A DYNAMIC PROGRAMMING LABELING ALGORITHM TO OPTIMIZE THE TRANSPORTATION OF ORGANS FOR TRANSPLANTATION

Isaac Balster

Dissertação de Mestrado apresentada ao Programa de Pós-graduação em Engenharia de Transportes, COPPE, da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários à obtenção do título de Mestre em Engenharia de Transportes.

Orientadores: Glaydston Mattos Ribeiro
Laura Silvia Bahiense da Silva Leite

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Examinada por:

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Prof. Glaydston Mattos Ribeiro, Ph.D.

____
Prof. Laura Silvia Bahiense da Silva Leite, D.Sc.

____
Prof. Edilson Fernandes de Arruda, D.Sc.

____
Prof. Basílio de Bragança Pereira, Ph.D.

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Balster, Isaac

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Laura Silvia Bahiense da Silva Leite

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UM ALGORITMO DE PROGRAMAÇÃO DINÂMICA COM *LABELING* PARA OTIMIZAR O TRANSPORTE DE ÓRGÃOS PARA TRANSPLANTE

Isaac Balster

Fevereiro/2019

Orientadores: Glaydston Mattos Ribeiro
Laura Silvia Bahiense da Silva Leite

Programa: Engenharia de Transportes

Quando um órgão se torna disponível para transplante, um receptor deve ser selecionado, e, como doador e receptor estão por vezes geograficamente separados, o transporte do órgão deve ser planejado e executado dentro da janela de tempo imposta pelo tempo máximo de preservação do órgão, o que pode impactar na seleção do receptor. Reduzir o tempo decorrido entre a remoção cirúrgica do órgão e o seu transplante, conhecido como Tempo de Isquemia Fria - TIF, aumenta significativamente os resultados do transplante. Portanto, de forma a minimizar o TIF, o transporte aéreo é geralmente a melhor opção, e por vezes o único modo capaz de entregar o órgão antes que pereça. Planejar o transporte de um órgão significa escolher entre milhares de sequências de voos possíveis, a que entrega o órgão o mais rápido possível em seu destino. Este problema pode ser modelado como um problema de caminhos mínimos com restrição de recursos. Dada a urgência e a importância desta tarefa, que é resolvida de forma manual no Brasil, essa Dissertação apresenta um algoritmo com *labeling* para encontrar a sequência ótima de voos. Testes computacionais feitos em 25 casos reais brasileiros mostraram uma redução, em média, de 37,46% para os TIF e de 44,17% para os tempos de transporte.

Abstract of Dissertation presented to COPPE/UFRJ as a partial fulfillment of the requirements for the degree of Master of Science (M.Sc.)

A DYNAMIC PROGRAMMING LABELING ALGORITHM TO OPTIMIZE THE TRANSPORTATION OF ORGANS FOR TRANSPLANTATION

Isaac Balster

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Advisors: Glaydston Mattos Ribeiro
Laura Silvia Bahiense da Silva Leite

Department: Transportation Engineering

When an organ becomes available for transplantation, a recipient must be selected, and, since donor and recipient are sometimes geographically apart, the transportation of the organ must be planned and executed within the time window imposed by the maximum preservation time of the organ, which can impact recipient selection. Reducing the time elapsed between the surgical removal of the organ and its transplantation, known as the Cold Ischemia Time - CIT, significantly improves transplantation outcomes. Therefore, in order to minimize CIT, air transportation is generally the best option, and sometimes the only mode able to deliver the organ before perishing. Planning the transportation of an organ means choosing among thousands of possible sequences of flights, the one that delivers the organ as fast as possible to its destination. This problem can be modeled as a resource constrained shortest path. Given the urgency and importance of this task, which is solved manually in Brazil, this Thesis presents a labeling algorithm to find the optimal sequence of flights. Computational tests performed on 25 Brazilian real cases showed a reduction, on average, of 37,46% for the CITs and 44,17% for the transportation times.

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Chapter 1

Introduction

Since the first successful kidney transplant in 1954, organ transplantation has saved and improved the quality of life of thousands of patients. It is the best life-saving treatment for end-stage organ failure, and has been successfully performed in 111 countries [26]. Organs can be donated from living or deceased persons with reported brain death, the latter being the major source of organs for transplantation. Even though one deceased donor can donate up to eight lifesaving organs, the demand is generally larger than the offer, and waiting lists continue to grow each year [27].

In addition to cultural issues such as family refusal for organ donation, the donation of an organ can represent a logistics challenge, since organs lose viability once they are removed from the donor's body (at a organ-specific rate), as illustrated in Figure 1.1 [29].

Figure 1.1: Maximum organ preservation times [22]

In order to achieve the maximum preservation times (Figure 1.1), organs are kept chilled in preserving solutions from their retrieval from the donor to their implantation in the recipient. Since donor and recipient are sometimes far apart, organs have to be properly stored and transported. In countries with continental dimensions such as Brazil, air transportation is often the only option capable of meeting the maximum preservation time constraint. Consequently, in 2001, the Brazilian Ministry of Health established a cooperation agreement with airports, the Brazilian Air Force and airlines to transport tissues, organs and medical staff for transplantation purposes through military or commercial flights voluntarily and free of charge [1, 19]. The National Transplantation Central (*Central Nacional de Transplantes - CNT*) is responsible for the procurement and distribution of organs and tissues for transplantation among the Brazilian states, managing and controlling receiver waiting lists at the state, regional and national levels [1].

This agreement, however, is potentially underused because the planning of the transportation is performed manually by CNT technicians, without any automation, despite being a very complex and delicate task. Organs are shipped from the origin airport and must arrive within the time window imposed by the maximum preservation time of the organ in the destination airport. However, the faster the organ arrives, the better transplantation outcomes tend to be, due to lower Cold Ischemia Times - CITs [57]. Ideally, this transportation should be performed with the least possible number of flights in order to minimize the handling of the organ and the probability of unforeseen events.

To avoid confusion or misuse of some terms, some definitions follow. The Cold Ischemia Time - CIT is the time interval between the blood supply cut off and its restoration in an organ or tissue [2]. As stated in [51, 52, 57], it varies with the time necessary to transport an organ for transplantation [52]. The maximum preservation times are assumed to be organ dependent fixed values, for which they remain viable. From now on, these definitions will be used throughout the text.

As [45] states, software support systems could help speed up and simplify some of the operations of the organ procurement phase, guaranteeing a better use of resources and increasing the chances of success. Choosing an adequate trade-off between speed and robustness from a myriad of possible paths, each combining a subset of hundreds of possible flights, is indeed a daunting - not to mention unfair - task. In order to automate the CNT technicians' work, which must be completed in minutes, and mathematically determine the shortest path between origin and destination airports, [38] proposed a Mixed Integer Linear Programming - MILP model to optimally solve the transportation of organs for transplantation.

These authors showed that the mathematical model could reduce the transportation times and result in a more fair choice of the recipient, when compared to the real decisions previously taken. Their work is also to be praised due to its novelty, since the scientific literature on operations research applied to the organs transplantation context has mainly focused on designing location-allocation of health care facilities or on optimizing organ transplant supply chains [54]. However, for some instances, [38] report that a commercial solver could not prove optimality or even find a feasible solution in ten minutes of execution, the amount of time available to plan the organ transportation.

The MILP Model proposed by [38] falls into the shortest path problem category, as one can use nodes and arcs as abstractions for airports and flights. However, one should not forget the constraint imposed by the maximum preservation time, resulting in a shortest path with resource constraints problem, which according with [49] can be solved using pseudo-polynomial algorithms.

Consequently, this work aims at the implementation of a dynamic programming labeling algorithm to optimally, and efficiently, solve the transportation of organs for transplantation problem. The dynamic programming solution approach can be simply understood as breaking a problem into smaller parts, which have the property of being themselves optimal, and solving this parts recursively [34]. Labels are used to store information, such as time and distance, from a path arriving at a given node [41].

The motivation of this Thesis resides in the relevance of the nature of the problem and its potential to save and increase the life quality of many Brazilian citizens. Additionally, since a previous attempt in the literature failed at optimally solving larger instances through the use of a commercial solver, bridging this gap further justifies this research.

The remainder of this work is organized as follows. Chapter 2 presents organ transplantation definitions and concepts, relevant transplantation management systems examples across the world, and a brief review of operations research applications in the organ transplantation context. Chapter 3 presents a classical shortest path formulation and the MILP model presented in [38]. Chapter 4 shows a methodology for solving the shortest path problem and its resource constrained variant by means of dynamic programming. Furthermore, two variants of the dynamic programming labeling algorithm are presented, as well as their pseudocodes. Chapter 5 presents a brief comparison between the two algorithm variants and, for the best performing variant, presents the performance of the dynamic programming labeling algorithm for all instances proposed in [38], comparing the required execution time and the quality of the solutions with the results shown in [38]. Finally, Chapter 6 presents the conclusions and outlines future research directions.

Chapter 2

Organs transplantation and literature review

This chapter provides a basic understanding of organ transplantation, its management systems and how operations research addresses their inherent challenges. First, the basic definitions concerning organ transplantation, as well as donation, are shown. Then, some relevant transplantation systems around the world are presented. Finally, a brief literature review on operations research applied to organ transplantation is provided.

2.1 Organ transplantation concepts

According to the World Health Organization - WHO, an organ is a differentiated and vital part of the human body, formed by different tissues, that maintains its structure, vascularisation and capacity to develop physiological functions with an important level of autonomy. Transplantation is defined as the transfer of human cells, tissues or organs from a donor to a recipient with the aim of restoring function(s) in the body [23]. Organ transplantation has become a consolidated therapy over the past 50 years, representing nowadays the best, or sometimes, the only available treatment for end-stage organ failure [26].

Organ transplantation involves two actors: a donor, a living or deceased human being who is the source of tissues and organs; and a recipient, to whom organs are transplanted [23, 33]. For reasons such as minimizing the inherent risks to live donors [24] and even the fact that some organs are vital and singular, organs from deceased persons correspond to the majority of transplants [8, 11]. Moreover, in the case of a living donor, both donor and recipient can be transported to the hospital where the surgery is to be performed, thus eliminating the need for organ transportation. Since the goal of this work is to optimize the transportation of organs by air, it focuses on the transplantation of organs from deceased donors.

A favorable aspect of organ transplantation is that one single deceased donor can potentially save many lives by donating of up to eight life-saving organs, as depicted in Figure 2.1. However, donation from deceased individuals occurs only in very specific conditions: cardiac death (Donor after Cardiac Death - DCD), when death occurs by cardio-pulmonary causes, or brain death (Donor after Brain Death - DBD), when death is attested by means of neurological criteria [23]. In such cases, despite the poor medical condition of a patient, when blood and oxygen keep flowing through organs (by natural or artificial means) so that they remain viable, e.g., when an individual has a severe head trauma that later results in brain death, donation from a deceased person remains possible.

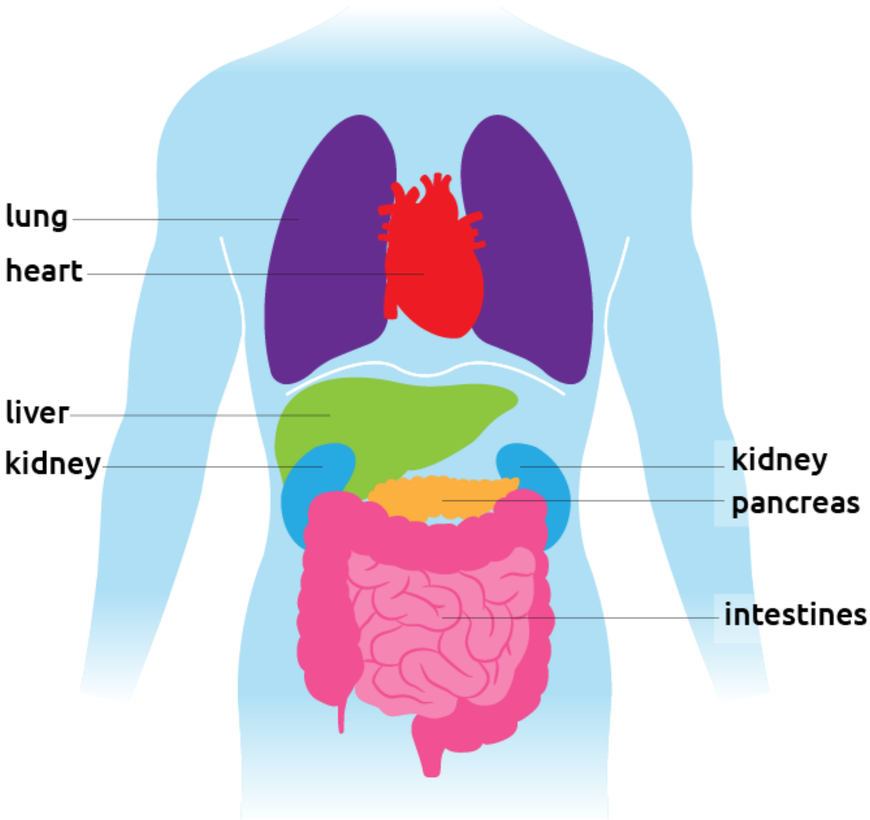

Figure 2.1: Organs that can be donated [13]

Advances in transplantation techniques and anti-rejection medications have ensured that more people benefit from transplantation [33]. The growth of transplantation surgery indications combined with factors such as the specificity of the medical conditions in which organs are viable for transplantation, have created an organ shortage. Demand has greatly outpaced the supply and transplantation waiting lists have spread worldwide [29, 33]. Other issues pertain this matter, such as when deceased's family does not consent with organ donation (in the absence of the patient's manifest willingness to become a donor via registry or where the family consent is mandatory), the logistics challenge to transport the organ to its recipient in viable time, cultural choices or myths that affect the choice towards donation, or other questions that can led to organ wastage [10, 26, 38].

To deal with these questions, each country develops its own education campaigns, organ allocation policies and measures pertinent to its culture, size, etc. To illustrate some differences in organ transplantation management systems and policies, some examples are shown in the next section.

2.2 Organ transplantation management systems

Organ transplantation requires a balance between fairness and medicine to decide upon the effective recipient [45]. Some medical factors are the first in line to determine if a person in the waiting list is a potential recipient: blood type, weight, height, age, etc [22]. Some of these characteristics can determine a definite incompatibility, e.g. blood type, while others, such as weight and height, may indicate how suitable the organ is for the recipient [45]. In addition, patients with a higher urgency, with higher estimated chances of survival and benefit normally appear on top when the ranked list of candidates is generated [22].

The idea of a static queue where a patient waits in line for an organ does not apply. Instead, each time an organ is available for transplantation a ranked list is generated based on the organ allocation policy. The differences in the level of policies, educational campaigns, governance, management systems within distinct regions and countries leads to a scenario where the rates of organ donation heavily varies around the world.

As Figure 2.2 illustrates, Spain is the country with the highest donation rates in the world, and is taken as an example by many countries. Another country with high donation rates and with the particularity of being large-sized, what must be taken into consideration due to the time-sensitive nature of organs, is the United States of America. Brazil, which is the object of study in this Thesis, possesses low rates, so there is much room for improvement.

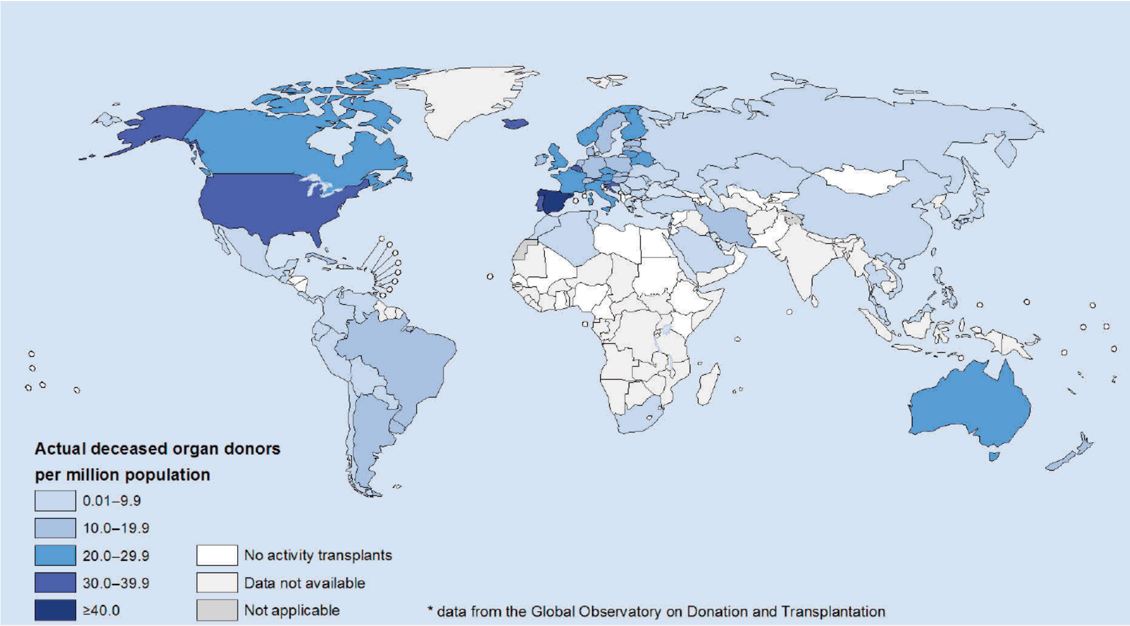

Figure 2.2: Organ donation rates from deceased donors (*per million population - p.m.p*), 2016 [25]

To illustrate the differences and similarities among countries, a brief discussion about organ donation policies and management systems is presented in the next sections.

2.2.1 The Spanish Model

Spain is the world leading country in organ donation and transplantation policies. However, it has not been always so. The *Organización Nacional de Trasplantes - ONT* was created in 1989, and since then Spain has increased its donation rates from 14 *p.m.p* to 47 donors *p.m.p*, the highest in the world. The reason of its success resides in a set of actions taken to increase the donation rates, known as the Spanish Model [5].

The Spanish Model is a multidisciplinary approach that encompasses legal, economic, political and medical aspects [6]. Some relevant points of this model are the presence of three coordination levels (national, regional and hospital), the existence of a proper legislation, a quality assurance program, hospital reimbursement for donation activities, the investment in communication and educational campaigns, a coordinator for each transplantation hospital (it is mandatory that this professional is a medic who works part-time at this function) and the ONT as a central agency, coordinating the waiting lists, organ allocation, transportation planning, statistics and actions that can contribute to the organ donation and transplantation process [6].

An outcome of the Spanish Model can be seen in Figure 2.3, as Spanish rates are far better than those of the majority of European countries.

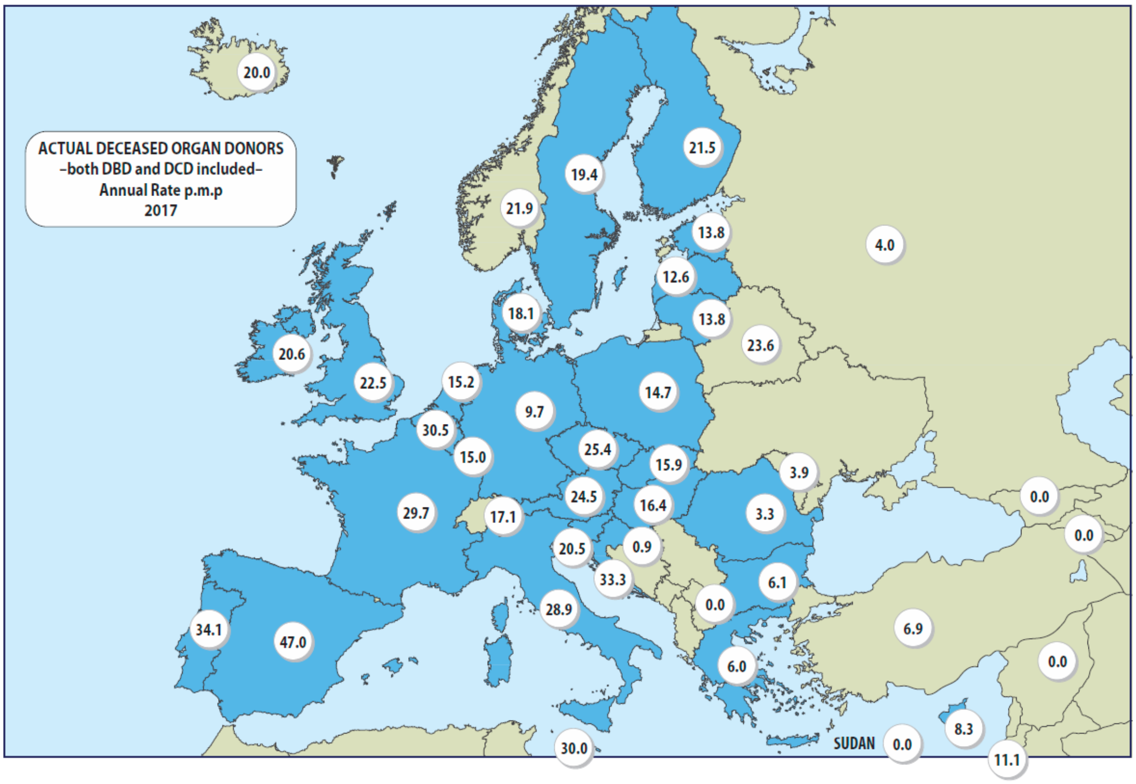

Figure 2.3: European donation rates (*per million population - p.m.p*), 2017 [25]

ONT argues that the Spanish Model is applicable to other countries, provided that some premises that can influence its success are maintained [7]. Indeed, much of its principles can be seen in other organ donation and transplantation management systems around the world.

The USA and Brazil, countries that perform the largest number of transplantation procedures in absolute numbers, have much of the Spanish Model in their organ transplantation management systems.

2.2.2 The United States organ transplantation system

The United States of America is the country with the highest numbers of donations and transplantations in the world, in absolute terms [25]. Figure 2.4 shows USA data on transplantations in 2017. With a total of 10,286 deceased organ donors, which corresponds to a rate of 31.7 donors *p.m.p*, a number of 33,506 patients were transplanted. The mismatch between these two numbers highlights that one donor can donate multiple organs. The number of transplants performed for each organ can also be observed in Figure 2.4.

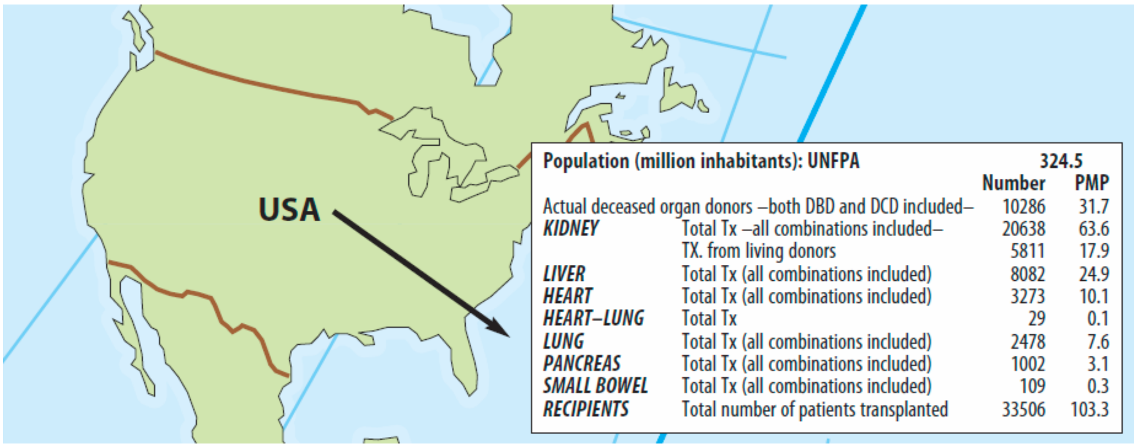

Figure 2.4: USA donation and transplantation numbers, 2017 [25]

In the USA, the organization governing the donation and transplantation of organs in the local scale is the Organ Procurement Organization - OPO. There are 58 OPOs across the United States, each one of them responsible for increasing the number of registered donors and coordinating the donation process within his designated service area [12]. The United Network for Organ Sharing - UNOS is responsible for the management of the organ transplant system through a computer network, managing the national transplant waiting list, matching donors to recipients and assisting with the transportation of organs [4, 20]. OPOs and UNOS are private, non-profit organizations.

When an organ becomes available, OPO staff ensures that the decision to donate is consented, conducts a medical and social history research on the potential donor to determine the suitability of their organs for transplantation, and enters the donation information into the UNOS computer to find potential receivers for the donated organs [4, 21]. Each organ has its own criteria and organ allocation policies (see [15] for details). In the United States organ allocation policy, geography plays key role [22]. First, organs are offered locally; if no match is found, the organ is offered regionally, and finally, nationally, until a recipient is found.

Figure 2.5 shows the division of the USA territory in 11 Regions for transplantation purposes.

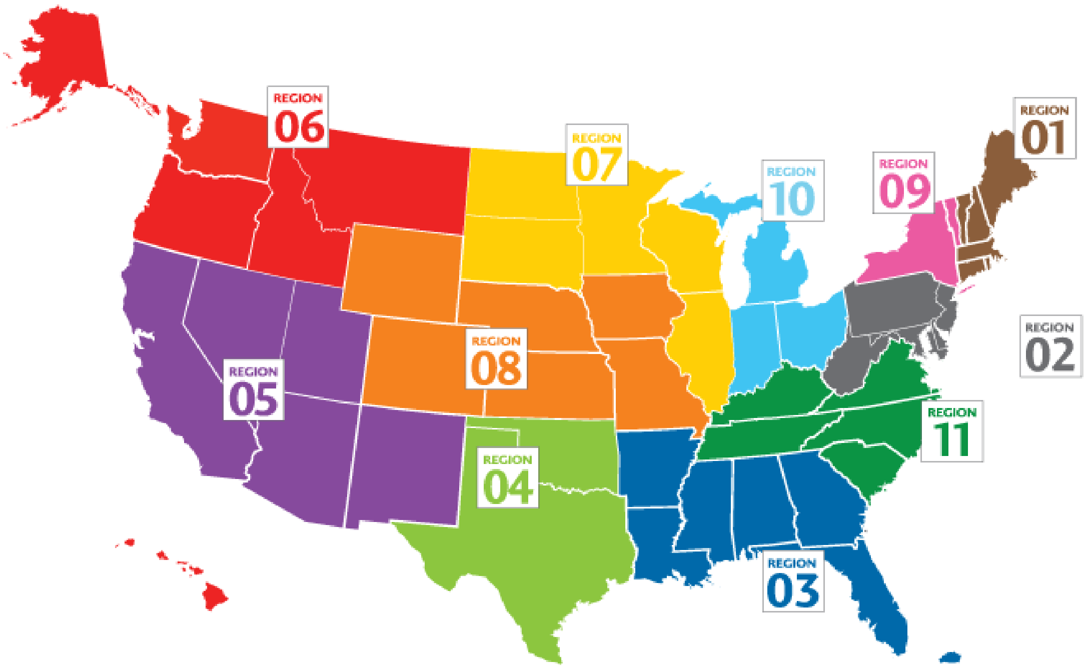

Figure 2.5: USA donation regions [16]

As UNOS advertises in a promotional video, the number of persons transplanted in the United States has grown over the last years. Figure 2.6 shows data on the growth of the number of transplants in the USA.

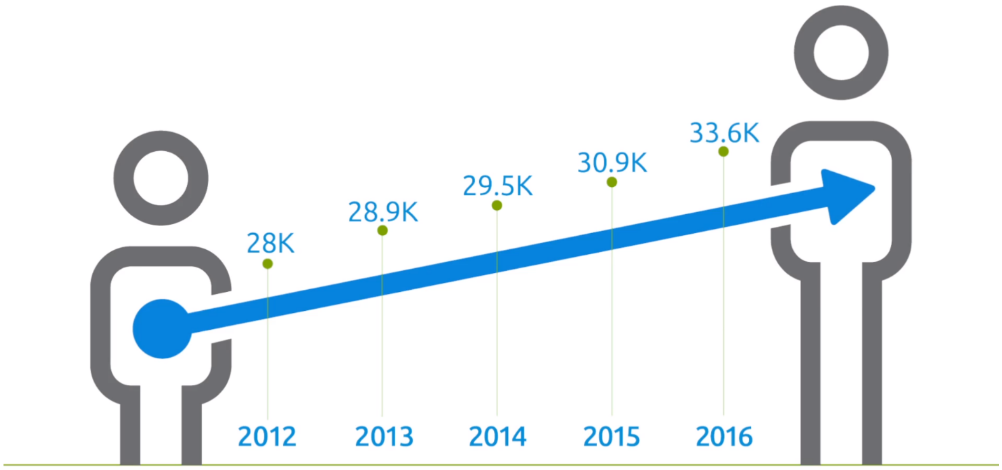

Figure 2.6: Growth of the number of transplants in the USA [22]

2.2.3 The Brazilian organ transplantation system

Brazil owns the world's largest public transplantation system, as 96% of its transplantation proceedings are publicly funded [3]. In absolute numbers, Brazil scores the second largest number of transplants in the world, just behind the USA [3, 25].

However, in terms of donation rates, Brazil still has much room to develop. As Figure 2.7 shows, in 2017 Brazil had a deceased organ donors rate of 16.3 *p.m.p*, far from the USA (31.7 *p.m.p*) and Spanish (47.0 *p.m.p*) rates, and behind his South American neighbor Uruguay (18.9 *p.m.p*).

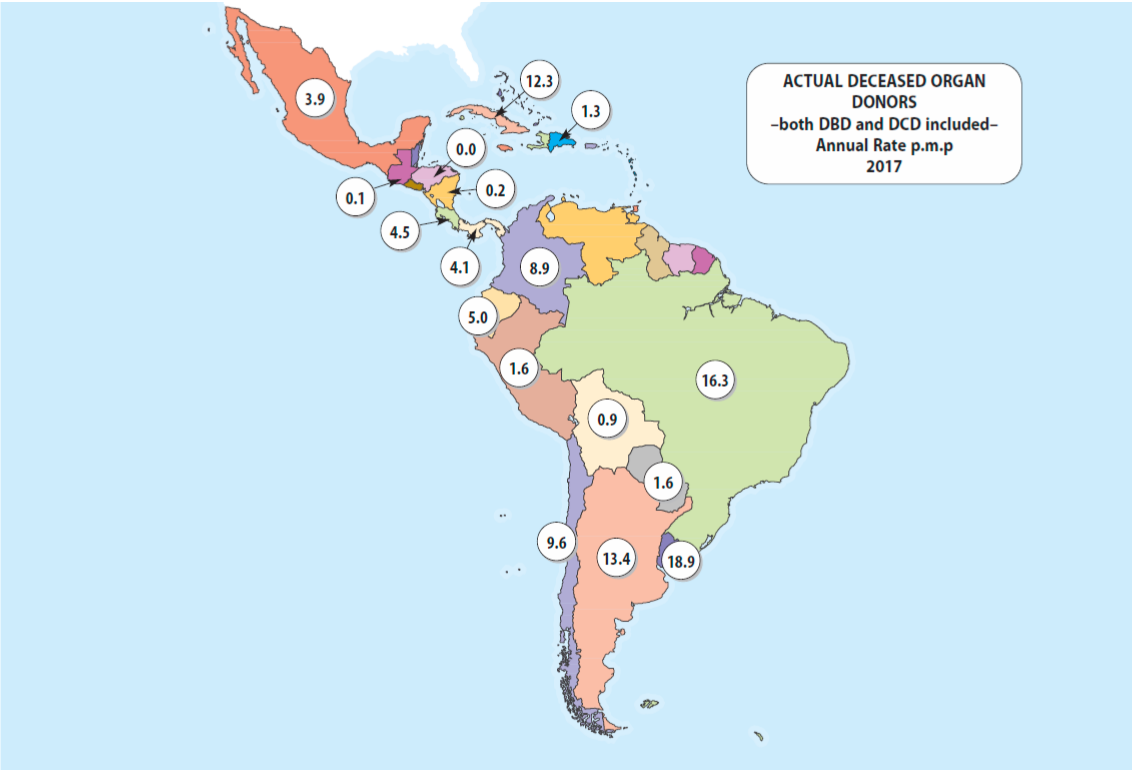

Figure 2.7: Donation rates in Central and South America (*per million population - p.m.p*), 2017 [25]

Again, the donation process begins with the identification of a potential donor. After brain death is diagnosed, family is informed of the death and a trained staff from the *Comissões Intra-hospitalares de Doação de Órgãos e Tecidos para Transplante - CIHDOTT* asks for the family's approval to donate the organs of the deceased. As the family consents and organs become available for transplantation, the local *Central de Notificação, Captação e Distribuição de Órgãos e Tecidos - CNCDO* is contacted. The CNCDO is responsible for the coordination of the transplantation activities in a state scale, and there is one operating at each state and in the federal district (*Distrito Federal - DF*) [1, 17].

With some differences regarding organs and tissues, Brazil adopts a regional allocation policy [9, 18]. Besides the geographical division in 26 states and a Federal District, for organ allocation purposes the CNT adopts the following macroregions [1, 17].

- Region I - Rio Grande do Sul, Santa Catarina and Paraná;

- Region II - Rio de Janeiro, Minas Gerais and Espírito Santo;
- Region III - Goiás, Mato Grosso do Sul, Mato Grosso, Distrito Federal, Tocantins, Amazonas, Pará, Acre, Roraima, Rondônia, Amapá and São Paulo; and
- Region IV - Bahia, Sergipe, Alagoas, Pernambuco, Paraíba, Rio Grande do Norte, Ceará, Maranhão e Piauí.

When an organ becomes available, the priority is to allocate it for a recipient within the same state. When this is not possible, the next step is to allocate the organ for a recipient in the same Region. At last, when no potential recipient is found, the organ becomes available in the national level [18]. In that sense, the cooperation agreement firmed between the Ministry of Health and Airlines is of great importance.

Despite the absolute numbers, Brazil has much room to increase donation rates. While the State of Paraná boasts a donor rate of 50.6 $p.m.p$, far superior to the Spanish average, the country as a whole is still below 20 donors $p.m.p$ [14]. It is also important to inform and educate the population, since a large number of families does not consent with the donation, with a refusal rate reaching 42.3% (cf. 13.0% in Spain [25]).

2.3 Operations research approaches for organ transplantation

Operations research has been widely applied in the healthcare domain, with applications that range from optimal location of hospitals and emergency vehicles, patient and medical staff scheduling, to disease diagnosis (see [59]). In this Section, a literature review on optimization applied to organ transplantation is provided.

Taking into consideration organ shortage and the time-sensitive nature of the problem, issues such as efficiency and fairness naturally arise. Most authors in the literature attempt to address these questions through location-allocation models and discussions regarding organ allocation policies.

[39] presents three basic facility location models, namely set covering, maximal covering and p-median formulations, which according to the authors, form the heart of location planning models in healthcare. A newer and extensive review of healthcare facility location, including organ transplant centers, can be found in [28].

[36] presents a model aimed at optimally organizing an organ transplant system. The authors analyze the Italian case, where different regions of the country have different waiting times. The location-allocation model proposes a reorganization

of the transplant system and an augment on regional equity through the selection of a set of locations that will result in the shortest maximum waiting list for all regions. The model was experimentally validated in the Italian transplantation system, showing a potential to better spatially distribute transplant centers.

[33] presents a MILP facility location model that aims at minimizing the waiting time from the moment an organ becomes available until implantation by looking for the optimal set of transplant centers to open for each organ. The MILP model even takes into consideration the waiting time until the organ removal surgery, which are less important, and therefore, should have reduced weight in the objective function summation. The model was applied to different scenarios based on Belgian real data from 2004-2009. The authors conclude that if the objective function aims at minimizing only the CIT, few transplant centers are opened, leading to a centralization scenario. However, if the total time is minimized, there is a trend to open many transplant centers, leading to a decentralized scenario. They also report that all instances were solved to optimality with very small computational times.

A bi-objective mixed-integer programming model for the multi-period location-allocation problem of designing a transportation network is presented in [64]. The formulation proposed in the paper takes into consideration uncertainties such as fluctuations in demands and supplies. The first objective function minimizes the total cost, composed of costs such as transplantation centers establishment costs and transportation costs among facilities, while also taking into consideration the possibility of integrating facilities and saving costs. The second objective function minimizes the total time, including surgery times, transportation times and transplantation waiting times. To efficiently deal with large-sized instances, the authors presented two metaheuristic algorithms, a Simulated Annealing - SA based one, and a second named self-adaptive differential evolution algorithm. The model was applied to a case study in Iran and showed potential to provide a more efficient transplant network.

[37] presents a model to optimize the distribution of aircraft in a set of hubs over Italy, which falls in the uncapacitated facility location category. Instances are based on the Italian database from June 2015 to May 2016. Two scenarios were modelled: two hubs and three hubs. Six aircraft were necessary to cover transportation requests in both scenarios. The authors concluded that a larger number of hubs would allow a reduction in the total distance flown, and consequently less fuel consumption and polluting emission.

An analysis of the Italian organ transportation logistics chain is presented by [54]. All transport activities over 44 Italian transplant centers and the related airport network were monitored in real-time, investigating parameters such as origin and destination of the organ, transport type, times, etc. The data was collected between

June and July 2015 and corresponds to 128 organ transportation events. A further study containing Italian data between June 2015 and July 2016 is presented in [55]. In this period a total of 617 organs were transported by air and in 417 cases the organs were accompanied by medical staff.

[38] presents a model to optimize the transportation of organs by air through the utilization of commercial flights in Brazil. The model was solved with CPLEX in instances based on data regarding 25 transplanted organs, collected from the National Transplantation Central (*Central Nacional de Transplantes - CNT*). The execution times vary from 5 seconds to 10 minutes (the maximum execution time allowed). The authors suggest that a shortest path with resource constraints algorithm could reduce the execution time and ensure optimality for all instances. This Thesis is dedicated to investigate the possibility.

Shortest path algorithms applied to healthcare, however, are not a novel approach. A shortest path analysis of the spatial accessibility of healthcare services in the Sichuan Province can be found in [56]. This method, which was implemented in a GIS-based environment, represents a more sophisticated analysis in comparison with the current regional availability approach used by policy makers, which solely calculates the ratio between population and healthcare services within administrative boundaries. According to the authors, this approach could provide useful information for healthcare planning and public health policies, as it identifies that the accessibility is highly uneven throughout the province. In the same sense and also in China, [65] presents an evaluation of the spatial accessibility to beds, doctors and nurses in Shenzen. The analysis was performed, among others, with the shortest path method, which was used to examine the geographical potential of hospital utilization.

A Bellman-Ford implementation to solve a sequence of shortest path problems that arise in the pricing problem of a column generation scheme can be found in [31]. The Column Generation algorithm aims to solve a set-partitioning formulation to locate a given number of roadside clinics in Africa. The mathematical model aims to provide equal access for truck drivers along different truck routes in Sub-Saharan Africa, since they should be sufficiently close to these facilities at every moment during their trips in order to their treatments to be effective. Computational tests were performed in 59 randomly generated instances, and the authors report near-optimal solutions within an acceptable amount of time for large sized instances, outperforming a previously direct approach. In addition, they report that considerable gains in terms of equity can be achieved.

Finally, an stochastic shortest path model to find an optimal sequence of tests to confirm or discard a disease, regarding an optimal testing policy, can be found in [32]. The model proposed in this work takes Bayesian statistics to, after one test, sequentially derive the posterior probability of a disease. The authors report that the model is related to sequential hypothesis testing, but with fundamental differences, such as a limited number of tests, each can be applied just once, and an individual cost for each test, thus not imposing any constraint in the cost function. The model is applied to compare tests for Coronary artery disease. Tests for an optimal costs policy and a optimal diagnosis policy are performed, showing a small difference in the probability of a correct diagnosis, but larger differences regarding to costs. Although there is no official guideline in Brazil, the authors report that the consensual strategy among physicians is to prioritize costly tests, in a similar diagnosis policy fashion. The authors affirm that the model can be applied to evaluate new technologies for disease detection.

2.4 Final considerations

As outlined in this chapter, organ scarcity can be seen everywhere. However, despite the fact that surgical techniques are well disseminated, there are considerable differences concerning donation and transplantation rates around the world. The influence of the successful Spanish Model is easily identified in the USA and Brazil, with the presence of three coordination levels — hospital, regional and national (central), the latter coordinating organ allocation, waiting lists and tasks such as planning organ transportation.

Even with the presence of this central agency coordinating actions among local, regional and national levels, rates and numbers vary within countries. Not surprisingly, most attempts in the operations research literature try to address these differences and increase regional equity through location-allocation models. Although organ transportation is tangent to these models, an approach which solely focuses on the transportation of organs through regions can be found in [38].

In Chapter 3, the mathematical model developed in [38] is presented, as a classic shortest path problem formulation, which is the base of the formulation proposed. Subsequently, based on the approach proposed by [38], Chapter 4 presents the solution methodology used in this Thesis to efficiently plan the transportation of organs through commercial flights in Brazil.

Chapter 3

Mathematical formulation

The problem approached in this Thesis is similar to the shortest path problem, one of the most simple and applicable problems in combinatorial optimization [63]. This Chapter presents its classical formulation and then shows the Mixed-Integer Linear Programming model proposed in [38], designed to optimally solve the transportation of organs for transplantation purposes.

3.1 The classic shortest path problem

The shortest path problem is a network flow problem which can be represented by a digraph. Here, we present its mathematical formulation as shown in [62].

First, let $D = (V, A)$ be a directed graph where V stands for the set of nodes, while A corresponds to the set of arcs. Let $s, t \in V$ be two distinguished nodes named source and sink, respectively. Let $k \in \mathcal{V}^+(i)$ and $k \in \mathcal{V}^-(i)$ be the set off all k arcs leaving from and arriving at a given node i, respectively. All arcs $(i, j) \in A$ have nonnegative costs c_{ij}. The shortest path problem aims to find the minimum cost path between s and t.

Arcs costs are a flexible way to compute the shortest path considering different criteria without compromising flow conservation constraints. Costs (c_{ij}) can easily be replaced by distances (d_{ij}), times (t_{ij}) or other resources (r_{ij}) that are accumulated, or consumed, along arcs and nodes.

Although simple, the classic shortest path problem formulation presented here constitutes a solid foundation for many practical applications, such as [32, 38]. The bridge between these formulations is to be seen and explained next. Differences reside on the fact that in the real problem there are multiple arcs linking each node, representing multiple flights linking airports troughout the day. Furthermore, the problem addressed here has a time-constrained nature, requiring side constraints on the resource time. Although unconstrained, the number of arcs taken from source to sink node is also of practical importance.

Finally, the shortest path problem formulation, and the mathematical model proposed in [38], follows.

$$z = Min \sum_{(i,j)\in A} c_{ij}x_{ij} \tag{3.1}$$

Subject to:

$$\sum_{k\in\mathcal{V}^+(s)} x_{sk} - \sum_{k\in\mathcal{V}^-(s)} x_{ks} = 1 \tag{3.2}$$

$$\sum_{k\in\mathcal{V}^+(i)} x_{ik} - \sum_{k\in\mathcal{V}^-(i)} x_{ki} = 0 \qquad \forall i \in V\backslash\{s,t\} \tag{3.3}$$

$$\sum_{k\in\mathcal{V}^+(t)} x_{tk} - \sum_{k\in\mathcal{V}^-(t)} x_{kt} = -1 \tag{3.4}$$

$$x_{ij} \in \{0,1\} \qquad \forall (i,j) \in A : i \neq j \tag{3.5}$$

The objective function (3.1) sums the costs of all arcs selected ($x_{ij} = 1$) in the path from s to t. Constraint (3.2) ensures that one arc is chosen outwards the source node s but none is chosen towards it. The set of Constraints (3.3) ensures the conservation of flow in all intermediate nodes $i \in V\backslash\{s,t\}$. Constraint (3.4) ensures that one arc arrives at the sink node t but none is chosen to leave it. At last, Constraints (3.5) are related to the domain of the binary decision variables x_{ij}.

[38] used the basic concepts of the mathematical formulation (3.1) - (3.5) to propose a model for the problem considered in this Thesis, which is presented in the next section.

3.2 A mathematical formulation to the transportation of organs for transplantation

Let $\mathcal{G} = (\mathcal{V}, \mathcal{A})$ be a directed graph, where $\mathcal{V}$ and $\mathcal{A}$ correspond to the sets of nodes (airports) and arcs (flights), respectively. The airport of origin (source node) is denoted by s and the destination airport (sink node) is denoted by t, while the set of candidate airports to intermediate stops, or transshipment nodes, is denoted by $\mathcal{V}_\Gamma$. Thus, $\mathcal{V}$ can be rewritten as $\mathcal{V} = \mathcal{V}_\Gamma \cup \{s,t\}$. Let $\mathcal{A}_{ij}$ be the set of all arcs available from a node $i \in \mathcal{V}$ to a node $j \in \mathcal{V} : i \neq j$. Thus, $\mathcal{A}$ can be written as $\mathcal{A} = \bigcup_{(i,j)} \mathcal{A}_{ij}, \forall i,j \in \mathcal{V} : i \neq j$.

For each arc $a \in \mathcal{A}_{ij}$, which corresponds to a flight from i to j, there is an associated departure time h^a_{ij} and a flight duration d^a_{ij}. According to the organ to be transplanted, there is a period of time D_{max} to transport the organ from the origin airport s to the destination airport t, which is related to the maximum preservation time of the organ. The organ is ready to be transported from time $H_{available}$ and must arrive in the airport t in a moment T_t not superior to the maximum possible time H_{t_max}.

When a stop in one or more airports from the set $\mathcal{V}_\Gamma$ is made, it must be guaranteed that there is enough time to handle the organ in an appropriate manner when an exchange of aircraft is necessary. The time required for these operations is represented by parameter τ_{ij}. [38] uses 30 minutes for all pairs of airports.

Even with the accounting of this handling time by the formulation, ideally, stopovers should be avoided to reduce the manipulations of the organ and also the possibilities of unforeseen events. In order to choose a solution with a good balance between the earliest arrival time at the destination airport and the fewest number of flights along the path from s to t, a penalty P, adjustable by the modeler, is added.

In respect to the decision variables, let $T_i \geq 0$ represent the time when the organ leaves node $i \in \mathcal{V} \backslash \{t\}$. When the airport into consideration is the origin s, it must be guaranteed that the flight chosen leaves the airport after the organ is available for transportation, $T_s \geq H_{available}$. Thus, let x_{ij}^a be a binary decision variable that assumes 1 if the arc (flight) $a \in \mathcal{A}_{ij}$ is chosen to make the trip between the nodes $i \in \mathcal{V}$ and $j \in \mathcal{V}$, and 0 otherwise.

Taking into account the definitions above, the mathematical model proposed by [38] is presented below.

$$Min\ z = T_t + P \sum_{i \in \mathcal{V} \backslash \{t\}} \sum_{j \in \mathcal{V} \backslash \{s\}: i \neq j} \sum_{a \in \mathcal{A}_{ij}} x_{ij}^a \tag{3.6}$$

Subject to:

$$\sum_{j \in \mathcal{V} \backslash \{s\}} \sum_{a \in \mathcal{A}_{sj}} x_{sj}^a = 1 \tag{3.7}$$

$$\sum_{i \in \mathcal{V} \backslash \{t\}} \sum_{a \in \mathcal{A}_{it}} x_{it}^a = 1 \tag{3.8}$$

$$\sum_{i \in \mathcal{V} \backslash \{j,t\}} \sum_{a \in \mathcal{A}_{ij}} x_{ij}^a = \sum_{i \in \mathcal{V} \backslash \{j,s\}} \sum_{a \in \mathcal{A}_{ji}} x_{ji}^a \qquad \forall j \in \mathcal{V}_\Gamma \tag{3.9}$$

$$x_{ij}^a (T_i + d_{ij}^a - T_j + \tau_{ij}) \leq 0 \qquad \forall i \in \mathcal{V} \backslash \{t\}, j \in \mathcal{V} \backslash \{s\}, a \in \mathcal{A}_{ij} \tag{3.10}$$

$$T_i = h_{ij}^a x_{ij}^a \qquad \forall i \in \mathcal{V} \backslash \{t\}, j \in \mathcal{V} \backslash \{i\}, a \in \mathcal{A}_{ij} \tag{3.11}$$

$$T_s \geq H_{available} \tag{3.12}$$

$$T_t \leq H_{t\_max} \tag{3.13}$$

$$x_{ij}^a \in \{0,1\} \qquad \forall i \in \mathcal{V} \backslash \{t\}, j \in \mathcal{V} \backslash \{i\}, a \in \mathcal{A}_{ij} \tag{3.14}$$

$$T_i \geq 0 \qquad \forall i \in \mathcal{V} \backslash \{t\} \tag{3.15}$$

The objective function minimizes the sum in (3.6), which corresponds to the arrival time at the destination airport T_t plus the number of flights taken multiplied by a penalty P. Constraints (3.7) and (3.8) correspond to constraints (3.2) and (3.4) in the classical shortest path formulation, and are responsible for the outflow and inflow at the source and sink nodes, respectively, guaranteeing that a flight leaving s and a flight arriving at t are going to be selected. The set of Constraints (3.9), on the other hand, can be associated to Constraints (3.3) and ensures the conservation of flow at the transshipment nodes. The set of Constraints (3.10) is responsible for the right accounting of time, ensuring that the organ is available for transportation from a destination j at least τ_{ij} minutes after its arrival, destined for the handling of the organ. The set of Constraints (3.11) sets the departure time at a given node equal to the departure time of the flight, i.e. arc, chosen to leave the node. Constraint (3.12) ensures that the organ leaves the origin airport only after the moment it is available for transportation, while Constraint (3.13) ensures that the organ must arrive at the destination t before the maximum arrival time. This pair of constraints over the resource time leads the problem to a different shortest path variation, what is further explained in Chapter 4. At last, Constraints (3.14) and (3.15) are associated with the decision variables domains.

The mathematical model (3.6)-(3.15) is nonlinear because of the set of Constraints (3.10), however, these constraints can be linearized as follows:

$$T_j \geq T_i + d_{ij}^a + \tau_{ij} - M_{ij}(1 - x_{ij}^a) \qquad \forall i \in \mathcal{V}\backslash\{t\}, j \in \mathcal{V}\backslash\{s\}, a \in \mathcal{A}_{ij} \tag{3.16}$$

where M_{ij} is a sufficiently large constant.

This model yields the shortest path between two airports, taking also into account the number of flights necessary to traverse this path. The answer consists of a sequence of flights within the time window imposed by the maximum preservation time of the organ transported. However, as reported in [38], the solution of the model becomes complex if the number of flights and nodes increase.

In order to mitigate the effects of the growth of the number of decision variables, since the processing time is limited to, for example, ten minutes, a dynamic programming algorithm, dedicated to this problem, is presented in the next chapter.

Chapter 4

Solution approaches

This chapter presents the dynamic programming labeling algorithm to solve the transportation of organs for transplantation. As in Chapter 3, first, a methodology to algorithmically solve the shortest path problem in its unconstrained version, without constraints or upper bounds in the consumption of resources (e.g. time, distance, flights etc.), is presented. Then, differences on unconstrained and resource constrained versions are explained, and the most recent attempts to solve its constrained version efficiently are presented. Having this foundation in mind, it is explained how the practical problem here addressed fits into the resource constrained shortest path problem. At last, necessary mathematical definitions are made and two variants of the dynamic programming labeling algorithm are formally presented.

4.1 Solving the shortest path problem

As stated in [46], all solution algorithms for the shortest path problem are derived from a single procedure, differing from each other mainly in the data structures used to implement the set of candidate nodes, i.e. nodes to be selected for treatment according to a defined criteria. This procedure corresponds to a dynamic programming algorithm, capable of finding the optimal solution for the shortest path problem through a recursion, building paths from the origin node s to the destination node t [41, 48, 62]. The effectivity of dynamic programming algorithms to solve the shortest path problem relies on the *Principle of Optimality*, which corresponds to the property of having an optimal substructure, where pieces of an optimal solution are themselves optimal [62].

The solution of the shortest path problem is a directed spanning tree T of $G = (V, A)$ rooted at the source node s [41, 46]. Let l_{ij} be the length of the arc (i, j) and the length of a path be the sum of the lengths of its arcs. It is necessary to assume that there is no directed paths with negative costs in G, which is achieved assuming that there is no arc with negative costs, i.e. lengths. Let d_v be the length of a path from the root s up to node $v \in V$. T is a shortest path tree rooted at s ($T = T^*(s)$) if and only if the Bellman's optimality condition holds:

$$d_i + l_{ij} - d_j \geq 0 \qquad \forall (i,j) \in A. \tag{4.1}$$

Having in mind the variables and the optimality condition, [46] presents the following operations as a general procedure whereby most shortest path algorithms can be derived:

1. Initialize a directed tree T rooted at s and for each $v \in V$, and let d_v be the length of the path from s to v in T;

2. Let $(i, j) \in A$ be an arc for which condition (4.1) is not satisfied, i.e. $d_i + l_{ij} - d_j < 0$, then update the path setting $d_j = d_i + l_{ij}$, and update the tree T replacing the arc incident into node j by the new arc (i, j); and

3. Repeat step 2 until optimality conditions (4.1) are satisfied for all arcs.

The key in the implementation of this procedure is the way arcs which do not satisfy the optimality conditions (4.1) are selected at step 2 [41, 46]. The behavior of the algorithm is deeply affected by the way in which this operation is performed [46]. Since the number of nodes is normally smaller than the number of arcs ($|V| \leq |A|$), it seems reasonable that in most algorithms a node v is selected and treated, i.e. step 2 is performed for all arcs $(v, j) \in A$ [41, 46].

Considering this node treatment discipline, let U be the set of unprocessed nodes and P be the set of processed, treated nodes. The following node selection criteria are presented in [41] as the most usual:

1. *FIFO (First-In-First-Out):* the oldest node in U is selected and treated. The data structure used to represent U is therefore a queue, where new nodes enter the queue at his end and the node at the front of the queue is treated;

2. *LIFO (Last-In-First-Out):* the newest node in U is selected and treated. The data structure used to represent U is therefore a stack, where new nodes are inserted at his top and the node to be treated is picked from the top of the stack; and

3. *Best-First:* the cheapest node $v \in U$ is selected and treated.

The definitions and procedures above should be enough to provide a foundation to understand solution approaches to solve the shortest path problem. With subtle differences, they belong to the core references for the shortest path problem in the literature, such as [58], [53], [35], [44] and [43]. However, for the practical application presented in this work, it is necessary to expand definitions and concepts, as shown in this next section.

4.2 Solving the resource constrained shortest path problem

In a classical shortest path problem formulation, the cost of a solution is equal to the sum of the costs of the edges used to traverse the optimal path from the source to the sink node. These costs can be seen as lengths, e.g., when the graph corresponds to a mathematical abstraction representing a roadway network, or in a more general sense, they can be interpreted as the consumption of a resource. A resource corresponds to a quantity that varies along the path, such as distance, time, load, etc. [49].

Variants of the shortest path problem in which one has to deal with a set of constrained resources are known as the *shortest path problem with resource constraints* - SPPRC. As in the unconstrained version, paths are built in a stepwise approach, but this time a multi-dimensional resources vector is accumulated and constrained at each node, introducing the concept of feasibility. Since two paths are incomparable when the first path is better than a second in the consumption of a resource and worse in the consumption of another resource, it is necessary to consider all uncomparable paths arriving at a given node. This observation provides an initial insight into the SPPRC's complexity [49].

An early attempt to solve a side constrained shortest path problem was presented in [50], where arcs were characterized by cost and a nonnegative second variable, with the optimal path being the most economical that satisfies a constraint requiring that the sum of these arc's second variables must be greater than or equal to a defined parameter. In a similar sense, [47] and [30] present a shortest path formulation with an additional knapsack constraint, addressing the problem with Lagrangean relaxation and implicit enumeration algorithms, respectively. [47] suggests that this additional constraint can be interpreted as a total time constraint in a transportation network, what points out in the direction of what perhaps is the most valuable resource, and therefore, the one which motivates most researches and applications: time.

First studied in [42], the *shortest path problem with time windows* - SPPTW is a time-constrained variant of the shortest path problem with time window constraints at each node. Time windows are an efficient way to model allowable delivery times of customers in many routing and scheduling problems [41]. The problem was generalized and addressed with an algorithm in [40, 41] for the case with several constrained resources (SPPRC).

Resource-constrained shortest path problems are very common as subproblems in several column generation and branch-and-price schemes to solve routing and scheduling problems, having contributed to the success of these methods as a flexible tool to model cost structures and feasibility rules of routes and schedules, and because there are efficient algorithms for its most important variants [49]. In respect to efficiency, the permanent labeling algorithm proposed by [41] is said to run in pseudo-polynomial time, solving instances with up to 2500 nodes and 250.000 arcs. This kind of algorithm starts with an empty and trivial path at the source node and calculates labels iteratively as paths are built [41].

More recently, [60] presented a bounded bi-directional dynamic programming algorithm for the *elementary shortest path problem with resource constraints*, where in order to minimize the growth of the number of labels along the path construction, a forward and a backward path are built from the source and sink node, respectively, and then these two paths are joined together. The bi-directional implementation [60] has been shown to outperform the mono-directional one. In the same effort to minimize labels growth, [61] experimentally observed that the forward and backward label extensions are unbalanced, and then proposed a dynamic half-way point based on the current state of the solved forward and backward paths. The dynamic half-way point implementation has shown to speed up the computational time in up to 41% when compared with the previous static bi-directional implementation.

After a brief review of SPPRC, we present in the next section the algorithm implemented to solve the transportation of organs for transplantation.

4.3 The dynamic programming labeling algorithm

The dynamic programming labeling algorithm uses the same directed graph $\mathcal{G} = (\mathcal{V}, \mathcal{A})$ introduced in Section 3.2, where $\mathcal{V}$ corresponds to the nodes (airports) and $\mathcal{A}$ corresponds to arcs (flights). Since there are different flights between two airports over the day, and that implies multiple arcs between two nodes, it is not possible to represent a path by just a sequence of nodes. Therefore, a *path* $P = (a_0, \dots, a_p)$ with length p is represented by a sequence of arcs (flights) where the arrival airport (head node) of $a_i \in \mathcal{A}$ has to be equal to the departure airport (tail node) of $a_{i+1} \in \mathcal{A}$ for all $i = 0, \dots, p-1$. There are no path-structural constraints (see [49] for more details), i.e. all paths are feasible.

Feasibility appears in the form of a time window imposed by the maximum preservation time of the organ to be transported. Time is the most important resource for this application, and all nodes are constrained by the time window $[H_{available}, H_{t\ max}]$. Another resource taken into consideration at the judgment of the solution is the number of flights used from the origin airport s to the destination t. Despite being an unconstrained resource, a good trade-off between the number of flights and the arrival time at t can be interpreted as an attempt to avoid unforeseen events and minimize the necessity of handling the organ, which is clinically not recommended. This trade-off is modeled through the use of a penalty P at the pricing of the solution, following the objective function (3.6) from Section 3.2.

As described above, the SPPRC variant for the transportation of organs deals with two resources: *time* and *flights*. Thus, a label (time, flights) is associated for each feasible path P_{sj} from the origin s to a node j, storing the arrival time at the node j and the number of flights taken up to j. A label representing a path P_{sj} from the origin s to a node j will be denoted by (T_j^k, F_j^k), where k corresponds to the k^{th} path from s to j. To understand the number of labels k that have to remain stored at each node, it is necessary to define the concepts of label efficiency and dominance between labels.

For two different paths P_{sj}^1 and P_{sj}^2 from s to j with two respectively associated labels (T_j^1, F_j^1) and (T_j^2, F_j^2), P_{sj}^1 is said to dominate P_{sj}^2 if and only if $T_j^1 \leq T_j^2$ and $F_j^1 \leq F_j^2$. In the case of a multidimensional resource vector R, P_{sj}^1 would dominate P_{sj}^2 if and only the set of inequalities $r_j^1 \leq r_j^2$ holds for every resource $r \in R$, which is equivalent to saying that the consumption of each resource at the path P_{sj}^1 would have to be less or equal the consumption of the same resource at the dominated path P_{sj}^2. For a given node j, a label (T_j^k, F_j^k) is said to be efficient if no other label at j dominates it. Similarly, a path P_{sj}^1 is said to be efficient if its associated label (T_j^1, F_j^1) is efficient.

Non-efficient labels, i.e. labels that are dominated by others from the set of labels of the same node, can be discarded in a label treatment step. Even treating labels and discarding some of them, their number can grow rapidly and increase the processing time of the algorithm, since labels represent paths that have to be extended until the destination t is reached. The way how paths are extended and resource consumption is accumulated throughout the path construction depends on the resource extension functions defined.

A *resource extension function* - REF $f_{ij}^r : \mathbb{R} \rightarrow \mathbb{R}$, defined over a resource r, depends on the consumption of the resource r accumulated along the path from the origin s until the node j and normally extends the consumption of this resource with the amount used at arc (i, j). For each resource taken into account at the dynamic programming algorithm implemented to solve the transportation of organs for transplantation, i.e. *time* (T) and *flights* (F), a REF is defined as follows:

$$f_a(T_j^k) = h_{ij}^a \ + \ d_{ij}^a \qquad \forall i \in \mathcal{V}\backslash\{t\}, j \in \mathcal{V}\backslash\{s\}, a \in \mathcal{A}_{ij}, k \in \mathbb{N} \tag{4.2}$$

$$f_a(F_j^k) = F_i^k \ + \ 1 \qquad \forall i \in \mathcal{V}\backslash\{t\}, j \in \mathcal{V}\backslash\{s\}, a \in \mathcal{A}_{ij}, k \in \mathbb{N}. \tag{4.3}$$

The time resource extension function (4.2) calculates the arrival time at j by summing up the departure time from a previous node i, h_{ij}^a, with the duration of the flight from i to j, d_{ij}^a. The usage of the resource time at a given label k of j, T_j^k, which corresponds to the arrival time at j, must lie within the time window $[H_{available}, H_{t\ max}]$, otherwise the path extension from a previous node i towards j is not feasible and will not be performed. The flights resource extension function (4.3) calculates the number of flights used at a given label k of j by adding 1 to the total number of flights used at the label k from the previous node i. One should remind that the resource flights is unconstrained.

The time window $[H_{available}, H_{t\ max}]$ defined over all nodes is enough to satisfy the sets of constraints (3.12) and (3.13) from the mathematical formulation presented at Section 3.2. However, it is not enough to satisfy the set of constraints (3.16), which requires that the organ is available for transportation from a transshipment node $i \in \mathcal{V}_\Gamma$ to node $j \in \mathcal{V}_\Gamma$, only τ_{ij} minutes after its arrival. In order to expand paths and keep them feasible in respect to these three sets of constraints, flights with departing time that do not satisfy this constraint will be discarded through preprocessing.

Besides embedding (3.12), (3.13) and (3.16), the preprocessing is also able to choose a single feasible and dominant arc (when there is at least one feasible) among all arcs available to expand the path P_{si}^k until P_{sj}^k. We can observe easily that the number of flights F_j^k will be the same for a path extension from i towards j arising from the path $P_{si}^k = (T_i^k,\ F_i^k)$, since it depends only on F_i^k. With that in mind, one can observe that a feasible flight, i.e. one that satisfies the sets of constraints, that results in the earliest arrival time T_j^k would generate a dominant label $P_{sj}^k = (T_j^k,\ F_j^k)$ when compared with the other feasible arcs, thus being not necessary to consider more than just one arc for each path extension between two nodes.

A path extension in all directions, i.e. towards all nodes $v \in \mathcal{V}$, can be understood as processing a path, or treating a label. Let $\mathcal{U}$ be the set of *untreated labels* and $\mathcal{P}$ be the set of *treated labels*. The main aspect of labeling algorithms is an efficient manipulation of these two sets. Since the number of labels can grow rapidly, it is also important to apply dominance rules and discard non-efficient labels. As labels are extended and discarded throughout the execution of the algorithm, the sets $\mathcal{U}$ and $\mathcal{P}$ change dynamically. Briefly explained, the algorithm starts with the trivial path P_s^0 in the unprocessed set $\mathcal{U}$, and the set $\mathcal{P}$ empty, and terminates when there are no more labels to treat, i.e the set $\mathcal{U} = \varnothing$.

The pseudo-code presented in Algorithm 1 can give a better idea on the functioning of the dynamic programming algorithm implemented for the transportation of organs for transplantation.

Algorithm 1 is heavily based on [49] with adjustments to the organs transportation variant, previously described. Nevertheless issues related to the implementation make it necessary to expand the explanation and further present a second variant implemented.

Algorithm 1: *SPPRC Dynamic Programming Labeling Algorithm - Version 1*

/* Initialization step */
SET $\mathcal{U} = \{P_s^0\}$ and $\mathcal{P} = \varnothing$
while $\mathcal{U} \neq \varnothing$ **do**
  CHOOSE the least cost path P $\in \mathcal{U}$ and **REMOVE** P from $\mathcal{U}$
  forall $v \in \mathcal{V}$ **do**
    /* Preprocessing step */
    FIND a feasible and dominant arc $a^* \in \mathcal{A}_{ij}$ towards v from the head node of P, when there is at least one
    /* Path extension step */
    if $\exists\ a^*$ **then**
      EXTEND P towards v and **ADD** the resulting path P_{sv}^k to the set $\mathcal{U}$
    end
  end
  ADD P to the set $\mathcal{P}$
  /* Dominance step */
  forall $v \in \mathcal{V}$ **do**
    APPLY a dominance algorithm between all k paths P_{sv}^k from $\mathcal{U} \cup \mathcal{P}$ ending at v and **DISCARD** all dominated paths
  end
end
/* Pricing step */
PRICE all k paths $P_{st}^k \subseteq \mathcal{P}$ arriving at the destination node t and **RETURN** the optimal, i.e. least cost path P_{st}^*, when there is at least one

The code was fully implemented in C programming language and the data structure used to represent the paths was a multi-dimensional array of the nodes. For each node, it is possible to store a limited number of labels `MAXLABELS`, which is a compiling parameter defined by the modeler. Since the reallocation of the nodes array was not implemented, the `MAXLABELS` parameter has to be large enough to avoid the discarding of an efficient label, and as low as possible to keep the code computationally efficient.

The dominance step can be applied at every iteration or be delayed to a point when there is a chance to remove several non-efficient labels before they are processed in the path extension step [49]. In the Algorithm 1 implementation, the dominance step is applied at every iteration. For small values of `MAXLABELS`, this has not compromised performance, but as `MAXLABELS` is increased it was observed that this could compromise the processing time needed. However, for small values of `MAXLABELS` an efficient label can be discarded since there is no space to store the label, in this case optimality cannot be ensured and Algorithm 1 displays a message in that sense together with the best answer found.

To tackle suboptimality, while keeping a good performance, the strategy adopted was to embed the dominance step inside the path extension step. This was achieved by comparing the candidate label with all labels already stored in the node the path is moving towards. If the candidate label dominates a previously stored label, it replaces the latter, which is discarded, thus not occupying an empty label position. Otherwise, if the candidate label is dominated by a previously stored label, it is discarded and also does not occupy any used or empty label position. Finally, if the candidate label neither dominates nor is dominated by a previously stored label, it is stored in an empty label position, when there is at least one available.

Algorithm 2 shows the improved version of Algorithm 1. A performance comparison between Algorithm 1 and Algorithm 2 as the parameter `MAXLABELS` increases is presented in Chapter 5.

Since there is no trigger point in the algorithm to terminate the execution when one or more feasible paths arriving at the destination node t are found, the complete execution of the algorithm calculates the shortest paths between all nodes $v \in \mathcal{V}$. When all paths are evaluated, the algorithm prices all paths arriving at the destination node t. However, the algorithm could return the shortest path from s to any other node without having to be recalculated. This is specially useful when a list of destinations sorted in order of priority is provided, and, in the absence of a feasible path towards the first node of the list, the algorithm jumps to the next candidate destination until a feasible path is found or until there is no more candidate destination. This could happen in a very constrained scenario, e.g. when an organ with a short maximum preservation time imposes a narrow time window above all nodes and the priority receptor is geographically very far from the donor.

Algorithm 2: *SPPRC Dynamic Programming Labeling Algorithm - Version 2*

/* Initialization step */
SET $\mathcal{U} = \{P_s^0\}$ and $\mathcal{P} = \varnothing$
while $\mathcal{U} \neq \varnothing$ **do**
    CHOOSE the least cost path P $\in \mathcal{U}$ and **REMOVE** P from $\mathcal{U}$
    forall $v \in \mathcal{V}$ **do**
        /* Preprocessing step */
        FIND a feasible and dominant arc $a^* \in \mathcal{A}_{ij}$ towards v from the head node of P, when there is at least one
        /* Path extension step */
        if $\exists\ a^*$ **then**
            EXTEND P towards v
            if the resulting path P_{sv}^k is dominated by a previously stored label $P_{sv}^i : i \in \{0, ..., \texttt{MAXLABELS}\}$ **then**
                DISCARD P_{sv}^k
            end
            if the resulting path P_{sv}^k dominates a previously stored label $P_{sv}^i, i \in \{0, ..., \texttt{MAXLABELS}\}$ **then**
                DISCARD P_{sv}^i, **STORE** the resulting path P_{sv}^k in the *i–th* position and **ADD** P_{sv}^k to the set $\mathcal{U}$
            end
            if the resulting path P_{sv}^k neither dominates nor is dominated by a previously stored label P_{sv}^i **then**
                if there is at least one empty label position **then**
                    STORE the resulting path P_{sv}^k and **ADD** P_{sv}^k to the set $\mathcal{U}$
                end
                if there is no empty label position **then**
                    DISCARD P_{sv}^k and **PRINT** the following message to the user: `An efficient label was discarded! The modeler must increase the parameter MAXLABELS to ensure optimality!`
                end
            end
        end
    end
    ADD P to the set $\mathcal{P}$
end
/* Pricing step */
PRICE all k paths $P_{st}^k \subseteq \mathcal{P}$ arriving at the destination node t and **RETURN** the optimal, i.e. least cost path P_{st}^*, when there is at least one

4.4 Final remarks

In this chapter, solution methodologies to solve the shortest path in its unconstrained and constrained versions were presented.

In its unconstrained version, there is no upper bound on the total amount of a quantity, such as time or distance, consumed to traverse paths. In that sense, there are no infeasible paths once the graph is connected. In addition, the judgement criteria of the optimal path depends on the consumption of a single quantity, and therefore, it is necessary to store just one single label per node.

On the other hand, in the constrained version, at least one quantity is limited to an upper bound, what introduces the concept of feasibility for paths. Moreover, the optimal path is calculated based on the consumption of more than one of these quantities, making necessary to store multiple labels arriving at each node, what augments the complexity of the problem and potentially the processing time required.

In order to obtain optimal answers as fast as possible, the algorithm implemented takes advantage of the constrained nature of the problem and also of the fact that optimal solutions are calculated with respect to two resources, namely time and flights. To minimize increase in the number of labels, the multiple arcs between two nodes are preprocessed, remaining at most one. Concerning computational efficiency, it was observed that the dominance step could compromise the performance of Algorithm 1 if one desires to ensure optimality in larger instances. Therefore, Algorithm 2 embedded dominance rules into the path extension step. This allowed the allocation of sufficiently large arrays, which are necessary to ensure optimality, without significant compromise of the algorithm performance.

In the next chapter, the difference in the performance of these two variants implemented is discussed, in order to justify the choice of one variant over the other. For the best performing variant, tests were made in the whole set of instances available and proposed in [38]. The performance of the algorithm is then shown and compared with the results previously obtained in [38].

Chapter 5

Computational results

The dynamic programming labeling algorithm presented in the previous chapter was tested on real instances introduced in [38]. First, a performance comparison between the two variants of the algorithm is shown. Then, the results obtained with the best performing variant are compared to those in [38] for the same set of instances. Furthermore, a comparison between the routes taken on these real cases and the ones obtained with the aid of the dynamic programming algorithm is presented. Additionally, the effect of the penalty in the solutions is shown.

5.1 Case study

The dynamic programming labeling algorithm was written in C, using the gcc 5.4.0 compiler with –O3 option. We used a computer with an AMD Athlon™ 64 X2 6000+ 3.0 Ghz dual core processor, 8.0 Gb of RAM, and Linux Ubuntu 16.04.11 LTS operating system. The results from [38] were obtained in up to 10 minutes of execution of the formulation (3.6)-(3.15) by the solver ILOG CPLEX 12.5 using a computer with an Intel® Celeron® M 540 1.81 Ghz processor, 2.0 Gb of RAM, and Windows 7 operating system. The MFlops relation between the two computers is approximately equal to 0.3 (1.81/2x3.0). Thus, in order to fairly compare the results, the computational times of [38] were multiplied by this factor. All the computational times are expressed in seconds.

Before presenting the results obtained with the dynamic programming labeling algorithm, it is important to compare the performance of Algorithm 1 and Algorithm 2 variants as the parameter `MAXLABELS` is increased in order to ensure optimality. Variants were executed for different values of `MAXLABELS` for the whole set of instances presented in [38]. Table 5.1 shows the mean and the standard deviation (σ) of the execution times required to process those instances.

Table 5.1: Algorithm variants performance for different values of the MAXLABELS parameter.

Algorithm Variant	**MAXLABELS**	**Execution Time $\pm$ σ (s)**
Algorithm 1 $-$ *Version* 1	10	0.003553 $\pm$ 0.001457
	100	0.091609 $\pm$ 0.030957
	1000	8.518455 $\pm$ 2.819210
	10000	841.583881 $\pm$ 277.893114
Algorithm 2 $-$ *Version* 2	10	0.001653 $\pm$ 0.000699
	100	0.003765 $\pm$ 0.001355
	1000	0.022822 $\pm$ 0.007012
	10000	0.216972 $\pm$ 0.066800

Table 5.1 shows that Algorithm 2 clearly outperforms Algorithm 1 when both variants are executed for the same value of MAXLABELS. It is also noteworthy that Algorithm 2 presented acceptable execution times as the parameter MAXLABELS grows. This parameter has to be large enough to store a number of efficient labels arriving at each node, ensuring optimality in large sized instances. For such reasons, Algorithm 2 was chosen and from now on can be referred as the dynamic programming labeling algorithm. For the computational tests that follow, the value of the parameter MAXLABELS assumed was 10, which was enough to ensure optimality for the set of instances available.

Instances are based on real data collected in [38] with the CNT from February 27 to March 20, 2014. Each instance corresponds to a real case in which an organ was available for transplantation and a list of possible destinations, in order of priority, was provided. The airport network is composed by 32 Brazilian airports, one airport for each state capital plus some airports considered relevant, e.g. an airport base of a Brazilian airline. The flight network is composed of all commercial flights operated by Brazilian airlines between these 32 airports.

Instances names are composed by a C letter followed by two numbers representing the number of the case (e.g. C01). For each case, instances were created from the priority destination until the real destination chosen. Table 5.2, which is adapted from [38], illustrates these cases and shows in bold and red the real destinations chosen by CNT.

Table 5.2: Cases and destination chosen by CNT among a ranked receivers list.

Case	Organ	Origin	Priority order of destination								
			1^{st}	2^{nd}	3^{rd}	4^{th}	5^{th}	6^{th}	7^{th}	8^{th}	9^{th}
C01	Kidney	SBSV	SBRF	SBFZ	SBRJ	**SBVT**	SBBH				
C02	Kidneys	SBRJ	SBVT	SBBH	SBRF	SBCT	**SBPA**				
C03	Kidneys	SBFZ	**SBRF**	SBRJ	SBVT	SBBR					
C04	Kidney	SBSV	SBRF	SBFZ	**SBPA**	SBBR	SBBH				
C05	Liver	SBBH	**SBVT**	SBRJ	SBCT	SBRF	SBPA				
C06	Kidneys	SBBH	SBRJ	SBVT	**SBPA**						
C07	Liver	SBCG	SBRF	**SBBR**	SBRJ	SBVT	SBBH	SBPA			
C08	Heart	SBCG	**SBSP**	SBBR							
C09	Kidneys	SBCG	**SBSP**	SBEG	SBBE	SBBR	SBGO	SBRF			
C10	Liver	SBSV	**SBRF**	SBFZ	SBRJ	SBCT	SBVT	SBBR	SBBH		
C11	Kidney	SBRB	**SBRF**	SBBR	SBBE	SBGO					
C12	Kidney	SBRB	SBRF	**SBGR**	SBBR	SBBE	SBGO				
C13	Liver	SBRB	**SBBR**	SBRJ	SBVT	SBRF	SBFZ				
C14	Liver	SBNT	SBSV	SBRF	**SBFZ**	SBRJ	SBBR	SBCT	SBVT		
C15	Kidney	SBFL	**SBSP**	SBPA	SBCT	SBRJ	SBRF	SBBH	SBBE	SBVT	
C16	Kidney	SBFL	SBPA	**SBCT**	SBRJ	SBRF	SBBH	SBBE	SBVT		
C17	Kidney	SBFL	SBRF	**SBSP**	SBPA						
C18	Liver	SBNT	SBRF	**SBFZ**	SBRJ	SBBR	SBVT	SBCT			
C19	Liver	SBNT	**SBGR**	SBRF	SBFZ	SBCT	SBRJ	SBBR	SBVT		
C20	Liver	SBSV	**SBFZ**	SBRF	SBRJ	SBBR					
C21	Kidney	SBFZ	SBSV	SBMO	**SBPA**	SBRJ	SBBE	SBTE	SBJP	SBRF	SBSL
C22	Kidneys	SBFZ	SBSV	SBMO	SBJP	SBRF	SBNT	**SBTE**			
C23	Heart	SBGO	**SBBR**								
C24	Lung	SBGO	**SBBR**								
C25	Liver	SBGO	**SBBR**	SBRJ	SBVT	SBPE	SBCE	SBPR			

The destination choosing task was performed manually by CNT technicians as they search for flights on the major Brazilian airlines websites, which can easily incur in a not fair choice in respect to priority and a suboptimal route. In fact, one can observe in Table 5.2 that in twelve cases the first priority receiver was not contemplated. This reality, however, can be changed by the algorithm results.

5.2 Results of the dynamic programming labeling algorithm

Before presenting the results, it is necessary to state that the answers presented in the following tables were obtained with the penalty parameter P equal to 30 minutes.

In addition, the times involved in the transplantation process have to be defined. Let D_{cg} be an organ dependant time required to perform the removal surgery. Let D_{hs} be the time necessary to transport the organ from the donor's hospital to the origin airport s, and D_{th} be the time necessary to transport the organ from the destination airport t to the recipient's hospital. Let D_{st} be the time elapsed since the moment an organ is available for transportation at the origin airport s ($H_{available}$) until its arrival in the destination airport t (T_t). Let D_{max} be the maximum time available to perform the transportation from airport s to airport t. Therefore, the following inequality holds: $D_{st} \leq D_{max}$. Finally, let the maximum cold ischemia time - CIT_{max} be a variable which corresponds to the organ maximum preservation time. Table 5.3 presents the values assumed for this parameter, as in [38].

Table 5.3: Composition of times and values assumed in cases proposed in [38].

Organ	$\mathbf{CIT_{max}}$	$\mathbf{D_{cg}}$	$\mathbf{D_{hs}}$	$\mathbf{D_{th}}$	$\mathbf{D_{max}}$
Heart	04:00	00:30	00:30	00:30	02:30
Lung	06:00	00:30	00:30	00:30	04:30
Liver	12:00	00:40	00:30	00:30	10:20
Pancreas	20:00	01:00	00:30	00:30	18:00
Kidney	36:00	01:20	00:30	00:30	33:40

Table 5.4 shows the comparison between the paths built by CNT and those provided by the dynamic programming labeling algorithm for the same destination, with differences highlighted in bold and red. Column Difference shows the difference in the transportation times (D_{st}) between routes built manually and the ones

provided by the algorithm. In cases where the transportation was made by a charter aircraft or by an aircraft from the Brazilian Air Force (FAB), it is not possible to calculate this difference. However, except for case C08, one can observe that it would be possible to perform this transportation with the aid of commercial flights. In addition, the CIT reduction column shows the percentage gain in the cold ischemia time. In cases where it is possible to compare paths and times, the algorithm has been shown to reduce the CIT by 37,46% on average. When only the time to transport the organ from the origin airport to the destination airport (D_{st}) is analyzed, the reduction increased to 44,17% on average.

Table 5.4: Comparison between the paths built by CNT and the ones provided by the algorithm for the same destination. Adapted from [38].

	Real path			Shortest path (algorithm)				
Case	**Path**	$\mathbf{D_{st}}$	**CIT**	**Path**	$\mathbf{D_{st}}$	**CIT**	**Difference**	**CIT Reduction (%)**
C01	SBSV-**SBBH**-SBVT	08:11	10:31	SBSV-**SBGR**-SBVT	05:18	07:38	02:53	27,42
C02	SBRJ-SBPA	17:42	20:02	SBRJ-SBPA	02:38	04:58	15:03	75,12
C03	SBFZ-SBRF	09:51	12:11	SBFZ-SBRF	03:55	06:15	05:55	48,56
C04	SBSV-SBGR-SBPA	19:50	22:10	SBSV-SBGR-SBPA	04:35	06:55	15:14	68,72
C05	SBBH-SBVT	07:03	08:43	SBBH-SBVT	05:29	07:09	01:34	17,97
C06	**SBBH-SBSP**-SBPA	06:51	09:11	**SBBH**-SBPA	05:35	07:55	01:15	13,61
C07	SBCG-SBBR	FAB	aircraft	SBCG-**SBKP**-SBBR	05:25	07:05	N/A	N/A
C08	SBCG-SBSP	Charter	aircraft	**Infeasible**	N/A	N/A	N/A	N/A
C09	SBCG-SBSP	Charter	aircraft	SBCG-SBSP	10:35	12:55	N/A	N/A
C10	SBSV-SBRF	06:21	08:01	SBSV-SBRF	04:52	06:32	01:28	18,30
C11	SBRB-SBBR-SBRF	09:18	11:38	SBRB-SBBR-SBRF	09:18	11:38	00:00	0,00
C12	SBRB-SBBR-SBGR	08:30	10:50	SBRB-SBBR-SBGR	08:13	10:33	00:16	2,46
C13	SBRB-SBBR	06:45	08:25	SBRB-SBBR	06:41	08:21	00:03	0,59
C14	SBNT-SBFZ	06:37	08:17	SBNT-**SBRF**-SBFZ	04:39	06:19	01:58	23,74
C15	SBFL-SBSP	15:44	18:04	SBFL-SBSP	01:35	03:55	14:08	78,23
C16	SBFL-**SBPA**-SBCT	16:47	19:07	SBFL-**SBSP**-SBCT	03:13	05:33	13:33	70,88
C17	SBFL-SBSP	17:10	19:30	SBFL-SBSP	03:11	05:31	13:58	71,62
C18	SBNT-SBFZ	03:54	05:34	SBNT-SBFZ	03:43	05:23	00:10	2,99
C19	SBNT-SBGR	06:32	08:12	SBNT-SBGR	04:22	06:02	02:10	26,42
C20	SBSV-**SBNT**-SBFZ	04:07	05:47	SBSV-SBFZ	02:15	03:55	01:51	31,99
C21	SBFZ-SBGR-SBPA	20:05	22:25	SBFZ-SBGR-SBPA	06:20	08:40	13:44	61,26
C22	SBFZ-**SBBR**-SBTE	21:33	23:53	SBFZ-SBTE	04:23	06:43	17:09	71,81
C23	SBGO-SBBR	FAB	aircraft	SBGO-SBBR	02:24	03:54	N/A	N/A
C24	SBGO-SBBR	FAB	aircraft	SBGO-SBBR	02:24	03:54	N/A	N/A
C25	SBGO-SBBR	FAB	aircraft	SBGO-SBBR	02:14	03:54	N/A	N/A

N/A - Not Available. It was not possible to calculate the Difference column because there is no data available on Charter or Military flights.

Although these results are promising, they were already achieved in [38]. The main contribution of this work resides on the fact that the algorithm can compute the shortest path between all airports in a fraction of the time required to solve a single instance of the mathematical model with the aid of a commercial solver. The algorithm can almost instantly return different solutions in respect to the penalty P and ensure optimality. In addition, it is free and does not incur additional costs, such as the cost of a solver license acquisition by the CNT.

Table 5.5 shows for all instances the paths found by the dynamic programming algorithm, the instant of time when the organ was available for transportation at the origin airport ($H_{available}$), the arrival time in the destination airport (T_t), the difference between these times, which correspond to the transportation time (D_{st}), and the execution time of the dynamic programming algorithm. One may observe that the set of instances on which the algorithm is tested corresponds to all Cases presented in Table 5.2. For each Case, instances were generated from the origin to destination airports in increasing order of priority, up to the real destination chosen by CNT was reached.

Table 5.5: Results and execution time of the dynamic programming labeling algorithm.

Instance	Path	$\mathbf{H_{available}}$	$\mathbf{T_t}$	$\mathbf{D_{st}}$	Execution Time (s)
C01 SBRF	SBSV-SBRF	02:42	07:27	04:45	0.002050
C01 SBFZ	SBSV-SBRF-SBFZ	02:42	09:24	06:42	0.002061
C01 SBRJ	SBSV-SBRJ	02:42	07:23	04:41	0.001948
C01 SBVT	SBSV-SBGR-SBVT	02:42	08:00	05:18	0.001973
C02 SBVT	SBRJ-SBVT	06:49	08:23	01:33	0.002354
C02 SBBH	SBRJ-SBBH	06:49	08:18	01:28	0.001976
C02 SBRF	SBRJ-SBRF	06:49	10:21	03:31	0.001912
C02 SBCT	SBRJ-SBCT	06:49	08:18	01:28	0.002014
C02 SBPA	SBRJ-SBPA	06:49	09:28	02:38	0.002058
C03 SBRF	SBFZ-SBRF	09:34	13:29	03:54	0.001884
C04 SBRF	SBSV-SBRF	13:34	15:48	02:13	0.002108
C04 SBFZ	SBSV-SBFZ	13:34	15:10	01:35	0.001885
C04 SBPA	SBSV-SBGR-SBPA	13:34	18:10	04:35	0.001503
C05 SBVT	SBBH-SBVT	02:52	08:21	05:28	0.001015
C06 SBRJ	SBBH-SBRJ	03:31	07:09	03:37	0.001964
C06 SBVT	SBBH-SBVT	03:31	08:21	04:49	0.002006
C06 SBPA	SBBH-SBPA	03:31	09:07	05:35	0.002192
C07 SBRF	SBCG-SBGR-SBRF	18:45	02:03*	07:18	0.001752
C07 SBBR	SBCG-SBKP-SBBR	18:45	00:10*	05:25	0.001542
C08 SBGR	Infeasible	18:34	N/A	N/A	0.000113
C08 SBKP	SBCG-SBKP	18:34	20:33	01:58	0.000115

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Table 5.5 – continued from previous page

Instance	Path	$H_{available}$	T_t	D_{st}	Execution Time (s)
C08 SBRP	Infeasible	18:34	N/A	N/A	0.000123
C08 SBSP	Infeasible	18:34	N/A	N/A	0.000117
C09 SBGR	SBCG-SBGR	19:25	21:22	01:57	0.001951
C09 SBKP	SBCG-SBGR-SBCY-SBKP	19:25	04:42*	09:17	0.002147
C09 SBRP	SBCG-SBGR-SBRP	19:25	23:16	03:51	0.002223
C09 SBSP	SBCG-SBSP	19:25	06:00*	10:35	0.002646
C10 SBRF	SBSV-SBRF	02:34	07:27	04:53	0.001046
C11 SBRF	SBRB-SBBR-SBRF	01:30	10:48	09:18	0.001809
C12 SBRF	SBRB-SBBR-SBRF	01:30	10:48	09:18	0.001951
C12 SBSP	SBRB-SBBR-SBSP	01:30	09:58	08:28	0.001922
C12 SBKP	SBRB-SBBR-SBKP	01:30	09:52	08:22	0.001874
C12 SBRP	SBRB-SBBR-SBGR-SBRP	01:30	11:57	10:27	0.002136
C12 SBGR	SBRB-SBBR-SBGR	01:30	09:43	08:13	0.001978
C13 SBBR	SBRB-SBBR	00:49	07:31	06:41	0.000399
C14 SBSV	SBNT-SBRF-SBSV	04:45	08:52	04:07	0.001468
C14 SBRF	SBNT-SBRF	04:45	07:22	02:37	0.001118
C14 SBFZ	SBNT-SBRF-SBFZ	04:45	09:24	04:39	0.001192
C15 SBGR	SBFL-SBGR	16:19	18:10	01:50	0.001870
C15 SBKP	SBFL-SBKP	16:19	21:12	04:52	0.001769
C15 SBRP	SBFL-SBSP-SBRP	16:19	20:16	03:57	0.001831
C15 SBSP	SBFL-SBSP	16:19	17:56	01:36	0.001983
C16 SBPA	SBFL-SBPA	16:19	18:33	02:13	0.002748
C16 SBCT	SBFL-SBSP-SBCT	16:19	19:33	03:14	0.002059
C17 SBRF	SBFL-SBGR-SBRF	14:04	21:37	07:33	0.002546
C17 SBGR	SBFL-SBGR	14:04	16:42	02:37	0.002113
C17 SBKP	SBFL-SBKP	14:04	21:12	07:07	0.002219
C17 SBRP	SBFL-SBSP-SBRP	14:04	20:16	06:12	0.002969
C17 SBSP	SBFL-SBSP	14:04	17:16	03:11	0.001918
C18 SBRF	SBNT-SBRF	11:48	16:16	04:28	0.000760
C18 SBFZ	SBNT-SBFZ	11:48	15:31	03:43	0.000839
C19 SBSP	SBNT-SBRJ-SBSP	00:52	07:31	06:38	0.000744
C19 SBKP	SBNT-SBKP	00:52	05:33	04:40	0.000685
C19 SBRP	SBNT-SBGR-SBRP	00:52	08:52	07:59	0.000716
C19 SBGR	SBNT-SBGR	00:52	05:15	04:22	0.000700
C20 SBFZ	SBSV-SBFZ	12:55	15:10	02:14	0.000914
C21 SBSV	SBFZ-SBRF-SBSV	16:49	20:49	04:00	0.002304
C21 SBMO	SBFZ-SBRF-SBMO	16:49	20:42	03:52	0.002255
C21 SBPA	SBFZ-SBGR-SBPA	16:49	23:10	06:20	0.002330
C22 SBSV	SBFZ-SBNT-SBSV	01:49	06:04	04:15	0.002222
C22 SBMO	SBFZ-SBGR-SBMO	01:49	08:57	07:08	0.001899
C22 SBJP	SBFZ-SBRJ-SBJP	01:49	11:00	09:10	0.001959
C22 SBRF	SBFZ-SBNT-SBRF	01:49	07:22	05:33	0.001871
C22 SBNT	SBFZ-SBNT	01:49	03:10	01:20	0.001758

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Table 5.5 – continued from previous page

Instance	Path	$H_{available}$	T_t	D_{st}	Execution Time (s)
C22 SBTE	SBFZ-SBTE	01:49	06:13	04:24	0.002068
C23 SBBR	SBGO-SBBR	04:36	07:00	02:24	0.000121
C24 SBBR	SBGO-SBBR	04:36	07:00	02:24	0.000339
C25 SBBR	SBGO-SBBR	04:46	07:00	02:13	0.001378

* the organ arrives the day after departure.

The results from Table 5.5 can be compared with the results in [38]. The authors report times of execution varying from 5 seconds to 10 minutes, depending on the instance, but since 10 minutes was defined as the maximum time of execution of the MILP formulation by solver ILOG CPLEX 12.5 and the authors reported optimization GAPs for some instances, for the sake of comparison, the performance of the algorithm will be compared with the upper bound.

For most instances the results are the same, although it is not possible to know if CPLEX proved optimality within the 10 minutes execution time. The dynamic programming algorithm proposed in this Thesis, however, has found the optimal solution, always equal or better than the obtained by the solver, almost instantly. Table 5.6 shows cases where the solution found by the algorithm differs from those obtained with the aid of CPLEX. Since these latter solutions are not optimal, one can deduce that the solver ran for 10 minutes and provided a suboptimal solution. However, it is important to remind that this time value (600 seconds) must be multiplied by the computers conversion factor, equal to 0.3, thus resulting in execution times of 180 seconds.

Table 5.6: Paths and time comparison between CPLEX and algorithm solutions, respectively.

Instance	MILP formulation with ILOG CPLEX 12.5			Dynamic programming labeling algorithm		
	Path	$\mathbf{T_t}$	**Time (s)**	**Path**	$\mathbf{T_t}$	**Time (s)**
C01 SBRJ	SBSV-SBKP-SBRJ	07:22	180‡	SBSV-SBRJ	07:23	0.001948
C07 SBRF	No viable solution found	N/A	180‡	SBCG-SBGR-SBRF	02:03*	0.001752
C09 SBKP	SBCG-SBKP	12:10*	180‡	SBCG-SBGR-SBCY-SBKP	04:42*	0.002147
C17 SBKP	SBFL-SBPA-SBKP	21:16	180‡	SBFL-SBKP	21:12	0.002219
C22 SBMO	SBFZ-SBNT-SBRF-SBMO	08:40	180‡	SBFZ-SBGR-SBMO	08:57	0.001899
C22 SBJP	SBFZ-SBNT-SBSV-SBMO-SBJP	11:00	180‡	SBFZ-SBRJ-SBJP	11:00	0.001959

* the organ arrives the day after departure.

‡ the computational times of [38] were multiplied by 0.3 in order to fairly compare the results, as mentioned in the beginning of this chapter.

5.3 The effect of the penalty

As stated before, for Tables 5.4, 5.5 and 5.6, all solutions presented were calculated with the penalty parameter P equal to 30 minutes. For instance, one can observe that in Table 5.6, the solutions provided by the algorithm for instances C01 SBRJ and C22 SBMO reach the final airport destination later when compared to the solutions provided by CPLEX. However, the solutions found by CPLEX prescribe more flights, and therefore represent suboptimal solutions.

One can remember that the addition of the penalty intended to give solutions a better balance between arrival time and the number of flights. To better visualize this effect when choosing the optimal solution, Table 5.7 shows the solutions with the penalty P equals to zero and 30 minutes, where they differ. To facilitate the understanding of choosing one solution over the other, column f_{obj} shows the value of the solution, calculated by summing the arrival time in the destination airport (T_t) with the number of flights multiplied by the value of the penalty P, as in Objective Function (3.6).

Table 5.7: The effect of the penalty in solutions.

	P = 0				P = 30 minutes			
Instance	**Path**	$\mathbf{T_t}$	**Flights**	$\mathbf{f_{obj}}$	**Path**	$\mathbf{T_t}$	**Flights**	$\mathbf{f_{obj}}$
C01 SBRJ	SBSV-SBKP-SBRJ	07:22	2	08:22	SBSV-SBRJ	07:23	1	07:53
C07 SBRF	SBCG-SBKP-SBRJ-SBRF	01:53*	3	03:23*	SBCG-SBGR-SBRF	02:03*	2	03:03*
C09 SBSP	SBCG-SBGR-SBCY-SBSP	05:57*	3	07:27*	SBCG-SBSP	06:00*	1	06:30*
C17 SBKP	SBFL-SBSP-SBRJ-SBKP	20:23	3	21:53	SBFL-SBKP	21:12	1	21:42
C22 SBMO	SBFZ-SBNT-SBRF-SBMO	08:40	3	10:10	SBFZ-SBGR-SBMO	08:57	2	09:57

* the organ arrives the day after departure.

As the number of flights required to traverse the path from the origin to the destination airport increases, the probability of an unforeseen event, such as a flight cancellation due to bad weather or even a delay, also increases. In addition, flight connections require a handling of the organ, which also must be avoided. For such reasons, taking into account that connections should be avoided when possible, Table 5.7 shows how the penalty can help in providing better solutions.

In instance C01 SBRJ, the addition of the penalty in the objective function provides an optimal path that arrives just one minute later but uses one less flight in comparison with the optimal solution for $P = 0$. In that sense, the effect of the penalty in instance C09 SBSP is even more dramatic. Instead of providing the earliest arrival time in a chain of 3 flights for $P = 0$, the dynamic programming labeling algorithm with $P = 30\ minutes$ provides a solution that uses one direct flight from the origin to the destination airport with the cost of arriving just 3 minutes later.

Chapter 6

Conclusions

This Thesis presented a dynamic programming labeling algorithm to solve the transportation of organs for transplantation problem. The algorithm minimizes the arrival time and the total number of flights used. Based on the literature review of resource-constrained shortest path problems, this approach differs from the previous attempt on the literature to solve this problem since it does not depends on a commercial solver and can provide the optimal path (if one exists) with low execution times.

As reported in [38], the commercial solver CPLEX could not solve some instances to optimality within 10 minutes of execution. It is also reported in [38] that for some instances CPLEX ran more than two hours without finding the optimal solution. The dynamic programming labeling algorithm, however, has found the optimal solution for all instances.

Comparing the algorithm's solutions with the routes taken in reality, shows, on average, a potential to reduce the CIT by 37,46% and the transportation time by 44,17%. The results also show that the automation of the task performed by CNT technicians could lead in a more fair choice of the receiver in respect to the priority list.

It is also noteworthy to mention that the algorithm computes all solutions from the origin towards all airports and can price them according to the penalty defined by the modeler. For instance, in case C22 the algorithm found the optimal solution for six possible destinations with the penalty $P = 0$ and $P = 30$ *minutes*. In a commercial solver utilization context, this would be equivalent to twelve instances, which would require to be solved one at a time.

The dynamic programming labeling algorithm can solve the problem efficiently and could have a great impact on the quality of the job performed by CNT technicians and in the post intervention life of organ receivers. Naturally, a future step is the implementation of this algorithm in the CNT system, which requires the development of an user-friendly graphical user interface whereby technicians can easily enter data such as organ, origin and a ranked list of destinations. As mentioned before, the algorithm can be adapted to check if it is possible to transport an organ for a potential recipient, and, in the absence of a feasible chain of flights, check the next candidate, until a recipient is found.

In that sense, it is important to reaffirm that the algorithm could return paths between multiple origin-destination pairs without having to be recalculated. Since the CNT system has access to all flights being operated between Brazilian airports, the number of nodes and arcs is expected to have a sharp increase in comparison with the instances proposed in [38], consequently requiring higher execution times. In order to investigate the performance of the algorithm in larger air transportation networks, a next and necessary step is the generation of larger instances of the problem.

In addition, as seen in Table 5.4, in one case the recipient could not be reached with commercial flights but the organ was transported in feasible time by a charter aircraft. Before offering an organ to a next recipient, it is necessary to contact the current candidate and ask if he is able to cover the transportation costs in order to be transplanted. This is useful in restricted operating scenarios but also requires further adjustments of the algorithm before its release in the CNT system.

Finally, the implementation of the algorithm and its use by CNT technicians will enable further research on organ transportation, the algorithm efficiency in practice and its effects in transplantation rates and outcomes in the mid and long terms.

Bibliography

[1] "Central Nacional de Transplantes (CNT)". Ministério da Saúde - Go-verno Federal - Brasil http://portalms.saude.gov.br/saude-de-a-z/doacao-de-orgaos/central-nacional-de-transplantes. (Accessed on 02/02/2019).

[2] "Definition of cold ischemia time - The NCI Dictionary of Cancer Terms". National Cancer Institute (NCI) https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cold-ischemia-time. (Accessed on 02/03/2019).

[3] "Doação de Órgãos: transplantes, lista de espera e como ser doador". Ministério da Saúde - Governo Federal - Brasil http://portalms.saude.gov.br/saude-de-a-z/doacao-de-orgaos. (Accessed on 02/03/2019).

[4] "Learn about the Donor Matching System - OPTN". Organ Procurement and Transplantation Network https://optn.transplant.hrsa.gov/learn/about-transplantation/donor-matching-system/. (Accessed on 02/03/2019).

[5] "El Modelo Español - ONT". Organización Nacional de Trasplantes http://www.ont.es/home/Paginas/ElModeloEspanol.aspx. (Accessed on 02/03/2019).

[6] "¿En qué consiste exactamente el modelo español? - ONT". Organización Nacional de Trasplantes http://www.ont.es/home/Paginas/Enqueconsiste.aspx. (Accessed on 02/03/2019).

[7] "¿Es trasladable este modelo a cualquier país? - ONT". Organización Nacional de Trasplantes http://www.ont.es/home/Paginas/Estrasladable.aspx. (Accessed on 02/03/2019).

[8] "Living donation". United Network for Organ Sharing https://unos.org/donation/living-donation/. (Accessed on 12/28/2018).

[9] "Regulamento Técnico do Sistema Nacional de Transplantes - PORTARIA N^o 2.600, DE 21 DE OUTUBRO DE 2009". Ministério da Saúde - Governo Federal - Brasil http://bvsms.saude.gov.br/bvs/saudelegis/gm/2009/prt2600_21_10_2009.html. (Accessed on 02/03/2019).

[10] "Myths and misconceptions". Australian Organ and Tissue Donation and Transplantation Authority https://donatelife.gov.au/about-donation/get-facts/myths-and-misconceptions. (Accessed on 01/05/2019).

[11] "Organ Donation and Transplantation Statistics". National Kidney Foundation https://www.kidney.org/news/newsroom/factsheets/Organ-Donation-and-Transplantation-Stats. (Accessed on 12/27/2018).

[12] "Find your Local Organ Procurement Organization". U.S. Government Information on Organ Donation and Transplantation https://www.organdonor.gov/awareness/organizations/local-opo.html. (Accessed on 02/03/2019).

[13] "Organ facts and surgeries - Transplant Living". United Network for Organ Sharing https://transplantliving.org/organ-facts/. (Accessed on 01/02/2019).

[14] "Paraná tem o maior perfil de doadores de órgãos do País". Folha de Londrina https://www.folhadelondrina.com.br/geral/parana-tem-o-maior-perfil-de-doadores-de-orgaos-do-pais-1016550 html. (Accessed on 02/03/2019).

[15] "Policies - OPTN". Organ Procurement and Transplantation Network https://optn.transplant.hrsa.gov/governance/policies/. (Accessed on 02/03/2019).

[16] "Regions - UNOS". United Network for Organ Sharing https://unos.org/transplantation/matching-organs/regions/. (Accessed on 02/03/2019).

[17] "Sistemas integrados viabilizam os transplantes no País". Governo Federal - Brasil http://www.brasil.gov.br/noticias/saude/2016/09/sistemas-integrados-viabilizam-os-transplantes-no-pais. (Accessed on 02/03/2019).

[18] “Portaria N^o 91/GM de 23 de janeiro de 2001”. Ministério da Saúde - Governo Federal - Brasil http://www.saude.ba.gov.br/wp-content/uploads/2017/07/TRANSPLANTES_PORTARIAGM_91_23JANEIRO2001.pdf. (Accessed on 02/03/2019).

[19] “Transporte aéreo de órgãos e tecidos para transplantes em 2017 já é maior do que em 2016”. Ministério da Infraestrutura - Governo Federal - Brasil http://www.transportes.gov.br/ultimas-noticias/6421-n. (Accessed on 02/02/2019).

[20] . “United Network for Organ Sharing - UNOS”. https://unos.org/about/, . (Accessed on 02/03/2019).

[21] . “Frequently asked questions - Matching organs - Saving lives”. United Network for Organ Sharing https://unos.org/transplantation/faqs/, . (Accessed on 02/03/2019).

[22] . “Matching organs”. United Network for Organ Sharing https://unos.org/transplantation/matching-organs/, . (Accessed on 01/05/2019).

[23] . “Global Glossary of Terms and Definitions on Donation and Transplantation - Geneva - November 2009”. World Health Organization and others https://www.who.int/transplantation/activities/GlobalGlossaryonDonationTransplantation.pdf?ua=1, . (Accessed on 11/26/2018).

[24] . “Donation and transplantation”. World Health Organization https://www.who.int/transplantation/donation/en/, . (Accessed on 12/27/2018).

[25] . “NEWSLETTER TRANSPLANT - International figures on donation and transplantation”. European Directorate for the Quality of Medicines & HealthCare of the Council of Europe https://www.organdonation.dk/siteassets/tal/nogletal-europa/nogletal-2018newsletter/newsletter-transplan-2017-volume-23-2018.pdf, . (Accessed on 11/26/2018).

[26] . “Guide to the Quality and Safety of Organs for Transplantation - 7th edition”. European Directorate for the Quality of Medicines & HealthCare of the Council of Europe https://www.edqm.eu/en/news/

new-release-7th-edition-guide-quality-and-safety-organs-transpla
. (Accessed on 11/26/2018).

[27] "Organ Donation Statistics". U.S. Government Information on Organ Donation and Transplantation https://www.organdonor.gov/statistics-stories/statistics.html. (Accessed on 11/26/2018).

[28] AHMADI-JAVID, A., SEYEDI, P., SYAM, S. S., 2017, "A survey of healthcare facility location", *Computers & Operations Research*, v. 79, pp. 223 – 263. ISSN: 0305-0548. doi: https://doi.org/10.1016/j.cor.2016.05.018. Available at: <http://www.sciencedirect.com/science/article/pii/S0305054816301253>.

[29] ALAGOZ, O., SCHAEFER, A. J., ROBERTS, M. S., 2009, "Optimizing organ allocation and acceptance". In: *Handbook of optimization in medicine*, Springer, pp. 1–24.

[30] ANEJA, Y., AGGARWAL, V., NAIR, K., 1983, "Shortest chain subject to side constraints", *Networks*, v. 13, n. 2, pp. 295–302. doi: 10.1002/net.3230130212.

[31] ARES, J. N., DE VRIES, H., HUISMAN, D., 2016, "A column generation approach for locating roadside clinics in Africa based on effectiveness and equity", *European Journal of Operational Research*, v. 254, n. 3 (nov), pp. 1002–1016. doi: 10.1016/j.ejor.2016.04.031. Available at: <https://doi.org/10.1016/j.ejor.2016.04.031>.

[32] ARRUDA, E. F., PEREIRA, B. B., THIERS, C. A., et al., 2018, "Optimal testing policies for diagnosing patients with intermediary probability of disease", *Artificial Intelligence in Medicine*, (dec). doi: 10.1016/j.artmed.2018.11.005. Available at: <https://doi.org/10.1016/j.artmed.2018.11.005>.

[33] BELIËN, J., BOECK, L. D., COLPAERT, J., et al., 2013, "Optimizing the facility location design of organ transplant centers", *Decision Support Systems*, v. 54, n. 4, pp. 1568 – 1579. ISSN: 0167-9236. doi: https://doi.org/10.1016/j.dss.2012.05.059. Available at: <http://www.sciencedirect.com/science/article/pii/S0167923612001807>. Rapid Modeling for Sustainability.

[34] BELLMAN, R., 1954, *The theory of dynamic programming.* Technical report, RAND Corp Santa Monica CA.

[35] BELLMAN, R., 1958, "On a routing problem", *Quarterly of applied mathematics*, v. 16, n. 1, pp. 87–90.

[36] BRUNI, M. E., CONFORTI, D., SICILIA, N., et al., 2006, "A new organ transplantation location–allocation policy: a case study of Italy", *Health Care Management Science*, v. 9, n. 2 (may), pp. 125–142. doi: 10.1007/s10729-006-7661-z. Available at: <https://doi.org/10.1007/s10729-006-7661-z>.

[37] CACCHIANI, V., MALANDRI, C., MANTECCHINI, L., et al., 2018, "A study on the optimal aircraft location for human organ transportation activities", *Transportation Research Procedia*, v. 30, pp. 314 – 323. ISSN: 2352-1465. doi: https://doi.org/10.1016/j.trpro.2018.09.034. Available at: <http://www.sciencedirect.com/science/article/pii/S2352146518301078>. EURO Mini Conference on "Advances in Freight Transportation and Logistics".

[38] CARRARA, B. A., RIBEIRO, G. M., JUNIOR, I. C. L., et al., 2018, "OPTIMIZING THE ORGAN TRANSPORTATION FOR TRANSPLANT IN BRAZIL BY COMMERCIAL DOMESTIC FLIGHTS", *International Journal of Transport Economics*, v. XLV, n. 2, pp. 185–210. doi: 10.19272/201806702001.

[39] DASKIN, M. S., DEAN, L. K., 2005, "Location of health care facilities". In: *Operations research and health care*, Springer, pp. 43–76.

[40] DESROCHERS, M., 1986, *La fabrication d'horaires de travail pour les conducteurs d'autobus par une méthode de génération de colonnes.* Université de Montréal, Centre de recherche sur les transports.

[41] DESROCHERS, M., SOUMIS, F., 1988, "A Generalized Permanent Labelling Algorithm For The Shortest Path Problem With Time Windows", *INFOR: Information Systems and Operational Research*, v. 26, n. 3, pp. 191–212. doi: 10.1080/03155986.1988.11732063.

[42] DESROSIERS, J., PELLETIER, P., SOUMIS, F., 1983, "Plus court chemin avec contraintes d'horaires", *RAIRO-Operations Research*, v. 17, n. 4, pp. 357–377.

[43] DIJKSTRA, E. W., 1959, "A note on two problems in connexion with graphs", *Numerische mathematik*, v. 1, n. 1, pp. 269–271.

[44] FORD JR, L. R., FULKERSON, D. R., 2015, *Flows in networks*. Princeton university press.

[45] FUZZATI, R., 2005, *Organ Transplantation Management. Swiss Federal Institute of Technology Lausanne (EPFL)*. Technical report, Technical Report.

[46] GALLO, G., PALLOTTINO, S., 1986, "Shortest path methods: A unifying approach". In: *Mathematical Programming Studies*, Springer Berlin Heidelberg, pp. 38–64. doi: 10.1007/bfb0121087.

[47] HANDLER, G. Y., ZANG, I., 1980, "A dual algorithm for the constrained shortest path problem", *Networks*, v. 10, n. 4, pp. 293–309. doi: 10.1002/net.3230100403.

[48] IOACHIM, I., GÉLINAS, S., SOUMIS, F., et al., 1988, "A dynamic programming algorithm for the shortest path problem with time windows and linear node costs", *Networks*, v. 31, n. 3, pp. 193–204. doi: 10.1002/(SICI)1097-0037(199805)31:3⟨193::AID-NET6⟩3.0.CO;2-A.

[49] IRNICH, S., DESAULNIERS, G., 2005, "Shortest Path Problems with Resource Constraints". In: *Column Generation*, pp. 33–65, Boston, MA, Springer US. ISBN: 978-0-387-25486-9. doi: 10.1007/0-387-25486-2_2.

[50] JOKSCH, H., 1966, "The shortest route problem with constraints", *Journal of Mathematical Analysis and Applications*, v. 14, n. 2, pp. 191–197. doi: 10.1016/0022-247X(66)90020-5.

[51] KAYLER, L., YU, X., CORTES, C., et al., 2017, "Impact of Cold Ischemia Time in Kidney Transplants From Donation After Circulatory Death Donors", *Transplantation Direct*, v. 3, n. 7 (jul), pp. e177. doi: 10.1097/txd.0000000000000680. Available at: <https://doi.org/10.1097/txd.0000000000000680>.

[52] KAYLER, L. K., LUBETZKY, M., YU, X., et al., 2017, "Influence of Cold Ischemia Time in Kidney Transplants From Small Pediatric Donors", *Transplantation Direct*, v. 3, n. 7 (jul), pp. e184. doi: 10.1097/txd.0000000000000668. Available at: <https://doi.org/10.1097/txd.0000000000000668>.

[53] KRUSKAL, J. B., 1956, "On the shortest spanning subtree of a graph and the traveling salesman problem", *Proceedings of the American Mathematical society*, v. 7, n. 1, pp. 48–50.

[54] MANTECCHINI, L., PAGANELLI, F., MORABITO, V., et al., 2016, "Transportation of Organs by Air: Safety, Quality, and Sustainability Criteria", *Transplantation Proceedings*, v. 48, n. 2, pp. 304 – 308. ISSN: 0041-1345. doi: https://doi.org/10.1016/j.transproceed.2015.12.050. Available at: <http://www.sciencedirect.com/science/article/pii/S0041134516000713>.

[55] MANTECCHINI, L., PAGANELLI, F., PERITORE, D., et al., 2017, "Transport of Human Organs in Italy: Location, Time, and Performances", *Transplantation Proceedings*, v. 49, n. 4, pp. 622 – 628. ISSN: 0041-1345. doi: https://doi.org/10.1016/j.transproceed.2017.02.033. Available at: <http://www.sciencedirect.com/science/article/pii/S0041134517301689>.

[56] PAN, J., LIU, H., WANG, X., et al., 2015, "Assessing the spatial accessibility of hospital care in Sichuan Province, China", *Geospatial Health*, v. 10, n. 2 (nov). doi: 10.4081/gh.2015.384. Available at: <https://doi.org/10.4081/gh.2015.384>.

[57] PONTICELLI, C. E., 2015, "The impact of cold ischemia time on renal transplant outcome", *Kidney International*, v. 87, pp. 272 – 275. ISSN: 0085-2538. Available at: <https://doi.org/10.1038/ki.2014.359>.

[58] PRIM, R. C., 1957, "Shortest connection networks and some generalizations", *Bell system technical journal*, v. 36, n. 6, pp. 1389–1401.

[59] RAIS, A., VIANA, A., 2010, "Operations Research in Healthcare: a survey", *International Transactions in Operational Research*, v. 18, n. 1, pp. 1–31. doi: 10.1111/j.1475-3995.2010.00767.x. Available at: <https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1475-3995.2010.00767.x>.

[60] RIGHINI, G., SALANI, M., 2006, "Symmetry helps: Bounded bi-directional dynamic programming for the elementary shortest path problem with resource constraints", *Discrete Optimization*, v. 3, n. 3, pp. 255–273. doi: 10.1016/j.disopt.2006.05.007.

[61] TILK, C., ROTHENBÄCHER, A.-K., GSCHWIND, T., et al., 2017, "Asymmetry matters: Dynamic half-way points in bidirectional labeling for solving shortest path problems with resource constraints faster", *European Journal of Operational Research*, v. 261, n. 2, pp. 530–539. doi: 10.1016/j.ejor.2017.03.017.

[62] WOLSEY, L., 1998, *Integer programming*. New York, Wiley. ISBN: 978-0-471-28366-9.

[63] WOLSEY, L. A., NEMHAUSER, G. L., 1999, *Integer and Combinatorial Optimization*. Wiley-Interscience. ISBN: 0471359432.

[64] ZAHIRI, B., TAVAKKOLI-MOGHADDAM, R., MOHAMMADI, M., et al., 2014, "Multi-objective design of an organ transplant network under uncertainty", *Transportation Research Part E: Logistics and Transportation Review*, v. 72, pp. 101 – 124. ISSN: 1366-5545. doi: https://doi.org/10.1016/j.tre.2014.09.007. Available at: <http://www.sciencedirect.com/science/article/pii/S1366554514001616>.

[65] ZHU, L., ZHONG, S., TU, W., et al., 2019, "Assessing Spatial Accessibility to Medical Resources at the Community Level in Shenzhen, China", *International Journal of Environmental Research and Public Health*, v. 16, n. 2 (jan), pp. 242. doi: 10.3390/ijerph16020242. Available at: <https://doi.org/10.3390/ijerph16020242>.