Composite Facility Location Problems: A Case Study of Personalised Medicine

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***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. In this paper we introduce a multi-objective mathematical model for the FLP in personalised medicine, and apply 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 in a multi-stage manner, each stage optimising a sub-space of the larger decision space. In each stage we free up more decision variables to optimise, until eventually all decision variables defining the complete problem are made available for optimisation. A variant of the NSGA-II algorithm is used as solution method to solve both the complete problem and the different problem stages. Our results suggest that the multi-stage approach is able to find better solutions when compared to an approach that is given an equivalent number of evaluations but optimises the complete problem at once.**

***Index Terms*—supply chain, personalised biopharmaceuticals, multi-objective optimisation, multi-stage algorithms**

I. Introduction

Supply chain optimisation problems are continuously extended, e.g. with new decision variables, constraints and objectives, to simulate the increasing complexity of challenges faced by businesses. Case studies of supply chain management, such as facility location, scheduling, or inventory management, often have complex variants, 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 [11].

One such example of complex real-world supply chain is the case of personalised biopharmaceuticals based on genes or human cells, referred to as *Advanced Therapy Medicinal Products* (ATMPs) [28]. 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 [15], Parkinson, Alzeheimer, or muscular atrophy [13]. While the clinical developments of ATMPs are impressive, their commercialisation has turned out to be difficult [18]. The optimisation of existing pharmaceutical and healthcare supply chains are already considered challenging and constitute a topic of continuous research [25]. 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. There is thus a need for new mathematical optimisation models that account for these additional challenges in order 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 are the patient's cells, which are then processed and later returned to the same patient. Each patient's cells constitute an ATMP order. For processing, the cells are transported from the hospital to an independent manufacturing facility (MF). Each MF has a manufacturing mode which is directly responsible for the duration and success rate of the ATMP process [19]. Between the hospital and the MF, there can be an intermediary cryopreservation facility (CF). The CF freezes the living cells to ensure that they remain viable until arriving at the MF. The construction and operation of a CF extends 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 [4]. 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. Nonetheless, solving multi-objective problems with large decision spaces and a high number of decision variables remains difficult. A sacrifice on either the quality of the solutions, the computational resources, or both becomes

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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 to be optimised at a time. For simplicity, we only apply a 3-stage process. In the *first stage*, we reduce the problem to the classic uncapacitated facility location problem (FLP) [1], 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 hospitals 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 II. A brief literature review of relevant studies is presented in Section III. The stages break-down of the problem and the algorithms are explained in Section IV. The case study data and the experimental results are presented in Sections V and VI. The paper concludes in Section VII with an overall discussion and recommendations for future research.

II. 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 hospital and the CF must be no more than 24 hours, which is typically shorter than the shelf-life, which ensures 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, then no transportation takes place. 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. 1.

Manufacturing an ATMP is a lengthy and complex process. There are different production modes 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, then the manufacturing process has failed and the entire supply chain, starting from cells 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 tells us whether the demand of hospital i is processed by any MF and any CF (z_i^{M} and z_i^{C}, respectively):

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

The objectives are given by:

Objective 2. The number of hospitals whose demand can be processed corresponds to those hospitals that have 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. For consistency with other objectives, we convert this objective to minimisation and measure it as the *ratio of uncovered hospitals*.

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

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

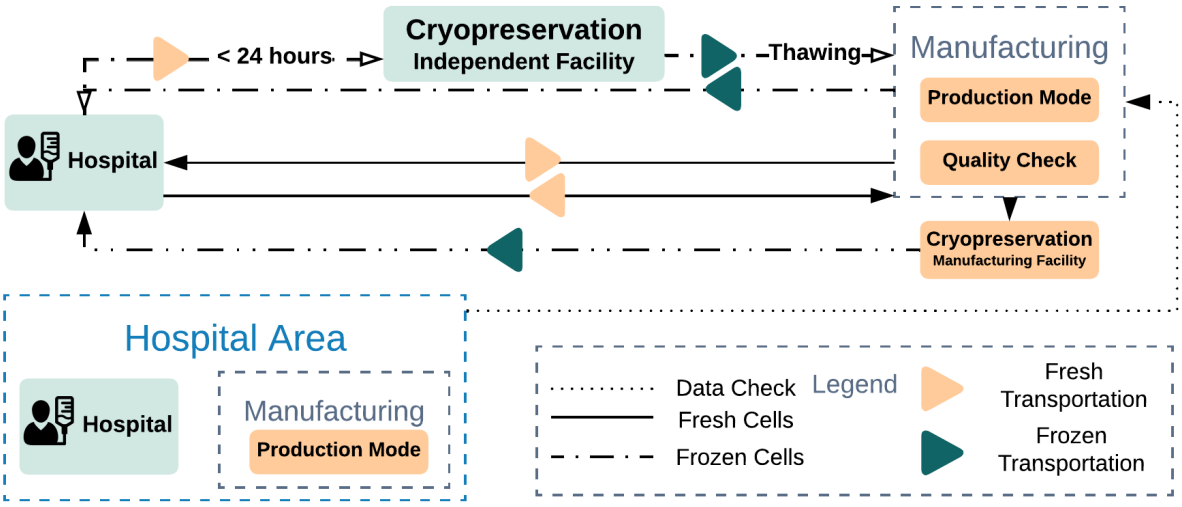

Fig. 1: Centralised and integrated supply chain configuration for personalised ATMPs. If a hospital has an integrated cryopreservation, then the route followed is the same as for fresh transportation for hospitals with no integration.

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

where *TotalTime* is the total delivery time:

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

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 in 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, thus we multiply it by a *failure rate* FR_j given by:

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

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

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

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

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 3, we do not consider here the production and delivery costs for simplicity.

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

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

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

Constraint 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. 1), it also enforces that a hospital cannot be assigned to more than one MF and CF.

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

The following constraint ensures that if a hospital at location i is allocated to a CF, it must be allocated to an MF:

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

Constraint 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:

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

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

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

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

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:

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

III. 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) [24]. This algorithm is based on a series of linearizations and constraint relaxations, by dividing the original problem into two synchronised sub-problems. A modified version of the BD has been used to solve to optimality large-scale single-objective uncapacitated FLPs [12] or covering location problems [7]. 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 [2]. 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 [23]), a sub-category of hierarchical FLPs. With few exceptions, most of the 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 [17, 20] or local search algorithms [21].

While a series of divide-and-conquer algorithms were used for variations of the MLFLP, most of them created the sub-problems by individually optimising the facilities at each level [23]. This approach was feasible as the allocation in MLFLPs is usually done sequentially, 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, that is independent of the actions at previous or later stages.

IV. Methodology

To solve the proposed mathematical model, we use the *Non-dominated Sorting Genetic Algorithm II* (NSGA-II) [8], which is a well-known multi-objective evolutionary algorithm (MOEA) 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 [5, 27] and hub location [9, 10] problems, and generally found to be a robust approach for multi-objective optimisation.

A. Solution Methodology

1) 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 I. For the production modes, we consider the three levels of automation described by Lopes et al. [19], namely, *manual, semi-automatic, and automatic*. The implications of each of them on the failure rate are described later in Section V.

	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 I: Integers representation for the candidate locations and hospitals solution vector.

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

2) 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.

3) Crossover and mutation: The crossover applied here is a variant of uniform crossover [26]. 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 2 indices is 0 (i.e., there is no facility open in that location). A graphical representation of the above on a toy example is presented in Figure 2. We preferred this approach as the operators used only apply to MFs and hence 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 an 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.

The results shown 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 IV, with a population size of 100. Each stage was

Fig. 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).

ran for 500 generations thus running for the complete problem required 1500 generations to match the number of solution evaluations.

V. Case Study

To test the proposed model, we chose a case study of a cell-based gene ATMP with market approval. Kymriah is a personalised therapy used in the treatment of adults with B-cell non-Hodgkin lymphomas and children and young adults up to 25 years old with B-cell acute lymphoblastic leukaemia [6]. Following these two designations, we estimated the global demand using data from the Institute for Health Metrics and Evaluation [14]. 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 needs to have FACT accreditation. The geographical distribution of the FACT hospitals globally are shown in Table II.

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

One of the main limitations with 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 in which the demand of personalised medicine can be allocated 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., intention of use for a particular diseases). The later can happen either geographically, for example, a therapy can get approval to deliver their product in a new country, or clinically when the product gets market approval to expand their 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 I. 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, will need to be re-produced. For *semi-automatic* the range is between 3% and 10% and for *automatic* it is between 1% and 5% [19].

Finally, the transportation time between any 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 nor our proposed algorithm.

VI. Results

The non-dominated solutions generated by NSGA-II over the 20 runs are presented in Figures 3 and 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. 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 integrated manufacturing in the solutions, and an ineffectiveness in rapidly reducing the cost by adding CFs.

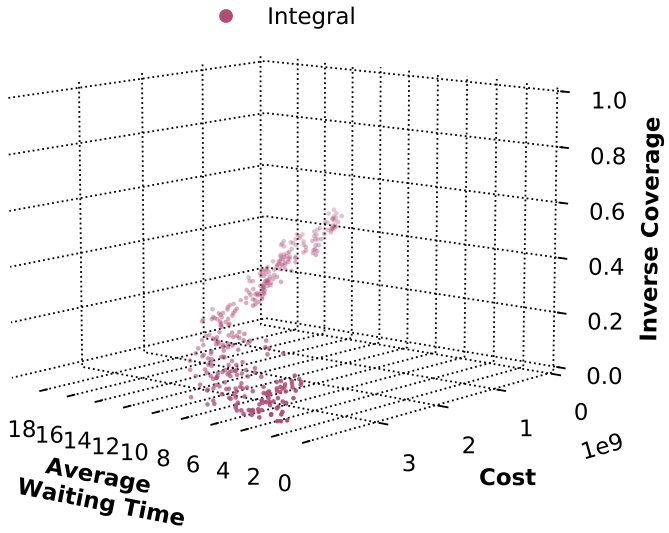

Fig. 3: Non-dominated solutions obtained from NSGA-II for the complete problem

The algorithm finds a better approximation of the Pareto front when the problem is solved in stages (Figure 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 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.

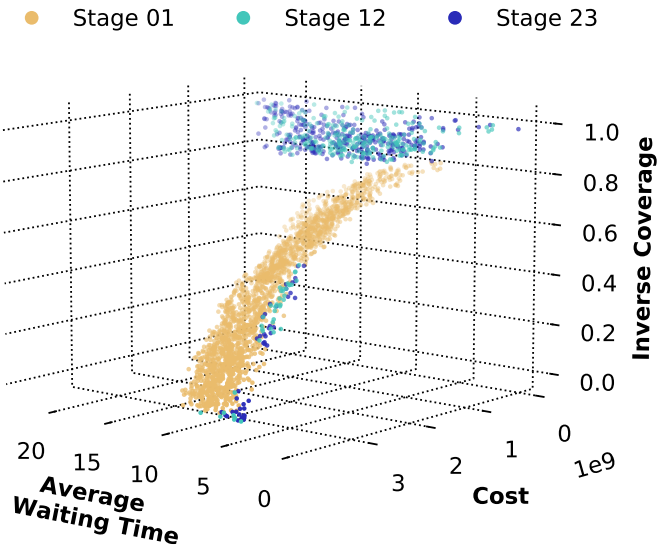

Fig. 4: Non-dominated solutions obtained from NSGA-II over the three stages.

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 5 shows this set after applying non-dominated sorting to it. As previously mentioned, optimising the complete problem starts with an advantage in terms of the waiting time objective by placing a high number of 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 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 hypervolume (HV). The HV is a popular metric used in multiobjective 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 that is worse than any solution under comparison. Higher HV values correspond to better approximations of the Pareto front. It provides a measure of both closeness to the Pareto front, good distribution and spread. The relative HV is reported in relation

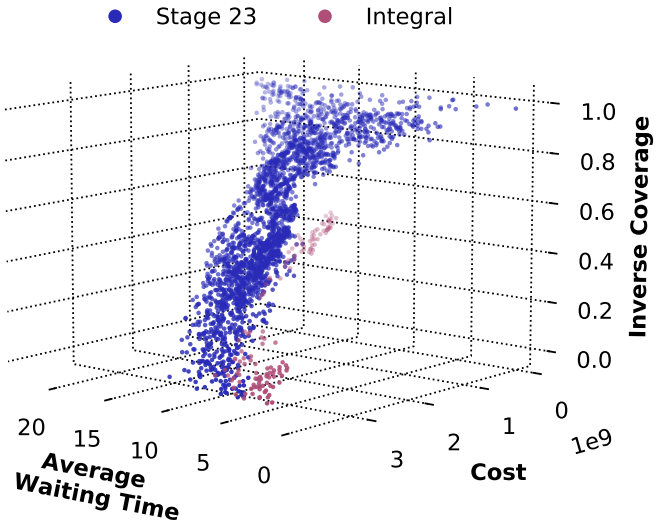

Fig. 5: Non-dominated solutions for NSGA-II between the Pareto front approximation of the last stage and the one of the complete problem

to the HV of a high-quality Pareto front approximation obtained by merging all solutions ever obtained by any approach in any run. We set the reference point 10% higher than the nadir point of this Pareto front approximation.

The descriptive statistics for the relative HV are shown in Table III. In line with the results shown in the previous figures, the HV suggests that the NSGA-II is able to 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 $\pm$ 0.06	0.33	0.68
Stage 1	0.31	0.63 $\pm$ 0.16	0.7	0.81
Stage 2	0.64	0.82 $\pm$ 0.01	0.82	0.82
Stage 3	0.22	0.82 $\pm$ 0.02	0.82	0.82

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

VII. Discussion and Conclusion

Supply chain management optimisation has been attracting increased attention in the recent years in the context of pandemic disruptions [22]. 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 [16]. 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 have solved the problem using a multi-stage approach. The results obtained from dividing the problem into multiple stages were superior to the results obtained by running the same algorithms on the complete problem. Moreover, having multiple stages allows the decision maker to change or conclude the optimisation process at key moments, such as when a good enough solution was 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-window classifications.

Several limitations pointing towards directions for future research have been highlighted throughout the paper. The ATMP supply chain has a number of 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 center, or the implementation of a public ATMP network able to manufacture and deliver multiple products.

Future research could also look at including 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 patients allocation could be prioritised to a hospital that has 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. To increase the role of the decision maker and potentially lead to better solutions towards different parts of the Pareto front, different approaches can be applied. For example, one might decide to 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 has been found to be superior when initially placing CF facilities [3].

The 3 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 have 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 does not have a strong enough impact on the overall objectives as each hospital can process only its own demand. Hence, the progress between stages 2 and 3 is not as substantial as the one between stages 1 and 2. A division of the problem in more stages with smaller decision spaces could mitigate this and allow the algorithm to further improve the solutions obtained in the last stage.

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