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PhD PROGRAMME IN COMPLEX SYSTEMS FOR PHYSICAL, SOCIO-ECONOMIC AND LIFE SCIENCES

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IMPROVING THE OPERATIONS MANAGEMENT IN OUTPATIENT CHEMOTHERAPY ONCOLOGY DEPARTMENTS FOR REDUCING THE PATIENT WAITING TIME

PHD THESIS

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1. Introduction

In the last years, the number of cancer diseases is steadily growing into the worldwide population. According to the statistical report of Siegel et al. (2021) of January 2021, it was estimated to detect 1,898,160 new cases in 2021 in the United States. Due to these numbers, the demand of healthcare services in the oncology centres is higher, but often such increasing demand is not properly compensated by an improvement in the service level of the oncology department. The outcomes of this dichotomy are a higher workload for staff in the oncology units and, above all, a dramatic growth of the patient waiting time for receiving the treatment. Reducing patient waiting time was recognized as an important factor to increase the patient satisfaction and well-being. Considering that cancer strongly affects the physical and emotional status of the patient, it is necessary to realize a patient-centred service in the oncology department for making the daily experience of the patient better and less stressful. Therefore, reducing the patient waiting time has to be the leading objective for improving the quality level in the outpatient cancer treatment facilities (Gesell and Gregory, 2004).

The oncology patients can undergo different types of treatment, including the chemotherapy one. When chemotherapy treatment is required, the patient spends lots of time in the oncology department, since the therapy administration can vary from few minutes to more than 6 hours. The chemotherapy oncology process also includes the medical consultation with an oncologist and the therapy preparation performed by a pharmacy department. When the oncology departments daily receive several patients, there are high probabilities to generate bottlenecks in the process and delays in healthcare service delivery. Furthermore, chemotherapy delivery is challenging due to the wide variation of chemotherapy treatments to be scheduled and the collaboration with the pharmacy department. Due to aforementioned features of the process, the oncology department can be considered as a complex system. Therefore the healthcare managers have to face several challenges to enhance the performance of the oncology units. These operational challenges are consequences not only of an imbalance between resource capacity of the oncology unit and increasing demand of patients but also a result of inefficient process configuration and chemotherapy appointment scheduling (Liu et al., 2019a).

In order to address the complexity of the oncology process and to enhance the patient satisfaction in the oncology units, in the last years, the healthcare managers are looking at the operations management field. The operations management concerns with managing the operations and process of a system to achieve the highest level of efficiency of the organization. In the oncology units, the operations management faces different type of problems, which can be classified in five groups:

1. **Planning problem:** it determines the days in which the patient has to undergo to the oncology unit to receive the treatment;
2. **Scheduling problem:** it consists of defining the appointment time for each patient in a specific single day;
3. **Patient flow management problem:** it aims at studying the current configuration of the investigated oncology department and finding new corrective actions that allow managers to improve the performance of the unit.
4. **Healthcare system design problem:** it deals with identifying the optimal number of resources that characterize the oncology departments;
5. **Healthcare supply chain problem:** it concerns with improving the flow management of medical materials and services in the healthcare network from manufacturer to patients.

The aim of the thesis is to cope with all the problems of the operations management in chemotherapy oncology units with the aim of proposing innovative techniques and guidelines for healthcare managers and stakeholders. In particular, the thesis discusses the outcomes arising from two projects with the oncology units of Catania and Ragusa (both in Southern Italy), in which it was addressed the patient flow management problem for reducing the patient waiting time. These real-life case studies represented a source of inspiration during the doctoral research. In fact, the research works dealing with scheduling and healthcare design system were developed as a straight continuation of the previous works in patient flow management. The planning problem was not studied since, in the real-life case studies, the patient appointment days are decided by the oncologists in respect of the chemotherapy protocol.

Finally, the supply chain problem is arising a growing attention in the healthcare context due to the high complexity of the problem compared to the other industries (Chen et al., 2013). Kochan et al. (2018) identified four sources of complexity, which

are the following: *i*) the high value of healthcare material and services (such as therapys, vaccines or medical devices); *ii*) the inventory management decisions taken by multiple healthcare stakeholders that have no experience with supply chain management; *iii*) the uncertain delivery lead-time of healthcare material and services; *iv*) the increasing and unpredictable patient demand. Therefore, it was pointed out the importance of enhancing the operations management in the healthcare supply chain. We faced the supply chain topic in collaboration with the Industrial Management Research Group of the University of Seville and, in particular, with Prof. Jose M. Framinan, which published several scientific articles and a seminal book in the supply chain dynamics field (Framinan, 2022). The partnership was also enriched by a 4-months visiting research period of the PhD candidate and author of the thesis. The thesis also presents the findings arising from the research works concerning the supply chain dynamics problem in which the analytical models of the literature were enriched by providing models that considers new constraints related to the production tasks and uncertainties of the system. The future objective will be to adapt these new supply chain models to the healthcare operations management field.

1.1 Research objectives

The research objectives (*RO*) of the thesis can be summarized as follows:

RO1: systematically studying the literature related to the operations management of chemotherapy oncology departments;

RO2: solving the patient flow management problem by identifying the best techniques and methodologies to evaluate the current process and proposing new configurations of oncology units;

RO3: solving the outpatient chemotherapy appointment scheduling problem in oncology departments;

RO4: providing guidelines to support managers in the decision-making process related to healthcare system design of oncology units;

RO5: proposing a new realistic supply chain dynamic model that will be used for the healthcare context.

1.2 Summary of research contributions

With regard to the research objectives outlined in Section 1.1, the contributions of this thesis are the following:

- A systematic literature review regarding the papers tackling the operations management in the chemotherapy oncology units was proposed. Firstly, all the key performance indicators utilized by academics and practitioners were classified and described. Then, some statistical analysis about the state of art were accomplished to demonstrate the increasing attention of managers in the topic under investigation. Finally, the papers were briefly described based on the specific problem addressed;
- A novel perspective of lean application on the specific case of the oncology units is proposed. The oncology department of a hospital located in Catania (Southern Italy) was studied to find lean improvement solutions. A Value Seam Map (VSM) integrated with a Discrete Event Simulation (DES) model is proposed, called as DVSM. The DVSM was used to study the service improvement of the oncology department with the objective of increasing the patient satisfaction. A Design of Experiments (DOE) was developed and, then, 72 Future Dynamic Value Stream Maps (FDVSM) were evaluated. Finally, an ANOVA analysis allowed us to statistically study the impact of all the factors in the system and to identify the best FDVSM;
- Simulation models are considered an effective tool for identifying potential ways to improve the patient flow in an oncology unit. To this end, we present a new agent-based simulation model designed to be configurable and adaptable to the needs of the oncology departments that have to interact with an external pharmacy. When external pharmacies are utilized, a courier service is needed to deliver the individual therapies from the pharmacy to the oncology department. An oncology unit located in Ragusa (Southern Italy) was studied through the simulation model and different scenarios were compared with the aim of selecting the ward configuration capable of reducing the waiting time of patients;
- Inspired by a real-world context and differently from the other studies, we modelled a multi-stage chemotherapy ward for the chemotherapy outpatient scheduling (COS) problem in which the pharmacy is located away from the

treatment area and therapies are delivered by batch. Processes in oncology wards are characterized by several sources of uncertainty that increases the complexity of the problem; thus, a stochastic approach was preferred to study the outpatient scheduling problem. To generate effective appointments schedules, we moved in two directions. First, we adopted a late-start scheduling strategy to reduce the idle times within and among the different stages, namely medical consultation, therapy preparation and treatment administration. Then, since the problem is NP-hard in strong sense, we developed a novel self-adaptive harmony search metaheuristic whose effectiveness was proved through an extended numerical analysis involving the standard harmony search and another optimization technique from the relevant literature. Also, a stochastic programming model of the problem under investigation was provided to preliminarily validate the attitude of the tested metaheuristics in solving the problem at hand. The outcomes from the numerical experiments confirmed the efficacy of the proposed scheduling model and the self-adaptive metaheuristic algorithm as well;

- The healthcare system design problem of outpatient chemotherapy oncology departments was investigated with the aim of providing guidelines for the decision-makers. Precisely, the goal is to drive the healthcare managers towards the selection of the alternative resource configurations able to assure a target level in terms of average number of patients cared in a given day and patient waiting time as well. A stochastic simulation model based on discrete time recursive equations was developed to emulate the patient flow in the oncology units. The simulation model was combined with a DOE to evaluate the impact of several different configurations on three key performance indicators: the patient waiting time, the number of patients and a trade-off indicator. The analysis of variance and Tukey tests were used to identify the influence of each experimental factors on the performance measures. Furthermore, we adopted a multi-objective Pareto approach and a well-detailed abacus of results to identify the non-dominated Pareto solutions and to easily evaluate the performances provided by each specific configuration considered in the experimental campaign. Finally, a multiple non-linear regression model was defined to estimate the performance of the outpatient chemotherapy oncology units;

- We investigated a two-echelon, two-product Supply Chain (SC) inspired by a real-world production/distribution firm, in which the product changeover time, necessary to switch from a product to another, induces a variable capacity in the factory. Such a varying production capacity is further exacerbated by the machine breakdowns that may occur in the manufacturing system. Since the two products share the same production system, a production control policy (PCP) has to be executed to decide the changeover, *i.e.* to select the product to be manufactured over time. An extended experimental campaign and ANOVA analysis were performed to investigate how the Fill Rate (FR) of the SC and the standard deviation of inventories vary as a series of operational and tactical parameters changes. Furthermore, we investigated the impact in terms of FR of four PCPs in the two-product, two-echelon supply chain dynamic problem with production capacity. We compared the well-known Hedging Corridor Policy (HCP) with two variants, namely Modified Hedging Corridor Policy (MHCP) and Improved Modified Hedging Corridor Policy (IMHCP), and Demand-Driven Material Requirements Planning (DDMRP) policy. Firstly, we used the Response Surface Methodology to calibrate the endogenous factors for each strategy. Then, through an extended full-factorial Design Of Experiments, we evaluated the effectiveness of the production control policies for several operational and market scenarios defined by varying exogenous factors. Finally, we proposed a new production control strategy, named Adaptive Hedging Corridor Policy (AHCP), which was compared with the well-established HCP.

1.3 Organization of the thesis

This section describes the structure of the thesis. Chapter 2 deals with the systematic literature review of the papers dealing with the operations management in chemotherapy oncology units. Chapter 3 describes the oncology process and provide a mathematical formalization of the problem at hand. Chapter 4 presents how lean methodology and simulation model can be combined to improve the performance of an oncology unit located in Catania (Southern Italy). This chapter is based on the following paper:

Fichera, S., Costa, A., Corsini, R. R., & Parrinello, V. (2021). "Application of lean techniques and simulation to improve efficiency of oncology department." International Journal of Services and Operations Management, In Press.

Chapter 5 presents a new configurable agent-based simulation model developed with the aim of being used by the managers for the patient flow management problem. The chapter also discusses of how the simulation model was used to identify the best configuration of an oncology unit situated in Ragusa (southern Italy). This chapter is based on the following paper:

Corsini, R. R., Costa, A., Fichera, S., & Pluchino, A. (2022). "A configurable computer simulation model for reducing patient waiting time in oncology departments." Health Systems, 1-15.

Chapter 6 reports the mathematical model and metaheuristic algorithm developed to face the chemotherapy outpatient scheduling problem in the oncology department. This chapter is based on the following paper:

Corsini, R. R., Costa, A., Fichera, S., & Parrinello, V. (2021). "Scheduling chemotherapy outpatient appointments: a self-adaptive metaheuristic approach." Annals of Operations Research, Under Review.

Chapter 7 reports the guidelines for healthcare managers that have to face the healthcare system design problem in the oncology units. This chapter is based on the following paper:

Corsini, R. R., Costa, A., Fichera, S., Pluchino, A., & Parrinello, V. (2021). "System design of outpatient chemotherapy oncology departments through simulation and design of experiments." Operations Management Research, Under Review.

Chapter 8 describes the new two-product two-echelon supply chain dynamics model and reports the findings arising from the comparison between the production control policies in a supply chain context. This chapter is based on the following papers:

Costa, A., Cannella, S., Corsini, R. R., Framinan, J. M., & Fichera, S. (2020). Exploring a two-product unreliable manufacturing system as a capacity constraint for a two-echelon supply chain dynamic problem. International Journal of Production Research, 1-29.

Corsini, R. R., Costa, A., & Fichera, S. (2021, August). Comparing production control policies in two-product supply chain dynamics. In 2021 IEEE 17th International Conference on Automation Science and Engineering (CASE) (pp. 1002-1007). IEEE.

Corsini, R. R., Costa, A., Cannella, S., Framinan, J. M. (2021). Analyzing the impact of production control policies on the dynamics of a two-product supply chain with capacity constraints, International Journal of Production Research. Under Review

Corsini, R. R., Fichera, S., & Costa, A. (2022). Assessing the Effect of a Novel Production Control Policy on a Two-Product, Failure-Prone Manufacturing/Distribution Scenario. In Selected Topics in Manufacturing (pp. 1-20). Springer, Cham.

Finally, Chapter 9 provides concluding remarks and new prospective for future research.

2. State of the art

Cancer patients can be treated from different specialists with different types of treatments. The chemotherapy is one of the major methods used to cure the cancer patients (Liang et al., 2015). Specifically, the chemotherapy treatment consists of using drugs to treat cancer patients with the aim of: *i*) stopping or slowing the tumour growth, *ii*) controlling or preventing the spread of cancer cells, *iii*) alleviating the cancer symptoms (Turkcan et al., 2012). However, the chemotherapy drugs not only destroy the cancer cells, but also affect the healthy cells. For this reason, chemotherapy drugs are administered in cycles with periods of recovery for the patient before the next treatment is given (Barton-Burke et al., 2002). In order to plan these cycles, the oncologists define a specific chemotherapy protocol for each patient on the basis of different factors such as the type of disease or the patients' health status. The protocol provides several information as for example the frequency of the chemotherapy appointments, the type of drugs and doses to be used. In particular, the protocol determines the days in which the patient has to undergo the treatment. The directions of the protocol have to be strictly respected.

In the treatment days, the patients undergo personalized drug therapy, administered in the oncology department under the care of a nurse, and, when the treatment is finished, he/she returns home. In brief, the main steps of the daily process in an outpatient chemotherapy oncology clinic are: i) the medical consultation with the oncologist; ii) the therapy preparation performed by the pharmacy; iii) the therapy administration monitored by the nurse. Specifically, in the first step, during the medical consultation, the oncologist monitors the health status of the patient and evaluates the results coming from the blood exams. After that, the oncologist sends to the pharmacy the information about the type and dose of the therapy to be prepared. When the pharmacy receives the request, the pharmacy technicians start the therapy preparation process. Therefore, the patient has to wait that the therapy was delivered from the pharmacy to the oncology department for starting the treatment. Moreover, a nurse has to be available since she/he has to prepare and monitor the patient. Finally, when the therapy process is completed, the same nurse releases the patient who can leave the oncology department and come back home.

On the basis of the day in which the patients undergo the medical consultation, there exist two different strategies that characterize the process of the oncology unit:

1. **Next-day:** the medical consultations are processed the day before the treatment. In this case, whether the results of the blood tests of the patients executed in the previous days in an external laboratory are acceptable, the pharmacy department prepared some doses in advance. Furthermore, another condition to prepare the therapies in advance depends on the cost of the therapy. In fact, the therapy can be prepared in advance only if it is not too expensive (Lamé et al., 2020). Although this strategy apparently enables reducing the patient waiting time, it is worth noting that patients have to go to the clinic on two consecutive days and that could be not so practical if they live far from the clinic;
2. **Same-day:** the medical consultations are carried out on the same day of the treatment administration. This strategy is quite diffused in the real-world oncology clinics as it is also preferred by patients (Lau et al., 2014) and prevents any waste of expensive drugs in case of deferral of patients or no-show at the infusion stage (Benzaid et al., 2020).

If the *same-day* strategy is adopted, some patients do not need to undergo all the stages of the oncology process (*i.e.*, medical consultation, therapy preparation and treatment administration). Indeed, patients can be classified into three categories depending on their daily pathway (Liang et al., 2015; Baril et al., 2017):

1. **Standard patients** or *patients POC*: go through all the stage of the oncology unit;
2. **Repetitive patients** or *patients PC*: are allowed to skip the medical consultation, since they have already met the oncologist and have received the treatment the day before;
3. **Control patients** or *patients PO*: do not need any treatment since they have successfully completed the provided chemotherapy protocol and they only require a periodical medical consultation.

Finally, the patients are also classified as **new patients**, *i.e.*, patients that go to the oncology unit to receive the treatment for the first time, or **follow-up patients**, *i.e.*, patients that have underwent the treatment at least once (Gocgun and Puterman, 2014; Le et al., 2015).

2.1 Performance measures

The problem of improving the operations in the chemotherapy oncology outpatient oncology departments can be faced by evaluating different performance measures, also called as key performance indicators (KPIs). Based on the stakeholder that can benefit from the KPIs improvement, the performance measure can be classified as patient perspective KPIs and management perspective KPIs (Alvarado et al., 2018).

Intuitively, the patient perspective KPIs are the performance measures aiming at enhancing the patient perception of the quality service in the oncology units. There are two performance measures that are classified as patient perspective KPIs, *i.e.*, treatment delay and flowtime (or waiting time). The treatment delay indicates the delay between the day of the patient appointment and the target day recommended by the oncologist in the protocol. This performance measure has to be minimized since if the treatment is not administered in the recommended day, the effectiveness of the therapy could be reduced negatively affecting the patient health status. However, in some situations, the protocol provides some tolerance limits for each treatment. Then, the treatment could be administered some days in delay by respecting the tolerance limit indicated by the oncologist. The flowtime derives from the manufacturing context and consists of the time a job (*e.g.*, raw material or semi-product) spends in the production system, *i.e.*, it represents the time between arrival and departure of the job from the manufacturing system (Baker and Trietsch, 2013). Likewise in healthcare system, the flowtime, also named in literature as length of stay, is the total time a patient spends in the oncology unit, *i.e.*, the time interval ranging from the time the patient is registered at the reception to the end of the chemotherapy treatment. Since the flowtime considers the entire patient flow in the oncology units, minimizing the flowtime corresponds to the reduction of the patient waiting time, which is the main cause of patient complaints. Some works adopted directly the patient waiting time as KPI and it measures the total time a patient waits for a medical consultation and for a treatment administration in the oncology unit.

In a managerial point of view, the oncology departments have to provide a cost-efficient service that simultaneously guarantees quality of care for the patient and employee satisfaction. To this end, five different management perspective KPIs can be pursued, *i.e.*, patient throughput, chair utilization, nurse utilization, nurse

overtime and makespan. The patient throughput indicates the number of patients cared in the chemotherapy oncology outpatient unit in a day. It represents a measure of the daily capacity of the system. It can be also considered as a patient perspective KPIs since a higher patient throughput allows the scheduler to reduce the postponement of patient appointments. The chair utilization, also denoted as bedload, measures the utilization time in percentage of the chairs in respect of the total working hours. Similarly, the nurse utilization, also denoted as workload, represents the utilization time in percentage of the nurses in respect of the total working hours. These two KPIs allow also understating if the number of chairs or the number of nurses are adequate to fulfil the daily patient demand. Notably, the nurse utilization can be also measured by referring to the total acuity level of the system, which is a measure related to the attention required by a patient treatment during the monitoring performed by the nurse. The nurse overtime is the extra working time of the nurses in respect to the standard working hours. The makespan is the closing time which consists of the completion time of the last treatment in a day. A reduction of these two last management perspective KPIs allow the managers to not pay the cost of work for the extra-hours and, simultaneously, to increase the nurse satisfaction and reduce the resource idle time. Finally, the total completion time is the total sum of the treatment completion time of the patients received in a day. Table 2.1 sums up the performance measures described above and used in the chemotherapy oncology outpatient units. Interestingly, Figure 2.1 depicts the number of articles that decided to adopt each KPI. It can be noticed that the patient waiting time is the most utilized performance measure. This trend of the literature justifies the objective of the thesis of reducing the patient waiting time by improving the operations management of oncology units.

Performance measures	Description
Patient perspective KPIs	
Treatment delay	Delay between the day of the patient appointment and the target day recommended by the oncologist in the protocol.
Flowtime or waiting time	The flowtime is the total time a patient spends in the oncology unit, while the waiting time is the total time a patient waits for a medical consultation and for a treatment administration in the oncology unit.
Management perspective KPIs	
Patient throughput	Number of patients cared in the chemotherapy oncology outpatient unit in a day.
Chair utilization or bedload	Utilization time in percentage of the chairs in respect of the total working hours.
Nurse utilization or workload	Utilization time in percentage of the nurses in respect of the total working hours or the total acuity level.
Nurse overtime	Extra working time of the nurses in respect to the standard working hours.
Makespan	Closing time which consists of the completion time of the last treatment in a day.
Total completion time	Total sum of the treatment completion time of the patients received in a day.

Table 2.1 Performance measure to evaluate the service in the oncology units

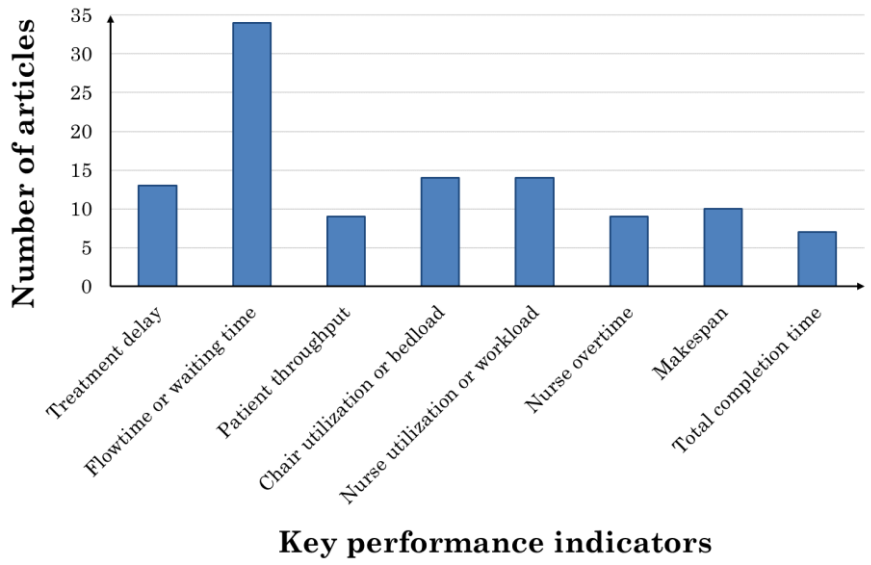


Figure 2.1 Frequency related to the key performance indicators

2.2 Background and related works

Managing the process of a chemotherapy oncology unit is challenging due to several factors that was thoroughly explained by Liu et al. (2019a). First of all, there exist several chemotherapy protocols that differ from each other. The chemotherapy treatment must be administered in the indicated days and only a short tolerance limit is accepted whether approved by the oncologist (Gocgun and Puterman, 2014). Any treatment administered in days outside the tolerance limit can undermine the effectiveness of the cure. Consequently, the wide variations resulting from the amount of different protocols complicate the operations required to indicate for each patient the days and times for administering the chemotherapy treatment. On the other hand, the oncology unit is coordinated with the operations carried out by the pharmacy. This interdependency between the departments increases the complexity of the problem since there are also variable conditions that affects the therapy preparation process performed by the pharmacy. In turn, possible delays on delivery the therapies from the pharmacy to the oncology department have a negative impact on the performance of the oncology unit (*e.g.*, a worsening of patient waiting time or an increase of clinic overtime) (Liu et al., 2019a). In the last years there was an increasing interest on applying Operation Research/Management Science (OR/MS) techniques to support the decision-making the problem at hand. On this regard, Sepúlveda et al. (1999) can be considered the pioneers of decision-making in oncology units. Nowadays, this study still represents a source of inspiration for researchers that aim to investigate the patient flow and operations in oncology departments.

In order to summarize the previous works on the application of operation research to support the operations management in oncology units, a systematic literature review is here proposed. To do this, it was browsed the SCOPUS database by adopting keywords related to the problem at hand. A number of 65 articles emerged by the search and by investigating the related citations. Figure 2.2, Figure 2.3 and Figure 2.4 are provided to better interpret the results of that research. In particular, Figure 2.2 highlights the growing interest on that topic by showing the number of papers published per years. Figure 2.3 compares the 15 most cited works in terms of the citation score and the number of citations (recorded by SCOPUS on the date 10/06/2021). The citation score is an indicator proposed by Glock and Grosse (2021), here calculated in Eq. 2.1 as follows:

$$\text{Citation score} = \frac{\text{Number of citations}}{\text{Current year-Year of publication+1}} \qquad (2.1)$$

As for example, the work of Santibáñez et al. (2009) was mentioned by 108 papers and was published in 2009, thus achieving a citation score of 8.31. Finally, Figure 2.4 shows the countries where the problem at hand was investigated by studying and enhancing the operations management of real-life oncology unit. From this figure it can be noticed that Canada, France and USA are the countries that provided more contribution to this research area, while there are no academic papers related to case studies in Italy.

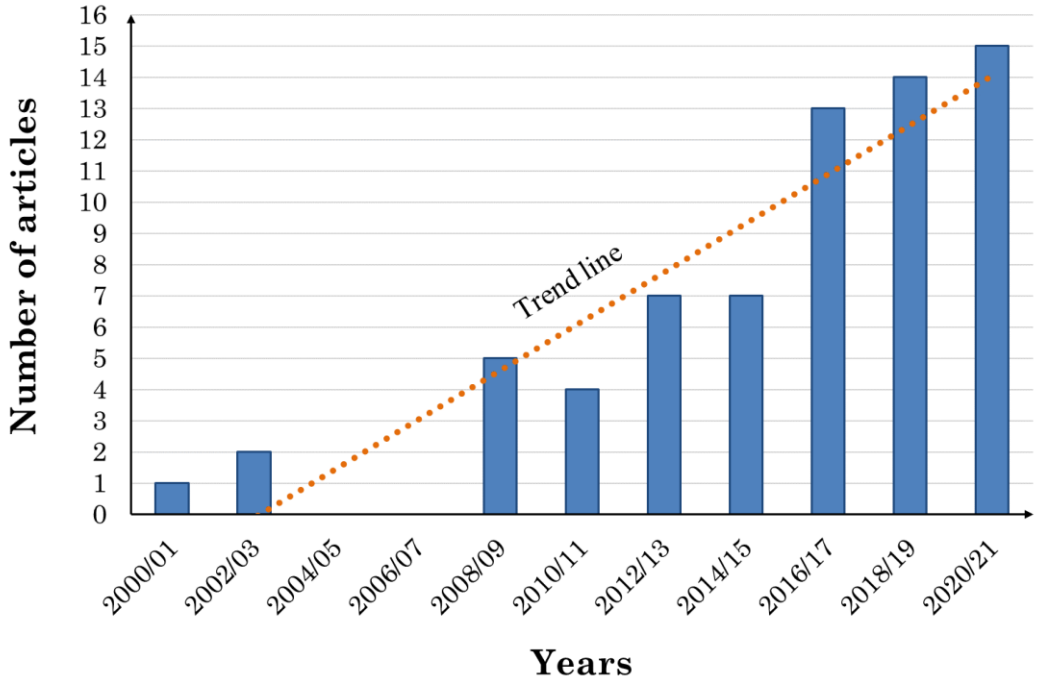


Figure 2.2 Number of articles in the last 20 years

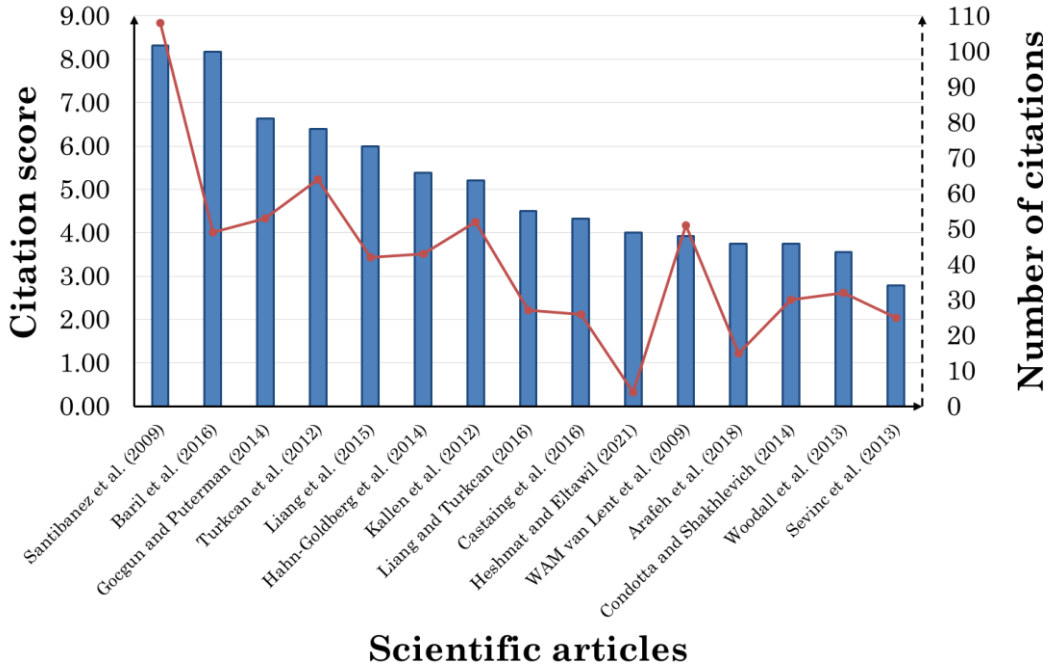


Figure 2.3 The most cited articles

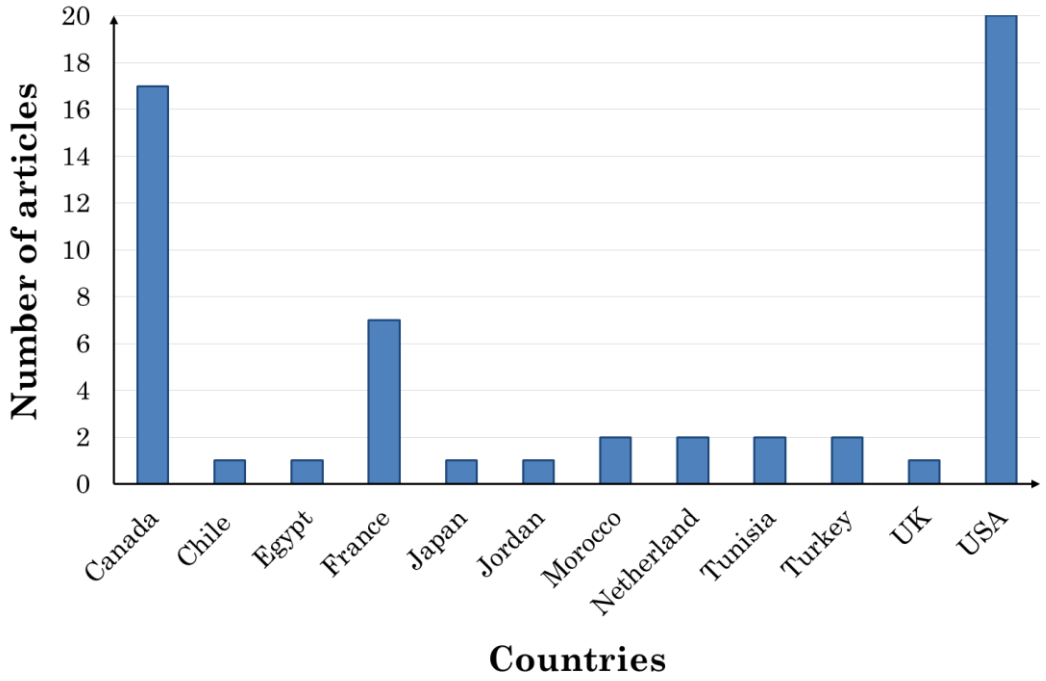


Figure 2.4 Countries of case studies in literature

In general, the 68 articles founded through the SCOPUS database can be classified in accordance with the specific type of problem investigated in the oncology unit, *i.e.*, planning, scheduling and patient flow management problem (see Chapter

1). Table 2.2 classifies the different sources of literature on the basis of the type of operations management problem addressed in chemotherapy oncology units. It can be noticed that some authors have faced different problems in the same work. The healthcare design system and supply chain problems are not discussed in this chapter since there is no relevant literature in chemotherapy oncology units. Chapter 7 and Chapter 8 report brief introductions of the state of art in healthcare regarding these two topics.

Classification criteria	**Related sources**
Planning	Alabdulkarim (2018); Gocgun and Puterman (2014); Gocgun (2018); Heshmat and Eltawil (2017, 2018); Ma et al. (2016); Mazier and Xie (2009); Sadki et al. (2010a, 2010b); Sadki et al. (2013).
Scheduling	Ahmed et al. (2011); Bouras et al. (2017, 2021); Castaing et al. (2016); Demir et al. (2021); Dobish (2003); Edwards et al. (2017); Garaix et al. (2020); Hahn-Goldberg et al. (2014); Hesaraki et al. (2019); Heshmat et al. (2017,2018); Huang et al. (2018, 2019); Huggins and Claudio (2019); Huggins et al. (2014); Liang and Turkcan (2016); Liang et al. (2015); Liu et al. (2019a); Mandelbaum et al. (2020); Sadki et al. (2011); Sevinc et al. (2013); Slocum et al. (2021); Suss et al. (2017, 2018); Yokouchi et al. (2012).
Planning and scheduling	Alvarado and Ntaimo (2018); Alvarado et al. (2018); Benzaid et al. (2020); Condotta and Shakhlevich (2014); Heshmat and Eltawil (2021); Hooshangi-Tabrizi et al. (2020); Issabakhsh et al. (2018, 2021); Le et al. (2015); Ramos et al. (2020); Santibáñez et al. (2012); Turkcan et al. (2012); Woodall et al. (2013).
Patient flow management	Aboumater et al. (2008); Ahmed et al. (2011); Alvarado et al. (2018); Arafeh et al. (2018); Baesler and Sepúlveda (2001); Baril et al. (2016a, 2016b, 2017, 2020); Bernatchou et al. (2017a, 2017b); Gruber et al. (2003, 2008); Hamad and El-Kilany (2020); Jane Vortherms et al. (2015); Kallen et al. (2012); Kang and Haswell (2020); Lamé et al. (2020); Liang et al. (2015); Liu et al. (2019a); Santibáñez et al. (2009); Suss et al. (2017); van Lent et al. (2009); Woodall et al. (2013); Yokouchi et al. (2012); Yu et al. (2021).

Table 2.2 Classification of the scientific articles

2.3.1 Planning problem

The chemotherapy planning decision problem determines the days in which the patient has to undergo to the oncology unit to receive the treatment. To guarantee the effectiveness of the treatment, these appointments should be planned as close as possible to the day indicated in the protocol. Only a short tolerance limit approved by the oncologist can be accepted (Alvarado et al., 2018; Gocgun and Puterman, 2014). The planning problem assumes a finite time horizon of several days or months. Optimization methods and heuristic algorithms were used by the literature to plan the treatment days according to protocol. Mazier and Xie (2009) are the firsts to solve the chemotherapy planning problem. They developed a mixed integer programming (MIP) model to construct a solution for achieving a better-balanced workload of physician and bedload. The works of Sadki et al. (2010a, 2010b) can be considered a continuation follow-up of the paper of Mazier and Xie (2009). In fact, they used the MIP model to define both oncologist and patient schedules with the objective of balancing the daily bedload. However, they stated that the MIP model requires high computational times to solve the problem due to large number of variables and constraints. To overcome this issue, they propose new heuristic algorithms as solving methodologies of the chemotherapy planning problem. Differently from the other works, Gocgun and Puterman (2014) focused only on the treatment administration stage, without considering the oncologists on the mathematical formalization of the problem. They used Markov decision process (MDP) for the chemotherapy planning problem. Due to the complexity of solving the problem with MDP, they employed linear-programming-based Approximate Dynamic Programming (ADP) to obtain approximate solutions. They also used a simulation model to demonstrate the effectiveness ADP by comparing it with easy-to-use heuristic decision rules. The objective of their work was to define the day of the patient appointment respecting the tolerance limit of the protocol. The work was improved by the paper of Gocgun (2018) in which the uncertainties deriving from the possible cancellations of the appointment were added in the model. Another stream of the literature on the chemotherapy planning problem deals with the definition of the treatment day of new patients. Sadki et al. (2013) focused on the planning problem of the new patients without changing the schedule of the existing patients and assuming that the oncologist schedules is a-priori known. The planning problem

of new patients was addressed also in the work of Ma et al. (2016). They used a simulation model to compare different decision policies and oncologist specialization configurations with the aim of efficiently use the resources of the oncology unit. A mathematical model was also provided to optimally solve the problem. Heshmat and Eltawil (2017) studied the planning problem of new patients by neglecting the medical consultation stage and including the therapy preparation process performed by the pharmacy. They proposed a MIP model to assign the starting days of treatment of new patients with the aim of achieve two different objectives, *i.e.*, minimizing the total completion time of the oncology unit and the treatment delay of the new patients. One year later, Heshmat and Eltawil (2018) published a new work that also addresses the problem of finding the optimum drug infusion doses to specify in the protocol. Finally, Alabdulkarim (2018) combined simulation and optimization to plan the starting days of the new patients. Specifically, they developed a system dynamics (SD) simulation model to find the critical days for the new patients and a mixed-integer programming (MIP) model to define the optimal start days.

2.3.2 Scheduling problem

The chemotherapy outpatient scheduling (COS) decision problem consists of defining the starting time of the appointment for each patient in a specific single day. In fact, the time horizon of the scheduling is of one day. Furthermore, the aim of the scheduling problem is to allocate the patients to the available resources of the oncology unit. The scheduling problem is strongly affected by the strategy that characterizes the process in the oncology unit, *i.e.*, next-day or same-day (see Section 2.1). In the next-day chemotherapy, the medical consultations are processed the day before the treatment. In this case, the scheduling problem just consists in allocating patients to chairs, assigning them a nurse and defining the starting times of the treatments. In the same-day chemotherapy strategy, the medical consultations are carried out on the same-day of the chemotherapy treatment and then it should be considered in the scheduling process.

The literature background reveals that the COS problem can be viewed under two different perspectives, namely off-line or on-line scheduling. As for the off-line scheduling, the daily list of patients is known in advance and the scheduler usually generates the appointment schedule a few days before the treatment. Instead, in the

on-line scheduling the appointment time is communicated to the patient immediately after his request or shortly after (*e.g.*, no later than 24 hours) by employing a properly designed template in which a series of vacant appointment slots, preliminarily generated on the basis of a specific criterion, have to be filled by the patient requests. Several solving approaches were employed by the literature to cope with the COS problem. The contribution by Dobish (2003) can be considered as the seminal research on the problem under investigation in which they adopted a next-day scheduling method based on a timetable for each day of the week. Similarly, Edwards et al. (2017) made use of a specific template or ad-hoc rules, based on the acuity level.

From then on, most literature recognized the need of explicitly considering the patient flow to improve the performance of oncology units. Indeed, some works developed simulation models to investigate the effectiveness of diverse scheduling rules on the performance of the oncology units (Ahmed et al., 2011; Yokouchi et al., 2012; Huggins et al., 2014; Liang et al., 2015; Liu et al., 2019a; Slocum et al., 2021). However, the mathematical programming was identified as the leading methodology for solving the COS problem. In this regard, Sadki et al. (2011) studied the same-day appointment scheduling problem with two major resources, namely oncologists for consultation and beds for injection, and proposed a combination of heuristics based on the Lagrangian relaxation to minimize patient waiting time and makespan. DES modelling and mathematical programming were used by Liang et al. (2015) to compare the proposed appointment scheduling tool with the current practice under a series of operational measures such as, patient waiting times, clinic total working time and resource utilization. Notably, they solved a linear programming model to schedule patient appointments according to a same-day off-line strategy. Liang and Turkcan (2016) distinguished between functional and primary care delivery models to provide chemotherapy treatments to cancer patients, depending on the availability of nurses. They considered a single-stage system where a set of patients have to be scheduled off-line on the same-day only for the infusion phase and proposed two multi-objective optimization models based on mathematical programming that ignore both oncology consultation and lab test. Suss (2017, 2018) proposed an algorithm that considers the classification of patient and the capacity of each stage of the process. Heshmat et al. (2017) improved the scheduling model proposed by Turkcan et al. (2012) in their hierarchical approach (see Section 2.3.3)

so that it can be solved in a smaller computational time also for larger-sized instances. Constraint programming was applied by Hahn-Goldberg et al. (2014) to the next-day outpatient scheduling problem considering the on-line approach. A similar approach for the same-day case can be attributed to Huang et al. (2018, 2019), who developed a chemotherapy outpatient scheduling template by reducing the violation between resource assignment and treatment requirements. Bouras et al. (2017) introduced a mixed integer programming (MIP) model for reducing the patient waiting time of a same-day off-line COS problem on a real-life oncology unit. In particular, they modelled the whole set of system stages, namely oncology consultation, therapy preparation and injection, also considering the limited number of resources at the different stages. To reduce the number of binary variables and constraints, thus enhancing the computational efficiency of their COS approach, Heshmat et al. (2018) devised a two-stage COS method, properly inspired by cellular manufacturing systems, which involves a clustering phase and a mathematical programming phase, for the minimization of the total completion time referred solely to the injection stage of an oncology unit. Another valuable contribution in the COS scenario is attributable to Hesaraki et al. (2019), who focus on the infusion stage to generate an on-line scheduling method subject to the nursing constraint. They used integer programming to design a template of vacant appointment slots that follows a bi-criteria objective based on the combination of weighted flow time and makespan. A different perspective emerged from the research by Huggins and Claudio (2019). They presented a mathematical model for the next-day COS problem that manages the chemotherapy patient appointments while taking into consideration the workload of nurses and pharmacy technicians as a constraint of the optimization problem in a cancer clinic. Recently, Bouras et al. (2021) published a paper, which can be considered the straight continuation of their previous work (Bouras et al., 2017), where a tabu search inspired metaheuristic algorithm was developed to overcome the computational time issue arising from the use of the MIP model.

All the aforementioned works make use of deterministic model to solve the COS problem. However, human factor may have a notable impact on the chemotherapy path of oncology outpatients, so deterministic models could represent a strong simplification. Mandelbaum et al. (2020) exploited the principles of queueing theory for the off-line appointment sequencing problem by engaging a large number of servers (chairs) and customers (patients) in a stochastic system wherein service

duration and punctuality are subject to a significant uncertainty. They proposed a data-driven approach based on the infinite-server queues whose effectiveness was proved by testing their approach against near-optimal algorithms. Both in deterministic and in stochastic mathematical programming models, the time to converge drastically depends on the number of patients and on the number of resources as well. Hence, heuristic or metaheuristic algorithms may represent a valid alternative to achieve a perfect compromise between qualities of solutions and computational times in solving COS problems. To this end, Sevinc et al. (2013) proposed a two-phase approach for the next-day COS problem. They used a specifically devised heuristic algorithm for handling the appointment scheduling for the laboratory tests, and two heuristics based on the multiple knapsack problem for the second phase in which patients have to be on-line assigned to the infusion seats. Castaing et al. (2016) presented a two-stage stochastic programming (SP) model for the next-day COS problem of an oncology unit located in USA. Since this optimization method requires a prohibitive computational time to be solved, the authors introduce a heuristic algorithm to find approximate solutions in a reasonable time. The work of Garaix et al. (2020) represented a valuable contribution adopting a metaheuristic algorithm in the field of the stochastic COS problem. In fact, they developed a GRASP algorithm to generate sub-optimal lists of patients for consultation and treatment phases in a same-day chemotherapy treatment scenario. Finally, Demir et al. (2021) formulated a two-stage stochastic programming model for the same-day COS problem focusing only on the treatment stage, in order to optimize a multi-criteria objective function, *i.e.*, the weighted sum of nurse overtime, chair idle time and patient waiting time. However, since they experienced high computational times to solve real-life instances, they developed a heuristic method based on a progressive hedging algorithm.

2.3.3 Integrated planning and scheduling problem

The previous sections discussed the methodological approach adopted by the literature to address the planning problem (in Section 2.3.1) and the scheduling problem (in Section 2.3.2). However, some works presented methodologies aiming at solving simultaneously both the planning and scheduling problem of the oncology units. In this end, some authors presented an integrated approach involving both planning and scheduling phases under a unique solving method. Le et al (2015)

proposed a tabu search based metaheuristic algorithm to solve the integrated planning and scheduling problem with the aim of maximizing the number of patients scheduled over a planning horizon, minimizing the overtime and finding a balanced nurse workload. Issabakhsh et al. (2018) developed a MIP model to reduce patient waiting time and makespan along several days planning horizon. This work was recently improved by the same authors in which they also proposed a robust scheduling heuristic based on adaptive large neighbourhood search to solve medium-large instances problem (Issabakhsh et al., 2021). Finally, Hooshangi-Tabrizi et al. (2020) presented an adaptive and flexible procedure, which combines two optimization models. The first model is aimed at dynamically schedule incoming appointment requests, while the second model is utilized for rescheduling already booked appointments to better allocate resources.

Other authors used a sort of hierarchical approach wherein the first stage is used to identify the day of the appointment while, in the second stage, the appointment starting time and the assignment of chairs and nurses are defined (Santibáñez et al., 2012). Turkcan et al. (2012) was the first study that hierarchically solved the planning and scheduling problem for chemotherapy treatment. They used two diverse mathematical programming models to tackle both planning and scheduling of chemotherapy patients. They proposed a MIP model to define the treatment days of new patients without adjusting the plans of existing patients. In this stage, the performance measures are the minimization of treatment delays and the workload of resources. The second model was used to find the resource requirements and acuity level for the scheduling problem of new patients. Woodall et al. (2013) focused on the nurse assignment by making use of MIP model to optimize the weekly and monthly scheduling of different types of nurses. Then, they proposed a simulation-optimization approach model to optimize the starting times of nurse shifts. Condotta and Shakhlevich (2014) exploited the mathematical programming for generating a multilevel template, which aimed at minimizing the patient waiting times and the nurse workload for an outpatient clinic. Notably, the template was specifically used to book new patient chemotherapy treatment. Alvarado and Ntaimo (2018) used a mean-risk SP model powered by a specific heuristic to schedule patient appointments and resources under uncertain conditions (such as acuity levels and availability of nurses) for reducing patient waiting time and nurse overtime. To evaluate the effectiveness of the solution arising from the SP model, they used the

simulation model developed by Alvarado et al. (2018). Benzaid et al. (2020) proposed a three-stage procedure to solve the planning and scheduling problem. Specifically, the first two stages address the problem of determining a date and start time for each new patient and assigning patients to nurses. The last stage is devoted to solve the scheduling problem by simulating last-minute changes due to cancellations and uncertainties on nurse availabilities. Similarly to the other works, Ramos et al. (2020) and Heshmat and Eltawil (2021) proposed a two-stage solving approach for the planning and scheduling problem, but, interestingly, they included the therapy preparation process performed by the pharmacy in the problem formulation. In particular, Heshmat and Eltawil (2021) used a DES model for the scheduling problem considering the drug availability and pharmacy technicians working-hours.

2.3.4 Patient flow management problem

The literature focused also in studying the patient flow of the chemotherapy oncology units to propose corrective actions and new configurations of the process with the aim of enhancing the performance measures. In this context, Gruber et al. (2003) were one of the firsts to point out the need of redesign the patient flow in the chemotherapy oncology outpatient unit by leading a project (called "Perfect day") which had the objective of improving the quality of the healthcare services provided. Some years later, Gruber et al. (2008) conducted a new project to enhance performance measure related to a managerial viewpoint. Precisely, they aimed at avoiding the barriers to increase patient throughput (*i.e.*, total number of patients cared in a day) and resource utilization while not compromising patient safety. Aboumater et al. (2008) implemented an electronic system to decide the priority of therapies to be prepared by the pharmacy that based on anticipated patient arrival at the chemotherapy oncology outpatient unit. Kallen et al. (2012) delineated corrective actions to increase appointment process efficiency, enhance the communication between department and employ an information technology system in the pharmacy unit. Jane Vortherms et al. (2015) carried out a project to implement an oncology outpatient staffing system with the goals of maximizing patient satisfaction, employee engagement, and finding a balanced workload distribution.

However, the works in literature mainly use DES modelling and compare alternative configurations by varying the number of resources, operational or scheduling policies and arrival rate for the patients. Sepúlveda et al. (1999) and

Baesler and Sepúlveda (2001) can be considered the pioneers of using simulation modelling for the patient flow management problem. On the other hand, considering that the paper of Santibáñez et al. (2009) is the most cited in this topic (108) and it has the highest value of citation score (8.31), their work is a seminal paper concerning the decision-making through simulation in oncology units. Nowadays, these studies still represent a source of inspiration for researchers that aim to investigate the patient flow in oncology departments. Some research work handle simulations to examine the performance of the ward by focusing primarily on the administration of chemotherapy treatment. Ahmed et al. (2011) and Yokouchi et al. (2012) employed simulation to propose new appointment scheduling rules with the aim of increasing both number of patients per day and bedload and reducing patient waiting time. Alvarado et al. (2018) developed a simulation model to analyse operational strategies related to the planning of patient appointments in an oncology clinic. Woodall et al. (2013) and Liu et al. (2019a) also included the activities of the pharmacy, which consists of preparing the therapies required by the oncology unit. The former considered the pharmacy operations in the simulation model to define the best daily shift start time in oncology unit. The latter performed a process analysis and a simulation study to evaluate the influence of simultaneous changes in demand level, chemotherapy staffing levels and appointment scheduling practice on the clinic overtime and patient waiting time. Baril et al. (2020) examined the workload of nursing staff in relation to the administration of patient treatments, considering both physical and mental workload. On the other hand, other works in the literature considered all the stage of the same-day oncology process (*i.e.*, medical consultation, therapy preparation and therapy administration) to improve patient flow and balance resource utilization in oncology clinics. Interestingly, Liang et al. (2015) proposed a robust DOE so as to support healthcare managers in the decision-making process by investigating the impact of various experimental factors on such things such as the number of patients per day or number of chairs. Baril et al. (2016b) combined simulations with a business game in a Kaizen event, *i.e.*, a workshop whose goal is to encourage the continuous improvement of a specific area or process. The authors compared a series of alternative management configurations and pointed out the need to include pharmacy technicians in the Kaizen event. Baril et al. (2016a, 2017) studied the nurse tasks in an oncology department with the goal to reduce their workload. Bernatchou et al. (2017a, 2017b) developed a DES

simulation to emulate the actual configuration of an oncology department and to evaluate the effect of different arrival patterns on patient waiting time and resource utilization. Suss et al. (2017) constructed a DES model to identify the elements that cause long patient waiting time and of one another to test hypotheses about potential improvements. Hamad and El-Kilany (2020) built a simulation model to compare two different scenarios with the aim of avoiding unnecessary delays. Differently from the other works, Kang and Haswell (2020) developed the simulation model on the basis of real-time data, while Lamé et al. (2020) merged the DES model with soft system methodology and ethnographic observations. Interestingly, inspired by the work of van Lent et al. (2009) that applied lean thinking to increase the efficiency of oncology units, Arafeh et al. (2018) and Yu et al. (2021) are the unique to merge the methods of six sigma and lean manufacturing with simulation to study the patient flow and improve the performance of oncology units.

3. Problem statement

3.1 Problem description

The health service of the chemotherapy oncology departments considered in this thesis is defined as *day-hospital* and the patients are named as *outpatients* since they receive the treatment and leave the hospital in the same day. Furthermore, the thesis is focused on the *same-day* chemotherapy oncology units (see Chapter 2 for the difference between *same-day* and *next-day*). The *same-day* oncology process consists of three main steps, *i.e.*, the medical consultation, the therapy preparation process and the chemotherapy administration. For this reason, it is usually considered as the counterpart of a three-stage hybrid flow shop of a manufacturing system (Bouras et al., 2017, 2021; Hahn-Goldberg et al., 2014) with limited human resources, denoted in literature as *HFS/HR* problem (Costa et al., 2013).

Figure 3.1 shows the sequence of steps that a patient undergoes during the treatment day, which can be described in detail as follows:

1. **Medical consultation:** Each patient arrives at the department and meets the nurse at reception for the registration. The first time a patient goes for a medical consultation, she/he is assigned a referee oncologist, which defines the chemotherapy protocol. From that moment on, every time the patient goes to the oncology unit, she/he always consults the same referee oncologist so as to be assured the continuity of care of the patient. During the medical consultation, the oncologist reviews the results of the blood test that the patient preliminary underwent in the same hospital or in an external laboratory. Then, the referee oncologist carries out a medical examination of the patient health status. Based on the outcomes coming from the blood test and the current health status of the patient, the oncologist decides if the patient is ready to receive the treatment in that working day. If the oncologist assesses that the patient is not able to undergo the treatment, the patient is deferred and the appointment is postponed to another day. Finally, based on the patient health conditions, the oncologist sends the request to the pharmacy of both type and doses of the therapy to be injected;
2. **Preparation of therapies:** The requests of therapy are processed by the pharmacy. In some cases, the pharmacy has to satisfy the orders coming from

different departments of the hospital. However, it usually gives priority to the preparation of chemotherapy therapies (Garaix et al., 2020; Lamé et al., 2020). The requests sent by the oncologists are processed in chronological order. In general, the pharmacy disposes of pharmacy technicians, which are engaged to prepare the therapies, and pharmacy assistants, which have the role of processing the requests, picking up the drugs from the inventory and providing them to the pharmacy technicians for the preparation of the therapy. When the therapy is ready, it is delivered to the oncology department. The therapy delivery time is strictly related to the location of the pharmacy and, thus, on its distance from the oncology department. In fact, if the pharmacy is *in-house*, *i.e.*, in the same floor or building of the oncology unit, the therapies are delivered by a nurse or through a conveyor belt as soon as they were prepared (Aboumatar et al., 2008). On the other hand, if the pharmacy is detached from the oncology unit, the therapies are gathered in several batches by the pharmacy assistants and a courier service is needed to transport the batch of therapies with a vehicle;

3. **Chemotherapy administration:** The patients need two different resources to receive the treatment in the oncology department: *i*) the treatment chair or bed that accommodate the patient during the therapy administration; *ii*) a nurse that has to prepare and monitor the patient. Therefore, once the therapy was delivered to the oncology unit, the chemotherapy treatment of patient may start if both a nurse and a treatment chair are available. In this case, the setup task can be accomplished by a nurse, which prepares the patient for the chemotherapy treatment. Every nurse can prepare only one patient at a time. During the treatment time of patients, any nurse is in charge to simultaneously monitor more than one patient. The limit of number of patients that a nurse can monitor simultaneously in literature is usually set to four (see for example Baesler and Sepulveda, 2001 or Baril et al., 2020 among the others). Finally, when the therapy process is completed, the patient discharges the oncology department.

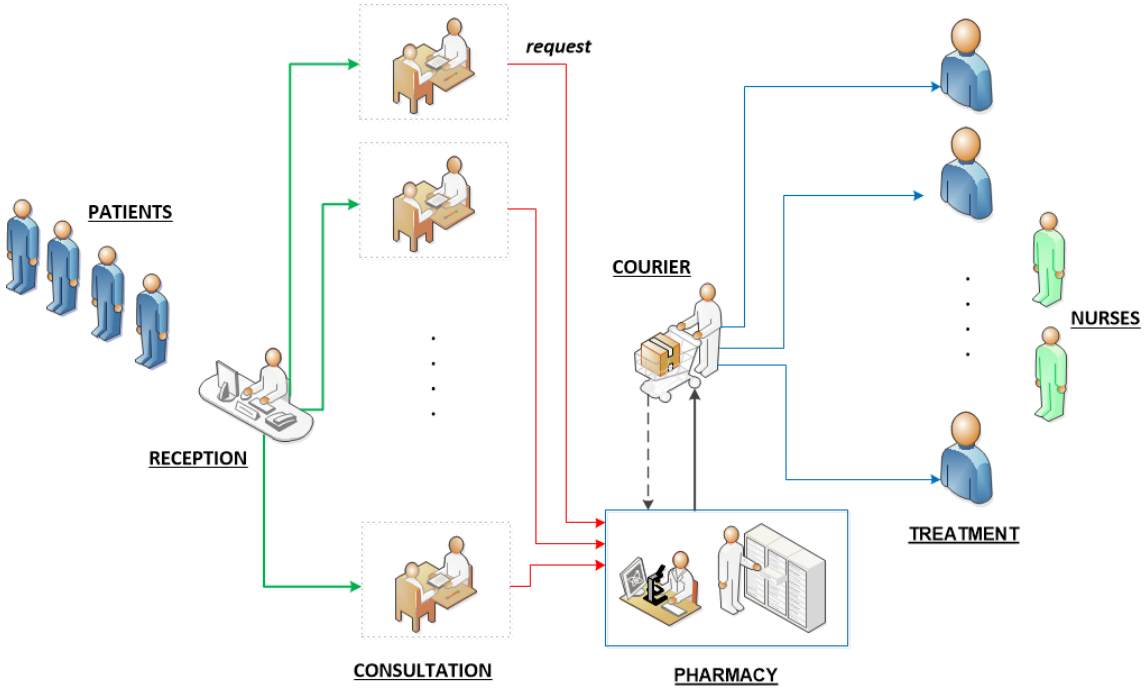


Figure 3.1 Patient flow in the oncology unit

3.2 Mathematical notation of the problem

This section reports the mathematical notation that is used along the whole thesis:

p	Patient $p=1,\ldots,P$, where $P = POC + PO + PC$
POC	Total number of standard patients
PO	Total number of control patients
PC	Total number of repetitive patients
o	Oncologist $o=1,\ldots,O$
d	Pharmacy technician $d=1,\ldots,D$
a	Auxiliary courier $a=1,\ldots,A$
b	Batch $b=1,\ldots,B$
c	Chair for the treatment $c=1,\ldots,C$
n	Nurse $n=1,\ldots,N$
Cl_p	Classification of patient p ($Cl_p \in \{POC; PC; PO\}$)
Op_p	Oncologist assigned to the patient p ($Op_p \in O$)
Ato_o	Available time of oncologist o
r_p	Arrival time of patient p
Sc_p	Medical consultation starting time of patient p
Dc_p	Duration of medical consultation of patient p

Cc_p	Medical consultation completion time of patient p
Atd_d	Available time of pharmacy technician d
Sp_p	Therapy preparation starting time of patient p
Dp_p	Duration of therapy preparation of patient p
Cp_p	Therapy preparation completion time of patient p
Ata_a	Available time of auxiliary courier a
Sb_b	Therapy delivery starting time of batch b
CAP_b	Batch size of batch b
TD_b	Therapy delivery duration of batch b
Cb_b	Therapy delivery completion time of batch b
$Atnset_n$	Available time of nurse n for the setup
Atc_c	Available time of chairs for treatment c
N_{max}	Maximum number of patients monitored by a nurse
$Sset_p$	Setup starting time of patient p
$Dset_p$	Duration of setup of patient p
$Cset_p$	Setup completion time of patient p
Si_p	Treatment starting time of patient p
Di_p	Duration of treatment of patient p
Ci_p	Treatment completion time of patient p

3.3 General simulation pseudo-code of the problem

The description of the problem can be formalized through a pseudo-code that is reported in Table 3.1. This pseudo-code was used to develop the simulation models described in the next chapters. A unique difference exists between the simulation models used for the patient flow management problem (see Chapter 4 and Chapter 5) and the simulation model of the metaheuristic algorithms used for the patient appointment scheduling problem (see Chapter 6). In fact, in the first problem the patient arrival time is described by a stochastic distribution arising from the historical data collected in the real-life oncology units. In the second case, the decisional problem consists of indicating the arrival time to the patients (through scheduling algorithms) so as to enhance the performance of the oncology units.

Firstly, the number of resources of the oncology units and pharmacy, *i.e.*, number of oncologists O, number of pharmacy technicians D, number of auxiliary couriers A,

number of nurses N and number of chairs for the treatment C, have to be introduced in the algorithm. Based on the statistical analysis of the historical data of the problem, the total number of patients and the variables that vary for each patient or each batch have to be defined by using deterministic values stochastic distributions. Then, the available time variables (*e.g.*, Ato_o or Atc_c), which indicated the time when the resources are available for the next patient, are set to zero.

From rows 4 to 14 the table describes the code that computes the starting time and the completion time of the medical consultation. Precisely, for each patient p that is classified as standard patient (*POC*) or control patient (*PO*), the medical consultation starting time depends on the arrival time of patient p (the time in which the patient is available to meet the oncologist) and the available time of the oncologist assigned to the patient p. The medical consultation completion time is the sum of the starting time and the duration of the meeting with the oncologist. Once concluded the medical consultation of patient p, the available time of the oncologist assigned to patient p has to be updated. As for the repetitive patients (*PC*), they skip the medical consultation and, then, their medical consultation completion time is assumed to be equal to their arrival time. Finally, the patients are ordered using the First-In-First-Out (FIFO) policy that refers to the medical consultation completion time.

From rows 15 to 23 the code describes the code that computes the starting time and the completion time of the therapy preparation process performed by the pharmacy technicians. This stage refers to the patients *POC* and *PC* since the control patients (*PO*) go back home after the medical consultation. The therapy preparation process can start as soon as the therapy request is sent by the oncologists. It is assumed that it happens when the medical consultation time is concluded (*i.e.*, medical consultation completion time). Therefore, in order to start the therapy preparations process, the pharmacy has to have received the therapy request from the oncologist (*i.e.*, Cc_p) and one of the pharmacy technicians has to be available to prepare the therapy (*i.e.*, $\min\{Atd_d\}$). The therapy preparation completion time is calculated by summing the starting time and the duration of the therapy preparation process and it is used to update the available time of the pharmacy technician. Finally, the patients are ordered using the FIFO rule based on the therapy preparation completion time.

From rows 24 to 36 the code evaluates the therapy delivery process for each patient that have to undergo the treatment administration (*i.e.*, patients *POC* and *PC*). Firstly, an auxiliary variable *'batch'* is initialized to record the patients' therapies that compose the batch. The pharmacy has to follow a serial-batching delivery approach. Even if a therapy is ready, the therapy batch has to be filled before being delivered. Therefore, the batch will be delivered when the last therapy of the batch is ready. As in serial-batch scheduling problem, the completion times of the therapies in a batch correspond to the completion time of the last therapy of the batch (Shabtay, 2014). When the size of the batch coincides with the maximum batch size CAP_b, then, the therapy delivery starting time is computed. It depends on the first available time between the couriers and the time in which the batch is completed. Then, the therapy delivery completion time is computed through the sum between the therapy delivery starting time and the therapy delivery duration of the batch b. The therapy delivery duration indicates the time spent by the courier to go from the pharmacy to the oncology unit. To update the courier available time, it has to be also considered the time needed to come back from the oncology unit to the pharmacy. Notably, if the pharmacy is *in-house* (*i.e.*, it is situated in the same floor or building of the oncology unit), the therapies are delivered as soon as they are ready without being collected in batches. In this scenario, *CAP* is equal to one and, then, the batch is composed by only one therapy.

Finally, from rows 37 to 48 the code describes the procedure of the treatment administration. For patients *POC* and *PC*, the chemotherapy treatment can start if the therapy was delivered in the oncology unit, a nurse is available to prepare and monitor the patient p and a chair is free for the treatment. Precisely, the nurse can prepare or setup one patient at a time and can monitor N_{max} patients simultaneously. However, the number of nurses of the oncology unit is usually set equal or greater than C/N_{max}. Therefore, a nurse will be always available to monitor a new patient. The setup duration ($Dset_p$) is used to compute the setup completion time ($Cset_p$) and the time availability of the nurse n for the setup ($Atnset_n$), while, the treatment duration (Di_p) is used to calculate the treatment completion time (Ci_p). The treatment completion time (Ci_p) also represents the time in which the patient p leaves the oncology unit and comes back home. As for the patient *PO*, the treatment completion time (Ci_p) is equal to the medical completion time (Cc_p) since they go to the oncology unit only for the medical consultation.

Algorithm 6.1 Simulation pseudo-code

```
1:  Define the number of resources: O, D, A, N, C.
2:  Define the historical data: P, r_p, Op_p, Dc_p, Dp_p, CAP_b, TD_b, Dset_p, Di_p
3:  Set the available time of the resources (i.e., Ato_o, Atd_d, Ata_d, Atn_n, Atc_c) equal to zero
4:  MEDICAL CONSULTATION
5:  for p = 1 to P
6:      Sc_p = max {r_p; Ato_o} | o = Op_p
7:      if Cl_p = POC or Cl_p = PO
8:          Cc_p = Sc_p + Dc_p
9:      else
10:         Cc_p = Sc_p
11:     end
12:     Ato_o = Cc_p
13: end
14: Order the patients using the FIFO policy
15: THERAPY PREPARATION
16: for p = 1 to P
17:     if Cl_p = POC or Cl_p = PC
18:         Sp_p = max {Cc_p; min{Atd_d}}
19:         Cp_p = Sp_p + Dp_p
20:         min{Atd_d} = Cp_p
21:     end
22: end
23: Order the patients using the FIFO policy
24: THERAPY DELIVERY
25: batch = 0
26: for p = 1 to P
27:     if Cl_p = POC or Cl_p = PC
28:         batch = batch + p
29:         if length(batch) = CAP_b
30:             Sb_b = max{min{Ata_a}; max{Cp_p}} ∀ p=1,…,P | p ∈ b
31:             Cb_b = Sb_b + TD_b
32:             min{Ata_a} = Cb_b + TD_b
33:             batch = 0
34:         end
35:     end
36: end
37: TREATMENT ADMINISTRATION
38: for p = 1 to P
39:     if Cl_p = POC or Cl_p = PC
40:         Si_p = max{Cb_b; min{Atnset_n}; min{Atc_c}} ∀ b=1,…,B | p ∈ b
41:         Sset_p = Si_p
42:         Cset_p = Sset_p + Dset_p
43:         min{Atnset_n} = Cset_p
44:         Ci_p = Si_p + Di_p
45:     else
46:         Ci_p = Cc_p
47:     end
48: end
```

Table 3.1 Simulation pseudo-code

4. Patient flow management problem: the case study of Catania

4.1 Introduction

New technologies and new researches in the field of healthcare allow more effective treatments and have improved the quality of life of many patients. The improvement of the health system corresponds to a significant increase in investments to guarantee a high level of service accessible to the greatest number of people. Unfortunately, the frequent economic crises have limited or even reduced the resources available for public services, including health services. Managers study new solutions to make the healthcare system more efficient and find innovative tools for improvement (Patri and Suresh, 2019; Toussaint and Berry, 2013). The problem is therefore to reduce costs but, at the same time, improve services. This apparent contradiction is one of the basic principles proposed by Lean Manufacturing.

Lean management basic assumptions originate from the Toyota Production System described in the famous book of Womack et al. (1991), *i.e.*, "*The Machine That Changed the World*". The core of the lean philosophy is to continually improve a process by either increasing customer value or reducing non-value adding activities (Muda), process variation (Mura), and poor work conditions (Muri) (Radnor et al., 2012). The basic principles of Lean management are six (Toussaint and Berry, 2013):

1. Lean Is an Attitude of Continuous Improvement;
2. Lean Is Value-Creating;
3. Lean Is Unity of Purpose;
4. Lean Is Respect for the People Who Do the Work;
5. Lean Is Visual;
6. Lean Is Flexible Regimentation.

To implement these principles, quantitative and non-quantitative tools and methods were proposed that concern all levels of the organization (Henrique and Godinho Filho, 2020). Nowadays, it is more appropriate to speak of lean culture, which is the synthesis of different methods of improving production systems. An example is the Lean Six sigma that combines lean methodologies with the statistical process control (De Koning et al., 2006). Lean methodologies originating in the automotive sector

were applied in other sectors such as aerospace or garment industry (Kumar et al., 2020b).

Lean methodologies developed in an automotive industrial context have recently been applied in healthcare with significant success. First of all the Institute for Healthcare Improvement, USA (Womack et al., 2005) and the Institution for Innovation and Improvement supported the use of lean methodologies. Young et al. (2004) published one of the first papers about Lean Healthcare. They proposed the use of industrial process to improve patient care identifying the weak links or bottlenecks and take appropriate remedial action. Lean Healthcare was widely applied in public and private hospitals so as to improve the performance of the emergency care services (Oh et al., 2016), intensive care units (Trzeciak et al., 2018), operating room units (Collar et al., 2012) and gynaecologic oncology unit (Kumar et al. 2019). The reviews of Augusto and Tortorella (2019) and D'Andreamatteo et al. (2015) demonstrate the widespread use of lean in the health sector. Robinson et al. (2012) classifies the lean tool utilised in the healthcare context into three groups. Assessment tools, such as process mapping, are used to review the performance of existing organisational processes in terms of their waste, flow or capacity to add value. Improvement tools are used to improve processes developing and redesigning processes through problem solving or housekeeping tools such as 5S (sorting, setting in order, sweeping, standardising and sustaining). Finally, monitoring tools, such as visual management, are used to measure and monitor the processes and their improvement. One of the most effective assessment lean tool is the Value Stream Map, VSM, used to identify all types of waste in the value stream and to take steps to try and eliminate these (Rother and Shook, 2003). VSM was successfully applied to analyse different healthcare organizations as Shou et al. (2017) highlighted in their cross-sector review on the use of value stream mapping. Lummus et al. (2006) studied a physician clinic, Cookson et al. (2011) studied an emergency department and Tortorella et al. (2017) provided a detailed description of VSM applied in a hospital sterilisation unit. An important support to help improve the delivery of healthcare is process simulation in particularly the DES. White et al. (2011) developed an empirically based discrete-event simulation to examine the interactions between patient appointment policies and capacity allocation policies (*i.e.*, the number of available examination rooms) and how they jointly affect various performance measures, such as resource utilization and patient waiting time. Baril

et al. (2014) used DES to model outpatient flows in an orthopaedic clinic. They simulated different scenarios in order to evaluate the best assignment of resource to each orthopaedist and the best appointment scheduling rules. Oh et al. (2016) used a simulation-based decision support model in the redesigning of an emergency department to improve the patient throughput time. Famiglietti et al. (2017) developed a DES to model a radiation oncology centre with the aim of increasing the efficiency of the system and achieving the quality improvement. Recently, Robinson et al. (2012) demonstrated theoretically and empirically the complementary roles of simulation and lean in healthcare. They proposed a 'SimLean' framework and demonstrated that fusion of simulation with lean improves the impact of lean. In the literature the Value Stream Map is the lean tool that was mainly used to integrate simulation and lean methodologies. First of all, the common approach of the proposed papers is to evaluate the current and future Value Stream Map of the process under examination. Then, the effects of the Future Stream Map are simulated through a discrete event simulator to analyse and choose the best future scenarios. Abo-Hamad et al. (2012) applied Value Stream Mapping to analyse the therapy delivery process in a hospital, so they simulated the process to evaluate the performance of three possible improvement scenarios. The emergency departments are studied by Bal et al. (2017). They evaluate the impact of the Future Stream Map on emergency departments overcrowding and patient waiting times by means of a simulation model applied to two different scenarios. Doğan and Unutulmaz (2016) applied the Value Stream Map and simulation procedure at the Physical Therapy and Rehabilitation (PT&R) department of a public hospital.

As for the outpatient chemotherapy oncology department, to the best of our knowledge, the Value Stream Map integrated with the discrete event simulation has not yet been studied to improve the activities of the oncology department (see Section 2.3.4). It represents the aim of the proposed paper. According to Lean Healthcare, it is necessary to eliminate all that is waste or all those activities that do not have value for the patient such as waiting times for health services. The Value Stream Map (VSM) is a Lean technique that allows the decision-maker to focus on the activities that generate value and not value for the patient. It traces the flow of the patient and at the same time the patient information, such as medical reports. The VSM identifies the resources used during the health service and the patient waiting time and therefore, it permits to identify possible improvement actions. Healthcare

services can be interpreted as complex systems because there is a significant interaction between service actors, patients, nurses and doctors and all events are affected by significant variability such as, for example, the duration of a medical examination. Furthermore, the best tool for correctly analysing patient flow and evaluating performance indicators is the simulation modelling, since it permits to evaluate the effect of organizational changes or investments in new resources. One of the aims of the paper is to propose a methodology to define a Future Value Stream Map (FVSM) that represents a new possible configuration of the process that allows the health facility to improve the patient satisfaction. In some situations, FVSM can be developed with little effort, but, in complex cases such as the problem under investigation in an oncology department, it is not easy to predict future performances. The Discrete Event Simulation (DES) model, which is one of the simulation techniques, allows us to handle uncertainty and forecast events in the oncology department creating different FVSM (Abdulmalek and Rajgopal, 2007).

In this paper a VSM integrated with a discrete event simulator is proposed and defined as Dynamic Value Stream Map (DVSM). DVSM was used to study the service improvement of an oncology department with the objective to increase the patient satisfaction. In the daily patient flow, the value time for the patient is the time spent on the medical consultation and the chemotherapy treatment, while, the non-value time is the waiting time. The Current Dynamic Value Stream Map (CDVSM) identifies the actual state of the oncology department under study so as to evaluate the patient waiting time by adopting the flowtime as KPI. All the alternative scenarios to improve the service were considered with several Future Dynamic Value Stream Maps (FDVSM) and the ANOVA analysis made it possible to identify the improvement actions with the greatest impact on the KPI. The best FDVSM was reported with all the identified changes and the new performances of the oncology department. Finally, we have developed a multiple non-linear regression model that supports the healthcare managers in the decision-making process, which allows them to easily evaluate all the proposed FDVSMs. The remainder of the paper is organised as follows. The problem statement is explained in detail in Section 4.2. In Section 4.3, the details of the dynamic value stream map are explained. The design of experiments, the results including statistical tests and a discussion are presented in Section 4.4. Section 4.5 provides the managerial implication, while Section 4.6 summarizes the concluding remarks.

4.2 Problem statement

This research was conducted for the oncology department of a hospital located in Catania (Southern Italy). The department provides health services for patients who need to receive chemotherapy treatment. The working day in the oncology unit starts at 08:00 AM and finishes when all the patients have left the department. We have conducted several audits and interviews with the staff of the department in order to well define the process under study. The oncology process under investigation can be classified as *same-day*. The description of the patient is reported in Chapter 3. It has to be specified that the oncology unit and the pharmacy unit are situated in two different buildings. Then, the pharmacy disposes of an auxiliary courier to deliver the therapies from pharmacy to the oncology department. He goes by walk and the absence of vehicle for transporting therapies involves long delivery time. In the real-life scenario, the patients are classified as standard, repetitive or control. However, the approach described in this work focuses only on the standard patients, because the aim of the research is to improve the whole pathway in the oncology department. All the repetitive patients arrive at the opening hour of the department and, since they do not receive the medical examination, they directly wait for the therapy preparation process. They are scheduled in the first slots of the first come first served list of the pharmacy and, consequently, they are the first patients to receive the treatment. Then, their pathway is fast and the waiting times are not long. Moreover, the percentage of repetitive patients is a low value and, thus, the probability that a patient is classified as a repetitive is negligible. As for the control patients, they do not require the chemotherapy treatment. For the medical examination, the oncologists give priority to the standard patients in order to allow them to complete the treatment until the end of the working day. Consequently, the medical examinations of the control patients do not affect the waiting times of the patients that need the treatment. The research project aims at reducing the patient waiting time. Therefore, the mean flowtime (see Section 2.1) is used as key performance indicator. It is calculated in Eq. 4.1 as follows:

$$\overline{F} = \frac{\sum_{p=1}^{P} Ci_p \cdot r_p}{P} \tag{4.1}$$

Other important indicators in the lean manufacturing philosophy is the mean Non-Value Time ($\overline{NVT}$). In Lean Manufacturing context, the Non-Value Time represents all the events in which the time is considered a waste for the customer. In the case under study, the Non-Value Time is the patient waiting time and, then, it can be also defined as mean Waiting Time ($\overline{WT}$). The Non-Value Time (calculated in Eq. 4.2) is the sum of the waiting time for the medical examination and the chair for treatment:

$$\overline{NVT} = \frac{\sum_{p=1}^{P} Si_p\text{-}Cc_p + Sc_p\text{-}r_p}{P} \tag{4.2}$$

On the other hand, the mean Value Time, ($\overline{VT}$), indicates all the events with value-added for the patients. Then, it is the sum of the duration of medical examination and the duration of the treatment. It is calculated in Eq. 4.3 as follows:

$$\overline{VT} = \frac{\sum_{p=1}^{P} Ci_p - Si_p + Cc_p - Sc_p}{P} \tag{4.3}$$

Finally, the efficiency of the Oncology Department is defined in Eq. 4.4 as follows:

$$Eff = \frac{\overline{VT}}{\overline{F}} = \frac{\overline{F}\text{-}\overline{NVT}}{\overline{F}} \tag{4.4}$$

As it is possible to note since the times of medical examination, therapy preparation and treatment of each patient are fixed, minimizing the flow time means minimizing the Non-Value Time and, consequently, the waiting times of the patients. Moreover, in this case, the efficiency will increase because the mean Value Time will be the same.

4.3 Dynamic Value Stream Map

The objective of this work is the formulation of a methodology to decrease the duration of the patient recovery and, at the same time, increase the productivity of the department. The duration of the patient recovery can decrease thus minimizing the patient waiting time that represent time wasted for patients. This approach is a typical topic of Lean Management: the elimination of wasted time. The tool that permits to highlight the wasted time for the patients is the Value Stream Map. The oncology department consists of processes that are subject to variability and are

interconnected, which leads to complexity. Queues emerge within the process and the performance is difficult to predict. Simulation of process in particular DES modelling can allow a robust what-if analysis by changing the parameters of the system. In order to realize a simulator, a four-steps procedure was developed: *i*) collection all the data of the process; *ii*) model construction; *iii*) verification of the model; *iv*) model validation. As described previously, in this work, VSM was integrated with DES and a Dynamic Value Stream Map (DVSM) was realized .

4.3.1 Data collection

All the activities of the oncology department were taken over for four weeks. During the four weeks, the activities were normally carried out and the number of oncologists and pharmacy technicians was normally in service. The patients observed had known pathologies and there were no particular cases. The data collected, in accordance with the mathematical model, are:

- The total number of patients arriving each morning, considering all the categories;
- The arrival time of each patient;
- The number of oncologists;
- The starting time and the durations of medical consultations;
- The number of patients visited daily by each oncologists;
- The number of pharmacy technicians;
- The durations of therapy preparation;
- The batch size of the therapies to deliver from the pharmacy to the oncology units;
- The duration of the therapy delivery;
- The number of chairs available for treatments;
- The starting time and the durations of the oncology treatments;

Some of the detected values are considered as simulator parameters, while other values are used to generate the input data and, then, to calculate the simulated performance and to verify if the simulator is actually able to replicate the activities of the oncology department.

4.3.2 Model construction

All the stages of the oncology process, as the durations of treatments, are affected by a great variability. In order to correctly simulate the process, the input parameters are considered as determinations of stochastic distributions. The distribution of each parameter was estimated based on the data collected as described in the previous paragraph. Table 4.1 reports the stochastic distributions used in the simulation model. Firstly, Table 4.1 shows the distributions to generate the total number of patients. In the special case of the arrival time of the patients at the oncology unit, three distributions with an a priori probability level were considered. Therefore, the arrival time is randomly associated with one of the three distributions and, then, on the basis of the distribution considered, the value is determined. Notably, the first group represents all the patients that arrives at the opening hour of the department, i.e. at 08:00 AM. The oncologists present different duration of the medical examination and number of patients to visit daily. Then, each oncologist presents a normal distribution and a probability to be assigned to a patient. Finally, the table reports the duration of the medical consultation, the duration of the treatment and the data that describes the pharmacy process.

Processes	Distribution
Patients	
Total number of patients	Normal(30.87,2.02)
Arrival time of the patients	
Group 1	Deterministic(0) – probability = 46.62 %
Group 2	Normal(47.63,7.75) – probability = 32.54%
Group 3	Gamma(14.87,9.77) – probability = 20.84%
Duration of medical consultations	
Oncologist 1	Normal(27.54,4.11) – probability = 9.29%
Oncologist 2	Normal(14.21,3.02) – probability = 30.71%
Oncologist 3	Normal(18.32,3.81) – probability = 13.82%
Oncologist 4	Normal(22.45,3.98) – probability = 13.62%
Oncologist 5	Normal(27.04,4.09) – probability = 11.81%
Oncologist 6	Normal(27.79,4.16) – probability = 20.75%
Therapy preparation process	
Duration of the therapy preparation	Deterministic(5)
Therapy batch size	Uniform(4,11)
Duration of therapy delivery	Deterministic(20)
Treatment administration	
Duration of oncology treatment	Gamma(1.9,52.37)

Table 4.1 Distributions of the simulation parameters

4.3.3 Model verification and validation

The model representative of the oncology department was coded on Arena® software platform. Figure 4.1 and Figure 4.2 depicts the graphic visualization in 2D and 3D of the simulation model. In order to verify that the simulator output results are representative of reality, a model verification and validation was performed. The verification was carried out by consulting the heads of the oncology unit to confirm the flow of patients and the interaction of the oncology department with the pharmacy. The logical model of the simulator was judged to be consistent with the actual reality of the department. As regards with the validation step, Sargent (2013) proposed several approaches to demonstrate the effectiveness of a simulation model,

particularly the "*historical data validation*" approach was considered. Validation was performed by comparing the values of the performance indicators measured in the real case study with those obtained from the simulator based on the input data collected and estimated statistically. Table 4.2 shows the real performances of the Oncology Department under study and those obtained from the simulation. The absolute deviations between the two values are always less than a few percentage points and, then, it is possible to state that the simulator correctly represents the real system. The validation of the DES model allows it to be used for the construction of CDVSM.

	Real data	**Simulated data**	**Error [%]**
Mean Flowtime	291.40	290.67	00.25
Non-Value Time	170.30	171.17	00.51
Value Time	121.10	119.50	01.32
Efficiency [%]	41.56	41.10	01.10

Table 4.2 Validation of the DES model

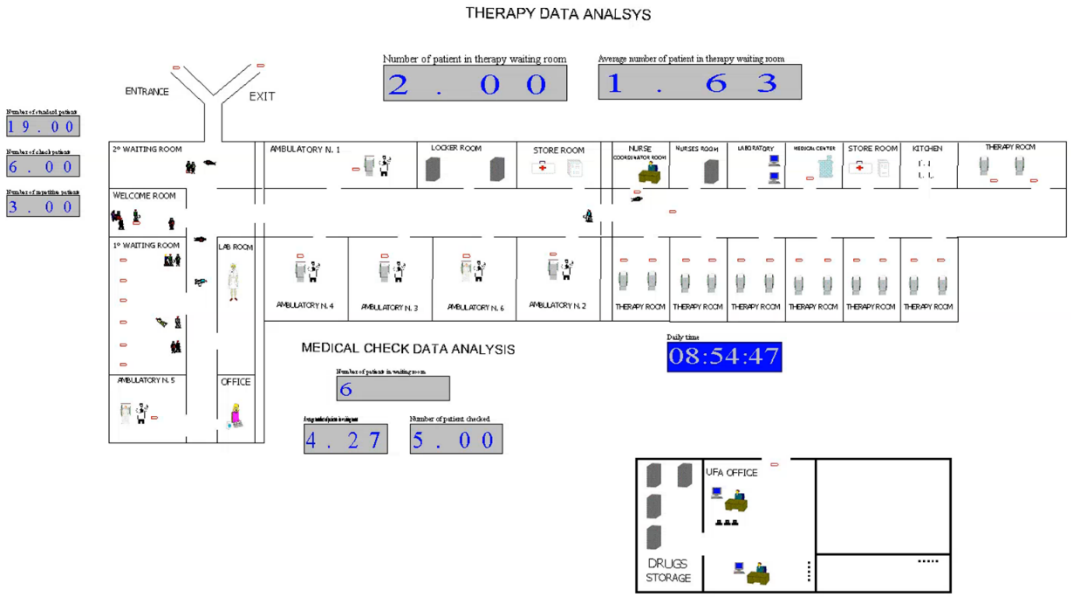


Figure 4.1 2D graphic visualization of the simulation model developed in Arena®

Figure 4.2 3D graphic visualization of the simulation model developed in Arena®

4.3.4 Current Dynamic Value Stream Map

The Current Dynamic Value Stream Map (CDVSM) that represents the actual condition of the oncology department is built using simulator outputs. The DVSM allows us to easily evaluate the flow of the events in the process and, then, the flow of material and information through the value chain. It provides to all the stakeholders a global vision of the activities and it enables the decision-makers to easily identify the wasted sources (Lacerda et al., 2016). In the CDVSM (see Figure 4.3) the physical flow of patients and therapies, and the information flow are reported. In particular, the rectangular boxes indicate the activities in the oncology department, the triangular boxes represent the waiting area of the patients. In the stage between the pharmacy and the chemotherapy treatment, two icons are reported representing the batch of therapies and the auxiliary worker that delivers the batch from the pharmacy to the oncology unit. The bottom line indicates the value and non-value time. The times corresponding to reception, medical consultation and chemotherapy treatment on the lower line are the value time. The other values on the upper line are the non-value times. All the values reported in CDVSM are the average values of all patients considered during the simulation period.

As also depicted in Figure 4.3, currently, the mean flow time is 4 hours and 51 minutes and the mean no value time is 2 hours and 50 minutes. The oncology department has an efficiency of 41.56%. This means that patients on average spend

58.44% of the total time waiting for the health services. Starting from actual organization of the oncology department it was necessary to evaluate the possible decision-making alternatives to improve the process.

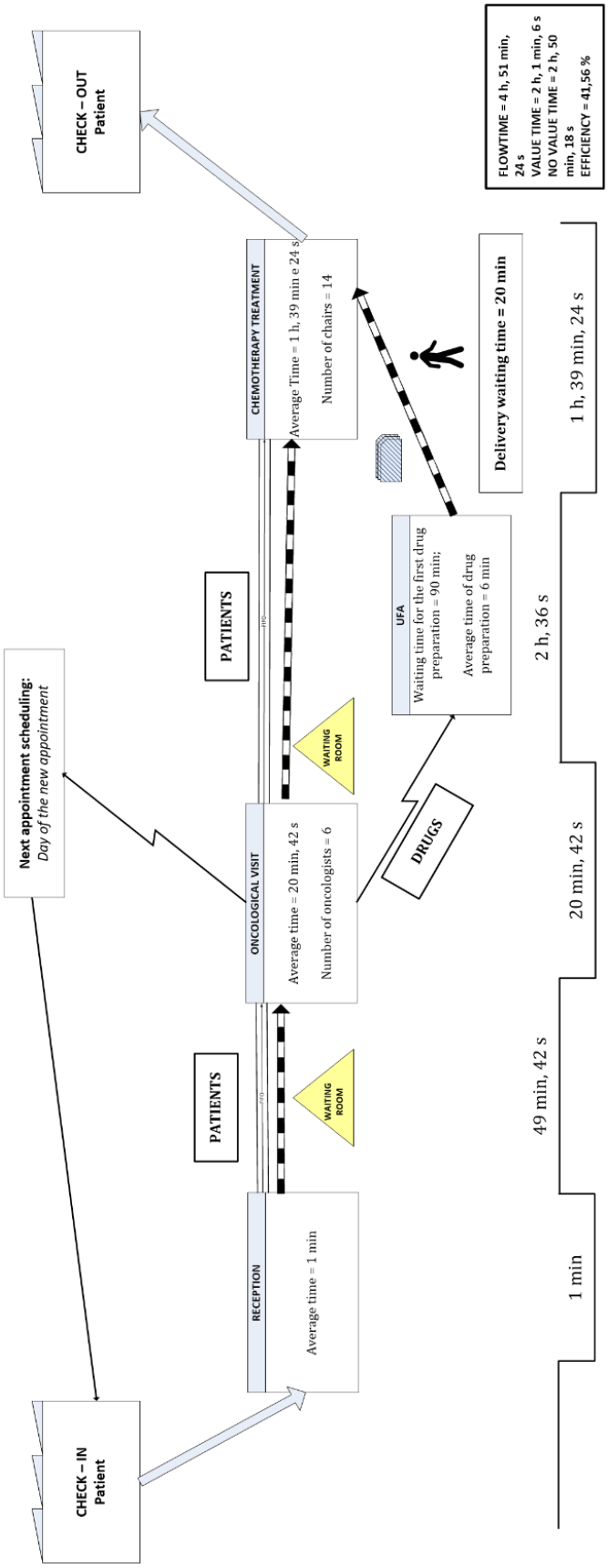


Figure 4.3 Current Dynamic Value Stream Map

4.4 Experiments and Future Dynamic Value Stream Map

The objective of the next step is to identify the corrective actions in order to enhance the performance of the oncology department and create the FDVSM. For this purpose, after a meeting with the oncologist of the department and the evidence of the CDVSM, the critical factors were identified. In order to evaluate their impact on the performance of the process, the mean flowtime, an appropriate Design of Experiments (DOE) was developed. All the results generated by several scenarios, each one simulated with the DVSM, are evaluated. Then, the best combination of the factors permits to define the FDVSM. Finally, we have proposed a regression model to support the optimization process of the system.

4.4.1 Design of Experiments

A full-factorial DOE (reported in Table 4.3) was developed in order to create a robust campaign of new possible processes of the oncology department. From the observation of the ward, in collaboration with the oncologists of the department, it was possible to identify five factors that can determine a decrease in terms of the mean flowtime and, therefore, an increase of the efficiency of the system and the quality of health service. Two or three different levels were identified for the five proposed factors corresponding to the different modalities to change the oncology department. Factors α and β concern the therapy preparation process performed by the pharmacy technicians. Specifically, factor α is the starting time of the activities of the pharmacy which can be at 8:30 or 9:30 AM. Factor β concerns the methodology adopted to deliver the therapies from pharmacy to the oncology unit. For this factor, level 1 is the current approach: the ready therapies are delivered in batch with random size and the auxiliary worker of the oncology department is called from pharmacy for delivering only when it is necessary. It involves a duration of the delivery equal to 20 minutes, Level 2 is a possible modification of this approach in which the size of the delivery batch is fixed a priori and equal to three therapies and the auxiliary worker is always available in pharmacy allowing to reduce the duration of the delivery from 20 minutes to 10 minutes. At level 3 the therapy is delivered when it is ready. Then, delivery batch is composed by only one therapy and the

auxiliary works can use a vehicle in order to deliver the therapies in only 3 minutes. The γ factor concerns the methods of arrival of the patients in the morning: level 1 is the current situation and foresees a random arrival as previously explained. Level 2, on the other hand, provides a calendar of appointments and, then, an arrival time is previously communicated to the patients. The δ factor concerns the priority rules for assigning precedence for the arrival of patients to the oncology department. The priority is assigned according to the expected duration of the chemotherapeutic treatment of each patient. Level 1, *i.e.*, Long Processing Time rule (LPT), gives priority to patients with longer durations, while level 2, *i.e.*, Short Processing Time rule (SPT), gives priority to patients with shorter durations. Level 3 represents the current situation that gives priority to patients with longer durations with some exceptions. The last factor ε concerns the number of chairs available for the treatment. Currently the oncology department dispose of 14 chairs, level 1, but, as reported by the level 2, in according to the layout of the department, an increase to 17 chairs is possible. In total, we have evaluated 72 possible scenarios and, therefore, 72 different FDVSMs. In order to evaluate the effect of the factors and define the best FDVSM, an Analysis of Variance (ANOVA) was carried out. For each scenario, 1000 simulations were performed. Each simulation corresponds to a working day as the oncology department carries out the day-hospital service. At the end of each day, based on the DVSM, it is possible to calculate the mean flowtime. The performances of the scenario is evaluated considering the average of the mean flowtime of all 1000 simulations. The simulation of each scenario was replicated five times. Then, $72 \cdot 1000 \cdot 5 = 360000$ simulations were launched.

Notation	Factors	Level 1	Level 2	Level 3
α	Pharmacy starting time	At 08:30 AM	At 09:30 AM	-
ß	Pharmacy process	Actual	Batch prefixed	Lean
γ	Patient's arrival management	Actual	Appointments	-
δ	Scheduling rules	LPT	SPT	Actual
ε	Number of chairs	14	17	-

Table 4.3 Design of Experiments

4.4.2 Analysis of variance

In order to identify the impact of the proposed factor an ANOVA analysis at 95% level and a statistical analysis was executed through Minitab®17. The impact of each factor proposed in the DOE is reported in the ANOVA table, Figure 4.4. The Figure 4.5 reports the main effect plots and the Figure 4.6 the interactions plots. Interestingly, the ANOVA table points out that the value of the R-squared is higher than the 95%. The R-squared is a statistical measure that represents the percentage of the response variables variation. When the value of R-squared is higher, it means that the model fits the data. In this case, the value of R-squared allows us to state the robustness of the proposed model. Moreover, the ANOVA table reports the p-value of all the factors. All the p-values are equal to zero and, then, all the factors significantly impact on the mean flowtime. Instead, the F-value enables to identify the factors with the higher influence. The factors α and β report the highest F-value, respectively equal to 2204972.83 and 177358.97. With the main effect plots we have established the levels that enables the oncology department to achieve the best performance and, then, to define the best FDVSM. The level 1 of α and the level 3 of β significantly decrease the mean flowtime. It highlights the importance of the synchronization between the oncology department and pharmacy. The level 2 of γ points out the benefits to implement an appointment system to lead the time arrivals of the patients, while the SPT rules, *i.e.*, the level 2 of δ, reduces the mean flowtime of the patients. Finally, an increase of number of chairs also improves the performances of the system. Then, the best FDVSM is defined as follow: level 1 of α, level 3 of β, level 2 of γ, level 2 of δ, level 2 of ε. As regards with the interactions, each of them is influent (p-values = 0) but no interesting trends were highlighted by the interaction plots.

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	71	477452	6725	37515.18	0.000
Linear	7	473199	67600	377121.23	0.000
α	1	395246	395246	2204972.83	0.000
β	2	63584	31792	177358.97	0.000
γ	1	6733	6733	37559.57	0.000
δ	2	5767	2883	16086.01	0.000
ε	1	1869	1869	10426.24	0.000
2-Way Interactions	19	3580	188	1051.10	0.000
α*β	2	128	64	358.41	0.000
α*γ	1	262	262	1459.34	0.000
α*δ	2	521	261	1453.61	0.000
α*ε	1	60	60	335.94	0.000
β*γ	2	60	30	168.72	0.000
β*δ	4	161	40	224.48	0.000
β*ε	2	37	19	103.89	0.000
γ*δ	2	403	202	1124.31	0.000
γ*ε	1	8	8	43.27	0.000
δ*ε	2	1939	969	5408.26	0.000

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.423382	99.99%	99.99%	99.98%

Figure 4.4 ANOVA table

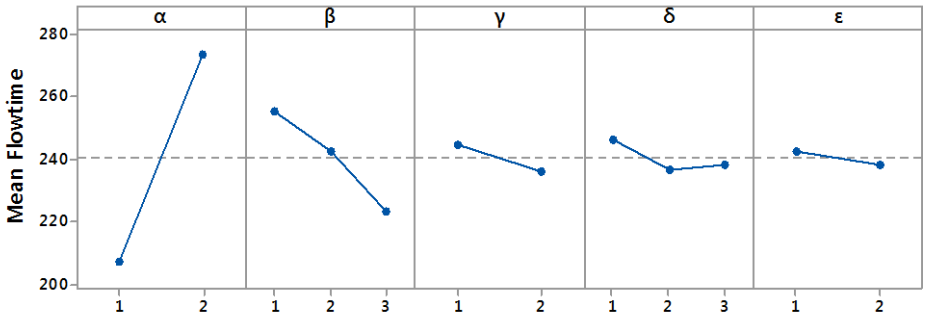


Figure 4.5 Main effect plots

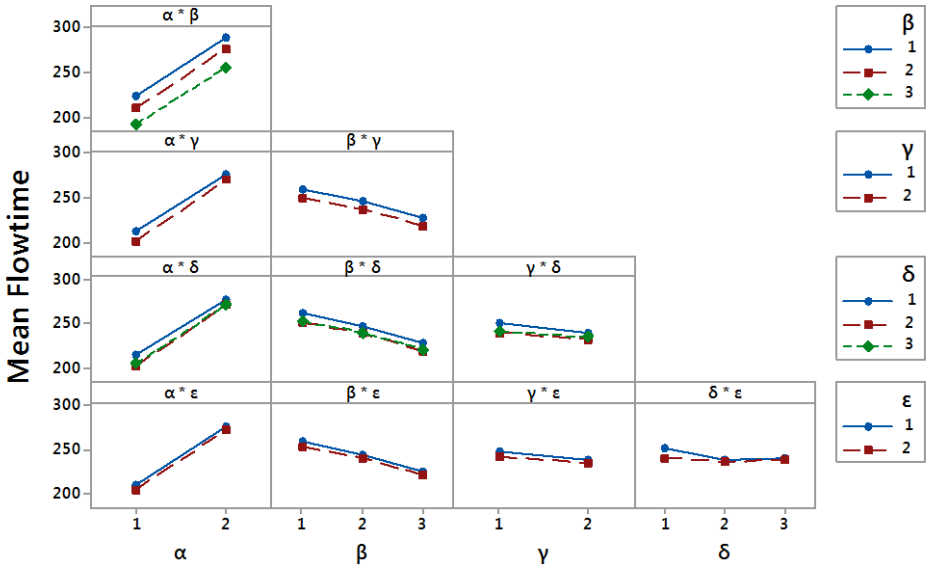


Figure 4.6 Interactions plots

4.4.3 Future Dynamic Value Stream Map

With the support of the ANOVA analysis, the best FDVSM is constructed. It is the value map that reports all the changes necessary to improve the performances of the oncology department. Table 4.4 compares the performance of the CDVSM with the FDVSM. In the first part, the table reports the levels of the factors that define the two DVSMs, while in the second part the performances are represented. The improvement in terms of reducing waiting time and the difference of the efficiency are highlighted. Through the implementation of the best FDVSM, the average patient waiting time will decrease by 112 minutes, *i.e.*, almost 2 hours. This result can be obtained only reducing the non-value times with a better configuration of the system. Interestingly, the proposed approach allows improving the efficiency from 41.56% to 67.72%. Finally, Figure 4.7 depicts the selected FDVSM. Differently from the CDVSM, the therapy delivery process is different. Indeed, the icons between the pharmacy stage and the treatment stage represent the delivery of therapies when it is ready and the vehicle that supports the auxiliary worker, reducing the transportation time from 20 minutes to 3 minutes. Moreover, the preparation of the therapies at pharmacy starts at 08:30 AM, the number of available chairs is equal to 17, the priority rules used for the arrival times of the patients is the SPT and the arrival times of the patients are managed with a schedule. Considering the high-

value of the R-squared reported by the ANOVA table and the normal probability plots of the residuals considering the mean flowtime as response of the model (see Figure 4.8), a multiple non-linear regression model with categorical predictors and interactions of the second order (see Eq. 4.5) was developed:

$$\overline{F}=242.69+57.38\cdot\alpha -17.63\cdot\beta -21.62\cdot\gamma -18.11\cdot\delta -17.83\cdot\varepsilon -1.078\cdot\alpha\cdot\beta +3.410\cdot\alpha\cdot\gamma+ +1.738\cdot\alpha\cdot\delta\ 1.636\cdot\alpha\cdot\varepsilon +0.951\cdot\beta\cdot\gamma +0.529\cdot\beta\cdot\delta +0.395\cdot\beta\cdot\varepsilon+2.537\cdot\gamma\cdot\delta+ +0.587\cdot\gamma\cdot\varepsilon +4.576\cdot\delta\cdot\varepsilon \quad (4.5)$$

The model allows forecasting the mean flowtime each of the 72 different FDVSMs and supports the healthcare managers in order to improve the process.

The multiple non-linear regression model was validated by comparing the performance of the regression model with 10 DVSMs. These are composed by the CDVSM, the best FDVSM and 8 FDVSMs randomly chosen. Table 4.5 reports the comparison. The values of the deviation are always less than a few percentage points, and, confirms the effectiveness of the proposed approach. Moreover, the table highlights the average error that is equal to 1.22% and then we can state that the regression model is effective for the real case study under investigation.

DVSM	**Factors**					**KPIs**			
	α	β	γ	δ	ε	$\overline{F}$ [min]	$\overline{NVT}$ [min]	$\overline{VT}$ [min]	Eff [%]
CDVSM	2	1	1	3	1	291.40	170.30	121.10	41.56
FDVSM	1	3	2	2	2	178.83	57.74	121.10	67.72
			Improvement			**112.57 min**			**26.16**

Table 4.4 Improvement with the Future Dynamic Value Stream Map

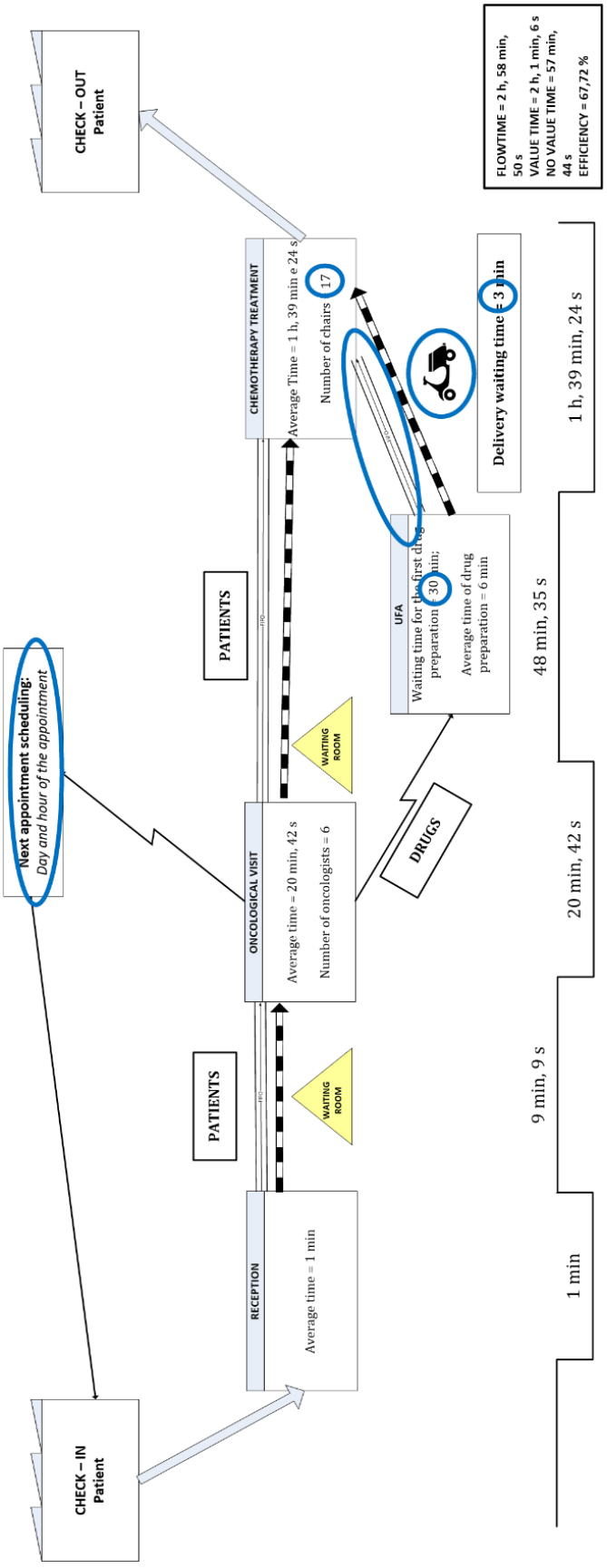


Figure 4.7 The best Future Dynamic Value Stream Map

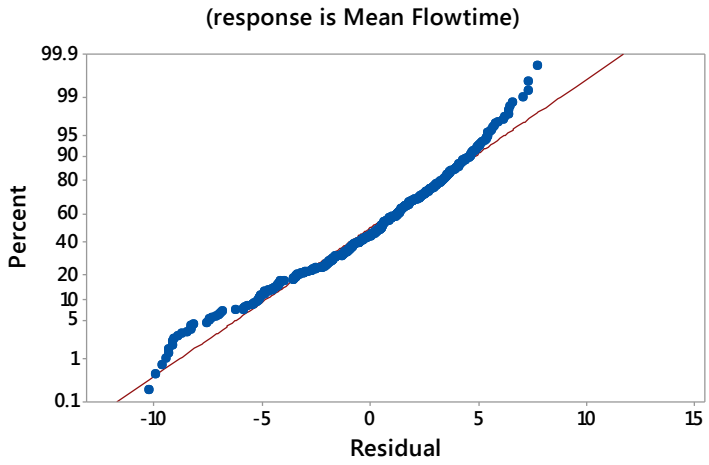


Figure 4.8 Normal Probability Plot of the residuals

Scenarios	**Factors**					**Mean Flowtime**		**Error**
	α	β	γ	δ	ε	DVSM [min]	Regression [min]	[%]
1	2	1	1	3	1	291.40	289.26	0.73
2	1	3	2	2	2	178.83	184.44	3.14
3	2	2	1	1	2	287.91	276.73	0.78
4	1	1	2	3	1	215.46	213.64	0.84
5	2	3	2	3	2	249.91	253.34	1.37
6	1	2	2	1	1	213.83	210.14	1.73
7	2	1	2	3	2	282.5	284.35	0.65
8	1	3	1	1	1	211.69	206.5	2.45
9	2	3	1	3	1	256.47	255.48	0.35
10	1	2	1	2	2	209.85	209.46	0.19
							Average	**1.22**

Table 4.5 Validation of the regression model

4.5 Managerial implications

Once completed the process of improvement and identified the actions for changing the process, the results were reported with the managers of the oncology department detailing the optimization approach and the future performances of the ward with the Lean actions. Moreover, according to the Lean Methodology, the whole proposal can be applied with minimal costs. The healthcare managers approved and decided to perform some improvement actions tests, considering the interactions between oncology department and pharmacy, before changing the system in accordance with the FDVSM. The ANOVA analysis has demonstrated that the lack of synchronization between the two departments negatively affects the outcomes of the whole system. Then, the working hour of the pharmacy technicians is changed for the tests in order to allow to setup the pharmacy workstations and start to prepare the therapies at 08:30 AM. Moreover, the auxiliary workers were supported by vehicles to reduce treatment delivery times. When these actions will become definitive part of the oncology department the managers will proceed with the other actions proposed with the FDVSM. The first results confirm the effectiveness of the new configuration.

4.6 Conclusions

In this work, a novel perspective of Lean application on the specific case of the oncology units was studied. The oncology department of a hospital located in Catania (Southern Italy) was studied to find lean improvement solutions. First of all, several audits and interviews with the oncologist to well define the process under investigation was conducted. A mathematical formulation is proposed to complete the description of the problem. Moreover, this formulation has supported the developing of the DES model. A combination of VSM with the stochastic simulation thus generating the DVSM was proposed. To allow this, a four-weeks campaign of collecting data was conducted. The data collected were statistically analysed and stochastic distributions were defined. A part of data, *e.g.*, number of patients, number of oncologists, represent the parameters of the simulation model, while, other data represented by stochastic distribution generate the input data. The use of stochastic model allows to consider the strong variability of this complex system and to reduce the effect of randomness. After the validation of the DES model, the

CDVSM highlighted the actual performances of the oncology department and the sources of patient waiting times. In the actual situation, the mean flowtime is about 5 hours and the efficiency is equal to 41.56%. It means that on average the patients spend more time on waiting than on receiving the health services. A DOE was developed and, then 72 FDVSMs were evaluated. The ANOVA analysis allows to statistically study the impact of all the factors in the system and to identify the best FDVSM. The best FDVSM was reported pointing out that with the Lean actions, the mean flowtime can be reduced by 112 minutes and the efficiency can increase with a value equal to 67.72%. To complete the improvement procedure, we have developed and validated a multiple non-linear regression model with categorical predictors that enables the managers to easily evaluate all the 72 FDVSM. Finally, through meeting with the managers, a gradual implementation procedure of the improvement actions was defined.

5. Patient flow management problem: the case study of Ragusa

5.1 Introduction

While tackling high healthcare costs and restricted budgets, oncology departments have had to face new managerial challenges, which stem from the need to satisfy ever increasing amount of patient demands. Moreover, the oncology process involves diverse resources, both human and none, along with cooperation from pharmacies all of which increases the complexity of the system. To this end, the healthcare community looks for an improvement of service levels, which in turn impacts on the life-quality of patients. Simulation modelling represents a risk-free and low budget method to assess the impact of potential changes on healthcare systems before implementing any intervention (Cassidy et al., 2019). Therefore, simulation modelling appears to be an effective tool to support decision-making policies. In fact, simulation tools were increasingly used in healthcare management, along with other Operational Research/Management Science (OR/MS) methods (as for example the dynamic optimization in the work of Hahn-Goldberg et al., 2014 or the stochastic programming in the work of Demir et al., 2021). Often, computer simulation is employed to virtually evaluate 'what-if' configurations of health departments, so that healthcare managers can assess the impact of potential changes on health systems without implementing them in the real systems (Cassidy et al., 2019; Gunal, 2012; Salleh et al., 2017). In general, computer simulation can be classified as: Discrete Event Simulation (DES), System Dynamics (SD) and Agent-Based Simulation (ABS).

In healthcare environments, DES is widely used for modelling and optimizing hospital workflows and other processes. DES methodology deals with real systems which have a strong queue structure that can be modelled in discrete periods, where the process can be described stochastically. According to this approach, variables and states change after a set of events happen at discrete time points and entities are simply data objects influencing system decision processes. Patients are represented by 'entities' that go through different processes of the system. In the healthcare context, Abo-Hamad and Arisha (2014) and Demir et al. (2017) merged the DES model with typical decision support tools (*e.g.*, balanced scorecard) in an emergency

department, while Luo et al. (2018) applied DES in a radiology department to study how to reserve capacity for emergency and non-emergency patients.

On the other hand, SD technique is typically adopted to model health systems at an aggregate level. Introduced by Forrester (1958), it is based on differential equations and is used to capture the macro-level dynamics of a complex system under study. In this respect, Rashwan et al. (2015) modelled the flow of elderly patients to study the impact of various system parameters on the issue of acute bed blockage in the Irish healthcare system, while Edaibat et al. (2017) used SD simulations to assess the impact of health information exchange (HIE) adoption policies in hospitals located in the State of Maryland.

Finally, a considerable attention has being focused on ABS modelling in the OR context (Abar et al., 2017; Siebers et al., 2010) and for health systems as well (Cassidy et al. 2019; Gunal, 2012; Sulis et al., 2020). ABS modelling allows users to write specific instructions that control the actions and interactions of autonomous agents, in order to handle the behaviour of a complex system (Gunal, 2012; Mustafee et al., 2010). In healthcare contexts, persons (*e.g.*, patients, doctors) can be represented by agents with an individual behaviour, but it is also possible to model rescue service vehicles and other resources using agents (Djanatliev and German, 2013). Several contributions reveal that ABS modelling is used to enhance the performance of healthcare departments, as follows. Yousefi and Ferreira (2017) combined ABS with decision-making techniques to re-allocate resources in an emergency department. Fragapane et al. (2019) developed an ABS model to enhance internal hospital logistics by examining the status of the goods' delivery system and evaluating potential improvements. Saeedian et al. (2019) and Ajmi et al. (2019) used the ABS approach to reduce indicators related to patients' pathways, such as total waiting time or length of stay, in surgery and emergency departments, respectively. As far as oncology departments are concerned, Sepúlveda et al. (1999) and Baesler and Sepúlveda (2001) can be considered the pioneers of decision-making through simulation in oncology units. Nowadays, these studies still represent a source of inspiration for researchers that aim to investigate the patient flow in oncology departments.

Inspired by the studies performed on a real-life oncology unit located in Ragusa (Southern Italy), the work proposed in this chapter presents a novel computer simulation model, which is configurable and adaptable to the needs of oncology

departments cooperating with a pharmacy far from the oncology unit. To the best of our knowledge, the work proposed in this chapter is the first in which an agent-based simulation model was developed so as to investigate oncology chemotherapy departments where agents reproduce patients, doctors, nurses and auxiliary resources (see Section 2.3.4 for the state of art in the patient flow management problem). Although, several agent-based packages are available both in the market and in the web, we deployed Netlogo® modelling software as it is considered a user-friendly tool that makes it possible for anyone to simulate any complex physical system (Cabrera et al., 2012; Chiacchio et al., 2014; Liu et al., 2017; Saeedian et al., 2019; Sulis et al. 2020; Taboada et al., 2011, 2012; Yousefi & Ferreira, 2017).

The presented model was designed to allow healthcare managers to recreate their oncology unit in a virtual environment and to easily test new configurations of the oncology process with the goal of reducing patient waiting time. The effectiveness of the proposed simulation model was verified through a case study of the oncology unit located in Ragusa. It is worth noting that, unlike similar configurations described in the literature, our model also considers the case in which the pharmacy unit is detached from the oncology department and, therefore, therapies are gathered in batches by pharmacy technicians and delivered through a courier. Once the proposed simulation model was validated, it was used to compare several 'what-if' configurations to identify better ward configurations that minimize the patient waiting times. The configurability and the free availability of the Netlogo® agent-based framework as well as the validation based on a real-life case study all represent the strengths of the proposed research. As follows, this work provides several contributions to the scientific community.

i) It represents the first attempt to use an agent-based simulation model to investigate outpatient flow in a multi-stage oncology department where the pharmacy is detached from the ward itself;
ii) It provides a configurable and adaptable tool that easily can be used by stakeholders for investigating alternative ward configurations and for optimizing the service level as well;
iii) A real-life situation is presented with the aim of testing and validating the effectiveness of the proposed approach;

iv) A series of findings arising from an ANOVA analysis allows the readers to assess how some organizational aspects may affect the performance of oncology departments.

The work is organized as follows. The proposed simulation model is introduced and described in detail. Then, the application to the case study is presented and the model is validated by comparing the behaviour of the real oncology unit and the simulated one. Finally, a Design Of Experiments (DOE) was carried out with the aim of identifying more effective configurations of the oncology unit under investigation. The best configuration in terms of patient waiting time reduction was identified and the managerial implications resulting from the present study were further discussed. Finally, the conclusions were summarized.

5.2 The agent-based simulation model

The proposed simulation model refers to the problem described in Chapter 3. A healthcare setting can be seen as a complex system and the computer simulation represents a valued tool to support the decision-making since it allows users to identify the factors that influence the patient waiting time and possible bottlenecks in the systems under investigation. Figure 5.1 represents the graphical visualization of the proposed simulation model developed in the agent-based Netlogo® environment (Wilensky, 1999), including a key depicting the model agents. The main features are described in the next sections.

5.2.1 Layout of the model

A general layout of the model was defined to emulate the patient flow in the oncology departments. Considering that the patient waiting time does not depend on the location of the rooms in the ward, there is no need to import the exact layout of an oncology unit in the simulation model. To this end, two main assumptions can be considered in the model: *i*) the layout of the model is qualitative; *ii*) the time needed for each patient to reallocate from one room to another is negligible. The layout of the model includes the following main rooms:

- The welcome room, where the patient meets the nurse at reception for the registration;
- The first waiting room, where the patient waits for the medical consultation;

- The oncologist room, where the patient meets the oncologist for the medical examination;
- The nurse room, where the courier delivers the batches of therapies;
- The second waiting room, where the patient waits for the treatment;
- The treatment room, where the patient undergoes the treatment monitored by the nurses.

The object located in the top-right corner of the simulation framework is the pharmacy. Finally, the simulation time clock, of which the time unit is the second, is visible on the top-right side of the agent-based simulation model.

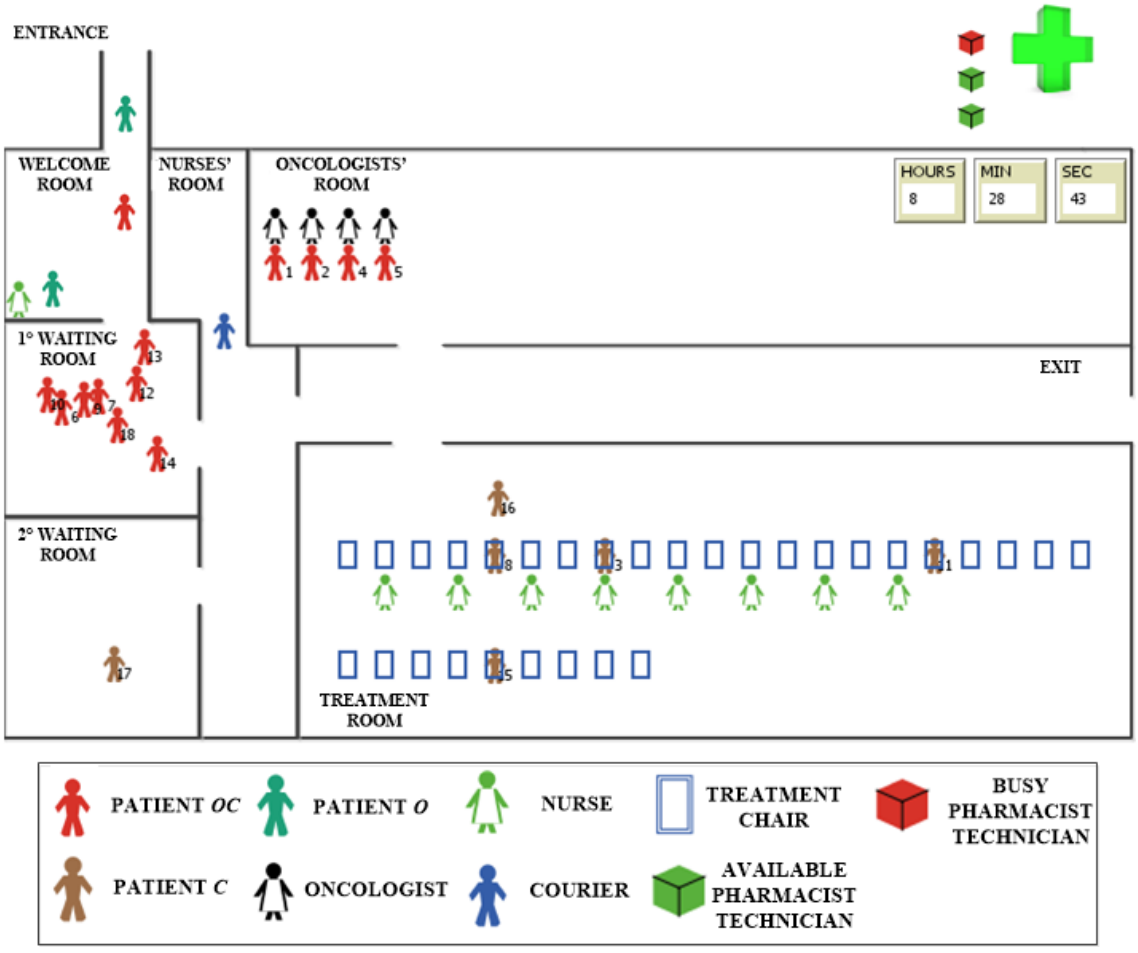


Figure 5.1 Agent-based framework of the simulation model

5.2.2 Modelling agents

Each simulation run represents a single day in the oncology unit, which starts at 08:00 AM and ends when all the treatments are concluded, which is exactly the same thing that happens in a real-life scenario. Patients and human resources are represented by two types of agents: moving agents, *i.e.*, agents that move freely within the system or fixed agents that occupy a specific location. Specifically, the patients and the courier act as moving agents, while the other resources play as fixed agents. For each simulation run, every patient agent is created in accordance with a vector of patient arrival times, defined as *arrival_time_list*. The patient p can move through the rooms previously described, following a path that depends on his/her classification, indicated by the agent's colour. Red agents are the standard patients *POC*, the brown ones are the repetitive patients *PC* and the green ones are the control patients *PO*. Each patient may interact with four types of resources: a nurse at reception, the oncologist for the medical consultation, the chair and the nurse for the treatment. According to the problem formulation in Chapter 3, patients *POC* follow the whole therapy pathway, patients *PO* are discharged after the medical consultation and patients *PC* are allowed to skip the medical consultation. All the patients start the medical consultation or the treatment based on the status of the resources involved in the related processes, which can be denoted as 'busy' or 'available'. In the case of the medical consultation, a patient p_k is allowed to enter his/her oncologist's room o_j (p_k) only if the latter is available. The First In First Out (FIFO) policy is adopted to decide the order of patients for the oncologist visit. Finally, a patient of the *POC* or *PC* group goes to the treatment room if at least one chair c and one nurse n are 'available' and the courier has delivered the therapy as well. As described in the model description (see Section 3.1), the nurse can setup only one patient at a time and can simultaneously monitor up to N_{max} persons. In this regard, the nurse's agent is characterized by a *setup_status* and a *monitor_status* that can be 'busy' or 'available'. In fact, a patient starts the treatment if both *setup_status* and *monitor_status* of a nurse are simultaneously 'available'. A vector called *monitoring_patient_list* is created to record the patients monitored by the nurse. If the length of *monitoring_patient_list* is lower than provided limit, *i.e.*, N_{max}, then the *monitor_status* is 'available'. With respect to pharmacy resources, each pharmacy technician, which is handled as a fixed agent, can prepare only one

therapy at a time and pre-emption is not allowed. In Figure 5.1, the pharmacy technicians are represented by three boxes, whose colour indicates when each of them is available/unavailable (i.e., green/red) to prepare therapies. The behaviour of agents related to the pharmacy strictly depends on the specific list of therapy requests coming from the oncologists, named *request_list*. If the list is empty, the agents are 'available' and the related box of the simulation framework becomes green. Otherwise, the agents status returns to 'busy' and the box are coloured to red. In this case, the therapy being prepared is registered in a vector called *wip_list*. When the preparation of a therapy is completed, another vector named *ready_list* is updated with the information of the therapies, which need to be delivered. Once the length of the *ready_list* equals the provided batch size, the courier picks up the ready batch and deliver it from the pharmacy to the oncology department. At this point, a new vector denoted as *delivery_list* contains the information of the therapies that are being transported by the courier. Simultaneously, these therapies are removed from the *ready_list* and a new batch size is defined for the next therapies to be prepared and delivered. As mentioned earlier, the courier for delivering the therapies is configured as a moving agent and is depicted in blue in Figure 5.1. It is assumed that the courier is exclusively engaged only to carry the therapy batches to the oncology department. The proposed simulation model also handles the round-trip of the courier from the oncology unit to the pharmacy. The courier delivery time TD_b is an input variable, which must be set by the analyst. Interestingly, if TD_b is set to zero, an in-house pharmacy could be modelled. When the courier arrives to the oncology department, a specific *therapy_flag* becomes 'true' to indicate that the patient's treatment may start.

5.2.3 Communication between agents

The simulation model is characterized by multiple interactions between agents. When communication exists between agents, one agent sends an input to another agent, causing an output, i.e., a certain behaviour of the latter agent. The model includes three types of communication (Yousefi & Ferreira, 2017): *i*) one-to-one; *ii*) one-to-n; *iii*) one-to-location. One-to-one communication happens when a single agent interacts with another agent, as in the case of the interaction between a patient and an oncologist. In this case, the arrival of the patient in the oncologist's room (input) makes the status of the oncologist 'busy' (output). One-to-n

communication occurs when a single agent communicates with a group of agents (for example, the communication between the courier arriving in the department and the group of nurses to notify that the batch of therapies was delivered). Finally, one-to-location communication exists when an agent communicates with agents in a different location, such as when an oncologist communicates with the pharmacy technicians in the pharmacy in order to request the preparation of the patient's treatment. Table 5.1 shows the kinds of communications involved in the simulation model for oncology units.

Input agent	**Output agent**	**Type of communication**	**Description**
Nurse at reception	Patient	One-to-n	The nurse at reception registers patients according to a FIFO rule.
Oncologist	Patient	One-to-n	Each oncologist receives a patient on the basis of the FIFO rule.
Patient	Oncologist	One-to-one	The arrival of the patient in the oncologist's room makes the assigned oncologist busy.
Oncologist	Pharmacy	One-to-location	The oncologist sends a request for a new treatment preparation to the pharmacy.
Pharmacy technician	Courier	One-to-one	A pharmacy technician notifies the courier that the batch is ready to be delivered.
Courier	Nurse	One-to-n	The courier arrives at the department and notifies the group of nurses that the therapies were delivered.
Nurse	Patient	One-to-n	Nurses allow patients to start the treatment once the therapy is at the ward and a chair is available. Again, the first patient arrived at the waiting room is the first served.
Patient	Nurse	One-to-one	The arrival of the patient in the treatment's room makes the nurse busy.

Table 5.1 Communication between agents in the proposed simulation model

5.3 Case study

The proposed simulation model was applied to improve the quality of services provided by a real-world oncology unit located in Ragusa (Southern Italy). The goal of the project is to analyse the performance of the oncology unit in its current configuration and, subsequently, to find new configurations capable of reducing the patient waiting times. The preliminary phases of the project were the following. First, briefings with the clinic's employees were held to define: *i*) the features of the oncology unit; *ii*) the key performance indicators. Over a three-week period, the project team, which includes clinicians, members of the oncology department and developers of the simulation model, performed an intense time study on the tasks related to the different oncology processes described earlier. Once the data had been collected, a statistical analysis was performed with the aim of finding the stochastic distributions of the main input variables of the simulation model.

5.3.1 Key Performance Indicators (KPIs)

It is well known that cancer diseases dramatically affect the physical and emotional status of suffering individuals. In this context, reducing the patient waiting time is the main objective so as to enhance the quality of cancer treatment within facilities (Gesell and Gregory, 2004), which is recognized as the primary source of patient dissatisfaction (Aboumatar et al., 2008; Edwards et al., 2017; Gourdji et al., 2003). In light of the previous considerations, in this work the total flowtime F (*i.e.*, the sum of the length of stay of patients) was adopted as a key performance indicator (KPI). The total flowtime consists of the total time a patient spends in the oncology unit, *i.e.*, the time interval ranging from the time he/she is registered at reception to the end of the chemotherapy treatment. Particularly, the mean flow time, from now on denoted as $\overline{F}$, was selected to measure the performance of any ward configuration in the successive analyses (see Section 4.3). Furthermore, two additional indicators were engaged to compare the status-quo of the oncology department with the simulated configurations, namely the mean patient waiting time $\overline{WT}$, which corresponds to the Non-Value Time in the lean philosophy, and the system efficiency *Eff*.

5.3.2 Data collection and statistical distributions

A time study covering three working weeks was carried out to collect the experimental data related to the ward status-quo. During that period, the healthcare unit, which consisted of 3 oncologists, 13 chairs, 1 nurse at reception and 3 nurses for the treatment, received 28 patients on average per day. Four patients who are receiving treatment simultaneously are monitored by one nurse. A single pharmacy technician working in an external pharmacy is dedicated to the preparation of the oncology therapies. A single auxiliary courier is employed to deliver the therapy batches from the pharmacy to the oncology department. Table 5.2 reports model parameters and stochastic distributions obtained by analysing the aforementioned status-quo related data. The number of patients per day is derived from a normal distribution with mean 28.07 and standard deviation 3.94. As stated above, usually these patients undergo two different processing stages: medical consultation and chemotherapy administration, which starts after the therapy delivery. Among the patients, 22.32% needs only the medical consultation (*PO*), while 6.18% attend only the chemotherapy's administration monitored by the nurse (*PC*), while the remaining 71.50% are classified as standard patients (*POC*). The experimental analysis revealed that the arrival times for each type of patient can be handled by considering five time windows, each one related to a different occurrence probability. Therefore, once the time interval is selected, every patient arrival time is drawn from an uniform distribution U[0, 59] in minutes. For *PO* and *POC*, the oncologist is assigned to the patient by using a random criterion as soon as the patient agent is created. The duration of the medical consultation is derived from a uniform distribution U[5,35], in minutes. This uniform distribution is adopted for both patients *POC* and *PO*. The order of patients for the medical consultation is decided by using the FIFO policy. Regarding the therapy's preparation, they can be classified into three typologies based on preparation time (short, medium and long); they are delivered in batch sizes, which may vary between 2 and 12 therapies, depending on courier availability and on pharmacy workload. A batch might contain any type of therapy, while the batch size may vary at every courier pick up. The courier takes 10 minutes to deliver the therapies to the ward and another 10 minutes to return to pharmacy. However, a 26.53% probability of delay due to traffic congestion may happen in both directions. Finally, the experimental studies conducted on the ward

showed that the treatments can be classified into five types, each one involving a different time duration. Notably, each treatment can be executed according to a specific occurrence probability and its duration implies the setup time. It is assumed that there is no relationship between the treatment duration and the therapy's preparation time. The time needed by a nurse to release a patient after the treatment can be considered negligible (Hesaraki et al., 2019).

Descriptors of process	Values or probability distribution
Patients	
Number of patients	N(28.07,3.94)
Classification of patient	
Standard patient	71.50%
Repetitive patient	6.18%
Control patient	22.32%
Arrival time	
08:30-09:30	56.58%
09:31-10:30	12.54%
10:31-11:30	5.81%
11:31-12:30	13.76%
12:31-13:30	11.31%
Registration	
Number of nurses at reception	1
Duration (min) of registration	1
Medical consultation	
Number of oncologists	3
Duration (min) of medical consultation	U(5,35)
Assignment of patient-oncologist	Random
Therapy preparation process	
Number of pharmacy technician	1
Duration (min) of therapy's preparation	
Short preparation	U(1,5)
Medium preparation	U(6,10)
Long preparation	U(11,27)
Probability of typology of therapy's preparation	
Short preparation	71.38%
Medium preparation	20.34%
Long preparation	8.28%
Therapy delivery	
Number of couriers	1
Batch size	U(2,12)
Duration (min) of delivery	
Delivery without delay	10
Delivery with delay	10 + U(2,10)
Probability of delay in delivery	
Delivery without delay	73.47%
Delivery with delay	26.53%
Treatment administration	
Number of chairs	13
Number of nurses	3
Treatment duration (min)	
Type 1	U(15,60)
Type 2	U(61,120)
Type 3	U(121,180)
Type 4	U(181,240)
Type 5	U(241,300)
Probability of treatment occurrence	
Type 1	30.13%
Type 2	38.91%
Type 3	14.23%
Type 4	12.13%
Type 5	4.60%

Table 5.2 Model descriptors

5.4 Experimental results

The verification and validation processes were the first step of the project development. This was done to verify if the simulation model was consistent with the problem description and if the outcomes of the simulations reproduced the status quo of a typical day in the oncology unit. Then, a DOE was arranged so as to use the validated simulation model for testing different ward configurations and improving the performance of the unit. In light of the multitude of stochastic parameters, a stochastic simulation approach was adopted for all the numerical investigations to assure the robustness of the proposed analysis. Therefore, each KPI was evaluated in terms of its expected value as in Eq. 5.1:

$$E(KPI) = \frac{\sum_{\omega=1}^{\Omega} KPI(\omega)}{\Omega} \tag{5.1}$$

where ω is the replicate of a certain ward configuration and Ω is the whole set of replicates.

5.4.1 Verification and validation of the simulation model

A preliminary step of any simulation model consists in demonstrating that it provides credible results (Balci, 2003; Roza et al., 2013). To this end, Verification and Validation (V&V) techniques are generally carried out to assure the effectiveness of a simulation model (Kleijnen, 1995). Specifically, the verification process assures that the conceptual model of the problem was transformed into a computer simulation model with sufficient accuracy (Robinson, 1997). The well-structured debug tool of NetLogo® and its model visualization were used to perform a dynamic verification test of the simulation model, which is widely used in literature (Sargent, 2013). Validation is necessary to demonstrate the efficacy of the model in reproducing the actual performance of the system under investigation with a satisfactory approximation. Sargent (2013) classified several validation techniques that can be applied to a given simulation model. In this work we adopted the 'Historical data validation' technique, which compares the key performance indicators obtained by the presented simulation model with one obtained by analysing the status-quo related configuration, as shown in Table 5.3. Looking at the numerical outcomes, the actual performance of the oncology unit in terms of the aforementioned KPIs are as follows:

- the mean flowtime $\overline{F}$ is equal to 265.46 minutes, with a 95% confidence intervals (CI) equal to [243.00; 287.92];
- the mean patient waiting time $\overline{WT}$ is equal to 138.28 minutes, with a 95% CI equal to [123.14; 153.42];
- the efficiency *Eff* is equal to 47.97%, with a 95% CI equal to [45.41%; 50.53%];

For both the real and the simulation configurations, Table 5.3 reports the expected KPIs, the confidence intervals at 95% and the percentage deviation (*Dev*). *Dev* is calculated in Eq.5.2 as follows:

$$Dev = \left| \frac{E(KPI_{sim}) - KPI_{real}}{KPI_{real}} \cdot 100 \right| \tag{5.2}$$

where $E(KPI_{sim})$ is the expected KPI resulting from the simulation model, while KPI_{real} is the KPI's value of the status-quo of the oncology unit. Interestingly, the percentage deviation values (*Dev*) reported in Table 5.3 confirm the validity of the developed simulative procedure. To further strengthen this outcome, the last column of the table reports the *p*-values resulting from the paired t-tests carried out for each KPI. The paired t-tests are used in order to assess if there exists any statistically significant difference between the means of the real and simulated configurations; p-values greater than 0.05 for each test pointed out the effectiveness of the proposed simulation model in simulating the dynamics of the oncology unit under investigation.

KPIs	**Real**	**95% CI**	**Simulated (E(KPI))**	**95% CI**	***Dev***	**p-value**
Mean Flowtime	265.46	(243.00;287.92)	259.50	(242.30;276.70)	2.25%	0.684
Mean Waiting Time	138.28	(123.14;153.42)	133.99	(116.54;151.44)	3.10%	0.730
Efficiency	47.91%	(45.41;50.53)	48.84%	(45.21;52.47)	1.94%	0.742

Table 5.3 Validation of the simulation model with historical data (results from 15 working days of measurements)

5.4.2 Design of Experiments (DOE)

In order to explore alternative configurations of the oncology department, a full-factorial DOE was developed. DOE is a statistical method which enables the identification of the impact of a series of experimental factors on a response variable. The influence factors, shown in Table 5.4, were suggested by the medical staff and were taken into consideration since the costs of implementation were low or negligible. Briefly, such factors can be described as follows:

- **The number of couriers (α)**. It refers to the number of couriers employed to deliver the batches of therapies to the oncology unit. Since only one resource is currently available for this task (level A in Table 5.4), the aim is to evaluate how an additional resource (level B) would affect the patient waiting time;
- **The batch size (β)**. The second factor consists of the number of therapies that can be collected in a batch. Currently, the batch size is not fixed and the number of therapies can vary from two to twelve therapies. The objective is to assess if a fixed batch size can enhance the adopted KPIs and, at the same time, to evaluate if a smaller batch size is better than a larger one. To this end, three levels were considered: (A) fixed batch sized with three therapies; (B) fixed batch size with six therapies; (C) variable batch size (i.e., corresponding to the current configuration);
- **The appointment distribution (γ)**. The first level (A) provides three time-windows of one hour and thirty minutes, each one with the same probability of occurrence equal to 33%. Similarly, the second level (B) consists of five time-windows of one hour, each with a probability of 20%. Level C entails the current case according to which patients arrive at the oncology unit conforming to five time-windows characterized by different occurrence probability (see Table 5.2);
- **The daily number of patients (δ)**. The last factor represents the average number of patients for each working day. Currently, every day the department takes care of about 28 patients (level A). The goal is to analyse how the performance changes considering a higher number of patients. To this end, an additional level (B) with 31 individuals is considered, which corresponds to an increase of about 10% of patients per day. It is worth

specifying that both levels refer to the mean of the normal distribution related to the number of patients per day (see Table 5.2) , while the standard deviation is kept constant at 3.94.

Notably, the current configuration of the oncology unit is {A-C-C-A}, considering a one-to-one correspondence with the set of experimental factors {α-β-γ-δ}, respectively. We defined a full-factorial DOE, which involves $3^2 \cdot 2^2 = 36$ different configurations of the oncology unit, in order to study the influence of the experimental factors on the performance of the ward. In addition, to make the statistical analysis robust enough, $\Omega = 5{,}000$ different replicates at varying random seeds, each one simulating a different working day, were executed, thus achieving a number of $5{,}000 \cdot 36 = 180{,}000$ experiments. The DOE was performed by means of five virtual machines installed on a workstation equipped with an INTEL i9-9900 3.6 GHz 10 core CPU, 32Gb DDR4 2,666MHz RAM and Win 10 PRO OS. Since the computational time required to simulate each configuration is equal about to 5 seconds, approximately two days were needed to accomplish the whole DOE. Only the expected mean flowtime $E(\overline{F})$ was used as KPI, since the expected mean waiting time $E(\overline{WT})$ and the expected efficiency $E(Eff)$ are strictly related to the former. However, the KPIs will be used in the next analysis to stress the difference between the best configuration and the status quo.

(*) time intervals with different occurrence probabilities as for the status quo configuration (see Table 5.2).

Factors		**Levels**		
Symbols	Description	A	B	C
α	Number of couriers	1	2	-
β	Batch size	3	6	U(2,12)
γ	Appointment distribution	3	5	5*
δ	Capacity of the department	28	31	-

Table 5.4 Factors/levels involved in the design of experiments

5.4.3 Analisys of results and managerial implications

The analysis of variance (ANOVA) determines if the experimental factors statistically influence the key performance indicators. To this end, an ANOVA analysis at 95% level of confidence was carried out in Minitab® 2017 commercial package to evaluate the statistical significance of each factor. The numerical outputs from the ANOVA (see Table 5.5) show the results concerning the main effects. The plots related to the main effects are reported in Figure 5.2. The 2-way interactions are not reported in the table (but are available upon request) since no relevant findings were detected. Looking at the condensed ANOVA table, it is worth pointing out that the adjusted R-squared, *i.e.*, the adjusted coefficient of determination, is larger than 95%. A higher value of the R-squared demonstrates that the model fits the data of the analysis thus confirming the robustness and the consistency of the proposed approach. With regards to the experimental factors, the p-value below 0.05 implies that they are statistically significant for the expected mean flowtime $E(\bar{F})$ at 95% confidence level. The significance of the influencing factors on the mean flowtime is further exacerbated by related F-values. Indeed, the most important factors are usually identified by an F-value larger than 50 (Yu et al., 2018). The very low F-value associated to factor α reveals that the number of couriers might have a weak effect on the performance of the system, as confirmed by the related main effect plots in Figure 5.2. To this end, a paired t-test at 95% confidence was performed and confirmed that the null hypothesis assuming that the mean difference between the paired samples is zero (*i.e.*, H_0: μ_d=0) can be rejected. In conclusion, the mean flow time is statistically insensitive to factor α. Interestingly, Figure 5.2related to factor β shows that fixing the batch size at the lowest value (level A) would favour the mean flow time reduction, while the current strategy based on a random batch size (level C) negatively biases the mean waiting time of patients. As for γ, rendering the arrival of the patients smoother by introducing new appointment distribution strategies (*e.g.*, levels A and B) makes the service level better than the actual one (level C). In particular, the strategy corresponding to level B reduces patient waiting time by approximately 20 minutes on average. Finally, as for factor δ, an increment in the number of patients (level B) slightly increases the patient waiting time but, on the other hand, it can be adequately compensated by a larger number of patients that can be accepted daily without worsening the current performance of the oncology

unit. Table 5.6 shows the expected mean flowtime $E(\bar{F})$ over the $\Omega = 5{,}000$ simulation replicates, performed for each combination of experimental factors. Notably, the performance of the status quo configuration is illustrated in the first row of the table, while the other configurations were sorted in ascending order of expected mean flowtime. Also, the confidence intervals of the expected mean flowtime for each configuration are reported in the last column. Looking at the table, configuration number 21 indicates the 'best configuration' characterized by factors {B-A-B-A} and an expected mean flowtime $E(\bar{F}_{21})$ equal to 208.53. However, it is worth noting that the status quo configuration is one of the worst in terms of expected mean flowtime, along with the last four configurations in which the β factor always is set to the C level. To sum up, the following managerial implications would arise from the proposed numerical analysis:

(1) On the daily basis, the oncology unit could save 40 minutes of patient waiting time by passing from a random batch size to a fixed batch size with three therapies. This improvement could be realized without investing additional funds;

(2) Focusing on the patients' appointments could also reduce the patient waiting time. A uniform distribution of patients' arrival times through five time-windows of one hour emerges as a valid alternative to enhance the performance of the ward without investing additional funds;

(3) Looking at the best configuration, an increase in the number of patients per day (configuration number 22) would involve a slight increment of expected patient waiting time to about ten minutes on average. However, configuration number 22 remains more successful than the status-quo configuration in terms of patient waiting time;

Since the number of couriers does not influence the expected mean flowtime, there would be no benefit from the addition of new resources dedicated to the therapy delivery.

Finally, Table 5.7 compares the best simulated configuration and the simulated status quo in terms of expected mean flowtime $E(\bar{F})$, expected mean waiting time $E(\overline{WT})$ and expected efficiency $E(Eff)$. Notably, Table 5.7 also report the related 95% confidence intervals (CI) and the percentage deviations (*Dev*). The percentage deviations reveal that the best configuration reduces the expected flowtime $E(\bar{F})$ of

19.85%, the expected mean waiting time $E(\overline{WT})$ of 37.73% and increases the expected efficiency $E(Eff)$ of 24.77%.

Source	DF	F-value	p-value
Model	19	40299.03	0.000
α	1	42.99	0.000
β	2	292158.50	0.000
γ	2	52500.10	0.000
δ	1	73713.83	0.000
			Adjusted R^2 > 95%

Table 5.5 ANOVA table

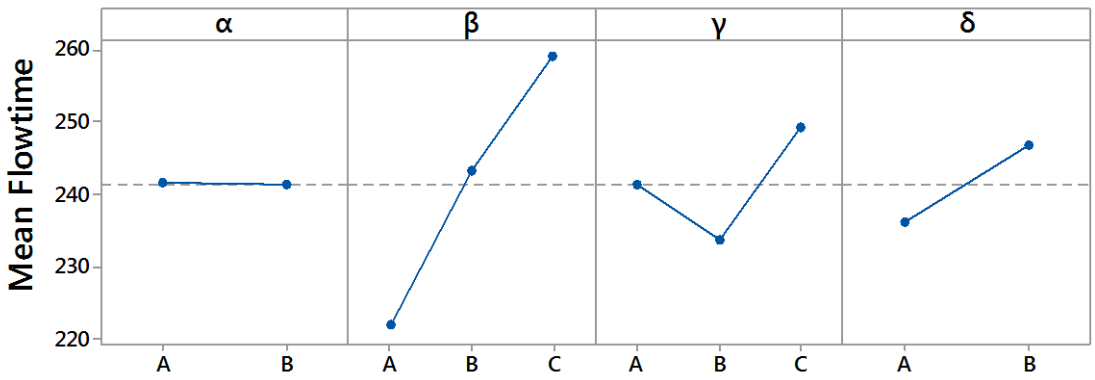


Figure 5.2 Main Effect Plots

Configuration	Factors				$E(\bar{F})$	95% CI
No.	α	β	γ	δ	[minutes]	[minutes]
17 (status-quo)	A	C	C	A	260.17	(259.22;261.12)
21	B	A	B	A	208.53	(207.83;209.23)
3	A	A	B	A	209.05	(208.34;209.75)
19	B	A	A	A	216.07	(215.34;216.80)
1	A	A	A	A	216.61	(215.88;217.34)
22	B	A	B	B	218.16	(217.42;218.91)
4	A	A	B	B	218.71	(217.97;219.46)
23	B	A	C	A	223.29	(222.41;224.17)
5	A	A	C	A	223.81	(222.93;224.69)
20	B	A	A	B	226.71	(225.94;227.48)
2	A	A	A	B	227.27	(226.50;228.04)
27	B	B	B	A	231.02	(230.30;231.74)
9	A	B	B	A	231.13	(230.41;231.84)
24	B	A	C	B	237.48	(236.53;238.43)
6	A	A	C	B	238.05	(237.11;239.00)
25	B	B	A	A	238.34	(237.61;239.08)
7	A	B	A	A	238.46	(237.73;239.20)
28	B	B	B	B	240.09	(239.35;240.83)
10	A	B	B	B	240.2	(239.46;240.94)
29	B	B	C	A	244.69	(243.80;245.58)
11	A	B	C	A	244.78	(243.89;245.67)
33	B	C	B	A	247.5	(246.67;248.33)
15	A	C	B	A	247.64	(246.81;248.47)
26	B	B	A	B	248.45	(247.68;249.22)
8	A	B	A	B	248.56	(247.79;249.34)
31	B	C	A	A	253.99	(253.14;254.84)
13	A	C	A	A	254.13	(253.28;254.98)
34	B	C	B	B	255.93	(255.07;256.78)
16	A	C	B	B	256.05	(255.20;256.91)
30	B	B	C	B	257.66	(256.70;258.62)
12	A	B	C	B	257.76	(256.80;258.72)
35	B	C	C	A	260.17	(259.21;261.12)
32	B	C	A	B	263.63	(262.74;264.52)
14	A	C	A	B	263.76	(262.88;264.65)
36	B	C	C	B	272.56	(271.54;273.59)
18	A	C	C	B	272.69	(271.67;273.71)

Table 5.6 Results of expected mean flowtime from the experimental campaign (5,000 replicates)

KPIs	Simul. status quo	95% CI	Simul. best config.	95% CI	*Dev*
$E(\bar{F})$	260.17 min	(259.22;261.12)	208.53 min	(207.83;209.23)	19.85%
$E(\overline{WT})$	136.87 min	(136.01;137.73)	85.23 min	(84.66;85.80)	37.73%
E(Eff)	47.39%	(47.21;47.57)	59.13%	(58.96;59.30)	24.77%

Table 5.7 Simulation results: status quo Vs best configuration

5.5 Conclusions

In this study, we developed a computer agent-based simulation model explicitly designed to be configurable and adaptable to the needs of oncology departments. The case in which the pharmacy is detached from the oncology unit and, therefore, a courier service to deliver batches of therapies is used is considered. The validity of the proposed model was demonstrated through a statistical analysis based on a set of experimental data obtained by studying an oncology unit located in Ragusa (Southern Italy). Consequently, a series of alternative configurations was tested through a robust simulation campaign based on a full-factorial design of experiments. The results were evaluated through an ANOVA analysis, revealing that a fixed batch size with a low number of therapies and an effective appointment strategy significantly decrease the patient waiting time. The best simulated configuration was selected and compared with the status quo by means of three main key performance indicators. This comparison shows that the expected patient waiting time can be reduced by 37.7% in percentage deviation and the expected ward efficiency can be increased by 24.8%.

6. Chemotherapy outpatient appointment scheduling problem

6.1 Introduction

Oncology outpatients may often receive a series of treatments (*e.g.*, chemotherapy or radiotherapy) for several periods, which in turns require different health services, such as physical and lab exams, therapy preparation and chemotherapy infusion. Despite the complexity and the multitude of tasks to be performed in a chemotherapy ward, reducing the patient waiting time is the leading objective for improving the quality level in the outpatient cancer treatment facilities (Gesell and Gregory, 2004). Scheduling outpatients that have to undergo chemotherapy treatments is a sensitive as much as challenging issue that was capturing the attention of both scholars and stakeholders in the healthcare landscape. In fact, building an effective schedule of patients allows reducing their waiting times on the one hand, and increasing the number of treatments in the working shift on the other hand. To strengthen this thought, the health wards may exploit an appointment scheduling approach to improve the efficiency of their services, thus increasing the patient satisfaction and the service rate as well (Gupta and Denton, 2008).

In brief, the main steps to generate a daily schedule of appointments in an oncology clinic are the following. The oncologists plan the days of treatment for each patient through a specific medium-term care protocol that defines all the necessary information, *e.g.*, date and duration of treatments, type and doses of drugs. Subsequently, the oncology unit communicates to the patients the appointment time for a given day. Since each patient may have a different disease history, thus requiring a different care path, the time she/he needs to receive the oncology treatment, which goes from the medical visit to the end of treatment, can be highly variable and the interaction with the other patients can strongly bias his/her length of stay in the clinic. Hence, an effective method for scheduling the patient appointments may positively impact on the performance of the clinic and on the patient satisfaction as well.

This work is inspired to the health services provided by the oncology units described in Chapter 4 and Chapter 5. A simulation framework based on discrete time recursive equations was adopted for modelling the patient flow in the oncology

clinic. All the steps of the daily oncology process were handled as resource-constrained stages since the number of oncologists, pharmacy technicians and nurses affect the service rate of their respective working areas. In particular, an eligibility constraint among patients and oncologists exists. Since the pharmacy and the oncology department are not located in the same building, the therapies are delivered by batches and, as a result, the delivery time may influence the system dynamics and the performance of the clinic as well. The simulation model works as an evaluative method embedded into a generative optimization technique consisting of a novel self-adaptive harmony search. It is noteworthy to highlight that the Chemotherapy Outpatient Scheduling (COS) problem in oncology clinics is stochastic in nature (Alvarado and Ntaimo, 2018), since some parameters of the problems, such as the deferral probability for each patient or the medical consultation time, are uncertain and cannot be exactly determined in advance. Therefore, a stochastic approach was formulated in order to properly run such sources of uncertainty. In brief, this work pursues a triple objective:

i) introducing a Stochastic Programming (SP) model of a multi-stage oncology ward in which the pharmacy is detached from the oncology department and therapies are delivered by batches;
ii) adopting a stochastic scheduling strategy able to reduce the idle times of patients among the stages;
iii) developing a new metaheuristic algorithm to solve the COS problem for the minimization of the patient waiting time.

To point out the novelty of the proposed work, Table 6.1 aims to retrieve the main literary contributions on the optimization of the COS problem (see also Section 2.3.2) and adopts a series of classification criteria to stress the difference among the different approaches with each other and the proposed study as well. The first two classification criteria refer to the way the medical consultation is run and to the scheduling strategy, respectively. A distinction between deterministic and stochastic approaches (type of model) is also indicated along with the adopted solving method. The objective function is defined as Key Performance Indicator (KPI). The kind of resources explicitly involved in the model can be the following: oncologists for the consultation phase (O), pharmacy technicians for the therapy preparation stage (D)

and nurse at the treatment stage (N). Finally, the last column points out the models able to run the therapy transportation time and the transportation batch as well. Notably, the proposed algorithm, namely a novel Self-Adaptive Harmony Search (SAHS), was compared with both a regular Harmony Search (HS) and a specific Greedy Randomized Adaptive Search Procedure (GRASP) algorithm already used by the literature in the same field of research. Preliminarily, the effectiveness of the aforementioned metaheuristics was properly validated by comparing the obtained solutions with the ones achieved by the SP model, considering a set of very small sized issues. Subsequently, a benchmark of larger-sized instances was generated, and an extended comparison analysis was carried out with the aim of demonstrating the outperformance of the proposed optimization technique over the other competitors.

The rest of the work is organized as follows. The problem statement also including the basic assumptions and the objective function are described in Section 6.2, while the SP model is introduced in Section 6.3. Then, the major components characterizing the proposed self-adaptive harmony search are dealt with in Section 6.4. Section 6.5 explains as the numerical experiments were handled. For a fair comparison analysis involving other metaheuristics two stopping criteria were calibrated on the basis of a proper analysis of convergence, as reported in Section 6.6. The output from the comparison analysis are discussed in Section 6.7. Finally, conclusions are in Section 6.8.

Reference	Medical consultation	Scheduling strategy	Type of model	Solving method	KPI	Limited resources			Therapy transp.
						O	D	N	
Alvarado and Ntaimo (2018)	Next-day	Off-line	S	SP	WT, WL			✓	
Bouras et al. (2017)	Same-day	Off-line	D	MP	WT	✓	✓	✓	
Castaing et al. (2016)	Next-day	Off-line	S	SP, HE	WT, TCT			✓	
Condotta nad Shakhlevich	Next-day	Off-line	D	MP, T	WT, WL			✓	
Demir et al. (2021)	Same-day	Off-line	S	SP, HE	WT, CU,			✓	
Dobish (2003)	Next-day	Off-line	D	T	WT, WL			✓	
Edwards et al. (2017)	Next-day	Off-line	D	T	CU, P			✓	
Garaix et al. (2020)	Same-day	Off-line	S	SP, GRASP	M	✓		✓	
Hahn-Goldberg et al. (2014)	Next-day	On-line	D	CP, DT	M		✓	✓	
Hesaraki et al. (2019)	Same-day	On-line	D	MP, DT	FW, M			✓	
Heshmat et al. (2017)	Next-day	Off-line	D	MP, CL	TCT			✓	
Heshmat et al. (2018)	Next-day	Off-line	D	MP, CL	TCT			✓	
Huang et al. (2019)	Same-day	Off-line	D	CP, T	WL			✓	
Huggins and Claudio (2019)	Next-day	Off-line	D	MP	P		✓	✓	
Liang and Turkcan (2016)	Same-day	Off-line	D	MP	WT, WL,			✓	
Liang et al. (2015)	Same-day	Off-line	D	MP	WL	✓		✓	
Mandelbaum et al. (2020)	Same-day	Off-line	S	IR	WT, OT				
Sadki et al (2011)	Same-day	Off-line	D	LR	WT, M	✓			
Sevinc et al. (2013)	Next-day	On-line	D	HE	CU				
Turkcan et al. (2012)	Same-day	Off-line	D	MP	TCT			✓	
This study	**Same-day**	**Off-line**	**S**	**SP, SAHS**	**F**	✓	✓	✓	✓

Legend: CL: Clustering; CP: Constraint Programming; CU: Chair Utilization; DT: Dynamic Template; F: Flowtime; FW: Weighted Flowtime; GRASP: Greedy Randomized Adaptive Search Procedure; HE: Heuristics; IR: Infinite-server Relaxation; LR: Lagrangian Relaxation; M: Makespan; MP: Mathematical Programming; OT: Overtime of resources; P: Number of Patients; SAHS: Self-Adaptive Harmony Search; SP: Stochastic Programming; T: Template; TCT: Total Completion Time; WL: Work Load; WT: Waiting Time.

Table 6.1 Optimizing the COS problem: classification of the relevant references

6.2 Problem statement

The oncology department under consideration can be considered as the counterpart of a three-stage hybrid flow shop manufacturing system in which the first stage is related to the medical consultation, the second stage consists of the pharmacy laboratory and, finally, the third stage involves a set of chairs in parallel for the chemotherapy treatment (Bouras et al., 2017; Hahn-Goldberg et al., 2014). In general, the description of the problem is reported in Chapter 3. However, this work introduced a new feature of the problem regarding the medical consultation. A referee oncologist assists the patient during the whole therapeutic path, in accordance to the care protocol. Hence, the long/medium-term appointment-planning phase is managed by the referee oncologist, who decides upon the days any patient undergoes the therapy. For that reason, the set of patients to be treated every day is known a-priori. When the patient meet the oncologist for the medical consultation, a decision on the chemotherapy is taken by the assigned oncologist based on the health status of the patient and on the blood tests executed by the patient in the same hospital or in an external laboratory. Therefore, there exists a deferral probability (Heshmat and Eltawil, 2019; Garaix et al., 2020) that the patient is not ready to receive the chemotherapy on the same-day. In case the medical consultation is successful, the referee oncologist sends a request (*i.e.*, a prescription) to the pharmacy, which includes type and doses of the therapy and the patient can undergo the treatment administration. Otherwise, the patient appointment is postponed since the patient health status was not evaluated properly good to receive the treatment. The objective is to minimize the average patient waiting time over the provided time horizon, which consists of one working day.

6.2.1 Problem assumptions

To thoroughly describe the problem under investigation, also in regard to the real-life ward we observed, the following assumptions can be summarized as follows:

1. The number of patients to be treated at a given day is known in advance as it arises from the planning phase, conforming to the patient care protocol decided by the oncologist;
2. Arrival times of patients are initialized to zero (r_p=0, $\forall p$=*1,..,P*);
3. Each patient is assigned to a referee oncologist for the medical consultation;

4. Cancellations and no-shows at the consultation session are disregarded;
5. The desk registration time is negligible;
6. Therapy preparation devices never break down;
7. Each pharmacy technician can prepare a therapy at a time;
8. Pre-emption on the different activities is not allowed;
9. Chairs are identical;
10. Every chair can accommodate a patient at a time;
11. Nurses have identical skills, *i.e.*, each patient can be treated by any available nurse;
12. Each nurse can prepare only a patient at a time;
13. A nurse can monitor at most four patients simultaneously;
14. The time any patient needs to leave the chair is negligible.

However, most of these assumptions are common to several literary contributions (Baril et al., 2016a; Demir et al., 2021; Garaix et al., 2020; Hesaraki et al, 2019; Sadki et al., 2011). Due to the stochastic approach we adopted for coping with COS problem at hand, the way the uncertainty is modelled and the stochastic counterpart of the objective function are discussed in the following subsections.

6.2.1 Modelling uncertainty

The COS problem is characterized by several sources of uncertainty. To model the uncertainties of the problem, the Sample Average Approximation framework is adopted (Denton et al., 2007). It consists of generating a finite number of scenarios Ω in which stochastic parameters are independently sampled from the corresponding stochastic distributions, while deterministic parameters are kept unchanged for each scenario ω (ω=1,...,Ω). The same approach was already used for scheduling outpatient appointments in oncology units (Castaing et al., 2016). Four distinct sources of uncertainty characterize the problem under investigation.

1. Every oncologist reviews the results of the patient blood test, carries out a medical examination of the patient health status and makes a decision on the dosage of the drugs to be prepared by the pharmacy. Therefore, the duration of each medical consultation cannot be determined a-priori and, as a consequence, it is a stochastic descriptor of the oncology process: Dc_p^{ω} is the medical consultation time of patient p at scenario ω.

2. Based on the outcome of the visit, the oncologist may decide if the patient is able to receive the treatment or if she/he has to be deferred. The probability a patient p at scenario ω is deferred, is denoted as $\lambda_p^\omega \in U[0,1]$. If λ_p^ω is lower than or equal to $\bar{\lambda}$, that is the experimental value arisen from the experimental observation, the patient is deferred, otherwise it is able to undergo the treatment. Hence, for each patient p and at each scenario ω the following deferral coefficient δ_p^ω can be introduced as in Eq. 6.1:

$$\delta_p^\omega = \begin{cases} 1 & if\ \lambda_p^\omega \leq \bar{\lambda} \\ 0 & otherwise \end{cases} \quad (6.1)$$

3. Since the pharmacy is detached from the ward, the time required to deliver the therapies from the pharmacy to the oncology ward can be significantly uncertain due to several factors such as urban traffic. Particularly, therapies prepared by the pharmacy are gathered in batches and delivered to the oncology unit by means of a courier service. Thereby, the batch transportation time is a stochastic descriptor and TD_b^ω denotes the time to deliver a batch b of therapies at scenario ω.
4. Setup time of patients for the chemotherapy treatment may be subject to variability due to many factors. So, Ds_p^ω is another stochastic descriptor denoting the setup time of patient p at scenario ω.

Conversely, conforming to our experimental observations, the therapy preparation time Dp_p and the treatment time Di_p are handled as deterministic factors, similarly being done by the relevant literature (Benzaid et al., 2020; Garaix et al., 2020; Hesaraki et al., 2019; Masini et al., 2014).

6.2.2 Objective function

The objective to be pursued consists of scheduling the outpatient appointments so as to reduce the patient waiting time. To this end, the total flow time was adopted, hereinafter denoted as F, that implies the reduction of the patient waiting time (Chonde et al., 2013; Hesaraki et al., 2019; Li and Chai, 2019; Taheri et al., 2012), and can be calculated as in Eq. 6.2:

$$F = \sum_{p=1}^{P} (Ci_p - r_p) \quad (6.2)$$

As mentioned earlier, patients' arrival times are initialized to zero (r_p=0, $\forall p$=1,..,P). Then, once a sequence of patients was scheduled, the corresponding appointment schedule is generated and the total flow time can be calculated by replacing the release dates r_p with the consultation starting time Sc_p, as in Eq. 6.3:

$$F = \sum_{p=1}^{P} (Ci_p - Sc_p) \tag{6.3}$$

The stochastic counterpart of the total flow time is the expected total flowtime $E(F)$, which depends on the set of scenarios Ω (ω=1,...,Ω), as in Eq. 6.4:

$$F = \frac{1}{\Omega} \sum_{\omega=1}^{\Omega} F(\omega) \tag{6.4}$$

6.3 Stochastic programming model

In order to optimally solve small-sized instances of the COS problem under investigation, we used the sample average approximation method to develop a SP model working by means of a time-slot based technique. Each time-slot is set to 5 minutes (Sadki et al., 2011). Notations and mathematical model are in the following:

Parameters

ω	Scenario ω=1,...,Ω
p	Patient p=1,…,P
o	Oncologist o=1,…,O
d	Pharmacy technician d=1,…,D
b	Batch b=1,…,B
c	Chair c=1,…,C
n	Nurse n=1,…,N
s	Time slot s=1,…,S
Op_p	Oncologist assigned to patient p
Dp	Duration of therapy preparation
Di_p	Duration of treatment for patient p
CAP	Batch size
M	A big number

Stochastic parameters

Dc_p^{ω}	Duration of medical consultation for patient p at scenario ω
$\delta_p^{\omega} \in \{0,1\}$	Deferral coefficient of patient p at scenario ω

TD_b^{ω} Duration of therapy delivery for batch b at scenario ω

$Dset_p^{\omega}$ Duration of setup for patient p at scenario ω

Decision variables

$\varphi_{p,o,s}^{\omega} \in \{0,1\}$ 1 if the oncologist o starts the medical consultation of the patient p in the time slot s at scenario ω, 0 otherwise

$\theta_{p,d,s,b}^{\omega} \in \{0,1\}$ 1 if the pharmacy technician d starts to prepare the therapy of the patient p of the batch b in the time slot s at scenario ω, 0 otherwise

$a_{p,n,s}^{\omega} \in \{0,1\}$ 1 if the nurse n starts the setup of the patient p in the time slot s at scenario ω, 0 otherwise

$\beta_{p,c,s}^{\omega} \in \{0,1\}$ 1 if the treatment of the patient p starts in the chair c in the time slot s at scenario ω, 0 otherwise

Auxiliary variables

Sc_p^{ω} Consultation starting time of the patient p at scenario ω

$Sp_{p,b}^{\omega}$ Therapy preparation starting time for the patient p of the batch b at scenario ω

Cb_b^{ω} Delivery completion time of the batch b at scenario ω

$Sset_p^{\omega}$ Setup starting time of the patient p at scenario ω

Si_p^{ω} Treatment starting time of the patient p at scenario ω

Objective and constraints

$$min \sum_{\omega=1}^{\Omega} \left(\sum_{p=1}^{P} \left[\left(Si_p^{\omega} + Di_p + Dset_p^{\omega} - Sc_p^{\omega} \right) \cdot \delta_p^{\omega} \right] \right) / \Omega \tag{6.5}$$

Subject to

$$\sum_{s=1}^{S} \varphi_{p,Op_p,s}^{\omega} = 1 \quad \forall p=1,\ldots,P, \ \omega \in \Omega \tag{6.6}$$

$$\sum_{p=1}^{P} \sum_{t=s-Dc_p^{\omega} \mid t>0}^{s-1} \varphi_{p,o,t}^{\omega} \leq 1 \quad \forall s=1,\ldots,S, \ o=1,\ldots,O \mid Op_p=o, \ \omega \in \Omega \tag{6.7}$$

$$Sc_p^{\omega} = \sum_{s=1}^{S} \varphi_{p,Op_p,s}^{\omega} \cdot s \quad \forall p=1,\ldots,P, \ \omega \in \Omega \tag{6.8}$$

$$Sc_p^{\omega} + Dc_p^{\omega} \leq \sum_{b=1}^{B} Sp_{p,b}^{\omega} \quad \forall p=1,\ldots,P, \ \omega \in \Omega \tag{6.9}$$

$$\sum_{s=1}^{S} \sum_{d=1}^{D} \sum_{b=1}^{B} \theta_{p,d,s,b}^{\omega} = 1 \quad \forall p=1,\ldots,P, \ \omega \in \Omega \tag{6.10}$$

$$\sum_{p=1}^{P}\sum_{t=s-Dp\cdot\delta_p^{\omega}\,|\,t>0}^{s-1}\sum_{b=1}^{B}\theta_{p,d,t,b}^{\omega}\leq 1 \qquad \forall s=1,\ldots,S,\ d=1,\ldots,D,\ \omega\in\Omega \tag{6.11}$$

$$Sp_{p,b}^{\omega}=\sum_{s=1}^{S}\sum_{d=1}^{D}\theta_{p,d,s,b}^{\omega}\cdot s \qquad \forall p=1,\ldots,P,\ b=1,\ldots,B,\ \omega\in\Omega \tag{6.12}$$

$$\sum_{p=1}^{P}\sum_{d=1}^{D}\sum_{s=1}^{S}\left(\theta_{p,d,s,b}^{\omega}\cdot\delta_p^{\omega}\right)\leq CAP \qquad \forall b=1,\ldots,B,\ \omega\in\Omega \tag{6.13}$$

$$Cb_b^{\omega}\geq\left(Sp_{p,b}^{\omega}+Dp\right)\cdot\delta_p^{\omega}+TD_b^{\omega} \qquad \forall p=1,\ldots,P,\ b=1,\ldots,B,\ \omega\in\Omega \tag{6.14}$$

$$M\cdot\sum_{d=1}^{D}\sum_{s=1}^{S}\theta_{p,d,s,b}^{\omega}+Cb_b^{\omega}-Sset_p^{\omega}\leq M \qquad \forall p=1,\ldots,P,\ b=1,\ldots,B,\ \omega\in\Omega \tag{6.15}$$

$$\sum_{s=1}^{S}\sum_{n=1}^{N}a_{p,n,s}^{\omega}=1 \qquad \forall p=1,\ldots,P,\ \omega\in\Omega \tag{6.16}$$

$$\sum_{p=1}^{P}\sum_{t=s-Dset_p^{\omega}\cdot\delta_p^{\omega}}^{s-1}a_{p,n,t}^{\omega}\leq 1 \qquad \forall s=1,\ldots,S,\ n=1,\ldots,N,\ \omega\in\Omega \tag{6.17}$$

$$\sum_{p=1}^{P}a_{p,n,s}^{\omega}\leq 1 \qquad \forall s=1,\ldots,S,\ n=1,\ldots,N,\ \omega\in\Omega \tag{6.18}$$

$$Sset_p^{\omega}=\sum_{s=1}^{S}\sum_{n=1}^{N}a_{p,n,s}^{\omega}\cdot s \qquad \forall p=1,\ldots,P,\ \omega\in\Omega \tag{6.19}$$

$$Sset_p^{\omega}\leq Si_p^{\omega} \qquad \forall p=1,\ldots,P,\ \omega\in\Omega \tag{6.20}$$

$$\sum_{s=1}^{S}\sum_{c=1}^{C}\beta_{p,c,s}^{\omega}=1 \qquad \forall p=1,\ldots,P,\ \omega\in\Omega \tag{6.21}$$

$$\sum_{p=1}^{P}\sum_{t=s-(Di_p+Dset_p^{\omega})\cdot\delta_p^{\omega}\,|\,t>0}^{s-1}\beta_{p,c,t}^{\omega}\leq 1 \qquad \forall s=1,\ldots,S,\ c=1,\ldots,C,\ \omega\in\Omega \tag{6.22}$$

$$\sum_{p=1}^{P}\beta_{p,c,s}^{\omega}\leq 1 \qquad \forall s=1,\ldots,S,\ c=1,\ldots,C,\ \omega\in\Omega \tag{6.23}$$

$$Si_p^{\omega}=\sum_{s=1}^{S}\sum_{c=1}^{C}\beta_{p,c,s}^{\omega}\cdot s \qquad \forall p=1,\ldots,P,\ \omega\in\Omega \tag{6.24}$$

$$Si_p^{\omega}+Di_p\leq S \qquad \forall p=1,\ldots,P,\ \omega\in\Omega \tag{6.25}$$

The objective function (see Eq. 6.5) consists in the minimization of the total flowtime for a given scenario. Constraint 6.6 ensures that each patient receives only one medical consultation during the day. Constraint 6.7 states that each oncologist visits no more than one patient at a time. Constraint 6.8 calculates the medical consultation starting time. Constraint 6.9 ascertains that the completion time of the medical consultation is less or equal to the therapy preparation starting time. As regards the pharmacy stage, Constraint 6.10 assures that the pharmacy technicians

can prepare only one therapy for each patient and each patient can be assigned to only one batch. Constraint 6.11 guarantees that each pharmacy technician can prepare only a single therapy at time. Constraint 6.12 computes the therapy preparation starting time. Through the Constraint 6.13, the maximum capacity of a batch is respected, while the Constraint 6.14 states that the delivery completion time is equal to the completion time of the batch plus the delivery time of the considered batch. Specifically, the completion time of the batch is equal to the completion time of the last therapy loaded into the batch. Constraint 6.15 makes use of the big M to check out that the setup operations start if the therapies are shipped to the department. Constraint 6.16 affirms that each patient can be prepared for the treatment only one time, while Constraint 6.17 and Constraint 6.18 assures that each nurse can setup only one patient at time. Constraint 6.19 determines the setup starting time. As concerns the last stage, Constraint 6.20 creates the timing relationship between the setup operations and the starting time of the treatment. Constraint 6.21 specifies that each patient can receive only one chemotherapy administration, while Constraint 6.22 and Constraint 6.23 imposes that each chair can accommodate only one patient at time. Constraint 6.24 computes the treatment starting time. Finally, the Constraint 25 ascertains that the completion times of each patients respect the total number of slots.

6.4 Metaheuristic algorithms for solving the COS problem

As mentioned earlier, the COS problem can be considered as a deterministic hybrid flow shop problem, which is NP-hard in the strong sense, even when there are two resources at the first stage (Gupta et al., 1997). As a result, only very small-sized instances can be optimally solved with reasonable computational time. Besides, due to the stochastic configuration of the problem at hand, the computational time required to solve an instance dramatically increases with the number of scenarios (Birge and Louveaux, 2011; Demir et al., 2021). As a result, either heuristic or metaheuristic algorithms are needed to solve large-sized instances in a reasonable computational time (Costa et al., 2013).

In this section, two metaheuristic algorithms are proposed, namely the Harmony Search (HS) algorithm and the Self-Adaptive Harmony Search (SAHS). The Harmony search (HS) is a metaheuristic algorithm inspired by the musical

performance process of a musician searching for a better state of harmony (Geem et al., 2001). It is an effective and efficient evolutionary technique able to solve different kinds of engineering problems (Manjarres et al., 2013), which showed better performance than other well-known optimization methods (Abdel-Raouf and Metwally 2013). Several research contributions also demonstrated that the evolutionary mechanism of HS is faster than genetic algorithms (Lee et al., 2005; Omran and Mahdavi, 2008).

However, the calibration procedure needed to choose the optimal set of parameters for metaheuristic algorithms has a considerable impact on their search performance. Within the field of evolutionary algorithms, the "Self-Adaptation" approach becomes popular. This consists of encoding the algorithm's parameters alongside the candidate solution that change with the evolution of the algorithm (Smith, 2008). To this end, a new self-adaptive version of the HS algorithm (namely SAHS) is here proposed to solve the COS problem. The following subsections deal with the rationale of the decoding procedure employed for evaluating any solution of the COS problem. Subsequently, the standard HS is presented, and the self-adaptive structure is thoroughly explained, respectively.

6.4.1 Decoding procedure

Any metaheuristic algorithm generates several candidate solutions for the problem under investigation with the aim of identifying the best near-optimal solution. In the case of the COS problem, any solution is represented by a permutation sequence of patients $\boldsymbol{\pi}$ to be processed for every scenario ω. Consequently, a decoding procedure is needed to evaluate the expected total flowtime associated to $\boldsymbol{\pi}$. The decoding procedure for the multi-stage COS problem at hand entails two distinct phases: the Early-Start (ES) scheduling and the Late-Start (LS) scheduling. The former follows a regular scheduling strategy; every patient preliminarily assigned to a specific oncologist starts the visit as early as possible, when his/her referee oncologist is available for the medical consultation. Once all patients were processed at the consultation stage, the First Come First Served (FCFS) policy is applied to schedule therapy preparations at the pharmacy stage and again the patients at the treatment stage, conforming to the delivery time of the therapies arranged in batches. The latter phase aims at reducing the patients' waiting time. In fact, the LS approach works by adjusting the ES schedule on the basis of a backward rule. In brief, the

activities scheduled at the treatment stage remain the same while, going backward from the therapy preparation to the consultation stage, the related operations are shifted as much as possible ahead, conforming to the provided constraints. As a result, the starting time of the medical consultation for some patients can be postponed, thereby favouring a consequent reduction of the total flowtime for each scenario. At the same time, the chemotherapy outpatient schedule is generated by matching the consultation starting time with the patient arrival times. Finally, the total expected flowtime *E(F)* can be computed by considering the single flowtime contributions pertaining to each scenario ω (see Eq. 6.4)

6.4.2 The Harmony Search Algorithm

In the HS algorithm, each harmony consists of an n-dimensional real-coded vector. Let us suppose a single harmony is denoted as $x = (x_1,...,x_j,...,x_n)$ such that each variable is defined in the domain $[LB_j, UB_j] \in \mathbb{R}$ and $f(x)$ is the related objective function value. Since the healthcare scheduling problem under investigation can be classified as a combinatorial issue, each real-coded solution has to be converted into a sequence of patients. To this end, we employed a well-known mechanism based on the smallest position value (SPV) rule (Komaki et al., 2014), which allows converting any real-valued harmony vector into a discrete job permutation. In brief, such rule, which works by means of a sorting procedure, enables the algorithm to switch from a conventional scheme to a discrete one. As for example, Table 6.2 shows a generic real-encoded harmony $\boldsymbol{x}$ corresponding to the permutation solution {7-6-2-1-8-4-3-5} after the SPV conversion is executed. The computational procedure of the basic HS algorithm is explicated by the pseudo-code in Table 6.3. After a preliminary initialization phase, in which a number of control parameters has to be set (namely harmony memory consideration rate *HMCR*, pitch adjustment *PAR* and bandwidth *BW*) a set of *HMS* randomly generated solutions (harmonies) are stored in the Harmony Memory (*HM*). The generation of the initial population, (*i.e.*, the initial *HM*) may assume a strategic role for the search ability of an evolutionary algorithm. Conforming to the seminal paper of Geem et al. (2001) and after a series of trial-and-error tests, we set the harmony memory size (*HMS*) to 60. The whole set of harmonies are randomly generated. However, to enhance the quality of the initial *HM*, two harmonies are replaced by two well-known heuristics, namely Short

Processing Time (SPT) and Long Processing Time (LPT), which consider only the treatment times.

After the initial *HM* was created, the decoding procedure is employed by the Harmony Search for evaluating the *HM*. A variable evals is updated to record the number of evaluations carried out by the algorithm. Then, a new harmony vector $\boldsymbol{x}^{new}$ is stochastically generated by applying three operators (improvisation phase): harmony memory consideration, pitch adjustment and random selection. If the new candidate harmony performs better than the worst one $\boldsymbol{x}^{worst}$ in the *HM*, then the latter is replaced by the new one. In this fashion, the harmony memory is constantly updated. A variable iter is used to record the number of improvisations. To boost the search ability of the proposed metaheuristic, two computational techniques were embedded into the HS structure, denoted as Local Search and Reinitialization, properly described in the following subsections. Finally, the HS algorithm stops once one of the termination criteria is satisfied (see Section 6.6).

$\boldsymbol{\pi}$	1	2	3	4	5	6	7	8
$\boldsymbol{x}$	0.14	-0.74	1.11	0.98	2.32	-1.54	-2.24	0.78

Table 6.2 Illustrative example of encoded solution x

Algorithm: Harmony Search

1: Step 1: Initialization and setting of control parameters, namely HMS, HMCR, PAR, BW,
2: $\forall$ j=1,…,n; iter = 0
3: Step 2: Generate the initial population, i.e., the HM, and calculate the objective function
4: harmony vector
5: Step 3: Improvise a new harmony $\mathbf{x}^{\mathbf{new}}$ as follows:
6: **for** i = 1 : HMS
7: **for** j = 1 : n
8: **if** rand< HMCR
9: $x_{ij}^{new} = x_{aj}$ where a $\in$ (1,…, HMS)
10: **if** rand< PAR
11: $x_{ij}^{new} = x_{ij}^{new} \pm$ rand · BW
12: **end**
13: **else**
14: $x_{ij}^{new} = LB_j$ + rand · (UB_j - LB_j)
15: **end**
16: **end**
17: **end**
18: Step 4: Compute the objective function $f(x^{new})$
19: Step 5: Update HM by $\mathbf{x}^{\mathbf{worst}} \leftarrow \mathbf{x}^{\mathbf{new}}$ if $f(x^{new}) < f(x^{worst})$
20: Step 6: iter = iter + 1
21: Step 7: **if** the exit criterion is satisfied
22: Stop the algorithm; Return the best harmony vector $\mathbf{x}^{\mathbf{best}}$ and $f(x^{best})$
23: **else**
24: Goto Step 3
25: **end**

Table 6.3 The Harmony Search algorithm

6.4.2.1 Local search

In the local search, at each iteration, a harmony $\boldsymbol{x_r}$ is randomly extracted from the current harmony memory, thus working as starting seed of this procedure. Two well-known perturbation methods, namely insertion and swap, are applied to the seed according to an adaptive probability equal to 1-[(*iter*/*Max_iter*)], where *Max_iter* is equal to (*PAT* · 1000)/*HMS*. In brief, being the insertion method more explorative than swap, it has a higher probability to be used at the early stages of the evolutionary path. Insertion consists in randomly selecting a digit and inserting that into a random position of the harmony vector. Swap means to exchange two randomly selected digits of the harmony vector. If the perturbed harmony $\boldsymbol{x_s}$

performs better than the original one, then the seed is replaced. The local search is outlined in Table 6.4. Besides, if the new harmony improves the best solution achieved so far, the new local optimum is updated and the worst solution of the harmony memory is replaced by the new best solution properly reinitialized.

Algorithm: Local Search		
1:	Step 1:	Select randomly a harmony in the current HM: $\mathbf{x_r} \mid r \in int(U[1,HMS])$
2:	Step 2:	flag_impr = 0
3:	Step 3:	**for** q = 1 : n
4:		**if** rand < 1-(iter/Max_iter)
5:		$\mathbf{x_s} \leftarrow$ insertion($\mathbf{x_r}$)
6:		**else**
7:		$\mathbf{x_s} \leftarrow$ swap($\mathbf{x_r}$)
8:		**end**
9:		**if** $f(x_s) < f(x_r)$
10:		$\mathbf{x_r} \leftarrow \mathbf{x_s}$; $f(x_r) \leftarrow f(x_s)$
11:		**if** $f(x_s) < F_{best}$
12:		flag_impr = 1
13:		$\mathbf{x^{best}} \leftarrow \mathbf{x_s}$; $f(x^{best}) \leftarrow f(x_s)$
14:		$\mathbf{x_s^*} \leftarrow$ reinitialize(x_s)
15:		$\mathbf{x^{worst}} \leftarrow \mathbf{x_s^*}$
16:		$\mathbf{F^{worst}} \leftarrow f(x_s)$
17:		**end**
18:		**end**
19:	**end**	

Table 6.4 The local search algorithm

6.4.2.2 Reinitialization

Reinitialization is a novel strategy we propose to enhance the exploration ability of SAHS. Once a reference harmony is selected, it generates a random harmony and rearranges the digits so that the SPV rule yields the same permutation solution of the reference harmony. Whether the local search does not yield any improvement in the local optimum *flag_impr*=0, the whole harmony memory is reinitialized. The reinitialization strategy aims at regenerating the information stored in each harmony vector; thus, reinitializing the current HM would reduce the risk of remaining prematurely trapped into a local optimum. In fact, every permutation solution obtained by applying the SPV rule to the real encoded vector just depends on the sorted information and not on the specific values assumed by each digit.

Hence, similarly to a well-known restart mechanism often embedded in the metaheuristic algorithms (Dao et al., 2017), reinitialization would allow the algorithm to improve the exploration ability over the space of solutions. Table 6.5 should clarify how a reference harmony x can be reinitialized by $\boldsymbol{x_{rein}}$, which in turn is obtained by sorting the information of a new randomly generated vector $\boldsymbol{x_r}$. For the sake of clarity, the reinitialization procedure is reported in Table 6.5.

Algorithm: Harmony Reinitialization		
1:	Step 1:	Select a harmony $\mathbf{x}$
2:	Step 2:	Generate the corresponding permutation harmony by applyingi SPV on $\mathbf{x}$:[~, $\mathbf{x_{perm}}$] = sort($\mathbf{x}$)
3:	Step 3:	Generate a random harmony $\mathbf{x_r}$
4:	Step 4:	Sort $\mathbf{x_r}$ values: $\mathbf{x_{r\_sort}}$ = sort($\mathbf{x_r}$)
5:	Step 5:	Sort $\mathbf{x_r}$ values through: $\mathbf{x_{perm}}$: $\mathbf{x_{rein}}(\mathbf{x_{perm}}) = \mathbf{x_{r\_sort}}$
6:	Step 6:	Reinitialize the harmony: $\mathbf{x} \leftarrow \mathbf{x_{rein}}$

Table 6.5 Harmony reinitialization

Vectors	**Values**			
$\boldsymbol{x}$	0.45	0.62	-0.12	0.33
$\boldsymbol{x_{perm}}$	3	4	1	2
$\boldsymbol{x_r}$	0.61	0.27	0.82	-0.23
$\boldsymbol{x_{rein}}$	0.61	0.82	-0.23	0.27

Table 6.6 Example of Harmony reinitialization

6.4.3 The proposed Self-Adaptive Harmony Search

To assure the maximum performance, metaheuristics require a set of control parameters to be preliminarily set, according to the kind of problem to be addressed. An accurate selection of such control parameters allows metaheuristics to find the best balance between exploration and exploitation, also called intensification and diversification (Blum and Roli, 2003). During the diversification phase, different solutions are generated to support the exploration of the search space on a global scale, while intensification consists of a search in a smaller region pertaining to a local optimum. In order to overcome any trial-and-error approach as well as any tedious calibration analysis concerning the selection of control parameters, a self-

adaptive harmony search algorithm (SAHS), inspired by the self-adaptive differential evolution proposed by Brest et al. (2006), was devised (the pseudo-code of SAHS is in Table 6.7).

To configure a self-adaptive mechanism for tuning the provided control parameters, with exception of the population size, each harmony in the HM is extended by three values, namely *HCMR*, *PAR* and *BW*, as in Eq. 6.26:

$$\begin{bmatrix} x_{1,1}\ldots x_{1,n} \mid x_{1,n+1}, x_{1,n+2}, x_{1,n+3} \\ x_{2,1}\ldots x_{2,n} \mid x_{2,n+1}, x_{2,n+2}, x_{2,n+3} \\ \ldots \\ x_{HMS,1}\ldots x_{HMS,n} \mid x_{HMS,n+1}, x_{HMS,n+2}, x_{HMS,n+3} \end{bmatrix} = \begin{bmatrix} x_1 \mid HMCR_1, PAR_1, BW_1 \\ x_2 \mid HMCR_2, PAR_2, BW_2 \\ \ldots \\ x_{HMS} \mid HMCR_{HMS}, PAR_{HMS}, BW_{HMS} \end{bmatrix} \quad (6.26)$$

The best values of control parameters lead to better harmonies, which in turn have much more chances to survive, thereby propagating such better parameter values in the next generations. For the sake of clarity, hereinafter the generic vector of control parameter $[x_{i,n+1}, x_{i,n+2}, x_{i,n+3}]$ will be denoted as $y_i = [y_{i1}, y_{i2}, y_{i3}]$.

Algorithm Self-Adapative Harmony Search

1: *Step 1:* Initialization and setting of the control parameters, namely HMS, $HMCR_{max}$, $HMCR_{min}$, PAR_{max}, PAR_{min},

2: BW_{max}, BW_{min}, (LB_j, UB_j) $\forall$ $j=1,\ldots,n$; Max_ev and Max_ct; $iter = 0$.

3: *Step 2:* Generate randomly the initial harmony memory HM and calculate the objective function of each harmony

4: vector. Generate randomly a vector of control parameters related to each harmony vector: $y_{i1} \in U$

5: $[HMCR_{min}, HMCR_{max}]$; $y_{i2} \in U$ $[PAR_{min}, PAR_{max}]$; $y_{i3} \in U$ $[BW_{min}, BW_{max}]$, $\forall$ $i=1,\ldots,HMS$; initialize number

6: of evaluated solutions: $evals = 0$.

7: *Step 3:* Replace 2 randomly selected harmonies with SPT, and LPT solutions. Convert the permutation solution into

8: real encoded solutions. Compute their fitness function of such heuristic solutions. Set the best solution $\boldsymbol{x}^{best}$

9: and the best expected total flowtime $E(F_{best})$. Set the worst solution $\boldsymbol{x}^{worst}$ and the worst expected total

10: flowtime $E(F_{worst})$. Set control parameters associated to the best solution: $\boldsymbol{y}^{best}$.

11: *Step 4:* Improvise a new harmony $\boldsymbol{x}^{new}$ as follows:

12: **for** $i = 1 : HMS$

13: **for** $j = 1 : n$

14: **if** $rand < y_{i1}$

15: $x_{ij}^{new} = x_{aj}$, where $a \in (1, \ldots, HMS)$

16. **if** $rand < y_{i2}$

17: $x_{ij}^{new} = x_{ij}^{new} \pm rand \cdot y_{i3}$

18: **end**

19: **else**

20: $x_{ij}^{new} = LB_j + rand \cdot (UB_j - LB_j)$

21: **end**

22: **end**

23: **end**

24: *Step 5:* Compute the objective function $f(x^{new})$

25: *Step 6:* Update control parameters (see Section 6.4.3.2)

26: *Step 7:* Update HM as follows:

27: **if** $f(\boldsymbol{x}^{new}) < E(F_{worst})$

28: $\boldsymbol{x}^{worst} \leftarrow \boldsymbol{x}^{new}$; $E(F_{worst}) \leftarrow f(\boldsymbol{x}^{new})$

29: **if** $f(\boldsymbol{x}^{new}) < E(F_{best})$

30: $\boldsymbol{x}^{best} \leftarrow \boldsymbol{x}^{new}$; $E(F_{best}) \leftarrow f(\boldsymbol{x}^{new})$

31: **end**

32: **end**

33: *Step 8:* Local Search

34: *Step 9:* Reinitialization

35: *Step 10:* $iter = iter + 1$; Update $evals$

36: **if** $evals \leq Max\_ev$ **or** $time \leq Max\_ct$

37: Stop the algorithm; return the best harmony vector $\boldsymbol{x}^{best}$ and $E(F_{best})$

38: **else**

39: Goto *Step 4*

40: **end**

Table 6.7 Pseudo-code of SAHS

6.4.3.1 Setting control parameters

In the proposed self-adaptive metaheuristic each harmony is composed by an n-dimensional vector and three additional digits concerning *HMCR*, *PAR* and *BW*, respectively. Each control parameter may vary within a specific domain to be preliminarily defined on the basis of what the literature experienced so far. A large value of *HMCR* enhances the local search ability of HS, while a smaller value would raise the diversity of the harmony memory. Conforming to Luo (2013), *HMCR* should be chosen in the range [0.5, 1.0] even if most literature adopts a value greater than or equal to 0.9, as reported in Kattan and Abdullah (2013) and Omran and Mahdavi (2008). Consequently, we assumed *HMCR* varying in [0.70, 0.99] for the proposed SAHS. As far as *PAR* is concerned, it is in charge to tune the level of diversification of the harmony memory. Generally, it can be set in the range [0, 1] (Pan et al., 2010) even though intermediate values would be preferable, as indicated in the comparison analyses proposed by Kattan and Abdullah (2013) and Zhao et al. (2017). In this research, the *PAR* related domain is set to [0.40, 0.90]. A finer intensification of the search mechanism depends on the bandwidth parameter *BW* that frequently is set to very low positive values (Kattan and Abdullah, 2013; Mahdavi et al., 2007; Pan et al., 2010). To this end, it is varied in the range [0.001, 0.1], conforming to Pan et al. (2010).

6.4.3.2 Updating control parameters

Control parameters pertaining to each harmony vector are dynamically updated according to a twofold rule. Notably, a sort of global search mechanism drives the parameter updating with an adaptive probability equal to 1-(1/*iter*). The rationale is that control parameters of the best solution (y_1^{best},y_2^{best},y_3^{best}) should be able to bias much more those of the other harmonies as much as the iterations increases. Therefore, for a generic harmony vector $\boldsymbol{x_i}$, if *rand* ≤ 1-(1/*iter*):

for k = 1:3
  if $y_{ik} \leq y_k^{best}$
    $y_{ik}^{new} = y_{ik} + rand \cdot (y_k^{best} - y_{ik})$
  else
    $y_{ik}^{new} = y_{ik} - rand \cdot (y_{ik} - y_k^{best})$
  end
end

On the other hand, to avoid of being trapped into a premature uniformity of control parameters, a diversification strategy is assured when the aforementioned adaptive probability is not satisfied, as follows:

for k = 1:3
  if rand ≤ 0.5
    $y_{ik}^{new} = y_{ik} + \text{rand} \cdot (\max_i y_{ik} - y_{ik})$
  else
    $y_{ik}^{new} = y_{ik} - \text{rand} \cdot (y_{ik} - \min_i y_{ik})$
  end
end

6.5 Numerical experiments

In order to prove the effectiveness of the proposed SAHS in solving the COS problem under investigation, several data sets of numerical instances were generated. We considered three classes of problems at varying problem size, namely small (P=15), medium (P=40) and large (P=70), where P indicates the number of patients. For each of them, a Design of Experiments (DOE) was performed by involving four factors (*i.e.*, number of oncologists O, number of chairs C, therapy batch size CAP and the interval of the uniform distribution related to the batch delivery time U(TD)) varied at two levels, low (L) and high (H), respectively. Hence, a total amount 2^4=16 configurations for each class of problem were considered. Since ten instances were randomly generated for each configuration, 3 ·16 ·10 = 480 runs were executed. Table 6.8 reports the different factors/levels, whose values were fixed on the basis of the benchmark problems addressed by the literature so far (please see Castaing et al., 2016; Garaix et al., 2020; Heshmat and Eltawil, 2021; Heshmat et al., 2017,2018; Ramos et al., 2020; Yokouchi et al., 2012 among the others). Indeed, since both the therapy transportation and the batch size related issues never were investigated by literature so far, their values were set on the basis of a brief survey involving the medical staff. The number of nurses N was set by considering that the ratio N/C is usually fixed to 1/4 to respect the assumption that one nurse can monitor at most four patients simultaneously (Hesaraki et al., 2019; Benzaid et al., 2020). Finally, to balance the pharmacy capability on the problem size, a different number of pharmacy technicians D={1,2,3}was assigned to each class of problems, respectively. The therapy preparation time Dp_p is set to 5 minutes for each patient, while the treatment time Di_p is drawn from a gamma distribution Γ(1.9, 52.37),

selected according to a series of empirical observations. Due to the stochastic feature of the proposed COS problem, the number of scenarios Ω to evaluate any candidate solution is set to 300, though it is reduced to 30 when the time-consuming SP model is used to solve small-sized issues (Liu et al., 2019b). The stochastic parameters of the COS problem under investigation were set as follows:

- the medical consultation time Dc_p^{ω} of the patient p at scenario ω depends on an $N(22.83, 3.19)$ normal distribution;
- the deferral coefficient δ_p^{ω} of the patient p at scenario ω arises from $\lambda_p^{\omega} \in U[0,1]$ with $\bar{\lambda}$ equal to 0.20 (see Sec. 3.1);
- the delivery time TD_b^{ω} of the batch b at scenario ω is derived from a uniform distribution as in Table 6.8;
- the setup time Ds_p^{ω} of the patient p at scenario ω is derived from an $U(5, 15)$ uniform distribution;
- at each scenario ω, every patient p is randomly assigned to a referee oncologist Op_p.

The type of the statistical distributions mentioned above refers to the results of an extensive time-study carried out in a chemotherapy unit located in the Southern Italy. Each metaheuristic algorithm was coded in Matlab®R2019b and executed on a 4GB RAM-2 processors virtual machine embedded on a workstation equipped with an INTEL i9-9900 3.6 GHz 10 core CPU, 32Gb DDR4 2,666MHz RAM and Win 10 PRO OS. Although the expected total flowtime *E(F)* is the objective function of the COS problem under investigation, the Relative Percentage Deviation (*RPD*) function (see Eq.6.27) is handled to compare the results obtained by the tested optimization techniques.

$$RPD=\frac{ALG_{sol} - BEST_{sol}}{BEST_{sol}} \cdot 100 \tag{6.27}$$

where ALG_{sol} is the $E(F)$ value achieved by a certain algorithm, while $BEST_{sol}$ is the best expected solution achieved by the algorithms related to the same instance. As concerns the exit criterion, we decided to implement two triggers, the former being the maximum number of evaluations (*Max_ev*), the latter depending on the maximum computational time (*Max_ct*). Both of them were fixed after a preliminary computational analysis described in the following section.

CLASS	**Small (*P*=15)**		**Medium (*P*=40)**		**Large (*P*=70)**	
Factor/Levels	L	H	L	H	L	H
O	2	3	4	6	6	9
C	5	10	10	15	15	20
CAP	2	4	2	4	2	4
U(TD)	*U*[8,12]	*U*[18,22]	*U*[8,12]	*U*[18,22]	*U*[8,12]	*U*[18,22]

Table 6.8 Classes of problems and related parameters

6.6 Setting the exit criteria of the algorithms

To establish the values to be assigned to *Max_ev* and *Max_ct*, we used a specific data set composed by 10 instances for each class of problems. Problem size and level of each factor related to each instance were randomly selected conforming to Table 6.8. The rationale to determine *Max_ct* is to launch the SAHS many times, by adopting a stopping criterion that varies with the maximum number of evaluations, and then to identify the value of *Max_ev* which assures the convergence of the proposed metaheuristic algorithm. Particularly, we used a parameterized exit criterion based on $Max\_ev(\gamma) = \gamma \cdot P$, where P is the problem size and γ is varied in the set {30, 60, 90, 120, 150, 180, 210, 240, 270, 300}. Once *Max_ev* is known, we determine *Max_ct* by rounding the maximum computational time down to the lowest integer value. Then, the values of *Max_ev* and *Max_ct* identified for each class of problems are adopted as exit criteria for each metaheuristic algorithm.

For each class of problems, Figure 6.1 shows the box plots related to the *RPD* values as γ changes and, as expected, reveals that the number of evaluations required to reach the convergence as the problem size changes. Notably, the first flat boxplot on each diagram means that $Max\_ev(\gamma)$ does not yield any further significant variation on the *RPD* indicator and the convergence is achieved. Graphically, Figure 6.1 allows detecting the γ values at varying the problem size. In fact, γ has to be set to 210 for small class of problems (Figure 6.1-a) and to 240 for medium and large-sized problems (Figure 6.1-b and Figure 6.1-c). Figure 6.1 reports average and maximum computational times (in brackets) for each class of problem at varying γ values. The bold outputs highlight the values corresponding to the selected values of γ. Therefore, we decided to set *Max_ct* to 272, 1154 and 2674 seconds for the small, medium and large classes of problem, respectively.

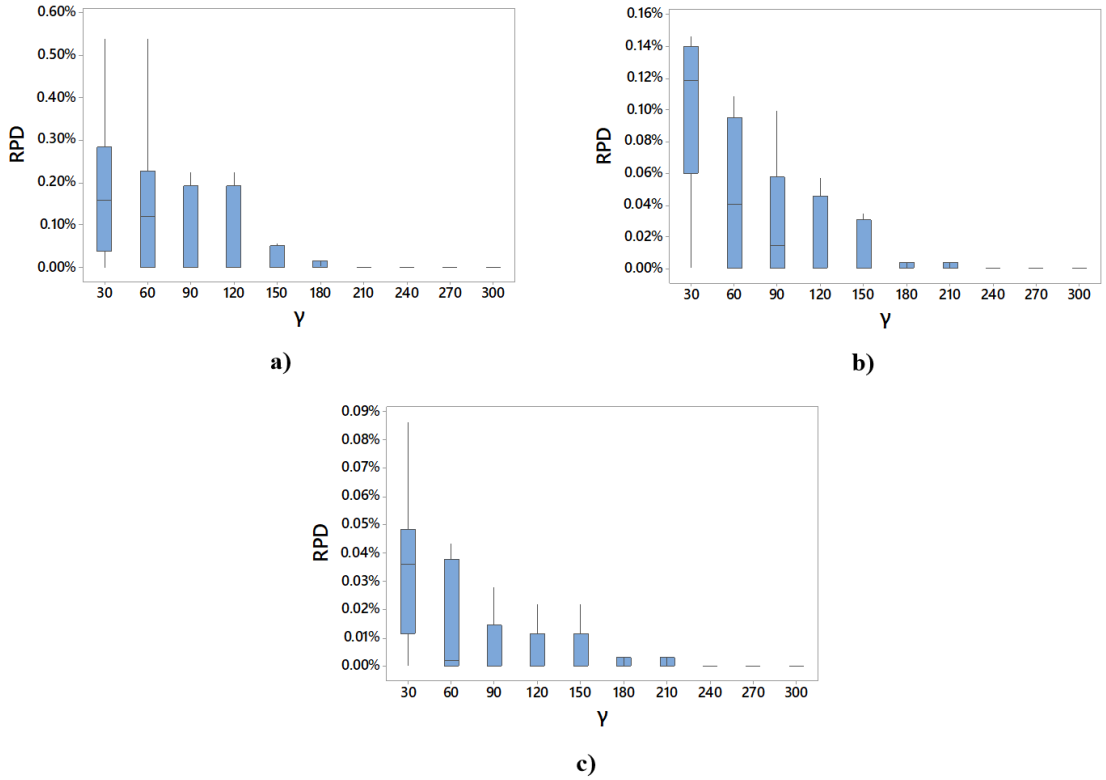


Figure 6.1 The patient flow in the oncology department

γ / Class	Small	Medium	Large
30	43.92 (50.71)	148.41 (155.57)	339.89 (366.24)
60	80.34 (85.29)	282.45 (300.02)	664.20 (696.74)
90	117.11 (125.54)	419.56 (4358.83)	981.68 (1025.38)
120	156.38 (165.95)	557.58 (582.53)	1305.35 (1354.21)
150	190.08 (197.42)	693.59 (723.13)	1629.79 (1683.50)
180	231.29 (238.67)	832.80 (872.94)	1955.50 (2018.25)
210	**268.36 (272.22)**	966.29 (1004.26)	2276.30 (2346.44)
240	304.25 (317.16)	**1105.71 (1154.21)**	**2593.21 (2674.36)**
270	341.81 (350.57)	1238.30 (1285.66)	2912.70 (3002.35)
300	380.06 (384.77)	1377.84 (1435.81)	3233.32 (3330.08)

Table 6.9 Average (maximum) computational time measure in seconds for each class of problems as parameter γ changes

6.7 Comparative analysis

This section deals with the numerical analyses we performed to demonstrate the ability of the proposed SAHS in solving the stochastic COS problem. First, the design phase of HS and SAHS was performed. Since the proposed metaheuristics employ both a set of heuristics for improving the initial population and a specific local search during the evolutionary path, their effect on the quality of solutions was preliminary tested. Subsequently, to demonstrate both efficacy and efficiency of the self-adaptive mechanism embedded in the SAHS, we calibrated a static configuration of the proposed metaheuristic, in which any self-calibration of control parameters is disabled. Finally, once the ability of SAHS in solving the COS problem under investigation was proved, two comparison analyses involving SAHS, a static configuration of harmony search and a GRASP algorithm from the relevant literature on the same topic (Garaix et al., 2020) were carried out. The former analysis aims to compare the different algorithms with the solutions obtained by solving the SP model for a set of very-small scenario problems. The latter comparison consists in an extended experimental campaign where the full factorial experimental plans were employed for assessing the effectiveness of the tested metaheuristic algorithms in solving larger-sized instances.

6.7.1 Comparing different variants of SAHS

To support the choice of the proposed SAHS, three alternative configurations of SAHS were compared with the proposed metaheuristic. A benchmark of 15 instances involving three classes of problems and based on a full factorial experimental plan as in Table 6.8 was engaged. The first configuration denoted by SAHS_NH consists of the SAHS with no heuristic solutions in the initial population. In the second variant of SAHS, named SAHS_NL, the local search is disabled, while in the last algorithm denoted as SAHS_NHL both heuristic solutions and local search are excluded. Table 6.10 allows comparing the different algorithms in terms of *RPD* for each instance. Besides, regardless of the problem size, the global median on the *RPDs* (RPD_{med}), and the maximum *RPD* (RPD_{max}) are reported. As the reader can notice, the positive effect of heuristic solutions on the initial population is quite weak. On the other hand, the local search significantly affects the quality of solutions. However, bold values in Table 6.10 confirm the outperformance of SAHS with respect

to the rest of competitors and justify the use of heuristic solutions into the initial population and the local search as well.

Instance	SAHS [%]	SAHS_NH [%]	SAHS_NL [%]	SAHS_NHL [%]
1	**0.00**	**0.00**	0.05	0.01
2	**0.00**	0.02	0.02	0.36
3	0.03	0.02	0.04	**0.00**
4	**0.00**	**0.00**	0.07	0.43
5	**0.00**	**0.00**	0.04	0.04
6	**0.00**	0.03	0.12	0.13
7	0.08	**0.00**	0.49	2.37
8	**0.00**	**0.00**	0.18	0.20
9	**0.00**	0.02	0.17	0.14
10	0.02	**0.00**	0.06	0.10
11	**0.00**	**0.00**	0.80	6.06
12	**0.00**	0.15	1.72	2.51
13	**0.00**	**0.00**	0.07	0.06
14	0.01	**0.00**	0.31	0.30
15	**0.00**	**0.00**	0.13	0.55
RPD_{med}	**0.01**	0.02	0.28	0.88
RPD_{max}	**0.08**	0.15	1.72	6.06

Table 6.10 Design of SAHS: *RPD* values

6.7.2 Calibrating the static Harmony Search

A major target of any self-adaptive metaheuristic is to achieve at least the same performance as the one working by static control parameters. Likewise, the effectiveness of any metaheuristic algorithm strongly depends on the values assigned to control parameters, which should assure a suitable balance between exploration and exploitation.

This section aims to calibrate a static version of the proposed SAHS, hereinafter denoted as HS, which disregards any self-adaptive mechanism to regulate control parameters. The harmony memory size was fixed to 60, conforming to SAHS. The rest of control parameters, namely *HMCR*, *PAR* and *BW*, were varied at three levels,

as reported in Table 6.11, and a full factorial plan was engaged to select the most suitable control parameters. For each configuration and for each class of problems, three instances were randomly generated similarly to what we did for setting the exit criteria of SAHS (see Section 6.6)

To sum up, $3^3 \cdot 3 \cdot 3 = 243$ runs were executed for calibration purposes and the *RPD* measure was adopted as response variable. For the sake of brevity, the outputs from the ANOVA analysis, whose related model resulted significant with p-value = 0.000, were omitted, while the main effects plot is depicted in Figure 6.2. The selected values are as follows: *HMCR* = 0.90; *PAR* = 0.20; *BW* = 0.10.

Factor	Description	Values
HMS	HM Size	60
HMCR	HM Consideration Rate	0.50, 0.70, 0.90
PAR	Pitch Adjustment Rate	0.20, 0.50, 0.80
BW	Bandwidth	0.001, 0.01, 0.10

Table 6.11 Experimental plan for the calibration of the Harmony Search

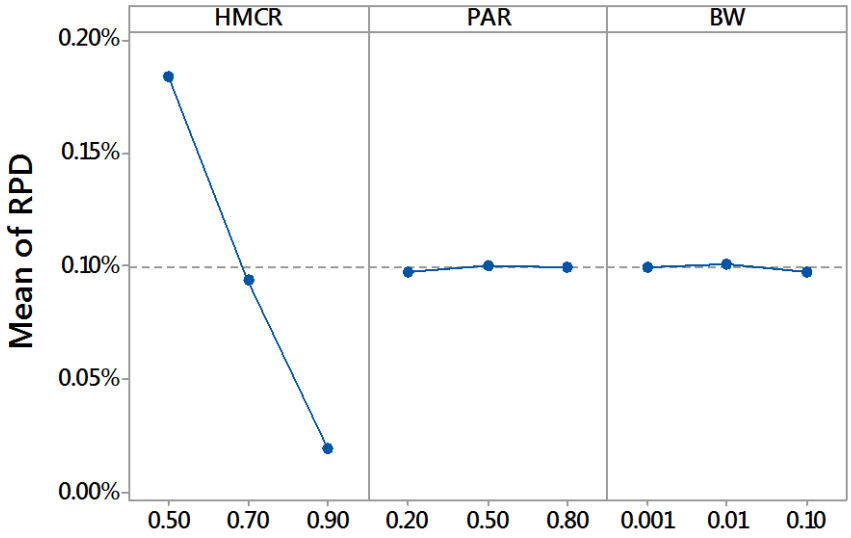


Figure 6.2 Main effects plot of HS algorithm parameters

6.7.3 Comparison with the SP model

A numerical analysis involving the SP model was accomplished to validate the effectiveness of the metaheuristic algorithms to be compared. Twenty very-small-sized instances involving 10 and 12 patients, respectively, were considered. The low values of the smallest class of problems in Table 6.8 were selected to define the factors characterizing each instance, such as number of oncologists and number of chairs. The SP model was implemented on IBM Cplex12 Optimizer® installed on the workstation mentioned earlier. Due to the complexity of the problem under investigation, a time limit equal to 1,200 seconds was set. Once again, the *RPD* was used to compare the different algorithms. Table 6.12 shows the minimum expected total flowtime value (*E(F)min*), expressed in minutes, achieved either by the SP model or by a metaheuristic, the *RPDs* for the metaheuristic algorithms and the SP model, and the gap of the solution obtained by the SP model from the optimal solution. It is worth noting that the SP model never converges within the provided time limit (Gap greater than zero), thereby confirming the complexity of the combinatorial problem at hand and the need of a performing metaheuristic algorithm able to find a near optimal solution in a reasonable time. As for the 10 patients related class of problem, SP assures the best performance as it reaches the best solution, likely the global optimum, seven times out of ten. The median values in italics confirm the outperformance of the SP approach, even if both HS and SAHS are quite effective. Looking at the numerical results involving 12 patients, HS and SAHS dominate the other approaches as they are not so dissimilar under the *RPD* viewpoint, while GRASP outperforms SP which likely would require a higher computational time to converge to better solutions. In fact, the percentage gap from the optimal solution (Gap[%]) of the SP optimization proves that the complexity of the problem strictly depends on the number of patients. On the other hand, the GRASP algorithm seems reducing the gap form the other competitors as the problem size grows, as emerges from the median values as the class of problem changes.

P	Instance	$E(F)_{min}$	SAHS	HS	GRASP	SP	Gap [%]
10	1	1361.67	0.05%	0.05%	0.47%	**0.00%**	19.39%
	2	1078.00	**0.00%**	**0.00%**	0.28%	0.02%	24.72%
	3	1133.67	0.01%	**0.00%**	0.04%	0.09%	22.51%
	4	1370.67	0.64%	0.64%	0.79%	**0.00%**	12.07%
	5	1080.83	0.49%	0.49%	0.65%	**0.00%**	11.63%
	6	1129.33	0.28%	0.28%	0.30%	**0.00%**	25.50%
	7	1187.83	0.01%	**0.00%**	0.03%	**0.00%**	19.23%
	8	1160.83	**0.00%**	**0.00%**	0.23%	**0.00%**	20.41%
	9	1152.33	0.01%	0.01%	0.30%	**0.00%**	26.62%
	10	1275.33	**0.00%**	**0.00%**	0.25%	0.22%	18.18%
	median		0.01%	0.01%	0.29%	**0.00%**	19.90%
12	1	1558.33	0.02%	**0.00%**	0.20%	0.61%	34.98%
	2	905.83	**0.00%**	0.03%	0.00%	0.06%	33.62%
	3	1090.83	**0.00%**	**0.00%**	0.03%	0.06%	55.44%
	4	1604.17	0.05%	**0.00%**	0.29%	0.94%	34.70%
	5	1339.33	**0.00%**	**0.00%**	0.01%	0.41%	50.72%
	6	1556.67	**0.00%**	**0.00%**	0.05%	1.03%	33.05%
	7	1061.50	0.02%	**0.00%**	0.24%	0.24%	40.24%
	8	1125.67	**0.00%**	**0.00%**	0.07%	0.13%	34.90%
	9	1566.17	0.05%	**0.00%**	0.19%	1.21%	36.73%
	10	1584.33	0.04%	**0.00%**	0.15%	1.42%	42.06%
	median		0.01%	**0.00%**	0.11%	0.51%	35.85%

Table 6.12 Comparison among the metaheuristics and the SP model

6.7.4 Extended comparison campaign

After the validation phase involving the SP model, the different metaheuristics were compared on the basis of a newly generated full factorial experimental plan, as indicated in Table 6.8. To sum up, three classes of problem at varying P were considered, each one involving 16 factor configurations and ten numerical instances randomly generated. Hence, 480 runs were elaborated by each algorithm. For each class of problem, Table 6.13 reports the median *RPD* values each configuration, computed over the provided 10 instances, each one entailing 300 scenarios.

The numerical outputs reveal the outperformance of SAHS and HS over the GRASP algorithm. The minimum *RPD* values for each configuration are highlighted in bold and all of them are in the SAHS or in HS related column. Regardless of the problem configurations, the median *RPD* (RPD_{med}) and the maximum *RPD* (RPD_{max}), support the primacy of SAHS and HS over the GRASP algorithm. Moreover, both SAHS and HS achieve an RPD_{med} value equal to zero for each class of problems, revealing that the major target of SAHS to achieve at least the same performance of HS was reached. Looking at the RPD_{max} values it is clear that the SAHS algorithms slightly improves its performance as the problem size increases; conversely, the GRASP technique worsens as the complexity of the problem rises up.

To infer about the statistical difference between SAHS and HS a series of non-parametric tests were performed by means of Minitab17® statistical software. Figure 6.3 shows the output from a Mann-Withney test on the median *RPDs* related to the small (Figure 6.3-a), medium (Figure 6.3-b) and large (Figure 6.3-c) classes of problems and confirms there is not a statistical difference between the two algorithms. Interestingly, there is no configuration in which the GRASP algorithm is able to equal the two competitors, at least. Since the GRASP algorithm works by successive constructions of a greedy randomized solution, which in turn is improved by a semi-greedy constructive procedure, the time required to build a solution results considerably high. Therefore, the weakness of GRASP in comparison with the other techniques can be mostly explained by the lower number of solutions it evaluates within *Max_ct*.

Finally, the SAHS algorithm was compared with the LPT rule, that is the strategy adopted by the staff of the oncology unit under investigation. For the sake of brevity, the numerical results from the LPT rule have not been included into the comparison

analysis. However, the experiments demonstrate that SAHS algorithm outperformances the LPT approximately of 7% on the average *RPD*. These results are consistent with the comparison between the metaheuristic algorithm and LPT method shown in the work of Garaix et al. (2020).

Class	**Small**			**Medium**			**Large**		
Config./algo	SAHS	HS	GRASP	SAHS	HS	GRASP	SAHS	HS	GRASP
1	**0.00%**	**0.00%**	0.65%	**0.00%**	0.01%	0.91%	0.02%	**0.00%**	2.86%
2	0.02%	**0.00%**	0.28%	**0.00%**	0.01%	0.85%	0.01%	**0.00%**	1.77%
3	0.02%	0.00%	0.79%	**0.00%**	**0.00%**	1.11%	**0.00%**	**0.00%**	1.92%
4	**0.00%**	**0.00%**	0.55%	**0.00%**	**0.00%**	1.21%	**0.00%**	0.03%	1.30%
5	**0.00%**	0.01%	0.18%	**0.00%**	**0.00%**	0.11%	**0.00%**	**0.00%**	0.12%
6	**0.00%**	**0.00%**	0.16%	**0.00%**	0.01%	0.12%	**0.00%**	**0.00%**	0.09%
7	**0.00%**	**0.00%**	0.23%	0.02%	**0.00%**	0.24%	**0.00%**	**0.00%**	0.31%
8	0.01%	**0.00%**	0.29%	0.02%	**0.00%**	0.19%	**0.00%**	**0.00%**	0.23%
9	**0.00%**	**0.00%**	0.18%	**0.00%**	**0.00%**	0.52%	**0.00%**	0.03%	0.89%
10	**0.00%**	**0.00%**	0.05%	**0.00%**	**0.00%**	0.56%	0.01%	**0.00%**	0.79%
11	**0.00%**	**0.00%**	0.09%	**0.00%**	**0.00%**	0.51%	0.02%	**0.00%**	1.01%
12	**0.00%**	**0.00%**	0.14%	**0.00%**	**0.00%**	0.65%	**0.00%**	**0.00%**	0.75%
13	**0.00%**	**0.00%**	0.11%	0.01%	**0.00%**	0.11%	**0.00%**	**0.00%**	0.32%
14	0.02%	**0.00%**	0.09%	**0.00%**	**0.00%**	0.12%	**0.00%**	**0.00%**	0.74%
15	0.01%	**0.00%**	0.15%	**0.00%**	**0.00%**	0.15%	**0.00%**	**0.00%**	0.43%
16	**0.00%**	**0.00%**	0.16%	**0.00%**	**0.00%**	0.18%	**0.00%**	0.01%	0.69%
RPD_{med}	**0.00%**	**0.00%**	0.19%	**0.00%**	**0.00%**	0.27%	**0.00%**	**0.00%**	0.63%
RPD_{max}	0.02%	**0.01%**	0.79%	0.02%	**0.01%**	1.21%	**0.02%**	0.03%	2.86%

Table 6.13 Median RPDs and global indicators to compare SAHS, HS and GRASP

```
        N   Median
HS    160  0.00000
SAHS  160  0.00000


Point estimate for η1 - η2 is 0.00000
95.0 Percent CI for η1 - η2 is (-0.00000;-0.00000)
W = 25172.0
Test of η1 = η2 vs η1 ≠ η2 is significant at 0.5198
The test is significant at 0.4641 (adjusted for ties)
```

a)

```
        N   Median
HS    160  0.00000
SAHS  160  0.00000


Point estimate for η1 - η2 is 0.00000
95.0 Percent CI for η1 - η2 is (-0.00000;-0.00000)
W = 25124.5
Test of η1 = η2 vs η1 ≠ η2 is significant at 0.5024
The test is significant at 0.4526 (adjusted for ties)
```

b)

```
        N   Median
HS    160  0.00000
SAHS  160  0.00000


Point estimate for η1 - η2 is 0.00000
95.0 Percent CI for η1 - η2 is (0.00000;0.00000)
W = 25040.0
Test of η1 = η2 vs η1 ≠ η2 is significant at 0.4396
The test is significant at 0.3949 (adjusted for ties)
```

c)

Figure 6.3 Mann-Withney non-parametric tests between HS and SAHS

6.8 Conclusions

In this work, the same-day off-line stochastic chemotherapy outpatient appointment scheduling problem inspired by a real-world oncology department was investigated. Differently from the rest of the literature on this topic, we stochastically modelled all the stages provided by the chemotherapy process and, in addition, several sources of uncertainty (*e.g.*, deferrals and medical consultation times) were taken into account. Particularly, since the pharmacy is located far away from the treatment unit, we considered the real-life scenario in which a therapies delivery service is a time-consuming task needed to take the therapies to the ward.

A stochastic scheduling approach was adopted to cope with the uncertainty of the problem. Since the problem under investigation can be assimilated to a hybrid flow shop scheduling problem with resource related constraints, several idle times may occur among the stages. Therefore, to improve the quality of any appointment

schedule, we implemented a LS scheduling strategy on the decoding algorithm for the minimization of the objective function, *i.e.*, the expected total flowtime.

The outpatients scheduling problem was extensively studied by literature and most authors used the mathematical programming applied to relaxed models for generating optimal solutions. Since the problem under investigation in NP-hard in strong sense, we developed a novel Self-Adaptive Harmony Search named SAHS that is able to auto-calibrate the control parameters during the evolutionary path. To demonstrate both efficacy and efficiency of the proposed metaheuristic, several comparison analyses, also involving a GRASP algorithm from the relevant literature on the same topic, were carried out. In addition, we performed a preliminary validation of the tested metaheuristics by solving a set of small instances through a SP model we developed ad-hoc for the problem under investigation.

The quality of solutions assured by the new SAHS as well as its computational efficiency were tested by the staff of the chemotherapy clinic, which decided to replace the LPT appointment strategy adopted so far with the proposed self-adaptive metaheuristic approach.

7. Healthcare system design problem of the chemotherapy oncology departments

7.1 Introduction

Healthcare departments are complex to design due to the high amount of different resources involved in the processes and the uncertainties that characterize the healthcare systems (Young et al., 2009). The growing demand for healthcare services and rising costs are causing a situation of considerable pressure to the healthcare managers (Dabhilkar and Svarts, 2019). On the other hand, public healthcare systems should provide quality care as quickly as possible. It means that the healthcare managers and decision-makers have to design healthcare systems able to increase patient satisfaction by caring the highest number of patients in a given time period and, simultaneously, minimizing patient waiting time (Ahmed and Alkhamis 2009). Therefore, the main goal of the healthcare system design is to enable continuous patient flow and efficient performance in terms of high quality patient care (Molema et al., 2007; McDermott et al., 2011; De Regge et al., 2015). To achieve this, healthcare managers and decision-makers are bringing attentions on new methods that allow them to assure quality healthcare in timely manner and enhance the efficiency of healthcare systems (Abo-Hamad and Arisha 2013; Dai and Tayur, 2020).

In particular, these increasing pressures to ensure the most efficient and effective healthcare services encourage the decision-makers to adopt Operations Research (OR) solutions (Pitt et al., 2016; Dhiaf et al., 2021). In fact, OR systematically support the decision-making process through efficient modelling techniques or methods of OR (e.g., linear programming, simulation models) or coming from related fields that can be integrated in the final solution (e.g., regression from statistics) (Capan et al., 2017). Ahmed and Alkhamis 2009 were the firsts to adopt OR techniques in a healthcare system design problem. They combined system simulation with optimization to define the optimal number of resources in an emergency department, such as doctors and nurses, with the objectives of maximizing the number of patients cared in a day and reducing the patient time in the system. Baril et al. (2014) used a combination of design of experiments and discrete event simulation to design an outpatient orthopedic clinic and enhance its performance. Ghanes et al. (2015)

proposed a simulation-based optimization to find the optimal resource staffing levels in an emergency department where the performance indicators were the average length of stay and the average door-to-doctor time for urgent patients. Uriarte et al. (2017) discussed the benefits of supporting the decision-making in healthcare systems design through system modelling. They proved nearly optimal solutions and design rules for the optimal number of resources in an emergency department for reducing the patients' time in the system. In the last years. Farid et al. (2020) provided a novel application of System Dynamics in healthcare in order to evaluate the relation between healthcare system design and nurses' wellbeing, while Xiao and Yoogalingam (2021) adopted a solution approach that merges simulation and optimization to assess the operational impact of reserving capacity in operating rooms system for emergency patients. Finally, Ordu et al. (2021) made use of a hybrid model, which is a combination of forecasting, simulation and optimization, for identifying bed capacity and staff levels needed by a mid-size hospital in England. Among the healthcare departments, the oncology units have to face new managerial challenges due to the need of facing the increasing incidence of cancer and restricted budgets. Wilson et al. (2019) estimated that the incidence of cancer will rise from 17 million to 26 million between 2018 and 2040, causing an increase of demand of oncology services. Moreover, the patient satisfaction in an outpatient oncology department is considered important for reducing the social burden of therapy and for maintaining the quality of life among these patients (Katayama et al. 2021). The oncology process involves several human and material resources and the cooperation with the pharmacy for the therapy preparation increases the complexity of the system. In brief, the main steps of the daily process in an outpatient chemotherapy oncology clinic are: *i*) the medical consultation with the oncologist; *ii*) the therapy preparation performed by the pharmacy; *iii*) the therapy administration monitored by the nurse. Specifically, in the first step, during the medical consultation, the oncologist monitors the health status of the patient and evaluates the results coming from the blood exams. After that, the oncologist sends to the pharmacy the information about the type and dose of the therapy to be prepared. When the pharmacy receives the request, the pharmacy technicians start the therapy preparation process. Therefore, the patient has to wait that the therapy was delivered from the pharmacy to the oncology department for starting the treatment. Moreover, a nurse has to be available since she/he has to prepare and monitor the

patient. Finally, when the therapy process is completed, the same nurse releases the patient who can leave the oncology department and come back home.

The healthcare managers should consider several factors during the decision process of designing the best configuration of the oncology unit. The literature uses simulation techniques, particularly Discrete Event Simulation (DES), to identify opportunities of improvement for the investigated oncology unit. As for example, Liang et al., (2015) developed a mathematical programming model for the appointment scheduling problem of medical consultations and chemotherapy treatments and a DES model to identify initiatives for improvement in process flow and enhance the operational performance of the oncology clinic. Alvarado et al. (2018) proposed a configurable DES model that allows for assessing scheduling algorithms using both patient and management perspectives. Recently, Baril et al. (2020) combined design of experiments and simulation to study the relation between the physical and mental nurse workload with the administration of chemotherapy treatments. Finally, Fichera et al. (2021) and Yu et al. (2021) made use of lean techniques and simulation models to provide initiatives for improvement to healthcare managers of the oncology units investigated.

To the best of our knowledge, there is no work in literature specifically dealing with the healthcare system design of oncology departments. This work, inspired to the healthcare services provided by an outpatient chemotherapy oncology unit of a hospital located in (to be revealed if the paper will be accepted in respect of the double-blind peer review policy of the journal), presents the results of a multi-objective analysis conducted by means of a combination of stochastic simulation and experimental design, with the aim of working as a guideline for the healthcare managers and decision-makers. Notably, the outcomes from the aforementioned analysis would drive the stakeholders towards the selection of the alternative resource configurations able to assure a target level in terms of average number of patients cared in a given day and patient waiting time as well.

Specifically, we developed a stochastic simulation model based on discrete time recursive equations able to emulate the daily patient flow in an outpatient chemotherapy oncology unit. To make a further contribution to scientific research and to elaborate the guideline for the decision-makers, we arranged a robust statistical analysis of the results obtained by combining a full-factorial Design Of Experiments (DOE) with simulations. We investigated how the resources of the

oncology department affect the performances of the department through an Analysis of Variance (ANOVA) analysis. Once identified the influence of the factors and their interactions, we established the multi-objective Pareto analysis and a well-detailed abacus. Interestingly, the firsts allowed us to identify the non-dominated Pareto solutions; the latter can be considered as a guideline for the healthcare managers, which enables them to easily estimate the performances of the oncology clinic for each specific configuration investigated. Finally, we defined the multiple non-linear regression model to estimate the performance of an outpatient oncology unit with an adequate approximation.

The work is organized as follows. First, Section 7.2 describes the stochastic simulation model of the outpatient chemotherapy oncology unit. Section 7.3 defines the DOE and the response variables considered in the problem at hand. Section 7.4 reports the analysis of the results coming from experimental campaign of simulations. Finally, the conclusions of the work are outlined in Section 7.5.

7.2 Model development

We developed a stochastic simulation model based on discrete time recursive equations using Matlab®2021 to study the healthcare system design problem of the oncology departments. The simulation model respects the features of the problem in the oncology department described in Chapter 3. The simulation model was verified and validated in the work of Chapter 4. For the healthcare system design problem, we assumed that the medical consultation can be carried out only in the morning (until the time indicated with *T1*), since usually the oncologists dedicates the afternoon to other activities, such as visiting the patients that need only a medical consultation for controlling their health status (Liang et al., 2015). As for the chemotherapy treatment, the oncology department works with work-shift equal to *T2*. In order to evaluate the maximum number of patient *P* cared in a day, the simulation model generates a large number *M* of patients. However, only the patients that conclude the medical consultation within *T1* and the chemotherapy treatment within *T2* are considered in the computation of the key performance indicators. The simulation model considers other assumptions that are the following:

- The registration time is neglected;

- The blood exams are executed in the previous days and therefore the results are available for the medical consultation;
- The deferral probability, *i.e.*, the probability that the oncologist decides to postpone the treatment of the patient due to her/his weak health status (Garaix et al., 2020), is neglected;
- The oncologists, the pharmacy technicians and the nurses are always available;
- The devices for the therapy preparation process never break down during the given day;
- The time needed by the nurse to release the patient after the therapy administration is considered negligible.

In order to create a general model able to replace the overall process of an oncology department we used stochastic distributions derived from the seminal works of Liang et al. (2015) and Turkcan et al., (2012). Table 7.1 reports the stochastic distributions used in the simulation model. The assignment of the patient to an oncologist is random. The arrival time r_p depends on the agenda of appointments of the assigned oncologist Op_p, in which each appointment is scheduled with a time interval of 10 minutes (that is the minimum medical consultation time). During the chemotherapy treatment, the maximum number of patients that a nurse can simultaneously monitor N_{max} is set to 4 (Baril et al., 2020). It can be noticed that distribution of the treatment time is divided in four groups (*i.e.*, G1, G2, G3 and G4) depending on the type of patient disease. The probabilities that a patient can be associated with a group are as follows: *i*) 41.84% for group 1; *ii*) 25.40% for group 2; *iii*) 7.17% for group 3; *iv*) 25.59% for group 4. Finally, the total number of patients generated in the simulation model M is set to 300 and the work-shift of the oncology department is as follows: *T1*=240 minutes; *T2*=600 minutes (Hesaraki et al., 2019).

Although one of the main goals in healthcare management is to guarantee a rewarding quality of service to patients, which also entails a reasonable waiting time, the daily number of patients that the department is able to receive is another undeniable indicator of its efficiency. For this reason, two main key performance indicators are pursued. The first indicator is the mean flowtime (also defined as length of stay) that allows evaluating how many times a patient spends in the department (Ghanes et al., 2015; Uriarte et al., 2017; Hesaraki et al., 2019). The

minimization of the mean flowtime $\overline{F}$ directly involves the reduction of the mean patient waiting time (see Section 4.2). The second indicator is the throughput of the system, also indicated as the maximum number of patients P cared in the given day (Ahmed and Alkhamis 2009). Furthermore, a third key performance indicator is defined specifically for the problem at hand. It is a trade-off indicator to minimize that consists of the ratio between mean flowtime $\overline{F}$ and number of patients P cared in the given day ($\overline{F}/P$).

Stage	**Distribution [min]**
Medical consultation	Uniform (10,30)
Therapy preparation time	Weibull (10.5,1.42)-1.5
Setup time	Triangular (5,10,15)
Therapy duration for group 1	Triangular (15,74,240)
Therapy duration for group 2	Triangular (15,63,240)
Therapy duration for group 3	Triangular (60,98,180)
Therapy duration for group 4	Triangular (75,137,255)

Table 7.1 Stochastic distributions used in the simulation model

7.3 Design of Experiments

We disposed a full-factorial DOE in which the experimental factors are: *i*) number of oncologists (O); *ii*) number of chairs for the treatment (C); *iii*) the ratio between the number of nurses and the number of chairs for the treatment (N/C); *iv*) number of pharmacy technicians (D); *v*) therapy transportation time (TD). Hence, we adopt five distinct factors as independent variables, wherein the first factor varies at four levels, the second factors at five levels, the third factors at two levels and the rest at three levels, as illustrated by Table 7.2. We set up the values of each level on the basis of real case studies addressed by the scientific literature so far (please see Alvarado et al. 2018; Garaix et al., 2020; Hesaraki et al., 2019; Turkcan et al., 2012 among the others). Based on our experience on the field, there exist alternative scenarios for the delivery of therapies from the pharmacy to the oncology unit. When the oncology department disposes of an in-house pharmacy, the therapy transportation time TD is set to 3 minutes. When the pharmacy is situated in a different location from the oncology unit, there could be a medium or a high distance

between the departments. As for the medium distance, the therapy transportation time *TD* is set equal to 10 minutes and the batch size *CAP* is equal to 3 therapies. In the case of high distance, *TD* and *CAP* are equal to 20 minutes and 7 therapies, respectively (Fichera et al., 2021). As for the response variable, three key performance indicators are considered: i) the mean flowtime ($\overline{F}$); ii) the number of patients (P); iii) a trade-off indicator ($\overline{F}/P$). Then, the proposed approach involves $5 \cdot 4 \cdot 3^2 \cdot 2 = 360$ scenarios or different configurations of the oncology unit. To make the analysis robust enough, we consider 1,000 replicates of each scenario so as to achieve a total of 1,000 · 360 = 360,000 experimental runs. The experimental campaign was launched on a 4GB RAM-2 processors virtual machine embedded on a workstation equipped with an INTEL i9-9900 3.6 GHz 10 core CPU, 32Gb DDR4 2,666MHz RAM and Win 10 PRO OS.

Factors	**Level 1**	**Level 2**	**Level 3**	**Level 4**	**Level 5**
Number of doctors (O)	4	6	8	10	-
Number of chairs (C)	10	15	20	25	30
Number of nurses / Number of chairs (N/C)	0.25	0.33	-	-	-
Number of pharmacy technicians (D)	1	2	3	-	-
Therapy transportation time (TD)	3	10	20	-	-

Table 7.2 Design of Experiments

7.4 Analysis of results

This section reports the results arising from the experimental approach and arguments the findings related to the healthcare system design of the oncology departments. To individuate the impact of each factor on the three key performance indicators and to understand the interactions among them, we executed an ANOVA analysis described in Section 7.4.1. Subsequently, in Section 7.4.2 we analyse the outcomes through a multi-objective Pareto analysis so as to identify the non-dominated solutions and the corresponding configurations. To further elaborate the discussion, in Section 7.4.3 we also provide an abacus of results, which would drive the stakeholders towards the selection of the alternative resource configurations. Finally, the multiple non-linear regression models for each performance measures are given in Section 7.4.4.

7.4.1 ANOVA analysis

The ANOVA analysis allows determining if the experimental factors statistically bias the response variables. In this work, three ANOVA analyses at 95% confidence level were carried out to discuss the influence of each experimental factor on the three response variables. To do this, we have adopted Minitab 17® commercial package as statistical tool of the analyses. For the sake of brevity, the ANOVA analyses were limited until the second order interactions of the experimental factors.

7.4.1.1 Patient flowtime

Figure 7.1 reports the numerical outcomes resulting from the ANOVA analysis for the mean patient flowtime F performance measure. The ANOVA table shows that the model is statistically significant at 95% confidence level since the p-value of the model is equal to zero. The robustness of the model is also confirmed by the value of R-sq equal to 98.53%. All the independent variables significantly influence the performance measure with significance level of 0.05, except for N/C that reports a p-value equal to 0.42. Looking at the F-values, the number of oncologists O and the number of pharmacy technicians D are the experimental factors that have the most relevant impact on mean flowtime. In order to better interpret the results, Figure 7.2 depicts the graphs related to the ANOVA analysis, *i.e.*, the main effect plot in Figure 7.2-a, the Tukey pairwise comparison in Figure 7.2-b, the most interesting interactions plot that are between O and C in Figure 7.2-c and between C and D in Figure 7.2-d.

These outcomes suggest that the patient waiting time mainly depends on the number of resources available in the first two stages of the oncology process: *i.e.*, the medical consultation and the therapy preparation process. In particular, it can be deduced by the main effect plot (Figure 7.2-a) that high number of oncologists increases the mean patient flowtime. It means that there will be a high number of patients that wait for receiving the treatment, when the number of oncologists O is set to the highest level. Figure 7.2-b reports the Tukey test for each experimental factor to further support the ANOVA analysis. Specifically, when different levels of the same experimental factors do not share the same letter, it means that the levels are significant different. For the number of oncologists, the Tukey test points out that increasing the number of oncologists from 8 to 10 does not induce a significant

increase on mean flowtime. On the other hand, a high level of number of pharmacy technicians *D* improves the mean value of patient flowtime. Also, the therapy transportation time *TD* and the number of chairs for the treatment *C* have a relevant impact on mean flowtime. As expected, a low value of *TD* and a high value of *C* lead a reduction of the patient waiting time. Specifically, it can be noticed from the Tukey Test that a statistical reduction of patient waiting time is obtained passing from 20 minutes to 10 minutes of *TD* and from 15 to 25 of *C*.

Finally, Figure 7.2-c and Figure 7.2-d illustrate the most interesting 2-order interaction plots: i) the interaction between the number of oncologists and the number of chairs (*O***C*); ii) the interaction between the number of chairs and the number of pharmacy technicians (*C***D*). Interestingly, the interaction plots show that the impact of the number of chairs becomes relevant when the oncology unit disposes of a low number of oncologists. Indeed, if the oncology department disposes of 4 oncologists, the increase the number of chairs for treatment from 10 to 30 chairs allows reducing F of more than 50 minutes on average. Similarly, selecting the appropriate number of chairs is needed when the pharmacy is composed by 2 or more pharmacy technicians. If the pharmacy disposes of only one pharmacy technician, it becomes irrelevant for the patient flowtime to increase the number of chairs.

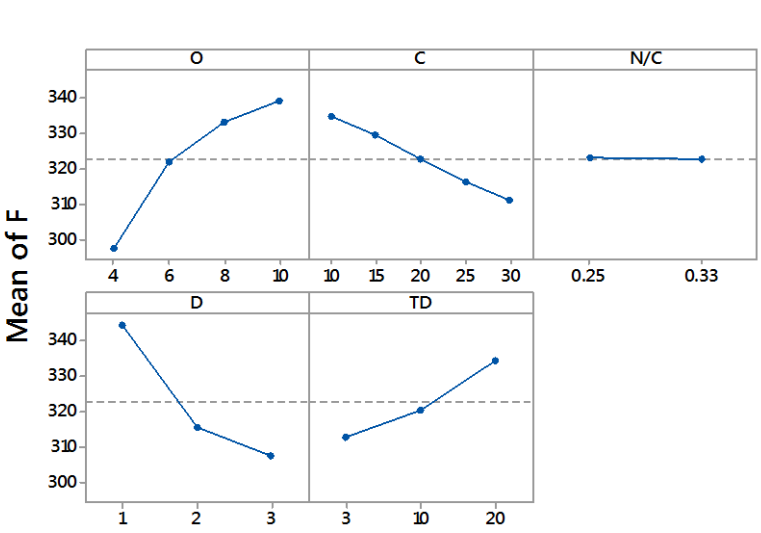
Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	67	274396	4095.5	292.14	0.000
Linear	12	241328	20110.7	1434.54	0.000
O	3	92154	30717.9	2191.18	0.000
C	4	26261	6565.3	468.32	0.000
N/C	1	9	9.1	0.65	0.420
D	2	93276	46638.2	3326.81	0.000
TD	2	29627	14813.7	1056.70	0.000
2-Way Interactions	55	33068	601.2	42.89	0.000
O*C	12	15230	1269.1	90.53	0.000
O*N/C	3	1	0.2	0.01	0.998
O*D	6	3519	586.4	41.83	0.000
O*TD	6	454	75.7	5.40	0.000
C*N/C	4	8	2.1	0.15	0.964
C*D	8	13255	1656.8	118.19	0.000
C*TD	8	28	3.5	0.25	0.981
N/C*D	2	1	0.4	0.03	0.973
N/C*TD	2	7	3.3	0.23	0.793
D*TD	4	567	141.8	10.11	0.000
Error	292	4094	14.0		
Total	359	278490			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
3.74418	98.53%	98.19%	97.77%

Figure 7.1 ANOVA table for flowtime



O	Inst	Mean	Grouping
10	90	338.95	A
8	90	332.86	A
6	90	321.74	B
4	90	297.09	C

C	Inst	Mean	Grouping
10	72	334.43	A
15	72	329.22	A
20	72	322.67	A B
25	72	316.22	B
30	72	310.75	B

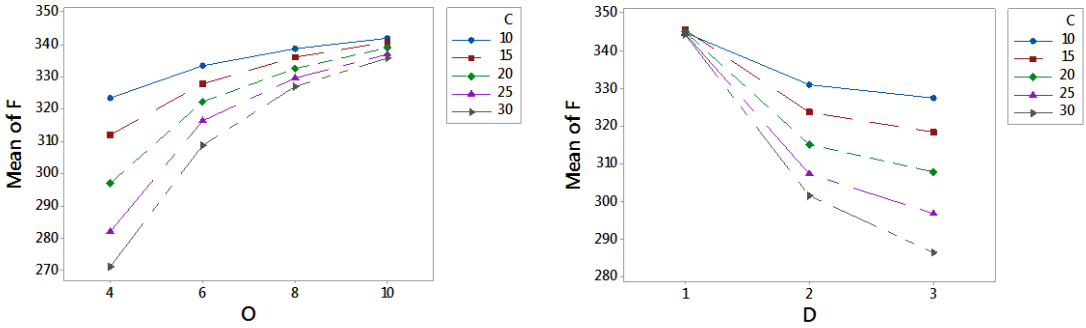
N/C	Inst	Mean	Grouping
0.25	180	322.82	A
0.33	180	322.50	A

D	Inst	Mean	Grouping
1	120	344.90	A
2	120	315.72	B
3	120	307.35	C

TD	Inst	Mean	Grouping
20	120	334.65	A
10	120	320.62	B
3	120	312.71	B

(a) Main effect

(b) Tukey pairwise



(c) Interaction plot

(d) Interaction plot

Figure 7.2 Analysis of results for flowtime

7.4.1.2 Number of patients

The second performance indicator analysed is the number of patients cared in a day in the oncology unit. Through the ANOVA analysis, we investigated how the experimental factors influence this performance measure. The ANOVA table is reported in Figure 7.3 and shows the validity of the model since the p-value is zero and the R-sq is equal to 98.53%. *N/C* is the unique experimental factor that does not have a relevant impact *P*, while all the other considered factors are statistically significant at 95% confidence level. The most relevant factor to increase the number of patients visited in the same day is the number of chairs for treatment *C* with a F-value of 3159.51. Also, the number of pharmacy technicians has a strong impact on *P* performance indicator (*F*-value = 1708.28).

Figure 7.4-a and Figure 7.4-b show the main effect plot and the Tukey test, respectively, supporting the analysis of the experimental factors effects on *P*. As expected, a high number of oncologists allows increasing the number of patients cared in a day. However, the Tukey test demonstrates that increasing the number of oncologists from 8 to 10 does not involve a significant improvement of *P*. A high level of *C* allows increasing the *P* indicator. Looking at the Tukey test, it can be noticed that each level is classified in a different group. It means that each level of the number of chairs induces a significant increment on the number of patients cared in a day. As for the number of pharmacy technicians *D*, a significant increment of *P* is obtained by passing from 1 to 2 pharmacy technicians. On the other hand, the Tukey test suggests that it is not statistically significant to increase the number of pharmacy technicians from 2 to 3. Finally, the low value of *TD* involves a slight improvement on the response variable *P*.

As for the mean flowtime indicator, the most relevant interaction plots (*i.e.*, *O***C* and *C***D*) are reported (see Figure 7.4-c and Figure 7.4-d). Figure 7.4-c demonstrates that, when the oncology department disposes of 4 oncologists, the maximum number of patients care in a day can be obtained with 25 chairs. In this specific case, there is no statistical difference between 25 and 30 chairs. A similar trend can be observed in the interaction between the number of chairs *C* and the number of pharmacy technicians *D*. In fact, if the pharmacy is composed by only 1 pharmacy technician, there is no benefit in terms of *P* performance measure to have more than 20 chairs for the treatment.

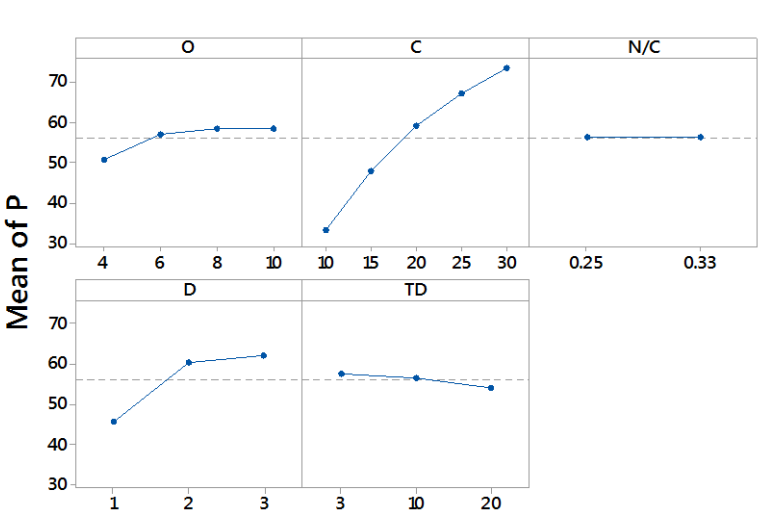
Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	67	116142	1733.5	292.80	0.000
Linear	12	99718	8309.9	1403.61	0.000
O	3	3803	1267.7	214.13	0.000
C	4	74821	18705.3	3159.51	0.000
N/C	1	0	0.1	0.01	0.910
D	2	20227	10113.6	1708.28	0.000
TD	2	866	433.2	73.17	0.000
2-Way Interactions	55	16424	298.6	50.44	0.000
O*C	12	3619	301.6	50.94	0.000
O*N/C	3	0	0.0	0.00	1.000
O*D	6	1496	249.3	42.10	0.000
O*TD	6	28	4.7	0.80	0.570
C*N/C	4	0	0.1	0.01	1.000
C*D	8	11238	1404.7	237.27	0.000
C*TD	8	17	2.1	0.36	0.940
N/C*D	2	0	0.0	0.00	0.996
N/C*TD	2	0	0.1	0.02	0.984
D*TD	4	26	6.4	1.09	0.364
Error	292	1729	5.9		
Total	359	117871			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
2.43317	98.53%	98.20%	97.77%

Figure 7.3 ANOVA table for number of patients



(a) Main effect plot

O	Inst	Mean	Grouping
10	90	58.52	A
8	90	58.28	A
6	90	57.09	A B
4	90	50.56	B

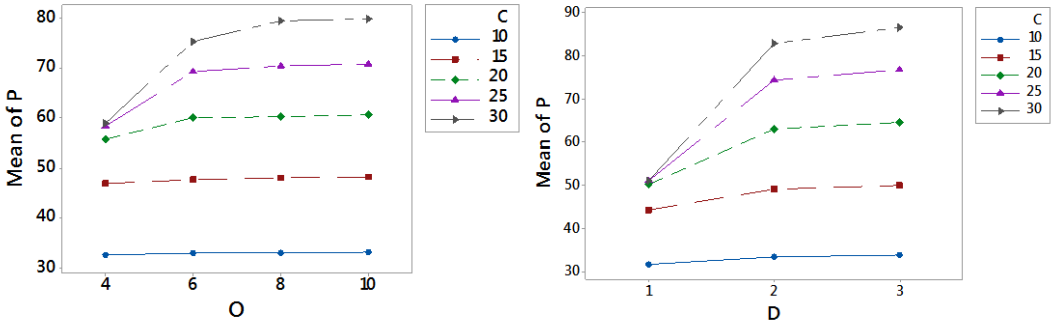
C	Inst	Mean	Grouping
30	72	73.41	A
25	72	67.27	B
20	72	59.191	C
15	72	47.743	D
10	72	32.960	E

N/C	Inst	Mean	Grouping
0.33	180	56.13	A
0.25	180	56.10	A

D	Inst	Mean	Grouping
3	120	62.31	A
2	120	60.47	A
1	120	45.568	B

TD	Inst	Mean	Grouping
3	120	57.82	A
10	120	56.45	A
20	120	54.07	A

(b) Tukey pairwise



(c) Interaction plot

(d) Interaction plot

Figure 7.4 Analysis of results for number of patients

7.4.1.3 Trade-off indicator

In order to consider simultaneously both the patient and the managerial point of views, we have included a trade-off performance indicator in the analysis, defined as $\overline{F}/P$. The ANOVA table in Figure 7.5 demonstrates the consistency of the model since it reports a p-value of the model equal to zero and a R-sq equal to 99.92%. With the exception of N/C, all the experimental factors are statistically significant since their p-values are equal to zero. The F-values suggest that C, D and TD are the most impacting experimental factors. On the other hand, the influence of the number of oncologists O on $\overline{F}/P$ can be considered weak in comparison with the other F-values. It can be also seen graphically through the mean effect plots in Figure 7.6-a. As for the number of chairs, a high number of chairs allows reducing the $\overline{F}/P$ indicator. It means that increasing the number of chairs for the treatment C allows enhancing the performance of the oncology unit both in a patient and managerial perspective.

However, the Tukey test in Figure 7.6-b suggests that there is no more benefits in terms of $\overline{F}/P$ when the oncology unit disposes of more than 25 chairs. Similarly, a higher number of pharmacy technicians D allows enhancing the $\overline{F}/P$ indicator, but there is no statistical difference between 2 and 3 pharmacy technicians. Finally, it can be denoted from both Figure 7.6-a and Figure 7.6-b that reducing the therapy transportation time is needed to reduce $\overline{F}/P$. As concerns the 2-way interactions, Figure 7.6-c depicts the most significant interaction plot between the number of chairs and the number of pharmacy technicians (F-value=1264.22). Interestingly, it can be noticed that when the pharmacy disposes of only one pharmacy technician, there is no improvement in terms of $\overline{F}/P$ if the oncology unit has more than 20 chairs for the treatment.

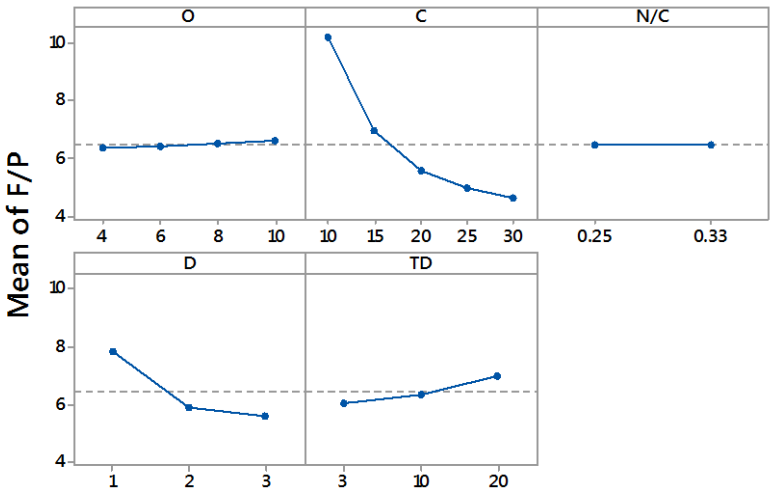
Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	67	1980.34	29.557	5742.03	0.000
Linear	12	1909.00	159.084	30904.85	0.000
O	3	3.09	1.030	200.04	0.000
C	4	1490.34	372.585	72381.20	0.000
N/C	1	0.02	0.020	3.81	0.052
D	2	359.87	179.934	34955.39	0.000
TD	2	55.69	27.845	5409.35	0.000
2-Way Interactions	55	71.33	1.297	251.96	0.000
O*C	12	2.81	0.234	45.43	0.000
O*N/C	3	0.00	0.001	0.17	0.918
O*D	6	2.48	0.413	80.30	0.000
O*TD	6	0.04	0.006	1.21	0.300
C*N/C	4	0.04	0.009	1.72	0.145
C*D	8	52.06	6.508	1264.22	0.000
C*TD	8	6.78	0.847	164.60	0.000
N/C*D	2	0.00	0.000	0.05	0.948
N/C*TD	2	0.01	0.006	1.23	0.293
D*TD	4	7.12	1.780	345.79	0.000
Error	292	1.50	0.005		
Total	359	1981.84			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.0717463	99.92%	99.91%	99.88%

Figure 7.5 ANOVA table for trade-off indicator



(a) Main effect

O	Inst	Mean	Grouping
10	90	6.574	A
8	90	6.492	A
6	90	6.371	A
4	90	6.344	A

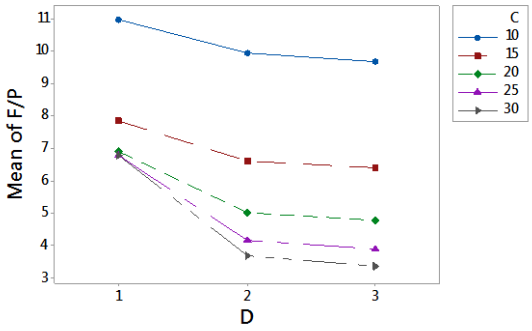
C	Inst	Mean	Grouping
10	72	10.185	A
15	72	6.9437	B
20	72	5.563	C
25	72	4.938	D
30	72	4.597	D

N/C	Inst	Mean	Grouping
0.25	180	6.453	A
0.33	180	6.438	A

D	Inst	Mean	Grouping
1	120	7.851	A
2	120	5.872	B
3	120	5.613	B

TD	Inst	Mean	Grouping
20	120	6.970	A
10	120	6.343	A B
3	120	6.023	B

(b) Tukey pairwise



(c) Interaction plot

Figure 7.6 Analysis of results for trade-off indicator

7.4.2 Pareto analysis

The managers may evaluate both mean flowtime, $\overline{F}$, and the number of patients, P, so as to define the best configuration of the oncology department. However, the ANOVA analysis discussed above indicates that in some cases there is no configurations able to improve simultaneously the two performance measures. For this reason, a trade-off indicator, $\overline{F}/P$, was introduced and evaluated. Now, we would further discuss this trade-off by employing the multi-objective Pareto approach. To this end, 360 scenarios investigated are graphically reported through the Pareto diagram (see Figure 7.7) in which the x and y axes are represented by P and $\overline{F}$ indicators, respectively. A trading-off is necessary to move from one solution to another. This process obviously involves an improvement of a performance measure and, at the same time, the worsening of the other performance indicator. The Pareto

diagram is here adopted since it allows us to identify the non-dominated solutions (highlighted with the red points), also defined as Pareto solutions. Table 7.3 reports the values of the experimental factors for each non-dominated solution and the corresponding mean and standard deviation values of the performance indicators. In order to isolate the Pareto solutions and their standard deviations, Figure 7.8 shows merely their mean values and the error bars.

As suggested by the ANOVA analysis of the trade-off indicator, *i.e.*, F/P, the Pareto analysis points out the strong dependence of the performance of the oncology unit on the number of chairs (C), the number of pharmacy technicians (D) and the therapy transportation time (TD). In fact, the non-dominated solutions can be achieved only with the highest values of C and D (except for the second scenario wherein the number of chairs is set to 20) and the lowest values of TD. Furthermore, as previously suggested by the main effect plot and Tukey test of $\overline{F}/P$, the number of oncologists (O), and the ratio between the number of nurses and chairs (N/C), are not significantly influent and there is no statistically difference in means among their levels. These results further confirm the validity of the proposed trade-off indicator $\overline{F}/P$.

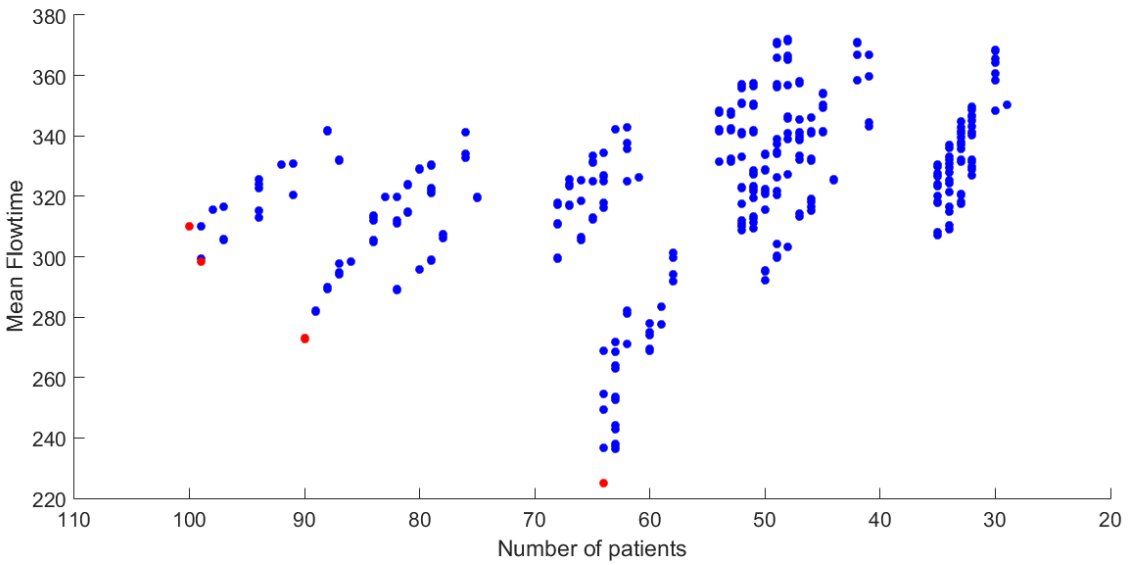


Figure 7.7 Pareto diagram

Scenarios	Factors					KPIs				
	O	C	N/C	D	TD	$\overline{F}$	P	$\overline{F}/P$	$\sigma(\overline{F})$	$\sigma(P)$
1	4	30	0.25	3	3	225.06	64	3.54	14.15	6.41
2	6	20	0.33	3	3	272.81	90	3.03	14.22	5.29
3	8	30	0.25	3	3	298.42	99	3.02	11.53	5.13
4	10	30	0.33	3	3	309.96	100	3.11	9.58	5.05

Table 7.3 Configurations and performances of the non-dominated solutions

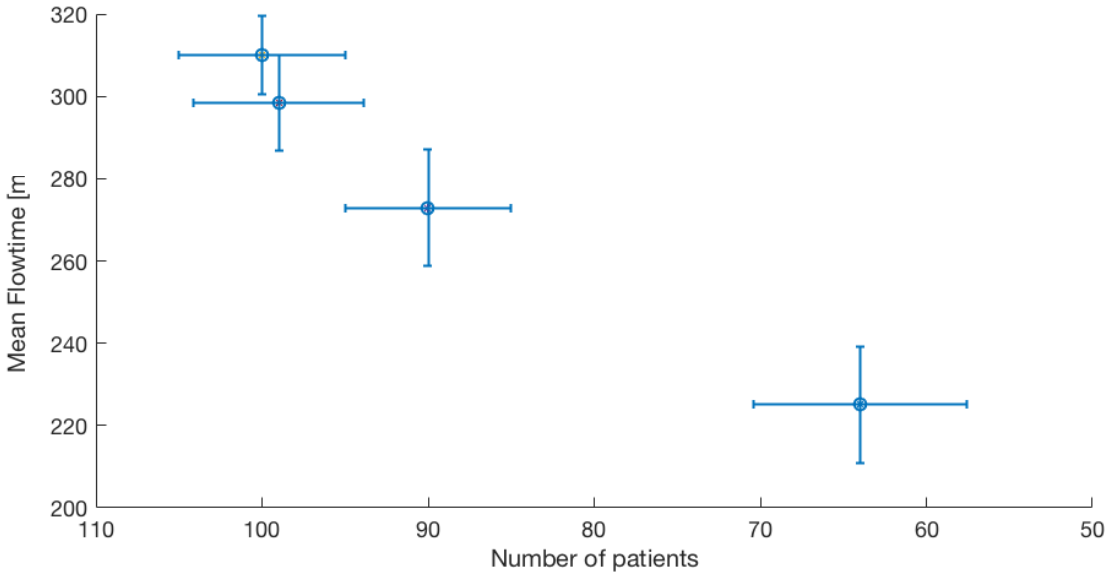


Figure 7.8 Error bars of the non-dominated solutions

7.4.3 Abacus of results

To further support the stakeholders in the decision-making process of the healthcare system design of an oncology unit, we provide an abacus of results reported in Table 7.4. This abacus enables obtaining a comprehensive overview of the outcomes coming from the alternative configurations. The abacus is composed of two levels in the x-axis and three levels in the y-axis. Precisely, in the first level of the x-axis there is the number of chairs (C), while in the second level there is the therapy transportation time (TD). As concerns the y-axis, it is composed by the number of oncologists (O) in the first level, the ratio nurses-chairs (N/C) in the second level and the number of pharmacy technicians (D) in the third level. For each configuration of the oncology unit, the abacus reports the mean and the standard deviation values of $\overline{F}$ and P (the standard deviation values are recorded into the brackets). To facilitate the consultation of the abacus, we arrange the table with a scale of colors, which depends

on the values of *P* indicator (the explanation of the scale of colors is reported in the caption of Table 7.4). The findings arising from the abacus can be summarized on the basis of the colours as follows:

- From *P* = 20 to *P* = 39 patients (yellow cells): these configurations strictly depend on the number of chairs. In fact, these values of P are obtained with C=10, regardless of the values of the other factors;
- From *P* = 40 to *P* = 59 patients (green cells): as for the previous case, when the oncology unit disposes of 15 chairs, it will be not able to receive more than 59 patients, independently from the values of the other experimental factors. Furthermore, if the oncology unit has more than 15 chairs and the pharmacy is composed of only one pharmacy technician (*i.e.*, *D* = 1) the oncology department can receive at most 59 patients in a day. Another configuration able to care at most 59 patients in a day consists of 20 chairs, 4 oncologists, and therapy transportation time at least equal to 10 minutes. In this specific case, the performance in terms of number of patients is independent from the number of pharmacy technicians *D*;
- From *P* = 60 to *P* = 79 patients (light blue cells): the oncology units can care a number of patients between 60 and 79, when the oncology unit disposes of:
    - 20 chairs, 2 or 3 pharmacy technicians, 4 oncologists and the therapy transportation time is equal to 3 minutes;
    - 20 chairs and the number of oncologists is equal to or more than 6;
    - 25 chairs, 6 oncologists, 2 pharmacy technicians and the therapy transportation time is equal to 3 minutes;
    - 25 chairs, 2 pharmacy technicians and the therapy transportation time is equal to or more than 10 minutes;
    - 25 chairs, at most 8 oncologists, 3 pharmacy technicians and the therapy transportation time is equal to 20 minutes;
    - 25 or 30 chairs, 2 or 3 pharmacy technicians and 4 oncologists;
- *P* > 80 patients (dark blue cells): in all the other cases considered in the DOE, the oncology units are able to receive more than 80 patients in a given day. In particular, it can be noticed that *O*, *C* and *D* have to be at least equal to 6, 25 and 2, respectively.

		C	10			15			20			25			30		
O	N/C	D-TD	3	10	20	3	10	20	3	10	20	3	10	20	3	10	20
10	0.33	3	327 (9.3)	332 (9.7)	343 (10.4)	323 (6.2)	328 (6.5)	337 (6.9)	318 (4.7)	323 (4.8)	333 (5.1)	314 (3.7)	320 (3.9)	329 (4.1)	310 (3.1)	316 (3.2)	326 (3.5)
			35 (15.4)	34 (15.5)	33 (16)	52 (13.4)	51 (13)	49 (12.7)	68 (11.6)	67 (11.9)	65 (11.5)	84 (10.7)	83 (10.7)	80 (10.6)	99 (10.3)	98 (9.9)	94 (10.8)
		2	331 (9.5)	336 (9.9)	349 (10.8)	327 (6.4)	334 (6.7)	346 (7.2)	325 (4.9)	331 (5.1)	342 (5.5)	324 (4)	330 (4.2)	341 (4.5)	324 (3.4)	331 (3.6)	342 (3.9)
			35 (16.2)	34 (15.6)	32 (16.4)	51 (13.1)	50 (13.3)	48 (13.9)	66 (12.2)	65 (11.8)	63 (12.7)	81 (11.1)	79 (11.1)	76 (11.5)	94 (11.4)	91 (11.2)	88 (11.3)
		1	341 (10.2)	349 (10.8)	368 (12.4)	345 (7.4)	354 (7.9)	371 (8.8)	348 (6.6)	357 (7)	372 (7.8)	348 (6.5)	356 (6.9)	371 (7.6)	348 (6.5)	357 (6.9)	371 (7.6)
			33 (17.2)	32 (16.3)	30 (17.6)	47 (15.1)	45 (15.5)	42 (16.2)	53 (15.4)	51 (15.8)	48 (16.4)	54 (15.9)	52 (16.3)	49 (17.2)	54 (15.6)	52 (16)	49 (16.8)
	0.25	3	328 (9.4)	333 (9.7)	345 (10.4)	323 (6.2)	329 (6.5)	339 (7)	317 (4.6)	324 (4.8)	334 (5.2)	313 (3.7)	320 (3.9)	329 (4.1)	310 (3.1)	317 (3.3)	326 (3.5)
			35 (16.2)	34 (15.7)	33 (15.6)	52 (12.9)	51 (12.9)	49 (13.1)	68 (12.1)	67 (11.4)	64 (11.8)	84 (11.1)	82 (10.1)	80 (11.1)	100 (9.6)	97 (10.9)	94 (10.3)
		2	330 (9.5)	337 (10)	349 (10.8)	327 (6.4)	334 (6.7)	346 (7.3)	326 (4.9)	331 (5.1)	343 (5.5)	324 (4)	331 (4.2)	341 (4.5)	323 (3.4)	331 (3.6)	342 (3.9)
			35 (15.4)	34 (16.5)	32 (16.3)	51 (13.7)	50 (13.1)	48 (13.5)	67 (12.4)	65 (12)	62 (12.6)	81 (11.5)	79 (11.2)	76 (11.7)	94 (11.1)	92 (11.3)	88 (11.4)
		1	341 (10.3)	350 (10.9)	369 (12.4)	346 (7.4)	354 (7.9)	371 (8.9)	347 (6.6)	357 (7)	372 (7.8)	348 (6.5)	356 (6.9)	371 (7.6)	348 (6.5)	357 (6.9)	370 (7.6)
			33 (16.4)	32 (16.8)	30 (18)	46 (14.8)	45 (15.2)	42 (16.2)	53 (15.7)	51 (16)	48 (16.4)	54 (16.6)	52 (16.2)	49 (17.5)	54 (15.8)	52 (16.7)	49 (17)
8	0.33	3	323 (9.2)	330 (9.6)	340 (10.3)	318 (6.1)	323 (6.3)	334 (6.8)	311 (4.6)	317 (4.8)	327 (5.1)	305 (3.6)	312 (3.8)	321 (4)	298 (3)	306 (3.2)	315 (3.4)
			35 (16)	34 (15.9)	33 (16.1)	52 (12.5)	51 (13.1)	49 (12.8)	68 (12.3)	67 (12.2)	64 (11.7)	84 (11.3)	82 (11.2)	79 (11)	99 (11.5)	97 (10.8)	94 (10.4)
		2	327 (9.4)	332 (9.8)	345 (10.7)	322 (6.3)	328 (6.6)	341 (7.2)	319 (4.8)	325 (5)	336 (5.4)	315 (3.9)	322 (4.1)	334 (4.4)	313 (3.3)	320 (3.5)	332 (3.8)
			35 (15.9)	34 (16.2)	32 (16.2)	51 (13)	50 (13)	48 (13.6)	66 (12.2)	64 (12.8)	62 (12.8)	81 (12.5)	79 (11.9)	76 (11.8)	94 (11.4)	91 (11.4)	87 (12.4)
		1	338 (10.2)	346 (10.8)	364 (12.2)	341 (7.3)	350 (7.8)	367 (8.8)	343 (6.5)	351 (6.9)	366 (7.7)	342 (6.4)	351 (6.8)	365 (7.5)	341 (6.3)	351 (6.8)	366 (7.6)
			33 (17.3)	32 (16.7)	30 (17.8)	46 (14.5)	45 (15.2)	41 (16.3)	53 (15.8)	51 (15.8)	48 (16.9)	53 (16.8)	52 (16.9)	48 (17.6)	54 (16.1)	52 (17.4)	48 (17.3)
	0.25	3	324 (9.3)	331 (9.7)	341 (10.4)	318 (6.1)	323 (6.4)	335 (6.9)	311 (4.6)	317 (4.8)	327 (5.1)	305 (3.6)	311 (3.8)	321 (4)	299 (3)	306 (3.2)	315 (3.4)
			35 (16.3)	34 (16)	33 (15.4)	52 (13.6)	51 (13)	49 (13.6)	68 (11.4)	67 (12.1)	64 (11.8)	84 (11.2)	82 (11)	79 (11.5)	99 (11.2)	97 (10.7)	94 (10.8)
		2	327 (9.4)	333 (9.8)	346 (10.8)	322 (6.3)	329 (6.6)	341 (7.2)	319 (4.8)	325 (5)	338 (5.5)	315 (3.9)	323 (4.1)	333 (4.4)	313 (3.3)	320 (3.5)	332 (3.8)
			35 (16)	34 (16.1)	32 (16.1)	51 (13.2)	50 (13.2)	47 (13.5)	66 (12.4)	65 (12.8)	62 (12.6)	81 (11.6)	79 (11.7)	76 (12.2)	94 (11.6)	91 (11.7)	87 (12)
		1	338 (10.2)	347 (10.9)	365 (12.3)	342 (7.4)	349 (7.8)	367 (8.8)	342 (6.5)	350 (6.9)	367 (7.7)	342 (6.4)	351 (6.7)	366 (7.5)	342 (6.4)	351 (6.8)	366 (7.6)
			33 (17)	32 (16.7)	30 (17.8)	46 (15.2)	45 (15.4)	42 (15.8)	53 (16.1)	51 (16.2)	48 (16.8)	54 (16.2)	52 (16.7)	49 (17.3)	54 (16.8)	52 (16)	49 (17)
O	N/C	D-TD	3	10	20	3	10	20	3	10	20	3	10	20	3	10	20
		C	10			15			20			25			30		

		C	10			15			20			25			30		
O	N/C	D-TD	3	10	20	3	10	20	3	10	20	3	10	20	3	10	20
6	0.33	3	318 (9.1)	324 (9.5)	336 (10.3)	309 (6)	316 (6.3)	326 (6.7)	299 (4.4)	305 (4.6)	316 (4.9)	289 (3.5)	296 (3.7)	307 (4)	273 (3)	282 (3.2)	295 (3.4)
			35 (15)	34 (15.3)	33 (15.6)	51 (13.6)	50 (13.5)	49 (13.5)	68 (12.6)	66 (12.2)	64 (12.3)	82 (12.2)	80 (11.9)	78 (11.8)	90 (14.3)	89 (13.5)	87 (13.3)
		2	320 (9.3)	328 (9.7)	341 (10.6)	313 (6.2)	320 (6.5)	332 (7)	306 (4.6)	312 (4.8)	325 (5.3)	299 (3.8)	306 (3.9)	320 (4.3)	289 (3.3)	299 (3.5)	312 (3.7)
			35 (16.7)	34 (16.3)	32 (15.5)	51 (13.3)	49 (13.5)	47 (14.2)	66 (12.9)	65 (12.2)	62 (12.6)	79 (12.6)	78 (13.1)	75 (13.2)	88 (15.5)	86 (14.6)	84 (13.8)
		1	332 (10)	340 (10.6)	359 (12)	332 (7.2)	341 (7.6)	358 (8.6)	333 (6.3)	342 (6.7)	357 (7.6)	332 (6.2)	341 (6.6)	357 (7.4)	332 (6.2)	341 (6.6)	357 (7.4)
			33 (16.6)	32 (17.6)	30 (18.7)	46 (15.2)	45 (15.2)	42 (16.1)	52 (16.4)	51 (16.5)	47 (17.2)	54 (16.6)	52 (17.2)	48 (18.2)	53 (15.8)	51 (17)	49 (17.7)
	0.25	3	318 (9.1)	325 (9.6)	337 (10.3)	309 (6)	316 (6.3)	327 (6.8)	300 (4.4)	306 (4.6)	318 (5)	289 (3.5)	296 (3.7)	307 (4)	273 (3)	282 (3.2)	294 (3.4)
			35 (16.5)	34 (16)	33 (15.6)	52 (13.9)	50 (14.1)	48 (13.2)	68 (11.8)	66 (12.4)	64 (12.2)	82 (12.5)	80 (12.6)	78 (11.9)	90 (14.2)	89 (13.5)	87 (13.6)
		2	321 (9.3)	328 (9.8)	343 (10.8)	313 (6.2)	322 (6.5)	333 (7.1)	306 (4.6)	313 (4.9)	326 (5.3)	299 (3.8)	307 (4)	320 (4.3)	290 (3.3)	298 (3.4)	313 (3.7)
			34 (16.5)	34 (15.5)	32 (16.6)	51 (13.5)	49 (14.2)	47 (14.3)	66 (12.8)	65 (12.4)	61 (12.6)	79 (13.1)	78 (13.4)	75 (12.7)	88 (15.1)	87 (15.2)	84 (14.1)
		1	332 (10.1)	341 (10.6)	361 (12.1)	332 (7.2)	342 (7.7)	360 (8.7)	332 (6.3)	341 (6.7)	358 (7.6)	332 (6.2)	341 (6.6)	356 (7.3)	333 (6.2)	341 (6.6)	356 (7.3)
			33 (17)	32 (17.4)	30 (18.6)	46 (15.9)	45 (16.2)	41 (16.1)	53 (16.3)	51 (16.1)	47 (16.9)	53 (17)	52 (17.2)	49 (17.7)	53 (16.8)	52 (17)	49 (17.3)
4	0.33	3	307 (8.9)	317 (9.4)	327 (10.2)	292 (5.8)	300 (6.1)	313 (6.6)	269 (4.5)	278 (4.7)	292 (5)	244 (3.9)	254 (4)	271 (4.3)	225 (3.5)	237 (3.8)	255 (4)
			35 (16.6)	34 (16)	32 (16.6)	50 (14.7)	49 (14.6)	47 (13.8)	60 (17)	60 (16.2)	58 (14.9)	63 (16.8)	63 (16.1)	62 (15.1)	64 (14)	63 (14)	64 (13.6)
		2	309 (9)	318 (9.6)	331 (10.5)	295 (5.9)	303 (6.3)	318 (6.9)	274 (4.6)	283 (4.8)	300 (5.2)	253 (4)	263 (4.2)	281 (4.5)	238 (3.7)	249 (3.9)	269 (4.2)
			34 (16.1)	33 (16.7)	32 (16.3)	50 (15.4)	48 (14.8)	46 (14.6)	60 (16.6)	59 (16.3)	58 (15.4)	63 (18.5)	63 (17.5)	62 (16.8)	63 (17.1)	64 (16.1)	64 (17.1)
		1	321 (9.8)	329 (10.3)	348 (11.8)	317 (6.9)	326 (7.3)	343 (8.3)	311 (6.1)	322 (6.5)	339 (7.3)	311 (6)	322 (6.4)	339 (7.1)	310 (6)	321 (6.4)	339 (7.1)
			33 (18.4)	32 (17.7)	30 (19.1)	46 (17.1)	44 (16.7)	41 (17.7)	51 (18)	50 (17.8)	47 (18.5)	52 (18.6)	50 (18.7)	48 (20.2)	52 (19.1)	50 (19.1)	47 (19)
	0.25	3	308 (8.9)	315 (9.4)	329 (10.2)	292 (5.8)	300 (6.1)	314 (6.7)	270 (4.5)	278 (4.7)	294 (5.1)	243 (3.8)	253 (4)	272 (4.3)	225 (3.5)	237 (3.7)	254 (4)
			35 (16.6)	34 (15.7)	32 (15.9)	50 (14.2)	49 (14.1)	47 (14.5)	60 (16.9)	59 (16)	58 (14.1)	63 (16.7)	63 (16.3)	63 (15.7)	64 (14.2)	64 (14)	63 (13.3)
		2	310 (9.1)	318 (9.5)	332 (10.5)	295 (5.9)	304 (6.2)	319 (6.9)	275 (4.6)	283 (4.8)	301 (5.2)	253 (4)	264 (4.2)	282 (4.5)	237 (3.8)	249 (3.9)	268 (4.3)
			34 (16.6)	33 (16.4)	32 (17)	50 (15.1)	49 (14.9)	46 (14.5)	60 (17.2)	59 (16.8)	58 (15.7)	63 (17.9)	63 (18.2)	62 (16.4)	63 (16.1)	64 (16.7)	63 (16.3)
		1	321 (9.8)	330 (10.4)	350 (11.9)	315 (6.8)	325 (7.3)	345 (8.4)	312 (6.1)	321 (6.5)	341 (7.3)	310 (6)	321 (6.4)	340 (7.2)	310 (6)	319 (6.3)	339 (7.1)
			33 (17.7)	32 (18)	29 (18.2)	46 (16.3)	44 (17.2)	41 (17.7)	52 (18.5)	50 (18.4)	47 (18.7)	52 (19)	50 (19)	47 (19.3)	52 (18.8)	51 (18.6)	47 (18.9)
O	N/C	D-TD	3	10	20	3	10	20	3	10	20	3	10	20	3	10	20
		C	10			15			20			25			30		

80 or more patients
60 – 79 patients
40 – 59 patients
20 – 39 patients

Table 7.4 Abacus of results

7.4.4 Multiple non-linear regression model

The performances of the oncology unit can be estimated through a multiple non-linear regression (MNLR) model. Specifically, a MNLR model is a mathematical function that non-linearly combines the experimental factor with different weight

coefficients to forecast the key performance indicator of the problem (Fan and Ding, 2019). The adjusted R-squared indicator reported in the ANOVA analyses indicates how much the output data fit with the regression line. The values of the adjusted R-squared for each response variable is higher than 95% demonstrating a high significance of the proposed regression model. As in the ANOVA analysis, only two orders of interactions are considered for each regression model. The experimental factor N/C is not included in the MNLR model since it does not affect the performances. In general, the response variables can be predicted using the model reported in Eq. 7.1:

$$Y=w_1+w_2\cdot O+w_3\cdot C+w_4\cdot D+w_5\cdot TD+w_6\cdot O^2+w_7\cdot C^2+w_8\cdot D^2+w_9\cdot TD^2+ w_{10}\cdot O\cdot C+w_{11}\cdot O\cdot D+w_{12}\cdot O\cdot TD+w_{13}\cdot C\cdot D+w_{14}\cdot C\cdot TD+w_{15}\cdot D\cdot TD \quad (7.1)$$

wherein y indicates the response variables and wi stands for the weight coefficients of the experimental factors. The set of weight coefficients are reported in Table 7.5. Finally, the MNLR models were compared with the values of the KPIs of 10 random scenarios resulting from the simulation model. Table 7.6 shows the results and the deviation calculated as in Eq. 7.2:

$$Deviation = \frac{KPI_{MNLR} - KPI_{simulated}}{KPI_{simulated}} \% \quad (7.2)$$

From the table it can be noticed that the average deviations (reported in the last row) present low values and, then, it can be stated that the regression models can be properly adopted for the problem under investigation.

y	$\overline{F}$	P	$\overline{F}/P$
w_1	329.40	2.13	18.23
w_2	13.44	1.839	0.1563
w_3	-1.856	1.534	-0.8424
w_4	-46.90	10.35	-2.899
w_5	1.770	-0.071	0.1325
w_6	-1.1598	-0.3936	0.00340
w_7	-0.00125	-0.05905	0.018734
w_8	10.405	-6.532	0.8602
w_9	0.01592	-0.00252	0.001008
w_{10}	0.3869	0.1640	-0.00406
w_{11}	1.312	0.908	-0.03779
w_{12}	-0.0665	-0.0158	-0.00060
w_{13}	-1.0171	0.8641	-0.05728
w_{14}	0.00225	-0.00366	-0.002512
w_{15}	-0.2124	0.0458	-0.02277

Table 7.5 Coefficients of the regression models

Scenarios	**Factors**					**Simulation**			**Regression**			**Deviation**		
	O	C	N/C	D	TD	$\overline{F}$ [min]	P	$\overline{F}/P$ [min]	$\overline{\overline{F}}$ [min]	P	$\overline{\overline{F}}/P$ [min]	$\overline{F}$ [%]	P [%]	$\overline{\overline{F}}/P$ [%]
1	4	10	0.25	1	20	350.32	29.32	11.95	352.63	31.77	11.48	0.66	8.34	3.92
2	4	20	0.33	2	10	283.47	59.14	4.79	288.40	58.36	4.72	1.74	1.32	1.38
3	4	30	0.25	2	20	268.40	63.07	4.26	280.82	65.37	4.50	4.63	3.65	5.68
4	6	30	0.33	3	20	294.89	87.35	3.38	288.54	83.99	3.47	2.15	3.84	2.52
5	6	25	0.25	1	10	341.31	51.57	6.62	338.83	53.54	6.17	0.73	3.82	6.85
6	8	15	0.33	3	10	322.92	50.96	6.34	327.60	52.59	6.67	1.45	3.20	5.17
7	8	25	0.25	2	3	314.66	80.73	3.9	313.60	77.59	3.78	0.34	3.89	3.18
8	10	15	0.33	3	10	328.00	50.77	6.46	330.88	52.15	6.74	0.88	2.72	4.37
9	10	20	0.25	2	3	325.66	66.58	4.89	323.28	67.66	4.66	0.73	1.62	4.63
10	10	30	0.33	3	3	309.91	99.37	3.12	309.60	99.88	3.22	0.10	0.51	3.11
											Average	**1.34**	**3.29**	**4.08**

Table 7.6 Validation of the multiple non-linear regression model

7.5 Conclusions

In this work, we addressed the healthcare system design problem of outpatient chemotherapy oncology departments. This work, inspired to the healthcare services provided by an outpatient chemotherapy oncology unit of a hospital located in (to be revealed if the paper will be accepted in respect of the double-blind peer review policy of the journal), presents the results of a multi-objective analysis conducted by means of a combination of stochastic simulation and experimental design, with the aim of working as a guideline for the healthcare managers and decision-makers. In order to consider both the quality of service to patients and the efficiency of the systems, the performances of the chemotherapy oncology units were evaluated based on three different key performance indicators: the patient waiting time, the number of patients and a trade-off indicator. A stochastic simulation model based on discrete time recursive equations was developed and combined with a DOE to emulate several different configurations. An ANOVA analysis, supported with main effect plots, Tukey tests and interaction plots, allows identifying the impact of each experimental factors on the performance of the oncology units. In general, the analysis pointed out that selecting the adequate number of chairs for treatment and the number of pharmacy technician are essential to achieve the best performance both in terms of patient waiting time and number of patients cared in a day. On the other hand, a high number of oncologists allow the oncology unit to increase the number of patient cared in a day. However, in this case, the oncology department has to dispose of an adequate number of pharmacy technicians and chairs for treatment to avoid that exists a bottleneck after the medical consultation. The analysis of results was also supported by a multi-objective Pareto approach, a well-detailed abacus and a MNLR model. In particular the abacus of results was built to support the managers and to easily evaluate the performances provided by each specific configuration considered in the DOE.

8. Supply chain dynamics problem

8.1 Introduction

A supply chain (SC) can be defined as a network of firms that transmit goods to each other and share information on their capabilities and resources in order to provide value to the final consumer (Disney and Lambrecht, 2008). SCs are highly non-linear, as they present the characteristics of complex systems, and evolve through non-trivial interactions between the nodes of the network (Surana et al., 2005). A source of complexity in the SC context is due to the capacity constraints that are widely usual in the real-world applications and may expose firms to unpredictable disturbances as well as to economic losses. For these reasons, such perturbations have to be promptly managed thorough specific protocols so to mitigate their impact on the whole distribution network (Shukla and Naim, 2017). Another perspective in terms of complexity is attributable to supply chain disruptions, *i.e.*, events that temporarily change structural design and operational policies of SCs with significant resilience impact (Kinra et al., 2020). According to the definition of Chakraborty et al. (2020), a supply related disruption may occur when suppliers are unable to fulfil the orders placed with them. Likewise, the supply disruption can be considered as the risk of interrupting the supply of a product, which in turn may yield uncertainty and loss of balance between the supplied quantity and the order size placed. Over the past few years the management of supply chain disruption has gained a lot of attention from both practitioners and academics. Vulnerability of supply chains and propagation of a disruption through the distribution network, also denoted as ripple effect, were investigated by several authors (*e.g.*, Dolgui et al., 2020, Hosseini et al., 2020 and Xu et al., 2020).

However, though the SC disruption surely represents a hot topic in the international research landscape, none of the aforementioned contributions explicitly considers the production planning issue in the factory node as a capacity constraint and a source of vulnerability for the entire supply chain as well. Production and distribution are the two primary internal elements of the supply chain and a proper integration between them plays a leading role in the development of quantitative approaches capable of accurately investigating the performance of supply chains (Kumar et al., 2020a). The research contributions investigating the

impact of capacity restrictions on SC performance are relatively scarce and most of them adopt a simplified approach to model the relationship between lead-times and capacity. The majority of the early studies considers the capacity limit implicitly connected to exogenous factors such as the order rate or to endogenous sources as production and transportation channels, also assuming that the lead time is an independent parameter. On the other hand, the emerging trend in modelling the capacity constraint bids on a more consistent approach focused upon a cause-effect relationship that treats lead times as load-dependent variables (Cannella et al., 2018). Although these recent studies have remarkably improved the modelling assumptions related to the capacitated SC problems, the complexity of some real-world manufacturing systems cannot be properly captured by relaxed or approximate approaches, thus requiring a more explicit capacity model to faithfully emulate the operational implications typical of the shop floors. In other words, an innovative methodology capable of accurately reproducing the realistic aspects of production capacity (such as the effects of multi-product processes, setup-times and machine breakdowns), would be necessary to go beyond the conventional models, most of which set the capacity limit to a constant value and use a single-product flow in an aggregate manner. As a matter of fact, Potter et al. (2009) encourage a multi-product perspective for exploring bullwhip in SC. They state that various clusters of products may have quite different types of SC, depending upon either the customer or the product type and, as a result, each cluster can be subject to a different bullwhip phenomenon.

In light of the previous considerations and inspired by the activities of local companies, to bridge the gap between the capacity modelling assumptions employed by literature so far and a novel approach able to stress the operational issues pertaining to the real-life manufacturing contexts, the following features should be explicitly modelled: *i*) different products or families of product sharing the same manufacturing system, *ii*) decision-making issues related to the selection of the product to be manufactured; *iii*) production planning and control strategies to run product changeovers; *iv*) machine/equipment breakdowns; and *v*) production lead times depending on both the work-in-progress and on the layout of the manufacturing system. Motivated by the aforementioned considerations, the following research questions motivate the present work:

1) Considering the methodologies proposed by literature so far, is there an alternative way consistently simulate the effects of a limited production capacity on the SC dynamics?

2) Can a more realistic factory model, in which changeover tasks and machine breakdowns may occur, bring out new insights on the theme of capacitated SCs?

3) Which variables connected to a holistic factory model should be explored to investigate the service levels as well as the variability of inventories in a multi-echelon SC context?

4) Is there a specific production control strategy that allows improving the performance of the whole SC?

The research work presented in this chapter aims to answer to these challenging queries by adopting a new methodology, as follows. We explore a two-echelon (*i.e.*, factory, retailer and customer), two-product SC in which the product changeover requirement acts as a variable capacity on the factory node. To this end, we explicitly consider a single-facility two-product manufacturing system subject to non-negligible random breakdowns and product changeovers, which dynamically may generate considerable throughput reductions and stock-outs over time. Specifically, a well-established production control policy (PCP), named Hedging Corridor Policy (HCP, see Elhafsi and Bai, 1996) is engaged to simulate the decision-making issues connected to a two-product manufacturing environment, while the retailer generates orders according to a proportional controller-based Order-Up-To policy. Because of the exploratory nature of this study, we adopt a suitable methodology for studying the dynamics of SCs, *i.e.*, computer simulation and more specifically the discrete-time recursive equations modelling approach. Such an explicit two-product capacity model may induce a significant disturbance into the factory node, under several viewpoints. Indeed, deciding for a product changeover means to undergo a temporary production stoppage and a consequent throughput decay on the outgoing product. On the other hand, during any steady-state phase of production, failures may occur and the output rate of the factory temporarily decreases, thus affecting the replenishment of the downstream supply chain. In order to infer how such a realistic capacity model biases the whole supply chain, the effect of several operational parameters (*e.g.*, inventory threshold to enable the changeover, changeover duration and failure rate) as well as their interactions with other leading factors (*e.g.*,

customer demand, safety stock factor, proportional controller and so on) should be thoroughly investigated. To this end, an extended experimental campaign and a proper analysis of variance (ANOVA) were arranged with the aim of disclosing how these parameters, pertaining to both production control and replenishment policies, impact on three distinct performance indicators, *i.e.*, the fill-rate and the standard deviations of inventory regarding to both the retailer and the factory.

Furthermore, this chapter contributes to the literature of both supply chain dynamics and production control problem by comparing four PCPs, *i.e.* HCP, Modified-HCP (MHCP) (Gharbi et al., 2006), Improved Modified HCP (IMHCP) (Assid et al., 2014) and Demand Driven Material Requirements Planning (DDMRP) (Ptak and Smith, 2011). Specifically, we compare in depth the PCPs in a capacitated multi-echelon SC in terms of customer service level (*i.e.*, fill rate) and internal operational performance of the factory. The aim is to assess both academics and industrial practitioners to select specific production control policy capable of properly supporting the SC strategy. Specifically, if the SC management strategy is oriented towards cost reduction, it should be preferred a PCP that can dampen both average and variability of the inventory level to generate lower holding costs. Conversely, if the SC strategy is focused on customer service level, it should be adopted a PCP able to increase the fill rate performance indicator.

The performance of the SCs is influenced by endogenous factors (such as proportional controller, safety stock factor and so on), which can be adjusted by the SC manager (decision-maker), and exogenous factors (such as transportation lead-time, production flow time, etc.), which are considered intrinsic features of the SC under investigation (Costas et al., 2015; Puche et al., 2019). In this regard, we conduct two sets of experiments to make the comparison as exhaustive as possible. First, a Response Surface Methodology (RSM) was used to identify the most suitable values of the endogenous factors for each PCP. Then, a full-factorial experimental design, which involves all exogenous factors, was carried out to investigate the effectiveness of each PCP with respect to several SC scenarios. All in all, we argue that the comparison of the PCPs extends the current state-of-art in the field of manufacturing systems and supply chain dynamics and provide practical guidelines for practitioners to adopt most appropriate PCPs, depending on the operational and market environment (*e.g.*, turbulence of the customer demand, geographical

dispersion of the network, capacity dimension of the production system, etc.) and firm strategies (*e.g.*, cost-reduction vs. customer-focus orientation).

Finally, a new production control policy called Adaptive Hedging Corridor Policy (AHCP) is proposed. It can be considered as a variant of HCP, since it consists in building positive inventory levels through a variable inventory threshold that protects against inventory shortages due to production changeovers and failures. The adaptive aspect consists of continuously changing the inventory threshold by estimating the demand. For this purpose, the variable demand of the distribution chain is estimated using the exponential smoothing forecasting technique. AHCP was compared with HCP to maximize the fill rate when a highly variable demand arises from the downstream players. For this purpose, the two PCPs were compared through several scenarios and a proper ANOVA analysis and a series of interval plots at 95% confidence intervals were arranged to evaluate the impact and effectiveness of the two PCPs on the FR indicator as well as the interactions among the adopted experimental factors.

The reminder of the work is as follows. Section 8.2 presents the review of literature related to the two main research streams involved in the work, namely SCs with capacity constraint and production planning and control policy. Section 8.3 describes the proposed SC dynamic model wherein the capacity restrictions are motivated by an unreliable manufacturing system able to produce two distinct products. Section 8.4 explains the structure of each PCP. In Section 8.5 we present the numerical results and the findings arising from different experimental campaigns and provide research and managerial implications. Finally, Section 8.6 deals with the conclusions.

8.2 State of art

This section presents the literature background regarding the two main research streams involved in this chapter, the former being related to the SC dynamics with capacity constraints, the latter concerning the optimal production planning and control policies, specifically oriented to failure-prone and multi-product scenarios. Due to their heterogeneous contents, two distinct sub-sections were provided, as follows.

8.2.1 The capacity constraint in SC dynamics

Considering any capacity constraint in the study of SCs means introducing a source of non-linearity that significantly augments the complexity of the problem. Indeed, the study of capacitated SCs is still a poorly explored research stream, and most academics make full use of simulation-based techniques to investigate such a demanding issue. A way to model the capacity constraint in SC dynamics lies in limiting the transportation flows (*e.g.*, Wilson, 2007; Juntunen and Juga, 2009; Spiegler and Naim, 2014; Spiegler et al., 2016a; Spiegler et al., 2016b; Shukla and Naim 2017). On the other hand, an alternative approach widely spread in the literature consists in assigning the capacity restriction to incoming orders or production flows. To better catch the added-value of the proposed research, Table 8.1 retrieves the most relevant studies on the SC dynamics with capacity constraints at the factory level. Each reference is classified on the basis of two criteria, namely the way the capacity constraint is modelled, and the number of products distributed along the network. Notably, capacity constraints limiting that work by limiting orders or production rate to a constant value are denoted as Limits Orders (LO) constraints, while any capacity restriction depending on the accumulated work-in-progress, which in turn may affect the lead-time, is indicated as a Load-Dependent Lead Times (LDLT) constraint.

In other words, the research contributions adopting a LO method dictate a specific threshold to the production rate or to any order placed to the supplier (see *e.g.*, Evans and Naim, 1994; Chen and Lee, 2012; Hussain et al., 2016; Ponte et al., 2017; Lin and Naim, 2019; Lin et al., 2020). In this area, to the best of our knowledge, the work of Evans and Naim (1994) represents the seminal study investigating the effect of capacity restrictions in the SC context. They compare eight three-echelon SCs with different assumptions regarding their capacity, and discover that the unconstrained configuration is unable to assure the best performance among the tested SCs. Likewise, subsequent studies point out the same finding, *i.e.*, SC models adopting a capacity threshold on orders or production rate reveal a significant reduction of the bullwhip effect with respect to the unconstrained scenario. Such phenomenon was widely investigated by scholars and most of them claim that the capacity restriction applied to the order rate acts as a bullwhip damper, which also enable a smoothing effect upon orders and production flows (Evans and Naim, 1994; Cannella et al.,

2008; Chen and Lee, 2012; Ponte et al., 2017). However, despite the capacity limitation exerts a positive influence under the bullwhip effect viewpoint, it usually deteriorates the SC performance in terms of inventory and customer service levels (Evans and Naim, 1994; Nepal et al., 2012; Hussain et al., 2016; Ponte et al., 2017).

The LDLT models consider lead-times as a function of the load (*i.e.*, orders and work-in progress) on the production-distribution system. As a result, such approach allows emulating the negative effect that the capacity saturation may induce on the lead-times, as experienced in the real-life networks wherein any decrease in the production capacity tends to increase the lead-times throughout the entire SC (Yang, 2007; Orcun et al., 2009). To the best of the authors' knowledge, only four studies explore the SC behavior under load-dependent lead times, namely Helo (2000), Boute et al. (2009), Framinan (2017) and Cannella et al. (2018). Specifically, Helo (2000) use a system dynamics based method to model the lead-time in terms of backlog/capacity ratio, and show that a lower capacity detriments the agility of the whole supply chain. Boute et al. (2009) study a two-echelon SC with the aim of analyzing the impact of the retailer replenishment policy on the performance of the distribution system. They find out that a lower flexibility under the capacity viewpoint implies stochastic lead times, which in turn increase inventory requirements and SC costs. Framinan (2017) provides an analytical model to derive the bullwhip effect considering that capacity depends on the current/past orders and/or demand. Finally, Cannella et al. (2018) make full use of a non-linear difference equations based model to emulate a single-echelon SC in which lead-times are derived by the well-known cycle time-throughput (CT-TP) curve (Mönch et al., 2012). They show that capacity restrictions can have a detrimental impact in terms of both order variance, inventory stability and service level. Differently from the contributions adopting the LO capacity constraint policy, the LDLT models - which allow a more realistic representation of the capacitated distribution network - reveal that capacity restrictions negatively affect the operational cost and increase the bullwhip effect along the SC.

Regardless of the conflicting results emerged from the two mentioned approaches, it is worth noting that both LO and LDLT models operate on a single-product environment. Although this assumption is largely adopted in the related literature and produced remarkable insights so far, a multi-product model would be able to accurately capture the dynamics of the real-life manufacturing environments such

as the one inspiring our research, in which decisional aspects, product changeovers and further operational issues may explicitly affect the production rate of a factory and its effect on the downstream flow. After a thorough review of literature, we may affirm that the work pertaining to Potter et al. (2009) is the only study that debates about the trade-off between bullwhip and inventory in a multi-product environment where some batching is inevitable. Properly supported by three case studies in UK and New Zealand, they focus on different SC scenarios, each one characterized by a number of different products sharing the same capacity asset, and assert that a significant difference in the level of bullwhip may exist for distinct clusters of products. However, that research consists of a pure empirical study and any insight about how the capacity constraint should be modelled in a multi-product SC context is out of the scope of their work.

In light of the aforementioned considerations, and considering that, in many real-life manufacturing environments, capacity limitations are strictly connected to a series of operational implications, the present study aims to propose a novel approach for modelling the capacity restrictions in SCs, hereinafter denoted as Explicit Production and Operations (EXPO) model. Table 8.1 summarizes the contributions on SC dynamics with capacity restrictions discussed above, and allows to easily detect the novelty of the proposed research with respect to existing ones.

Reference	Capacity constraint modeling criterion			Assumption on the number of product	
	LO	*LDLT*	*EXPO*	*SP*	*MP*
Evans and Naim (1994)	✓			✓	
Helo (2000)		✓		✓	
Cannella et al. (2008)	✓			✓	
Boute et al. (2009)		✓		✓	
Chen and Lee (2012)	✓			✓	
Nepal et al. (2012)	✓			✓	
Hussain et al. (2016)	✓			✓	
Spiegler et al. (2016b)	✓			✓	
Framinan (2017)		✓		✓	
Ponte et al. (2017)	✓			✓	
Shukla and Naim (2017)	✓			✓	
Cannella et al. (2018)		✓		✓	
Lin and Naim (2019)	✓			✓	
Lin et al. (2020)	✓			✓	
This study			✓		✓

- *LO - Limiting Orders*. Limitation on orders placed to suppliers or orders' acceptance channel. Under this assumption, capacitated SCs may benefit from an improved dynamic performance in comparison to unconstrained systems
- *LDLT - Load-Dependent Lead Times*. Modeling lead-times (production and/or transportation) as a function of the load (*i.e.*, orders, work-in progress) of the production-distribution system (*e.g.*, lead time modeled as a CT-TP curve, or as function of the current/past orders). Under this assumption, capacity restriction can deteriorate the operational cost and increase the bullwhip effect
- *EXPO - EXplicit Production and Operations*. Emulating the capacity constraints by explicitly modeling operations typical of real-world production systems (e.g., product changeovers, failures and maintenance activities that may significantly reduce the nominal capacity of a production plant).
- *SP/MP*. Single Product/Multi-Product SC modeling.

Table 8.1 Review of capacity constraints in supply chain dynamics

8.2.2 The production control policies

The production control problem consists of selecting the best strategy, or PCP, to carry out manufacturing activities in a production system subject to unforeseen events. The literature on the production control problem can be divided into two streams, depending on the number of products handled by the manufacturing system. The first stream refers to single-product manufacturing systems where in most contributions the unforeseen events are machine failures or breakdowns. In this respect, the Hedging Point Policy (HPP) was widely adopted in the literature (Kimemia and Gershwin, 1983; Restrepo et al., 2016; Hatami-Marbini et al., 2020) to properly set the production rate so as to avoid the risk of inventory shortages due to failures in single-product manufacturing system with a constant demand. HPP was also used to manage the production operations of a factory in a single-product SC scenario (Hajji et al., 2009; Turki and Rezg, 2017).

The second stream concerns the production control problem of manufacturing systems that handle two different product types. In such circumstances, changeover operations, which are required to switch from one product type to another, represent the main source of disruption. In this case, the PCP adopted by the factory node must decide the product type to be manufactured and the sequence of product changeovers. The Hedging Corridor Policy (HCP) was developed by Elhafsi and Bai (1996) to conduct the decision-making process in two-product manufacturing systems. It can be considered as the multi-product version of HPP since, similarly, it aims at achieving a target inventory level or inventory threshold as soon as possible to protect against inventory and capacity shortages. The authors proved that HCP is optimal for minimizing the inventory costs of a single-machine two-product manufacturing system with a constant demand. HCP was also proved to be optimal for a cost-based objective function, which indirectly considers changeover costs, for unreliable single-machine two-product manufacturing systems with constant demand (Bai and Elhafsi, 1997). Then, extended versions of HCP were proposed to manage production systems with non-negligible changeover times. Gharbi et al. (2006) proposed the Modified Hedging Corridor Policy (MHCP) for a single-echelon multiple-machine manufacturing system with constant demand, in which the objective was to minimize setup and inventory costs. In this case, MHCP allows anticipating the product changeovers when there subsist inventory shortages

for one product type. On the other hand, Assid et al. (2014) presented a new modified version of MHCP, named as Improved Modified Hedging Corridor Policy (IMHCP) in the work of Assid et al. (2015), with the aim of reducing the total costs incurred by a factory characterized by an unreliable manufacturing system with constant demand. Differently from MHCP, IMHCP triggers the changeover to a product before the inventory level of this product becomes negative. However, the majority of the works on the production control problem for a multi-product scenario deal with single-node manufacturing companies facing a constant demand.

Recently, Polotski et al. (2020) pointed out that the production control problem with uncertain or variable demand can be faced through two different approaches. The first one, defined as 'guaranteed approach', consists of implementing production control policies, such as HPP and HCP, which can be considered 'good on average' solutions. This means that these policies guarantee the best possible results when applied several times. The second approach is defined as 'adaptive approach' and concerns with a strategy that uses some information about a source of uncertainty to create a rule that varies according to such information. In this regard, they propose an adaptive approach based on a Kalman filter-based technique as an estimator for a failure-prone single-machine single-product manufacturing system where the demand is uncertain.

A never-ending interest towards new hybrid/integrated approaches, *e.g.*, inspired to Theory Of Constraints (TOC) and Just-In-Time (JIT) paradigms, was emerging from the literature on production control and replenishment management. Recently, the Demand-Driven MRP (DDMRP) strategy proposed by Ptak and Smith (2011), which combines MRP logic, TOC and some principles of lean manufacturing and distribution resource planning, has captured the attention of both practitioners and academics (Velasco Acosta et al., 2020). The goal of this strategy is to manage the flow of materials in manufacturing systems exposed to uncertainties and high variability. DDMRP mainly consists of three steps (Ptak and Smith, 2016). The first step deals with decoupling and strategic positioning of buffers in order to cope with the variability along the whole manufacturing system. The second step involves defining the buffer profiles that are used to decide how to rebuild the inventory level. The third step refers to dynamically adjust the buffer profiles and levels to fit with the demand variability and market changes. The superiority of DDMRP was proved by the literature when applied to manufacturing systems characterized by high-

volume production and subject to internal and external uncertainty. Particularly, Miclo et al. (2019) and Thürer et al. (2020) demonstrated that DDMRP performs better than other methods, e.g. MRP II and Kanban/Lean production or Optimized Production Technology (OPT). Velasco Acosta et al. (2020) used DDMRP in a complex manufacturing environment with the aim of reducing lead time and inventory level. However, they pointed out that the success of DDMRP strongly depends on the strategic positioning of the buffers. As for HCP and its variants, DDMRP was applied only in a single-echelon manufacturing system and, moreover, the relationship between changeover operations and DDMRP has never been studied.

8.3 Modelling a multi-product supply chain model with capacity restrictions

Figure 8.1 gives an overview of the proposed SC model reporting both material and information flows. The first node of the proposed SC involves a manufacturing plant able to manufacture two different products. In brief, two products or two families of products share the same manufacturing system and, as a consequence, a variable production capacity would fulfil the demand coming from the downstream node. The factory always has raw material for production; thus, it does not place any order. The retailer stage emits orders to the factory and upgrades its inventory. To place the orders, the retailer follows a smoothing replenishment rule (Boute et al., 2009). The following paragraphs introduce the general assumptions of the proposed SC model and later a detailed explanation of an analytical model based on discrete time difference equations will be presented. The nomenclature adopted along the chapter is reported in Table 8.2.

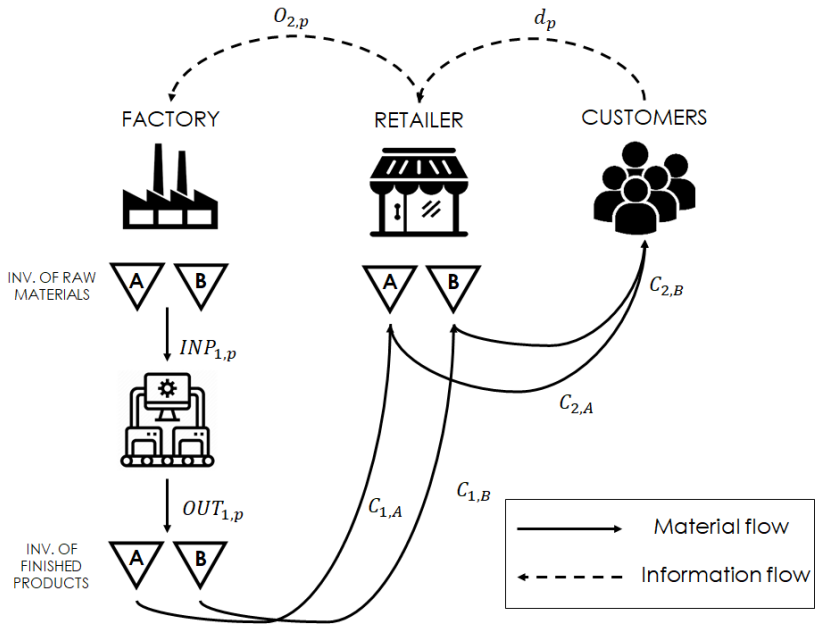


Figure 8.1 The two-product two-echelon supply chain model

Indices, parameters and statistics			
α_{ret}	Forecasting smoothing factor of retailer	t	time period
α_{fact}	Forecasting smoothing factor of factory	T	Time horizon
α_p	Minimum inventory threshold of product p	TOG_p	Top of green of product p
β	Proportional controller	TOR_p	Top of red of product p
b_p	Safety inventory threshold of product p	TOY_p	Top of yellow of product p
δ	Changeover time	φ	Factor of minimum inventory threshold
ε	Safety stock factor	χ_p	Nominal production capacity of product p
F	Flow time	z	Threshold of inventory factor
F_l	Flow time factor	Z_p	Maximum inventory threshold of product p
F_v	Variability factor	μ_{d_p}	Mean customer demand of product p
i	Echelon's position	$\sigma^2_{d_p}$	Variance customer demand of product p
k	Threshold of lost sales factor	FR	Fill Rate
λ	Failure rate	μI_{fact}	Average value of factory inventory level
LT	Delivery lead-time	ΣI_{fact}	Standard deviation of factory inventory level
p	Product type	ΣI_{ret}	Standard deviation of retailer inventory level
p'	Alternative product type		

Variables			
$C_{i,p}(t)$	Units of product type p delivered to echelon i at time t	$O_{2,p}(t)$	Order quantity of product type p issued by the retailer at time t
$CO_{1,p'p}(t)$	Residual changeover time to switch from product type p' to p in the factory at time t	$OUT_{1,p}(t)$	Output quantity of product type p in the factory at time t
$d_{i,p}(t)$	Demand of product type p in echelon i at time t	$t_R(t)$	Repair time in the factory
$\hat{d}_{i\,p}(t)$	Demand of product type p forecasted by echelon i at time t	$TI_{2,p}(t)$	Target inventory of product type p in the retailer at time t
$I_{i,p}(t)$	Inventory level of product type p in echelon i at time t	$TW_{2,\,p}(t)$	Target work in progress of product type p in the retailer at time t
$\hat{I}_{1,p}(t)$	Forecasted inventory level of product type p in the factory at time t	$W_{i,p}(t)$	Work in progress of product type p in echelon i at time t
$INP_{1,p}(t)$	Input quantity of product type p in the factory at time t		

Table 8.2 Supply chain nomenclature

8.3.1 Modelling the factory capacity

Assuming a single product and a variable lead-time is a way to faithfully represent the sources of uncertainty typical of capacitated manufacturing environments (Boute et al., 2009; Cannella et al., 2018). Of course, such an aggregate approach could represent a too approximate perspective to investigate in-depth the SC dynamics, especially when two or more products share the same production equipment and machine breakdowns/failures may occur. To this end, the more realistic EXPO model was proposed in the present work. The following assumptions were considered to model the factory node at hand:

- Let us suppose a process-oriented manufacturing system able to produce two distinct types of product or, alternatively, two different product families; thus, the two part-types share the same manufacturing equipment, which produces at maximum production rate.
- A non-negligible setup time is required whenever a product changeover is needed. When a changeover occurs, the semi-finished product along the line has to be processed entirely.
- Failures may randomly occur and production has to be temporary stopped.
- A production planning strategy is employed to jointly cope with the capacity shortage deriving from both setups and failures.

- The time each product spends to go through the production line is the flow time, hereinafter denoted as F, also called production lead time. Thereby, it denotes the time interval between launching a workpiece down the line and removing the finished product from the line, and it is known in advance. As for example, that is the case of paced assembly lines (Scholl, 1999), textile industry (Aldas et al., 2018) and semi-conductors wafer fabrication (Haller et al., 2003; Lee et al., 2008).
- At each time period t, a quantity of product INP_p enters the production system and will take F time periods to be completed (Stadnicka and Litwin, 2019). Generally, the variable INP_p equals the nominal production capacity χ_p and the maximum WIP level for each product can be computed as $F \cdot \chi_p$, accordingly. Such maximum WIP level, that keeps unchanged until an adverse event such as failure or product changeover occurs, will be denoted as WIP-CAP hereinafter.

To sum up, in steady-state conditions (if no adverse event such as failures or changeovers happen) the input rate INP_p, *i.e.*, the quantity of product feeding the system, is equal to the nominal production capacity χ_p and the WIP lays on the maximum value WIP-CAP. When a failure happens or a setup is required, both the WIP level of the in-process product and the throughput are reduced. Figure 8.2 shows a graph wherein the WIP level $W_p(t)$ of each product p varies over the time because of the product changeovers. Besides, the maximum WIP, *i.e.*, the expected $WIP\text{-}CAP_p$ for each product p can be detected. When a changeover is needed, the WIP level of the outgoing product rapidly decreases while, once the provided setup time δ elapsed, the WIP related to the incoming product suddenly grows.

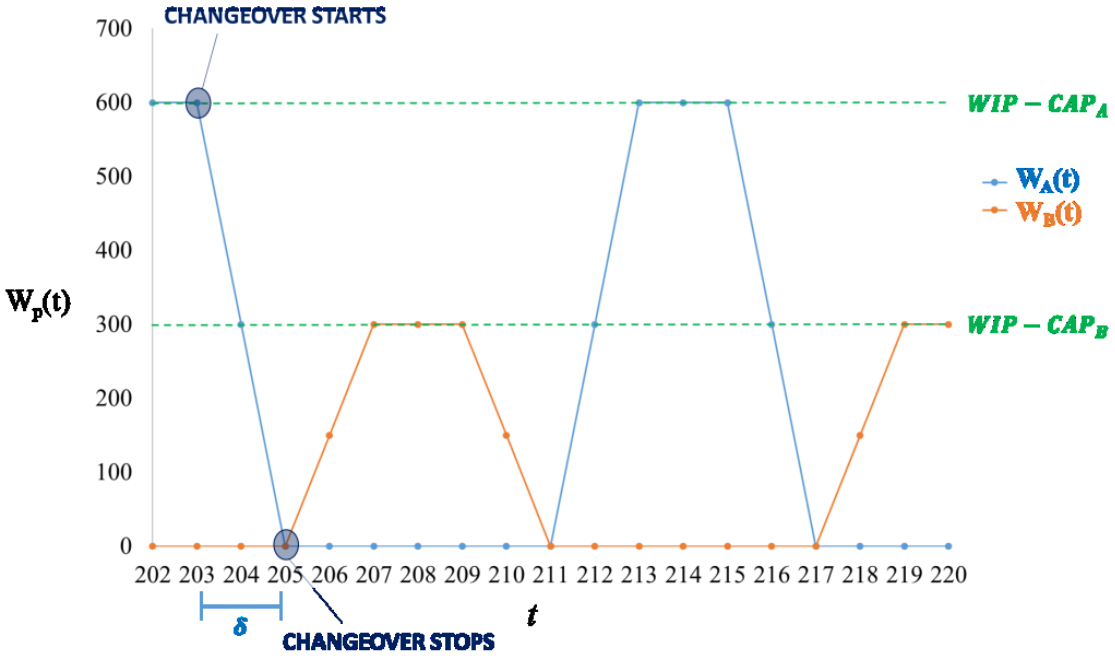


Figure 8.2 Variation of WIP level (when $\delta=F$)

To better explain the proposed factory model, Figure 8.3 refers to a production system able to produce two distinct products, denoted as *A* and *B*, respectively. Let us suppose 300 units of product *A* and 150 units of product *B* can be alternatively produced at each time period *t* (*i.e.*, $\chi_A=300$, $\chi_B=150$), and both products have a flow time equal to two time units ($F=2$). At each time unit, the quantity of product in terms of work-pieces or raw materials feeding the production system is equal to the corresponding nominal capacity, that is $Inp_p(t)=\chi_p \mid p\in(A,B)$. Whether no changeover is required, the input quantity $Inp_p(t)$ will be processed and then released by the production system after *F* time units. Let us suppose product *A* is being processed as first. Whether a product changeover is needed (at time $t=3$), a setup time δ equal to one-time unit is required; thus, the production system cannot process any product and the $W_A(t)$ level of the outgoing product (*i.e.*, the product *A*) decreases from 600 to 300 units. At time $t=4$, once the changeover task is completed, *i.e.*, after $\delta=1$ time units, 150 work-pieces of product *B* enter the system and $W_B(t)$ starts to increase until the steady-state conditions are achieved. For the sake of clarity, Table 8.3 refers to the example described by Figure 8.3 and displays the following variables: $Inp_p(t)$, work in process $W_{1,p}(t)$, output quantity $OUT_p(t)$ as well as the changeover variable

$CO_{pp'}(t)$, which assumes a value equal to one whenever a switch from product p=A to product p'=B (and vice-versa) is required.

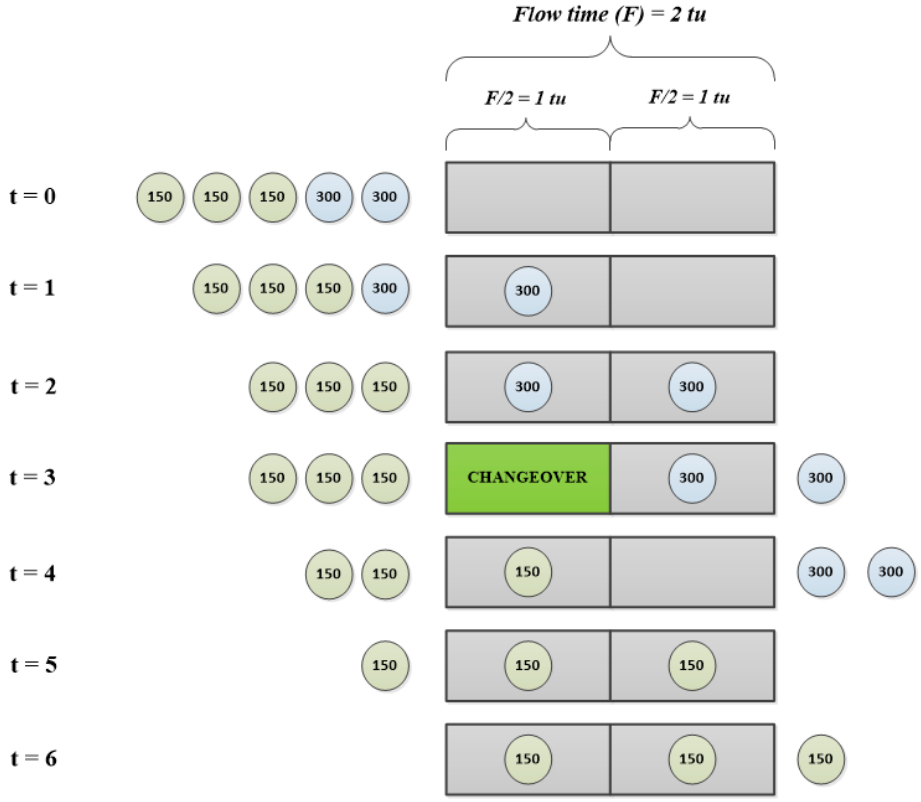


Figure 8.3 Example of manufacturing stage with changeover

t	$CO_{AB}(t)$	$CO_{BA}(t)$	$INP_A(t)$	$INP_B(t)$	$W_A(t)$	$W_B(t)$	$OUT_A(t)$	$OUT_B(t)$
0	0	0	0	0	0	0	0	0
1	0	0	300	0	300	0	0	0
2	0	0	300	0	600	0	0	0
3	1	0	0	0	300	0	300	0
4	0	0	0	150	0	150	300	0
5	0	0	0	150	0	300	0	0
6	0	0	0	150	0	300	0	150

Table 8.3 Numerical example of product changeover

Disregarding any preventive maintenance strategy, failures may occur randomly, according to a failure rate equal to δ. Conforming to Chiu et al. (2019), when a machine breakdown occurs, failures are instantaneously detected and the machine repair operation starts right away. The manufacturing process resumes to work

when the repair task is accomplished, *i.e.*, after a certain amount of time called machine repair time $t_R(t)$. Failures are supposed to happen just at the first stage of the production line. Figure 8.4 illustrates how the proposed simulation approach runs a failure. Let us suppose the flow time is again F=2 and the nominal production capacities for the two products are χ_A=300 and χ_B=150, respectively. At time t=1 product A is being processed and the related input quantity $INP_A(1)$ is equal to χ_A. At time t = 2 a failure happens. Whether the machine repair time $t_R(t)$ is equal to 0.8, properly extracted by a uniform distribution $U(0,1)$, since the failure is supposed to happen at the first production stage, the corresponding input quantity $INP_A(2)$ reduces to $(1\text{-}t_r(2))\cdot 300=60$ product units, which later will be processed by the downstream stages of the production system.

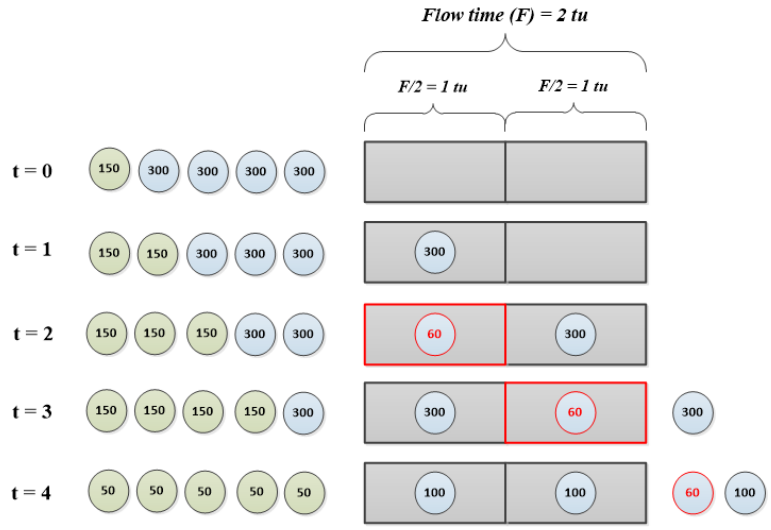


Figure 8.4 Example of manufacturing stage with failures

8.3.2 General assumption of the supply chain model

To model the SC dynamics of the problem under investigation, a set of discrete time difference equations was developed and implemented by means of Matlab r2020®. The simulations were run on a workstation equipped with a INTEL i9-9900 3.6 GHz 10 core CPU, 32Gb DDR4 2,666MHz RAM and Win 10 PRO OS. In order to fulfill both the dynamic feature of the proposed simulation approach as well as the aspects typical of real-life SCs, the following general assumptions, most of them employed by the relevant literature (Chatfield et al., 2004; Cannella et al., 2010; Dominguez et al., 2019), were considered:

1. Two distinct types of product flow through the SC;

2. The downstream node places orders for each product to the next upstream node, which fulfills those orders. The customer node does not fill orders;
3. The factory always has raw material for production. Thereby, it does not place any order;
4. The factory has a constrained capacity as two products share the same manufacturing equipment;
5. Stocking and transportation capacities are unlimited;
6. For each product, the demand received by a node equals the orders received by the downstream stages;
7. Lead time related to the last echelon is neglected. Conversely, the lead time from factory to retailer is the sum of two constant contributions, the former being the production flow time F, the latter being the transportation lead time LT.
8. When the stock is not enough to completely fill an order, a stock-out is generated and partial replenishment is used;
9. Backlogging is allowed as a consequence of stockholding;
10. Returns of excess inventory to upstream partners are not permitted;
11. At period t and for each product p, the customer places an independent stochastic demand following a normal distribution with mean μ_{d_p}, and variance $o_{d_p}^2$;
12. At period t and for each product p, the throughput of the factory depends on the nominal production capacity χ_p and it is reduced in case of product changeovers or failures.
13. The exponential smoothing is adopted as forecasting method for estimating demand.

A production control policy (PCP) is employed to manage the product changeover decision-making issue (see Section 8.4). To this end, the decision on the product type to be manufactured and product changeovers depend on the PCP adopted. In order to match the recent studies on capacitated SC dynamics with a more realistic model of production capacity, this work proposes modified PCPs, in which both WIP and production flow time may affect the stock level of the two part-types. Therefore, a changeover from a generic product p to another p' is performed by considering the forecasted inventory of finished products $\hat{I}_{1,p}(t)$. In turn, the WIP level as well as the

flow time of each product may significantly influence the mentioned forecasted inventory levels.

8.3.3 Dynamic modelling

This section deals with the time-dependent equations supporting the dynamic model of the proposed two-product SC with production capacity constraints.

8.3.3.1 Factory related dynamics

At each time period, the factory performs the following sequence of actions:

1. ***Finished products*** $OUT_{1,p}(t)$. The output quantity of product p at time t is equal to the input quantity of the same product at time t-F, where F is the production flow time.

$$OUT_{1,p}(t)=INP_{1,p}(t-F) \tag{8.1}$$

2. ***Number of delivered units*** $C_{1,p}(t)$. It consists of the number of product p units delivered by the factory at period t to satisfy the retailer order quantity $O_{2,p}(t-1)$. Two events may occur:
    a. The factory inventory level is greater than the retailer order at time t: $(I_{1,p}(t-1)+OUT_{1,p}(t) \geq O_{2,p}(t-1))$. Therefore, it is capable to satisfy the retailer requests without generating any backorder.
    b. The factory has a lower inventory level and it is not able to satisfy the retailer order: $(I_{1,p}(t-1)+OUT_{1,p}(t) < O_{2,p}(t-1))$. Then, it delivers the whole stock quantity.

    Whether the available inventory level assumes a negative value, that is a backlog, no finished products can be delivered to the retailer and the variable $C_{1,p}(t)$ will be equal to 0.

$$C_{1,p}(t)=max\{min[I_{1,p}(t-1)+OUT_{1,p}(t);O_{2,p}(t-1)];0\} \tag{8.2}$$

3. ***Inventory of final products*** $I_{1,p}(t)$. The inventory level at time t increases by the output quantity $OUT_{1,p}(t)$ and decreases by the order $O_{2,p}(t-1)$ coming from the retailer, as reported in Eq. 8.3. According to Sajadi et al. (2011),

stock-outs cannot be higher than a limit denoted as threshold of lost sales ($k \cdot \mu_{d_p}$), so that orders from retailer cannot be accepted any more. This assumption can be further justified if cost of backorders is higher than the cost of lost sales.

$$I_{1,p}(t)=max\left\{I_{1,p}(t-1)+OUT_{1,p}(t)-O_{2,p}(t-1);-k\cdot\mu_{d_p}\right\} \quad (8.3)$$

4. ***Forecast of future inventory levels*** $\hat{I}_{1,p}(t)$. Differently from the canonical application of PCPs, the product changeover is enabled by the predicted inventory level, which in turn depends on the provided production lead time F. In particular, the difference between the nominal capacity χ_p and the expected demand of product p, *i.e.*, $\hat{d}_{1,p}(t)$, has to be added to the current stock level.

$$\hat{I}_{1,p}(t)=max\left\{I_{1,p}(t)+F\cdot(\chi_p-\hat{d}_{1,p}(t));-k\cdot\mu_{d_p}\right\} \quad (8.4)$$

The forecast demand coming from the retailer can be expressed by the following relation:

$$\hat{d}_{1,p}(t)=\alpha_{fact}\cdot O_{2,p}(t-1)+\left(1-\alpha_{fact}\right)\cdot\hat{d}_{1,p}(t-1) \quad (8.5)$$

where the forecasting smoothing factor α_{fact} is a design parameter ranging in [0,1] (Cannella et al., 2018).

5. ***Input quantity*** $INP_{1,p}(t)$**.** Generally, the quantity of product feeding the production system ($INP_{1,p}$) fits the nominal production capacity (χ_p). In turn, under these circumstances, the output rate $OUT_{1,p}$, *i.e.*, the throughput of product p, is equal to the nominal capacity if no adverse event happens. Two categories of events, namely changeovers and failures, may bias the productivity of the factory. Therefore, $INP_{1,p}(t)$ is equal to zero when a product changeover occurs or, alternatively, when a different product p' is being processed. The failure repair time $t_R(t)$ reduces the input quantity accordingly.

$$INP_{1,p}(t) = \begin{cases} x_p \cdot \left(1 - CO_{1,p'p}(t)\right) \cdot (1 - t_R(t)) & \text{if the system is producing p} \\ 0 & \text{otherwise} \end{cases} \quad (8.6)$$

where,

$$CO_{1,p'p}(t) = \begin{cases} \delta & \text{if a decision on changeover is made} \\ max\{CO_{1,p'p}(t\text{-}1)\text{-}1;\ 0\} & \text{otherwise} \end{cases} \quad (8.7)$$

$$t_R(t) = \begin{cases} U \in (0,1) & \text{if } rand \leq \lambda \text{ and no changeover event} \\ 0 & \text{otherwise} \end{cases} \quad (8.8)$$

6. ***Work in process quantity*** $W_{1,p}(t)$. The work in process $W_{1,p}(t)$ consists of the in-process inventory at time t, as follows:

$$W_{1,p}(t)=W_{1,p}(t\text{-}1)+INP_{1,p}(t)\text{-}OUT_{1,p}(t) \quad (8.9)$$

8.3.3.2 Retailer related dynamics

At each time period, the retailer performs the following sequence of actions, similarly being done by Cannella and Ciancimino (2010):

1. ***Number of delivered units*** $C_{2,p}(t)$. It is the minimum between the demand required by the customer $d_p(t)$ and the available inventory $I_{2,p}(t\text{-}1)+C_{1,p}(t\text{-}LT)$. Alternatively, in case of any backlog, it is equal to zero.

$$C_{2,p}(t)=max\{min[I_{2,p}(t\text{-}1)+C_{1,p}(t\text{-}LT);\ d_p(t)];\ 0\} \quad (8.10)$$

2. ***WIP level*** $W_{2,p}(t)$. It models the work in progress quantity $W_{2,p}(t)$at time t.

$$W_{2,p}(t)=W_{2,p}(t\text{-}1)+C_{1,p}(t)\text{-}C_{1,p}(t\text{-}LT) \quad (8.11)$$

3. ***Inventory of final products*** $I_{2,p}(t)$**.** It is similar to the factory related rule (see Eq. 8.3), the only difference being that the retailer inventory at the previous time is increased by the units delivered by factory to retailer $C_{1,p}(t\text{-}LT)$ after the lead-time LT is elapsed.

$$I_{2,p}(t)= \max\left\{I_{2,p}(t\text{-}1)+C_{1,p}(t\text{-}LT)\text{-}d_p(t);\ -k\cdot\mu_{d_p}\right\} \quad (8.12)$$

4. ***Forecasting of the future demand*** $\hat{d}_{2,p}(t)$**.** As in Eq. 8.5, the forecast demand can be expressed by:

$$\hat{d}_{2,p}(t)= a_{ret}\cdot d_p(t)+(1-a_{ret})\cdot \hat{d}_{2,p}(t-1) \quad (8.13)$$

5. ***Target inventory*** $TI_{2,p}(t)$ ***and Target work in progress*** $TW_{2,p}(t)$.

$$TI_{2,p}(t)=\varepsilon\cdot \hat{d}_{2,p}(t) \quad (8.14)$$

$$TW_{2,p}(t)=LT\cdot \hat{d}_{2,p}(t) \quad (8.15)$$

The safety stock factor ε is a parameter to be a-priori defined by the analyst (Cannella et al., 2018).

6. ***Replenishment order*** $O_{2,p}(t)$. It is the sum of three components: forecast demand $\hat{d}_{2,p}(t)$; work in progress gap $\beta\cdot\left(TW_{2,p}(t)-W_{2,p}(t)\right)$ and inventory gap $\beta\cdot\left(TI_{2,p}(t)-I_{2,p}(t)\right)$, where the proportional controller parameter ranges in [0,1]. If $\beta=1$ is equal to one the classical Order-Up-To policy holds, otherwise, the smoothing replenishment rule is enabled (Disney and Lambrecht, 2008). Furthermore, negative orders are not allowed (Chatfield and Pritchard, 2013).

$$O_{2,p}(t)=max\left\{\hat{d}_{2,p}(t)+\beta\cdot\left(TW_{2,p}(t)-W_{2,p}(t)+TI_{2,p}(t)-I_{2,p}(t)\right);0\right\} \quad (8.16)$$

8.4 Description of the production control policies

A PCP is needed by the factory to address the inventory and capacity shortages due to changeover times and failure events. In fact, at each time t, the PCP makes decision on both the product type that has to feed the production line and consequently the product changeover. In this study, five PCPs are considered, namely the Hedging Corridor Policy (HCP) (Elhafsi and Bai, 1996), the Modified Hedging Corridor Policy (MHCP) (Gharbi et al., 2006), the Improved Modified Hedging Corridor Policy (IMHCP) (Assid et al., 2014), the Demand-Driven Material Requirement Planning (DDMRP) (Ptak and Smith, 2011), the Adaptive Hedging Corridor Policy (AHCP) (proposed in this work for the first time). Each PCP is

adapted in the SC context in order to respect the features and the assumptions of the *EXPO* SC model. In particular, the decision-making of each PCP is carried out using the forecasted inventory level $\hat{I}_{1,p}(t)$ since the manufacturing system is characterized by the production flow time F and the production work-in-progress in the production line. The PCPs are described in the following sections.

8.4.1 Hedging Corridor Policy

The Hedging Corridor Policy (HCP) consists of setting a target inventory level to be reached by the forecasted inventory level of a product type so as to switch to the production of the other product type. The target inventory level is defined as maximum inventory threshold (Z_p) and depends on a control parameter, named the inventory threshold factor (z), and the mean value of the customer demand (μ_{d_p}):

$$Z_p = z \cdot \mu_{d_p} \tag{8.17}$$

Figure 8.5 shows the variation of the current and forecasted inventory levels when HCP is used as PCP by the factory. The continuous line is the current inventory level $I_{1,p}(t)$, while forecasted inventory level $\hat{I}_{1,p}(t)$ is depicted with the dashed line. The blue bar indicates the changeover time to switch from product type A to product type B, while the yellow bar is for the changeover time to switch from B to A. As described in Eq. 8.7, when a decision on product changeover is made, the residual changeover time $CO_{1,p'p}(t)$ is set equal to the changeover time δ. When the decision on product changeover is conducted by the HCP, the Eq. 8.7 can be expressed as follows:

$$CO_{1,p'p}(t) = \delta \quad if\ INP_{1,p'}(t\text{-}1) > 0\ and\ \hat{I}_{1,p'}(t) \geq Z_{p'} \tag{8.7.a}$$

In fact, the decision to switch from product type p' to product type p is made by comparing the forecasted inventory $\hat{I}_{1,p'}(t)$ of the product p' being manufactured (verified by $INP_{1,p'}(t\text{-}1) > 0$) and the maximum inventory threshold $Z_{p'}$. When the forecasted inventory $\hat{I}_{1,p'}(t)$ of the product p' being manufactured exceeds the corresponding maximum inventory threshold $Z_{p'}$ (see mark 1 in the Figure 8.5), a decision on product changeover is made and, thus, $CO_{1,p'p}(t)$ assumes a value equal to δ (in this example, δ=1). Consequently, the output quantity $OUT_{1,p'}(t)$ turns to zero causing a decrease of both the current and the forecasted inventory level. On

the other hand, the production line is processing the other product type p (*i.e.*, $INP_{1,p}(t)>0$) and the related inventories increase after F time units (in this example, $F=1$).

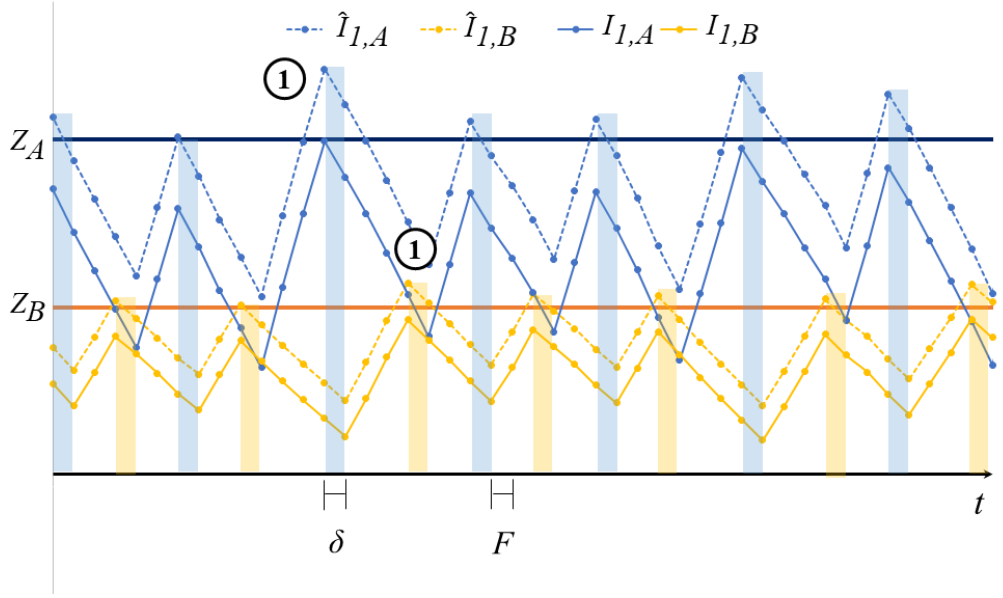


Figure 8.5 Variation of current and forecasted inventories of the factory by using HCP

8.4.2 Modified Hedging Corridor Policy

The Modified Hedging Corridor Policy (MHCP) is characterized by two thresholds: the maximum inventory threshold Z_p and the minimum inventory threshold α_p (where $\alpha_p < Z_p$). The Z_p is calculated as in Eq. 8.17. The minimum inventory threshold α_p depends on a parameter φ in $[0,1[$. α_p is calculated as follows:

$$\alpha_p = \varphi \cdot Z_p \tag{8.18}$$

The value of φ used for MHCP is equal to 0.77 and coincides with the optimal value found in the work of Gharbi et al. (2006). Figure 8.6 shows the variation of the current and the forecasted inventory levels due to the usage of MHCP. The current inventory level $I_{1,p}(t)$ is represented by the continuous line, while the dashed one shows the variation of the forecasted inventory level $\hat{I}_{1,p}(t)$. The blue and yellow bars indicate the changeover time needed to switch from one product type to another. The decision on product changeover is made in accordance with two alternative conditions and, thus, in the case of MHCP, Eq. 8.7 can be described as follows:

$$CO_{1,p'p}(t) = \delta \quad if\ INP_{1,p'}(t\text{-}1) > 0\ and \begin{cases} \hat{I}_{1,p'}(t) \geq a_{p'}\ and\ I_{1,p}(t) < 0 \\ \hat{I}_{1,p'}(t) \geq Z_{p'} \end{cases} \qquad (8.7.b)$$

The first condition simultaneously considers the forecasted inventory of the product type *p'* being manufactured (verified by $INP_{1,p'}(t\text{-}1) > 0$) and the current inventory level of the alternative product type *p*. As indicated by mark 1 in Figure 8.6, a decision on product changeover is made when $\hat{I}_{1,p'}(t)$ exceeds the minimum inventory threshold $a_{p'}$ and, at the same time, the inventory level of the alternative product $I_{1,p}(t)$ becomes negative, involving a backlog scenario. The alternative condition, represented by the mark 2 in Figure 8.6, consists of comparing the forecasted inventory level of product type *p'* being manufactured $\hat{I}_{1,p'}(t)$ with the maximum inventory threshold $Z_{p'}$. In this respect, the changeover event occurs when $\hat{I}_{1,p'}(t)$ exceeds the maximum inventory threshold $Z_{p'}$. During the changeover, the inventories of all the product types decrease since there is a production stoppage due to setup operations for a period equal to δ (in this example, δ=*1*). When the changeover procedure is finished, the inventory of the product being manufactured increases after *F* time units (in this example, *F*=*1*).

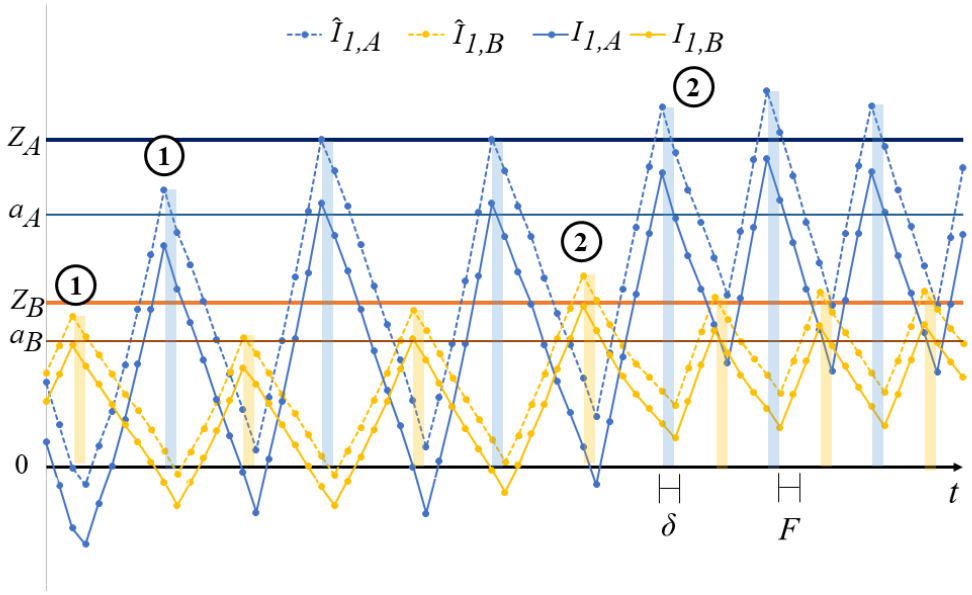


Figure 8.6 Variation of current and forecasted inventories of the factory by using MHCP

8.4.3 Improved Modified Hedging Corridor Policy

The Improved Modified Hedging Corridor Policy (IMHCP) is described by three thresholds. The first threshold is the maximum inventory threshold Z_p, which is

computed as in Eq. 8.17. The second is the minimum inventory threshold a_p calculated as in Eq. 8.18. The value of φ used for IMHCP coincides with the optimal valued defined by the work of Assid et al. (2014) (*i.e.*, $\varphi = 0.63$). Finally, a new threshold is named safety threshold b_p, and is calculated by using δ and μ_{d_p} as follows:

$$b_p = \delta \cdot \mu_{d_p} \tag{8.19}$$

Figure 4 depicts the variation of the current and forecasted inventory levels by using IMHCP. The current inventory level $I_{1,p}(t)$ is depicted by the continuous line and the dashed line represents the variation of the forecasted inventory level $\hat{I}_{1,p}(t)$. The blue and yellow bars are the changeover time needed to switch from one product type to another, as in Figure 8.5 and Figure 8.6. The decision about product changeover is based on two alternative conditions:

$$CO_{1,p'p}(t) = \delta \quad if\ INP_{1,p'}(t\text{-}1) > 0\ and \begin{cases} \hat{I}_{1,p'}(t) \geq a_{p'}\ and\ I_{1,p}(t) < b_p \\ \hat{I}_{1,p'}(t) \geq Z_{p'} \end{cases} \tag{2.c}$$

The first condition enables conducting a changeover if the forecasted inventory level $\hat{I}_{1,p'}(t)$ being manufactured (verified by $Inp_{1,p'}(t\text{-}1) > 0$) exceeds the minimum inventory threshold $a_{p'}$ and, simultaneously, the current inventory of finished product of the other product type $I_{1,p}(t)$ is less than the safety threshold b_p (see mark 1 in Figure 8.7). On the other hand, a decision on product changeover is made if the forecasted inventory level $\hat{I}_{1,p'}(t)$ of the product being manufactured is equal to or larger than the maximum inventory threshold $Z_{p'}$ (see mark 2 in Figure 8.7). When the changeover procedure is triggered, the inventories decrease for a period equal to δ (in this example, δ=*1*) and, therefore, the inventories of the product being manufactured increase after F time units (in this example, F=*1*).

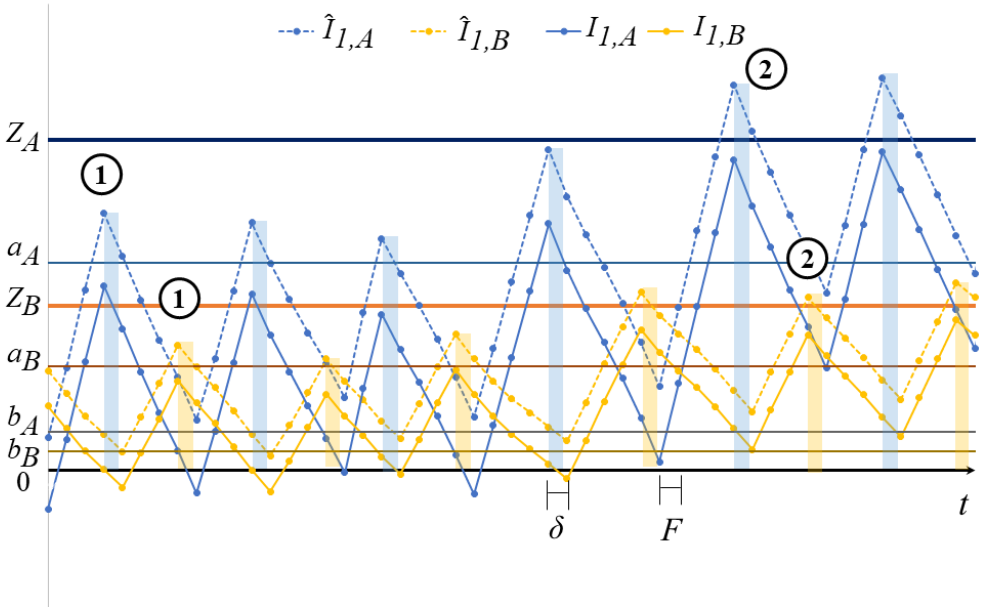


Figure 8.7 Variation of current and forecasted inventories of the factory by using IMHCP

8.4.4 Demand Driven Material Requirements Planning

DDMRP usually consists of three main steps: *i*) positioning the buffers; ii) defining the buffer profiles and levels; *iii*) dynamically adjusting the buffer profiles. However, in the problem at hand, the first step is not considered since the factory is only composed by a production line and an inventory of finished products. As for the second step, the DDMRP buffer, here denoted as inventory, is characterized by three profiles or zones, *i.e.*, green, yellow and red zones. Specifically, the green zone represents the ideal factory inventory level, the yellow zone works as an alert advertising the need of rebuild the inventory level and the red zone indicates a scenario in which the inventory level is too high or it risks to collapse in a backlog situation (Ptak and Smith, 2011, 2016). Each zone in turn is limited by different thresholds, denoted as top of red (TOR_p), top of yellow (TOY_p) and top of green (TOG_p). These thresholds are defined according to the type of item, the lead time and the variability (Velasco Acosta et al., 2020). In this context, the lead time was configured as flow time. Finally, the thresholds are dynamically adjusted by using the forecasted demand computed through the exponential smoothing method. Then,

the thresholds are calculated as follows (see for example Ptak and Smith, 2016; Lee and Rim, 2019; Velasco Acosta et al., 2020):

$$TOR_p(t) = [(\widehat{d}_{1,p}(t) \cdot F) \cdot F_l] \cdot (1 + F_v) \quad (8.20)$$

$$TOY_p(t) = TOR_p(t) + (\widehat{d}_{1,p}(t) \cdot F) \quad (8.21)$$

$$TOG_p(t) = TOY_p(t) + [(\widehat{d}_{1,p}(t) \cdot F) \cdot F_l] \quad (8.22)$$

where F_l is the flow time factor and F_v is the variability factor. The values of these factors were set to 1.00 after consulting the work of Ptak and Smith (2016) and on the basis of trial-and-error preliminary tests. Figure 8.8 shows the variation of both current and forecasted inventory levels by using the DDMRP strategy. As in the previous figures, the continuous line represents $I_{1,p}(t)$, the dashed line is for $\hat{I}_{1,p}(t)$ and blue and yellow bars are used to represent the changeover time. For the sake of clarity, Figure 8.8 reports only the thresholds related to product A. The decision concerning the product changeover is based on two alternative conditions:

$$CO_{1,p'p}(t) = \delta \quad if\ INP_{1,p'}(t\text{-}1) > 0\ and \begin{cases} \hat{I}_{1,p'}(t) \geq TOY_{p'}(t) \ \ and\ I_{1,p}(t) < TOY_p(t) \\ \hat{I}_{1,p'}(t) \geq TOG_{p'}(t) \end{cases} \quad (8.2.d)$$

Hence, the product changeover may occur when the forecasted inventory level $\hat{I}_{1,p'}(t)$ being currently manufactured (verified by $INP_{1,p'}(t\text{-}1) > 0$) exceeds $TOY_{p'}(t)$ and, simultaneously, the current inventory level of the other product type $I_{1,p}(t)$ is lower than $TOY_p(t)$ (see mark 1 in Figure 8.8). Alternatively, a decision can be made when the forecasted inventory level $\hat{I}_{1,p'}(t)$ of the product being manufactured risks to be too high since it exceeds $TOG_{p'}(t)$ (see mark 2 in Figure 8.8).

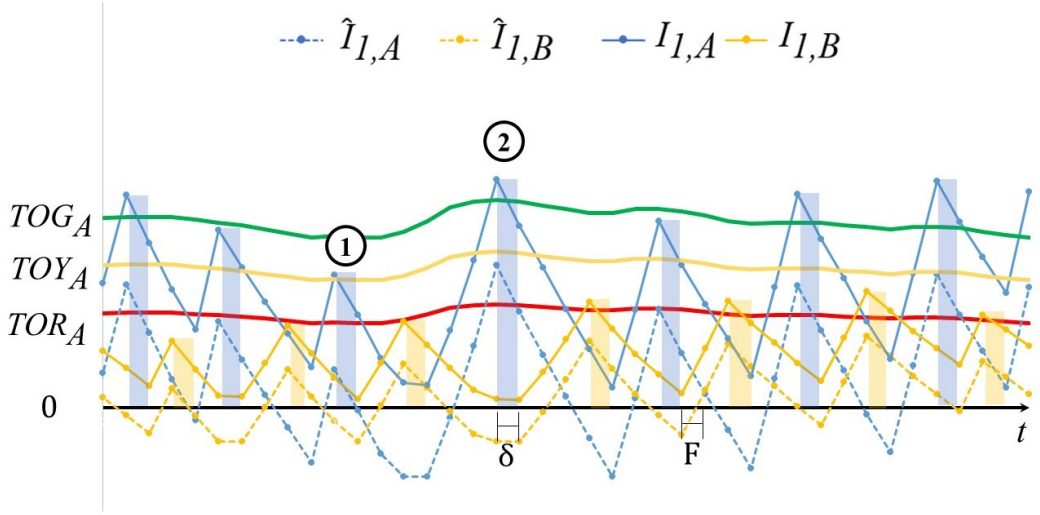


Figure 8.8 Variation of current and forecasted inventory levels of the factory by using DDMRP

8.4.5 Adaptive Hedging Corridor Policy

AHCP is a new version of HCP proposed in this work to deal with the uncertainty of the variable demand coming from the distribution chain. Different from HCP, $Z_p(t)$ is calculated at each time t and depends on the inventory threshold factor (z), which can be adjusted by managers, and the forecasted demand $\hat{d}_{1,p}(t)$, which is calculated in each period by using the exponential smoothing method, as in Eq. 8.5. Therefore, the inventory threshold $Z_{p,t}$ is defined as:

$$Z_p(t) = z \cdot \hat{d}_{1,p}(t) \tag{8.23}$$

Figure 8.9 shows the variation of the forecasted inventory level $\hat{I}_{1,p'}(t)$ when AHCP is applied. When the decision on product changeover is conducted by the HCP, the Eq. 8.7 can be expressed as follows:

$$CO_{1,p'p}(t) = \delta \quad if\ INP_{1,p'}(t\text{-}1) > 0\ and\ \hat{I}_{1,p'}(t) \geq Z_{p'}(t) \tag{8.7.e}$$

It is noteworthy that the threshold is not linear but assumes a variable trend. As in HCP, when a decision on the product changeover is taken, the forecasted inventory level of product p' decreases and, on the other hand, the forecasted inventory level of the other product type p increases.

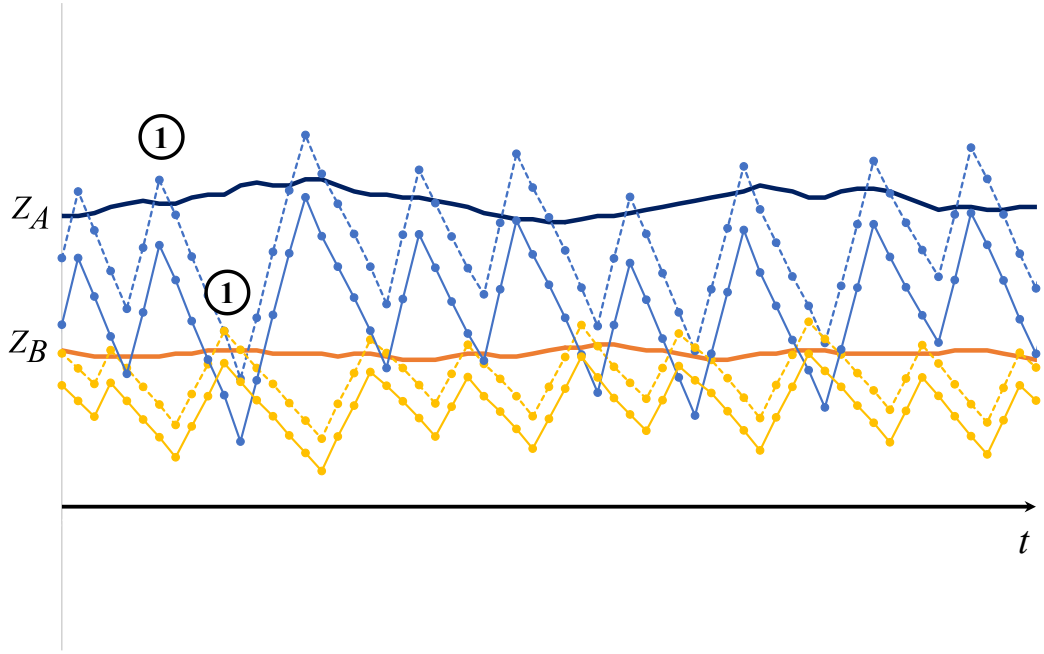


Figure 8.9 Variation of current and forecasted inventory levels of the factory by using AHCP

8.5 Experiments and analysis of results

This section presents the experimental resolution approach adopted to address the two-product two-echelon SC dynamics problem with production capacity constraints. Three different specific problems were faced:

1. The first step was to evaluate the performance of the proposed two-product SC with realistic capacity restrictions, in which the well-established HCP was selected as production control policy;
2. The second step was to compare the four production control policies provided by the literature in order to identify the best policy based on the SC strategy (customer-oriented or focused on the minimization of operational cost);
3. The last step was to evaluate the effectiveness of the new adaptive production control policy proposed for the first time in this work. The adaptive HCP was compared with the original HCP in terms of fill rate.

8.5.1 Experimental campaign with the new SC model with realistic capacity constraints

A full-factorial Design of Experiments (DOE) was arranged to evaluate the performance of the proposed two-product SC with realistic capacity restrictions. Notably, seven distinct factors, five of them varied at three levels and the rest at two

levels were adopted as independent variables. Hence, the influence of those factors on three dependent variables, namely, Fill Rate (*FR*), standard deviation of inventory of both retailer ($\sum I_{ret}$) and factory ($\sum I_{fact}$), was investigated. The Fill Rate response variable refers to the customer service level, *i.e.*, the percentage of orders delivered on time (Ponte et al., 2017). It is calculated as the ratio between the mean number of units of product delivered by the retailer $C_{2,p}(t)$ and the customer mean demand $d_p(t)$, as follows:

$$FR_p = \left(\frac{1}{T} \sum_{t=1}^{T} \frac{C_{2,p}(t)}{d_p(t)} \right) \% \tag{8.24}$$

The standard deviation of inventories, denoted as $\sum I_{ret}$ and $\sum I_{fact}$, was used for investigating the inventory level variability of factory and retailer over the time (Zanoni et al., 2006). It is able to measure the inventory holding cost at each stage of the SC, also capturing the detrimental consequences of the bullwhip effect (Dominguez et al., 2019; Hosoda and Disney, 2018).

Table 8.4 reports the list of parameters and influencing factors considered in the DOE. Notably, the threshold factor of lost K_p sales was varied at 2 levels (1 and 2, respectively) since cost of backlogs were considered remarkably higher than cost of lost sales. Moreover, it is assumed that the values of α_{ret} and α_{fact} are equal and, then, they can be generally expressed as α. To make the analysis robust enough, the full factorial design was replaced five times for each experiment; thus, a total of $3^5 \cdot 2^4 = 3{,}888$ scenarios were investigated, and $5 \cdot 3{,}888 = 19{,}440$ runs were executed. The time length (T) of each simulation run consists of 2.000 periods and a warm-up period of 200 time units was excluded from the response variables computation. To assure the repeatability of the experiments, a set of variables has to be initialized as follows:

- p at time $t = 1$ is randomly chosen between 1 or 2;
- $I_{i,p}(1) = \varepsilon \cdot \mu_{d_p}$;
- $\hat{I}_{i,p}(1) = \varepsilon \cdot \mu_{d_p}$;
- $\hat{d}_{i,p}(1) = \mu_{d_p}$;
- $INP_{1,p}(1) = \chi_p$;
- $W_{1,p}(1) = \chi_p$;

All the other variables were set to zero.

Parameters	**Values**		
Lead time transportation (LT)	2		
Flow time (F)	2		
Mean demand product A (μ_{d_A})	100		
Mean demand product B (μ_{d_B})	50		
Machine repair time ($t_R(t)$)	$U \in (0,1)$		
FACTORS	***Level 1***	***Level 2***	***Level 3***
Safety stock factor (ε)	1.00	1.50	2.00
Proportional controller (β)	0.20	0.40	0.60
Demand smoothing forecast factor (α)	0.30	-	0.60
Nominal capacity / Mean demand (χ_p/μ_{d_p})	3.00	3.25	3.50
St. Dev. Demand / Mean demand (σ_{d_p}/μ_{d_p})	0.10	-	0.30
Inventory threshold factor (z)	9.00	11.00	13.00
Threshold factor of lost sales factor (k)	1.00	-	2.00
Changeover time (δ)	0.50	1.00	2.00
Failure rate (λ)	0.03	-	0.10

Table 8.4 Parameters and factors involved concerning with the DOE

8.5.1.1 Analysis of numerical results

A series of analyses of variance (ANOVA) at 95% level of confidence were performed to infer about the statistical influence of several factors over the three response variables. Minitab®17 commercial package was engaged as statistical tool and interactions until the second order were assessed. Although the work deals with a two-products SC problem, the numerical analysis refers just to one product (product *A*), since no significant differences were detected for the other one

As for the fill rate (*FR*) performance indicator, Figure 8.10 refers to the output from the ANOVA, while Figure 8.11 depicts the main effect plots. For the sake of brevity, a stepwise ANOVA table ignoring the statistically irrelevant first- and second-order factors is reported. All independent variables statistically bias the fill rate indicator, with exception of the demand smoothing forecast factor α. Interestingly, both the safety stock factor ε, that expands the target inventory $TI_{2,p}(t)$ (see Eq. 8.14), and even more the proportional controller β negatively

influences the fill rate; in fact, the customer satisfaction decreases as much as ε decreases and/or the replenishment policy of the retailer tends to the Order-Up-To strategy. Such an unpredictable result can be justified as follows. Whenever a higher proportional controller β is employed, the order to the factory not only consists of the expected customer demand, but also includes two contributions depending on the expected WIP level and the inventory level, respectively (see Eq. 8.16). This last implicitly depends on the safety stock factor that, in this case, works as an amplification factor of β, as emerges in the following.

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	104	1418160	13636	239.86	0.000
Blocks	4	36	9	0.16	0.960
Linear	14	535422	38244	672.73	0.000
ε	2	6513	3257	57.29	0.000
β	2	125236	62618	1101.47	0.000
α	1	14	14	0.25	0.615
χ_p/μ_(d_p)	2	182150	91075	1602.04	0.000
σ_(d_p)/μ_(d_p)	1	4941	4941	86.92	0.000
z	2	33786	16893	297.15	0.000
k	1	111947	111947	1969.18	0.000
δ	2	63669	31835	559.98	0.000
λ	1	7165	7165	126.03	0.000
2-Way Interactions	86	882702	10264	180.55	0.000
ε*β	4	35892	8973	157.84	0.000
ε*α	2	360	180	3.17	0.042
ε*χ_p/μ_(d_p)	4	34708	8677	152.63	0.000
ε*σ_(d_p)/μ_(d_p)	2	21016	10508	184.84	0.000
ε*z	4	178	44	0.78	0.536
ε*k	2	20072	10036	176.54	0.000
ε*δ	4	344	86	1.51	0.195
ε*λ	2	91	46	0.80	0.448
β*α	2	209	105	1.84	0.159
β*χ_p/μ_(d_p)	4	197493	49373	868.49	0.000
β*σ_(d_p)/μ_(d_p)	2	34275	17138	301.46	0.000
β*z	4	3139	785	13.80	0.000
β*k	2	120157	60079	1056.80	0.000
β*δ	4	9188	2297	40.41	0.000
β*λ	2	2926	1463	25.74	0.000
α*χ_p/μ_(d_p)	2	301	150	2.64	0.071
α*σ_(d_p)/μ_(d_p)	1	59	59	1.03	0.310
α*z	2	170	85	1.49	0.225
α*k	1	56	56	0.98	0.322
α*δ	2	150	75	1.32	0.268
α*λ	1	7	7	0.12	0.735
χ_p/μ_(d_p)*σ_(d_p)/μ_(d_p)	2	39931	19965	351.20	0.000
χ_p/μ_(d_p)*z	4	19579	4895	86.10	0.000
χ_p/μ_(d_p)*k	2	162132	81066	1425.98	0.000
χ_p/μ_(d_p)*δ	4	45785	11446	201.34	0.000
χ_p/μ_(d_p)*λ	2	4553	2277	40.05	0.000
σ_(d_p)/μ_(d_p)*z	2	102	51	0.90	0.406
σ_(d_p)/μ_(d_p)*k	1	19074	19074	335.52	0.000
σ_(d_p)/μ_(d_p)*δ	2	2416	1208	21.25	0.000
σ_(d_p)/μ_(d_p)*λ	1	1	1	0.02	0.892
z*k	2	18363	9181	161.50	0.000
z*δ	4	41290	10322	181.58	0.000
z*λ	2	1664	832	14.63	0.000
k*δ	2	37804	18902	332.49	0.000
k*λ	1	4411	4411	77.58	0.000
δ*λ	2	4806	2403	42.27	0.000
Error	19335	1099183	57		
Total	19439	2517343			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
7.53985	56.34%	56.10%	55.86%

Figure 8.10 ANOVA analysis for the fill rate

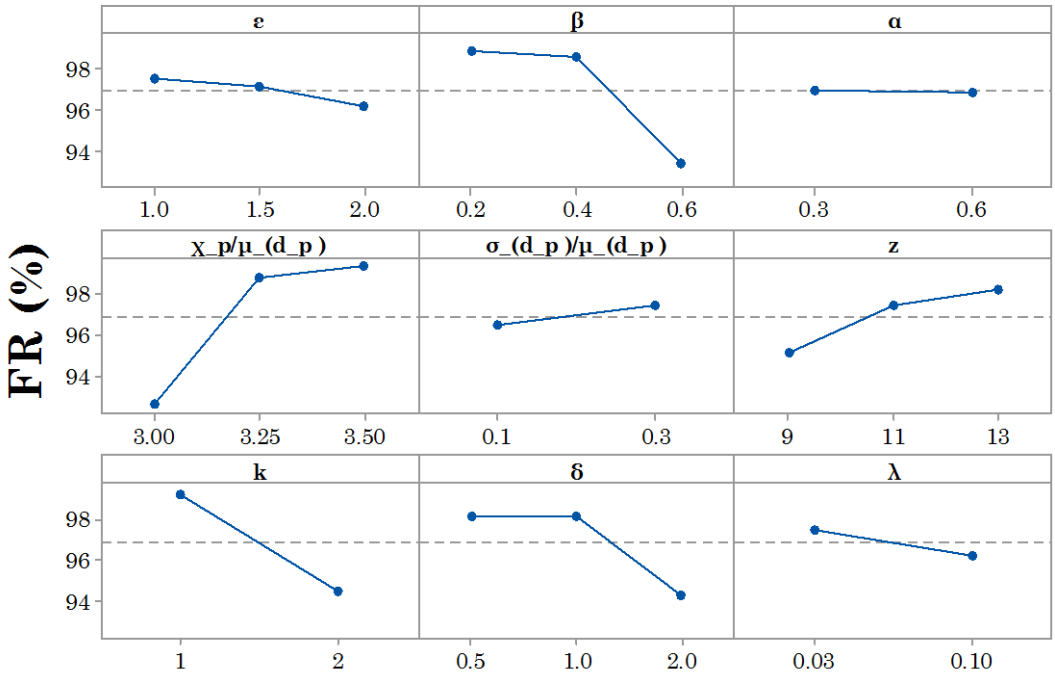


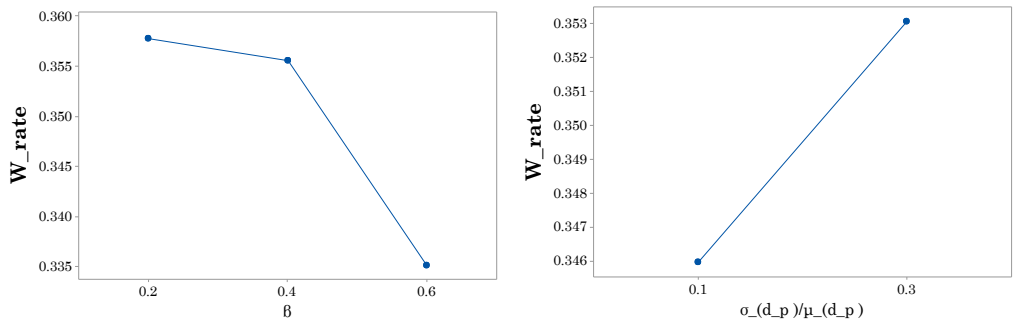
Figure 8.11 Main effect plots for the fill rate

A higher value of β implies a greater demand from retailer to factory and, especially when the production capacity χ_p/μ_{d_p} is set to a lower value, the capacitated production system takes more time to achieve the changeover threshold Z_p. Such situation makes the production runs longer (*i.e.*, fewer changeovers) and, as a consequence, severe backlogs for the other (waiting) product may occur. To further infer about the aforementioned affirmation, a specific metric denoted as working rate (W_{rate}) was properly designed, as follows:

$$W_{rate}=\frac{N_{CO}*\delta}{T\text{-}Tw} \tag{8.25}$$

where N_{CO} is the number of changeover events occurred during the entire simulation time T, which has to be depurated of the warm-up time T_w. In words, it consists of the ratio between the total changeover time and the net simulation time. Figure 8.12-a) shows the box plot related to the mean W_{rate} as the proportional controller value changes. As the reader can notice, W_{rate} decreases as β grows, thus confirming that a greater β would lead to fewer setups, *i.e.*, longer production runs, to achieve the changeover threshold. Under this perspective, a higher safety stock factor would increase the target inventory and the replenishment order as well, thus reinforcing

the risk of incurring in a severe backlog. In other words, chasing the changeover threshold for a product implies to increase the risk of stock-out for the other one, thereby reducing the service level to customers.



a) b)

Figure 8.12 Box plot of mean W_{rate} as β changes a) and as σ_{d_p}/μ_{d_p} changes b)

No noteworthy effect merges for α, as depicted in the related main-plot diagram, while the ratio between input rate and mean customer demand χ_p/μ_{d_p} significantly affects the FR response variable, as confirmed by the corresponding F-value in Figure 8.10. An appropriate production capacity allows the factory to better satisfy the retailer orders, also reducing the production runs and increasing the number of product changeovers. It is worth noting as the fill rate is less insensitive to higher values of χ_p/μ_{d_p} (see Figure 8.11). Another unforeseen finding regards the variability of the customer demand ratio σ_p/μ_{d_p}that positively affects the fill rate objective. In fact, the fourth main plot in Figure 8.11 reveals that the higher is the standard deviation of the customer demand the better is the customer service level. To infer on such unexpected outcome, the working rate indicator was observed again. Figure 8.12-b) points out that W_{rate} increases as much as the variability of the customer demand grows too. Briefly, when the customer demand has a lower variability, the HCP provides longer production runs and as smaller number of changeovers are executed. On the other hand, also supported by the provided limit on the backlogs, a higher demand variability favors the achievement of the changeover threshold, which reduces the production runs and improves the responsiveness to customers.

The inventory threshold factor z, which drives the production control policy, positively biases the fill rate. In fact, the higher z the higher will be the factory inventory level, which allows to promptly satisfy the customer demand.

Looking at the F-values of Figure 8.10 the threshold factor of lost sales is the most influencing factor for the fill rate indicator. As expected, a higher value of k remarkably reduces the service levels since it controls the maximum stock-out quantity. In fact, under such a limited capacity condition, a higher k implies a higher allowed stock-out and a poorer service level as well.

The last two factors, *i.e.*, changeover time δ and failure rate λ remarkably influence the customer service level, as expected. Notably, the changeover time has a really negative impact on the fill rate, even though there is not a significant difference between δ=0.5 and δ=1.0. As for the failure rate, a greater value means a higher probability to reduce the throughput, which leads to a lower service level.

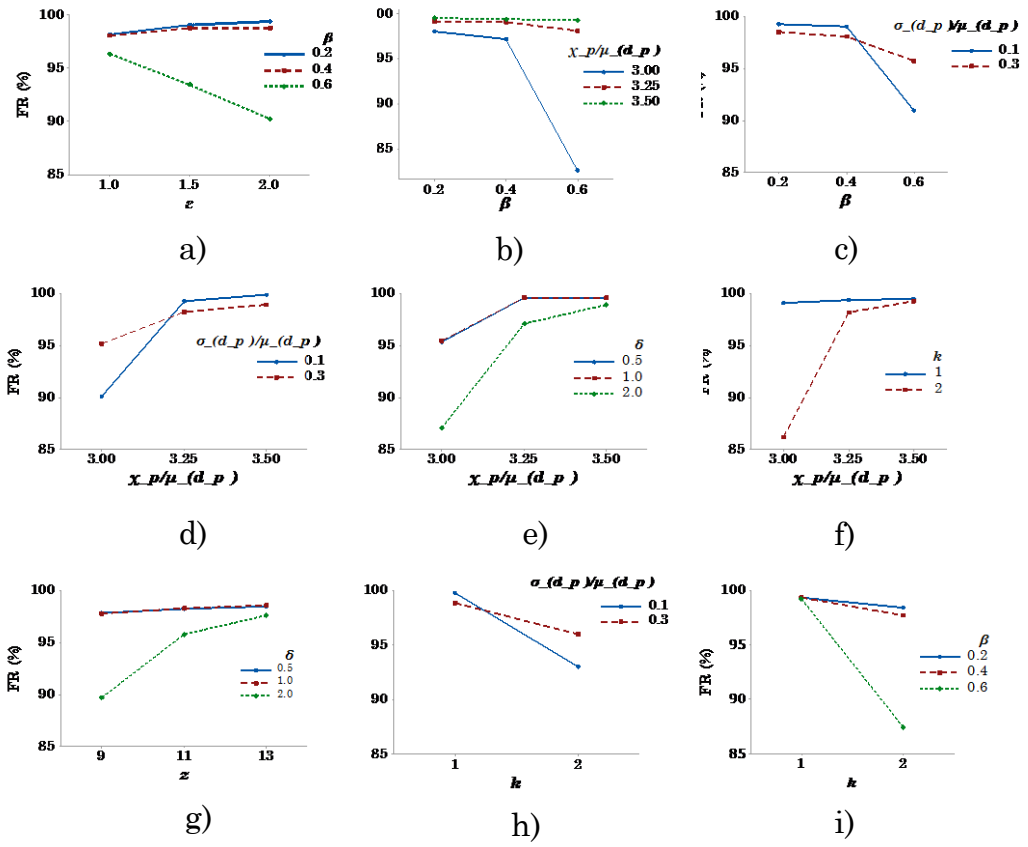


Figure 8.13 Interaction plot for the fill rate

As far as the second-order interactions are concerned, Figure 8.13 reports the most representative plots, most of them selected on the basis of the largest F-values from the ANOVA table (Figure 8.10). Lower values of β (*i.e.*, 0.2 or 0.4) combined with any value of ε do not harm the fill rate significantly (see Figure 8.13-a). Conversely, whether β assumes the highest value (*i.e.*, 0.6) the fill rate reduces as much as the

safety stock factor is set to a lower value. Similarly, the interaction plot between β and the nominal capacity/mean demand ratio χ_p/μ_{d_p} (see Figure 8.13-b) shows that the fill rate drastically falls down if the proportional controller takes a high value and the nominal capacity is set at the lowest level. Another interesting insight concerns the interaction between the proportional controller β and the customer demand variability σ_{d_p}/μ_{d_p} (see Figure 8.13-c). In fact, regardless of the demand variability, a minor impact on the fill-rate appears when β assumes lower values, while the same response variable undergoes a strong degradation as the demand variability reduces and β takes the highest value. The negative effect of a lower demand variability can be observed in combination with the lowest nominal capacity/mean demand ratio χ_p/μ_{d_p} (see Figure 8.13-d). Figure 8.13-e) depicts the joint role of changeover time δ and production capacity ratio χ_p/μ_{d_p} on the fill-rate. As expected, the service level decreases as much as the nominal capacity reduces but a higher changeover time further encourages the degradation of the fill-rate. The strong effect of the lost sales threshold factor k on the FR can be observed in connection with the nominal capacity ratio. If k is set to the lowest value no significant impact occurs on the FR as the nominal capacity varies. Instead, a higher value of k has a detrimental influence on the fill rate as much as the manufacturing capacity reduces (see Figure 8.13-f). The harmful effect on the service level achieved by merging a lower nominal capacity with a higher proportional controller is visible in Figure 8.13-g). The implications of the customer demand variability on the fill rate depends on the value assumed by the threshold factor of lost sales (see Figure 8.13-h). Finally, another interesting finding comes out by considering the interaction between the changeover threshold and its duration. In fact, the fill rate is almost insensitive to z except when δ assumes a higher value (see Figure 8.13-i).

Figure 8.14 refers to the ANOVA table for the retailer inventory's standard deviation, while Figure 8.15 depicts the related main effect plots. Differently from the fill rate analysis, the safety stock factor positively biases the standard deviation of the retailer inventory $\sum I_{ret}$ level. In fact, a lower safety stock factor, which also reduces the weight of the target inventory on the replenishment policy, determines a lower variability of the retailer stock level. Lower values of the proportional controller β generate a favorable effect on the fill rate and on the inventory standard deviation as well. So, a replenishment policy considerably far from the order-up-to

strategy would imply a lower variability of the stock level. When the production capacity decreases, the factory might not be able to properly support the incoming replenishment orders. As a consequence, the retailer inventory is subject to a higher variability, which in turn affects the fill rate, as mentioned in the previous analysis. As expected, the ratio σ_{d_p}/μ_{d_p} strongly impacts on $\sum I_{ret}$; thus, the higher is the ratio between standard deviation and mean of customer demand σ_{d_p}/μ_{d_p} the greater the variability of the retailer inventory. The dependent variable $\sum I_{ret}$ seems to be remarkably sensitive to the changeover threshold Z_p/μ_d; in fact, the retailer inventory variability reduces as much as such threshold rises.

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	104	15773919	151672	800.28	0.000
Blocks	4	8671	2168	11.44	0.000
Linear	14	12304619	878901	4637.39	0.000
ε	2	288368	144184	760.77	0.000
β	2	982859	491429	2592.95	0.000
α	1	91398	91398	482.24	0.000
χ_p/μ_(d_p)	2	789599	394800	2083.10	0.000
σ_(d_p)/μ_(d_p)	1	8417425	8417425	44413.23	0.000
z	2	356334	178167	940.07	0.000
k	1	563619	563619	2973.85	0.000
δ	2	762493	381247	2011.59	0.000
λ	1	52523	52523	277.13	0.000
2-Way Interactions	86	3460629	40240	212.32	0.000
ε*β	4	95252	23813	125.65	0.000
ε*α	2	1583	791	4.18	0.015
ε*χ_p/μ_(d_p)	4	86827	21707	114.53	0.000
ε*σ_(d_p)/μ_(d_p)	2	13113	6556	34.59	0.000
ε*z	4	4618	1154	6.09	0.000
ε*k	2	57309	28654	151.19	0.000
ε*δ	4	10867	2717	14.33	0.000
ε*λ	2	229	114	0.60	0.547
β*α	2	35412	17706	93.42	0.000
β*χ_p/μ_(d_p)	4	525125	131281	692.69	0.000
β*σ_(d_p)/μ_(d_p)	2	28508	14254	75.21	0.000
β*z	4	1656	414	2.18	0.068
β*k	2	394643	197322	1041.14	0.000
β*δ	4	15562	3891	20.53	0.000
β*λ	2	1301	651	3.43	0.032
α*χ_p/μ_(d_p)	2	100	50	0.26	0.769
α*σ_(d_p)/μ_(d_p)	1	9477	9477	50.00	0.000
α*z	2	339	169	0.89	0.409
α*k	1	32	32	0.17	0.681
α*δ	2	484	242	1.28	0.279
α*λ	1	131	131	0.69	0.407
χ_p/μ_(d_p)*σ_(d_p)/μ_(d_p)	2	125363	62682	330.73	0.000
χ_p/μ_(d_p)*z	4	78137	19534	103.07	0.000
χ_p/μ_(d_p)*k	2	580506	290253	1531.48	0.000
χ_p/μ_(d_p)*δ	4	280505	70126	370.01	0.000
χ_p/μ_(d_p)*λ	2	7024	3512	18.53	0.000
σ_(d_p)/μ_(d_p)*z	2	12645	6322	33.36	0.000
σ_(d_p)/μ_(d_p)*k	1	54459	54459	287.34	0.000
σ_(d_p)/μ_(d_p)*δ	2	9046	4523	23.86	0.000
σ_(d_p)/μ_(d_p)*λ	1	196	196	1.04	0.309
z*k	2	97150	48575	256.30	0.000
z*δ	4	553361	138340	729.93	0.000
z*λ	2	19463	9731	51.35	0.000
k*δ	2	276213	138107	728.70	0.000
k*λ	1	15292	15292	80.69	0.000
δ*λ	2	68702	34351	181.25	0.000
Error	19335	3664470	190		
Total	19439	19438389			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
13.7668	81.15%	81.05%	80.94%

Figure 8.14 ANOVA analysis of $\sum I_{ret}$

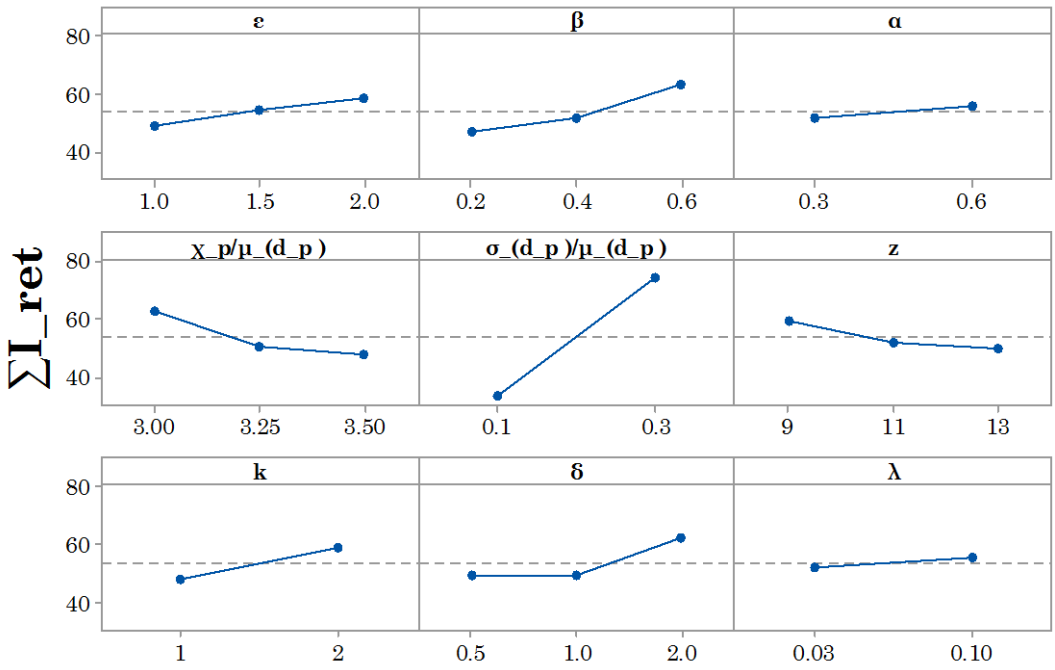


Figure 8.15 Main effect plots of $\sum I_{ret}$

The whole set of independent variables affects the standard deviation of the retailer inventory $\sum I_{ret}$. The variability of the customer demand exerts a strong influence, while this time the demand smoothing forecast factor weakly impacts on the performance measure at hand. Similarly, to the previous analysis on the fill rate, the first two levels of changeover time δ do not affect the standard deviation of the retailer inventory. On the other hand, a detrimental impact on the inventory variability emerges when δ is equal to its highest value. Finally, the probability of failure moderately impacts on the $\sum I_{ret}$ objective, as confirmed by the smallest F-value in the ANOVA table. As expected, a higher failure rate implies a higher stock variability.

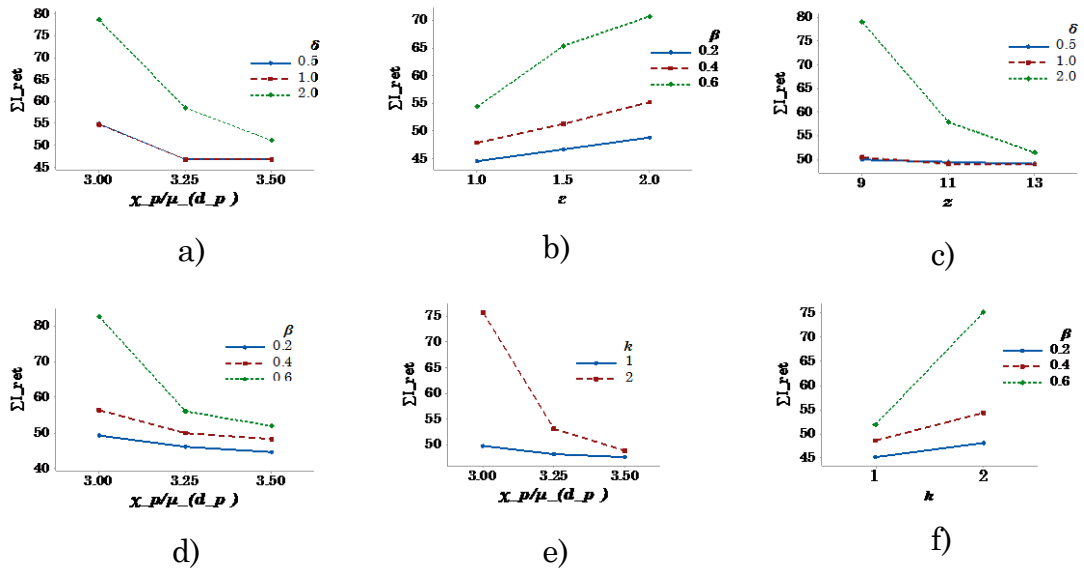


Figure 8.16 Interaction plot of $\sum I_{ret}$

Figure 8.16 retrieves the most interesting interaction plots concerning the highest F-values in Figure 8.14. The first plot regards the interaction between the nominal capacity/mean demand ratio χ_p/μ_{d_p} and the changeover time δ (see Figure 8.16-a). The lower the production capacity the greater the standard deviation of the retailer inventory, though such phenomenon is amplified as the changeover time increases. It is worth noting how such factors working at the factory level significantly affect the variability of the retailer inventory. Figure 8.16-b) highlights that the negative influence of ε on $\sum I_{ret}$ increases as much as the proportional controller β grows. Similarly to what we described earlier for the FR performance measure, $\sum I_{ret}$ is almost insensitive to the changeover threshold if such task has a lower duration. The interval plot involving the changeover threshold Z_p/μ_{d_p} and the changeover time δ are worthy to be investigated. Although both factors regard the production flow, their effect is remarkably reflected on the retailer level. Indeed, if the changeover time is set to a low or medium level, *i.e.*, δ=0.5 or δ=1.0, $\sum I_{ret}$ is quite insensitive to the changeover threshold variability. Conversely, if δ takes the highest value (δ=2.0), the inventory variability drastically increases as much as Z_p/μ_{d_p} reduces. (see Figure 8.16-c). A similar effect on $\sum I_{ret}$ emerges from the interaction plots involving the nominal capacity with β and k, respectively (see Figure 8.16-d and Figure 8.16-e). Interestingly, β acts as an amplification factor of k for the objective function under consideration Figure 8.16-f).

Figure 8.17 shows the results from the analysis of variance on the factory inventory variability $\sum I_{fact}$. Again, the whole set of factors influences the factory inventory variability in a statistically significant manner. The main effect plots in Figure 8.18 are consistent with the ones observed in the retailer-related indicator $\sum I_{fact}$. Therefore, most previous considerations about $\sum I_{ret}$ can be extended to the $\sum I_{fact}$ indicator. The main differences concern the safety stock factor ε, the customer demand variability ratio σ_{d_p}/μ_{d_p} and the inventory threshold factor z, whose effects appear less significant than in the $\sum I_{ret}$ related analysis, as confirmed by the corresponding F-value in the ANOVA table (see Figure 8.17) and the main effect plots (see Figure 8.18). Interestingly, it is worth noting that the mean value of $\sum I_{fact}$ (shown in dashed line in Figure 8.18) is roughly three times greater than the mean $\sum I_{ret}$ (Figure 8.15); thereby, the inventory standard deviation can be considered as a way to assess the bullwhip effect. Since the changeover time δ takes the highest F-values in the ANOVA table, it can be considered as the most influencing factor. In fact, whenever a changeover occurs, such stoppage generates a sudden reduction of the throughput and the factory stock level as well, which amplifies the variability of the factory inventory. The impact of the failure rate λ can be considered as comparable to the one observed for the $\sum I_{ret}$ performance indicator.

In line with the previous analyses, only the main second-order interactions on the mean $\sum I_{fact}$ will be investigated in the following. Considering the highest F-values of the 2-way interactions in Figure 8.17, Figure 8.19 depicts four interaction plots involving the following factors: proportional controller β, safety stock factor ε, nominal capacity/mean demand ratio χ_p/μ_{d_p} and demand variability ratio σ_p/μ_{d_p}. The mean inventory standard deviation dramatically increases when the nominal production capacity is at the lowest level and the proportional controller at the highest one (see Figure 8.19-a). Large values of β yield a relevant increase in the standard deviation of factory inventory as the safety stock factor increases too (Figure 8.19-b). However, without loss of generality, it is possible to state that the combination of large values of β and small values of χ_p lead to critical conditions for the service level and variability inventories as well. Figure 8.19-c) highlights that the harmful effect of higher values of proportional controller on $\sum I_{fact}$ is exacerbated by the threshold factor on lost sales. It is worthy to note that the safety stock factor has a different impact on $\sum I_{fact}$ depending on the variability of the customer demand.

In particular, if σ_p/μ_{d_p} assumes a lower value the effect of ε is quite uncertain, while $\sum I_{fact}$ almost linearly grows when σ_p/μ_{d_p} and ε are set to the highest levels (Figure 8.19-d).

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	104	73294065	704751	1214.53	0.000
Blocks	4	17557	4389	7.56	0.000
Linear	14	68363628	4883116	8415.30	0.000
ε	2	188898	94449	162.77	0.000
β	2	2552243	1276121	2199.20	0.000
α	1	420055	420055	723.90	0.000
χ_p/μ_(d_p)	2	3390870	1695435	2921.82	0.000
σ_(d_p)/μ_(d_p)	1	3970695	3970695	6842.88	0.000
z	2	39061	19531	33.66	0.000
k	1	903619	903619	1557.25	0.000
δ	2	55793815	27896907	48076.05	0.000
λ	1	1104373	1104373	1903.22	0.000
2-Way Interactions	86	4912879	57127	98.45	0.000
ε*β	4	121217	30304	52.22	0.000
ε*α	2	1197	599	1.03	0.356
ε*χ_p/μ_(d_p)	4	88881	22220	38.29	0.000
ε*σ_(d_p)/μ_(d_p)	2	100510	50255	86.61	0.000
ε*z	4	9083	2271	3.91	0.004
ε*k	2	54197	27098	46.70	0.000
ε*δ	4	23110	5777	9.96	0.000
ε*λ	2	3167	1584	2.73	0.065
β*α	2	26935	13467	23.21	0.000
β*χ_p/μ_(d_p)	4	1007753	251938	434.18	0.000
β*σ_(d_p)/μ_(d_p)	2	122693	61347	105.72	0.000
β*z	4	23230	5808	10.01	0.000
β*k	2	724902	362451	624.63	0.000
β*δ	4	30798	7700	13.27	0.000
β*λ	2	927	463	0.80	0.450
α*χ_p/μ_(d_p)	2	4690	2345	4.04	0.018
α*σ_(d_p)/μ_(d_p)	1	115198	115198	198.53	0.000
α*z	2	1337	669	1.15	0.316
α*k	1	1018	1018	1.75	0.185
α*δ	2	9270	4635	7.99	0.000
α*λ	1	126	126	0.22	0.641
χ_p/μ_(d_p)*σ_(d_p)/μ_(d_p)	2	104527	52263	90.07	0.000
χ_p/μ_(d_p)*z	4	32967	8242	14.20	0.000
χ_p/μ_(d_p)*k	2	911604	455802	785.50	0.000
χ_p/μ_(d_p)*δ	4	949391	237348	409.03	0.000
χ_p/μ_(d_p)*λ	2	13285	6642	11.45	0.000
σ_(d_p)/μ_(d_p)*z	2	3481	1741	3.00	0.050
σ_(d_p)/μ_(d_p)*k	1	22818	22818	39.32	0.000
σ_(d_p)/μ_(d_p)*δ	2	2580	1290	2.22	0.108
σ_(d_p)/μ_(d_p)*λ	1	2547	2547	4.39	0.036
z*k	2	27807	13903	23.96	0.000
z*δ	4	86112	21528	37.10	0.000
z*λ	2	2229	1114	1.92	0.147
k*δ	2	167813	83906	144.60	0.000
k*λ	1	12495	12495	21.53	0.000
δ*λ	2	102985	51492	88.74	0.000
Error	19335	11219448	580		
Total	19439	84513513			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
24.0887	86.72%	86.65%	86.58%

Figure 8.17 ANOVA analysis of $\sum I_{fact}$

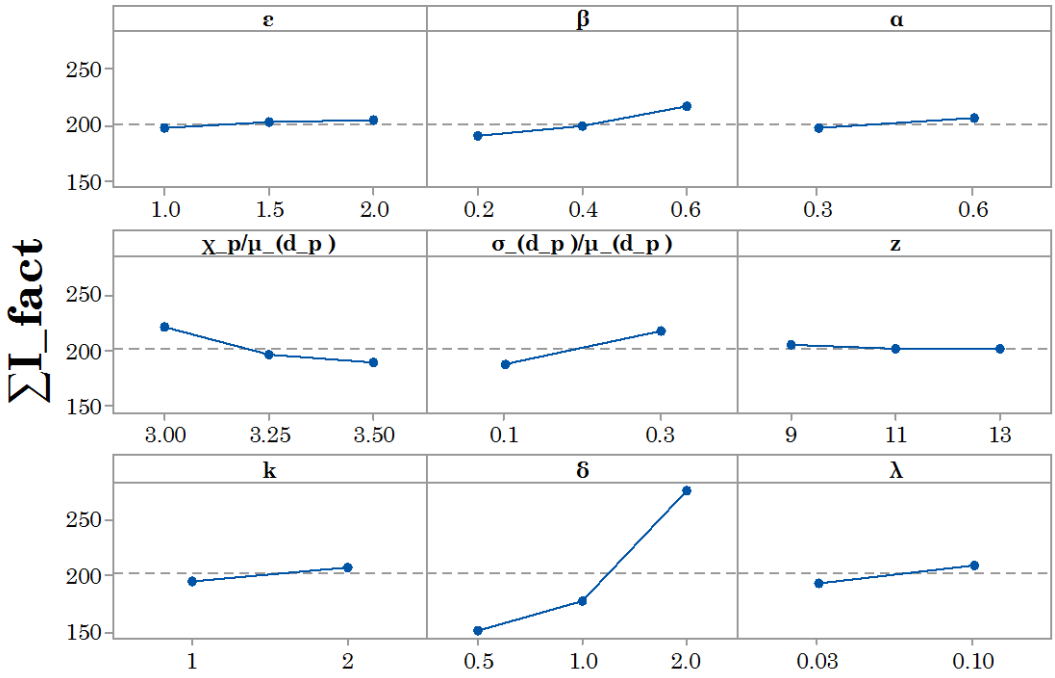


Figure 8.18 Main effect plots of $\sum I_{fact}$

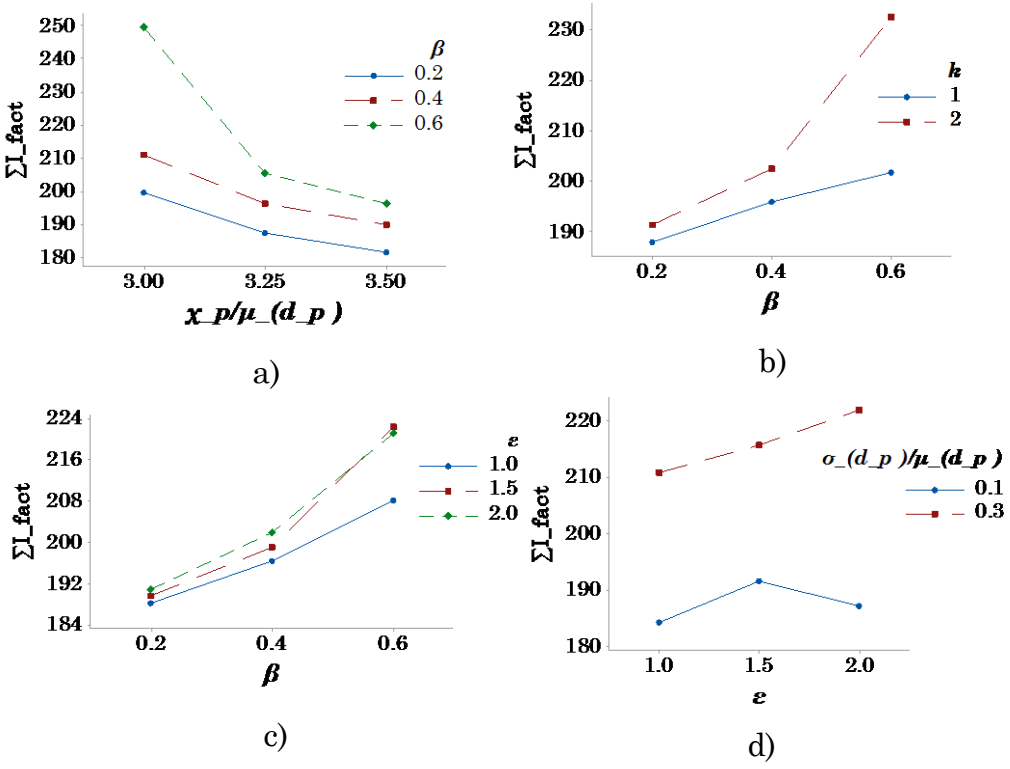


Figure 8.19 Interaction plots of $\sum I_{fact}$

8.5.1.2 Managerial and theoretical implications

Most findings arising from the previous DOE are in line with the body of literature involved on both constrained and unconstrained SC dynamics. Failures can exacerbate the instability in the SC, and the high variability of the customer demand as well (Fan et al., 2010; Ivanov et al., 2015). In this fashion, this work reasserts that the assumption of a single product in the capacitated SC model works well and is able to capture the impact of both exogenous (*e.g.*, parameters of the replenishment policy, capacity of the production line, changeover rule) and endogenous factors (variability of customer demand, failure rate) on the SC performance. On the other hand, the adopted replenishment rule, and specifically the proportional controller, reveal a peculiar effect on the performance of the proposed SC that, to the best of our knowledge, has not been detected so-far in single-product cases.

According to the literature, properly tuning this the proportional controller is an effective bullwhip-limiter method, as it can smooth the members' over-reaction/under-reaction to the variability of demand and thus limit both the propagation of the amplification of orders in upstream direction and the variability of inventories (Disney and Lambrecht, 2008; Priore et al., 2019). However, it may have negative impact on the customer service level (Dominguez et al., 2019), as excessive smoothing of the order rate could generate several stock-out events (Cannella and Ciancimino, 2010). In this study, we note that, by reducing the smoothing effect produced by the proportional controller (*i.e.*, shifting from β=0.1 to β=0.6), not only the variability of the inventory at the factory stage increases – confirming the literary findings – but also the customer service level remarkably deteriorates, in countertendency with the state-of-art in SC dynamics. This atypical phenomenon occurs because higher values of the proportional controllers induce longer production runs, thus reducing changeovers events and, as a consequence, increasing the risk of severe stock-outs for the other product. This result may have noteworthy implications for both practitioners and researchers. Specifically, from a theoretical viewpoint, we argue that modeling multi-product SCs may contribute to discover peculiar features of the inventory control policies that cannot emerge in single-product environments. Accordingly, this work would suggest that further efforts are needed to capture the dynamics of the advocated, novel and complex SCs

(*i.e.*, closed-loop SCs, additive manufacturing-based SCs, industrial symbiosis networks, etc.).

From a managerial perspective, this result would stimulate practitioners to pay special attention to the dynamics of the replenishment rule adopted downstream the SC. Depending on the typology of production system, decisions about the proportional controllers in the retailer may produce a detrimental effect for all members of the SC. To avoid this negative impact on the entire SC, a viable solution can be represented by the adoption of collaboration mechanisms such as the Vendor Managed Inventory VMI strategies (Yalcin et al., 2018), which allows to generate orders at the retailer stage on the basis of real-time operational data (*e.g.*, customer demand, current inventories, availability of the production line). However, the practical implementation of collaboration in SC is often impractical, since it is deemed too costly or too risky (Geunes et al., 2016; Huang et al., 2016). Thus, an alternative strategy may consist in working with smaller product batches or according to a production leveling strategy, such as heijunka, – particularly when the nominal production capacity is quite limited – as this dangerous effect could be determined by a saturation of the production line generated by an overreaction to the demand variability at the retailer stage. In fact, heijunka (hi-JUNE-kuh) is a Japanese word that means leveling. It is a well-known paradigm of the lean manufacturing that helps organizations to fulfill unpredictable customer demand patterns and eliminate production waste by leveling both type and quantity of production output over a fixed period of time.

8.5.2 Comparison between the production control policies

In Section 8.4 HCP, MHCP, IMHCP and DDMRP were described and identified as PCPs that can be adopted by the factory to manage the production capacity constraint. This section addresses the experimental approach defined to investigate the impact of the selected PCPs on the two-product, two-echelon SC model under investigation. For this purpose, the main response variable considered is the Fill Rate (*FR*, see Eq. 8.24). The impact of each PCP on *FR* may depend on several factors that outlines the dynamics of the SC system. In fact, the SC is described by endogenous factors, *i.e.*, control parameters whose value can be selected by the managers, and exogenous factors, which describe intrinsic features of the system. To make the comparison as exhaustive as possible, a two-stage experimental analysis

was performed. Depending on the values of the control parameters, each PCP can differently affect the *FR* indicator. Therefore, the first stage aims at selecting the most suitable values of the endogenous factors for each PCP. The second stage deals with the comparison between HCP, MCHP, IMHCP and DDMRP used with their own calibrated control parameters. This comparison is executed through an extended experimental campaign, involving several SC scenarios obtained by varying all the exogenous factors. In this last stage, the four PCPs were compared also by evaluating two further key performance indicators, *i.e.*, the average value and the standard deviation of the factory inventory level, (respectively indicated as μI_{fact} and ΣI_{fact}). Each simulation should be long enough to ensure that the outcomes are not affected by the warm-up period. In this regard, as in the previous work, the time horizon T of each simulation is 2,000 periods and the warm-up period is equal to 200 time units. Moreover, in order to start the simulations successfully, a set of variables has to be initialised (see Section 8.5.1). The initial values of all other variables are set to zero. Finally, it should be noted that the statistical analysis discussed in the next subsection deals with the first product (A), since no significant difference was encountered between the results of the two products.

8.5.2.1 Calibration of endogenous factors

The SC model is characterized by four endogenous factors (employed as control parameters), *i.e.*, the forecasting parameter used by the retailer α_{ret}, the forecasting parameter used by the factory α_{fact}, the proportional controller β and the safety stock factor ε. In particular, α_{ret} and α_{fact} are used in the smoothing method to forecast the demand coming from the downstream node, while β and ε are used to define the order quantity that the retailer places in accordance with the smoothing Order-Up-To policy.

Each endogenous factor can assume different values within a certain range. Therefore, a set of experiments are required to identify the most suitable values of each endogenous factor that allows each PCP to enhance its effectiveness in a SC scenario. For this purpose, the Box-Behnken Design (BBD) was used to define a matrix of 29 experiments, as shown in Table 8.5. α_{ret}, α_{fact}, and β are in the range of 0.1 and 0.9, as they are used as "smoothing" techniques, while ε is in the range of 0.5 and 2.5. For each experiment, 1,000 random combinations of exogenous factors,

properly drawn in the ranges indicated in the next section (see Table 8.5), were configured to consider their effect on the selection of the endogenous parameters. Therefore, Table 8.5 reports the mean value over the 1,000 combinations of the *FR* for each experiment. Since four PCPs have to be studied, the BBD matrix of experiments were used four times, one for each PCP. In order to distinguish the outcomes in relation to each PCP, the experiments are hereinafter denoted as follows: *i*) HCP model, *ii*) MHCP model, *iii*) IMHCP model, *iv*) DDMRP model. Design Expert 12® allowed carrying out the statistical study.

Considering the experimental results coming from the simulation runs, the reduced cubic model was included in the statistical analysis. The ANOVA methodology, listed in Table 8.6, was used for each PCP to investigate the validity of the proposed SC model and to determine the influence of each endogenous factor on the FR. The statistical significance of the model is shown by the *F*-values (equal to 117.63 for the HCP model, 119.39 for the MHCP model, 317.99 for the IMHCP model and 129.91 for the DDMRP model) and by the *p*-values ($p < 0.0001$ for each model). Focusing on the terms of the model, the endogenous factors are significant since their *p*-values are less than 0.05, except ε that is not statistically significant in the DDMRP model. Moreover, it can be noticed that $\alpha_{fact} \cdot \beta$ and $\beta \cdot \varepsilon$ are the most interesting interactions to analyse. The values of the three R^2 allow us to show that the model fit is effective. In fact, the values of R^2 of 99.27% for the HCP model, 99.28% for the MHCP model, 99.73% for the IMHCP and 99.34% for the DDMRP model imply that the predicted response and the experimental results are strongly correlated. This is also confirmed by the values of adjusted R^2 and the predicted R^2 since their difference is less than 20% for each model. In this regard, RSM was employed to perform the statistical analysis, described in the next lines.

The effects of each endogenous factor on the FR indicator are represented by the Main Effect Plots, which can be seen in Figure 8.20. Each column indicates the model under study, while each row represents the control parameters analysed. Specifically, the first row shows the effects of α_{ret}, the second row illustrates the influence of α_{fact}, the third row reports the effects of β, and, finally, the last row illustrates the influence of ε. The figure reveals that higher values of α_{ret} allow achieving larger values of *FR*. Instead, when the value of α_{fact} and ε are close to its lowest level, it increases the effectiveness of PCP in terms of *FR*. As for β, the highest

performance is guaranteed when it is set between 0.3 and 0.5 in the HCP and MHCP models, or between 0.5 and 0.7 in the case of the IMHCP and DDMRP models.

To examine the interaction between the endogenous factors, the contours and 3D response surface plots of the significant interactions were presented in Figure 8.21-a for the HCP model, Figure 8.21-b for the MHCP model, Figure 8.21-c for the IMHCP model and Figure 8.21-d for the DDMRP model. In these plots, the control parameters, which are not considered, were held constant at the mean value. These figures show that, if the interaction between the factors is significant, it is necessary to explore these curves to further identify the SC's performance variation. Looking at the colour gradient, one can immediately deduce that the HCP is able to assure the best performance in comparison with the other PCPs. The curves related to the HCP and MHCP models are similar and, therefore, a single brief discussion can be conducted. Focusing on the first interaction, it can be deduced that the values of *FR* strictly depend on β. In fact, the best performances are obtained when β is in the range of 0.3 and 0.5. It is interesting to note that when α_{fact} and β assume high values (*e.g.* 0.9), the *FR* decreases below 50%. A similar phenomenon is seen in the interaction between β and ε. However, high values of ε in combination with β, which is in the range of 0.2 and 0.5, allow the effectiveness of PCPs and, thus, the FR of the SC to be enhanced. As for HCP and MHCP, also IMHCP and DDMRP models report similar trends. In this case, the interaction strongly depends on the β values. In fact, the *FR* increases when β is in the range of 0.5 and 0.7.

Once the effects of the endogenous factors and their interactions were studied, the final step of this analysis is to estimate the calibrated values of each control parameter. In this regard, the statistical tool generated a list of several potential values. A set of suitable values was selected considering the knowledge obtained through the RSM analysis as follows: α_{ret}=0.90, α_{fact}=0.10, β=0.50 and ε=1.00 for the HCP model, α_{ret}=0.90, α_{fact}=0.10, β=0.51 and ε=1.00 for the MHCP model, α_{ret}=0.90, α_{fact}=0.13, β=0.28 and ε=1.16 for the IMHCP model, α_{ret}=0.90, α_{fact}=0.10, β=0.60 and ε=1.05 for the DDMRP model. A series of experiments were conducted with the random values and the calibrated values of the endogenous factors to validate the estimated set of optimal parameters.

No. experiment	Endogenous factors				FR (%)			
	α_{ret}	α_{fact}	β	ε	HCP	MHCP	IMHCP	DDMRP
1	0.5	0.5	0.1	0.5	43.00%	41.26%	30.41%	29.55%
2	0.5	0.1	0.5	0.5	54.94%	52.61%	47.39%	50.52%
3	0.1	0.5	0.5	0.5	54.30%	51.61%	47.15%	48.40%
4	0.9	0.5	0.5	0.5	53.75%	51.19%	46.67%	47.74%
5	0.5	0.9	0.5	0.5	53.04%	50.07%	45.51%	45.39%
6	0.5	0.5	0.9	0.5	44.24%	42.00%	39.09%	40.14%
7	0.5	0.1	0.1	1.5	50.18%	46.82%	34.28%	37.17%
8	0.1	0.5	0.1	1.5	50.82%	47.60%	35.19%	38.54%
9	0.9	0.5	0.1	1.5	50.53%	47.54%	35.46%	38.32%
10	0.5	0.9	0.1	1.5	50.67%	47.50%	35.67%	38.39%
11	0.1	0.1	0.5	1.5	52.96%	50.61%	46.08%	50.25%
12	0.9	0.1	0.5	1.5	54.93%	52.42%	47.86%	51.99%
13	0.5	0.5	0.5	1.5	52.66%	49.88%	46.14%	48.26%
14	0.5	0.5	0.5	1.5	52.63%	49.89%	45.97%	48.18%
15	0.5	0.5	0.5	1.5	52.69%	50.00%	45.96%	48.37%
16	0.5	0.5	0.5	1.5	52.52%	49.95%	45.90%	48.26%
17	0.5	0.5	0.5	1.5	52.38%	49.72%	45.98%	48.34%
18	0.1	0.9	0.5	1.5	50.89%	48.06%	43.97%	45.36%
19	0.9	0.9	0.5	1.5	52.39%	49.43%	45.11%	45.96%
20	0.5	0.1	0.9	1.5	45.87%	44.29%	41.85%	44.95%
21	0.1	0.5	0.9	1.5	43.55%	41.38%	39.09%	40.69%
22	0.9	0.5	0.9	1.5	44.58%	42.38%	39.90%	41.43%
23	0.5	0.9	0.9	1.5	42.76%	40.30%	37.81%	37.83%
24	0.5	0.5	0.1	2.5	54.89%	50.84%	39.82%	45.07%
25	0.5	0.1	0.5	2.5	51.40%	49.21%	45.62%	49.46%
26	0.1	0.5	0.5	2.5	49.08%	46.85%	43.66%	45.80%
27	0.9	0.5	0.5	2.5	50.92%	48.32%	45.16%	47.44%
28	0.5	0.9	0.5	2.5	49.19%	46.43%	43.24%	44.75%
29	0.5	0.5	0.9	2.5	43.67%	41.54%	39.61%	41.37%

Table 8.5 Box-Behnken Design matrix of experiments and FR for each PCP

Source	HCP model		MHCP model		IMHCP model		DDMRP model	
	***F*-value**	***p*-value**	***F*-value**	***p*-value**	***F*-value**	***p*-value**	***F*-value**	***p*-value**
Model	117.63	< 0.0001	119.39	< 0.0001	317.99	< 0.0001	129.91	< 0.0001
a_{ret}	10.43	0.0066	10.66	0.0062	15.98	0.0015	3.22	0.0958
a_{fact}	44.19	< 0.0001	80.15	< 0.0001	87.31	< 0.0001	155.52	< 0.0001
β	431.69	< 0.0001	351.11	< 0.0001	443.29	< 0.0001	82.12	< 0.0001
ε	123.28	< 0.0001	128.50	< 0.0001	77.59	< 0.0001	6.97	0.0204
$a_{ret} \cdot a_{fact}$	0.2349	0.6360	0.2317	0.6383	0.7897	0.3903	0.8352	0.3774
$a_{ret} \cdot \beta$	1.80	0.2031	1.36	0.2641	0.5376	0.4765	0.6113	0.4483
$a_{ret} \cdot \varepsilon$	5.90	0.0304	4.27	0.0594	7.43	0.0173	3.45	0.0861
$a_{fact} \cdot \beta$	13.37	0.0029	25.96	0.0002	55.77	< 0.0001	45.70	< 0.0001
$a_{fact} \cdot \varepsilon$	0.1005	0.7563	0.0718	0.7929	0.4845	0.4986	0.1136	0.7415
$\beta \cdot \varepsilon$	160.32	< 0.0001	120.72	< 0.0001	149.28	< 0.0001	134.05	< 0.0001
a_{fact}^2	0.3234	0.5793	0.5686	0.4643	0.2157	0.6501	0.0006	0.9814
a_{fact}^2	0.8122	0.3839	1.01	0.3327	1.60	0.2287	0.0013	0.9721
β^2	776.27	< 0.0001	891.21	< 0.0001	3511.61	< 0.0001	1249.28	< 0.0001
ε^2	12.21	0.0040	9.30	0.0093	4.76	0.0481	10.70	0.0061
$\beta^2 \cdot \varepsilon$	249.63	< 0.0001	215.86	< 0.0001	263.34	< 0.0001	158.71	< 0.0001
R^2	99.27%		99.28%		99.73%		99.34%	
Adjusted R^2	98.42%		98.45%		99.41%		98.57%	
Predicted R^2	93.77%		94.54%		98.34%		95.98%	

Table 8.6 ANOVA analysis

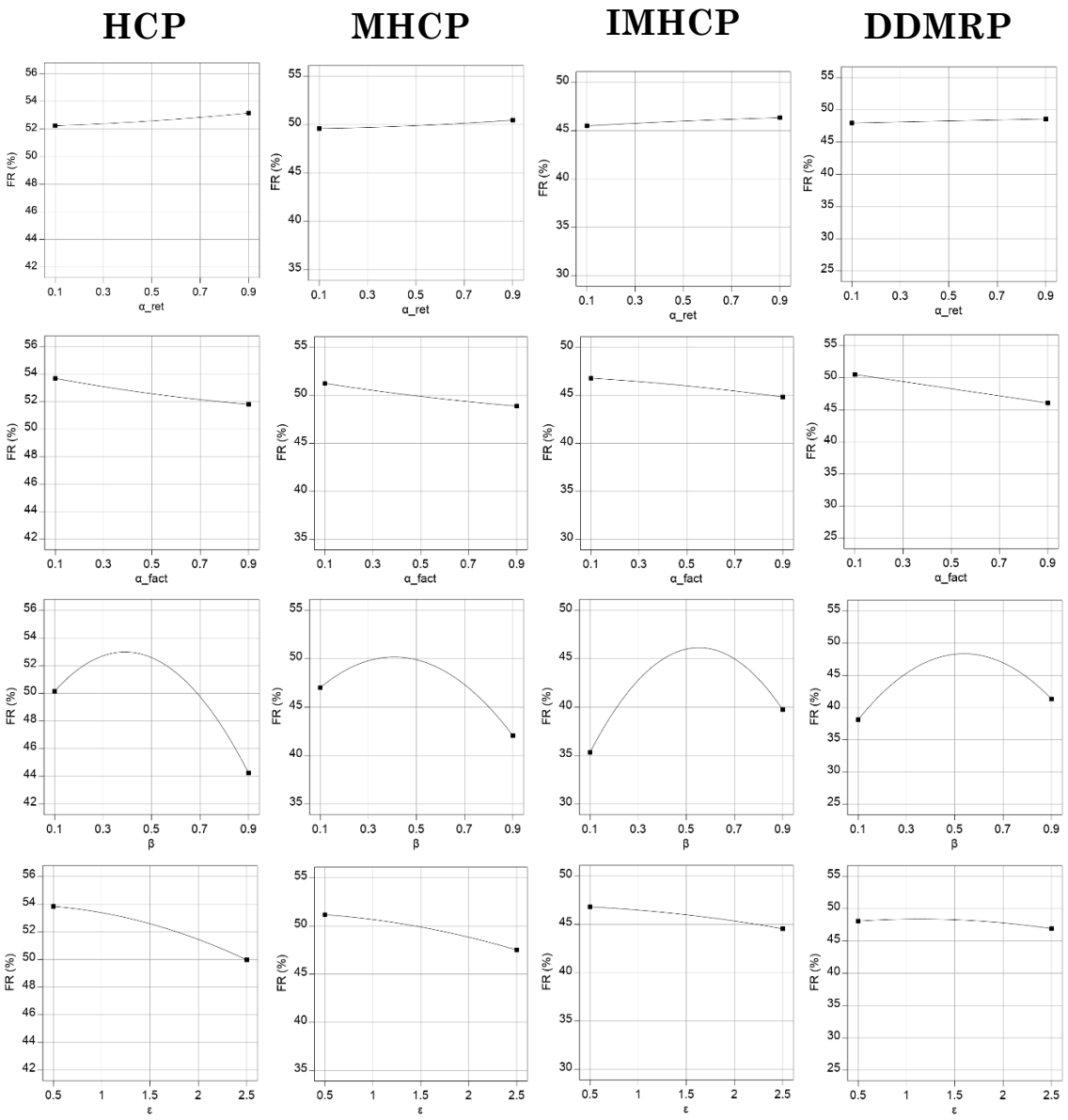


Figure 8.20 Main Effect Plots of the endogenous factors

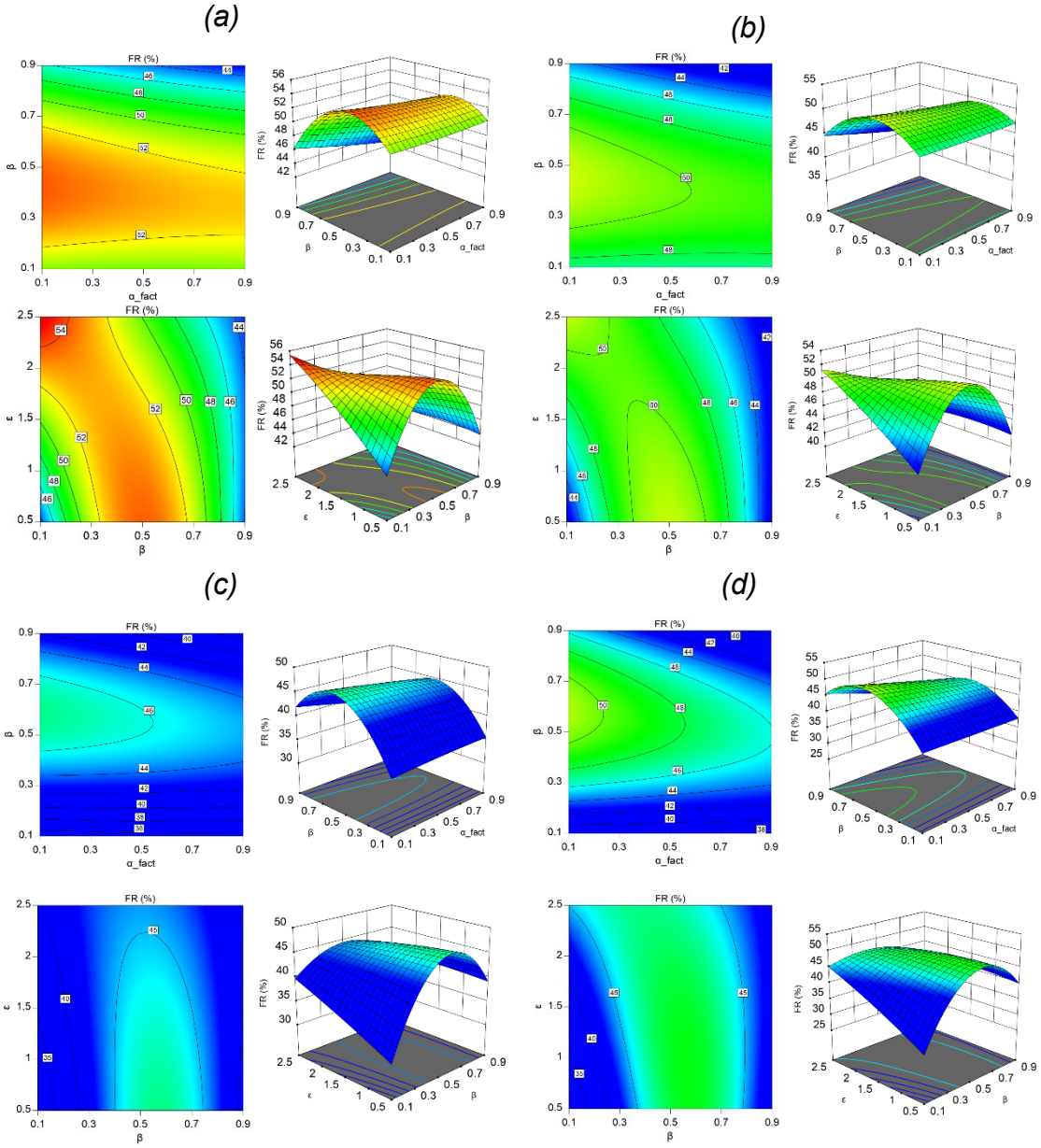


Figure 8.21 Contour and 3D Surface Plots

8.5.2.2 Analysis with the exogenous factors

In order to perform the second step of the extended comparison between the four PCPs, a full-factorial DOE was constructed, as shown in Table 8.7. In particular, DOE contains the eight exogenous factors that characterize the SC model, *i.e.*, the ratio between the standard deviation and the mean of the customer demand σ_{d_p}/μ_{d_p}, the delivery lead-time LT, the production flow time F, the ratio between the nominal production capacity and the mean of the customer demand χ_p/μ_{d_p}, the changeover time δ, the threshold of lost sales factor k, the inventory threshold factor z and the

failure rate λ. The unique data of the problem fixed ex-ante are the mean customer demand of both products, which are equal to 100 and 50 respectively. The values of these exogenous factors are consistent with relevant studies from the literature dealing with multi-echelon SC dynamics problem (as for example Sterman, 1989; Chatfield et al., 2004; Dejonckheere et al., 2004). The endogenous factors were fixed in accordance with the values selected in Section 8.5.2.1. All experimental factors are varied in three levels. Therefore, $3^8 = 6{,}561$ scenarios were considered. To increase the robustness of the analysis, the experimental campaign was replicated 10 times. The set of experiments was used for each PCP and, thus a total of $3^8 \cdot 10 \cdot 4 = 262{,}440$ simulation runs were performed.

In order to identify the impact of the exogenous factors on *FR* for each SC model, an ANOVA analysis at 95% confidence level was performed. Table 8.8 shows the results of the ANOVA analysis. The statistical analysis refers to the quadratic models. For the sake of brevity, the table does not report the *F*-values and *p*-values of the two-way interactions. However, the interactions among the exogenous factors and each PCP are depicted by the interval plots in Figure 8.22 and Figure 8.23.

The model investigated is statistically significant since the *p*-values are less than 0.05. R^2 is equal to 89.09%, 89.16%, 92.28% and 94.02%, respectively for HCP, MHCP, IMHCP and DDMRP models. They show a good fit since, in general, a substantial level of R^2 is obtained for value higher than 67% (Henseler et al., 2009). The difference between the values of adjusted R^2 and predicted R^2 is less than 20%, thus confirming the effectiveness of each model. Finally, looking at the *p*-values it can be noticed that the impact of all the exogenous factors is statistically significant. It has to be noticed that the inventory threshold factor *z* was not considered in the DDMRP model since it is not used by this PCP and, then, it does not bias the effectiveness of DDMRP.

Parameters	**Symbol**	**Value**			
Mean demand of product A	μ_{d_A}	100			
Mean demand of product B	μ_{d_B}	50			
Endogenous factors	**Symbol**	**HCP**	**MHCP**	**IMHCP**	**DDMRP**
Forecasting factor (retailer)	α_{ret}	0.90	0.90	0.90	0.90
Forecasting factor (factory)	α_{fact}	0.10	0.10	0.13	0.10
Proportional controller	β	0.50	0.51	0.58	0.60
Safety stock factor	ε	1.00	1.00	1.16	1.05
Exogenous factors	**Symbol**	**Low value**	**Medium value**	**High value**	
St. Dev. Demand / Mean Demand	σ_{d_p}/μ_{d_p}	0.05	0.10	0.20	
Transportation lead-time	LT	1.00	2.00	4.00	
Production flow time	F	1.00	2.00	3.00	
Nominal production capacity / mean demand	χ_p/μ_{d_p}	3.00	3.50	4.00	
Changeover time	δ	1.00	2.00	3.00	
Threshold of lost sales factor	k	1.50	2.00	2.50	
Inventory threshold factor	z	8.00	9.00	10.00	
Failure rate	λ	0.05	0.10	0.20	

Table 8.7 Full-factorial DOE

Source	HCP model		MHCP model		IMHCP model		DDMRP model	
	***F*-value**	***p*-value**	***F*-value**	***p*-value**	***F*-value**	***p*-value**	***F*-value**	***p*-value**
Model	3900.58	0.000	3929.71	0.000	5715.47	0.000	7520.22	0.000
σ_{d_p}/μ_{d_p}	37.12	0.000	29.72	0.000	1188.90	0.000	1896.05	0.000
LT	6626.00	0.000	5327.25	0.000	1984.98	0.000	3518.17	0.000
F	1980.54	0.000	1352.03	0.000	2771.36	0.000	86382.30	0.000
χ_p/μ_{d_p}	35115.98	0.000	41814.47	0.000	72420.73	0.000	100927.37	0.000
δ	96554.42	0.000	91889.23	0.000	101657.11	0.000	44158.89	0.000
k	47505.24	0.000	57118.44	0.000	119299.79	0.000	141825.56	0.000
z	10737.51	0.000	9729.99	0.000	5802.06	0.000	-	-
λ	8774.74	0.000	8578.02	0.000	6399.14	0.000	8634.26	0.000
R^2	89.09%		89.16%		92.28%		94.02%	
Adjusted R^2	89.06%		89.13%		92.27%		94.01%	
Predicted R^2	89.04%		89.11%		92.25%		94.00%	

Table 8.8 ANOVA table for *FR*

The factors that mainly affect *FR* are χ_p/μ_{d_p}, δ and k, as also confirmed by the *F*-values in Table 8.8. In the case of DDMRP, the main significant factor is *F* since it is used to calculate the thresholds. However, it is worthwhile to study the interactions of each exogenous factor with the PCPs through interval plots. The interval plots, that are depicted in two different figures, *i.e.*, Figure 8.22 and Figure 8.23, also report the interaction between the exogenous factors and PCPs in terms of μI_{fact} and ΣI_{fact}. The x-axis and y-axis refer to the considered exogenous factor and KPIs respectively. HCP is represented with a red line, MHCP with a green line, IMHCP with an orange line and DDMRP with a blue line. To easily identifying the exogenous factors that mostly affect the key performance indicators, the y-axes of the interaction plots present the same scales. It can be noticed that, on average, HCP achieves the best performance in terms of *FR*. However, HCP presents the highest values of μI_{fact}. As for the factory inventory variability, the interval plots reveal that DDMRP involves the highest values of ΣI_{fact}. Finally, it can be noticed that IMHCP assures the best performances in terms of both μI_{fact} and ΣI_{fact}.

Figure 8.22-a shows that there is no appreciable effect from σ_{d_p}/μ_{d_p}, as the FR maintains approximately the same percentage. However, it can be noticed a slight improvement that emerges when the SC is characterized by the high value of the demand variability (*i.e.*, $\sigma_{d_p}/\mu_{d_p} = 0.2$). The high demand's variability induces the factory to increase the number of changeovers that, consequently, to improve the responsiveness of the SCs. On the other hand, it also involves an increase in terms of μI_{fact} and ΣI_{fact}. In particular, it can be seen that the factory is more sensible to high values of σ_{d_p}/μ_{d_p} in terms of ΣI_{fact} when IMHCP or DDMRP are adopted.

As expected, a long transportation lead-time LT negatively biases the performance of the SC (see Figure 8.22-b). In fact, when the delivery lead-time sharply increases (*i.e.*, $LT = 4$), for each PCP it can be revealed a 5% of reduction of FR on average. High values of LT also increase the variability of the factory inventory, in particular for the case of DDMRP, while no significant difference it can be noticed in terms of μI_{fact}.

Figure 8.22-c shows that the values of flow time F strongly affects the FR of the SC when DDMRP is adopted, since the flow time F is used to calculate the thresholds. Therefore, when F is set to the highest value (*i.e.*, $F = 3$), DDMRP is characterized by a higher inventory level that allows the factory to hedge against the uncertainties. This is confirmed by the interval plot concerning μI_{fact} in which the highest value of F involves an average factory inventory level of about 500. As concerns the variability of the factory inventory level, higher values of F induce an increase of ΣI_{fact} for each PCP.

A high production capacity of the manufacturing system allows the SC to face the disruption events of the factory. This is demonstrated by Figure 8.22-d, in which a value of the ratio between the nominal production capacity and the customer mean demand χ_p/μ_{d_p} equal to 4 guarantees high FR for each PCP. Moreover, when the value of production capacity χ_p is high, the choice between HCP and MCHP becomes indifferent. When the production capacity χ_p is tight, the SC is stressed and its performance gets worse, also in terms of ΣI_{fact}. On the other hand, as expected, higher values of production capacity χ_p induces an increment in terms of μI_{fact}.

As concerns the changeover time δ, a low value of δ allows the factory node to exploit the production capacity. In fact, HCP or MHCP allows the SC to yield a FR

close to 100%. Notably, when $\delta = 1$, IMHCP performs better than DDMRP, achieving a *FR* between 85 and 90%. Increasing the changeover time has a negative impact on the performance of the SC, since the factory is subject to long production stoppages. Moreover, Figure 8.23-a shows that δ strongly damages the effectiveness of IMHCP. The increase of the changeover time δ has a strong impact also in the other KPIs, causing a reduction of μI_{fact} and an increase of ΣI_{fact} for each PCP. However, DDMRP is less sensitive to the changeover values compared to the other PCPs, particularly in terms of μI_{fact}.

The trend characterizing the exogenous factor k (see Figure 8.23-b) involves interesting findings, as also shown in the relevant literature (see *e.g.* Disney et al., 2021). Notably, HCP outperforms the other PCPs to improve the *FR* indicator. When the threshold of lost sales assumes low values, the *FR* is in the range of 90% and 100% for HCP and MHCP, while IMHCP enables achieving values close to 85%. When k is set to the highest values (*i.e.*, $k = 2.5$), the FR deeply decreases, especially for IMHCP where the *FR* is almost of 50%. As for the other experimental factors, an increase of FR induces higher values of μI_{fact}. The variability of the factory inventory becomes larger for high values of k. Notably, the figure reveals that there is no relevant difference between HCP and its variants in terms of ΣI_{fact} when k is lower than 2.5.

Figure 8.23-c shows that the highest values of the inventory threshold factor z positively affect the *FR* and increase the μI_{fact}. This means that higher values of z enable the factory to better satisfy the orders placed by the retailer. Interestingly, the inventory threshold factor z does not present a relevant influence on ΣI_{fact}. Finally, it has to be pointed out that z is not used to define the thresholds of DDMRP and, therefore, there is no interaction among them.

Finally, the failure rate λ negatively affects the *FR*, as expected. Figure 8.23-d highlights that HCP outperforms the other PCPs in terms of *FR* and demonstrates that the differences between the PCPs remain constant for each value of λ and for each investigated KPI.

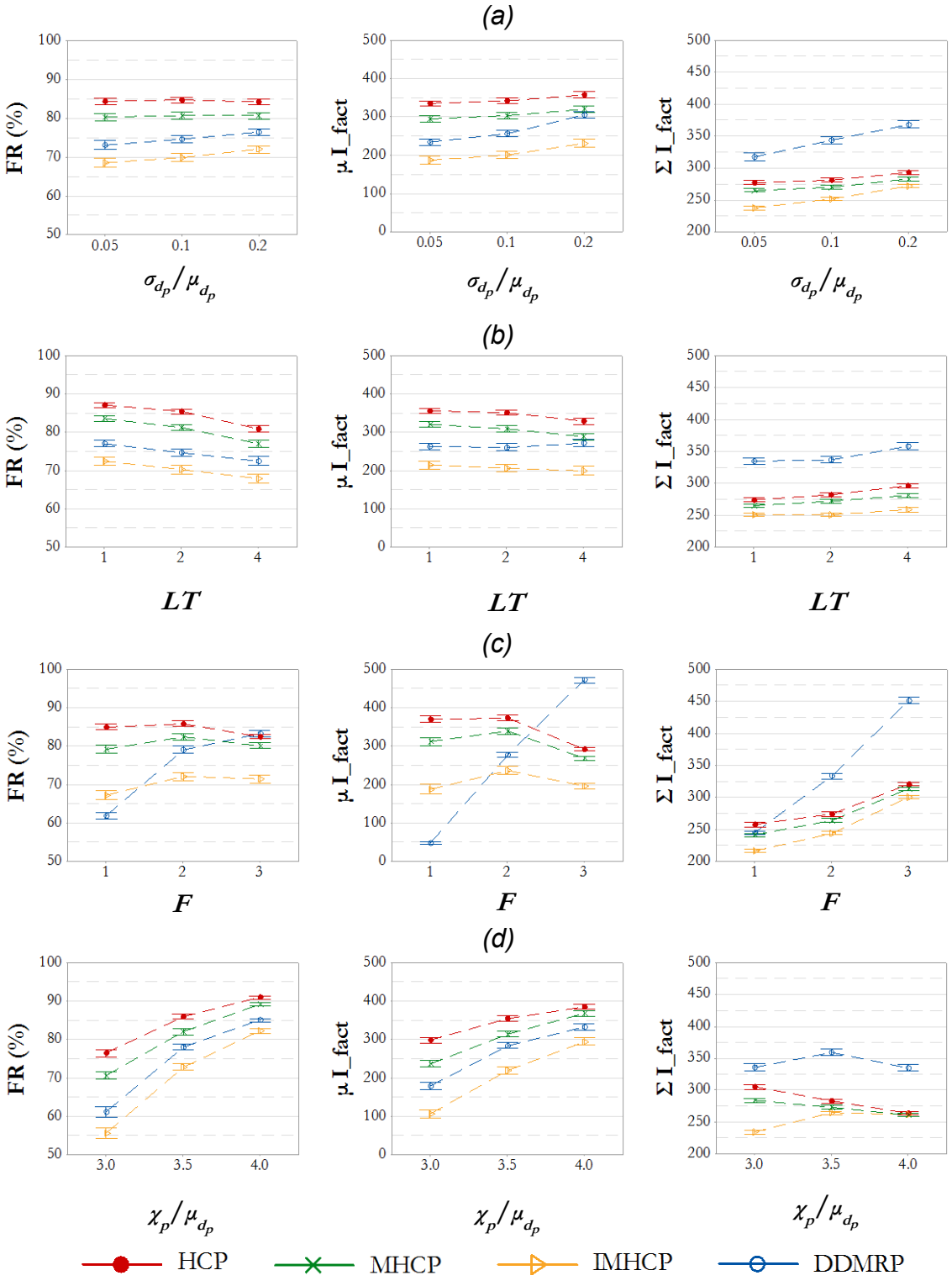


Figure 8.22 Comparison between PCPs in terms of *FR*, μI_{fact} and ΣI_{fact} considering σ_{d_p}/μ_{d_p}, *LT*, *F* and χ_p/μ_{d_p}

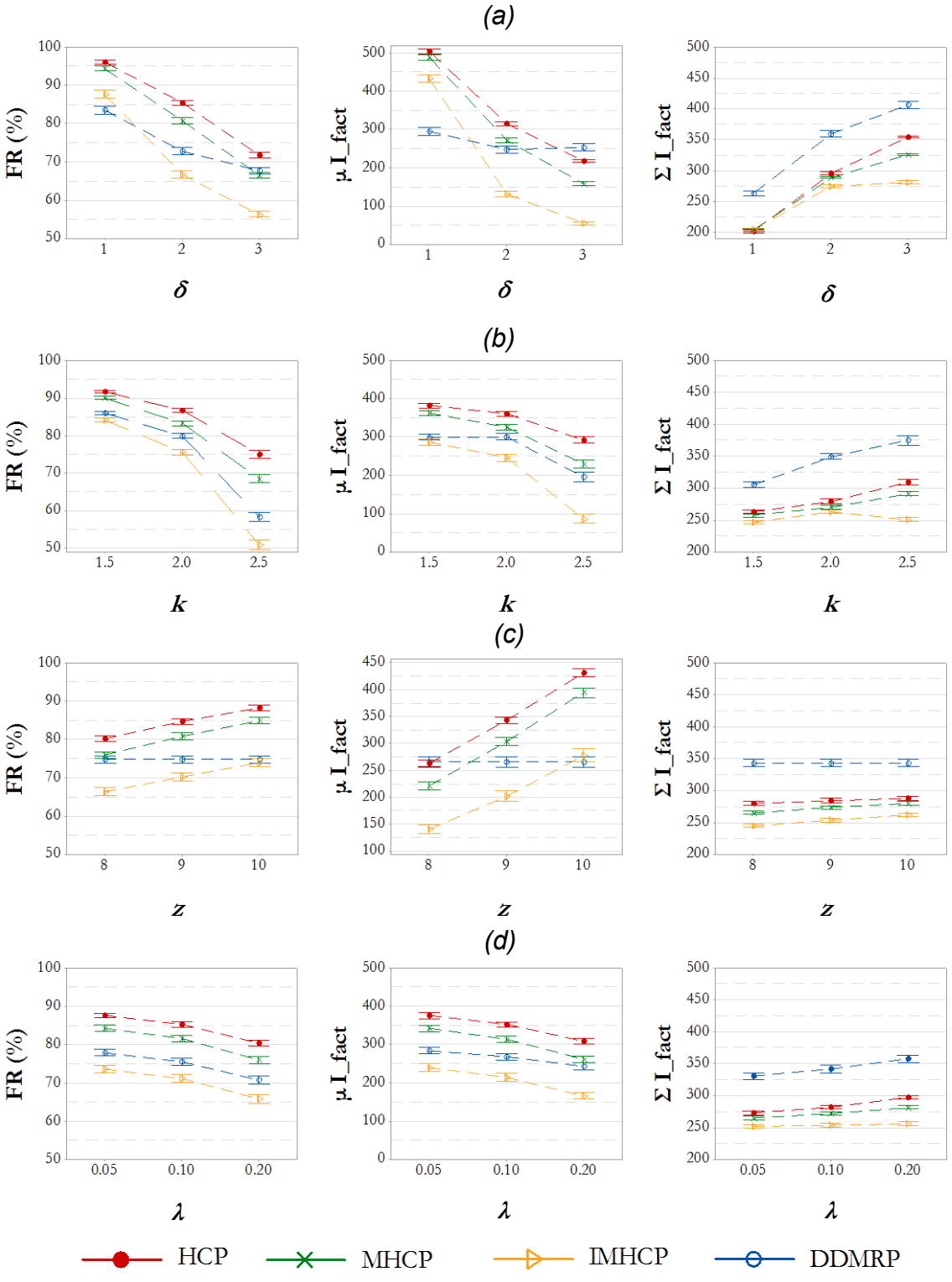


Figure 8.23 Comparison between PCPs in terms of *FR*, μI_{fact} and ΣI_{fact} considering δ, k, z and λ

8.5.2.3 Managerial and theoretical implications

The findings of this work provide several implications for SC management, under a variety of operational and market conditions. The implications are summarized as follows:

1. The first implication regards the PCP to be adopted and integrates the findings formerly introduced by the literature regarding factory node with capacity constraints. Indeed, the previous papers demonstrate that the two variants of HCP, *i.e.*, MHCP and IMHCP, allow minimizing the total costs incurred by the factory in a single-echelon system with a constant demand. Our study provides novel insights on the impact of the PCPs in more complex SCs (*i.e.*, a two-product two-echelons) subjected to the intrinsic stochasticity of the real-life environments (*e.g.*, the factory has to face a variable demand). Specifically, we show that the HCP generally outperforms MHCP, ~~and~~ IMHCP and DDMRP in terms of customer service level of the whole SC. However, results also show that the effectiveness of HCP and MHCP could be similar in some scenarios. The results speak for the fact that internal (*i.e.*, intra-company) operational efficiency in terms of costs minimization is not necessarily aligned with systematic (*i.e.*, SC-wide) efficiency in terms of customer service. These finding should be taken into account by managers in order to design and operate efficient, customer-centric SCs;
2. In order to study the operational efficiency of the factory in a two-product two-echelon SC context, two additional key performance indicators were also evaluated, *i.e.*, the average value and the variability of the factory inventory level. The analysis pointed out that IMHCP is the strategy that performs better from the viewpoint of the internal operational efficiency. Moreover, it can be noticed that the average value of the factory inventory level presents an opposite trend in comparison with the fill rate of the SC. It means that the factory needs to increase the intra-company costs to improve the SC-wide efficiency. Finally, DDMRP is the strategy that involves a larger variability of the factory inventory level.
3. Another interesting finding regards both the market in which the SC is operating and the operational contexts. Results show that both the variability of the customer demand and the production flow time do not have a strong

impact on customer service level, as compared to the other exogenous factors (*i.e.*, the transportation lead-time, the production capacity, the changeover time, the threshold of lost sales factor, the inventory threshold factor and the failure rate). In this fashion, these results suggest that the SC adopting the HCP is more resilient, with respect to variants, to the turbulence of the market demand and the production flow time. A different brief discussion has to be conducted for the flow time when DDMRP is adopted by the factory. In fact, the flow time is used to calculate the thresholds of this strategy and, therefore, its impact becomes relevant on the dynamics of the whole SC. In particular, the analysis revealed that high values of flow time allow the factory to create an inventory level that hedges against the disruptive events. However, it also involves a remarkable increase of the factory inventory level and variability.

4. Moreover, the transportation lead-time negatively affects the customer service level when it assumes the highest values. HCP seems to be the most effective PCP for each value of transportation lead-time in terms of FR. Thus, it can be reasonable to consider that both geographically dispersed and closed SCs should favor the adoption of HCP policy.
5. A further important implication concerns capacity management. We note that high values of production capacity allow coping with the disruptive events due to changeovers and failures. In this scenario, it seems to be indifferent to use HCP and MHCP. On the other hand, IMHCP is not able to achieve a *FR* larger than 60% for tight production capacities. These results suggest that an increase of production capacity could represent a suitable strategy to cope with the detrimental effects produced by uncontrollable, disruptive phenomena. However, increasing the capacity can produce other relevant unnecessary costs for SCs (*i.e.,* increase of underutilization and fixed costs) (Disney and Lambrecht 2008; Cannella et al. 2018; de Matta 2019). This is confirmed by the increase of the average factory inventory level resulting from the scenario characterized by high values of production capacity. However, in this context, it can be noticed an interesting reduction in terms of variability of the factory inventory level when HCP and MHCP are used.

6. Concerning both changeover time and failure events, we note that the increase of their occurrences indisputably deteriorate the performance of the whole SC. The results clearly show that low values of changeover time and low failure probability enable the SC to achieve a higher customer service level. Notably, *FR* is almost equal to 95% when the changeover time is set to its lowest value and the factory adopts HCP or MHCP. Thus, managers should consider undertaking all possible actions to reduce the occurrences of both phenomena, for instance by adopting robust preventive maintenance programs and/or by investing in technical improvement, *e.g.,* Single Minute Exchange of Die (Da Silva and Godinho Filho 2019), which can reduce the changeover time.
7. A predictable result regards the impact of backlogs on the performance of the SC. When the threshold of lost sales is higher, the customer service level deeply decreases. Also in this case, the HCP is the most effective policy among the four. Despite the adopted PCP, the results show that the backlog could be reduced by increasing the available capacity. However, this decision should be based on a robust trade-off analysis between the penalty costs associated to the backlog and the fixed capacity costs.
8. Regarding the inventory threshold factor, it is to note that, when HCP, MHCP or IMHCP were chosen as PCP, higher values of this parameter allow the factory to achieve a positive inventory that hedges against the adverse events, thus assuring higher customer service levels. Again, the HCP policy represents the best option to be adopted. As for DDMRP, the inventory threshold factor does not influence the performance, since it is not used to calculate the inventory thresholds of this PCP.
9. A final implication is devoted to the endogenous variables of the SC. With the RSM we show that identifying the optimal values of the control parameters is necessary to increase the effectiveness of the PCP. For instance, the proper tuning of the proportional controller can enhance the customer service level since it smooths the variability of orders coming from the retailers.

8.5.3 Evaluation of the new adaptive production control policy

The previous work revealed that HCP is the best rule to improve the *FR* of two-product two-echelon SCs. The aim of this section is to perform a comparison between

HCP and the new adaptive HCP (*i.e.*, AHCP) that is proposed for the first time. To make this comparison, we considered a DOE that entails four independent variables: production control policy (PCP), the ratio between nominal production capacity and the mean of the customer demand (χ_p / μ_{d_p}), changeover time (δ) and inventory threshold factor (z). The production control policy is varied at two levels (HCP and AHCP) while the other independent variables at three levels. A number of $2 \cdot 3^3 = 54$ scenarios were considered. To avoid randomness biasing the results, 30 replications were adopted for each scenario. Therefore, $30 \cdot 54 = 1620$ simulation runs were performed. The values of the model parameters are shown in Table 8.9, while the independent variables are reported in Table 8.10. The production control policies were tested by investigating the *FR* as response variable of the experimental campaign (see Eq. 8.24). As in the previous works, the simulation time T is equal to 2,000 periods, also including a warm-up time of 200 periods.

Model parameters	**Symbol**	**Values**
Machin repair time	tr	U∈[0,1]
Smoothing forecasting factor	α	0.30
Standard deviation of demand / Mean demand	σ_{d_p}/μ_{d_p}	0.10
Delivery lead time	LT	2.00
Production flow time	F	2.00
Failure rate	λ	0.10
Threshold of lost sales factor	k	2.00
Proportional controller	β	0.20
Safety stock factor	ε	1.00
Mean demand of product A	μ_{d_A}	100
Mean demand of product B	μ_{d_B}	50

Table 8.9 Model parameters

Independent variables	Symbol	Levels		
		I	II	III
Production control policy	PCP	HCP	AHCP	-
Nominal production capacity / Mean demand	x_p/μ_{d_p}	3.00	3.50	4.00
Changeover time	δ	1.00	2.00	3.00
Inventory threshold factor	z	7.00	9.00	11.00

Table 8.10 Design Of Experiments

8.5.3.1 Analysis of numerical results

To evaluate the significance of the model and the independent variables on the *FR*, an ANOVA analysis with 95% confidence interval was performed by using the commercial package Minitab 17® as a statistical tool. The outcomes resulting from this analysis are shown in Figure 8.24. For the sake of simplicity, statistical analysis just refers to the results of the first product (hereinafter denoted as product A) since no significant difference was found between the two types of products.

Firstly, it can be observed that the p-value of the model and the blocks (i.e., replications) are equal to 0 and 1, respectively. These demonstrate that the proposed simulation model is statistically significant and the randomness does not affect the results. R-sq is equal to 95.15% and therefore the quadratic model fit is effective.

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	54	39.5008	0.73150	568.56	0.000
Blocks	29	0.0062	0.00021	0.17	1.000
Linear	7	32.3601	4.62286	3593.12	0.000
PCP	1	2.4039	2.40392	1868.45	0.000
χ_p⁄μ_(d_p)	2	2.1296	1.06479	827.61	0.000
δ	2	19.2207	9.61034	7469.64	0.000
z	2	8.6059	4.30294	3344.46	0.000
2-Way Interactions	18	7.1346	0.39637	308.08	0.000
PCP*χ_p⁄μ_(d_p)	2	0.0097	0.00486	3.77	0.023
PCP*δ	2	1.2982	0.64912	504.53	0.000
PCP*z	2	0.6453	0.32267	250.80	0.000
χ_p⁄μ_(d_p)*δ	4	0.9930	0.24824	192.95	0.000
χ_p⁄μ_(d_p)*z	4	0.0874	0.02185	16.98	0.000
δ*z	4	4.1009	1.02523	796.86	0.000
Error	1565	2.0135	0.00129		
Total	1619	41.5143			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.0358690	95.15%	94.98%	94.80%

Figure 8.24 ANOVA table

Moreover, the predicted R-sq is in reasonable agreement with the adjusted one since their difference is less than 20% (R-sq(adj) – R-sq(pred) = 0.18%). Finally, all independent variables and 2-way interactions have p-values lower than 0.05, thus resulting statistically significant at a 95% confidence level.

Figure 8.25 depicts the main effects plots of the ANOVA analysis and Table 8.11 reports the mean values of the *FR* for each level of the independent variables studied. The most interesting findings come out from the main effects plot of the production control policy PCP. In general, the analysis shows that the new AHCP strategy is more effective than the HCP rule. Indeed, AHCP allows gaining a mean value of *FR* of 90.39%, while HCP allows achieving a mean value of *FR* of 82.69%. It is worth highlighting the effect of the nominal production capacity (χ_p) on *FR*. A higher nominal production capacity (χ_p) protects the manufacturing plant against inventory shortages. In fact, an adequate production capacity allows the inventory levels of each type of product to quickly reach the inventory threshold. Therefore, the manufacturing plant easily meet the retailer orders throughout the time horizon, thus increasing the *FR* indicator of the distribution chain. In confirmation of this, the mean value of *FR* is equal to 90.20% when the nominal production capacity of the manufacturing system is set to the highest level (i.e., $\chi_p/\mu_{d_p} = 4.00$). Moreover, it can be noticed that the *FR* indicator is more sensitive to lower values of χ_p/μ_{d_p}. In fact, *FR* deeply decreases moving from $\chi_p/\mu_{d_p} = 3.50$ (where the mean value of *FR* is equal 87.81%) to $\chi_p/\mu_{d_p} = 3.00$ (where the mean value of *FR* is equal to 81.60%).

Looking at the *F*-values in the ANOVA table (see Figure 8.24), the changeover time (δ) is the most influential independent variable. higher δ has a negative impact on the *FR* indicator. Confirming this, there is a relevant difference in terms of *FR* (*i.e.*, $\Delta FR \cong 27\%$) between the lowest value of changeover time ($\delta = 1.00$) and highest one ($\delta = 3.00$). It is noteworthy that when the changeover time (δ) is equal to one, disruptive phenomena are not significant since the *FR* indicator is close to 100%.

Interestingly, the inventory threshold factor (z) positively affects the performance indicator at hand. Although it might be better to maintain a lower inventory level, a higher inventory threshold assures a better performance in terms of *FR*. In fact, the *FR* indicator moves from a value of 77.06%, when the inventory threshold factor (z) is set to 7 to a value almost equal to 95% when z is set to 11.

Finally, in order to make the comparison between production control policies more robust, a series of interval plots illustrating the interactions between HCP and AHCP with the adopted experimental factors are presented in the following lines. More specifically, Figure 8.26 reports the interaction between PCP with the ratio between the nominal production capacity and the mean demand (χ_p/μ_{d_p}), Figure 8.27 shows the interval plot involving the changeover time (δ) while Figure 8.28 depicts the interaction with the inventory threshold factor (z).

Interesting insights are obtained from the interval plot illustrated in Figure 8.26. In general, the trends emerged by the main effects plot (depicted in Figure 8.25) of the production control policies (PCP) and the nominal production capacity (χ_p) are confirmed in the interval plot. Indeed, the interval plot points out that the adaptive approach, *i.e.*, AHCP, outperforms the traditional rule, *i.e.*, HCP, in terms of *FR* for each value of nominal production capacity (χ_p).

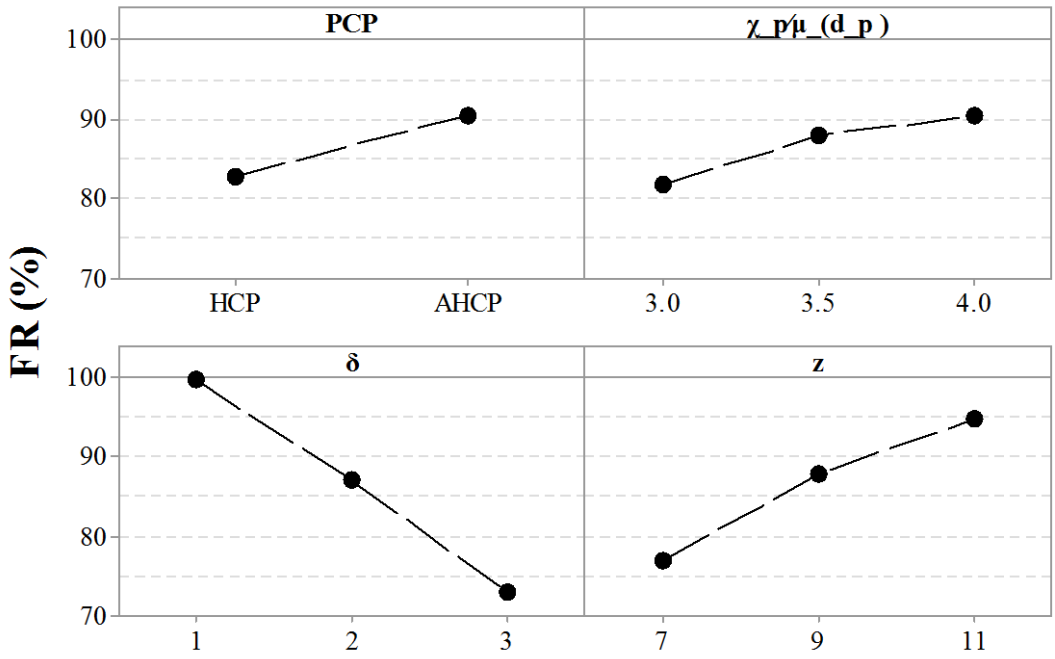


Figure 8.25 Main effects plots

Independent variables	Symbol	Mean *FR*		
		Lev. I	Lev. II	Lev. III
Production control policy	*PCP*	82.69%	90.39%	-
Nominal production capacity / Mean demand	χ_p/μ_{d_p}	81.60%	87.81%	90.20%
Changeover time	δ	99.61%	87.06%	72.95%
Inventory threshold factor	z	77.06%	87.78%	94.78%

Table 8.11 Mean values of FR for each level of DOE

Furthermore, it is worth noting that the AHCP rule allows the manufacturing plant and the distribution chain to achieve a *FR* larger than 85% for each value of the ratio between the nominal production capacity and the mean demand (χ_p/μ_{d_p}). Interestingly, the performance achieved by AHCP with $\chi_p/\mu_{d_p} = 3$ is mostly equal to the *FR* achieved when the manufacturing system with $\chi_p/\mu_{d_p} = 4$ adopts the traditional HCP (see Figure 8.26). This means that the adaptive rule allows the manufacturing system to achieve the same performance of a manufacturing system with a larger nominal production capacity (χ_p) that adopts the HCP as production control policy.

The effectiveness of the production control policy also strictly depends on the time taken to perform the changeover operations (δ). When the changeover time is low ($\delta = 1$), there is no difference in the *FR,* regardless of the production control policy (PCP) adopted. In fact, in this case, the *FR* is almost equal to 100% when both HCP and AHCP are used. On the other hand, the highest changeover time (δ) leads to a large decrease in the *FR* indicator. Such detrimental effect depends on the production control policy chosen. In fact, when the changeover time (δ) is larger than one, Figure 8.27shows that AHCP is always more effective in terms of *FR*. Finally, regarding the inventory threshold factor (z), lower values of z emphasize the difference in terms of *FR* between AHCP and HCP. As shown in Figure 8.28, the difference in *FR* is more than 10% when $z = 7$, while, when $z = 11$, the performances of the two production control policies are similar.

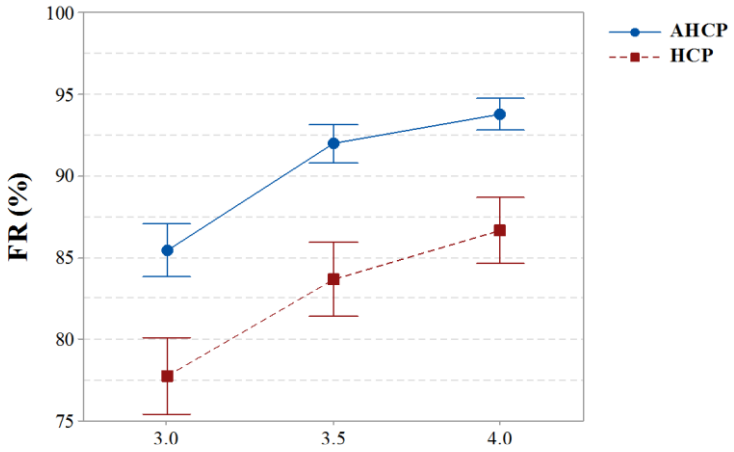


Figure 8.26 Interval plot of production control policies for different levels of χ_p/μ_{d_p} to analyse the effect on the *FR*

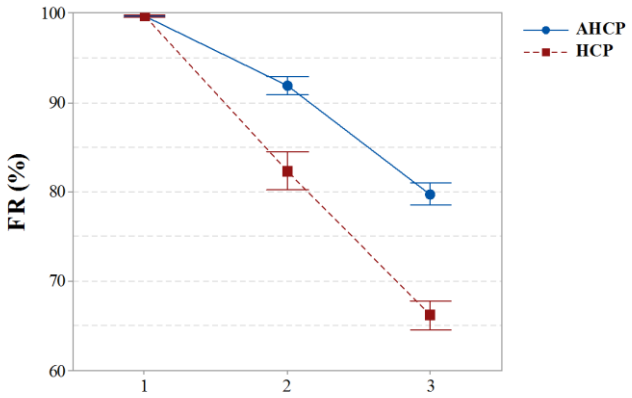


Figure 8.27 Interval plot of production control policies for different levels of δ to analyse the effect on the *FR*

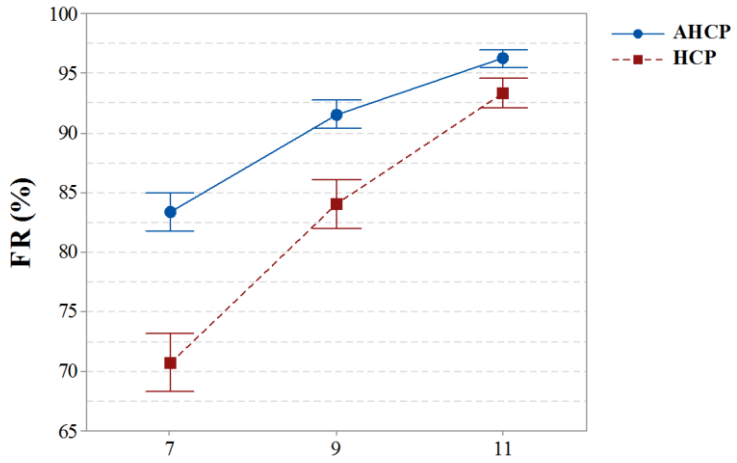


Figure 8.28 Interval plot of production control policies for different levels of z to analyse the effect on the *FR*

8.5.3.2 Managerial and theoretical implications

Here, the main findings that emerge from the comparison of the two PCPs are summarized. Some of these findings can be considered relevant as they extend the literature of production control of two-product manufacturing systems by evaluating the effect of an adaptive strategy on the *FR* performance measure. Such findings are:

(1) The adaptive AHCP strategy outperforms traditional HCP to improve the *FR* performance measure.

This research should motivate practitioners to implement the proposed adaptive production control strategy to manage multi-product manufacturing systems with non-negligible changeover times. The results of the statistical analysis show that significant benefits may arise from employing an adaptive PCP focused on the *FR*. Such benefits were emphasized by comparing two alternative PCPs, namely AHCP and HCP, in various scenarios where nominal production capacity, changeover time and inventory threshold were varied.

(2) The adaptive PCP approach is able to reduce shortages due to a lower production capacity.

The results of the analysis show that the AHCP can achieve higher values of the *FR* indicator than the HCP for each value of nominal production capacity. It is worth noting that, the AHCP with $\chi_p/\mu_{d_p} = 3$ assures almost the same *FR* of HCP when the ratio χ_p/μ_{d_p} is set to 4. Therefore, practitioners managing production systems with

lower production capacity might be encouraged to adopt an adaptive control approach rather than investing in expanding the capacity of the manufacturing system.

(3) The choice of production control strategy requires a strong consideration of the changeover time required by the production system.

Depending on the changeover time (δ), the production control strategies can involve different effects on the *FR* indicator. The results of this study show that there is no significant difference between the use of AHCP or HCP when the manufacturing system is characterized by a low changeover time (*e.g.*, $\delta = 1$). On the other hand, the production control strategy assumes a crucial role when the manufacturing system is described by long changeover times (*e.g.*, $\delta = 3$) and, thus, the adaptive approach allows achieving higher values of *FR* then the HCP.

(4) Setting the inventory threshold is a key-factor to improve the *FR* indicator.

The choice of an appropriate inventory threshold factor (z) is relevant. In fact, higher inventory threshold allows enhancing the *FR* performance measure. As concerns the production control policies, the analysis of results highlights that AHCP emerges to be an effective strategy for each value of inventory threshold factor (z) considered in the investigated DOE.

(5) Investigating explicit multi-product models of unreliable manufacturing systems is needed to faithfully evaluate the impact of the production control policies in industrial contexts.

From a theoretical viewpoint, our study reveals that modelling multi-product manufacturing systems may provide new findings regarding the production control policies that cannot be discovered in aggregated single-product industrial scenarios. Then, the present work would suggest that further studies may contribute to capture the impact of production control policies in unreliable multi-product manufacturing systems.

8.6 Conclusions

In this work, a variable capacity SC problem was explored. The objective of the proposed research consists of introducing a novel and realistic two-product SC

capacity model, defined as EXPO, subject to a set of unexplored operational parameters. The leading contribution of the proposed approach relies on the integration between a two-echelon SC context and a well-known near-optimal production planning policy, denoted as hedging corridor policy, whose role is to decide on the product changeover. Several ANOVA analyses revealed a strong interaction between the production planning model and the adopted smoothing replenishment strategy, which remarkably affects the performance of the SC. Interestingly, a higher value of the proportional controller negatively affects the service levels since the adopted PCP, under these circumstances, tends to encourage longer production runs for a certain product and, consequently, persistent stock outs for the other one.

Furthermore, we provided a systematic analysis of four PCPs (*i.e.*, HCP, MHCP, IMHCP and DDMRP), usually applied in manufacturing systems, in a two-product two-echelon SC system where the factory node has to satisfy a variable demand resulting from orders placed by the downstream echelon, *i.e.* the retailer. To the best of our knowledge, the literature demonstrated that MHCP and IMHCP allow the factory managers to minimize the total costs incurred, and DDMRP allows enhancing the performance of manufacturing systems exposed to uncertainties and high variability. However, to the best of our knowledge, the two variants of HCP were only tested in a single-echelon system that has to face a constant demand, while DDMRP never was employed to control the product changeovers in multi-product unreliable manufacturing systems. By adopting the SC *EXPO* model (see Section 8.3, Costa et al. 2020) that explicitly emulates the capacity constraints of the real-life production systems, in this work we investigate the effectiveness of the four PCPs on the customer service level via the *FR* indicator of a two-products, multi-echelon SC, in which the factory has to satisfy a variable demand resulting from the orders issued by the downstream node. Interestingly, the results of this study reveal that the HCP outperforms the other PCPs in terms of *FR*, while IMHCP allows the factory to improve its internal operational efficiency. Particularly, through the study of μI_{fact} and ΣI_{fact}, it can be noticed that the PCPs that improve for the intra-company internal efficiency in terms of inventory costs minimization not necessarily enhance the SC systemic efficiency in terms of customer service. Also, we showed that endogenous and exogenous variables can noticeably affect the customer service level when considering a PCP.

Finally, this work proposes a new PCP, called Adaptive Hedging Corridor Policy (AHCP). AHCP was compared with the well-known Hedging Corridor Policy (HCP), which is often used in manufacturing systems where the changeover time to switch from one type of product to another is not negligible. The interactions between PCP and experimental variables that characterize the production capacity and inventory of the manufacturing plant were considered.

9. Conclusions of the thesis

This thesis dealt with the operations management of the outpatient chemotherapy oncology departments. The operations management concerns with managing the operations and process of a system to achieve the highest level of efficiency of the organization. The operations management in oncology units is challenging due to the complex nature of the oncology process, which can be considered as complex system. In fact, the oncology units are characterized by several stages and resources shared among patients, high variability and uncertainties in the process, and cooperation with the pharmacy departments. All these features increase the complexity in managing the operations of the outpatient chemotherapy oncology unit. Furthermore, in the last years, the operations management in the oncology units becomes more complex due to the increasing of demand of healthcare services arising from growing number of cancer cases.

The aim of the thesis was to provide innovative methodologies and tool to support the healthcare managers in the operations management of the chemotherapy oncology units so as to reduce the patient waiting time. A summary of the proposals and findings of the thesis is provided in Section 8.1, while Section 8.2 reports some future research directions of the operations management in the oncology units.

8.1 Summary

The structure of the thesis respects the research objective fixed in Section 1.1. The first research objective was:

RO1: systematically studying the literature related to the operations management of chemotherapy oncology departments.

Chapter 2 provided a systematic literature review regarding the papers tackling the operations management in the chemotherapy oncology units. A detailed problem description was described involving all the aspects considered in literature (*e.g.*, process and patient classification). Then, the chapter reported all the key performance indicators adopted by academics and practitioners by classifying them based on the patient and managerial perspective. Statistical analysis about the state of art were proposed to demonstrate the increasing attention of managers in the topic. The operations management in chemotherapy oncology unit were classified as

planning, scheduling and patient flow management problem. A literature review for each problem was provided.

Chapter 3 dealt with the mathematical formalization of the problem. Specifically, the chapter denoted the specific problem statement and mathematical notation adopted in the whole thesis. Finally, a general pseudo-code simulation model of the patient flow in the oncology unit was provided.

The second research objective was:

RO2: solving the patient flow management problem by identifying the best techniques and methodologies to evaluate the current process and proposing new configurations of oncology units.

During the doctoral research period, two real-life case studies were addressed: an oncology department situated in Catania and a second one located in Ragusa (both locations are in Southern Italy). Differently from the literature, both these two departments are characterized by pharmacy departments situated far from the oncology units. In fact, they need a courier service that uses a vehicle to deliver the therapies from the pharmacy to the oncology department. This aspect was not previously considered in the literature and represents a new features that increase the complexity of the system. The two case studies were faced with different approaches, which were described in Chapter 4 and Chapter 5.

Chapter 4 coped with the case study of Catania in which it was proposed a methodology that merges Lean methodology with Discrete Event Simulation (DES). Specifically, we adopted a combination of Value Stream Maps with the stochastic simulation thus generating the Dynamic Value Stream Map. Firstly, the current process of the oncology unit was replaced by the DES model, thus creating the Current Dynamic Value Stream Map, which reports the current performances of the department in terms of mean flowtime, mean patient waiting time and efficiency of the system. Then, a Design of Experiments (DOE) was defined to evaluate and compare 72 Future Dynamic Value Stream Maps. The best FDVSM was identified through the ANOVA analysis and was proposed to the healthcare managers. To this end, the DES model was developed in the Arena® platform, since it provides a 3D virtual visualization that allows the healthcare managers to easily comprehend the benefits of our proposal.

Chapter 5 faced the case study of Ragusa, in which it was proposed a configurable and adaptable agent-based simulation model of the oncology unit. The aim was to develop a user-friendly simulation model that makes it possible for any healthcare managers to evaluate different corrective actions in the oncology process. This is the first time that an agent-based simulation approach in this topic. The simulation model was delivered to the healthcare managers who implemented the "best configuration" to the chemotherapy unit at hand. Due to the COVID pandemic we are not allowed to visit the ward, but we received positive feedback from the medical staff regarding a significant improvement in service level. Hopefully, further data will be collected in the near future to support the validity of the proposed research.

The third research objective was:

RO3: solving the outpatient chemotherapy appointment scheduling problem in oncology departments.

Usually, the patients arrive at the hospital in the first hours of the day without respecting an agenda of appointment and generating long queues before the treatment. Then, the chemotherapy outpatient scheduling problem is recognized as a leading strategy to pursue the objective of reducing the patient waiting time. Chapter 6 dealt with the same-day off-line stochastic chemotherapy outpatient appointment scheduling problem inspired by a real-world oncology department was investigated. Differently from the rest of the literature on this topic, we stochastically modelled all the stages provided by the chemotherapy process and, in addition, several sources of uncertainty (*e.g.*, deferrals and medical consultation times) were considered. Furthermore, as for the patient flow management problem, this is the first time that the scheduling problems consider a pharmacy is located far from the oncology unit and the courier service to deliver the therapies (as in real-life scenarios of Catania and Ragusa). Firstly, we proposed a stochastic mathematical programming to optimally solve the small instances of the problem at hand. Since the problem under investigation in NP-hard in strong sense, the metaheuristic approach was provided to solve medium-large instances. Specifically, we developed a novel Self-Adaptive Harmony Search named SAHS that was compared with the original version named Harmony Search and with the Greed Randomized Adaptive Search Procedure utilized in literature. Moreover, to improve the quality of any

appointment schedule, we adopted the LS scheduling strategy on the decoding algorithm.

The fourth research objective was:

RO4: providing guidelines to support managers in the decision-making process related to healthcare system design of oncology units.

Chapter 7 addressed the healthcare system design problem of outpatient chemotherapy oncology departments. As in the scheduling problem, the patient flow was replaced by using a stochastic simulation model based on discrete-time recursive equations. This approach allows us to execute a huge number of simulations with small computational times. In order to consider both the quality of service to patients and the efficiency of the systems, the performances of the chemotherapy oncology units were evaluated based on three different key performance indicators: the patient waiting time, the number of patients and a trade-off indicator. A DOE was defined with the aim of considering oncology units of small, medium and large sizes. Firstly, we adopted the ANOVA analysis and Tukey tests to outline the impact of the number of resources on the key performance indicators. This analysis was supported by generating the Pareto graphs to identify the non-dominated solutions. After that analysis, an abacus of results was provided with the intent of supporting the healthcare managers in the decision-process of the healthcare system design of oncology units. In fact, the abacus is easy to read and enables the decision-makers to easy understand what the best configuration is for achieve some target performance levels. Finally, a multiple non-linear regression model was provided to estimate the performance of any oncology unit with an adequate approximation.

The last research objective was:

RO5: proposing a new realistic supply chain dynamic model that will be used for the healthcare context.

Chapter 8 explored a new simulation model based on discrete time difference equations for two-product two-echelon supply chain dynamics problem where a set of unconventional variables (*e.g.*, the changeover time, changeover threshold, failure rate, flow time) drastically affect the performance of the entire supply chain. Then, an extended experimental campaign involving several independent factors was performed to infer on how a series of operational and tactical parameters, related to

both manufacturing and replenishment issues, may affect the performance of the capacitated two-echelon SC at hand. The statistical analysis over the obtained numerical results highlighted that the interaction of the HCP policy with the replenishment policy has a peculiar effect on the performance of the distribution network, which has not emerged up-to-now from the relevant literature based on a single-product flow. As for instance, a partially counterintuitive role of the replenishment smoothing factor emerges from the numerical analysis. In fact, if the smoothing effect induced by the proportional controlled is reduced, not only the inventory variability at the factory stage increases – confirming findings of the literature – but also the fill rate significantly deteriorates. Moreover, the way several operation parameters (*e.g.*, the nominal capacity, the lost sales threshold factor, the changeover duration and the threshold value for enabling the changeover task) impact on the performance measures investigated may represent a valuable contribution for the related literature. Furthermore, we provided a systematic analysis of four PCPs (*i.e.*, HCP, MHCP, IMHCP and DDMRP), usually applied in manufacturing systems, in a two-product two-echelon SC system where the factory node has to satisfy a variable demand resulting from orders placed by the downstream echelon, *i.e.* the retailer. We assessed the impact of the four policies in terms of customer service level by evaluating the most commonly adopted key performance indicator for customer-oriented purpose, *i.e.*, the *FR*. Firstly, we identified the most suitable set of values of the endogenous factors for each PCP and, then, we performed a comparison of the four PCPs, under several scenarios obtained by varying all the exogenous factors that characterize real-life SCs. The PCPs were compared also evaluating the internal operational efficiency of the factory, represented by the average value and the standard deviation of the factory inventory level, respectively μI_{fact} and ΣI_{fact}. Finally, a new production control policies, called Adaptive Hedging Corridor Policy, was proposed. The work demonstrated that AHCP can assure best performance in terms of customer service level compared to the well-established HCP.

8.2 Future research directions

Different future research directions can be highlited and summarized as follows:

- In the patient flow management problems, the proposed experimental campaigns were defined jointly with the healthcare staff of the two oncology units, with the aim of identifying an improved service configuration, without investing additional funds (according to lean principles). However, in accordance with the managing staff, further efforts will be dedicated to future projects for assessing in the real case study the impact of additional resources (*e.g.*, the number of pharmacy technicians or treatment chairs) and different queuing mechanisms on the performance of the oncology department, also taking benefit from the findings of the work regarding the healthcar system design of oncology units (see Chapter 7). To this end, future research can be oriented towards either simulation-optimization approaches or hybrid simulation models, capable of adequately capturing macro- and micro-level dynamics of such complex healthcare systems.
- As for the scheduling problem, alternative metaheuristic algorithms, a multi-objective approach involving more objective functions or further constraints on the system modelling could be considered as new opportunities for future research in the chemotherapy outpatient scheduling topic.
- In the healthcare system design problem, alternative methods of the Operations Research (OR) and new constraints of the model can be considered as new opportunities for future research in the healthcare system design problem of outpatient chemotherapy oncology departments.
- Finally, the innovative methods and findings arising from the works in the supply chain dynamics problem can be applied for a real-life healthcare supply chain management problem so as to assure the best health service and to enhance the performance indicators both in patient and managerial perspectives.

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