ORPHAN DRUG LOGISTICS

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By
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Orphan Drug Logistics
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We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

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ABSTRACT

ORPHAN DRUG LOGISTICS

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"Orphan drugs" are medical products that are developed to treat orphan diseases. Since they are required by a small number of population, the pharmaceutical industry is not interested much in them. Hence they are produced in small amounts and they are difficult to attain. Moreover, patients may need them urgently. There are regulations for the transportation of orphan drugs to the patient. Those regulations differ among the countries. In this thesis, we focus on the logistics of the orphan drugs motivated by the application in Turkey. We analyze the implementation dynamics of Turkey and define related Operational Research (OR) problems. The overall problem can be considered as an application of location-routing problem. We identify four performance measures based on urgency and ambulance scarcity. The primal aim in the current system is to serve the patient in need at short notice. Therefore, the minimization of the total distance is chosen to be the first performance measure. However, due to scarcity of ambulances in each city, the total extra disturbance, the maximum extra disturbance and the total number of cities disturbed are also analyzed. The problem includes multi-criteria optimization and the ϵ-constraint method is used to analyze the Pareto-optimal solutions. Turkey case is considered for computational analysis.

Keywords: Healthcare Systems, Orphan drugs, Multi-criteria optimization, Pareto analysis.

ÖZET

YETİM İLAÇLARIN LOJİSTİĞİ

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"Yetim ilaçlar" yetim hastalıklarını tedavi etmek için geliştirilen tıbbi ürünlerdir. Az sayıda hasta bu tarz ilaçlara ihtiyaç duyduğu için, ilaç endüstrisi yetim ilaçlar ile pek ilgilenmemektedir. Bu nedenle küçük miktarlarda üretilmektedirler ve tedarik edilmeleri zordur. Ayrıca, bazı durumlarda yetim ilaçların hastalara acil olarak ulaştırılması gerekmektedir. Yetim ilaçların hastaya ulaştırılması için bazı düzenlemeler vardır. Bu düzenlemeler ülkeler arasında farklılık göstermektedir. Bu tezde, Türkiye özelindeki uygulama kapsamında yetim ilaçların lojistiğine odaklanılmıştır. Türkiye'deki uygulama dinamiklerini analiz edilmiştir ve ilgili Yöneylem Araştırması (YA) problemi tanımlanmıştır. Genel problem konumlandırma ve rotalama probleminin bir uygulaması olarak düşünülebilir. Aciliyet ve ambulans azlığına göre dört performans ölçütü tespit edilmiştir. Mevcut sistemdeki temel amaç ilaca ihtiyacı olan hastaya kısa sürede ilacı yetiştimektir. Bu nedenle, toplam mesafenin en aza indirilmesi ilk performans ölçütü olarak seçilmiştir. Ancak, her şehirdeki ambulansların azlığından dolayı, toplam ekstra rahatsızlık, maksimum ekstra rahatsızlık ve rahatsız edilen toplam şehir sayısı da analiz edilmiştir. Bu problem kapsamında, çok amaçlı optimizasyon yapmakla beraber Pareto-optimal çözümlerini analiz etmek için ϵ-kısıt yöntemi kullanılmıştır. Türkiye örneği üzerinden hesaplamalar ve analizler yapılmıştır.

Anahtar sözcükler: Sağlık Sistemleri, Yetim İlaçlar, Çok Amaçlı Optimizasyon, Pareto analizi.

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Chapter 1

Introduction

Orphan drugs are medical products that are developed to treat specific orphan diseases. Aldurazyme, haem arginate, ibuprofen and pralidoxime are examples of orphan drugs. We will refer to them as orphan drugs in general. The reason for the “orphan” label is because those diseases were orphaned by the pharmaceutical industry until the 1980s. Orphan diseases affect 6-8 % of the total population in the world. Around 5000 orphan diseases are listed in the medical literature. 80% of these diseases are rooted in genetic origins. Some of the orphan diseases are identified to be results of bacterial or viral infections and allergies. Further, they can be rooted due to degenerative and proliferative causes. Genetic diseases, rare cancers, congenital malformation, auto-immune diseases, toxic diseases and degenerative diseases can be classified as orphan diseases as many others.

Orphan diseases are associated with a variety of symptoms that differ among patients. Orphan diseases may be misdiagnosed due to relatively common symptoms with other diseases. In that case, orphan diseases may be obscured by common symptoms. There are approximately between 3000 and 7000 orphan diseases around the world. However, only 5% of orphan diseases have proper treatment procedure.

There are challenges in assessing clinical relevance and lack of knowledge and training on orphan diseases. Thus, the pharmaceutical industry is not interested much in orphan drugs. The stakeholders do not show interest in the orphan drug market

due to its small size. Moreover, production cost of orphan drugs is too expensive. As a result, the profits of firms and shareholders' return on the investments can be endangered. Since the number of patients is small, the pharmaceutical industry does not grow much interest to produce or develop drugs for orphan diseases. Due to those reasons, these drugs are difficult to attain.
Before the 1980s, the orphan drug and orphan disease notions were not notified. Then at the 1980s, the legislations as laws and policies established a ground for the development and improvement of orphan drugs. The legislations prompted stakeholders to show interest in orphan drugs as a new market. The US Orphan Drug Act in 1983 was the first legislation about orphan drugs and it leads to similar successful enactments in Singapore, Japan, Australia and Europe around 1990s [1].
Through the acts in different countries, the different definitions for orphan diseases are formed for each country. The definitions differ based on the number of people affected or important factors such as the severity of disease and the existence of adequate treatments. In the US, the orphan disease is defined as "the disease that has a low prevalence such as almost 7 cases per 10.000 people" while in Japan, the definition is given as "the disease is classified as an orphan if it has a prevalence of 4 cases per 10.000 people"[2]. In Singapore, if the disease has a prevalence of 37 cases per 100.000, the disease is called orphan disease. In Australia, the prevalence is 1 case per 10.000 people and in the EU, the prevalence is 5 case per 10.000 people for orphan disease definition [1].
There are different procedures and approaches in different countries. Therefore, the logistics of orphan drugs are challenging. The problem is analyzed and defined based on the application in Turkey and possible performance measures are discussed on in Chapter 2. Four performance measures are identified based on urgency and ambulance scarcity. Furthermore, the problem is described in OR context. A multi-criteria location and routing problem is defined. After problem definition, a review of the literature is given in Chapter 3. The problem defined in Chapter 2 can be positioned within healthcare literature and the OR problem can be classified as an application of minimum cost network flow problems. Therefore, the literature review is divided into two main parts: healthcare logistics and minimum cost network flow problems. In Chapter 4, the mathematical models are developed based on a specialized network for the Turkey case. The motivations

of each performance measure and the related mathematical models are given in Chapter 4. The Turkey application data is described and provided in Chapter 5. Due to operational dynamics, there are two main parameters: distance matrix and boolean neighbourhood relation matrix. It is challenging to create a boolean neighbourhood relation matrix which requires analysis of the distance matrix. After analysis of data, Chapter 6 presents the computational analysis. The mathematical models are solved and Pareto-optimal solutions found by ϵ-constraint method are analyzed. Finally, the conclusions are summarized in Chapter 7.

Chapter 2

Application in Turkey

The accessibility of orphan drugs is controlled by rules and legislation which differ among countries. In this chapter, we will discuss the implementation dynamics of the application in Turkey. In Turkey, orphan drugs can only be stored at specific types of hospitals which are called as third level health institutions. Those health facilities are located in 31 cities in Turkey. In the current system, among the 31 cities, there are 15 cities where third level health institutions are used for storage of orphan drugs. The current active cities can be seen in Table B.1 in Appendix B.

The orphan drugs are not easily accessible since they are not stocked in every hospital. In case of an emergency, they should be transmitted to patients urgently. There are regulations for the transmission of orphan drugs. The law states that orphan drugs can only be transported via a specific type of ambulances. Describing the functions of ambulances are crucial to clarify the significance of the ambulance type which is used during orphan drug transportation. Therefore, we now provide general information about ambulances.

In Turkey, there are three types of ambulances based on their transportation type: highway, marine and airway ambulances. Airway ambulances have two types: aeroplane and helicopter ambulances. Aeroplane ambulances are used for patient transfer and emergency medical aid. There are a total of two aeroplane ambulances in Turkey which are located in Ankara airport. There are also helicopter ambulances as airway ambulances. The main aim of helicopter ambulances is to increase the response time in the case that highway transportation for urban areas is hard. However, helicopter ambulances have small area and transfer is shaky. Therefore the medical aid is not safe and possible. There are in total 17 helicopter ambulances in Turkey. In addition to airway ambulances, there are marine ambulances that are used for patient transfer in the case that there is an obstacle like river, lake and sea that separate the towns[3].

The third type is the highway ambulances. There are 7 types of highway ambulances including emergency, patient transfer and specially designed ambulances. The differences between the ambulances depend on their functions. The specially designed ambulances are designed for special purposes or functions. They are designed depending on both the age, physical and medical condition of the patient and the geographical features of the area. The ambulances with intensive care unit, the ambulances with incubators for newly-born, ambulances for obese people, tracked terrain ambulances, multi-emergency ambulances and motor ambulances are the specially designed ambulances. The ambulances with intensive care unit have both luminous red and blue stripes. In those ambulances, at least three staffs including one doctor and emergency care technician are on duty. The ambulances with incubators for newly-born do not include any medical material that is required to aid adult patients. The ambulances for obese people have their special system of crane that is used for patients who cannot be carried by two people. The tracked terrain ambulances are classified as snow-tracked ambulances for the areas with heavy snow. The multi-emergency ambulances are used when the patient number is more than one and they are required to be transferred emergently. The maximum limit of those ambulances is four patients per ambulance and it includes equipment that is enough to aid four patients. Motor ambulances are used as a supporting unit for ambulances without doctors and to arrive at the scene of an event with teams including a doctor. Also, they are used for transportation of medical personnel and medical material in extreme cases or during disasters [4]. The patient transfer ambulances are used for transportation of non-urgent patients. They require at least two staff performing the duty. They have luminous blue stripes that distinguish them from the other types [3].

Finally, there are emergency ambulances which are used during the transportation of orphan drugs. In general, emergency ambulances are used for patients who need emergency medical intervention. In terms of physical difference from other ambulance types, they have luminous red strips that distinguish them. There should be one doctor, one emergency care technician and one emergency medical technician performing duty as staff in the emergency ambulances when the ambulance is active. Moreover, they are used for transportation of orphan drugs because emergency ambulances are active for 24 hours. Therefore, they can react quickly to emergent cases [3], unlike other ambulance types. More detailed classification of ambulance types can be seen in Appendix A.1. Since emergency ambulances are used for emergent cases, they are required to stay within the cities and they are not allowed to leave the city.

The restriction of "ambulances not leaving the city borders" puts a great challenge in transferring orphan drugs. The drugs need to move between ambulances at city borders. Due to the functional properties of emergency ambulances, during the transportation of orphan drugs, the ambulances of cities meet at borders. After meeting at borders, the transfer of orphan drug occurs between ambulances at the city border. Then, the ambulances return to hospitals that they are assigned. The whole staff is included in transportation because there might be an emergent case to interfere on their way to border and on their way to the hospital. Therefore, for an emergent response, the staff is required to interfere.

We now detail the operational dynamics of the logistics of orphan drugs. We explain how drugs will be sent to patients when a need arises, in the next section in more detail.

2.1 Operational Dyamics

In the current structure, orphan drugs are immediately available in 15 cities of Turkey. If there is a patient at a city where orphan drugs are not stored, the drug needs to be transported from its assigned city among the 15 cities. As explained before, due to legislations, orphan drugs are transported via emergency ambulances. However, emergency ambulances are restricted to serve within the city borders of their assigned city. In this case, they are not allowed to leave the city and therefore, the orphan drug transportation is made at borders by ambulances.

If the city where the orphan drug is stored and the city where a patient needs the orphan drugs are not bordered neighbours, the ambulances of intermediate cities are also used during transportation of the orphan drug. The ambulance of the city where the orphan drug is stored meet at borders with the ambulances of the intermediate cities. The final transmission occurs and the orphan drugs are transmitted to the patient by the ambulance of the city where it is required.
It is better to clarify operational dynamics through an example. For instance, if a patient in Ağrı needs an orphan drug and it is not stored in any health institution in Ağrı, then it should be transported from the assigned third level health institution. If it is stored in the health institution in Erzurum then the orphan drug needs to be transported from Erzurum. During the transfer, the emergency ambulances of Ağrı and Erzurum are used. Each emergency ambulances in both cities meet at the border to transfer the orphan drug.

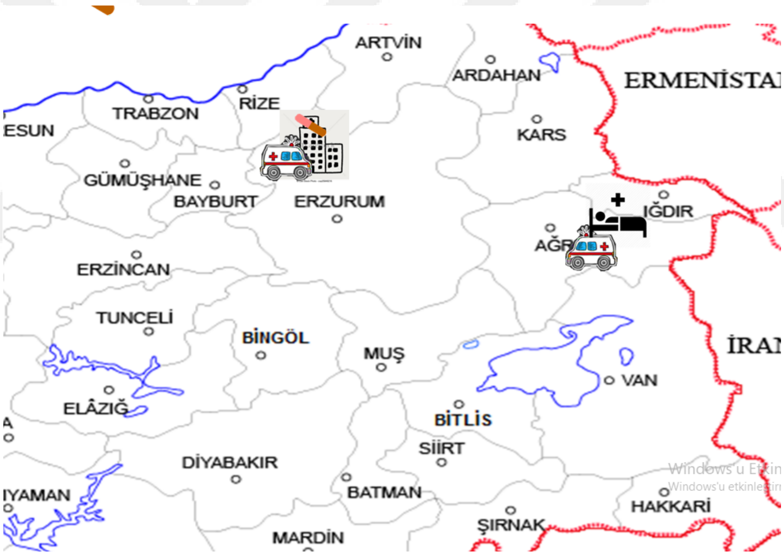


Figure 2.1: Transportation between cities which are bordered neighbours

In the case where cities are not bordered neighbours, transportation is still possible. However, in this case, the ambulances of cities in between these cities are also included. For example, let us say, an orphan drug is required in a health institution in Van for a patient and not stored in any health institution in Van. Erzurum is the assigned city of Van. Van and Erzurum are not bordered neighbours and the shortest path between them passes through Ağrı. Then, the ambulance from Erzurum (E) and an ambulance from Ağrı (A) go to the border of Erzurum and Ağrı. Ambulance (E) transfers the orphan drug to ambulance(A) then ambulance (A) goes to the border of Ağrı and Van. An ambulance from Van (V) also is transported to the border of Ağrı and Van. Ambulance (A) and ambulance (V) meet. Then, the drug is transferred from the ambulance (A) to ambulance (V). Finally, ambulance (V) transports the orphan drug to the patient in need.

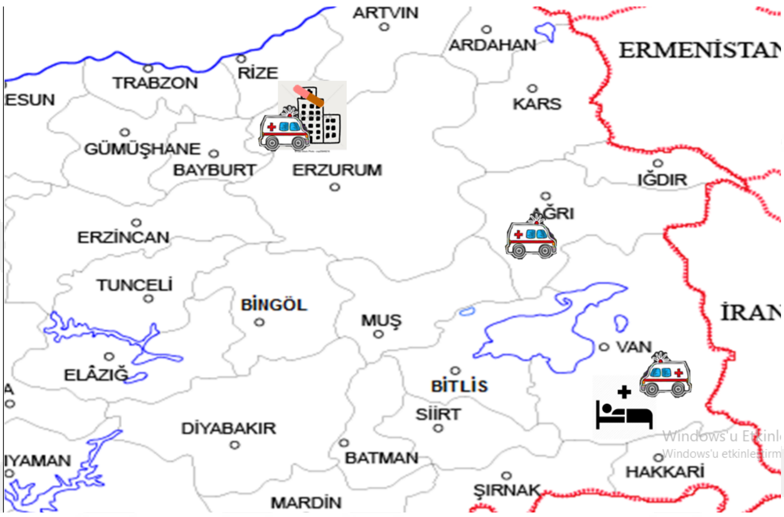


Figure 2.2: Transportation between cities which are not bordered neighbours

If there are more than one intermediate nodes, the intermediate nodes are used if they share borders. For example, let us say, an orphan drug is required in a health institution in Hakkari for a patient and not stored in any health institution in Hakkari. Hakkari is assigned to Erzurum to get service. There are more than one intermediate node between Hakkari and Erzurum. Let us say that the route between Hakkari and Erzurum is decided through both Van and Ağrı. Then, the ambulance from Erzurum (E) and an ambulance from Ağrı (A) go to the border of Erzurum and Ağrı. Ambulance (E) transfers the orphan drug to ambulance(A) then ambulance (A) goes to the border of Ağrı and Van. An ambulance from Van (V) also is transported to the border of Ağrı and Van. Ambulance (A) and ambulance (V) meet. Then, the drug is transferred from the ambulance (A) to ambulance (V). Then ambulance (H) goes to the border of Van and Hakkari. An ambulance from Hakkari (H) also is transported to the border of Van and Hakkari. Ambulance (V) and ambulance (H) meet. Then, the drug is transferred from the ambulance (V) to ambulance (H). Finally, ambulance (H) transports the orphan drug to the patient in need. Therefore, the transporation can occur if the intermediate cities are sharing borders.

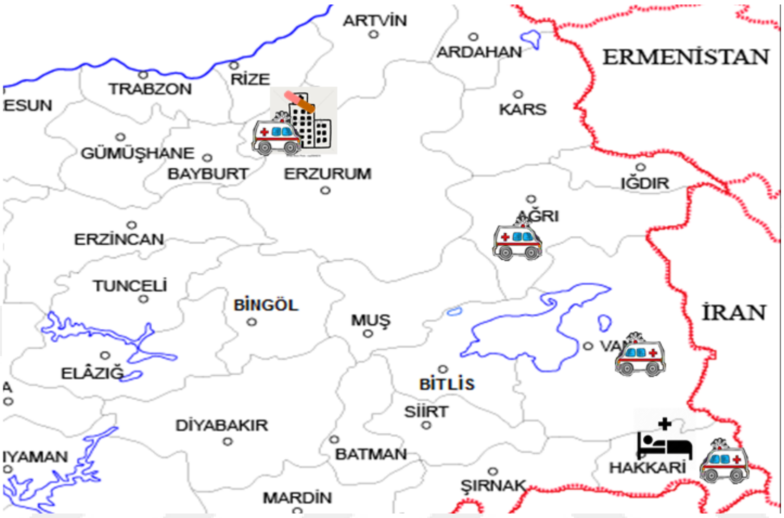


Figure 2.3: Transportation between cities which require more than one intermediate node

Even though the operational dynamics are instructed as given above, for the current system, only location and allocation decisions are provided in legislation depicted as in Table B.1 in Appendix B. However, due to operational dynamics, the routing decision is also critical. In the current system, the routing decision is left to the hospital management. This brings a challenging decision: If there are intermediate cities, how should the drug be routed since all cities passed through during the transportation needs to send their ambulances.

Their main aim is to serve the patient as quickly as possible during urgency. There are only 15 cities active for storage of orphan drugs. However, there are third-level health institutions in 31 cities of Turkey in total and they are not used for this purpose. If we include all 31 cities as a candidate city in location decision, the

optimal location and allocation decision might enlarge. Also, for different performance measures, alternative location and allocation decisions can be given.
When these facts are considered, it cannot be affirmed that the current system is well structured. Therefore, in this study, the aim is to find the best locations for storage of orphan drugs and corresponding routing and allocation decisions considering orphan drug transportation dynamics.
This thesis study proposes mathematical models to reorganize the orphan drugs transportation system at the strategic and tactical level. The locations for orphan drugs storage and allocation of cities to those storage locations will be decided through mathematical modelling. In mathematical models, the demand levels are neglected and each city is assumed to have 1 unit of demand because the demand data was not available. Additionally, alternative location and routing decisions can be given for different performance measures. There is not a commonly used objective function for this kind of problem. We have defined the performance measures based on urgency and ambulance scarcity. We now detail the performance measures, in the next section.

2.2 Performance Measures

After defining the problem, we introduce performance measures based on operational dynamics. In the current system, the primal aim is to transmit the orphan drug as quickly as possible. To transport the orphan drug quickly, it is fair to use the shortest path to serve the patient. Therefore, the distance travelled by ambulances is one of the performance measures. However, the dynamics of the system is not only related to urgency.
The number of ambulances is limited in each city. Also, emergency ambulances are responsible for reacting to urgent cases. During transportation, ambulances leave the service area they are responsible for. In such cases, there might be a vulnerability in terms of arriving on the scene on time. Therefore, due to the dynamics of the system, ambulance scarcity is another important aspect to consider. There may be different performance measures related to ambulance scarcity. We will introduce the "extra disturbance" term for the performance measures. The

extra disturbance refers to the number of ambulances used in a city other than the city where orphan drugs are stored and the city where a patient is in need. Each city can dispatch more than one ambulance if they are using as intermediate cities during the transportation. We distinguish the “extra disturbance” as an additional metric since those cities are disturbed only because they are on the way. With this metric, different measures can be defined. We consider the minimization of the total extra disturbance, minimization of the maximum extra disturbance, and minimization of the number of cities disturbed.

The total extra disturbance is considered to find the total number of ambulances required through the intermediate cities during the orphan drug transportation. Moreover, the maximum extra disturbance is considered to find the maximum amount of ambulances that each intermediate city can dispatch during transportation.

The final performance measure is introduced to find the number of cities where an extra ambulance is dispatched. Different from the previous two performance measures, it is not related to the number of ambulances used. However, it considers the cities which dispatch ambulances. In this case, the intermediate cities during transportation are analysed.

Through the small data, the differences on the location and allocation decisions for those performance measures are constructed. The data set is constructed for 15 nodes and there are 4 candidate cities in which the hospitals can store orphan drugs. The candidate cities are Adana, Gaziantep, Konya, Yozgat. In this context, we will give location and allcoation decisions when 2 of the candidate cities are selected for orphan drug storage.

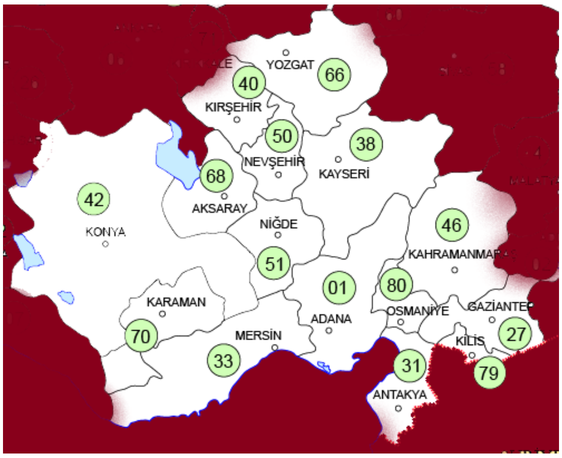


Figure 2.4: Data set with 15 nodes

For each performance measure, the location and allocation decisions are given in Tables 2.1a- 2.1d. In the small data, when the total distance, total extra disturbance and maximum extra disturbance are minimized, the cities that are chosen to store orphan drugs are Adana and Yozgat. However, allocation decision for each performance measure changes. Also, when the number of cities disturbed is minimized, the cities that are chosen to store orphan drugs are Konya and Gaziantep. The allocation decisions are given in Table 2.1.

(a) Location and Allocation decisions for small data with minimization of total distance

Cities chosen to store orphan drugs	Allocated cities
Adana	Adana, Gaziantep, Antakya, Mersin, Konya, Kahramanmaraş, Niğde, Karaman, Kilis, Osmaniye
Yozgat	Yozgat, Kayseri, Kırşehir, Nevşehir, Aksaray

(b) Location and Allocation decisions for small data with minimization of total extra disturbance

Cities chosen to store orphan drugs	Allocated cities
Adana	Adana, Gaziantep, Antakya, Mersin, Konya, Kahramanmaraş, Nevşehir, Niğde, Aksaray, Karaman, Kilis, Osmaniye
Yozgat	Yozgat, Kayseri, Kırşehir

(c) Location and Allocation decisions for small data with minimization of maximum extra disturbance

Cities chosen to store orphan drugs	Allocated cities
Adana	Adana, Gaziantep, Antakya, Mersin, Konya, Nevşehir, Niğde, Aksaray, Karaman, Kilis, Osmaniye
Yozgat	Yozgat, Kayseri, Kırşehir, Kahramanmaraş

(d) Location and Allocation decisions for small data with minimization of the number of cities disturbed

Cities chosen to store orphan drugs	Allocated cities
Konya	Konya, Adana, Mersin, Kayseri, Kırşehir, Nevşehir, Niğde, Yozgat, Aksaray, Karaman
Gaziantep	Gaziantep, Antakya, Kahramanmaraş, Kilis, Osmaniye

Table 2.1: Location and Allocation decisions on small data for different performance measures

We have introduced those four performance measures namely: i)-minimization of the total distance, ii)-minimization of the total extra disturbance, iii)-minimization of the maximum extra disturbance, iv)-minimization of the number of cities disturbed based on operational dynamics. Moreover, those performance measures are helpful to analyze the problem in different perspectives. We now present problem definition in OR context, in the next section.

2.3 Problem Definition in OR

The problem described above can be classified as a multi-criteria location and routing problem. The allocation decision is made as an intermediate decision along with location and routing decisions. Moreover, the performance measures introduced in the subsection 2.2 will be used for multi-criteria optimization. The performance measures are used to analyze different aspects of the problem. The sets of solutions for each performance measure are found by ϵ-constraint method and the Pareto-optimal solutions are found as a measure of efficiency in this multi-criteria problem. This thesis aims to make an analysis of distance and ambulance scarcity about orphan drug logistics in multi-criteria context.

Chapter 3

Literature Review

Orphan drugs and ambulances are parts of healthcare systems and the problem defined in Chapter 2 is related to healthcare logistics. Thus the problem studied can be positioned within healthcare logistics. The OR problem can be classified as minimum cost network flow problem. Thus, in this section, we provide a review of the literature on healthcare logistics and minimum cost network flow problems in sections 3.1 and 3.2. The healthcare logistics literature in section 3.1 is investigated in three main categories which are patient, drug and hospital logistics.

3.1 Healthcare Logistics Literature

The healthcare logistics literature can be separated into three main topics which are patient, drug and hospital logistics. The main reason for this categorization is operational dynamics. Further details will be given in the appropriate subsections.

3.1.1 Patient Logistics

In our categorization, the first one is patient logistics. This category is divided into two main subcategories: emergent and non-emergent patient logistics. We further classify the papers in the emergent patient logistics into ambulance location, ambulance relocation and patient survivability.

The location of ambulances and ambulance stations are the main strategical decisions while the sizing of the fleet of ambulances and allocations of ambulances to stations are part of tactical decisions. Moreover, which ambulances should be dispatched to a call and the reallocations of ambulances are included as operational decisions. The pioneering works in ambulance location problems are Set Covering Location Problem (SCLM) by Toregas et al. [5] and the Maximal Covering Location Problem by Church and Revelle [6]. To cover the demand by enough number of vehicles, (SCLM) by Toregas et al. [5] can be used as a planning tool. Besides, inspired by the location set covering problems, Shiah and Chen [7] have developed ambulance allocation capacity models in which they use capacity as the probability of the availability of an ambulance. Leknes et al. [8] present a new problem for the strategical decisions mentioned earlier and it can be referred to as Maximum Expected Performance Location Problem for Heterogeneous Regions. The model decides on strategical decisions and calculates service and arrival rates for each station along with probabilities that a call is served by a particular station. Furthermore, rapid response to medical emergencies is one of the main goals of the Emergency Medical Service and response time is affected by fleet size and locations of ambulances.

In literature generally, the ambulance location problems are combined with coverage problems including maximum coverage problems. Owen and Daskin et al. [9] present a study on the ambulance facility location. Daskin and Stern [10] formulate hierarchical objective covering problem in the context of EMS vehicles. They consider the maximization of the extent of multiple coverages of zones and minimizing the number of vehicles that are required to cover all zones.

Later, coverage models are expanded and double coverage models are included in literature and by Gendreau et al. [11], it is applied to EMS vehicles. Ingolfsson et al. [12] describe the model for ambulance location to minimize the number of ambulances that are required to provide a certain service level. The model considers response time as a composition of random delays and random travel time. There are a total of three uncertainties reflected the model and they are uncertainty in response time, delay time and ambulance availability. By modelling all three uncertainties together provides a more realistic ambulance location problem.

Degel et al. [13] propose a data-driven optimization approach to maximize the flexible empirically determined required coverage. This new approach has a similar idea with double coverage. However, since double coverage is not reflecting observable temporal variations of the demand in emergency and the speed of ambulances, it causes miscalculation, which leads to uncovering of some districts. It is not static like double coverage. By this approach, the EMS system is prevented from the unavailability of ambulances by the parallel operations to improve the coverage of the planning area. Also, this formulation is better at reacting to real demand. Besides, Brotcorne et al. [14] present a paper on ambulance location and relocation models. It includes the evolution of ambulance location and relocation models over the past 30 years. There are two main types of models: deterministic and probabilistic. While deterministic models are used at the planning stage, probabilistic models reflect the fact that the ambulances may be unavailable as servers. Additionally, recently dynamic models emerged to update the ambulance location periodically throughout the day. Also, similar analyses are made by Li et al. [15].

The second classification for emergent patient logistics is ambulance relocation problems. This subcategory can further be divided into two: periodic redeployment and real-time ambulance relocation. Generally, the models assume that each demand point generates a specific amount of calls per period. Daskin [16] presents Maximum Expected Covering Location Problems that focuses on the expected outcome instead of deterministic outcome and focuses on the fact that ambulances can be busy. All ambulances are assumed to have the same probability of being busy and assume to be all independent. Daskin [16] considers periodic redeployment of ambulances in which the planning horizon is divided into discrete-time intervals and the static ambulance location problem is solved more than once. The outcome is the minimum number of ambulances while increasing service coverage up to a satisfactory level.

Gendreau et al.[17] and Gendreau et al. [18] propose a dynamic redeployment problem. In [17], the model avoids the movement of the same ambulances repeatedly, for round and long trips. In [18], the aim is to maximize the expected covered demand while the number of waiting site relocations is controlled. Jagtenberg et al. [19] consider the ambulance redeployment problem with the main objective of minimizing the expected fraction of late arrivals and van Barneveld et al. [20] consider the same problem with the main aim of maximization of the expected performance of the service provider. The times that an event occurs, the times that an ambulance is dispatched or the times that an ambulance is newly free to decide the relocation decisions. van Barneveld et al. [21] focus on real-time ambulance relocation which bases the decisions depending on the state of the system throughout the day. In the paper by van Barneveld et al.[21], the dynamic ambulance relocation problem is analysed by combining two methods proposed by Jagtenberg et al. [19] and van Barneveld et al. [20]. van Barneveld et al. [22] propose the minimum expected penalty relocation problem (MEXPREP) as an extension of the model by [18]. Also, van Barneveld et al. [22] consider survival probabilities as a different performance measure related to response times.

The final classification of emergent patient logistics is patient survivability. Erkut et al. [23] propose new location models for EMS and the new models consist of existing coverage problems with survival function which decreases monotonically as a function of response time. The survival function gives the probability of survival of patient by the response time of ambulances. The survival maximizing models are better fit for the EMS system to respond to the differentiation in response times. Knight et al. [24] propose a new model The Maximal Expected Survival Location Model for Heterogeneous Patients (MESLMHP) in which the allocation of ambulances across a network is allowed. Knight et al. [24] consider multiple classes of patients where patients are categorized according to medical conditions with a corresponding survival function. The main aim is to maximize the overall expected patient survival. Later, McCormack and Coates [25] integrate heterogeneous survival functions and demands on two EMS vehicles: ambulances and rapid response cars. Zaffar et al. [26] analyse the recent ambulance allocation models with patient survivability objective showing better results on both coverage and survivability metrics.

Our second subcategory of patient logistics is non-emergency patients. The non-emergent patient logistics can further be divided into two: in-house hospital transportation and transportation to a hospital. Beaudry et al. [27] and Hanne et al.[28] represent in-house hospital transportation. Beaudry et al. [27] propose a two-phase heuristic to solve a dynamic dial-a-ride problem in a hospital context. The hospital-specific features increase the complexity of the problem. The aim is to provide an efficient transport service for patients within the hospital. In [28], a dynamic DARP is proposed related to German hospitals.
The second classification of non-emergency patient logistics is transportation to the hospital. Toth and Vigo [29] present Pickup and Delivery Problem with Time Windows and it presents an optimal schedule for vehicles to transport handicapped persons in an urban area. Furthermore, Melachrimoudis et al. [30] propose a dial-a-ride model with soft time windows and the model is applied to a non-profit organization. The aim is to minimize both transportation cost and client inconvenience time which includes excess riding time, early/late delivery time before service and late pickup time after service. Bowers et al. [31] propose a Dial-a-Ride problem with the constraint of the maximum diversion from a patient's direct route to the hospital. Zhang et al. [32] address a real-life public patient transportation problem as a multi-trip dial-a-ride problem (MTDARP). The model designs several routes for each ambulance. The routes start and terminate at the hospital as the depot. Since each ambulance is scheduled with several routes to prevent the spread of disease, the ambulances are required to be disinfected between two consecutive trips. Detti et al. [33] consider non-emergent patient transportation with constraints such as heterogeneous vehicles, vehicle-patient compatibility constraints, quality of service requirements, patients' preferences, tariffs depending on the vehicles' waiting. Molenbruch et al. [34] take into account the tradeoff between operational efficiency and service quality.

3.1.2 Drug Logistics

The second main category of healthcare logistics literature is drug logistics. The literature on drug logistics can further be divided into two sub-sections based on

the problem considered: distribution and storage. The studies related to drug distribution will be given initially.
Swaminathan [35] considers the efficiency, effectiveness, and equity of the drug-allocation process by a multiobjective optimization model. Michelon et al. [36] compare two delivery system and evaluate the number of carriers required by the new system. Periodic home health care logistics in France is considered by Liu et al. [37] and Liu et al. [38]. The study in [37] and [38] includes material pickup and delivery among pharmacy, patients, hospital, and lab. In [37], the visit days of each patient and the vehicle routes are optimized and in [38], the aim is to minimize the total vehicle cost while satisfying the demands of patients. Chahed et al. [39] focus on the anti-cancer drugs' supply chain.
Furthermore, Kergosien et al. [40] propose a two-level vehicle routing problem. The problem has time windows, a heterogeneous fleet, and multi-depot, multi-commodity and split deliveries. The first level of VRP considers the routing problem for vehicles which deliver medicines, clean linen, meals, various supplies, patient files and picks up waste and dirty linen while the second level considers the routing of employees between buildings within a hospital. A simultaneous facility location and vehicle routing problem in the healthcare context is modelled and solved by Veenstra et al. [41] and a fast and effective hybrid heuristic is proposed to solve the problem. Kotavaara et al. [42] allocate centralised warehousing functions by long delivery distances and the trade-off between service level and geographic reach was controlled with delivery costs-efficiency and share of deliveries constraints. Liu et al. [43] propose a deterministic model for medical resources order and shipment and later a stochastic model is developed for the uncertain demand.
Afterwards, the studies related to drug storage will be given. Little and Coughlan [44] propose an optimal inventory policy and the aim is to maximize the average and minimum service level. Dynamic economic lot size models are considered by Fleischhacker and Zhao et al. [45] under the risk of demand failure. Also, it is shown that stochastic failure-risk models can be transformed into deterministic Wagner–Whitin models. Lapierre and Ruiz [46] focus on scheduling decisions instead of multi-echelon inventory decisions and they represent two modelling approaches with a tabu search metaheuristic. Kelle et al. [47] determine the reorder point and order up to level and focus on tradeoffs amongst the expected number

of daily refills, the service level, and the storage space utilization.

3.1.3 Hospital Logistics

Hospital logistics is the third main category of healthcare logistics. Hospital logistics can further be narrowed down to scheduling and routing of medical-crew.
This sub-section of hospital logistics includes studies related to routing and scheduling of medical crew. Cheng and Rich [48] propose scheduling by separating nurses into two groups: full-time and part-time nurses and the aim is to minimize the amount of overtime and part-time worked. Bertels and Fahle [49] propose a heuristic algorithm via hybridizing constraint and some heuristic techniques similar to [48]. Wirnitzer et al. [50] propose a MIP-approach to generate a nurse roster and the main aim is to provide maximal continuity of care considering nurse availabilities, patient-nurse compatibilities. Also, the objective is to reduce the total number of nurses assigned to each cluster. Bennett and Erera [51] propose a Home Health Nurse Routing and Scheduling (HHNRS) problem which is a dynamic periodic fixed appointment time routing problem. The objective is to maximize the number of patients served per nurse. Nowak et al. [52] find some significant savings while assigning nurses to patients with longer planning horizons. Moreover, the number of allowed nurses per patient is limited by hard constraint and the nurses' workload is balanced in a study by Cappanera and Scutellà [53]. Eveborn et al. [54] focus on home care in Sweden while Akjiratikarl et al. [55] focus on home care in the UK. In [54], VRP is applied with synchronization constraints to reduce total costs while in [55], the main aim is to minimize the total distance travelled with capacity and delivery time window constraints.

3.2 Minimum Cost Network Flow Literature

The minimum cost network flow problem has been studied widely in the literature with many applications. In this section, papers on bi-objective and multi-objective

MCNF are detailed in the context of transportation problems due to its relevance to our problem.

In general, in transportation problems, bi-objective problems, are studied. Aneja and Nair [56] propose a bi-objective minimum cost flow problem where continuous variables are used. Also, all non-dominated points in objective space are found. Malhotra and Puri [57] propose a generalization of the out-of-kilter method for bi-objective minimum cost flow problem (BCNF). Lee and Pulat [58] combine BCNF with the out-of-kilter method. Likewise, Lee and Pulat [59] propose a method for integer BCNF and Pulat et al. [60] propose a parametric analysis for BCNF. Sedeño-Noda and Gonzàlez-Martin [61] propose a method which finds all efficient extreme points in the objective space. Furthermore, the method in [61] is based on the method of Lee and Pulat [58]. Similar to [61], Sedeño-Noda and Gonzàlez-Martin[62] present a method which finds all the efficient integer points in the objective space and the flow variables are integer-valued. Later, Przybylski et al. [63] show the incorrectness of [62] by giving a counterexample where all efficient points in objective space could not be found. Raith and Ehrgott [64] represent a two-phase method to compute all non-dominated extreme points in phase 1 and the remaining non-dominated points in phase 2. Keshavarz and Toloo [65] deal with the bi-objective minimum cost-time network flow problem (BOMCFT) and use the weighted sum scalarization technique to convert BOMCFT into minimum cost network flow with a single objective.

Calvete and Mateo [66] propose Multiobjective Network Flow with pre-emptive priorities and use specialized versions of general primal-dual and out-of-kilter methods. For a multi-objective transportation problem, an algorithm is developed by [67] to identify the non-dominated solutions. Klingman and Mote [68] represent a special version of the Multiobjective Simplex method that is proposed by Yu and Zeleny [69]. Ringuest and Rinks [70] propose two interactive algorithms for multiple objective transportation problem. Eusébio and Figueira [71] propose an algorithm to find all supported non-dominated vectors/efficient integer solutions for multi-objective integer network flow problems (MOINF). More detailed review on theory and algorithms to solve the multi-objective minimum cost flow problems (MMCNF) is given by Hamacher et al. [72]. According to the classification given by [72], this study can be classified as integer MCNF with a method based on linear programming.

In this thesis, orphan drug logistics for Turkish application is defined. The orphan drugs are transported via emergency ambulances if they are required in a city other than those candidate cities. Moreover, emergency ambulances are restricted to serve within the city borders. Thus, routing decisions are crucial. As detailed in Chapter 2, the problem needs to be considered under different performance measures. The related performance measures are decided based on urgency and ambulance scarcity. The primal aim is to save lives, therefore the first performance measure is the minimization of distance travelled. However, due to ambulance scarcity, the number of ambulances should be also considered. The performance measures that are related to the ambulance scarcity are: the minimization of the total extra disturbance, minimization of the maximum extra disturbance, and minimization of the number of cities visited. The extra disturbance refers to the number of ambulances used in a city other than the city where orphan drugs are stored and the city where a patient is in need. This thesis aims to make an analysis of distance and ambulance scarcity in orphan drug logistics and the studies in this section are useful to design basis of the problem. Our contribution to the literature include the analysis of the operational dynamics of the orphan drug system in Turkey, introduction of new performance measures and representing a new area of application for MCNF Problems. Also, we established models based on both performance measures and operational dynamics of the system and solved models. Furthermore, the Pareto optimal points are found by the ϵ-Constraint method and analysis is done.

Chapter 4

Mathematical Formulation

In this chapter, we will introduce the mathematical models for the problem defined in Chapter 2. More specifically, we aim to decide on the storage location of drugs, service allocation of cities and routing decisions of the ambulances for the transportation under different performance measures. For this purpose, a linear integer mathematical formulation is developed and the details of this formulation are explained in this chapter. Mathematical models are coded in JAVA with solver library of IBM CPLEX 12.8.1. The instances for different values of p are tested on a Linux OS with Dual Intel Xeon E5-2690 v4 14 Core 2.6GHz processors with 128 GB of RAM.

Even though the problem is location and routing problem, due to the restrictions on the transportation it can also be defined as an MCNFP for different performance measures: being minimization of distance, the total number of extra disturbance, the maximum number of extra disturbance in each city and number of cities visited in total. The performance measures are detailed in Chapter 2. For the problem defined in this study, there is not a specific objective function. In order to represent the operational dynamics of orphan drug logistics, a special network is constructed and the mathematical model is established based on this network. The network constructed is given in Figure 4.1.

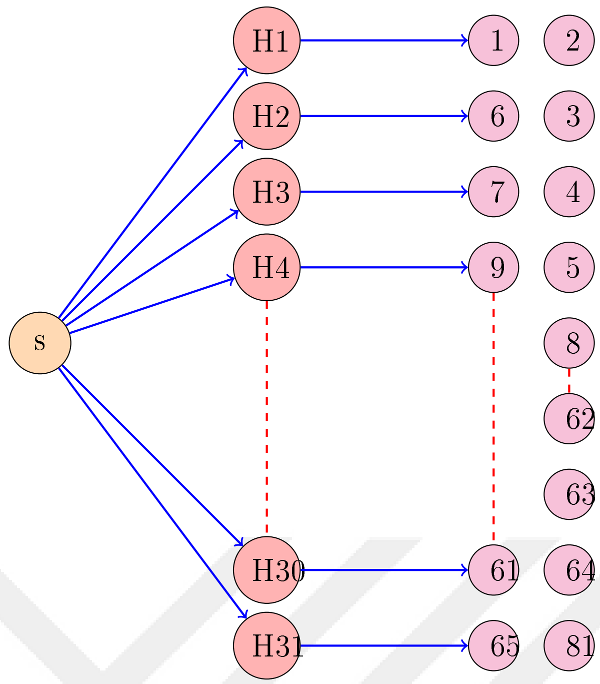


Figure 4.1: The network structure for the problem

Based on the problem defined, in Turkey, orphan drugs are located at third level health institutions. In the current system, there are 15 cities where third level health institutions are used for storage of orphan drugs. There are 31 cities in Turkey where third level health facilities are located. Therefore, in this study, the candidate number of cities for the location decision of orphan drug storage is extended to 31 cities.

In figure 4.1, s is considered as the start and supply node. The candidate cities which have proper hospital to store orphan drugs are: Adana(1), Ankara(6), Antalya(7), Aydın(9), Balıkesir(10), Bursa(16), Denizli(20), Diyarbakır(21), Elazığ(23), Erzurum(25), Eskişehir(26), Gaziantep(27), Antakya(31), Mersin(33), İstanbul(34), İzmir(35), Kayseri(38), İzmit(41), Konya(42), Malatya(44), İzmir(45), Kahramanmaraş(46), Mardin(47), Muğla(48), Ordu(52), Adapazarı(54), Samsun(55), Tekirdağ(59), Trabzon(61), Şanlıurfa(63), Van(65). Those candidate cities are represented by H1, H2, ... H31. The number of cities among the candidate cities that are chosen for location decisions is represented by p in parameters.

The rest of the nodes are the demand nodes representing the cities that should receive service. The demand nodes are named starting from 1 to 81 which correspond to the registration numbers for each city. For the flow balance, node s delivers 81 units of flow via H1, H2, ..., H31. The net flow on H1, H2, ..., H31 nodes is 0 since they are transhipment nodes. Finally, the demand of each node 1, 2, 3, 4, ..., 81 is -1.
In the network, the nodes $H1, ..., H31$ are the representation of the candidate cities. For example, 1 indicates the city Adana and H1 is the duplicated node of Adana to represent Adana as one of the candidate cities. Therefore, in the network constructed, H1 has only connection to node 1. $H1, ..., H31$ are the transhipment nodes and H1 is chosen as a city which can store the orphan drugs then it will serve itself. Moreover, if H1 is not chosen as a city which can store the orphan drugs, then it will not affect the flow sent to Adana through another city. The similar link structure is constructed with $H2, ..., H31$. Finally, the start node s has only links with $H1, ..., H31$. It is the supply node and $H1, ..., H31$ are the transhipment nodes. The start node sends flows to the candidate cities to chose the cities that can store orphan drugs among them. The neighbourhood relation contructed within the demand nodes are explained in Chapter 5. The distance data for demand cities are direclty taken from the website of General Directorate for Highways [73] however, in the models, the distance between duplicated nodes are taken as 0. For instance, the distance between node $H1$ and node 1 is taken as 0 since they are the duplicates. Also, the distances between the start node s and the nodes $H1, ..., H31$ are taken as 0.

The common parameters and decision variables of each model are given as:

Sets:

I= The set of nodes.

Parameters:

$D = [d_{ij}]$ where d_{ij} denotes the shortest distance between cities i and j, $i, j \in I$

$A = [a_{ij}]$ where a_{ij} denotes the boolean neighbourhood relation between cities i and j, $i, j \in I$.

$$b_l = \begin{cases} 81, & l = 1 \\ 0, & l = 2...32 \\ -1, & l = 33...113 \end{cases}$$

p= the number of cities that is selected for locating the orphan drugs.

The parameter p is required to analyze location and routing decisions for different number of candidate cities. It indicates the number of cities chosen among the candidate cities with the third level health institutions. In the network constructed, the supply node s is dummy start node and indexed as 1 in the parameter b_l. Also, the candidate cities are indicated as transhipment nodes. There are 31 candidate cities in total. They are shown as $H1, ..., H31$ in the network given in Figure 4.1 and they are indexed from 2 to 32 in the parameter b_l. The rest of the nodes starting from 33 in the model are the demand nodes. Since in total there are 81 cities, they are indexed from 33 to 113 in the parameter b_l and in the network given in Figure 4.1, they are shown as nodes 1...81.

Decision Variables:

Y_{kl} = the amount of flow to be routed from city k to city l, $k, l \in I$

$$X_l = \begin{cases} 1, & \text{If the hospital in city } l \text{ is used as storage hospital for orphan drugs, } l \in I \\ 0, & \text{otherwise} \end{cases}$$

We now provide the mathematical model. The models will be given with different performance measures under different sections.

4.1 Minimization of Total Distance (M1)

The first performance measure that we considered is the minimization of the total distance travelled. The mathematical model is constructed as below:

$$(M1)\min \quad f_1 = \sum_{k\in I}\sum_{l\in I} D_{kl}Y_{kl} \tag{4.1}$$

subject to

$$Y_{kl} \leq MA_{kl} \qquad \forall k,l \in I \tag{4.2}$$

$$\sum_{k\in I} Y_{lk} - \sum_{k\in I} Y_{kl} = b_l \qquad \forall k,l \in I \tag{4.3}$$

$$Y_{1l} \leq MX_l \qquad \forall l \in I \tag{4.4}$$

$$\sum_{l\in I} X_l = p \tag{4.5}$$

$$Y_{kl} \geq 0 \qquad \forall k,l \in I \tag{4.6}$$

$$X_l \in \{0,1\} \qquad \forall l \in I \tag{4.7}$$

The objective function (4.1) minimizes the total distance travelled by all ambulances. Constraints (4.2) ensure that if the cities i and j are not bordered neighbours, there will be no flow going through (i,j) arc. Constraints (4.3) is the flow balance for the system. Constraints (4.4) ensure that if a candidate city is not selected for storage of orphan drugs, then there will be no flow going from node s to that candidate city. The node s is indexed as 1. Constraints (4.5) ensure that the number of cities that is selected for storage of orphan drugs should be exactly p. Those constraints will be useful to analyze the location and routing decisions for the different number of cities with third level health institutions. Lastly, constraints (4.6) and (4.7) are the domain constraints for the decision variables.

4.2 Minimization of Total and Maximum Extra Disturbance (M2)

Minimizing total distance is the primal objective due to life-saving. However, if an emergent case occurs within the city during transportation, there might be a vulnerability in terms of arriving on the scene on time due to ambulance scarcity. In terms of ambulance scarcity, two new performance measures are considered: minimization of the total extra disturbance and the minimization of maximum extra disturbance. To express new performance measures, new decision variables and constraints are added.

Additional Decision Variables:

Z_l = the number of ambulances used in the city l, $l \in I$

$$(M2)\min \quad f_2 = \sum_{l \in I} Z_l \tag{4.8}$$

$$f_3 = \max_{l \in I} \quad Z_l \tag{4.9}$$

subject to

(4.2) – (4.7)

$$Z_l = \sum_{\substack{k \in I \\ k \geq 33}} Y_{kl} - 1 \qquad \forall l \in I \quad \& \quad l \geq 33 \tag{4.10}$$

$$Z_l = X_l \qquad \forall l \in I \quad \& \quad l < 33 \tag{4.11}$$

$$Z_l \in \mathbb{Z} \qquad \forall l \in I \tag{4.12}$$

There are two objective functions related to number of extra disturbance. The second objective function is the minimization of total extra disturbance and represented by (4.8). Also, the third objective function is the minimization of the maximum extra disturbance used and represented by (4.9). The objective function (4.9) minimizes the maximum number of ambulances used in each city and the objective function (4.8) minimizes the total number of ambulances used. Contraints (4.2), (4.3), (4.4), (4.5), (4.6) and (4.7) from the basic model. Constraints (4.10) and (4.11) define the decision variable Z_l as the number of extra ambulances used during the transportation for city l. Constraints (4.10) define Z_l as $\sum_{\substack{k\in I\\ k\geq 33}} Y_{kl} - 1$. In constraints (4.10), $\sum_{\substack{k\in I\\ k\geq 33}} Y_{kl}$ implies for the flow entering the node l and -1 is used to subtract the demand of the node l. In the network constructed, there is a supply node s which is dummy start node. Moreover, there are 31 candidate cities which are indicated as transhipment nodes and they are indexed from 2 to 32 in the model. The demand nodes 1,...,81 are indexed from 33 to 133 in the model and therefore the model looks for the extra disturbance of the demand nodes. Constraints (4.12) are the domain constraint for the decision variable, Z_l.

4.3 Minimization of Number of Cities Disturbed (M3)

Finally, related to the ambulance scarcity, there is a fourth performance measure which is the number of cities visited/disturbed as extra during the transportation. To express the new performance measure, new constraints and decision variable are added and model is constructed as below:

Additional Decision Variable:

$$w_l = \begin{cases} 1, & \text{If city } l \text{ is used as an of intermediate city during transportation of} \\ & \quad \text{orphan drugs between two different cities , } l \in I \\ 0, & \text{otherwise} \end{cases}$$

$$(M3)\min \quad f_4 = \sum_{\substack{l \in I \\ l \geq 33}} w_l \tag{4.13}$$

subject to

(4.2) – (4.7), (4.10), (4.11), (4.12)

$$Z_l \geq 1 - M\left(1 - w_l\right) \qquad \forall l \in I \quad \& \quad l \geq 33 \tag{4.14}$$

$$Z_l \leq M w_l \qquad \forall l \in I \quad \& \quad l \geq 33 \tag{4.15}$$

$$w_l = 0 \qquad \forall l \in I \quad \& \quad l < 33 \tag{4.16}$$

$$w_l \in \{0, 1\} \qquad \forall l \in I \tag{4.17}$$

In this model, the main aim is to minimize the number of cities disturbed during the transportation. In this case, again new decision variable along with new constraints are defined. The objective function (4.13) minimizes the total number of cities disturbed in the system. Constraints (4.14) ensure that the if the city is used during the transportation, the extra ambulances used by that city should be more than one. Constraints (4.15) ensure that the if the city is not used during the transportation, the extra ambulances of that city cannot be used for transportation. Constraints (4.16) equalize w_l to zero value for simplicity. Lastly, constraints (4.17) are the domain constraint for the decision variable, w_l.

4.4 The Overall Model

We have defined four different performance measures. In this section, we will analyze the behaviour of the solutions with respect to each of the objectives. We will also provide a Pareto analysis. The overall model is given below:

$$
\begin{aligned}
(M4)\ \min \quad & f_1 = \sum_{k \in I} \sum_{l \in I} D_{kl} Y_{kl} && && (4.1)\\
& f_2 = \sum_{l \in I} Z_l && && (4.8)\\
& f_3 = \max_{l \in I} \quad Z_l && && (4.9)\\
& f_4 = \sum_{\substack{l \in I \\ l \geq 33}} w_l && && (4.13)\\
& \text{subject to} && && \\
& Y_{kl} \leq M A_{kl} && \forall k, l \in I && (4.2)\\
& \sum_{k \in I} Y_{lk} - \sum_{k \in I} Y_{kl} = b_l && \forall k, l \in I && (4.3)\\
& Y_{1l} \leq M X_l && \forall l \in I && (4.4)\\
& \sum_{l \in I} X_l = p && && (4.5)\\
& Z_l = \sum_{\substack{k \in I \\ k \geq 33}} Y_{kl} - 1 + X_l && \forall l \in I \quad \& \quad l \geq 33 && (4.10)\\
& Z_l = X_l && \forall l \in I \quad \& \quad l < 33 && (4.11)\\
& Z_l \geq 1 - M\,(1 - w_l) && \forall l \in I \quad \& \quad l \geq 33 && (4.14)\\
& Z_l \leq M w_l && \forall l \in I \quad \& \quad l \geq 33 && (4.15)\\
& w_l = 0 && \forall l \in I \quad \& \quad l < 33 && (4.16)\\
& Y_{kl} \geq 0 && \forall k, l \in I && (4.6)\\
& X_l \in \{0, 1\} && \forall l \in I && (4.7)\\
& Z_l \in \mathbb{Z} && \forall l \in I && (4.12)\\
& w_l \in \{0, 1\} && \forall l \in I && (4.17)
\end{aligned}
$$

To make decisions under multi-criteria, we should focus on the solution set that defines the best trade-off between the competing objective functions. The goodness of the solution in multi-criteria optimization is determined by dominance. If the objective vector of a solution x is not worse than that of another solution y under all criteria and solution x is strictly better than the solution y in at least one criterion, then the objective vector of solution x dominates that of solution y. If there are more than one conflicting objectives, Pareto optimization reduces the huge feasible set of decisions into much smaller subsets. Those subsets are useful to choose the best feasible option that fits all performance measures. This method determines the set of Pareto-optimal solutions. Pareto-optimal solutions or non-dominated solutions cannot be improved in any objective without degenerating another objective. In other words, the other solutions are dominated by Pareto-optimal solutions and therefore those solutions are worse than Pareto-optimal solutions. There are some methods used to find the Pareto-optimal solutions and ϵ-constraint method is considered in this paper. Haimes et al. [74] proposed the ϵ-constraint method. In the ϵ-constraint method, only one of the performance measures is selected to be optimized. The other performance measures are added to model constraints.

Chapter 5

Data

In this chapter, we will introduce the data used in this study. As the overall study is motivated for the Turkish application, we created a real data set. There are two main attributes of data used and therefore we have two main parameters: distance matrix and boolean neighbourhood relation or link relation matrix. The distance data is taken from the website of General Directorate for Highways [73]. The distance data shows the shortest distance between two cities. Even though the distance attribute shows the shortest path between two cities, it does not show whether the cities have links/ borders. Therefore, the distance attribute is not enough for representing the operational dynamics of an orphan drug logistics problem. To use the distance attribute, the neighbourhood relation between the cities is required. The neighbourhood relation shows whether the cities share a border or not.

The operational dynamics require the relation showing borders between cities for the routing decision. To establish a neighbourhood relation between two cities, we have conducted an analysis of the distance data. If the city (A) has borderline to a city (B), then the city (A) has a link to that city (B). However, there have been other cases to consider. On the map, there are some cities which have no border to the city (B) and are very close to the city (B). Let us say city (A) and city (B) are very close and on the map, they are shown to have no border. In that case, it is expected that to travel between those two cities, an intermediate city should be used. However, when we analyze the distance between the city (A) and city (B) through any intermediate city, it is recognized that the distance between the city (A) and city (B) given in the distance matrix is always smaller than the distance calculated through an intermediate city. Therefore, it is considered that they have a link or shared border. Similar to the previous case, there might be two cities that do not have a borderline on the map and they may be close to each other. However, in this case, in order to travel between those cities, an intermediate city can be visited. Let us say city (A) and city (B) are very close and on the map, they are shown to have no border. When we analyze the distance between the city (A) and city (B) through any intermediate city, it is recognized that the distance between the city (A) and city (B) given in the distance matrix is equal to the distance calculated through an intermediate city. Therefore, it is considered that they do not have a shared border. Also, there might be two cities which have borderlines. However, when the distance is analyzed, it is considered that they do not have a link. Because to travel between those cities, another city should be visited. Let us say city (A) and city (B) on the map are shown to share a border however when we analyze the distance between the city (A) and city (B) through any intermediate city, it is recognized that the distance between the city (A) and city (B) given in the distance matrix is equal to the distance calculated through an intermediate city. Therefore, it is considered that they do not have a shared border. To make it more clear, we will represent examples of the cases that are encountered.

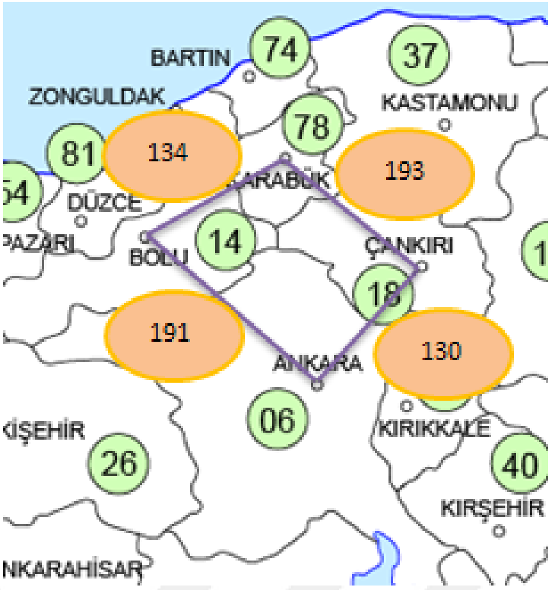


Figure 5.1: Neighbourhood relation between Ankara and Karabük

The first example is about neighbourhood relation between Ankara and Karabük. In the distance matrix, the distance between Ankara and Karabük is 215 km and on the map, there is no borderline between those two cities but they are close to each other. When we analyse the borders of Ankara and Karabük, both Çankırı and Bolu share a border with Ankara and Karabük. Since between Ankara and Karabük, there is no border, we are analyzing whether the distance between Ankara and Karabük is greater than or equal to the total distance of Ankara-Çankırı-Karabük or Ankara-Bolu-Karabük. The distances for each pair of cities with borders are:
Ankara-Çankırı:130 km
Çankırı- Karabük:193 km
Ankara- Bolu :191 km
Bolu- Karabük:134 km
When we analyse the distance between Ankara and Karabük over Çankırı, the distance is 323 km and over Bolu, the distance is 325 km. However, in the distance data obtained from General Directorate for Highways [73], the distance between Ankara and Karabük is given as 215 km. The distance is given by assuming that the distance data is taken from the centroid of each city. While travelling from

Ankara to Karabük, the city centres of neither Çankırı nor Bolu are visited. Therefore, it is assumed that Ankara and Karabük share a border that allows travelling directly. In this case, even though they do not have borderlines on the map, they are assumed to share borders connecting each other. Thus, in the boolean neighbourhood (link) relation matrix, the value for Ankara and Karabük is given as 1.

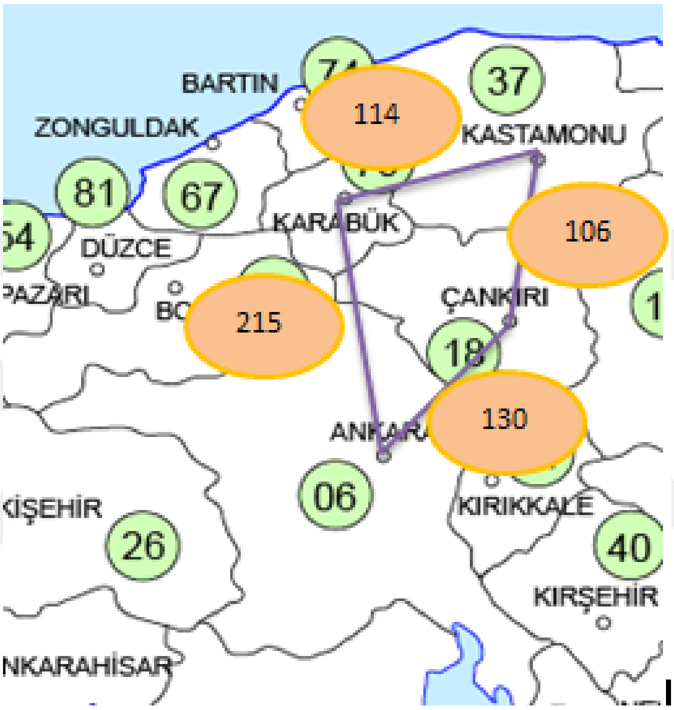


Figure 5.2: Neighbourhood relation between Ankara and Kastamonu

A similar situation is observed between Ankara and Kastamonu. Ankara and Kastamonu do not have borderlines on the map but they are close to each other. Also, both Çankırı and Karabük have links to Ankara and Kastamonu. Let us analyse the distance between those city pairs:

Ankara- Çankırı:130 km

Çankırı- Kastamonu:106 km

Ankara-Karabük:215 km

Karabük- Kastamonu: 114 km

When we analyse the distance between Ankara and Kastamonu over Çankırı, the distance is 236 km and over Karabük, the distance is 329 km. In the distance data obtained from General Directorate for Highways [73], the distance between Ankara and Kastamonu is given as 236 km. In this case, it can be verified that Ankara and Kastamonu do not share a border that can connect them because, in order to travel to Kastamonu from Ankara, Çankırı should be used.

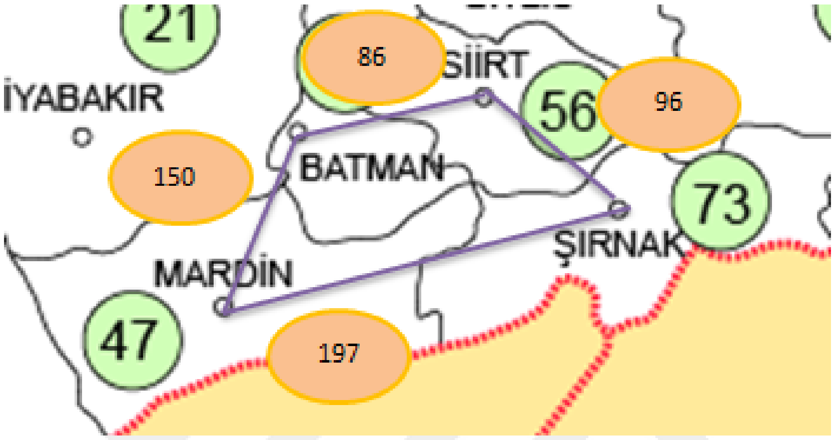


Figure 5.3: Neighbourhood relation between Batman and Şırnak

As an example for the final case, Batman and Şırnak seem to share a border on the map. Also, both Batman and Şırnak have borderlines to Siirt and Mardin. The distances for each pair of cities with borders are:
Batman-Siirt :86 km
Siirt- Şırnak :96 km
Batman- Mardin :150 km
Mardin- Şırnak :197 km
When we analyse the distance between Batman and Şırnak over Siirt, the distance is 182 km and over Mardin, the distance is 347 km. In the distance data obtained from General Directorate for Highways [73], the distance between Batman and Şırnak is given as 182 km. Therefore, even though those two cities seem to have borderline, according to distance data, in order to travel between those cities, Siirt should be visited. While analyzing the data, all such cases are considered and neighbourhood relation matrix is created as described above.
Thus, we created a real data set to use in our mathematical models. Two main

parameters are constructed: distance matrix and boolean neighbourhood relation or link relation matrix.

Chapter 6

Computational Analysis

In this chapter, we will analyze the performance measures defined in Chapter 4. The performance measures are the total distance travelled by ambulances, the number of extra disturbance and the number of cities visited in total during the transportation of the orphan drugs. We present how the results change. At first, we analyze each performance measure independently to find the best values for each measure. Moreover, this analysis is done for different number of cities with third level health institutions (denoted as p). Then bi-criteria optimization is done. The performance measure to be optimized was determined to be the minimization of total distance since transmitting the orphan drugs as rapidly as possible is crucial. Therefore, performance measures other than the minimization of distance were restricted as constraints one by one by ϵ-constraint method. Afterwards, a similar analysis is done through three performance measures for each value of p. In this analysis, two performance measures were kept as constant and Pareto-Frontiers are found.

6.1 Analysis on Performance Measures

Firstly, in this chapter, the models (M1), (M2), (M3) are solved independently. The aim is to find the best values for each performance measure as a different number of cities with third level health institutions(denoted as p). Since the number of cities with third level health institutions is 31, the value of p ranges between 1 to 31. Moreover, the objective function values of each performance measure are depicted along with solution times as seen in the tables 6.1a, 6.1b, 6.1c. In table 6.1b, there are two different performance measures and solution times of those performance measures because there are two different objective functions in the model (M2). Therefore, in model (M2), we are solving two different problems. The instances are solved upto 32 threads.

(a) Solution time for solving the model (M1) with minimization of total distance

Number of cities with Hospitals	Solution Time (sec.)	Total Distance (Objective Value)
1	0.43	46986 (Kayseri)
2	0.53	30206 (Ankara, Diyarbakır)
3	6.24	24606
4	8.21	21297
5	13.17	18730
6	12.63	16825
7	11.94	15352
8	7.31	14260
9	6.28	13366
10	3.69	12524
11	3.60	11875
12	3.33	11308
13	2.98	10815
14	2.23	10393
15	2.67	9984
16	1.49	9578
17	1.59	9294
18	1.68	9039
19	1.44	8846
20	1.50	8655
21	1.79	8474
22	1.13	8299
23	0.98	8128
24	1.33	7987
25	1.58	7856
26	1.51	7757
27	1.25	7659
28	0.94	7583
29	0.65	7514
30	0.43	7473
31	0.09	7438

The total distance is important in terms of transmitting the orphan drug as rapidly as possible. The table 6.1a represents the objective values when the total distance is minimized. As the value of p increases, the objective value decreases. However, the decrement is sharp while p changes from 1 to 2. Moreover, the decrement amount also decreases as p-value increases. The decrement amount is lowest while p changes from 30 to 31. So, the gains in distance reduction as p increases has a diminishing return. Also, the model is solved in short solution time for all p values. However, the largest solution time is observed when p =5. While changing the value of p from 2 to 3, the sharpest increment in solution value is observed. On the other hand, the sharpest decrement occurs while changing the value of p from 9 to 10. Also, along with the objective values, the location decisions for p=1 and p=2 are given in paranthesis.

(b) solution time for solving the model (M2) with minimization of total extra disturbance and maximum extra disturbance

Number of cities with Hospitals	solution Time (sec.)	Total Extra Disturbance (Objective Value)	solution Time (sec.)	Maximum Extra Disturbance (Objective Value)
1	0.45	197 (Konya)	0.94	9 (Ankara)
2	4.11	102 (Erzurum, Konya)	4.44	4 (Erzurum, Konya)
3	23.38	76	3.95	3
4	27.05	59	2.86	2
5	105.03	47	2.03	2
6	96.05	37	4.23	2
7	736.23	29	1.11	1
8	13.09	21	0.63	1
9	112.09	16	0.33	1
10	31.19	13	0.31	1
11	16.27	10	0.23	1
12	3.64	8	0.28	1
13	1.67	6	0.27	1
14	1.31	5	0.25	1
15	1.86	5	0.23	1
16	1.38	5	0.28	1
17	1.98	5	0.31	1
18	1.55	5	0.25	1
19	1.19	5	0.23	1
20	1.22	5	0.20	1
21	1.42	5	0.23	1
22	1.17	5	0.25	1
23	1.17	5	0.28	1
24	1.17	5	0.27	1
25	1.23	5	0.17	1
26	0.98	5	0.28	1
27	1.20	5	0.19	1
28	0.78	5	0.19	1
29	0.33	5	0.11	1
30	0.20	5	0.17	1
31	0.08	5	0.09	1

The model (M2) is solved for two objective functions: the total extra disturbance and maximum extra disturbance. The total extra disturbance is important in terms of determining the number of ambulances that should be used while transmitting the orphan drug. In the table 6.1b, objective function values for both performance measures are represented. For both performance measure, as the value of p increases, the objective values decrease. The sharpest decrement occurs when p changes from 1 to 2 in both measures. Similar to pattern in the table 6.1a, the decrement amount also decreases as p-value increases until a value of p. The objective function values stabilize after a certain value of p for each performance measure. For the total extra disturbance, after p=13, the objective function values stabilize at 5. The cities which dispatch ambulances with total extra disturbance for different values of p are Bitlis, Çankırı, Çorum, Nevşehir, Yozgat, Aksaray, Kırıkkale, Şırnak, Karabük, Düzce. However, Çankırı is used only when p =22 and Aksaray is only used when p=19. Çorum, Kırıkkale, Şırnak and Karabük are the cities that dispatch ambulances when value of p is equal to 25, 26, 28, 29 and 30. Moreover, for each value of p, when we analyse the results, we observe that starting from p =14 until p=31, the city Karabük is always used as an extra disturbance. However, between two intervals of values of p, Karabük is used twice as an intermediate city, implying that it dispatches two ambulances for transportation of orphan drugs. This case happens when p ranges from 14 to 22 and from 25 to 30. However, when p is 23 and 24, Karabük also dispatches one ambulance. Moreover, when p=31, Karabük dispatches three ambulances. When p ranges from 15 to 31, there is no other city which dispatches more than one ambulance other than Karabük. These results imply that after certain value of p, the total extra disturbance does not change. As the number of cities for orphan drugs storage increases, the allocation and routing decision can be made such a way that the requirement for intermediate cities is more insignificant. Furthermore, for the maximum extra disturbance, after p=7, the objective function values stabilize at 1. In this case, the model finds a result such a way each city dispatches at most 1 ambulance however the number of cities which dispatches ambulances increases. As the ambulance number per city is decreased, to serve each city, the routing decisions will be made such a way that more intermediate cities are required to be used. Also, along with the objective values, the location decisions for p=1 and p=2 are given in paranthesis for both performance measures.

(c) Solution time for solving the model (M3) with minimization of the number of cities disturbed

Number of cities with Hospitals	Solution Time (sec.)	Number of cities disturbed (Objective Value)
1	15960.62	23 (4.35% gap) (Denizli)
2	21657.40	20 (9.51% gap) (Konya, Tekirdağ)
3	11502.00	18 (5.56% gap)
4	45663.16	16
5	357.26	14
6	52.53	12
7	17.44	10
8	7.28	9
9	12.53	8
10	45.25	7
11	34.36	6
12	5.30	5
13	2.08	4
14	1.22	3
15	0.70	3
16	0.36	3
17	0.36	3
18	0.25	3
19	0.22	3
20	0.17	3
21	0.23	3
22	0.16	3
23	0.22	3
24	0.19	3
25	0.17	3
26	0.11	3
27	0.14	3
28	0.14	3
29	0.08	3
30	0.16	3
31	0.20	3

Table 6.1: Solution time for solving the performance measures

The number of cities disturbed is important in terms of finding the number of cities where an extra ambulance is dispatched. In the table 6.1c, objective function values of this performance measure is represented. As the value of p increases, the objective value decreases. For p=1 to p=3 takes a long time to get results, therefore a time limit of 6 hours is forced on CPLEX to get the results for those value of p. The results with gaps are given in the Table 6.1c and the gap percentages are given in paranthesis. In the table 6.1c, the decrement amount decreases as the value of p increases until a certain value of p. The objective function values stabilize after a certain value of p. After p=13, the objective function values stabilize at 3. The cities which dispatch ambulances for different values of p are Bitlis, Nevşehir, Yozgat, Aksaray, Kırıkkale, Batman, Şırnak, Karabük. For different value of p there are different combinations of those cities as a group of 3. When p ranges between 19 to 25, the cities which are disturbed together are Aksaray, Çankırı and Karabük. Also, when p ranges between 26 to 30, the cities which are disturbed together are Nevşehir, Batman and Karabük. Moreover, Karabük is the city which is used in each p-value ranging between 13 to 31. We can summarize the table 6.1c: as the number of cities for orphan drugs storage increases, the allocation and routing decision can be made such a way that the number of cities disturbed is getting more insignificant. Therefore, the maximum extra disturbance and total extra increase simultaneously to serve each city and to decrease the number of cities disturbed. Also, along with the objective values and gap percentages, the location decisions for p=1 and p=2 are given in paranthesis for the number of cities disturbed.

The models M1, M2 and M3 are constructed by the different performance measures and solved as single-objective optimization problems. All the models are solved for all values of p within short solution times which were expected and it was supported by the results. The results in Tables 6.1 is significant to find the best values for each performance measure. However, the solution set for single-objective problem is not optimal for other performance measures. For instance, when the model (M3) is solved for p=31 with the objective function of the number of cities disturbed, the total distance is found as 9613 and maximum extra disturbance is 3. Nevertheless, those values are not optimal for those performance measures. Therefore, we aim to find alternative solution sets where the other performance measures are also optimized or close to the optimal solution. Next, we

find alternative optimal solutions through bi-criteria optimization.
We use bi-criteria optimization to find alternative solutions for total distance while setting other performance measures to the best value for each values of p. The orphan drug system aims to transmit the orphan drug to the patient quickly. Therefore, the distance travelled is chosen to be the performance measure to be optimized in bi-criteria optimization. Furthermore, the best solution for distance travelled will be found within the alternative solution sets. Also, for the rest of the thesis, the analysis will be done for specific values of p such as 5, 8, 10, 13, 15, 18 and 20. Since the current system involves 15 cities as location decision, the analysis will be done within the range it is included. In the Algorithm 1, we present the methadology used by optimizing the total distance through bi-criteria optimization with respect to the other performance measures. In the Algorithm 1 if $j = 2$, then it represents the total extra disturbance. Also, if $j = 3$, then it represents the maximum extra disturbance. Finally, if $j = 4$, then it represents the number of cities disturbed. In the Algorithm 1, the methadology that is used to find the best alternative solutions for the first performance measure by setting the other performance measures to their best values is explained. Firstly, we set the value of p to a certain value. Then, we solve the model (M4) by optimizing f_1 subject to the additional constraints that $f_j = b_j$. $(\min_{x \in X}\{f_1 | f_j = b_j\})$. b_j is used to refer to the best values of each performance measures for different values of p and it can be referred as f_j^* . In these cases, the best values are the values that are found in Table 6.1.

Algorithm 1 Algorithm for Bi-criteria Optimization with respect to total extra disturbance

Require:
Set the value of p to a certain value.
1: **for** $j = 2 \to 4$ **do**
2: Set b_j to the best value of the performance measure j.
3: Solve the model (M4) by optimizing f_1 subject to the additional constraints that $f_j = b_j$. $(\min_{x \in X}\{f_1 | f_j = b_j\})$
4: **end for**
5: Find the alternative solution set for the first performance measure by setting the j^{th} perofrmance measure to its best value for the certain value of p.
6: Change the value of p and apply the algorithm again.

(a) Comparision of performance measures with the best values under total distance

Number of cities with Hospitals	Objective Value (Total Distance)	Total Extra Disturbance (Best Value)	Maximum Extra Disturbance (Best Value)	Number of Cities Disturbed (Best Value)
5	18730	71(47)	8(2)	29(14)
8	14260	38(21)	5(1)	22(9)
10	12524	22(13)	3(1)	15(7)
13	10815	13(6)	3(1)	8(4)
15	9984	10(5)	3(1)	7(3)
18	9039	10(5)	3(1)	7(3)
20	8655	9(5)	3(1)	6(3)

Table 6.2: The comparision of performance measures

In Table 6.2a, when the main performance measure is the total distance, the values of the other criteria are also given with the best values that they can take in the given value of p. The best values of each criterion can be seen in Tables 6.1 and those values for the given values of p are given in parenthesis in Table 6.2a. As can be seen, the total distance decreases with an increase in the number of hospitals. Moreover, all other criteria decrease with the increase in the value of p. However, it can be recognized that, after a certain value of p, the maximum extra disturbance is stabilizing. Even though there is stabilization, total extra disturbance, maximum extra disturbance and number of cities disturbed are not getting equal to the best values. The location, allocation and routing decisions for the total distance travelled and given p values can be seen in the Figures C.1- C.7 in Appendix C. In Table 6.2a, only total distance is minimized and bi-criteria optimization is not used.

For the following tables, the bi-criteria method will be used. In the Algorithm 1, the methadology for optimization of the first performance measure through bi-criteria optimization with respect to the other performance measures is given. In order to apply the Algorithm 1 for the total extra disturbance, it is important to set $j = 2$. Firstly, we set the value of p to a certain value. Then, we solve the model (M4) by optimizing f_1 subject to the additional constraints that $f_2 = b_2$.

($\min_{x\in X}\{f_1|f_2 = b_2\}$). b_2 is used to refer to the best value of total extra disturbance for different values of p. The best values for total extra disturbance are taken from Table 6.1b. For example, we first set p equal to 5 and then in order to solve the model (M4), we set the value of the total extra disturbance to its best value which is 47 in this example. After solving the model (M4), the solution is noted in Table 6.2b. By changing the value of p, the same methadology is applied for different value of p and those solutions are also noted in Table 6.2b. Next, we present the results found by the methadology metioned in Algorithm 1 for total extra disturbance (when $j = 2$).

(b) Comparision of performance measures with the best values under total extra disturbance

Number of cities with Hospitals	Total Distance (Best Value)-(Deviation)	Objective Value (Total Extra Disturbance)	Maximum Extra Disturbance (Best Value)	Number of Cities Disturbed (Best Value)
5	21575(18730)-(15%)	47	5(2)	28(14)
8	15253(14260)-(7%)	21	2(1)	16(9)
10	13245(12524)-(6%)	13	2(1)	11(7)
13	11234(10815)-(4%)	6	1(1)	6(4)
15	10344(9984)-(4%)	5	1(1)	5(3)
18	9231(9039)-(2%)	5	1(1)	5(3)
20	8777(8655)-(1%)	5	1(1)	5(3)

Table 6.2: The comparision of performance measures

The second performance measure is the total extra disturbance. The first performance measure is optimized through the bi-criteria optimization with respect to the second performance measure. In Table 6.2b, when the second performance set to its optimal value for each value of p, the values of other performance measures are provided along with the best values that are found in the Table 6.1.

A similar trend in Table 6.2a can be seen also in Table 6.2b. While the number of hospitals to be opened is increased, the total distance decreases. The deviation from the best value for total distance is no higher than 15%. All other criteria decrease with the increase in the value of p and it can be recognized that after a certain value of p, the maximum extra disturbance and number of cities disturbed are stabilizing again. However, in this case, maximum extra disturbance values reach the best values when p is greater than and equal to 13. On the other hand, the number of cities disturbed cannot reach down to the best value, but the stabilization happens when p is 13. The deviations from best values are smaller than the cases when the objective is to minimize the total distance. In Table 6.2b, it could be suggested that if we restrict the total extra disturbance to its best value, the maximum extra disturbance is also getting closer and equal to its best value as p increases. The location, allocation and routing decisions for the total extra disturbance and given p values can be seen in the Figures C.8- C.14 in the Appendix C.

In order to apply the Algorithm 1 for the maximum extra disturbance, it is important to set $j = 3$. Firstly, we set the value of p to a certain value. Then, we solve the model (M4) by optimizing f_1 subject to the additional constraints that $f_3 = b_3$. $(\min_{x \in X}\{f_1 | f_3 = b_3\})$. b_3 is used to refer to the best value of maximum extra disturbance which are taken from Table 6.1b. For example, we first set p equal to 5 and then in order to solve the model (M4), we set the value of the maximun extra disturbance to its best value which is 47 in this example. After solving the model (M4), the solution is noted in Table 6.2c. By changing the value of p, the same methadology is applied for different values of p and those solutions are also noted in Table 6.2c. Next, we present the results found by the methadology metioned in Algorithm 1 for maximum extra disturbance (when $j = 3$).

(c) Comparision of performance measures with the best values under maximum extra disturbance

Number of cities with Hospitals	Total Distance (Best Value)-(Deviation)	Total Extra Disturbance (Best Value)	Objective Value (Maximum Extra Disturbance)	Number of Cities Disturbed (Best Value)
5	20462(18730)-(9%)	53(47)	2	36(14)
8	15092(14260)-(6%)	23(21)	1	23(9)
10	12864(12524)-(3%)	16(13)	1	16(7)
13	11005(10815)-(2%)	9(6)	1	9(4)
15	10107(9984)-(1%)	7(5)	1	7(3)
18	9162(9039)-(1%)	7(5)	1	7(3)
20	8777(8655)-(1%)	5(5)	1	5(3)

Table 6.2: The comparision of performance measures

The third performance measure is the maximum extra disturbance. The first performance measure is optimized through the bi-criteria optimization with respect to the third performance measure. In Table 6.2c,when the third performance set to its optimal value for each value of p, the values of other performance measures are provided along with the best values that are found in the Table 6.1.
While the number of hospitals to be opened is increased, the distance decreases. The deviations from the best values for total distance are no higher than 9% and there is stabilization on total distance deviation after p=15. Also, all other criteria decrease with the increase in the p-value, however, it can be seen that there is a pattern of stabilization for the total disturbance and number of cities disturbed after a certain p-value. In Table 6.2b, it could be suggested that minimizing the total extra disturbance also minimizes the maximum extra disturbance, however,

it cannot be deducted from Table 6.2c. Also, the best value of maximum extra disturbance for values of p ranging from 8 to 20 in Table 6.2c is 1. When we analyze the cities for values of p ranging from 8 to 20, the most common ones are Düzce, Karabük, Batman, Nevşehir, İzmit, Çankırı. Those cities dispatch one ambulance for the specified values of p. Moreover, the location, allocation and routing decisions under maximum extra disturbance and given p values can be seen in the Figures C.15- C.21 in Appendix C. In the figure C.16, it can be seen that even though the maximum extra disturbance is 1, Adana receives flows both from Antakya and Osmaniye. There is an exceptional situation. Adana can get orphan drugs from Kahramanmaraş either through Osmaniye or Antakya. However, only one of them gives service to Adana. Let us say that Adana receives service from Osmaniye, then according to the results, Antakya gives service to Mersin through Mersin. However, in this transportation, it does not use the ambulance from Adana. The ambulance of Antakya travels through Adana to meet ambulance of Mersin. The similar case also was seen in the Figure C.15 when p=5 and the maximum extra disturbance is equal to 2. In the Figure C.15, let us assume that Ankara gives service to Bartın and Kastamonu through Karabük. Also, let us assume that Ankara gives service to Yozgat and Çorum through Kırıkkale. Then to give service to Sinop and Samsun, there are exceptional cases. To serve Sinop through Kastamonu, the ambulance of Çankırı travel through Kastamonu to the border of Sinop for transmission of an orphan drug. Also, to give service to the patient in Samsun, the ambulance of Çankırı travels through Çorum to meet with the ambulance of Samsun for transmission of an orphan drug.

In order to apply the Algorithm 1 for the number of cities disturbed, it is important to set $j = 4$. We set the value of p to a certain value and solve the model (M4) by optimizing f_1 subject to the additional constraints that $f_4 = b_4$. $(\min_{x\in X}\{f_1|f_4 = b_4\})$. b_4 is used to refer to the best value of maximum extra disturbance which are taken from Table 6.1c. For instance, we first set p equal to 5 and then in order to solve the model (M4), we set the value of the number of cities disturbed to its best value which is 14 in this example. After solving the model (M4), the solution is noted in Table 6.2d. By changing the value of p, the same methadology is applied for different values of p and those solutions are also noted in Table 6.2d. Next, we present the results found by the methadology metioned in Algorithm 1 for the number of cities disturbed (when $j = 4$).

(d) Comparision of performance measures with the best values under number of cities disturbed

Number of cities with Hospitals	Total Distance (Best Value)-(Deviation)	Total Extra Disturbance (Best Value)	Maximum Extra Disturbance (Best Value)	Objective Value (Number of Cities Disturbed)
5	infeasible (18730)	infeasible (47)	infeasible (2)	infeasible
8	17396 (14260)-(22%)	33(21)	7(1)	9 (12.10% gap)
10	13696(12524)-(9%)	15(13)	3(1)	7
13	11380(10815)-(5%)	8(6)	3(1)	4
15	10570(9984)-(6%)	6(5)	3(1)	3
18	9457(9039)-(5%)	5(5)	3(1)	3
20	9003(8655)-(4%)	5(5)	3(1)	3

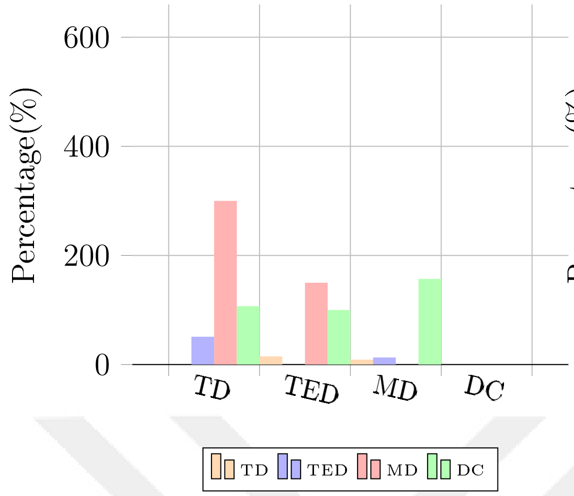
Table 6.2: The comparision of performance measures

The final performance measure is the total number of cities disturbed. The first performance measure is optimized through the bi-criteria optimization with respect to the fourth performance measure. In Table 6.2d, when the fourth performance set to its optimal value for each value of p, the values of other performance measures are provided along with the best values that are found in the Table 6.1. When p= and p=8, it takes too long to get the results, therefore for those values of p, a time limit of 6 hours is forced on CPLEX. Witin 6 hour time limit, when p=5, infeasible solution is found through bi-criteria optimization. Even though there is a feasible solution when p=5 in Table 6.1, through bi-crtieria optimization with time limit, a feasible solution could not be found.
While the number of hospitals to be opened is increased, the distance decreases. The deviation from the best value for total distance is no higher than 9%. Also,

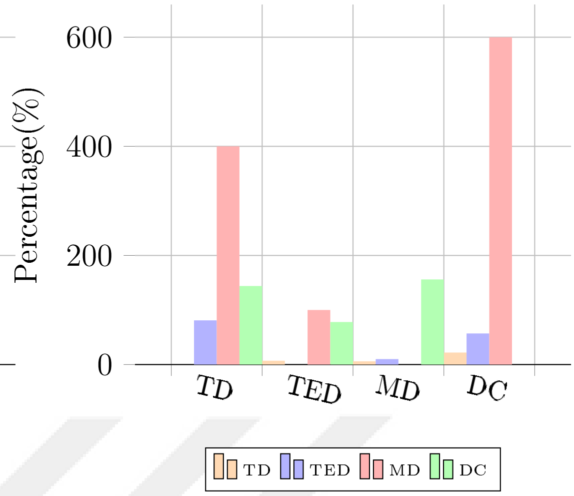
all other criteria decrease with the increase in the p-value, however, it can be seen that there is a pattern of stabilization for the total disturbance and number of cities disturbed after a certain p-value. For maximum extra disturbance, the stabilization occurs after p=10 while for total extra disturbance, the stabilization occurs after p=18. The location, allocation, routing decisions for the number of cities disturbed and given p values can be seen in the Figures C.22- C.26 in Appendix C.

We now provide a visual representation of the information provided in Tables 6.2. The percentage deviations in Tables 6.2 are visualized in two ways. The first visualization of figure 6.1 is based on the behaviour of the values of the performance measures for different values of p. In each graph 6.1, the visual representation of percentage deviations of the four bi-criteria optimization for different values of p are provided. The performance measures are set to their best values and the bars for each performance measure show the deviation of other performance measures from their optimum value on the specific value of p. For example, in Figure 6.1a, the percentage deviations for p=5 is shown. Under the performance measure of TD, the total distance is minimized and the bars are the percentage deviation values of other performance measures. The blue bar represents the percentage deviation of total extra disturbance (TED) measure when we minimize the total distance. The red bar represents the percentage deviation of maximum extra disturbance (MD) measure when we minimize the total distance. Finally, the green bar represents the percentage deviation of the total number of cities disturbed. The orange bar represents the percentage deviation of total distance (TD) measure but there is no bar for total distance under the performance measure of TD since the best value of the total distance is found.

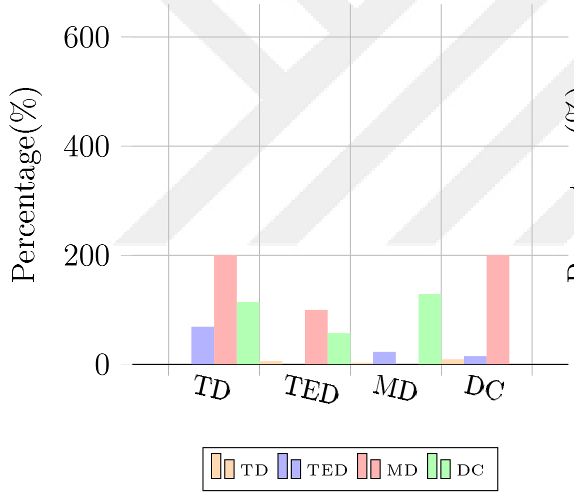
Under the performance measure of TED, the total distance is minimized with bi-criteria optimization by setting the total extra disturbance to the best value. Then the deviations of other performance measures from their best values are given other than total extra disturbance since it is set to its optimal value. Therefore, there is no blue bar since it represents the total extra disturbance. Similarly, when the perofrmance measure is MD, the total distance is minimized with bi-criteria optimization by setting the maximum extra disturbance to the best value. Then the deviations of other performance measures from their best values are given other than maximum extra disturbance since it is set to its optimal value. Therefore, there is no red bar since it represents the total extra disturbance.



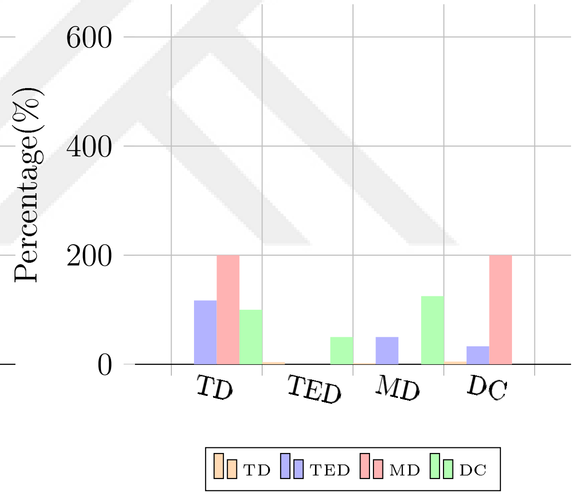
(a) Percentage Deviation when p=5



(b) Percentage Deviation when p=8

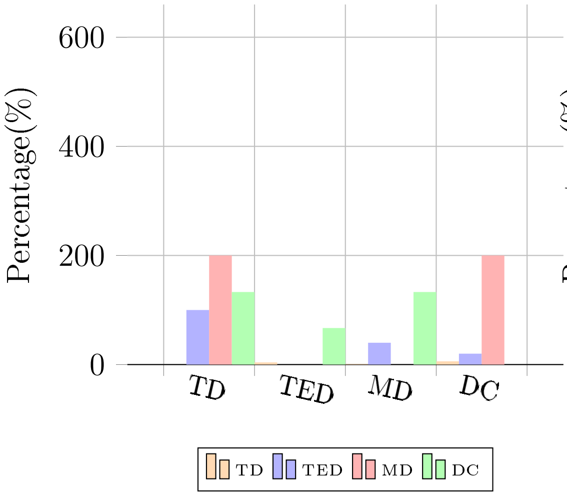


(c) Percentage Deviation when p=10

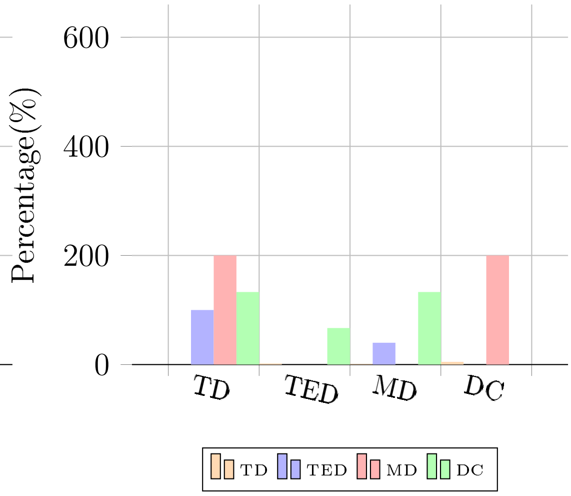


(d) Percentage Deviation when p=13

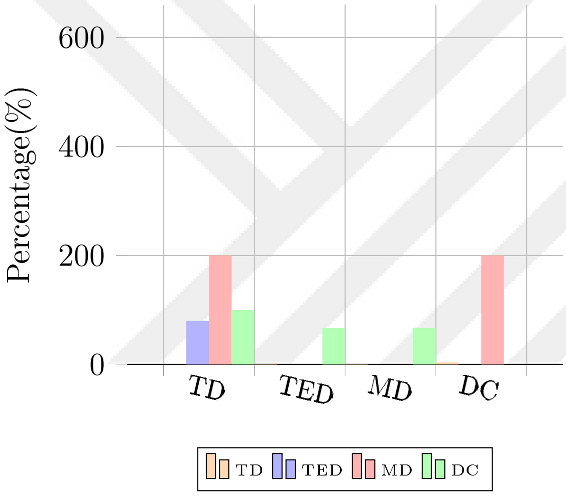
Figure 6.1: The Percentage Deviation



(e) Percentage Deviation when p=15



(f) Percentage Deviation when p=18



(g) Percentage Deviation when p=20

Figure 6.1: The Percentage Deviation

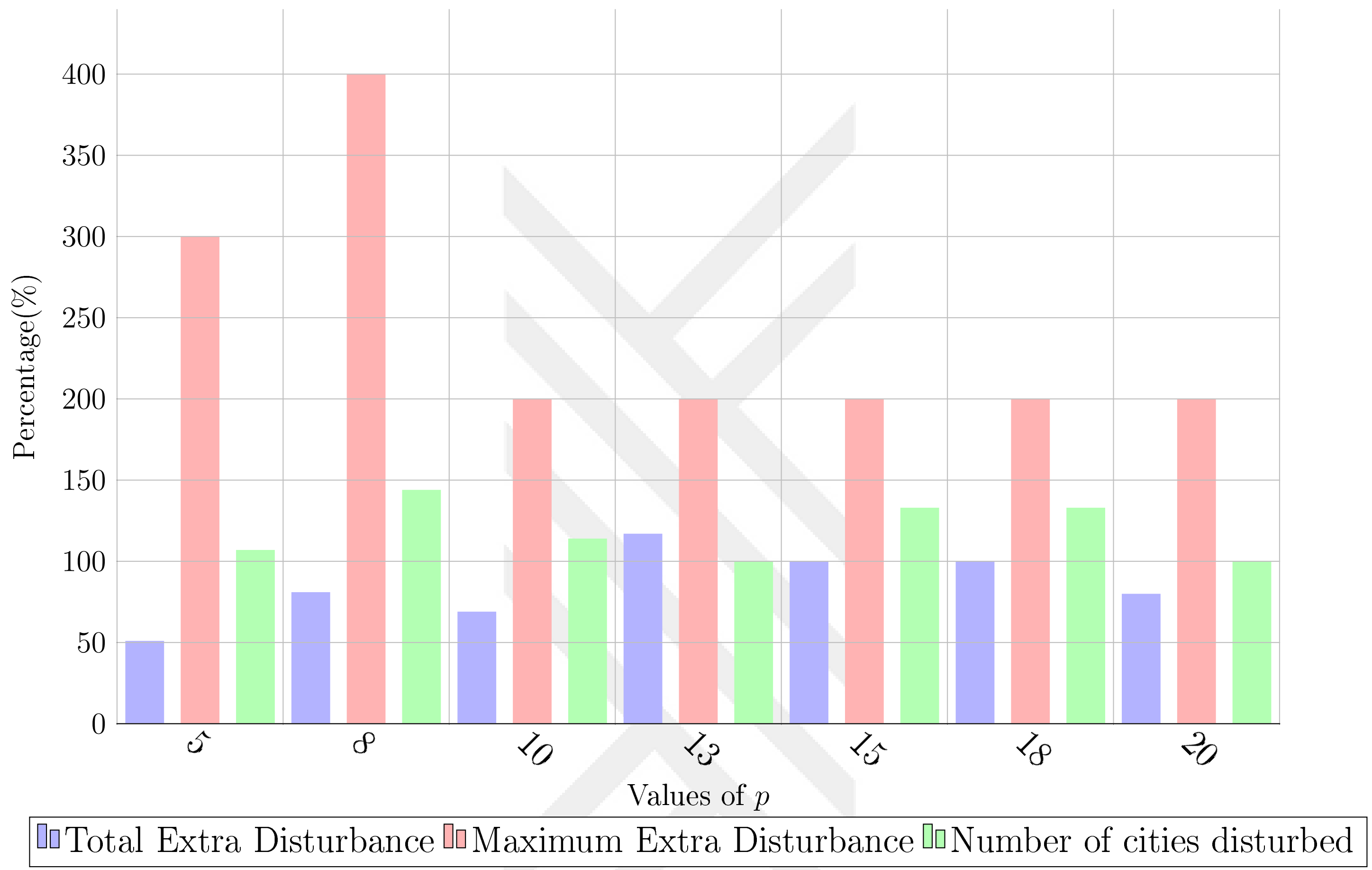
This representation is applied to different values of p. In the graphs, it can be seen that maximum extra disturbance is the performance measure which has generally the highest deviation from the best value for the given values of p. Also, under the performance measure TD, the deviation of total extra disturbance is higher than the cases under the performance measure MD and the performance measure DC for given p values.

As the value of p increases, the percentage deviation of the total distance from the best value decreases for any performance measure. When the performance measures are TED and MD, the deviation for the total distance decreases from 15% and 9% respectively to 1%. However, when the performance measure is DC, the deviation decreases from 9% to 4%. It implies that the percentage deviation for the total distance is not getting as small as other performance measure under DC

The percentage deviation of total extra disturbance does not show a recognizable pattern. Under any performance measure, there are increments and decrements in the deviation of total extra disturbance as the values of p changes.

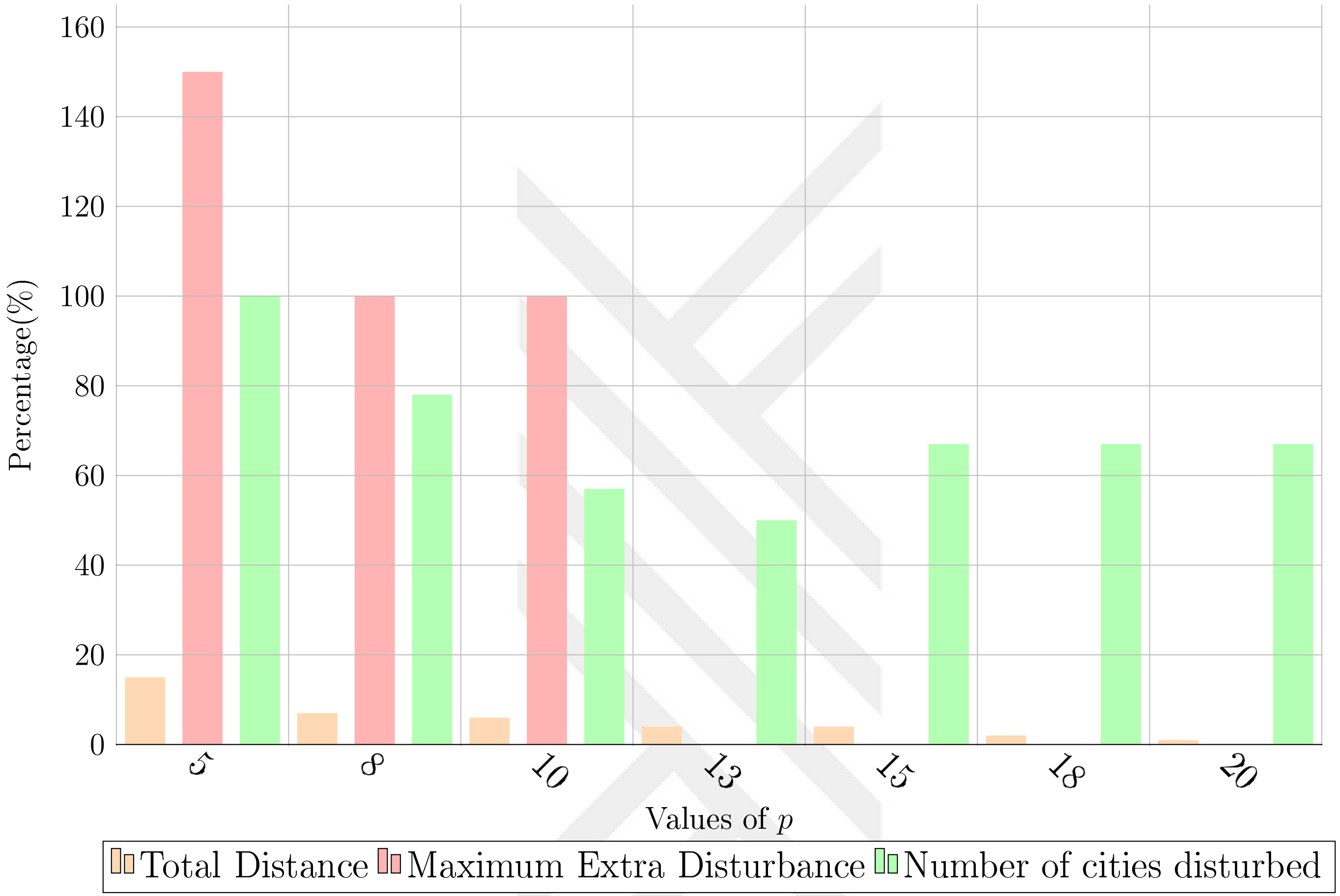
As the value of p increases, the percentage deviation of maximum extra disturbance from the best value decreases generally for any performance measure. There is only one exception when p=8 and under performance measure TD, it increases. When the performance measure is TED, the deviation decreases drastically and the deviation becomes 0% implying the optimal value for the maximum extra disturbance. Furthermore, the percentage deviation of the number of cities disturbed has lower values under the performance measure MD. However, in general, the results could imply that the number of cities disturbed may not reach optimality as p increases, however, the deviation decreases.

Next, we provide another visual representation for the information provided in Tables 6.2. In the second visualization of percentage deviations, the difference with respect to change in p is analyzed and all values of p for the other three criteria are shown in a graph for a certain main performance measure. Those representations are given in graphs 6.2a for total distance, 6.2b for total extra disturbance, 6.2c for maximum extra disturbance, 6.2d for the number of cities disturbed.



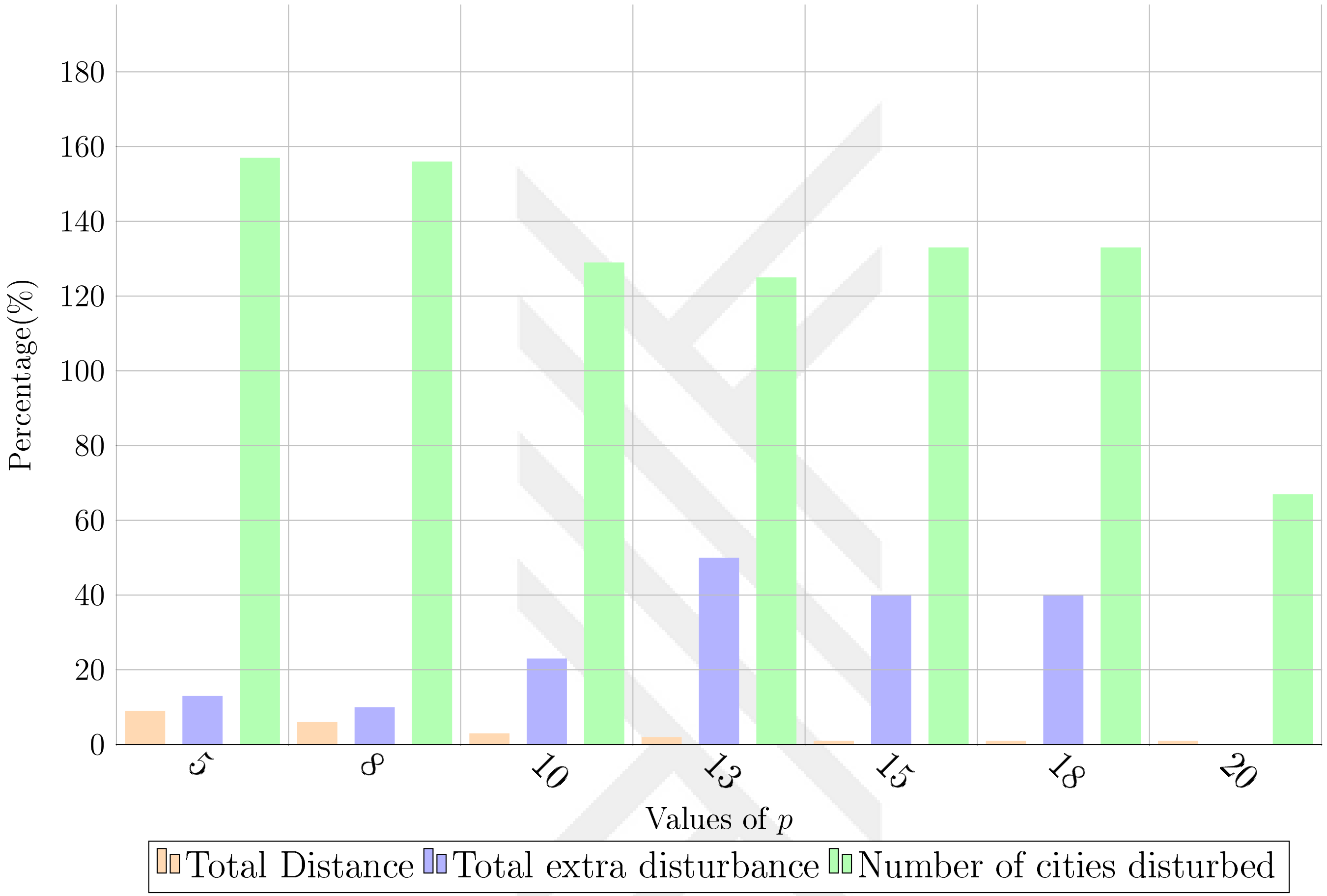
(a) Percentage Deviation When Main Performance Measure is to Minimize Total Distance

Figure 6.2: The Percentage Deviation for different p values



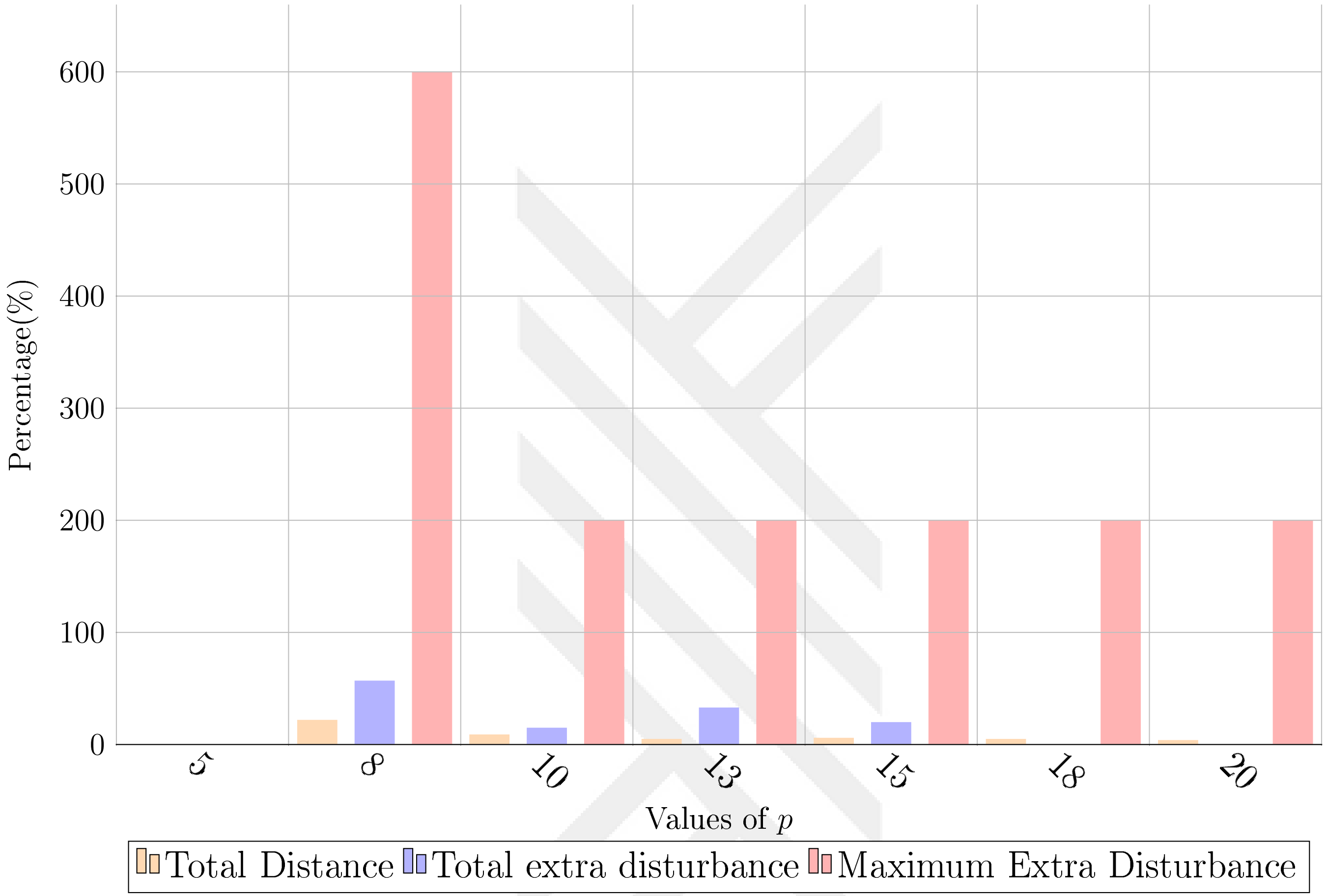
(b) Percentage Deviation When Main Performance Measure is to Minimize Total Extra Disturbance

Figure 6.2: The Percentage Deviation for different p values



(c) Percentage Deviation When Main Performance Measure is to Minimize Maximum Extra Disturbance

Figure 6.2: The Percentage Deviation for different p values



(d) Percentage Deviation When Main Performance Measure is to Minimize Number of Cities Disturbed

Figure 6.2: The Percentage Deviation for different p values

As it can be seen in graphs 6.2b, 6.2c, 6.2d, the percentage deviations of the total distance are below 20% for different p values given under all other three performance measures. Next, we analyze the percentage deviation of total extra disturbance under other three performance measures (total distance in graph 6.2a , maximum extra disturbance in graph 6.2c, number of cities disturbed in graph 6.2d). The percentage deviation of total extra disturbance is generally higher when the main performance measure is the total distance than other performance measures. Moreover, when we analyze the graphs 6.2a, 6.2b and 6.2d, the percentage deviation of maximum extra disturbance is generally low under the minimization of total extra ambulance(6.2b). However, there is not a pattern for the percentage deviation of the maximum extra disturbance. Finally, the percentage deviation of the number of cities disturbed generally lower under total extra ambulances(6.2b) than other performance measures. The location, allocation and routing decisions for each performance measure and given p values can be seen in Appendix C.

6.2 Pareto-Frontiers

For Pareto-optimal solutions, ϵ-Constraint method is used and the performance measure to be optimized is total distance while the other performance measures are added as constraints to the model. In the ϵ-Constraint method the total distance is selected to be optimized with respect to the other three performance measures. For the other three performance measures, a range is set and we find Pareto-optimal solutions which are the non-dominated solutions of the entire feasible decision space. Also, they are the solutions which cannot be improved without degregading at least one of the performance measures. The range varies between the best value of each performance measure and the value of performance measure when the total distance is minimized. The ranges can be taken from the Table 6.2a for the three performance measure. For a certain value of p, the upper limits for total extra disturbance can be decided by the values in the coloumn of total extra disturbance in the Table 6.2a. Also, the lower limit can be decided by the objective value represented in Table 6.2a by the best value in the coloumn of total extra disturbance. For example, we want to find the Pareto-Frontier for p=5 for the first

and second performance measures (total distance and total extra disturbance). Then, the range for total extra disturbance is set as 47 to 71 by the Table 6.2a. The optimal value of total extra disturbance is 47 and we set the lower limit (l_2). Moreover, when only the total distance is minimized, the value of total extra disturbance is 71. In this case, we set the upper limit (u_2) for the range of total extra disturbance. Moreover, when p=5, the highest maximum extra disturbance value is 8 from Table 6.2a and the lowest maximum extra disturbance value is 2 from Table 6.2a. Then, we set the range for the number of cities disturbed. When p=5, the range for total extra disturbance is set as 14 to 29 by the Table 6.2a. For each performance measure and for different values of p, the ranges are as explained. After deciding the ranges, we have used ϵ-Constraint method for different values of p and different performance measures.
The algorithm that is used for ϵ-Constraint method is given in Algorithm 2. Firstly, we set the number of cities with proper hospitals to a certain value. Then for a certain value of p, we find an optimal solution x^1 for the total distance f_1 in the model (M4). For the same value of p, the upper limits for other three performance measures (f_j) are defined as u_j as explained previously. For example, when p=5, the upper value (u_2) for total extra disturbance (f_2) is 71. Then, ϵ_j is set to the u_j for each f_j. For ϵ-Constraint method, the step size for each performance measure is determined. Then we solve the model (M4) by optimizing the total distance by adding additional constraints $f_j \leq \epsilon_j$. After solving the model, the ϵ_j is decreased by the decrement amount. Algorithm continues as long as there are feasible points. After completing all steps, the Pareto-Frontiers with respect to first and j^{th} performance measures are drawn. Then, by changing the values of p, the same procedure is applied again. The Pareto-frontier for p=5 can be seen in graph 6.3. For clarity, we can represent the Algorithm 2 for the Pareto-frontier in the graph 6.3. The Algorithm 3 is the representation of the Algorithm 2 for the Pareto-frontier in the graph 6.3.

Algorithm 2 Algorithm for ϵ-Constraint Method

Require:

Set the value of p to a certain value.

Find x^1 an optimal solution for f_1 by the model (M4) for certain value of p.

for $j = 2 \rightarrow 4$ **do**

  Determine u_j values.

  Set ϵ_j to u_j. ($\epsilon_j \leftarrow u_j$)

  Determine the step size for each performance measure f_j. (It is decided as 1 for each performance measure)

  while $\min_{x \in X}\{f_1 | f_j \leq \epsilon_j\}$ is feasible **do**

    Solve the model (M4) by optimizing f_1 subject to the additional constraints that $f_j \leq \epsilon_j$. ($\min_{x \in X}\{f_1 | f_j \leq \epsilon_j\}$)

    Change the value of ϵ_j by step size which is 1. ($\epsilon_j \leftarrow \epsilon_j - stepsize$)

    The Pareto-optimal solutions are found for the first and for the j^{th} performance measures for the certain value of p.

  end while

end for

Change value of p and apply the algorithm again.

From the graph 6.3, it can be seen that as the value of total extra disturbance increases, the total distance travelled decreases. For other p-values, the Pareto-frontiers for the first and second performance measures are also drawn and they are shown in Appendix C.27- C.32. Similarly, the Pareto-Frontiers for different p-values for total distance and maximum extra disturbance are drawn and the graphs can be seen in Appendix C.33 - C.39. Finally, the Pareto-Frontiers for different p-values for total distance and number of cities disturbed are drawn and the graphs can be seen in Appendix C.40- C.44.

Algorithm 3 Algorithm for ϵ-Constraint Method- Sample Application for p=5 with respect to total extra disturbance

Require:

Set value of p to 5.

Find x^1 an optimal solution for f_1 by the model (M4) for p=5.

for $j = 2$ **do** $\triangleright$ $j = 2$ is representation of the total extra disturbance

  Determine u_2 value.

  Set ϵ_2 to u_2. ($\epsilon_2 \leftarrow u_2$)

  Determine the step size for total extra disturbance f_2. $\triangleright$ decided as 1.

  while $\min_{x \in X}\{f_1 | f_2 \leq \epsilon_2\}$ is feasible **do**

    Solve the model (M4) by optimizing f_1 subject to the additional constraints that $f_2 \leq \epsilon_2$. ($\min_{x \in X}\{f_1 | f_2 \leq \epsilon_2\}$)

    Change the value of ϵ_2 by step size which is 1. ($\epsilon_2 \leftarrow \epsilon_2 - 1$)

    The Pareto-optimal solutions are found for the first and for the 2^{nd} performance measures for p=5.

  end while

end for

Change the value of p and apply the algorithm again.

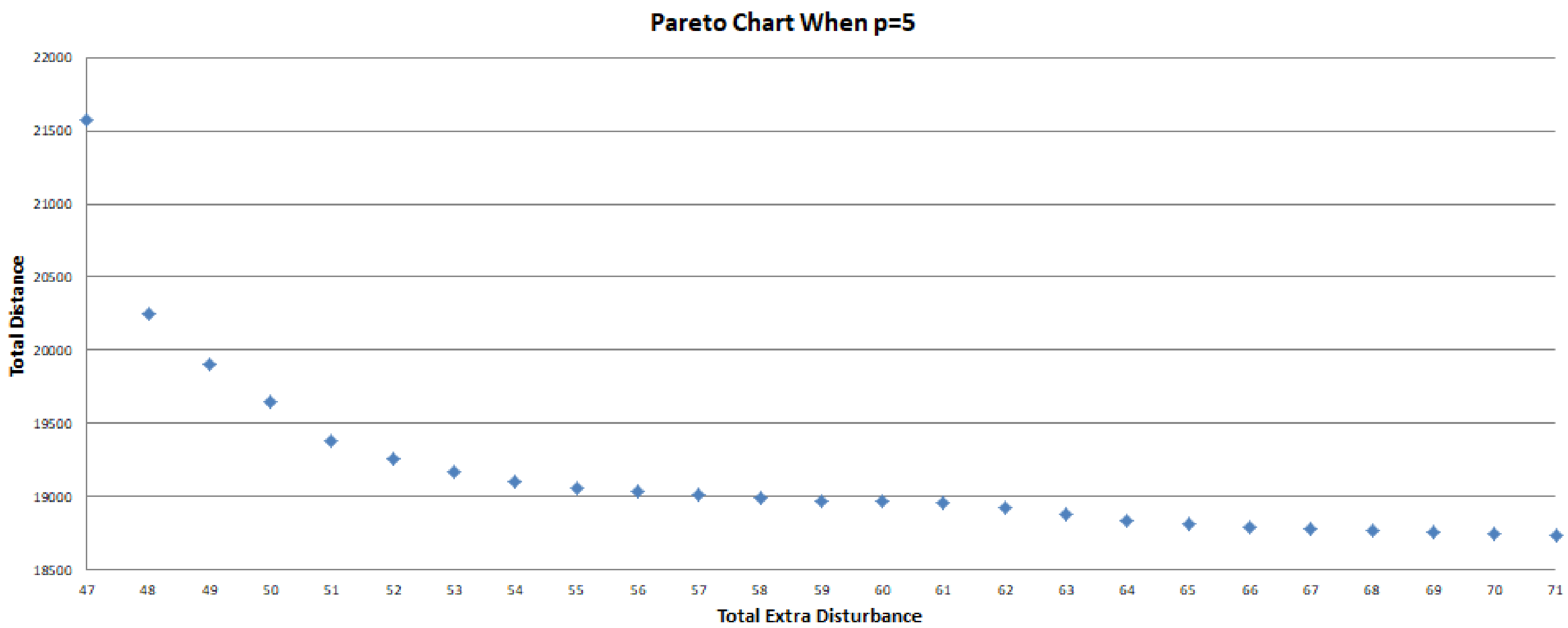


Figure 6.3: Pareto chart for TDE as Epsilon constraint When p=5

Thus far, Pareto-frontiers are drawn between only two performance measures. One of them is optimized while the other performance measure is added as a constraint. Since we are dealing with multiple performance measures, we will extend the analysis further by including four performance measures. There will be one performance measure to be optimized, one performance measure to be added as a constraint and finally, the other two performance measures to be kept as constant. Therefore, we will reduce problems by fixing the two of the performance measures constant. In order to decide which performance measures to choose for fixing, we analyzed each performance measure. Since the primal performance measure is the total distance, it will be the main one to be optimized. Throughout the analysis so far, it is been noticed that values for total extra disturbance deviate less from the best values when compared with third and fourth performance measures. Therefore, ϵ-constraint method is used with the total extra disturbance. In that case, the fixed performance measures are chosen to be both maximum extra ambulance and the number of cities disturbed and the ranges are set for them.

The range for each constant criterion at each value of p is decided by the values in Tables 6.2a, 6.2c, 6.2d. For example, when p=8, the highest DC value is 22 from Table 6.2a and the lowest DC value is 9 from Table 6.2d. First, the number of cities disturbed will be kept constant at 22. Then, we set the range for the maximum extra disturbance. When p=8, the maximum extra disturbance criteria have taken values ranging from 1 to 6 at different DC values.

When the objective is the minimization of the number of cities disturbed, the DC value is getting its lowest value. The same logic is applied for maximum extra disturbance criteria. When the objective is the minimization of the maximum extra disturbance, the objective value is the lower bound for this criteria as it can be seen in Table 6.2c. Also, since our primal objective is the total distance, the maximum extra disturbance upper value is decided by the value in Table 6.2a. The range for each performance measure in different values of p are decided in this manner. As another example, when p=10, the upper value of DC is 15 and the lower value of DC is 7. On the other hand, when p=10, the upper value of MD is 3 and the lower value of MD is 1.

The algorithm that is used for ϵ-Constraint method by keeping 2 of the performance measure constant is given in Algorithm 4. In this part, we look for Pareto-Frontiers for total distance and total extra disturbance by keeping maximum extra

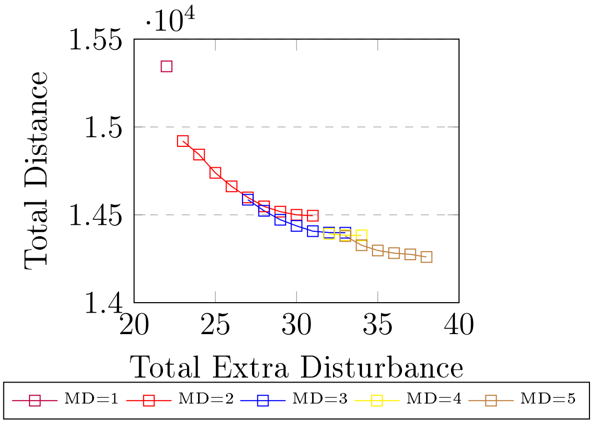
disturbance and the number of cities disturbed constant. Firstly, again, we set the number of cities with proper hospitals to a certain value. Then, for a certain value of p, we set range for the number of cities disturbed as explained in the Algorithm 2. Also, for a certain value of p, we set range for the maximum extra disturbance as mentioned in the Algorithm 2. Afterwards, we find an optimal solution x^1 for the total distance f_1 in the model (M4) by keeping both f_4 and f_3 constant at their upper limits. For example, when p=8, the lower value (l_4) for the number of cities disturbed f_4 is 22 while the upper value (u_4) for the number of cities disturbed (f_4) is 8. Then, we set the number of cities disturbed equal to the upper value (22). The lower value (l_3) for the maximum extra disturbance f_3 is 1 while the upper value (u_3) for the maximum extra disturbance (f_3) is 5. Then, we set the maximum extra disturbance equal to the upper value (5).
Since we try to find the Pareto-Frontiers for total distance and total extra disturbance, ϵ_2 for total extra disturbance is set to the u_2. Then, for ϵ-Constraint method, the step size for total extra disturbance is determined. The step-size is determined to be 1. Then we solve the model (M4) by optimizing the total distance by adding additional constraints $f_2 \leq \epsilon_2$. After solving the model, ϵ_2 is decreased by 1 (step size). As long as there are feasible points, algorithm continues. After completing all steps, the Pareto-Frontiers with respect to first and j^{th} performance measures for the certain value of p are drawn. After drawing Pareto-Frontiers for $j = 2, 3, 4$, the value of p is changed and the same procedure is applied again. Algorithm 4 is a version of Algorithm 2 for two specific performance measures.

Algorithm 4 Algorithm for ϵ-Constraint Method by keeping two performance measures constant-Pareto Charts based on the Number of Cities Disturbed

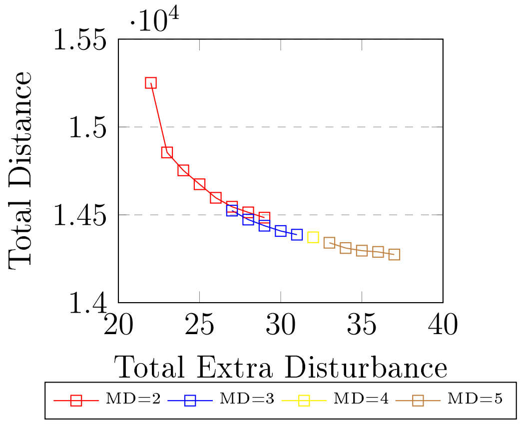
Require:

Set value of p to a certain value.
Set ϵ_2 to u_2 for the given value of p. ($\epsilon_2 \leftarrow u_2$)
Set ϵ_4 to u_4 for the given value of p. ($\epsilon_4 \leftarrow u_4$)
Set ϵ_3 to u_3 for the given value of p. ($\epsilon_3 \leftarrow u_3$) Determine the step size for total extra disturbance f_2.

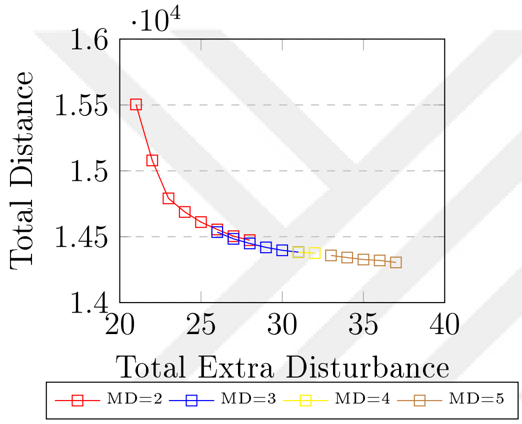
```
for f_4 = ε_4 do
    for f_3 = ε_3 do
        while min_{x∈X}{f_1 | f_2 ≤ ε_2, f_3 = ε_3, f_4 = ε_4} is feasible do
            Solve the model (M4) by optimizing f_1 subject to the additional
            constraints that f_2 ≤ ε_2, f_3 = ε_3, f_4 = ε_4. (min_{x∈X}{f_1 | f_2 ≤ ε_2, f_3 = ε_3, f_4 = ε_4})
            Change the value of ε_2 by step size. (ε_2 ← ε_2 − stepsize)
            The Pareto-optimal solutions are found for the first and the second
            performance measures by the constant values of third and fourth performance
            measures for the certain value of p
        end while
        Change the value of ε_3 by the step size which is 1.
    end for
    Change the value of ε_4 by the step size which is 1.
    Set ε_3 to u_3 for the next value of the number of cities disturbed (ε_3 ← u_3)
end for
Change the value of p and apply the algorithm again.
```



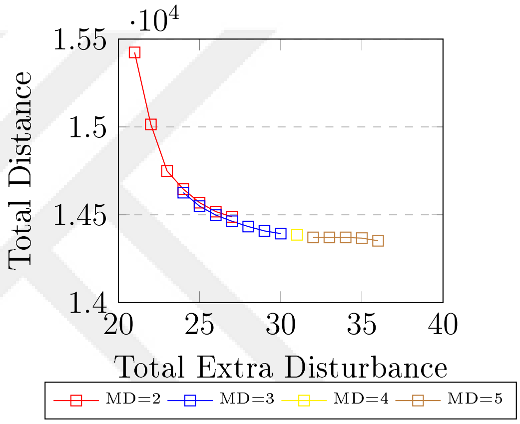
(a) p=8 & Number of Disturbed Cities is 22



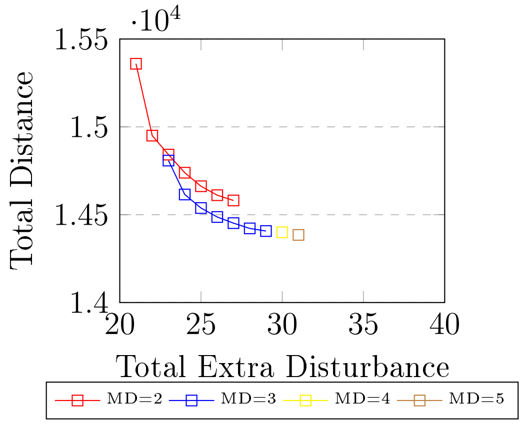
(b) p=8 & Number of Disturbed Cities is 21



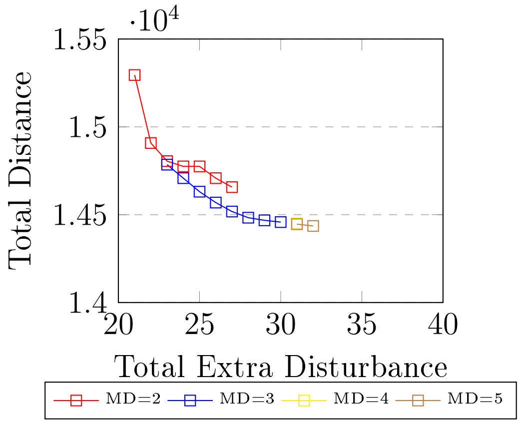
(c) p=8 & Number of Disturbed Cities is 20



(d) p=8 & Number of Disturbed Cities is 19

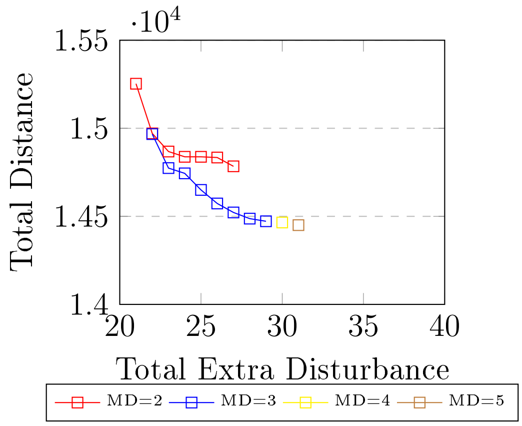


(e) p=8 & Number of Disturbed Cities is 18

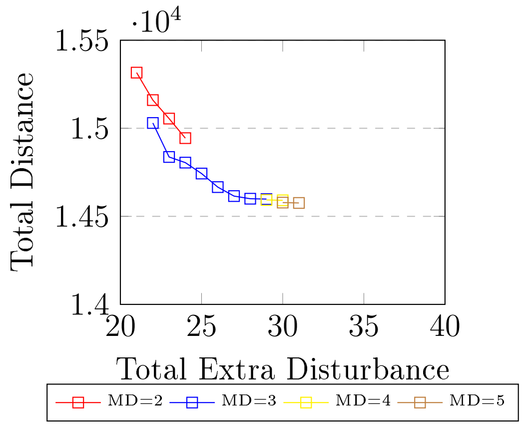


(f) p=8 & Number of Disturbed Cities is 17

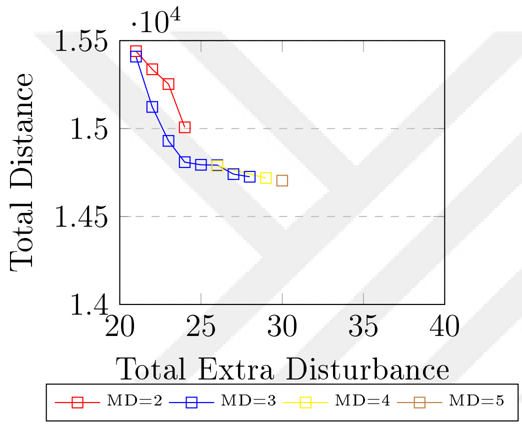
Figure 6.4: Pareto Charts on disturbed city values when p=8



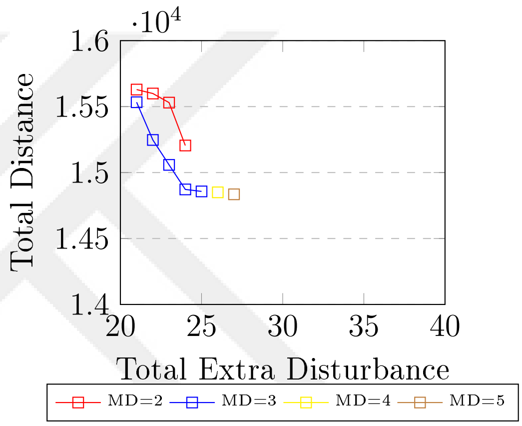
(g) p=8 & Number of Disturbed Cities is 16



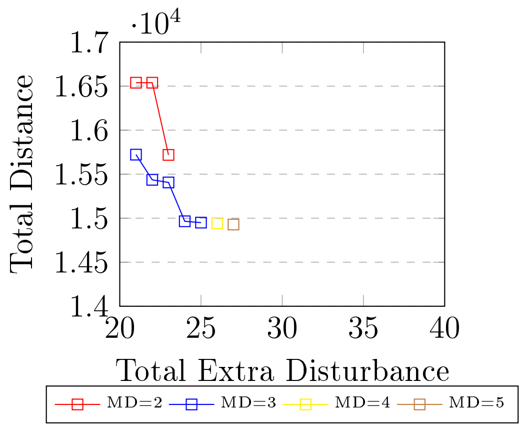
(h) p=8 & Number of Disturbed Cities is 15



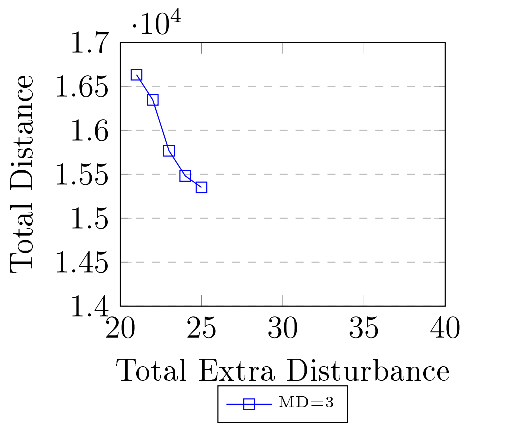
(i) p=8 & Number of Disturbed Cities is 14



(j) p=8 & Number of Disturbed Cities is 13

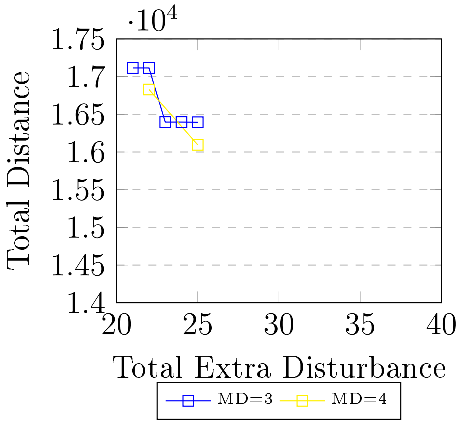


(k) p=8 & Number of Disturbed Cities is 12

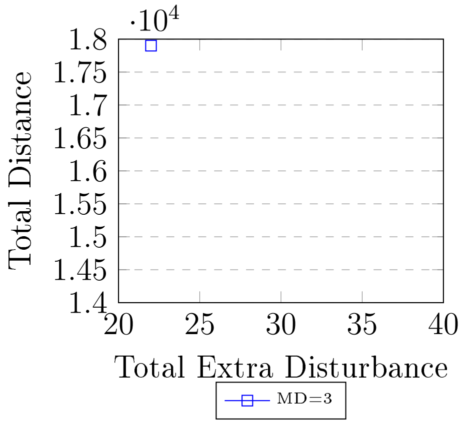


(l) p=8 & Number of Disturbed Cities is 11

Figure 6.4: Pareto Charts on disturbed city values when p=8



(m) p=8 & Number of Disturbed Cities is 10

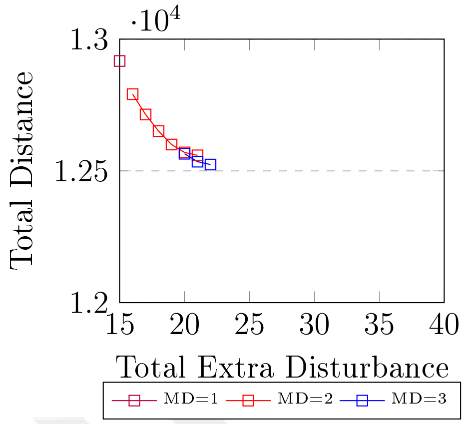


(n) p=8 & Number of Disturbed Cities is 9

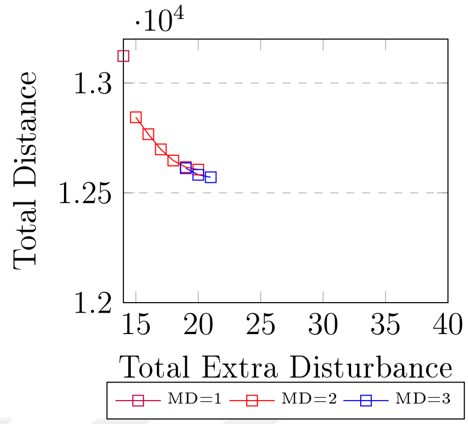
Figure 6.4: Pareto Charts on disturbed city values when p=8

In the graphs 6.4, when DC is ≥17 for maximum extra disturbance(MD) around 2 and 3, the total extra disturbance does not exceed 30 and the total distance does not exceed 15504. For higher maximum extra disturbance values such as 4, 5 and 6 the total extra disturbance does not exceed 40. Also, when MD=4 the number of solutions are very limited. The number of Pareto-optimal solutions of MD=5 is usually more than the number of Pareto-optimal solutions of MD=4. It can be said that MD=4 is not a very good choice due to the limited number of solutions. When p=8 and DC is $\geq$ 17, for all maximum extra disturbance values, the total distance gets smaller values as total extra disturbance value increases. However, when the maximum extra disturbance is 3, the values of total distance is lower than the values in case of maximum extra disturbance of 2. As maximum extra disturbance increases along with the total extra disturbance, the total distance gets smaller values. However, the Pareto-optimal solutions are very limited when the maximum extra disturbance is 4 and 5. Also, if the total extra disturbance is not preferred to be more than 23, the first objective is feasible only when MD=2. When DC is ≤16 and DC is ≥12, the Pareto charts show values from MD=2 to MD=5. Again, when MD=3, the total distance is lower than the points when MD=2. It can be interpreted that as total extra disturbance increases, the first objective gets lower values with larger maximum extra disturbance values. Also, after DC ≤11, the charts do not show any pattern. Similar charts are derived for

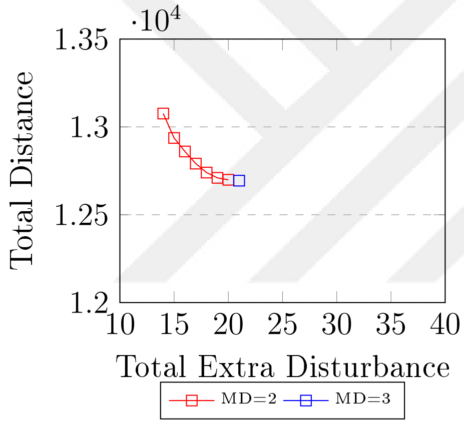
p=10 and depicted in Figures 6.5.



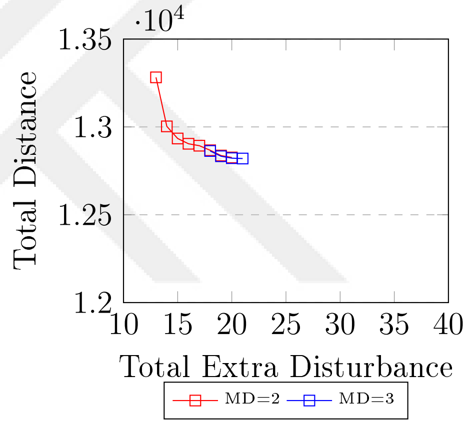
(a) p=10 & Number of Disturbed Cities is 15



(b) p=10 & Number of Disturbed Cities is 14

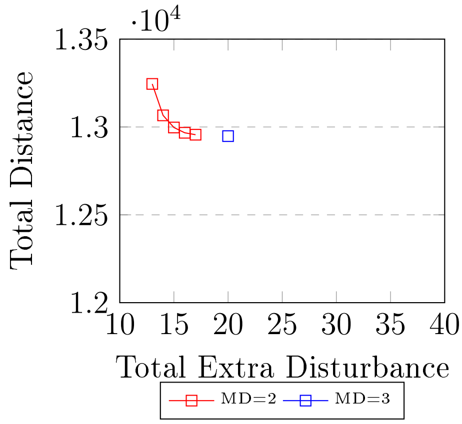


(c) p=10 & Number of Disturbed Cities is 13

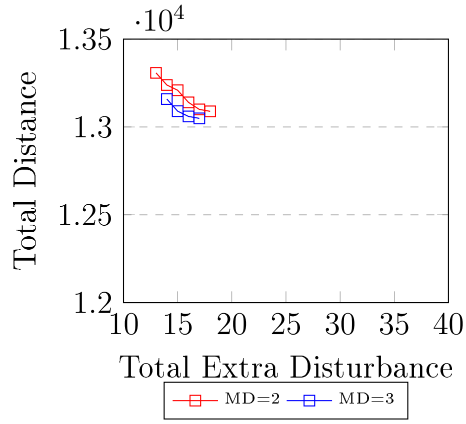


(d) p=10 & Number of Disturbed Cities is 12

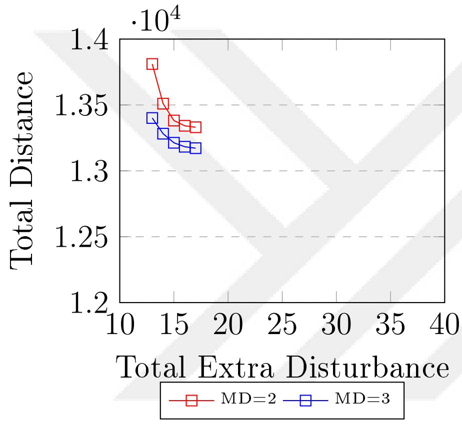
Figure 6.5: Pareto Charts on disturbed city values when p=10



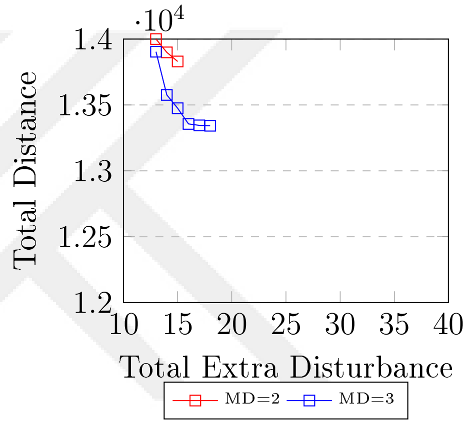
(e) p=10 & Number of Disturbed Cities is 11



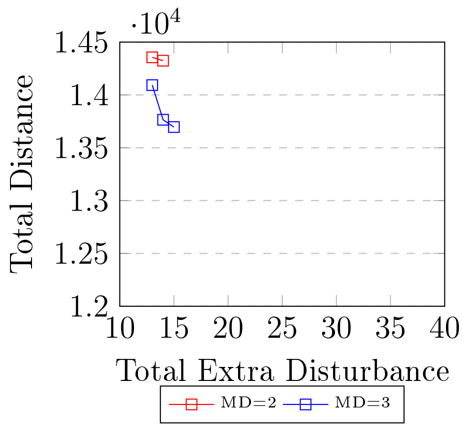
(f) p=10 & Number of Disturbed Cities is 10



(g) p=10 & Number of Disturbed Cities is 9



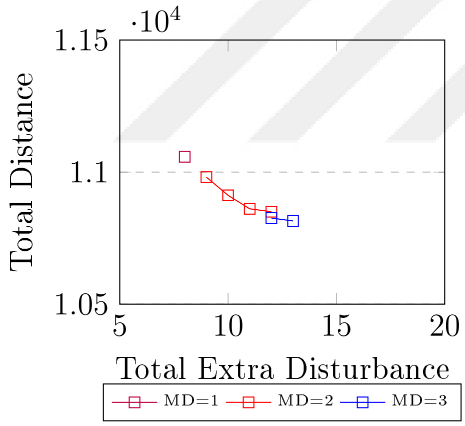
(h) p=10 & Number of Disturbed Cities is 8



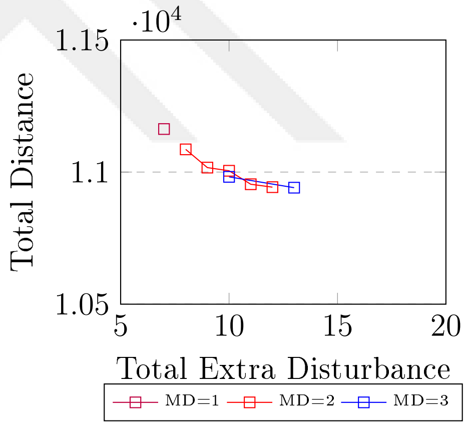
(i) p=10 & Number of Disturbed Cities is 7

Figure 6.5: Pareto Charts on disturbed city values when p=10

In the graphs 6.5, when DC is ≥14, for maximum extra disturbance around 2 and 3, the total extra disturbance does not exceed 30 and the total distance does not exceed 13000. In this case, the MA values cannot get higher values than 3, therefore, the maximum extra disturbance cannot take values such as 4, 5 and 6. Moreover, in Pareto charts 6.5, when MD=3 the number of Pareto-optimal solutions are smaller than the Pareto-optimal solution of MD=2. When p=10 and DC is ≥ 14, for all maximum extra disturbance values, the total distance gets smaller value as total extra disturbance value increases. However, when the maximum extra disturbance is 3, the total distance is better than the values in case of maximum extra disturbance of 2. As maximum extra disturbance increases along with the total disturbance, the total distance gets smaller values. When DC is ≤13 and DC is ≥11, when MD=3, the value of total distance is lower than the values of total distance when MD=2. Moreover, when DC is ≤10 and MD=3, the total distance gets lower values. Next, similar charts derived for p=13 are analyzed and those charts are depicted in Figures 6.6.

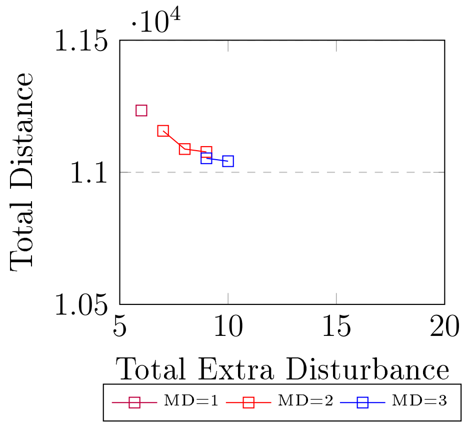


(a) p=13 & Number of Disturbed Cities is 8

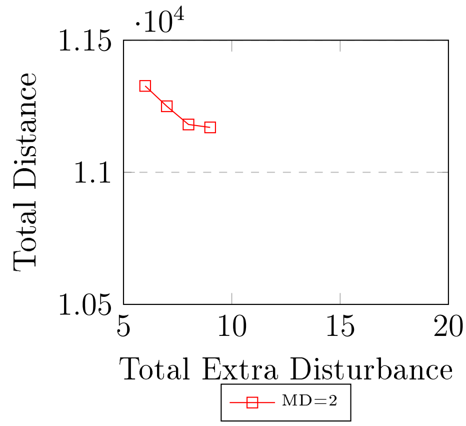


(b) p=13 & Number of Disturbed Cities is 7

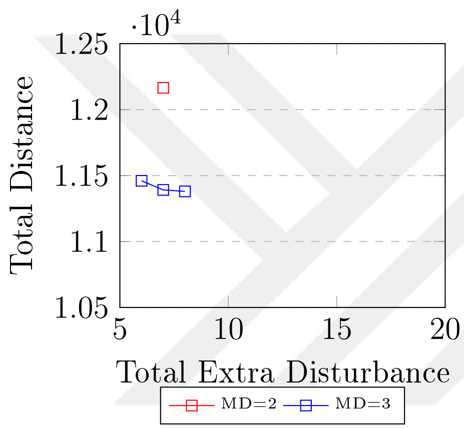
Figure 6.6: Pareto Charts on disturbed city values when p=13



(c) p=13 & Number of Disturbed Cities is 6



(d) p=13 & Number of Disturbed Cities is 5



(e) p=13 & Number of Disturbed Cities is 4

Figure 6.6: Pareto Charts on disturbed city values when p=13

In the graphs 6.6, when DC ranges between 4 and 8, the MA takes values of 2 and 3. The number of Pareto-optimal solutions is decreasing as value of p increases. When DC is equal to 8, 6 and 4, the total distance gets lower values with MD=3. Furthermore, in Pareto charts 6.6, when MD=3 the number of Pareto-optimal solutions are generally less than the Pareto-optimal solution of MD=2. However, when DC is equal to 5, there are no Pareto-optimal solutions for MD=3. In general, it can be interpreted that as total extra disturbance increases, the maximum extra disturbance should increase for lower value of first objective value.
For p=15, those Pareto charts are put into Appendix ranging from C.45a to C.45d

and for p=18, those Pareto charts are put into Appendix ranging from C.46a to C.46e. Similar analysis can be done for those charts.
Next, we analyze the Pareto Charts constant value of the maximum extra disturbance criteria. In those charts, we add Pareto-Charts for the distinct constant value of the number of cities disturbed and for specific value of maximum extra disturbance. The Pareto charts are given in figures 6.7, 6.8, 6.9, 6.10. Those charts are actually similar to the previous Pareto charts for different values of p. The range for maximum extra disturbance and the number of disturbed cities from the previous charts are applied. Then, the maximum extra disturbance and the number of cities disturbed are kept constant, however the Pareto charts for a specific value of the maximum extra disturbance and different values of the number of cities disturbed are drwn together. The Pareto-optimal solution for the first and second performance measures are drawn when MD=2 for different number of cities disturbed. Then, for MD=3, the similar procedure is applied and Pareto-optimal solutions are drawn and added to the same graph with MD=2. As the value of maximum extra disturbance increased, the number of cities disturbed is changed and the Pareto optimal solutions for first and second performance measure are drawn. Another algorithm that is used for ϵ-Constraint method by keeping 2 of the performance measure constant is given in Algorithm 5. In this part, again we look for Pareto-Frontiers for total distance and total extra disturbance by keeping maximum extra disturbance and the number of cities disturbed constant. However, the performance measure that we keep constant initially changes and therefore the visual presentation of the graphs change. Also, for this analysis, the value of maximum extra disturbance 1 is not included.

Algorithm 5 Algorithm for ϵ-Constraint Method by keeping two performance measures constant-Pareto Charts based on Maximum Extra Disturbance

Require:

Set the value of p to a certain value.
Set ϵ_2 to u_2 for the given value of p. ($\epsilon_2 \leftarrow u_2$)
Set ϵ_3 to u_3 for the given value of p. ($\epsilon_3 \leftarrow u_3$)
Set ϵ_4 to u_4 for the given value of p. ($\epsilon_4 \leftarrow u_4$) Determine the step size for total extra disturbance f_2.

for $f_3 = \epsilon_3$ **do**
  for $f_4 = \epsilon_4$ **do**
    while $\min_{x \in X}\{f_1 | f_2 \leq \epsilon_2, f_3 = \epsilon_3, f_4 = \epsilon_4\}$ is feasible and $\epsilon_3 > 1$ **do**
      Solve the model (M4) by optimizing f_1 subject to the additional constraints that $f_2 \leq \epsilon_2, f_3 = \epsilon_3, f_4 = \epsilon_4$. ($\min_{x \in X}\{f_1 | f_2 \leq \epsilon_2, f_3 = \epsilon_3, f_4 = \epsilon_4\}$)
      Change the value of ϵ_2 by step size. ($\epsilon_2 \leftarrow \epsilon_2 - stepsize$)
    end while
    The Pareto-optimal solutions are found for the first and the second performance measures by the constant values of third and fourth performance measures for the certain value of p.
    Change the value of ϵ_4 by the step size which is 1.
  end for
  Change the value of ϵ_3 by the step size which is 1.
  Set ϵ_4 to u_4 for the next value of the number of cities disturbed ($\epsilon_4 \leftarrow u_4$)
end for
Change the value of p and apply the algorithm again.

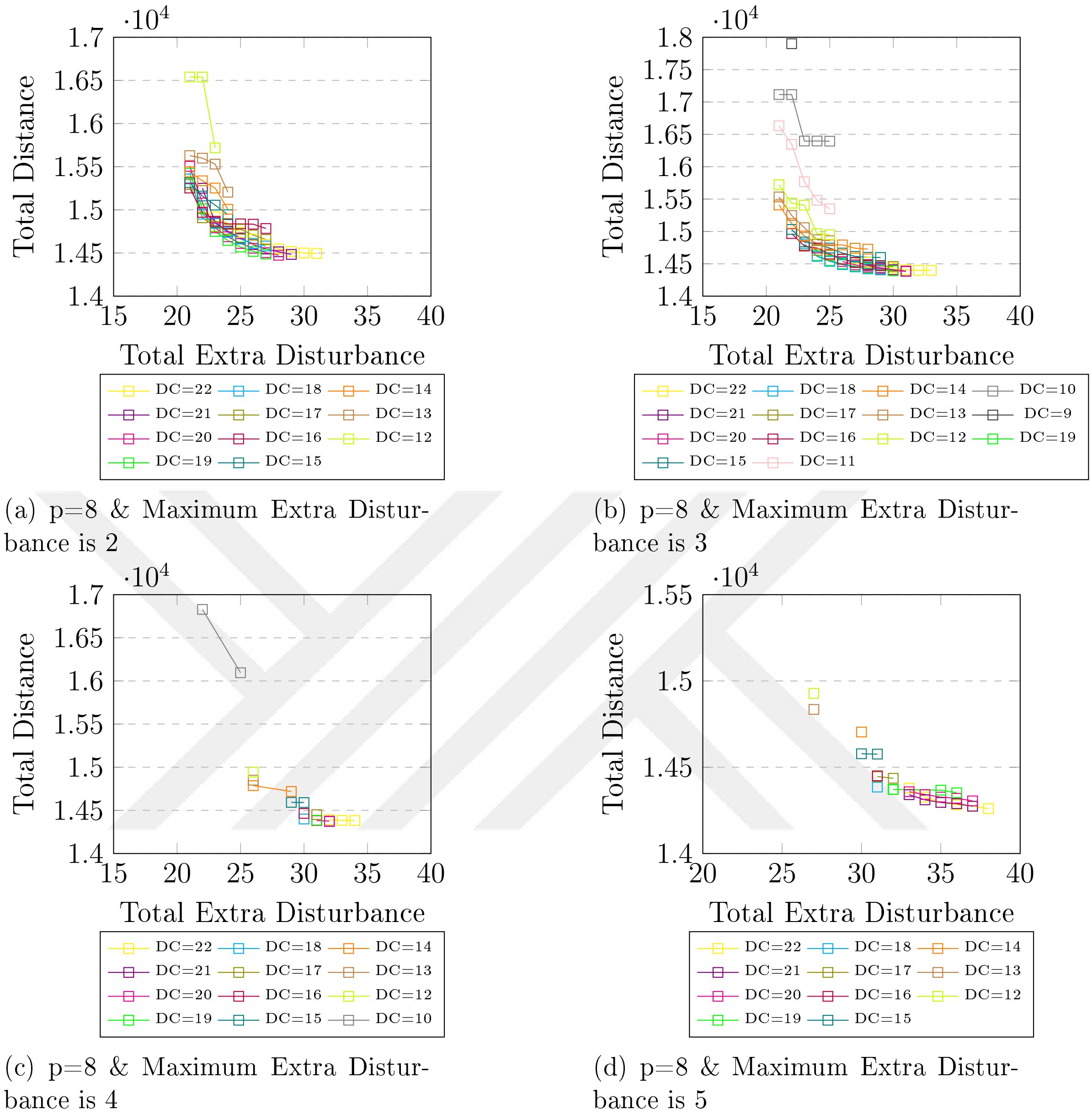
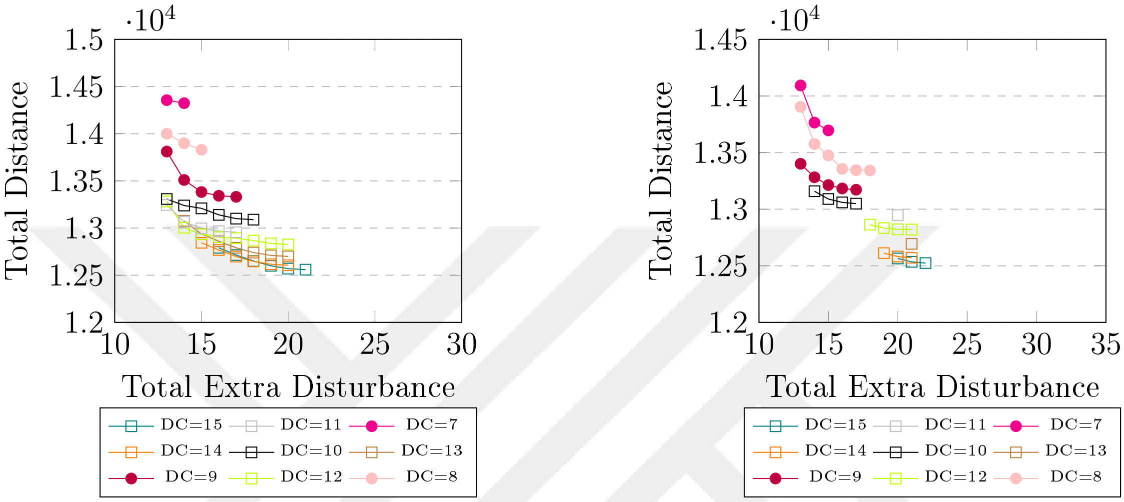


Figure 6.7: Pareto Charts on maximum extra disturbance values when p=8

In graph 6.7a, when the number of cities disturbed is 16 and the total extra disturbance is 21, the first objective gets lower value: 15253. When the number of cities disturbed is 17 and the total extra disturbance is 22 the first objective gets lower value 14908. When the number of cities disturbed is 19 and the total extra disturbance ranges from 23 to 27, the first objective gets lower values: 14749, 14646, 14569, 14518 and 14488, respectively. In graph 6.7b, when the number of cities disturbed is 18 and total extra disturbance ranges from 24 to 29, the first objective gets lower values: 14615, 14538, 14487, 14452, 14422 and 14407 respectively. Similar analysis is done for p=10 and the graphs are depicted in Figures 6.8.

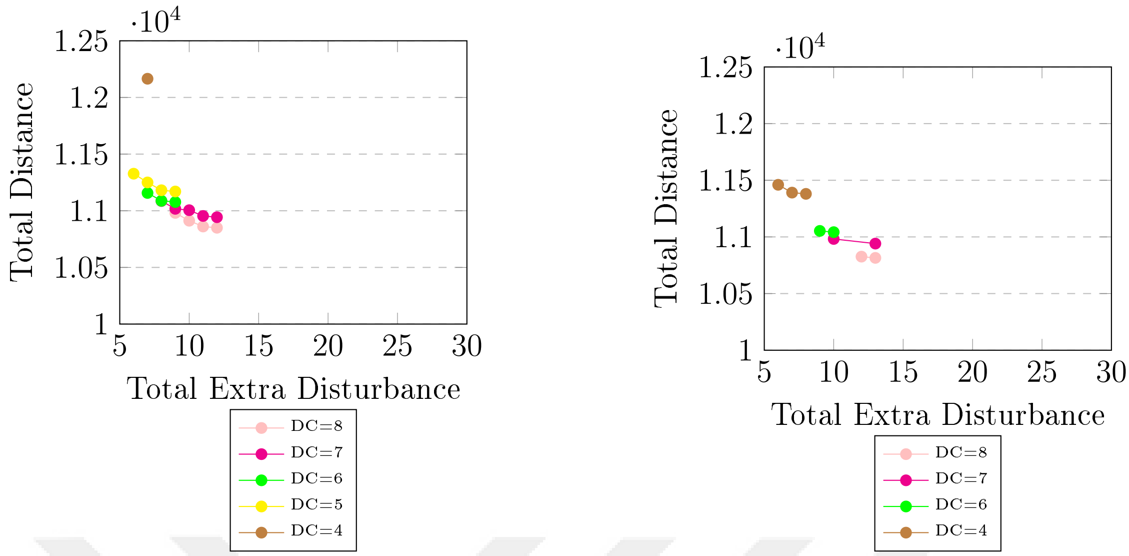


(a) p=10 & Maximum Extra Disturbance is 2

(b) p=10 & Maximum Extra Disturbance is 3

Figure 6.8: Pareto Charts on maximum extra disturbance values when p=10

In graph 6.8a, when the number of cities disturbed is 14 and total extra disturbance ranges from 15 to 18, the first objective gets lower values: 12844, 12767, 12698, 12647 respectively. Also, in graph 6.8b, when the number of cities disturbed is 15 and total extra disturbance ranges from 20 to 22, the first objective gets lower values: 12565, 12535, 12524 respectively. Similar analysis can be done for p=13.

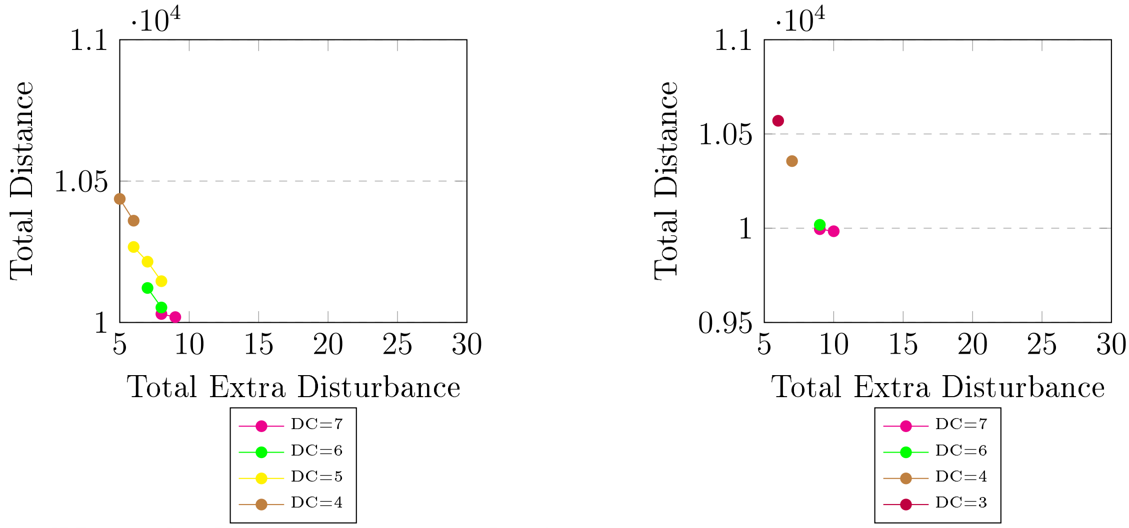


(a) p=13 & Maximum Extra Disturbance is 2

(b) p=13 & Maximum Extra Disturbance is 3

Figure 6.9: Pareto Charts on maximum extra disturbance values when p=13

In graph 6.9a, when DC=6 the values of total distance, are lower than the values of total distance when DC=5 if the range of total extra disturbance is between 7 and 9. After the total extra disturbance of 9, the values of total distance for DC=8 are lower than the other points.



(a) p=15 & Maximum Extra Disturbance is 2

(b) p=15 & Maximum Extra Disturbance is 3

Figure 6.10: Pareto Charts on maximum extra disturbance values when p=15

In graph 6.10a, the values of the total distance for DC=7 are lower than the values of the total distance for DC=5 and DC=5.

Chapter 7

Conclusion

Orphan drugs are medical products that serve only for orphan diseases and they are difficult to attain. The pharmaceutical industry is not interested much in orphan drugs due to small market size. They are produced in small amounts. Additionally, they may be required urgently for patients. There are procedures and approaches developed for storing, transporting and delivering orphan drugs. Depending on the country, there are regulations for the transportation of orphan drugs to the patient. In this study, we investigate the procedure utilized in Turkey .

In Turkey, orphan drugs are stored at third level health institutions. There are a total of 31 cities which have third level health institutions however only 15 of them are active in the current system. Orphan drugs are transported by emergency ambulances and those ambulances are restricted to stay within their respective city limits. Therefore, the transmission of the drug happens at city borders between the ambulances of neighbouring or bordering cities. Even though there is an active system with location and allocation decisions, the routing decision is left to the hospital administration. Due to the operational dynamics of the problem, the routing decision is crucial. To represent the operational dynamics of the orphan drug logistics, we have constructed a special network and we introduced four different performance measures for alternative location and routing decisions.

For such problems, there is not a commonly used objective function. Therefore, we have introduced the performance measures based on urgency and ambulance scarcity. The proposed performance measures are the minimization of total distance, minimization of total extra disturbance, minimization of extra disturbance and minimization of the number of the cities disturbed. Based on the network constructed and the performance measures defined, mathematical models are developed.

We have analyzed the behaviour of solutions concerning each performance measure. By analyzing each performance measure independently, we aim to find the best values for each performance measure as the value of p changes. Also, the solution times are reported for each value of p and each performance measure. For all performance measures, as the value of p increases, the objective function values decreases. Moreover, after some value of p the objective functions stabilize for all performances measures except the total distance travelled. However, the values of other performance measures when one of them is optimized are not optimal for those performance measures. Hence, alternative solution sets are found through bi-criteria optimization and Pareto-optimal solutions are found by the ϵ-Constraint method. In both cases, the performance measure to be optimized is total distance while the other performance measures are added as constraints to the model. The reason is that the orphan drug system aims to serve the patient as quickly as possible. Thus, throughout the multi-criteria optimization, we compared the results for each value of p and analyzed different performance measures.

While dealing with multi-criteria optimization, the set of solutions for one performance measure is not optimal for another performance measure. Therefore, bi-criteria optimization is solved by prioritizing the minimization of the total distance since the aim of the orphan drug system is to transmit the orphan drug as quickly as possible to the patient. In bi-criteria optimization, the strictly dominated solutions are eliminated. The analysis for those results is done for p values of 5, 8, 10, 13, 15, 18 and 20.

In bi-criteria optimization between the total distance and the total extra disturbance, the total distance decreases as value of p increases. The deviation from the best value is not more than 15%. Also, after a certain value of p, both the maximum extra disturbance and the number of cities disturbed stabilizes. During the stabilization, the maximum extra disturbance reaches to its best value but the number of cities disturbed does not reach to its best value. In this case, the results may imply that by restricting the total extra disturbance to the best value, the maximum extra disturbance gets equal to the best value as value of p increases. However, a similar relationship cannot be deducted through the bi-criteria with respect to the maximum extra disturbance. Also, while p equals to 5 and 8, there are some exceptional routing decisions. The exceptional decisions imply that there some cases in which the ambulance of a city should leave its city and move through an intermediate city to meet with the ambulance of the city after the intermediate city that moved through. Finally, with respect to the bi-criteria optimization with number of cities distured as the second objective, the distance decreases decreases as value of p increases and the deviation from the best value is not more than 9%. For each bi-criteria optimization, the location and routing decisions are given in Appendix C. Moreover, we provided visual reprsentations of the deviations for each performance measure for each value of p in each bi-criteria optimization.

Lastly, Pareto-optimal solutions are found by ϵ-Constraint method. The main performance measure is again the minimization of the total distance. The range is set for other performance measures and within those ranges the Pareto-frontiers are found. In each of the Pareto charts, it is observed that as the value of performance measure increases, the value of total distance decreases. The analysis extended further and total extra disturbance is selected to be added as constraint while the other two performance measures are kept as constant in ϵ-contraint method. Accordingly, the Pareto-optimal solutions are found and Pareto-charts are drawn for specific values of p.

Demand levels can be added to the problem as an extension of the study. For more realistic scenarios, the demand data can be provided. In the case of demand data, the previous instances and the demands could be analyzed and it would be better in terms of making estimations on patient demand at a strategical level.

The mathematical model can be extended further by adding time limit. In this case, the main can be defined to find the minimum number of cities with third level health institutions to store the orphan drugs. However, the transportation of the orphan drugs can occur within a time limit. The additional restriction is the time limit to transmit drug to a patient. It can be assumed that there is an average time limit to transmit the drug from a third level health institution to save the life of a patient. Let us say, the time limit is t hours. The time limit is converted to distance constraint by assuming that the ambulances will travel with speed of K km per hour. Then, the time limit is converted as distance limit, T km. The model can be extended as given below:

Additional Parameter:

T = The distance limit

Additional Decision Variable:

$$YZ_{kl} = \begin{cases} 1, & \text{If the } (k,\ l) \text{ is used as during transportation, } k, l \in I \\ 0, & \text{otherwise} \end{cases}$$

u_l = Time when node l is left, $l \in I$

$$(M5)\ \min \quad f_1 = \sum_{k \in I} \sum_{l \in I} D_{kl} Y_{kl} \tag{4.1}$$

subject to

(4.2) – (4.7), (4.10), (4.11), (4.12), (4.14) – (4.17)

$$YZ_{kl} \leq Y_{kl} \quad \forall k, l \in I \tag{7.1}$$

$$MYZ_{kl} \geq Y_{kl} \quad \forall k, l \in I \tag{7.2}$$

$$u_k - u_l + TYZ_{kl} \leq T - D_{kl} YZkl \quad \forall k, l \in I \quad k \neq l \tag{7.3}$$

$$0 \leq u_l \leq T \quad \forall l \in I \tag{7.4}$$

In this model, the main aim is to minimize the total distance travelled by all ambulances within a time limit. The objective function (4.1) minimizes the total distance travelled by all ambulances. Constraints (7.1) ensure that if there is no flow through (k, l) then (k, l) is not used during transporation. Constraints (7.2) assure that if arc (k, l) is used, then there should be flow going through (k, l). Constraints (7.3) and (7.4) are distance version of Miller-Tucker-Zemlin subtour elimination constraints used in Distance Constrained VRP.

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Appendix A

Ambulance Scheme

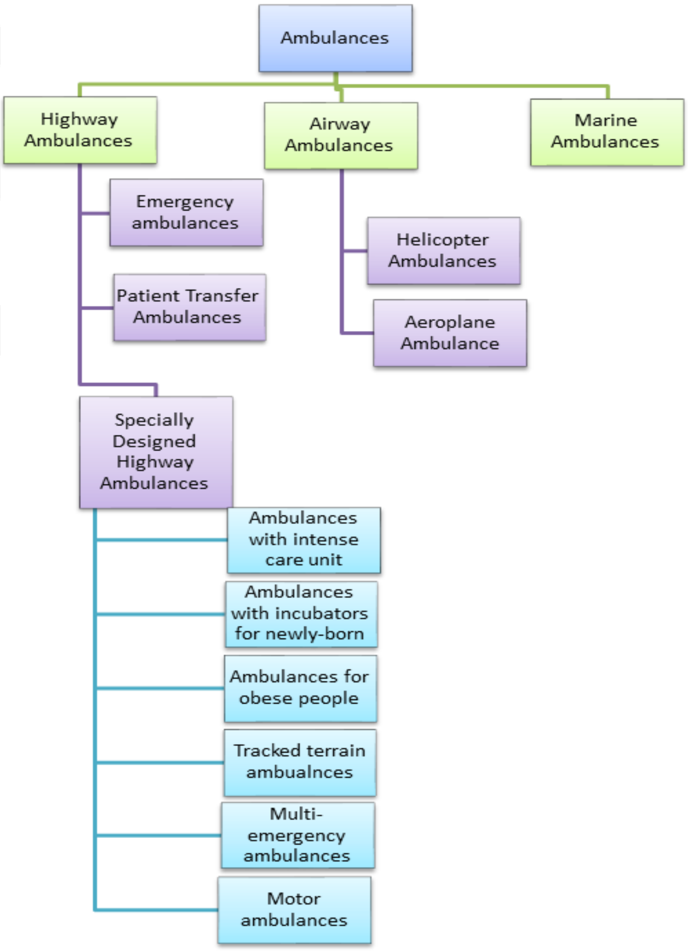


Figure A.1: Ambulance Scheme

Appendix B

Current Location and Allocation

Storage City	Allocated cities to the storage city
Adana	Adana
	Osmaniye
	Hatay
	Mersin
	Kahramanmaraş
	Gaziantep
	Kilis
Antalya	Antalya
	Isparta
	Burdur
Aydın	Aydın
	Denizli
	Muğla
Bursa	Bursa
	Çanakkale
	Balıkesir
	Yalova
Diyarbakır	Diyarbakır
	Batman
	Mardin
	Siirt
	Şırnak
	Adıyaman
	Şanlıurfa
Erzurum	Erzurum
	Erzincan
	Bayburt
	Ardahan
	Kars
İstanbul	İstanbul
	Kocaeli
	Sakarya
	Düzce
İzmir	İzmir
	Manisa
	Uşak
Kayseri	Kayseri
	Sivas
	Yozgat
	Nevşehir
	Aksaray
	Niğde
	Karaman
	Konya

Storage City	Allocated cities to the storage city
Samsun	Samsun
	Sinop
	Amasya
	Ordu
	Tokat
	Giresun
Tekirdağ	Tekirdağ
	Edirne
	Kırıklareli
Trabzon	Trabzon
	Gümüşhane
	Rize
	Artvin
Van	Van
	Hakkari
	Bitlis
	Muş
	Ağrı
	Iğdır
Ankara	Ankara
	Kütahya
	Bilecik
	Eskişehir
	Afyonkarahisar
	Bolu
	Zonguldak
	Bartın
	Karabük
	Kastamonu
	Çankırı
	Çorum
	Krıkkale
	Kırşehir
Elazığ	Elazığ
	Malatya
	Bingöl
	Tunceli

Table B.1: Current Location and Allocation

Appendix C

Decisions on Maps

Figure C.1: Decisions under Total Distance minimization When p=5

Figure C.2: Decisions under Total Distance minimization When p=8

Figure C.3: Decisions under Total Distance minimization When p=10

Figure C.4: Decisions under Total Distance minimization When p=13

Figure C.5: Decisions under Total Distance minimization When p=15

Figure C.6: Decisions under Total Distance minimization When p=18

Figure C.7: Decisions under Total Distance minimization When p=20

Figure C.8: Decisions under Total Extra Disturbance minimization When p=5

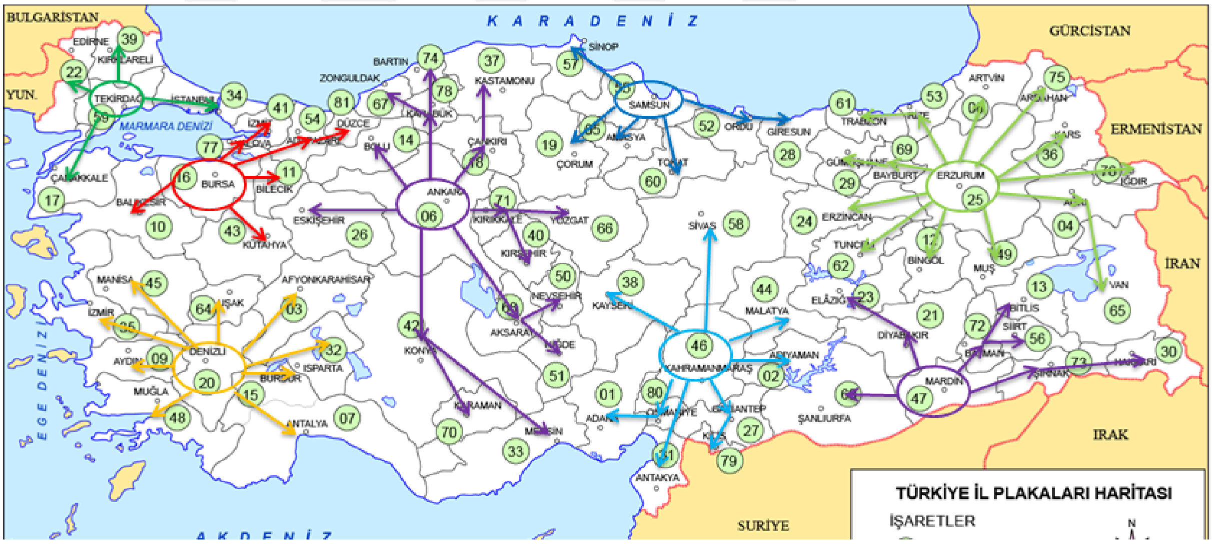


Figure C.9: Decisions under Total Extra Disturbance minimization When p=8

Figure C.10: Decisions under Total Extra Disturbance minimization When p=10

Figure C.11: Decisions under Total Extra Disturbance minimization When p=13

Figure C.12: Decisions under Total Extra Disturbance minimization When p=15

Figure C.13: Decisions under Total Extra Disturbance minimization When p=18

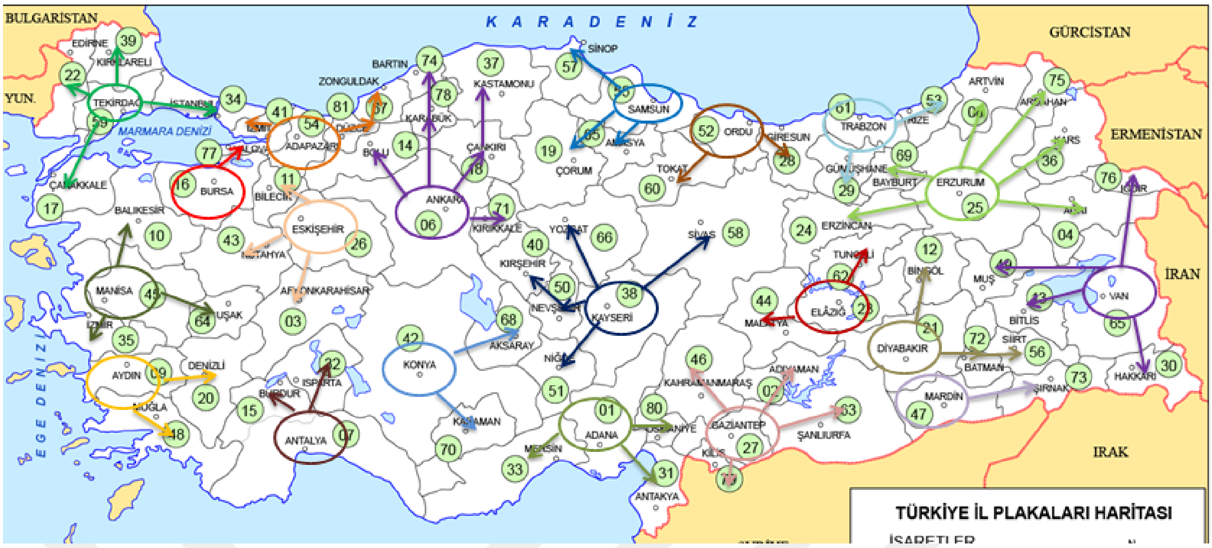


Figure C.14: Decisions under Total Extra Disturbance minimization When p=20

Figure C.15: Decisions under Maximum Extra Disturbance minimization When p=5

Figure C.16: Decisions under Maximum Extra Disturbance minimization When p=8

Figure C.17: Decisions under Maximum Extra Disturbance minimization When p=10

Figure C.18: Decisions under Maximum Extra Disturbance minimization When p=13

Figure C.19: Decisions under Maximum Extra Disturbance minimization When p=15

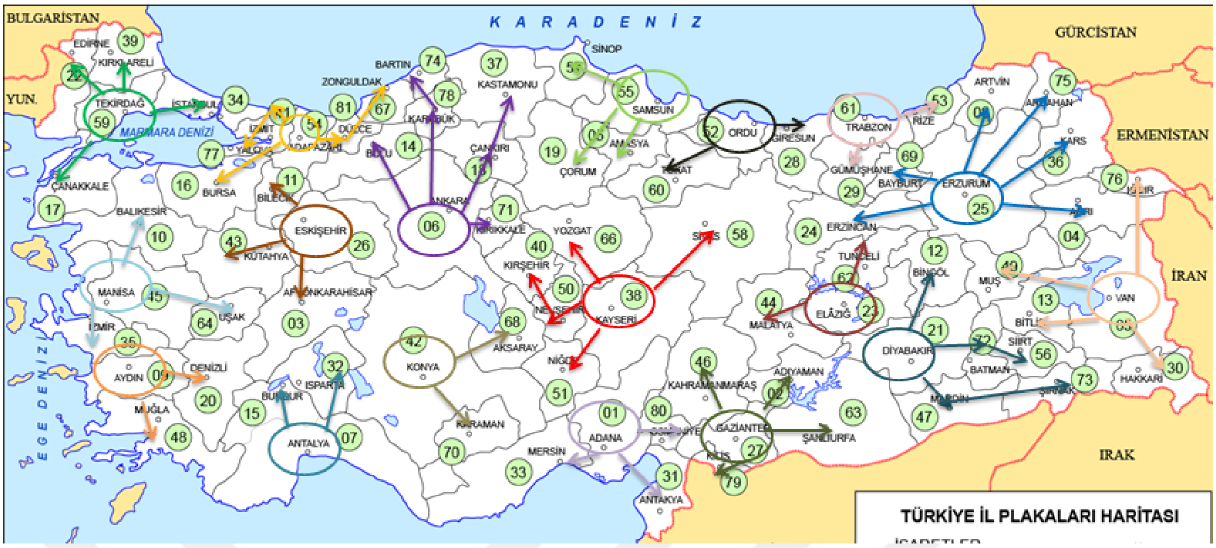


Figure C.20: Decisions under Maximum Extra Disturbance minimization When p=18

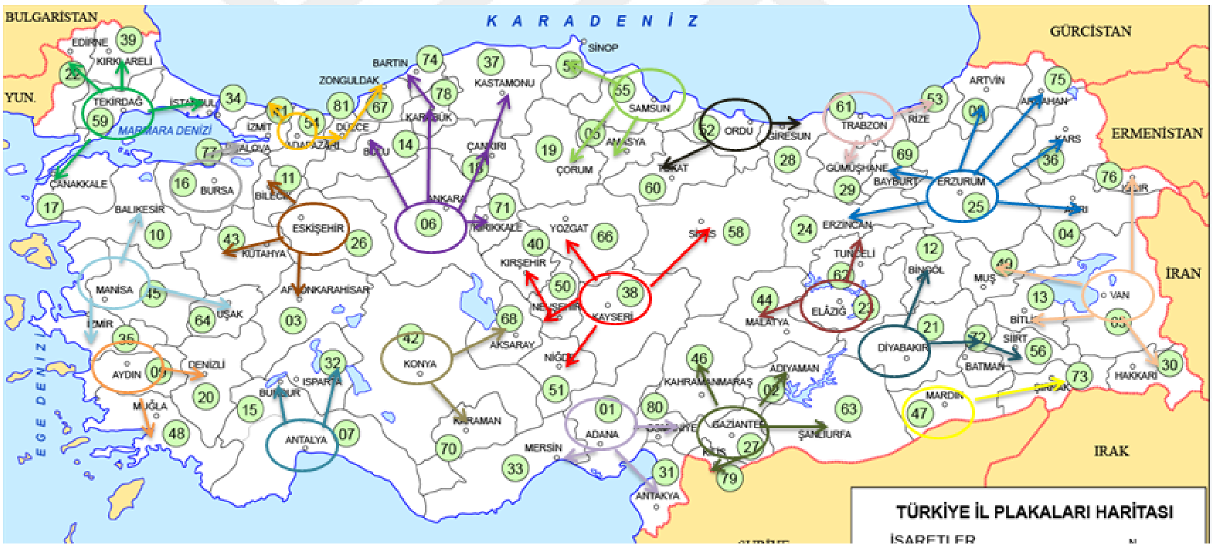


Figure C.21: Decisions under Maximum Extra Disturbance minimization When p=20

Figure C.22: Decisions under Minimiation of Total Number of Cities Disturbed When p=10

Figure C.23: Decisions under Minimiation of Total Number of Cities Disturbed When p=13

Figure C.24: Decisions under Minimiation of Total Number of Cities Disturbed When p=15

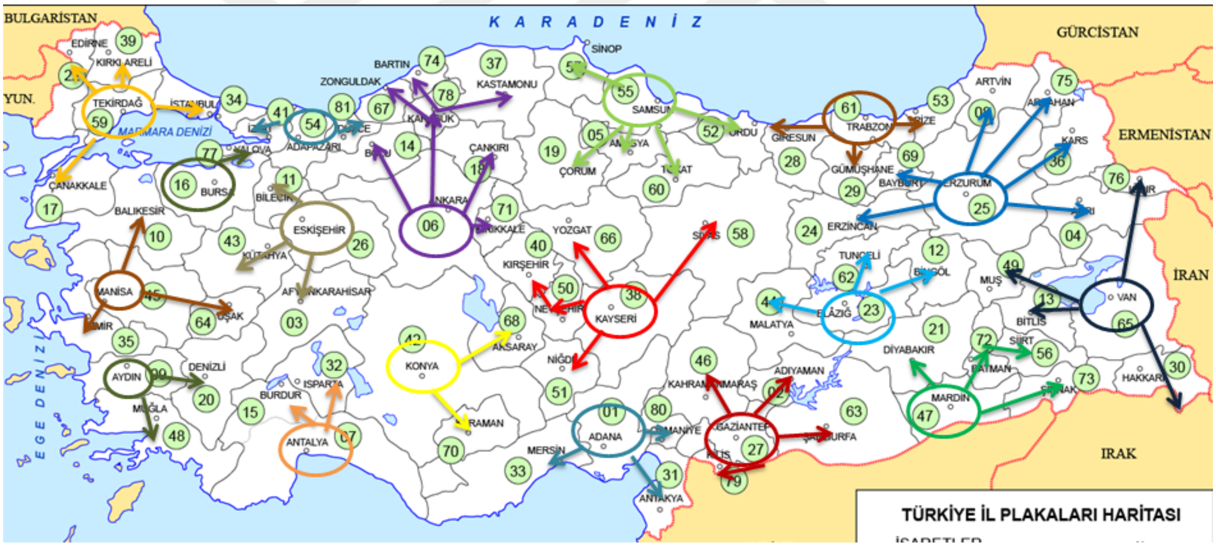


Figure C.25: Decisions under Minimiation of Total Number of Cities Disturbed When p=18

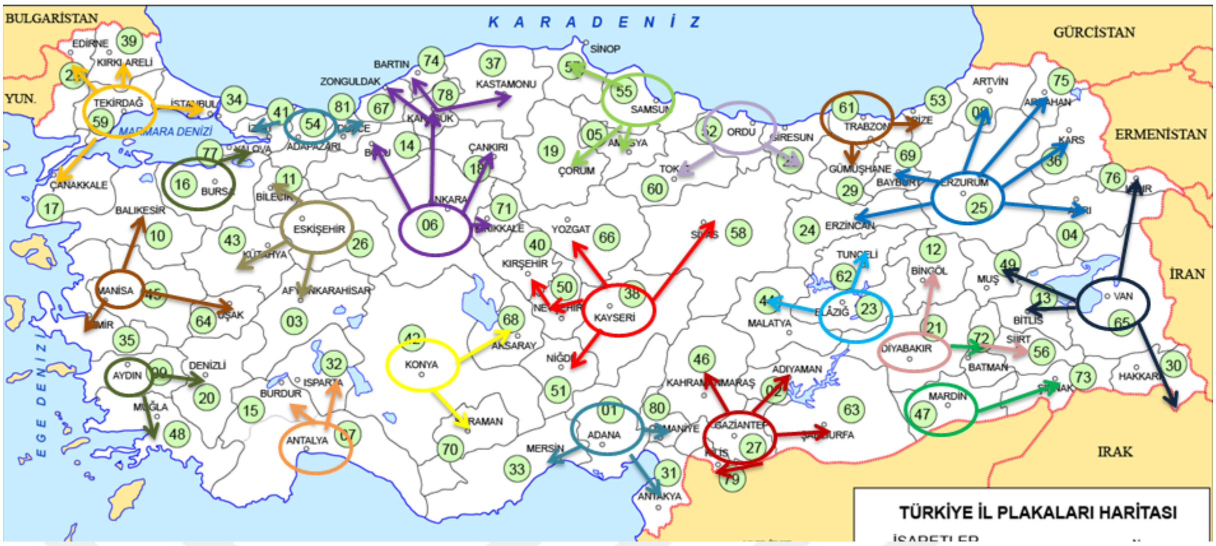


Figure C.26: Decisions under Minimiation of Total Number of Cities Disturbed When p=20

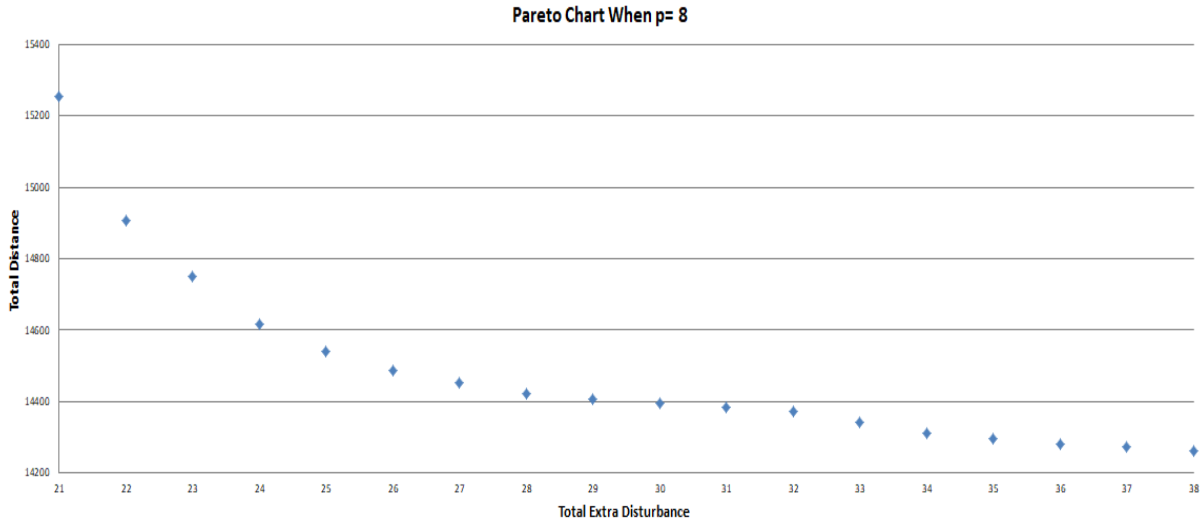


Figure C.27: Pareto chart for TDE as Epsilon constraint When p=8

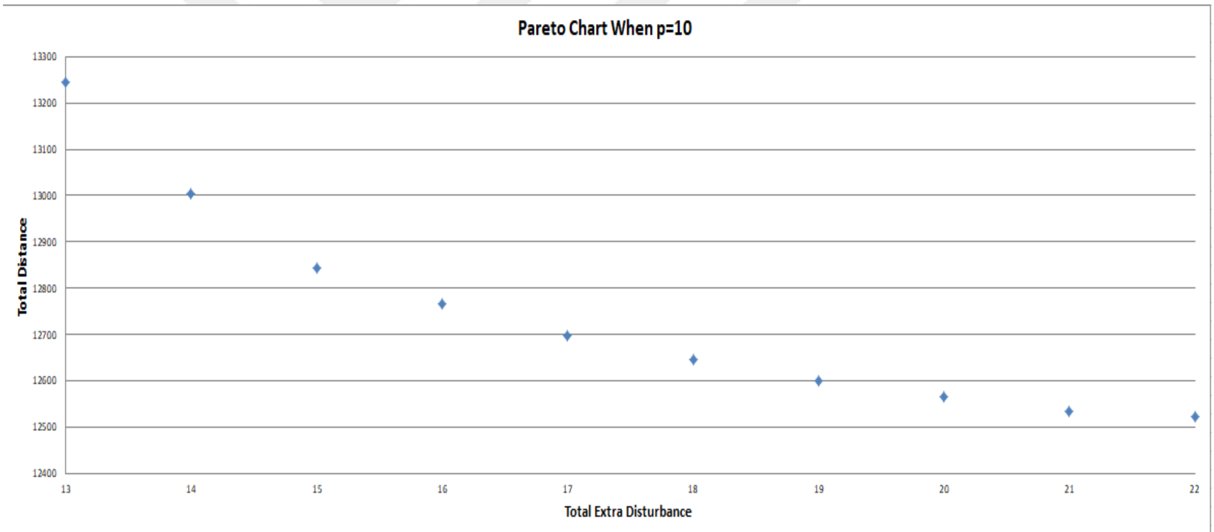


Figure C.28: Pareto chart for TDE as Epsilon constraint When p=10

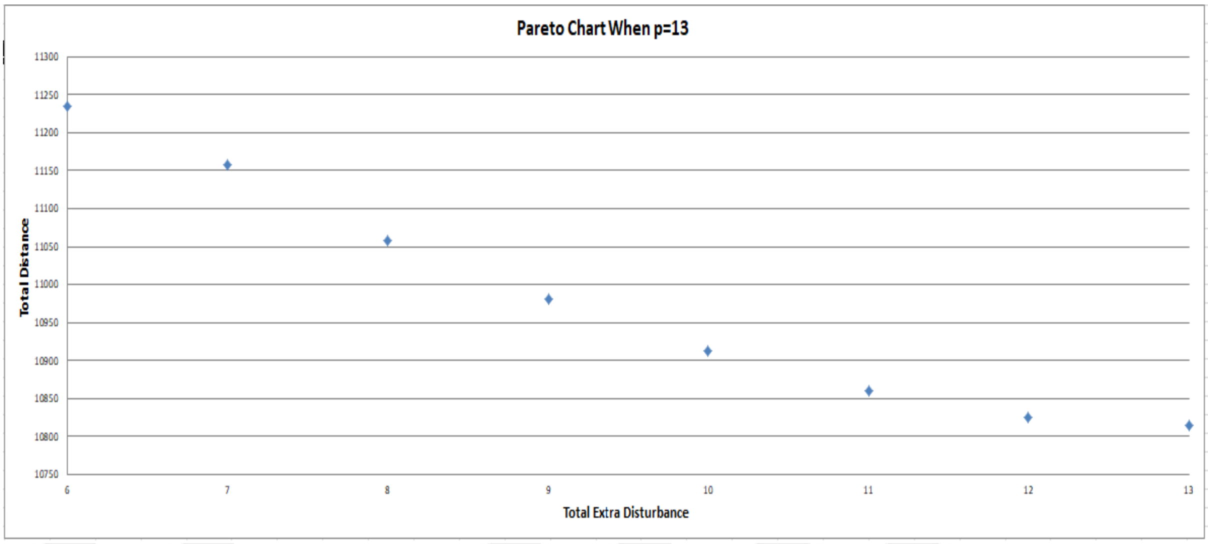


Figure C.29: Pareto chart for TDE as Epsilon constraint When p=13

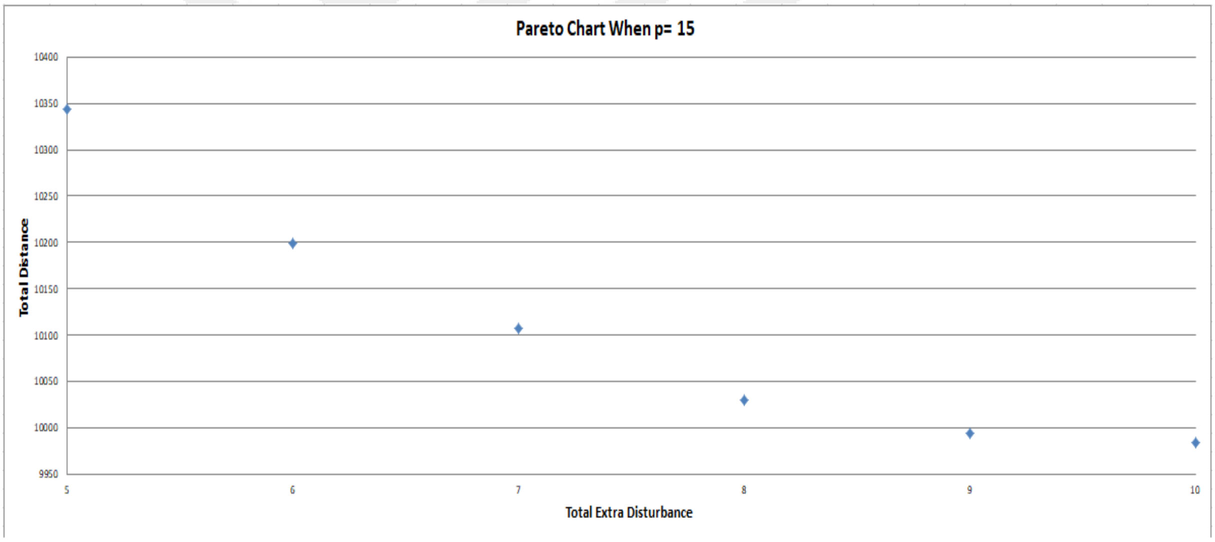


Figure C.30: Pareto chart for TDE as Epsilon constraint When p=15

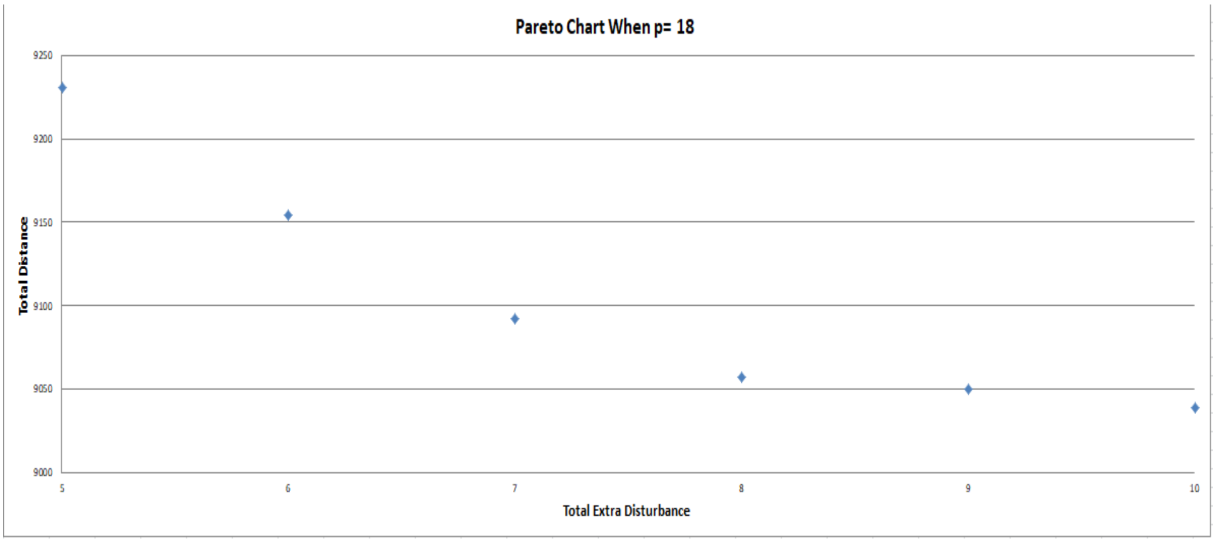


Figure C.31: Pareto chart for TDE as Epsilon constraint When p=18

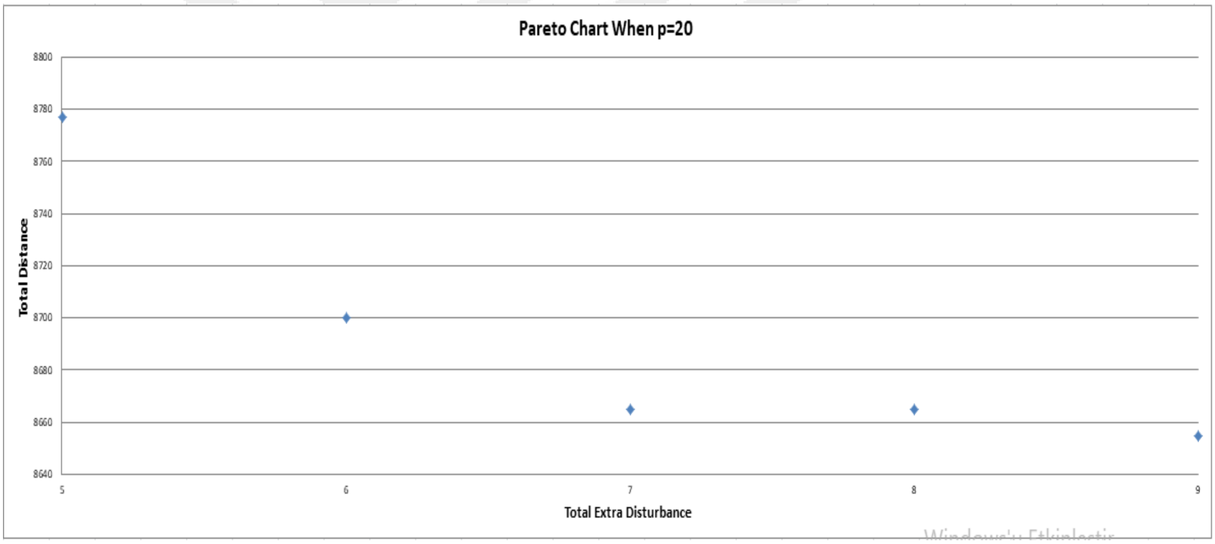


Figure C.32: Pareto chart for TDE as Epsilon constraint When p=20

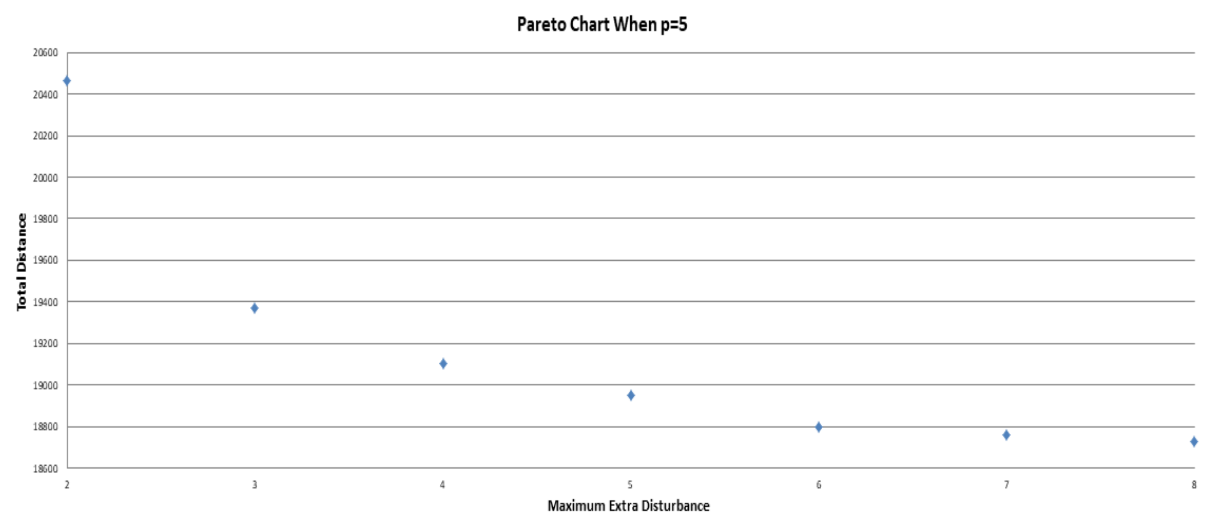


Figure C.33: Pareto chart for MD as Epsilon constraint When p=5

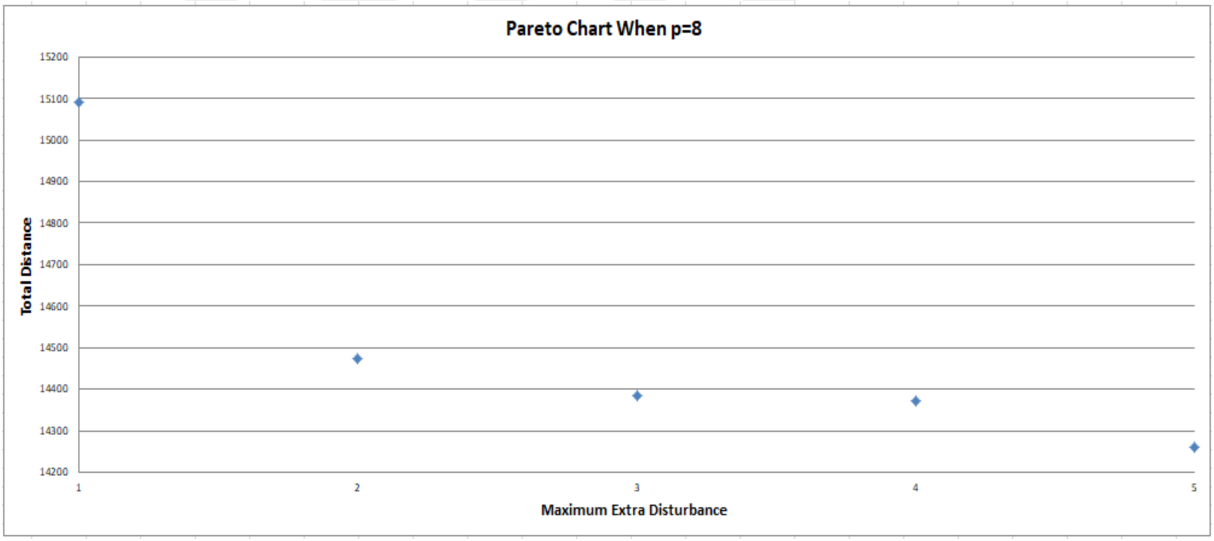


Figure C.34: Pareto chart for MD as Epsilon constraint When p=8

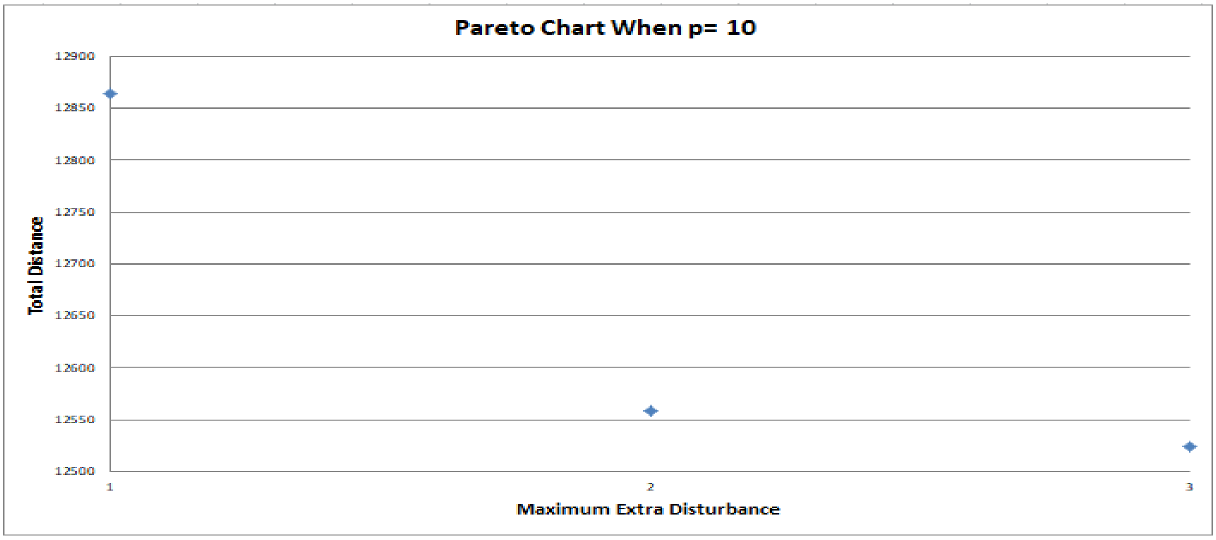


Figure C.35: Pareto chart for MD as Epsilon constraint When p=10

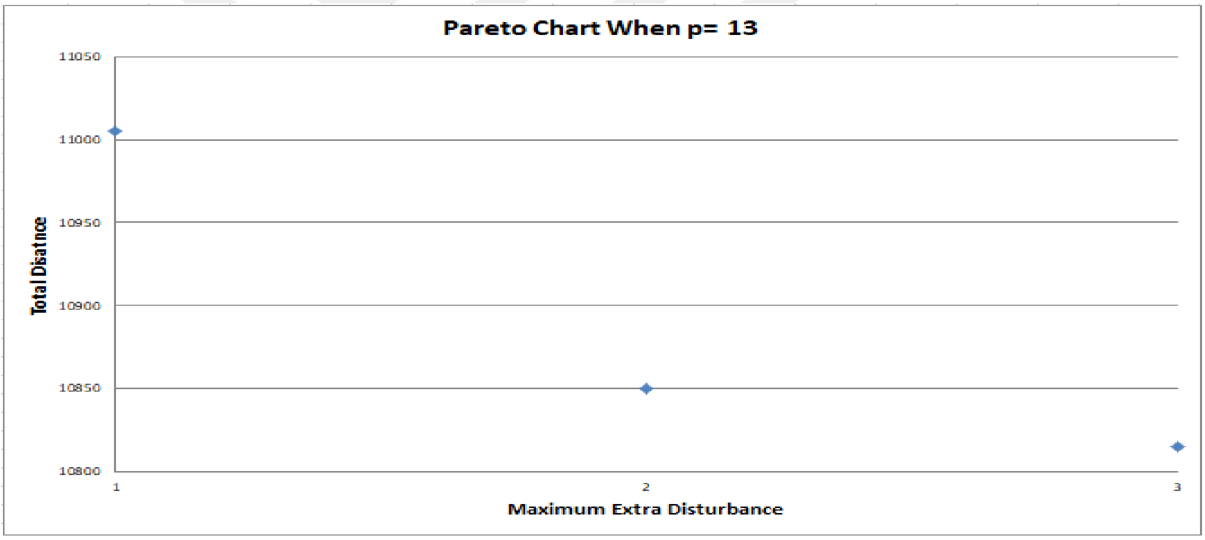


Figure C.36: Pareto chart for MD as Epsilon constraint When p=13

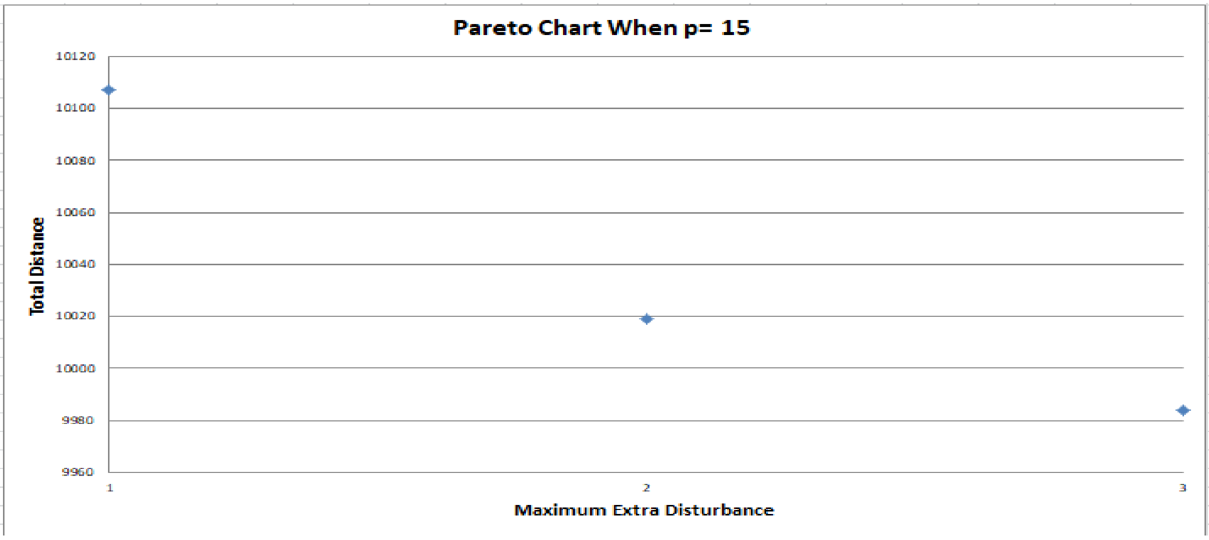


Figure C.37: Pareto chart for MD as Epsilon constraint When p=15

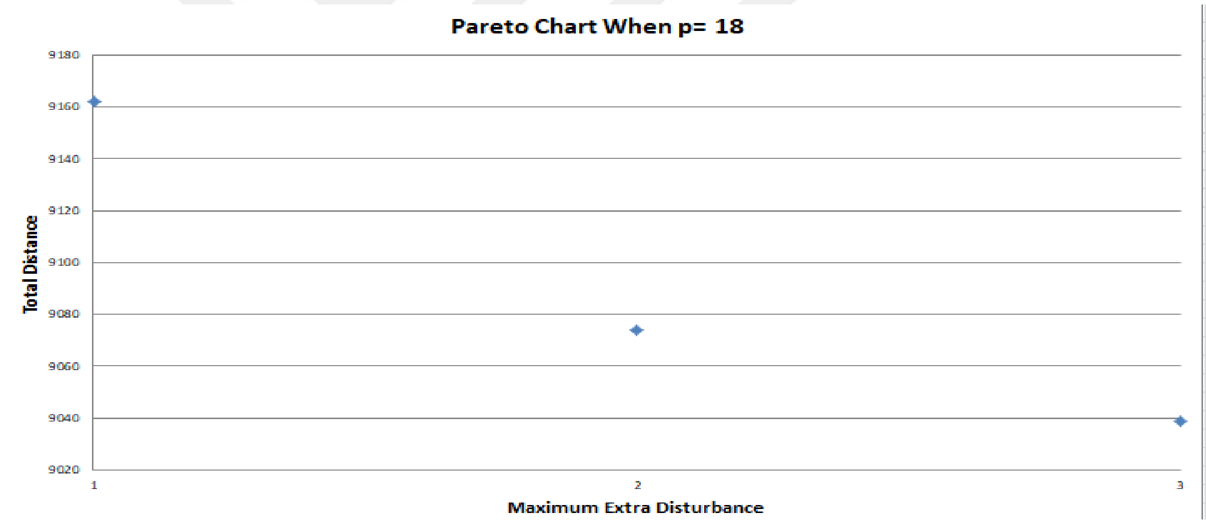


Figure C.38: Pareto chart for MD as Epsilon constraint When p=18

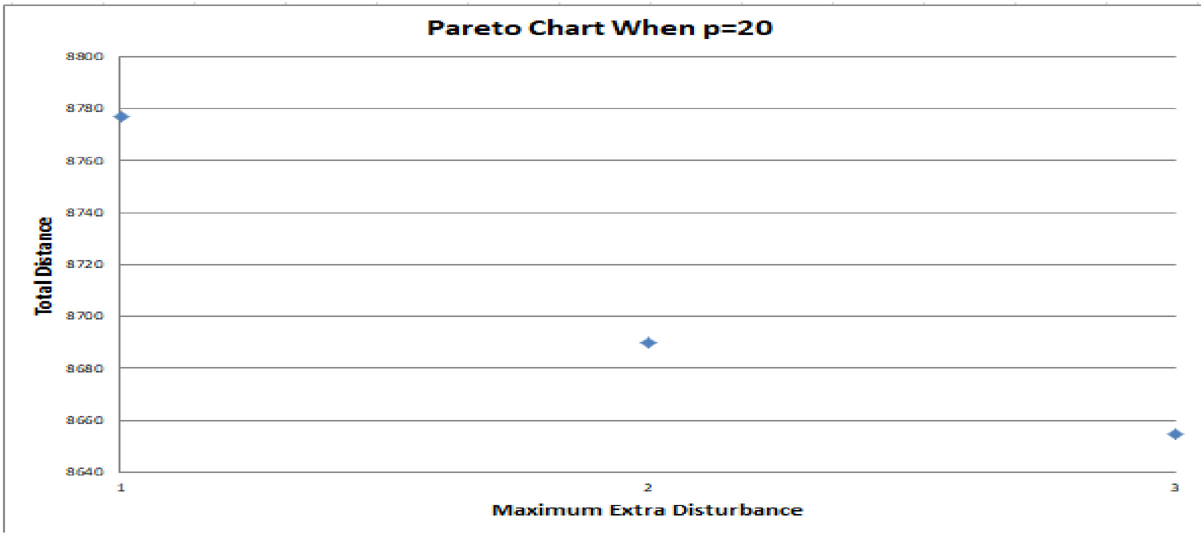


Figure C.39: Pareto chart for MD as Epsilon constraint When p=20

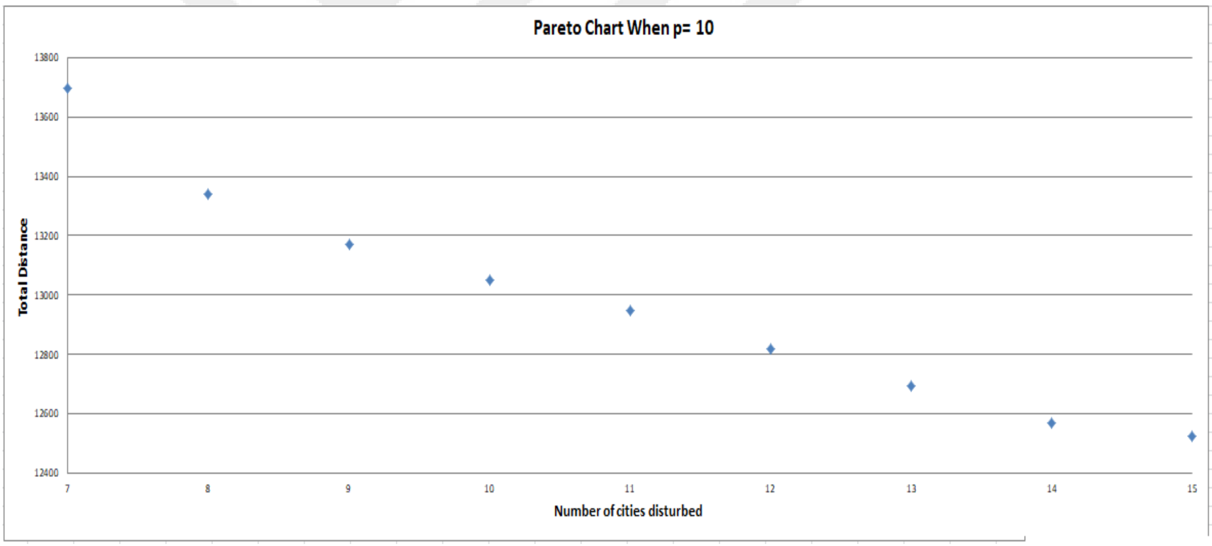


Figure C.40: Pareto chart for DC as Epsilon constraint When p=10

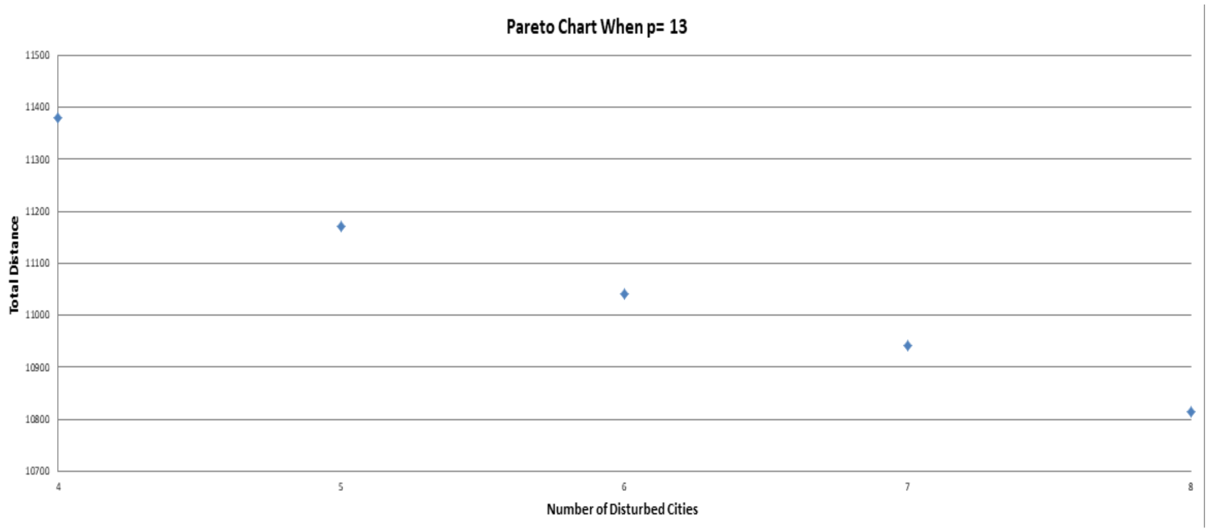


Figure C.41: Pareto chart for DC as Epsilon constraint When p=13

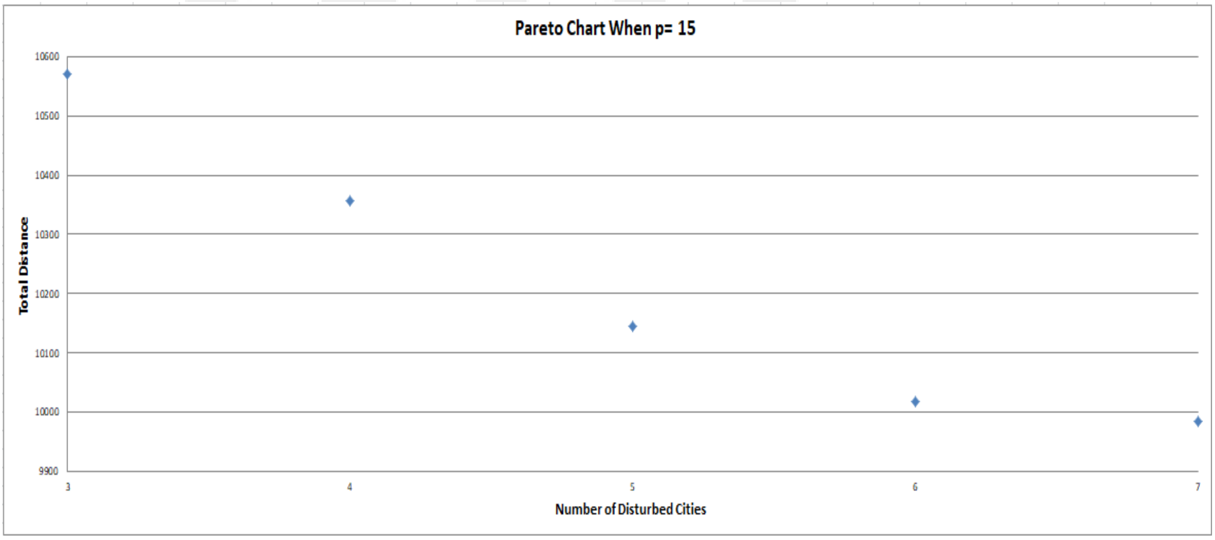


Figure C.42: Pareto chart for DC as Epsilon constraint When p=15

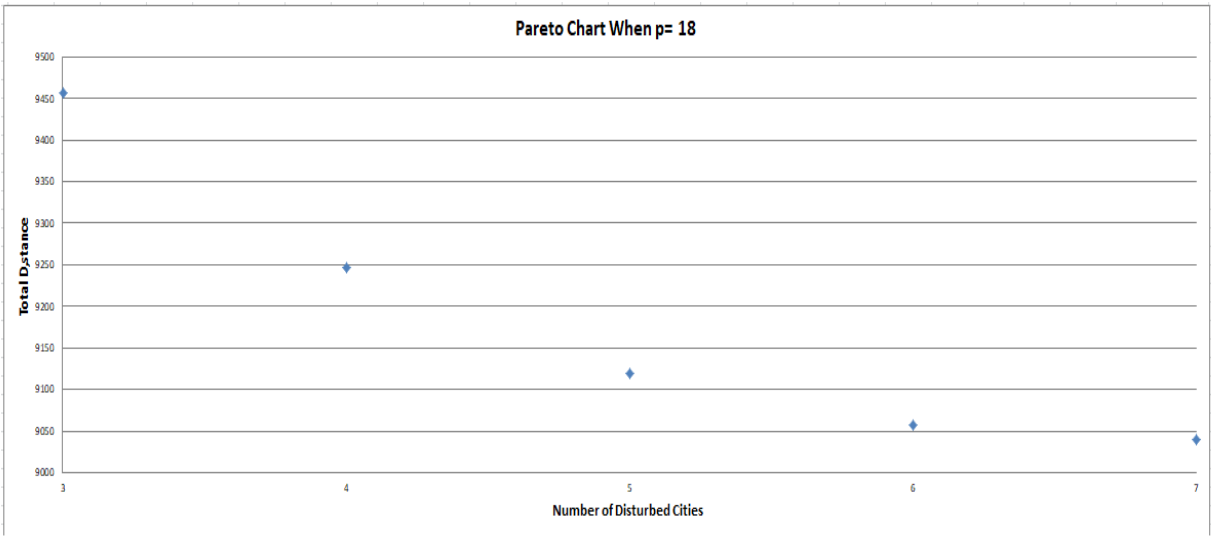


Figure C.43: Pareto chart for DC as Epsilon constraint When p=18

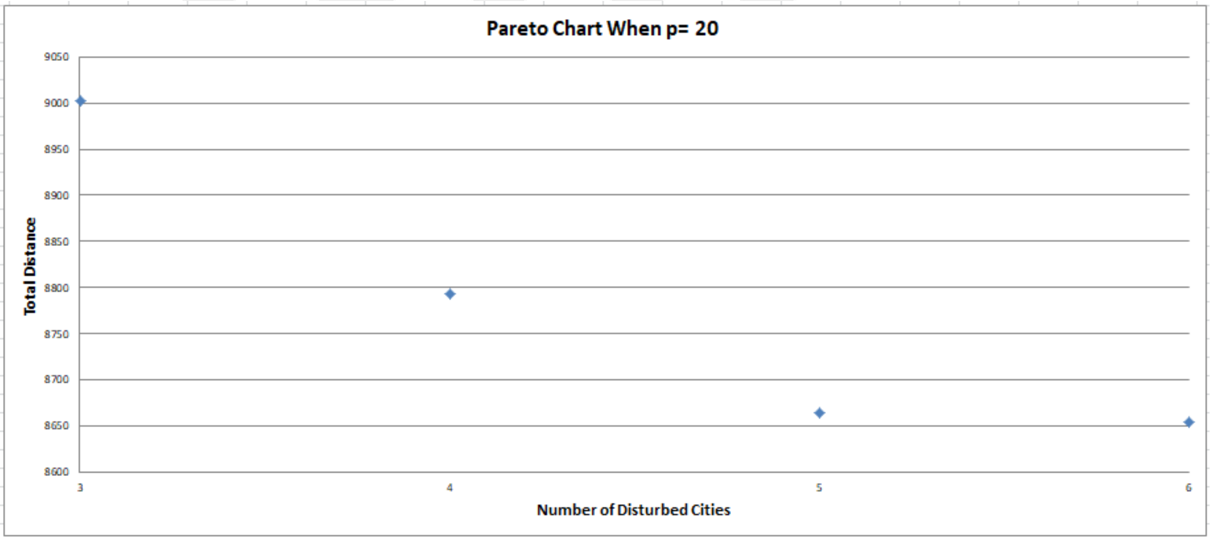
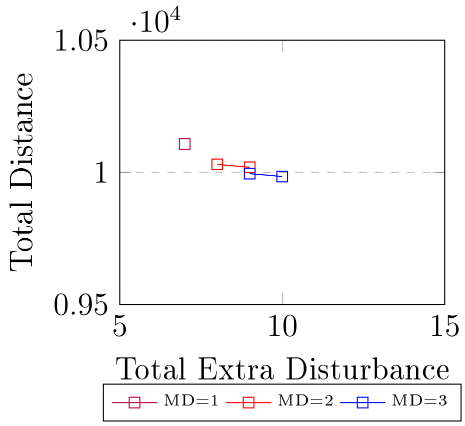
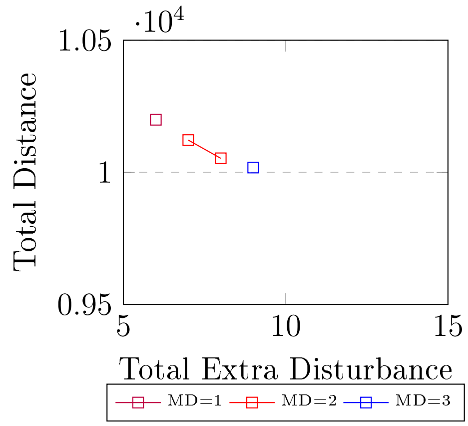


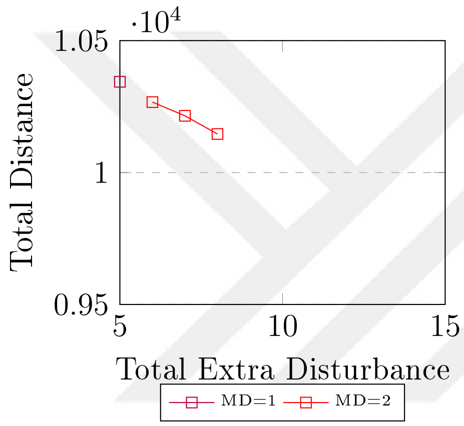
Figure C.44: Pareto chart for DC as Epsilon constraint When p=20



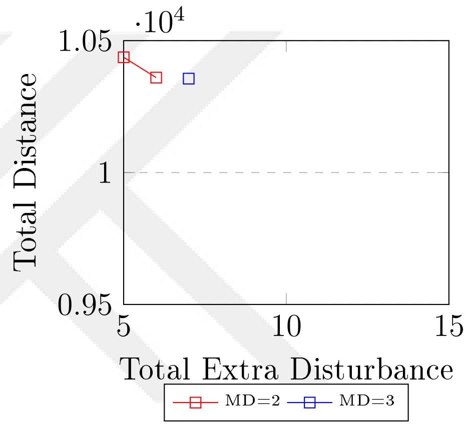
(a) p=15 & Number of Disturbed Cities is 7



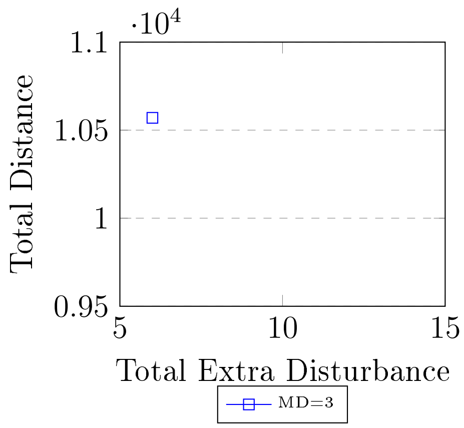
(b) p=15 & Number of Disturbed Cities is 6



(c) p=15 & Number of Disturbed Cities is 5

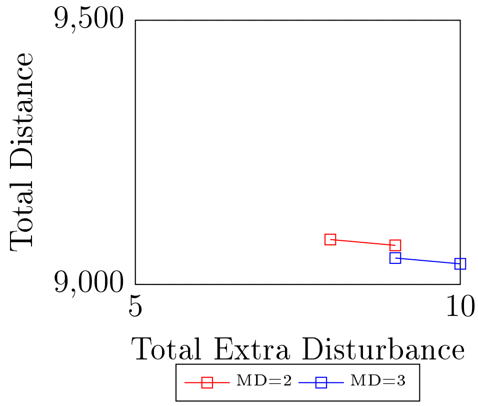


(d) p=15 & Number of Disturbed Cities is 4

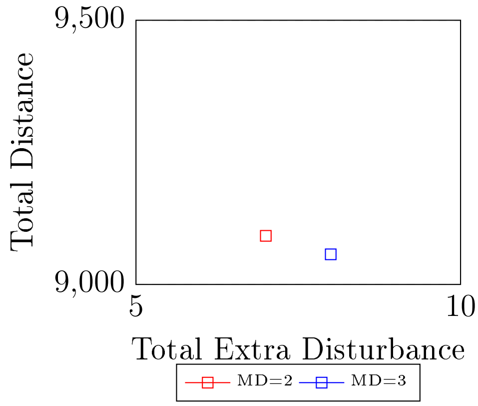


(e) p=15 & Number of Disturbed Cities is 3

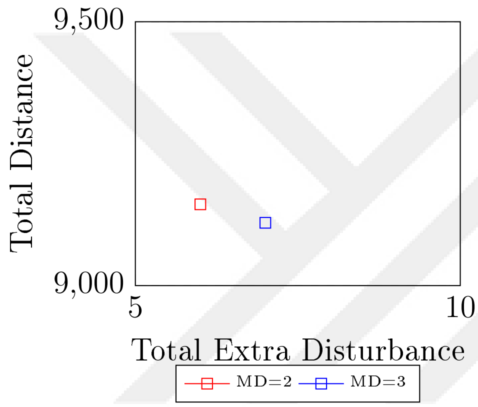
Figure C.45: Pareto Charts on disturbed city values when p=15



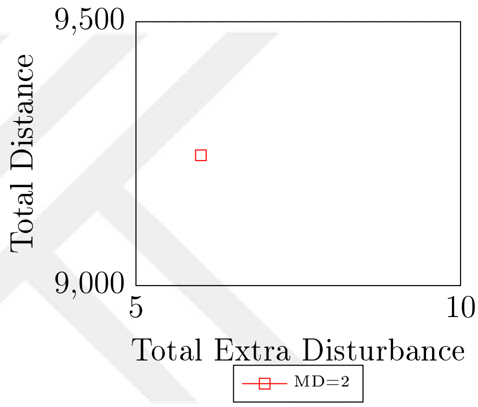
(a) p=18 & Number of Disturbed Cities is 7



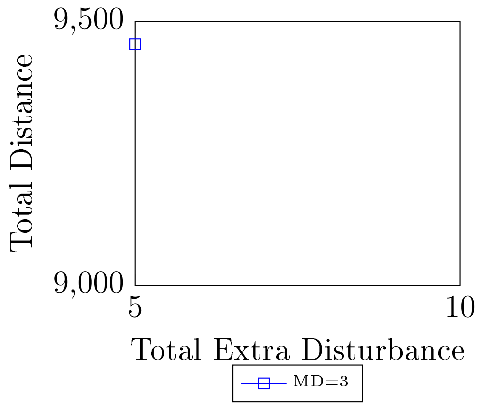
(b) p=18 & Number of Disturbed Cities is 6



(c) p=18 & Number of Disturbed Cities is 5



(d) p=18 & Number of Disturbed Cities is 4



(e) p=18 & Number of Disturbed Cities is 3

Figure C.46: Pareto Charts on disturbed city values when p=18