to the second process and so on. At each process, value is added to the product by performing certain operations. Typically, a product quality characteristic is inspected at each respective process, and compared with pre-defined specifications. When the quality characteristic falls within the acceptable range, the product is accepted at the respective process and then transferred to the next process, and when the part finishes process four, it is then moved to the finished goods storage. On the other hand, when the product falls outside the acceptable range, it could be either reworked or scrapped, depending on the value of the quality characteristic. If a product falls in the rework range at any given process, the product is re-entered into the process to be reprocessed and re-inspected against the same specification limits. A scrapped part is a part the falls in the scrap range of the specifications, and it could not be reworked, and hence will be discarded from the production line. Figure 4.2 shows a flow diagram of four processes in a serial configuration.

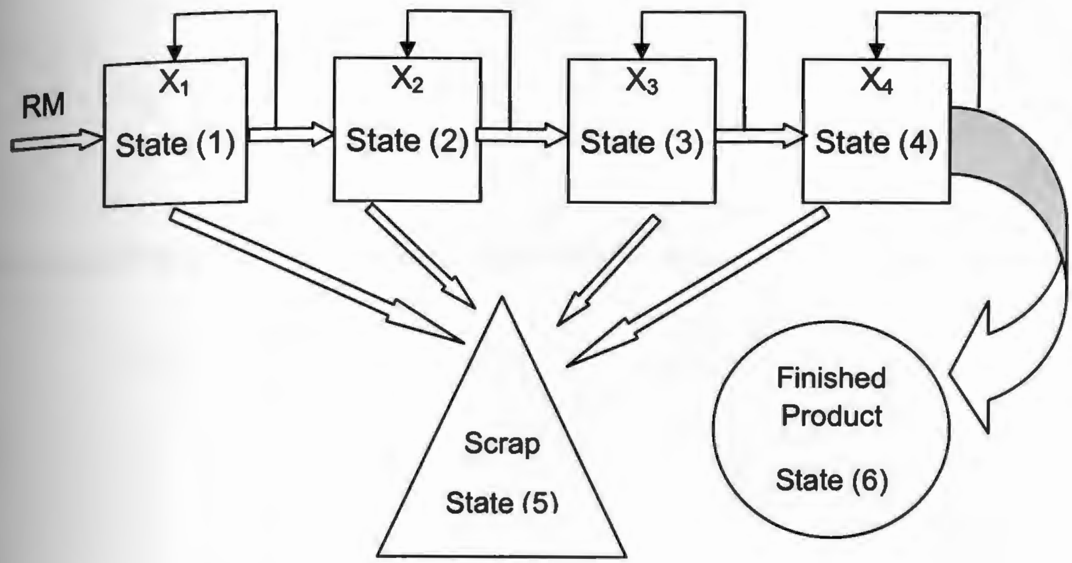


Fig. 4.2: Four process production system in series

Processes one through four represent the transition states (1), (2), (3), and (4) respectively in the Markov chain, where the scrap is considered as an absorption state (5) and the finished product as an absorption state (6). Probabilities of transferring between states are used as the inputs for the transition probability matrix *P*.

4.3.1 Building Absorbing Markov Chain Matrices

The transition probability matrix is:

$$
P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{array}
\begin{array}{c}
\begin{array}{cccc:cc} 1 & 2 & 3 & 4 & 5 & 6 \end{array} \\
\left[\begin{array}{cccc:cc}
P_{11} & P_{12} & 0 & 0 & P_{15} & 0 \\
0 & P_{22} & P_{23} & 0 & P_{25} & 0 \\
0 & 0 & P_{33} & P_{34} & P_{35} & 0 \\
0 & 0 & 0 & P_{44} & P_{45} & P_{46} \\
\hdashline
0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 1
\end{array}\right]
\end{array}
\qquad (4.1)
$$

By subtracting the Q matrix from the 4x4 identity matrix, the I - Q matrix becomes:

$$
(I-Q)=\begin{bmatrix}
1-P_{11} & -P_{12} & 0 & 0 \\
0 & 1-P_{22} & -P_{23} & 0 \\
0 & 0 & 1-P_{33} & -P_{34} \\
0 & 0 & 0 & 1-P_{44}
\end{bmatrix}
$$

And hence:

$$
A=(I-Q)^{-1}=
$$

$$
\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array}
\begin{array}{c}
\begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\
\begin{bmatrix}
\dfrac{1}{(1-P_{11})} & \dfrac{P_{12}}{(1-P_{22})(1-P_{44})} & \dfrac{P_{12}P_{23}}{(1-P_{11})(1-P_{22})(1-P_{33})} & \dfrac{P_{12}P_{23}P_{34}}{(1-P_{11})(1-P_{22})(1-P_{33})(1-P_{44})} \\
0 & \dfrac{1}{(1-P_{22})} & \dfrac{P_{23}}{(1-P_{22})(1-P_{33})} & \dfrac{P_{23}P_{34}}{(1-P_{22})(1-P_{33})(1-P_{44})} \\
0 & 0 & \dfrac{1}{(1-P_{33})} & \dfrac{P_{34}}{(1-P_{33})(1-P_{44})} \\
0 & 0 & 0 & \dfrac{1}{(1-P_{44})}
\end{bmatrix}
\end{array}
$$

(4.2)

Then:

$$B=(1-Q)^{-1}R=$$

$$\begin{array}{c} \\ 1 \\ \\ 2 \\ \\ 3 \\ \\ 4 \end{array}
\begin{array}{c} 5 \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad 6 \\
\begin{bmatrix}
\frac{P_{15}(1-P_{22})(1-P_{33})(1-P_{44})+P_{12}P_{25}(1-P_{33})(1-P_{44})+P_{12}P_{23}P_{35}(1-P_{44})+P_{12}P_{23}P_{34}P_{45}}{(1-P_{11})(1-P_{22})(1-P_{33})(1-P_{44})} & \frac{P_{12}P_{23}P_{34}P_{46}}{(1-P_{11})(1-P_{22})(1-P_{33})(1-P_{44})} \\
\frac{P_{25}(1-P_{33})(1-P_{44})+P_{23}P_{35}(1-P_{44})+P_{23}P_{34}P_{45}}{(1-P_{22})(1-P_{33})(1-P_{44})} & \frac{P_{23}P_{34}P_{46}}{(1-P_{22})(1-P_{33})(1-P_{44})} \\
\frac{P_{35}(1-P_{44})+P_{34}P_{45}}{(1-P_{33})(1-P_{44})} & \frac{P_{34}P_{46}}{(1-P_{33})(1-P_{44})} \\
\frac{P_{45}}{(1-P_{44})} & \frac{P_{46}}{(1-P_{44})}
\end{bmatrix}
\end{array}$$

(4.3)

4.3.2 Resource Consumption Models

Equations (4.2) and (4.3) are used to build the models for cost of quality, productivity, and cycle time for the four stage serial configuration system.

4.3.2.1 Cost of Quality Model

Since there are four processes in the considered production system, the expected scrap and rework could exist at any of these processes, and hence the cost of quality model is:

Quality Cost = Rework Cost + Scrap Cost

$$QC=f(RC_1)+f(RC_2)+f(RC_3)+f(RC_4)+f(SC_1)+f(SC_2)+f(SC_3)+f(SC_4) \quad (4.4)$$

Where:

$$f(RC_1)=(a_{11}-1)RC_1 \tag{4.5}$$

$$f(RC_2)=(1-b_{15})(a_{22}-1)RC_2 \tag{4.6}$$

$$f(RC_3)=(1-b_{15})(1-b_{25})(a_{33}-1)RC_3 \tag{4.7}$$

$$f(RC_4)=(1-b_{15})(1-b_{25})(1-b_{35})(a_{44}-1)RC_4 \tag{4.8}$$

$$f(SC_1)=b_{15}SC_1 \tag{4.9}$$

$$f(SC_2)=(1-b_{15})b_{25}SC_2 \tag{4.10}$$

$$f(SC_3)=(1-b_{15})(1-b_{25})b_{35}SC_3 \tag{4.11}$$

$$f(SC_4)=(1-b_{15})(1-b_{25})(1-b_{35})b_{45}SC_4 \tag{4.12}$$

4.3.2.2 Productivity Model

The productivity of a system of four processes in series is simply the multiplication of the probabilities of acceptance at each state.

Productivity =

[(probability of accepting item at X_1) x (probability of accepting item at X_2) x (probability of accepting item at X_3) x (probability of accepting item at X_4)]

$$\text{Productivity} = (1-b_{15})(1-b_{25})(1-b_{35})(1-b_{45}) \tag{4.13}$$

4.3.2.3 Cycle Time Model

The cycle time is the total time of processing and reworking at each process, and then:

$$\text{Total Cycle Time} = CT_1 + CT_2 + CT_3 + CT_4 \quad (4.14)$$

Therefore:

$$CT_1 = PT_1 + (a_{11} - 1)RT_1 \quad (4.15)$$

$$CT_2 = PT_2 + (a_{22} - 1)RT_2 \quad (4.16)$$

$$CT_3 = PT_3 + (a_{33} - 1)RT_3 \quad (4.17)$$

$$CT_4 = PT_4 + (a_{44} - 1)RT_4 \quad (4.18)$$

4.3.3 Numerical Example (1)

Assume there is a production system with four serial machining processes (A, B, C, and D). Each process adds a new feature to the product. The mean, standard deviation, and the specification limits of the key quality characteristic at each process are summarized in table 4.1, where they are used to calculate the probability of accepting, scrapping, and reworking parts at each process. The table also includes rework costs, scrap costs, processing times, and rework times at each process.

The assumptions are:

- The quality characteristics of all processes follow the normal distribution.
- A part is considered to be acceptable if it falls within the specification limits, scrap if it falls below the lower specification limit and rework if it falls above the upper specification limit.
- The sequence of the processes is: A, B, C, and then D.

Table 4.1 Numerical example (1)

	Process A	Process B	Process C	Process D
Mean	5	7	9	12
StDev	0.4	0.4	0.4	0.8
Upper limit	6.2	8	10.5	13.6
Lower limit	4	6.2	8.4	10.6
P(rework), above USL	0.0013	0.0062	0.0001	0.0228
P(accept)	0.9924	0.9710	0.9331	0.9372
P(scrap), below LSL	0.0062	0.0228	0.0668	0.0401
RC ($/item)	1	1.5	1.5	2
SC ($/item)	2	3.2	3.7	4
PT (min/item)	3	4	4	5
RT (min/item)	2	3	3	3.5
Number of entered RM	10000	---	---	---

The *P*, *A*, and *B* matrices are:

$$P=\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{array}\begin{array}{c} \begin{array}{cccccc} 1 & 2 & 3 & 4 & 5 & 6 \end{array} \\ \begin{bmatrix} 0.0013 & 0.9924 & 0 & 0 & 0.0062 & 0 \\ 0 & 0.0062 & 0.9710 & 0 & 0.0228 & 0 \\ 0 & 0 & 0.0001 & 0.9331 & 0.0668 & 0 \\ 0 & 0 & 0 & 0.0228 & 0.0401 & 0.9372 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

$$A=\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array}\begin{array}{c} \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \begin{bmatrix} 1.0014 & 0.9999 & 0.9711 & 0.9272 \\ 0 & 1.0062 & 0.9772 & 0.9331 \\ 0 & 0 & 1.0001 & 0.9549 \\ 0 & 0 & 0 & 1.0233 \end{bmatrix} \end{array}$$

$$B=\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array}\begin{array}{c} \begin{array}{cc} 5 & 6 \end{array} \\ \begin{bmatrix} 0.1310 & 0.8690 \\ 0.1256 & 0.8744 \\ 0.1051 & 0.8949 \\ 0.0410 & 0.9590 \end{bmatrix} \end{array}$$

By applying the models from section 4.3.2, cost of quality, productivity, and cycle time can be found. For the cost of quality model, rework costs and scrap costs are found by applying equations 4.5 through 4.8 and 4.9 through 4.12, respectively:

$f(RC_1) = 0.0014$, $f(RC_2) = 0.0081$, $f(RC_3) = 0.0001$, $f(RC_4) = 0.0317$

$f(SC_1) = 0.2620$, $f(SC_2) = 0.3491$, $f(SC_3) = 0.2954$, $f(SC_4) = 0.1115$

Then:

QC = \$1.06 per part (by applying equation 4.4)

By applying equation (4.13):

Productivity = 0.6522 = 65.22%.

By applying equations (4.15 through 4.18):

$CT_1 = 3.0027$, $CT_2 = 4.0187$, $CT_3 = 4.0003$, $CT_4 = 5.0815$.

Then:

The total cycle time = 16.10 minutes per part (by applying equation 4.14).

4.4 One Stage Parallel System with Four Processes

Consider four processes in parallel, where raw material enters each process which is capable of performing all required operations to produce a finished product. Parts from each process could be finished product if they meet the predetermined specifications, or can be reworked or scrapped if they do not meet specifications. Figure 4.3 shows a flow diagram of a configuration with four processes in parallel. As in the serial configuration the production processes are considered as transition states ((1), (2), (3), and (4)), where the scrap and finished product are considered as the absorption states (5) and (6) respectively.

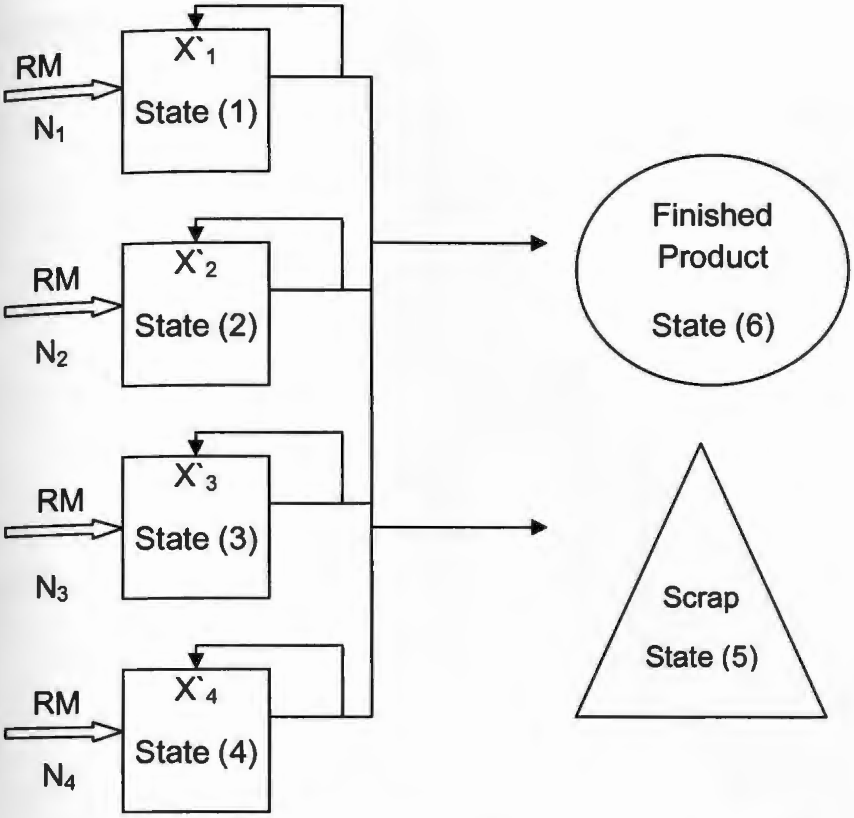


Fig. 4.3: Four processes production system in parallel

4.4.1 Building Absorbing Markov Chain Matrices

The transition probability matrix P is:

$$P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{array} \begin{array}{c} \begin{array}{cccc|cc} 1 & 2 & 3 & 4 & 5 & 6 \end{array} \\ \left[\begin{array}{cccc|cc} P_{11} & 0 & 0 & 0 & P_{15} & P_{16} \\ 0 & P_{22} & 0 & 0 & P_{25} & P_{26} \\ 0 & 0 & P_{33} & 0 & P_{35} & P_{36} \\ 0 & 0 & 0 & P_{44} & P_{45} & P_{46} \\ \hline 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{array}\right] \end{array} \qquad (4.19)$$

The $(I - Q)$ matrix becomes:

$$(I-Q)=\begin{bmatrix} 1-P_{11} & 0 & 0 & 0 \\ 0 & 1-P_{22} & 0 & 0 \\ 0 & 0 & 1-P_{33} & 0 \\ 0 & 0 & 0 & 1-P_{44} \end{bmatrix}$$

And hence:

$$A=(I-Q)^{-1}= \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{array}{c} \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \begin{bmatrix} \frac{1}{(1-P_{11})} & 0 & 0 & 0 \\ 0 & \frac{1}{(1-P_{22})} & 0 & 0 \\ 0 & 0 & \frac{1}{(1-P_{33})} & 0 \\ 0 & 0 & 0 & \frac{1}{(1-P_{44})} \end{bmatrix} \end{array} \tag{4.20}$$

Then:

$$B=(1-Q)^{-1}R= \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{array}{c} \begin{array}{cc} 5 & 6 \end{array} \\ \begin{bmatrix} \frac{P_{15}}{(1-P_{11})} & \frac{P_{16}}{(1-P_{11})} \\ \frac{P_{25}}{(1-P_{22})} & \frac{P_{26}}{(1-P_{22})} \\ \frac{P_{35}}{(1-P_{33})} & \frac{P_{36}}{(1-P_{33})} \\ \frac{P_{45}}{(1-P_{44})} & \frac{P_{46}}{(1-P_{44})} \end{bmatrix} \end{array} \tag{4.21}$$

4.4.2 Resource Consumption Models

Equations (4.20) and (4.21) are used to build the resource consumption models for the parallel configuration system with four processes.

4.4.2.1 Cost of Quality Model

Each of the four processes contributes to the total quality cost per item which is the summation of the rework and scrap cost for all processes.

$$QC = f(RC_1)+f(RC_2)+f(RC_3)+f(RC_4)+f(SC_1)+f(SC_2)+f(SC_3)+f(SC_4) \quad (4.22)$$

Where:

$$f(RC_1)=\frac{N_1(a_{11}-1)RC_1}{(N_1+N_2+N_3+N_4)} \quad (4.23)$$

$$f(RC_2)=\frac{N_2(a_{22}-1)RC_2}{(N_1+N_2+N_3+N_4)} \quad (4.24)$$

$$f(RC_3)=\frac{N_3(a_{33}-1)RC_3}{(N_1+N_2+N_3+N_4)} \quad (4.25)$$

$$f(RC_4)=\frac{N_4(a_{44}-1)RC_4}{(N_1+N_2+N_3+N_4)} \quad (4.26)$$

$$f(SC_1)=\frac{N_1 b_{15} SC_1}{(N_1+N_2+N_3+N_4)} \quad (4.27)$$

$$f(SC_2)=\frac{N_2 b_{25} SC_2}{(N_1+N_2+N_3+N_4)} \quad (4.28)$$

$$f(SC_3)=\frac{N_3 b_{35} SC_3}{(N_1+N_2+N_3+N_4)} \quad (4.29)$$

$$f(SC_4)=\frac{N_4 b_{45} SC_4}{(N_1+N_2+N_3+N_4)} \quad (4.30)$$

4.4.2.2 Productivity Model

The productivity of the production system that consists of four processes in parallel is the expected number of finished products divided by the total number of raw material parts that enter the system. Based on that:

Productivity = [(N_1 x probability an item from process $X`_1$ is accepted) +

(N_2 x probability an item from process $X`_2$ is accepted) +

(N_3 x probability an item from process $X`_3$ is accepted) +

(N_4 x probability an item from process $X`_4$ is accepted)] /

(N_1 + N_2+ N_3 + N_4)

Therefore:

$$\text{Productivity} = \frac{N_1(1-b_{15})+N_2(1-b_{25})+N_3(1-b_{35})+N_4(1-b_{45})}{(N_1+N_2+N_3+N_4)} \qquad (4.31)$$

4.4.2.3 Cycle Time Model

The cycle time is the summation of processing and reworking times at each of the four processes weighted to account for the proportion of raw material in each process path, therefore:

$$\text{Expected Cycle Time} = \frac{N_1CT_1+N_2CT_2+N_3CT_3+N_4CT_4}{N_1+N_2+N_3+N_4} \qquad (4.32)$$

Where:

$$CT_i = PT_i + (a_{11} - 1)RT_i \tag{4.33}$$

4.4.3 Numerical Example (2)

Assume there is a production system with four parallel machining processes (A`, B`, C`, and D`). Each process can perform all production operations that are required to produce a finished product. Table 4.2 includes all required data, where the assumptions are:

- The quality characteristics of all processes follow the normal distribution.
- The considered quality characteristics at A`, B`, C`, and D` are the same as process D in the serial configuration system in example 1 and the specification limits are equal to those for process D.
- A part is considered to be acceptable if it falls within the specification limits, scrap if it falls below the lower specification limit and rework if it falls above the upper specification limit.
- A`, B`, C`, and D` each has the same mean, standard deviation, specification limits, processing and rework times, and rework and scrap costs.
- The process time at each of the processes A`, B`, C`, and D` equals the summation of process times at processes A, B, C, and D in example 1.

- The rework time at each of the processes A`, B`, C`, and D` equals the summation of rework times at processes A, B, C, and D in example 1.
- The rework cost at each of the processes A`, B`, C`, and D` equals the summation of rework costs at processes A, B, C, and D in example 1.
- The scrap cost at each of the processes A`, B`, C`, and D` equals the summation of scrap costs at processes A, B, C, and D in example 1.

Table 4.2 Numerical example (2)

	Process A`	Process B`	Process C`	Process D`
Mean	12	12	12	12
StDev	0.8	0.8	0.8	0.8
Upper limit	13.6	13.6	13.6	13.6
Lower limit	10.6	10.6	10.6	10.6
P(rework), above USL	0.0228	0.0228	0.0228	0.0228
P(accept)	0.9372	0.9372	0.9372	0.9372
P(scrap), below LSL	0.0401	0.0401	0.0401	0.0401
RC ($/item)	6	6	6	6
SC ($/item)	12.9	12.9	12.9	12.9
PT (min/item)	16	16	16	16
RT (min/item)	11.5	11.5	11.5	11.5
Number of entered RM	2500	2500	2500	2500

The *P*, *A*, and *B* matrices are:

$$P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{array} \begin{array}{c} \begin{array}{cccccc} 1 & 2 & 3 & 4 & 5 & 6 \end{array} \\ \begin{bmatrix} 0.0228 & 0 & 0 & 0 & 0.0401 & 0.9372 \\ 0 & 0.0228 & 0 & 0 & 0.0401 & 0.9372 \\ 0 & 0 & 0.0228 & 0 & 0.0401 & 0.9372 \\ 0 & 0 & 0 & 0.0228 & 0.0401 & 0.9372 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

$$A = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{array}{c} \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \begin{bmatrix} 1.0233 & 0 & 0 & 0 \\ 0 & 1.0233 & 0 & 0 \\ 0 & 0 & 1.0233 & 0 \\ 0 & 0 & 0 & 1.0233 \end{bmatrix} \end{array}$$

$$B = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{array}{c} \begin{array}{cc} 5 & 6 \end{array} \\ \begin{bmatrix} 0.0410 & 0.9590 \\ 0.0410 & 0.9590 \\ 0.0410 & 0.9590 \\ 0.0410 & 0.9590 \end{bmatrix} \end{array}$$

The cost of quality, productivity, and cycle time can be found using the models from section 4.4.2. For the cost of quality model, rework costs and scrap costs are found by applying equations 4.23 through 4.30:

$f(RC_1) = f(RC_2) = f(RC_3) = f(RC_4) = 0.0349$.

$f(SC_1) = f(SC_2) = f(SC_3) = f(SC_4) = 0.1322$.

Then:

QC = $0.67 per part (by applying equation 4.22).

By applying equation (4.31): Productivity = 0.9590 = 95.90%.

The expected cycle time = 16.27 minutes per part (by applying equation 4.32).

4.5 Two Stage Serial-Parallel System with Four Processes (without Crossover)

Consider two parallel lines with two serial processes each, where raw material parts enter the first process of each line and then are processed and moved to the second process if they meet the quality specifications. If they do not meet specifications, they are scrapped or reworked. Parts from the first stage can only go to the next process in the same line and can not crossover to the second line. Figure 4.4 shows a flow diagram of the two parallel lines that consist of two serial processes each. Processes $\hat{X}_1$, $\hat{X}_2$, $\hat{X}_3$, and $\hat{X}_4$ are considered as transition states ((1), (2), (3), and (4)), where the scrap and finished product are considered as the absorption states (5) and (6) respectively.

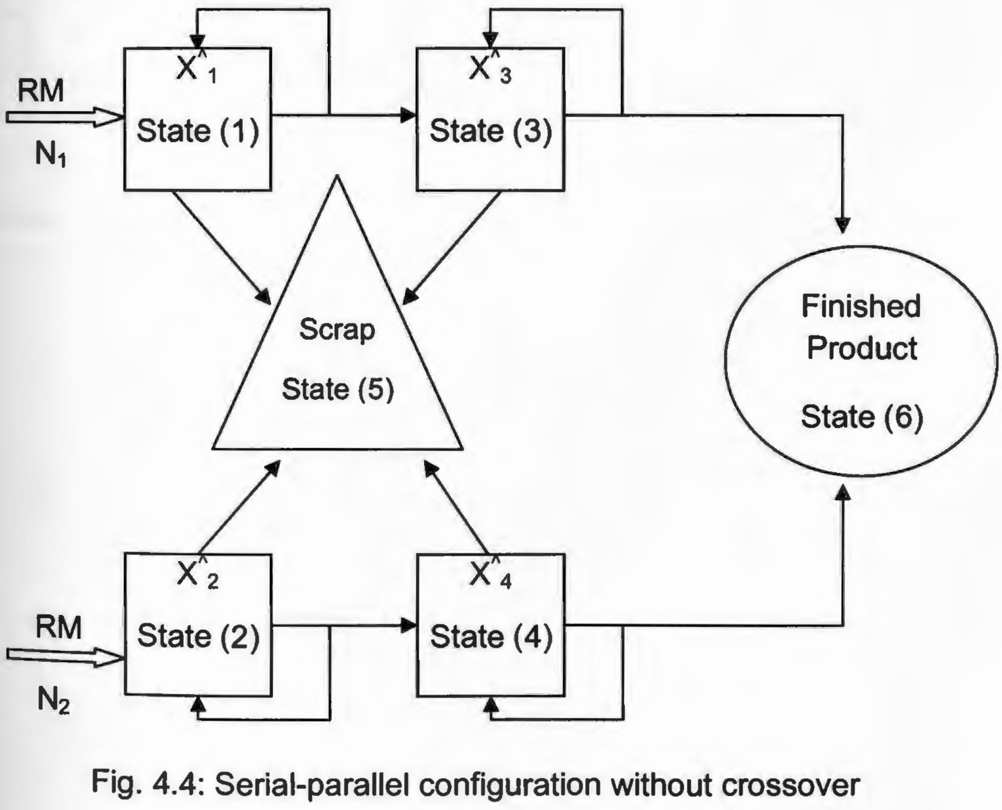


Fig. 4.4: Serial-parallel configuration without crossover

4.5.1 Building Absorbing Markov Chain Matrices

The transition probability matrix P is:

$$P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{array} \begin{array}{c} \begin{array}{cccc:cc} 1 & 2 & 3 & 4 & 5 & 6 \end{array} \\ \left[\begin{array}{cccc:cc} P_{11} & 0 & P_{13} & 0 & P_{15} & 0 \\ 0 & P_{22} & 0 & P_{24} & P_{25} & 0 \\ 0 & 0 & P_{33} & 0 & P_{35} & P_{36} \\ 0 & 0 & 0 & P_{44} & P_{45} & P_{46} \\ \hdashline 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{array}\right] \end{array} \qquad (4.34)$$

The $I - Q$ matrix is:

$$(I - Q) = \begin{bmatrix} 1-P_{11} & 0 & -P_{13} & 0 \\ 0 & 1-P_{22} & 0 & -P_{24} \\ 0 & 0 & 1-P_{33} & 0 \\ 0 & 0 & 0 & 1-P_{44} \end{bmatrix}$$

And hence:

$$A = (I - Q)^{-1} = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{array}{c} \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \begin{bmatrix} \frac{1}{(1-P_{11})} & 0 & \frac{P_{13}}{(1-P_{11})(1-P_{33})} & 0 \\ 0 & \frac{1}{(1-P_{22})} & 0 & \frac{P_{24}}{(1-P_{22})(1-P_{44})} \\ 0 & 0 & \frac{1}{(1-P_{33})} & 0 \\ 0 & 0 & 0 & \frac{1}{(1-P_{44})} \end{bmatrix} \end{array} \qquad (4.35)$$

$$B=(1-Q)^{-1}R=\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array}\begin{bmatrix} 5 & 6 \\ \frac{P_{15}(1-P_{33})+P_{13}P_{35}}{(1-P_{11})(1-P_{33})} & \frac{P_{13}P_{36}}{(1-P_{11})(1-P_{33})} \\ \frac{P_{25}(1-P_{44})+P_{24}P_{45}}{(1-P_{22})(1-P_{44})} & \frac{P_{24}P_{46}}{(1-P_{22})(1-P_{44})} \\ \frac{P_{35}}{(1-P_{33})} & \frac{P_{36}}{(1-P_{33})} \\ \frac{P_{45}}{(1-P_{44})} & \frac{P_{46}}{(1-P_{44})} \end{bmatrix} \quad (4.36)$$

4.5.2 Resource Consumption Models

Equations (4.35) and (4.36) are used to build the resource consumption models for a serial-parallel production system with four processes when there is no crossover.

4.5.2.1 Cost of Quality Model

Each of the four processes at stages one and two contributes to the total quality cost per part:

$$QC=f(RC_1)+f(RC_2)+f(RC_3)+f(RC_4)+f(SC_1)+f(SC_2)+f(SC_3)+f(SC_4) \quad (4.37)$$

Where:

$$f(RC_1)=\frac{N_1(a_{11}-1)RC_1}{(N_1+N_2)} \quad (4.38)$$

$$f(RC_2)=\frac{N_2(a_{22}-1)RC_2}{(N_1+N_2)} \quad (4.39)$$

$$f(RC_3)=\frac{N_1(1-b_{15})(a_{33}-1)RC_3}{(N_1+N_2)} \quad (4.40)$$

$$f(RC_4)=\frac{N_2(1-b_{25})(a_{44}-1)RC_4}{(N_1+N_2)} \quad (4.41)$$

$$f(SC_1)=\frac{N_1 b_{15} SC_1}{(N_1+N_2)} \quad (4.42)$$

$$f(SC_2)=\frac{N_2 b_{25} SC_2}{(N_1+N_2)} \quad (4.43)$$

$$f(SC_3)=\frac{N_1(1-b_{15})b_{35} SC_3}{(N_1+N_2)} \quad (4.44)$$

$$f(SC_4)=\frac{N_2(1-b_{25})b_{45} SC_4}{(N_1+N_2)} \quad (4.45)$$

4.5.2.2 Productivity Model

The productivity is the ratio between the finished products delivered from processes $\hat{X}_3$ and $\hat{X}_4$ and the total raw material parts that enter the two parallel lines, therefore:

Productivity = [(N_1 x probability an item is accepted at $X^\wedge_1$ and $X^\wedge_3$) +

(N_2 x probability an item is accepted at $X^\wedge_2$ and $X^\wedge_4$)] / (N_1 + N_2)

Then:

$$\text{Productivity} = \frac{N_1(1-b_{15})(1-b_{35}) + N_2(1-b_{25})(1-b_{45})}{(N_1+N_2)} \tag{4.46}$$

4.5.2.3 Cycle Time Model

For the parallel configuration without crossover, the expected cycle time becomes:

$$\text{Expected Cycle Time} = \frac{N_1(CT_1+CT_3)+N_2(CT_2+CT_4)}{N_1+N_2} \tag{4.47}$$

Where:

$$CT_i = PT_i + (a_{11}-1)RT_i \tag{4.48}$$

4.5.3 Numerical Example (3)

Assume that there is a production system with four machining processes ($A^\wedge$, $B^\wedge$, $C^\wedge$, and $D^\wedge$). Processes $A^\wedge$ and $C^\wedge$ are parallel to processes $B^\wedge$ and $D^\wedge$. Each pair of processes can perform all production operations that are required to produce a finished product. Table 4.3 includes all required data, where the assumptions are:

- The quality characteristics of all processes follow the normal distribution.
- The considered quality characteristics at $A^{\wedge}$ and $B^{\wedge}$ are the same as in process B in the serial configuration system in example 1 (the specification limits are equal to those for process B). On the other hand, the considered quality characteristics at $C^{\wedge}$ and $D^{\wedge}$, are the same as in process D in example 1.
- A part is considered to be acceptable if it falls within the specification limits, scrap if it falls below the lower specification limit and rework if it falls above the upper specification limit.
- Processes $A^{\wedge}$ and $B^{\wedge}$ have the same mean, standard deviation, specification limits, processing and rework times, and rework and scrap costs. The process time, rework time, rework cost, and scrap cost for each process equals, respectively, the summation of process time, rework time, rework cost, and scrap cost of that for processes A and B in example 1.
- Processes $C^{\wedge}$ and $D^{\wedge}$ have the same mean, standard deviation, specification limits, processing and rework times, and rework and scrap costs. The process time, rework time, rework cost, and scrap cost for each process equals, respectively, the summation of process time, rework time, rework cost, and scrap cost of that for processes C and D in example 1.

Table 4.3 Numerical example (3)

	Process A^	Process B^	Process C^	Process D^
Mean	7	7	12	12
StDev	0.4	0.4	0.8	0.8
Upper limit	8	8	13.6	13.6
Lower limit	6.2	6.2	10.6	10.6
P(rework), above USL	0.0062	0.0062	0.0228	0.0228
P(accept)	0.9710	0.9710	0.9372	0.9372
P(scrap), below LSL	0.0228	0.0228	0.0401	0.0401
RC ($/item)	2.5	2.5	3.5	3.5
SC ($/item)	5.2	5.2	7.7	7.7
PT (min/item)	7	7	9	9
RT (min/item)	5	5	6.5	6.5
Number of entered RM	5000	5000		

The *P*, *A*, and *B* matrices are:

$$P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{array}\begin{array}{c} \begin{array}{cccccc} 1 & 2 & 3 & 4 & 5 & 6 \end{array} \\ \begin{bmatrix} 0.0062 & 0 & 0.9710 & 0 & 0.0228 & 0 \\ 0 & 0.0062 & 0 & 0.9710 & 0.0228 & 0 \\ 0 & 0 & 0.0228 & 0 & 0.0401 & 0.9372 \\ 0 & 0 & 0 & 0.0228 & 0.0401 & 0.9372 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

$$A = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array}\begin{array}{c} \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \begin{bmatrix} 1.0062 & 0 & 0.9999 & 0 \\ 0 & 1.0062 & 0 & 0.9999 \\ 0 & 0 & 1.0233 & 0 \\ 0 & 0 & 0 & 1.0233 \end{bmatrix} \end{array}$$

$$B = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{array}{c} \begin{array}{cc} 5 & 6 \end{array} \\ \begin{bmatrix} 0.0629 & 0.9371 \\ 0.0629 & 0.9371 \\ 0.0410 & 0.9590 \\ 0.0410 & 0.9590 \end{bmatrix} \end{array}$$

By applying the models from section 4.5.2:

$f(RC_1) = f(RC_2) = 0.0078$, $f(RC_3) = f(RC_4) = 0.0382$ (by applying equations 4.38 through 4.41).

$f(SC_1) = f(SC_2) = 0.1637$, $f(SC_3) = f(SC_4) = 0.1479$ (by applying equations 4.42 through 4.45).

Therefore:

QC = $0.72 per part (by applying equation 4.37).

By applying equation (4.46): Productivity = 0.8986 = 89.86%.

By applying equations 4.48:

$CT_1 = CT_2 = 7.0312$, $CT_3 = CT_4 = 9.1513$.

Then:

The expected cycle time = 16.18 minutes per part (by applying equation 4.47).

4.6 Two Stage Serial-Parallel System with Four Processes (with Crossover)

Consider two parallel lines with two serial processes each, where raw material parts enter the first process of each line and then are processed and moved to the second process. This configuration is similar to the one in section 4.5, where the only difference is that in this configuration parts from stage one could proceed to any process in stage two. Figure 4.5 shows the flow diagram for this type of system configuration (there is only one scrap state, but it is represented twice in the figure).

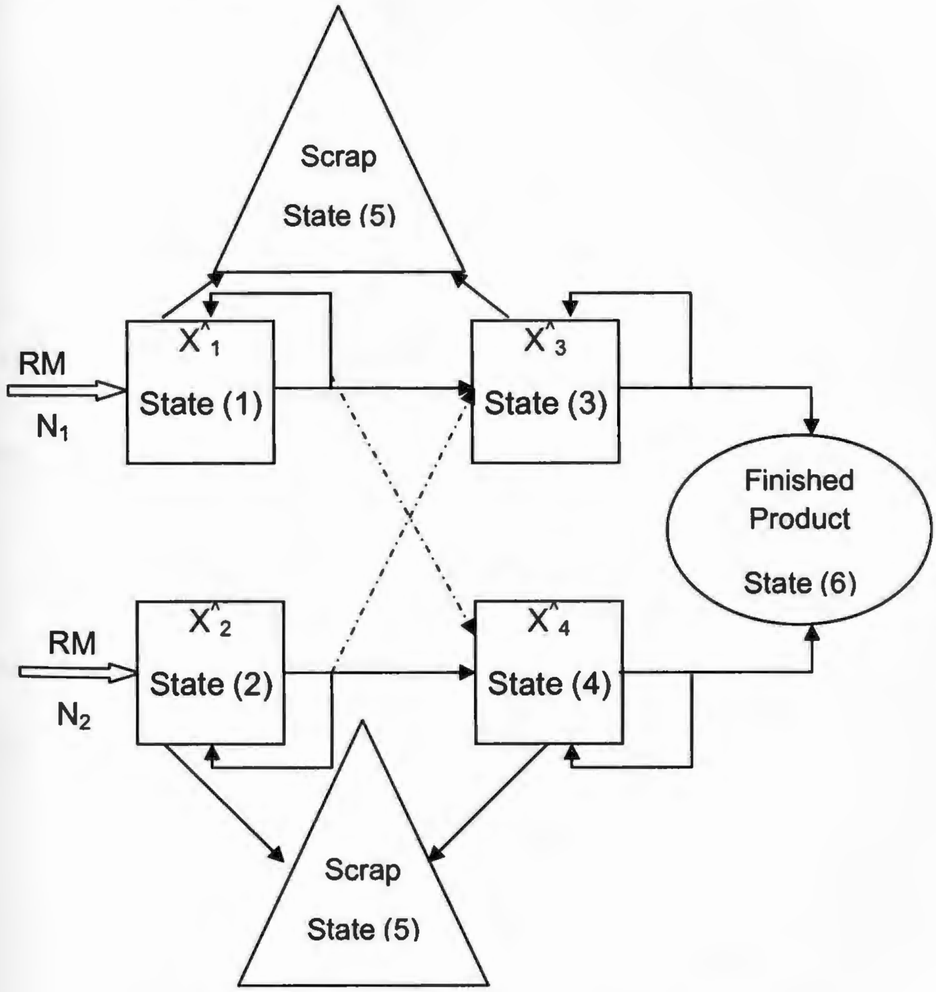


Fig 4.5: Serial-parallel configuration with crossover

4.6.1 Building Absorbing Markov Chain Matrices

The transition probability matrix P is:

$$P = \begin{array}{c|cccc|cc} & 1 & 2 & 3 & 4 & 5 & 6 \\ \hline 1 & P_{11} & 0 & P_{13} & P_{14} & P_{15} & 0 \\ 2 & 0 & P_{22} & P_{23} & P_{24} & P_{25} & 0 \\ 3 & 0 & 0 & P_{33} & 0 & P_{35} & P_{36} \\ 4 & 0 & 0 & 0 & P_{44} & P_{45} & P_{46} \\ \hline 5 & 0 & 0 & 0 & 0 & 1 & 0 \\ 6 & 0 & 0 & 0 & 0 & 0 & 1 \end{array} \qquad (4.49)$$

The $I - Q$ matrix is:

$$(I-Q) = \begin{bmatrix} 1-P_{11} & 0 & -P_{13} & -P_{14} \\ 0 & 1-P_{22} & -P_{23} & -P_{24} \\ 0 & 0 & 1-P_{33} & 0 \\ 0 & 0 & 0 & 1-P_{44} \end{bmatrix}$$

And hence:

$$A = (I-Q)^{-1} = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{array}{c} \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \begin{bmatrix} \frac{1}{(1-P_{11})} & 0 & \frac{P_{13}}{(1-P_{11})(1-P_{33})} & \frac{P_{14}}{(1-P_{11})(1-P_{44})} \\ 0 & \frac{1}{(1-P_{22})} & \frac{P_{23}}{(1-P_{22})(1-P_{33})} & \frac{P_{24}}{(1-P_{22})(1-P_{44})} \\ 0 & 0 & \frac{1}{(1-P_{33})} & 0 \\ 0 & 0 & 0 & \frac{1}{(1-P_{44})} \end{bmatrix} \end{array} \qquad (4.50)$$

$$B=(1-Q)^{-1}R=$$

$$
\begin{array}{c}
\\ 1 \\ \\ 2 \\ \\ 3 \\ \\ 4
\end{array}
\begin{array}{cc}
5 & 6 \\
\left[\begin{array}{cc}
\dfrac{\text{[redacted]}-P_{33})(1-P_{44})+P_{13}P_{35}(1-P_{44})+P_{14}P_{45}(1-P_{33})}{(1-P_{11})(1-P_{33})(1-P_{44})} & \dfrac{P_{13}P_{36}(1-P_{44})+P_{14}P_{46}(1-P_{33})}{(1-P_{11})(1-P_{33})(1-P_{44})} \\
\dfrac{\text{[redacted]}-P_{33})(1-P_{44})+P_{23}P_{35}(1-P_{44})+P_{24}P_{45}(1-P_{33})}{(1-P_{22})(1-P_{33})(1-P_{44})} & \dfrac{P_{23}P_{36}(1-P_{44})+P_{24}P_{46}(1-P_{33})}{(1-P_{22})(1-P_{33})(1-P_{44})} \\
\dfrac{P_{35}}{(1-P_{33})} & \dfrac{P_{36}}{(1-P_{33})} \\
\dfrac{P_{45}}{(1-P_{44})} & \dfrac{P_{46}}{(1-P_{44})}
\end{array}\right]
\end{array}
$$

(4.51)

4.6.2 Resource Consumption Models

Equations (4.50) and (4.51) are used to build the models of quality cost, productivity, and cycle time for the serial-parallel production system with four processes when there is crossover.

4.6.2.1 Cost of Quality Model

Since the processes at stage two, $X^{\wedge}_3$ and $X^{\wedge}_4$, could receive parts from either process $X^{\wedge}_1$ or $X^{\wedge}_2$, weights are given to identify the proportion of parts which enter $X^{\wedge}_3$ and $X^{\wedge}_4$. "w_{ij}" term is used to represents the weights, where:

w_{ij}: the percentage of accepted parts from process $\hat{X}_i$ that go to process $\hat{X}_j$.

$$QC = f(RC_1) + f(RC_2) + f(RC_3) + f(RC_4) + f(SC_1) + f(SC_2) + f(SC_3) + f(SC_4) \quad (4.52)$$

For this type of system configuration:

$$f(RC_1) = \frac{N_1(a_{11} - 1)RC_1}{(N_1 + N_2)} \quad (4.53)$$

$$f(RC_2) = \frac{N_2(a_{22} - 1)RC_2}{(N_1 + N_2)} \quad (4.54)$$

$$f(RC_3) = \frac{N_1(1 - b_{15})(w_{13}) + N_2(1 - b_{25})(w_{23})}{(N_1 + N_2)} \times (a_{33} - 1)RC_3 \quad (4.55)$$

$$f(RC_4) = \frac{N_1(1 - b_{15})(w_{14}) + N_2(1 - b_{25})(w_{24})}{(N_1 + N_2)} \times (a_{44} - 1)RC_4 \quad (4.56)$$

$$f(SC_1) = \frac{N_1 b_{15} SC_1}{(N_1 + N_2)} \quad (4.57)$$

$$f(SC_2) = \frac{N_2 b_{25} SC_2}{(N_1 + N_2)} \quad (4.58)$$

$$f(SC_3) = \frac{N_1(1 - b_{15})(w_{13}) + N_2(1 - b_{25})(w_{23})}{(N_1 + N_2)} \times b_{35} SC_3 \quad (4.59)$$

$$f(SC_4) = \frac{N_1(1 - b_{15})(w_{14}) + N_2(1 - b_{25})(w_{24})}{(N_1 + N_2)} \times b_{45} SC_4 \quad (4.60)$$

4.6.2.2 Productivity Model

System productivity is the ratio between the finished products delivered from processes $X^{\wedge}_3$ and $X^{\wedge}_4$ and the total raw material parts that enter the two parallel lines. When considering the weights given to identify proportions of parts that enter $X^{\wedge}_3$ and $X^{\wedge}_4$ from $X^{\wedge}_1$ and $X^{\wedge}_2$, the system productivity becomes:

Productivity =

[illegible] $$\frac{\ldots_{15})(w_{13})+N_2(1-b_{25})(w_{23})]\times(1-b_{35})+[N_1(1-b_{15})(w_{14})+N_2(1-b_{25})(w_{24})]\times(1-b_{45})}{(N_1+N_2)}$$

(4.61)

4.6.2.3 Cycle Time Model

The expected Cycle Time=

[illegible] $$\frac{\ldots_1 + (N_1 w_{13} + N_2 w_{23})CT_3) + (N_2 CT_2 + (N_1 w_{14} + N_2 w_{24})CT_4)}{N_1 + N_2} \quad (4.62)$$

Where:

$$CT_i = PT_i + (a_{11} - 1)RT_i \quad (4.63)$$

4.6.3 Numerical Example (4)

The assumptions in this example are similar to that in example 3, except that parts from either process in stage one can go to any process at stage two.

75% of parts that are accepted at process A^ proceed to C^ and 25% proceed to D^, whereas 50% of parts that are accepted at process B^ proceed to C^ (assuming C^ has higher capacity than D^) and 50% proceed to D^. Table 4.3 includes all required data for this example.

Table 4.4 Numerical example (4)

	Process A^	Process B^	Process C^	Process D^
Mean	7	7	12	12
StDev	0.4	0.4	0.8	0.8
Upper limit	8	8	13.6	13.6
Lower limit	6.2	6.2	10.6	10.6
P(rework), above USL	0.0062	0.0062	0.0228	0.0228
P(accept)			0.9372	0.9372
P(accepted then go 1st process at 2nd stage)	0.7283	0.4855	---	---
P(accepted then go 2nd process at 2nd stage)	0.2428	0.4855	---	---
P(scrap), below LSL	0.0228	0.0228	0.0401	0.0401
RC ($/item)	2.5	2.5	3.5	3.5
SC ($/item)	5.2	5.2	7.7	7.7
PT (min/item)	7	7	9	9
RT (min/item)	5	5	6.5	6.5
Number of entered RM	5000	5000		

The *P*, *A*, and *B* matrices are:

$$P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{array} \begin{array}{c} \begin{array}{cccccc} 1 & 2 & 3 & 4 & 5 & 6 \end{array} \\ \begin{bmatrix} 0.0062 & 0 & 0.7283 & 0.2428 & 0.0228 & 0 \\ 0 & 0.0062 & 0.2428 & 0.7283 & 0.0228 & 0 \\ 0 & 0 & 0.0228 & 0 & 0.0401 & 0.9372 \\ 0 & 0 & 0 & 0.0228 & 0.0401 & 0.9372 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

$$A = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array}\begin{array}{c} \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \begin{bmatrix} 1.0062 & 0 & 0.7499 & 0.2500 \\ 0 & 1.0062 & 0.2500 & 0.7499 \\ 0 & 0 & 1.0233 & 0 \\ 0 & 0 & 0 & 1.0233 \end{bmatrix} \end{array}$$

$$B = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array}\begin{array}{c} \begin{array}{cc} 5 & 6 \end{array} \\ \begin{bmatrix} 0.0629 & 0.9371 \\ 0.0629 & 0.9371 \\ 0.0410 & 0.9590 \\ 0.0410 & 0.9590 \end{bmatrix} \end{array}$$

$f(RC_1) = f(RC_2) = 0.0078$, $f(RC_3) = 0.0477$, $f(RC_4) = 0.0286$ (by applying equations 4.53 through 4.56).

$f(SC_1) = f(SC_2) = 0.1637$, $f(SC_3) = 0.1849$, $f(SC_4) = 0.1109$ (by applying equations 4.57 through 4.60).

Then:

QC = $0.72 per part (by applying equation 4.52).

By applying equation (4.61), the system productivity = 0.8986 = 89.86%.

$CT_1 = CT_2 = 7.0312$, $CT_3 = CT_4 = 9.1514$ (by applying equation 4.63).

Then:

The expected cycle time = 16.18 minutes per part (by applying equation 4.62).

4.7 Summary of the Numerical Example Results:

Table 4.5 summarizes the results from examples 1, 2, 3, and 4. For the machining production system that is assumed in the four examples, we can conclude that:

Table 4.5 Summary table

Configuration	QC ($)	Productivity (%)	Cycle time (min./part)
Serial	1.06	65.22	16.10
Parallel	0.67	95.90	16.27
Serial-parallel with crossover	0.72	89.86	16.18
Serial-parallel without crossover	0.72	89.86	16.18

Based on the data and assumptions, serial-parallel with crossover and serial-parallel without crossover configurations have same quality cost, productivity, and total cycle time. Their total quality costs are equal, although their $f(RC_3)$ and $f(RC_4)$ values are not the same. The quality cost, productivity, and cycle time equations for the system with crossover are not the same as that for the system without crossover (as shown in section 4.5 and 4.6 respectively), which in turn indicates that the result in this example is just a special case where the two configurations perform the same due to the assumptions that the processes at each stage are similar in terms of the parameters used in the three models

In terms of the quality cost, the parallel configuration has the lowest cost, followed by the serial-parallel configurations, and then the serial configuration. In terms of productivity, the parallel configuration has the highest value, followed by the serial-parallel configurations, and then the serial configuration. In terms of total cycle time, the serial configuration has the lowest time, followed by the serial-parallel configurations, and then the parallel configuration.

In summary, the parallel configuration of the assumed production system has the best performance in terms of quality cost and productivity, followed by the serial-parallel configurations and then the serial configuration. On the other hand, the serial configuration has the best performance in terms of total cycle time followed by the serial-parallel configurations and then the parallel configuration.

CHAPTER FIVE

METHODOLOGY: MODEL FOR n PROCESS PRODUCTION SYSTEM

5.1 Abstract

In chapters three and four, the resource consumption models are developed for two and four process production systems respectively, while in this chapter the work is extended to build a general model for n process production systems for each of the serial, parallel, and serial-parallel without crossover configurations.

5.2 Introduction about Building the n Model

It can be concluded from the models for two and four process production systems (in chapters three and four) that there are only two terms needed to develop the resource consumption models:

1- a_{ii} from matrix *A*, where i= 1,2,.., n , and n = number of the processes.

2- $b_{i(n+1)}$ from matrix *B*, which is the long term probability that an item from state i will end up as scrap, where state (n+1) is the scrap state and state (n+2) is the finished goods state. For example, when the production system consists of two processes (n=2), then b_{13} is the long term probability that an item from process 1 (state 1) ends as scrap.

Mathematica® software is used to generate the model for different values of n, and then the trend for both of a_{ii} and $b_{i(n+1)}$ is analyzed to generate a general expression. For the definitions of the notations in next sections, refer to section 4.2 in chapter four.

5.3 Serial Production System with n Processes

Figure 5.1 represents a production system with n processes arranged in series.

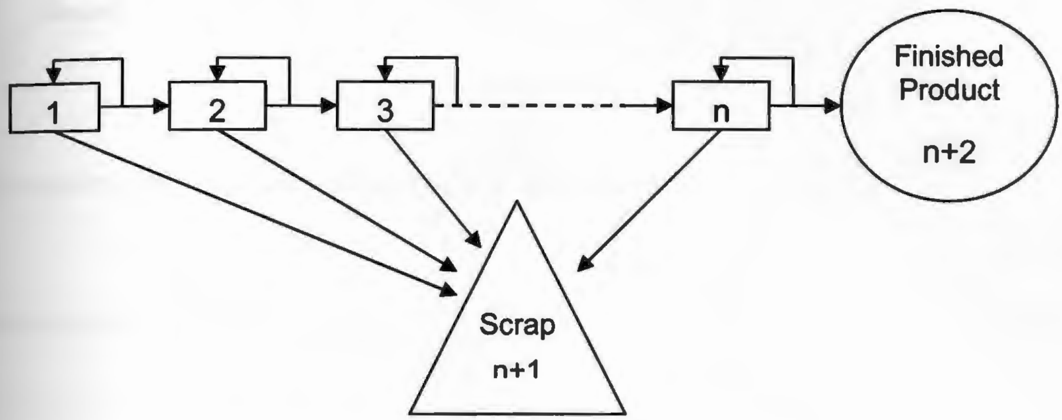


Fig. 5.1 Pure serial configuration for n process

The general expression for a_{ii} is:

$$a_{(i)(i)} = \frac{1}{(1 - P_{(i)(i)})} \tag{5.1}$$

The general expression for $b_{i(n+1)}$ is:

$$b_{(i)(n+1)} = \frac{\sum_{j=i}^{n} \left(\left(P_{(j)(n+1)}\right) \left(\prod_{k=2}^{j} P_{(k-1)(k)} \right) \left(\prod_{y=j}^{n-1} \left(1 - P_{(y+1)(y+1)}\right) \right) \right)}{\left(\prod_{z=2}^{i} P_{(z-1)(z)} \right) \left(\prod_{w=i}^{n} \left(1 - P_{(w)(w)}\right) \right)} \tag{5.2}$$

The general expression for the cost of quality model is:

$$QC = \sum_{i=1}^{n} \left(\left(\left(a_{(i)(i)} - 1\right) RC_{(i)} + b_{(i)(n+1)} SC_{(i)} \right) \prod_{k=2}^{i} \left(1 - b_{(k-1)(n+1)}\right) \right) \tag{5.3}$$

The general expression for the productivity model is:

$$\text{Prductivity} = \prod_{i=1}^{n} \left(1 - b_{i(n+1)}\right) \tag{5.4}$$

The general expression for the cycle time model is:

$$\text{Cycle Time} = \sum_{i=1}^{n} \left(PT_{(i)} + RT_{(i)} \left(a_{(i)(i)} - 1\right)\right) \tag{5.5}$$

As an example, suppose there is a production system with 5 processes (n=5), and the *P* matrix that includes the probabilities of the transitions between states is:

$$P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \end{array} \begin{array}{c} \begin{array}{ccccccc} 1 & 2 & 3 & 4 & 5 & 6 & 7 \end{array} \\ \begin{bmatrix} 0.02 & 0.97 & 0 & 0 & 0 & 0.01 & 0 \\ 0 & 0.06 & 0.91 & 0 & 0 & 0.03 & 0 \\ 0 & 0 & 0.05 & 0.93 & 0 & 0.02 & 0 \\ 0 & 0 & 0 & 0.04 & 0.95 & 0.01 & 0 \\ 0 & 0 & 0 & 0 & 0.04 & 0.03 & 0.93 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

Where:

States 1, 2, 3, 4, and 5 represent the states of a part being processed at workstations 1, 2, 3, 4, and 5 respectively. State 6 represents the scrap and state 7 represents the finished goods.

Assume that:

The rework costs are: RC_1 = \$4/part, RC_2 = \$3/part, RC_3 = \$3/part, RC_4 = \$1/part, and RC_5 = \$2/part;

the scrap costs are: SC_1 = \$5/part, SC_2 = \$5.5/part, SC_3 = \$6.2/part, SC_4 = \$6.5/part, and SC_5 = \$7/part;

the processing times are: PT_1 = 3 min/part, PT_2 = 2 min/part, PT_3 = 2 min/part, PT_4 = 1min/part, and PT_5 = 1.5 min/part;

and the rework times are: RT_1 = 2.5 min/part, RT_2 = 2 min/part, RT_3 = 1.5 min/part, RT_4 = 1 min/part, and RT_5 = 1.5 min/part.

Therefore, by applying equations 5.3, 5.4, and 5.5 respectively the quality cost, productivity, and cycle time can be found:

Total rework costs = \$0.48 per part

Total scrap costs = \$1.63 per part

Therefore, the QC = \$2.11 per part

Productivity = 71.21%

Cycle time = 9.86 minutes per part

5.4 Parallel Production System with n Processes

Figure 5.2 represents production system with n processes arranged in parallel.

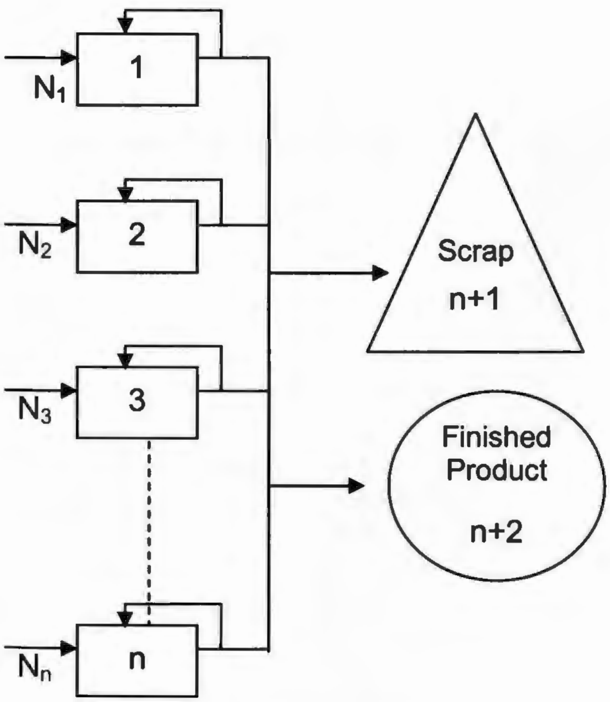


Fig. 5.2 Pure parallel configuration for n process

The general expression for a_{ii}, $b_{i(n+1)}$, and the resource consumption models are:

$$a_{(i)(i)} = \frac{1}{(1 - P_{(i)(i)})} \tag{5.6}$$

$$b_{(i)(n+1)} = \frac{P_{(i)(n+1)}}{(1 - P_{(i)(i)})} \tag{5.7}$$

$$QC = \frac{\sum_{i=1}^{n} (N_i((a_{(i)(i)} - 1)RC_i + b_{i(n+1)}SC_i))}{\sum_{k=1}^{n} N_k} \tag{5.8}$$

$$\text{Productivity} = \frac{\sum_{i=1}^{n} (N_i(1 - b_{(i)(n+1)}))}{\sum_{k=1}^{n} N_k} \tag{5.9}$$

$$\text{Cycle time} = \frac{\sum_{i=1}^{n} (N_i(PT_i + (a_{(i)(i)} - 1)RT_i))}{\sum_{k=1}^{n} N_k} \tag{5.10}$$

For example, assume there is a production system with 3 processes, and the transition probability matrix is:

$$P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} \begin{array}{c} \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0.15 & 0 & 0 & 0.04 & 0.81 \\ 0 & 0.1 & 0 & 0.07 & 0.83 \\ 0 & 0 & 0.05 & 0.08 & 0.87 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

If:

The rework costs are: $RC_1 = RC_2 = RC_3 = \$6$/part

The scrap costs are: $SC_1 = SC_2 = SC_3 = \$7$/part

Processing times are: $PT_1 = PT_2 = PT_3 = 10$ min/part

Rework times are: $RT_1 = RT_2 = RT_3 = 8$ min/part

$N_1 = N_2 = N_3 = 20$ parts

Then:

QC = \$1.17 per part.

Productivity = 93%

Expected cycle time = 10.91 minutes per part

5.5 Serial-Parallel Production System with n Processes (Without Crossover)

Figure 5.3 shows a serial-parallel configuration without crossover with n processes, arranged in two parallel lines. For each process, a product can get accepted and sent to the next process, reworked, or scrapped. The total number of processes in both lines is n, where the number of processes in each line could vary between 1 to n-1, while the rest of the processes exist in the other line. In other words, n processes can be distributed between the two lines such that there should be at least one process in each line. A line with no processes would convert this configuration into a pure serial.

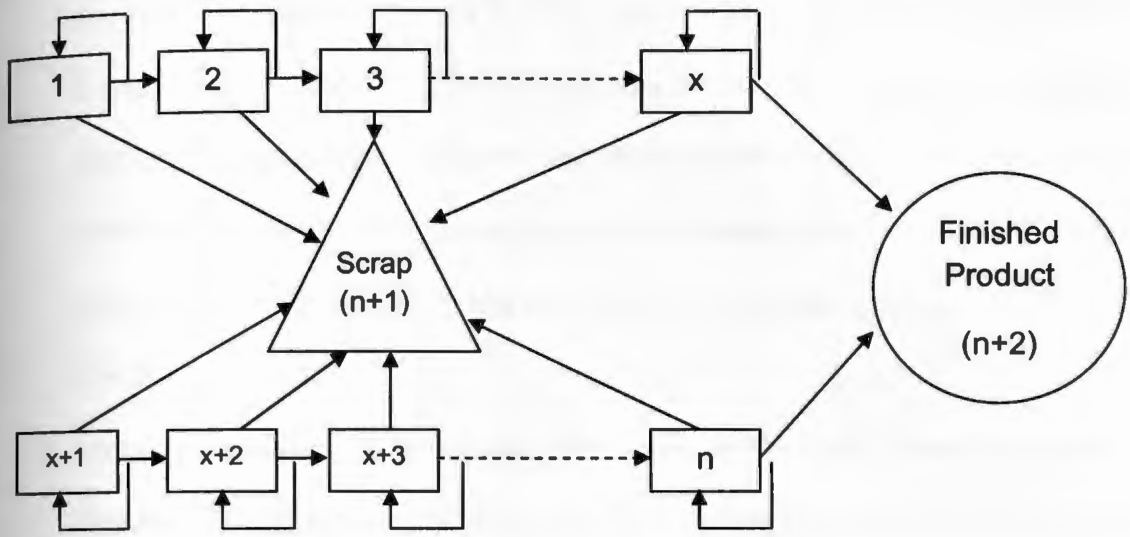


Fig.5.3: Serial-Parallel configuration for n processes, arranged in two parallel lines

To define the resource consumption models, the following conditions should be fulfilled:

1- If n processes are to be modeled, and they are distributed in two production lines, namely line #1 and line #2, the number of processes in one line can be n-1 or fewer, while the rest of the processes are located in the other line. For example, if n = 6, then line #1 can have 2 processes, and line #2 can have 4 processes; another combination could be 1 process in line #1, and 5 processes in line #2, etc...

2- If the number of processes in lines 1 and 2 are not equal, then virtual processes must be added to the shorter line in order to use the developed models. For example, for n = 6, if the production line is arranged to contain 2 processes in line #1, and 4 processes in line #2, then we will need to add 2 virtual processes to line #1, so that both lines will have 4 processes, and then hence, m = 8. Generally, in any configuration, m equals 2 times the number of processes in the longer line. In the example above, m = 2 X 4 = 8

3- Virtual processes are processes which exist at the end of each line when needed. In the above example, line #1 contains processes 1 and 2, and then contains virtual processes 3 and 4, while line #2 has processes 5 through 8.

4- Virtual processes should fulfill the following conditions:

   a. Processing time = 0
   b. Rework time = 0
   c. Probability of scrap = 0
   d. Probability of rework = 0
   e. Probability of acceptance = 1

Figure 5.4 expands on figure 5.3, shown after adding the virtual processes.

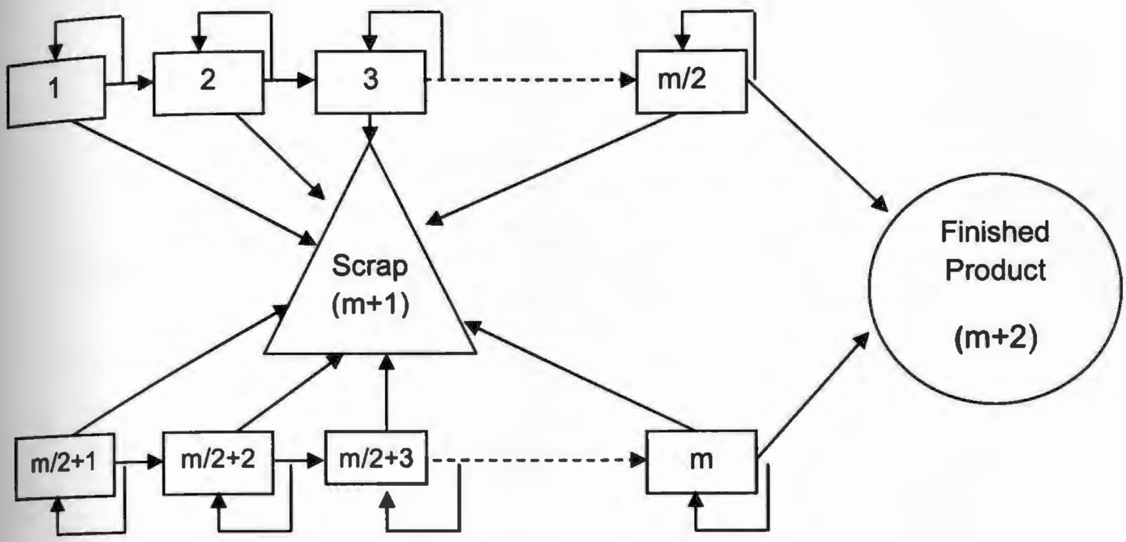


Fig.5.4: Serial-Parallel configuration for m processes, with added virtual processes

Based on the above explained methodology, a_{ii}, $b_{i(n+1)}$ and the resource consumption models become:

$$a_{(i)(i)} = \frac{1}{(1 - P_{(i)(i)})} \qquad (5.11)$$

$b_{i(m+1)} =$

$$
\left\{
\begin{array}{l}
IF\ \left(i \le \frac{m}{2}\right) \\[2ex]
b_{i(m+1)} = \dfrac{\sum_{j=i}^{m/2} \left(P_{j(m+1)}\right)\left(\prod_{k=2}^{j} P_{(k-1)(k)}\right)\left(\prod_{y=j}^{m/2-1}\left(1 - P_{(y+1)(y+1)}\right)\right)}{\left(\prod_{z=2}^{i} P_{(z-1)(z)}\right)\left(\prod_{w=i}^{m/2}\left(1 - P_{(w)(w)}\right)\right)} \\[6ex]
IF\ \left(i > \frac{m}{2}\right) \\[2ex]
b_{i(m+1)} = \dfrac{\sum_{j=i}^{m} \left(P_{j(m+1)}\right)\left(\prod_{k=2}^{j} P_{(k-1)(k)}\right)\left(\prod_{y=j}^{m-1}\left(1 - P_{(y+1)(y+1)}\right)\right)}{\left(\prod_{z=2}^{i} P_{(z-1)(z)}\right)\left(\prod_{w=i}^{m}\left(1 - P_{(w)(w)}\right)\right)}
\end{array}
\right\}
$$

(5.12)

$$
\begin{aligned}
QC = {} & \left(\frac{N_1}{N_1 + N_2}\right) \sum_{i=1}^{\frac{m}{2}} \left(\left(\left(a_{(i)(i)} - 1\right) RC_{(i)} + b_{(i)(m+1)} SC_{(i)} \right) \prod_{k=2}^{i} \left(1 - b_{(k-1)(m+1)}\right) \right) \\
& + \left(\frac{N_2}{N_1 + N_2}\right) \sum_{h=\frac{m}{2}+1}^{m} \left(\left(\left(a_{(h)(h)} - 1\right) RC_{(h)} + b_{(h)(m+1)} SC_{(h)} \right) \prod_{k=\frac{m}{2}+2}^{h} \left(1 - b_{(k-1)(m+1)}\right) \right)
\end{aligned}
$$

(5.13)

$$\text{Productivity} = \left(\frac{N_1}{N_1+N_2}\right)\prod_{i=1}^{m/2}\left(1-b_{(i)(m+1)}\right)+\left(\frac{N_2}{N_1+N_2}\right)\prod_{h=m/2+1}^{m}\left(1-b_{(h)(m+1)}\right) \quad (5.14)$$

$$CT = \left(\frac{N_1}{N_1+N_2}\right)\sum_{i=1}^{m/2}\left(PT_i+\left(a_{(i)(i)}-1\right)RT_i\right)+\left(\frac{N_2}{N_1+N_2}\right)\sum_{h=m/2+1}^{m}\left(PT_h+\left(a_{(h)(h)}-1\right)RT_h\right) \quad (5.15)$$

As an example, suppose that there are five machines arranged in two parallel lines with three processes in the first line and two processes in the second line. Table 5.1 shows the probabilities of scrap, rework, and acceptance for each machine. It also includes rework and scrap costs, and processing and reworking times.

Table 5.1 Data for serial-parallel production system with 5 processes

	Process 1	Process 2	Process 3	Process 4	Process 5
P(rework)	0.1	0.05	0.06	0.07	0.1
P(scrap)	0.02	0.04	0.09	0.03	0.03
P(accepted)	0.88	0.91	0.85	0.9	0.87
RC ($/part)	1	2	3	1.5	4
SC ($/part)	4	4.2	4.5	5	5.4
PT (min/part)	6	7	4	3	7
RT (min/part)	4	5	3	2	2

m = 3*2 = 6 processes

Figure 5.5 shows the configuration of the 5 main processes and the virtual process (number 6).

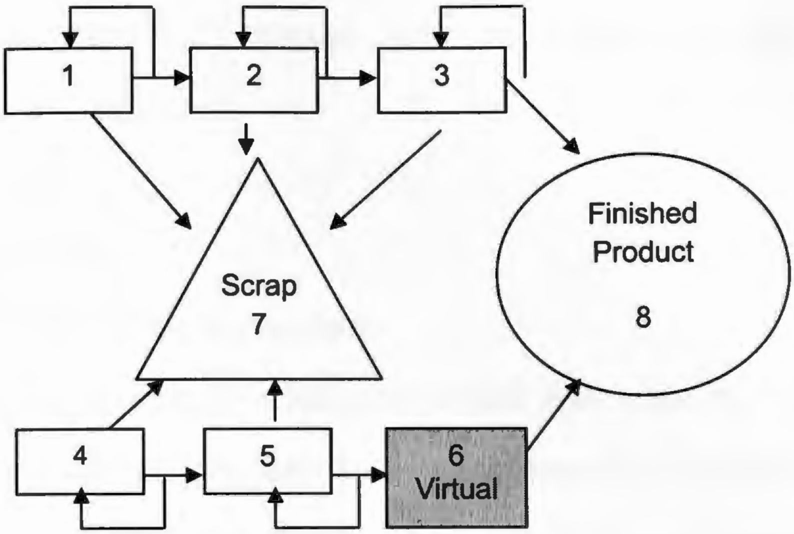


Fig.5.5: Serial-Parallel configuration for 5 processes, with added virtual processes

The transition matrix for the 6 processes becomes:

$$
P = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \end{array}
\begin{array}{c}
\begin{array}{cccccccc} 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \end{array} \\
\begin{bmatrix}
0.1 & 0.88 & 0 & 0 & 0 & 0 & 0.02 & 0 \\
0 & 0.05 & 0.91 & 0 & 0 & 0 & 0.04 & 0 \\
0 & 0 & 0.06 & 0 & 0 & 0 & 0.09 & 0.85 \\
0 & 0 & 0 & 0.07 & 0.90 & 0 & 0.03 & 0 \\
0 & 0 & 0 & 0 & 0.1 & 0.87 & 0.03 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}
\end{array}
$$

State 6 represents a part at process 6, which is the virtual process in this example. Note that the rework and scrap probabilities for process 6 equal zero, whereas the acceptance probability equals 1.

By applying equations 6.13 through 6.15 respectively the quality cost, productivity, and cycle time are:

QC = $1.23 per part

Productivity = 82.40%

Expected cycle time = 12.88 min per part

The n process serial-parallel configuration with crossover involves a complicated model for the long term scrap probabilities $b_{i(n+1)}$ as well as more complicated resource consumption models. However, there is an example of four process serial-parallel configuration with crossover in section 4.6, and an example of six process serial-parallel configuration with crossover in section 6.5.2, which can be used for similar production systems in each case. The level of complexity and difficulty to follow a pattern in the probability matrices and the resource consumption models is too high and it is advised that the reader uses mathematical software packages to help develop the model for configurations with a large number of processes.

CHAPTER SIX

CASE STUDY AT BIOPHARMACEUTICAL COMPANY

6.1 Abstract

The methodologies and models in this thesis are applied in a biopharmaceutical industry case study. Two production systems from a biopharmaceutical company have been utilized to apply the serial-parallel model (with and without crossover), and the serial model. This chapter includes a brief background about the company and the description and analysis of the two production systems.

6.2 Company Background

XY Company is a fast growing biopharmaceutical company that develops and produces drug products. It has many locations outside and inside the United State. It has short and long term objectives that aim to satisfy their customer with a high quality product that meets the Good Manufacturing Practices (GMPs), established by the Food and Drug Administration (FDA), in all aspects, and hence it maintains the safety, identity, strength, quality, and purity of its products.

As in many biopharmaceutical companies, the main processes for producing the drug products are preparing media, cell culture, preparing buffer, purification, and filling and packaging as shown in figure 6.1. The focus of this case study is to apply the methodologies and analysis on the Media and cell culture processes.

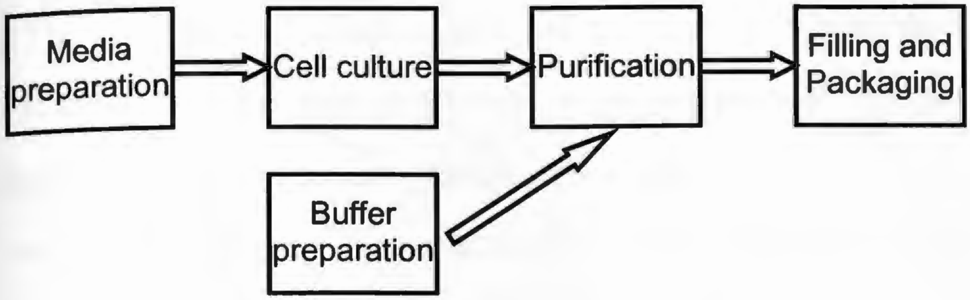


Fig. 6.1: Main production processes

6.3 Media Preparation Production System

Media is defined as: "a (usually sterile) preparation made for the growth, storage, maintenance, or transport of microorganisms or other cells" (Odum, 2002). Different types of biopharmaceutical products need different types of media, and for each product there are two types of media, growth and production media. Figures 6.2 and 6.3 show the value stream map (VSM) for producing 750 liters of media starting from the point the raw material is received to the point where finished media is ready to be transferred to the internal customer (cell culture department).

The media production system consists of two preparation tanks, two hold tanks, and transfer lines as show in figure 6.4. Media is prepared at tanks A and B, where the components are added to WFI (Water for Injection) followed by titrating the solution to adjust the pH value. The holding tanks (A' and B') are used to keep the media under pressure after going through the filters at the transferring lines. Filters should pass two tests, pre-test and post-test, to ensure that they were in good condition and did not cause any contamination of the media. To meet the GMP requirements and avoid cross contamination, CIP (Clean in Place) and SIP (Steam in Place) processes are applied to clean the tanks and the transfer lines before producing the media.

As can be seen from figures 6.2 and 6.3, the VSM tracks all activities occurring at preparation tanks A and B, and hold tanks A` and B`. Both figures show the percentage of value added time at each tank. For example, hold tank A' has 65% value added time whereas hold tank B` has 5% value added time, which is the lowest percent. The two most common non-value adding activities are different types of waiting and paperwork.

6.4 Media Production System Configuration

Two types of media, L and M, are used in this case study, where both are used for the same drug product. As shown in figure 6.4, the production system of media L or M consists of three main production stages. The first stage is preparing media at tank A or B by adding chemicals and serum to WFI. The second stage is titrating the media at tank A or B, and the third stage is filtering and transferring the media to holding tank A` or B`. The system configuration is considered to be serial-parallel, where there are two parallel lines, and each line consists of three processes. Crossover may also happen between the processes at stages two and three. That means the media after titration could be transferred to either of A' or B' as shown in figure 6.4.

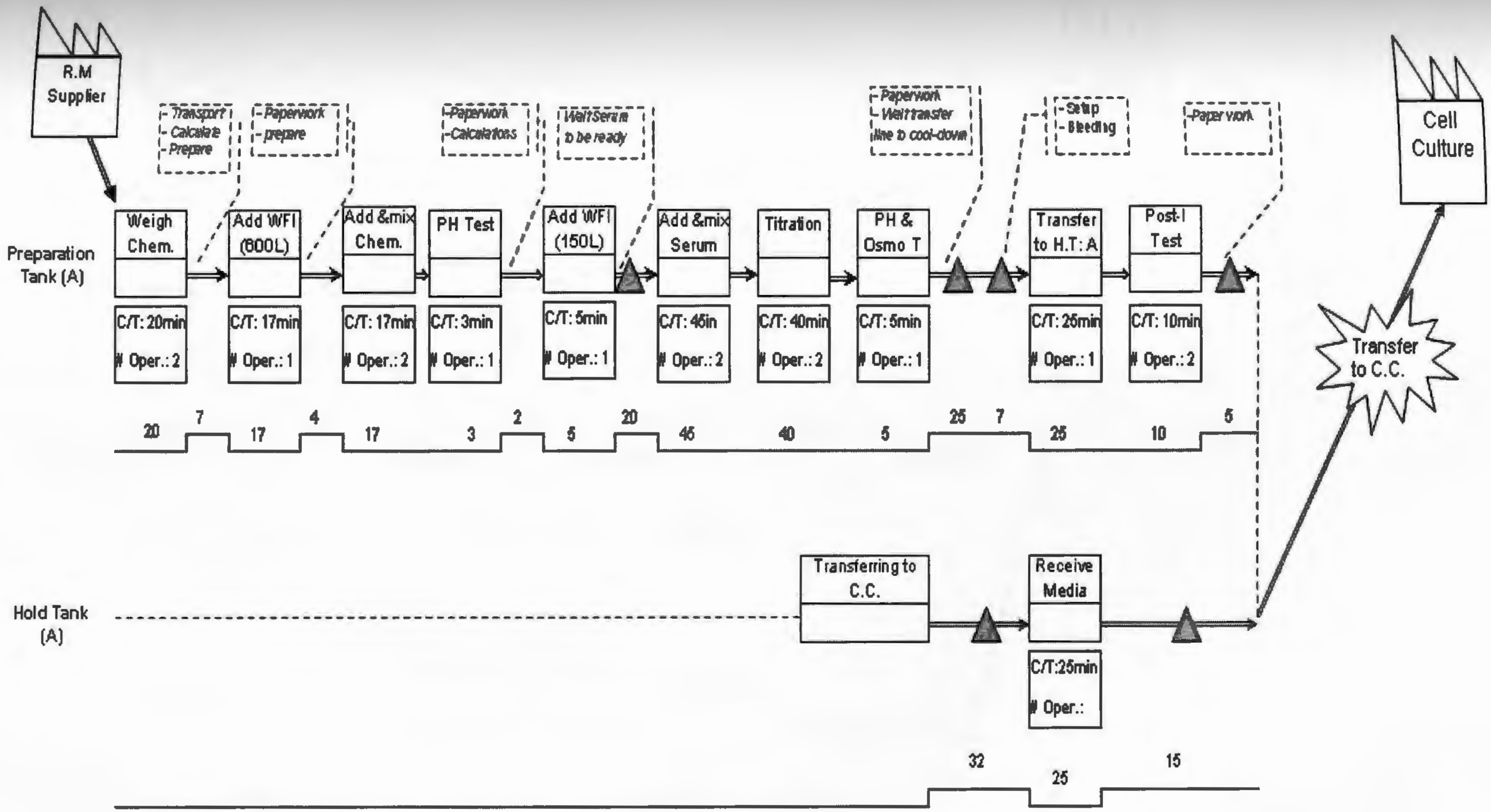


Fig. 6.2: Value stream mapping (VSM) for media production system (part 1)

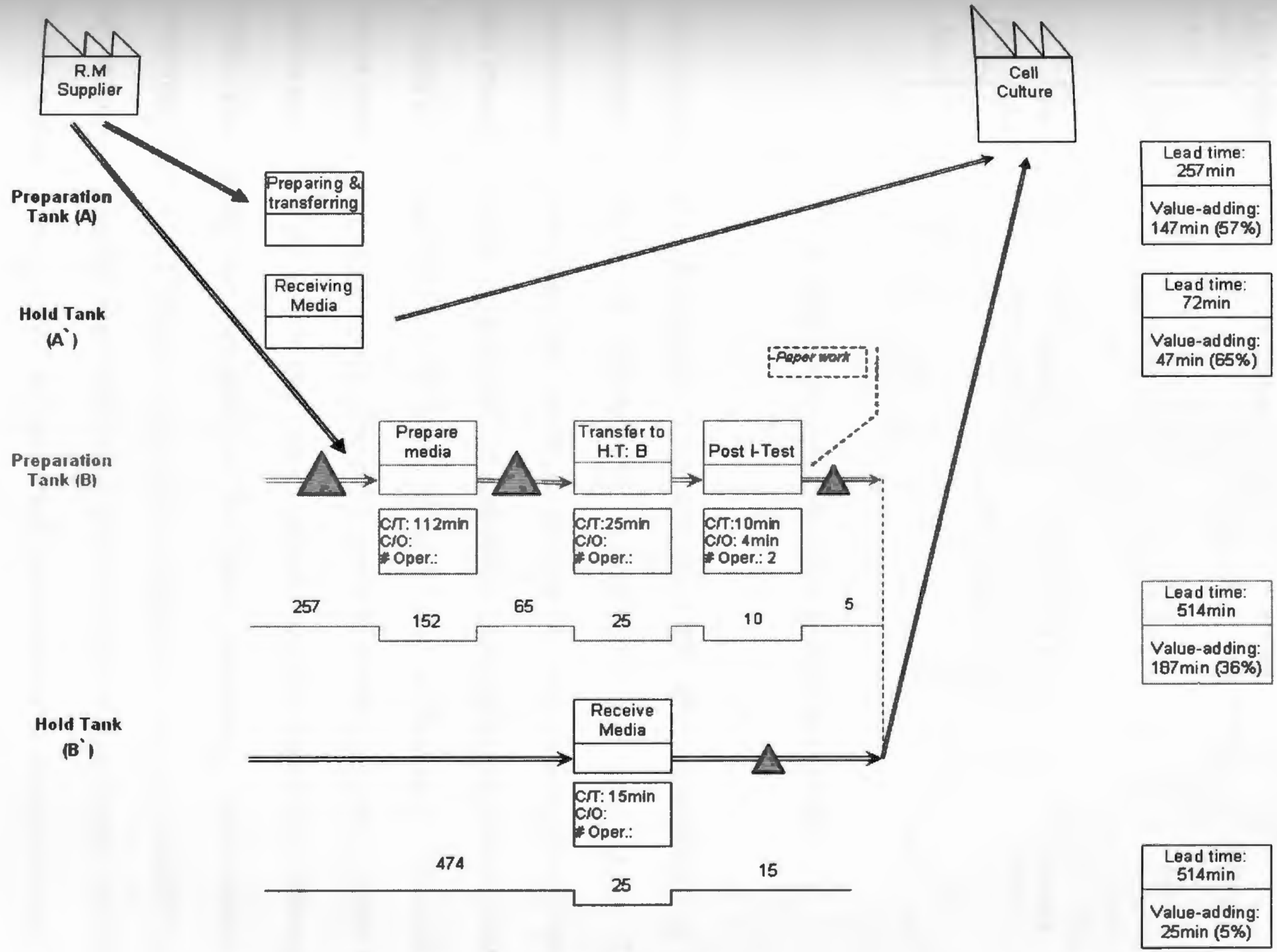


Fig. 6.3: Value stream mapping (VSM) for media production system (part 2)

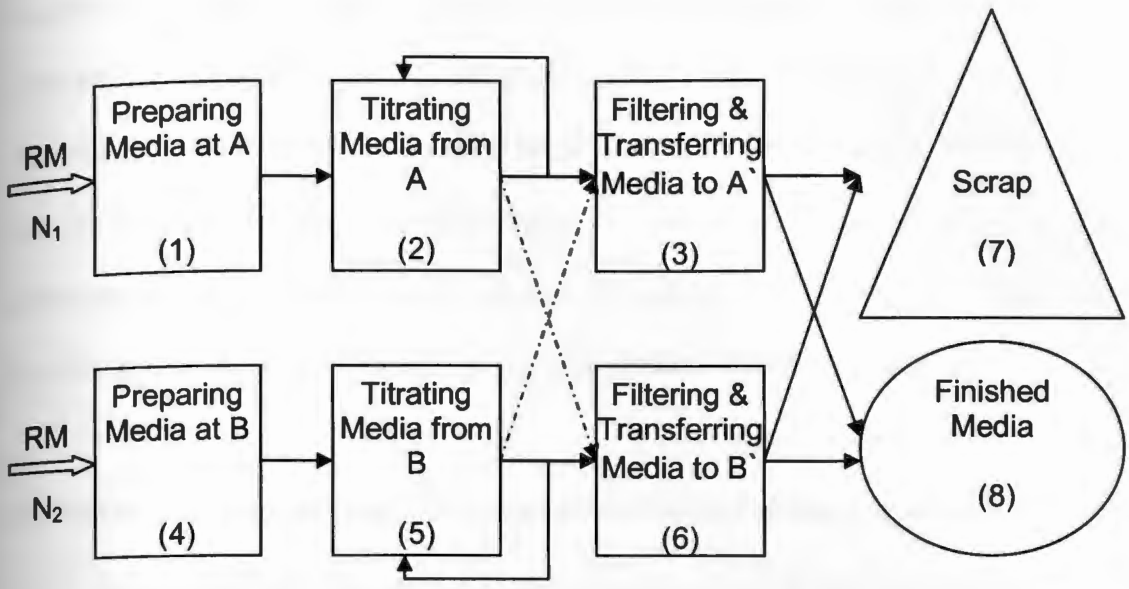


Fig. 6.4: Configuration of the media production system

Two configuration alternatives are analyzed to find the performance of each alternative in terms of quality cost, productivity, and cycle time. These configuration alternatives are, serial-parallel without crossover and serial-parallel with crossover. In the case of this specific production system it is not appropriate to arrange the six processes into a pure parallel configuration, because this would violate the requirement of filtering the media before it enters the hold tanks and is ready for use by the cell culture department. In other words, filtering the media should not be performed in the same processing stage where it is prepared. Arranging them in a pure serial configuration is not applicable as well. For example, if the two processes in the preparing media stage were arranged in series where adding water is performed at tank A and adding chemicals is performed at tank B, then that will be not feasible since water has to be transferred again from tank A to tank B in order to be able to add chemicals, and hence filling water into tank A becomes meaningless. That means that preparing and transferring the media can only be performed by three stages, not one stage (as in a pure parallel configuration) or six stages (as in a pure serial configuration). The models developed in chapter five for the "three stage serial-parallel system with six processes" can be applied in this case study.

6.5 Resource Consumption Models at the Media Production System

In this section the resource consumption models are applied to the two alternative configurations, and then the results are used to analyze their performance.

6.5.1 Serial-Parallel Configuration (without Crossover)

The required data to build the resource consumption models have been collected, with the exception of data that are related to costs because this is not available to be included in the thesis. As a starting point, the types of media that are used in this case study are identified. After that, the key quality characteristic for each process is defined, and then the short term probabilities of acceptance, rework, and scrap are determined.

6.5.1.1 Quality Characteristics and Short Term Probabilities

Figure 6.4 shows states 1 through 8 that are used in developing the Markov chain model. At the first processing stage (state (1) and (4)), the operator should make sure that the total amount of WFI is within the acceptance range after adding the chemicals. OIT (Operation Interface Terminal) technology is used to control the amount of added WFI before and after adding the chemicals, so at this process all of the prepared media is accepted, since it always falls within the pre-specified range, and moved to the titration stage.

At titration, the considered quality characteristic is the pH value. The prepared media can not proceed to the next stage unless the pH value at titration falls within a given acceptance range. The solution is re-titrated until pH falls within this range; hence, there is no scrap from this stage. Once the media is accepted at titration it is then filtered and transferred to the hold tanks.

There is no rework at stage three (filtering and transferring media). The amount of scrapped media at stage three could range from a few liters up to all of the prepared media. If the filters do not pass the post-test, the media is considered to be non-qualified media and is all scrapped. Although losing the entire amount of media rarely happens, there are always small amounts lost during the filtering and transferring process.

Historical data for the pH values at the titration stage are collected in order to find the rework rate. Minitab software is used to find the probability distribution that the data follows. Data for media L shows that the pH value of the titrated media from tank A (state 2) fits the normal and lognormal distributions, whereas the pH value of the titrated media from tank B (state 5) fits the lognormal distribution (figures 6.5 and 6.6 show part of the Minitab outputs for finding the best distribution. The figures of other distributions are attached in the appendix).

Figures 6.7 and 6.8 show the pH value histograms for the titration processes.

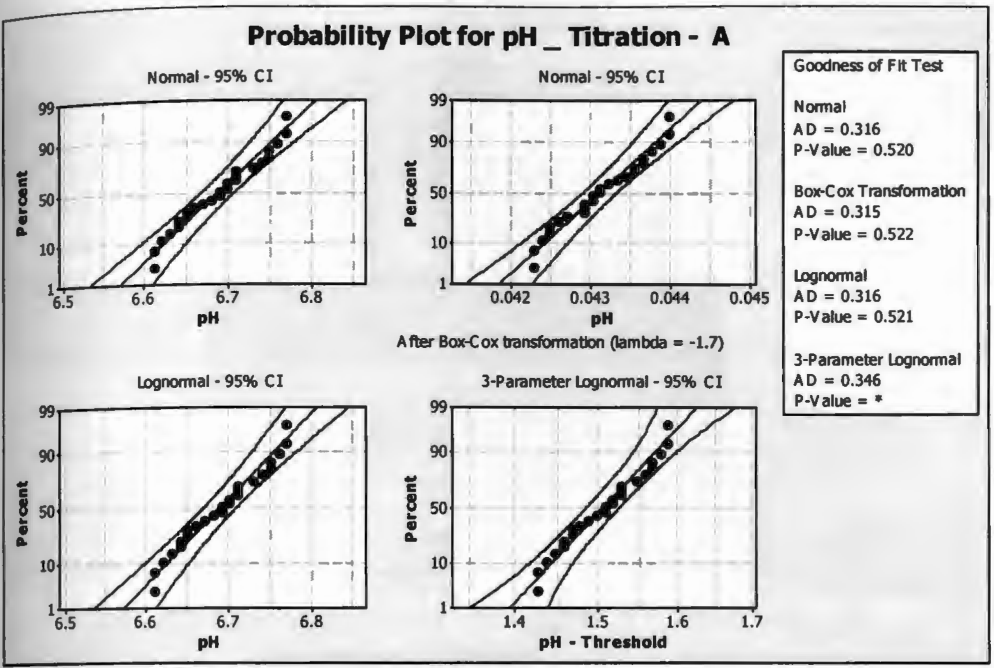


Fig. 6.5: Probability plot for pH values from titration process
(for media L prepared at tank A)

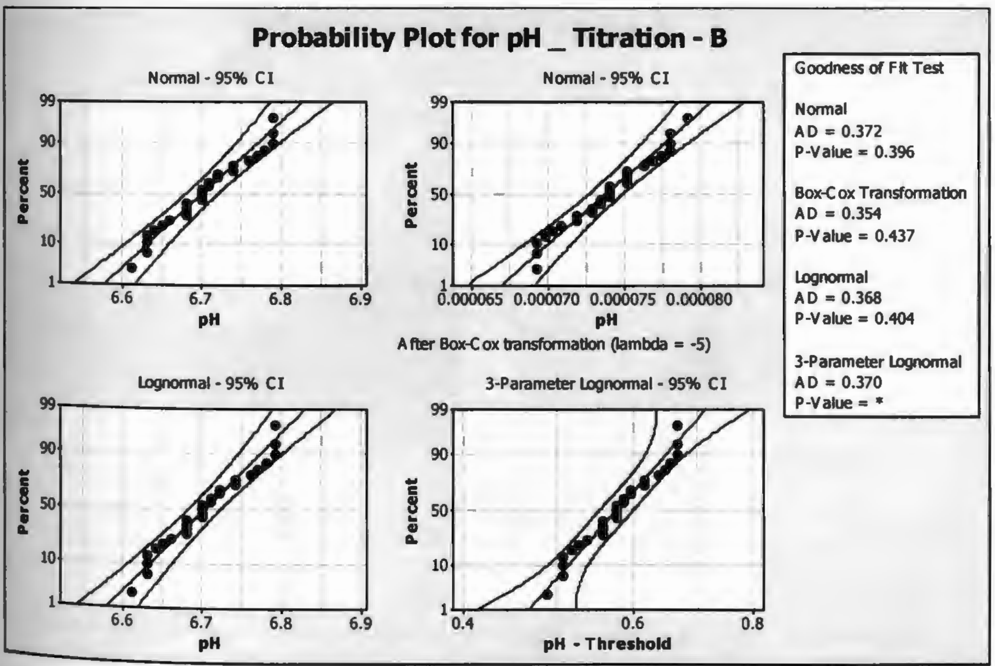


Fig. 6.6: Probability plot for pH values from titration process
(for media L prepared at tank B)

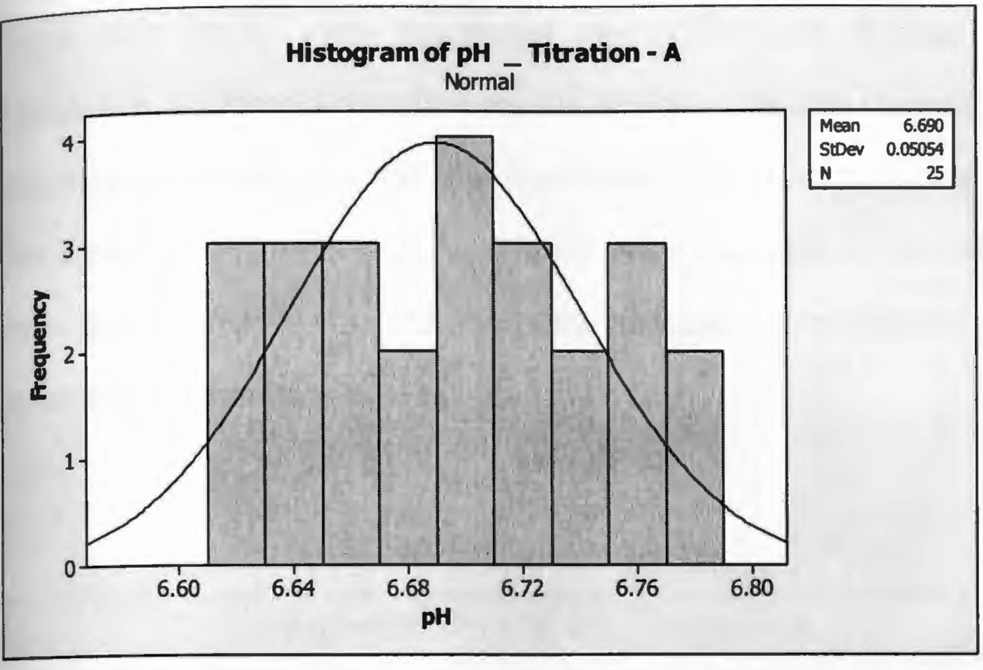


Fig. 6.7: Histogram for pH values from titration process (for media L prepared at tank A)

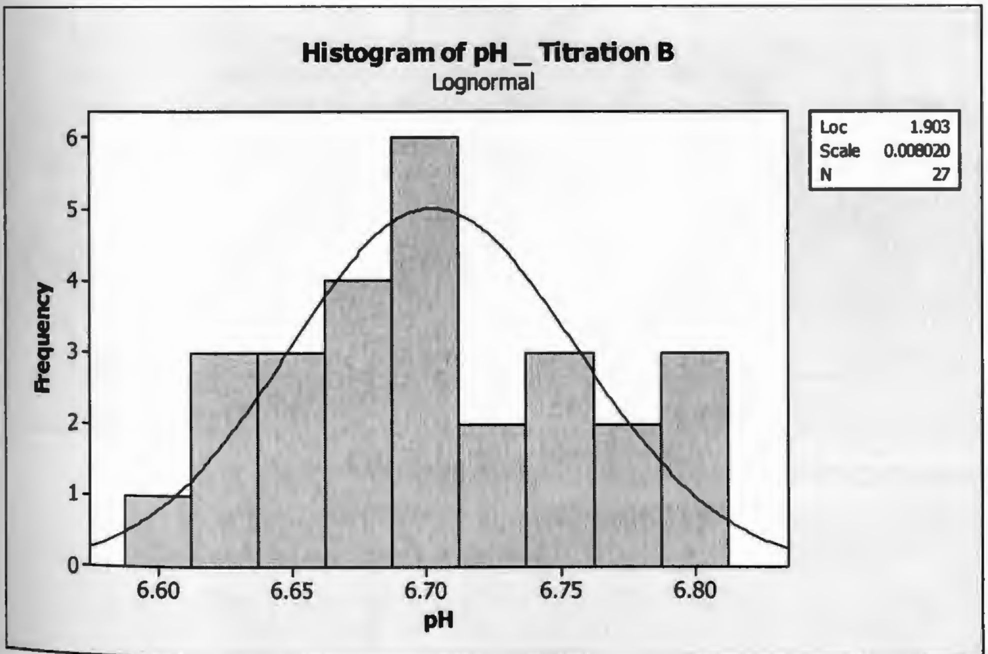


Fig. 6.8: Histogram for pH values from titration process (for media L prepared at tank B)

For media M, the titrated media from tank A (figure 6.9) fits the largest extreme value distributions, while the titrated media from tank B does not fit any distribution, so Johnson transformation is applied to the data (figure 6.10) and the resulting P-Value is accepted (the figures for other distributions are attached in the appendix). Figure 6.11 shows the pH value histogram for the titrated media from tank A, while figure 6.12 shows the histogram of the transformed data of titrated media from tank B.

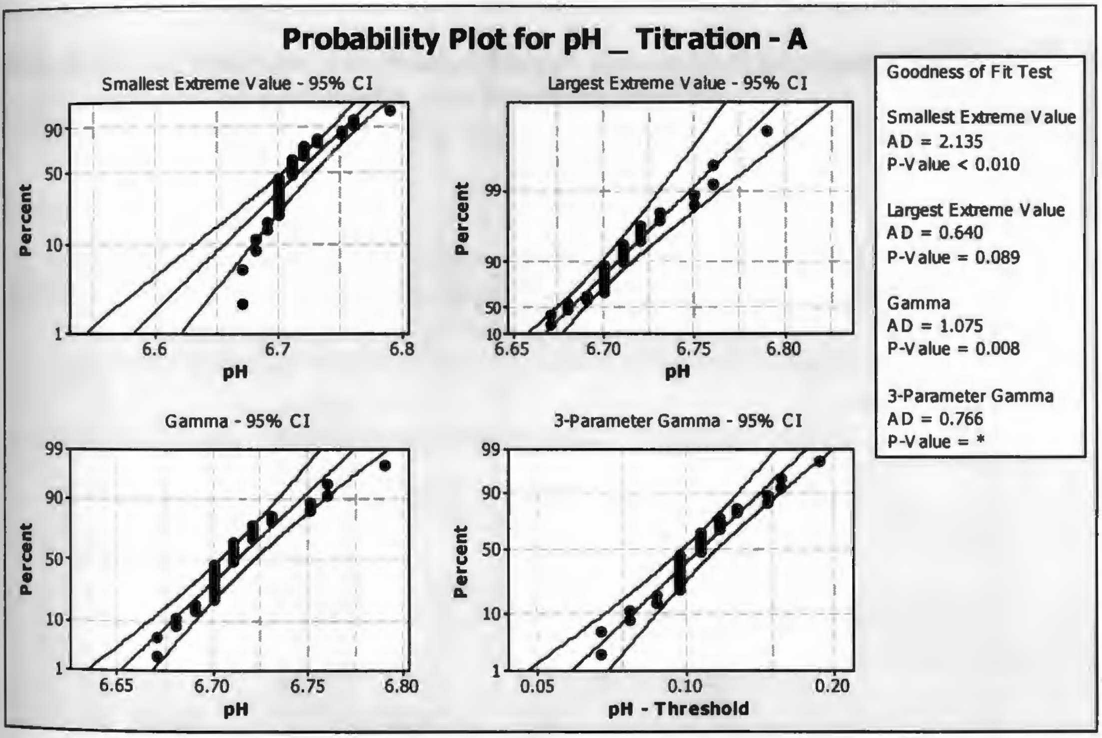


Fig. 6.9: Probability plot for pH values from titration process (for media M prepared at tank A)

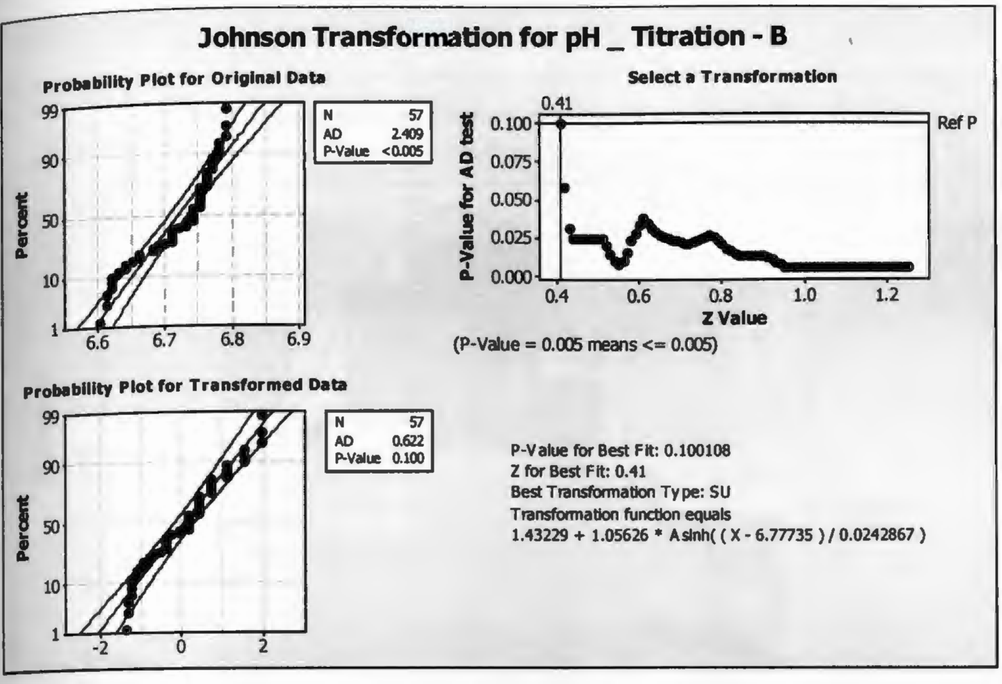


Fig. 6.10: Johnson transformation for pH values from titration process (for media M prepared at tank B)

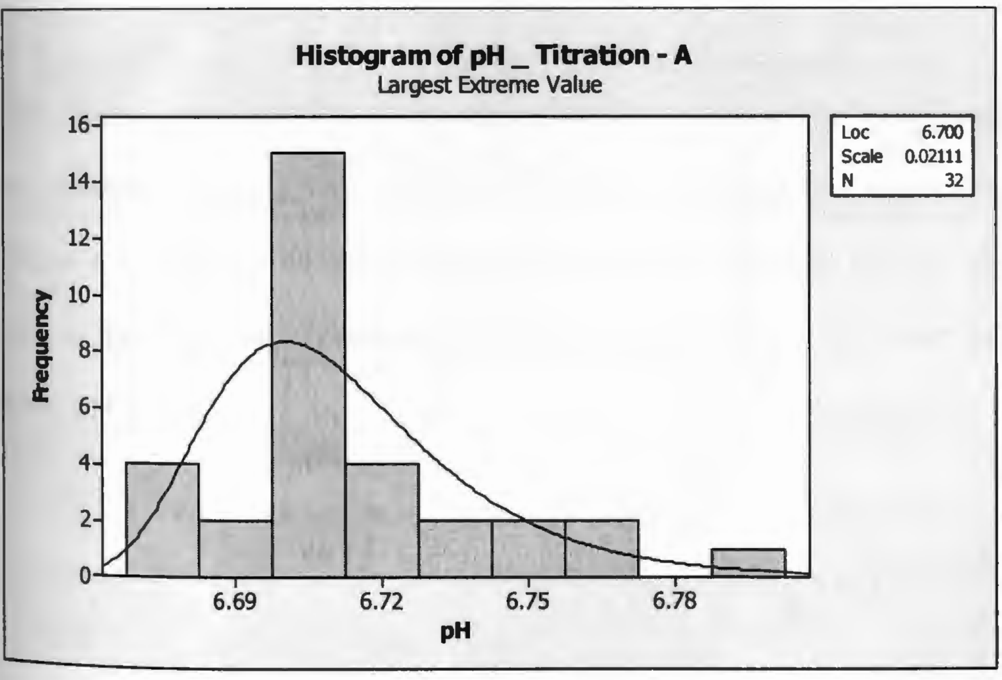


Fig. 6.11: Histogram for pH values from titration process (for media M prepared at tank A)

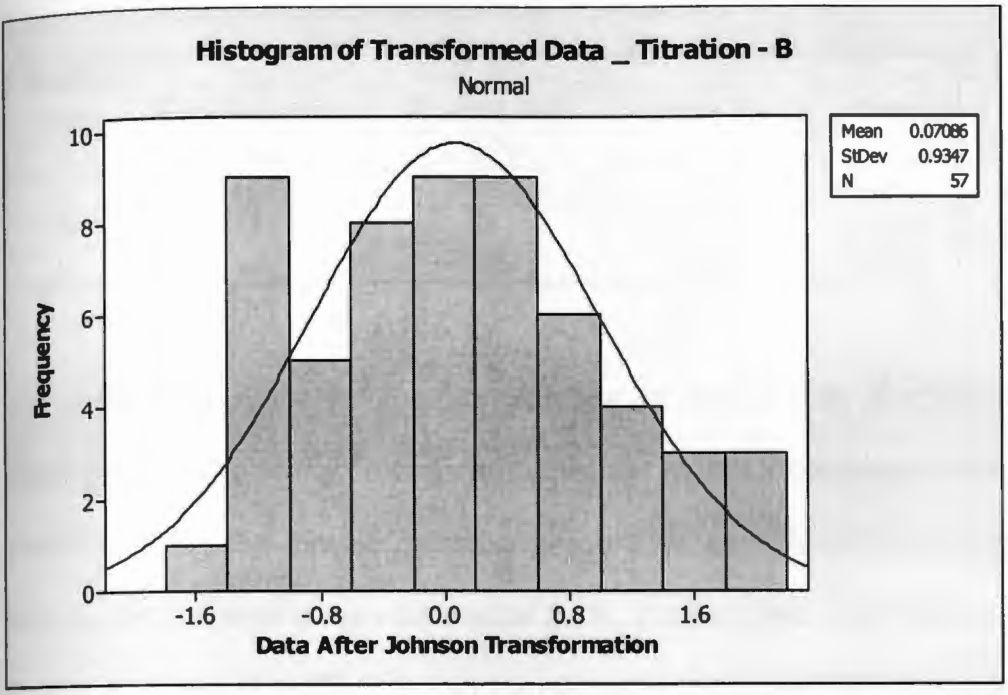


Fig. 6.12: Histogram of the transformed data after using Johnson transformation (for media M prepared at tank B)

After finding the distributions for the pH data, the probability of rework at each of the titration processes for both types of media is calculated, and summarized in Table 6.1. The probability of rework is the probability that the pH value will be above the upper specification limit (pH = 6.8) or below the lower specification limit (pH = 6.6).

Table 6.1: Rework probabilities at titration processes

Media type	Process/sate	P(pH<LSL)	P(pH>USL)	Total
L	3	0.038	0.015	0.053
L	4	0.024	0.041	0.065
M	3	0	0.009	0.009
M	4	0.057	0.008	0.065

Historical data for the percentages of media that are lost during the filtering and transferring process are collected to find the average scrap rate. For media L, when the titrated media is prepared at tank A and transferred to hold tank A\` the average scrap rate equals 3.2%. On the other hand, when the titrated media is prepared at Tank B and transferred to hold tank B\`, the average scrap rate equals 12.3%. For media M, the scrap rate values for hold tanks A' and B' are 1.6% and 2.3%, respectively.

Each campaign of the selected product includes, on average, seven lots of type L and fifteen lots of type M. The rework time and processing time for the titration process are almost equal. Since cost data is not available, the rework cost at any process is measured by the labor time in minutes at that process. On the other hand, the scrap cost is measured by the labor time in minutes consumed for producing the media starting from receiving the raw material to the point where the scrap happens. Tables 6.2 and 6.3 summarize all of the data that is required to apply the resource consumption models for the production system of media L and M.

Table 6.2: Data summary for media L

	Preparing Media at A, B		Titrating Media from A, B		Filtering /Transferring to A`, B`	
	State 1	State 4	State 2	State 5	State 3	State 6
P(rework)	0	0	0.053	0.065	0	0
P(accept)	1	1	0.947	0.935	0.968	0.877
P(scrap)	0	0	0	0	0.032	0.123
RC (labor min/unit media)	0	0	45	45	0	0
SC (labor min/unit media)	0	0	0	0	257	257
PT (min/ unit media)	140	140	45	45	72	72
RT (min/ unit media)	0	0	45	45	0	0
Number of lots per campaign (N)	3	4				

Table 6.3: Data summary for media M

	Preparing Media at A, B		Titrating Media from A, B		Filtering /Transferring to A`, B`	
	State 1	State 4	State 2	State 5	State 3	State 6
P(rework)	0	0	0.009	0.065	0	0
P(accept)	1	1	0.991	0.935	0.984	0.977
P(scrap)	0	0	0	0	0.016	0.023
RC (labor min/unit media)	0	0	45	45	0	0
SC (labor min/unit media)	0	0	0	0	257	257
PT (min/ unit media)	140	140	45	45	72	72
RT (min/1 media)	0	0	45	45	0	0
Number of lots per campaign (N)	5	10				

From the data presented in this section, the short term probabilities can be summarized in the transition probability matrix (P), where P_L and P_M are the transition probability matrices for media L and M respectively:

$$
P_L = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \end{array}
\begin{array}{c}
\begin{array}{cccccccc} 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \end{array} \\
\begin{bmatrix}
0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0.053 & 0.947 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0.032 & 0.968 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0.065 & 0.935 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0.123 & 0.877 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}
\end{array}
$$

$$
P_M = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \end{array}
\begin{array}{c}
\begin{array}{cccccccc} 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \end{array} \\
\begin{bmatrix}
0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0.009 & 0.991 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0.016 & 0.984 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0.065 & 0.935 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0.023 & 0.977 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}
\end{array}
$$

6.5.1.2 Quality Cost, Productivity, and Cycle Time

The procedure used in previous chapters is used to find the cost of quality, productivity, and cycle time models.

1- Cost of Quality Model:

$$QC = \sum_{i=1}^{6} f(RC_i) + \sum_{i=1}^{6} f(SC_i)$$, where:

$$f(RC_1) = \frac{N_1 * (a_{11} - 1)RC_1}{(N_1 + N_2)}$$

$$f(RC_2) = \frac{N_1(1 - b_{17})(a_{22} - 1)RC_2}{(N_1 + N_2)}$$

$$f(RC_3) = \frac{N_1(1 - b_{17})(1 - b_{27})(a_{33} - 1)RC_3}{(N_1 + N_2)}$$

$$f(RC_4) = \frac{N_2(a_{44} - 1)RC_4}{(N_1 + N_2)}$$

$$f(RC_5) = \frac{N_2(1 - b_{47})(a_{55} - 1)RC_5}{(N_1 + N_2)}$$

$$f(RC_6) = \frac{N_2(1 - b_{47})(1 - b_{57})(a_{66} - 1)RC_6}{(N_1 + N_2)}$$

$$f(SC_1) = \frac{N_1 b_{17} SC_1}{(N_1 + N_2)}$$

$$f(SC_2) = \frac{N_1(1 - b_{17})b_{27} SC_2}{(N_1 + N_2)}$$

$$f(SC_3) = \frac{N_1(1 - b_{17})(1 - b_{27})b_{37} SC_3}{(N_1 + N_2)}$$

$$f(SC_4) = \frac{N_2 b_{47} SC_4}{(N_1 + N_2)}$$

$$f(SC_5) = \frac{N_2(1 - b_{47})b_{57} SC_5}{(N_1 + N_2)}$$

$$f(SC_6) = \frac{N_2(1 - b_{47})(1 - b_{57})b_{67} SC_6}{(N_1 + N_2)}$$

(Refer to the definitions of a_{ii}, and b_{ij} from section 4.2).

2- Productivity Model:

$$\text{Productivity} = \frac{N_1(1-b_{17})(1-b_{27})(1-b_{37}) + N_2(1-b_{47})(1-b_{57})(1-b_{67})}{(N_1+N_2)}$$

3- Cycle Time Model:

$$\text{Expected Cycle Time} = \frac{N_1(CT_1+CT_2+CT_3) + N_2(CT_4+CT_5+CT_6)}{N_1+N_2}$$

Where:

$CT_i = PT_i + (a_{ii} - 1)RT_i$

Table 6.4 summarizes the calculated quality cost, productivity, and cycle time after applying the equations.

Table 6.4: Without crossover configuration

	Quality Cost (labor min/ unit media)	Productivity (100%)	Expected Cycle Time (min / unit media)
Media L	19.81	77.42	259.87
Media M	7.26	93.93	259.22

6.5.2 Serial-Parallel Configuration (with Crossover)

In this configuration the titrated media from stage two can proceed to any process in stage three. That means that there are four possible paths for the produced media:

Prepared at tank A – titrated – filtered and transferred to Tank A`

Prepared at tank B – titrated – filtered and transferred to Tank A`

Prepared at tank A – titrated – filtered and transferred to Tank B`

Prepared at tank B – titrated – filtered and transferred to Tank B`

6.5.2.1 Quality Characteristics and Short Term Probabilities

The considered quality characteristics are the same as in section 6.5.1 when crossover is not allowed between stage three and stage four. The probability of re-titrating the prepared media does not change (table 6.1). The only change is the scrap rates during the filtering and transferring process. Table 6.5 shows the percentages of titrated media from Tanks A and B that is filtered and transferred to the hold tanks A` and B`.

Table 6.5: Percentage of accepted parts that go from one process to another

	A`	B`
A	80%	20%
B	42%	58%

For media L, when hold tank A` receives media from both processes in the previous stage, the average scrap rate becomes 11.2%. On the other hand, when hold tank B` receives media from both processes in the previous stage, the average scrap rate becomes 8.0%. For media M, the scrap rate values are 2.23% and 1.65 % respectively for hold tanks A' and B'.

Therefore, the new P matrices become:

$$P_L = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \end{array}\begin{array}{c} \begin{array}{cccccccc} 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \end{array} \\ \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0.053 & 0.758 & 0 & 0 & 0.189 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0.112 & 0.888 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0.393 & 0 & 0.065 & 0.542 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0.080 & 0.920 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

$$P_M = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \end{array}\begin{array}{c} \begin{array}{cccccccc} 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \end{array} \\ \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0.009 & 0.7928 & 0 & 0 & 0.1982 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0.0223 & 0.9777 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0.3927 & 0 & 0.065 & 0.5423 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0.0165 & 0.9835 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

6.5.2.2 Quality Cost, Productivity, and Cycle Time

1- Cost of Quality Model:

$QC = \sum_{i=1}^{6} f(RC_i) + \sum_{i=1}^{6} f(SC_i)$, where:

$$f(RC_1) = \frac{N_1(a_{11} - 1)RC_1}{(N_1 + N_2)}$$

$$f(RC_2) = \frac{N_1(1 - b_{17})(w_{12}) + N_2(1 - b_{47})(w_{42})}{(N_1 + N_2)} \times (a_{22} - 1)RC_2$$

$$f(RC_3)=\frac{(N_1(1-b_{17})(w_{12})+N_2(1-b_{47})(w_{42}))(1-b_{27})(w_{23})}{(N_1+N_2)}\times(a_{33}-1)RC_3+$$

$$\frac{(N_1(1-b_{17})(w_{15})+N_2(1-b_{47})(w_{45}))(1-b_{57})(w_{53})}{(N_1+N_2)}\times(a_{33}-1)RC_3$$

$$f(RC_4)=\frac{N_2(a_{44}-1)RC_4}{(N_1+N_2)}$$

$$f(RC_5)=\frac{N_1(1-b_{17})(w_{15})+N_2(1-b_{47})(w_{45})}{(N_1+N_2)}\times(a_{55}-1)RC_5$$

$$f(RC_6)=\frac{(N_1(1-b_{17})(w_{12})+N_2(1-b_{47})(w_{42}))(1-b_{27})(w_{26})}{(N_1+N_2)}\times(a_{66}-1)RC_6+$$

$$\frac{(N_1(1-b_{17})(w_{15})+N_2(1-b_{47})(w_{45}))(1-b_{57})(w_{56})}{(N_1+N_2)}\times(a_{66}-1)RC_6$$

$$f(SC_1)=\frac{N_1b_{17}SC_1}{(N_1+N_2)}$$

$$f(SC_2)=\frac{N_1(1-b_{17})(w_{12})+N_2(1-b_{47})(w_{42})}{(N_1+N_2)}\times b_{27}SC_2$$

$$f(SC_3)=\frac{(N_1(1-b_{17})(w_{12})+N_2(1-b_{47})(w_{42}))(1-b_{27})(w_{23})}{(N_1+N_2)}\times b_{37}SC_3+$$

$$\frac{(N_1(1-b_{17})(w_{15})+N_2(1-b_{47})(w_{45}))(1-b_{57})(w_{53})}{(N_1+N_2)}\times b_{37}SC_3$$

$$f(SC_4)=\frac{N_2b_{47}SC_4}{(N_1+N_2)}$$

$$f(SC_5)=\frac{N_1(1-b_{17})(w_{15})+N_2(1-b_{47})(w_{45})}{(N_1+N_2)}\times b_{57}SC_5$$

$$f(SC_6)=\frac{(N_1(1-b_{17})(w_{12})+N_2(1-b_{47})(w_{42}))(1-b_{27})(w_{26})}{(N_1+N_2)}\times b_{67}SC_6+$$

$$\frac{(N_1(1-b_{17})(w_{15})+N_2(1-b_{47})(w_{45}))(1-b_{57})(w_{56})}{(N_1+N_2)}\times b_{67}SC_6$$

(Refer to the definitions of a_{ii}, b_{ij} , and w_{ij} from section 4.2).

2- Productivity Model:

Productivity =

$$\frac{\left(N_1(1-b_{17})(w_{12})+N_2(1-b_{47})(w_{42})\right)(1-b_{27})(w_{23})+\left(N_1(1-b_{17})(w_{15})+N_2(1-b_{47})(w_{45})\right)(1-b_{57})(w_{53})}{(N_1+N_2)}\times(1-b_{37})+$$

$$\frac{\left(N_1(1-b_{17})(w_{12})+N_2(1-b_{47})(w_{42})\right)(1-b_{27})(w_{26})+\left(N_1(1-b_{17})(w_{15})+N_2(1-b_{47})(w_{45})\right)(1-b_{57})(w_{56})}{(N_1+N_2)}\times(1-b_{67})$$

3- Cycle Time Model:

Expected Cycle Time=

$$\frac{\left(N_1 CT_1 + (N_1 w_{12} + N_2 w_{42})CT_2 + \left((N_1 w_{12} + N_2 w_{42})w_{23} + (N_1 w_{15} + N_2 w_{45})w_{53}\right)CT_3\right)+}{N_1 + N_2}$$

$$\frac{\left(N_2 CT_4 + (N_1 w_{15} + N_2 w_{45})CT_5 + \left((N_1 w_{12} + N_2 w_{42})w_{26} + (N_1 w_{15} + N_2 w_{45})w_{56}\right)CT_6\right)}{N_1 + N_2}$$

Where:

$$CT_i = PT_i + (a_{ii} - 1)RT_i$$

Table 6.6 summarizes the results of applying the equations of quality cost, productivity, and cycle time for serial-parallel system configurations with crossover:

Table 6.6: With crossover configuration

	Quality Cost (labor min/ unit media)	Productivity (100%)	Expected Cycle Time (min / unit media)
Media L	23.11	73.33	259.87
Media M	7.05	94.20	259.22

Charts 6.13, 6.14, and 6.15 show the difference in performance of the two configurations in terms of quality cost, productivity, and cycle time, respectively.

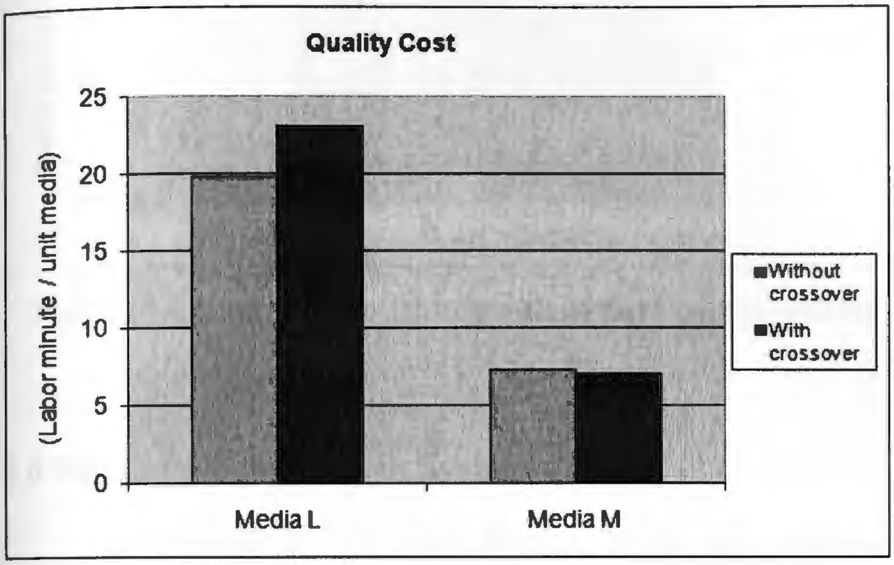


Fig. 6.13 Quality cost for two system configurations

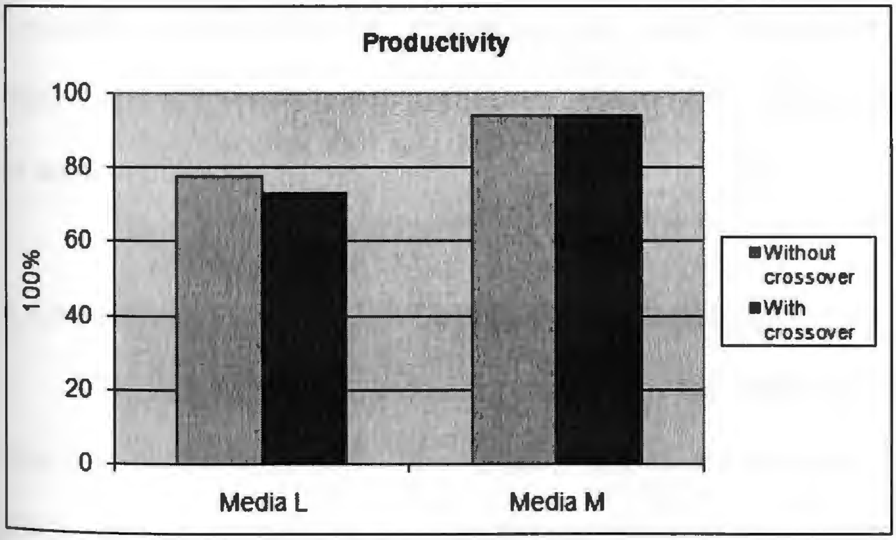


Fig. 6.14 Productivity for two system configurations

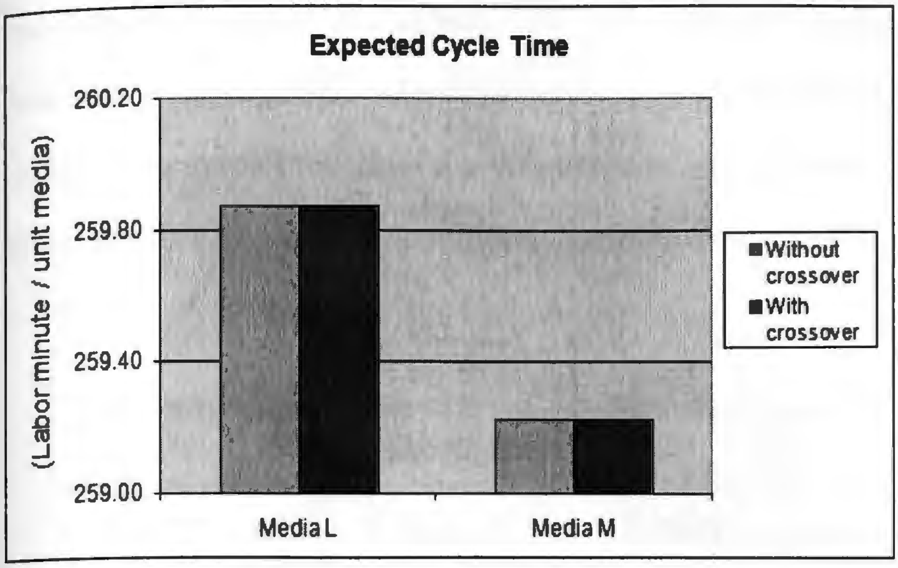


Fig. 6.15 Expected cycle time for two system configurations

6.6 Cell Culture Production System

Odum, 2002 defined cell culture as: "Cells taken from a living organism and grown under controlled conditions ("in vitro"). Method used to maintain cell lines or strains". There are four main stages which happen during the cell culture production system: initiation, cell expansion, refeed, and harvest. A brief description of the production processes for two types of drug products is shown in section 6.6.1.

6.6.1 Process Flow for Cell Culture Production System

The production for product 1 starts with the initiation process followed by four cell expansions (CE), one refeed, and finally fourteen harvest processes (HA), with an average processing time of 76 days, as shown in figure 6.16. On the other hand, the production for product 2 includes one initiation process, three cell expansions (CE), one refeed, and three harvest processes (HA), with an average processing time of 56 days, as shown in figure 6.17. During the initiation and cell expansion processes the growth media is used, where during the refeed and harvests processes the production media is used instead.

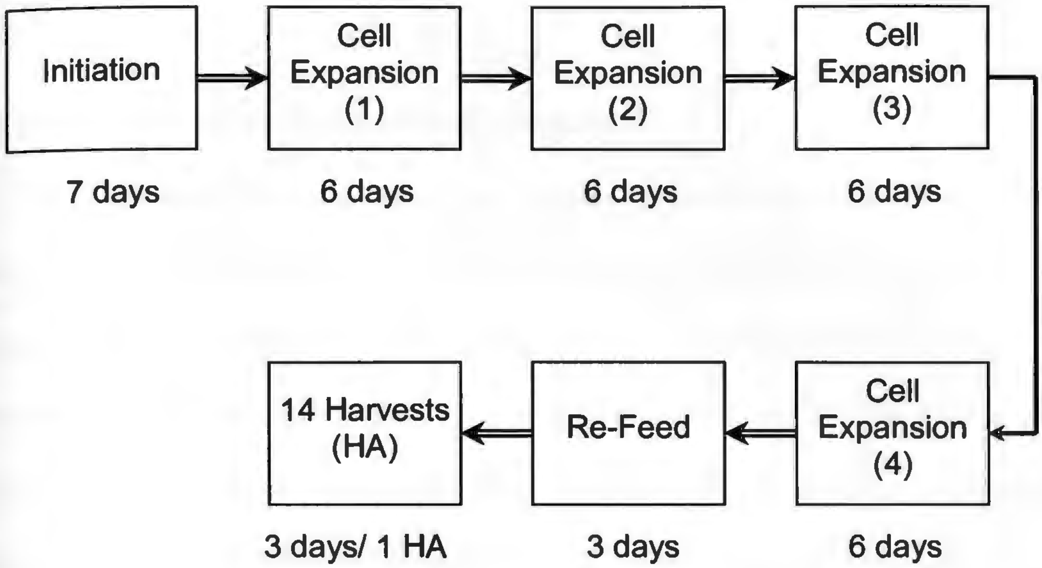


Fig. 6.16: Process flow for product #1

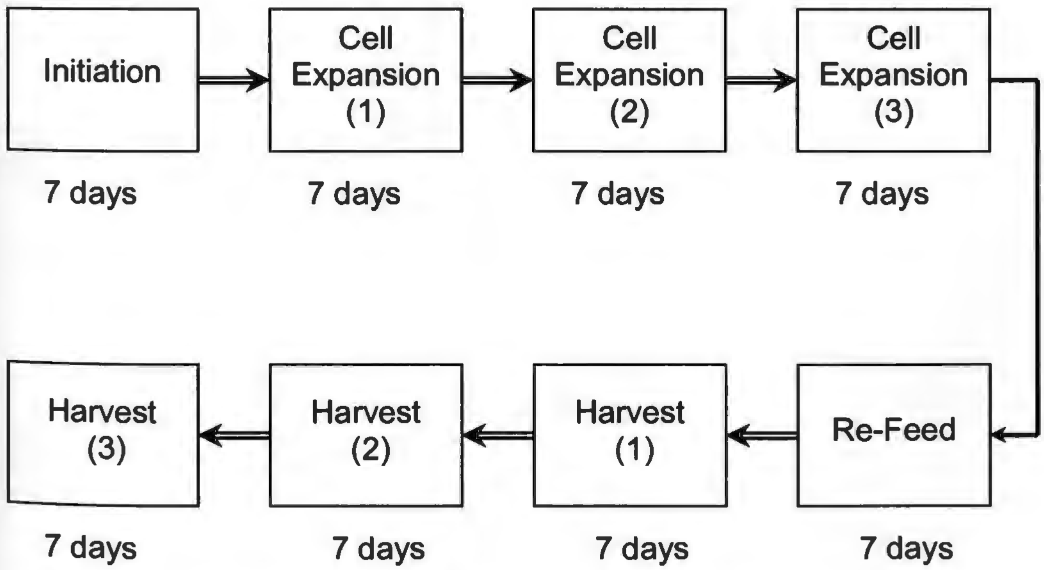


Fig. 6.17: Process flow for product #2

Each campaign of product 1 includes six lots; three as main lots and three as back-up lots that proceed only to cell expansion three. Each campaign of product 2 includes seven lots; five as main lots and two as back-up lots that proceed only to cell expansion two. The back-up lots are only used if any of the main lots are lost because of a bioburden or contamination problem.

6.6.2 Initiation and Cell Expansion Processes

The cells are seeded inside the media to grow other cells. The media with the cells inside are saved inside roller bottles (RB). Figures 6.18 and 6.19 show, on average, the number of seeded bottles per lot at each of the initiation and cell expansion processes and show how many of them proceed to the next process. After the final cell expansion process for the main lots, the number of seeded RB stays constant unless a contaminated RB is found in a subsequent process. The back-up lots are discarded if none of the main lots are lost.

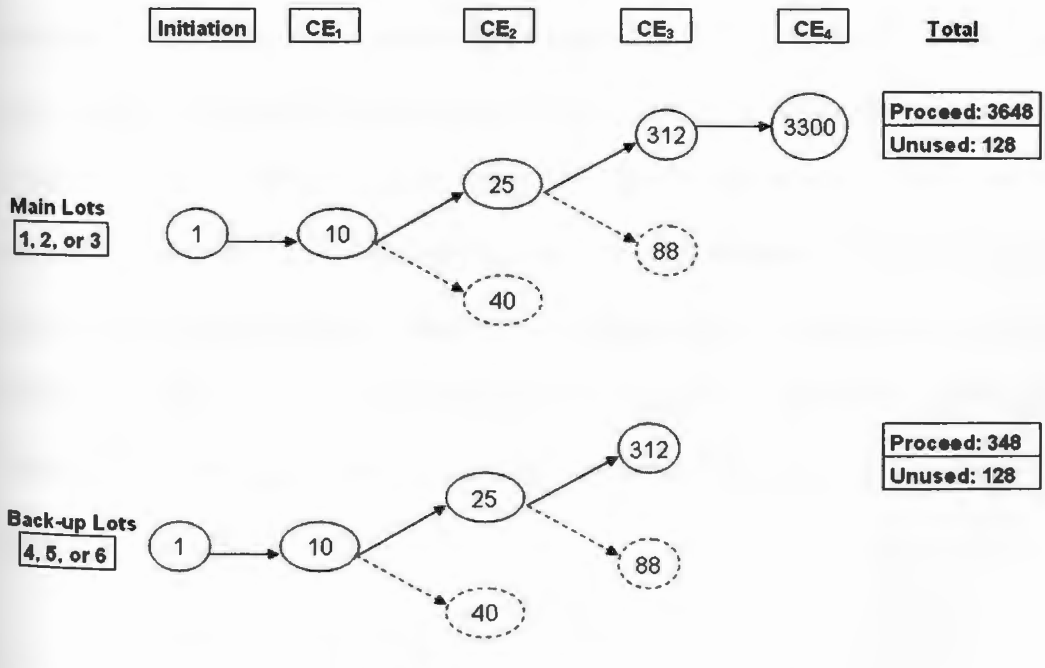


Fig. 6.18 Number of RB for product 1

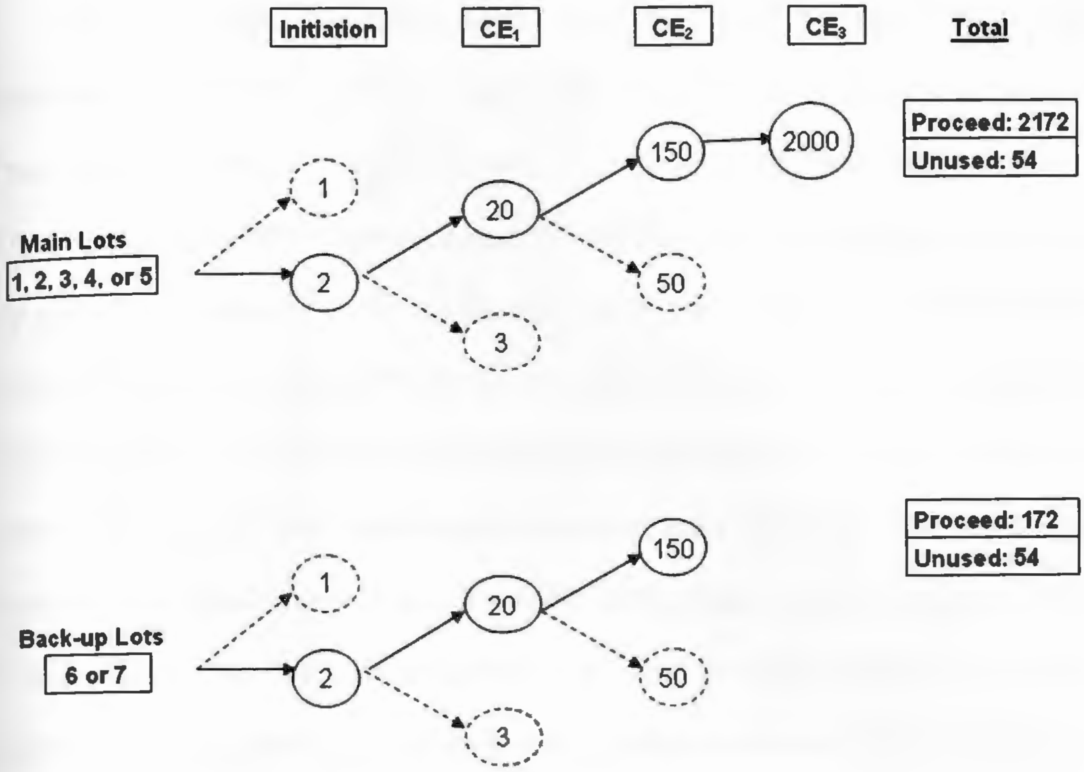


Fig. 6.19 Number of RB for product 2

Reviewing the historical data shows that using the back-up lots rarely happens, and most of the time the back-up lots end up discarded. The total number of seeded bottles for each back-up lot is 476 RB for product 1 (from initiation, CE_1, CE_2, and CE_3) and 226 RB for product 2 (from initiation, CE_1, and CE_2). Since each campaign of product 1 has three back-up lots, the total quantity of seeded bottles (which will be mostly discarded) becomes 1,428 RB, and since each campaign of product 2 has 2 back-up lots, the total quantity of seeded bottles becomes 452 RB.

Through an online search for the market price of the empty RB, it can be assumed that its price from the supplier equals $5 (http://www.coleparmer.com). Then, the total cost of empty RB that are used in the back-up lots becomes $7,140 per single campaign of product 1, and $2,260 per campaign of product 2. By adding the costs of labor hours, overhead, and other raw material, the total cost becomes even larger. This is an example that shows the type of challenges and difficulties that the biopharmaceutical industry faces to be competitive and meet the market needs. Back-up lots that cost a lot of money are produced just to make sure that the company will not risk a shortage of critical product available in the market for their patients which in turns means loosing the customer satisfaction, not helping the patients, and loosing millions of dollars. Tables 6.7 and 6.8 include the total number of RB per campaign for product 1 and product 2.

Table 6.7: Number of RB per campaign of product 1

		1 lot	Total (3 main lots)	Total (3 back-up lots)	Total (per campaign)
Initiation	proceed	1	3	3	6
	unused	0	0	0	0
CE_1	proceed	10	30	30	60
	unused	0	0	0	0
CE_2	proceed	25	75	75	150
	unused	40	120	120	240
CE_3	proceed	312	936	936	1872
	unused	88	264	264	528
CE_4	proceed	330	990	-	990
	unused	0	-	-	-

Table 6.8: Number of RB per campaign of product 2

		1 lot	Total (5 main lots)	Total (2 back-up lots)	Total (per campaign)
Initiation	proceed	2	10	4	14
	unused	1	5	2	7
CE_1	proceed	20	100	40	140
	unused	3	15	6	21
CE_2	proceed	150	750	300	1050
	unused	50	250	100	350
CE_3	proceed	2000	10000	-	10000
	unused	0	-	-	-

The percentages of discarded RB per campaign at each initiation and cell expansion processes are now found. The discarded RB are the unused seeded RB from main lots and all RB from the back-up lots. Table 6.9 includes the total non-discarded and discarded RB for each process.

Table 6.9: Total non-discarded and discarded RB per campaign

		Product 1		Product 2	
		Non-Discarded	Discarded	Non-Discarded	Discarded
Initiation	main	3	0	10	5
	back up	0	3	0	6
	total	3	3	10	11
CE_1	main	30	0	100	15
	back up	0	30	0	46
	total	30	30	100	61
CE_2	main	75	120	750	250
	back up	0	195	0	400
	total	75	315	750	650
CE_3	main	936	264	10000	-
	back up	0	1200	0	0
	total	936	1464	10000	-
CE_4	main	990	-	-	-
	back up	0	0	-	-
	total	990	0	-	-

As can be seen in table 6.9, 50% of RB at initiation, 50% of RB at CE_1, 81% of RB at CE_2, and 61% of RB at CE_3 are discarded per campaign of product 1. For product 2, 52% of RB at initiation, 38% of RB at CE_1, and 46% of RB at CE_2, are discarded per campaign.

Each of the cell expansion processes includes two steps, trypsinization and inoculation. The final expansion before the refeed is performed by robots, whereas all of the previous cell expansions are performed manually. When the robots perform the trypsinization, some RB might be discarded if any problem happens during this semi-automated process. There is no available historical data regarding how many RB each robot might loose during the process, but based on two days of personal observations the percentage of the discarded bottles from all robots during the last cell expansion averages 1.57% for product 1 and 6.14% for product 2. Assuming that these observations are representative of typical production, and based on figures 6.15 and 6.16, the percentages of the discarded RB for each of the main lots at each of the initiation and cell expansion processes can be found. Table 6.10 summarizes these percentages for product 1 and product 2.

Table 6.10: Percentage of discarded RB per lot
(at initiation and cell expansions)

	Initiation	CE_1	CE_2	CE_3	CE_4
Product 1	0	0	0.6250	0.2200	0.0157
Product 2	0.3333	0.1304	0.2500	0.0614	-

6.6.3 Refeed and Harvest Processes

The refeed and harvest processes follow the cell expansion processes. The refeed process involves replacing the media in the RB and returning the RB back to the storage room to continue growing the cell. The harvest processes include collecting product from the RB, adding new media, and then returning them back to the storage room. The process flow is shown in detail in figure 6.20.

During the refeed and harvest processes the roller bottles (RB) are visually checked to determine if any is contaminated. An RB is discarded if its contents are contaminated or damaged by an operator or robot, or if the bottle itself is damaged. Two years of historical data for the number of discarded bottles at refeed and harvest were used to calculate the average percentage of discarded RB for each process. Since the discarded RB does not add value to the finished product, they will be considered to be waste or scrap. Table 6.11 shows the percentage of discarded RB (scrap rate) for refeed and all harvest processes of product 1 and product 2.

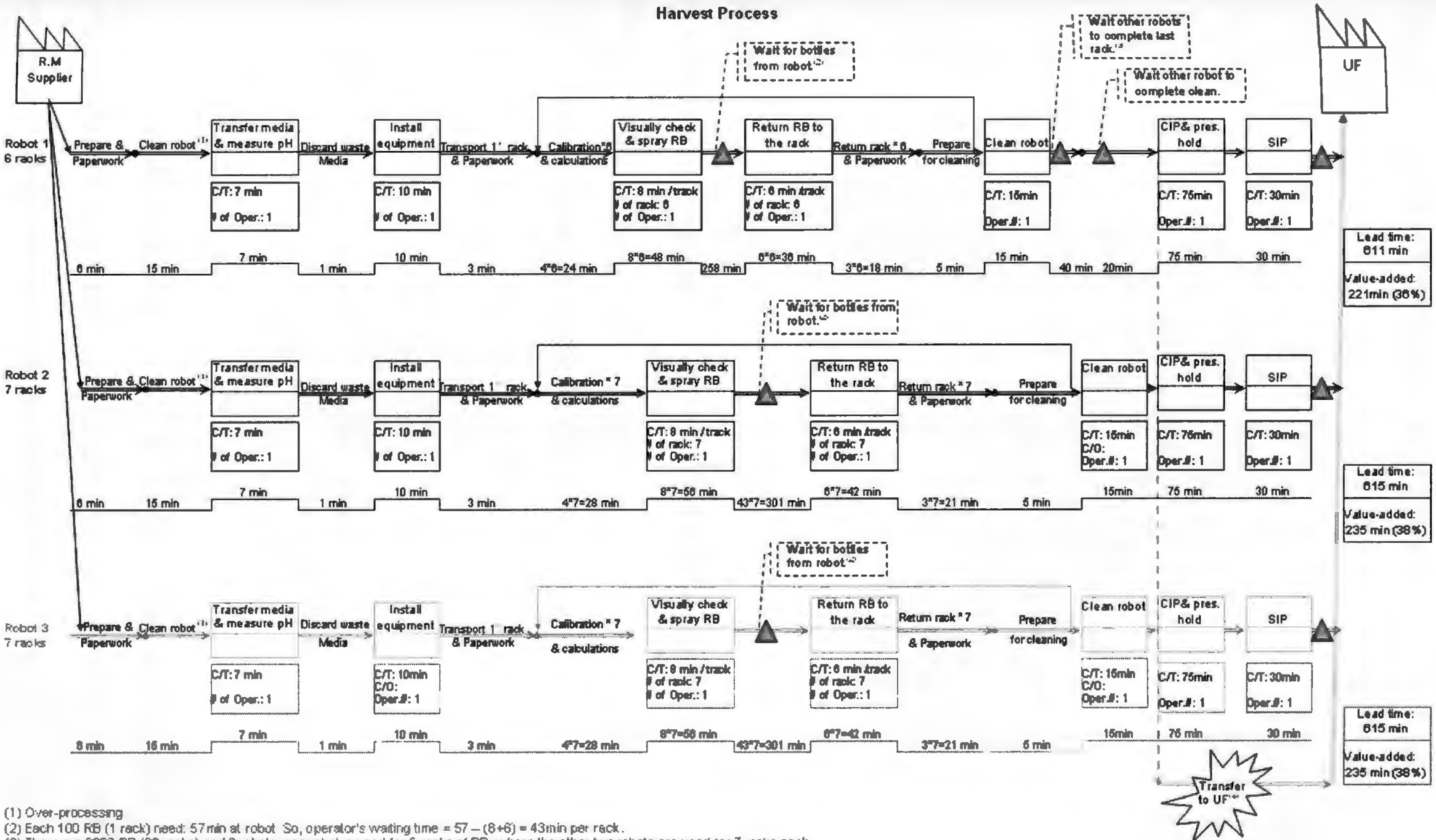
The data describing the number of discarded RB at all processes of cell culture (initiation, cell expansions, refeed, and harvests) are used to develop a transition probability matrix for the serial configuration of the entire cell culture production system. Then, the quality cost, productivity, and the cycle time can be found.

Table 6.11: Percentage of discarded RB per lot (at refeed and harvests)

	Product 1	Product 2
Refeed	0.0009	0.0012
HV1	0.0007	0.0007
HV2	0.0010	0.0005
HV3	0.0021	0.0002
HV4	0.0008	-
HV5	0.0014	-
HV6	0.0006	-
HV7	0.0009	-
HV8	0.0011	-
HV9	0.0010	-
HV10	0.0008	-
HV11	0.0008	-
HV12	0.0009	-
HV13	0.0026	-
HV14	0.0005	-

6.6.4 Resource Consumption Models for the Cell Culture System

The initiation and cell expansion processes (except the last cell expansion) are not considered in the *P* matrix in developing the Markova chain, but they will be considered in determining the quality cost, productivity, and cycle time. That is because at each of these processes the scrap rate is based on a constant quantity that is needed to be achieved each time and it could not be variable with time, so it will not be changed in long run. On the other hand, scrap at the last cell expansion, refeed, and harvest processes is caused by robot, operator, or contamination, so it may vary with time. The transition probability matrix is developed based on data shown in tables 6.10 and 6.11. Since any RB with any quality problem will be discarded to maintain the highest possible production quality, there is no rework in the cell culture production system.



(1) Over-processing
(2) Each 100 RB (1 rack) need: 57min at robot. So, operator's waiting time = 57 – (8+6) = 43min per rack.
(3) There are 2000 RB (20 racks) and 3 robots: one robot is used for 6 racks of RB, where the other two robots are used for 7 racks each.
(4) Before transferring: wait 15 min before taking sample, and wait 5 min to confirm from UF. Transferring takes: 90 min on average

Fig. 6.20: Value stream mapping (VSM) for harvest process

The transition probability matrix for product 1 is:

P_1 =

	CE	RF	HA1	HA2	HA3	HA4	HA5	HA6	HA7	HA8	HA9	HA10	HA11	HA12	HA13	HA14	SC	FG
CE	0	.9843	0	0	0	0	0	0	0	0	0	0	0	0	0	0	.0157	0
RF	0	0	.9991	0	0	0	0	0	0	0	0	0	0	0	0	0	.0009	0
HA1	0	0	0	.9993	0	0	0	0	0	0	0	0	0	0	0	0	.0007	0
HA2	0	0	0	0	.9990	0	0	0	0	0	0	0	0	0	0	0	.0010	0
HA3	0	0	0	0	0	.9979	0	0	0	0	0	0	0	0	0	0	.0021	0
HA4	0	0	0	0	0	0	.9992	0	0	0	0	0	0	0	0	0	.0008	0
HA5	0	0	0	0	0	0	0	.9986	0	0	0	0	0	0	0	0	.0014	0
HA6	0	0	0	0	0	0	0	0	.9994	0	0	0	0	0	0	0	.0006	0
HA7	0	0	0	0	0	0	0	0	0	.9991	0	0	0	0	0	0	.0009	0
HA8	0	0	0	0	0	0	0	0	0	0	.9989	0	0	0	0	0	.0011	0
HA9	0	0	0	0	0	0	0	0	0	0	0	.9990	0	0	0	0	.0010	0
HA10	0	0	0	0	0	0	0	0	0	0	0	0	.9992	0	0	0	.0008	0
HA11	0	0	0	0	0	0	0	0	0	0	0	0	0	.9992	0	0	.0008	0
HA12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	.9991	0	.0009	0
HA13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	.9974	.0026	0
HA14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	.0005	.9995
SC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
FG	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Where:

INT: initiation, CE: cell expansion, RF: refeed, HA: harvest, SC: scrap, and FG: finished goods.

The transition probability matrix for product 2 is:

P =

	CE	RF	HA1	HA2	HA3	SC	FG
CE	0	0.9386	0	0	0	0.0614	0
RF	0	0	0.9988	0	0	0.0012	0
HA1	0	0	0	0.9993	0	0.0007	0
HA2	0	0	0	0	0.9995	0.0005	0
HA3	0	0	0	0	0	0.0002	0.9998
SC	0	0	0	0	0	1	0
FG	0	0	0	0	0	0	1

A modified model for the n stage serial configuration is used by considering the short term probabilities for the initiation and cell expansion processes (except the final cell expansion) and the long term probabilities for the rest of the processes obtained from the Markov chain model. Table 6.12 summarizes the results of applying the resource consumption models for the serial configuration cell culture system.

Table 6.12: Result of resource consumption models for products 1 and 2

	Quality Cost (hr/ lot)	Productivity (100%)	Expected Cycle Time (hr / lot)
Product 1	105.72	24.84	1824
Product 2	99.95	40.51	1344

6.7 Cell Expansion 3 for Product 2

In this section another case study is developed for the final cell expansion process in producing product 2. The final cell expansion process is performed by three robots, and it includes trypsinization and then an inoculation process. Three robots are used to perform the cell expansion, robots X, Y and Z. Based on observations, the percentage of wasted RB during the trypsinization step is assumed to be 10.71% at robot X, and 3.8% at robots Y and Z. On the other hand, the scrap rate during the inoculation process is assumed to be 0.0025% for robot X, while it is 0% for robots Y and Z. Robot X has some operation problems caused by different factors such as the sensor, robot arm, or keyboard.

During the trypsinization process the cell suspension is prepared in a spinner, and then at the inoculation process the spinner content is distributed to empty bottles in order to expand the cells. Table 6.13 includes the average time required to perform the trypsinization and inoculation processes when they are completed at the same robot.

Table 6.13: Processing time for cell expansion 3

Trypsinization	Time (min/spinner)	Inoculation	Time (min/spinner)
Setup	30	Calibrations	32
Material handling and paperwork	16	Material handling and paperwork	28
Robot's operations	40	Robot's operations	166
Samples	3		
Cell count	15		
Total	**104**		**226**

Different alternative configurations are considered, and then the resource consumption models are applied. Since Robots Y and Z are similar in terms of the scrap rate, the number of alternatives is reduced to eight, as shown in figure 6.21. The current configuration is a pure parallel, by which both trypsinization and inoculation are performed at the same robot. On the other hand, the other alternative configurations have a combination where the two processes could be performed at the same robot or at two different robots. If the inoculation is performed at different robot from the one that performs the trypsinization, then the average time for inoculation is assumed to be increased by 10 minutes for material handling and setup.

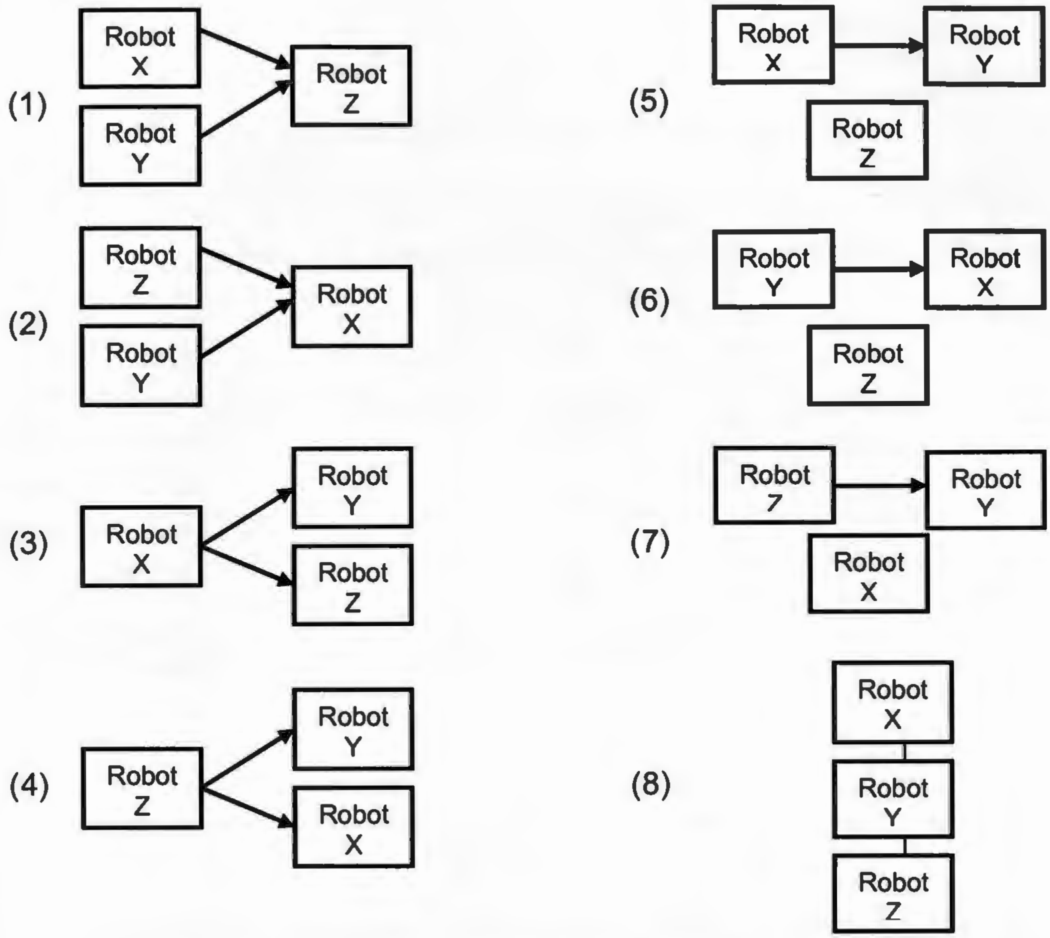


Fig. 6.21: Eight configuration alternatives for CE_3

6.7.1 Quality Cost, Productivity, and Cycle Time for All Alternative Configurations

To develop the results for the eight configurations the model from chapter three for the pure serial and serial-parallel configurations is used assuming that the appropriate process has zero parameters. For example, in configuration #5, a hypothetical process of zero parameters is assumed to be in series with process Z. Table 6.14, and figures 6.22, 6.23, 6.24 summarize the results for all configurations.

Table 6.14: Result of resource consumption models for different alternative configurations

	Quality Cost (min/ 1 spinner)	Productivity (min/ 1 spinner)	Cycle Time (min/ 1 spinner)
Configuration 1	7.57	92.72	340
Configuration 2	4.82	95.67	340
Configuration 3	11.13	89.30	340
Configuration 4	4.41	95.91	340
Configuration 5	11.92	92.73	335
Configuration 6	8.76	95.91	335
Configuration 7	19.66	92.73	335
Configuration 8	15.37	95.40	330

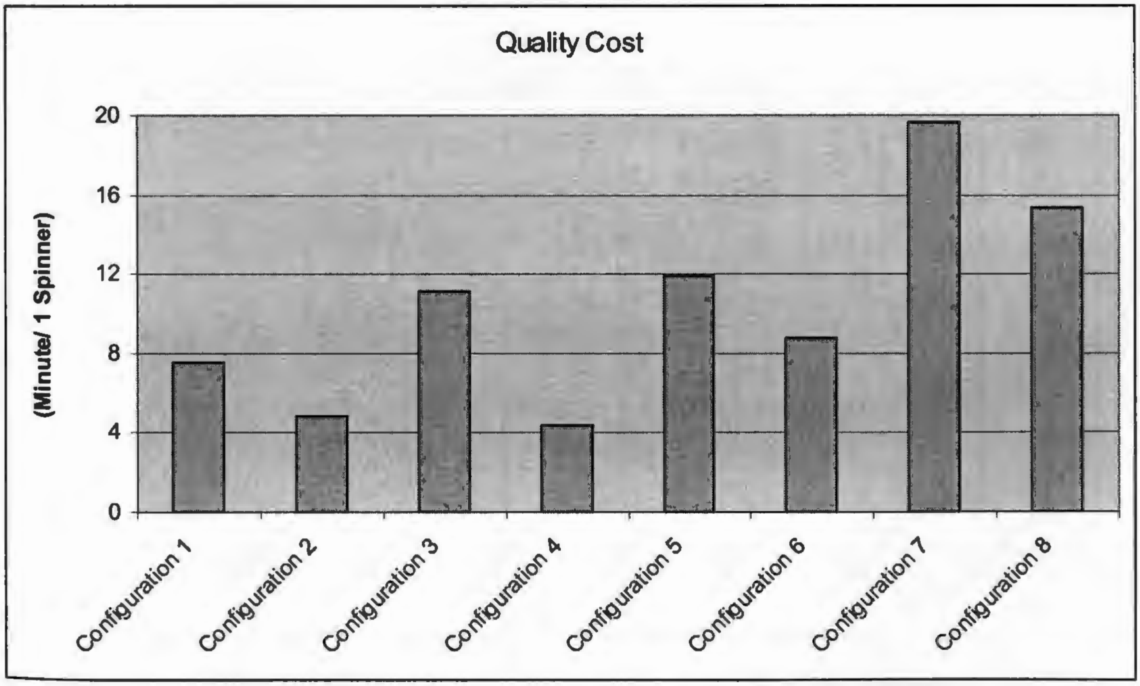


Fig. 6.22: Quality Cost for all alternative configurations

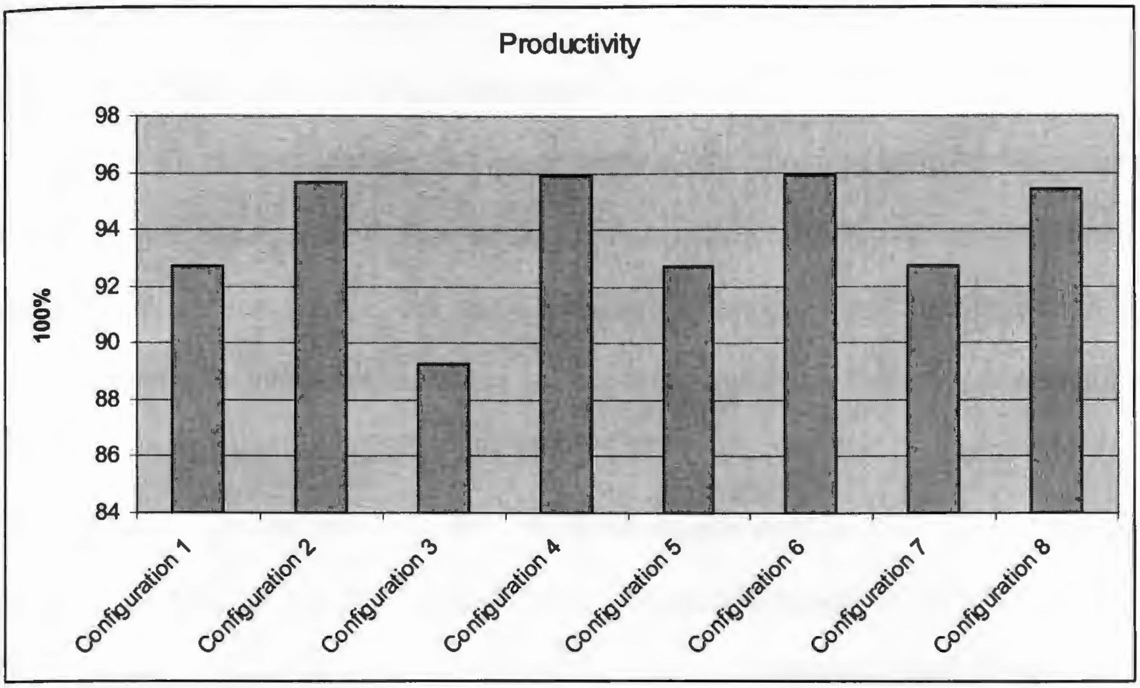


Fig. 6.23: Productivity for all alternative configurations

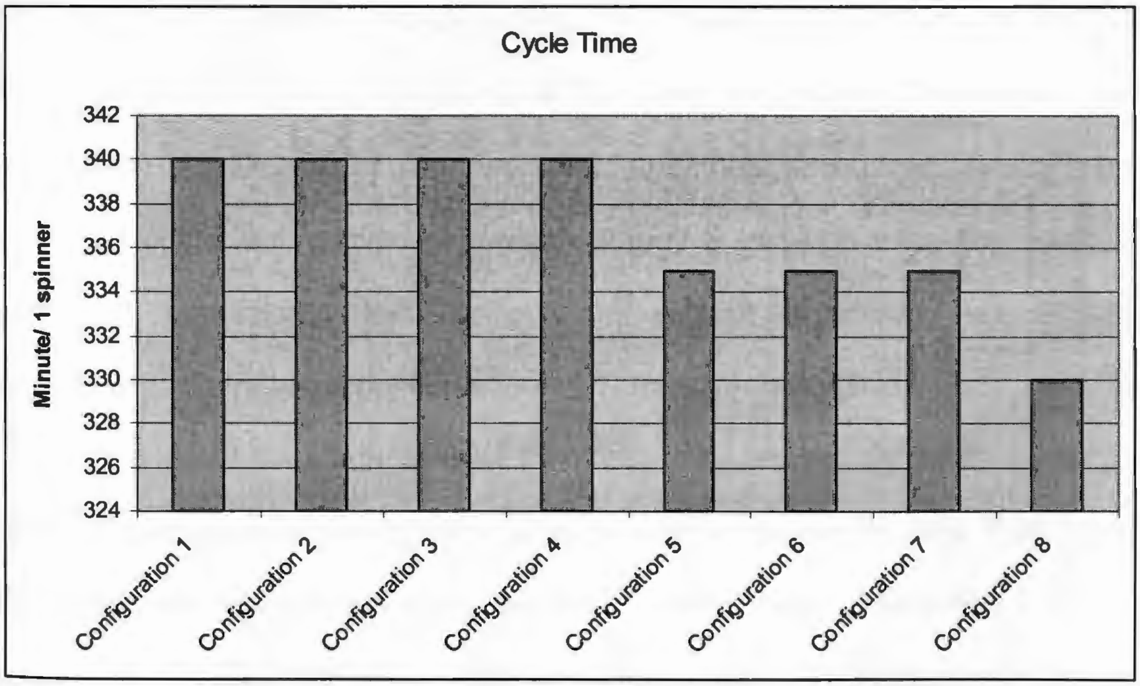


Fig. 6.24: Cycle time for all alternative configurations

6.8 Summary and Conclusions

6.8.1 Case Study One: Media Production System

The production system for two different types of media is analyzed, where there are two configuration alternatives: serial-parallel with crossover and serial-parallel without crossover. All data required to model each configuration is collected, and then the productivity, quality cost, and cycle time are determined for each alternative.

The results for media L show that the quality cost is 19.81 (labor minute per unit of media) for the serial-parallel configuration without crossover, and 23.11 (labor minute per unit of media) for the serial-parallel configuration with crossover. The total expected time to produce one unit of media for both configurations is 259.87 minutes, so this indicates that 19.81 minutes is 7.62% and 23.11 minutes is 8.89% of the total time that is required to produce one unit of media. In other words, 7.62% and 8.89% of the total time required to produce 1 unit of media is a waste because of the scrap and rework. Converting labor minutes to labor costs of two operators, and then adding the material and overhead costs, will indicate how much money is lost due to quality costs. In terms of productivity, the configuration without crossover has 77.42% productivity, whereas the configuration with crossover has 73.33%.

The results for media M show that the quality cost per unit of media is 7.26 (labor minutes) when the configuration is without crossover, and 7.04 (labor minutes) when there is crossover, which are, respectively, 2.80% and 2.72% of cycle time (259.22 minutes). When the configuration is without crossover the productivity is 93.93%, while it is 94.20% when the configuration is with crossover.

As a conclusion, the cost of quality and productivity for the media M production system is better than that for media L, since the rework and scrap rates are different as shown in Tables 6.2 and 6.3. The without-crossover configuration of media L has a lower cost of quality and higher productivity than a configuration with crossover, while the expected cycle time is the same for both configurations. On the other hand, for the media M production system, a configuration with crossover performs slightly better than a configuration without crossover by generating less cost of quality and higher productivity. The expected cycle time, however, is the same for with and without crossover configurations of media M.

6.8.2 Case Study Two: Cell Culture Production System

The cell culture production system has a serial configuration and this is the only applicable configuration, because of the nature of the product, where cells should stay for a certain amount of time after each process to keep growing before proceeding to next process. The developed resource consumption models for serial configuration still can be used to find the quality cost, productivity and cycle time for product 1 and product 2 production systems.

For product 1 the scrap rates at cell expansions 2 and 3 are the highest and they affect the quality cost and productivity more than the remaining processes. The cycle time equals 1824 hours (76 days), which is just the summation of the processing time at each process since there is no rework time. The quality cost is 105.72 hours per lot (approximately 4 day and 10 hours per lot), which is 5.8 % of the total time. The productivity is only 24.84% and that is obviously because of the high scrap rate at many processes.

For product 2 the Initiation, cell expansions 1, and cell expansion 2 processes have the highest scrap rate, so they have greatest effect on quality cost and productivity more than the remaining processes. The quality cost is 99.95 hours per lot (approximately 4 days and 4 hours per lot), which is 7.44 % of the total time. The productivity is only 40.51% which is better than that for product 1 but still not high. There is no rework in producing product 2, so the cycle time equals the summation of the processing time at each process which is 1344 hours (56 days). The company should consider improving the processes to reduce the scrap rate especially for processes that have the highest rates, in order to reduce the quality cost and increase productivity.

6.8.3 Case Study Three: Cell Expansion

Different alternative configurations are analyzed to find which one performs better. Figures 6.22 shows that configuration 4 is the best in term of quality cost since it has the lowest quality cost, while configuration 7 is the worst since it has the highest quality cost. Figure 6.23 shows that configurations 4 and 6 have the highest productivity and hence they perform best, while configuration 3 has the lowest productivity so it is the worst one. Figure 6.24 shows that configuration 8 has the lowest cycle time so it is the best, while configurations

1,2, 3, and 4 have the highest cycle time so they are the worst. Table 6.15 includes the ranks of the eight configurations from best to worst.

Table 6.15: Ranking the different configurations

Rank	Quality Cost	Productivity	Cycle Time
8 (best)	4	4, 6	8
7	2	2	5, 6, 7
6	1	8	1, 2, 3, 4
5	6	5, 7	
4	3	1	
3	5	3	
2	8		
1 (worst)	7		

It can be concluded from table 6.15 that although performance metrics may involve trade off, it is possible to achieve multiple goals at the same time. For example, configuration 4 performs the best in term of two metrics: quality cost and productivity. Configuration 8, which is the current configuration, has the best performance only in term of cycle time. Selecting the best configuration depends on the metrics that the management wants to consider in improving the production system performance. The managers also could give weights to the performance measures depending on the importance of each measure. For example, if the weights for the quality cost, productivity, and cycle time are 0.4, 0.4, and 0.2 respectively, then table 6.16 shows that in terms of all metrics, configuration 4 performs the best while configuration 7 performs the worst. The applicability of each alternative should also be considered before selecting the best one.

Table 6.16: Assigning weights to select the preferred configuration

Configuration	Rank * Weight			Total
	Quality Cost	Productivity	Cycle Time	
1	2.4	1.6	1.2	5.2
2	2.8	2.8	1.2	6.8
3	1.6	1.2	1.2	4
4	**3.2**	**3.2**	**1.2**	**7.6**
5	1.2	2	1.4	4.6
6	2	3.2	1.4	6.6
7	0.4	2	1.4	3.8
8	0.8	2.4	1.6	4.8

CHAPTER SEVEN

DISCUSSION AND CONCLUSION

This chapter provides a summary of the results obtained, with a comprehensive discussion. The conclusions are then proposed.

7.1 Summary and Discussion

A summary of the numerical example results for the two process production system (using a numerical example as shown in sections 3.3.4 and 3.4.4) is shown in table 7.1.

Table 7.1: Resource consumption summary for two process production system example

Configuration	Serial	Parallel
Cost of Quality ($/item)	0.33	0.25
Productivity (%)	79.03	93.16
Cycle Time (min/item)	8.10	8.13

The results show that the selection of the better alternative depends on the performance measure of interest. For example, if this manufacturer is interested in reducing the cost of quality, then the parallel configuration performs better than the serial, or in other words, changing the production configuration from serial to parallel can save 24.2% of the quality cost. Such an improvement is also combined with an increase in the productivity of the production system from 79.03% (serial) to 93.16% (parallel). However, the cycle time slightly increases using the parallel configuration. The manufacturer can make a decision based on the performance target of interest.

Next, a full summary of the sensitivity analysis for the two process numerical example is shown in tables 7.2, 7.3, and 7.4. Note that the results apply for the ranges of parameters selected for the sensitivity analysis. Table 7.2 indicates that the parallel configuration performs better than the serial configuration when rework costs change, while the preferred configuration depends on the value of the scrap costs. Table 7.3 indicates that the parallel configuration performs better than the serial configuration when means and standard deviations change. Table 7.4 shows that the serial configuration performs slightly better than the parallel configuration when the processing times change, while the preferred configuration depends on the value of the rework times of processes 1 and 2.

Table 7.2: Sensitivity analysis summary for quality cost of the two process production system example

Parameters	Results summary
RC_1	Parallel has lower QC than the serial
RC_2	Parallel has lower QC than the serial
SC_1	Parallel has lower QC than the serial at high SC_1
SC_2	Parallel has lower QC than the serial at low SC_2

Table 7.3: Sensitivity analysis summary for productivity of the two process production system example

Parameters	Results summary
$Mean_1$	Parallel has higher productivity than the serial
$Mean_2$	Parallel has higher productivity than the serial
$StDev_1$	Parallel has higher productivity than the serial
$StDev_2$	Parallel has higher productivity than the serial

Table 7.4: Sensitivity analysis summary for cycle time of the two process production system example

Parameters	Results summary
PT_1	Serial has slightly lower cycle time than the parallel
PT_2	Serial has slightly lower cycle time than the parallel
RT_1	Serial has lower cycle time than the parallel at low RT_1
RT_2	Serial has lower cycle time than the parallel at low RT_2

With a two process production system, there are only two possible configurations to be applied, pure serial and parallel. In the following discussion, a four process production system is analyzed, and the four possible configurations are implemented, which are pure serial and pure parallel, and serial-parallel with and without crossover. Table 7.5 summarizes the results of the resource consumption models using a numerical example as in sections 4.3.3, 4.4.3, 4.5.3, and 4.6.3.

Table 7.5: Resource consumption summary for four process production system example

Configuration	Serial	Parallel	Serial-parallel without crossover	Serial-parallel with crossover
Cost of Quality ($/item)	1.06	0.67	0.72	0.72
Productivity (%)	65.22	95.90	89.86	89.86
Cycle Time (min/item)	16.10	16.27	16.18	16.18

Similarly, the selection of any given configuration depends on the performance target a ssigned by the manufacturer. The parallel configuration shows the highest productivity and the lowest cost of quality compared to the other alternatives, while the serial process flow has the lowest cycle time.

In table 7.5, the results show that the serial-parallel configurations (with and without crossover) performed the same, based on the assumptions and parameters used for that example. However, when applying the serial-parallel models (with and without crossover) on the case study analysis at a biopharmaceutical company in Chapter 6, results were different between the two alternatives. The parameters used to develop the case study were based on actual production data, where results were dependent on the operating parameters, assumptions, and production constraints. A production line for two media products containing six processes was analyzed, utilizing serial-parallel configurations (with and without crossover). Referring to section 6.5, table 7.6 summarizes these results. Note that media L and M are two different products that are manufactured on the same production system.

Table 7.6: Resource consumption summary for serial-parallel configuration of Media L and M of the case study

	Media L		Media M	
Configuration	without crossover	with crossover	without crossover	with crossover
Cost of Quality (labor min/unit media)	19.81	23.11	7.26	7.05
Productivity (%)	77.42	73.33	93.93	94.20
Cycle Time (labor min/ unit media)	259.87	259.87	259.22	259.22

Table 7.6 shows that the results for configurations with and without crossover are different. In terms of cost of quality and productivity, the configuration without crossover for media L performs better, while the configuration with crossover for media M performs better. However, the cycle time remains the same between the two configurations for each media type, because the processing time and rework parameters - including the rework time and probabilities - stays the same when changing configurations.

In another case study implemented at the same biopharmaceutical company, three robots within cell expansion 3 are arranged into all possible configurations of pure parallel and serial-parallel configurations. Note that the model was adjusted so that it can be used for configurations of any number of processes, odd or even, by making the appropriate assumptions and adding virtual processes. Based on the performance target, the eight different configurations were ranked to achieve the best production output.

7.2 Conclusions

This thesis provides an analytical approach to model a production system and select the preferred configuration. There is a relationship between the configuration of any production line and the performance. Based on the production and operating parameters, the preferred configuration could vary accordingly. Cost of quality, productivity, and cycle time are three important metrics in measuring the system performance. They are affected by the system configuration and the operating parameters. Besides the transition probabilities between the states of the production system, the main parameters that affect the quality cost are rework and scrap costs, while the main parameters for cycle time are the processing time and rework time. An n process general model can be applied for odd or even numbers of processes in any production line, with direct calculations for the resource consumption models which provides great benefits for analyzing large production systems. This thesis provides an excellent reference for the biopharmaceutical industry, with models that are applicable for the performance analysis of both continuous and discrete production systems.

7.3 Future Work

Based on the results obtained, the following are suggested as possible extensions to the research in this thesis:

1- Use a simulation tool to model the production flows of the four different system configurations and then to verify the proposed resource consumption models.

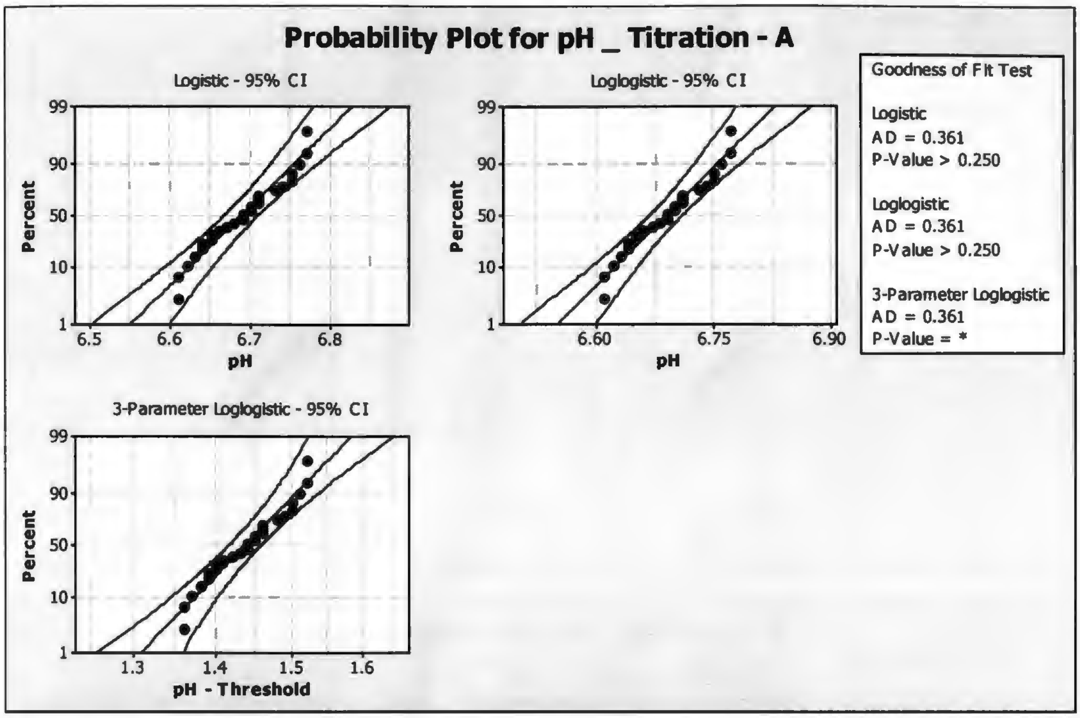
2- Include the short term probability factor in the sensitivity analysis.

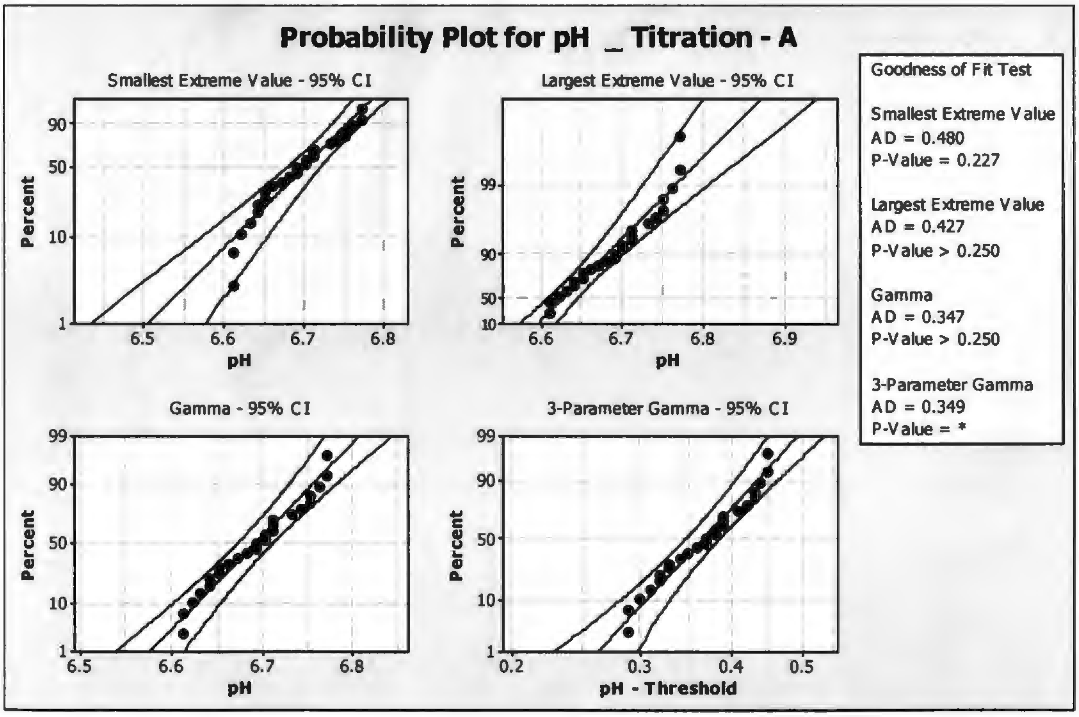
3- Extend the sensitivity analysis by utilizing the design of experiment approach to reveal more information about th e significant factors that affect each model.

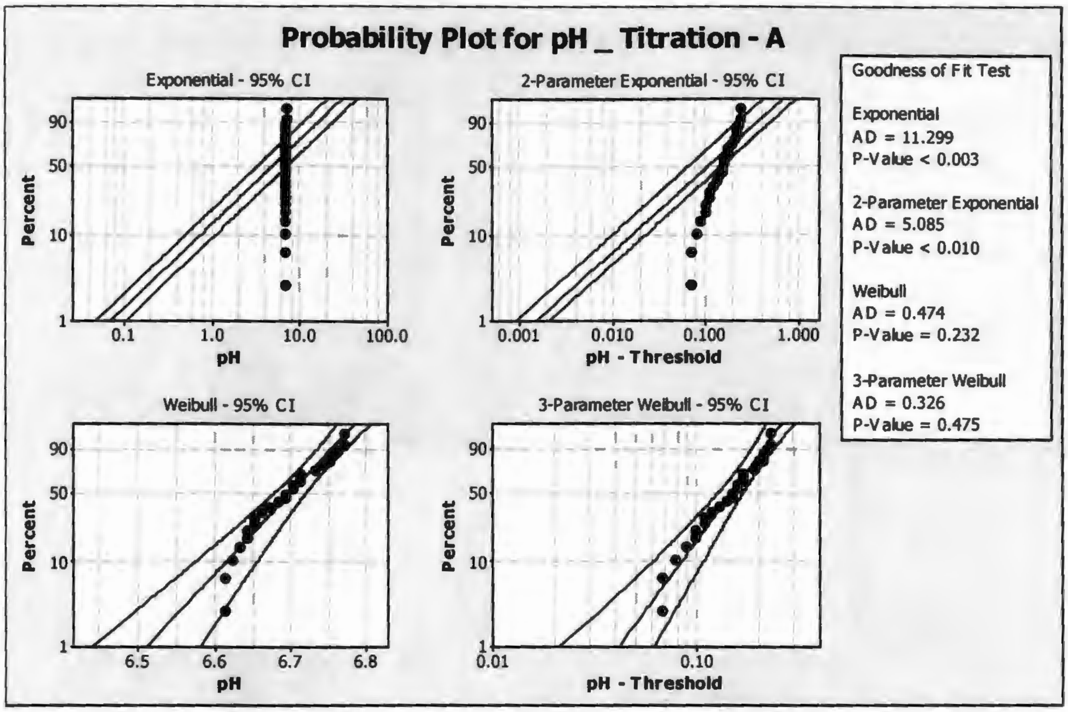
4- Extend the study to include more metrics that are important to the biopharmaceutical industry.

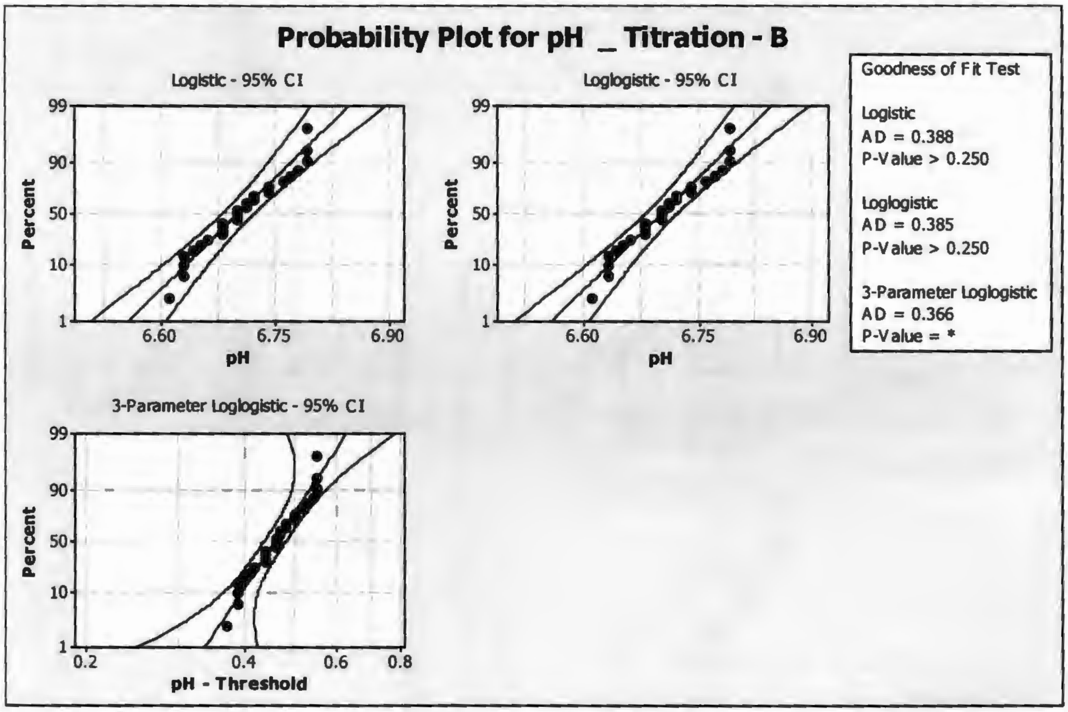
Appendix

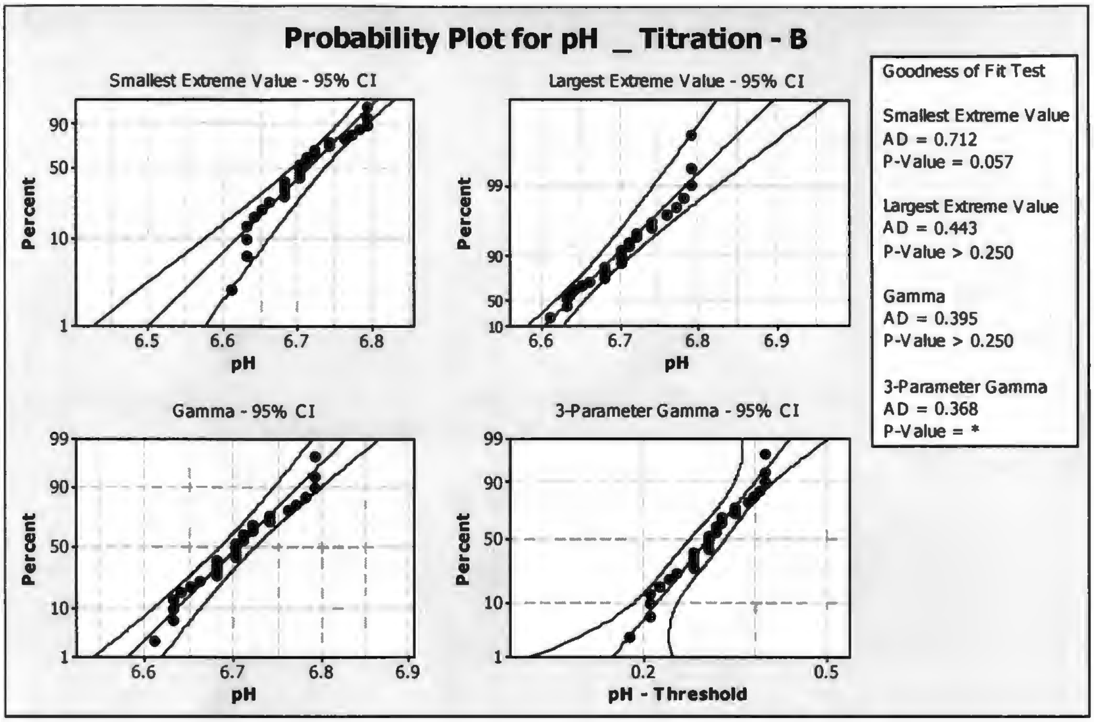
Media L:






Probability Plot for pH _ Titration - A
Exponential - 95% CI
2-Parameter Exponential - 95% CI
Weibull - 95% CI
3-Parameter Weibull - 95% CI
Percent
pH
pH - Threshold
Goodness of Fit Test
Exponential
AD = 11.299
P-Value < 0.003
2-Parameter Exponential
AD = 5.085
P-Value < 0.010
Weibull
AD = 0.474
P-Value = 0.232
3-Parameter Weibull
AD = 0.326
P-Value = 0.475


Probability Plot for pH _ Titration - B
Logistic - 95% CI
Loglogistic - 95% CI
3-Parameter Loglogistic - 95% CI
Percent
pH
pH - Threshold
Goodness of Fit Test
Logistic
AD = 0.388
P-Value > 0.250
Loglogistic
AD = 0.385
P-Value > 0.250
3-Parameter Loglogistic
AD = 0.366
P-Value = *


Probability Plot for pH _ Titration - B
Smallest Extreme Value - 95% CI
Largest Extreme Value - 95% CI
Gamma - 95% CI
3-Parameter Gamma - 95% CI
Percent
pH
pH - Threshold
Goodness of Fit Test
Smallest Extreme Value
AD = 0.712
P-Value = 0.057
Largest Extreme Value
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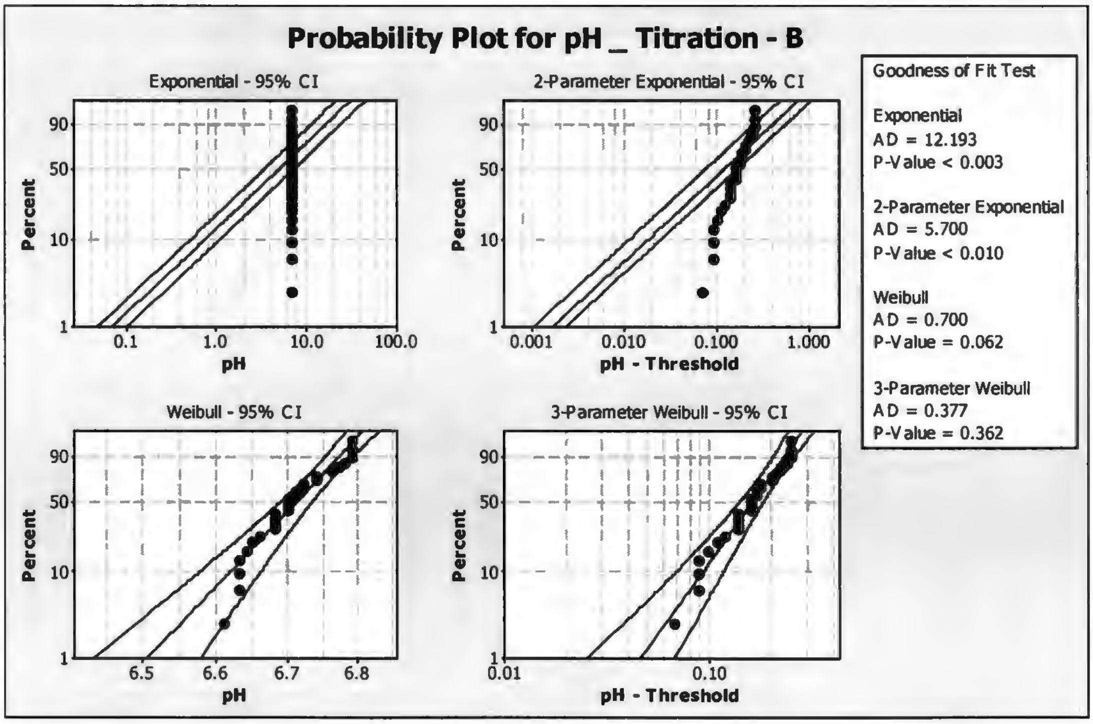
P-Value > 0.250
Gamma
AD = 0.395
P-Value > 0.250
3-Parameter Gamma
AD = 0.368
P-Value = *


Probability Plot for pH _ Titration - B
Exponential - 95% CI
2-Parameter Exponential - 95% CI
Weibull - 95% CI
3-Parameter Weibull - 95% CI
Percent
pH
pH - Threshold
Goodness of Fit Test
Exponential
AD = 12.193
P-Value < 0.003
2-Parameter Exponential
AD = 5.700
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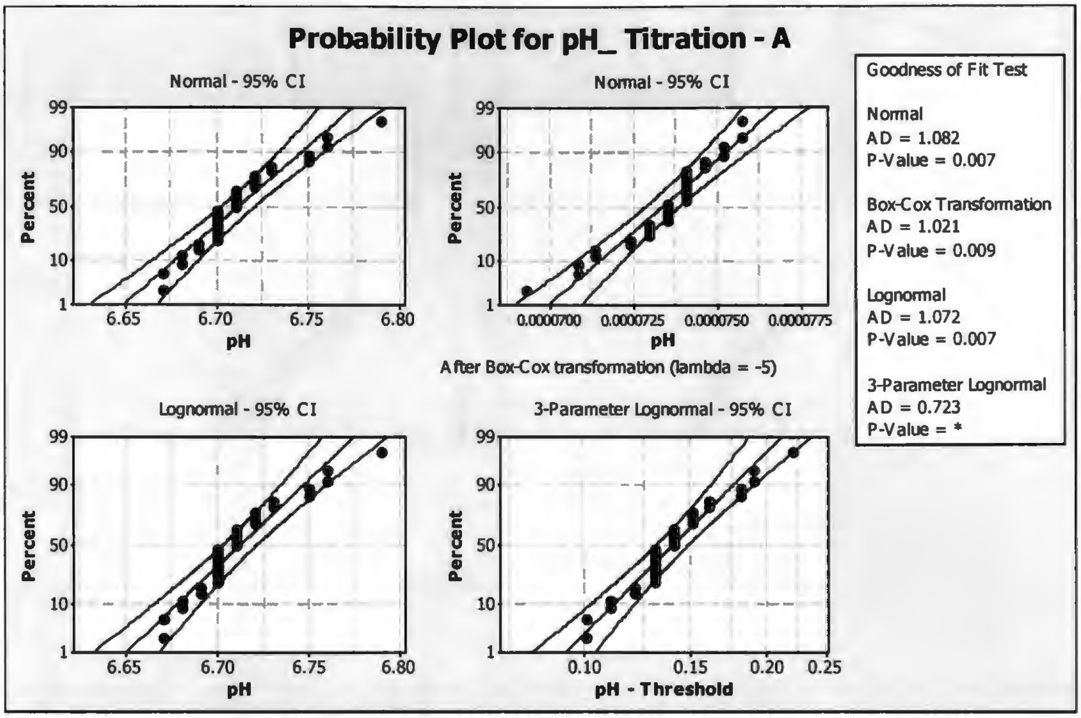
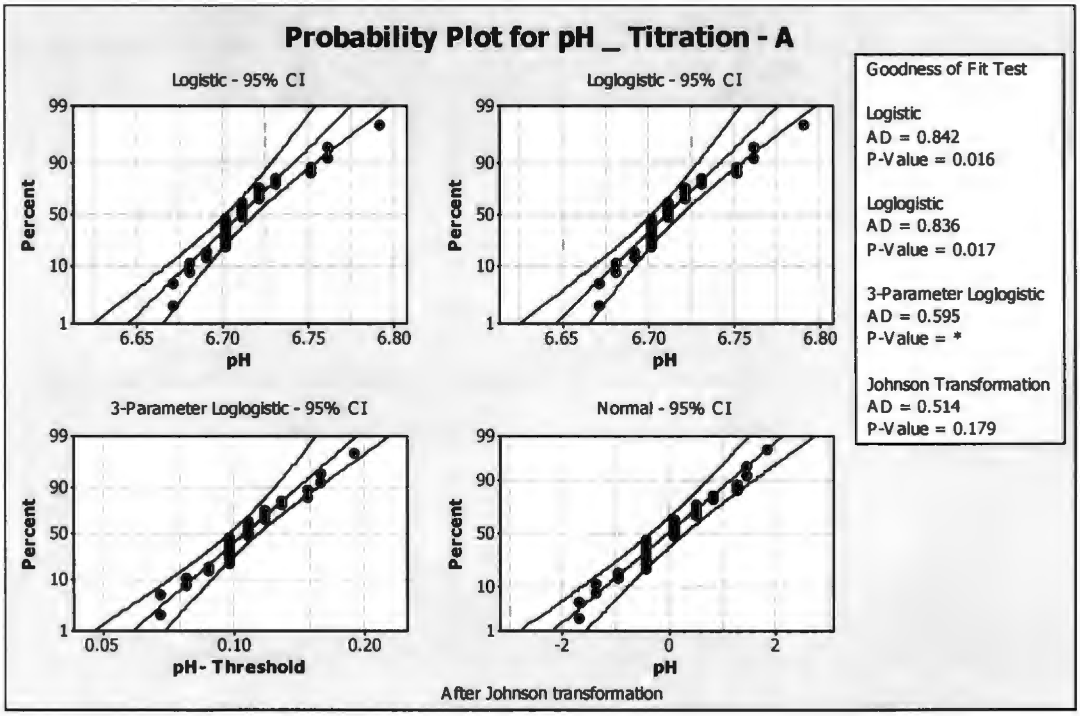
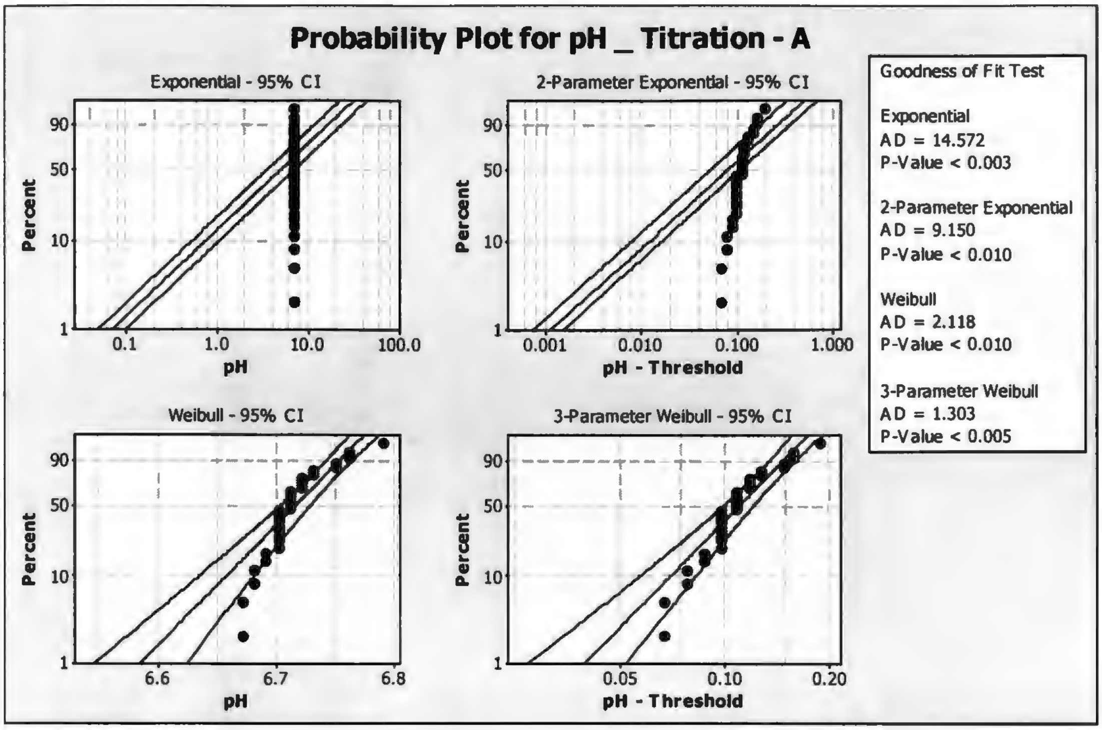
Weibull
AD = 0.700
P-Value = 0.062
3-Parameter Weibull
AD = 0.377
P-Value = 0.362

Media M:


Probability Plot for pH_ Titration - A
Normal - 95% CI
Normal - 95% CI
Lognormal - 95% CI
3-Parameter Lognormal - 95% CI
Percent
pH
pH - Threshold
After Box-Cox transformation (lambda = -5)
Goodness of Fit Test
Normal
AD = 1.082
P-Value = 0.007
Box-Cox Transformation
AD = 1.021
P-Value = 0.009
Lognormal
AD = 1.072
P-Value = 0.007
3-Parameter Lognormal
AD = 0.723
P-Value = *


Probability Plot for pH _ Titration - A
Logistic - 95% CI
Loglogistic - 95% CI
3-Parameter Loglogistic - 95% CI
Normal - 95% CI
Percent
pH
pH- Threshold
After Johnson transformation
Goodness of Fit Test
Logistic
AD = 0.842
P-Value = 0.016
Loglogistic
AD = 0.836
P-Value = 0.017
3-Parameter Loglogistic
AD = 0.595
P-Value = *
Johnson Transformation
AD = 0.514
P-Value = 0.179


Probability Plot for pH _ Titration - A
Exponential - 95% CI
2-Parameter Exponential - 95% CI
Weibull - 95% CI
3-Parameter Weibull - 95% CI
Percent
pH
pH - Threshold
Goodness of Fit Test
Exponential
AD = 14.572
P-Value < 0.003
2-Parameter Exponential
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P-Value < 0.010
Weibull
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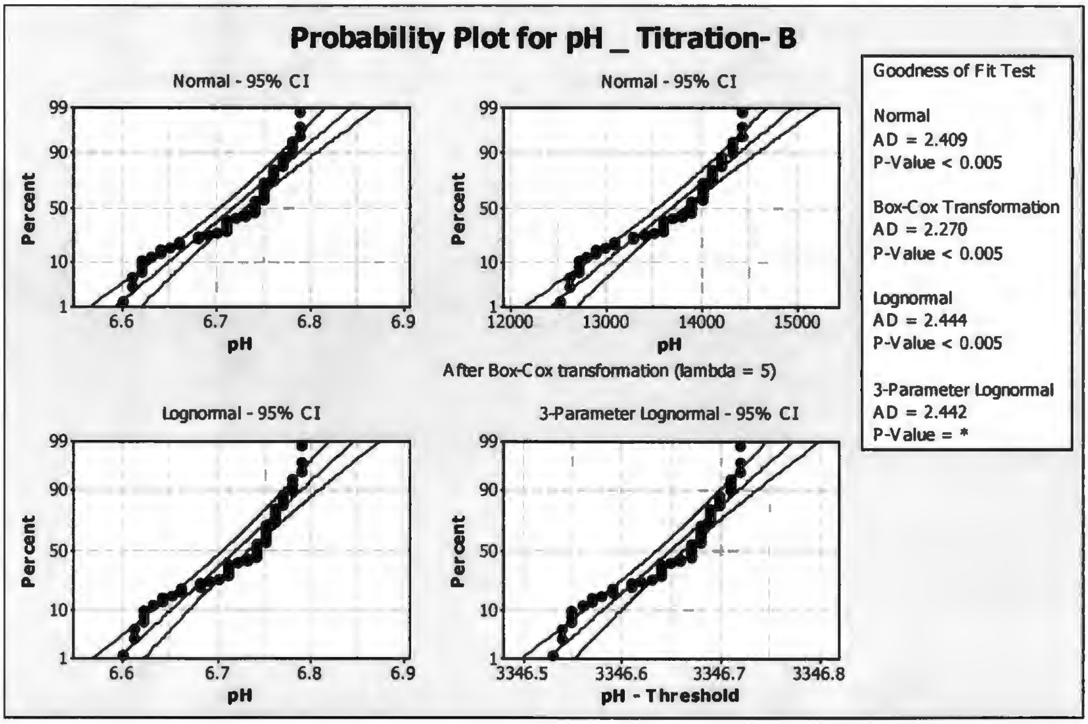
P-Value < 0.010
3-Parameter Weibull
AD = 1.303
P-Value < 0.005


Probability Plot for pH _ Titration- B
Normal - 95% CI
Normal - 95% CI
After Box-Cox transformation (lambda = 5)
Lognormal - 95% CI
3-Parameter Lognormal - 95% CI
Percent
pH
pH - Threshold
Goodness of Fit Test
Normal
AD = 2.409
P-Value < 0.005
Box-Cox Transformation
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P-Value < 0.005
Lognormal
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P-Value < 0.005
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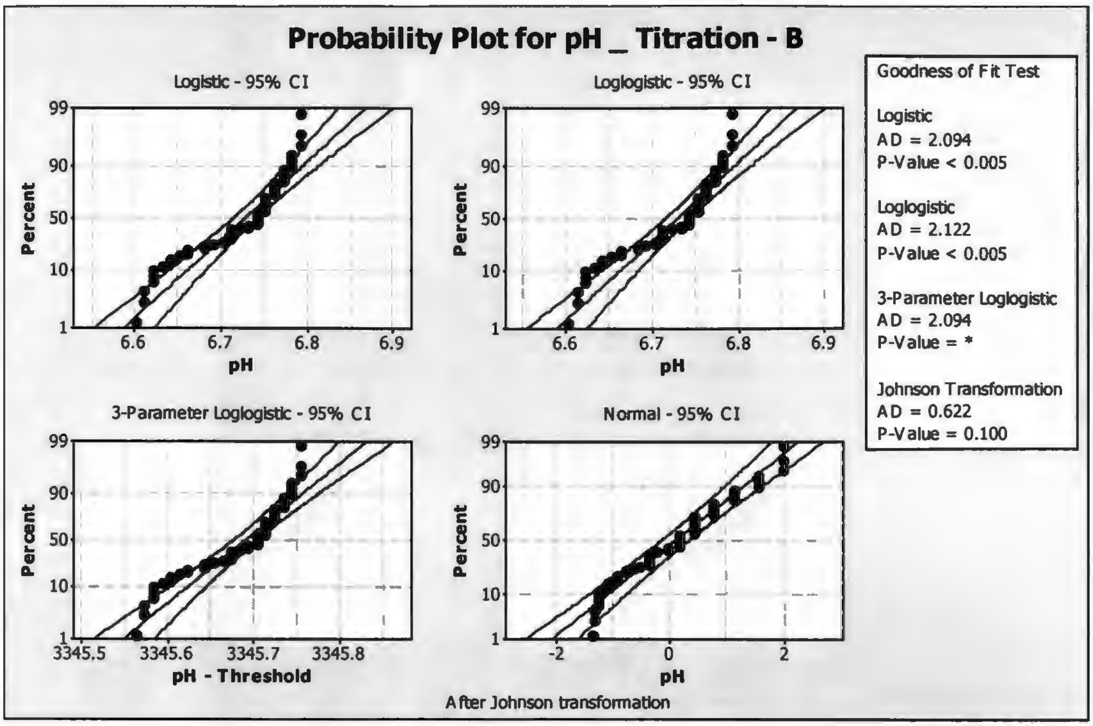
P-Value = *


Probability Plot for pH _ Titration - B
Logistic - 95% CI
Loglogistic - 95% CI
3-Parameter Loglogistic - 95% CI
Normal - 95% CI
Percent
pH
pH - Threshold
After Johnson transformation
Goodness of Fit Test
Logistic
AD = 2.094
P-Value < 0.005
Loglogistic
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P-Value < 0.005
3-Parameter Loglogistic
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P-Value = *
Johnson Transformation
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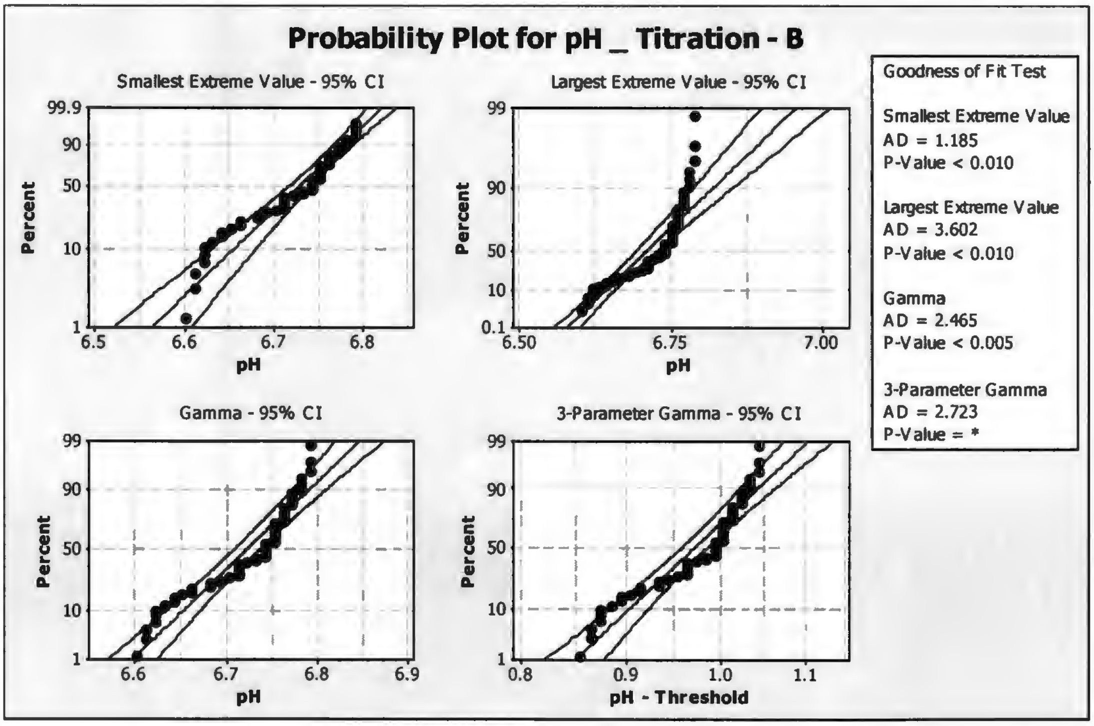
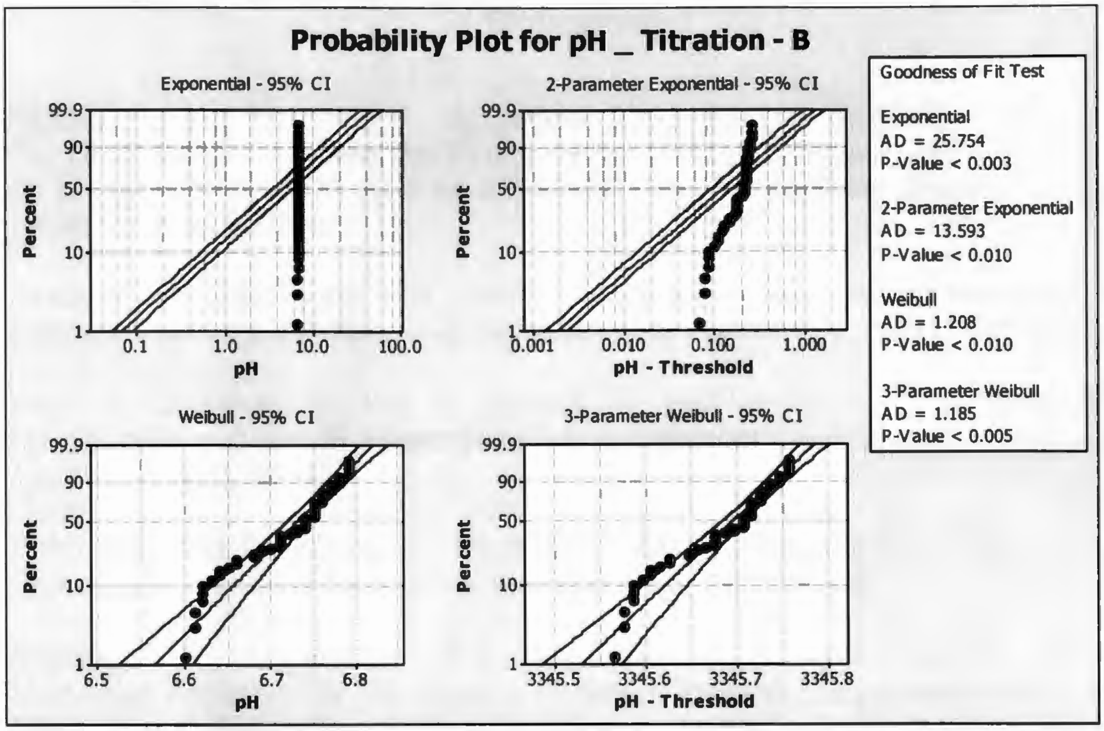

Probability Plot for pH _ Titration - B
Smallest Extreme Value - 95% CI
Largest Extreme Value - 95% CI
Gamma - 95% CI
3-Parameter Gamma - 95% CI
Percent
pH
pH - Threshold
Goodness of Fit Test
Smallest Extreme Value
AD = 1.185
P-Value < 0.010
Largest Extreme Value
AD = 3.602
P-Value < 0.010
Gamma
AD = 2.465
P-Value < 0.005
3-Parameter Gamma
AD = 2.723
P-Value = *



Probability Plot for pH _ Titration - B
Exponential - 95% CI
2-Parameter Exponential - 95% CI
Weibull - 95% CI
3-Parameter Weibull - 95% CI
Percent
pH
pH - Threshold
Goodness of Fit Test
Exponential
AD = 25.754
P-Value < 0.003
2-Parameter Exponential
AD = 13.593
P-Value < 0.010
Weibull
AD = 1.208
P-Value < 0.010
3-Parameter Weibull
AD = 1.185
P-Value < 0.005

Bibliography

Abboud, L. and Hensley, S., September 2003, Factory Shift: New Prescription For Drug Makers: Update the Plants - After Years of Neglect, Industry Focuses on Manufacturing; FDA Acts as a Catalyst -The Three-Story Blender, *The Wall Street Journal*, 293(84).

Azab, A. and ElMaraghy, H.A., 2007, Mathematical Modeling for Reconfigurable Process Planning, *CIRP Annals-Manufacturing Technology*, 56(1), 467-472.

Basu, P., Joglekar, G., Rai, S., Suresh, P., and Vernon, J., 2008, Analysis of Manufacturing Costs in Pharmaceutical Companies, *Journal of Pharmaceutical Innovation*, 3(1), 30-40.

Bohn, R.E. and Terwiesch, C., December 1999, The Economics of Yield-Driven Processes, Journal of Operations Management, 18(1), 41-59.

Bowling, S.R., Khasawneh, M.T., Kaewkuekool, S., and Cho B.R, 2004, A Markovian Approach to Determining Optimum Process Target Levels for a Multi-Stage Serial Production System, *European Journal of Operational Research*, 159(3), 636-650.

Buzacott, J.A. and Shanthikumar J.G., 1993, *Stochastic Models of Manufacturing Systems*, Englewood Cliffs, New Jersey: Prentice Hall, Inc.

Cole-Parmer, 2009, Corning ® Roller Bottles, http://www.coleparmer.com/catalog/product_view.asp?sku=0183600, accessed on May, 2009.

Colledani, M. and Tolio, T, 2005, A Decomposition Method to Support the Configuration / Reconfiguration of Production Systems, *CIRP Annals-Manufacturing Technology*, 54(1), 441-444.

Colledani, M. and Tolio, T., 2006, Impact of Quality Control on Production System Performance, *CIRP Annals-Manufacturing Technology*, 55(1), 453-456.

Daellenbach, H.G. and George, J.A., 1978, *Introduction to Operations Research Techniques*, Boston, MA: Allyn and Bacon, Inc.

Davis, R.P. and Kennedy, W.J., 1987, Markovian Modelling of Manufacturing Systems, *International Journal of Production Research*, 25(3), 337-351.

Djurdjanovic, D. and Jun Ni, 2006, Stream-of-Variation (SoV)-Based Measurement Scheme Analysis in Multistation Machining Systems, *IEEE Transaction on Automation Science and Engineering*, 3(4), 407-422.

Freiheit, T., Shpitalni, M., Hu, S.J., and Koren, Y., 2003, Designing Productive Manufacturing Systems without Buffers, *CIRP Annals-Manufacturing Technology*, 52(1), 105-108.

Hamamoto, S., Yih, Y., and Salvendy, G., 1999, Development and Validation of Genetic Algorithm-Based Facility Layout - a Case Study in the Pharmaceutical Industry, *International Journal of Production Research*, 37(4), 749–768.

Hassan, M., 1994, Machine Layout Problem in Modern Manufacturing Facilities, *International Journals of Production Research*, 32(11), 2559-2584.

Hon, K.K.B. and Xu, S., 2007, Impact of Product Life Cycle on Manufacturing Systems Reconfiguration, *CIRP Annals-Manufacturing Technology*, 56(1), 455-458.

Hu, S.J. and Koren, Y, 1997, Stream-of-Variation Theory for Automotive Body Assembly, *CIRP Annals-Manufacturing Technology*, 46(1), 1-6.

Juran, J.M., Gryna, M., and Bingham, R.S., 1974, *Quality Control Handbook*, 3rd edition, New York, NY: McGraw-Hill, Inc.

Kaebernick, H., Bazargan-Lari, M., and Arndt, G., 1996, An Integrated Approach to the Design of Cellular Manufacturing, *CIRP Annals-Manufacturing Technology*, 45(1), 421-425.

Klampfl, E., Gusikhin, O., and Rossi, G., 2005, Optimization of Workcell Layouts in a Mixed-Model Assembly Line Environment, *International Journal of Flexible Manufacturing System*, 17(4), 277-299.

Kochhar, J.S. and Heragu S.S., 1999, Facility Layout Design in a Changing Environment, *International Journal of Production Research*, Vol. 37(11), 2429 – 2446.

Koren, Y., Heisel, U., Jovane, F., Moriwaki, T., Pritschow, G., Ulsoy, G., and Brussel, H.V., 1999, Reconfigurable Manufacturing Systems, *CIRP Annals - Manufacturing Technology*, 48(2), 527-540.

Koren, Y., Hu, S.J., and Weber, T.W., 1998, Impact of Manufacturing System Configuration on Performance, *CIRP Annals-Manufacturing Technology*, 47(1), 369-372.

Maier-Speredelozzi, V., Koren, Y., and Hu, S.J., 2003, Convertibility Measures for Manufacturing Systems, *CIRP Annals-Manufacturing Technology*, 52(1), 367-370.

Newcombe, A., Watson, K., and Newcombe, C., March/April 2008, Biopharmaceutical Process Characterization: Defining the Design Space, *Pharmaceutical Engineering- ISPE*, 28(2).

Odem, J.N. May/June 2002, Biotech Glossary of Terms, *Pharmaceutical Engineering-ISPE*, 70-80.

Odem, J., March/April 2005, Trends in Biopharmaceutical Manufacturing Facility Design: What's Hot!, *Pharmaceutical Engineering-ISPE*, 25(2).

Oh, S.K.W., Kuek, K.H., and Wong, V.V.T., 2004, Design, Simulation, and Optimization of a Large-Scale Monoclonal Antibody Production Plant: Upstream Design, *Pharmaceutical Engineering-ISPE*, 24(6), 42-60.

Pillai, V.M. and Chandrasekharan, M.P., 2008, An Absorbing Markov Chain Model for Production Systems with Rework and Scrapping, *Computers and Industrial Engineering*, 55(3), 695-706.

Shabaka, A. I. and Elmaraghy H.A., 2007, Generation of Machine Configurations Based on Product Features, *International Journal of Computer Integrated Manufacturing*, 20(4), 355 – 369.

Spicer, P., Koren, Y., Shpitalni, M., and Yip-Hoi, D., 2002, Design Principles for Machining System Configurations, *CIRP Annals-Manufacturing Technology*, 51(1), 275-280.

Suh, N.P., Cochran, D.S., and Lima, P.C., 1998, Manufacturing System Design, *CIRP Annals-Manufacturing Technology*, 47(2), 627-639.

Sun, Ji-wen, Xi, Li-feng, Du, Shi-chang and Ju, Bo, 2008, Reliability Modeling and Analysis of Serial-Parallel Hybrid Multi-Operational Manufacturing System Considering Dimensional Quality, Tool Degradation and System Configuration, *International Journal of Production Economics*, 114(1), 149-164.

Winston, W., 2004, *Operation Research Applications and Algorithms*, 4th Ed., Belmont, CA: Thomson-Brooks/Cole.

Zhong, W., Maier-Speredelozzi, V., Bratzel, A., Yang, S., Chick, S.E., and Hu, S.J., 2000, Performance Analysis of Machining Systems with Different Configurations, *Japan-USA Symposium on Flexible Manufacturing conference*, Ann Arbor, Michigan