**Faculdade de Engenharia da Universidade do Porto**

U. PORTO
FEUP FACULDADE DE ENGENHARIA
UNIVERSIDADE DO PORTO

# Strategic collaborative approaches for enhanced Supply Chain resiliency

José Pedro Matos Soares Pereira

Master in Electrical and Computer Engineering

Supervisor: Catarina Moreira Marques

June 30, 2023

# Resumo

Uma vez que as cadeias de abastecimento da indústria farmacêutica estão expostas a elevados níveis de incerteza, não só devido a um ambiente altamente dinâmico, mas também a eventos inesperados, é fundamental assegurar que os níveis de capacidade de resposta necessários são atingidos.

A resiliência é muito importante nesse sentido e pode ser alcançada, não só através da capacidade de antecipar o comportamento da cadeia de abastecimento em ambiente estocástico, mas também através da sua aptidão para resistir a eventos disruptivos. Neste sentido, a flexibilidade também desempenha um papel fundamental nas cadeias de abastecimento farmacêutico, juntamente com aspetos de sustentabilidade, tais como preocupações ambientais e sociais.

Assim, o principal objetivo deste trabalho é explorar técnicas de simulação para desenvolver uma ferramenta de apoio à decisão capaz de ajudar na tomada de decisões e na implementação de estratégias eficientes, visando melhorar a resiliência global e a flexibilidade numa cadeia de abastecimento no setor da indústria farmacêutica.

# Abstract

As pharmaceutical supply chains are exposed to high levels of uncertainty due not only to a highly dynamic environment but also to unexpected events, it is critical to ensure the required levels of responsiveness are met.

Resiliency is very much important in that sense and can be achieved, not only through the capacity to anticipate the behavior of the supply chain in a stochastic environment but also through its ability to withstand disruptive events. In this regard, flexibility also plays a key role in the pharmaceutical supply chains together with sustainability aspects, such as environmental and social concerns.

Therefore, the main goal of this work is to explore simulation techniques to develop a decision-support tool able to assist decision-making and effective strategies regarding design and capacity management to improve the overall resiliency and flexibility in a pharmaceutical supply chain.

# Agradecimentos

Em primeiro lugar, gostaria de agradecer à Doutora Catarina Moreira Marques por toda a disponibilidade e orientação na realização da dissertação, que foram fulcrais para me guiar no rumo certo.

Agradeço também à Mestre Ana Carolina Silva por todos os esclarecimentos e pela ajuda disponibilizada ao nível da simulação, ao Professor Doutor Jorge Pinho de Sousa e ao Mestre Romão Santos pelo apoio e pelos conselhos sempre pertinentes.

Ao INESC TEC (Instituto de Engenharia de Sistemas e Computadores, Tecnologia e Ciência), particularmente a todos os membros do CESE (Centro de Engenharia de Sistemas Empresariais), onde tive o prazer de realizar a dissertação, o meu agradecimento pela oportunidade proporcionada e pelo acolhimento.

Por último, mas não menos importante, o meu especial agradecimento à minha família e amigos, que sempre me apoiaram e me deram força quando mais precisava.

# Contents

# List of figures

# List of tables

# Abbreviations

| | |
|---|---|
| ABS | Agent-Based Simulation |
| API | Active Pharmaceutical Ingredient |
| BPMN | Business Process Modelling Notation |
| DES | Discrete Event Simulation |
| EPC | Event-driven Process Chain |
| FP | Final Product |
| ICU | Intensive Care Unit |
| KPI | Key Performance Indicator |
| MCDM | Multi-Criteria Decision-Making |
| PSC | Pharmaceutical Supply Chain |
| SC | Supply Chain |
| SCM | Supply Chain Management |
| SCOR | Supply-Chain Operations Reference |
| SD | System Dynamics |
| UML | Unified Modelling Language |

# 1. Introduction

This chapter aims to introduce the dissertation “Strategic collaborative approaches for enhanced Supply Chain resiliency”. A contextualization of the problem is presented in section 1.1, the motivation in section 1.2, and the main objectives of the work are described in section 1.3. In section 1.4, the methodological approach is outlined, and finally the main structure of the dissertation is presented in 1.5.

## 1.1. Contextualization

Managing a Supply Chain  in todays troubling environment is a complex endeavor for companies, particularly in highly complex and global sectors such as the pharmaceutical industry. This sector is specially critical, because the failure on a Pharmaceutical Supply Chain (PSC) would delay the delivery of medicines that people need in a daily basis.

Therefore, it is important to have a resilient SC, because the ability to deal with disruptive events and to anticipate them leads to the minimization of the impacts on the SC responsiveness. In the particular case of the PSC, enhancing the resiliency and flexibility through collaborative-based strategies, will provide more robust distribution networks able to reduce medicines shortages.

In this context, this work aims to exploit simulation techniques to address the PSC’s operational performance under several scenarios, in order to support an integrated decision-making process towards more resilient and sustainable SC operations. The developed approach will be especially focused on SC network design and dynamic capacity management decisions through collaborative strategies between the SC key players. In the end, the output of the work will be a decision support system that can somehow contribute to the resiliency and flexibility of the distribution network.

## 1.2. Motivation

Being the pharmaceutical industry indispensable to people’s life as it is responsible for the supply of medicines that people need daily, it is fundamental that the PSC works well. However, there are ever more disruptive events difficult to predict, both in terms of timing and impact, that can trigger major changes in the PSC operations. For example, the COVID-19 pandemic has been a great challenge to all SC in general, not only because the timing was unpredictable, but also because of the world-wide scale of this disease. As the pharmaceutical industry played a vital role in this event, the scale of its impact was significant, exposing important SC vulnerability ties that still remain.

Therefore, to anticipate unexpected disruptions on the PSC, it is fundamental to raise its preparedness through sound contingency plans and network design strategies. Although resiliency has been calling the attention of researchers for decades, there is a clear lack of effective solution approaches, and, therefore, still remaining an important open challenge.

## 1.3. Objectives

The aim of this work is to address this challenge by developing new decision-support solutions to cope with different disruptive scenarios, so that pharmaceutical industry, which is key on people's life, does not have a breakdown when facing unexpected events.

By designing a tool, based on simulation approaches, to support high-level decision-making and design effective strategies to improve PSC resiliency, the best decisions are expected to be made at the right time. To ensure the required levels of responsiveness and flexibility, collaborative-based strategies will be particularly explored and assessed through several scenarios.

## 1.4. Methodological approach

Firstly, a bibliographical review is done, consisting in an analysis of the most relevant published works, in order to contextualize the problem in the current state-of-the-art and to possibly contribute to a future solution.

Then, to better understand and analyse the impacts of disruptive events in a PSC, a simulation model will be developed, particularly focused on the exploitation of Agent-Based simulation techniques. A base case will be structured in order to validate the simulation model, and several problem instances are expected to be tested and simulated under different scenarios. The main goal will be the development of a multi-agent simulation model able to support the deployment of different strategies and policies that may contribute to higher levels of SC resiliency.

## 1.5. Dissertation structure

This dissertation is divided in five chapters.

In this first chapter, the introduction of the work is outlined, addressing a contextualization of the work proposal, its objectives, motivation, possible applications and implications, and how it will be the methodological approach.

In chapter two, some theoretical aspects are detailed in order to present a full perception of what the work will be based on. It is done a literature review, in which, the most relevant published work is analysed, as well as the proposed.

In the third chapter, the problem is defined through its definition and conceptualization. Besides that, it is presented and explained the approach used in the simulation model.

In the fourth chapter, the results of the base case, of the disruptive event applicated to the base case, and of some mitigation measures made in order to reduce the disruption, are presented and analysed.

The fifth chapter presents the conclusions and future work and, finally, the references used in this dissertation are listed.

# 2. Background and Literature Review

This chapter refers to the theoretical of background concepts and literature review in order to contextualize and present the main topics of the dissertation. The main concepts are centred in the Supply Chain Management (2.1), resiliency (2.2), pharmaceutical industry (2.3), and finally in simulation (2.4).

## 2.1. Supply Chain Management

### 2.1.1. Definition

Back in the 1980's, with the introduction of the concept of Supply Chain Management (SCM), it was needed to distinguish between this concept and the concept of logistics. After different opinions, the concept of SCM was redefined "from integrating logistics across the supply chain to the current understanding of integrating and managing key business processes across the supply chain" [4]. Since then, the Council of Logistics Management defined logistics management as a part of SCM.

In fact, nowadays, individual businesses are no longer seen as autonomous entities, but in an overall perspective as a SC of interconnected elements. As it gets more complex, the more difficult is to manage all those entities due to, not only, the network of complex relationships between them, but also the interactions with and ever more dynamic business context ([4]).

### 2.1.2. SCM conceptual framework

A conceptual framework of SCM can be done to emphasize the relation between elements of a SC, as depicted in Figure 1.

The SC Network Structure consists in all entities that are part of a SC that need to be managed from the supplier to the end-customer and how those entities are linked. The criteria to decide takes into consideration multiple factors, such as "the complexity of the product, the number of available suppliers, and the availability of raw materials" [4]. Depending on which SC members are identified and what are the main ones, the weight of the connections between them can be different from one to another.

There are also three structural dimensions of the network – horizontal structure, vertical structure, and the entities' horizontal position within the SC, according to [4].

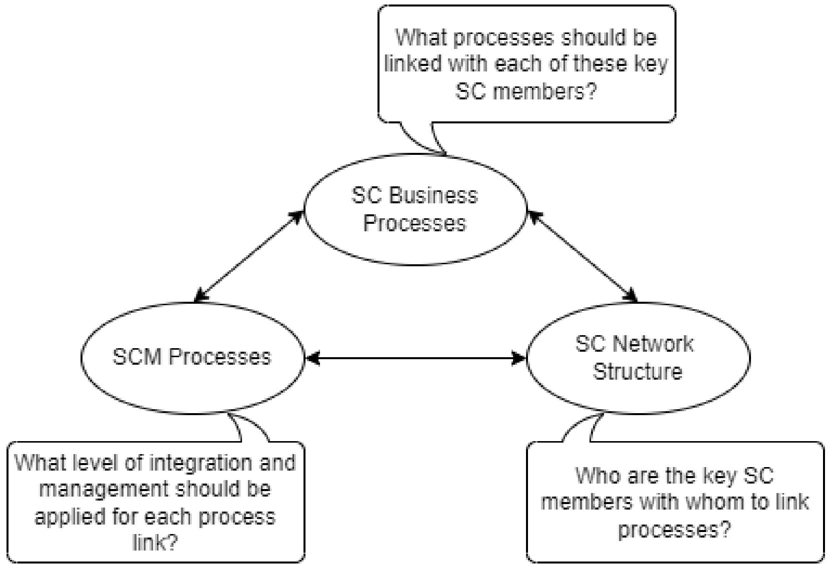


**Figure 1 - Conceptual framework of SCM (proposed by [4])**

The SC Business Processes consist in the decision-making process about the association between each key SC member and the different types of processes ([4]) which are represented in Figure 2.

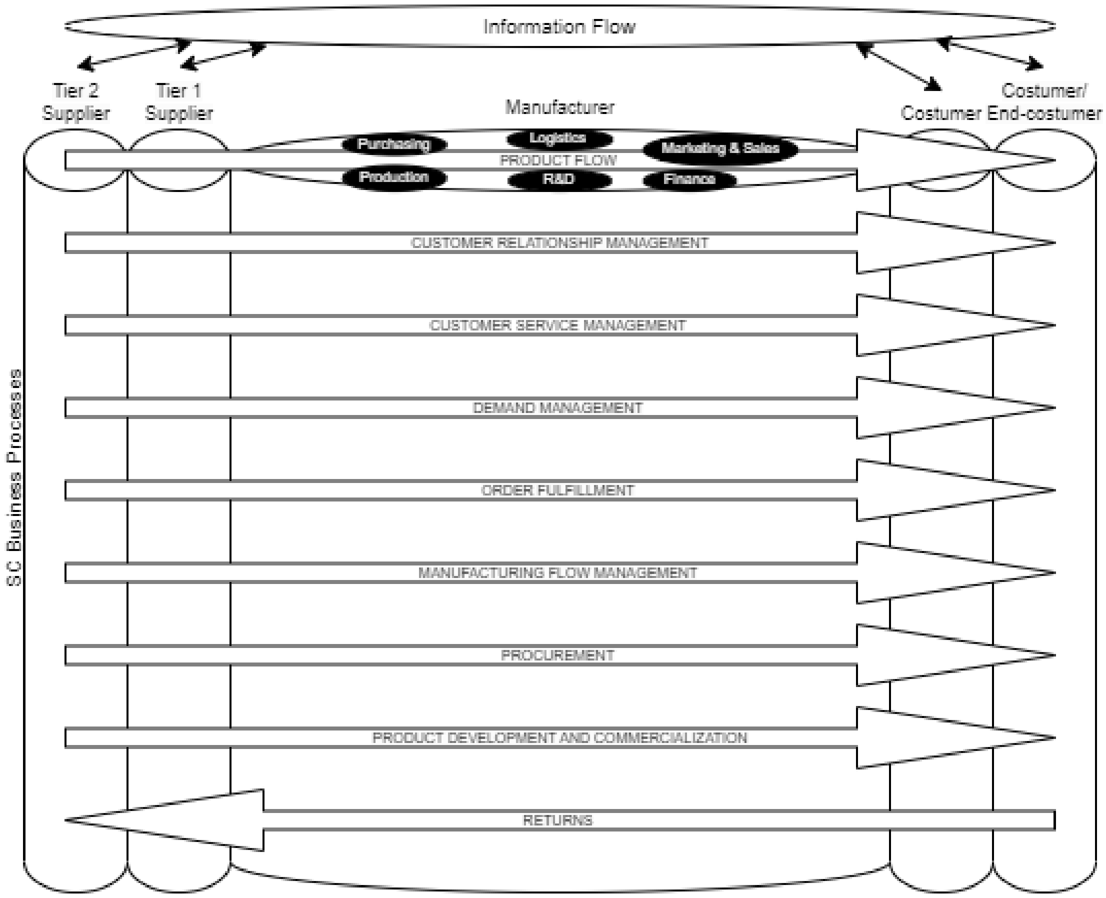


**Figure 2 - SC Business Processes Management (proposed by [4])**

In fact, SC Business Processes involve actions, events, and decisions according to the discipline of business process management. They may include a number of actors who are responsible for carrying out different tasks and making decisions ([19]).

In order to represent business processes as diagrams in the context of SC Business Process modelling, some visual representation techniques are used, such as flowchart diagrams, dataflow diagrams, Business Process Modelling Notation (BPMN), Event-driven Process Chain (EPC), and UML (Unified Modelling Language). Furthermore, Supply-Chain Operations Reference (SCOR) is now an international standard for SC management and planning across industries ([20], [21]). SC Business Process modelling is a crucial component of business process management. The integration and redesign of the business processes within a SC are also included in SC Business Process modelling and management.

The SC Management Components are nine and they are related to the connections between SC members and which level should be associated to each link ([4]). Those management components are represented in Figure 3.

Since managing the entire SC from end-to-end is impractical to manage all suppliers and costumers, management techniques "link-by-link, relationship-by-relationship" ([22]) should be adopted. Thus, by identifying members, determining management levels, and implementing necessary processes, relationships should be managed properly and not equally ([22]).

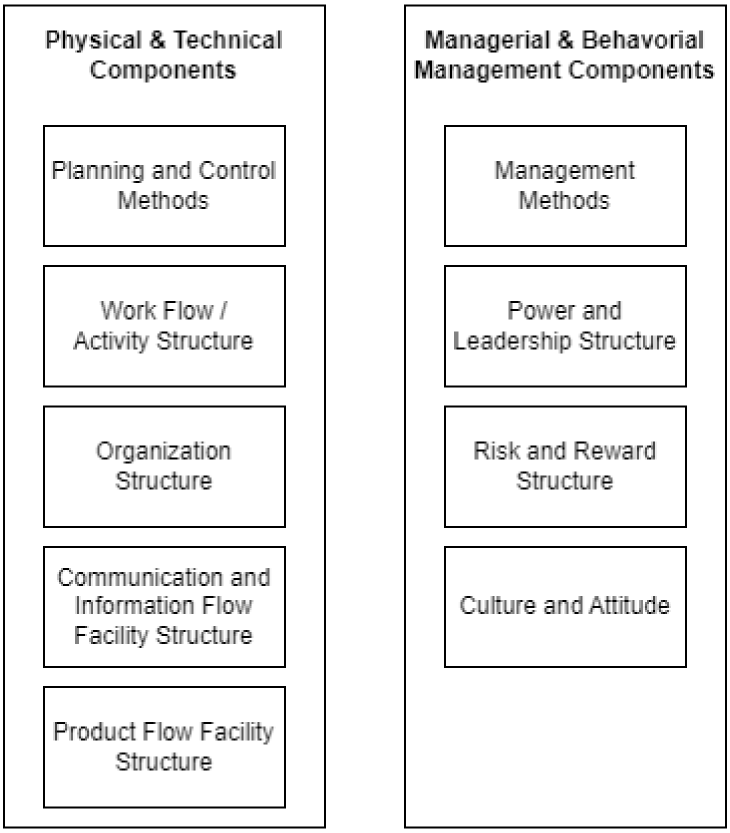


**Figure 3 - SC Management Components (proposed by [4])**

However, all these frameworks do not represent constraints in the SC, and the related uncertainty. Those models assume that every demand is accomplished in the right time and that the order is placed in the SC as soon as the order is done by the customer. Those issues should be considered in more innovative and sophisticated approaches ([4]).

### 2.1.3. Decision-making processes in SCM

To improve SC operational performance, decision-support processes are important to achieve more informed and efficient planning decisions. Due to the complexity of SC operations, management decisions are typically embedded in matrices and frameworks organized in short-term, mid-term, and long-term decision levels. Those models are done through a vertical hierarchical structure which represents complex decision problems in different decision levels and their representation tends to solve subproblems sequentially. As those subproblems start to get solved, the complexity tends to reduce. However, the interactions between the decision levels are not considered as it should be ([6]).

For example, according to [24], "the supplier selection is one of the most important decision-making issues in supply chain management field", also impacting decisions regarding collaborative strategies. Traditionally supplier selection has been driven by several conventional criteria, according to [23], such as quality, delivery, reliability, flexibility, service level, demand, production capacity, and price/cost.

However, businesses have become considerably more devoted to taking environmental issues into account ([23], [25]). In fact, green supplier selection is linked with sustainability factors and its decisions are done through a multi-criteria decision-making (MCDM) technique. This approach is gaining research interest, involving environmental, economic, social, and operation criteria, and various decision-makers. The optimal supplier selection is complex due to high uncertainty and conflicting attributes ([23]).

## 2.2. Resiliency

### 2.2.1. Supply Chain Resiliency

When facing disruptive events, businesses can be strongly impacted, in terms of their ability to fulfill the demand needed. So, being resilient means that a SC have strategies in place to effectively manage operations when one of those events happens. Depending on their scale, the consequences in a SC can be more or less negative. So, simulating different possible scenarios that support decision-making processes, the SC can improve their resiliency.

The first definition of SC resiliency, according to [29], appeared in 2004 ([28]), when the notion of SC was still “a relatively new addition to the lexicon of management” and the isolated concept of resiliency had already been approached by other researchers. In [28], SC resiliency is defined as “the ability of a system to return to its original state or move to a new, more desirable state after being disturbed”. However, papers regarding this topic have grown exponentially and more definitions have been emerging ([29]).

Latest publications are more focused on sustainable and resilient SC network design, especially after the COVID-19 pandemic, where the resiliency is defined as “the ability of a system to detect, adapt, and react to disturbances in order to restore its original structure and functions” ([27]).

The topic of resiliency has been attracting the attention of research communities for some decades as can be highlighted by some comprehension reviews ([2], [3], [8], and [9]).

According to [2], the resiliency of a SC accommodates four phases: readiness, response, recovery, and growth. Furthermore, it was defined a proactive strategy related to the first phase through collaboration, human resource management, inventory management, predefined decision plans, redundancy, and visibility. It was also defined a reactive strategy related to the other phases through agility, collaboration, flexibility, human resource management, and redundancy.

In the work presented in [3], those phases are anticipation, resistance, recover and response. Besides that, principles were defined, and they are based on SC reengineering, collaboration, agility, and SC risk management culture. Through the years and through the analysis of different authors, those principles have been modeled and developed and it was possible to build a SC resiliency principles framework, as seen in Figure 4.

According to Figure 4, “collaboration” is one of the key principles to account for in SC resiliency.

Through strategic collaborative approaches with both costumers and suppliers, or even third-party logistics providers ([43]), the resiliency in a SC can be enhanced, by reducing costs and having a more sustainable SC ([26]). In fact, [43] mentions that the SCM “success requires close collaboration and intensive information exchange”, while [26] states the collaboration with suppliers, the use of outside resources and the encouragement of SC sustainable product development. Furthermore, in [35], a green SC intends to enhance operations with integration techniques, such as information sharing and collaboration which are also promoted techniques through smart contracts for SC collaboration ([42], [44]).

Through different techniques, such as machine learning ([16]) and graph neural networks ([17]), the interactions between entities are easier to understand and to model. Thus, it helps to mitigate risks, due to the increase of the visibility of the SC. As seen in Figure 4, “visibility” is also one of the fundamental ideas to consider in SC resiliency. With the help of these techniques, disruptions are modeled, having an important role on the resiliency of the SC, as in [18].

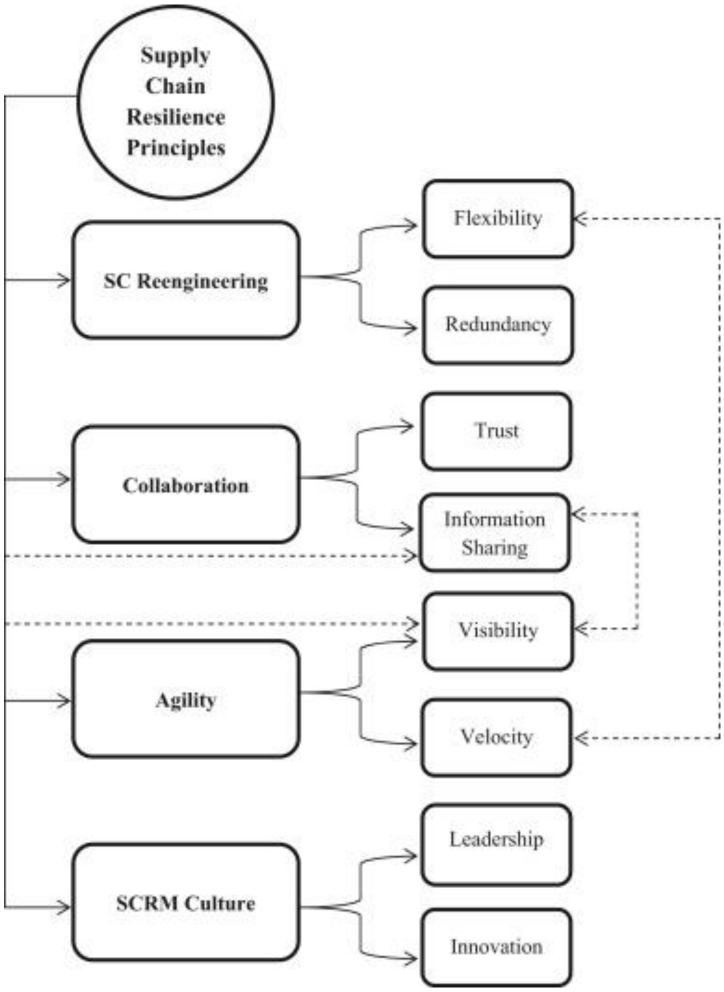


**Figure 4 – SC resiliency principles framework (proposed by [3])**

Analysing [9], the approach was based on observing the resiliency in material science, the human resiliency, the ecological and engineering resiliency, the information and communication resiliency, the business resiliency and, finally, a general definition of a resilient system.

From the analysis of the different references, it is possible to note that there is no universal definition for SC resiliency. As stated by [8], it “can hardly be considered as an isolated term, as it is a product of industry and business evolution and needs”. Moreover, it should be seen from different perspectives because its definition is complex as there are many interactions between elements and many scenarios.

Even though there is no unique definition, the challenge of resiliency assurance in a SC is well known, as well as its importance in human well being indirectly.

### 2.2.2. Resiliency measurement

The most of many resiliency studies are done using a qualitative approach, with theoretical and abstract results. However, it is necessary to have a sense about the real value of resiliency in a SC which is not easy to measure in a quantitative way. Although important contributions have been made over the last years, an effective way of measuring resiliency quantitatively is still lacking and remains as an important open challenge. Those ways of measurement vary from one to another.

In [10], it is presented the case of *halal* pharmaceuticals in Malaysia. In order to measure the resiliency of their SC, researchers prioritized the "identification of the capabilities and vulnerabilities". The capabilities are the potential Key Performance Indicators (KPIs) that a SC needs to have to withstand disruptive events, while the vulnerabilities are the factors that can expose the SC to those disruptions. After these identifications, it is done a survey whose target are the pharmaceutical manufacturing companies responsible for this type of medicines. This questionnaire, whose answers are on a scale of 1 to 5 in a time horizon, is done through the revision of experts after their analysis of the vulnerabilities and capabilities previously defined. Based on the mean and the standard deviation of the results, the company is able to make thoughtful decisions in order to anticipate and overcome disruptions.

A different perspective of how resiliency should be measured is done in [12], where four approaches are presented based on its companies' resiliency indexes. Linking the recovery time with the disruption severity, along the time horizon and the fulfilment rate respectively, the area of the triangle presented in Figure 5 is intended to minimize. As the resiliency increases, the triangle becomes lower.

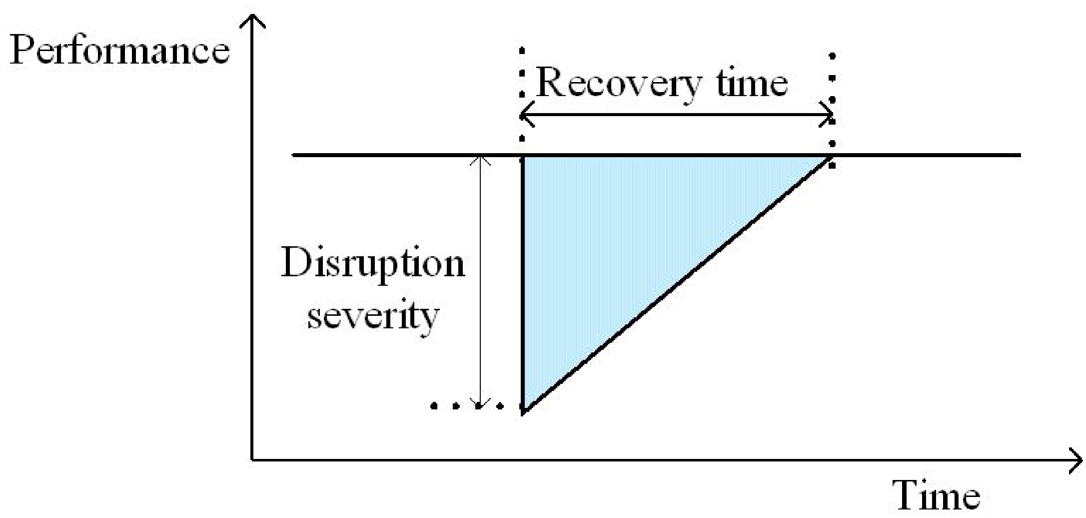


**Figure 5 - Resiliency triangle (proposed by [12])**

Analysing [31], the resiliency loss is represented by the shaded area in Figure 6, through the different amounts of shortages and recovery times. Then, the resiliency can be obtained through the following expression:

$$\psi = 1 - \frac{\rho}{T \times Q}$$

In this equation, $\rho$ represents the resiliency loss, while "T and Q denote the expected length of recovery and amount of items, respectively" ([31]).

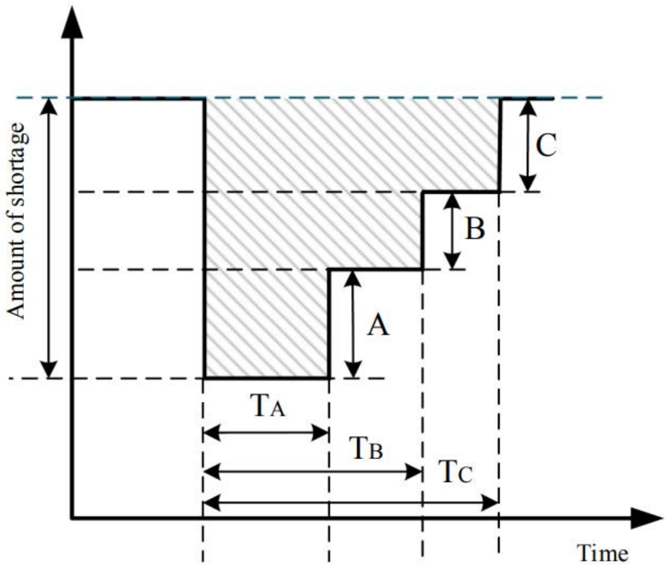


**Figure 6 - Resiliency loss (proposed by [31])**

## 2.3. The pharmaceutical industry

### 2.3.1. Introduction to the pharmaceutical industry

The pharmaceutical industry has a pivotal role, not only on people's health, but also on countries' economies. Besides that, this industry is also important on the reductions in the healthcare cost as the needs for expensive surgeries and long-term care in hospitals are lower ([6]).

The pharmaceutical sector is composed by different scales of companies and manufacturers and each type have a specific role in the overall production, supply, and distribution of pharmaceutical drugs. The main difference between them is related to the complexity of the PSC and, the bigger the complexity, the harder is to manage a PSC, and the bigger is the vulnerability to uncertainty and risk ([6]).

### 2.3.2. Pharmaceutical Supply Chain

The Pharmaceutical Supply Chain (PSC) encompasses some specific features when compared to other industrial sectors. A typical PSC is divided in two distinct phases: the drug development phase, and the marketing of the final product phase ([6]), as can be seen in Figure 7.

Focusing on the drug development phase, it involves the discovery part, the pre-clinical tests (done in animals to determine if it is safe for human use), the clinical trials on humans, and finally the product launch into the market (production process needs to be approved by the regulatory agencies). All this process together can be very expensive and take a long time ([6]).

Taking into consideration the marketing of the successful drugs, "success is not guaranteed" [6]. This may be because people want a better cost/benefit relation. Furthermore, it is needed to have the right scale production capacity, so that demand matches production. For that, it might be necessary to invest in new facilities ([6]).

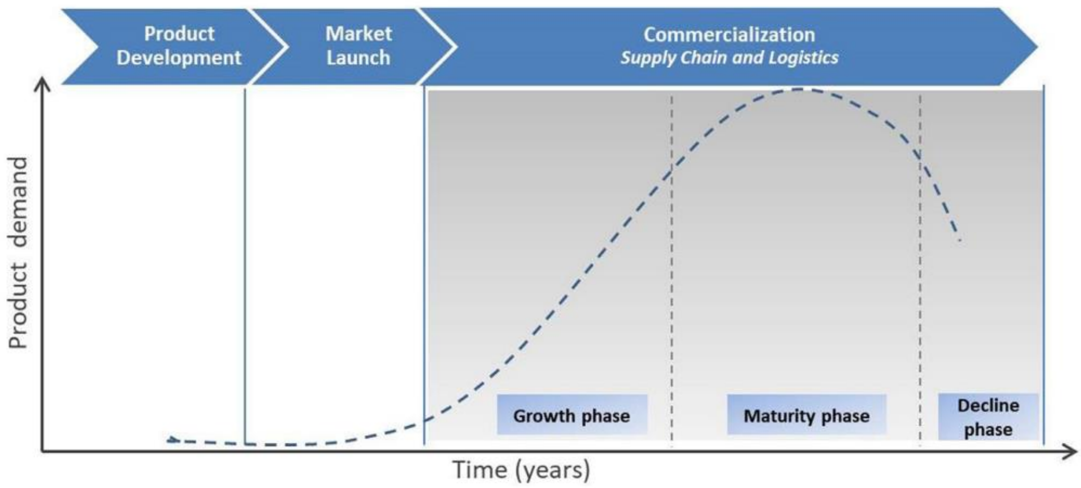


**Figure 7 - Pharmaceutical product life cycle (proposed by [6])**

A pharmaceutical drug manufacturing process is divided into two sequential stages: drug substance manufacturing and drug product manufacturing ([6]).

The first, which is the primary manufacturing, consists in the transformation of raw materials into Active Pharmaceutical Ingredients ([6], [32], [33]). Here, production is the result of expensive and time-consuming R&D projects, framed by extremely controlled manufacturing processes. Thus, this production stage, which employs a Make-to-Stock strategy, is often limited, and placed in a small number of locations ([33]).

Fermentation is frequently the first step, followed by purification. Multiple decoupling steps are possible, and there are cleaning and storage specifications along the way.

Before being released, all processes must receive regulatory authority approval and pass quality control ([32]).

In this process, since different products share available resources, low production volumes can be highly variable, leading to higher flexibility and efficiency. However, this gain of flexibility leads to higher prices in the complexity of the production system. Beyond these costs, inventory costs must be added, because it is necessary to the reliability and responsiveness, as the high customer service level is a key focus of this industry. Considering these factors and being the product lifetime usually short, primary production performance can be known as weak ([6]).

The second, which is the secondary production, consists in the transformation of the API into a product suitable to be sold. It is a combination between API and other non-therapeutic ingredients in the form of solid dosage commonly, but they can also be semi-solid or liquid dosage forms. The challenges and costs are not the same comparatively to the primary production since it is more about the costs of the manufacturing processes. In this case, the several decontamination methods and the cold chain distribution systems to measure the temperature sensitivity and control require a complex and expensive system ([6]).

According to [33], secondary manufacturers may adapt to sustainability market developments and implement a Make-to-Order strategy.

As wholesalers purchase inventory of the finished drug product from secondary manufacturers and distribute it to the retailers, they play a significant part in the SC. Finally, the retailers deliver the drug product to the end-consumer ([33]).

Being the PSC's network structure very complex and hard to manage, it is needed to be resilient, because the pharmaceutical area is not expected to fail, as it provides, for example, medicines indispensable for people's lives.

Therefore, resiliency is a very important topic that this work will focus on a sustainable way as well because sustainability is also a subject that is increasingly being addressed due to its importance on the environment and on countries' economies.

### 2.3.3. Decision-making challenges in the PSC

As seen in 2.1.3, MCDM approaches are gaining more and more interest and also in the PSC as studied in [34]. This study gives some suggestions for future research on the hybridization of MCDM techniques to address PSC issues which "would improve the effectiveness of decision-making processes" ([34]) in the PSC.

Analysing [37], 17 PSC indicators were identified based on four categories: technological, environmental, organisational and SC. The study shows that the last two influence the others.

In [36], the decision support framework covered three phases: sustainable and resilient supplier selection, order allocation, and the best solution selection.

Finally, there are also optimization and simulation techniques. The last one will be detailed in the next chapter as it will be used in this dissertation.

## 2.4. Simulation

### 2.4.1. Simulation as a tool for decision support systems

According to [41], simulation "is the imitation of the operation of a real-world process or system over time". In fact, in simulation, a system is given an artificial history that can be observed to learn more about how it operates. It is necessary for solving problems, evaluating behaviours, testing various scenarios, and supporting the design of practical systems ([41]).

In order to build valid and credible simulation models, by defining if it is an accurate representation of the real system that is wanted to be researched, [5] proposed a seven-step approach for conducting a successful simulation study, as seen in Figure 8.

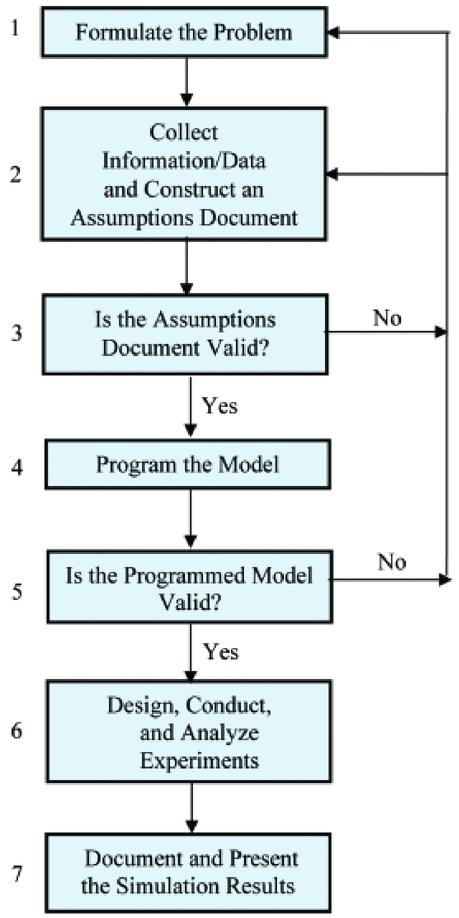


**Figure 8 - Seven-step approach (proposed by [5])**

Nowadays, by making it possible to synchronize and monitor physical systems, “through its data, advanced graphic resources, and constant support for decision making” ([39]), simulation is transforming the industrial environment. It is crucial in Industry 4.0, a new industrial age built on smart organizations and business processes that combine physical and digital worlds with cutting-edge technologies ([39]).

Furthermore, resiliency is also being studied in a simulation environment based on decision-making processes, in which simulations under a scenario pretend to enhance urban resiliency. By simulating various scenarios, the decision-making credibility increases ([31], [38]).

### 2.4.2. Simulation approaches

The simulation modelling is one step of big importance, since it is through those simulations that the proposal of the work will be studied and tested. There are three main approaches, which can also be combined, in simulation modelling: System Dynamics (SD), Discrete Event Simulation (DES), and Agent-Based Simulation (ABS).

The System Dynamics method includes general types of systems such as flows between stocks, the stocks themselves, and delays ([14]). Therefore, their values are used in stock and flow diagrams. Besides that, the identification of interacting feedback loops is also a methodology used in SD ([15]). According to [45], levels that describe the state of the system and rates that affect decision-making make up the two basic variables in feedback loops. Positive loops reinforce input, leading to exponential growth or decline, whereas negative loops demonstrate goal-seeking behaviour ([45]).

Furthermore, Discrete Event Simulation models entities and the flows between them, through flowcharts, for example ([1]). Thus, entities must transition between states. When describing the interaction between entities and events, the activity diagram is utilized as a conceptual model. The main objective is to illustrate the order of events and the interval between them so that the following event can be foreseen. To achieve reliable findings from DES, which might result in outputs like waiting time, resource utilization, and queue lengths, a significant amount of numerical data must be collected ([15]).

Finally, Agent-Based Simulation models entities working individually and independently of other ones with direct or indirect interactions between them ([1]), in which “the macro-level system behavior is a result of the micro-level behavior of the agents” ([45]). In fact, the agents are designed to reflect entities, such as "human beings, animals, or institutions” ([45]). It is an emerging operational research technique, in which autonomous agents obey predetermined rules to accomplish goals ([14]).

In this dissertation, the type of simulation modelling used is the Agent-Based Simulation, therefore it will be further detailed in the next sub-section.

### 2.4.3. Agent-Based Simulation

Agent-Based Simulation is a computational model that simulates the behaviour of autonomous agents (decision-making entities), and the relationships between them within a system, giving “the modeler the possibility to reproduce the reality at detailed level in a straightforward manner” ([13]).

In an ABS, agents are individual entities that are programmed to follow certain rules and interact with each other and their environment, even though each agent must have its own role in the model.

They are often used to study complex systems in the business area ([15]) using, not only traditional mathematical models, but also sophisticated simulation softwares such as *AnyLogic*, which is the software used in this dissertation. In fact, *AnyLogic* is frequently used in ABS, due to the transparency of the interaction between entities, to the use of intuitive programming languages, and to the option of 3D display ([15]).

ABS is commonly used in healthcare, as in [41] and [13]. In the work presented in [41], a hybrid DE and ABS is implemented for COVID-19 management regarding Intensive Care Unit (ICU) bed resources. ABS is used to model the to spread of the disease. In [13], the combination of the three methods presented in 2.4.2 pretends to foresee the effects of medical products and to identify the gaps and flaws in the health system.

Finally, in the batch chemical process industry ([7]), multi-agent systems are implemented and ABS “acts as the core of methodology by responding to uncertainties through local dispatching rules” ([7]). In [33], multi-agent systems are also implemented in the pharmaceutical industry. In this case, it is used a hybrid DE and ABS approach.

### 2.4.4. Multi-agent systems

The entities of a SC should make decisions independently of other ones as each entity represents one different department. Therefore, through multi-agent systems, where an agent can have many subagents, it is possible to solve more complex problems in a SC. A multi-agent framework was proposed by [7], as seen in Figure 9.

Despite this new approach, the systems in the chemical process industry are still limited and with a need to be improved.

With the intention to enhance these systems, their representation and, consequently, the SC analysis, the work was also focused on two important areas by [7]: environmental impact and finances.

Having these concerns and with the critical thinking of always trying to improve processes, the chemical process industry will also benefit from those improvements. Even though it is a complex system, in order to improve the resiliency on a SC, it is also important to minimize the complexity of it through decision-making processes.

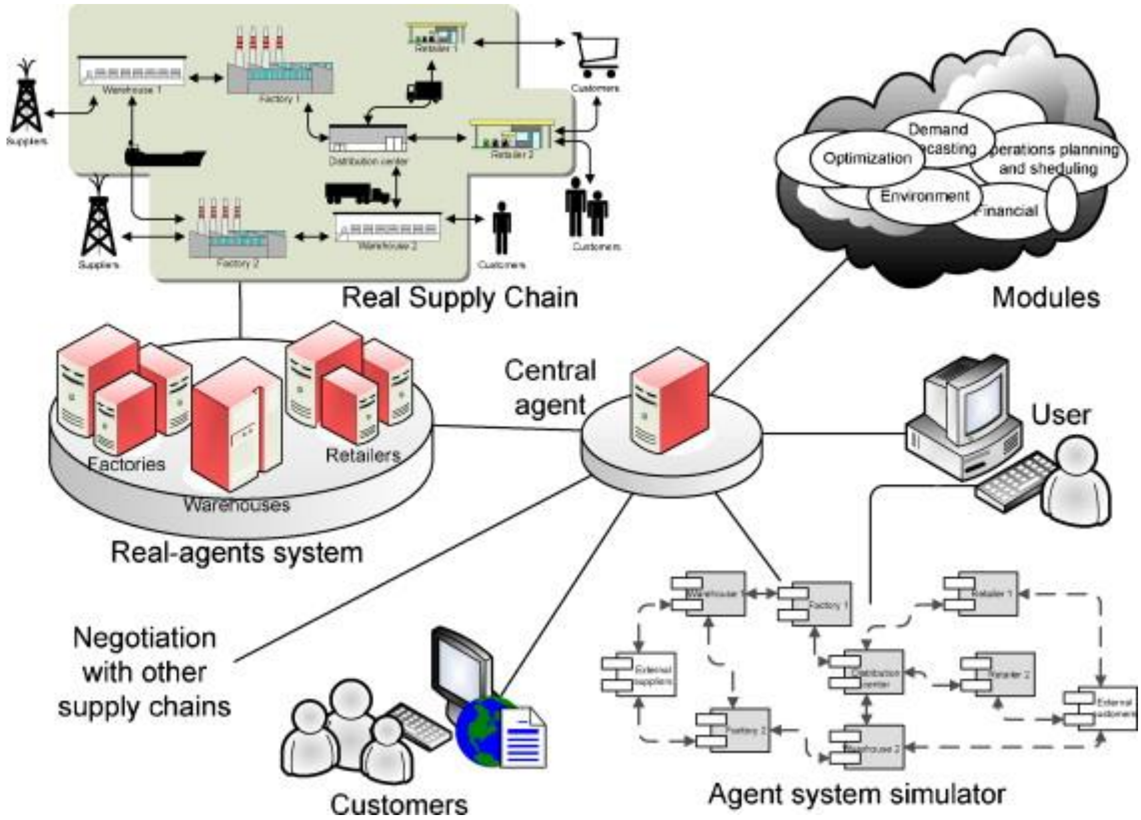


**Figure 9 - Multi-agent framework (proposed by [7])**

In this work, a multi-agent system will be developed to model a PSC, so that more complicated issues can be handled in a SC. Besides that, it is an approach that still requires development in the pharmaceutical sector. Thus, this work intends to contribute to the research in this type of system.

# 3. Problem Definition and Methodological Approach

In this chapter, the definition of the problem addressed in this dissertation is presented as well as the adopted methodology. The problem definition and its conceptualization is presented in sections 3.1 and 3.2, respectively, while the proposed methodology is detailed in section 3.3.

## 3.1. Problem definition

This work aims to study a typical PSC under uncertainty in order to dynamically implement strategies able to efficiently manage disruptions and enhance the overall SC resiliency.

As the main goal is to explore collaborative strategies and how these can be beneficial to achieve higher levels of resiliency, a set of manufacturers located in Europe will be considered as part of a possible collaboration agreement. Usually, the PSC is constituted by primary manufacturers, secondary manufacturers, wholesalers, and retailers, and therefore, these will be the main elements considered in this work (Figure 10).

Firstly, the primary manufacturer represents the transformation of raw materials in API product, that will be later consumed by the secondary manufacturer to transform it into the Final Product (FP) to be commercialized.

After the phase related to the manufacturing of the product, the product needs to be transported from the secondary manufacturer to a wholesaler to satisfy a certain product demand imposed by the retailers in specific markets. The decision related to which wholesalers the product should be sent is primarily based on its location, depending on its proximity to the retailer. The wholesalers are responsible for the supply of the final product to the retailers, while the retailers are responsible for the product distribution to the final end users (market).

Therefore, the flow of the products is the following:

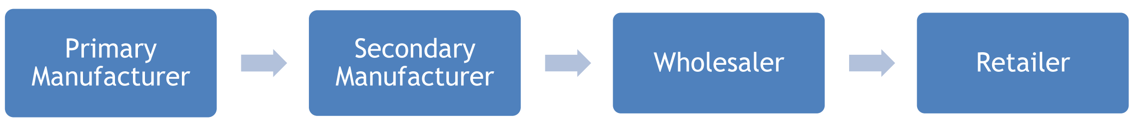


**Figure 10 - Product flow through the echelons of the SC**

On the other hand, the demand information follows in the reverse direction of the one depicted in Figure 10. The product demand is considered uncertain and following a normal distribution specific for each product considered. To satisfy the product demand, retailers need to have available stock, that is maintained by placing orders to the wholesalers. Likewise, wholesalers need to place orders to secondary manufacturers in order to ensure the required levels of inventory to satisfy demand as quickly as possible. Moreover, the material flows between all the SC entities are considered to be by truck transportation means.

## 3.2. Problem conceptualization

For the development of the simulation model some simplifications were considered. The first one is related to the primary manufacturing representation, that in this work was not explicitly modelled, but instead, only the arrival of API to the secondary manufacturer is represented with a defined supply rate. The problem considered here refers to a SC encompassing only the European geographical zone, and, finally, it is considered that the product demand in retailers needs to be immediately met or it is considered to be lost.

Therefore, the model is developed based on the entities depicted in Figure 10, with the exception of the primary manufacturer. Each entity is intended to be an agent in the simulation model, together with some other key elements of the present problem, namely:

- The main secondary manufacturer;
- The wholesalers geographical distributed;
- The retailers representing the markets;
- The products that are being produced and commercialized (API or FP);
- The orders that are made by the retailers to the wholesalers, and by the wholesalers to the secondary manufacturers;
- The alternatives to the secondary manufacturer that will be activated to collaborate in the SC whenever needed;

Starting by the common elements between echelons, all of them have the:

- Location;
- Facility information, regarding the name of its location and the names of the types of products that are being produced in the facility (secondary manufacturer), and that the facility can handle (wholesalers and retailers);
- Facility performance (service level and stock levels regarding each entity and product);

Both retailers and wholesalers place orders to the layer above (the retailer sends the order to the wholesaler, and the wholesaler sends it to the secondary manufacturer). The orders will be modelled as agents with the following parameters:

- The order size;
- The product that was ordered;
- The location of origin of the product;
- The location of destination of the product.

The “Product” agent has the following parameters:

- The product type;
- The lot size.

The overall SC performance is evaluated mainly through the service level which is defined by the following expression:

$$Service\ Level\ (\%)\ = \frac{Total\ Orders\ Fulfilled}{Total\ Orders} \times 100$$

Since this KPI is key in this sector, its value should be maintained as high as possible and, therefore, it was selected as the main resilient metric for the PSC.

## 3.3. Simulation Model

An Agent-Based simulation model is developed using the *AnyLogic* software. This is a “multi-method object-oriented tool” [30] that supports the three methods presented in 2.4.2 ([30]). Being a multi-paradigm simulation tool, makes it easy to change between approaches or even “combine different methods into one model” [30]. Furthermore, as a result of its Java/C++ core, *AnyLogic* is a popular choice for programming simulation models. Moreover, it has already proven to be efficient in previous works ([11], [33]) and has “the ability to rapidly compose industrial-strength agent based models within the same visual environment” [1]. Besides that, as seen in 2.4.3, *AnyLogic* is advantageous for ABS which is the method used in the simulation model.

The simulation model will be developed considering the diagram presented in Figure 11.

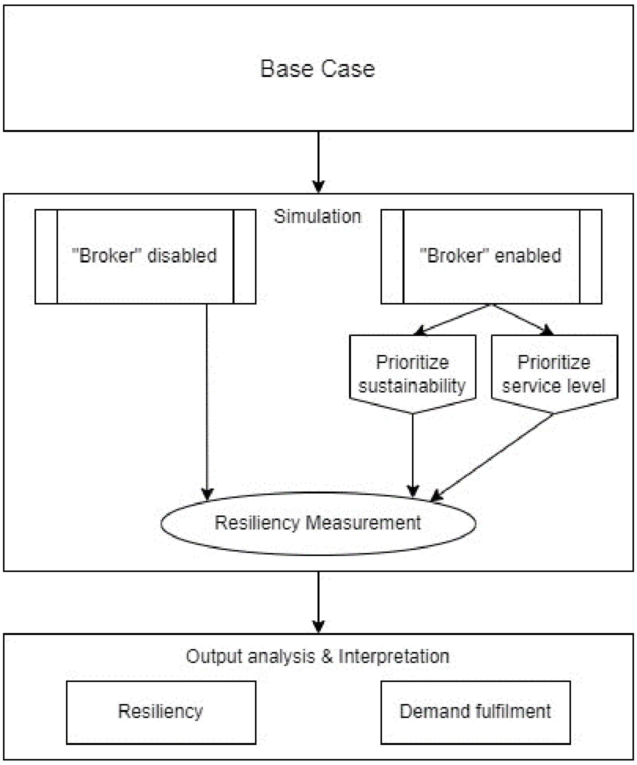


**Figure 11 - Adopted methodology diagram (based on [31])**

First, the base case will be deployed considering the problem definition and conceptualization previously described, and the respective performance will be assessed.

Then, a disruption scenario will be applied to the base case and the service level will be monitored by the "broker" agent. In case of any deviations from the defined target value for the service level, the agent proactively takes appropriate actions (based on the collaborative alternatives available) to mitigate risks and improve the SC performance towards resiliency. Depending on which KPI is intended to be prioritized (sustainability or service level), the collaborative mitigation measures will vary accordingly. Hence, the resiliency measurement will also differ, leading to different outputs, regarding the demand fulfilment and the resiliency itself, as seen in Figure 11.

### 3.3.1. Agent-Based modelling

As explained before in 3.2, each individual entity of the SC was modelled using the agent-based method, enabling the model to quickly simulate various strategies in each tier of the SC. The simulation in this case is based on three agents: one active secondary manufacturer, wholesalers, and retailers. They communicate with each other through orders represented by the "Order" agent.

The configuration of the secondary manufacturer has slightly differences compared to the alternative ones (backup secondary manufacturers). In fact, even though they all have a bidirectional connection with the wholesalers, only the main one is enabled in the beginning of the simulation (Figure 12). The alternatives (backup secondary manufacturers) are disabled (Figure 13). Depending on certain conditions, those connections can be activated or deactivated. This is due to the fact that only one secondary manufacturer should be activated and supplying products to the wholesalers.

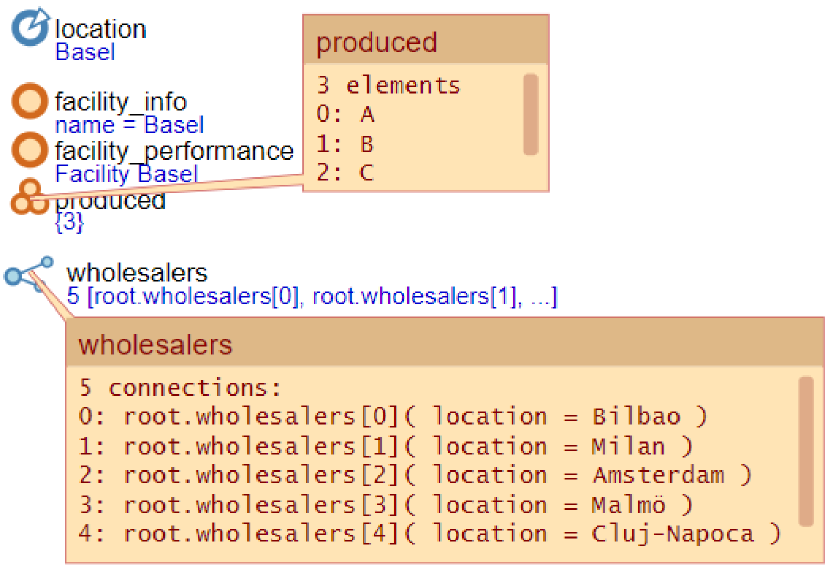


**Figure 12 - Connections between the main secondary manufacturer and wholesalers when activated**

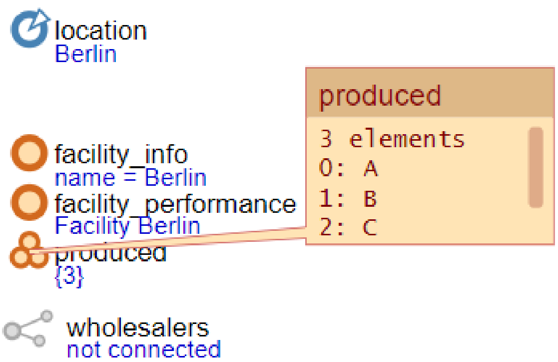


**Figure 13 - Connections between an alternative secondary manufacturer and wholesalers when deactivated**

On the one hand, the secondary manufacturer has initial stocks of API and FP to avoid the warm-up time of the SC. Otherwise, this period would have a slow service level growth. Instead, the SC has already products to satisfy the earliest demands, keeping the service level at ideal values. While the stock values are running out, the production of API into FP is in progress. The values of the initial stocks are specifically calculated, so that the time that takes to run out the stock meets the deliver to the general public of the first produced products.

On the other hand, since the alternatives to the secondary manufacturer are expected to replace the main one after a disruptive event, the production of FP from API in both facilities starts in the beginning of the simulation. Even though there are no initial stocks in those facilities, the production that takes place between the start of the simulation and the moment that the alternative is activated is kept in stock. Thus, as in the case of the principal secondary manufacturer, the warm-up time is avoided.

Regarding the product flow, it is somewhat similar between secondary manufacturers, despite the difference related to initial stocks (Figure 14 and Figure 15). Besides that, the orders that come from the wholesalers only arrive at the connected secondary manufacturer, and the hold blocks are only unblocked in the active agent.

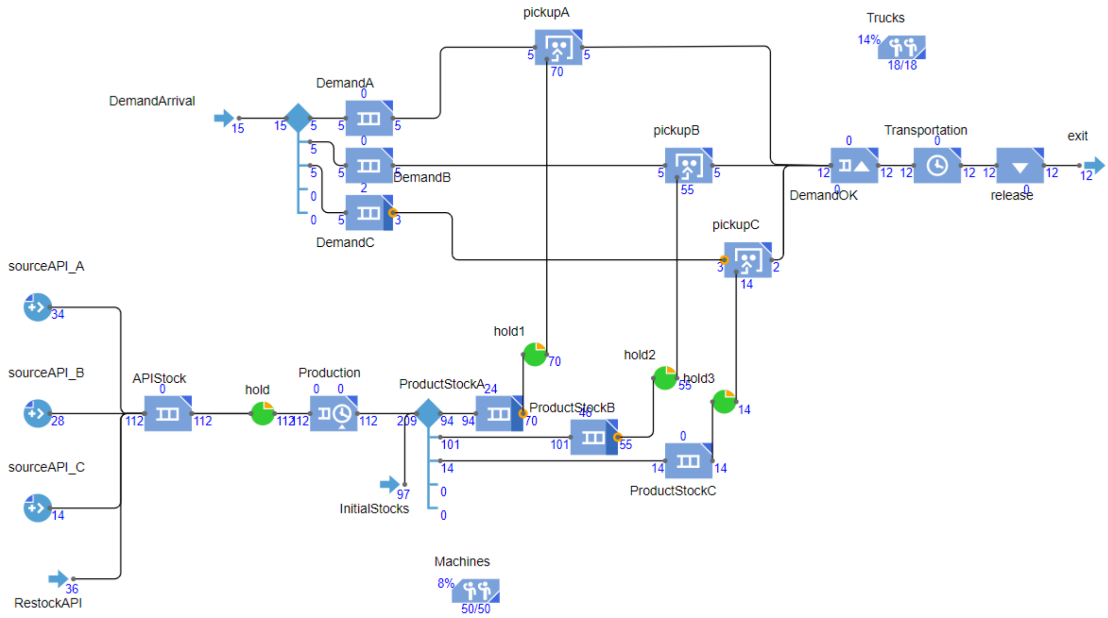


**Figure 14 - Product flow in the main secondary manufacturer when activated**

In fact, being the secondary manufacturers responsible for the production of FP through API, it is needed to be modelled in the respective agents. The source blocks “sourceAPI_A”, “sourceAPI_B”, and “sourceAPI_C” represent the arrival of API from the primary manufacturer which is stored in a queue block representing the API stock. After that, the service block “Production” is responsible for the production of FP from API with an associated resource pool which stands for the production machines. Then, the FP is stored in the queue block associated to the respective type of product. The order arrival to a facility is determined by a dynamic event “OrderProduct”, by receiving a message from the layer below. Then, if the order of each product type and its stock in the facility match the maximum of lot sizes in a container, its transportation to the tier below starts.

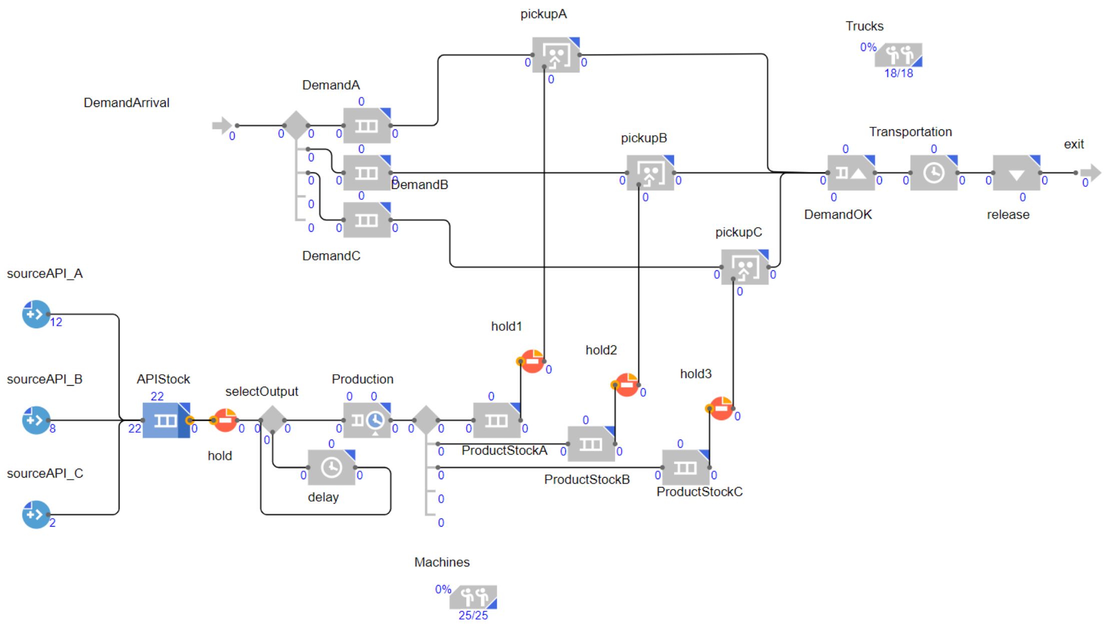


**Figure 15 - Product flow in an alternative secondary manufacturer when deactivated**

Both wholesalers and retailers are responsible for managing their inventory, which means that the monthly orders placed by wholesalers to the active secondary manufacturer (Figure 16) and by retailers to wholesalers (Figure 17) may not necessarily align with the monthly demand generated by the retailers. In fact, if a higher-tier inventory has enough stock to fulfill the demand of the lower-tier, there is no need to place orders with the higher-tier.

The inventory management carried out by wholesalers and retailers involves periodic stock checks and aims to regulate the monthly orders based on the following expression:

$$\text{Monthly Order} = \text{Minimum Monthly Stock} + \text{Average Monthly Demand} - \text{Current Stock}$$

Regarding the demand generation (Figure 17), the monthly demand follows a normal distribution where the mean value of this distribution varies over time to replicate the graph shown in Figure 27.

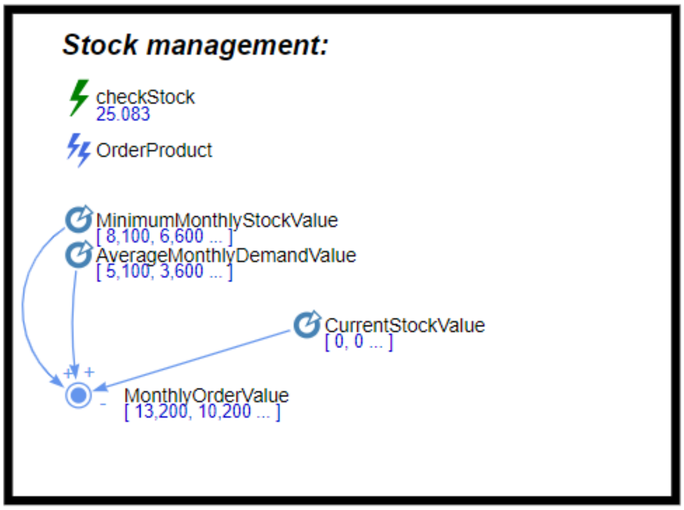


**Figure 16 - Stock management made by a wholesaler**

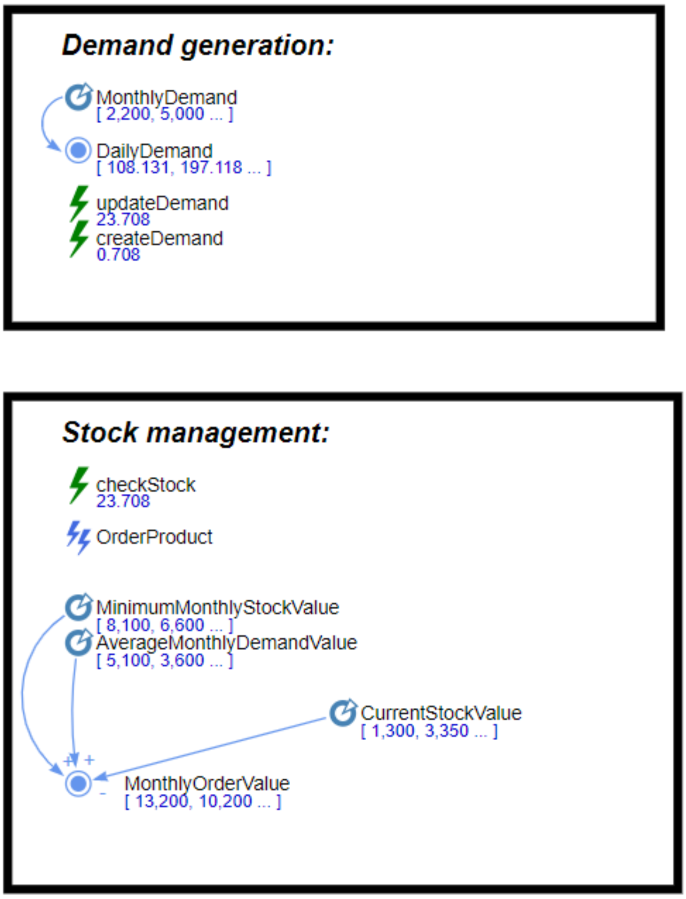


**Figure 17 - Demand generation and stock management made by a retailer**

A wholesaler has only one bidirectional connection with a secondary manufacturer enabled and a collection of bidirectional links with the retailers of its “group”. As in the connections from the secondary manufacturers, the main one is enabled in the beginning of the simulation and the alternatives are disabled. Depending on certain conditions, those links can be activated or deactivated. In Figure 18, it is represented the change between secondary manufacturers. On the left, the wholesaler is connected to the main secondary manufacturer. On the right, the same wholesaler is connected to the first alternative to the secondary manufacturer.

A retailer has only one bidirectional link with the respective wholesaler (Figure 19).


**Figure 18 - Representation of the links with a wholesaler**


**Figure 19 - Representation of the links with a retailer**

Regarding the product flow of the wholesalers and retailers (Figure 20 and Figure 21), it is somewhat similar comparatively with the main secondary manufacturer, even though the last one has the production of FP from API in the beginning of the process. The source blocks "sourceAPI_A", "sourceAPI_B", and "sourceAPI_C", the enter block "RestockAPI", the queue block "APIStock", the service block "Production", and the hold block between the queue and the service block are replaced by a enter block both in wholesalers and retailers representing the arrival of product from the tier above. Therefore, the exit block in the secondary manufacturers has a connection with the enter block "ProductArrival" in the wholesalers, and the exit block in the wholesalers with the enter block "ProductArrival" in the retailers.

Moreover, after the pickup, the retailers have a queue block followed by a sink block representing the deliver of the products to the end users. Furthermore, as the secondary manufacturers, the wholesalers have a seize block with an associated resource pool which stands for the trucks, and a delay block representing the transportation between a wholesaler and a retailer, and a release block before the exit block which stands for the unloading process. In the case of a secondary manufacturer, the transportation is between its facility and a wholesaler.

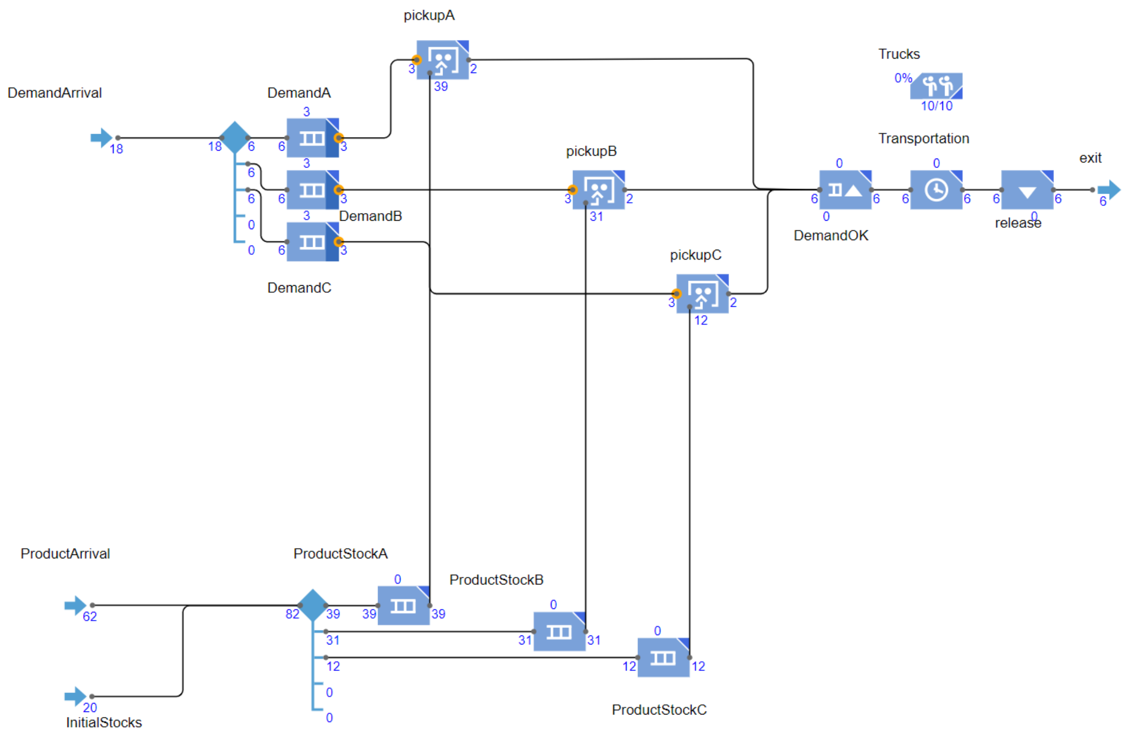


**Figure 20 - Product flow in a wholesaler**

As previously mentioned, the choice regarding the alternatives to the secondary manufacturer is made by a "broker" agent, depending if it is enabled and on the KPI that is intended to be prioritized in the initial configurations (Figure 22).

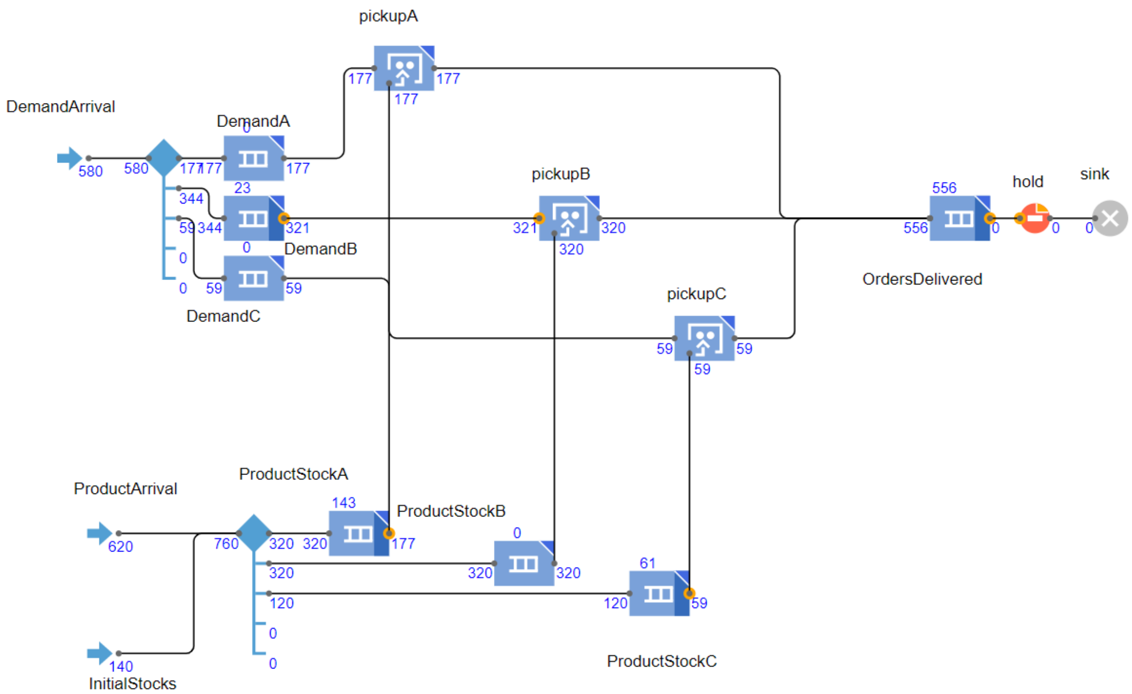


**Figure 21 - Product flow in a retailer**


**Figure 22 - PSC variable configurations**

It is represented by a boolean parameter that is true if the "broker" is activated, and an event that checks the current state of the SC by calling every hour a function responsible for changing the connections between secondary manufacturers and wholesalers if applicable (Figure 23).

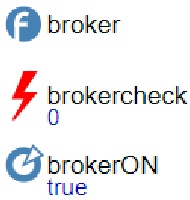


**Figure 23 - "Broker" agent**

Besides that, the performance metrics had to be created and updated on a daily basis, so that the service level can be calculated through the total orders made and the total orders answered, comprising all product types (Figure 24).

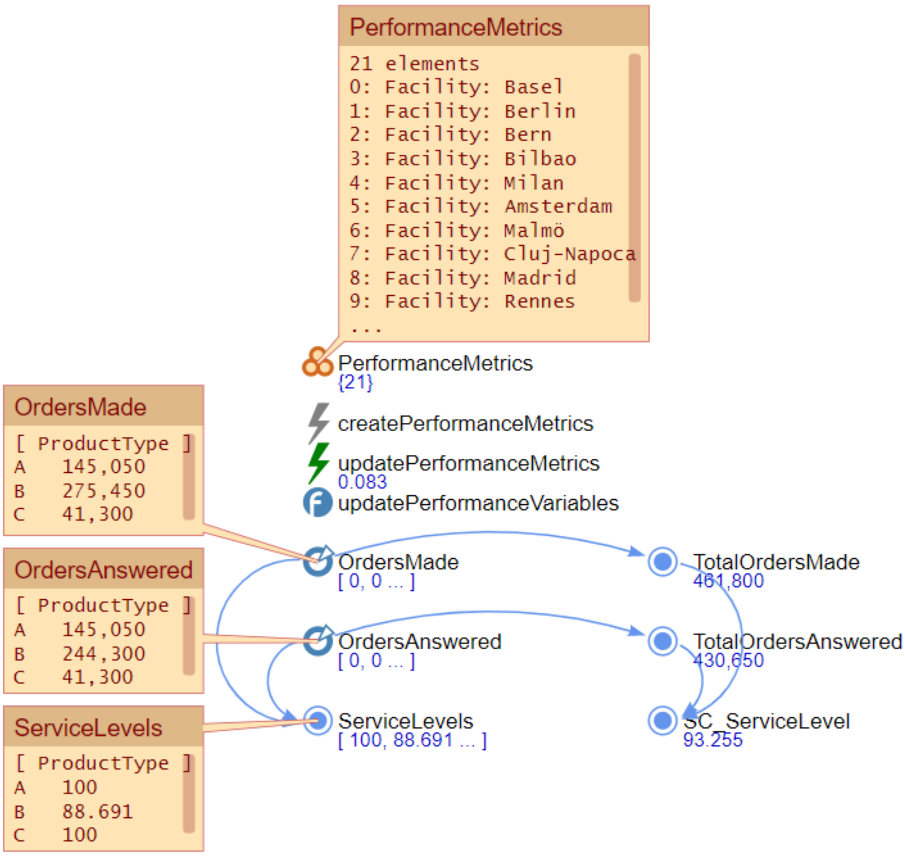


**Figure 24 - Performance Metrics and Service Level**

### 3.3.2. SC configuration

The SC configuration will follow a general case in the European market with only one active secondary manufacturer responsible to supply the final product to the wholesalers. Besides that, it is supposed that there are more retailers than wholesalers. In fact, there are five wholesalers and three of them are responsible to deliver the final product to three retailers and the other two wholesalers deliver it to two retailers.

The locations of these entities are depicted in Figure 25, where the red facility represents the secondary manufacturer, the yellow ones the wholesalers, and the green ones the retailers:

- The main secondary manufacturer is located in Basel (Switzerland).
- The wholesaler located in Bilbao (Spain) is connected to the retailers located in Madrid (Spain), Porto (Portugal), and Rennes (France);
- The wholesaler located in Cluj-Napoca (Romania) is connected to the retailers located in Bucharest (Romania), Kraków (Poland), and Kyiv (Ukraine);
- The wholesaler located in Milan (Italy) is connected to the retailers located in Lyon (France), Rome (Italy), and Zürich (Switzerland);
- The wholesaler located in Amsterdam (The Netherlands) is connected to the retailers in Leverkusen (Germany), and London (United Kingdom);
- The wholesaler located in Malmö (Sweden) is connected to the retailers in Oslo (Norway), and Riga (Latvia).

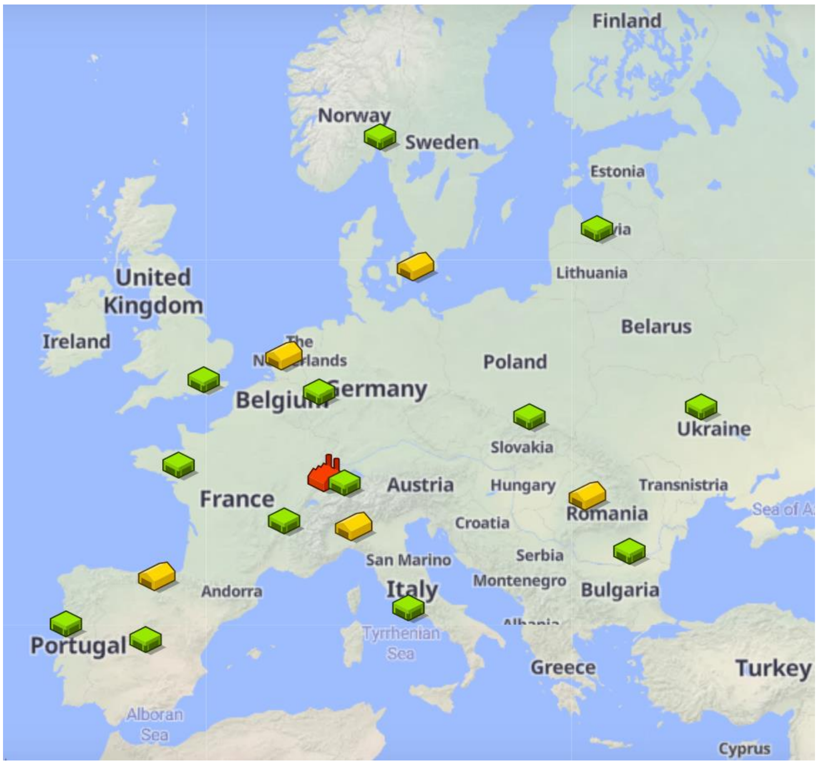


**Figure 25 - Facilities locations**

In addition, there are also two backup secondary manufacturers, and they are located in Berlin (Germany) and Bern (Switzerland), as seen in Figure 26. Those alternatives are part of an extension to the base case. They are also represented as agents that should only be activated if needed under a collaboration strategy to deal with disruptive events.

There are three types of products named as A, B, and C, that can be developed and distributed. Their demand profile over time differs from one to another. The time horizon considered is three years in order to be able to accommodate some disruptive event and its main impacts on the SC. The different demand profiles are depicted in Figure 27.


**Figure 26 - Locations of the alternatives to the secondary manufacturer**

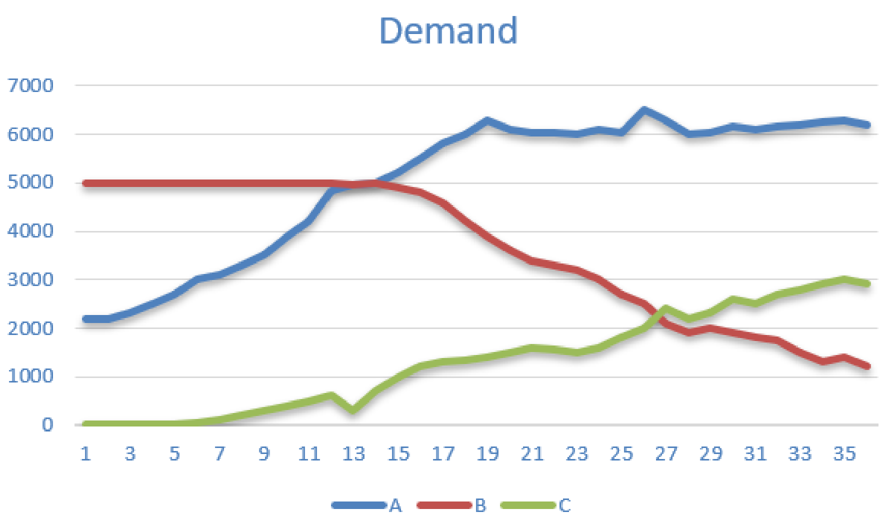


**Figure 27 - Demand of each type of product**

However, the monthly demand should not be equally distributed over all the days of the month. In fact, there is always an uncertainty associated to the daily demand (Figure 28). In order to represent it, a normal distribution is applied to the daily demand, as already mentioned. The mean of this distribution is given by the division of the monthly demand of that month by 30 (number of days in a month), and its standard deviation is 30.

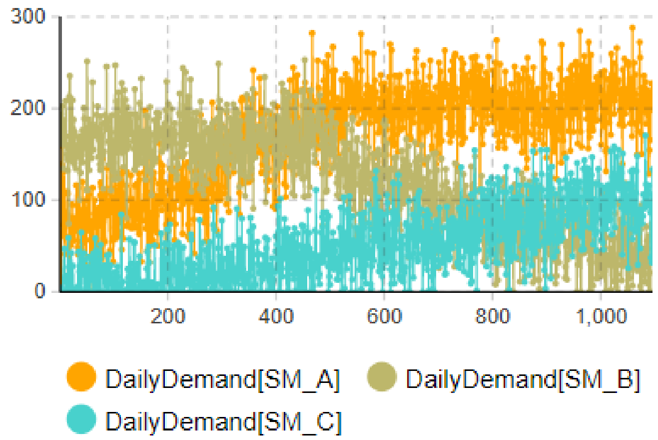


**Figure 28 - Daily demand with uncertainty**

According to the predicted monthly demand, the initial stocks of each product type in each phase of the development and distribution of the medicines were also defined. Initially, the product type C has no stock. Thus:

- The initial stocks of API in the secondary manufacturer are 11000 units of product A and 25000 units of product B;
- The initial stocks of Final Product (FP) in the same echelon are 49000 units of product A and 48000 units of product B;
- The initial stocks of FP in each wholesaler are 11000 units of product A and 9000 units of product B;
- The initial stocks of FP in each retailer are 2000 units of product A and 5000 units of product B.

Besides that, it was defined a minimum monthly stock in the wholesalers and retailers, which are the same between these echelons:

- 8100 units of product A;
- 6600 units of product B;
- 4400 units of product C.

In the source blocks of the secondary manufacturer, the arrivals of API product are defined by interarrival time of one week, meaning that each week a predetermined number of API products entities arrives to the secondary manufacturer. Those entities generated are set to be:

- API needed to produce 17 lots of FP per week of product A;
- API needed to produce 14 lots of FP per week of product B;
- API needed to produce 7 lots of FP per week of product C.

Furthermore, the delay time of the production in the secondary manufacturer and of the transportation from the secondary manufacturer to a wholesaler and from a wholesaler to a retailer follow a triangular distribution in which the most likely to happen is that these delays are half a day (12 hours) and has a minimum of 6 hours and a maximum of 18 hours.

Still regarding the production in the secondary manufacturer, there are 50 machines allocated and, regarding the transportation, there are 18 trucks allocated to the route from the secondary manufacturer to a wholesaler and ten allocated to the route from a wholesaler to a retailer. The speed of these trucks is 50 km/h.

Finally, the lot size in the secondary manufacturer and in the wholesaler is 1000 and in the retailer is variable with an initial value of 50.

# 4. Results

The base case was built in order to analyse the normal course of a medicine since an API until the commercialization of the final product. However, it is not realistic that the PSC works perfectly all the time without disturbances or mishaps. Therefore, with the use of *AnyLogic*, it was possible to add an extension to the base case, in which a disruptive scenario is introduced in the simulation.

## 4.1. Base Case

As seen in 3.2, the service level is expected to be high, and it can be obtained with the right configuration of the SC. Different scenarios regarding numbers of stocks, lot sizes, etc. have been tested, leading to the values referred in 3.3.2. The general service level obtained, which is the mean between the service level of all product types in all retailers, is represented in Figure 29, where it is visible that the service level stabilizes at 90% after the first months where the initial stocks allow the SC to have a higher service level.

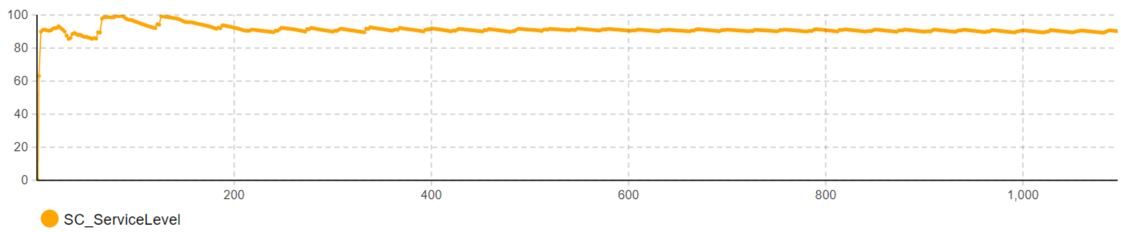


**Figure 29 - SC Service Level**

A more detailed perspective can be obtained if it is done an analysis of the service level of each type of product, as seen in Figure 30. It is possible to understand that the production of product B struggles to satisfy the demand. As the demand of this type of product decreases, its service level increases. On the other hand, as the demand of products A and C increases over time, their service level decreases.

The disadvantages of having three retailers allocated to one wholesaler instead of only two retailers can be seen in Figure 31 and in Figure 32. In fact, if a wholesaler is intended to fulfill the needs of three retailers, their service levels are lower.

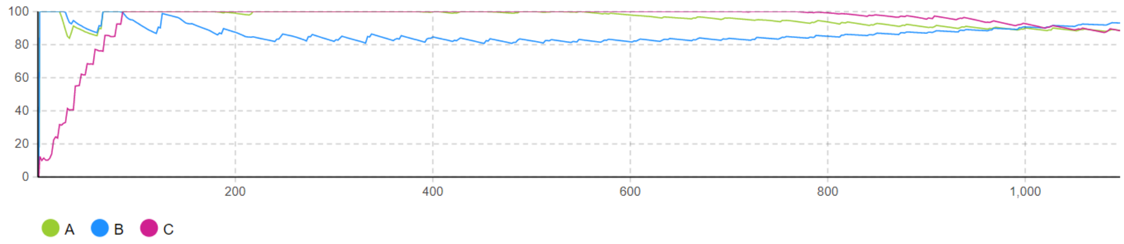


**Figure 30 - SC Service Level of each type of product**

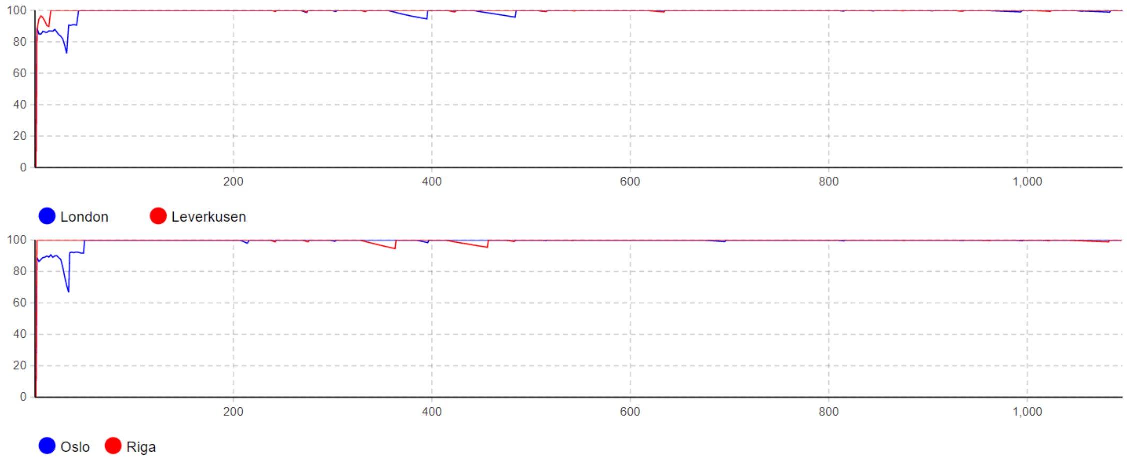


**Figure 31 - SC Service Level of “groups” with two retailers**

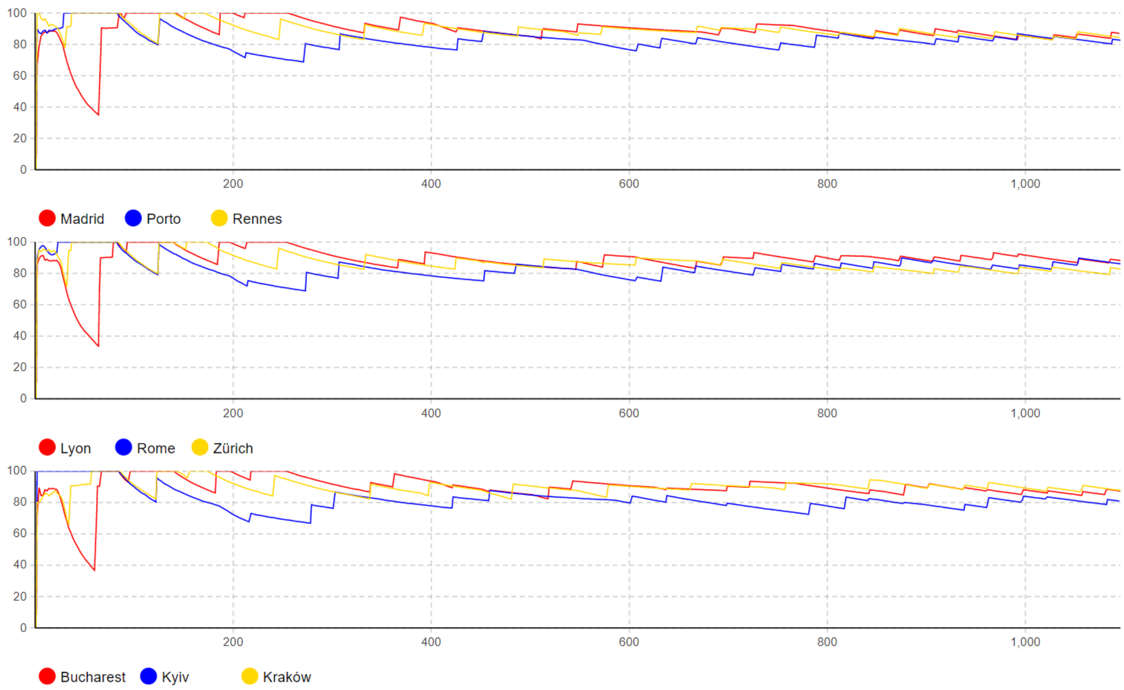


**Figure 32 - SC Service Level of "groups" with three retailers**

Analysing the stocks in the main secondary manufacturer (Figure 33), each type of product has a different evolution of their values, depending on the weekly arrival of API to the facility and the demand generated by the retailers.

However, a common feature between the different product types is their monthly consumption due to the monthly demand. Then, for one month, the stock increases until the next delivery to the tier below.

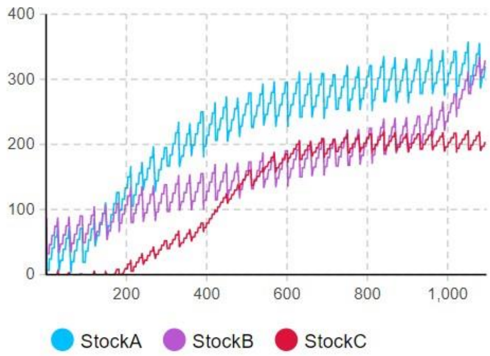


**Figure 33 - Stocks in the main second manufacturer**

## 4.2. Disruption Scenario

The extension to the base case consists in an event which stops the production of medicines in the secondary manufacturer at the end of the first year of the simulation. The production is resumed only after one year, remaining only one more year to the end of the simulation. Furthermore, the existing inventory in the secondary manufacturer is destroyed.

As seen in the analysis of the service level of the SC (Figure 34), the disruption event causes a decline that is damaging to the PSC.

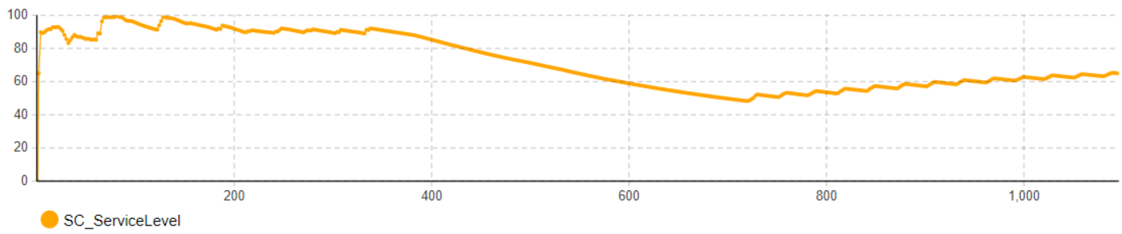


**Figure 34 - SC Service Level with a disruption event**

The service level decreases from 90% to 50% in one year, approximately. At the beginning of the third year, when the production is resumed, even though the capacity of production is the same as before the disruption, the secondary manufacturer struggles to correspond to the demand from the retailers. In fact, since there is no stock, because it was destroyed, it is only capable to deliver what is being produced along the third year, being able to increase approximately 15% until the end of the simulation time.

Furthermore, the level of stocks under a disruptive event is considered zero as the inventory in the main secondary manufacturer is destroyed at the start of the disruptive event.

## 4.3. Mitigation Measures

Since the decline of the service level is highly undesirable, it is needed to be stopped as soon as it is detected, so that its value remains acceptable. As the event is supposed to deeply affect the production in the main secondary manufacturer, the disruption is needed to be mitigated and the service level is expected to rise after the fall caused by the disruptive event, even though perhaps not reaching the usual values.

To do so, mitigation measures are made, in order to have automatic responses when an unexpected event occurs, being its impact lessened. Depending on the evolution of the service level and on certain criteria, a “broker” agent is expected to decide which measure is the most appropriated for each case. It was determined that the measure should be made as soon as the service level falls below 85%.

Since the simulated disruption affects the production in the secondary manufacturer, it was decided that there would be two more secondary manufacturers with the same function as the main one, but with different configurations. As part of the mitigating plan, it is considered that these two alternative manufacturers do not originally produce the same products but holds the main capabilities necessary for production. By strategically maintain a stock of critical components (such as the needed API), these backup manufacturers can quickly step in and initiate the required production. The amount of API and the capacity of production are not the same from one alternative to another, even though the product flow is the same.

Therefore, those two secondary manufacturers are alternatives to the main one. In case it fails, depending on certain criteria, one of the alternatives to the secondary manufacturer is activated in order to fulfil the demand. It was defined that these criteria should be based on sustainability and on the service level.

However, since those alternatives are not part of the PSC at the begging and they are producing for other ones, they cannot correspond to the needs immediately when activated. It was defined that those alternatives would take one month to adapt its operations, so that they could fit the PSC in their work environment. Through a delay block representing that one month, a “SelectOutput” block, which is responsible of deciding if a product entity delays its production in one month or if the production should start with the help of an auxiliary variable, it is possible to represent this adjustment of the new secondary manufacturer, as seen in Figure 35.

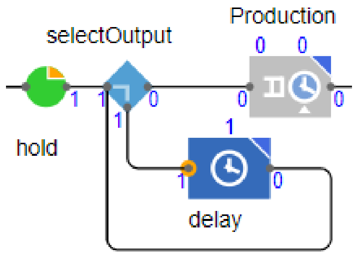


**Figure 35 - Delay of the production**

Thus, there are two mitigation measures related to the disruption scenario.

### 4.3.1. Mitigation measure 1: Prioritize Sustainability

The first alternative to the secondary manufacturer is geographically close to the main one. It was defined that the location would be Bern (in the same country as the main facility – Switzerland).

This facility has a lower capacity of production and a lower arrival of API to the facility. In the source blocks of this secondary manufacturer, the arrivals of API product are also defined by interarrival time of one week. However, those entities generated are set to be:

- The amount of API needed to produce 6 lots of FP per week of product A;
- The amount of API needed to produce 4 lots of FP per week of product B;
- The amount of API needed to produce 1 lot of FP per week of product C.

Furthermore, the delay time of the service block “Production” also follows a triangular distribution but with a bigger delay. In this case, the most likely to happen is that this delay is one day and has a minimum of half a day (12 hours) and a maximum of one day and a half (36 hours).

Finally, the last difference between the first alternative to the secondary manufacturer and the main one is the number of machines allocated to the process of production and their speed, which is 25 machines.

With this mitigation measure, the sustainability is prioritized, because trucks travel shorter distances, leading to an expected reduction of carbon footprint which is one of the main factors that must be considered when it comes to sustainability.

The evolution of the service level in this case is represented in Figure 36.

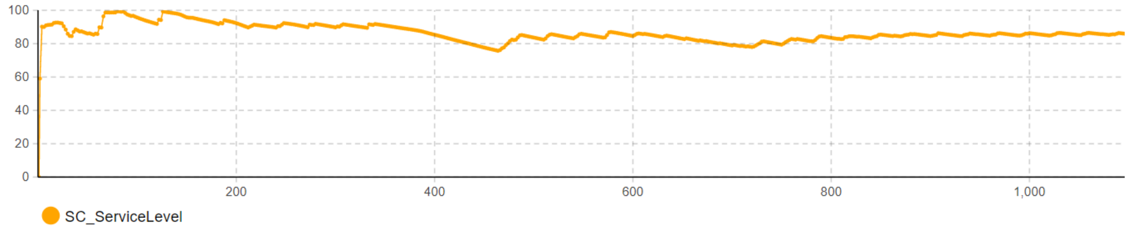


**Figure 36 - SC Service Level with "broker" prioritizing sustainability**

After the service level becomes lower than 85%, the secondary manufacturer located in Bern is activated and the main one deactivated, leading to the month in which the alternative is getting ready to supply the PSC. After that month, the API stock that is the result of the first 13 months of the simulation (the first year of the simulation plus the month delay), in which the API was just arriving and not being produced, starts to satisfy the demand. When the stock ends, there is a little decline of the service level, until the main secondary manufacturer is able to produce again and fulfil the PSC needs.

In Figure 37, it is possible to understand that, since API is arriving to the alternatives to the secondary manufacturer during the first 13 months, the values of the stocks of each product type are not null which leads to steep rise in the beginning of the first year. Then, due to the low capacity of production of this facility, the stock runs out quickly.

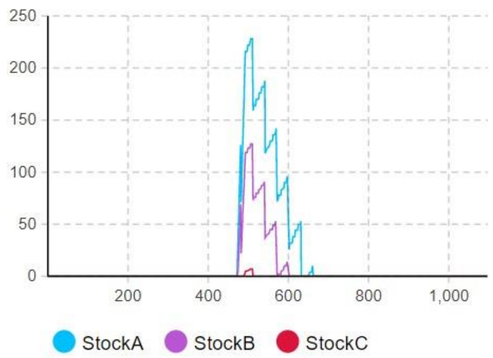


**Figure 37 - Stocks of each product type in the first alternative to the secondary manufacturer when activated**

### 4.3.2. Mitigation measure 2: Prioritize Service Level

The second alternative is further away in the map but has the same capacity of production as the main facility and the same amount of arrival of API to the facility. This arrival is also defined by interarrival time of one week. It was defined that the location would be Berlin (Germany).

Regarding delay times and number of machines allocated to the process of production, the values are the same compared to the principal secondary manufacturer.

With this mitigation measure, the service level is prioritized, because the capacity of production remains the same, even though the facility is further away from the wholesalers with the "groups" of three retailers. These "groups", compared with the "groups" of two retailers, have more problems in meeting the demand, as seen in Figure 31 and Figure 32, meaning that helps that the secondary manufacturer is closer to these wholesalers.

The evolution of the service level in this case is represented in Figure 38.

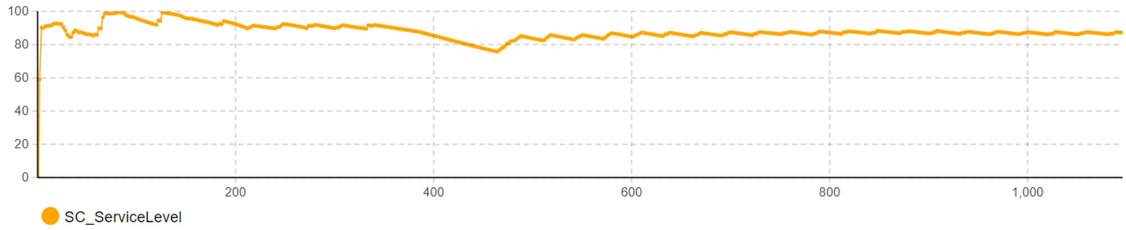


**Figure 38 - SC Service Level with "broker" prioritizing the service level**

After the service level becomes lower than 85%, the secondary manufacturer located in Berlin is activated and the main one deactivated, leading to the same evolution as in 4.3.1. However, contrarily to the other mitigation measure, as the capacity of production is the same as the principal facility, the stock is able to satisfy the demand until the main secondary manufacturer is able to produce again and fulfil the PSC needs (Figure 39).

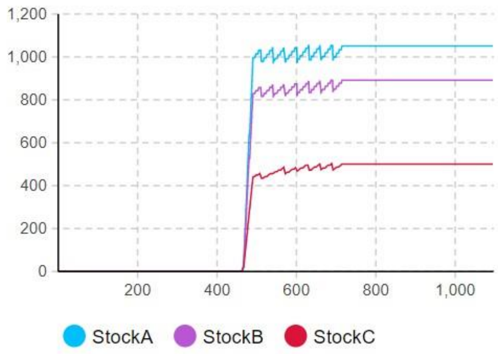


**Figure 39 - Stocks of each product type in the second alternative to the secondary manufacturer when activated**

Contrarily to the case of the first alternative to the secondary manufacturer, the second alternative has the capacity to produce and satisfy the PSC needs during the whole year in which it is activated. After that year, the facility still keeps stock of the different product types, as seen in Figure 39.

## 4.4. Results Analysis

A more detailed evaluation of the results can be done through a data set analysis. In fact, analysing the highlights of the simulation, a better perspective of what occurs with the "broker" disabled and for each collaborative approach (with the "broker" enabled) is obtained, as seen in Table 1.

**Table 1 - Results Analysis**

| Day | Service Level (%) | | |
|---|---|---|---|
| | "Broker" disabled | "Broker" enabled | |
| | | Prioritize Sustainability | Prioritize Service Level |
| 366 | 89,8 | 89,9 | 89,9 |
| ... | | | |
| 406 | | 84,9 | 84,9 |
| ... | | | |
| 466 | | 75,9 | 75,9 |
| ... | | | |
| 636 | | 84,2 | |
| ... | | | |
| 720 | 48,4 | | |
| ... | | | |
| 722 | | 77,0 | |
| ... | | | |
| 1096 | 65,3 | 82,8 | 86,7 |

When the "broker" is disabled, the overall service level starts to gradually decrease when the disruption event occurs which is approximately on day 366. Then, the service level reaches its lowest level almost one year later (near the end of the second year of the simulation). After the resume of the production in the main secondary manufacturer at the beginning of the third year, the service level starts to gradually increase until the end of the simulation.

If the "broker" is enabled, the difference between the disruption event and the moment the service level falls below 85% (the "broker" becomes active) is approximately 40 days. After that, the overall service level continues to decrease until the day 466 approximately (60 days after the "broker" becomes active). That is due to the one-month delay regarding the adjustment of the new secondary manufacturers plus the time that takes to product and deliver to the end users the first products demanded to the new facility. The development of the overall service level in the remaining time differs from one mitigation measure to another.

If the sustainability is prioritized, the stocks that remain from the first year before the disruption run out approximately on day 636 (230 days after the “broker” becomes active). Then, the service level decreases until near the end of the second year of the simulation, due to the weak capacity of production of the facility that is not able to satisfy the demand. When the production in the principal secondary manufacturer resumes, the overall service level starts to gradually increase until the end of the simulation.

On the other hand, if the service level is prioritized, the stocks from the first year before the disruption do not run out and the capacity of production of the facility is able to satisfy the demand. In fact, after the day 466 approximately, the overall service level increases gradually until the end of the simulation where its value is close to the values before the disruption.

Thus, the “broker” agent, allowing the PSC to meet its requirements and to have strategic collaborative approaches, is a helpful tool to make the right decisions, in terms of what is needed to improve the PSC resiliency.

Moreover, the stocks of FP lots in the backup secondary manufacturers can also be analysed for both mitigation measures, as seen in Table 2 and Table 3. The results (at the beginning of each month) are presented with an interval of two months between them. Since the production only starts one month after the activation of the alternative manufacturers and the first lots being produced will promptly satisfy the demand, the stocks of FP lots are null until the month 18 approximately.

Analysing the Table 2, it can be concluded that the stocks of Product A take longer to run out than the other product types due to its larger production in the facility, comparatively with the other product types, despite being lower than the other facilities. Besides that, as the capacity of production of Product C is even more limited and almost null, the stock of this type of product runs out very quickly.

**Table 2 - Stocks of FP lots in the first alternative secondary manufacturer of each product type when sustainability is prioritized**

| Month | Product A | Product B | Product C |
|---|---|---|---|
| 16 | 0 | 0 | 0 |
| 18 | 228 | 127 | 3 |
| 20 | 142 | 53 | 0 |
| 22 | 50 | 0 | 0 |
| 24 | 0 | 0 | 0 |

Finally, analysing the Table 3, it can be deduced that, even though the stocks are being consumed, the capacity of production of the second alternative facility is able to enlarge the amount of stocks. Since Product A has the largest production capacity and Product C has the least production capacity among all product types, the values of all stocks of FP lots make sense. Until the end of the simulation, the values of the stocks remain the same as the month 26, due to the resume of production in the principal facility and the respective end in the alternative one.

**Table 3 - Stocks of FP lots in the second alternative secondary manufacturer of each product type when service level is prioritized**

| Month | Product A | Product B | Product C |
|---|---|---|---|
| 16 | 0 | 0 | 0 |
| 18 | 1031 | 857 | 450 |
| 20 | 1044 | 873 | 479 |
| 22 | 1040 | 875 | 493 |
| 24 | 1053 | 891 | 503 |
| 26 | 1051 | 892 | 501 |

# 5. Conclusions and future work

## 5.1. Conclusions

This dissertation aimed to investigate the resiliency of a typical PSC under uncertainty and explore collaborative strategies to effectively manage disruptions. The study focused on a set of manufacturers located in Europe and examined their roles within the PSC, including secondary manufacturers, wholesalers, and retailers.

The base case analysis provided insights into the normal course of medicine production and distribution within the PSC. However, it is acknowledged that disruptions and mishaps are inevitable, and the PSC cannot always function flawlessly. To address this, a disruptive scenario was introduced using *AnyLogic* simulation software, where the production in the main secondary manufacturer was halted for one year and the existing inventory was destroyed.

To mitigate the negative impact of disruptions and improve the service level, a set of automatic responses and mitigation measures were implemented. A "broker" agent was responsible for deciding the most appropriate measure based on the service level and sustainability criteria. Two alternative secondary manufacturers were introduced, with one located geographically closer to the main facility and the other further away. The first alternative had a lower production capacity and a smaller arrival rate of API, prioritizing sustainability by predictably reducing carbon footprint. The second alternative had the same production capacity as the main facility and a comparable API arrival rate, prioritizing service level by ensuring a steady supply to wholesalers.

Upon the service level falling below 85%, the respective alternative secondary manufacturer was activated, allowing for a one-month adjustment period to fit into the PSC. The API stock accumulated during the first year of the simulation was then used to satisfy the demand until the main secondary manufacturer resumed production. In the case of the first alternative, the service level experienced a slight decline, while the second alternative maintained a stable service level throughout the activation period due to its production capacity.

Overall, the findings highlight the importance of proactive measures and collaboration in managing disruptions within the PSC. This dissertation makes a valuable contribution by employing strategic collaborative approaches and incorporating alternative secondary manufacturers, which effectively enhance the resiliency of the PSC and drive improvements in overall SC performance.

## 5.2. Future work

Future research can further explore additional mitigation measures and evaluate their effectiveness under various disruptive scenarios to support decision-making and optimize SC resiliency in the pharmaceutical industry.

Moreover, costs regarding production, inventory, or transportation can be associated to the study of resiliency in a SC. In fact, as they are important requirements for decision-making processes, costs can be helpful for a more developed “broker” agent, so that it can calculate costs and make the right decisions.

Finally, further analysis regarding the sustainability dimension should be made in order to understand how resiliency and sustainability can be addressed simultaneously in such a complex setting.

# 6. References


[1] Borshchev, A., Filippov, A. (2004). “From System Dynamics and Discrete Event to Practical Agent Based Modeling: Reasons, Techniques, Tools.” The 22nd International Conference of the System Dynamics Society. Oxford, England.

[2] Hohenstein N.-O., F., E., Hartmann, E., Giunipero, L. (2015). "Research on the phenomenon of supply chain resilience: A systematic review and paths for further investigation." International Journal of Physical Distribution & Logistics Management **45**(1/2): 90-117.

[3] Kamalahmadi, M., Parast, M. M. (2015). "A review of the literature on the principles of enterprise and supply chain resilience: Major findings and directions for future research." International Journal of Production Economics **17**: 116-133.

[4] Lambert, D. M., Cooper M. C. (2000). "Issues in Supply Chain Management." Industrial Marketing Management **29**: 65-83.

[5] Law, A. M. (2009). “How to build valid and credible simulation models.” Winter Simulation Conference, Austin, Texas, U.S.A., Institute of Electrical and Electronics Engineers (IEEE).

[6] Marques, C. M., Moniz, S., Sousa, J.P., Barbosa-Povoa, A. P., Reklaitis, G. (2020). "Decision-support challenges in the chemical-pharmaceutical industry: Findings and future research directions." **134**.

[7] Puigjaner, L., Guillén-Gosálbez, G. (2008). "Towards an integrated framework for supply chain management in the batch chemical process industry." Computers and Chemical Engineering **32**: 650-670.

[8] Ribeiro, J. P. (2018). "Supply Chain Resilience: Definitions and quantative modelling approaches - A literature review." Computers & Industrial Engineering **115**: 109-122.

[9] Wang, J., Muddada R. R., Wang, H., Ding, J., Lin, Y., Liu, C., and Zhang, W. (2016). "Toward a resilient holistic supply chain network system: Concept, review and future direction." IEEE Systems Journal **10**(2): 410-421.

[10] Aigbogun, O., Ghazali, Z., Razali, R. (2018). "Supply Chain Resilience and Measurement Dimensions: The Case of Halal Pharmaceuticals in Malaysia." Paper presented at the SHS Web of Conferences.

[11] Silva, A.C.T. (2022). "Dynamic Capacity Management in Pharmaceutical Supply Chains." Master, Faculty of Engineering of the University of Porto.

[12] Barroso, A.P., Carvalho, H., Machado, V.H., Cruz Machado, V. (2015). "Quantifying the Supply Chain Resilience." Chap. 2 In *Applications of Contemporary Management Approaches in Supply Chains*, 13-38.

[13] Djanatliev, A., German, R. (2013). "Prospective Healthcare Decision-Making by Combined System Dynamics, Discrete-Event and Agent-Based Simulation." Paper presented at the 2013 Winter Simulation Conference.

[14] Maidstone, R. (2012). "Discrete Event Simulation, System Dynamics and Agent Based Simulation: Discussion and Comparison." *System* 1, no. 6: 1-6.

[15]Sumari, S., Ibrahim, R., Zakaria, N.H., Ab Hamid, A.H. (2013). "Comparing Three Simulation Model Using Taxonomy: System Dynamic Simulation, Discrete Event Simulation and Agent Based Simulation." *International Journal of Management Excellence* 1, no. 3: 54-59.

[16]Kosasih, E.E., Brintrup, A. (2022). "A Machine Learning Approach for Predicting Hidden Links in Supply Chain with Graph Neural Networks." International Journal of Production Research 60, no. 17: 5380-93.

[17]Wichmann, P., Brintrup, A., Baker, S., Woodall, P., McFarlane, D. (2020). "Extracting Supply Chain Maps from News Articles Using Deep Neural Networks." International Journal of Production Research 58, no. 17: 5320-36.

[18]Zhao, P., Li, Z., Han, X., Duan, X. (2022). "Supply Chain Network Resilience by Considering Disruption Propagation: Topological and Operational Perspectives." *IEEE Systems Journal* 16, no. 4: 5305-16.

[19]Ahoa, E., Kassahun, A., Tekinerdogan, B. (2020). "Business Processes and Information Systems in the Ghana Cocoa Supply Chain: A Survey Study." *NJAS: Wageningen Journal of Life Sciences* 92, no. 1: 1-11.

[20]Kopp, A., Orlovskyi, D., Kuka, D. (2017). "An Approach to Forming Dashboards for Business Processes State Analysis." *Bulletin of the National Technical University "KhPI", Series: System Analysis Control and Information Technologies* 51, no. 1272: 44-52.

[21]Kopp, A., Orlovskyi, D., Syzonova, K. (2022). "Integration of Business Process and Inventory Management Models for Supply Chain Simulation." *Collection of scientific papers «SCIENTIA»*: 108-13.

[22]Enz, M.G., Lambert, D.M. (2023). "A Supply Chain Management Framework for Services." *Journal of Business Logistics* 44, no. 1: 11-36.

[23]Ghosh, S., Mandal, M.C., Ray, A. (2022). "Green Supply Chain Management Framework for Supplier Selection: An Integrated Multi-Criteria Decision-Making Approach." *International Journal of Management Science and Engineering Management* 17, no. 3: 205-19.

[24]Taherdoost, H., Brard, A. (2019). "Analyzing the Process of Supplier Selection Criteria and Methods." The 12th International Conference Interdisciplinarity in Engineering, Procedia Manufacturing, 32: 1024-1034.

[25]Žic, J., Žic, S. (2020). "Multi-Criteria Decision Making in Supply Chain Management Based on Inventory Levels, Environmental Impact and Costs." *Advances in Production Engineering & Management* 15, no. 2: 151-63.

[26]Hofmann, K.H., Jacob, A., Pizzingrilli, M. (2022). "Overcoming Growth Challenges of Sustainable Ventures in the Fashion Industry: A Multinational Exploration." *Sustainability* 14.

[27]Kiers, J., Seinhorst, J., Zwanenburg, M., Stek, K. (2022). "Which Strategies and Corresponding Competences Are Needed to Improve Supply Chain Resilience: A Covid-19 Based Review." *Logistics* 6, no. 1.

[28]Christopher, M. (2004). "Building the Resilient Supply Chain." *The International Journal of Logistics Management* 15, no. 2: 1-13.

[29]Pettit, T.J., Croxton, K.L., Fiksel, J. (2019). "The Evolution of Resilience in Supply Chain Management: A Retrospective on Ensuring Supply Chain Resilience." *Journal of Business Logistics* 40, no. 1: 56-65.

[30]Borshchev, A. (2014). "Multi-Method Modelling: Anylogic." In *Discrete-Event Simulation and System Dynamics for Management Decision Making*, 248-79.

[31]Moosavi, J., Hosseini, S. (2021). "Simulation-Based Assessment of Supply Chain Resilience with Consideration of Recovery Strategies in the Covid-19 Pandemic Context." *Computers & Industrial Engineering* 160.

[32]Lindahl, S.B., Babi, D.K., Gernaey, K.V., Sin, G. (2023). "Integrated Capacity and Production Planning in the Pharmaceutical Supply Chain: Framework and Models." *Computers & Chemical Engineering* 171.

[33]Silva, A.C.T., Marques, C.M., Sousa, J.P. (2023). "A Simulation Approach for the Design of More Sustainable and Resilient Supply Chains in the Pharmaceutical Industry." *Sustainability* 15, no. 9.

[34]Laganà, I.R., Colapinto, C. (2022). "Multiple Criteria Decision-Making in Healthcare and Pharmaceutical Supply Chain Management: A State-of-the-Art Review and Implications for Future Research." *Journal of Multi-Criteria Decision Analysis* 29, no. 1-2: 122-134.

[35]Wong, C.Y., Wong, C.W.Y., Boon-itt, S. (2020). "Effects of Green Supply Chain Integration and Green Innovation on Environmental and Cost Performance." *International Journal of Production Research* 58, no. 15: 4589-4609.

[36]Kayani, S.A., Warsi, S.S., Liaqait, R.A. (2023). "A Smart Decision Support Framework for Sustainable and Resilient Supplier Selection and Order Allocation in the Pharmaceutical Industry." *Sustainability* 15, no. 7.

[37]Khan, S.A., Gupta, H., Gunasekaran, A., Mubarik, M.S., Lawal, J. (2023). "A Hybrid Multi-Criteria Decision-Making Approach to Evaluate Interrelationships and Impacts of Supply Chain Performance Factors on Pharmaceutical Industry." *Journal of Multi-Criteria Decision Analysis* 30, no. 1-2: 62-90.

[38]Rezvani, S.M., Almeida, N.M., Falcao, M.J., Duarte, M. (2022). "Enhancing Urban Resilience Evaluation Systems through Automated Rational and Consistent Decision-Making Simulations." *Sustainable Cities and Society* 78.

[39]Santos, C.H., Queiroz, J.A., Leal, F., Montevechi, J.A.B. (2022). "Use of Simulation in the Industry 4.0 Context: Creation of a Digital Twin to Optimise Decision Making on Non-Automated Process." *Journal of Simulation* 16, no. 3: 284-97.

[40]Banks, J. (1999). "Introduction to Simulation." Paper presented at the Winter Simulation Conference.

[41]Anagnostou, A., Groen, D., Taylor, S.J., Suleimenova, D., Abubakar, N., Saha, A., Mintram, K., Ghorbani, M., Daroge, H., Islam, T., Xue, Y., Okine, E., Anokye, N. (2022). "Facs-Charm: A Hybrid Agent-Based and Discrete-Event Simulation Approach for Covid-19 Management at Regional Level." Paper presented at the 2022 Winter Simulation Conference.

[42]Agrawal, T.K., Angelis, J., Khilki, W.A., Kalaiarasan, R., Wiktorsson, M. "Demonstration of a Blockchain-Based Framework Using Smart Contracts for Supply Chain Collaboration." *International Journal of Production Research* (2022): 1-20.

[43]Czinkota, M., Kotabe, M., Vrontis, D., Shams, R. (2021). *Marketing Management*. Chapter 11 - Distribution and Supply Chain Management.

[44]Peng, X., Zhang, X., Wang, X., Li, H., Xu, J., Zhao, Z. (2022). "Multi-Chain Collaboration-Based Information Management and Control for the Rice Supply Chain." *Agriculture* 12, no. 5.

[45]Schieritz, N., Miling, P.M. (2003). "Modeling the Forest or Modeling the Trees - a Comparison of System Dynamics and Agent-Based Simulation." 21st International Conference of the System Dynamics Society, Manheim University.