Data-Driven Optimisation for the Development and Delivery of Personalised Medicine

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Abbreviations

Algorithms

irace Iterated Racing for Automatic Algorithm Configuration

A-MORS Archive Multi Objective Random Search

A-NSGA-II Archive Non-Dominated Sorting Genetic Algorithm II

EMOA Evolutionary Multiobjective Optimisation Algorithm

GA Genetic Algorithm

GVNS General Variable Neighborhood Search

HV hypervolume

MORS Multi Objective Random Search

NSGA-II Non-Dominated Sorting Genetic Algorithm II

R-NSGA-II Reference point based Non-Dominated Sorting Genetic Algorithm II

Countries

EU European Union

UK United Kingdom

USA United States of America

Diseases

ALL acute lymphoblastic leukaemia

DLBCL diffuse large B-cell lymphoma

NHL non-Hodgkin lymphoma cancer

PMBCL primary mediastinal large B-cell lymphoma

r/r refractory or relapsed

Other

CPLEX IBM ILOG CPLEX Optimization Studio

DM Decision Maker

MOO Multi-objective Optimisation

OR Operations Research

Pharmaceutical Legislation and Personalised Medicine

ATMP Advanced Therapy Medicinal Product

C&GT cell and gene therapy

CAR-T Chimeric antigen receptor T-cell therapy

CMC Chemistry, Manufacturing and Controls

CoC Chain of Custody

CoG Cost of Goods

CoI Chain of Identity

FACT Foundation for the Accrediation of Cellular Therapy

FDA Food and Drug Administration

ICER Institute for Clinical and Economic Review

IHME Institute for Health Metrics and Evaluation

IICC-3 International Incidence of Childhood Cancer

NICE National Institute for Health and Care Excellence

PM Personalised Medicine

QA Quality Assurance

QC Quality Control

R&D Research & Development

Problem Formulation

CF cryopreservation facility

CMC Centralised Model Configuration

CU integrated cryopreservation unit

DMC Decentralised Model Configuration

H hospital

h clinic

H^C hospital with integrated cryopreservation

H^M hospital with integrated manufacturing

IMC Integrated Model Configuration

MF manufacturing facility

MU integrated manufacturing unit

Supply Chain

BSC Biopharmaceutical supply chain

FLP Facility Location Problem

HSC Healthcare supply chain

SCM Supply Chain Management

SHO Supply Chain for Substances of Human Origin

SHOB Blood supply chain

SHOO Organ transplantation supply chain

VSC Vaccine supply chain

Abstract

The biopharmaceuticals developed under Personalised Medicine (PM) are the most promising medical treatments of this century, yet their commercialisation on large scale remains sub-optimal. The manufacturing and delivery of advanced therapy medicinal products created for individual patients rather than population groups are highly affected by worsened bottlenecks, such as low global demand, low shelf-lives, or increased product fragility. The current pharmaceutical supply chain configurations are optimised for mass delivery and, hence, they lead to long waiting times and high costs per patient in the delivery of PM, where each product corresponds to one exact patient.

This thesis argues for the immediate necessity of new decision-making frameworks adaptable to the requirements of PM. We compare the bottlenecks encountered in the new personalised medical products to the most common mature supply chains of the healthcare and pharmaceutical industries, highlighting their dissimilarities. We make an initial theoretical contribution by uncovering the need for a new supply chain in light of the rapid clinical developments of personalised medical products.

To address some of these challenges, we focus the rest of the thesis on the strategical level of the supply chain. Considering the expectations of the real-world, we propose several multi-objective mathematical models and solution methods for large scale facility location problems. Our formulations follow both centralised and decentralised networks and aim to find optimal locations for multiple types of interdependent facilities commonly met in the PM supply chain. The models and algorithms proposed are validated using data corresponding to products with current market approval and an estimation of global demand.

The results presented throughout the thesis are consistent with the current motivations and proposed directions of how the PM supply chain should look. We show that the benefits brought by considering PM as standalone and not part of the regulations of the more traditional pharmaceuticals overcome the disadvantages. The development of specialised decision support tools can lead to smaller costs for biopharmaceutical companies, lower delivery times, and overall better global coverage.

This research was in collaboration with an industrial partner, Biopharm Services, who has contributed to validating the mathematical formulations with respect to their practicality for biopharmaceutical companies and have provided part of the data used.

Declaration

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Dedication

To my grandparents.

Chapter 1

Introduction

This chapter will introduce the general background of Personalised Medicine (PM), its main commercialisation challenges, and its position in the context of Operations Research (OR) and Supply Chain Management (SCM) in Section 1.1. The motivation for the PhD project and the research questions are subsequently outlined in Section 1.2, while the overview of the thesis structure is presented in Section 1.3. Since this thesis follows the paper-based format, this introductory chapter concludes with an outline of the publications that resulted from this research and an indication of each author's contribution. The link between the objectives and each of the presented manuscripts is previously shown in Section 1.2.

1.1 Personalised Medicine Biopharmaceuticals

Personalised medicine (PM), also known as precision medicine, is a new healthcare model that acknowledges the inherent differences between patients due to variations in genetic and environmental conditions. This could translate into having lower or higher predispositions to certain illnesses or different reactions to certain medications between individuals or for the same person between two different periods. The focus is thus shifted from treating the disease, which is the prominent approach in the traditional healthcare system, to treating each patient with their individual-specific treatment designed to the patient's exact needs and surrounding factors. The medical treatments, the majority of

which are biopharmaceuticals, developed under personalised therapies have received considerable attention and breakthrough designation[1] strategies due to their ability to treat and even cure life-threatening diseases. These treatments are often used when no other treatment is available or everything has failed.

Personalised biopharmaceuticals are a particular type of Advanced Therapy Medicinal Products (ATMPs). These are medicines based on genes, tissues, or cells, derived from the patient and which, after in vitro manipulation, are administered back to the same individual. The ATMPs market is one of the fastest growing in the medical sector, with a market size value estimated at £7.8 billion, over 1,078 clinical trials globally, and expected to exceed £17.5 billion in the next 5 to 7 years (Grand View Research, 2021), more than half of which are personalised products (Ramezankhani et al., 2020).

The success of the ATMPs is partly due to the promising results highlighted in the past decade for some of the most complex diseases to treat. Examples include neurological and neurodegenerative diseases, such as Parkinson, Alzheimer, or Huntington's disease (Strafella et al., 2018; Rosser et al., 2022), or advanced-stage cancers (Yu et al., 2018). More recently, other applications have been proposed, such as treating COVID-19 (Golchin et al., 2020).

The commercialisation of pharmaceutical products is generally complex. Even though the global market exceeds £1 trillion, the supply chain of medicines is still prone to several challenges that have been extensively studied in OR. A sub-optimal strategic supply chain echelon becomes a significant cause of concern in the novel development of biopharmaceuticals targeted at individual patients under PM. For example, changes in demand patterns or slowed delivery impact manufacturers, hospitals, pharmacies, and

[1] offered to therapies that show in preliminary clinical results that the drug can provide significantly better treatment than the existing ones.

ultimately patients. More extreme scenarios, which will be explained in future chapters, can lead to the inability to provide the treatment to the patient, more often than not, due to the impossibility of recreating the ATMP.

1.2 Motivation and Research Questions

By 2050, it is projected that the number of people over 60 will double, exceeding 2 billion (World Health Organization, 2022), a more rapid increase rate than the overall population. The ageing population will have as a direct consequence an increment in the number of people living with a neurodegenerative disease, the number of seniors that die of Alzheimer, or the number of those affected by dementia-caused diseases, at a rate of 1 in 3 (Alzherimer's Association, 2022). Along the same lines, research around genetic conditions will continue to be an equally important focus in the following years. We are facing a substantial increase in genetic disorders we can identify and ultimately develop treatments for (Claussnitzer et al., 2020).

PM is currently the most promising line of research that can help not only with symptom alleviation or long-term treatments, leading to a cease of disease progression, but to complete cures and even regression of the illness. Successful cases have supported the above statement in different types of blood cancer (Micallef et al., 2022). Nonetheless, it has been repeatedly emphasised that the economic hurdle brought by the ATMPs, should they remain at the same costs, would exceed the medical reimbursement power of many countries. Consequently, regardless of their clinical potential, the ATMPs will not go beyond the accepted applications of last-case scenario therapies.

This thesis then aims to answer the key research question of **how the PM supply chain strategic level, focusing on facilities locations, can be modelled to lead to**

cost-effective, timely, and globally available personalised ATMP treatments.

The overarching problem addressed in this research was pursued along the following objectives:

1. Identify the similarities and differences between the main characteristics of the PM strategic supply chain and those of more mature healthcare networks, namely SHOB, SHOO, VSC, and HSC. **[Chapter 3]**

2. Develop a mathematical model and solution method for the centralised PM supply chain, and solve a large scale real-world case study of approved personalised ATMPs. **[Chapter 4]**

3. Extend the mathematical model of the centralised supply chain to account for the facility locations and decide on the facility-specific mode of production accounting for time, cost, and failure rates. [**Chapter 5**]

4. Understand the relationship between the different facility types and how these affect optimisation. In the ATMPs supply chain, alongside a production facility, there is the possibility to use helper facilities that can deal with some constraints, such as short shelf-life. Each facility will have characteristics that will influence one or more objectives. [**Chapter 5**]

5. Test the impact of different levels of decentralisation in terms of time, cost, and patient travel time. **[Chapter 6]**

6. Create a preference-based stage-wise approach that separates the above-formulated problems into smaller, independent parts, allowing the DM to interactively control the optimisation process and the configuration of the supply chain. **[Chapter 7]**

1.3 Thesis Structure

This thesis is structured following a journal format, consisting of standard chapters (Chapters 1, 2, and 8) and paper-based chapters (Chapters 3, 4, 5, 6, and 7). Since these chapters are self-contained papers, there is some repetition throughout the thesis, mostly related to the literature review and the supply chain configuration. Since the PM supply chain, as defined in this research, is not commonly known to the targeted audience, parts of it are explained in each chapter.

Chapter 1 is an introduction to PM and briefly discusses its supply chain, highlighting the thesis' motivation and research questions. It provides an overview of the thesis structure (Section 1.1) and the publications that resulted from it.

The aim of Chapter 2 is to establish the scope of the project and present the roadmap of the thesis, and the lack of mathematical formulations (Sarkis et al., 2021b) and solution methods for Facility Location Problems (FLPs) in the context of personalised ATMPs. An in-depth introduction to personalised therapies reveals a significant distinction between these products and other advanced therapies. The importance of supply chain optimisation for PM is further underlined and discussed in a brief overview of the development journey. Following this, we discuss the commercialisation challenges faced by personalised products and the existing decisional tools. Any published papers resulting from the research presented here have not been included in the analysis covered in this chapter.

Chapter 3 is a theory-focused chapter that distinguishes between the existent research in other healthcare supply chains and PM. It emphasises that even though there are shared characteristics between the different network configurations at the strategic level, none of the existing models can fully capture the challenges of a high level of personalisation in a time and temperature-sensitive biopharmaceutical network. As the primary target

audience of this research could be policymakers and companies in the pharmaceutical industries, literature that could be tangentially relevant, such as the make-to-order supply chains that are not part of the healthcare sector, was intentionally excluded.

Chapters 4 and 5 present the different mathematical formulations and their corresponding solution methods following the current centralised supply chain configuration used in the pharmaceutical industry, adapted to PM. The problem is formulated as multi-objective and solved using problem-specific initialisations and evolutionary algorithms. The objectives of interest are overall cost and average delivery time per patient minimisation and maximisation of the total hospitals' coverage. Chapter 4 shows some preliminary results using a small-scale case study following the demand of the USA. The USA was chosen as the country of reference as it has the highest number of hospitals and research institutes that can provide ATMPs. Chapter 5 extends the results previously found with an estimated global level demand for two case studies. We introduce multiple initialisation procedures and use automatic algorithm configuration with *irace* to find the best set of parameters for the problem. The overarching scope of this chapter is also to understand the interdependencies of the two facility types used and explain their role in a corresponding FLP.

Chapter 6 brings attention to the limitations of a centralised configuration in the context of PM and introduces possible extensions with a more decentralised network. The chapter extends the previously presented research and introduces more exhaustive, integrated and decentralised supply chain configurations. We then compare the models following the values of three objectives and the change in the decision space. In addition to the previous chapters, one of the objectives here is modified to reflect on the ethical concerns that might arise around partial hospital coverage.

Chapter 7 presents the importance of the DM in the optimisation process. We propose

a framework that allows the DM to easily create different supply chain configurations accounting for various levels of decentralisation. This approach ultimately leads to a flexible algorithm based on the preferences of the DM. We also divide the problem into smaller parts by reducing the number of decision variables optimised at once. Using an automatic parameter tuning tool, we show that the different facilities have unequal importance in optimisation.

Chapter 8 concludes the thesis with a summary of the research contribution, its limitations and the perspectives for future work. The thesis structure is also summarised in Figure 1.1.

1.4 Publications Resulting from the Thesis

CRediT author statement:

Andreea Avramescu: Conceptualization, Methodology, Software, Validation, Data curation, Writing - Original Draft, Visualization, Project administration.

Richard Allmendinger: Conceptualization, Methodology, Writing - Review & Editing, Supervision, and Project administration

Manuel López-Ibáñez: Conceptualization, Methodology, Writing - Review & Editing, Supervision, and Project administration

Adriana Lopes: Data curation, Methodology, Writing - Review. She also provided insights concerning the industry on behalf of Biopharm Services about the main constraints, objectives, and feasibility of the supply chain configurations applied in the papers.

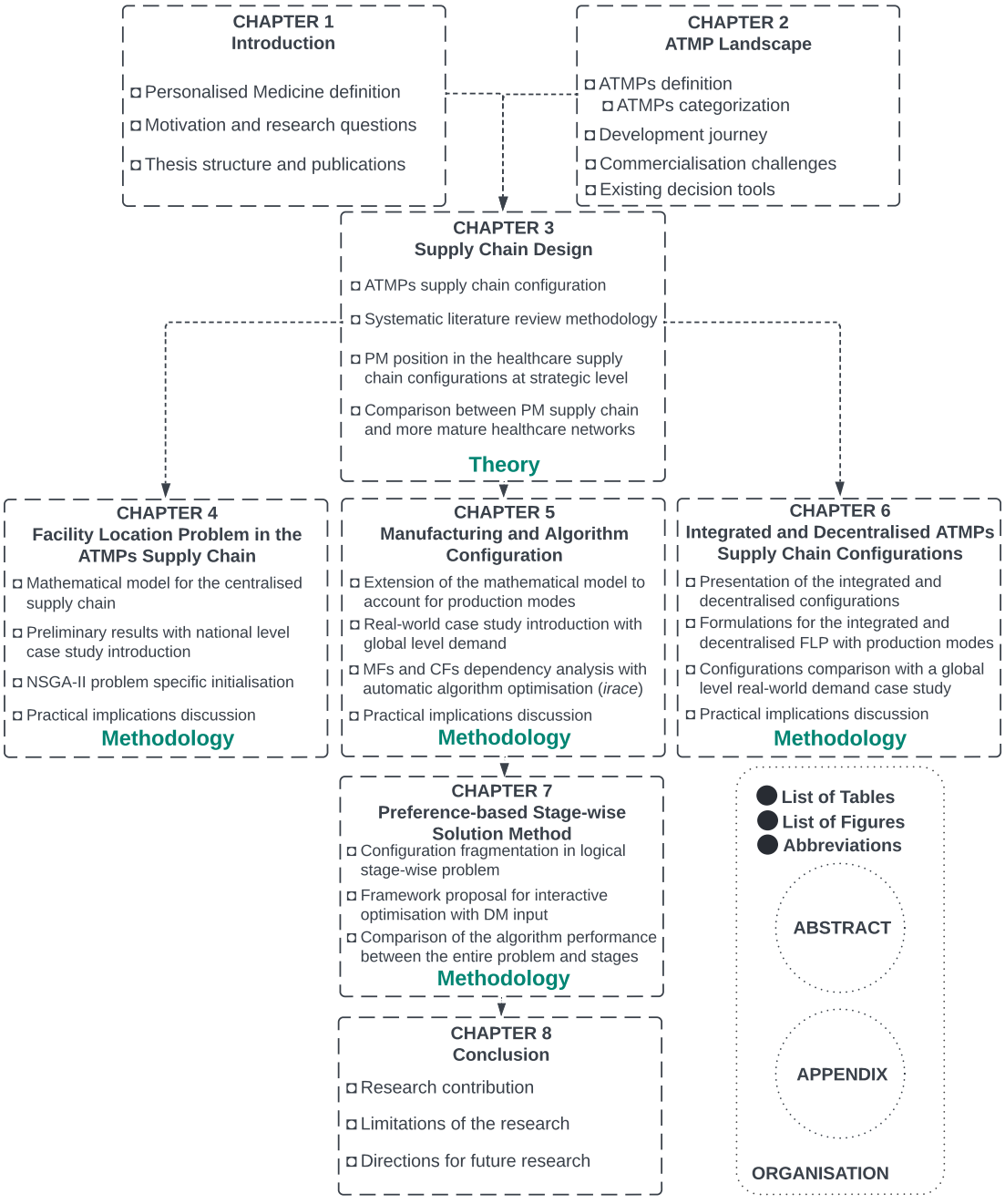


Figure 1.1: Thesis structure.

Journal Papers

[*Manuscript 1, Chapter 3*] A. Avramescu, R. Allmendinger, and M. López-Ibáñez. **Managing Manufacturing and Delivery of Personalised Medicine: Current and Future Models**. To be submitted.

[*Manuscript 3, Chapter 5*] A. Avramescu, R. Allmendinger, and M. López-Ibáñez. **Multi-objective Optimisation for Personalised Medicine Centralised Supply Chain**. To be submitted.

[*Manuscript 4, Chapter 6*] A. Avramescu, R. Allmendinger, and M. López-Ibáñez. **A Comparison between the Centralised, Integrated, and Decentralised Personalised Medicine Supply Chain Configurations**. To be submitted.

Conference Papers

[*Manuscript 2, Chapter 4*] A. Avramescu, R. Allmendinger, and M. López-Ibáñez. **A multi-objective multi-type facility location problem for the delivery of personalised medicine**. In P. Castillo and J. L. Jimenez Laredo, editors, *Applications of Evolutionary Computation*, volume 12694 of LNCS, pages 388–403. Springer, Cham, Switzerland, 2021. doi:10.1007/978-3-030-72699-7-25

[*Preliminary work, Chapter 7*] A. Avramescu, R. Allmendinger, M. López-Ibáñez, and A. Lopes. **Composite Facility Location Problems: A Case Study of Personalised Medicine**. In M. Chetty, J. Hallinan, S. Lim, A. Shatte, and C. Foale, editors, *19^{th} IEEE International Conference in Computational Intelligence in Bioinformatics and Computational Biology*. IEEE, 2022. doi:10.25955/1a39-wk54

[*Manuscript 5, Chapter 7*] A. Avramescu, M. López-Ibáñez, R. Allmendinger. **Interactive Stage-Wise Optimisation of Personalised Medicine Supply Chains**. In *Applications of Evolutionary Computation: 26th European Conference, EvoApplications 2023*. doi:10.1007/978-3-031-30229-9_46

Conference Abstracts and Short Papers

[*Preliminary work, Chapter 6*] A. Avramescu, R. Allmendinger, M. López-Ibáñez, and A. Lopes. **Towards a Holistic Supply Chain Model for Personalised Medicine**. In M. Chetty, J. Hallinan, S. Lim, A. Shatte, and C. Foale, editors, *18th IEEE International Conference in Computational Intelligence in Bioinformatics and Computational Biology*, Supplemental Proceedings of Short Papers, pages 5–6. IEEE, 2021.

[*Preliminary work, Chapters 4, 5, and 6*] A. Avramescu, R. Allmendinger, M. López-Ibáñez. **An analysis of the facility location problems in personalised biopharmaceuticals**, 2022. In *Proceedings of the 34th European Conference of Operational Research*.

Tutorials

[*Thesis overview, particularly Chapter 3*] A. Avramescu, R. Allmendinger, M. López-Ibáñez. **Personalized medicine: Introduction + Supply chain challenges + Optimization methods**, 2022. Part of the *19th IEEE International Conference in Computational Intelligence in Bioinformatics and Computational Biology*.

Chapter 2

Personalised Medicine Industry

The main focus of the research presented in this thesis is on personalised medical therapies. However, they are part of the broader spectrum of advanced medical products. While the supply chain of the personalised therapies will be described throughout the thesis, this chapter distinguishes between the different product types (Section 2.1) in terms of their development journey (Section 2.2) and their respective commercialisation (Section 2.3). As we move forward to analyse only the problem of facility location, we now give a brief overview of the existing decisional tools that can be used to optimise other aspects of the ATMP supply chain (e.g., manufacturing, supplier selection, scheduling) and how these could be integrated with the work presented here (Section 2.4).

2.1 Product Types

The ATMPs can be separated by the origin or type of the starting material, in allogeneic or autologous, and into cell therapies, gene therapies, cell and gene therapies, and tissue engineering, respectively.

Allogeneic therapies have as starting point a healthy donor. The donor can be unrelated to the patient, and the cells collected from one individual can be used to produce large batches and ultimately used to treat multiple patients. In other words, they follow a one-to-many model by relying on one collection source for creating multiple

batches of treatment (Farid and Jenkins, 2018). They can thus rely on an "off-the-shelf" supply model where the resulting product can be stored and used later. A major advantage of this technique is the possibility to use the ATMP as an emergency treatment. Nonetheless, this is not the case as most ATMPs is only partially used as a last resort treatment due to their high costs. In addition, while considered revolutionary therapies, the ATMPs can lead to significant side effects, which would be hard to control in a non-standard environment.

The advantages of allogeneic products are also brought by administering multiple doses over time. As multiple batches are created and stored, a patient journey looks similar to the traditional biopharmaceuticals, where the supervision of disease progression is continuous and additional treatments are prescribed (Depil et al., 2020). Nevertheless, an allogeneic medical product, organ transplantation or advanced therapy is always prone to rejection. An allorejection happens when an organism can distinguish between its tissue or cells and those of a foreign nature (Boardman et al., 2016). While medication to counter is continuously developed and constitutes an important research topic, a rejection can preclude a patient from getting similar treatment in the future or getting a lower dose (Caldwell et al., 2021). From a clinical perspective, increased persistence would be preferred to multiple administrations (Caldwell et al., 2021).

Autologous therapies have become an appealing alternative as they can alleviate the above concerns. As a result, the industry has shaped its interests towards developing more autologous than allogeneic therapies. For example, in Europe, for the past six years, more than 70% of the clinical trials for cell therapies (a type of ATMP) are autologous (Figure 2.1). Autologous products are derived from the patient himself. Instead of collecting cells from a healthy donor, the starting material is collected from the patient, and then, after ex-vivo processing, it is returned to the same patient in the form of an

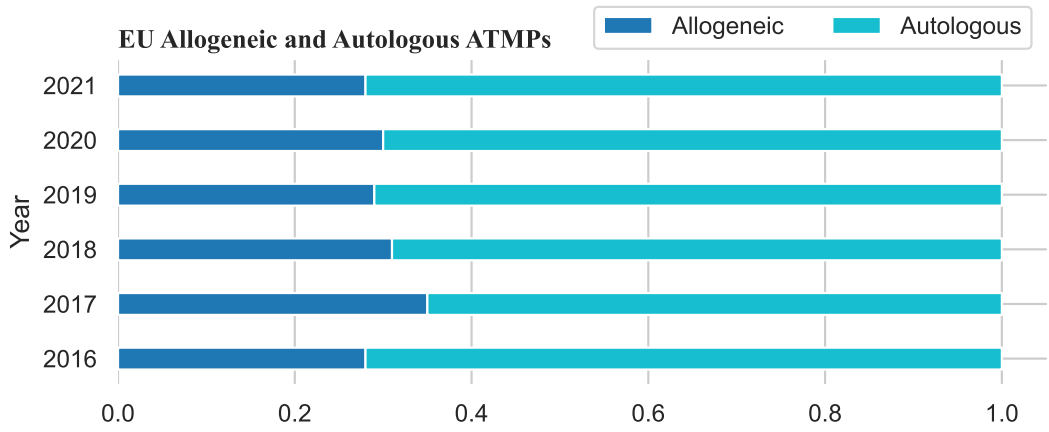


Figure 2.1: Allogeneic and autologous ATMPs in Europe. The data is obtained from the *Cell and Gene Therapy Catapult ATMP Clinical Trials Database 2021 (Catapult, 2021).*

ATMP. As a result, any risk associated with alloimmunization is avoided.

Nevertheless, it follows a one-to-one model where each product can only be used for one person without the possibility of an off-the-shelf supply model or long-term storage. A follow-up administration would then require creating a new product entirely (involving a new cell collection process). Despite this limitation, it was found that an autologous ATMP can remain viable for a considerably more extended period compared to an allogeneic product; patients were found to be in remission years after the initial administration (Maude et al., 2014).

The ATMPs of interest in this research is the fully personalised products (i.e., autologous). The following sections will briefly describe the allogeneic supply chain and development journey to compare and contrast with the autologous products.

Following the European Union (EU) regulations on ATMPs, these can be categorised into C&GTs (including cell therapies and gene therapies) and tissue engineering (The European Parliament and the Council of the European Union, 2007). Tissue engineering,

even though primarily these products have tissues as starting materials, they are sometimes derived from cells and genes and constitute the branch of ATMPs aiming to repair, regenerate or replace damaged human tissue. Important application areas were recorded in organ development (Mandrycky et al., 2017) and nerve and vascular grafts (Li et al., 2021; Kurobe et al., 2012). The global market size for tissue engineering is considerable and was estimated to be £8.2 billion in 2019, with over 14.7% compound annual growth, and is expected to surpass £24.6 billion by 2027 (Grand View Research, 2020). However, as tissue engineering is usually discussed under the umbrella of regenerative medicine rather than personalised, the case studies and supply chain design particularities referred to throughout Chapters 3 to 7 use C&GTs.

Cell therapy and gene therapy are overlapping fields. Unlike tissue engineering, they aim to treat or cure diseases that have an underlying genetic cause[1], but have also been successfully used to treat rapidly progressive diseases. The C&GTs account for the majority of the ATMPs (Figure 2.2). C&GTs has received extraordinary attention from researchers, clinicians, and patients due to their remarkable results in treating advanced diseases and illnesses with no previous cure, such as last-stage cancers (Singh and McGuirk, 2020). Moreover, their popularity was increased by showing potential in treating neurodegenerative diseases like Parkinson's and Alzheimer's in late clinical trials (Hitti et al., 2019). In light of their potential, rapid expansion in the past years, and hurdles for companies from a manufacturing and delivery perspective, the case studies of approved C&GTs were preferred when testing the proposed models and solutions methods presented throughout the thesis.

Finally, the in-vivo ATMPs, where the gene is delivered to the patient, usually through

[1]Genetic diseases are caused by one or multiple mutations, defined as changes in the DNA structure by substitution, depletion or duplication of genes.

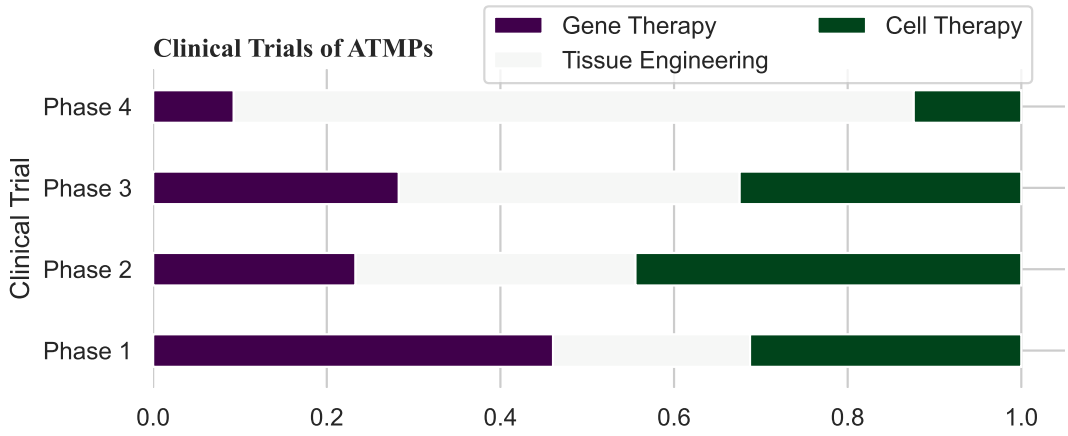


Figure 2.2: Clinical trials by phase for gene therapies, cell therapies, and tissue engineering ATMPs. The data is obtained from the *Cell and Gene Therapy Catapult ATMP clinical trials database 2021 (Catapult, 2021).* The *x-axis* shows the standardised values between 0 - 1 and indicates the relative number per ATMP type in each of the four clinical trials.

a virus without ex-vivo manipulation, is not considered. Their supply chain is strictly linked to the method of administration and its processing rather than the patient's cells, making it outside this research's scope.

2.2 Development Journey

The journey to the patient of a pharmaceutical or biopharmaceutical product is lengthy, complicated, and usually a costly process. A product becomes widely available to patients once it has obtained market authorisation. This dictates the designation for which the particular treatment can be used and usually needs to be brought in each country or region individually. The approval is obtained after three clinical trials have been successfully passed, as follows:

Phase 1: testing of the product's safety, including any potential side effects and any

other way the treatment can affect the body. The dose, number of treatments required, and the administration method are also covered.

Phase 2: administration of the drug to a higher number of patients and continuing to assess the effectiveness and safety of the drug.

Phase 3: administration of the product to a sample of a few thousand patients, continuous assessment of its safety. In addition, a comparison with other existing treatments for the same targeted disease is also conducted wherever possible.

Unlike traditional pharmaceuticals, the autologous ATMPs can have a faster development process. Most of the time, this is either because of a lack of available treatments to market, the impossibility of testing the product on healthy individuals in Phase 1, or their high clinical potential. The diseases targeted by the ATMPs make it inefficient and potentially dangerous for the treatment to be tested on healthy individuals. As a result, since patients are already involved in the first clinical trial, the efficiency and safety of the product can be assessed at this stage, and hence it is common for Phase 1 and Phase 2 to be conducted concomitantly.

An additional bottleneck in the patient sample is dictated by, to date, an ATMP that can only be offered as a potential medication after at least two lines of treatment have already failed (assuming treatment is available). Alongside the rare conditions, this leads to deficient global demand. As a result, biopharmaceutical companies are granted the option to apply for special regulatory approvals (Seimetz et al., 2019), such as orphan or rare disease and breakthrough designation. An orphan drug can be understood as a medical product whose designation target is a population small enough that it would not be profitable for the company to manufacture and deliver the drug without public and governmental assistance. The breakthrough designation is primarily used in the USA and

offered by the Food and Drug Administration (FDA). This recognises the potential of the therapy to treat life-threatening conditions, and preliminary results might be considered for expediting the drug authorisation to commercial use. Most of the ATMPs currently have market authorisations offered either one or both of the above exceptions. It is thus normal for the three-stage clinical phases to shift to only one or two phases.

The expedited clinical trials, in most cases, lead to a conditional marketing authorisation (The Commission of the European Communities, 2006). In the EU, the approval is only offered for one year, at the end of which, a new application for renewal needs to be made. In the one-year time frame, the authorisation holder (usually a biopharmaceutical company) must fulfil a series of obligations. The conditions imposed on companies are not entirely known, but in most cases, it is linked to providing additional data to support their medical benefit (Hoekman et al., 2016). Despite the potential to obtain faster market approval, the commercialisation issues met in the autologous ATMP supply chain are many, most of which have not been previously met in a healthcare network. Alongside meeting the yearly renewal requirement, the scale-up of the production has turned out to be difficult for most biopharmaceutical companies offering any personalised product.

2.3 Commercialisation Challenges

Commercialisation challenges of autologous ATMPs are partly due to the novel technologies they use for manufacturing and a high level of personalisation in a complex healthcare supply chain, which lead to issues related to high costs and reimbursement refusals.

A series of factors determine how an ATMP is processed through clinical trials and later on for commercial use. Usually, the main drivers are cost and turnaround time. The

manufacturing cost directly influences the product's price and includes the operational and running costs of materials, equipment, personnel, and facilities. Decisions such as the level of automation used to influence the production time and ultimately contribute to the waiting time for the patient. The persons treated with ATMPs are, in most cases, in a poor health conditions, and the time between cell collection and product administration is critical. The production duration and cost of an ATMP can then depend on how this is manufactured. Different production modes have been proposed in the literature (e.g. Lopes et al. (2020)); however, no research has so far looked at understanding the trade-off between these two objectives (i.e. cost and duration).

The patient's health condition is also creating the issue of product variability, which was not previously encountered to this extent in the pharmaceutical industry. Usually referred to as "the product is the process", each ATMP will have a certain quality and efficiency due to the variable condition of the cells of each individual (Heathman et al., 2016). For example, Novartis, the owner of the first approved C&GT, has struggled to maintain a low variability between the products, mentioning that the requirements in commercial production are more severe than in clinical trials (Southey, 2018). Moreover, by relying on the patient for the starting material, the success of the manufacturing of each product becomes critical, as a separate cell collection might not be possible.

Unlike allogeneic products, the quality control process also becomes labour intensive as each batch needs to be tested individually (Radrizzani et al., 2016). The level of automation used could then be a driving factor of whether an ATMP passes the efficiency requirements. While a high level of automation could lead to lower variability due to the small involvement of staff is preferable, the high price of setting up such a system can be economically inefficient in areas with low demand. Thus, a facility dependent production mode, which would allow the facilities with small demand to have a lower

construction cost, might be favoured compared to a supply chain wide mode. There is currently no available framework that could analyse whether the difference in demand (which is usually small in autologous ATMPs) is enough to justify the facility-based production mode in PM.

Allogeneic products imply an off-the-shelf business model, whereas autologous are service-based, which raises further questions about the design of the supply chain alongside production mode, and whether the configuration should follow a centralised or decentralised environment. The companies are now more prone to partnering with regional companies, such as the recent extension of Novartis in Asia C&GT (Keenan, 2022), which could potentially make decentralisation more appealing. Outsourcing is a relatively unusual approach for Big Pharma companies, which generally have comprehensive in-house Chemistry, Manufacturing and Controls (CMC) protocols. Outsourcing thus becomes a fundamental part of the biotech business, as ensuring large-scale development capabilities is a high priority in maintaining commercialisation abilities.

Supply chain management is also one of the key challenges in autologous ATMPs. The products cannot be scaled-up but rather scaled out where the focus is on expanding the capability of parallel processing (Gastelurrutia et al., 2021). The high Cost of Goods (CoG) and the need for fast manufacturing and logistics have led to the need to rethink the facilities' design and strategic locations. The centralised supply chain is inefficient as, unlike allogeneic products where the products can be stored (Abbasalizadeh et al., 2017), the process is continuous in this case. Once the product is manufactured, it is returned directly to the patient. The discussion around decentralisation has been proposed as an alternative (Harrison et al., 2018b,a). Constructing regional manufacturing centres or even integrating them at or near hospitals with high demand could decrease the supply chain's start-to-end duration, reduce the risks associated with transportation in an ultra

cold supply chain and reduce logistical costs. Nevertheless, more production sites usually translate to a higher risk of process variability. Increased efforts have been made towards developing automated and closed equipment, leading to more consistent production and reducing the risk of cross-contamination between the ATMPs. Theoretical debates and small case studies of whether a centralised or decentralised scenario would be a better alternative were proposed. Nevertheless, no optimisation framework that could generate a demand based supply chain network for specific ATMPs characteristics is yet widely available.

The final price of an ATMP can range from £310.000 (Yescarta®) - £395.000 (Kymriah®) to £2.3 million (Zolgensma®) - £2.9 million (Hemgenix®). The biotech companies argue that high prices lead to cost savings for the healthcare system since most of these products are a one-time treatment, eliminating the need for continuous supervision and ongoing regular interventions (Dean et al., 2021). Authorities responsible for the evaluation of the cost-effectiveness of these therapies, such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) and the Institute for Clinical and Economic Review (ICER) in the USA, are finding it difficult to approve reimbursement strategies and funding applications given the lack of historical data and proven market success and the continuous variability between each product. The cases of Provenge® and Glybera® are two of the prominent examples of ATMPs that, despite their clinical potential, were withdrawn from the market for not achieving costs to prove their commercial viability. Moreover, both NICE and the German health authorities declined the request of Zynteglo® for reimbursement, concluding that the £1.5 million price is not justified and supported by sufficient data (Federation, 2021; Pagliarulo, 2021).

2.4 Existing Decisional Tools

Decision-making refers to the process in which a decision needs to be reached by evaluating various factors that could influence the issue of interest. In supply chains, the decision-making process is complex and happens at all levels of the network. The decision-support tools or decisional tools are then commonly used in the biopharma sector to aid in assessing the feasibility of their strategy (e.g. Lim et al. (2005), Farid et al. (2005), Vieira et al. (2019b), Shirahata et al. (2019), Zürcher et al. (2020)), usually starting from the pre-commercialisation period. Identifying and mitigating potential problems that could endanger the route to market authorisation for a product is highly important in light of the substantial Research & Development (R&D) investment, often in the order of billions of dollars.

As expected, more decision tools for allogeneic products were developed than for autologous. On the one hand, this is a result of their earlier market approval. With few exceptions, most of these tools focus on the decision related to the manufacturing process. The lack of supply chain optimisation is partly due to the very similar configuration of allogeneic ATMPs to the traditional biopharmaceuticals. Nevertheless, important decision tools have moved the production of these therapies further. Simaria et al. (2014) and Hassan et al. (2015) were among the first to develop a decisional tool that aims to find the most optimal process flowsheet that leads to be lowest CoG. The development timeframe of interest in both studies is early clinical trials, consistent throughout the other academic and industry research. The CoG reduction in the manufacturing flowsheet of early development has received considerable attention, and a substantial number of decisional tools were developed. At later stages, the issues related to the reimbursement procedures were important driving factors for the need for particular decisional tools

able to estimate the CoG when different raw materials for manufacturing were used (e.g., Hassan et al. (2016); Jenkins and Farid (2018); Chilima et al. (2018)). A more detailed review of the existing decisional tools related to regenerative medicine manufacturing was created by Lam et al. (2018).

The number of decisional tools concerned with the production facilities is sparse for autologous ATMPs, despite the sub-optimal usage of the existing tools. A few papers analysed the impact of the geographical location of manufacturing facility (MF) using a scenario-based approach. At the same time, to the best of our knowledge, there is no such research around cryopreservation facility (CF) outside of the modelling presented in this thesis. Harrison et al. (2017) were among the first to raise the issues related to the location of production of ATMPs and its impact on the patients and the supply chain cost. They further continued their research and looked at understanding the differences between centralised and decentralised production for ATMPs in the UK (Harrison et al., 2018a), while Harrison et al. (2019) analysed the impact of offshore and onshore production in terms of transport, labour availability and facility costs in the USA, with potential production in Argentina and Mexico. Their conclusions are along the same lines with Lam et al. (2021) who, also using a UK demand-based case study, found that an increase in the geographical area of demand leads to a higher need for decentralisation; a centralised model is only efficient in small geographical areas.

The only decisional tools concerned directly with the optimisation of the facilities location in an autologous supply chain focused either only on MFs in a small case study (e.g. Wang et al. (2018b), Moschou et al. (2020)) or mobile medical units (e.g. Karakostas et al. (2020)). Nonetheless, the need for such models has been repeatedly highlighted (Sarkis et al., 2021b; Lam, 2021), and the research presented in this thesis aims to contribute towards the collective effort of providing decision support tools for

the facility location of autologous ATMPs.

Chapter 3

Supply Chain Design of Autologous ATMPs

3.1 Abstract

With almost 50% of annual commercial drug approvals being PM and its huge potential to improve quality of life, this emerging medical sector has received increasing attention from the industry and medical research, driven by health and care services, and us, the patients. Notwithstanding the power of ATMPs to treat progressive illnesses and rare genetic conditions, their large-scale delivery is still problematic. The biopharmaceutical companies are currently struggling to meet timely delivery and, given high prices of up to $2 million per patient, prove the cost-effectiveness of their ATMP. Consequently, in most cases, ATMPs is used as a last resort. ATMPs is at the intersection of multiple healthcare logistic networks, and due to their novelty, research around their commercialisation is still in its infancy from an operations research perspective. To accelerate technology adoption in this domain, we characterise pertinent practical challenges in a PM supply chain at the strategic level. The identified challenges will be contrasted with the literature on related supply chains regarding model formulations and suitable optimisation methods. Finally, needed technological advancements are discussed to pave the way to affordable commercialisation of PM.

3.2 Introduction

It is widely accepted that traditional pharmaceuticals are efficient for approximately 60% of the population only (Ermak, 2016). The "one-formula-fits-all" drugs and the currently reactive healthcare approach are following a trial-and-error prescription of medicines by having its primary focus on the disease rather than the patient (Agyeman and Ofori-Asenso, 2015). However, the past decades have seen increased interest in understanding patient variability. Evidence is being accumulated supporting that an organism's response to drugs is driven by genetic, environmental, and social conditions (Vogenberg et al., 2010). Among other factors, it was this evolution of pharmacokinetics ("what the body does to the drug") and pharmacodynamics ("what the drug does to the body") that allowed medical researchers to discuss new treatments and develop dedicated approaches known under the umbrella term of PM (Morse and Kim, 2015). With a thriving popularity in an industry that exceeds $250 billion worldwide (Moorkens et al., 2017), the advancement of innovative therapies in the medical sector has been rapid. By 2030, approximately 50,000 people could be treated yearly with over 60 approved treatments (Quinn et al., 2019).

Notwithstanding the potential of PM to treat and even cure patients where all other forms of treatment have failed, the number of individuals that had benefited from a personalised therapy is negligible (Meij et al., 2019). The delivery and development of PM treatments is still problematic. The current state of play is that simulation and optimisation of PM delivery relies heavily on models borrowed from the biopharmaceutical field. The PM therapies, known as personalised ATMP, are, however, complex and driven by a different set of constraints, forcing the pharmaceutical industry to rethink the development, manufacturing, and delivery of the products from a mass production,

off-the-shelf approach to a batch and on-demand model (Trainor et al., 2014). Without significant manufacturing and supply innovations in both the physical and digital space, the promise of targeted healthcare will remain accessible only on a small scale (Elverum and Whitman, 2019). From an operations research perspective, the field's novelty calls for extensive research and the implementation of holistic models.

ATMPs could be formally placed at the junction of multiple supply chains: those that support biopharmaceutical products and those that support the Supply Chains for Substances of Human Origin (SHOs), namely blood transfusions and organ transplantation (Rutherford et al., 2017). Critical concerns in the ATMPs, such as shelf life, patient stratification, and uncertain supply and demand, are also some of the principal bottlenecks of the SHOs supply chains. However, ATMPs have a distinctly fragile composition and, in most cases, are impossible to replace due to the advanced stage of a patient's disease. In addition, the responsive nature of PM acknowledges each person's characteristics as a clear indicator of how the treatment should be applied (Chouchane et al., 2011). In this sense, the patient has increasingly started to be active in the treatment and is now an integral supply chain factor. Unlike the more common biopharmaceuticals, in a personalised ATMP scenario, the individual's health condition is directly influencing the scheduling of the product, with the patient becoming one of the suppliers of raw materials and the main customer of the final product (Abou-El-Enein et al., 2016). All these lead to high costs and complex manufacturing processes, forcing these medicines to be used only as a last resort.

Despite its differences with other mature healthcare supply chains, ATMPs can also benefit from operations research and management perspectives by developing models capable of optimising the products. Hence, this paper presents the most common challenges the ATMP supply chain faces. The need for extensive reviews incorporating

literature from different fields to understand the potential impact of healthcare operations management has also been highlighted as a research priority by Kc et al. (2020).

The rest of the paper is structured as follows. Sections 3.3 and 3.4 describe the current PM landscape and its supply chain. The methodology for the systematic review is outlined in Section 3.5. The PM supply chain and its general integration in the wider field of healthcare supply chains are described in Section 3.6.1, while the complete literature review is presented in Section 3.6. Subsection 3.6.3 identifies gaps in the literature of the PM supply chain. The paper ends with a conclusion and directions for future research in Section 3.7.

3.3 Personalised Medicine Landscape

By 2020, there were 42 ATMPs approved to the market (Eder and Wild, 2019) and over 2,000 ongoing clinical trials in Europe alone (Alliance for Regenerative Medicine, 2019), becoming one of the fastest growing areas of the pharmaceutical industry. The rapid progression is unlikely to cease in the foreseeable future, given the ability of novel therapies to cure rare and genetic conditions. Namely, there are only 8% of the orphan diseases — a disease that affects approximately less than 200,000 people worldwide (Aronson, 2006) — that had at least one drug approved at the beginning of 2018 (Seoane-Vazquez et al., 2019).

The shift towards personalisation has important implications for patients and healthcare executives (Betcheva et al., 2020) and the general population. From a social sustainability perspective, personalised therapies have the potential to minimise the growing resistance of certain diseases to antibiotics and can potentially lead to their eradication (Moser et al., 2019). From an environmental perspective, the ATMPs can lead

the generally unsustainable pharmaceutical supply chains towards zero waste (Pastorino et al., 2021). As a result, breakthrough ATMPs have attracted the interest of researchers and scientists and the public's and government's attention. Through investments in projects such as The Precision Medicine Initiative in the USA (Collins and Varmus, 2015) and HORIZON2020 in Europe (Nimmesgern et al., 2017), PM has become one of the healthcare research priorities.

However, the current approach to the commercialisation of ATMPs has led to major challenges for some companies, such as the cases of Provenge (Jarosławski and Toumi, 2015) and ChondroCelect (Abou-El-Enein et al., 2016), or to lower quality treatments (Bersenev and Kili, 2018). The ATMP's are among the most expensive medical treatments. Their price tag is a reflection of (i) the high development cost through the clinical stages and up to commercialisation and (ii) the high manufacturing and delivery costs, given a low global demand and the need for cold chain logistics, i.e., temperature-controlled supply chain (Abou-El-Enein et al., 2016).

One of the most popular classes of ATMPs in the past few years has been the Chimeric antigen receptor T-cell therapy (CAR-T) therapies. With the first market authorisation in 2017 for paediatric patients with acute lymphoblastic leukaemia (ALL), it has since seen an increase in both products and treatment designations. The manufacturing locations of USAs worldwide are scarce. Novartis, the manufacturer of Kymriah, has the largest geographical network for CAR-Ts with five sites in New Jersey (USA), France and Switzerland, and via contract companies in Germany, and Japan (Stanton, 2020). The locations of the manufacturing sites are dictated not only by global demand but also by manufacturing authorisations. Given the lack of historical data, these authorisations are difficult to obtain. The ATMPs cost between a few hundred thousand and a few million dollars, so many countries are reluctant to offer market approval. For example, Kymriah

is currently the only CAR-T that is approved in Asia; Yescarta, the second biggest CAR-T with market authorisation has only three manufacturing sites in California and Maryland (USA), and the Netherlands (Hargreaves, 2020).

3.4 ATMPs Supply Chain Configuration

The generic supply chain configuration for autologous ATMPs is graphically presented in Figure 3.1. It starts with material collected from the donor (allogeneic process) or the patient (autologous process) through an apheresis procedure for products with blood as starting material or a biopsy for products using solid tumours. Through leukapheresis, components, such as plasma or white blood cells, are separated and stored in a special container, while the remainder of the blood is returned to the patient. These procedures can only be conducted at candidate hospitals that have obtained FACT approval. The collected product is then transported to a MF where it is genetically modified (Pörtner et al., 2018). Hence, finding optimal locations for the manufacturing facilities to optimise the delivery of the products is the first step in the supply chain network design.

Facility location problems have been studied extensively in the literature. However, the products' sensitivity to temperature variations challenges the ATMP delivery. Using living cells, the entire process until the ATMP is returned to the patient has a short shelf-life, from a few hours to a few days, depending on the product type. Therefore, transportation is commonly done within a cold supply chain between $-60°C$ and cryogenic temperatures. Freezing the material extends the preservation time frame and allows for off-the-shelf distribution, especially important for allogeneic products, relaxing the time constraints (Rafiq et al., 2017). Cryopreservation cannot always be conducted at the hospital, and it could be undertaken at an independent facility. These facilities

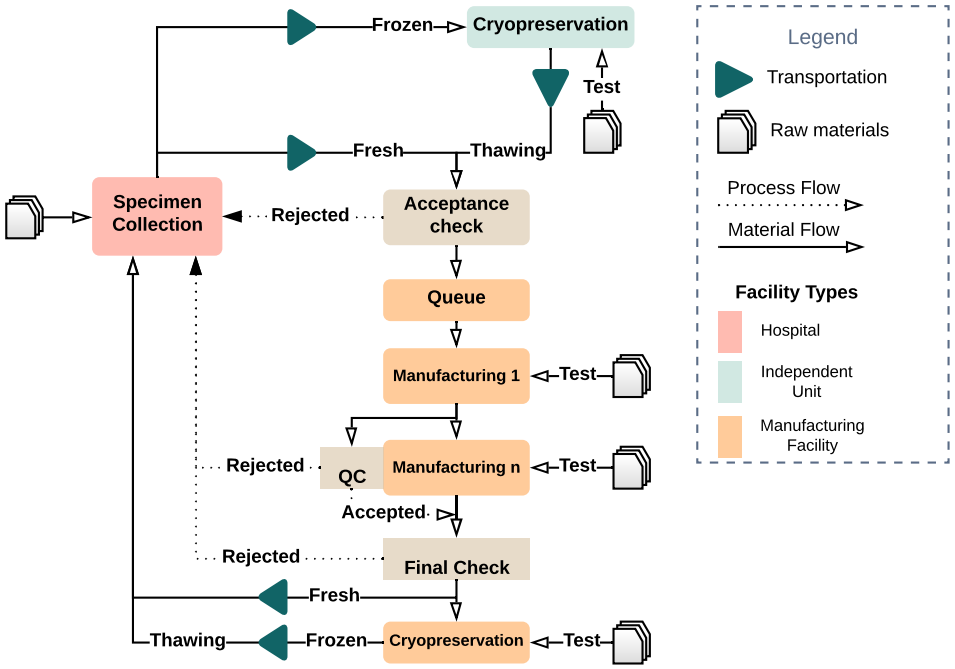


Figure 3.1: Schematic flowchart of the autologous supply chain for an ATMP, including independent cryopreservation unit, manufacturing steps, and failure possibility.

are relevant only before the cells arrive at a manufacturing site since these specialised facilities can always freeze the ATMP product for return. In an ATMP network, it is therefore important to optimise the locations of manufacturing and cryopreservation facilities simultaneously.

A cryopreserved product must be thawed before starting the manufacturing process and before the final administration at the hospital. Alongside poor logistics, this process increases the risk of damaging the ATMP (Woods et al., 2016). Maintaining the product viable is crucial as the possibility of replacements is minimal. The autologous process shown in Fig. 3.1 involves patients with advanced-stage diseases, and their poor health condition might preclude another apheresis procedure. In addition to thawing associated

risks, the failure rate of a product is also influenced by the way each step of the manufacturing process is organised. The processing tasks and their duration depend on the product but are mainly classified into four categories: cell and gene therapy, cell therapy, gene therapy, and tissue engineering. The manufacturing is currently labour-intensive and time-consuming, leading to a high CoG and a long processing time per product (Lipsitz et al., 2017). However, various automation modes of production are currently available, which can lower each task duration, ensuring a better standardisation between ATMPs, lower failure rates (Lopes et al., 2020), and relaxing the dependence on labour availability. Finding skilled workers in some geographical areas is challenging for the ATMP supply chain, given the emerging highly specialised systems they are working with. It is not always the case that staff trained to create pharmaceutical products would be able to oversee the production of ATMPs. The optimisation of the manufacturing process alongside facility location could then lead to a more efficient supply chain design. For example, locations that are expected to have a high demand could benefit from a higher automation level which can reduce the duration of the manufacturing for each product but assumes a large initial investment.

Each step of the manufacturing process is also influenced by various exogenous factors that can lead to lower quality therapies, ultimately making them inefficient (Lipsitz et al., 2016). One such factor specific to a personalised supply chain is the patient's health condition. As the starting material directly involves the patients, their health condition can influence the quality of the ATMP and the number of blood samples required to obtain a high-quality final product. The patient becomes an integral network factor for the first time in the literature and drives the entire scheduling of an ATMP. Finally, once the manufacturing process is completed, the ATMPs are transported to the patient, either fresh or frozen. The product is usually transported by cars whenever the

distance allows, however, given the low number of manufacturing sites in the world, in the past, air transportation has also been used for longer distances. For example, one of Yescarta's reasons for cryopreservation was the need for delivery from Europe to USA and return. At this step, cryopreservation occurs within the MF and not at an independent facility but still carries the abovementioned risks. The product is administered only if the patient's health condition allows it.

3.5 Methodology

The supply chain field has been defined in different ways (Swanson et al., 2018), but it mainly refers to at least two entities, whether these are organisations or individuals, which are involved in the suppliers (upstream) and distribution (downstream) and any other information to and from the customer (Mentzer et al., 2001). This review will only consider papers related to the subfields of SCM that are critical for the PM supply chain (Rutherford et al., 2017) on a strategic level. Specifically, these include facility location, logistics (storage, inventory, and transport), network-related risk (Ho et al., 2015), manufacturing and service processes, demand management and inventory planning. Throughout the paper, we will also be referring to "patient risk", which is defined based on each individual's health condition and its impact on the product's quality and the treatment's success rate.

To minimise the double review of articles considered in past studies, we have restricted the search to papers published between January 2015 and December 2020 that considered at least two supply chain echelons. Only journal papers written in English and from an operations research perspective were included in line with previous systematic reviews. Moreover, because the PM supply chains remain in place, papers that analysed

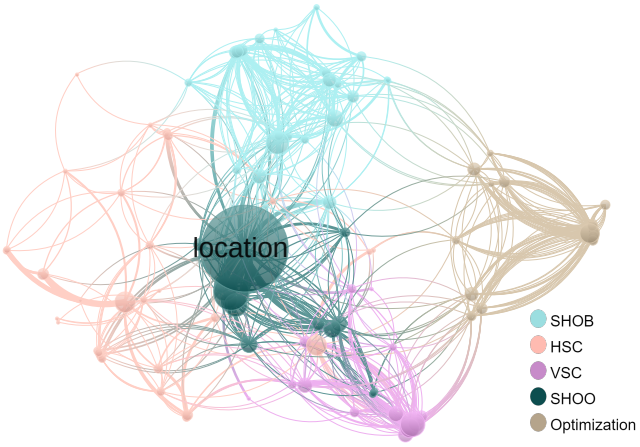
the healthcare emergency and humanitarian relief supply chains have not been considered. Finally, non-emergency healthcare supply chain papers focusing on non-medical products were excluded.

The search strategy is presented in Figure 3.2a. The keywords were chosen to start from the supply chains of interest, namely non-emergency HSC (including hospitals, nursing homes, and local treatment centres), those that support substances of human origin (SHO), such as blood supply chain (SHOB) and organ donation supply chain (SHOO), and vaccine supply chain (VSC). The initial search returned 226 papers for SHOB, 45 papers for SHOO, and 44 papers for VSC, among which 202, 43, and 41 were excluded for each area, respectively, due to non-relevance. For HSC supply chain, the search returned over 1000 papers, but only ten were included in the review due to non-relevance or duplication in other searches. In addition, two conference papers and a journal article focusing on optimising the CAR-T delivery, a class of autologous ATMP, were manually added to the bibliography. Finally, because the ATMPs are biopharmaceutical products, they share characteristics with the Biopharmaceutical supply chain (BSC), and even though it is not extensively analysed in this review, references to it will be made in Section 3.6.1.

The literature was inspected using text mining and network analysis on the title, keywords, and abstracts of the selected papers. The analysis returned five main clusters, colour-coded in Figure 3.2b. Each node's size represents a keyword's frequency in all papers. The distance between nodes relates to how related the terms are. SHOB, HSC, VSC, and SHOO clusters differentiate between the commonly used terms specific to each of the four supply chains, while the optimisation cluster belongs to modelling and solution methods. As expected, the keyword "location", forming the strategic level of these supply chains, is the most prevalent in the reviewed papers, indicating the high

	Healthcare Supply Chain	Vaccine Supply Chain	Blood Supply Chain	Organs Supply Chain
TITLE-ABS-KEY	healthcare OR healthcare network	vaccine OR vaccine supply chain OR immunization	blood OR blood supply chain OR platelets OR plasma	organ donation OR organs OR organ transplant
AND NOT	"review" OR "survey" OR "overview"			
AND	optim* OR stochastic OR uncertain OR analysis OR model OR analytic OR heuristic OR algorithm OR program OR simulation OR solution method OR mathematical OR formulation			
AND	process OR collection OR transport OR routing OR production OR inventory OR management OR distribution			
PUBYEAR	> 2014			

(a) Search Strategy



(b) Topic Clustering

Figure 3.2: Keywords search (Figure 3.2a) and bibliometric analysis (Figure 3.2b) for the blood (SHOB), healthcare (HSC), vaccine (VSC), and organ donation (SHOO) supply chains.

number of location problems in the field.

The complexity of the FLP and their important role in the supply chain design made them attract particular interest and often be considered separately. Nonetheless, oversimplification can lead to sub-optimal solutions that work in isolation but fail to render similar results on an extended multi-echelon problem (Shen and Qi, 2007). The increasing number of papers on integrated supply chains is also evident through the recent literature reviews, such as Sharkey et al. (2011)'s review on FLP with demand scheduling on predefined time windows; Kaviani (2009) and Farahani et al. (2014)'s discussions on facility location and inventory management problems, and Fahimnia et al. (2013)'s review on production-distribution planning.

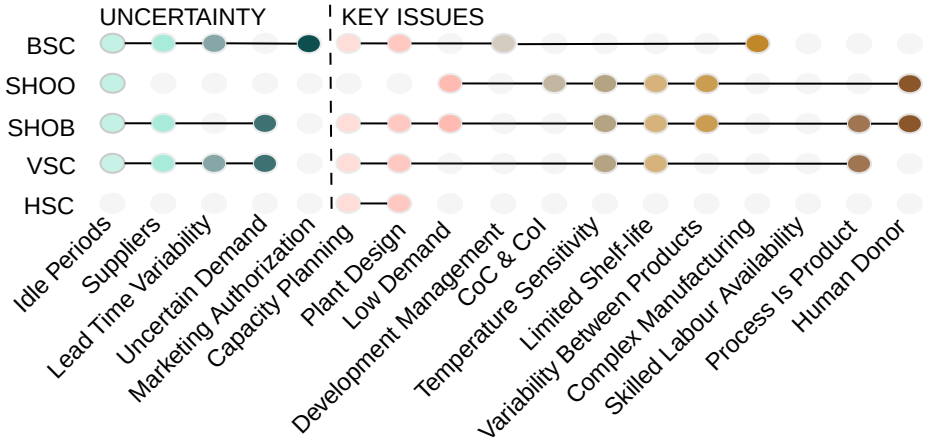


Figure 3.3: Comparative table showing the intersection of key issues and uncertainties between personalised medicine and other healthcare supply chains. CoC & CoI refer to Chain of Custody and Chain of Identity, respectively. *Variability Between Products* is specific to ATMPs and refers to the different qualities of the cells collected from the patient, which influence the final product.

3.6 Literature Review

3.6.1 Personalised Medicine Integration in Healthcare

There is a considerable number of surveys of operation research methods applied to healthcare supply chains (for reviews see, e.g., Ahmadi-Javid et al., 2017b; Duijzer et al., 2018; Pirabán et al., 2019). Medical product collection, storage, and transportation are mature and well-defined supply chains. Increased complexity is, however, brought by the ability of PM to create personalised re-engineered products that are autologous and force the medical treatment towards a patient-centred approach. The rest of this section discusses the uncertainties and key issues of the ATMP network design and how they intersect with those present in other healthcare supply chains. Figure 3.3 gives an overview of this intersection.

The PM supply chain is prone to several uncertainties. More widely researched within

the BSC, SHOs, and VSC supply chains, disruptions, idle periods, and supplier-related uncertainties are concerns for the ATMPs. Lead time variability is characteristic of the VSC and BSC, while the uncertain demand is challenging for the SHOB and VSC. Nonetheless, none of the latter two face a low demand that can lead to long periods of inactivity of parts of the supply chain. The autologous products typical of PM increase the difficulty of handling uncertainties. While SHOs involves human donors, the process is allogeneic. The patient's health condition is now driving both the supply and demand. Moreover, in most cases, the SHOs products can be derived from other individuals, which is impossible for autologous products.

The uncertain demand is strongly related to whether a product will obtain market authorization. Commercialisation approval is a lengthy process, dependent on the drug administration agencies. Together with the sensitive nature of their field, any changes in the manufacturing process of an ATMP after the initial commercial approval are highly regulated by authorities and require a lengthy reevaluation (Phillips et al., 2011; Iglesias-Lopez et al., 2019). This makes the supply chain need to be optimised before market release.

As a medical supply chain, PM shares common characteristics with other, more mature networks in the healthcare field. The first problem to be solved as part of the strategic level of the supply chain is a facility location problem. While the location of the hospitals is fixed, the location of manufacturing and cryopreservation facilities needs to be optimized. Except SHOO, the other supply chains are also concerned with facility location and design problems. Nevertheless, the highly personalised products lead to low global demand for PM therapies and, alongside a long development process (also encountered in the BSC), makes the FLP more challenging.

The PM has an agile supply chain driven by pull factors, meaning the production is

executed in response to a customer's needs. Using off-the-shelf products is no longer a viable approach in PM, and the patient's health condition determines the start and finish times of the supply chain. Similar to the SHOO, there is thus a need for a Chain of Custody (CoC) and Chain of Identity (CoI) to be always maintained. Nevertheless, the highly sensitive nature of genetic testing data that is usually associated with the ATMPs makes issues such as privacy protection of even higher importance for PM (Miller and Tucker, 2018). Moreover, using living cells, the entire process has a short shelf-life. Therefore, similar to the SHOO, SHOB, and VSC, transportation is commonly done within a cold supply chain. However, in comparison to the more traditional stratified products, ATMPs add to the supply chain a *complex manufacturing process* that is dictated by patient variability and the quality of the raw materials, which are characteristics of the BSC.

With the increasing number of commercial ATMPs and the rapid growth of new technologies, the manufacturing process also suffers from a lack of skilled labour (Lewis and Bradshaw, 2017). As a result, the shift towards a higher level of automation has received particular attention (Moutsatsou et al., 2019). As shown by Lopes et al. (2020), this could reduce both the duration of the supply chain and the CoGs. While the BSC also has manufacturing processes, the availability of skilled labours is not a major problem for any other healthcare supply chain. Additionally, as each stage of the manufacturing process is influenced by various exogenous factors that can influence the quality of the product (Lipsitz et al., 2016), it is common to refer to the product as the process itself. Ensuring that the variability between products is minimal is one key aspect that needs to be guaranteed should personalised medicine be widely implemented.

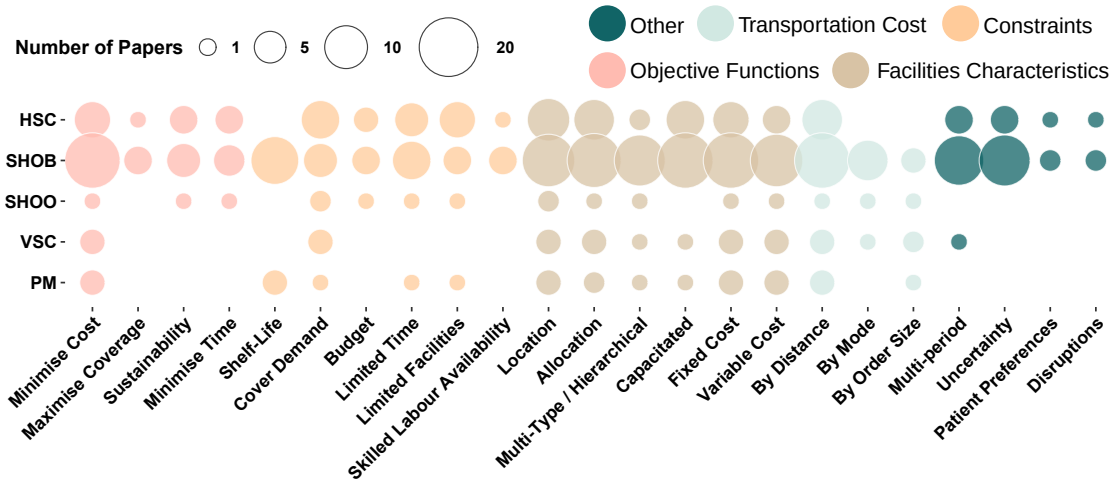


Figure 3.4: Bubble plot. *x-axis*: personalised medicine characteristics, *y-axis*: healthcare supply chains, *size*: frequency in healthcare academic literature after 2015.

3.6.2 Objectives and Constraints in Healthcare Supply Chains

Following our discussion above of the characteristics of PM supply chains, we now analyse which objectives and constraints are mentioned in the reviewed papers as being relevant for each supply chain. An overview of this analysis is shown in Figure 3.4, where each bubble indicates, for each supply chain, how many papers considered a particular objective or constraint. A further breakdown of each reviewed paper is presented in Tables 3.1 and 3.2. Table 3.1 shows the classification of objectives, constraints, and solution methods for papers of interest. Table 3.2 presents the distribution regarding the most common characteristics associated with the facilities and how the delivery costs are calculated. A miscellaneous category presents other related considerations in the supply chain, such as multi-period models, uncertainty, patient preferences, or disruptions.

Cost minimisation and profit maximisation were the most prevalent objectives across all four healthcare supply chains. In contrast to the public sector, which regulates most of the healthcare industry, the pharmaceutical sector is primarily driven by delivering

drugs at the right time while maintaining the benefits for all stakeholders (Rossetti et al., 2011). Maximising coverage and ensuring social sustainability have not been extensively considered. Access to healthcare is an important ethical issue, and without significant improvements in the delivery methods of the ATMPs, personalised medicine will contribute to widening this barrier (Chong et al., 2018). Ares et al. (2016), Eskandari-Khanghahi et al. (2018), Zhang and Atkins (2019) and Haeri et al. (2020) are the only ones to consider social sustainability, either as equity and efficiency (usually defined by the waiting time or product shortages) or social welfare (usually defined by the impact of the supply chain on staff jobs). Similarly, environmental sustainability was discussed only by Saif and Elhedhli (2016), Heidari-Fathian and Pasandideh (2018), and Hamdan and Diabat (2019). They analysed this aspect from a wastage perspective (CO2 emissions due to the cold supply chain) or the impacts of opening facilities.

3.6.3 Gaps in the Literature of Personalised Medicine Supply Chain

Generally, the non-emergency supply chains are designed considering a stable environment. The lack of demand, for example, is not of main concern. The reviewed studies do not consider other potential delays, such as workers' unavailability or equipment breakdown. With potentially disastrous consequences for the patient in case of interruptions, the supply chain resistance and recovery becomes highly relevant for ATMPs. Finally, transportation (modelled as a function of distance and, to a lesser extent, order size) has been largely considered using only one type of vehicle. It seems possible that this simplification results from the limited geographical areas considered in the papers. Most case studies are restricted to local or national areas and use a relatively sparse granularity.

As also emphasised in Subsection 3.6.1, the availability of skilled labour is the

Table 3.1: The distribution of characteristics between the blood (SHOB), organ donation (SHOO), personalised medicine (PM), vaccine (VSC), and non-emergency healthcare (HSC) supply chains - Part 1.

			Objective Functions					Constraints							
2015–2020	HSC, PM, SHOB, SHOO, VSC		Minimise Cost	Maximise Coverage	Social Sustainability	Environmental Sustainability	Minimise Time	Shelf-life	Cover Demand	Budget	Limited Time	Limited # of Facilities	Skilled Labour Availability	Case Study	Solution Method
	Mestre et al.		❍	❍			❍		❍		❍			❍	EM
	Shishebori and Babadi		❍							❍		❍		❍	EM
	Cardoso et al.		❍		❍				❍		❍	❍		❍	EM
	Ares et al.			❍	❍							❍		❍	AM
	Zarrinpoor et al.		❍						❍		❍	❍		❍	EM
	Wang and Ma		❍				❍		❍			❍		❍	AM
	Vieira et al.						❍		❍		❍	❍		❍	EM
	Zhang and Atkins				❍							❍		❍	AM
	Dogan et al.		❍				❍		❍	❍	❍			❍	EM
	Mendoza-Gómez et al.		❍						❍						AM
	Wang et al.		❍					❍							EM
	Moschou et al.		❍					❍						❍	EM
	Karakostas et al.		❍					❍	❍		❍				AM
	Zahiri et al.		❍					❍	❍	❍	❍	❍		❍	EM
	Elalouf et al.		❍											❍	EM
	Arvan et al.		❍					❍	❍	❍					EM
	Chaiwuttisak et al.		❍				❍	❍			❍			❍	EM
	Fahimnia et al.		❍				❍		❍		❍	❍			EM
	Osorio et al.		❍					❍	❍					❍	EM
	Ramezanian and Behboodi		❍	❍		❍		❍						❍	EM
	Ensafian and Yaghoubi			❍			❍	❍						❍	EM
	Zahiri and Pishvaee		❍					❍		❍		❍		❍	EM
	Ensafian et al.		❍					❍						❍	EM
	Attari et al.		❍				❍	❍			❍			❍	EM
	Eskandari-Khanghahi et al.		❍		❍	❍		❍							AM
	Heidari-Fathian and Pasandideh		❍		❍	❍		❍							EM
	Osorio et al.		❍						❍		❍			❍	EM
	Samani and Hosseini-Motlagh		❍					❍			❍			❍	EM
	Bruno et al.		❍								❍			❍	EM
	Hamdan and Diabat		❍			❍	❍	❍	❍			❍		❍	EM
	Haeri et al.		❍	❍	❍						❍			❍	EM
	Hosseini-Motlagh et al.		❍							❍	❍		❍	❍	EM
	Hosseini-Motlagh et al.		❍					❍	❍		❍	❍		❍	EM
	Rajmohan et al.						❍		❍			❍		❍	EM
	Rabbani and Talebi		❍		❍				❍	❍	❍			❍	EM
	Saif and Elhedhli		❍			❍			❍					❍	EM
	Lim et al.		❍						❍					❍	EM
	Yang et al.		❍						❍					❍	EM

Note: *Social Sustainability* includes efficiency and equity. For *Solution Method*, EM is Exact Methods, and AM is Approximate Methods.

least prevalent constraint in the reviewed papers. Hosseini-Motlagh et al. (2020a) are the only ones to consider skilled labours as part of their problem by directly linking the staff's proficiency to the patient's satisfaction. No reviewed paper was concerned with a lack of labour resources. Similarly, one of the biggest discrepancies between ATMPs and other supply chains, with few exceptions, is the lack of consideration for patient or user preferences. This is a direct consequence of the exclusive allogeneic (material collected from a donor) nature of the other supply chains, where an off-the-shelf approach with inventory management is implemented. If PM is to replace traditional

Table 3.2: The distribution of characteristics between the blood (SHOB), organ donation (SHOO), personalised medicine (PM), vaccine (VSC), and non-emergency healthcare (HSC) supply chains - Part 2.

		Facilities Characteristics						Delivery Cost				Other			
2015 / 2016 / 2017 / 2018 / 2019 / 2020	HSC / PM / SHOB / SHOO / VSC	Location	Allocation	Multi-Type / Hierarchical	Capacitated	Fixed Cost	Variable Cost	By Distance	By Mode	By Order Size		Multi-period	Uncertainty	Patient Preferences	Disruptions
Mestre et al.		○	○		○	○	○	○				○	○		○
Shishebori and Babadi		○			○			○							
Cardoso et al.		○	○		○	○	○	○							
Ares et al.		○						○					○		
Zarrinpoor et al.		○	○	○		○		○					○	○	
Wang and Ma		○	○	○	○	○									
Vieira et al.		○	○					○							
Zhang and Atkins		○	○		○			○				○		○	
Dogan et al.		○	○		○	○		○							
Mendoza-Gómez et al.			○		○	○	○	○				○	○		
Wang et al.		○				○	○	○		○					
Moschou et al.		○	○			○	○	○							
Karakostas et al.		○	○	○	○	○	○	○							
Zahiri et al.		○	○	○	○	○		○		○			○		
Elalouf et al.		○	○	○		○		○				○	○		
Arvan et al.		○	○	○	○	○	○	○							
Chaiwuttisak et al.		○		○	○	○	○	○	○						
Fahimnia et al.		○	○		○	○		○				○			
Osorio et al.		○	○		○		○						○		
Ramezanian and Behboodi		○	○	○	○	○	○	○	○			○	○		
Ensafian and Yaghoubi			○	○	○	○	○	○	○			○	○		
Zahiri and Pishvaee			○	○	○	○	○	○	○			○	○		
Ensafian et al.			○		○	○	○	○	○			○	○		
Attari et al.		○	○		○	○	○	○				○	○		
Eskandari-Khanghahi et al.		○	○	○	○	○	○	○	○	○		○	○		
Heidari-Fathian and Pasandideh		○	○	○	○	○	○	○	○	○		○	○		
Osorio et al.		○		○	○	○	○	○					○		
Samani and Hosseini-Motlagh		○	○	○	○	○	○	○				○	○		
Bruno et al.		○	○	○	○	○	○	○							
Hamdan and Diabat		○	○	○	○	○	○	○	○			○	○		
Haeri et al.		○	○	○	○	○	○	○				○	○	○	○
Hosseini-Motlagh et al.		○	○	○	○	○	○	○	○			○			○
Hosseini-Motlagh et al.		○	○	○	○		○	○		○	○	○	○		
Rajmohan et al.		○													
Rabbani and Talebi		○	○	○		○	○	○	○	○		○			
Saif and Elhedhli		○	○			○	○	○	○						
Lim et al.		○	○	○		○	○	○		○		○			
Yang et al.		○	○		○	○	○	○		○					

pharmaceutical products, the logistics of the supply chain will ultimately be the patient's choice. Understanding patient preferences (Liu et al., 2018) and ensuring fairness (Qi, 2017) has been considered in the past in the healthcare management and operations research literature but has not been directly considered about PM optimisation.

In the context of PM, Wang et al. (2018b); Moschou et al. (2020) and Karakostas et al. (2020) were the only ones that discussed the supply chain from an operations

research perspective. The three papers look at the supply chain of CAR-T, a type of autologous ATMP. Nevertheless, none of the proposed models is exhaustive. The papers do not consider patient preferences, disruptions, resource availability or different risk levels as part of their models. Except Wang et al. (2018b), which also aims to minimise the response time of the supply chain, the only objective is to minimise the cost of the network. Finding trade-offs between hospital coverage and the equity and efficiency of the supply chain alongside time and cost minimisation could potentially lead to more realistic models of PM supply chain. All papers related directly to optimising personalised ATMPs are discussed in more detail throughout the thesis.

3.7 Conclusion and Future Research

The treatments developed under PM have led to the need for an inclusive supply chain in the healthcare sector. The timely and cost-efficient delivery of biopharmaceutical products of human origin is challenged by aspects that have been researched only independently in the past. Our growing ability to develop ATMPs increases the need for a new cold supply chain which accounts for the delivery and manufacturing aspects. Furthermore, a new element is also brought by the concepts of ”living products”, and the ”process is product”, where the final ATMP is defined by the entire supply chain network and its configuration.

This paper presented a first systematic review of literature from an operations research perspective for the ATMPs supply chain in light of the current knowledge in the medical and pharmaceutical sectors. To understand the exact dissimilarities between the targeted sectors and ATMPs, the extensive literature mapping concentrated on the

recent publications in the traditional non-emergency healthcare networks from a modelling perspective. Our analysis suggests that, while the PM distribution shares common characteristics with other mature supply chains, none mirrors the PM network. The existing models in the literature were designed for mass delivery due to high demand and, as a consequence, are not appropriate to cover some of the key challenges of PM. The bibliographic and modelling analysis presented in this review indicates that, while the means for PM optimisation exist, more comprehensive research is necessary.

Our understanding of the commercialisation of PM products from an operations research perspective is still incipient and further research is deemed necessary. For instance, future mathematical models for PM can understand how patient prioritisation and risk analysis can lead to an equitable and fair supply chain. This way, we ensure that the entire process is designed for each individual and that the most at-risk patients can access timely personalised medical therapies.

Regarding solution methods, most of the studies analysed in this review used exact methods to solve the problems to optimality. Nevertheless, a real-world scenario for ATMPs has many decision variables, usually leading to intractable non-linear mathematical models. Using existing solvers and other exact methods becomes thus infeasible. Additionally, biopharmaceutical companies might not have access to the commercial solvers used in the papers, and a transposal of the corresponding algorithm can become challenging. This is something that should be borne in mind in future studies.

Chapter 4

Facility Location Problem in the ATMPs Supply Chain

MENTION: this chapter is an adapted version of the submitted paper "A. Avramescu, R. Allmendinger, and M. López-Ibáñez. **A multi-objective multi-type facility location problem for the delivery of personalised medicine**. In P. Castillo and J. L. Jimenez Laredo, editors, *Applications of Evolutionary Computation*, volume 12694 of LNCS, pages 388–403." (Avramescu et al., 2021b). This chapter differs from the previous work in the following ways:

- Problem formulation: the mathematical model has been standardised to match the rest of the thesis and mirror the more traditional notations used in the literature on facility location problems.
- Data: the size of the problem classes are described. The following sections will then briefly discuss how the problem size could have affected the algorithm's performance, which will be tackled in more detail in the later chapters.
- Methodology: a more detailed description of the algorithms used and the solution representation is provided here.

As a consequence, some of the other sections have suffered small modifications. The chapter follows the same structure as the paper, and the writing is the same.

4.1 Abstract

Advances in personalised medicine targeting specific sub-populations and individuals challenge the traditional pharmaceutical industry. With a higher level of personalisation, an already critical supply chain faces additional demands added by the very sensitive nature of its products. Nevertheless, studies on the efficient development and delivery of these products are scarce. Thus, this paper presents the case of personalised medicine and the challenges imposed by its mass delivery. We propose a multi-objective mathematical model for the location-allocation problem with two interdependent facility types for personalised medicine products. We show its practical application through a cell and gene therapy case study. A multi-objective genetic algorithm with a novel population initialisation procedure is used as a solution method.

4.2 Introduction

Personalised medicine, or precision medicine (PM), has been defined in numerous ways, and there is no standard understanding behind the new healthcare mantra (Redekop and Mladsi, 2013). In this paper, we focus on the ATMPs, i.e., the biopharmaceutical products created due to the development of PM. ATMPs use tissue, genes, or cells to treat progressive diseases like cancer and rare disorders. They can overcome the generally accepted fact that current drugs are not useful for the entire population, with some estimates pointing to a 60%

PM's development was enhanced by the completion of the Human Genome Project (Lander et al., 2001) and our subsequent ability to sequence a person's DNA set through a simple procedure (Wilson and Nicholls, 2015). The medical field has made considerable

progress concerning PM treatments and their ability to cure progressive diseases. In contrast, little research has been conducted regarding how these products should be manufactured and delivered. Using a high level of stratification and low global demand, the continuous, off-the-shelf, and mass production of traditional drugs is shifting towards a batch and on-demand model. Additionally, biopharmaceutical companies work with new technologies under highly regulated markets. As a result, ATMPs research followed a sparse approach that analysed different supply chain echelons independently without creating a holistic model.

The lack of optimisation models that consider the specific requirements of ATMPs means that decisions at strategic and operational levels are taken using existing pharmaceutical models. The current approach for the commercialisation of ATMPs has led to major challenges for some companies, such as the cases of Provenge (Jarosławski and Toumi, 2015) and ChondroCelect (Abou-El-Enein et al., 2016), or to lower quality treatments, such as the case of Kymriah (Bersenev and Kili, 2018). Additional consequences for the patients also include limited availability. The high costs, complex manufacturing processes, and the requirement for timely delivery in a cold supply chain,[1] restrict these medicines to being used only as a last resort.

This paper aims to contribute towards creating more specialised optimisation models capable of tackling the inherent complexities associated with the delivery of PM. Accordingly, we propose a Multi-objective Optimisation (MOO) model to find the location of two types of facilities required as part of the supply chain that minimises the cost and delivery time and maximises the demand covered while satisfying several constraints. Subsequently, we use a customised MOO algorithm to solve the problem. Our proposed algorithm is based on NSGA-II (Deb et al., 2002a) but uses customised strategies for the

[1] A temperature-controlled supply chain that maintains a product viable through temperature decreases.

population initialisation, mating and mutation of solutions, considering the dependency of one facility type on the other. Finally, we propose an algorithm based on states' proximity to obtain the demand allocation per hospital.

The remainder of this paper is organised as follows. Section 4.3 outlines the theoretical background and highlights the relevant literature. Section 4.4 describes the supply chain and introduces the proposed mathematical model for the given problem. Sections 4.5 and 4.6 describe the data and methodological approach, while the results are presented in Section 4.7. The paper ends with a summary of the main findings and suggestions for future work.

4.3 Related Work

PM lies at the core of multiple supply chains in the pharmaceutical and healthcare industries. Therefore, the relevant theoretical background encompasses different topics. Using living cells, its delivery process shares common characteristics with the substances of human origin, while the research on the supply chains supporting biopharmaceuticals helps optimise manufacturing. As a service-oriented supply chain, key social requirements within healthcare are equity and fairness in access to medications and preventing drug shortages (Nematollahi et al., 2017). The most common objectives are the guarantee of perfect demand coverage or maximising available backup assistance in case of disruptions. The societal impact was assessed through the cost-effectiveness of the products and the ability to create an affordable healthcare system for society and the patient. Such objectives are extensively reviewed by Pirabán et al. (2019) in the context of blood supply chains, and models of multiple healthcare supply chains are further outlined by Ahmadi-Javid et al. (2017b).

Most of the products (e.g. blood and pharmaceuticals) within the above mentioned supply chains are part of the essential and emergency medical system and are protected by fundamental human rights (Burkholder et al., 2019). This is not the case for ATMPs, and access to breakthrough therapies is not guaranteed. The high uncertainty in evidence regarding the efficiency on a large scale as an outcome of the low number of products approved and their short time frame on the market, combined with the products' complex and inefficient supply chains, makes numerous regulatory bodies reluctant to approve such therapies (Gonçalves, 2020). While capable of revolutionising treatment through a patient-centric approach, the requirements of PM are believed to widen the gap in access to healthcare (Weiss et al., 2018). To solve some of these problems, a scenario-based bi-objective facility-location problem formulation was proposed in Wang et al. (2018b). The paper aimed to maximise the net present value and minimise the average response time for patients. Nevertheless, to the best of our knowledge, the main constraints of the PM supply chain, concerning the product shelf-life and fragility, have not been addressed before from an operations research perspective.

FLP is a well-known class of NP-hard problems (Farahani et al., 2010). Therefore, solving the problems using exact solution methods is rarely feasible for real-world problem instances (Farahani et al., 2010). Different meta-heuristics have been applied for real-world scenarios, such as local search heuristics and various variants of Genetic Algorithms (Basu et al., 2015). The applications of GAs to this problem type (Yang et al., 2007; Rahmani and Mirhassani, 2014) and some of its extensions (Ardjmand et al., 2015; Hiassat et al., 2017) are prominent. When discussing the number of objectives, for bi- and multi-objective problems, the NSGA-II (Deb et al., 2002a) has been applied to problems such as uncapacitated facility location problem (Villegas et al., 2006), hub location (Eghbali et al., 2014) and hub maximal covering under uncertainty (Ebrahimi Zade

et al., 2014), warehouse location (Bhattacharya and Bandyopadhyay, 2010), gas field location (Wang et al., 2018b), location of public facilities in places prone to natural hazards (Doerner et al., 2008), and hospital waste management networks (Medaglia et al., 2009).

4.4 Problem Description

In this paper, we focus on the autologous supply chain of an ATMP (Papathanasiou et al., 2020) (Figure 4.1), i.e. the donor is the patient itself and, after being processed, the cells need to be returned to the same hospital from where they were collected. Thus, each patient's cells correspond to one *order* that needs to be processed. The process starts with material collection from the donor at a hospital that has FACT authorisation. The collected product is then transported to a MF where it is genetically modified. Using living cells, the entire process from hospital collection until the cells are returned to the patient must be shorter than the cells' shelf-life, between a few hours and a few days, depending on each product type. Otherwise, it is common that cells are frozen at an independent cryopreservation facility, and the transportation is done under cryogenic temperatures. Freezing the material extends the preservation time frame, relaxing the time constraints altogether. This paper considers the shelf-life redundant once the cells are cryopreserved. This scenario is realistic since we assume that once the cells are processed, they are automatically returned to the patient without long-term storage.

4.4.1 Mathematical Model

Starting from the above problem description, we aim to find an optimal location of MFs and CFs and allocate each patient's cells, typically from hospitals, accordingly. We

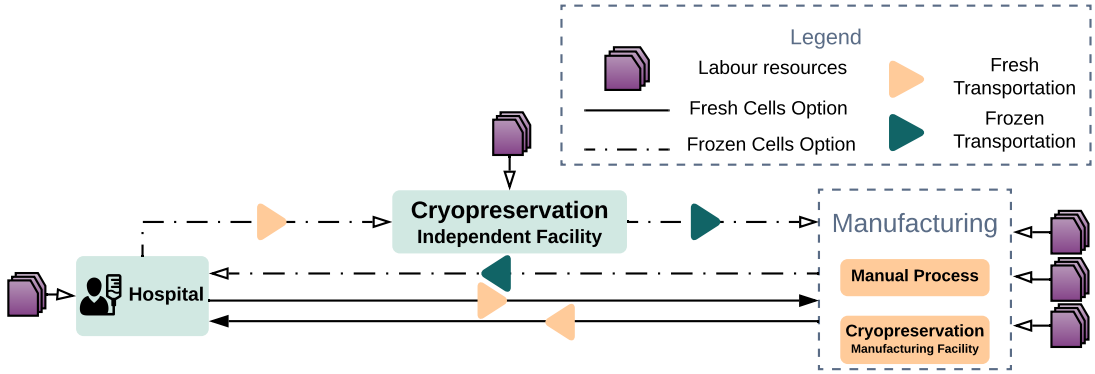


Figure 4.1: ATMPs supply chain network flow with three modes of production, separate and integrated cryopreservation facilities.

start with a pre-defined set of locations J, which can be any geographical point where a facility can be placed and a bunch of orders I. Each order has associated with a known geographical location, typically a hospital. We know the travel time between candidate locations and between candidate locations and hospitals denoted as t_{ij}, where $i \in I$ and $j \in J$. For simplicity, in this paper, we calculate the haversine distance t_{ij} by dividing the distance between any two locations or orders, i, j, by the average car driving speed in the USA. We model the PM supply chain as an MOO problem (see next page).

Objective (4.1) minimises the average delivery time per patient. As each order corresponds to one patient and has hospitals as starting point, the objective minimise the travel time from order i to its assigned MF located at j, possibly via a cryopreservation facility located at $j' \in J$ if $z_i = 1$. Objective (4.2) minimises the total cost of the supply chain, i.e., the cost of opening manufacturing and cryopreservation facilities, which is independent of the orders assigned to them, and the cost of operating the facilities, which depends on how many orders are assigned to them. The calculation of the costs is later explained in Section 4.5. Objective (4.3) maximises the number of patients receiving the therapies by maximising the number of processed orders.

Indices and Parameters

$i \in I$	Demand orders.
$j \in J$	Candidate locations for placing a facility.
$t_{ij}, t_{jj'}$	Travel time between locations J and from/to demand orders I, and in-between candidate locations where $i \in I$ and $j, j' \in J$.
γ	Shelf-life constant when order is processed as fresh.
$s_j^{\mathrm{C}}, s_j^{\mathrm{M}}$	Cost of opening a cryopreservation (C) or a manufacturing (M) facility at location $j \in J$.
$c_j^{\mathrm{M}}, c_j^{\mathrm{C}}$	Operating (M) or cryopreservation (C) cost of a facility placed at location $j \in J$ per unit.

Decision Variables

$y_{ij}^{\mathrm{M}}, y_{ij}^{\mathrm{C}}$	1 if order i is allocated to a manufacturing (M) or a cryopreservation (C) facility placed at location $j \in J$, 0 otherwise.
$x_j^{\mathrm{M}}, x_j^{\mathrm{C}}$	1 if a manufacturing (M) or a cryopreservation (C) facility is placed at candidate location $j \in J$, 0 otherwise.
z_i	1 if order $i \in I$ is delivered as frozen, 0 otherwise.

Objectives

$$\min \sum_{i\in I}\sum_{j\in J}\left(y_{ij}^{\mathrm{M}} \cdot ((1-z_i)t_{ij} + t_{ji}) + z_i y_{ij}^{\mathrm{C}} \cdot \left(t_{ij} + \sum_{j'\in J}(t_{jj'} \cdot y_{ij'}^{\mathrm{M}})\right)\right) \tag{4.1}$$

$$\min \sum_{j\in J}\left(s_j^{\mathrm{M}} \cdot x_j^{\mathrm{M}} + c_j^{\mathrm{M}} \cdot \left(\sum_{i\in I} y_{ij}^{\mathrm{M}}\right) + s_j^{\mathrm{C}} \cdot x_j^{\mathrm{C}} + c_j^{\mathrm{C}} \cdot \left(\sum_{i\in I} y_{ij}^{\mathrm{C}}\right)\right) \tag{4.2}$$

$$\max \sum_{i\in I}\sum_{j\in J} y_{ij}^{\mathrm{M}} \tag{4.3}$$

Constraints

$$2 \cdot (1-z_i)\sum_{j\in J}(t_{ij} \cdot y_{ij}^{\mathrm{M}}) + z_i \sum_{J\in J} t_{ij} \cdot y_{ij}^{\mathrm{C}} \leq \gamma \quad \forall i \in I \tag{4.4}$$

$$\sum_{j\in J} x_j^{\mathrm{M}} \geq 1 \tag{4.5}$$

$$\sum_{j\in J} y_{ij}^{\mathrm{M}} \leq 1 \quad \forall i \in I \tag{4.6}$$

$$\sum_{j\in J} y_{ij}^{\mathrm{C}} \leq z_i \quad \forall i \in I \tag{4.7}$$

$$y_{ij}^{\mathrm{M}} \leq x_j^{\mathrm{M}} \quad \forall i \in I, \forall j \in J \tag{4.8}$$

$$y_{ij}^{\mathrm{C}} \leq x_j^{\mathrm{C}} \quad \forall i \in I, \forall j \in J \tag{4.9}$$

$$x_j^{\mathrm{C}} + x_j^{\mathrm{M}} \leq 1 \quad \forall j \in J \tag{4.10}$$

$$y_{ij}^{\mathrm{M}},\ y_{ij}^{\mathrm{C}},\ x_j^{\mathrm{M}},\ x_j^{\mathrm{C}}, z_i \in \{0,1\} \tag{4.11}$$

The most important constraints in the PM supply chain are time constraints ensuring that each order is delivered within its respective shelf-life (4.4). Constraint (4.5) provides that at least one MF is placed; otherwise, orders cannot be processed. Constraint (4.6) does not allow orders to be assigned to more than one MF. In the case of (4.7), the order is only assigned to a CF if the order is cryopreserved. Constraints (4.8) and (4.9) limit orders to be assigned only to open facilities. Finally, we restrict that no more than one facility can be placed at each location (4.10).

4.5 Data

We test the proposed model using publicly available data of a PM product, Kymriah, manufactured and distributed by the biopharmaceutical company Novartis. Kymriah is a genetically engineered autologous cell therapy that first obtained market authorisation and the breakthrough therapy designation by the FDA in August 2017 (CBER, 2017a). While the product has recently obtained authorisation to expand its targeted patients, the demand data was calculated using only the designation for B-cell precursor ALL that is refractory or relapsed (r/r) in paediatric patients in the USA. The data was obtained from the International Incidence of Childhood Cancer (IICC-3) (Steliarova-Fourcher et al., 2017) and supplemented with expert opinions. It is estimated that about 80% of ALL cases are caused by B-precursor (Sexauer et al., 2020), and in paediatric patients, about 20% of these will be r/r (Sun et al., 2018). While we have used real data in this paper, the usage of a different production mode in their current supply chain than the one used in this paper makes a comparison with the current Kymriah distribution not possible.

The list of candidate hospitals that can accept patients for Kymriah was obtained from the official Novartis data and matched against the FACT accredited hospitals (Figure 4.2).

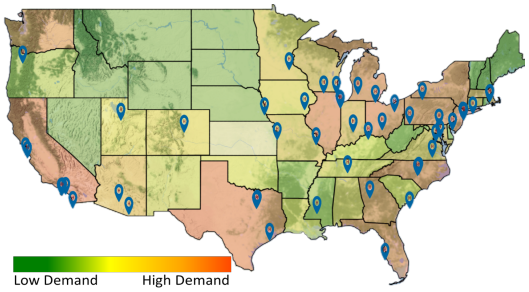


Figure 4.2: USA map with estimated Kymriah demand layer and candidate hospitals.

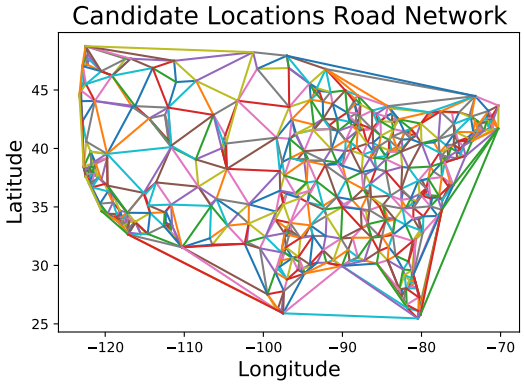


Figure 4.3: USA road network connections between the 1000 candidate locations.

The demand at the state level was then distributed using a uniform random allocation to the hospitals within the same state until the entire capacity was filled. The remaining demand was then allocated randomly to a hospital in one of the neighbouring states with remaining capacity. If no hospital was available in a neighbouring state, the allocation was moved to hospitals within the second-level neighbouring states. The candidate locations for both manufacturing and cryopreservation facilities (L) are the 1 000 largest cities of the USA; their network is presented in Figure 4.3.

As creating each ATMP requires a long production process, we have obtained the data for the corresponding manufacturing tasks using the Biosolve Process software (Sinclair and Monge, 2010). Finally, the hourly wage for the labour resources was obtained from the U.S. Bureau of Labor Statistics for each individual state. This data is used later to calculate the total cost for the PM supply chain (see Eq. 4.2), which comprises the cost of opening MFs and CFs, and the operating cost. The latter was defined as the total cost for manufacturing and transportation and calculated using a standard manual production setup as defined by Lopes et al. (2020). The exact staff allocation for each task is shown in Fig. 4.4. The light blue frames are processes outside of the MF, either at the hospital,

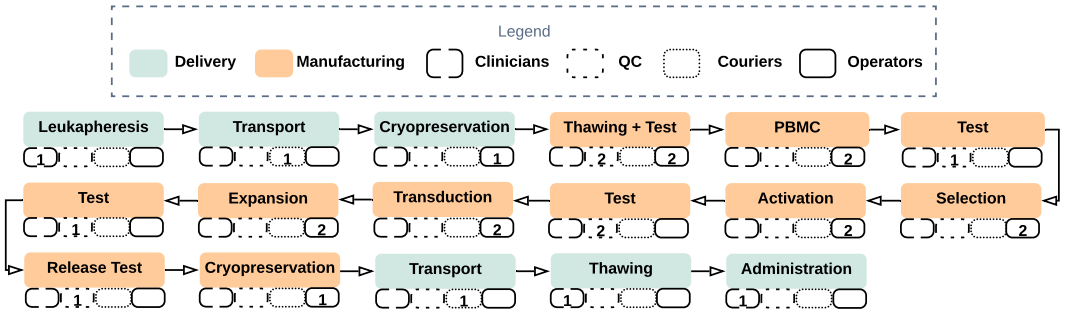


Figure 4.4: Cell and gene therapy traditional sequence of tasks with required resources.

CF or correspond to the delivery between facilities. The orange frames correspond to the manufacturing tasks, and in the manual production mode, they are all mandatory and performed in the exact sequence presented here.

4.6 Methodology

We consider two MOO algorithms to solve the PM supply chain problem defined in Section 4.4: MORS and a modified version of NSGA-II (Deb et al., 2002a). The performance of MORS shall serve as a baseline.

Before we explain both MOO algorithms, we describe a procedure (Algorithm 1) for determining the allocation of orders to manufacturing and/or CF based on the shelf-life. An order can only be allocated to a MF at a particular location (without cryopreservation)

Algorithm 1 Shelf-life Radius

Require: J, I, γ_i, t_{ij}

1: **for** $i \in L$ **do**
2: $\quad R_j^{\mathrm{M}} \leftarrow \{i \in I \mid t_{ij} < \gamma_i/2\}$
3: $\quad R_j^{\mathrm{C}} \leftarrow \{i \in I \mid t_{ij} < \gamma_i\}$
4: **end for**
5: **return** $R_j^{\mathrm{M}}, R_j^{\mathrm{C}}, j \in J$

Algorithm 2 Initial Population

Require: J; N (population size)
1: $P \leftarrow \varnothing$
2: **while** TRUE **do**
3: $M \leftarrow$ randomly selected subset of J
4: $C_{\text{full}} \leftarrow \text{ProgressiveCoverage}(M)$ ▷ See Algorithm 3
5: **for** $k = 1$ **to** $|C_{\text{full}}|$ **do**
6: $C \leftarrow \{c_1, \ldots, c_k\} \subseteq C_{\text{full}}$ ▷ First k elements
7: $s \leftarrow \{x_j^{\text{M}} = 1 \; \forall j \in M, x_j^{\text{C}} = 1 \; \forall j \in C \}$ ▷ Create partial solution
8: $P \leftarrow P \cup \{s\}$
9: **if** $|P| = N$ **then**
10: **return** P
11: **end if**
12: **end for**
13: **end while**

if the travel time from the order to the location is shorter than half its shelf-life. Similarly, an order can only be allocated to a CF at a particular location if the travel time from the order to the location is shorter than its shelf-life (once the order is cryopreserved, the shelf-life constraint is deactivated). We apply this procedure once before running an MOO algorithm to calculate, for each location $j \in J$, which orders in I could be assigned to a MF in location j without cryopreservation (line 3) and which orders could be assigned to a CF in that location (line 2). That is, $R_j^{\text{M}}, R_j^{\text{C}} \subseteq I$ are the orders that can be safely assigned to either a MF (without cryopreservation) or a CF located in $j \in J$.

Following the abovementioned allocation, we can apply an MOO algorithm to tackle the PM supply chain problem. The NSGA-II approach considered here differs from the standard one (Deb et al., 2002a) in the initialisation, mutation and crossover operators. At the same time, it maintains the non-dominated sorting procedure coupled with crowding distance and binary tournament selection. Our NSGA-II follows Algorithm 2 to create an initial population of size 500. Our initialisation aims to ensure that we have a mix of solutions representing different configurations regarding the number of MFs and CFs

Algorithm 3 Progressive Coverage

Require: $M \subset J$; $R_j^{\mathrm{M}}, R_j^{\mathrm{C}}\ \forall j \in J$

1: $C_{\text{full}} \leftarrow \varnothing$
2: $I_{\text{coverage}} \leftarrow \bigcup_{j \in M} R_j^{\mathrm{M}}$ ▷ R_j^{M} calculated by Algorithm 1
3: $\overline{I} \leftarrow I \setminus I_{\text{coverage}}$ ▷ Uncovered orders
4: $\overline{J} \leftarrow J \setminus M$ ▷ Available locations
5: **while** $\overline{I} \neq \varnothing$ **do**
6: $\quad J^* \leftarrow \arg\max_{j \in \overline{J}} |R_j^{\mathrm{C}} \cap \overline{I}|$ ▷ R_j^{C} calculated by Algorithm 1
7: $\quad j^* \leftarrow \arg\max_{J^*} |R_j^{\mathrm{C}}|$
8: $\quad C_{\text{full}} \leftarrow C_{\text{full}} \cup \{j^*\}$
9: $\quad \overline{I} \leftarrow \overline{I} \setminus R_{j^*}^{\mathrm{C}}$
10: $\quad \overline{J} \leftarrow \overline{J} \setminus j^*$
11: **end while**
12: **return** C_{full}

and their coverage levels. The algorithm can reach better solutions in fewer iterations by replacing the random initialisation with this approach. We use prior knowledge of the shelf-life and the radius of each facility to find a minimum number of CFs that can cover the demand. For placing the CFs, we employ the progressive coverage procedure outlined in Algorithm 3. It is important to note that since having a MF is a mandatory requirement for an order to be processed, we prioritise the placement of this facility type and construct the CF around it. For this, we use an iterative approach (Algorithm 3) to place the CFs: Looking at all orders that are not within the radius of any placed MF (M), a CF is positioned at the candidate location (J^*) that can safely cover the most orders with no coverage (line 6). If several candidate locations cover an equal number of uncovered orders, then the location j^* with the maximum number of potentially assigned orders would be selected (line 7). This approach was preferred to increase the supply chain's resilience in case of disruptions of any MFs. The process is repeated until the demand from all orders is covered. This results in multiple solutions containing CFs with different coverage levels for each potential assignment of MFs.

Our NSGA-II creates new solutions using crossover and mutation operators. As the CFs depend on having an assigned MF, the crossover ignores the former and considers only the latter type of facilities. If there is a common manufacturing location, the child inherits this facility, while the non-identical ones are inherited with a probability of 0.5 from either parent. As orders cannot be covered without processing, solutions without MFs are not allowed. For each solution, the mutation is applied randomly to a solution as follows. With the probability of 0.1, a MF is added or removed randomly. Removing a MF is not allowed if it is the only one in the solution. A second mutation, applied with a probability of 0.8, follows the network of candidate locations (Figure 4.3) and allows a MF to be moved at random only to one of the adjacent locations on the map. The orders are allocated to facilities after each mutation, with each order being assigned to the closest facility.

In this problem, we use two binary vectors to represent the decision of allocating a MF or CF, respectively, in the search space. In total, since we have 1000 locations and you cannot allocate both MF and CF to the same location, the problem size is 3^{1000}. If not otherwise stated, any results shown were obtained by running our two MOO approaches for 20 independent runs, each consisting of 800 generations (using a population size of 500).[2]

4.7 Results

We have tested the current case study by constraining the problem to three levels of coverage. The restrictions imposed a minimum of 50% or 80% coverage and a third

[2]Code for both MOO algorithms is available at doi: 10.5281/zenodo.4495163

scenario with no coverage restriction (i.e., no minimum number of orders). The non-dominated solutions generated by NSGA-II and MORS are presented in Figures 4.5 and 4.6 for two levels of minimum coverage. The three objectives (time, cost, and coverage) are represented on the plot axes, while the colour scheme corresponds to the number of MFs placed within each solution.

Several patterns can be observed from Figures 4.5 and 4.6. An increase in the coverage of orders leads to a rise in the cost but has no direct impact on the delivery time. This is influenced by the CFs, which allows an order to be covered even though the total distance travelled increases. The average delivery time and the cost are negatively correlated. This results from the higher costs of MFs compared to CFs. A higher number of MFs in a solution corresponds to a lower average delivery time, higher costs, and higher coverage. The best-known non-dominated solutions obtained by MORS are similar in slope and the tendency of the trade-offs between the objectives. However, MORS cannot find reasonable trade-off solutions between the cost and time objectives. Unlike NSGA-II, MORS does not use Algorithm 3 to optimise the number of cryopreservation locations. For this reason, MORS is more likely to find extreme solutions by selecting both MFs and CFs at random, regardless of the coverage.

Table 4.1 shows the best values from all 20 runs for each objective for the three coverage scenarios. These are only extreme examples, and the more realistic trade-off solutions are shown in Figures 4.5 and 4.6. When the coverage was not constrained, NSGA-II found better solutions for cost and time objectives. Both algorithms found solutions that covered the entire demand. Because multiple solutions had no uncovered demand, the second order sorting when selecting the solution was done by cost. For a minimum of 50% or 80% coverage, MORS returned a better minimum cost, but the difference was negligible when benchmarking with the covered demand and delivery time.

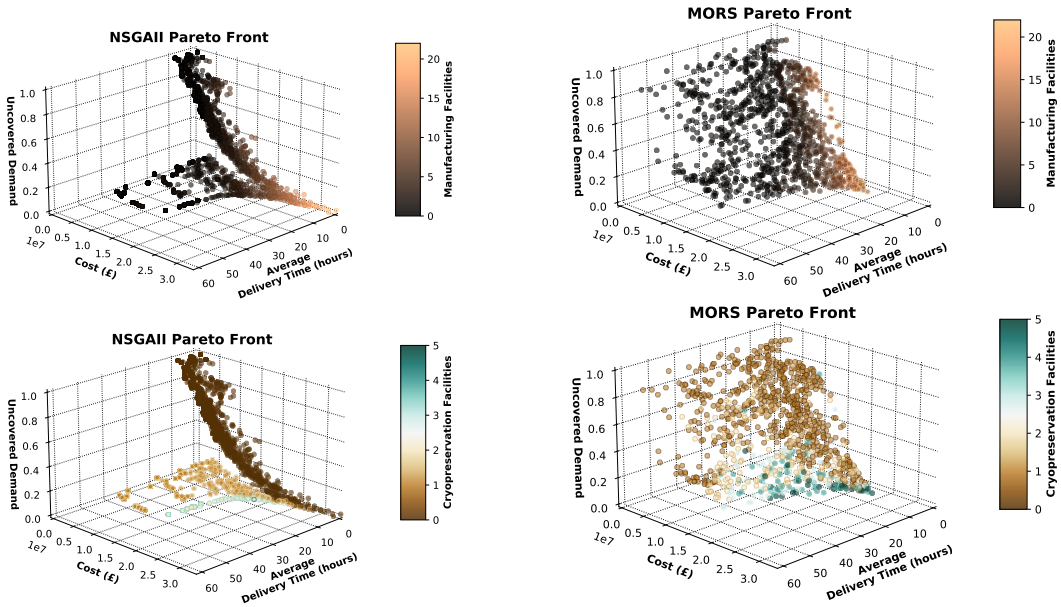


Figure 4.5: Non-dominated solutions obtained by NSGA-II (*left*) and MORS (*right*) when there are no coverage restrictions. The same solutions are shown in the top and bottom plots. The only difference is the colour that shows the number of manufacturing and CFs, respectively.

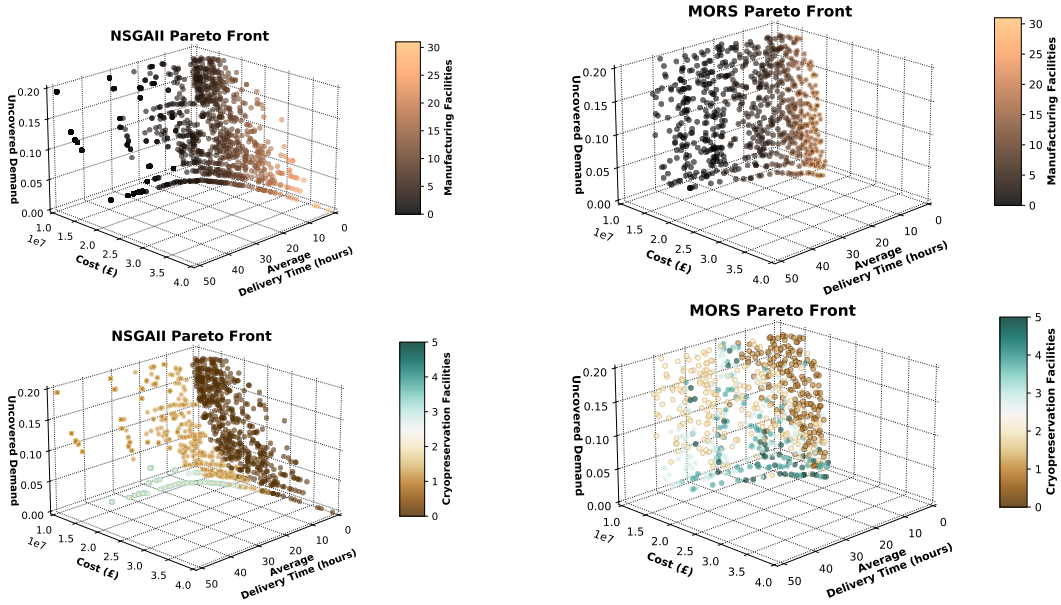


Figure 4.6: Non-dominated solutions obtained by NSGA-II (*left*) and MORS (*right*) when there is a minimum of 80% coverage restriction. The same solutions are shown in the top and bottom plots. The only difference is the colour that shows the number of manufacturing and CFs, respectively.

Table 4.1: Comparison of extreme solutions identified by NSGA-II and MORS for different coverage restrictions.

No Coverage Restrictions

	NSGA - II					MORS				
	Uncovered Demand	**Average Delivery Time**	**Total Cost**	**Configuration**		**Uncovered Demand**	**Average Delivery Time**	**Minimum Cost**	**Configuration**	
Minimum Cost	98%	6 hours	**£934,848**	Manufacturing Cryopreservation	1 0	93%	15.6 hours	£1,648,944	Manufacturing Cryopreservation	1 1
Minimum Average Delivery Time	95%	**40 minutes**	£2,336,130	Manufacturing Cryopreservation	2 0	75%	56 minutes	£8,322,743	Manufacturing Cryopreservation	6 1
Maximum Coverage	**0%**	21.7 hours	£12,969,249	Manufacturing Cryopreservation	1 2	**0%**	21 hours	£12,914,729	Manufacturing Cryopreservation	1 3

50% Coverage Restrictions

	NSGA - II					MORS				
	Uncovered Demand	**Average Delivery Time**	**Total Cost**	**Configuration**		**Uncovered Demand**	**Average Delivery Time**	**Minimum Cost**	**Configuration**	
Minimum Cost	50%	5 hours	£8,029,810	Manufacturing Cryopreservation	2 0	50%	27.7 hours	**£7,114,973**	Manufacturing Cryopreservation	1 1
Minimum Average Delivery Time	16%	**1.7 hours**	£20,631,568	Manufacturing Cryopreservation	22 0	31%	3 hours	£18,116,561	Manufacturing Cryopreservation	10 1
Maximum Coverage	**0%**	21.6 hours	£12,677,729	Manufacturing Cryopreservation	1 2	**0%**	23.4 hours	£13,238,729	Manufacturing Cryopreservation	1 3

80% Coverage Restrictions

	NSGA - II					MORS				
	Uncovered Demand	**Average Delivery Time**	**Total Cost**	**Configuration**		**Uncovered Demand**	**Average Delivery Time**	**Minimum Cost**	**Configuration**	
Minimum Cost	19%	30 hours	**£10,866,954**	Manufacturing Cryopreservation	1 1	20%	23.5 hours	**£10,443,065**	Manufacturing Cryopreservation	1 2
Minimum Average Delivery Time	3.6%	**36 minutes**	£34,589,842	Manufacturing Cryopreservation	6 0	16%	1.7 hours	£19,083,259	Manufacturing Cryopreservation	9 1
Maximum Coverage	**0%**	2.6 hours	£28,047,023	Manufacturing Cryopreservation	1 2	**0%**	20 hours	£12,969,729	Manufacturing Cryopreservation	1 3

For minimum delivery time, NSGA-II found better solutions than MORS with better coverage but overall worse total cost. Similar to the no coverage restriction scenario, both algorithms found solutions that covered the entire demand.

To exemplify one of the solutions in the Kymriah case study, we have filtered the solutions of both algorithms to match the current Novartis' location. Kymriah is manufactured at the Morris Plains, USA. Among our final solutions, NSGA-II had 68 unique solutions that had placed at least a MF within a 50 km radius of the above location for the 80% coverage restriction, 31 for the 50%, and 30 when no coverage restriction was imposed (MORS returned 28, 21, and 14 solutions respectively). The best solution in terms of coverage, breaking ties according to average delivery time, was returned by NSGA-II and the entire solution representation is shown in Figure 4.7.

The total cost of this solution is £32,850,481 with an average delivery time of approximately one hour. The solution has 6 MFs, one placed at the current Kymriah location, and 2 CFs. Given the higher number of hospitals on the eastern half of the USA, there were considerably more MFs placed here compared to the western side. This distribution leads to a lower average delivery time, but the overlapping of manufacturing radiuses indicates that it is possible to reduce the cost by gradually increasing the time objective. Finally, because we assume that the orders are assigned only from existing hospitals, there are areas of the USA uncovered. Since hospitals within those areas can obtain FACT authorisation, the demand coverage would be reduced. In terms of resiliency, this configuration has a high backup coverage in case of possible disruptions to one of the production sites, as all hospitals are within the shelf-life radius of a CF. Nevertheless, given the unbalanced distribution of hospitals between the two facilities, one might become overloaded, and the solution becomes infeasible should capacity constraints be considered.

The interpretations regarding absolute values for cost and time should be restricted only to the parameters and variables considered in the problem presented. The supply chain of ATMPs is more complex, and the final price of a product is usually a result of multiple factors, such as the quality of raw materials, supplier agreements, or Research and Development (R&D). The cost formulation in our problem considers only the production cost, which includes labour and one pre-defined quality of raw materials (previously detailed in Section 4.5).

Finally, we want to analyse the convergence behaviour of the two MOO algorithms. For this, Figure 4.8 shows the average hypervolume (HV) and the corresponding 95% confidence interval obtained by our NSGA-II and MORS. Our NSGA-II can achieve significantly higher HV values than MORS when compared with the same initialisation

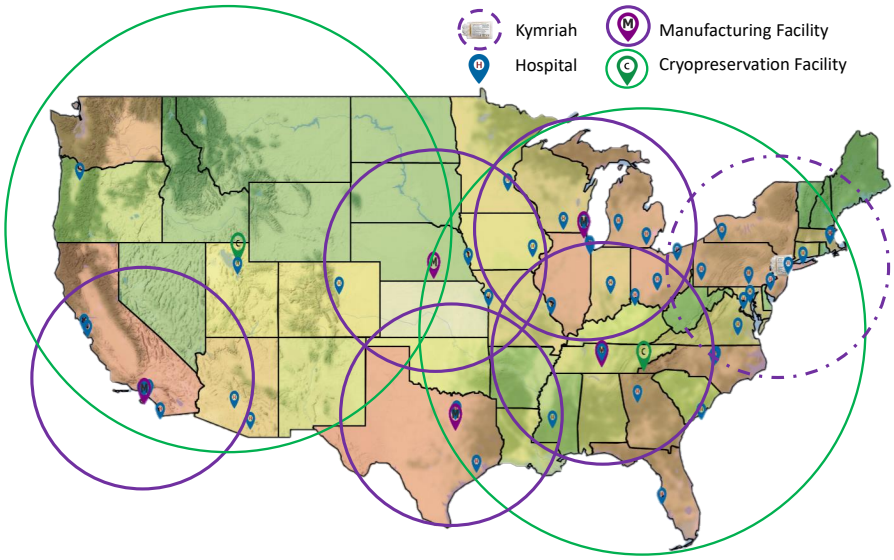


Figure 4.7: USA map with the demand layer, hospitals (order locations), manufacturing (shelf-life radius in purple) and cryopreservation (shelf-life radius in green) facilities. The dashed circle corresponds to the radius of the current location of Kymriah.

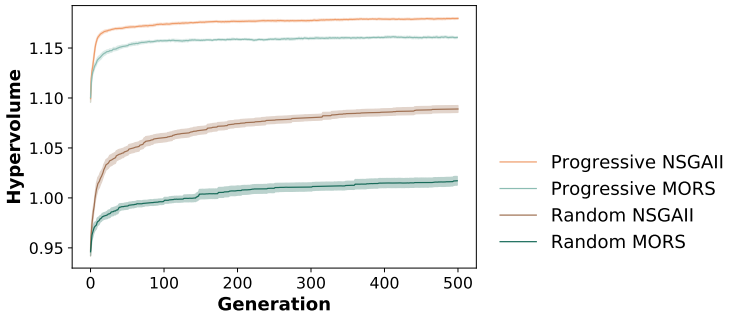


Figure 4.8: Algorithms performance comparison between NSGA-II and MORS using the two different initialisation procedures, progressive (Algorithm 3) or random.

procedure. However, the algorithms using the progressive coverage initialisation (Algorithm 3) perform better overall than those applying a random initialisation, which shows that the proposed initialisation is critical. Moreover, even though both algorithms are faster at the beginning, NSGA-II continues to improve, indicating that better solutions can be obtained using more generations.

4.8 Conclusion and Future Research

Progressing the field of PM has essential implications. Breakthrough therapies create possibilities to treat life-endangering diseases for which no other feasible treatment. Nevertheless, existing research in logistics and supply chain management does not provide sufficient knowledge to sustain personalised healthcare commercialisation. Novel formulations that integrate different supply chains and continuous theoretical development of the requirements of the PM products are essential.

We have presented a multi-objective mathematical model for a PM supply chain and analysed the performance of two MOO algorithms. A novel initialisation procedure considering progressive coverage of cryopreservation was also proposed and found to be superior to the random one for both algorithms. The model captured trade-offs between cost, delivery time, and demand coverage in FLP and was validated for three scenarios representing constraints on different coverage levels. Broadly translated, our findings indicate that the operations research field has the potential to help biopharmaceutical companies offer timely and cost efficient products, thus making revolutionary therapies more widely available.

The recommendations presented in this paper should be interpreted in light of the data and the search space used in solving the proposed formulation. The model does not perfectly mimic the real-world case where different production modes are used. We have also assumed a perfect turnover where no manufacturing fails, and hence all orders are returned to the patient without further delays. However, this is not always the case, and further extensions of this model can focus on integrating failure rates into the mathematical model. Moreover, we have also considered only a snapshot time period. However, the demand is usually fluctuating, and a more realistic approach to this problem

would be by integrating time periods and forecasted demand.

The current study has limitations and can be further developed using different approaches. For instance, the thawing necessary after freezing the product increases the risk of damaging the material (Panch et al., 2019; Hanley, 2019). Thus, future research considering cryopreservation methods with variable shelf-life might extend the current research towards a more resilient and safe supply chain. Maintaining the cells viable is crucial as the possibility of replacements is minimal. The autologous process involves patients with advanced stage diseases, and the poor health condition might preclude another apheresis procedure. Finally, the novelty of the products and the uncertain global demand require the implementation of stochastic models.

Chapter 5

Manufacturing and Algorithm Configuration for the Centralised Supply Chain

5.1 Abstract

Personalised biopharmaceuticals are some of the most promising treatments for curing progressive and rare genetic disorders. Nevertheless, patient level granularity complicates their commercialisation on a large scale. A low global demand, lengthy manufacturing processes, and the need for cold transportation are slowing down an already critical supply chain. Studies concerned with the optimisation of the delivery of these products are scarce and vital bottlenecks have not been sufficiently addressed. In this paper, we reformulate the strategic level of the personalised biopharmaceuticals supply chain and solve the corresponding FLP. To account for manufacturing production, we extend a previously proposed mathematical model for the FLP of the two main facility types in PM. We solve the problem using NSGA-II and MORS as benchmarks. We look at different algorithm configurations using *irace* to better understand the relationship between the two facility types. The data used to test the above formulation and their practical implications is made using three case studies of currently approved C&GTs for an estimated global demand. Our results suggest that using the current centralised supply chain model might be sub-optimal for PM.

5.2 Introduction

The biopharmaceuticals developed under PM, formally defined as autologous ATMPs, use a patient's cells, genes, or tissue to create therapies designed for each individual. In most cases, the ATMPs are breakthrough medicines tailored for progressive diseases, such as last stage cancer or rare genetic disorders. They could overcome the fact that traditional drugs are only efficient for 60% of the population (Ermak, 2016). Given their potential and recent clinical results, almost half of the yearly approved medicines are personalised. There are 42 ATMPs currently with commercial authorisation (Eder and Wild, 2019) and over 2000 clinical trials (Alliance for Regenerative Medicine, 2019).

Despite the clinical potential of the ATMPs, their global delivery has imposed significant challenges for biopharmaceutical companies and policymakers (Abou-El-Enein et al., 2016). The healthcare industry's mass-production and off-the-shelf supply chain model is not feasible for PM. The ATMPs are manufactured on-demand and in patient specific batches. The high-level stratification, alongside critical bottlenecks, such as short shelf-life, in a critical healthcare supply chain, make these products available only on a small scale.

The ATMPs supply chain usually starts at specialised hospitals that have obtained FACT approval (Warkentin, 2009). Here, the patient's blood is collected and, depending on the ATMP type, certain cells are separated through a leukapheresis process. The resulting product is transported to a MF, re-engineered before being returned to the same patient. The shelf-life of these cells between collection time and administration is short and varies between a few hours and a few days. For this reason, the ATMPs are usually transported under cryogenic temperatures to preserve the quality and validity of the cells. The ultra-cold supply chain adds additional difficulty as the cells are typically frozen at

an independent CF before being transported to the MF.

Research focused on the FLP of MFs and CFs of ATMPs is limited. In their majority, the existing studies do not consider the CFs or asn. In Avramescu et al. (2021b), we have previously proposed a mathematical model that considers both types of facilities; however, the manufacturing process was not considered. The case study was only presented at national demand for USA and did not resemble a real-world global demand scenario. In terms of solution methods, the standard FLP is a well-known NP-hard problem and using exact solution methods is usually feasible for problems with low complexity, such as small problem instances and a single objective (Melo et al., 2009). For multi-objective problems with heuristic methods were favourable for decision spaces, which is most commonly the case for real-world scenarios, heuristic methods were favourable, among which genetic algorithms were widely used (Ahmadi-Javid et al., 2017b). In addition to our previously proposed algorithms, we aim to improve their performance by testing different operators and initialisation procedures using automatic algorithm configurations with the *irace* package (López-Ibáñez et al., 2016). The CFs and MFs are not fully independent, so we hypothesise that the relationship between the two facility types if accounted for in the optimisation process, will lead to a faster convergence.

In summary, this paper makes the following contributions beyond our previous work:

- **Problem Formulation:** In this paper, we extend the initially proposed supply chain design to consider the manufacturing process. Previously, we have only looked at the delivery time between hospitals and the two types of facilities. However, each order needs to be re-engineered alongside transportation, which is a lengthy and expensive process. We look at understanding how different modes of production proposed in the literature will affect the location of the MFs based

on a mode-dependent failure rate, cost and process duration.

- **Applications:** In addition to the USA level demand of 1 ATMP that we initially analysed, we now look at the global demand of 2 ATMPs with different levels of authorisations, leading to 3 case studies in total. Accordingly, the sets of hospitals and candidate locations and the number and size of problem instances are more significant.

- **Solution Methods:** Previously, we have shown that due to the interdependence between CFs and MFs, an intelligent initialisation procedure for the two algorithms leads to significantly better results. We continue this research and apply automatic algorithm configuration methods using *irace* (López-Ibáñez et al., 2016) to analyse the performance of different operators and initialisation procedures.

The remainder of this paper is structured as follows. Section 5.3 will outline the current research on the PM supply chain, and, more generally, the FLP problems in some of the key healthcare sectors, such as VSC, SHOB or SHOO. Section 5.4 describes the supply chain design and the proposed mathematical model. The focus will be on the manufacturing extension, while a detailed description of the initial formulation is available in Avramescu et al. (2021b). Section 5.5 presents the data used for the case study, namely the demand estimation for each ATMP, the cost and duration of the manufacturing modes, and their corresponding failure rate, as well as the distribution of the hospitals and candidate locations. The algorithms and the proposed initialisations and operators are introduced in Section 5.6, with the experimental results discussed in Section 5.7. The paper concludes with an overall conclusion and directions for future research in Section 5.8.

5.3 Background

Discrete FLP is a class of optimisation problems that involve choosing locations for facilities from a given set of potential sites subject to one or multiple objective functions and constraints. It is one of the most widely studied topics in supply chains and has led to extensive literature. For this reason, in the broader context of the healthcare supply chain, we only focus our review on the differences between ATMPs and other medical products regarding objective functions and constraints to highlight the need for new supply chain configurations. For detailed surveys on medical applications in OR and FLP problems in healthcare, see Melo et al. (2009), Rais and Viana (2010) and Ahmadi-Javid et al. (2017a). We then present the existing research in optimisation related directly to ATMPs, considering both formulations and solution methods.

Objective Functions. The ATMPs are non-emergency biopharmaceuticals, and hence they share common characteristics with different healthcare supply chains, such as blood, vaccine or organ donation. Nevertheless, none of the existent models fully capture the inherent attributes of PM. For example, as service-oriented supply chains, one of the key requirements within healthcare is ensuring access to medicines and preventing drug shortages (Nematollahi et al., 2017). For this reason, the guarantee of perfect demand coverage is one of the main constraints considered in the literature, and it is rarely modelled as an objective alongside cost and time minimisation. The ATMPs are not part of the emergency and essential medical systems (Burkholder et al., 2019), and thus ensuring that all hospitals have access to the products is not a requirement. Furthermore, these therapies are usually a one-time treatment and relocating patients to hospitals that can offer ATMPs could lead to more cost-efficient and equitable supply chain configurations.

Constraints. Critical concerns for ATMPs, such as short shelf life, low demand, and the need for a cold supply chain, are also principal constraints in some more mature healthcare networks. Nevertheless, the ATMPs are distinctly fragile products that require transportation under cryogenic temperatures if a MF is not within the shelf-life radius of the collection hospital. Moreover, ATMPs require lengthy manufacturing processes, which is a constraint briefly met in the pharmaceutical industry, VSC, and to an even lesser extent in SHOB. Overall, little attention has been given to the supply chain of biopharmaceuticals (Kaminsky and Wang, 2015), which is now challenged by a high level of personalisation (Vieira et al., 2019a). The lack of an optimised supply chain leads to complex and inefficient manufacturing. Alongside a lack of historical data proving the products' efficiency due to the low number of approved therapies, many regulatory bodies are reluctant to offer market authorisations (Gonçalves, 2020). Iapplyingtimal to apply decision tools specifically developed for the more traditional healthcare supply chains in PM.

5.3.1 Facility Location Problems for ATMPs

The recent developments and the breakthrough authorisations pf ATMPs starting in 2017 (Ramezankhani et al., 2020) have recently led to increased attention to the requirements of PM from an OR perspective. Wang et al. (2018b) and Moschou et al. (2020) proposed scenario-based bi-objective FLP mathematical models for the delivery of CAR-T treatments, a type of ATMP. The studies aim to find the optimal location of MFs in a case study considering UK level of demand. Both models maximise the net present value (NVP, i.e., aiming to find whether the projected financial gains of the specified ATMP will outweigh the initial/current investment) while minimising the waiting time

per patient. The conclusions of the two studies align with the recommendations of Sarkis et al. (2021b), which suggest that the PM could benefit from further research on the optimisation of delivery and manufacturing. Nevertheless, both studies focused on small scale case studies with estimated demand, which were solved using exact solution methods.

As previously mentioned, FLP are NP-hard problems (Farahani et al., 2010) and using exact algorithms becomes quickly infeasible when considering real-world problems, such as the problem presented here and following a global medical demand. Karakostas et al. (2020) addressed this limitation in the case of FLP products using a General Variable Neighborhood Search (GVNS) algorithm. Moreover, compared to the above papers, which use a centralised supply chain network, this paper follows the SHOB models and tests the use of mobile medical units and local treatment facilities.

The limited number of papers investigating the ATMPs supply chain contrasts with the rapid developments from a medical perspective. This indicates the need for additional optimisation models and solution methods to assist with the delivery and development on a large scale of PM. Upon discussing the placement of facilities, all previous studies were limited to finding the optimal location of MFs or local treatment centres while disregarding CFs from the configuration or considering their location already known. This paper addresses this gap and proposes a model that optimises the location of both MFs and CFs while also optimising the type of MFs based on the mode of production. With one exception, the previous academic research on this topic focused on problem formulation, disregarding the large decision spaces inherent to the real-world scenario of ATMPs. Finally, the data was estimated at the national level or randomly generated. Therefore, we present two case studies of ATMPs with market authorisation using the

current global demand and treatment centres and solve them using two automatically-configured meta-heuristic algorithms.

5.4 Mathematical Model

The modelling work in this paper incorporates the view of a central decision maker, who aims to find optimal locations for the required facilities and assign the patients' orders. As part of the ATMP supply chain, MFs will process the product, while CFs can handle the temperature sensitivity and shelf-life constraints. The network configuration should lead to a low cost and waiting time and ensure that as many patients as possible can be offered the ATMP. Unlike the first two objectives, which are usual in the healthcare supply chain literature, the third objective is more commonly treated as a constraint. However, the current personalised ATMPs are unavailable at all hospitals. In our case, we do not ensure perfect coverage since we start the supply chain from the hospital and assume that patients could travel to the hospitals that can offer ATMPs. In other words, the coverage refers to the hospital, not the patients.

Our model's time and cost depend on the production mode used. A mode refers to the manufacturing steps necessary to produce an ATMP, from cell collection to administration. Biopharmaceutical companies constantly develop new manufacturing modes since optimising the manufacturing process is an active research area. To exemplify what different modes look like, we use the classification created by Lopes et al. (2020) into *fully manual*, *semi-automated*, and *fully automated* manufacturing. The three production modes differ in their reliance on automated systems and skilled labour resources. For instance, a fully automated process can increase the production capacity per facility, reduce the duration of the processing, and reliance on skilled labour. Nonetheless, the

high investment in automated systems required to operate such a facility might not be profitable in areas with very low demand, characteristic of PM products.

The production modes are also linked to the possibility of damaging the cells and can lead to product failure (Lopes et al., 2020). If an order does not pass the quality checks (Quality Assurance (QA) and Quality Control (QC), it cannot be returned to the patient, the ATMP is discarded, and the entire supply chain is restarted. In our model, we thus assume a corresponding failure rate for each production mode and increment the cost and the waiting time accordingly. This failure rate can, however, be extended in future models to account for the patient's health condition, which can affect the quality of the starting product.

Indices and Parameters

$i \in I$	Demand nodes (individual orders).
$j \in J$	Candidate facility locations.
$k \in K$	Manufacturing modes (e.g., manual, semi-automated, automated).
t_{ij}	Travel time between (facility or demand node) locations $i, j \in I \cup J$.
$s_j^{\mathrm{M}}, s_j^{\mathrm{C}}$	Setup cost (e.g., construction) of a facility at location $j \in J$.
$c_{ijk}^{\mathrm{f}}, c_{ijk}^{\mathrm{z}}$	Operation cost per fresh (f) and frozen (z) order covered that depends on the order i, location j and the mode k.
$p_k^{\mathrm{f}}, p_k^{\mathrm{z}}$	Production time per fresh (f) and frozen (z) order for mode $k \in K$.
r_k	Failure rate, within $[0, 1]$, of manufacturing for order $i \in I$ when using mode k.
γ	Shelf-life constant when order is processed as fresh cells.
T	Constant larger than any travel time.

Decision Variables

$x_j^{\mathrm{M}}, x_j^{\mathrm{C}}$	1 if a manufacturing (M) or cryo-preservation (C) facility is opened at candidate location $j \in J$; 0 otherwise.
$y_{ij}^{\mathrm{M}}, y_{ij}^{\mathrm{C}}$	1 if demand location $i \in I$ is covered by the manufacturing (M) or cryo-preservation (C) facility at candidate location $j \in J$; 0 otherwise.
z_i	1 if demand order $i \in I$ is cryo-preserved; 0 otherwise.
m_{jk}	1 if facility at location $j \in J$ is assigned a manufacturing mode $k \in K$; 0 otherwise.

Personalised Medicine Centralised FLP Model

$$
\begin{aligned}
&\text{Objectives} && \min\ W && && (5.1.1)\\
&&& \min\ C && && (5.1.2)\\
&&& \max\ V && && (5.1.3)\\
&\text{Constraints} && \sum_{j\in J} y^{\mathrm{M}}_{ij}\cdot t_{ij} \le \gamma + z_i\cdot T && \forall i\in I && (5.1.4)\\
&&& \sum_{j\in J} y^{\mathrm{C}}_{ij} t_{ij} \le 24\,\text{hours} && \forall i\in I && (5.1.5)\\
&&& \sum_{j\in J} y^{\mathrm{M}}_{ij}\cdot t_{ji} \le \gamma + z_i\cdot T && \forall i\in I && (5.1.6)\\
&&& \sum_{j\in J} y^{\mathrm{M}}_{ij} \le 1 && \forall i\in I && (5.1.7)\\
&&& \sum_{j\in J} y^{\mathrm{C}}_{ij} \le z_i && \forall i\in I && (5.1.8)\\
&&& y^{\mathrm{M}}_{ij} \le x^{\mathrm{M}}_{j} && \forall i\in I, j\in J && (5.1.9)\\
&&& y^{\mathrm{C}}_{ij} \le x^{\mathrm{C}}_{j} && \forall i\in I, j\in J && (5.1.10)\\
&&& x^{\mathrm{M}}_{j} + x^{\mathrm{C}}_{j} \le 1 && \forall j\in J && (5.1.11)\\
&&& \sum_{k\in K} m_{jk} = x^{\mathrm{M}}_{j} && \forall j\in J && (5.1.12)\\
&&& y^{\mathrm{M}}_{ij},\ y^{\mathrm{C}}_{ij},\ x^{\mathrm{M}}_{j},\ x^{\mathrm{C}}_{j}, z_i,\ m_{jk} \in \{0,1\} && && (5.1.13)
\end{aligned}
$$

Objective 1: Waiting Time. The waiting time is the time that a patient (represented by order $i \in I$) must wait from their cells being collected (leukapheresis) until the ATMP is administered. The steps differ slightly depending on whether the order is processed fresh or frozen.

Let us assume, for simplicity, that leukapheresis time is already included in all travel times starting from each demand location $i \in I$ since this is relatively constant between patients. Similarly, administration time is included in the travel times to each demand location for the same reason. Then, for a fresh order (f), the waiting time corresponds to the travel time from/to the demand location $i \in I$ and its assigned MF in location $j \in J$. It also accounts for its production time, which depends on the manufacturing mode $k \in K$. If the order is cryopreserved, we first visit a CF at location j' and then a MF at location j.

Therefore, by taking into account whether order i is cryopreserved (z_i) or not, the

waiting time for order i can be expressed as:

$$\sum_{j\in J} y_{ij}^{\mathrm{M}} \Big[\underbrace{(1-z_i)t_{ij} + z_i\Big(\sum_{j'\in J} y_{ij'}^{\mathrm{C}}(t_{ij'}+t_{j'j})\Big)}_{TimeToManufacture(i,j)} + \underbrace{\sum_{k\in K}\Big((1-z_i)p_k^{\mathrm{f}} + z_i p_k^{\mathrm{z}}\Big)m_{jk}}_{ProductionTime(i,j)} + \underbrace{t_{ji}}_{TimeToPatient(i,j)} \Big] \quad (5.1)$$

For each mode k at a facility location j, the failure rate $r_k \in (0,1)$ gives the probability of production failure. Therefore, assuming a single failure, the process leading to $TimeToPatient(i,j)$ will be multiplied by $1+r_k$ times. Thus the total waiting time is calculated as follows:

$$W = \sum_{i\in I}\sum_{j\in J} y_{ij}^{\mathrm{M}} \Big[\big(1+\sum_{k\in K} r_k m_{jk}\big)\big(TimeToManufacture(i,j) + ProductionTime(i,j)\big) + TimeToPatient(i,j)\Big] \quad (5.2)$$

Even though a perpetual failure is more likely in many industries, given the severity of the consequences on the patient and the high cost of the product, once an ATMP order fails, it is improbable to be allowed to happen again.

Objective 2: Cost. Each facility type has a setup cost $s_j^{\mathrm{M}}, s_j^{\mathrm{C}}$ that depends on the location and an operation cost $c_{ijk}^{\mathrm{f}}, c_{ijk}^{\mathrm{z}}$ that depends on the order i, the location j, the manufacturing mode k, and whether an order is fresh (f) or frozen (z). It already takes into account resources and transportation for each order. Thus, the total cost (without

considering failures) of the supply chain is given by:

$$\sum_{j\in J}\left(s_j^{\mathrm{M}}x_j^{\mathrm{M}}+s_j^{\mathrm{C}}x_j^{\mathrm{C}}\right)+\sum_{i\in I}\sum_{j\in J}\sum_{k\in K}y_{ij}^{\mathrm{M}}m_{jk}\left((1-z_i)c_{ijk}^{\mathrm{f}}+z_ic_{ijk}^{\mathrm{z}}\right) \tag{5.3}$$

If manufacturing fails, we need to process the complete order again, which can be modelled as a factor that increments the operation costs:

$$C=\sum_{j\in J}(s_j^{\mathrm{M}}x_j^{\mathrm{M}}+s_j^{\mathrm{C}}x_j^{\mathrm{C}})+\sum_{i\in I}\sum_{j\in J}y_{ij}^{\mathrm{M}}\sum_{k\in K}\left(1+r_k\right)m_{jk}\left((1-z_i)c_{ijk}^{\mathrm{f}}+z_ic_{ijk}^{\mathrm{z}}\right) \tag{5.4}$$

Objective 3: Coverage. Since each order must be fulfilled by one MF, the total coverage, that is, the number of demand orders that can be covered or, in other words, the number of patients that can receive the therapy is given by:

$$V=\sum_{i\in I}\sum_{j\in J}y_{ij}^{\mathrm{M}} \tag{5.5}$$

Constraints. The most critical constraints concern the shelf-life γ, typically no more than a few days, of the ATMP, corresponding to order $i\in I$, which represents the maximum travel time either to (5.1.4), or from (5.1.6) the MF. Regardless of the route taken, the return travel distance is always symmetric. The shelf-life to travel to a CF is more strict (preferably no more than 24 hours, which is always less than γ) to compensate for the damage caused by the freezing process (5.1.5). After cryopreservation, shelf-life is unlimited for all practical purposes. Hence, we disable constraints (5.1.4) and (5.1.6) using a very large shelf-life T if the order is cryopreserved ($z_i=1$). In our case, this is a realistic assumption since we do not consider any intermediary storage in the case of ATMPs, and, hence, the shelf-life of frozen cells would never be exceeded.

Other constraints ensure that each order is assigned to no more than one MF (5.1.7),

each order is assigned to no more than one CF only if the order is cryopreserved (5.1.8). Each order is assigned to a facility at a given location if a facility of that type is open at that location (5.1.9) and (5.1.10). Only one facility type may be opened at the same location (5.1.11), and one, and only one, production mode is assigned at each location, and only if there is an open MF at that location (5.1.12).

5.5 Data

We tested the applicability of the proposed model and the solution methods on two ATMPs, Kymriah and Yescarta. Kymriah was the first CAR-T therapy to obtain market authorisation in August 2017 in the USA (CBER, 2017a). The initial approval was for treating children and young adult patients (i.e., up to 25 years) suffering from ALL that is r/r (*case study one*). More recently, the approval was extended for the treatment of adult patients with r/r diffuse large B-cell lymphoma (DLBCL), a common type of a non-Hodgkin lymphoma cancer (NHL) (*case study two*) (Ali et al., 2020). Yescarta first obtained market authorisation in October 2017 for the treatment of adult patients with r/r DLBCL and primary mediastinal large B-cell lymphoma (PMBCL) after at least two lines of treatment have failed (CBER, 2017b) (*case study three*). We used these approvals as guidelines to calculate the global level of demand for each ATMP, separating adult and paediatric hospitals.

The commercialisation approval is a continuous process, both geographically and medically, which affects the countries where the ATMPs can be delivered and the number of patients (i.e., calculated based on the number of medical conditions and patient demographics). This study does not consider the gradual demand expansion usually caused by additional authorisations. We leave the integration of time periods for

future research, which will likely impact the facility's locations, should uncertainty and disruptions be considered.

The data used to calculate the demand for the two ATMPs was obtained from the Institute for Health Metrics and Evaluation (IHME) (Institute for Health Metrics and Evaluation (IHME), 2022). We used the prevalence (i.e. a measure of the frequency of disease at one point in time) of ALL and NHL, respectively. From the overall cases of ALL, around 80% are B-precursor (Sexauer et al., 2020) and about 20% of these will be r/r (Sun et al., 2018) in pediatric patients. DLBCL is one of the most common NHL types and accounts for 40% of all cases (Lukenbill and Hill, 2014), among which 30% will be r/r (Martelli et al., 2013). PMBCL is a rare cancer type and only accounts for about 4% of all NHL cases (Dabrowska-Iwanicka and Walewski, 2014).

The ATMPs can only be delivered to patients at FACT accredited hospitals. The list of hospitals that accept autologous ATMPs was obtained from FACT (Foundation for the Accreditation of Celular Therapy, 2021). The higher number of authorisations in the USA compared to other parts of the world leads to a larger density of FACT hospitals. The global demand for each ATMP was distributed equally to all hospitals. The set with candidate locations L for the MFs and CFs was created by assigning an equal number of locations randomly (following a uniform distribution) in each country (or state for the USA) that had demand for either ATMP up to 1 000.

5.6 Methodology

To solve the proposed model, we have used a multi-objective genetic algorithm, NSGA-II, and random search adapted for multi-objective problems (MORS) as the baseline.

NSGA-II is a popular fast sorting elitist genetic algorithm (Deb et al., 2002b). In

	Adult patients	Paediatric patients
Asia	5	1
Europe	16	0
Oceania	11	6
North America	124	83
South America	2	1
TOTAL	157	92

Table 5.2: Number of hospitals that accept autologous ATMPs for adult and paediatric patients with breakdown by continent.

the population used as a sample for optimisation at each generation, an individual (or solution) is said to be non-dominated if (i) its objective values are not strictly worse than the objectives of another solution and (ii) at least one of its objectives is better than that of another individual. Following this rule, the individuals are then divided into fronts. Front 1 contains all non-dominated individuals. Front 2 contains all individuals dominated only by the solutions in the first front, and so on. The higher fronts thus populate the next generation until the population size is reached. If the last front exceeds the population size, crowding distance is applied to the last inserted front. The crowding distance favours diverse solutions, i.e., those on more sparsely populated parts of the front.

To create new individuals NSGA-II uses crossover and mutation operators. From a list of proposed operators, we have then used *irace* to automatically choose the best algorithm configuration (López-Ibáñez et al., 2016), that is the combination of algorithm-initialisation-operators that lead to the best results.

As we have previously shown in Avramescu et al. (2021a), the **population initialisation** significantly impacted the quality of the solutions the algorithm found within a certain budget. The MFs are always placed randomly with a probability between (0, 1). To explore the impact of the number of each facility type in the initial population on the

optimisation process, we have further extended how the CFs are placed by comparing the following approaches.

- **Random:** the CFs are placed randomly with a probability of $1 - p$ where p is the probability of placing an MF. In our case, the random initialisation commonly used as starting point in iterative algorithms is placing both MFs and CFs in empty candidate locations. To not bias the algorithm's preference towards one facility type, both MFs and CFs have an equal probability of being located in a certain location.

  However, The above initialisation is more appropriate when there is either only one facility type or no interdependency between facilities. In PM, the CFs are used only as helper points for hospitals which are not within the shelf-life radius of a MFs, while for a product to be processed, it must be delivered to a MF thus, a CF is optional.

- **Progressive Coverage:** after the MFs are randomly located, calculate the remaining uncovered demand and order the candidate locations based on the highest coverage following the radius of CFs. A CF is then placed in the location that covers most hospitals. The process is repeated until all hospitals are covered. Each solution with MFs will have n solutions with CFs with different levels of coverage.

- **Change MFs to CFs:** after the MFs are randomly located, change n open MFs into CFs. The motivation behind this strategy is the influence of the MFs on the time and cost objective. A high number of MFs leads to a small delivery time, which is hard to be dominated by solutions in the following generations for that objective. A high number of MFs minimises the maximum distance to the closest

facilities, thus lowering the delivery time. However, they lead to a very high cost and configurations that are not applicable. Changing some MFs into CFs can then balance the number of facilities without adding additional ones. n is the number of MFs to be changed, and it can take any real number between 0 and the number of MFs placed in a solution minus 1. One facility should always exist in the solution, otherwise, that solution becomes invalid.

- **Change MFs to empty:** similarly to the above initialisation, after placing MFs, we calculate the demand allocated from hospitals to each facility (following a closest facility allocation rule) and using the same n parameter, we decide how many MFs to be closed.

For both initialisations that change MFs, we also apply an additional parameter that decides whether the MFs changed are the ones with the *highest* or the *lowest* demand.

The **crossover** is a genetic operator used to improve the quality of the solutions in the following generation by combining parts of the two parents from a current solution. We have used three popular crossover operators: one-point, two-point, and uniform crossover (Umbarkar and Sheth, 2015). In the first one, a point in the vector representation is selected randomly, and the tails of the chosen parent solutions are swapped. Similarly, a two-point crossover is a generalisation and splits the parent solutions at two randomly chosen points. The alternating segments are then swapped. The uniform crossover differs from the previous ones by treating each gene individually rather than as vector segments. In our case, the crossover is applied either to an MF or CF, and each gene represents a candidate location. Consequently, it uses a given probability to decide whether the two genes should be swapped. In our case, we have set the probability of applying a crossover equal to 0.5. The three crossovers are graphically presented using a toy example in

Figure 5.1.

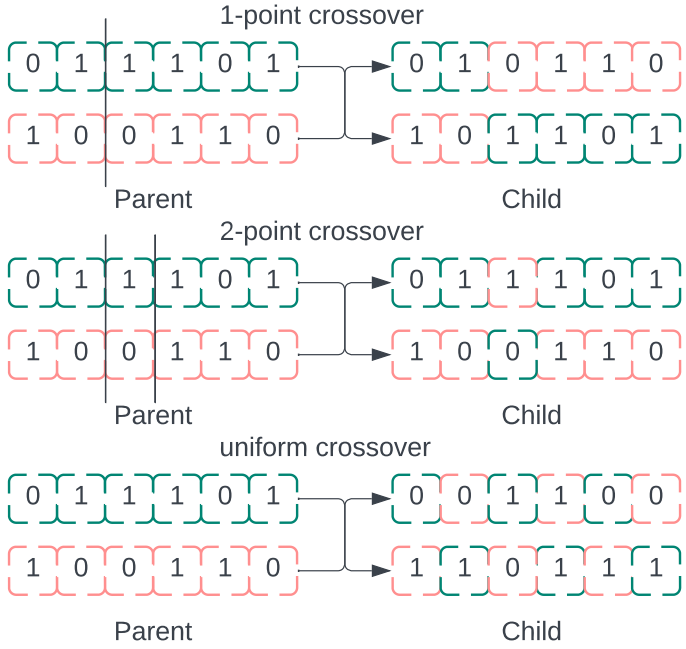


Figure 5.1: One and two-point crossovers.

The **mutation** is another genetic operator used to maintain diversity in the population between generations. The mutation we apply in this paper works by adding, removing, or moving a facility. Following the approach previously introduced in 4, we add a network-based move. It is an operation where the MF facility can be moved to an adjacent location. The network is a graph with the calculated distances between two adjacent candidate locations. In the network-based mutation, the swap can only happen to a location next to the one currently changed on the graph. Instead of comparing different mutations, we let *irace* decide the probability of adding and removing facilities with a choice between (0, 0.5) and step of 0.1. The probability of applying the network move is given by $1 - p_{add} + p_{remove}$ where p_{add} and p_{remove} are the probabilities of adding or removing a facility. The three mutations are graphically presented using a toy example

in Figure 5.2.

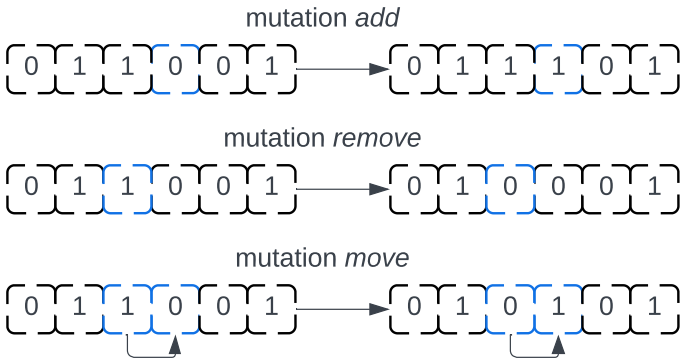


Figure 5.2: *Add*, *remove*, and *move* mutations.

Both genetic operators are applied only on the MFs vector and not on the CFs. This intentionally maintains the status of CFs only as helper facilities and maintains the problem as a variant of the uncapacitated FLP. All the moves executed on the CFs vector are a consequence of a previous move on the MFs. For example, if a MF is moved to a different location, then depending on the initialisation, the CF can also be moved to a location that leads to better objective values.

Another decision at each generation is whether to drop facilities with no demand allocated. We consider a facility to have demand if at least one hospital is allocated. At the end of each generation, the result population contains solutions with MF and CF opened, but that might not necessarily have any demand. We thus introduce a repair operator that allows *irace* to remove from each solution either the MFs or CFs, both, or neither facility types that do not have demand. While at the end of the optimisation process, it might always be desirable not to retain facilities with no demand since these would translate into construction costs without ever being functional throughout the algorithmic run, it can influence the algorithm's efficiency. The way the facilities are added to solutions would make the algorithms more prone to a lower number of facilities

since the only way to add MFs after the initial population is through the *add* mutation; there is no way to add CFs. A gradual probability for mutation and additional mutations that change based on the number of facilities in solutions could potentially prevent this issue, but these need to be problem specific.

The best algorithm configuration retrieved by *irace* on a budget of 1000 evaluations was then used. The generation number and population size were part of *irace* parameters set between (0, 10.000) and (2, 100), respectively. The following section will also analyse the behaviour of *irace* and the progress of the parameters throughout the evaluations. The complete list of parameters is shown in Table 5.3.

Parameter	**Option**	**Values**
Algorithm	choice	nsgaii, random
Initialisation CFs	choice	random, progressive, MFs to CFs, MFs to empty
Select number MFs	range	between 0 and 1
Manufacturing demand	choice	smallest, largest
Mutation *add*	choice	between 0.0 and 0.5, with step 0.1
Mutation *remove*	choice	between 0.0 and 0.5, with step 0.1
Crossover	choice	1-point, 2-point, uniform
Drop facilities	choice	both, MFs, CFs
Population size	range	between 2100
Generations number	range	between 50 and 6.000

Table 5.3: *irace* parameters.

Algorithm 5 presents the pseudocode for the NSGA-II, adapted from Coello et al. (2007). The parameters optimised by *irace* are underlined both here and in Algorithm 4, which presents the pseudocode for the various initialisations available.

To build up on the previous model introduced in Chapter 4, we have replaced the two binary vectors with an integer vector from 0 to 4 (0: empty; 1: CF, 2: MF with manual production mode, 3: MF with semi-automatic production mode, and 4: MF with

Algorithm 4 Initialisations

if random **then**
  Select MFs locations with probability *p*
  Select CFs locations in remaining locations with probability ***(1-p)/2***
else if progressive cryopreservation **then**
  Select MFs locations with probability *p*
  Add CFs using the progressive cryopreservation method ▷ calculated by Algorithm 3
else if MFs to CFs **then**
  Select MFs locations with probability *p*
  Compute allocated demand for each MF
  Select first/last r% of MFs by demand and transform them into CFs
else if MF to empty **then**
  Select MFs locations with probability *p*
  Compute allocated demand for each MF
  Remove first/last r% of MFs by demand
  Add CFs randomly
end if

Algorithm 5 NSGA-II

Create initial population with Algorithm 4
Drop unused facilities None/MF only/ CF only/ both and evaluate objectives
repeat
  Select parent population using non-dominating sorting and crowding distance
  Crossover
  Mutation
  Drop unused facilities None/MF only/ CF only/ both and evaluate objectives
until n^{th} generation is reached

automatic production mode). The decision to move from a binary representation to an integer vector was for ease of scalability of the problem for higher complexity. Like previously, we have 1000 locations, each with five facility possibilities. The problem size in this case is 5^{1000}.

5.7 Results and Discussion

5.7.1 Parameters Configuration

In a multi-objective problem, it is rarely the case that there is a single optimal solution, given that, in most cases, the objectives are conflicting. As a result, various set-quality indicators have been used to compare multiple algorithms. *irace* uses the HV which is a popular metric and commonly used in Evolutionary Multiobjective Optimisation Algorithms. The HV is a performance metric that measures the quality of a non-dominated approximation set. When assessing the algorithms' performance, it considers the spread and diversity of the solutions in the decision space and the approximation to the Pareto front (Guerreiro et al., 2020). The best algorithm configuration found using *irace* on the parameters presented above were as follows:

> A NSGA-II algorithm using a MF based initialisation with a probability 0.95 of placing a facility in an empty candidate location was preferred. Consequently, the CFs were placed by converting almost half of the MFs with the smallest allocated demand. The genetic operators are a classic uniform crossover with a variant of a two-point mutation where a MF is placed with 0.1 probability, removed with 0.2, and moved to an adjacent location with 0.7. The algorithm runs with a population size of 74 for 3313 generations. Only MFs with no allocated demand is dropped at each generation, while CFs are kept. The CFs with no demand are discarded in the last generation only.

The above configuration further suggests the importance of allocating the CFs only as helper facilities of MFs. Any random allocation that assumes the two facilities are independent was proven to lead to worse performance. The greedy coverage initialisation we have previously used does not correspond to the highest HV when extending the case study. Where the geographical space between facilities was limited, the greedy coverage created a few solutions with CFs for each solution with MF. Nonetheless,

a global level of demand automatically increases the number of facilities required to cover all hospitals. Greedy coverage will create many solutions with CFs for the same MF, slowing the algorithm's progress. Moreover, starting with a high number of MFs (e.g., 950/1000) means that the potential allocated demand is calculated for almost every candidate location. Creating a demand-based reduction of MFs will thus avoid placing facilities in areas with little coverage. Even though the best configuration is changing around half of the MFs to CFs, this number varies between 41% and 88% in the five best configurations (all elite configurations found by *irace* in the seven performed iterations can be found in Appendix A). This high percentage, together with the drop of MFs, is also a strong indicator that an increased number of such facilities does not lead to the best solutions. This is also the currently applied model in PM where a low number of MF locations are used, and the products are mostly cryopreserved at CFs rather than being directly transported as fresh cells.

5.7.2 Case Studies

Using the above best parameters for each problem instance, we did 15 independent algorithmic runs. To select the run that best mimics the average behaviour of the NSGA-II and to be in line with the performance indicator of *irace*, we continue to use the HV. The results presented onward correspond to the run whose HV was closest to the median value for each problem.

Figure 5.3 shows the candidate locations and their variance among the non-dominated solutions for each problem instance. The solution representation is a vector between 0 and 4, so a location can change to at most five values (0: empty, 1:CF, 2:MF with manual production mode, 3:MF with semi-automatic production mode, 4:MF with automatic

production mode). While the set of candidate locations between the 3 case studies is always the same, the location and number of hospitals vary. *Kymriah_ALL* can only accept paediatric patients where the hospitals are mainly distributed around North America, with only one hospital in Asia and 1 in South America. *Yescarta* has only adult patients, which can be accepted at a considerably higher number of hospitals, having coverage in Europe and Oceania as well. Finally, *Kymriah* refers to the current designation of the ATMP for ALL and DLBCL and hence can accept both paediatric and adult patients.

The 1000 candidate locations were chosen randomly from the 10.000 largest cities worldwide. Among these, more than half will never change their initial allocation. In other words, it means that if a solution starts with an MF in a certain location, then it is likely that the location will retain the MF position throughout the optimisation process. Similarly, as most of these are empty and far away from any hospital, many locations that do not have either an MF or CF in the initial population will not do so later. The placement of a CF close to the hospital is expected as the orders need to be transported within 24 hours. What is interesting is the low number of MFs that are outside the radius of their allocated hospitals. We expected more hospitals to share a MF than each of these demand locations to have an almost exclusive MF. This directly results from the high coverage rate in most non-dominated solutions. It is not common for the solutions with very high coverage to have a low number of MFs, indicating that most of the orders in these solutions would not need to first pass by a CF.

The overall number of CFs among the non-dominated solutions in any of the three problem instances is very low. Over 90% of the hospitals are allocated directly to an MF, and their orders are always transported as fresh. Moreover, none of the extreme solutions that show the values for each objective, in turn, shown in Table 5.4 have any CF. This result contrasts with the current PM configurations where almost all ATMPs with market

authorisation are first cryopreserved. A CF with a shelf-life of only 24 hours means it must be close to a hospital. It thus becomes quickly inefficient cost-wise to place many CFs despite their lower price compared to a MF since each CF could cover a low number of hospitals and hence a low demand. Moreover, whenever a candidate's location was near a hospital, for example, in the same city, that location almost always had a MF. These findings suggest that, for the current hospitals with FACT authorisation for personalised ATMPs, a fully centralised configuration that relies only on the placement of MFs and CFs to handle the production of the therapies seems to be sub-optimal.

The geographical distribution of hospitals for paediatric and adult patients is uneven between countries, leading to two possible main scenarios. The first scenario would create a supply chain with low construction costs. As the delivery time is usually short in these cases, any cost associated with transporting the patient cells and the ATMP would be negligible. Nevertheless, the number of hospitals that can be covered directly by a MF is small. The rest of the hospitals must pass by a CF, increasing the coverage but reducing the trade-off between cost and delivery time. The second scenario is focused more on maximising the coverage. In this case, the number of MFs necessary to be opened would be too high and correspondingly, the high cost reflected in the final price of the ATMP would be hardly justifiable.

5.8 Conclusion and Future Research

In this paper, we introduced an FLP problem for the PM with a focus on ATMPs that are fully personalised, having the patient and the donor as the same individual. The multi-objective formulation considers the two main facilities currently used in the ATMP supply chain, namely MFs and CFs. For each MF, we also looked at the best configuration in

	Minimum	Cost	Average Delivery Time	Uncovered Demand	Facilities			
					CF	MF with manual	MF with semi-automatic	MF with automatic
Kymriah ALL	**Cost**	**£ 7,113,396**	-	99%	0	1	-	-
	Average Delivery Time	£ 7,113,396	**-**	99%	0	1	-	-
	Coverage	£ 592,487,445	12h	**0%**	0	7	1	-
Yescarta	**Cost**	**£ 19,998,856**	22h	99%	0	1	-	-
	Average Delivery Time	£ 58,632,567	**-**	99%	0	1	-	-
	Coverage	£ 3,041,142,326	10h	**0**	0	7	5	1
Kymriah	**Cost**	**£ 7,071,396**	18h	99%	0	1	0	0
	Average Delivery Time	£ 64,994,963	**-**	98%	0	1	0	0
	Coverage	£ 3,627,637,771	8h	**0**	0	10	4	1

Table 5.4: Extreme solutions for cost, time, and coverage objectives for the three problem instances. The line (–) in "*Average Delivery Time"* indicates a rounding to 0 when the delivery was less than 1 hour. The rounding was preferred as, in all cases, a delivery time of less than 1 hour means that the MF was placed in the same city as the hospital, considering the set of candidate locations and the pre-calculated time.

manufacturing using a pre-defined set of manufacturing modes proposed in the literature. The aims of this paper were twofold. We wanted to understand better the relationship between the two facility types and how this influences the optimisation process. We did this by creating several initialisations for the NSGA-II with different levels of dependency between the MFs and CFs. Further, the three case studies used are existing ATMPs with commercial authorisation and were preferred compared to hypothetical scenarios to analyse the impact of the current supply chain on the cost, time, and the potential to cover all hospitals worldwide.

Our results suggest that treating the problem as a classic FLP disregarding the dependency between facilities might lead to sub-optimal results. Using *irace* to automatically configure the parameters available to the NSGA-II, we have shown that random initialisations that weight equally the MF and CF will take a longer computational time to find similarly good solutions than the use of problem specific initialisations. Moreover,

assuming that desirable solutions will not have a very large number of opened MFs due to their high construction costs, it was expected that the probability of placing a MF in a particular candidate location to be low. Nonetheless, this is not the case and an almost exhaustive demand calculation to possible candidate locations with a MF is preferred.

Based on these findings, we argue that PM supply chain, particularly at FLP level, could benefit further from an optimisation perspective, and the constituted problem has particularities that are worth researching further. Future research directions could focus on creating demand-based heuristics or interactive optimisation processes. For instance, similar to the initialisation used in this paper, one could consider combining multiple strategies that replace facilities based on certain conditions, such as minimum distance to a hospital or CF, a given number of MFs already existing in the solution, or changing facility type based on allocated demand. In addition, as the solutions found by any algorithm would eventually be used by a DM, using expert knowledge at the optimisation's beginning could lead to better or equally good solutions, but in less computational time and cost. One way to do that is to direct the algorithm towards finding solutions in one part of the Pareto front chosen by the DM.

It is worth noting that the results and conclusions made in this paper are based on the problem configuration and the assumptions made regarding demand, cost, and time. The data was built to reflect the current industry recommendations and the chosen case studies' inherent characteristics, such as demand and shelf-life. Nevertheless, different ATMPs can have more lenient or restrictive constraints to vary the supply chain configuration. Generally, the results obtained should remain the same given similar intervals presented in this paper, regardless of the exact costs. While the exact prices or delivery times can differ, a MF will always be more expensive to build and restrict the shelf-life constraint of the ATMP more than a CF.

Several research directions can be followed When looking at the application of the problem in the industry. Firstly, we restricted the MFs and CFs to be placed only in a set of 1000 possible locations. While this is a relatively large decision space, visualising the impact of changing the locations is worth investigating further. Many of the candidate locations used in this paper are outside the radius of MFs. These locations were not excluded since we assume that once the orders from a hospital are frozen (i.e., that hospital is within the radius of a CF), the shelf-life constraint is deactivated. However, the algorithm's tendency to place MFs close to hospitals rather than, for example, mid-way between clusters of hospital locations suggests that the set of candidate locations could be improved. Finally, this paper's findings align with industry discussions, which suggest that the centralised way of manufacturing, which is common in the pharmaceutical industry, is no longer appropriate for PM. Alternatively, the shift towards more decentralised configurations was proposed. Future research could expand the mathematical formulation presented in this paper to account for various levels of decentralisation. For example, the MFs or CFs opened near a hospital could be turned into smaller facilities integrated at the demand point. Moreover, the hospitals with available FACT authorisation are, in their majority, concentrated in small geographical areas, leaving many countries, such as those in Africa or South America, without the possibility to offer ATMPs treatments. Optimising not only the production facilities but also those that act as demand points could lead to more widely available and equitable supply chains for PM.

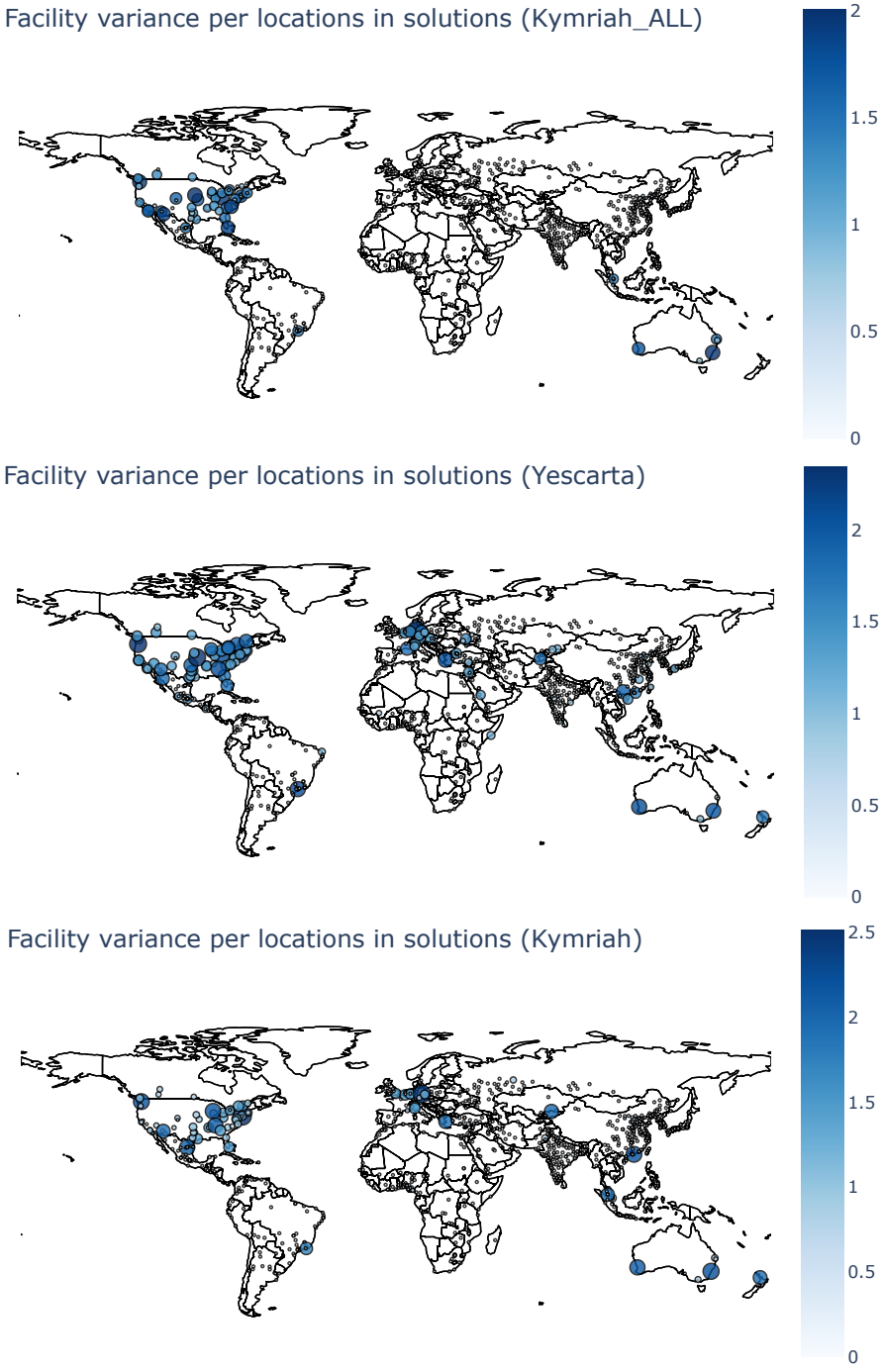


Figure 5.3: Variance of facilities on locations across the non-dominated solutions in the last generation for the three problem instances. The candidate locations represented by larger and darker blue show a higher density of either MF or CF placed in that location throughout the optimisation process.

Chapter 6

Multi-objective Optimisation for the Integrated and Decentralised ATMPs Supply Chain Configurations

6.1 Abstract

PM is a new area of the healthcare sector that promises to deliver treatments targeted to each patient. The biopharmaceuticals created under the PM paradigm can treat and even cure rare and progressive diseases, most of which have no other treatment currently available. Nevertheless, the prices of such therapies can reach up to $2 million. Consequently, many authorisation bodies and policymakers recommend PM treatments for commercialisation and use only when all other possibilities have failed. Part of this cost is due to the need for a new supply chain that disrupts the current medical delivery system from continuous and off-the-shelf to a patient dependent batch and on-demand model. This paper presents a centralised, integrated, and decentralised supply chain configuration, modelling it as a multi-objective problem considering the maximisation of coverage and minimisation of patient waiting time and costs. The mathematical models are solved using an NSGA-II.

6.2 Introduction

ATMPs are re-engineered biopharmaceutical products that use an individual's cells, genes, or tissues to cure progressive (such as late stage cancer) and genetic disorders. They were created under the umbrella term *precision medicine* or PM and are one of the fastest growing areas of healthcare. The global market size of ATMPs values more than $9.5 billion in 2021 and is expected to exceed $21.2 billion by 2028 (Grand View Research, 2021). Nevertheless, the shift from the traditional pharmaceutical treatments based on the "one-size-fits-all" model to an on-demand approach has raised considerable challenges for delivering ATMPs.

BSCs are usually created following a continuous mode of production aiming to limit the stockouts and disruptions of each product (Jaberidoost et al., 2013). This off-the-shelf and more lenient approach towards waste compared to the ATMPs has allowed strategic supply chain processes to follow a centralised model. In this case, the entire manufacturing process is conducted in one facility responsible for delivering the end product to customers (usually hospitals, clinics or pharmacies). The ATMPs constraints are, however, extending beyond the capabilities of central manufacturing; in addition to low global demand and the use of living cells, the ATMPs are delivered within a cold supply chain, having a temperature sensitive shelf-life.

The centralised production model has led to significant challenges for companies offering ATMPs, which had to either deliver lower quality products, sometimes free of charge (Lam et al., 2021), or to withdraw their product from the market (Seoane-Vazquez et al., 2019). In these circumstances, a shift towards decentralisation was proposed as a more sustainable alternative for the PM supply chain (Harrison et al., 2018a). This case emphasises smaller, local facilities closer to the patient, which could lead to lower

costs and delivery times and higher quality ATMPs. Nevertheless, while multiple supply chain configurations have been discussed, PM supply chain optimisation research is still scarce.

This paper focuses on the strategic-tactical levels of the personalised ATMP supply chain and proposes three novel mathematical models.

1. The first model follows the current personalised ATMPs supply chain configuration (centralised model). In this configuration, the patient can be assigned only to designated hospitals and the product is re-engineered at a MFs responsible for the entire production.

2. The second model is an extension of the centralised network and builds an integrated approach where the hospitals can act as manufacturing nodes (semi-decentralised model). In this scenario, the hospitals are still the only demand point to which the patients can be allocated. These facilities can also have integrated manufacturing units responsible for part of the production alongside the main manufacturing hubs.

3. The third model is a fully decentralised configuration, where the patient can be assigned to either a hospital or a clinic, and the product can be re-engineered at integrated or independent facilities.

The exact roles of each facility in the three configurations are explained in detail in Section 6.3. All models aim to find the trade-off between minimising the cost and delivery time of the supply chain and maximising the number of hospitals that can process the product. The paper will discuss the practical implications of the three supply chain configurations from the perspectives of decision-makers (i.e. biopharmaceutical companies, policymakers, and hospitals) and patients.

The rest of the paper is structured as follows. The following section provides a comprehensive explanation of the three supply chain configurations. The literature review is purposefully discussed in Section 6.4 and compares the existing models and solution algorithms proposed in other decentralised healthcare supply chains. The mathematical formulations of the three configurations will then be presented in Section 6.5. The procedure to obtain the data used in this paper and the solution methods are presented in Section 6.6. The results are shown in Section 6.7. Finally, the conclusions and limitations of this study, as well as future research directions, are given in Section 6.8.

6.3 Supply Chain Configurations

An ATMP is classified as autologous or allogeneic depending on the raw materials. In an allogeneic transplant, the cells are collected from a healthy individual and then administered to the patient. The allogeneic ATMPs are used in regenerative medicine. The ATMPs listed as PM uses an autologous process, meaning that the cells used to create the final product are collected from and administered to the same patient. The raw material is obtained through a leukapheresis process[1] where the necessary white blood cells are separated and stored, while the remainder of the blood is returned to the patient. These cells will be later re-engineered and returned to the same patient. Collection always occurs at a hospital or clinic approved by the FACT.

The cells collected undertake a complex manufacturing process at individual manufacturing facilities (MF). At this stage, the product is time- and temperature-sensitive, with a very short shelf-life. For this reason, it is common for the cells to be frozen at a

[1]A particular type of apheresis, where the white cells are separated from the blood sample. It is the first step in CAR-T and Dendritic cell autologous therapies.

cryopreservation facility (CF) and then transported under a cold supply chain. The manufacturing process is formed of complex and highly-regulated steps that include peripheral blood mononuclear cells (PBMC) production, isolation and activation, transduction and expansion, and several QC (i.e., batch validation and testing, and QA (i.e., documentation, supplier management, training and investigation procedures) tests (Pörtner et al., 2018). If all QC and QA tests are completed, then the ATMP is transported back, either fresh or frozen, to the same hospital where the product is administered.

For personalised ATMPs, various factors can lead to a QC or a QA test failing at any step of the manufacturing process or before the administration. For example, while freezing the material extends the product's shelf-life (Rafiq et al., 2017), the thawing necessary before manufacturing or administration can damage the cells (Woods et al., 2016). Autologous processes involve patients with advanced stage diseases, and their poor health condition might preclude another apheresis procedure. A patient's health condition also leads to variability in the raw material, often cited as the main reason for manufacturing failure (Kirouac and Zandstra, 2008; Lipsitz et al., 2016). Creating a personalised ATMP is currently a labour-intensive and time-consuming process (Lipsitz et al., 2017). The technologies biopharmaceutical companies are working with are new and highly-regulated, which has led to a shortage of specialised labour. Different modes of production to automate the manufacturing process have been proposed, which could lead to lower failure rates, minimisation of the variability between ATMPs, and lower dependency on skilled staff (Lopes et al., 2020). Nevertheless, the equipment used for each mode can influence the construction and operation costs.

Establishing a network of manufacturing and cryopreservation facilities and optimising the production mode could lead to more resilient and efficient supply chains. In this paper, we model and test three supply chain configurations, namely a Centralised

Model Configuration (CMC), an Integrated Model Configuration (IMC), and a fully Decentralised Model Configuration (DMC). The CMC is the configuration currently used and follows a mode of delivery closer to the traditional pharmaceuticals where each facility acts as a main hub responsible for both production and quality checks. The DMC contains several possible additional facilities and subsidiary roles for the facilities available in CMC. Nevertheless, the authorisation procedures required for implementing these configurations might not be possible for a single biopharmaceutical company. For this reason, we propose an IMC network that only extends the role of the hospitals to provide part of the manufacturing production. In this case, we aim to explore whether the gradual move towards a decentralised supply chain could still benefit patients and biopharmaceutical companies in delivering personalised therapies.

6.3.1 Centralised Model

In a centralised model, the MFs are responsible for the entire manufacturing process and act as production and quality assurance hubs. The CFs are independent facilities responsible for freezing the raw material such that the product's shelf-life is not exceeded. The raw materials (i.e. a patient's cells or tissue) can only be collected and administered at existing hospitals with FACT accreditation. In this scenario, we know the location of the hospitals. We need to find optimal locations for the CFs and MFs and optimise the production mode of MF such that we minimise the average waiting time per patient, the total cost of the supply chain, and maximise the number of hospitals that can offer personalised therapies. To be processed, an order must be delivered to an MF within its shelf-life radius with a specific manufacturing mode. If no MF is available, the cells can be first frozen at a CF within 24 hours and subsequently delivered to an MF. The CMC

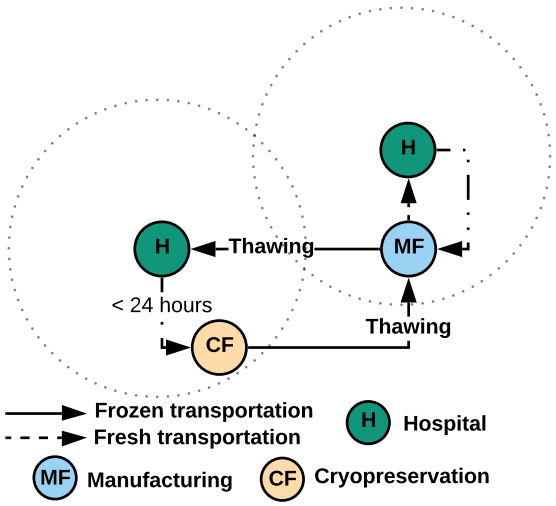


Figure 6.1: Centralised supply chain model with hospitals (Hs), manufacturing facilities (MFs) and cryopreservation facilities (CFs). It graphically represents a network of two hospitals, with the dotted circles representing their shelf-life radius.

approach is graphically presented in Figure 6.1, and a simplified version has already been modelled and solved in Avramescu et al. (2021b).

The total waiting time for an ATMP is calculated as the delivery duration (i.e., transportation time) and that of the re-engineering steps. In the CMC, the delivery time is calculated between a hospital and an MF, and possibly via a CF if the raw material is frozen. The re-engineering time is the total duration of the leukapheresis, cryopreserving (optional), manufacturing processes and administration. In this paper, we do not consider the other procedures that the patient might need to undertake, such as chemotherapy or additional surgeries, as these are usually done in parallel and hence do not influence the waiting time.

We only calculate the total supply cost, namely the construction and operational costs. It is worth mentioning that the final price of an ATMP usually includes the R&D costs throughout the development pipeline in clinical trials. However, these are hard to estimate and not something we optimise in this paper. The construction cost depends on

the facility type (MF or CF) and its location. The operational cost depends on whether the product is cryopreserved or not. It includes the salaries of the staff and the cost of the equipment/consumables associated with each task, as well as the transportation under the cold supply chain if required.

The shelf-life is usually product dependent, but we have set it as a constant for simplicity and given that the chosen case studies have a similar shelf-life. The cells will need to be delivered to a MF within their shelf-life[2]. If a MF is not within the radius of a hospital, then the order can still be processed if delivered within 24 hours to a CF. The 24-hour window is the preferred time for frozen cells to minimise any potential damage associated with cryopreserving (Tyagarajan et al., 2019).

We also consider a failure rate that depends on our manufacturing mode. The modes of production we use have been presented by Lopes et al. (2020), and each has an estimated percentage of orders that will fail. These include three levels of automation, namely a fully manual process where each manufacturing and QC steps are manually conducted, a partially automated level where some of the manufacturing steps are automatised, and fully automated - where the QC tests are the only manual processes. Possible cryopreservation damage is not yet considered a potential risk and is assumed never to fail or increase the chances of failure of a re-engineered order. If the manufacturing fails for any specific order, the product re-engineering is restarted with another leukapheresis. In the real world, failures that arise earlier in the manufacturing process possibly save some time and resources concerning those detected later. However, we assume any failure is observed in the last manufacturing step for simplicity. Hence, all orders assigned to a MF will always go through the entire re-engineering process. The

[2]Ideally, the manufacturing process should start within 24-48h from the collection as the viability of the cells decreases with time (Tyagarajan et al., 2019).

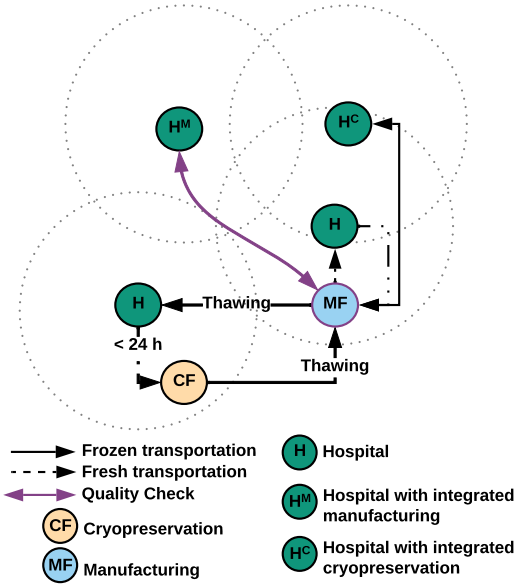


Figure 6.2: Integrated (semi-centralised) supply chain model with hospitals (Hs) and hospitals with integrated manufacturing (H^M), manufacturing facilities (MFs), and cryopreservation facilities (CFs).

cost and time objectives will be recalculated entirely. Even though this approach is more conservative, it was preferred given the available data.

6.3.2 Integrated Model

The IMC assumes that some manufacturing processes could also be conducted at hospitals with a small processing unit integrated. The IMC network is graphically presented in Figure 6.2. In this case, the CF would have the same role as in the CMC, but the MF will act as a central hub, and the orders assigned to a H^M (i.e., hospital with integrated manufacturing unit (MU)) would not need to be transported. The MF is still responsible for conducting the manufacturing for the hospitals that do not have a MU, as well as being responsible for the QC of the MFs.

In the case of an MU, only product samples would need to be delivered to an MF

for QC. If the QC is not passed, the manufacturing process fails and must be restarted. The QC sample must not be returned to the hospital. The hospitals without MU will follow the same network as in the CMC (that is, transport to a MF, possibly via a cryopreservation facility if the shelf-life constraint cannot be satisfied); the manufacturing hub is responsible for the entire process, including QC and, if the QC fails, then the process is restarted.

In the IMC, for MU, the delivery time becomes redundant, as the one-way transportation of samples for QC is done in parallel with the manufacturing. Since there is no delivery between facilities, no order needs to be frozen, so the time and cost are always the same as for fresh cells (i.e., they do not include freezing at a cryopreservation facility, thawing, freezing at a MF, and a final thawing at the hospital before administration). In addition to the construction costs of the CMC, the hospitals with MU will also have a one-time purchase cost associated with buying the integrated unit. This cost is always fixed regardless of the hospital location and considerably lower than for an MF.

The failure rate applies to both MU and MFs and depends on the production mode. We also assume that the MU can only process their own patients' cells due to capacity constraints and possible over-complication of the CoI and CoC.[3] This is because an order processed at an integrated hospital would still need to be administered at its original hospital and undertake QC at an MF.

6.3.3 Decentralised Model

The DMC is the most complex supply chain configuration for PM delivery. Decentralisation is not entirely new to the healthcare field and has been used in nuclear medicine,

[3]The Chain of Identity and Chain of Custody is related to the Quality Assurance process and concerned with documentation management aspects.

blood supply, and intravenous feeding (Harrison et al., 2018b). In this scenario, alongside the configurations available in the previous two models, there is also the possibility to conduct leukapheresis and administration at independent clinics whose location is to be decided. The clinics are small facilities that undertake the same role as a hospital (i.e. leukapheresis and product administration). Still, they need to be assigned to a hospital in case of emergencies. The clinics would help have supply points to patients nearer their location and minimise travel distance. The hospitals and clinics can also have integrated cryopreservation units (MU and integrated cryopreservation unit (CU), respectively).

Unlike our previous work (Avramescu et al., 2021b), where hospitals and their corresponding demand are assigned to cryopreservation and manufacturing facilities, in this paper, the assignment of patients to either a hospital or clinic is done first. A possible constraint could limit the distance between any patient and a hospital/clinic (i.e. a patient cannot be assigned to a facility unless it is within a total travel time).

We have built the decentralised configuration using existing literature. However, other possible configurations could be modelled. Likely, decentralisation scenarios can be made by simply using some parts of this model or re-assigning the tasks for each facility.

6.4 Literature Review

The PM network shares common characteristics with other, more mature healthcare and pharmaceutical supply chains, placing the body of literature at the intersection of those. Biopharmaceutical products produce living cells; therefore, aspects relevant to their delivery are also met in other networks targeting substances of human origin, such as organ transplantation or blood. A complete analysis of the similarities and

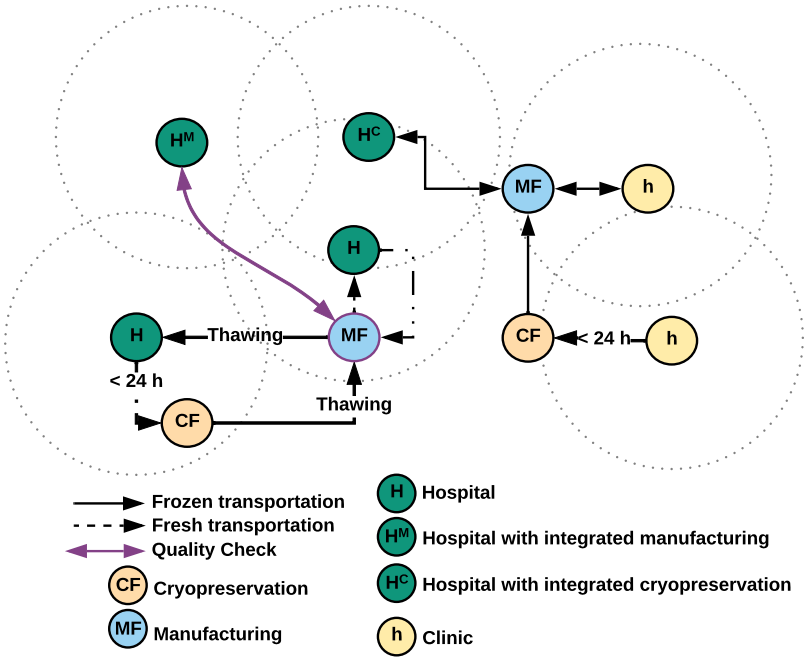


Figure 6.3: Decentralised supply chain model with hospitals (H), hospitals with integrated manufacturing (H^M) and hospitals with integrated cryopreservation (H^C), manufacturing facilities (MFs), cryopreservation facilities (CFs), and clinics (h).

differences between the aforementioned supply chains and PM is beyond the scope of this paper. Such reviews have been addressed in the past, see (Avramescu et al., 2021a), while surveys on the healthcare supply chains were created by Pirabán et al. (2019) and Ahmadi-Javid et al. (2017b). The rest of this section will focus on critically analysing the literature related to the problem of decentralisation in the healthcare industry, with a particular focus on PM applications.

The PM therapies that have obtained market authorisations or are in late stage clinical trials usually target patients with either rare or last-stage progressive diseases (such as cancer). The patients of interest thus lead to very sparse and low global demand, which is highly uncertain and generally fluctuates considerably between countries. The decisions about treatment approval are made individually for each patient and usually follow

guidelines provided at the national level. It has thus led to the impossibility of traditional centralised manufacturing that is generally adopted by pharmaceuticals to deliver timely and cost-efficient products while also remaining resilient to disruptions (Köhl et al., 2018; Buechner et al., 2018; Harrison et al., 2018a). The lack of a standardised reimbursement system for hospitals and patients worldwide further complicates these challenges.

A centralised manufacturing network for PM implies that the raw material is collected from the patient, delivered to a specialised facility (potentially cryopreserved before) for re-engineering, and then transported back to the same patient. The patient-specific batch and on-demand model of PM leads to the need for a strict CoI and CoC in a cold supply chain if the cells are cryopreserved. The additional costs and delivery time per patient are considerable and lead to ineffective and sub-optimal supply chains. For this reason, the shift towards decentralising the PM network has been proposed. The idea of redistributed manufacturing is not entirely new since it has been implemented in other critical healthcare supply chains, like nuclear medicine, blood transfusions, or intravenous feeding supplies (i.e., total parenteral nutrition) (Harrison et al., 2018b).

In the context of PM, Ran et al. (2020) looked at a case study of a Germany-based research centre specialised in personalised CAR-T manufacturing. Their results suggest that an in-house MF could lead to lower costs and potentially eliminate the need for cryopreservation since the delivery to an independent facility would be eliminated. This could also reduce the potential risks of damaging the cells during delivery, which usually leads to the need for a second round of cell collection from the patient and the restart of the supply chain. The authors use a fully-automatic mode of production where the entire re-engineering process is conducted with minimal intervention of specialists. Their results are supported by previous studies, such as Haddock et al. (2017), which believe that in-house automatic machines can minimise some of the risks associated with

delivery.

Simulation studies related to PM decentralisation were also conducted by Lam et al. (2021). The authors created a hypothetical UK based case study covering ten potential hospitals (demand points) with three nominal base demand cases of 100, 200 and 500 patients per year. Their conclusions iterate over the benefits of decentralisation as highlighted by Ran et al. (2020) of lower delivery time and reduction in cold chain transportation. Nevertheless, the authors did not find significant benefits in terms of cost for the decentralised model compared to centralised manufacturing.

Qiu et al. (2021) mention decentralisation as a possible solution for PM in long-term disruptions, such as the scenario of border closure and medical personnel reassignment brought by COVID-19. Many clinical trials were disrupted, which can lead to considerable delays in market approval of an already lengthy and complicated authorisation process. However, the authors focus more on follow-up schedules and the introduction of telemedicine rather than the treatment period itself.

The decentralisation of PM from a cost-analysis perspective was also researched by Lopes et al. (2020), who looked at three modes of production in a centralised and decentralised model on a small-scale case study, namely a manual, partially-automated and fully-automated production mode. The authors found that, even though a fully-automated production can reduce the overall cost by up to 10%, the lack of flexibility and control over the re-engineering process leads to a partially-automated mode being preferable. In this case, the automated process works in parallel with quality checks conducted by specialists.

The trade-off between the benefits of the two supply chain configurations lies around the consistency of quality, more straightforward automation (centralised) and less complex logistics, minimisation of cryopreservation and specialised airfreight (decentralised).

Doulgkeroglou et al. (2020) argue that, while a decentralisation of the supply chain could lead to better resilience, the optimisation of the modes of production is equally relevant and can ultimately lead to the reliability and consistency between patient-specific batches and a reduction in the Cost of Goods (e.g., storage, transport, production, raw materials).

The problem of decentralisation in the context of PM remains a research subject. The studies that have previously analysed the effect of either in-house or local manufacturing centres compared to the centralised, global approach have either looked at small-scale studies, did not consider different modes of production, or looked at the problem from a single- or bi-objective perspective. Harrison et al. (2018a, 2017) emphasise the importance of a decentralised network for PM not only in patient safety and cost efficiency but also in terms of environmental impact. Growing concern over the usage of energy and the waste of resources put long-distance temperature-controlled transportation under questionable relevance. Likewise, Harrison et al. (2019) argue that the savings in centralised manufacturing and the ability to standardise production might be insignificant when it is impossible to facilitate offshoring.

Previous studies have assumed a known location of the manufacturing facilities. However, the placement of facilities in a centralised or decentralised scenario remains suboptimal. Optimisation frameworks capable of finding the optimal number and location of manufacturing and cryopreservation facilities with their production mode could lead to optimal supply chain networks and a fair comparison between each configuration (Wang et al., 2019). Moreover, the problem of coverage remains completely unaddressed. A supply to all hospitals with the requirements to provide PM treatment is not mandatory, and patients could be reallocated to a nearby hospital. The trade-off between cost, time, and the number of hospitals that can be covered is worth exploring. Generally, these problems that analyse the fairness of supply chain management have received increased

attention in the past years.

6.5 Problem Formulation

This paper focuses on the PM supply chain, particularly on ATMPs. We aim to find the optimal location of different facilities for the three configurations introduced in Section 6.3, as well as the production mode of each facility with manufacturing (individual MF or hospital with integrated manufacturing). The resulting FLP will first allocate the patients to hospitals and clinics. We extend the initial CMC and IMC models previously introduced in Chapter 5 and Avramescu et al. (2022b) respectively. We model the problem as a multi-objective FLP, aiming to minimise the cost of the entire configuration and the waiting and travel time of the patients.

We start from a predefined set J with geo-located points where a MF or CF can be opened, and a set I of candidate locations for clinics and current locations of hospitals. The final set I is equivalent to the locations of the demand points. Each point in I has an associated demand a_i, the number of orders that must be manufactured at that location. We calculate the travel time by calculating the Haversine distance between any two points $i(j)$ and $j(j\prime)$ and using a constant average speed α. In addition to the transportation time, the waiting time for a patient is also dependent on the mode of production $k \in K$ and whether the product is fresh (f) β or frozen (z) γ.

The total cost of the supply chain is divided into construction (or setup) costs and operational costs. The construction cost is a one-time investment applied when a facility is opened or an integrated unit is assembled at a hospital, depending on the facility type. The operational cost depends on the production mode k and whether the product is fresh (f) t_k^f or frozen (z) t_k^z. Even though, in reality, the cost of the transportation can vary

depending on the quantity of the cells delivered, the transporter used, and the country, for simplicity, this variable was not taken into consideration in this model and could be integrated into future research.

Indices and Parameters

$j \in J$ the set of candidate locations for facilities (MF or CF).

$i \in I$ the union set of candidate locations for clinics $I = I^{\mathrm{h}}$ and hospitals I^{H} where $I = I^{\mathrm{h}} \cup I^{\mathrm{H}}$ and I^{h}, I^{H} are disjoint. Also, I_0 is the set of closed hospitals and clinics, while I_1^{H} is the set of open hospitals (we are never concerned with I_1^{h} because demand is never reallocated to an open clinic).

$d_{ij}, d_{jj'}$ Haversine distance from i (j) to j (j').

α avg. speed constant.

T large time constant.

r_k failure rate for production mode k.

$k \in K$ manufacturing modes.

a_i total ATMP orders at allocated hospital/clinic i.

$c_{ijk}^{\mathrm{f}}, c_{ijk}^{\mathrm{z}}$ Operation cost per fresh (f) and frozen (z) order that depends on the hospital i, MF at location j and the mode k.

p_k^f, p_k^z Operation time per fresh (f) and frozen (z) order that depends on the hospital i, MF at location j and the mode k.

β price per distance.

$s_i^{\mathrm{a}}, s_i^{\mathrm{c}}, s_i^{\mathrm{m}}$ Setup cost for a hospital/clinic i, with different integrations (in the order no integration, with cryopreservation, with manufacturing).

$s_j^{\mathrm{C}}, s_j^{\mathrm{M}}$ Setup cost for a facility in location j for cryopreservation or manufacturing.

Decision Variables

x_i^{a} 1 if a clinic/hospital at $i \in I$ with no integrated facilities is active in the ATMP supply chain, 0 otherwise.

x_i^{c} 1 if a clinic/hospital at $i \in I$ with integrated cryopreservation is active in the ATMP supply chain, 0 otherwise.

x_i^{m} 1 if a hospital at $i \in I^{\mathrm{H}}$ with integrated manufacturing is active in the ATMP supply chain, 0 otherwise.

x_i 1 if an active clinic/hospital of any type is open at i, 0 otherwise.

$x_j^{\mathrm{C}}, x_j^{\mathrm{M}}$ 1 if a CF / MF at j is active in the ATMP supply chain, 0 otherwise.

y_{ij},$y_{jj'}$ 1 if product is distributed from clinic/hospital i (or facility j) to facility j (another facility j'), 0 otherwise.

m_{jk} 1 if MF in location j is of production mode k, 0 otherwise.

z_i^{C} 1 if hospital/clinic type a is allocated to a CF, 0 otherwise.

z_i^{M} 1 if hospital/clinic type a or c is allocated to a MF, 0 otherwise.

6.5.1 Objective Functions

DELIVERY. For basic clinics/hospitals ($x_i^{\mathrm{a}} = 1$) the distance product delivery is:

$$CentralisedDeliveryProduct(i) = \sum_{j \in J} \underbrace{y_{ij} d_{ij}}_{I} + \underbrace{z_i^{\mathrm{C}} y_{ij} \sum_{j' \in J} y_{jj'} d_{jj'}}_{II} + \underbrace{y_{ij} d_{ji}}_{III} \tag{6.1}$$

where d_{ji} represents the return route from j to i. Note that d_{ij} and d_{ji} are symmetrical in our problem.

- I - product delivery to the first facility (constrained unless hospital/clinic has

integrated cryopreservation/manufacturing)

- II - optional product delivery from CF to MF
- III - product delivery to patient, from MF back to hospital/clinic

For clinics/hospitals with integrated cryopreservation ($x_i^{\mathrm{c}} = 1$) allocation to a CF is not necessary ($z_i^{\mathrm{C}} = 0$). Therefore the distance of product delivery is:

$$IntegratedDeliveryProduct(i) = \sum_{j \in J} \Big(\underbrace{y_{ij} d_{ij}}_{I} + \underbrace{y_{ji} d_{ji}}_{III} \Big) \tag{6.2}$$

For hospitals with integrated manufacturing ($x_i^{\mathrm{m}} = 1$) product delivery is not necessary ($z_i^{\mathrm{M}} = 0$).

$$TotalDelivery = \sum_{i \in I} a_i \times (1 - x_i^{\mathrm{m}}) \times CentralisedDeliveryProduct(i) \tag{6.3}$$

$$= \sum_{i \in I} a_i \times (1 - x_i^{\mathrm{m}}) \times \sum_{j \in J} \Big(\underbrace{y_{ij} d_{ij}}_{I} + \underbrace{z_i^{\mathrm{C}} y_{ij} \sum_{j' \in J} y_{jj'} d_{jj'}}_{II} + \underbrace{y_{ji} d_{ji}}_{III} \Big) \tag{6.4}$$

PRODUCTION TIME (PT) AND COST (PC): Production time and cost are the same regardless of location (MF). The only difference is between a fresh and frozen product.

$$ProductionTime(i,j) = \sum_{k \in K} y_{ji} m_{jk} [(1 - z_i^{\mathrm{C}}) p_k^f + z_i^{\mathrm{C}} p_k^z] \tag{6.5}$$

$$ProductionCost(i,j) = \sum_{k \in K} y_{ji} m_{jk} [(1 - z_i^{\mathrm{C}}) c_{ijk}^{f} + z_i^{\mathrm{C}} c_{ijk}^{z}] \tag{6.6}$$

CONSTRUCTION COSTS.

$$ConstructionCosts = \sum_{i \in I} \underbrace{\left(x_i^{\mathrm{a}} s_i^{\mathrm{a}} + x_i^{\mathrm{c}} s_i^{\mathrm{c}} + x_i^{\mathrm{m}} s_i^{\mathrm{m}}\right)}_{\text{clinic/hospital setup cost}} + \sum_{j \in J} \underbrace{\left(x_j^{\mathrm{C}} s_j^{\mathrm{C}} + x_j^{\mathrm{M}} s_j^{\mathrm{M}}\right)}_{\text{facility setup cost}} \tag{6.7}$$

FAILURE RATE. When the manufacturing process fails (with a rate of r_k), the time and cost of the manufacturing process are repeated.

Note: distance terms in the objective are divided by a constant average speed α to convert into time units

$$\begin{aligned} T_{wait} = \sum_{i \in I} a_i \sum_{j \in J} \Bigg[& \underbrace{\left(1 + \sum_{k \in K} r_k m_{jk}\right)}_{\text{Failure multiplier}} \\ & \times \Bigg[PT(i,j) + \alpha^{-1}(1 - x_i^{\mathrm{m}}) \Big(\underbrace{y_{ij} d_{ij}}_{I} + \underbrace{z_i^{\mathrm{C}} y_{ij} \sum_{j' \in J} y_{jj'} d_{jj'}}_{II} + \underbrace{z_i^{\mathrm{M}} y_{ji} \sum_{j' \in J} y_{jj'} d_{jj'}}_{IV} \Big) \Bigg] \\ & + \alpha^{-1}(1 - x_i^{\mathrm{m}}) \underbrace{y_{ji} d_{ji}}_{III} \Bigg] \end{aligned} \tag{6.8}$$

Note: distance terms for product delivery are multiplied by the β price per distance constant because of the different measurement units between the cost and distance.

$$C = \sum_{i \in I} a_i \sum_{j \in J} \Bigg[\underbrace{\Big(1 + \sum_{k \in K} r_k m_{jk}\Big)}_{\text{Failure multiplier}} \times \Big[[(1 - x_i^{\mathrm{m}})\beta] \underbrace{y_{ij} d_{ij}}_{I} + PC(i,j) + (1 - x_i^{\mathrm{m}}) \Big(\beta \underbrace{z_i^{\mathrm{C}} y_{ij} \sum_{j' \in J} y_{jj'} d_{jj'}}_{II} \Big) \Big] + \beta (1 - x_i^{\mathrm{m}}) \underbrace{y_{ji} d_{ji}}_{III} \Bigg] + ConstructionCosts \quad (6.9)$$

For every closed clinic/hospital $i \in I_0$, their demand is reallocated to the closest open hospital $i' \in I_1^{\mathrm{H}}$. The third objective is the total distance of reallocated demands.

$$T_{travel} = \sum_{i \in I_0} a_i \times \min_{i' \in I_1^{\mathrm{H}}} d_{ii'} \quad (6.10)$$

6.5.2 Constraints

Constraint 6.1.4 restricts the integrated manufacturing units to be placed only at hospitals H. Equations 6.1.5 and 6.1.6 are location constraints and allow only one facility type to be placed at each location i or j. As we assume that a product will follow the same delivery route to and from a facility, constraint 6.1.7 ensures that the distance between any two locations is symmetrical. However, a product does not need to follow the same path for return. For example, if a hospital is assigned to a CF, the orders will be returned directly to the hospital from the MF after being re-engineered. This is enforced by constraint 6.1.8. Constraints 6.1.9 and 6.1.10 restrict products to be delivered only to

active facilities. Constraints 6.1.11 and 6.1.12 ensure that if a clinic/hospital is active, it is assigned to only one facility j that satisfies delivery constraints. Constraint 6.1.13 ensures that if orders from either a clinic or a hospital must pass through an independent CF, those orders will be frozen. A CF is necessary for the supply chain of a clinic/hospital i only if it does not have any integrated units ($x_i^{\mathrm{a}} = 1$) (constraint 6.1.14). The time constraint of product delivery from clinic/hospital i to the first facility is 24h if the facility is CF ($z_i^{\mathrm{C}} = 1$), T otherwise; for any i where $x_i = 1$, otherwise $x_i = 0$ (constraint 6.1.16). Delivery restrictions between facilities are also ensured via constraint 6.1.18. CFs deliver products to only one other facility j' that satisfies delivery constraints. Once a product is re-engineered, it must return to the initial clinic/hospital if the clinic/hospital does not have integrated manufacturing ($x_i^{\mathrm{a}} = 1$ or $x_i^{\mathrm{c}} = 1$).

If the supply chain starting at clinic/hospital i passes through a MF, then equation 6.2.1 is enforced. Hospitals with MU ($x_i^{\mathrm{m}} = 1$) do not need a MF in their supply chain. Any clinics (since $x_i^{\mathrm{m}} = 0$ for $i \in I^{\mathrm{h}}$) or hospital that does not have MU may need a MF in their supply chain (constraint 6.2.2). Each MF should have precisely one production mode (contraint 6.1.17). If a clinic/hospital already exists but may not necessarily be in the ATMP supply chain is defined by equation 6.1.15.

Decentralised Personalised Medicine Supply Chain Model

Objectives	$\min\ T_{wait}$		(6.1.1)
	$\min\ C$		(6.1.2)
	$\min\ T_{travel}$		(6.1.3)
Constraints	$x_i^{\mathrm{m}} = 0$	$\forall i \in I^{\mathrm{h}}$	(6.1.4)
	$x_i = x_i^{\mathrm{a}} + x_i^{\mathrm{c}} + x_i^{\mathrm{m}} \leq 1$	$\forall i \in I^{\mathrm{h}}$	(6.1.5)
	$x_j = x_j^{\mathrm{C}} + x_j^{\mathrm{M}} \leq 1$	$\forall j \in J$	(6.1.6)
	$d_{ij} = d_{ji}$	$\forall i \in I, j \in J$	(6.1.7)
	$y_{ij} \neq y_{ji}$	$\forall i \in I, j \in J$	(6.1.8)
	$y_{ij} \leq x_j$	$\forall i \in I, j \in J$	(6.1.9)
	$y_{jj'} \leq x_{j'}$	$\forall j \in J$	(6.1.10)
	$y_{ij} \leq \sum_{j \in J} y_{ij} = x_i$	$\forall i \in I, j \in J$	(6.1.11)
	$x_i = \sum_{j \in J} y_{ij} \leq 1$	$\forall i \in I, j \in J$	(6.1.12)
	$z_i^{\mathrm{C}} = \sum_{j \in J} x_j^{\mathrm{C}} y_{ij} \leq 1$	$\forall i \in I, j \in J$	(6.1.13)
	$z_i^{\mathrm{C}} \leq x_i^{\mathrm{a}}$	$\forall i \in I$	(6.1.14)
	$s_i^{\mathrm{a}} = 0$	$\forall i \in I$	(6.1.15)
	$\alpha^{-1} \sum_{j \in J} y_{ij} d_{ij} \leq (24\mathrm{h}) z_i^{\mathrm{C}} + T(1 - z_i^{\mathrm{C}})$	$\forall i \in I, j \in J$	(6.1.16)
	$\sum_{k \in K} m_{jk} = 1$	$\forall k \in K$	(6.1.17)
	$x_j^{\mathrm{C}} = \sum_{j' \in J} y_{jj'} x_{j'}^{\mathrm{M}} \leq 1$	$\forall i \in I, j \in J$	(6.1.18)

$$z_i^{\mathrm{M}} = \sum_{j \in J} x_j^{\mathrm{M}} y_{ji} \leq 1 \qquad \forall i \in I, j \in J \quad (6.2.1)$$

$$z_i^{\mathrm{M}} \leq 1 - x_i^{\mathrm{m}} \qquad \forall i \in I \quad (6.2.2)$$

$$y_{ji} = x_i^{\mathrm{a}}[(1 - z_i^{\mathrm{C}}) y_{ij} + z_i^{\mathrm{C}} \sum_{j' \in J} y_{ij'} y_{j'j}] + x_i^{\mathrm{c}} y_{ij} \quad \forall i \in I, j \in J \quad (6.2.3)$$

6.6 Data

In this paper, the centralised and decentralised manufacturing models are the equivalents of hub-and-spoke (Elrod and Fortenberry, 2017) and hub-and-node models, respectively (Harrison et al., 2018a). In the hub-and-spoke model, a central facility conducts the start-to-end manufacturing process. The re-engineered ATMP is then delivered to the hospital. In contrast, the central facility in a hub-and-node model will only oversee the nodes that almost entirely undertake the manufacturing process.

We tested the applicability of the proposed model and the solution methods on two case studies of personalised ATMPs, Kymriah and Yescarta. Kymriah was the first CAR-T therapy to obtain market authorisation in August 2017 in the USA (Foundation for the Accreditation of Celular Therapy, 2021). The initial approval was for treating children and young adult patients (i.e., up to 25 years) suffering from B-cell ALL that is r/r. More recently, the approval was extended for the treatment of adult patients with r/r DLBCL, a common type of NHL. Yescarta first obtained market authorisation in October 2017 for the treatment of adult patients with r/r DLBCL and PMBCL after at least two lines of treatment have failed.

The data used to calculate the global demand for the two ATMPs was obtained from

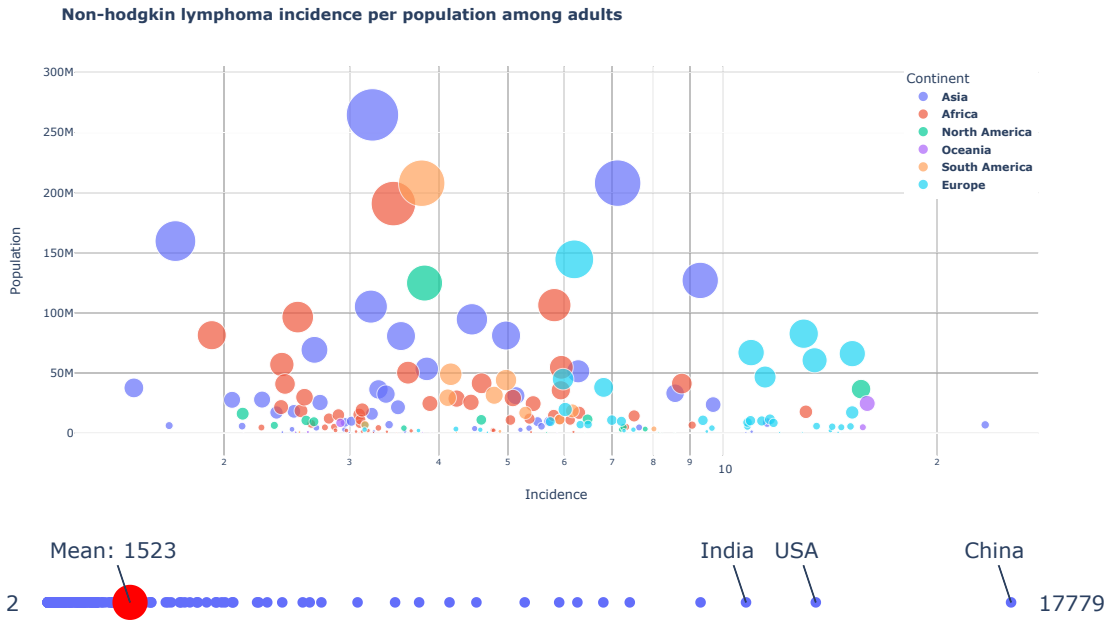


Figure 6.4: Incidence and Population by country and continent (upper graph) and Yescarta estimated demand where the red circle is the average value.

the IHME (Institute for Health Metrics and Evaluation (IHME), 2022). We used the prevalence (i.e. a measure of the frequency of disease at one point in time) of ALL and NHL, respectively. From the overall cases of ALL, around 80% are B-precursor (Sexauer et al., 2020) and about 20% of these will be r/r (Sun et al., 2018) in paediatric patients. DLBCL is one of the most common NHL types and accounts for 40% of all cases (Lukenbill and Hill, 2014), among which 30% will be r/r (Martelli et al., 2013). PMBCL is a rare cancer type and only accounts for about 4% of all NHL cases (Dabrowska-Iwanicka and Walewski, 2014). The final global demand calculated for Yescarta is shown in Figure 6.4.

The ATMPs can only be delivered to patients at FACT accredited hospitals. The list of hospitals that accept autologous ATMPs was obtained from the FACT at the University of Nebraska Medical Center (Foundation for the Accreditation of Celular Therapy, 2021).

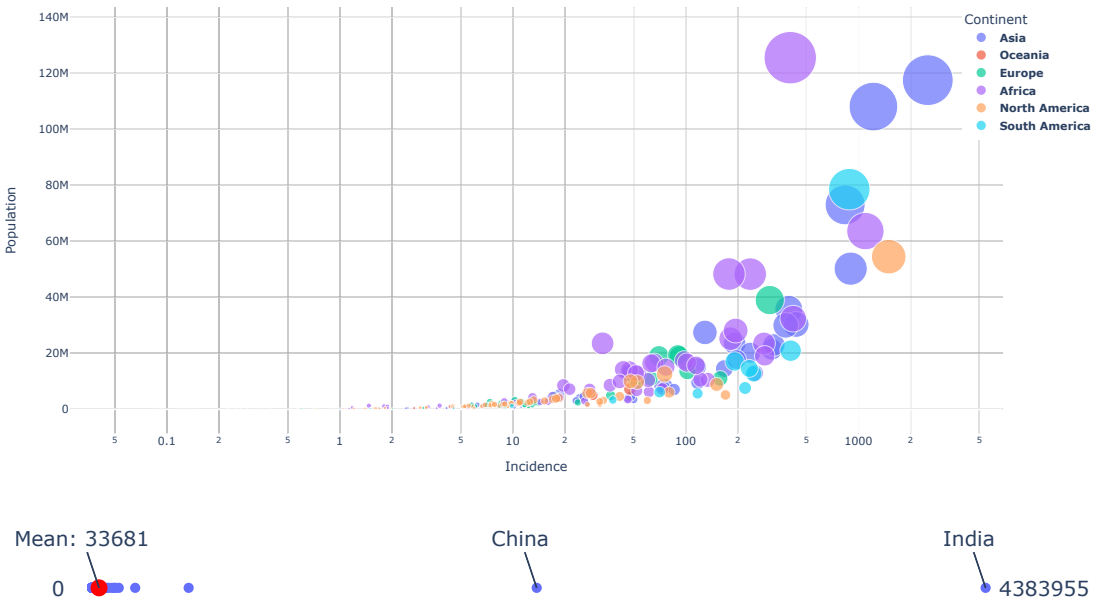


Figure 6.5: Incidence and Population by country and continent (upper graph) and Kymriah estimated demand where the red circle is the average value.

The higher number of authorisations in the USA compared to other parts of the world leads to a larger density of FACT hospitals. The location of the hospitals accepting adult and paediatric patients is presented in Figure 6.6, and the breakdown numbers per continent are presented in Table 6.3. The set with candidate locations J for the MFs and CFs was created by assigning an equal number of locations randomly, following a uniform distribution, in each country (or state for the USA) that had demand for either ATMP up to 1 000.

To solve the three supply chain configurations described in Section 6.3, we used NSGA-II (Deb et al., 2002b) and MORS as a benchmark. NSGA-II is a multi-objective genetic algorithm that uses non-dominated sorting and crowding distance to rank and preserve the best individuals. The initial population is always randomly created regardless of which of the three configurations is optimised. The facilities allowed to be placed in

	Adult patients	Paediatric patients
Asia	5	1
Europe	16	0
Oceania	11	6
North America	124	83
South America	2	1
TOTAL	157	92

Table 6.3: Number of hospitals that accept autologous ATMPs for adult and paediatric patients with breakdown by continent.

	Centralised	Integrated	Decentralised
Hospital	❍	❍	❍
MF	❍	❍	❍
CF	❍	❍	❍
MU		❍	❍
CU		❍	❍
Clinic			❍

Table 6.4: Facilities allowed in each of the three configurations.

each configuration are shown in Table 6.4. Every time a new population is initialised, a facility's opening probability is 0.5.

NSGA-II uses mutation and crossover to create new solutions. We apply three mutations randomly with the following probabilities. With an equal probability of 0.3, a facility is removed or added from a specific location. In the remaining instances, we use a network graph of candidate locations and allow a facility to be moved randomly to an adjacent location. For the crossover operator, a comparison between a one-point, two-point and uniform crossover was created, and the solutions presented in this paper use the two-point crossover resulting in the best hypervolume value.

MORS uses randomly generated solutions and ranks them using non-dominating sorting. The algorithm is run for several evaluations that match the number of generations $\times$ population size of the NSGA-II. Archive versions of the algorithms were used for both

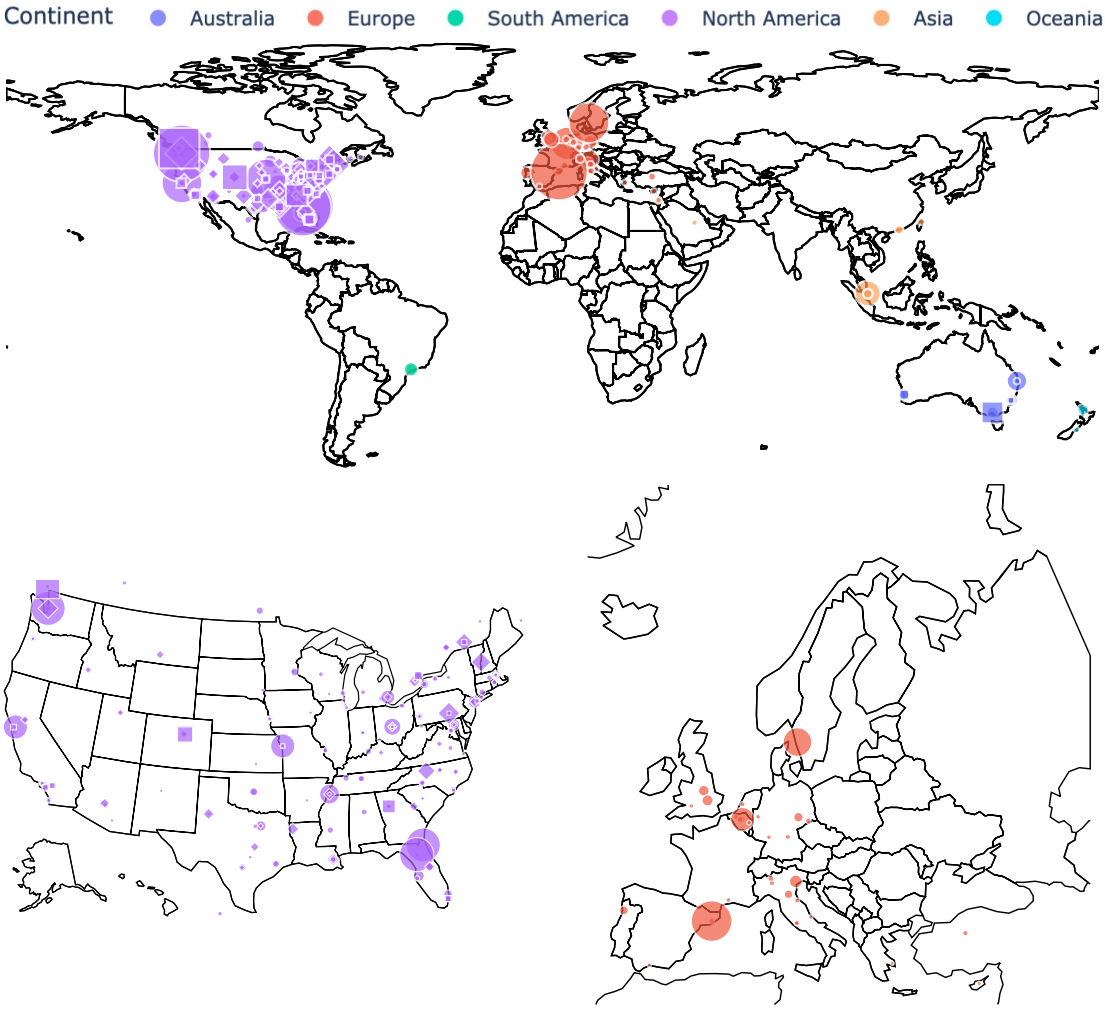


Figure 6.6: Clustering of FACT accredited hospitals per continent. The size of the bubbles corresponds to the inverse demand allocated to each hospital. The shapes correspond to the type of patient accepted, with diamond for adult, dotted circle for paediatric, and circle for both. Zoomed-in projections of the USA and Europe are also provided, given the higher density of hospitals in these areas.

MORS and NSGA-II. The archive will store the non-dominated solutions over the entire optimisation process, not just those in the last generation, referenced as A-NSGA-II and A-MORS.

The problem representation in this chapter maintains the integer vector introduced

in Chapter 5 (0: empty; 1: CF, 2: MF with manual production mode, 3: MF with semi-automatic production mode, and 4: MF with automatic production mode). In addition, alongside the vector for independent facilities, a second integer vector is used to represent the hospitals and the different levels of integration (0: empty; 1: CU, 2: MU with manual production mode, 3: MU with semi-automatic production mode, and 4: MU with automatic production mode, 5: not integrated). Finally, we have used a binary vector to represent whether a clinic is open at a certain location. The problem size in this case is $5^{1000} * 6^{249} * 2^{120}$.

6.7 Results

NSGA-II proved to be significantly better than the MORS regarding the number of non-dominated solutions found throughout the optimisation process. This is the case for both MORS and A-MORS. Similarly, the solutions found by A-NSGA-II almost entirely dominated the ones found by NSGA-II (see Appendix C) and, in consequence, the results presented in this section and any further discussion of the problem will be based on A-NSGA-II. Moreover, unless otherwise stated, all results were obtained by running the algorithm for 15 independent runs, for 10.000 generations, with a population size of 100. The hypervolume was used as a measure of comparison, and the run closest to the median hypervolume was always selected. Some example solutions chosen at random for the decentralised configuration are shown in Figures 6.7 and 6.8.

Figures 6.9 and 6.10 show the non-dominated solutions between the three configurations (CMC, IMC, and DMC) for Kymriah and Yescarta respectively. As expected, the current supply chain configuration for ATMPs is sub-optimal. A centralised delivery

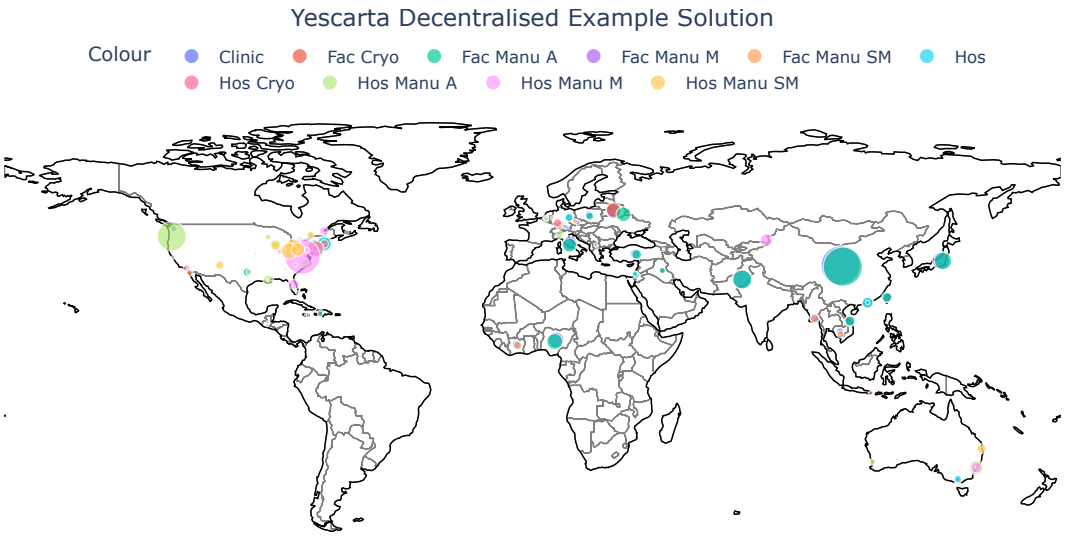


Figure 6.7: Example non-dominated solution using a decentralised configuration for Yescarta demand. The locations of the clinics and candidate locations for MFs and CFs are potential overlaps between the two.

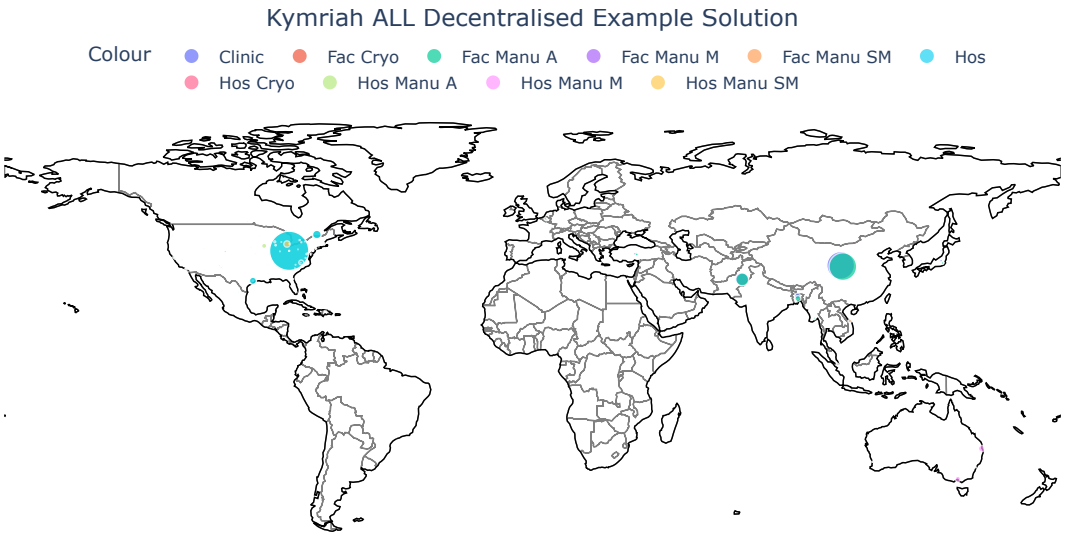


Figure 6.8: Example non-dominated solution using a decentralised configuration for Kymriah ALL demand.

mode where all products are manufactured in large-scale facilities is inefficient when considering a global coverage demand. With only several exceptions which are marginally

better in the cost objective, the solutions obtained following a CMC configuration are entirely dominated by either IMC or DMC for both Kymriah ALL and Yescarta. Moreover, the high number of hospitals in Europe and USA leads to a high patient distance for people outside these regions. The delivery time might not necessarily be affected in a centralised configuration by the sparse MFs or CFs or geographically grouped hospitals since it is calculated only as the time between hospitals and MF and the production time.

The differences between IMC and DMC bring a more interesting comparison. While the main scope of decentralisation is to reduce patient travel distance, the algorithm does not find many solutions that favour this objective. Even though, on average, the patient distance in the DMC is lower than in IMC, most non-dominated solutions are grouped around the same area of the Pareto, leading to a reasonable total cost. For Yescarta, the USA demand was aggregated to only one location on the East Coast to eliminate the bias brought by the state-level demand compared to other countries of similar geographical areas (such as Brazil, Russia, India, or China). The introduction of clinics becomes more relevant and finds solutions with higher total costs and lower patient travel distance. It can be suggested that a lower demand granularity (e.g., at the region or city level) compared to a country-based demand will be more indicative, and the DMC will find better solutions. This data is not publicly available for all countries, but biopharmaceutical companies could estimate their expected demand following results from clinical trials.

Some outlier solutions are present in both Figure 6.9 and even more prevalent in Figure 6.10. In this case, an outlier is defined as an extreme solution in the objectives or the number of facilities in the supply chain. The solutions were analysed separately, and the facility allocation for the solutions that lead to a very low patient distance are solutions with only one hospital with MU. Consequently, the total cost is minimal, and the delivery

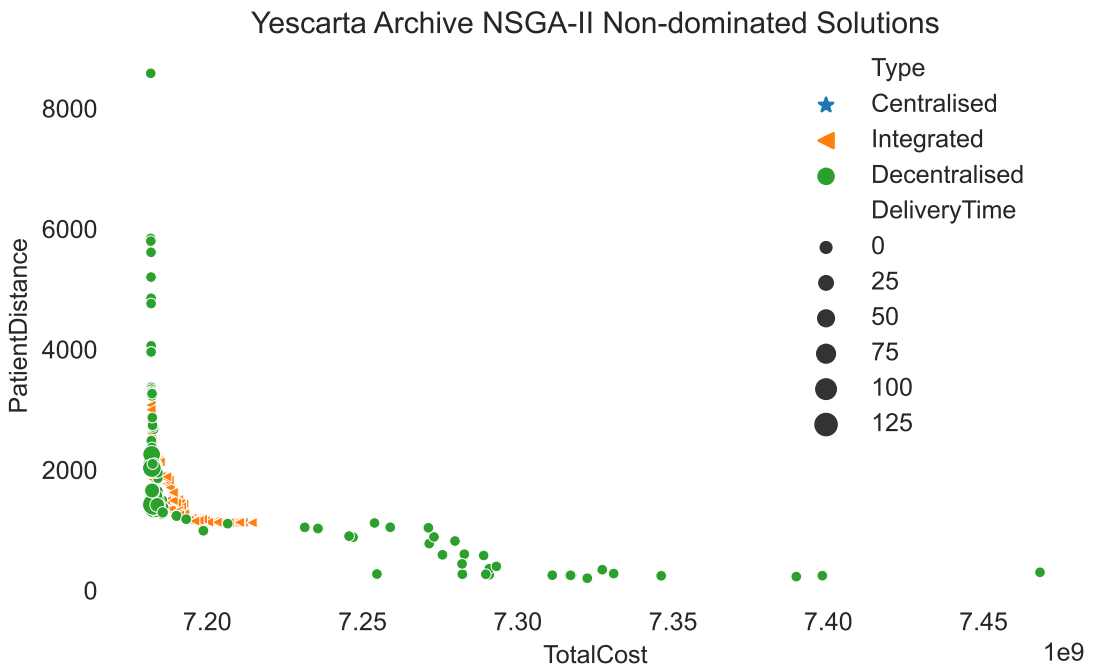


Figure 6.9: Yescarta non-dominated solutions using the NSGA-II algorithm with archive. The Delivery Time objective is shown with the bubble sizes, and each configuration (CMC, IMC, and DMC) is shown with different markers and colours. The best solutions in the CMC are almost all dominated by the other two configurations.

time is 0, as all orders are processed internally. These are feasible solutions to our problem but might be unrealistic from the point of view of the DM. As a simple example, these extreme solutions would become infeasible should capacity constraints be applied to hospitals. In reality, a hospital could not accept the yearly allocated few thousand patients. As we were interested primarily in comparing the possible configurations, namely CMC, IMC, and DMC, we decided to limit the number of restrictions only to hard constraints without which the supply chain would fail.

The lack of capacity constraints and the effect of demand distribution on the optimal configuration is also evident in Tables 6.6 and 6.5. The minimum number of MFs in each of the three configurations is always 1, which is to meet the production constraint where

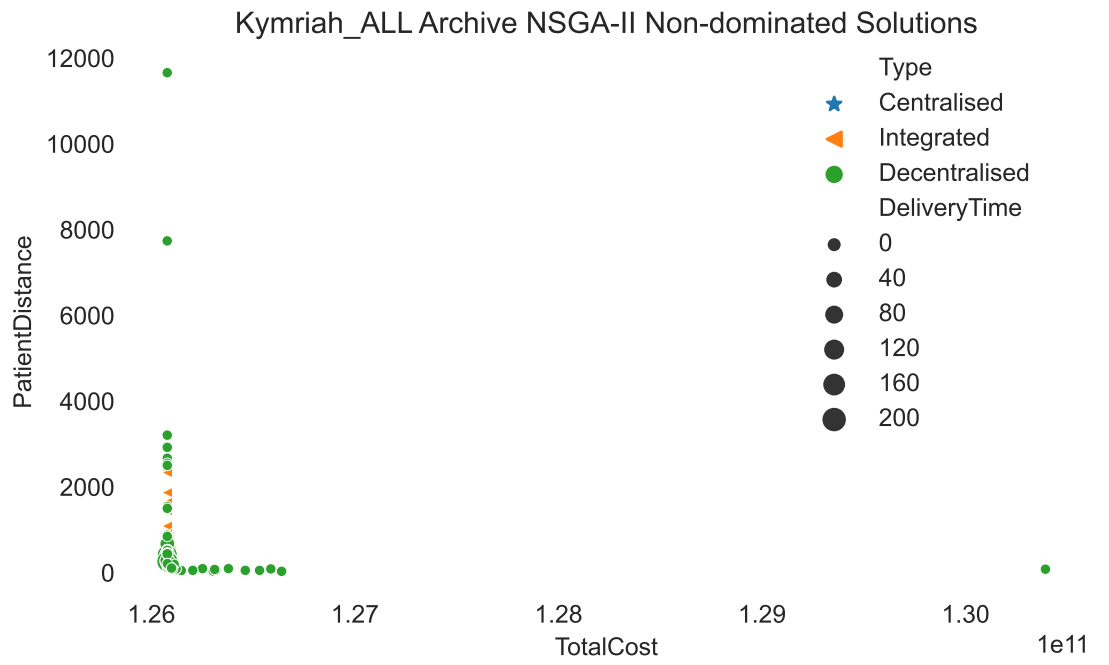


Figure 6.10: Kymriah ALL non-dominated solutions using the NSGA-II algorithm with archive. The Delivery Time objective is shown with the bubble sizes, and each configuration (CMC, IMC, and DMC) is shown with different markers and colours. The best solutions in the CMC are almost all dominated by the other two configurations.

Measurement	Configuration	Clinics opened	Hospitals opened (no integration)	Hospitals opened (with integration)	CFs opened	MFs opened
Minimum	Centralised	-	0	-	0	1
	Integrated	-	0	0	0	1
	Decentralised	0	0	0	0	1
Median	Centralised	0	20	-	0	6
	Integrated	-	20	34	0	1
	Decentralised	-	20	5	0	1
Maximum	Centralised	-	20	-	19	47
	Integrated	-	20	114	1	2
	Decentralised	26	20	74	15	48

Table 6.5: Yescarta minimum, maximum, and median number of facilities among the non-dominated solutions found by the A-NSGA-II.

at least 1 MF needs to exist in any solution, and for CFs is 0. These solutions have a small total cost but will always lead to a high patient travel distance, delivery time, or both. The integration at hospitals is also preferred in many cases, with an average of 34/158

Measurement	Configuration	Clinics opened	Hospitals opened (no integration)	Hospitals opened (with integration)	CFs opened	MFs opened
Minimum	Centralised	-	0	1	0	1
	Integrated		4	0	0	1
	Decentralised	17	0	0	0	1
Median	Centralised	0	76	-	0	6
	Integrated	-	80	6	1	1
	Decentralised	0	80	3	0	1
Maximum	Centralised	-	91	-	3	43
	Integrated	-	20	94	1	1
	Decentralised	23	91	52	6	45

Table 6.6: Kymriah ALL minimum, maximum, and median number of facilities among the non-dominated solutions found by the A-NSGA-II.

hospitals for Yescarta and 6/93 hospitals for Kymriah ALL. As the IMC incorporates all components of the centralised one (and the DMC further includes all components from the IMC), solutions that do not necessarily have any level of integration are allowed.

We have also analysed the influence of the candidate locations for MFs and CFs on the problem and whether all of them are relevant. We created the candidate locations using the 1000 biggest cities in the world. Figures 6.12 and 6.11 show the most favourable locations over the 15 algorithmic runs for DMC (the ones for CMC and IMC are shown in Figures D.1 to D.4). The colour represents the rank of the locations, where, for example, 0-3 means the three locations where most facilities were placed. With few exceptions, the most preferred locations always seem close to hospitals, given their very short distance, regardless of the configuration.

However, some patterns are clearly distinguished. In the USA, the East Coast has a higher chance of having a facility. It covers both the USA and Europe demand in such cases. Further, for IMC and DMC, there is a route between Europe - Asia - Oceania with the most important points at its two ends. A difference in favourable locations between configurations suggests that various candidate locations could potentially lead to faster converging by some configurations since many of the locations in CMC seem redundant in our case studies. This is something to be considered in future studies.

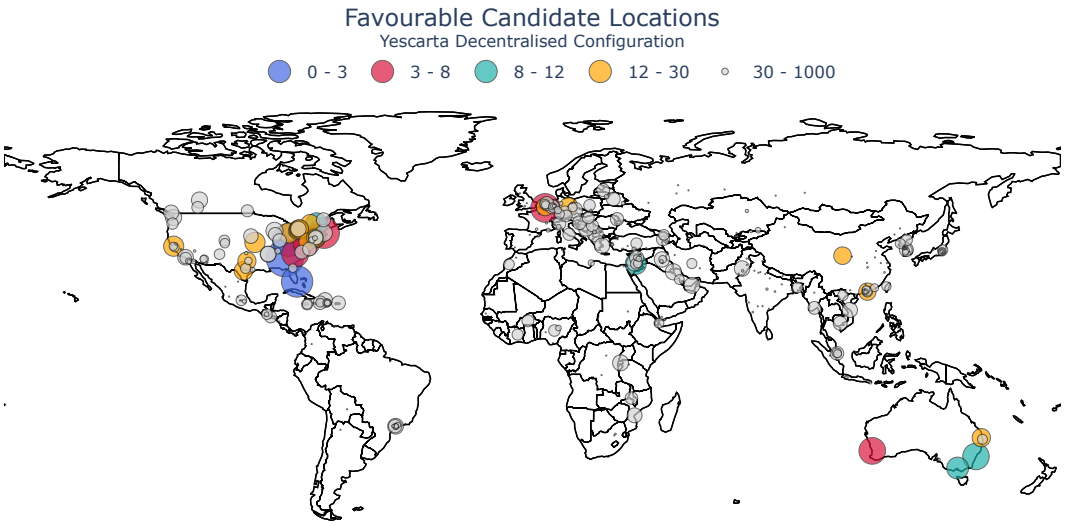


Figure 6.11: Favourable candidate locations for Yescarta Decentralised configuration for all types of manufacturing and cryopreservation.

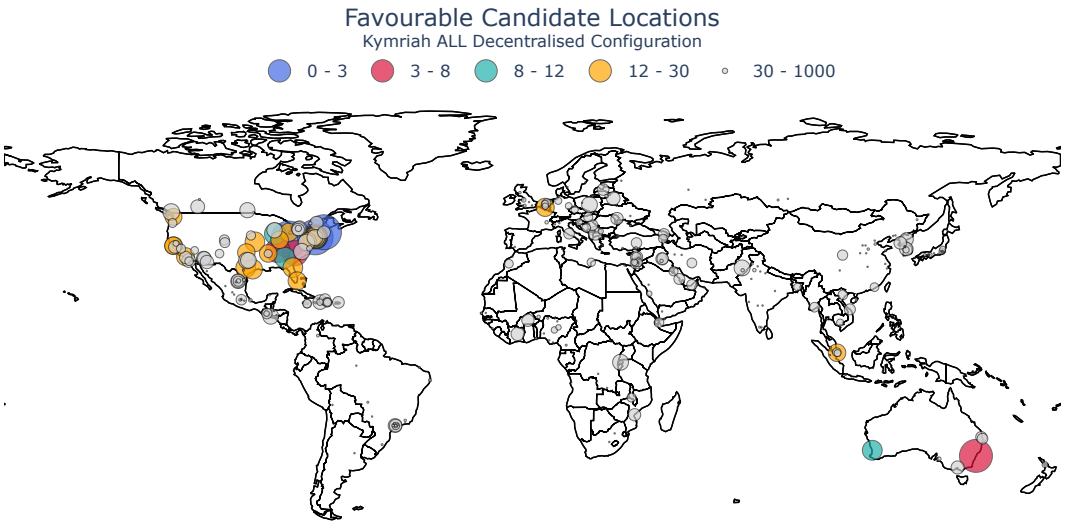


Figure 6.12: Favourable candidate locations for Yescarta Decentralised configuration for all types of manufacturing and cryopreservation.

6.8 Conclusion and Future Research

As the clinical development of PM and particularly of autologous revolutionary therapies is becoming increasingly central to medical treatments, it is essential to understand their commercialisation at a large scale. The low number of approved ATMPs has already met significant challenges in proving their cost effectiveness and the ability to deliver timely products, given a greater demand than the one encountered in clinical trials. With the products' medical potential, an increase in the number of academic papers concerned with the optimisation of different echelons of the supply chain is observed. Nevertheless, with few exceptions previously mentioned, the research around the optimal location of facilities and the analysis of multiple supply chain configurations has not been addressed.

In this paper, we have introduced from an OR perspective three possible such configurations, namely a fully centralised model which follows the traditional pharmaceutical network, an IMC which focuses on the advantages brought by lower scale manufacturing closer to the hospitals, and a fully DMC looking at expanding the demand locations and hence lead to a more accessible network for the patients.

The multi-objective formulation was created following the current market needs. The biopharmaceutical companies and the authorisation bodies are looking to reduce the cost of therapies to offer reimbursement contracts that benefit the population and the healthcare system. At the same time, given the gravity of the diseases, the ATMPs generally target, particularly the Yescarta and Kymriah case studies used, a fast turnaround time is of high priority. The substantial investment in manufacturing optimisation had as the main scope of these two objectives. We have also introduced a third objective which concerns the patient directly. Currently, only a few countries offer PM. On one side, this is because of the lengthy approval process, but mostly it is due to the lack of a broader image of how a

global PM network could look like. We have thus introduced the patient travel distance as a third objective.

Our results suggest that following the biopharmaceutical industry's existing supply chain strategies is insufficient for PM and will limit its availability on a large scale. A more decentralised configuration, whether through manufacturing and cryopreservation integration or/and an increase of locations that can offer ATMPs, can lead to a better time, cost, and distance. We have also shown that assuming a relatively small cost for clinics, they are a viable solution for PM. However, assumptions about their cost were made since this facility type does not yet exist in the ATMP supply chain. We have assumed that a clinic will have the same price as the ones from the blood supply chain, which might not end up not being the case for PM. This assumption was made since the clinics would be responsible for the leukapheresis and administration process, commonly met in the same format in blood bag transfusions.

From a practical perspective, we hope this research encourages the discussion towards creating a less rigid supply chain. What is, however, worth mentioning is that any analysis around the CoI and CoC, as well as how to maintain the variability between products in a decentralised network, is beyond the scope of this paper. However, these problems have been addressed in the past, and the general conclusion was that higher manufacturing automation could solve some of these concerns. Another limitation of the study is related to the data and the cost analysis. The paper focused more on introducing a framework to optimise the abovementioned decision variables. The costs were reported in this paper only as absolute values (rather than average like in the cases of the other two objectives) as, based on our analysis, we could only estimate a delivery and production cost per patient. The final price of an ATMP is usually influenced by a higher number of variables, such as the costs of R&D.

We propose two research streams as potential direct future research from this paper. Firstly, we assume a static demand. However, the market approval for ATMP is gradual. A company can extend their designation (i.e., the disease its product can treat) and the geographical area covered (i.e., obtaining approval from a different country). An example is the case of Kymriah, which got multiple authorisations over the past five years. A mathematical formulation that considers time windows could also indicate the location of the facilities and the order and the time at which these should be constructed, following, for example, a scenario-based expected approval.

Finally, the three configurations proposed cannot be further adjusted without considerable changes. However, the DM can decide whether some facilities are already optimised or should not be part of the supply chain. For example, the DM might be interested in only finding the location of MFs and hospital MF integration and their corresponding production modes. Different levels of integration could be applied. As the target user of these models would most likely be either a private biopharmaceutical company or a healthcare regulator, allowing the DM to interact with the optimisation process and the problem configuration could lead to better results in a comparable computational time.

Chapter 7

Preference-based Stage-wise Multi-objective Optimisation of ATMPs Supply Chains

MENTION: this chapter is an extension of the paper "A. Avramescu, M. López-Ibáñez, R. Allmendinger. **Interactive Stage-Wise Optimisation of Personalised Medicine Supply Chains**. In *Applications of Evolutionary Computation: 26th European Conference, EvoApplications 2023*. doi:10.1007/978-3-031-30229-9_46" (Avramescu et al., 2023). This chapter differs from the previous work in the following ways:

- Problem formulation: the problem presented here includes not only the CMC and IMC, but also DMC. The production time and total cost are maintained among the three objectives, but the demand coverage is changed to patient distance, and the demand nodes do not correspond to the hospitals. The demand needs to be allocated accordingly to either hospitals or clinics.
- Problem stages: an additional stage for the placement of clinics is introduced, which creates the DMC presented in Chapter 6.
- Methodology: A main focus of the paper is on dividing the problem into the facility location of logical supply chain phases that need to happen so the ATMP can be processed, such as MFs, CFs, etc. Previously, we have used a pre-defined order in which the various stages of the problem (i.e., the order in which different facilities are introduced in the supply chain) had to be run, as well as their switch point. In

this case, we build a more flexible framework allowing the DM to define these parameters. In this way, the DM is not restricted simply to the three configurations we have presented throughout this thesis but will be able to create additional levels of decentralisation.

As a consequence, the rest of the sections have seen small modifications. The chapter follows the same structure as the paper, and the writing is the same. A previous, published version (Avramescu et al., 2022a) of this work with preliminary results can be found in Appendix E

7.1 Abstract

PM is a new area of healthcare that has shown promising results in offering treatments for rare and advanced stage diseases. Nonetheless, their supply chain differs from the traditional healthcare model by adding a high level of complexity through product individualisation. The patient is also the donor and becomes part of a complex manufacturing and delivery system. PM biopharmaceuticals are cryopreserved (frozen) and re-engineered at specialised facilities before being returned to the same patient. The corresponding FLP consists of manufacturing and cryopreservation sites, having a set of constraints that are not met in other healthcare supply chains. As a result, the FLP in the context of PM has been only partially analysed, and additional research is still necessary to reach optimal network configurations. In this paper, we extend the solution methods previously proposed for PM FLP by using a stage-wise approach in which the (constrained binary multi-objective) problem is divided into smaller, logical parts. We approach the problem from the perspective of the DM and use the R-NSGA-II algorithm to find a set of desirable solutions. By optimising only part of the decision space at a time,

we reduce the complexity of the problem and allow the DM to compare the objective values obtained between different supply chain configurations. To further understand the impact of each stage (corresponding to each facility type), we use *irace* to automatically configure the order of the stages and their switching point. Our results suggest that allowing the DM to interact with the optimisation process can lead to good and desirable solutions in a shorter computational time and more flexible network configurations, such as the possibility of partial decentralisation.

7.2 Introduction

A sub-optimal supply chain can lead to considerable costs for businesses. However, for some fields, the consequences go beyond the economic perspective and directly influence the customers (patients). A prominent example that has received increased attention is the field of PM. PM focuses on the pharmaceuticals and biopharmaceuticals developed due to this new healthcare paradigm (Branke et al., 2016). These treatments are among the products with the highest re-engineering process, starting with raw cells from the patient. After complex manufacturing, they are returned to the same individual (Sarkis et al., 2021a). It is then for the first time that the donor and the recipient are the same person and become part of the healthcare supply chain.

The market value of personalised medicine biopharmaceuticals (ATMPs) is expected to surpass $2 billion (Grand View Research, 2021), with about 40 products approved for commercialisation (i.e. after proceeding through three clinical stages and obtaining the regulatory permissions) (Eder and Wild, 2019) and over 2000 in any of the three clinical trials in Europe (Alliance for Regenerative Medicine, 2019). Regardless of both economic and social promises of ATMPs (Di Sanzo et al., 2017), the companies

are struggling to offer the products globally. Causes of failure include the inability to ensure a timely and cost-efficient production that meets the quality standards reached in clinical trials. Market authorisation for medical products is a lengthy procedure that, once obtained, comes with a series of regulatory practices and quality assurance measurements that need to be met for each patient. Not meeting the constraints of the market authorisation can lead to partial or complete market withdrawal (Jarosławski and Toumi, 2015; Abou-El-Enein et al., 2016).

The current configuration for the personalised medicine biopharmaceuticals (ATMPs) delivery follows strategic and organisational decisions used for traditional pharmaceuticals. Nevertheless, ATMPs use novel technology and are among the newest products on the healthcare market. Research around its supply chain from an operations research perspective is still developing. A sub-optimal supply chain will further increase the gap in access to revolutionary healthcare and not advance the usage of personalised medicine beyond the current one, namely when everything else has failed.

The scope of this paper is to contribute to the development of more holistic supply chain models and solution methods specifically designed for the optimisation of ATMPs. We start from the mathematical formulations of a CMC (i.e. the demand and supply nodes are always different) introduced in (Avramescu et al., 2021b) and an integrated supply chain (demand and supply points can coincide) presented in (Avramescu et al., 2022b). In addition to the two configurations, we also use the concept of clinics from the DMC introduced in Chapter 6. Unlike the previous chapters focusing on the network design, we are now looking at the impact of the problem dimension and the ability to overcome it by limiting the search space with the support of a DM. In all cases, the problem is formulated as a multi-objective FLP consisting of one mandatory facility, which must process each product, and a helper facility that can reduce the impact of the

constraints.

The FLP is a known class of NP-hard problems. In the context of PM, exact solution methods have only been successfully applied for simple formulations with a small decision space. Suppose we consider the real-world demand for ATMPs with global coverage. In that case, the formulation leads to hundreds of demand nodes and thousands of candidate locations for multiple facility types. The large number of decision variables resulting from the large scale of the problem, alongside the formulation as multi-objective, makes the use of heuristics preferable.

This paper analyses the impact of the DM, usually a biopharmaceutical company, in the optimisation process. We divide the problem into logical stages that follow the facility types and reduce the number of decision variables that are optimised at once. This approach offers the DM the flexibility to create different supply chain configurations and stop the optimisation process when desirable solutions have been obtained. We use a reference-point-based algorithm, R-NSGA-II (Deb and Sundar, 2006), to get a set of non-dominated solutions for each of the six stages (each stage is explained later in Section 7.3). The R-NSGA-II was the preferred algorithm to allow the DM to express desirable solutions to be able to create a straightforward comparison with the NSGA-II. The two algorithms differ only in the way the crowding distance is calculated.

The rest of the paper is organised as follows. A summary of the ATMP decisions at the strategic level of the supply chain and the case study used in this paper is described in Section 7.3. Some of the academic research covering ATMP supply chain optimisation is presented in Section 7.4. Section 7.5 describes in more depth the problem stages, while Section 7.6 describes the exact problem formulation applied in this paper and the two algorithms used to solve it. The case study used to test the proposed approach is described in Section 7.7. The results are presented in Section 7.8 before the paper ends

with conclusions and directions for future research in Section 7.9.

7.3 Problem Formulation

The ATMPs supply chain follows a 1-to-1 model where each product is created individually, having the patient as starting and endpoint. The demand locations are usually hospitals, where the first step of the supply chain, leukapheresis, is conducted. Through leukapheresis, the cells required to create the ATMP are collected while the rest of the blood is returned to the patient. This initial step represents one of the reasons why the supply chain's success rate is critical. The cells undergo a manufacturing process where they are re-engineered to fight a specific disease. As with any production, manufacturing can fail at different steps for various reasons. If an ATMP manufacturing fails, the supply chain of that patient needs to be restarted. However, collecting a second set of cells might not always be possible, depending on the individual's health condition. The FLP models corresponding to the ATMPs supply chain can be divided into two broad categories, referred here as *CMC* and *IMC* based on the production model, and can be extended with a patient allocation *DMC*.

Centralised Supply Chain

The manufacturing process occurs at highly specialised MFs to which the cells are delivered from the hospital. After the manufacturing is finished, they are returned to the same patient. Usually, assuming the current workflow of public healthcare, this will coincide with the same hospital from which the cells were initially collected. The cells are time and temperature sensitive, with ATMPs being considered some of the most sensitive medical products. To mitigate the short shelf-life and risk to the quality

of the cells, a cryopreservation technique (the freezing process of the cells) is applied. The frozen cells then have an extended shelf-life that is generally not imposing a time restriction unless the product is stored. The shelf-life of frozen cells is long enough for the delivery between any two points to be met.

The cryopreservation process is conducted at the MFs once the re-engineering process is finished and at independent CFs after leaving the hospital. A more detailed description and the corresponding mathematical model for the above were defined in Chapter 5.

Integrated Supply Chain

Opening new MFs and CFs is expensive and has to consider several constraints, like obtaining regulatory approvals for each location. Moreover, each ATMP targets diseases with low global demand. A high initial investment might be economically inefficient for biopharmaceutical companies. Additionally, a large default delivery time is expected since placing many such facilities around the globe is not feasible. As an alternative, different levels of decentralisation have been proposed (Harrison et al., 2018b,a). We analyse the impact of smaller manufacturing and cryopreservation units (MUs and CFs) as possible integration at demand points (i.e. hospitals). In this scenario, either the cryopreservation or the manufacturing can occur directly at the hospital, providing a potential solution for locations with high demand or highly isolated. An integrated CU avoids the shelf-life constraint. An integrated MU also allows the completion of the manufacturing without needing transportation. A more detailed description of the IMC and its formulation were defined in (Avramescu et al., 2022b), and a simplified mathematical model is described below.

In line with the objectives from Chapter 6, the problem is formulated as a multi-objective FLP where we aim to:

1. *minimise the average patient distance*, calculated as the distance between the demand node and the closest opened clinic or hospital to which it is allocated;

2. *minimise the average waiting time per patient*, calculated as the total delivery and production time (excluding leukapheresis) divided by known total demand;

3. *minimise the total cost of the supply chain*, calculated as the cost of building the MFs and CFs, the integration cost at hospitals of MUs and CUs, and the production cost which is product dependent.

Objective 7.1 is 0 if a clinic or hospital is opened at the demand node. Otherwise, it is the Haversine distance between the demand node and its allocated facility. The demand node can only be reassigned to hospitals and not clinics unless a clinic is opened at its location. Partial demand coverage is not allowed, and it is assumed that the demand from a demand point is always assigned to the same facility. Likewise, if a demand point is not covered, those orders will be reallocated to the closest open hospital. The distance a patient can travel is unconstrained as the shelf-life only applies once the cells are collected. Objective 7.2 is the hospital's average delivery time. The hospitals that have an MU will have no delivery time, while those with CU will only have direct delivery to an allocated MF. Objective 7.3 is the sum of the construction cost for MFs and CFs and the cost of integration in the case of MUs and CUs, and production cost.

FR_j (Eq. 7.5) is the failure rate associated to each location. Equations (7.6) and (7.7) are classic FLP constraints and restrict one facility type to be opened at each location. This applies to both demand nodes and candidate locations. Similarly, if a hospital has an MU or CU, it cannot be allocated to an MF or CF, and it can only be assigned to either an MF or CF (7.8). All hospitals that are allocated to a CF must be allocated to an MF (7.9). Hospital allocation can only be done at open MFs or CFs (7.10). Equation (7.11) is the

shelf-life constraint. If the demand from a hospital is delivered to an MF via a CF, then the shelf-life constraint is deactivated. To enforce the IMC, all demand locations that do not have a hospital need to remain closed, as constrained by Equation (7.12). As specified above, those demand points will stay closed and have no demand as it was reallocated.

Indices and Parameters

$i \in I$ Demand nodes which can be hospitals (I^H) or locations that need to be reallocated as no facility can be opened here (I^h).

$j \in J$ Candidate locations for placing an MF/CF.

$k \in K$ Production modes of MU/MF such as manual, semi-automatic, and automatic ($k > 1$); the value $k = 1$ denotes cryopreservation (either CU or CF); the value $k = 0$ denotes no integration.

r_k Failure rate associated to each production mode ($k > 1$).

d_{ij}, $d_{ij'}$ Distances between facilities.

c_{ik} Production cost for hospital i with mode k, where k is either the production mode of the MU or of the allocated MF.

s_{ik}, s_{jk} Cost for building an MU ($k > 1$) or CU ($k = 1$), and cost for building an MF $(k > 1)$ or CF ($k = 1$) respectively.

γ Shelf life.

T Very large number.

a_i Total ATMP orders at allocated hospital i.

Decision Variables

h_{ik} 1 if an MU or CU is built at hospital $i \in I$, 0 otherwise; where $k \in K$ represents either CU ($k = 1$) or MU with various production modes ($k > 1$).

x_{jk} 1 if a MF or CF is placed at location $j \in J$, 0 otherwise; where $k \in K$ has the same meaning as above but now refers to independent facilities.

y_{ij} 1 if hospital i is allocated to either an MF or CF at location j, 0 otherwise.

The following helper variables are used to check if hospital i has an MU (h_i^{M}), it is

allocated to an MF (z_i^{M}) or to a CF (z_i^{C}):

$$h_i^{\mathrm{M}} = \sum_{k=2}^{K} h_{ik} \qquad x_j^{\mathrm{M}} = \sum_{k=2}^{K} x_{jk} \qquad z_i^{\mathrm{M}} = \sum_{j\in J} y_{ij} x_j^{\mathrm{M}} \qquad z_i^{\mathrm{C}} = \sum_{j\in J} y_{ij} x_{j1}$$

Objectives

$$\text{Minimise} \quad \sum_{i\in I} a_i \times \min_{i'\in I_1^{\mathrm{H}}} d_{ii'} \tag{7.1}$$

$$\text{Minimise} \quad \frac{TotalTime}{\sum_{i\in I} h_i^{\mathrm{M}} + z_i^{\mathrm{M}}} \tag{7.2}$$

$$\text{Minimise} \quad \sum_{i\in I}\sum_{k=1}^{K} s_{ik} h_{ik} + \sum_{j\in J}\sum_{k=1}^{K} c_{jk} x_{jk} + \sum_{i\in I} a_i c_{ik} \tag{7.3}$$

where:

$$TotalTime = \sum_{i\in I}(1-h_i^{\mathrm{M}}) \sum_{j\in J} y_{ij} x_j^{\mathrm{M}} \Big[d_{ji} + (1+FR_j) \cdot \Big((1-z_i^{\mathrm{C}}) d_{ij} + z_i^{\mathrm{C}} \sum_{j'\in J} y_{ij'} x_{j'1} (d_{ij'} + d_{j'j}) \Big) \Big] \tag{7.4}$$

$$FR_j = \sum_{k=2}^{K} r_k x_{jk} \tag{7.5}$$

$$\sum_{k=1}^{K} h_{ik} \leq 1 \quad \forall i \in I \tag{7.6}$$

$$\sum_{k=1}^{K} x_{jk} \leq 1 \quad \forall j \in J \tag{7.7}$$

$$h_i^{\mathrm{M}} + z_i^{\mathrm{M}} \leq 1, \quad h_{i1} + z_i^{\mathrm{C}} \leq 1 \quad \forall i \in I \tag{7.8}$$

$$z_i^{\mathrm{C}} \leq z_i^{\mathrm{M}} \leq 1 \quad \forall i \in I \tag{7.9}$$

$$y_{ij} \leq \sum_{k=1}^{K} x_{jk} \quad \forall i \in I, \forall j \in J \tag{7.10}$$

$$\sum_{j \in J} y_{ij} x_j^{\mathrm{M}} d_{ij} \leq z_i^{\mathrm{C}}(24 \text{ hours}) + (1 - z_i^{\mathrm{C}})\gamma + h_{i1} \cdot T \quad \forall i \in I \tag{7.11}$$

$$i = 0, \forall i \in I^h \tag{7.12}$$

Decentralised Supply Chain

As shown in Chapter 5, the hospitals that can accept patients for ATMPs treatment are not distributed equally globally. The issue of unfair access to PM is raised, with large geographical areas, such as almost Africa or South America, remaining primarily uncovered. The DMC aims to solve this problem by finding good locations for additional hospitals, following the same objectives as the two production models. In the DMC, the facilities opened with the same role as the existing hospitals are called clinics. This difference is made for two reasons. Firstly, the hospitals already have a FACT authorisation, while these new hospitals would need to go through the application process, and it is uncertain how long this would take. Secondly, they are thought to be smaller buildings which do not have the same competence and personnel as a hospital (e.g., operating rooms). The mathematical model for this configuration is described in Chapter 6.

7.4 Background

The FLP in ATMPs supply chain has been only recently approached from an optimisation perspective. Nonetheless, the papers that focused on either the mathematical modelling of the problem or the extension of solution methods have highlighted the impact of the supply chain on the availability of ATMPs (Sarkis et al., 2021b; Papathanasiou et al.,

2020).

Most of the papers on ATMPs FLP focus on optimising the centralised model. The first authors to propose a mathematical formulation were Wang et al. (2018a). They use a small case study of a CAR-T therapy with 11 demand points and six candidate locations for the MFs. Their formulation is a classical uncapacitated FLP, and considering the small decision space and linear model, it was solved using exact methods. In most of the papers, there has been little emphasis on the development of solution methods and more on the extension of the problem formulation, such as in the extension presented by Moschou et al. (2020) on a centralised model, and Bernardi et al. (2022), who introduce intermediate storage units as possible decentralisation.

Karakostas et al. (2020) presented a hypothetical configuration for the ATMPs supply chain, taking inspiration from supply networks for blood transfusion bags. They propose the use of local treatment facilities alongside specialised hospitals, as well as mobile medical units for treatment delivery. They were the first ones who did not use an exact solver and applied a GVNS to tackle a realistic-sized CAR-T case study.

Using an exact solver, such as IBM ILOG CPLEX Optimization Studio (CPLEX), was feasible as the linear formulations in previous papers had a relatively low number of decision variables, usually only one objective, and a small decision space. The applications of heuristics were proven to lead to reasonable non-dominated solutions in less computation effort when compared to exact methods given the complexity of multi-objective problems with large decision spaces (Ehrgott and Gandibleux, 2008).

Moreover, none of these papers considered the location of the CFs as part of the optimisation problems and did not look at integration levels for either MFs or CFs. The only model considering levels of integration at hospitals was proposed by Avramescu et al. (2022b), which considers both the optimisation of independent MFs/CFs and the

hospital's facility integration (MUs/CUs).

In addition to the expansion of the research focused on the development or analysis of existing solution methods for the proposed FLP problems in the context of PM, a topic of interest for PMs could be the integration of the DM preference in the optimisation process. The field of interactive optimisation has been of significant interest, particularly for problems that lead to solutions that will ultimately need to be used by a DM. Barbati et al. (2022) argue that, even though from a technical perspective, the use of heuristic methods had helped to reduce the computational complexity, the number of non-dominated solutions that are usually found by such algorithms in MOO is often confusing for the DM. Thus, taking advantage of the knowledge of the DM can restrict the search in the decision space to the preferable solutions. The authors distinguish between three methods, depending on the moment the DM is involved.

1. *A priori* will use prior knowledge of the DM about one or all objectives and can define one or more preferences before the optimisation process starts.

2. *Interactive* will have the DM actively changing its preferences throughout the optimisation process.

3. *A posteriori* when the DM is only asked to express their preferences at the end of the optimisation process, for example, ranking several solutions obtained by the algorithm.

In this paper, we then aim to understand the impact of the DM and use as *a priori* methods a set of reference points that are defined at the beginning of the optimisation, as well as the configuration of the supply chain and the order in which the facilities locations are being optimised. One of the main arguments against an *a priori* method is

that the DM might not know any information about the objectives before the optimisation. Hence, setting any desirable values for the objectives would be impossible. However, in the context of personalised ATMPs, there are several situations in which the DM could pre-define values of the objectives. For instance, the *delivery time* is strictly linked to the shelf-life and subsequent usage of the CFs. The DM might then prefer solutions that have a short delivery time.

Allowing the DM to choose the desirable configuration and restrict the decision space would lead to a smaller problem complexity. One example to illustrate the above could be that by not adding certain facilities such as CFs, these would not account towards the number of decision variables. Moreover, the DM can also set how many facilities are optimised at once, hence changing the variables during the search.

7.5 Problem Stages

The IMC is an extension of the CMC. Even though there may be a solution where the demand could be covered entirely by MUs, for it to be feasible, at least one MF needs to exist for purposes of quality check and quality assurance. In other words, the IMC will always need to comprise an MF from the CMC. This section describes the six stages we propose; three are part of the CMC and three of the IMC. The first stage of the CMC will be referred to later on as Stage 0 or Stage C1 as it is the only stage mandatory for the optimisation, and the DMC stage, which creates the DMC will become Stage 6 or Stage DMC. It is then possible to allow the DM to stop the optimisation process at different stages, with a different number of facility types, by dividing the problem into its logical sub-components, as follows:

I **Stage C1**: At this stage in the optimisation process, we only optimise the location

of the MFs, reducing the problem to the classic uncapacitated FLP (Cornuéjols et al., 1983). This is the only mandatory stage, as the production of a ATMP cannot happen unless the cells are re-engineered at one of the MFs. A default production mode chosen by the DM is set. In this paper, we have set this as a manual production mode.

II **Stage C2**: After the optimisation of the MFs, the DM can decide whether to accept any of the non-dominated solutions obtained in the previous step or add CFs. The CFs will increase the overall delivery time for a patient since the cells will need to be first frozen and then delivered to an MF. However, the CFs can reduce the cost of the supply chain by reducing the number of MFs while maintaining or increasing the number of hospitals that can accept ATMPs.

III **Stage C3**: The final stage of the CMC optimises the production modes of the MFs. Each mode of production has an associated construction, production cost, and failure rate. If the production of a ATMP fails, the entire supply chain for that patient needs to be restarted from leukapheresis, thus increasing the total time (Eq. 7.4).

Figure 7.1 shows the three stages' graphical representation.

Once the CMC is created, the DM can add different integration levels to the supply chain. In this paper, we have created the integration stages by mirroring the centralised ones to simplify the process for the DM. At the same time, this distribution creates the possibility of interchangeably switching between CMC or IMC at the beginning of the optimisation process. However, alternative levels of integration or order of stages could also be applied. The mirrored integrated stages are as follows:

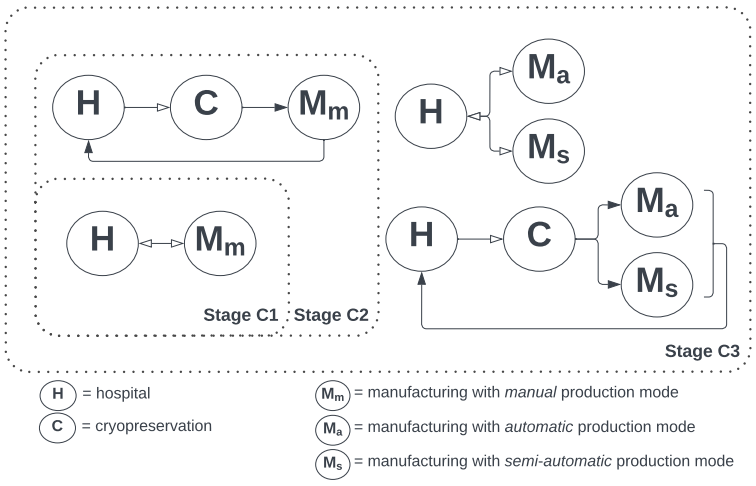


Figure 7.1: Facilities and network direction for the different stages in the centralised scenario where the integration model is not considered. Stage C3 can only happen if Stage C1 is already finished. Filled (resp. unfilled) arrows correspond to frozen (resp. fresh) delivery of cells.

IV **Stage I1**: Add MUs at hospitals. The cells can be processed on-site without delivery if a hospital has an MU. In this case, the obvious advantage would be a considerable decrease in delivery time for the patient and the elimination of the cryopreservation process. Even though a single MU cost is cheaper than an MF, this cost would be unprofitable for hospitals with low demand.

V **Stage I2**: Add CUs at hospitals. In this case, the cells can be transported to any MF without first passing by a CF. To simplify the CoI and CoC, we restrict the cells that come from a hospital with CUs only to be processed at MFs and not hospitals with MUs.

VI **Stage I3**: this final stage only optimises the production modes of the hospitals with MUs.

Figure 7.2 shows the route of the integrated hospitals. The stages can happen in any

order, except for Stage C1, which is always the first one, and the DM only has control over the default production mode of the MFs opened now.

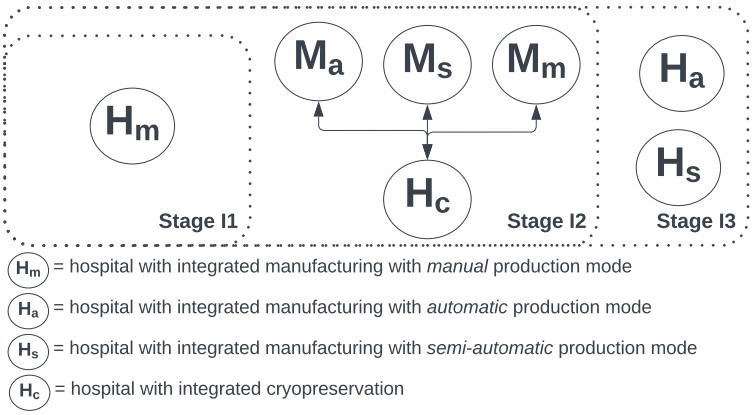


Figure 7.2: Facilities and network direction for the different stages in the integrated scenario. Stage I3 can only happen after Stage I1 has already finished. Filled (resp. unfilled) arrows correspond to frozen (resp. fresh) delivery of cells. No connection means no delivery occurs, and the facility acts as both demand and supply nodes.

Finally, the DMC is created by adding clinics that help with the demand (re)allocation but do not play an active role in the production of the ATMP. The clinics stage is not constrained in any way and can happen before any stages that build the CMC and IMC stages. At this stage, it is decided whether the patients (i.e. demand) from a certain location need to be reallocated to an open hospital or can be processed locally because a clinic has been opened here.

The level of decentralisation possible in the PM supply chain, and even more largely in the healthcare supply chains, depends on the needs, resources available, and restrictions of the DM. For instance, in the IMC, we assume that the DM would be allowed to integrate both MUs and CUs at hospitals. However, it might be that some countries, or some public hospitals, might not approve the addition of one or the either. It then becomes desirable to have a framework that would allow additional constraints, such

as some facilities not being added. Similarly the DM might only want to continue optimising an existing network, such as extending integrated into a centralised model, and not create an entire supply chain configuration.

7.6 Methodology

This paper aims to build an optimisation framework that a DM, for example, a biopharmaceutical company with a product in late clinical stages, can use to make different supply chain configurations. As the focus is on the DM, we are more interested in finding solutions that would be favourable to some pre-defined objective values (i.e. reference points) rather than finding a close approximation to the entire Pareto front. To achieve this, we use a reference point-based algorithm, R-NSGA-II (Deb and Sundar, 2006), which is a variant of the popular NSGA-II (Deb et al., 2002a).

By default, EMOAs try to approximate the entire Pareto front by distributing the non-dominated solutions evenly across the objectives (Deb, 2011). In comparison, a preference-based EMOA relying on reference points provided by a DM allows the DM to set ideal values for the objective functions, and the non-dominated solutions returned by the algorithm will then be concentrated around that particular region. R-NSGA-II is among the most popular reference point-based EMOA algorithms and differs from the classic NSGA-II in the crowding distance, which is calculated using the Euclidean distance from the reference points. We simulate a DM by defining four reference points as shown in Table 7.1. The four reference points were chosen to represent different preferences of the DM towards either of the three objectives, such as delivery time (i.e., Reference point #1), patient distance (i.e., Reference point #4), total cost (i.e., Reference point #2), and a more balanced distribution between the three objectives (i.e., Reference

Table 7.1: Reference point values for the three objectives.

	Time	**Cost**	**Distance**
Reference point #1	0	£6×10^7	1000
Reference point #2	5	£1×10^5	500
Reference point #3	10	£3×10^7	200
Reference point #4	50	£5×10^6	100

point #3). The results presented in the next section use these reference points.

Since the only requirement for a supply chain of ATMP to be feasible is to have an MF, the DM can decide (i) which other facilities alongside MF to be used such that solutions close to the desired objectives are found, (ii) the order in which the facilities are placed, and (iii) the length each stage should be optimised for. The scope of the second choice is to allow the DM to check the solutions obtained during the optimisation process and stop it should desired solutions be found. This approach could potentially lead to a reduction in the optimisation cost by stopping the algorithm sooner. The solutions presented to the DM are always the non-dominated solutions found before the termination. A solution is considered to be non-dominated if no other solution can obtain a better value for any of the objectives without worsening another objective function. The configurations used by the DM here are shown in Table 7.3. There were four reference points and four configurations (i.e., order of stages/facilities order), leading to 16 combinations.

R-NSGA-II is used as the primary solution method for all stages of the problem. At Stage C1, the initial population is created randomly by placing MFs with probability p in each candidate location. At Stages C2 and I2, the initialisation is done by adding CFs or CUs at empty locations or by changing some of the existing MFs or MUs (if any exist). This approach was preferred as compared to randomly placing CFs or CUs to avoid a drop in the solution quality at the first generation of the following stage. Adding facilities

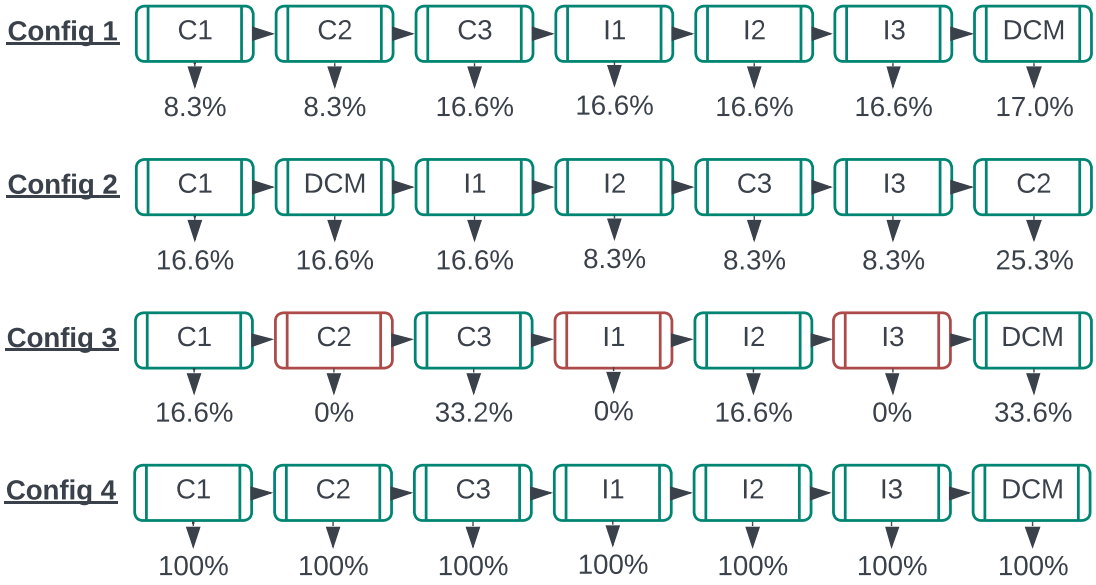


Figure 7.3: The order in which stages are run and the configurations the facility placements lead to. **Green** means that the stage is being optimised, while **red** means that the facilities part of that stage will not be taken into consideration. The percentages represent the length of generations for which each stage is optimised before being changed.

at random to an already optimised solution will, in most cases, lead to worse objective function values. Consequently, progress would stagnate until the values of the objectives reach at least the one obtained at the end of the previous stage. Stages C3 and I3 are only optimising the production modes of existing MFs or MUs (if any exist); the initialisation will also switch the mode from manual[1], to either semi-automatic or fully-automatic, rather than adding new facilities. The logic of the solution method, where all stages would be run in order, is shown in the flowchart in Figure 7.4.

[1]Default production mode used in this paper

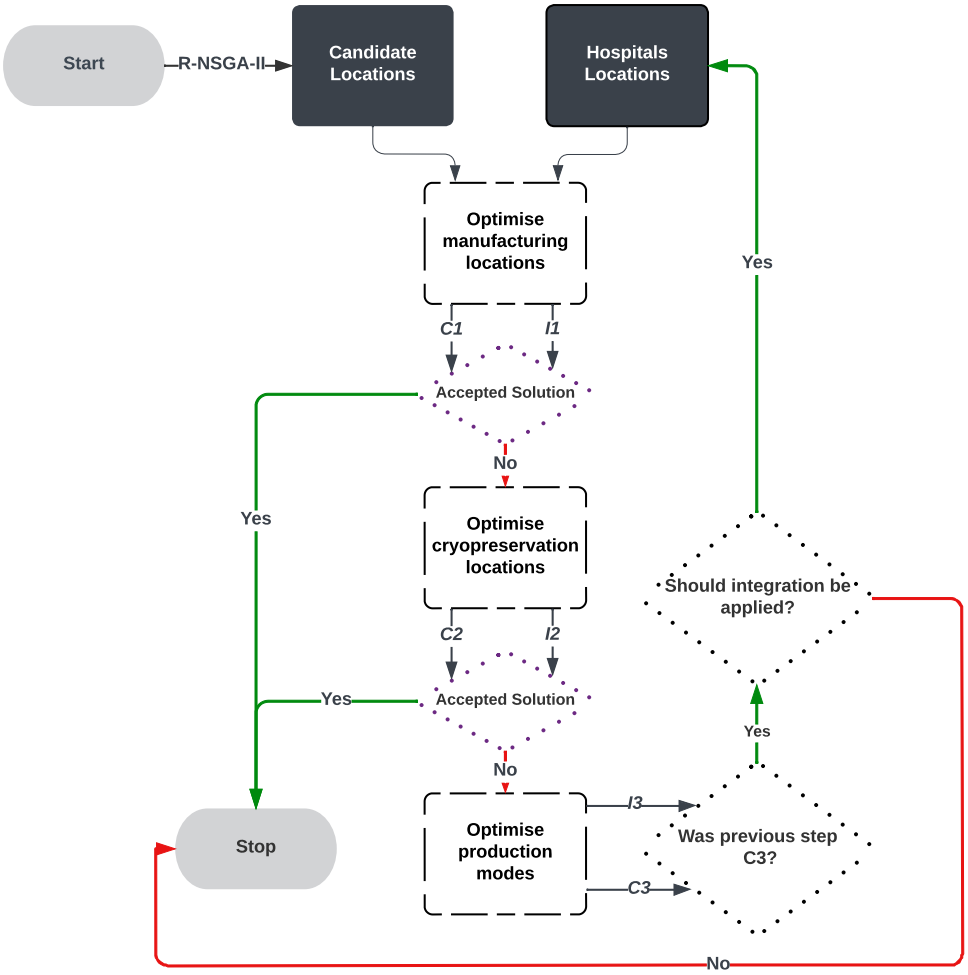


Figure 7.4: Flowchart of solution method highlighting the problem stages and the steps at which the DM can stop or continue the optimisation process using a standard Stage C1 to I3 running order. The red and green lines correspond to negative and positive decisions, respectively. The dotted shapes represent a decision that needs to be taken, either by the DM or is a change that can influence the algorithm, such as the stage at which the optimisation is at a certain moment. The coloured shapes of candidate and hospital locations show the locations affected by different stages.

The choices done by the DM regarding the order of the facilities and length of the optimisation process are fairly subjective and usually outside the scope of the DM. To gain an understanding of whether the order in which the facilities are placed, as well

as whether some facilities would have a stronger influence than others on the quality of the solutions, we use *irace* (López-Ibáñez et al., 2016) to automatically configure these parameters. To switch between the stages and the order, we simplify how *irace* manipulates the parameters, allowing it only to change the generation at which each stage starts. More concretely, if two stages start at the same generation, all decision variables in that stage will be optimised concomitantly. Similarly, if a stage is set to begin at the last generation or beyond, that stage will never be part of the supply chain configuration. For the experiments run using *irace*, we replace R-NSGA-II with NSGA-II and use the HV as a comparison metric, which is by default used by multi-objective *irace*. The HV is a commonly used performance measure in MOO to indicate the quality of a set with non-dominated solutions. It has become a popular measure as it can be used regardless of the number of objectives and does not require any prior knowledge related to the Pareto-optimal front. This becomes particularly important when working with real-world problems for which the Pareto front is usually unknown.

7.7 Data

To test the stage-wise approach proposed, we solved the problem using a case study of ATMP with market authorisation. The ATMP used is Yescarta, which is used for treating adults suffering from DLBCL. Like most of the ATMPs initial market authorisation, it can be used only after two lines of an alternative treatment have already been used. It is worth mentioning that the market authorisations usually take place gradually in different jurisdictions around the world; however, for simplicity, we assume that the supply chains of the two ATMPs would be constructed assuming global coverage and, hence, we do not consider time-periods in the problem.

The set of demand locations comprises all hospitals that can accept adult patients. In addition to the case study presented in this paper, only two more scenarios can be currently analysed given the PM landscape. An ATMP usually target either adult or paediatric patients. The set of hospitals that can treat one or the other is usually different (see Chapter 6 for a representation of the FACT accredited hospitals for each category). The few numbers of approved CAR-Ts make it rare for an ATMP to target both adult and paediatric patients (e.g., Kymriah). The hospitals could then have only the hospitals that accept adult patients, paediatric patients, and, more rarely, both. The distribution of hospitals for paediatric patients is more sparse than for adults; for example, having no hospitals in Europe and only one hospital in Asia or South America. Thus, using further case studies in this paper would lead to different values for the objectives, but it is unlikely that they would impact the proposed approach, which is independent of the set of hospitals.

The demand was calculated using estimated data from the IHME (Institute for Health Metrics and Evaluation (IHME), 2022). The locations of the hospitals are fixed, and we only decide whether it is efficient in terms of the three objectives (total cost, patient distance, and delivery time minimisation) for the hospital to be covered as part of the production. The clinics' locations correspond to the country's centre for which the IHME has publicly available data. As the two ATMPs target different diseases, we have discarded from our analysis any country for which data was not available to calculate the demand of both ATMPs. The candidate locations correspond to the 1000 biggest cities in the world (Opendatasoft, 2022).

The production modes were proposed in (Lopes et al., 2020), divided into manual, semi-automatic, and fully automatic. As each production mode has an associated failure rate that leads to the restart of the production for that patient, the corresponding

percentage of failed ATMPs per facility depending on the production mode is shown in Table 7.2. As previously mentioned, Stages C1 and I1 start with MFs with manual production mode.

Table 7.2: Lower and upper limits for the failure rate of each production mode defined by Lopes et al. (2020).

	Lower Limit	**Upper Limit**
Manual	5%	15%
Semi-automatic	3%	10%
Automatic	1%	5%

We have used common mutation and crossover operators for FLP to obtain new solutions. We have defined the mutation to remove and add facilities with a probability of 0.3 each or move a facility to a different location with a probability of 0.4. The mutation is applied for all facility types but depends on the stages to be optimised. A mutation will apply only to the stage that is currently being optimised, as well as all previous stages. As a consequence, it will never be used on facilities that are part of a stage that is yet to be optimised or that has been excluded. We also apply a uniform crossover (Syswerda, 1989) to the vectors of hospitals and locations separately with a probability of 0.5. The results were obtained by running R-NSGA-II for 6000 generations, with a population size of 50 ($50 \cdot 6000$ solution evaluations), over 15 independent runs. The parameters are also shown in Table 7.3.

Table 7.3: R-NSGA-II parameters.

Parameter		**Value**
Mutation	Mutation add	0.3
	Mutation remove	0.3
	Mutation move	0.4
Crossover		0.5
Population		50
Generation		6000
Independent runs		15

The solution representation in this chapter changes between the stages used and the moment in the optimisation process (i.e., how many stages have already been added to the problem). When all the stages are being optimised at the largest, the problem size is the same as the one introduced in Chapter 6.

7.8 Results

In a multi-objective problem, the result is a set of non-dominated solutions rather than a single optimal value. The DM would then be presented with solutions that cannot be improved in any of the objectives without sacrificing another one. In this section, we analyse the results of the stage-wise approach looking at the impact of the stages on the optimisation process (Subsection 7.8.1) and the impact of the facility order based on the results obtained from the automatic configuration with *irace* (Subsection 7.8.2).

7.8.1 Comparative Analysis of the Stages Behaviour using R-NSGA-II.

Figures 7.5 to 7.8 show the non-dominated solutions in the final generation obtained by R-NSGA-II. The axes of the 3D plots are consistent for each reference point for the three objectives. The colour dimension represents each stage; however, which stage is represented by which colour differs between plots. Each figure has four plots where the upper right is configuration 1, the upper left is configuration 4, the lower right is configuration 2, and the lower right is configuration three as defined in Figure 7.3 in the previous section. The reference points are not visually represented on the map as their optimistic scenario for the cost objective, in particular, does not allow the algorithm to find solutions very close to it. Subsequently, we preferred to show the zoomed-in solutions to visualise the change between stages. Otherwise, an extension of the y-axis on the plots would lead to an overlap between the solutions found, given the big difference in the objective. In case of stages missing from the plot but used in the optimisation, any others dominated all the solutions found at that step.

The results are consistent between the reference points used and suggest a pattern in the trajectory of the solution on the approximation set and that it might not always be necessary to use all facility types. The overlap between the different stages indicates this. Particularly prominent are the results following configuration 4, where the order of the facilities follows first a CMC. After the CMC is fully optimised, including MFs, CFs, and the modes of production for the MFs, the same steps are followed to create all stages of the IMC, namely MUs, CUs, and the production modes of MUs. The DMC created by adding the clinics is optimised at the end.

In this case, as expected, the MFs alone cannot lead to solutions close to the reference

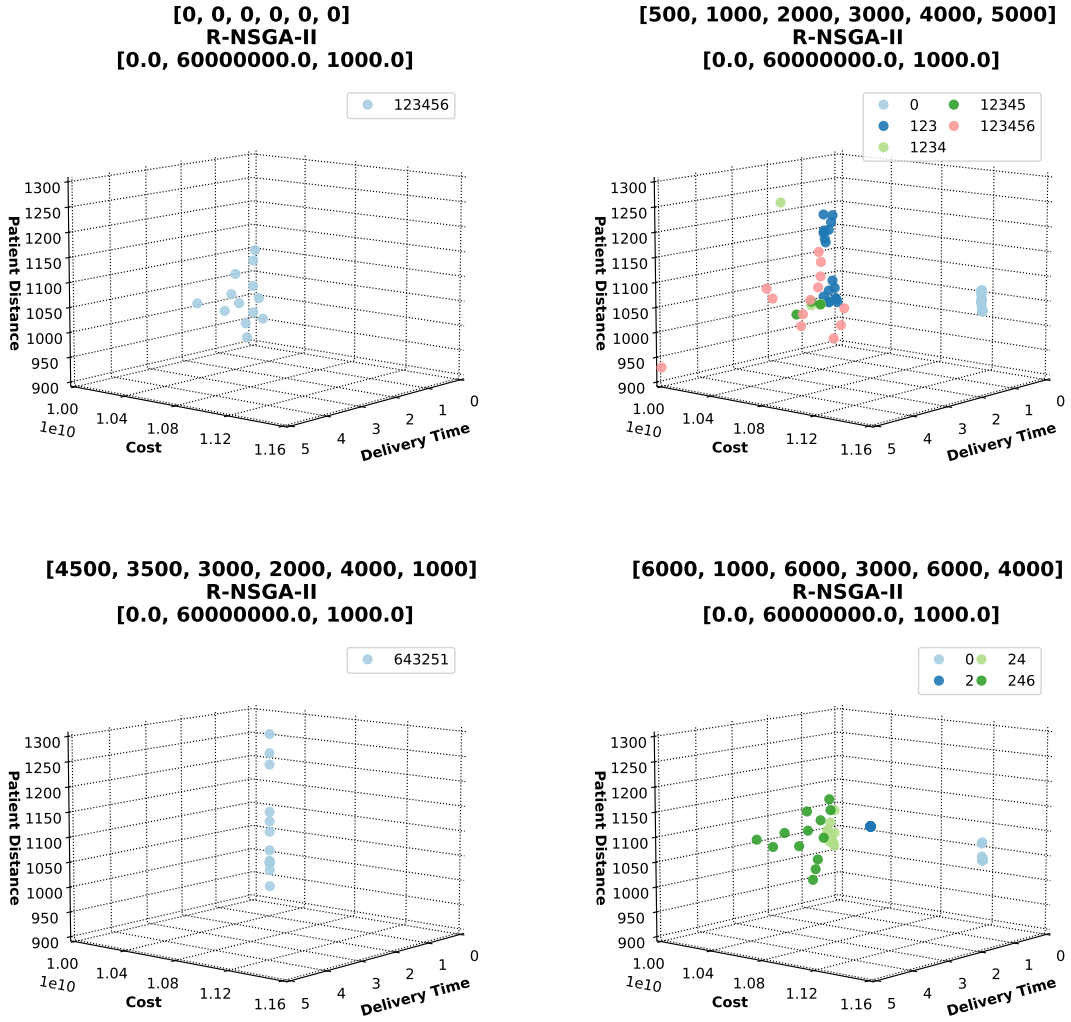


Figure 7.5: Comparative analysis of the behaviour of the stages using R-NSGA-II for Reference point #1 against the three objectives, cost minimisation (y-axis), delivery time minimisation (x-axis), and patient distance minimisation (z-axis). Stage 0 corresponds to C1, stage 1 to C2, stage 2 to C3, stage 3 to I1, stage 4 to I2, stage 5 to I3, and stage 6 to DMC. The stages are represented using the colour dimension, and the order of stages is shown in the legend. For example, 246 would mean that stages C2, I2, and DMC were the only ones run by that point in the optimisation.

point. One example is the lack of other facilities for a reference point whose delivery time objectives are not close to 0. The way the MF is built, it would have a very high

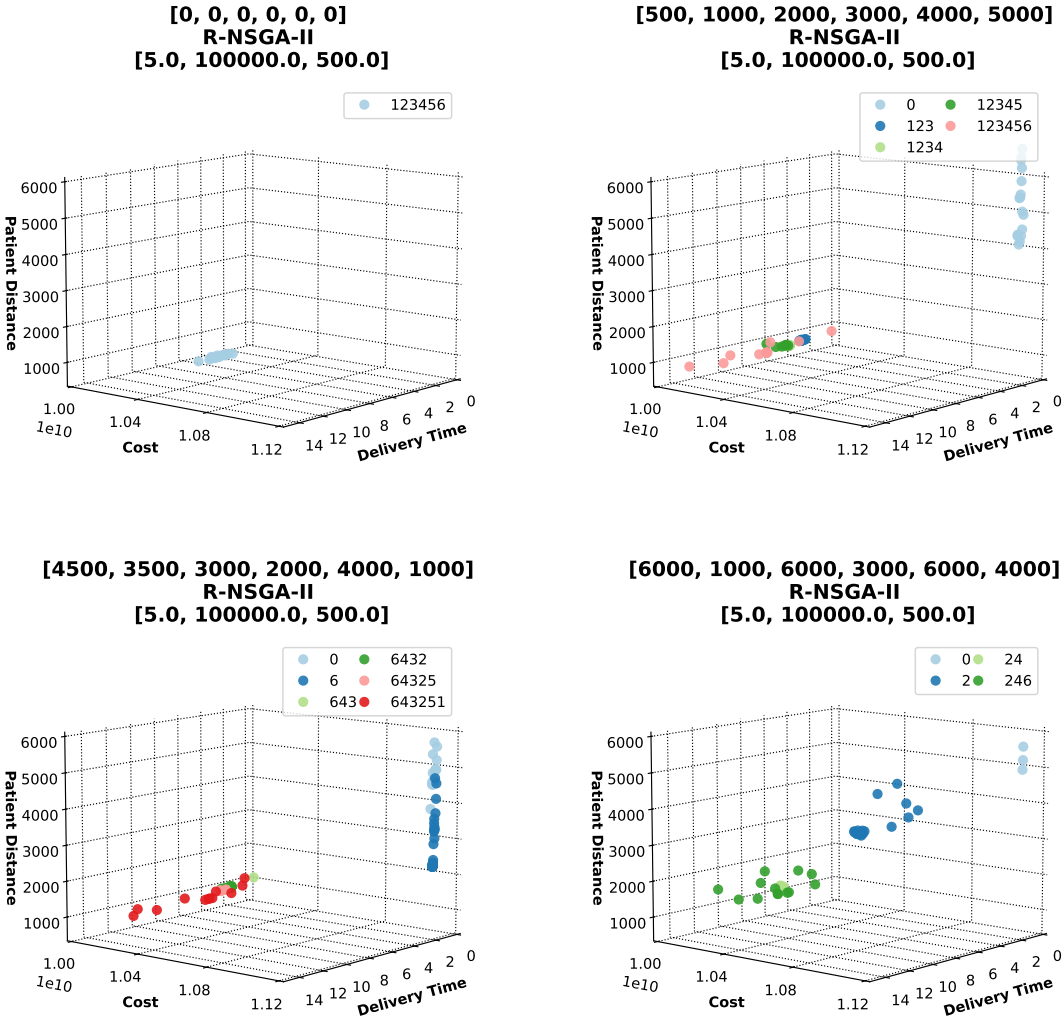


Figure 7.6: Comparative analysis for the behaviour of the stages using R-NSGA-II for Reference point #2 against the three objectives, cost minimisation (y-axis), delivery time minimisation (x-axis), and patient distance minimisation (z-axis). Stage 0 corresponds to C1, stage 1 to C2, stage 2 to C3, stage 3 to I1, stage 4 to I2, stage 5 to I3, and stage 6 to DMC. The stages are represented using the colour dimension, and the order of stages is shown in the legend. For example, 246 would mean that stages C2, I2, and DMC were the only ones run by that point in the optimisation.

cost and would need to be placed close to a hospital due to its small shelf-life. Thus, the high number of MFs needed to cover the entire demand would be high. However,

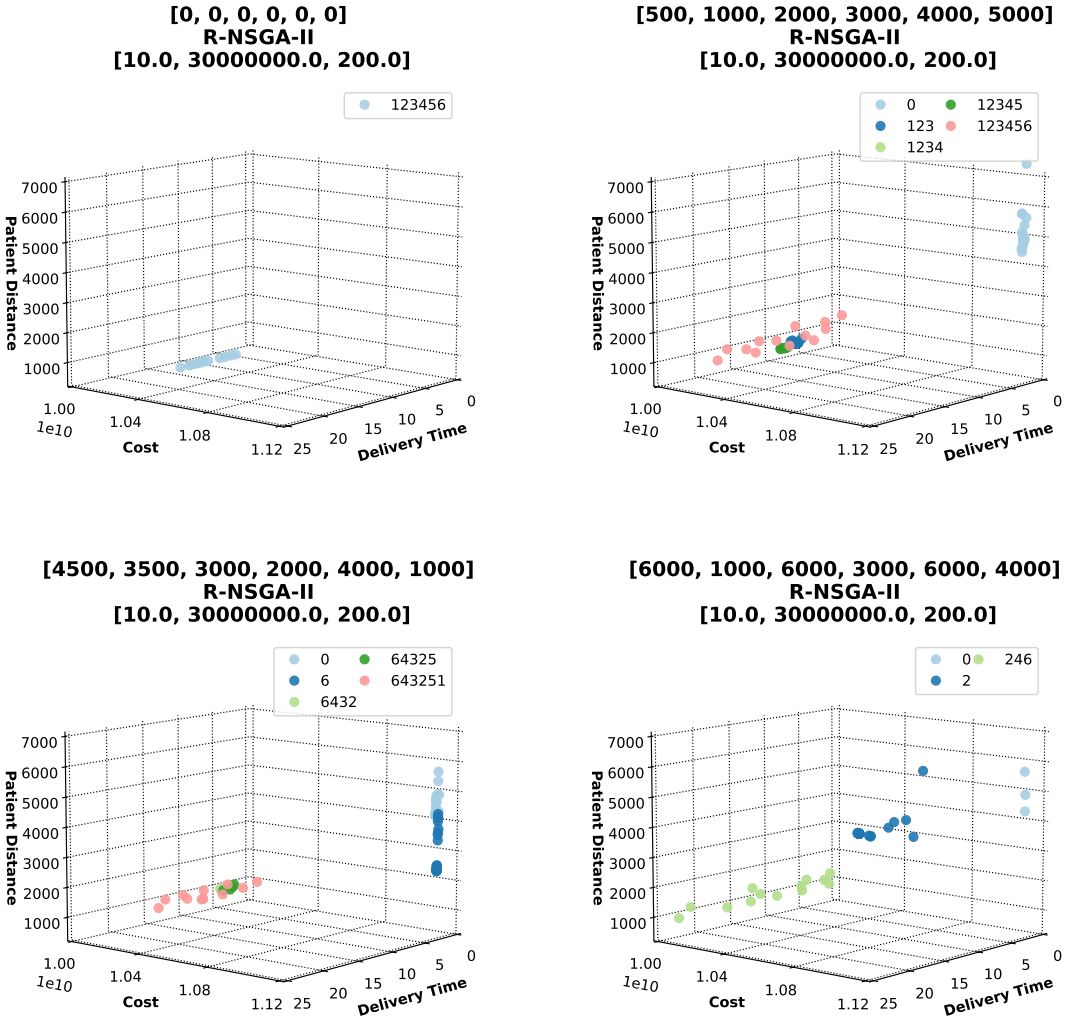


Figure 7.7: Comparative analysis for the behaviour of the stages using R-NSGA-II for Reference point #3 against the three objectives, cost minimisation (y-axis), delivery time minimisation (x-axis), and patient distance minimisation (z-axis). Stage 0 corresponds to C1, stage 1 to C2, stage 2 to C3, stage 3 to I1, stage 4 to I2, stage 5 to I3, and stage 6 to DMC. The stages are represented using the colour dimension, and the order of stages is shown in the legend. For example, 246 would mean that stages C2, I2, and DMC were the only ones run by that point in the optimisation.

the differences in objectives between the other stages, such as between CMC and IMC, might not be sufficient to convince the DM to add more facilities in the supply chain.

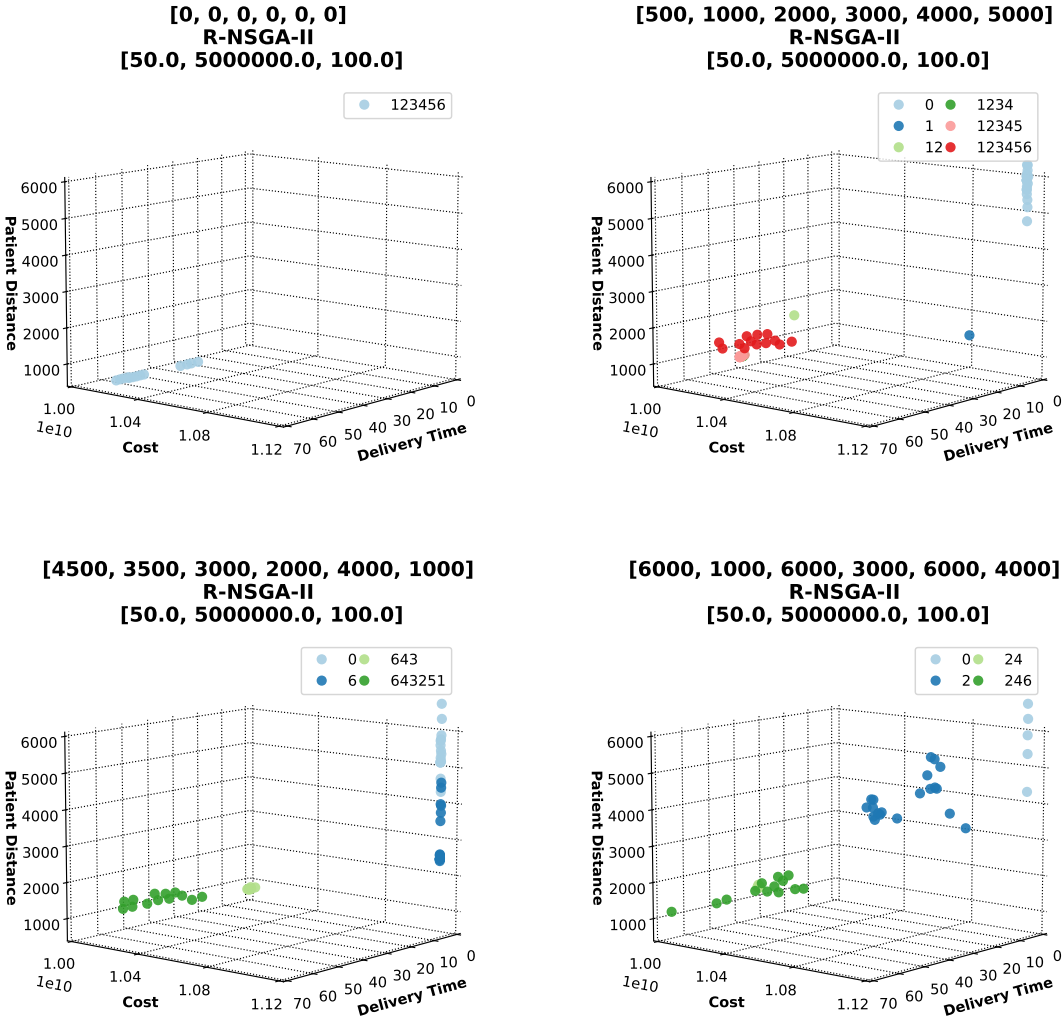


Figure 7.8: Comparative analysis for the behaviour of the stages using R-NSGA-II for Reference point #4 against the three objectives, cost minimisation (y-axis), delivery time minimisation (x-axis), and patient distance minimisation (z-axis). Stage 0 corresponds to C1, stage 1 to C2, stage 2 to C3, stage 3 to I1, stage 4 to I2, stage 5 to I3, and stage 6 to DMC. The stages are represented using the colour dimension, and the order of stages is shown in the legend. For example, 246 would mean that stages C2, I2, and DMC were the only ones run by that point in the optimisation.

The number of authorisations usually required for the use of any additional facility and the problem of product variability is not an objective or constraint we account for in this

problem, but that the DM could choose to consider when analysing the trade-off between solutions.

A breakdown in stages of the problem is also a good indicator of the role of each facility in the objectives. The clinics do not play an active role in the ATMP production, and hence they cannot influence the delivery time since this is calculated only after the cells have been collected from the patient and until administration. Likewise, the cost of building a clinic is considerably lower than, for example, and MF, so its impact on the cost objective is minimal. Nevertheless, they are the prime contributor to the reduction of patient distance since they can avoid the reallocation of the demand, especially useful for geographical areas with many patients but no hospital that can be opened.

Similarly, the stages part of the IMC is the one that can drive the cost reduction the most without sacrificing considerably the delivery time such that the solutions would be too far from the reference point. The lower plots in all stages figures with non-dominated solutions present this perspective most clearly. It is worth mentioning that once a stage is completed, there will be no significant changes to its facility type. However, small changes can still happen through mutation and crossover, leading to better configurations with those facilities. The lower right plot in all figures shows a distinct trajectory and close to solution clusters for each stage. The configuration shown in those plots only focuses on adding clinics, MFs and CUs. In other words, cryopreservation is allowed to happen exclusively at hospitals (each hospital being allowed only to cryopreserve the cells of its own patients), and the manufacturing is always off-site.

7.8.2 Facility Order Impact on the Algorithm

One of this paper's objectives was to understand each facility's effect on the optimisation process. Previous results (e.g., Chapter 5) suggested that in the PM supply chain, the FLP problem comprises multiple facility types that interact with each other and have a direct impact on the behaviour of the algorithm used to solve the problem. By dividing the problem into multiple stages, each optimising one facility type, we further investigate whether the order in which the facilities are added can lead to better algorithm configurations.

We do so by using *irace* to automatically configure the order of the problem and which facilities to be part of the supply chain. The results are presented in Table 7.4, where each iteration corresponds to a subsequent series of evaluations. The configurations are compared by *irace* using the HV metric. The values under each column correspond to the generation at which that particular stage is started. Stage C1 always starts at generation 0 as defined in the problem formulation since having an MF in the configuration is a hard constraint. Moreover, the soft constraint is deactivated, which does not allow the manufacturing modes to be optimised before the MF or MU is placed. Stage I3 still optimises semi-automatic and fully-automatic MFs, but the stage can be optimised before Stage I1. Stage C3 will always happen while C1 is being optimised or after it has finished. The manual production mode is being optimised independently despite the soft constraint since it is the most commonly used in practice nowadays.

There are a few conclusions that can be drawn from these experiments. Firstly, at all iterations, all stages are optimised. There is no instance in a configuration when a stage is missing and is part of the elite configurations found by *irace*. This aligns with previous findings presented in this thesis, which suggest that a move towards decentralisation

	C1	C2	C3	I1	I2	I3	DMC
ITERATION 1	0	1587	5227	701	4102	1358	2305
	0	2089	5605	5346	4940	2240	1222
	0	2651	5036	4611	2675	4269	1590
ITERATION 2	0	5906	4340	2542	4186	3837	902
	0	4791	4967	132	4435	1481	1751
	0	372	4733	521	3338	2402	2396
	0	1756	4885	527	3041	1300	2000
ITERATION 3	0	3799	4932	1879	2801	4248	767
	0	5997	4982	397	4330	774	3228
	0	400	3177	1187	2604	2979	1735
	0	4297	4759	1069	3846	629	2372
ITERATION 4	0	3937	5394	852	3427	220	2243
	0	3799	4932	1879	2801	4248	767
	0	4297	4759	1069	3846	629	2372
	0	5997	4982	397	4330	774	3228

Table 7.4: Automatic configuration of the stages order and optimisation duration using *irace* on the NSGA-II. Columns C1 to DMC correspond to the different stages/facility types optimised. Each iteration category between 1 and 4 will have a corresponding number of elite solutions represented by rows. The values in each cell are the generations at which that particular stage starts. For C1, the generation is always 0 as this is the only mandatory stage and is always optimised at the beginning.

could be a better alternative for PM compared to the CMC. Moreover, *irace* seems to be converging towards an optimisation of the stages that are part of the IMC, followed by DMC and, in the end, by CMC. This can be explained by the heavy influence of the demand at certain nodes on the subsequent location of production facilities (i.e., MFs and CFs for CMC; MUs and CUs for IMC).

The analysis shows the potential of integrating tools such as *irace* to optimise the more usual operators, such as crossover or mutation, and use it to design the problem itself and, consequently, the supply chain configuration. Despite the promising results, the number of possible combinations for tuning (6 stages $\times$ 7000 possible generations) makes it difficult for *irace* to converge in the allowed run time. Future research could look

at visualising whether running *irace* for longer would lead to one or few best facilities order and whether this depends on the case study used.

7.9 Conclusion

The overarching goal of this paper was to introduce the DM in the optimisation process of the supply chain of personalised medicine. We did so by dividing the problem into logical stages that can be optimised independently and allowing the DM to set expected values for the objective functions as reference points. The problem was solved using a popular preference-based EMOA, R-NSGA-II. Our results suggest that the supply chain of ATMPs could benefit from interactive optimisation methods. If the problem is further extended, for example, to include more decentralisation options, the involvement of the DM might avoid the need for implementation of problem-specific heuristics.

In this paper, we have introduced a flexible framework that allows the DM to choose the facilities that should be part of the supply chain and the order in which these should be added. Allowing the DM to set these two parameters could lead to more transparency in the optimisation process. The DM is permitted to check the solutions after each stage and decide whether the solutions obtained are a realistic target for them and sufficient in terms of the three objectives or whether to continue the process and add more facility types. Increasing the complexity level of the network with multiple facilities means, in many cases, more applications for authorisations between different countries. Improving the three objectives and the additional legal implications might not be desirable for a company.

We also allowed the DM to decide how long each stage should be optimised. However, this is not something that the DM is expected to be familiar with. We have then used an

automatic algorithm configurator, *irace*, to optimise the entire process. The difference between the various configurations found was, however, not significant. Hence, future work can consider two potential improvements of this work. The first would be to allow *irace* to run for a more extended period. The budget we have used was not enough for it to converge. A second approach could be to reduce the number of decisions that *irace* needs to make. For example, the DM can choose the facilities that should be part of the supply chain, and the order in which these should be introduced, and *irace* can optimise just the generation number at which a stage is switched.

Finally, more experiments are necessary to analyse the behaviour of the problem. The impact of each facility type on the objectives for each of the seven stages and the order in which they are added to the optimisation is still unclear. Studying the impact of the DM changing the reference point between the stages would also be useful. *irace* was ran using the classic NSGA-II rather than the reference point version. Further implementations could consider adjusting *irace* to use the distance to the reference point as performance measurement. Hence, it is possible to compare its results and the manual configurations of the DM.

Chapter 8

Conclusions and Future Work

The research objective of this thesis was to formally define the FLP for autologous medical therapies that were developed under the rapidly progressing PM. By analysing different supply chain configurations, we have concluded that the strategic location of different facility types used for ATMPs production can lead to not only cost-effective products but overall contribute to patients' satisfaction by being able to reduce the waiting time and ensure a point of collection closer to the patient.

The current models in other healthcare supply chains are insufficient for PM, but they share characteristics that can be further extended to create more exhaustive frameworks for ATMPs. Based on these findings, the rest of the thesis introduced new supply chain configurations and tested their applicability using real-world case studies.

8.1 Key concluding remarks

The conclusions of this thesis were twofold. On the one hand, we considered the main characteristics of PM and how to introduce them to the OR community. From this perspective, the following main conclusions are worth highlighting:

1. The OR research on the pharmaceutical supply chains is not always applicable for PM. The mode of production is shifted from mass production to an on-demand model. The constraints that can be borrowed from the pharma industry are becoming more critical in PM (e.g., shelf-life), and some others are entirely new.

2. The healthcare industry shares common characteristics with PM, but, except SHOO, none of these are as critical and potentially life-threatening. The other networks can work with an off-the-shelf system where the products can be stored for a determined period. This is not possible in autologous ATMPs.

3. We have introduced several mathematical models that can be applied for the optimisation of ATMPs FLP in Chapters 5-7. These have focused on three possible configurations and can be further extended to account for a higher number of more flexible modelling.

4. It is already known that FLP is a class of NP-hard problems. The dimensionality of the problems presented in this thesis is an impediment, and more advanced solution methods are necessary. The interdependency of the main, helper, and optional facilities leads to new algorithmic challenges.

5. In the literature of FLP, the effect of problem fragmentation on the optimisation process has been less researched. This could highlight the trade-off with the benefits it could bring to offering the DM a more transparent solution space. We believe this approach to be particularly useful in the case of PM, where multiple facilities play specific roles that might or might not be desired in the network configuration. We have shown that solving any of the specified supply chain configurations can lead to more flexible network configurations where the DM can decide, based on either objectives or regulatory constraints, whether to include some facilities.

6. Regarding the solution methods, our focus was on understanding the particularities of the problem and how to best extend the existing methods rather than developing

problem-specific algorithms. Namely, we have looked at the interdependency of the two main facility types (i.e., MFs and CFs) and proposed several strategies that were proven effective in different scenarios.

On the other hand, an important part of this research was to advance the current knowledge on the strategic level of the supply chain of PM with particular interest in the FLP. PM and the corresponding ATMPs developed under it are believed to be life-changing for many individuals. For that reason, it becomes of even greater importance to ensure that the supply chain, which is usually directed towards profit maximisation in the pharmaceutical industry, is now also taking into account the benefits of the patient, which becomes, for the first time an integral part of the delivery network. In this sense, the following practical conclusions can be drawn from this research:

1. A supply chain where the manufacturing is centralised at large facilities is often sub-optimal. It is a viable option only when the demand is geographically distributed in small areas, for example, looking only at national level demand.

2. In line with previous research around manufacturing optimisation and the advancement of automated and closed equipment, integrating such units at demand locations can benefit autologous ATMPs. Previously it was shown that it has benefits in minimising the risk of cross-contamination. We also believe it to be a cost-efficient approach that leads to shorter delivery times and could minimise the risk of cell damage through cryopreservation.

3. We have discussed the effect of extending the current hospital network for ATMPs (in our case referred to as clinics), assuming a global demand. We looked at paediatric (Kymriah case study) and adult hospitals (Yescarta case study). Currently,

most hospitals with authorisation for PM are concentrated in certain parts of the world that were involved in developing these medicines. As a global extension is sought after, we have shown possible strategical locations for opening more hospitals/clinics.

8.2 Future Work

This thesis presents a first attempt at introducing the corresponding FLPs for PM in healthcare supply chains. This research can be continued in terms of the strategic level, and, more generally, the PM supply chain could benefit from several research streams.

8.2.1 Strategic Level of ATMPs and PM

1. The research presented in this thesis was focused on formulating the problem and showing its value for the DMs in the biopharmaceutical industry and the policymakers. A secondary goal was to create an in-depth analysis of the existing solution methods and the development of new algorithms capable of helping with the complexities brought by the problem. Therefore, future research could look into other algorithm classes and the development of problem-specific heuristics. For example, one might consider implementing hybrid algorithms between population based and local search heuristics. Another research stream could also analyse the impact of other interactive methods (i.e., different than reference point-based algorithms), such as trade-offs, weights or classification of the three objectives (Xin et al., 2018), which would help the DM to navigate the decision space more efficiently.

2. Another interesting research stream discusses the combination of the FLP with the production. Considering the extensive body of research on manufacturing optimisation, the combination of the two problems was considered out of scope for this thesis. Instead, we have used pre-defined production modes. Further work could look into developing a framework that allows for a more flexible manufacturing process of each MF that allocated demand, capacity constraints, or the raw materials and labour availability could indirectly dictate.

3. We have also briefly discussed the importance of the candidate locations in the optimisation process. It is worth continuing this analysis to understand the feasibility of each candidate location in terms of supplier availability, offshore and onshore production, tax regulations between countries, or the differences in market approvals between countries.

4. The market authorisation process for ATMPs does not happen simultaneously in all countries and for all targeted diseases. It is a continuous process, and hence the addition of time windows that advise not only the location of the facilities but also the date (e.g. year) at which it should be opened could further benefit the DM. Moreover, the expansion in the medical designation could also indicate the size of the facility, the production modes, and whether an expansion will be desirable in the following years.

5. Even though this is not currently used in the pharmaceutical industry, it has been argued that PM products could benefit from a network of facilities that can be used for multiple products by one or multiple companies. The potential of this approach is also made evident by the shift to the use of contractors by biopharmaceutical companies. This model is not commonly used in the traditional pharma sector.

There is still a need to prove whether this approach could alleviate the consequences of low global demand per ATMP.

8.2.2 Tactical and Operational Levels of the ATMPs and PM

1. An area of research that has not yet been researched in ATMP is the scheduling of the patient. As the manufacturing of the product is directly linked to the collection procedure of the cells from the patient, the scheduling problem could aim to optimise both the prioritisation of the patient (e.g. following the severity of the condition) and the preferred manufacturing mode (e.g. if a second cells collection is not possible and thus a failed ATMP would have drastic consequences).

2. A more decentralised production was recommended as a potential alternative to the centralised pharmaceutical supply chain. We have shown in this thesis that different levels of decentralisation can lead to more efficient network configurations. Nevertheless, one of the main issues in the industry remains the problems related to product quality discrepancy due to patient and manufacturing diversity. These are already concerns in the current centralised model and will be heightened with increased decentralisation. While previous research has shown that higher manufacturing automation can help with these concerns, uncertainties remain and should be analysed further.

3. More generally, research around the regulations, intellectual property (IP), the timeline from market approval to the patent expiration date, and the capabilities of a higher level of digitalisation with the rapid expansion in the Internet of Things (IoT) for better ensuring the CoI and CoC are all important aspects of the PM supply chain that need further attention.

The research presented in this thesis brought attention to the need for building decision support tools to identify the inherent hurdles of personalised ATMPs. We have introduced the problem of PM supply chain at a strategic level and showed that the current FLPs met in other healthcare supply chains are not appropriate for the one-to-one supply model. We have also looked at understanding the role different configurations of the supply chain, such as CMC, IMC, or DMC could play in making PM more easily accessible to the patients at an affordable cost for the biopharmaceutical companies and ultimately to the general healthcare administrators. The OR community could significantly contribute to developing delivery and manufacturing strategies for ATMP, and more research is imperative in light of the new technologies these products use and, consequently, their specific bottlenecks from a supply chain perspective.

Chapter 9

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Appendix A

Elite configurations found by *irace*

configuration	*cryo*	*orderHeapq*	*select_manu*	*breed*	*pop*	*gen*	*mut_add*	*mut_remove*	*drop*	*prop_manu*
ITERATION 1										
14	greedyCryo	nlargest	0.7396	cxOnePoint	77	1540	0.1	0.5	cryo	0.9664
12	changeManuToCryo	nsmallest	0.6294	cxUniform	19	2407	0.2	0	both	0.6732
ITERATION 2										
14	greedyCryo	nlargest	0.7396	cxOnePoint	77	1540	0.1	0.5	cryo	0.9664
12	changeManuToCryo	nsmallest	0.6294	cxUniform	19	2407	0.2	0	both	0.6732
18	changeManuToCryo	nsmallest	0.6881	uniform	69	2034	0.1	0	manu	0.9144
ITERATION 3										
18	changeManuToCryo	nsmallest	0.6881	uniform	69	2034	0.1	0	manu	0.9144
14	greedyCryo	nlargest	0.7396	cxOnePoint	77	1540	0.1	0.5	cryo	0.9664
12	changeManuToCryo	nsmallest	0.6294	cxUniform	19	2407	0.2	0	both	0.6732
ITERATION 4										
18	changeManuToCryo	nsmallest	0.6881	uniform	69	2034	0.1	0	manu	0.9144

configuration	*cryo*	*orderHeapq*	*select_manu*	*breed*	*pop*	*gen*	*mut_add*	*mut_remove*	*drop*	*prop_manu*
14	greedyCryo	nlargest	0.7396	cxOnePoint	77	1540	0.1	0.5	cryo	0.9664
12	changeManuToCryo	nsmallest	0.6294	cxUniform	19	2407	0.2	0	both	0.6732
36	changeManuToCryo	nsmallest	0.6153	uniform	71	3618	0.1	0.2	manu	0.7529
ITERATION 5										
36	changeManuToCryo	nsmallest	0.6153	uniform	71	3618	0.1	0.2	manu	0.7529
18	changeManuToCryo	nsmallest	0.6881	uniform	69	2034	0.1	0	manu	0.9144
14	greedyCryo	nlargest	0.7396	cxOnePoint	77	1540	0.1	0.5	cryo	0.9664
ITERATION 6										
55	changeManuToCryo	nsmallest	0.6275	uniform	84	2147	0.2	0.1	manu	0.8364
65	changeManuToCryo	nsmallest	0.7945	uniform	93	1901	0.1	0	manu	0.9870
36	changeManuToCryo	nsmallest	0.6153	uniform	71	3618	0.1	0.2	manu	0.7529
62	changeManuToCryo	nsmallest	0.4970	uniform	87	2861	0.1	0	manu	0.7511
60	changeManuToCryo	nsmallest	0.5077	uniform	95	1257	0.1	0.1	manu	0.8808
ITERATION 7										
73	changeManuToCryo	nsmallest	0.4105	uniform	74	3313	0.1	0.2	manu	0.9583
65	changeManuToCryo	nsmallest	0.7945	uniform	93	1901	0.1	0	manu	0.9870
71	changeManuToCryo	nsmallest	0.8268	uniform	87	1894	0.3	0	manu	0.8626
69	changeManuToCryo	nsmallest	0.7167	uniform	91	1835	0	0.1	manu	0.9489
72	changeManuToCryo	nsmallest	0.8882	uniform	86	1204	0.2	0.1	manu	0.8975

configuration	*cryo*	*orderHeapq*	*select_manu*	*breed*	*pop*	*gen*	*mut_add*	*mut_remove*	*drop*	*prop_manu*

Table A.1: *irace* elite configurations in each of the 7 iterations.

Appendix B

Kymriah and Yescarta Global Demand

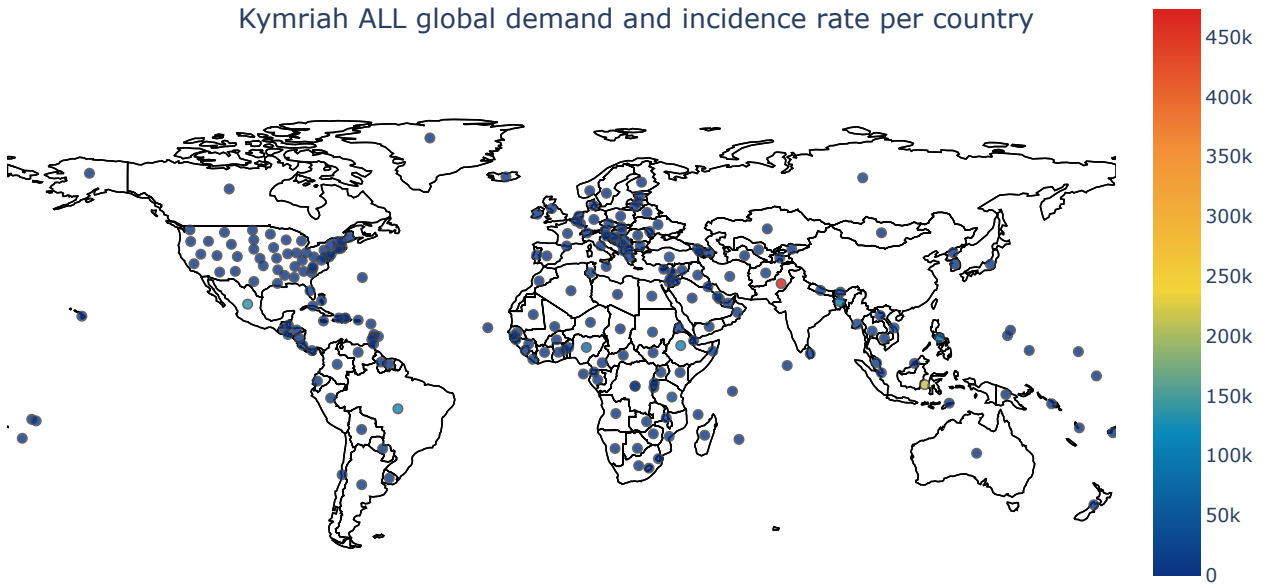

Figure B.1: Kymriah ALL global demand per country. The colour dimension shows the demand, while size corresponds to the incidence level.

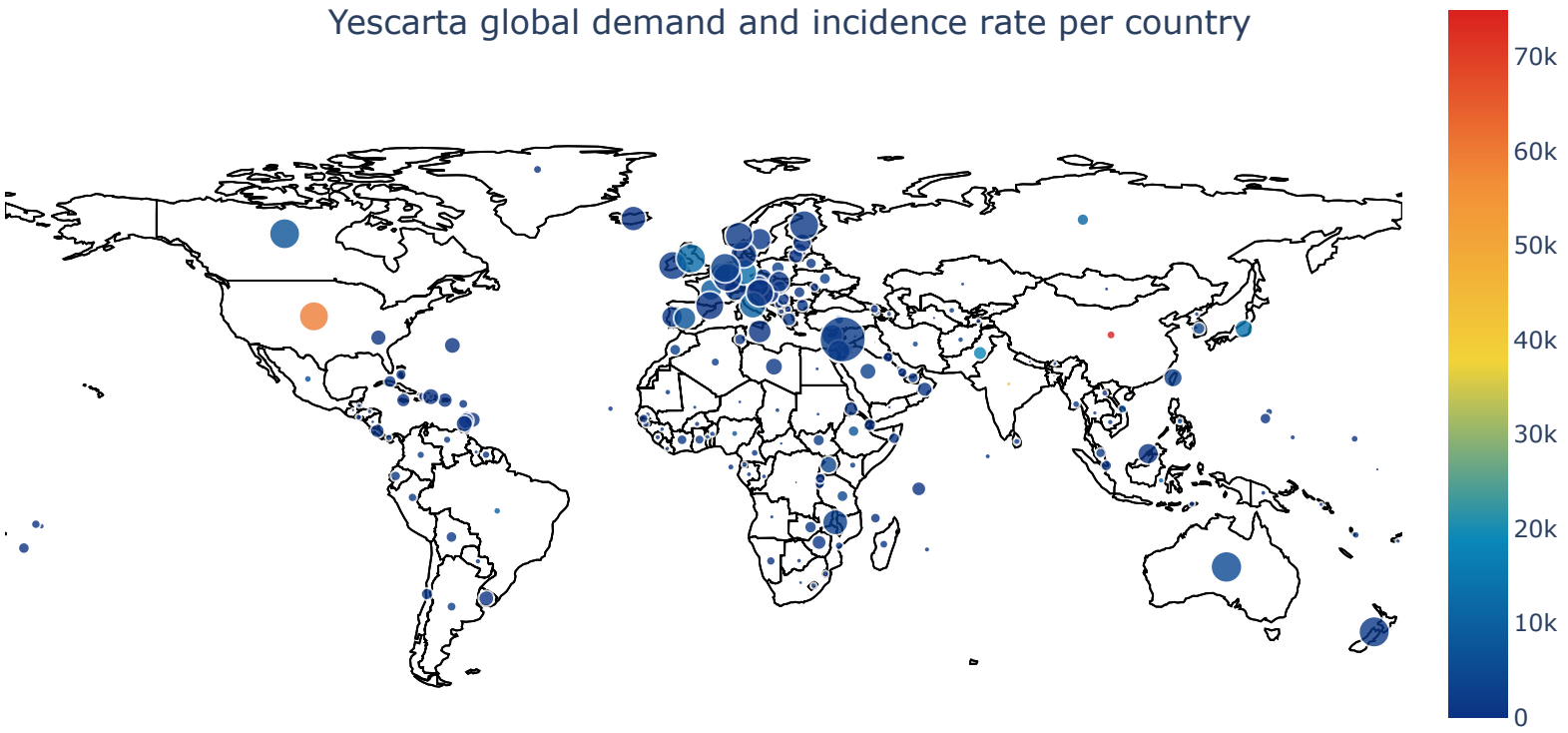

Figure B.2: Yescarta global demand per country. The colour dimension shows the demand, while size corresponds to the incidence level.

Appendix C

Centralised and Integrated Non-dominated Solutions

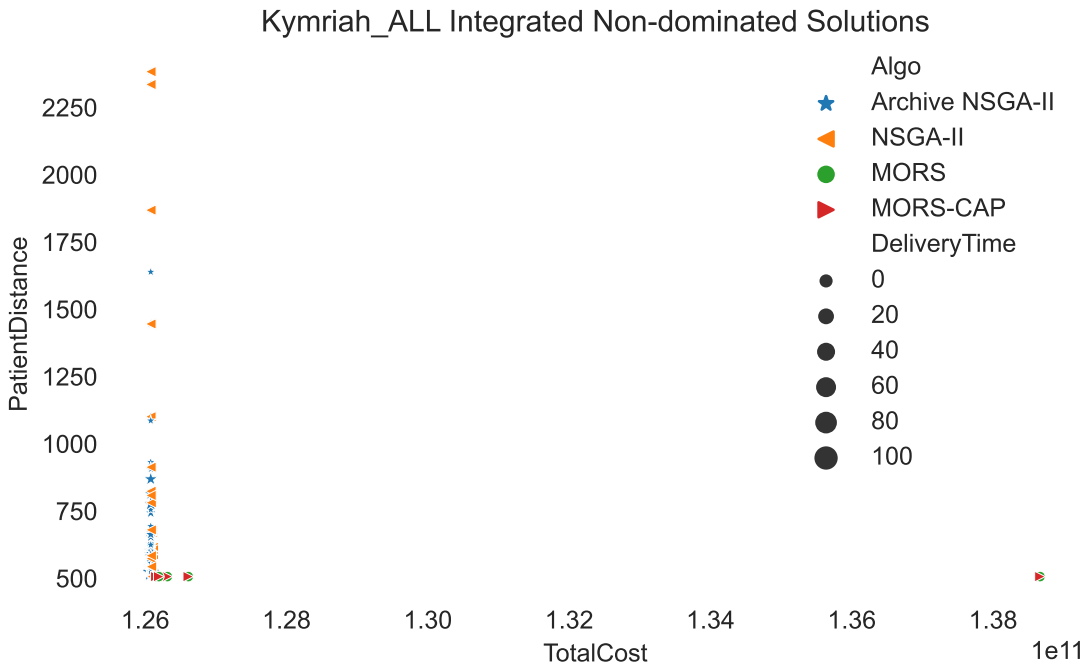

Figure C.1: Set of non-dominated solutions for the Kymriah ALL IMC case study between the A-NSGA-II, NSGA-II, MORS, and A-MORS over the three objectives. The total cost and patient distance objectives are shown on the x- and y-axes, while the delivery time is shown as the size of the bubbles.

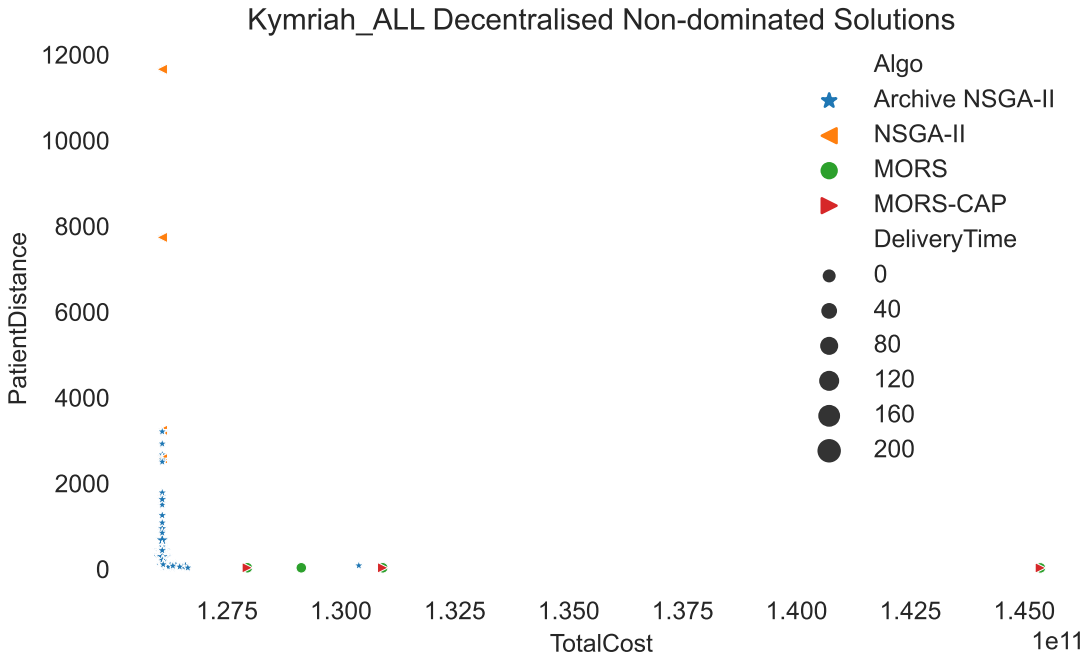

Figure C.2: Set of non-dominated solutions for the Kymriah ALL DMC case study between the A-NSGA-II, NSGA-II, MORS, and A-MORS over the three objectives. The total cost and patient distance objectives are shown on the x- and y-axes, while the delivery time is shown as the size of the bubbles.

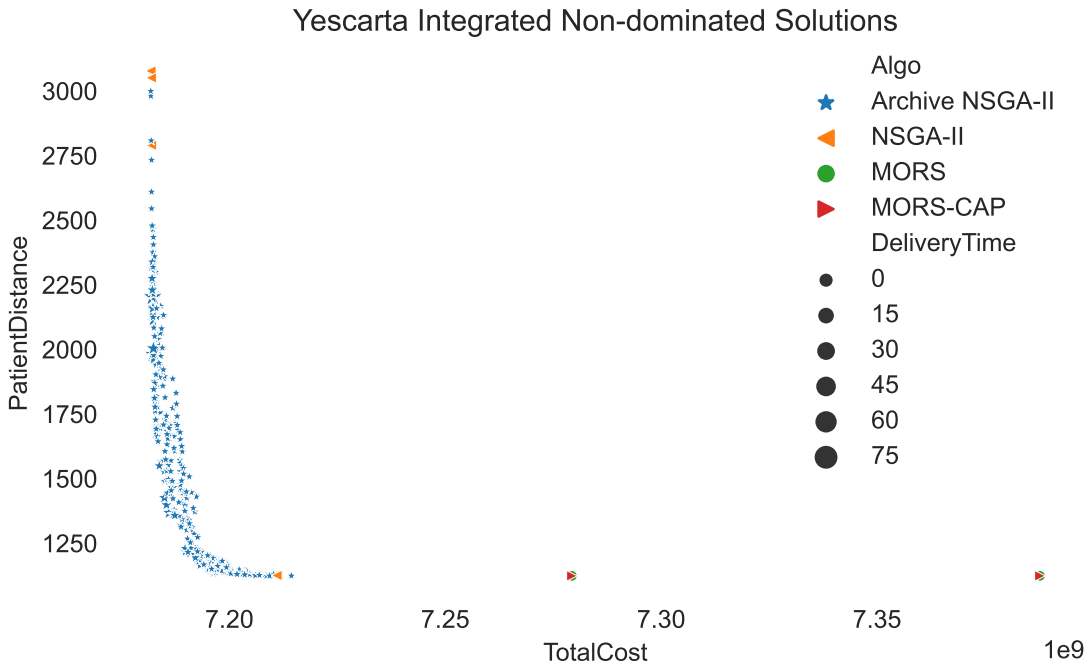

Figure C.3: Set of non-dominated solutions for the Yescarta IMC case study between the A-NSGA-II, NSGA-II, MORS, and A-MORS over the three objectives. The total cost and patient distance objectives are shown on the x- and y-axes, while the delivery time is shown as the size of the bubbles.

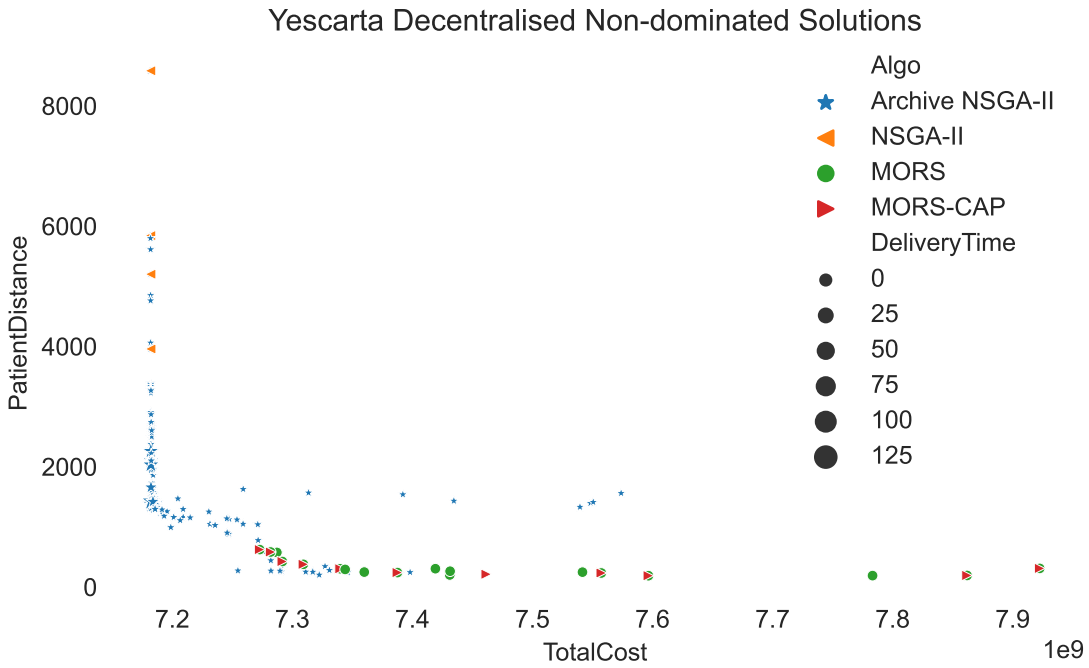

Figure C.4: Set of non-dominated solutions for the Yescarta DMC case study between the A-NSGA-II, NSGA-II, MORS, and A-MORS over the three objectives. The total cost and patient distance objectives are shown on the x- and y-axes, while the delivery time is shown as the size of the bubbles.

Appendix D

Favourable Locations in CMC and IMC

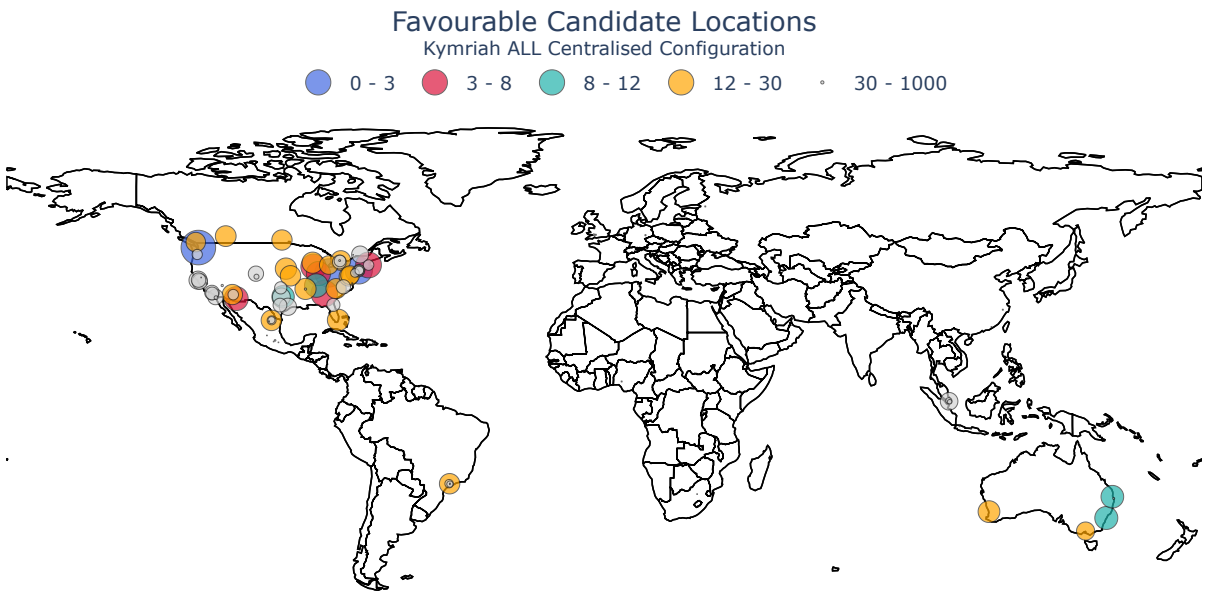

Figure D.1: Favourable candidate locations for Kymriah ALL Centralised configurations for all types of manufacturing and cryopreservation.

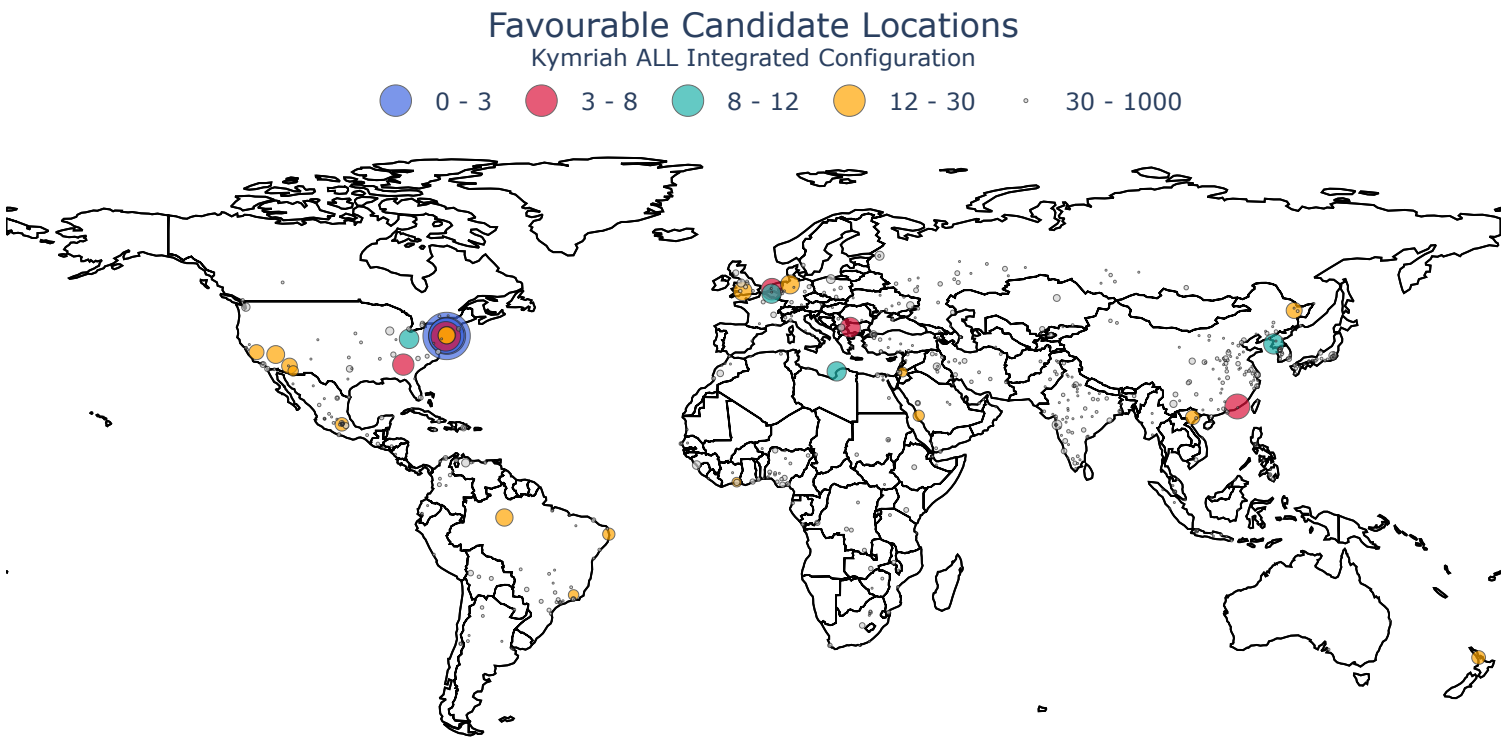

Figure D.2: Favourable candidate locations for Kymriah ALL Integrated configurations for all types of manufacturing and cryopreservation.

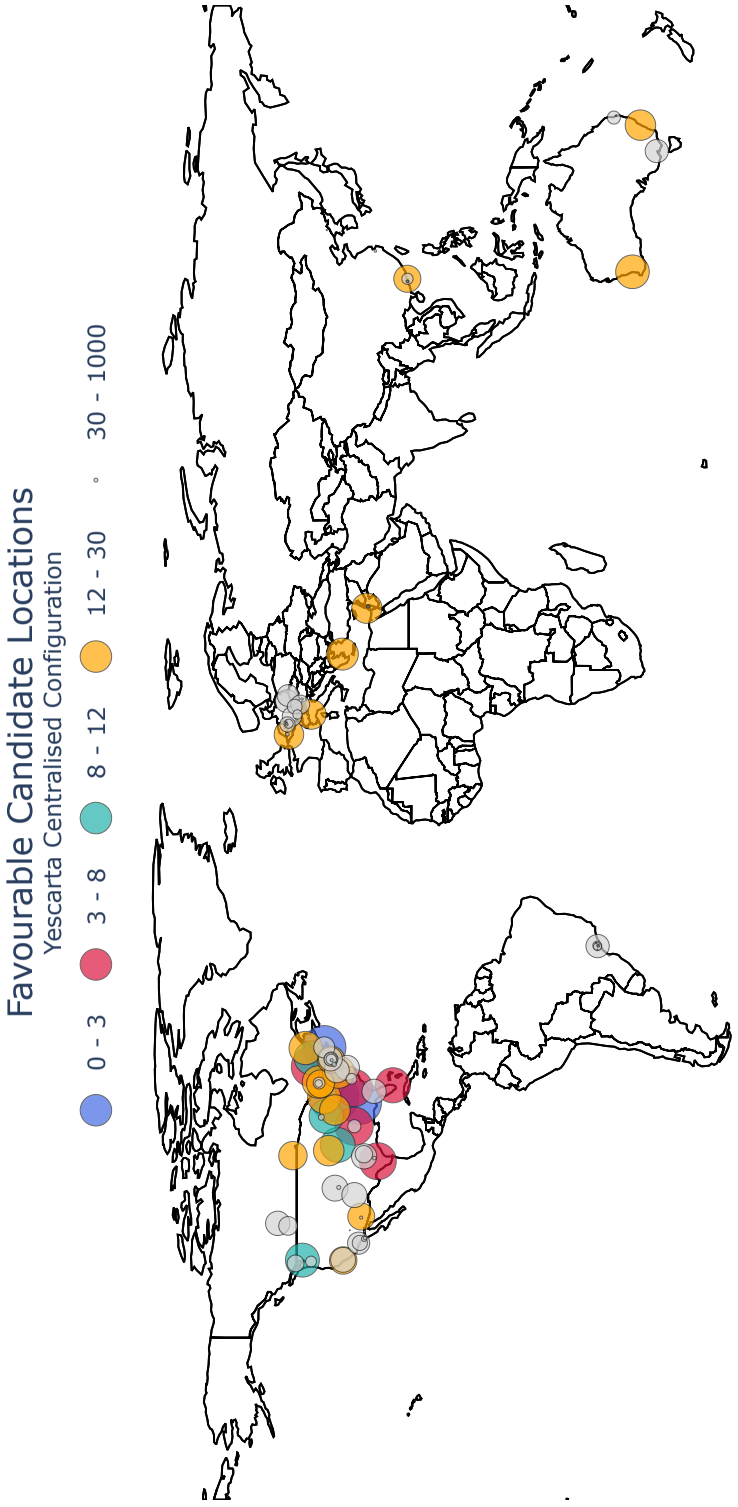

Figure D.3: Favourable candidate locations for Yescarta Centralised configurations for all types of manufacturing and cryopreservation.

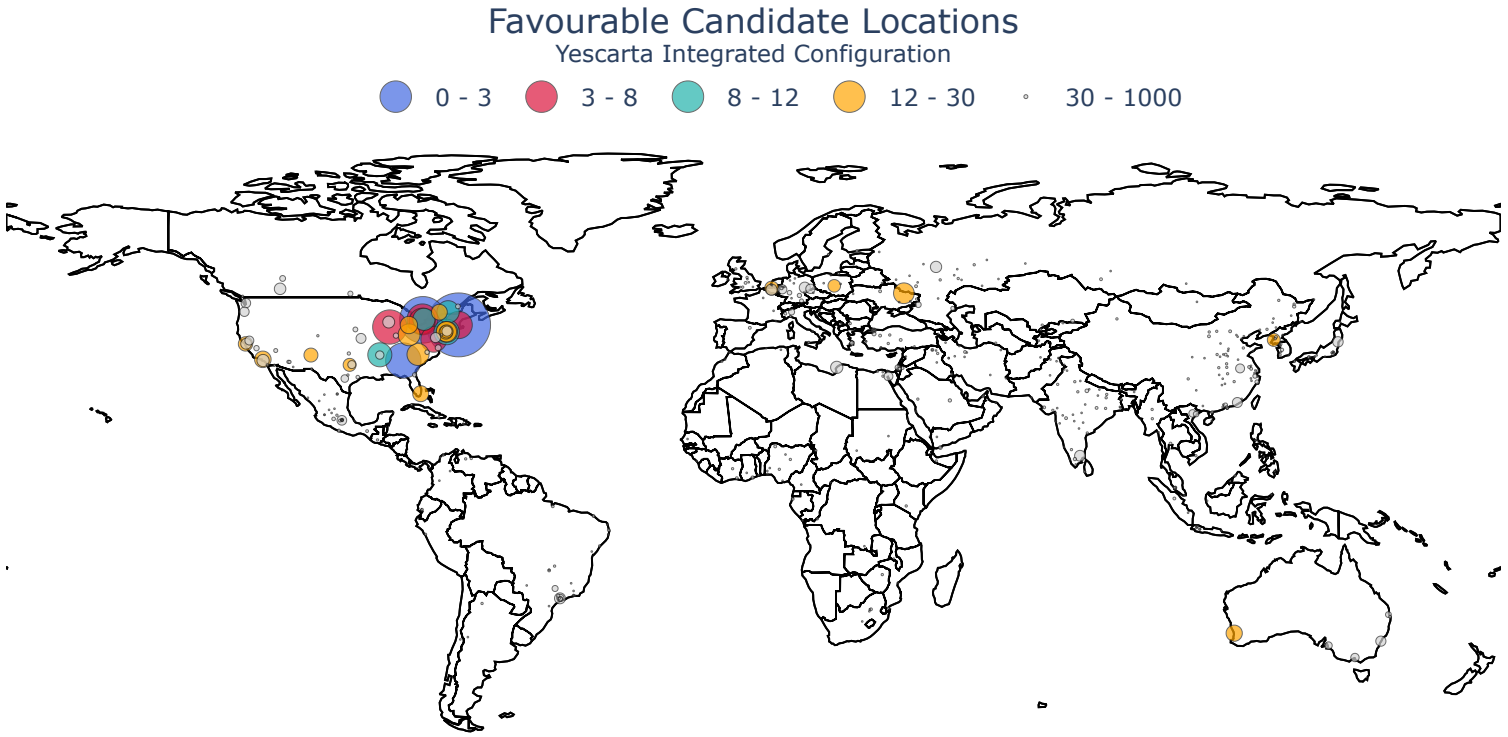

Figure D.4: Favourable candidate locations for Yescarta Integrated configurations for all types of manufacturing and cryopreservation.

Appendix E

Stage-wise Preliminary Work

E.1 Abstract

Facility location problems (FLPs) are one of the most studied problem classes in supply chain management. However, despite the high number of research outputs, complex FLPs with large decision spaces and multi-objective formulations remain hard to solve. This paper introduces a multi-objective mathematical model for the FLP in personalised medicine and applies a multi-stage algorithmic approach to solve it. In this case, the supply chain is circular and follows an on-demand and batch specific approach where the patient is also the donor. We solve the problem multi-stage, each stage optimising a sub-space of the larger decision space. In each stage, we free up more decision variables to optimise until all decision variables defining the complete problem are eventually made available for optimisation. A variant of the NSGA-II algorithm is used as a solution method to solve both the full problem and the different problem stages. Our results suggest that the multi-stage approach can find better solutions when compared to an approach that is given an equivalent number of evaluations but optimises the complete problem at once.

E.2 Introduction

Supply chain optimisation problems are continuously extended, e.g. with new decision variables, constraints and objectives, to simulate the increasing complexity of business challenges. Supply chain management case studies, such as facility location, scheduling, or inventory management, often have complex variants and multi-echelon formulations and usually involve large decision spaces, conflicting objectives and uncertainty. Even with our current computational resources and algorithmic knowledge, most of them remain hard to solve using existing exact methods (Farahani et al., 2019).

One such example of the complex real-world supply chain is the case of personalised biopharmaceuticals based on genes or human cells, referred to as ATMPs (Yu et al., 2018). These treatments are considered to be one of the most important developments in medicine, with promising results in treating and even curing rare, progressive, and degenerative diseases; examples include last stage cancers (Iancu and Kandalaft, 2020), Parkinson, Alzeheimer, or muscular atrophy (Hanna et al., 2016). While the clinical developments of ATMPs are impressive, their commercialisation has become difficult (Lam et al., 2020). The optimisation of existing pharmaceutical and healthcare supply chains is already considered challenging and constitutes a topic of continuous research (Singh et al., 2016). The ATMPs bring to these supply chains an extra level of difficulty with stricter bottlenecks, such as low global demand, limited shelf-life, and complex manufacturing. Thus, new mathematical optimisation models are needed to account for these additional challenges to design cost and time efficient delivery networks.

A personalised ATMP corresponds to only one patient. This means that part of the product's starting material is the patient's cells, which are then processed and returned to the same patient. Each patient's cells constitute an ATMP order. The cells are transported

from the hospital to an independent MF for processing. Each MF has a manufacturing mode which is directly responsible for the duration and success rate of the ATMP process (Lopes et al., 2020). Between the hospital and the MF, there can be an intermediary CF. The CF freezes the living cells to ensure they remain viable until arriving at the MF. The construction and operation of a CF extend the shelf-life based range of hospitals that are covered by an MF but increases the cost of the supply chain.

The above network follows a *centralised* configuration, which has so far turned out to be sub-optimal for personalised products (Avramescu et al., 2021c). Building an MF is expensive, and the delivery between hospitals, MFs, and CFs adds to the patient's waiting time. Hence, a network that is *integrated* (or semi-decentralised), comprising of both independent MFs and CFs, but also the possibility to integrate smaller units able to manufacture or freeze the cells at some hospitals could be a more cost-effective alternative.

When choosing the location of the different facilities, the decision maker looks at obtaining a low cost and low waiting time for the patient while supplying as many hospitals as possible. Solving multi-objective problems with large decision spaces and many variables remains difficult. A sacrifice on the quality of the solutions, the computational resources, or both becomes necessary. We thus propose in this paper a multi-stage approach for solving the above problem. Our multi-stage approach divides the decision space and fixes the number of variables that need optimisation at a time. For simplicity, we only apply a 3-stage process. In the *first stage*, we reduce the problem to the classic uncapacitated FLP (Ahmadi-Javid et al., 2017b), optimising only the location of MFs. Starting from one non-dominated solution obtained in Stage 1, in the *second stage*, we optimise the manufacturing modes and the location of CFs. Finally, in the *third stage*, we optimise the hospital's level of integration.

The rest of the paper is organised as follows. The vein-to-vein supply chain of ATMPs, together with the mathematical model, are presented in Section E.3. A brief literature review of relevant studies is presented in Section E.4. The stages breakdown of the problem and the algorithms are explained in Section E.5. The case study data and the experimental results are presented in Sections E.6 and E.7. The paper concludes in Section E.8 with an overall discussion and recommendations for future research.

E.3 Problem Definition

We model the design of an ATMP supply chain as a multi-objective FLP. We are given the fixed locations of the hospitals ($i \in I$) that we wish to supply and the candidate locations for placing either MFs or CFs ($j \in J$). The supply chain has two types of deliveries: fresh and frozen. In the *fresh route*, living cells are collected at a hospital i, transported to an MF located in j where the ATMP is manufactured and then delivered back to the same hospital i. The travel time from hospital to MF must be lower than the shelf-life of the living cells, denoted as a known constant θ. In the *frozen route*, the living cells are first transported to a CF, then to an MF and back to the same hospital. The travel time between the hospital and the CF must be no more than 24 hours, typically shorter than the shelf-life, ensuring that the cells are of high quality before cryopreservation. Once cryopreserved, there is no limitation in the travel time between CF and MF.

The above model corresponds to a *centralised scenario*, where MF and CF are independent facilities shared by multiple hospitals. In an *integrated scenario*, we may build an integrated manufacturing or cryopreservation unit at particular hospitals. If a hospital has an integrated MF, no transportation occurs. If a hospital has an integrated CF, then cells are transported frozen to an independent MF, and the shelf-life is irrelevant.

The possible configurations of the ATMP supply chain from the point of view of a hospital are shown in Fig. E.1.

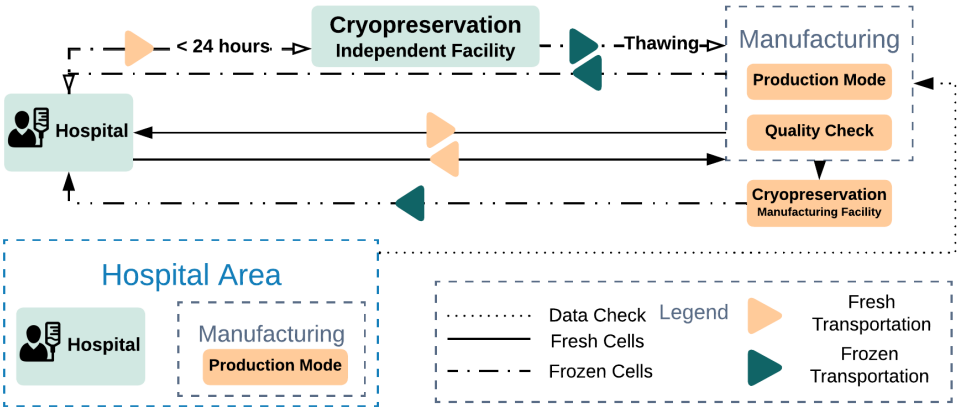

Figure E.1: Centralised and integrated supply chain configuration for personalised ATMPs. If a hospital has integrated cryopreservation, then the route followed is the same as fresh transportation for hospitals without integration.

Manufacturing an ATMP is a lengthy and complex process. Different production modes are available that differ in the level of automation and represent a trade-off between cost and success rate. Generally, a high cost lowers the manufacturing time but increases the probability that the order is defective. If the order is defective, the manufacturing process has failed, and the entire supply chain, starting from cell collection at the hospital, is restarted.

The main decisions in the above model are: what type of facility (MF or CF or none) should be open in each candidate location, what type of integrated facility should be built at each hospital (manufacturing, cryopreservation or none) and the production mode used for each independent or integrated MF built.

The main objectives are: (1) the maximisation of the *coverage*, that is, the number of hospitals whose demand can be processed because the hospital is within the range of a MF or CF, or the hospital has an integrated unit for either manufacturing or cryopreservation;

(2) the minimisation of the *average waiting time*, defined as the time from cell collection at a hospital to the delivery of the manufactured product at the same hospital, taking into account the expected additional time incurred due to the failures; and (3) the minimisation of the *total supply chain cost*, which is calculated as the total cost of construction of MFs, CFs, and integrated units at hospitals, where all costs depend on the location chosen and, in addition, the cost of constructing, an MF depends on its production mode.

Following the above description, we model the design of an ATMP supply chain as a multi-objective integer non-linear optimisation problem. We are given the fixed locations of the hospitals ($i \in I$) that we wish to supply and the candidate locations for placing either MFs or CFs ($j \in J$). The decision variables are given by:

Decision Variables

h_i^{M}, h_i^{C} 1 if an integrated manufacturing or cryopreservation unit is built at hospital $i \in I$, 0 otherwise.

x_j^{M}, x_j^{C} 1 if a MF or CF is open at location $j \in J$, 0 otherwise.

m_{lk} 1 if the MF at location $l \in I \cup J$ uses production mode $k \in K$, 0 otherwise.

y_{ij}^{M},y_{ij}^{C} 1 if the demand of hospital i is processed by the MF or CF at location j 0 otherwise.

For simplicity, we also define the following helper variables that tell us whether the demand of hospital i is processed by any MF and any CF (z_i^{M} and z_i^{C}, respectively):

$$z_i^{\mathrm{M}} = \sum_{j \in J} y_{ij}^{\mathrm{M}} \qquad z_i^{\mathrm{C}} = \sum_{j \in J} y_{ij}^{\mathrm{C}} \tag{E.1}$$

The objectives are given by:

Objective E.2. The number of hospitals whose demand can be processed corresponds to those with an integrated manufacturing unit or are assigned to some MF. We assume

that the entire demand of a hospital will be fully covered once any of the previous requirements are met. We convert this objective to minimisation for consistency with other objectives and measure it as the *ratio of uncovered hospitals*.

$$\min\ 1 - \frac{\sum_{i\in I} h_i^{\mathrm{M}} + z_i^{\mathrm{M}}}{|I|} \tag{E.2}$$

Objective E.3. The *average waiting time* is calculated by dividing the total delivery time by the number of hospitals covered. For simplicity, we do not consider the time associated with collection, production and administration in this work. The travel time between locations is given by $d_{ll'}$, $l, l' \in I \cup J$.

$$\min\ \frac{TotalTime}{\sum_{i\in I} h_i^{\mathrm{M}} + z_i^{\mathrm{M}}} \tag{E.3}$$

where *TotalTime* is the total delivery time:

$$TotalTtime = \sum_{i\in I}(1-h_i^{\mathrm{M}}) \sum_{j\in J} y_{ij}^{\mathrm{M}} \Big[d_{ji} + (1+FR_j) \cdot \Big((1-z_i^{\mathrm{C}}) d_{ij} + z_i^{\mathrm{C}} \sum_{j'\in J} y_{ij'}^{\mathrm{C}} (d_{ij'} + d_{j'j}) \Big) \Big] \tag{E.4}$$

where there is a delivery time only if the hospital i does not have an integrated manufacturing unit ($h_i^{\mathrm{M}} = 0$). Otherwise, the trip is divided into two legs. In the first leg, the manufactured product always has to travel back from the MF located at j assigned to hospital i (d_{ji}). In the second leg, either the hospital is not assigned to an independent CF and the order has to travel from the hospital to its assigned MF (d_{ij}); or the order has to travel to the CF located at j' ($d_{ij'}$) and from there to the MF located at j ($d_{j'j}$). The second delivery leg has to be repeated if manufacturing fails, and thus, we multiply it by

a *failure rate* FR_j given by:

$$FR_j = \sum_{k \in K} r_k m_{jk} \tag{E.5}$$

where r_k is the failure rate associated to production mode $k \in K$ and

Objective E.6. The *total supply chain cost* is given by:

$$\min \sum_{i \in I} (h_i^{\mathrm{C}} c_i^{\mathrm{C}} + \sum_{k \in K} c_{ik}^{\mathrm{M}} m_{ik}) + \sum_{j \in J} (x_j^{\mathrm{C}} c_j^{\mathrm{C}} + \sum_{k \in K} c_{jk}^{\mathrm{M}} m_{jk}) \tag{E.6}$$

where c_{ik}^{M} and c_i^{C} are, respectively, the construction cost of an integrated manufacturing and cryopreservation unit at hospital i. Similarly, c_{jk}^{M} and c_j^{C} are, respectively, the construction cost for an independent MF and CF at location j. Construction costs of manufacturing facilities depend on the production mode k employed. In line with objective E.3, we do not consider the production and delivery costs for simplicity here.

Constraints: Constraints E.7 and E.8 allow only one facility type to be open at each location i or j.

$$h_i^{\mathrm{C}} + h_i^{\mathrm{M}} \leq 1 \quad \forall i \in I \tag{E.7}$$

$$x_j^{\mathrm{M}} + x_j^{\mathrm{C}} \leq 1 \quad \forall j \in J \tag{E.8}$$

Constraint E.9 enforces that hospitals cannot be covered by both an independent and an integrated MF nor by both an independent and an integrated CF. In addition, due to the definitions of z_i^{M} and z_i^{C} (Eq. E.1), it also enforces that a hospital cannot be assigned to more than one MF and CF.

$$h_i^{\mathrm{M}} + z_i^{\mathrm{M}} \leq 1, \quad h_i^{\mathrm{C}} + z_i^{\mathrm{C}} \leq 1 \quad \forall i \in I \tag{E.9}$$

The following constraint ensures that if a hospital at location i is allocated to a CF, it

must be allocated to an MF:

$$z_i^{\mathrm{C}} \leq z_i^{\mathrm{M}} \quad \forall i \in I \tag{E.10}$$

Constraint E.11 does not allow assigning a hospital i to a facility type at location j if there is no such facility type at that location:

$$y_{ij}^{\mathrm{M}} \leq x_j^{\mathrm{M}}, \quad y_{ij}^{\mathrm{C}} \leq x_j^{\mathrm{C}} \quad \forall i \in I, \forall j \in J \tag{E.11}$$

The following constraint enforces the shelf-life limits according to the fresh or frozen routes:

$$\sum_{j \in J} y_{ij}^{\mathrm{M}} d_{ij} \leq z_i^{\mathrm{C}}(24 \text{ hours}) + (1 - z_i^{\mathrm{C}})\theta + h_i^{\mathrm{C}} \cdot T \quad \forall i \in I \tag{E.12}$$

where θ is the shelf-life of the cells when fresh and T is a very large time that effectively disregards the limit if the hospital has an CU.

Finally, the following constraints enforce that each MF either only has one production mode or none, depending on whether there is an MF at location j, and similarly for integrated manufacturing units at hospital i:

$$x_j^{\mathrm{M}} = \sum_{k \in K} m_{jk} \quad \forall j \in J, \qquad h_i^{\mathrm{M}} = \sum_{k \in K} m_{ik} \quad \forall i \in I \tag{E.13}$$

E.4 Related Work

If an FLP can be formulated using mixed-integer linear programming, a popular stage-wise solution method applied to instances with many variables is the Benders Decomposition (BD) Rahmaniani et al. (2017). This algorithm is based on a series of

linearisations and constraint relaxations, dividing the original problem into two synchronised sub-problems. A modified version of the BD has been used to solve large-scale single-objective uncapacitated FLPs Fischetti et al. (2017) or covering location problems Cordeau et al. (2019). Nevertheless, a BD approach requires that the sub-problem is a linear problem, which is not always achievable.

To the best of our knowledge, the integrated ATMP supply chain model described above constitutes a new FLP variant. However, there are various expansions of the FLP that meet some of the characteristics presented by ATMPs Avramescu et al. (2021a). We believe that the closest FLP class is the multi-level FLPs (MLFLPs) (also known in the literature as multi-echelon, multi-stage or multi-layer Ortiz-Astorquiza et al. (2018)), a sub-category of hierarchical FLPs. With few exceptions, most solution methods developed in the past years for variants of the MLFLPs are heuristics. For single-objective MLFLPs, a composite approach has been used to individually calculate the optimal location of facilities in each level, which was later used in genetic Maric (2010); Korac et al. (2013) or local search algorithms Marić et al. (2014).

While a series of divide-and-conquer algorithms were used for variations of the MLFLP, most created the sub-problems by individually optimising the facilities at each level Ortiz-Astorquiza et al. (2018). This approach was feasible as the allocation in MLFLPs is usually done sequentially, with each customer having to visit at least one facility at each level. In the integrated ATMP supply chain (independent or integrated), CFs are optional and only activated as helpers for MFs. As a result, there is an inter-dependency between MFs (with different manufacturing modes) and CFs. In the classical MLFLP, the different facility types have a separate cost or time independent of the actions at previous or later stages.

	Candidate locations vector	Hospitals integration vector
0	no facility is open	no integration
1	CF open	hospital with CF integration x
2	MF is *manual* MM open	hospital with MF with *manual* MM integration
3	MF is *semi-automatic* MM open	hospital with MF with *semi-automatic* MM integration
4	MF is it automatic MM open	hospital with MF with *automatic* MM integration

Note: MM stands for manufacturing mode

Table E.1: Integers representation for the candidate locations and hospitals solution vector.

E.5 Methodology

To solve the proposed mathematical model, we use the NSGA-II (Deb et al., 2002a), which is a well-known EMOA using elitism, non-dominated sorting and crowding distance to preserve good solutions in the following generations. The algorithm has been successfully applied to a range of supply chain management problems in facility (Bhattacharya and Bandyopadhyay, 2010; Wang et al., 2018b) and hub location (Eghbali et al., 2014; Ebrahimi Zade et al., 2014) problems, and generally found to be a robust approach for multi-objective optimisation.

E.5.1 Solution Methodology

Solution representation

Each solution is represented as two integer vectors, one for candidate locations of length $|J|$ and one for hospitals integration of length $|I|$. Each integer can take a value between [0, 4] as shown in Table E.1. For the production modes, we consider the three levels of automation described by Lopes et al. (2020), namely, *manual, semi-automatic, and automatic*. Their implications on the failure rate are described later in Section E.6.

The above does not apply to stage 1. In this stage, a binary vector is used to declare whether a MF with manual (default) production mode is open at a particular location. The cryopreservation, manufacturing modes, and integration levels are added in stages 2 and 3.

Population initialisation

The way the initial population is created depends on the problem stage. For *stage 1*, a random initialisation is used to open MFs at random locations. For all subsequent stages, a solution from the non-dominated set at the last generation of the previous stage is chosen randomly, and only the remaining facilities are optimised. Namely, in *stage 2*, based on a good solution with MFs, random manufacturing modes will be allocated to the available MFs and additional CFs are added at random free locations until the population limit is reached. No additional MFs are allowed to be inserted. Similarly, in *stage 3*, the CFs and the MFs with their corresponding manufacturing modes are fixed, and new solutions are created by adding different levels of integration to hospitals.

Purposely, each facility type was given an equal probability of being added to an initial solution and no constraint restricting an upper bound on the number of facilities was implemented.

Crossover and mutation

The crossover applied here is a variant of uniform crossover (Syswerda, 1989). Uniform crossover creates children solutions from a pair of parents by switching their indices between them with a given probability. Our uniform crossover differs from the original formulation by restricting the switch only if one of the two indices is 0 (i.e., no facility is open in that location). A graphical representation of the above on a toy example is

presented in Figure E.2. We preferred this approach as the operators used only apply to MFs. An exchange of nonzero values would not change the location or type of facility, but only the manufacturing mode.

The mutation operator randomly selects one position j of the locations vector, and either opens a MF ($x_j^{\mathrm{M}} = 1$) with probability 0.3, removes it ($x_j^{\mathrm{M}} = 0$) with probability 0.3 or moves the facility to an adjacent location with probability 0.4.

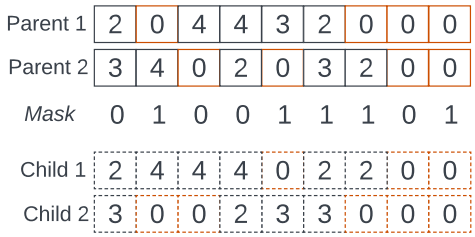

Figure E.2: Example of crossover operator on a sample of 8 indices. The *mask* dictates whether a switch can happen (*Mask* = 1) or not (*Mask* = 0).

The results were obtained over 20 independent algorithmic executions for the proposed NSGA-II on the complete problem and the composite sub-problems as defined in Section E.5, with a population size of 100. Each stage was run for 500 generations, running for the complete problem required 1500 generations to match the number of solution evaluations.

E.6 Case Study

We chose a case study of a cell-based gene ATMP with market approval to test the proposed model. Kymriah is a personalised therapy used in treating adults with B-cell non-Hodgkin lymphomas and children and young adults up to 25 years old with B-cell acute lymphoblastic leukaemia (CBER, 2017a). Following these two designations, we

estimated the global demand using data from the Institute for Health Metrics and Evaluation (Institute for Health Metrics and Evaluation (IHME), 2022). We then distributed the overall demand to hospitals that can accept patients for cell and gene therapies. For a hospital to be eligible for ATMP treatments, it must have FACT accreditation. The geographical distribution of the FACT hospitals globally is shown in Table E.2.

	Adult patients	**Paediatric patients**
Asia	5	1
Europe	16	0
Oceania	11	6
North America	124	83
South America	2	1
TOTAL	157	92

Table E.2: Number of hospitals that accept adult and paediatric patients for personalised ATMPs with breakdown by continent.

One of the main limitations of the above approach is that we assumed each hospital would accept an equal number of patients. This is not always true in real life, and future research could focus on identifying reliable ways to allocate the demand for personalised medicine to hospitals. The main uncertainties in doing so are the continuous approvals of FACT hospitals and the expansion or cease of biopharmaceutical designation (i.e., the intention of use for a particular disease). The latter can happen geographically; for example, a therapy can get approval to deliver its product in a new country or clinically when it receives market approval to expand its target patients.

Our instance has 1000 candidate locations (J) and 216 hospitals (I), which gives a search space of 5^{1216} solutions when considering the various facility types in Table E.1. The failure rates corresponding to each production mode are represented as a range with random probability for each manufacturing. For a *manual* production mode, between 5%

and 10% of the entire demand allocated to that facility will fail and, consequently, must be reproduced. For *semi-automatic*, the range is between 3% and 10% and for *automatic*, it is between 1% and 5% (Lopes et al., 2020).

Finally, the transportation time between two locations was estimated using the Euclidean distance and dividing it by a constant average speed. If a more precise estimation is available, it would not require changes to our mathematical model or our proposed algorithm.

E.7 Results

The non-dominated solutions generated by NSGA-II over the 20 runs are presented in Figures E.3 and E.4.

The three axes in the plot correspond to the time, cost, and coverage objectives. Throughout this section, solutions discovered for the different sub-problems will be shown using the following colour scheme: ● for the complete problem, ● for *stage 1*, ● for *stage 2* and ● for *stage 3*.

When running the algorithm on the complete problem (Fig. E.3), the distribution of the set with non-dominated solutions is directed towards solutions with high coverage, which also lead to a high cost and a relatively low average waiting time. The low time likely indicates a high number of MFs and hospitals with MU in the solutions and an ineffectiveness in rapidly reducing the cost by adding CFs.

The algorithm finds a better approximation of the Pareto front when the problem is solved in stages (Figure E.4). Particularly it finds solutions that have a lower coverage overall, which, given the low cost and slightly increased waiting time, have a higher number of CFs compared to anything found in the complete version. Nevertheless, there

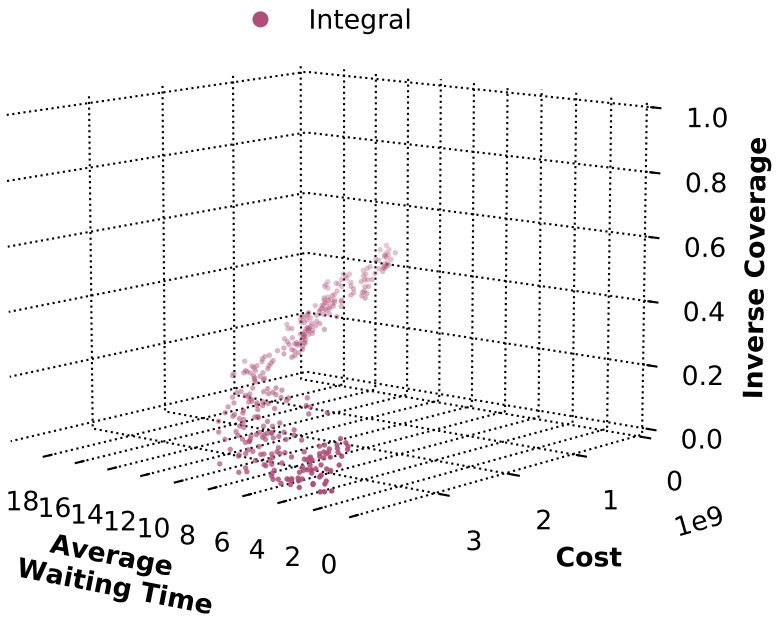

Figure E.3: Non-dominated solutions obtained from NSGA-II for the complete problem

are still patterns possibly unidentified. For example, a very low delivery time can be obtained by having a high level of hospitals with manufacturing integration. While these solutions would lead to a high cost, they should not be dominated. One explanation for NSGA-II not finding such solutions could be the still considerably large search space associated with the problem in stages 2 and 3. While the progress between stages 1 and 2 is evident, the progress in stage 3 is not considerable.

For a fair comparison between complete and staged solution approaches, we have labelled and combined the non-dominated solutions identified after the last stage (i.e., stage 3) and when solving the complete problem at once. Figure E.5 shows this set after applying non-dominated sorting. As previously mentioned, optimising the complete problem starts with an advantage regarding the waiting time objective by placing many facilities in the initial population. These solutions are not dominated throughout the generations or by running the algorithm in stages. While the staged approach also has an

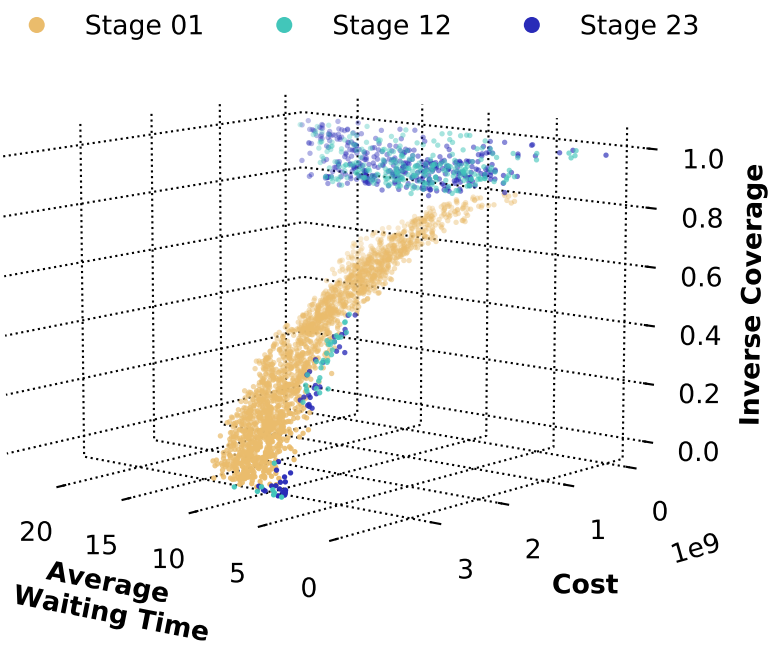

Figure E.4: Non-dominated solutions obtained from NSGA-II over the three stages.

equal probability for each facility type to be added, by not optimising certain facilities in some stages, the overall number of facilities in the initial population at each stage is always smaller.

To evaluate the performance of the NSGA-II on the different problem setups, we used the relative HV. The HV is a popular metric used in multi-objective optimisation to indicate the quality of the solutions obtained by an algorithm. It computes the hypervolume of the objective space weakly dominated by a set of solutions up to a common reference point worse than any solution under comparison. Higher HV values correspond to better approximations of the Pareto front. It provides a measure of closeness to the Pareto front, good distribution and spread. The relative HV is reported about the HV of a high-quality Pareto front approximation obtained by merging all solutions ever received by any approach in any run. We set the reference point 10% higher than the nadir point of this Pareto front approximation.

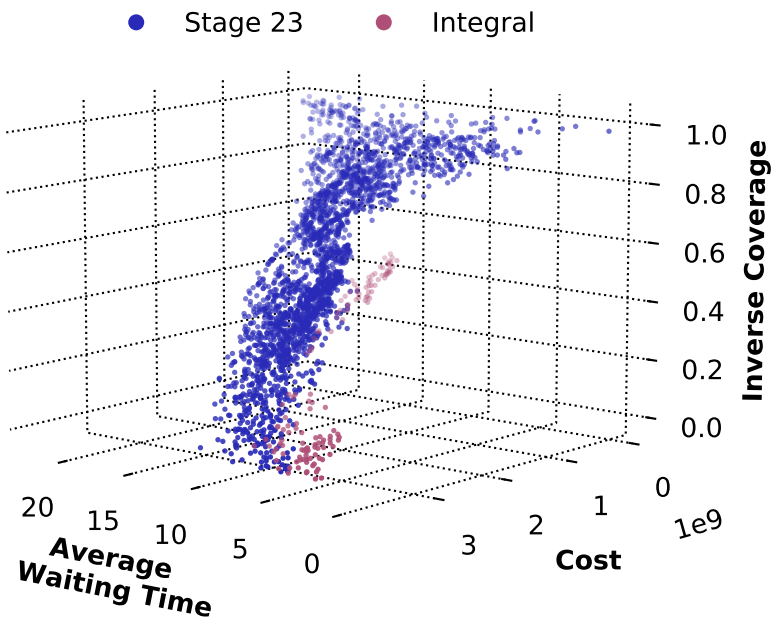

Figure E.5: Non-dominated solutions for NSGA-II between the Pareto front approximation of the last stage and the one of the complete problem

The descriptive statistics for the relative HV are shown in Table E.3. In line with the results shown in the previous figures, the HV suggests that the NSGA-II can converge faster and find a better approximation when dividing the decision space and solving the problem in stages. However, the HV points towards a lack of progress between stage 2 and stage 3. This is an expected outcome and is a direct result of the lack of operators, like crossover and mutation on the solution vector for the integrated hospitals.

	Minimum	Mean $\pm$ SD	Median	Maximum
Integral	0.20	0.34 ± 0.06	0.33	0.68
Stage 1	0.31	0.63 ± 0.16	0.7	0.81
Stage 2	0.64	0.82 ± 0.01	0.82	0.82
Stage 3	0.22	0.82 ± 0.02	0.82	0.82

Table E.3: Relative hypervolume statistics for the NSGA-II on the complete problem and the 3 stages.

E.8 Discussion and Conclusion

Supply chain management optimisation has attracted increased attention in recent years in the context of pandemic disruptions (Montoya-Torres et al., 2021). In particular, the healthcare supply chains were affected by the change in demand (i.e., increased demand for emergencies and lower demand for optional treatments), borders closure, and lockdowns (Khan et al., 2021). Real-world instances of problems such as FLP are becoming more complex to account for inter-dependencies like disruptions and allocations or a high level of personalisation of products, as in the case of ATMPs.

In this paper, we proposed a new mathematical formulation for the integrated supply chain of personalised biopharmaceuticals and solved the problem using a multi-stage approach. The results from dividing the problem into multiple stages were superior to those obtained by running the same algorithms on the complete problem. Moreover, multiple stages allow the decision maker to change or conclude the optimisation process at key moments, such as when a good enough solution is obtained. In the same way, having a clearer understanding of how the decision space evolves over evaluations can

potentially be useful in modelling uncertainty and time-period classifications.

Several limitations pointing towards directions for future research have been highlighted throughout the paper. The ATMP supply chain has several particularities that have not been extensively researched. Such cases involve the demand allocation of patients to hospitals, especially for the countries that do not have a FACT authorised medical centre or the implementation of a public ATMP network able to manufacture and deliver multiple products.

Future research could also include the patient's health conditions and prioritisation strategies in allocating the demand to manufacture. We assumed that the MFs are uncapacitated and can accept any demand level that is allocated to them. This is rarely the case, and should capacity constraints be enforced on multiple products supply chain, a fair allocation of patients with a higher risk or higher chance of having the cells damaged through freezing could be prioritised directly to an MF, rather than transported through CFs. Similarly, the patient allocation could be prioritised to a hospital with a level of integration with low failure risk.

Additional experiments should also be conducted to explore the behaviour of the problem. To generate the initial populations, we only used one solution chosen at random. It is, however, worth investigating to which extent different initialisations can impact the optimisation process. Different approaches can be applied to increase the decision-maker's role and potentially lead to better solutions towards different parts of the Pareto front. For example, one might choose the n solutions based on the number of MFs, their geographic location, the value of the objectives, or the HV contribution. In the same way, different initialisations of the additional facilities can be applied depending on the stage. In a previous work dealing with a simpler formulation of the problem, a greedy approach to the coverage is superior when initially placing CF facilities (Avramescu et al., 2021b).

The three stages of the problem were chosen by following the importance of each facility in the network. Nevertheless, other combinations of variables or a different number of stages could improve the results. In the ATMP case, the MFs has the highest cost and replacing MFs by CFs lowers the cost by increasing the delivery time. However, the integration levels for hospitals optimised in stage 3 do not have a strong enough impact on the overall objectives as each hospital can process only its demand. Hence, the progress between stages 2 and 3 is less substantial than between stages 1 and 2. A division of the problem into more stages with smaller decision spaces could mitigate this and allow the algorithm to improve further the solutions obtained in the last stage.