A novel combination of Cased-Based Reasoning and Multi-Criteria Decision Making approach to radiotherapy dose planning

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Abstract

In this thesis, a set of novel approaches has been developed by integration of Cased-Based Reasoning (CBR) and Multi-Criteria Decision Making (MCDM) techniques. Its purpose is to design a support system to assist oncologists with decision making about the dose planning for radiotherapy treatment with a focus on radiotherapy for prostate cancer.

CBR, an artificial intelligence approach, is a general paradigm to reasoning from past experiences. It retrieves previous cases similar to a new case and exploits the successful past solutions to provide a suggested solution for the new case. The case pool used in this research is a dataset consisting of features and details related to successfully treated patients in Nottingham University Hospital. In a typical run of prostate cancer radiotherapy simple CBR, a new case is selected and thereafter based on the features available at our data set the most similar case to the new case is obtained and its solution is prescribed to the new case. However, there are a number of deficiencies associated with this approach.

Firstly, in a real-life scenario, the medical team considers multiple factors rather than just the similarity between two cases and not always the most similar case provides with the most appropriate solution. Thus, in this thesis, the cases with high similarity to a new case have been evaluated with the application of the Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS). This approach takes into account multiple criteria besides similarity to prescribe a final solution. Moreover, the obtained dose plans were optimised through a Goal Programming mathematical model to improve the results. By incorporating oncologists' experiences about violating the conventionally available dose limits a system was devised to manage the trade-off

between treatment risk for sensitive organs and necessary actions to effectively eradicate cancer cells.

Additionally, the success rate of the treatment, the 2-years cancer free possibility, has a vital role in the efficiency of the prescribed solutions. To consider the success rate, as well as uncertainty involved in human judgment about the values of different features of radiotherapy Data Envelopment Analysis (DEA) based on grey numbers, was used to assess the efficiency of different treatment plans on an input and output based approach. In order to deal with limitations involved in DEA regarding the number of inputs and outputs, we presented an approach for Factor Analysis based on Principal Components to utilize the grey numbers. Finally, to improve the CBR base of the system, we applied Grey Relational Analysis and Gaussian distant based CBR along with features weight selection through Genetic Algorithm to better handle the non-linearity exists within the problem features and the high number of features.

Finally, the efficiency of each system has been validated through leave-one-out strategy and the real dataset. The results demonstrated the efficiency of the proposed approaches and capability of the system to assist the medical planning team. Furthermore, the integrated approaches developed within this thesis can be also applied to solve other real-life problems in various domains other than healthcare such as supply chain management, manufacturing, business success prediction and performance evaluation.

Keywords: CBR; MCDM; Radiotherapy dose planning; Organs at risks; TOPSIS; Goal Programming; DEA; FA; Grey numbers; GRA; Gaussian distance; Genetic Algorithm.

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To my parents for their inspirations …

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Chapter 1

Introduction

This thesis investigates the application of Multi-Criteria Decision Making (MCDM) techniques in hybridization with Cased-Based Reasoning (CBR) method to propose novel approaches to solve the radiotherapy dose planning problem for prostate cancer. The dataset available to this thesis, in order to test and measure the efficiency and applicability of the approaches, is provided by Nottingham University Hospital. The approaches developed in this thesis are all applied to the radiotherapy dose planning for the first time and are generic and transferable. These approaches can deal with the multicriteria nature of the problem at hand and furthermore, their applicability to other domains is possible through additional problem design. This chapter provides a brief background on the problem, the motivation for the research, research objectives and overall layout of the thesis.

1.1 Background

Cancer can be defined as a disease in which a group of cells in a part of the body proliferate uncontrollably despite the normal trends of cell division. Normal cells receive signals which indicate whether they should divide, transform or die, while cancer cells develop a degree of autonomy from mentioned signals which results in the overgrowth of them. This uncontrolled growth, if left untreated can be fatal to the

patient as the tumours created by abnormal proliferation can spread throughout the body (1). Cancer is usually named after the organ on which its growth was initiated. As an example, if the first cancer cells are being developed in lungs, the cancer is called lung cancer. Although it is not still of certainty and it remains impossible to indicate what makes a person develop cancer, there are factors contributing to increased risk of developing cancer. Apart from age which cannot be controlled, alcohol, being exposed to cancer-causing substances (chemical substances mostly), sunbeams, tobacco, chronic inflammation, hormones, diet, radiation, infectious agents, obesity and immunosuppression are the main contributors increasing the risk of developing cancer (2).

Cancer represents a major healthcare concern, both in the UK and globally. Every two minutes someone in the UK is diagnosed with a form of cancer (3). Mortality rates of cancer make it a substantial cause of death among people and a significant concern to researchers. In 2012, cancer caused 8.2 million loss of life: 4.7 million (57%) in males and 3.5 million (43%) among females (4). The highest cancer mortality rate in males (210 per 100,000) belongs to Armenia, while Zimbabwe possesses the highest rate among female population (146 per 100,000) (2012) (4).

In the year 2012, UK ranked 56th out of 84 countries worldwide regarding the cancer mortality rate among males, while the similar rank for females was 36th. 163,444 deaths by cancer have occurred in the UK in 2014 of which more than 46% have been due to lung, bowel, prostate and breast cancer. Furthermore, 368,560 new cancer cases have been diagnosed in the UK in 2014. The fact that more than 29% of the total deaths in 2011 in the UK has been caused by cancer can give us a better understanding of the significance of this class of diseases (3). Prostate cancer is the second most common cancer for adults in the UK and the most common cancer type for men in the UK.

Approximately 46,700 men are diagnosed with prostate cancer in the UK each year. That reflects 130 cases each day (3).

1.2 Motivation

The human body is a complex system and usually, tumours are located in close proximity to sensitive tissues or critical organs; thus, making the treatment planning an equally complex task. Radiotherapy is one of the major approaches to treat cancer patients. All radiotherapy types involve risk because even a small error in treatment planning, delivery, or dosimetry can lead to negative consequences (5). Radiotherapy treatment planning involves different stages and dose planning, the process of determining the precise effective dose plan to be delivered to tumours and surrounding area, is among the most important of them. Applying doses higher than necessary may lead to surrounding organ damages and applying doses less than the effective amount may lead to an incomplete tumour and cancer cells removal (6).

There has been much software developed to facilitate the task of treatment planning and are available in system planning markets. However, the radiotherapy process is performed differently in each hospital; thus, software is often specialized to find the treatment planning characteristics in different forms of outputs and based on different approaches. For example, in the Nottingham University Hospital oncologists consider a fixed number of beams (i.e. four beams) in prostate cancer treatment radiotherapy and therefore a software compatible with this approach is needed. Brainlab, Elekta, Philips, Prowess and Raysearch are among the most recognized software providers available in the market. Radiotherapy planning and the precise identification of values for different variables of the treatment is essentially an optimization process. However, the search space of this optimization problem is enormous and as a result, software applications commonly struggle with the problem of coming up with the global or near-

global optimum solution. When it comes to dose planning the final goal of the optimization procedure is to find highly effective, but not excessive and harmful, uniform dose values over the organ under radiotherapy to maximize the success rate of the cancer treatment (6).

Data imaging and information gathered from various simulation procedures form the basis of optimization algorithms in radiotherapy optimization software packages. However, due to numerous environmental factors in the radiotherapy process and complexities of human body organs, anticipating the outcome of a treatment plan is a highly difficult task, if not impossible. As a result, the success rate of a treatment plan can be significantly uncertain and it affects the confidence of oncologists in using the optimization packages (7). On the other hand, past oncologists' experiences can be extremely insightful in assisting researchers to anticipate the success rate of the treatment to some approximation.

The knowledge-based reasoning is a set of approaches that can utilize the previous knowledge gained by oncologists to new cases of patients (8). Thus, many researchers have focused on Cased-Based Reasoning, rule-based reasoning and hierarchical organization of knowledge to develop approaches which capture the experience gained by oncologists and generalize it to improve the treatment plan for a new cancer patient. However, still many issues and gaps have not been covered in the existing literature. The existing quantitative methods in the literature are commonly mathematical models or search algorithms which try to find an optimal solution in the search space area by just considering the amount of dose which is going to be radiated to the organ (a comprehensive list of research within this context can be found in table 2.3). There is lack of methods which considers multi-attribute nature of the dose planning problem and this was the main motivation of this PhD thesis. It is important to consider that,

complexities involve in health care decisions, necessitate the trade off between multiple and often conflicting criteria (9). Moreover, the literature is missing case evaluations based not only on the similarity measure of knowledge-based approaches but also on other available criteria. Consideration of multiple criteria results in consideration of multiple similar cases, and this increases the chance of obtaining better results by increasing the number of potential solutions (10).

1.3 Objectives

In this thesis, a decision support procedure based on the integration of MCDM techniques with CBR method has been developed for radiotherapy dose planning in prostate cancer. After a complete investigation of the radiotherapy dose planning problem, the literature related to this problem and the existing approaches developed and proposed to improve the accuracy of the treatment plan the following objectives have been defined and will be followed within this thesis:

1- To investigate the radiotherapy treatment planning and review the state-of-the-art literature with a focus on operational research approaches for radiotherapy dose planning of prostate cancer (chapter 2).

2- To explore the decision-making principles based on which oncologists decide in real-life scenarios and multi-criteria nature of the problem and incorporate them in a Decision Support System (DSS) to assists oncologists with their decisions (chapter 3, 5 and 6).

3- To model a mathematical programming model which can direct the final doses towards optimal dose plans considered by oncologists and increase the efficiency of the dose plans while simultaneously looking after the risks of the treatment (chapter 4).

4- To incorporate the existing uncertainties in oncologists' judgments about the values of different criteria and factors in dose planning and thus making the evaluations and models closer to real-life scenarios (chapter 5).

5- To develop a mechanism to assign optimal non-objective importance weight to each feature of the radiotherapy dose planning problem (chapter 6).

1.4 Layout of the thesis

This thesis is comprised of 7 chapters that are structured as follows (Figure 1.1): After this brief introductory chapter, the thesis continues with the second chapter focused on radiotherapy prostate cancer problem explanation and literature review on application of operation research in radiotherapy treatment planning. In chapter 3, a hybrid application of Cased-Based Reasoning and TOPSIS to prostate cancer radiotherapy dose planning is presented. Chapter 4 proposes a novel integrated Goal Programming optimization and case-base reasoning approach to optimize the doses in radiotherapy. In chapter 5 we develop an approach of Interval-valued Factor Analysis for variable reduction in grey Data Envelopment Analysis and its application in radiotherapy dose planning. Chapter 6 introduces two new similarity measures with better effectiveness for the data type used in this dissertation. A featuring weight mechanism through Genetic Algorithm has been embedded in each similarity calculation approach to find the optimal feature weights and increase the number of successful case retrieval. Finally, Chapter 7 includes the conclusion, limitations and suggested future works related to this research. This thesis can be divided into three main parts of introduction and literature review, the main body of empirical and methodological research and outputs and finally conclusion section. In figure 1.1 these three parts have been separated by a dashed line and where there is an original contribution of this research,

it is highlighted in grey and otherwise, where it exists in the literature it is shown in white.

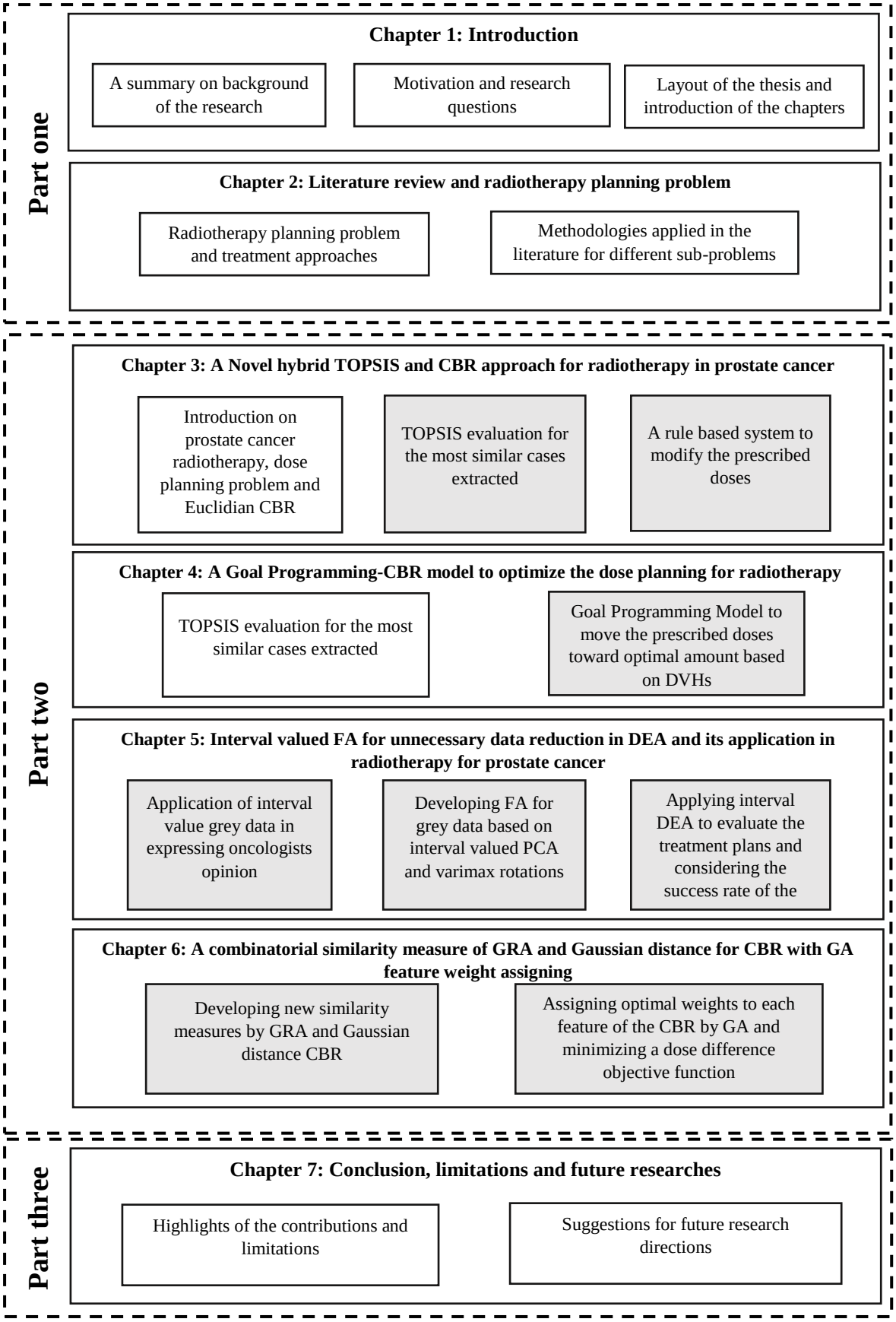

Figure 1.1 Overview of the thesis and contributions

1.5 Summary of the chapters

In this section, the summary of each chapter is given in order to lead the reader to a better understanding of the problem.

Chapter 2 ‘Literature review and radiotherapy problem explanation’: In this chapter, an overview of the magnitude and importance of the cancer diseases and in particular prostate cancer has been given. The treatment options, various type of radiotherapies, the treatment planning process and significant tasks related to it have been explained. Moreover, the methodologies related to different stages of the treatment planning and in detailed works in the literature about the application of operational research and knowledge-based techniques have been reviewed.

Chapter 3 ‘A novel hybrid TOPSIS and CBR approach for radiotherapy in prostate cancer’: Complexity of dose planning for radiotherapy has turned this process into a time and resource consuming task. Usually, oncologists use past experience and spend a large amount of time to determine the optimal combination of dose in phase I and II of treatment. In this chapter, a novel TOPSIS (Technique for Order Preference by Similarity to Ideal Solution) Cased-Based Reasoning (CBR) approach is proposed to capture the past experience and expertise of oncologists. Initially, cases that resemble new case are extracted from the database. Thereafter, inferred cases are evaluated using TOPSIS, a multi-criteria decision-making approach, to prescribe an optimal dose plan. Within this chapter hybridization of Multi-Criteria Decision Making and knowledge-based techniques has been utilized to improve the success rate of the CBR. Robustness of the proposed method is validated on data sets collected from the City Hospital Campus, Nottingham University Hospitals, NHS, UK, using leave-one-out strategy (the description of leave-one-out strategy can be found in chapter 3, section 3.6.2). In the experiment, the proposed methodology outperformed CBR approach. The

methodology is generic in nature and can help oncologists both new and experienced in dose planning process.

Chapter 4 ‘A Goal Programming-CBR model to optimize the dose planning for radiotherapy’: The main objective of dose planning process is to deliver high dose to the cancerous cells and simultaneously minimize the side effects of the treatment. In this chapter, a novel Cased-Based Reasoning and Goal-Programming approach have been proposed to optimize the dose plan for prostate cancer treatment. Firstly, a hybrid retrieval process TOPSIS-CBR is used to capture oncologists’ experience. Thereafter, the dose plans of retrieved cases are adjusted using Goal-Programming Mathematical model. This approach will not only help oncologists to make a better trade-off between different conflicting decision-making criteria but will also deliver a high dose to the cancerous cells with minimal unavoidable effect on surrounding organs at risk. The efficacy of the proposed method is tested on a real dataset collected from Nottingham City Hospital using leave-one-out strategy. In most of the cases, treatment plans generated by the proposed method are coherent with the dose plan prescribed by an experienced oncologist or even better. Developed decision support system can assist both new and experienced oncologists in the treatment planning process.

Chapter 5 ‘Interval valued Factor Analysis for variable reduction in grey Data Envelopment Analysis and its application in radiotherapy dose planning’: While in previous chapters and within the evaluation process all criteria were treated as the same, within this chapter they were divided into two groups of input and output. Also, we added an extra criterion of the success rate of the treatment which is based on the probability of return of cancer after treatment. Data Envelopment Analysis (DEA) is a non-parametric technique to evaluate the efficiency of a set of peer entities (options) in presence of several inputs and outputs of different types (11).

Here, DEA has been used to identify the best suited and efficient case among previously treated cases. In order to adopt the decision-making process close enough to real-world scenarios, we converted the outputs and inputs, considered for each case, to grey linguistic variables which can better justify the oncologists' judgments and include the uncertainty within their understanding of different factors. Thus, the use of interval DEA become necessary within our problem. By including a higher number of outputs and inputs in the DEA model it becomes possible to investigate the efficiency of treatment plans from more points of view. However, the problem of discrimination between efficient and inefficient DMUs in DEA occurs, when the number of variables is large relative to the number of units. To this end, Factor Analysis (FA) was developed and applied, a variable reduction technique, for interval variables in particular for grey numbers based on Principal Component Analysis (PCA) to deal with the aforementioned problem.

Chapter 6 'A combinatorial similarity measure of GRA and Gaussian distance for CBR with GA features' weight assigning': The non-linear relation between the clinical factors and solution of each case, the high number of clinical factors in comparison to the number of the cases in the case pool and the inability of Euclidean CBR in dealing with data distributions require the introduction of other similarity measures to obtain more precise and reliable results. In this chapter, a combined similarity measure by Grey Relational Analysis and Gaussian distance CBR was applied. Moreover, the features weights which also play an important role in case retrieval have been optimized by a proposed Genetic Algorithm to increase the success rate of the retrieval process. The individual and combinatorial performances of each approach have been thoroughly tested and compared to each other.

Chapter 7’Conclusion and future work’: In this chapter, a discussion about the effectiveness of the proposed approaches is done and a conclusion is presented to highlight the contributions of the thesis. Furthermore, the shortcomings of the thesis are being reviewed and future suggestions for the development of the research is presented.

In the following the outcomes of this thesis in terms of publications have been mentioned:

[1] Malekpoor, H., Mishra, N., Sumalya, S. and Kumari, S., 2017. An efficient approach to radiotherapy dose planning problem: a TOPSIS Cased-Based Reasoning approach. International Journal of Systems Science: Operations & Logistics, 4(1), pp.4-12.

In communication: Malekpoor, H., Mishra, N., Kumar, S. A novel TOPSIS-CBR Goal programming approach to sustainable healthcare treatment. (2017) *Annals of Operational Research* (revised and resubmitted, minor revisions)

Chapter 2

Literature review of radiotherapy planning problem for cancer

2.1 Introduction

Cancer is a crucial public health issue and a significant cause of morbidity and mortality, with around 14 million new cases diagnosed in 2012 and 8 million cancer-related deaths in the same year which reached to 8.8 million in 2015, affecting populations in all countries and all regions (3). Cancer has been recognised as the second cause of death globally and is responsible for 1 out of every 6 deaths (12) and the number of new cases is expected to be raised by 70% in the next two decades. Cancer is a disease where cells in a particular segment of the body proliferate abnormally. Globally, the most common types of cancer are Lung, Breast, Colorectum and Prostate (Figure 2.1).

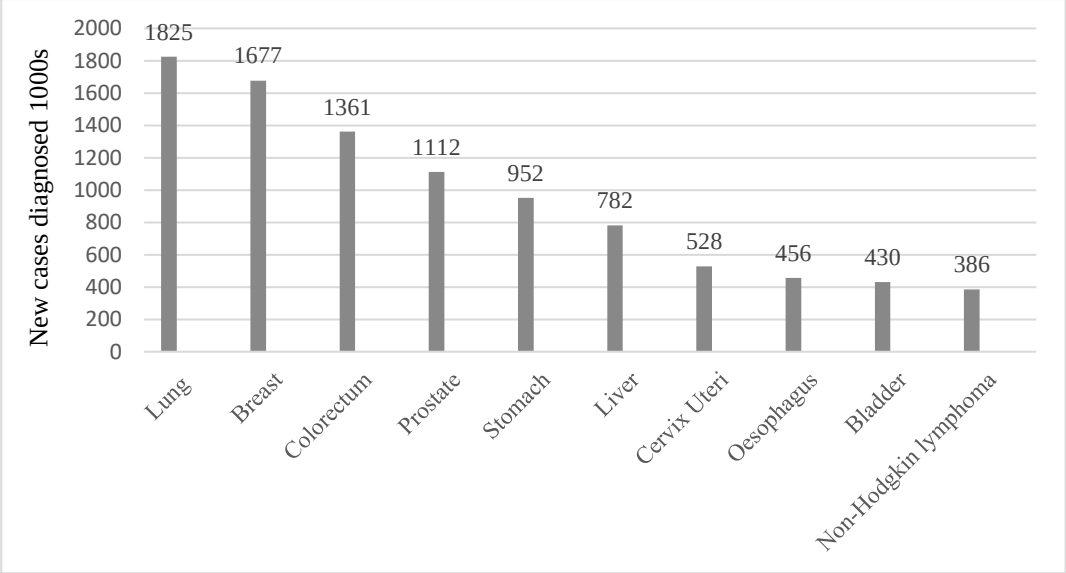

Figure 2.1 the most common cancer types diagnosed globally (13)

The mortality rate of the cancer is not the same in different countries. Asia, Africa, Central America and South America are associated with 70% of the cancer occurrence and 60% of the cancer-related deaths (2). The UK has 36th highest rate of mortality for females globally and among the European countries possesses a high mortality rate for both genders. Figure 2.2 illustrates the mortality age-standardized rate per 100 thousand in a sample of European countries and as can be seen, the UK has the second rank after Denmark.

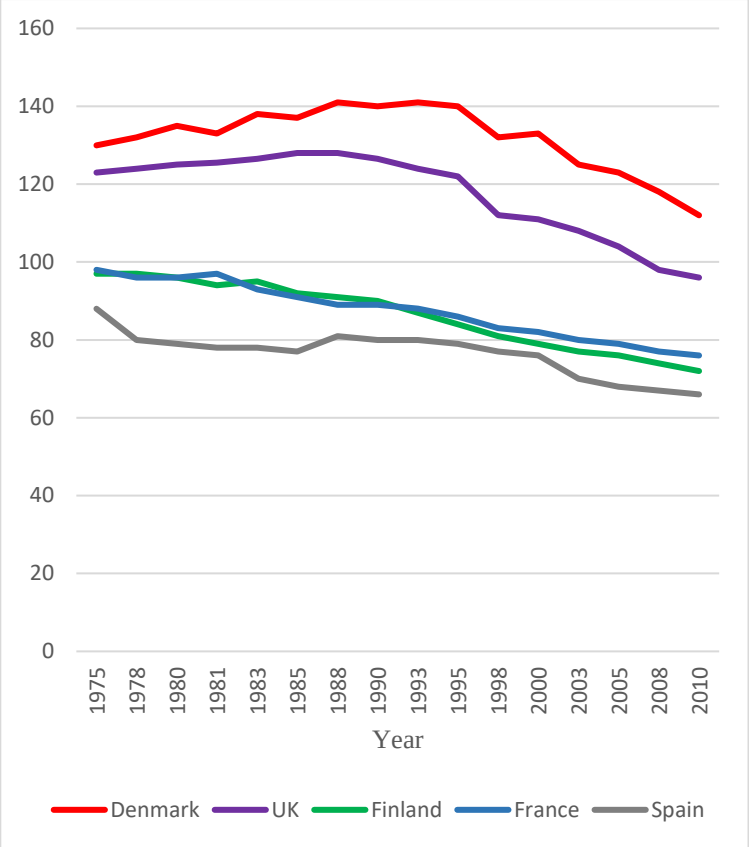

Figure 2.2 Mortality age-standardized rate of cancer in European countries (14)

Usually, cancer begins in one part of the body and spread to the other parts affecting the functionality of the host and surrounding healthy organs. This process is known as metastasis. In metastasis, cancer cells separate from the primary location where they initially formed and move through the blood or lymph system and create new tumours (metastatic tumours) in other parts of the body. A metastatic tumour has similar characteristics to the primary tumour type (2).

The initial phase of a cancer diagnosis is done through a lab test. High or low levels of certain substances in your body can indicate the presence of cancer. Thus, doctors seek assistance from lab tests of body fluids i.e. blood and urine in their diagnosis. However, as important as lab tests are, they are not the only source that doctors rely on. Imaging procedures are a set of useful diagnostic tools which create pictures of areas inside your body that help the doctors to see whether a tumour is present. Computerized

Tomography scan (CT scan), Nuclear scan, Positron Emission Tomography scan (PET scan), Magnetic Resonance Imaging (MRI) and ultrasound are among the most common imaging procedure tools. CT scan uses X-rays to make detailed pictures of parts of the body and the structures inside the body (15). In CT scan, several beams are sent simultaneously from different angles. This allows highly detailed images from within the body to be interpreted by doctors. However, it cannot distinguish between normal and pathological cells.

Therefore, MRI or in some cases a combination of MRI and Nuclear scans becomes necessary. MRI is a strong magnet linked to a computer that is used to make detailed pictures of areas in the human body. Also in Nuclear scans, a small amount of radioactive material is injected into the body. It flows through the bloodstream and accumulates in certain bones or organs. A scanning device detects and measures the radioactivity. The scanner creates pictures of bones or organs on a computer screen or on film. All the aforementioned tests are part of the diagnosis procedure and in order to reach a conclusive evidence about malignant cancer performing a Biopsy is essential (16). In Biopsy a small part of a tissue is removed as a sample to be further examined. A Pathologist then looks at the tissue under a microscope to confirm the existence of malignant cancer (17).

Treatment options depend on the type, size and stage of cancer and moreover, whether it has spread throughout the body, the level of spread and the patient's general health condition. Based on the abovementioned factors there exist a range of treatment methods that include surgery, chemotherapy or cancer drugs, hormone therapy and radiotherapy (2). Surgery is a primary treatment and is suggested by oncologists when the cancer is not spread and is in very first stages. In this treatment, the cancerous cells are physically removed. Chemotherapy literally means drug treatment (16). In cancer

treatment, it means using anti-cancer drugs to destroy cancer cells. One or a combination of several drugs is used to slow the growth or reducing the size of the tumours and in some more advanced cancer stages, it is done as a complementary treatment along with other treatment methods.

Hormone therapy blocks or lowers the amount of hormones in the body to stop or slow down the growth of cancer and it is usually applied to treat hormone-dependent cancers such as breast and prostate cancer (18). Hormone therapy stops the natural hormone production or prevents hormones from making cancer cells grow and reproduce. In radiotherapy, Gamma or X-rays are used to kill cancerous cells. Radiotherapy annihilates the cancer cells in the treated area by impairing the structure of DNA within these cells. About 4 out of 10 people struggling with cancer (40%) are prescribed to perform radiotherapy as a part of their treatment (3).

The purpose of radiotherapy is to eradicate cancer cells while causing as little damage as possible to healthy cells as radiations not only destroy the cancer cells but also affect the healthy surrounding cells which are exposed to it. The cells do not die at once and the process of dying usually takes up to a few weeks. During this period some of the damaged cells recover through reproduction. However, the recovery pace for healthy cells is much faster than the cancerous ones. Thus, the radiation is delivered to the patient in doses of approximately 2Gy each day over a course of several weeks to let the recovery of healthy cells be done appropriately. Gy (pronounced as Gray) is the unit to indicate the absorbed dose. One Gy is equal to one Joule (J) of energy deposited in one kilogram (kg) of matter (19).

There are various methods of radiotherapy being performed in hospitals based on existing circumstances and in different conditions. Depending on where oncologists

locate the radiation during treatment, we can classify radiotherapy into three main categories of external beam radiotherapy, internal radiation therapy or Brachytherapy and systemic radiation therapy.

In internal radiation therapy, the source of radiation is implanted inside the body in or near a tumour and depending on the cancer type and stage it could be temporary or permanent. In systemic radiation therapy, a radioactive drug (radiopharmaceuticals) through oral digestion or vein injection (IV) is delivered to the body (20). These kinds of drugs are sometimes bound to a special antibody (called a monoclonal antibody) that attaches to the cancer cells and it is more commonly in use for certain cancers, such as thyroid, bone, and prostate cancer. External radiation (or external beam radiation) is the most common type of radiation therapy used for cancer treatment (21). In this type of treatment, a machine called linear accelerator (Linac) aims high-energy rays (or beams) from outside the body into a tumour. Nowadays advancements in medical technologies allow oncologists to focus the beams with high precision on the tumours and thus reduce the side effects of treatment significantly (22). External beam radiotherapy is divided into several categories which are shown in table 2.1.

Table 2.1 Different types of external beam radiotherapy

Method	Description
Three-dimensional conformal radiation therapy (3D-CRT)	Radiation beams which are designed to match the tumour shape are delivered from different angles. The aim of this method is to deliver radiation to the gross tumour volume with a margin for microscopic tumour extension called the clinical target volume and a further margin uncertainty due to organ motion and setup variations called the planning target volume(23).
Intensity modulated radiation therapy (IMRT)	IMRT enables oncologists to create irregularities in the beam shapes and thus control the doses that conform to a tumour whilst simultaneously prevent damages to critical organs. Higher doses in necessary parts of the organ and lesser doses in some parts can significantly improve the results of the radiotherapy. Multi-leaf collimators are used to modulate the beam, by creating barriers in the beam path where necessary. This has improved the therapeutic ratio of the treatment for several tumour sites, such as head and neck cancers (24), prostate cancers(25) and gynaecological cancers (26).
Image-guided radiotherapy (IGRT)	IGRT is sort of a 3D-CRT in which imaging scans (e.g. a CT scan) are done prior to each treatment session. This allows the radiation oncologist to adjust the position of the patient to the most updated relevant position or alter the focus of beams to hit the essential targeted area of a tumour and restrain the extent of damages. This approach is becoming common in nearly all the IMRT treatments to increase the precision of the treatment (27).
Proton beam radiation therapy	In this method, proton beams are applied instead of electrons or x-rays. When proton beams are radiated to the body, they cause a minimal damage to the tissues they passed through, however they effectively eradicate the cells at the end of their path. This behaviour makes proton beams able to enhance the radiation delivery to the tumour target zone while reducing side effects on normal tissues. Special machines called cyclotron or synchrotron are used to put out the protons. Proton therapy is beneficial in particular to the patients with tumours near vital organs, such as base of the skull, and patients who are struggling with cancer at younger age and therefore minimization of the long-term effects of treatment is an advantage (such as hormonal imbalances, intellectual development delay and secondary cancers) (13).
Stereotactic body radiation therapy (SBRT)	Technological advances enable oncologists in cooperation with surgeons to precisely deliver high individual doses of radiation over only a few treatment fractions to ablate small, well-defined primary and oligometastatic tumours. Due to high doses used in this method any cell, healthy or cancerous adjusted by the radiation is going to be damaged, however, because of low rate existence of healthy cells in regions of high doses in this method, the damages to healthy cells are negligible (13).

Designing radiotherapy treatments is a complicated task and modern advancements in treatment technologies have made it even more complex, however more flexible for physicians to improve patients care. Consequently, treatment design is increasingly automated by means of optimization techniques, and many of the advances in the design process are accomplished by a collaboration between medical physicists, radiation oncologists, and optimization experts (28). While previously the treatment

design was done by physicians through trial and error with the help of operational researchers, the designing plan process has been becoming more optimized, automated and significantly improved. Each of the experts in a planning team has their specialized responsibility. While the oncologists diagnose the source of cancer, outline the tumour volume and prioritize the organs at risks, the medical physicists are in charge of the equipment needed to deliver the doses and perform the actual radiation delivery. The role of the operational researchers is to optimize all treatment stages through mathematical modelling, artificial intelligence methods and simulations in such a way that other experts can achieve their goals with the best possible results (29).

2.2 Radiotherapy planning process

The treatment plan for radiotherapy consists of three main steps of imaging and pre-planning, simulation and confirmation and execution. The main goal of radiation therapy is to damage the DNA of cancer cells and deprive them of their multiplication potential and eventually kill them. While doing so, the inevitable damage to healthy cells surrounding the tumour or standing in the way of radiation to reach a tumour must be minimized (30).

Observing symptoms related to cancer is the first step for diagnosis. Thereafter the patient is referred to imaging scanning or in some cases to biopsy to investigate the suspected lesion. The imaging process may be performed by CT scans, magnetic resonance imaging (MRI) or positron emission tomography (PET). Through consultation with oncologists for required details, each of the abovementioned options can provide unique information about the patient's condition. CT scans can provide bone anatomy and tissue density information. Information regarding the soft tissues can be obtained through MRI and PET and is useful in gaining functional information on the tumour metabolic activity. Information provided by imaging can be decisive in

selecting a treatment modality, the tissues that should be focused in radiotherapy and the ones that should be spared.

Gross Tumour Volume (GTV) is a primary tumour or other tumour mass which is identified either through imaging or examination under anaesthetic (EUA) (20). Clinical Target Volume (CTV) contains the GTV as well as other microscopic cancer cells which have to be eradicated in order to effectively treat cancer. Throughout the treatment due to patient's movements or changes in the size of different organs, the position of the CTV may also vary compared to its original position. It is necessary to deliver homogenous and sufficient radiation to the CTV thus a margin called Planning Target Volume (PTV) is defined and contains the CTV as well as a safe margin to ensure the delivery of the actual dose plan to CTV (Figure 2.3).

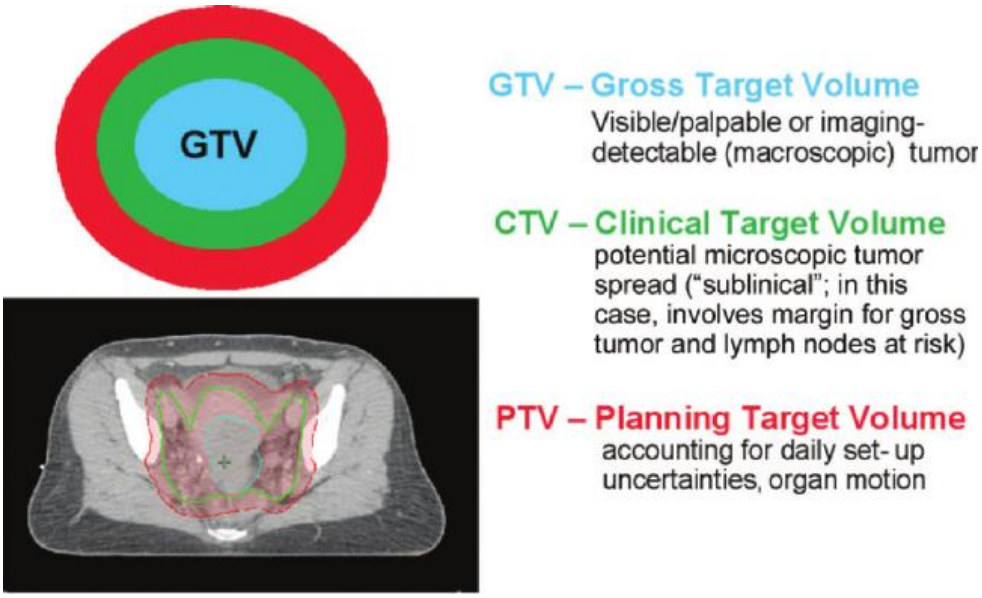

Figure 2.3 Different target volumes in radiotherapy (31)

After outlining different tumour volumes, oncologists begin to specify the Organs At Risks (OARs) and prioritize them based on the location of a tumour in the body, seen

in the images. There are critical normal tissues the vulnerability of which may force significant restriction so special care should be assigned to them. The next step is preparing and designing a treatment plan which is a collaboration between oncologists and medical physicists. This treatment plan should determine the amount of radiation dose to be received by different target volumes, the beams specifications including the shape, size number and their concentration target, number of wedges and the configuration and beam intensity profile for each beam. There are two different approaches for determining the treatment plan, namely forward and inverse planning. In forward planning physicists and oncologists manually select all the specification of the treatment and after that calculate how the radiation is absorbed and deposited in different organs. If the result is unsatisfactory then another treatment plan is created and this trial and error process continues until a near to satisfactory result is obtained. However, in reverse planning, the amount of optimum doses to be accumulated in the organs is prescribed and then the treatment specifications are calculated through algorithms and models. In this approach, the role of the operation researchers and mathematical models are more highlighted. Next is the simulation phase to examine the effects of the treatment on different organs within different volumes of them.

Dose Volume Histogram (DVH) has an important role in reviewing and simulating the treatment plan. DVH is a graphical representation of the dose that is received by normal tissues and target volumes within a 3-D radiation therapy plan. They provide information on the volume of a structure receiving a given dose over a range of doses (32). Based on the DVHs values and other circumstances a final treatment plan, which is both effective and minimizes the damages to surrounding healthy cells is suggested by the treatment plan team. Once the suggested treatment has been confirmed and finalized the radiation is delivered to the patient by using a linear accelerator or Linac.

In order to ensure the appropriate position of the patient during the treatment, some immobilization devices may be used. These immobilization devices can be a simple cotton band to fix the patients feet or in some more extreme sensitive cases like brain radiotherapy, it could be some pins placed into the skull to affix the patient's head in the right position.

Then Linac is equipped with a device called multi-leaf collimator. A multi-leaf collimator consists of individual leaves made up of a high atomic numbered material, i.e. tungsten. These leaves are responsible to block a portion of a particle beam by creating barriers in the beam path. Furthermore, most modern Linacs take digital images, which are called an EPI (Electronic portal image) or PI (portal image). These images are compared against those generated during the radiotherapy planning, by the radiographers and physicists, before they deliver any treatment as verification. A multi-leaf collimator is shown in figure 2.4.

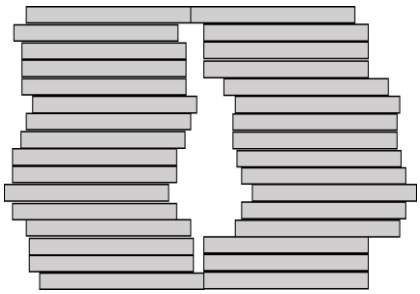

Figure 2.4 Multi-leaf collimator

Operational research is a very helpful instrumentation in assisting to find a solution to different problems in radiotherapy treatment planning and optimized a large number of parameters involved. The issues covered by the literature in radiotherapy planning problem and their summarized description is presented in table 2.2.

Table 2.2 Issues of the radiotherapy planning problem covered by literature

Problem investigated	Problem description	references
Geometry problem or beam configuration optimization problem	Selection of the optimal number of beams, determining the optimal angle between beams and the beams' weights	(33-70)
Wedges configuration problem	Find the optimal configuration of the wedges including their position, number and angle	(71-76)
Segmentation problem	Selection of optimal delivery sequence	(77-83)
Outline of the treatment volume and movement of organs	Determination of different treatment volumes, organs at risks and calculation of organ movements during a treatment	(84-109)
Dose Planning Problem	Obtaining the optimal dose plan to be delivered in different phases of the treatment to different treatment volumes	(45,110-130)

2.2.1 Beam configuration (Geometry problem):

Determination of an ideal beam configuration is an important step in radiotherapy planning and has significant influence in treatment quality both to enhance the eradication of the tumour cells and surrounding organ sparing. The main two objectives in beam configuration optimization are determining the optimal number of the beams and the perfect angle between them. Since the last decade, due to its advantages, application of IMRT in treating the patients has been increased. IMRT is being used most widely to treat certain types of cancer including prostate, head and neck, and central nervous system. If necessary and some limitations are satisfied, IMRT can also be used to treat breast, thyroid, lung, as well as in gastrointestinal, gynecologic malignancies and certain types of sarcomas. Pediatric malignancies can be also treated

effectively by IMRT in some limited situations. The main difference between traditional external radiotherapy methods with IMRT is in the number of the beams. In the traditional method, a few beams are used while IMRT delivers hundreds of small radiation beams with different intensities, entering the body from a number of different angles. In traditional treatment, the planning team usually sets their configuration through trial and error and based on previous experiences, however, in order to deliver the IMRT to the patient such a task is almost impossible manually and relying on past experiences.

Pugachev and Xing (37), developed a Simulated Annealing (SA) algorithm to search for the optimal set of beam configuration to speed up the beam configuration optimization. At first, they investigated the quality of each possible beam orientation by a method called beams-eye-view dosimetrics (BEVD) which was developed in Pugachev et al. (131). Then, after the optimal set of beam orientations was calculated by taking into account the BEVD scores of different incident beam directions. However, in this approach, the beams interactions with each other were not considered which can change the results significantly. Yang et al. (132) applied a mixed integer linear programming with binary variables to represent a candidate for beam orientation and a positive float variable to represent a beam weight. They solved their model by use of branch and bound method and the main goal of their research was to avoid the possibility of obtaining a local optimal solution instead of global optimal solution which can be a result of stochastic and heuristic search algorithms used by Hou et al. (133), Li et al. (134) and (33) in previous research. Although branch and bound method in comparison with random search algorithms can increase the solving time in presence of big solution space. Li and Lei (36) proposed a DNA genetic algorithm (DNA-GA) in order to improve the computation time of solving the beam angle problem (BAO).

A feasible mapping was constructed between the universal DNA-GA algorithm and the specified engineering problem of BAO. Experiments on clinical as well as simulated cases showed the efficiency of the proposed method can be higher than GA in some cases. Cabrera et al. (70) proposed a two-phase optimization process to solve the BAO problem by treating it as a multi-objective problem that takes into account the trade-off between different goals in radiotherapy. In the first phase by using a deterministic local search algorithm, they created a set of locally optimal beam angle configurations and in the second phase by performing a dominance analysis they presented the set of promising optimal solutions.

2.2.2 Wedges configuration

In radiotherapy treatment by high energy beams, the isodose distribution needs to be modified through compensating dose inhomogeneity. Wedges filters are a common instrument for this dose modification (135). Principally, wedges represent metallic absorbent blocks (lead or steel) and they are placed into the path of the X-ray beam at the output of a Linac. Nowadays, static wedges have been replaced by dynamic wedges which have improved the dose distribution and is capable of achieving any wedge angle by the movement of one pair of independent jaws of the wedge. To be more specific there are two main wedges uses:

- Wedges are used to compensate for a sloping surface, as for example in some cases for the missing tissues.
- Placing a wedge pair of beams which is most often used in the treatment of low lying lesions so that two beams can be set to form an angle of less than 180º (hinge angle).

Determining the number of wedges, their positions and their optimal angle is a complex and time-consuming task. The main goal of the operational research working in this

area is to set all the factors involved in this process in their optimal situation as well as reducing the time needed for calculation and decision making. Albertini et al. (136), studied various starting conditions in intensity modulated proton therapy (IMPT) based on different wedges features. Through the quasi-Newton method, they optimized the plans with different starting conditions and after finding local optimal solutions, they compared the results of the plans by considering the OARs vulnerabilities and determined the best starting conditions for IMPT.

2.2.3 Outline of the treatment volume and movement of organs

During a fractionated course of radiotherapy shifts in patient's position and also sometimes in alignments of the beams and thus unpredictable organ motions will happen. So, after initial imaging and determining different organ volumes, margins set up for CTV and PTV should account for the intra and inter-fractionally movements of organs and tumours during the treatment. These margins can compensate for the errors that happen systemically and randomly. While systematic errors are the results of incorrect data transfer between planning department and delivery team or inaccurate equipment set up are avoidable and have to be corrected, the random errors are due to changes in daily patient anatomy and are impossible to correct. So researchers, based on image-guided techniques and systems as well as circumstances of the tumours and organs involved, try to optimize to most efficient way to consider the necessary margins. Khan et al. (102) proposed a study to model inter-fraction CTV variation in patients with intact cervical cancer and design a PTV that minimizes normal tissue dose while maximizing CTV coverage. To do so they performed computed-tomography techniques to obtain a probability function that can predict the optimal volume targets. Lens et al. (109) introduced a probabilistic treatment planning approach that prospectively incorporates respiratory-induced motion in the treatment

plan optimization. They performed a comparison between two methods of probabilistic respiratory motion-included (RMI) approach and Internal Target Volume (ITV) approach by taking into account the information related to 18 pancreatic cancer patients. The comparison results revealed that by applying probabilistic treatment planning approach dose gradients are yielded significantly steeper and thus the dose damaging surrounding healthy tissues is lower comparing to ITV approach.

2.2.4 Dose planning problem

A critical step in radiotherapy treatment for cancer is determining the optimal dose plan in different phases of the treatment. After defining all the aforementioned parameters, including beam configurations, wedges configurations, outlining different treatment volumes, prioritizing organs at risks and obtaining DVHs of different organs, dose prescription is the next task to be done. Through CT scans the 3-D tumour information is provided to oncologists and they are in charge of prescribing a dose plan which can kill cancerous cells as much as possible while limiting damage to healthy organs, in particular, the ones lying next to the main tumour area. The oncologists are seeking to find a dose plan that does not impair the healthy cells, however, sometimes sacrifices are inevitable to deliver the effective dose of radiation to cancer cells so that the patient can be in a cancer-free condition in the future. Romeijn et al. (137) proposed a linear programming approach to radiotherapy dose planning problem. The main constraints of the developed model were hard bounds regarding the dose limits for normal and cancerous cells. In this approach, various dose-planning parameters were fixed before the optimization, which is a complex task. Their exact values may vary from patient to patient. Moreover, the proposed model is able to generate only one treatment plan for each run. In case of a need for multiple plans or necessary compromises, the planner is obligated to launch a series of experiment and the calculation time is going to be

increased. Zhang and Merritt (129) formulated a new least-squares model that can resolve the non-convexity and not be differentiable problems associated with objective functions of the previous models, caused by incorporating the dose-volume constraints (DVCs) into the problem in IMRT. They concluded that compared to a widely used existing model at the time, the new approach was capable of generating clinically relevant plans at a significantly faster speed. Modiri et al. (130) used particle swarm optimization (PSO) algorithm to solve a 4D radiation therapy (RT) inverse planning problem. By using respiratory motion as an additional degree of freedom in lung cancer radiotherapy, they tried to find an optimal dose plan and beam configuration for the treatment. To do so they proposed a new PSO algorithm and called it virtual search algorithm. This algorithm despite the previous algorithms (unconstrained and hard constrained) select one objective (based on different weighting approaches) as a critical objective and use it to navigate the search agents. The approach can reduce the calculation time for large-scale non-convex problems.

2.3 Operational research approaches applied in radiotherapy treatment planning process

Besides biological and laboratory research that were done to improve the treatment plans quality, the operational research techniques applied within this area can be classified into two major groups of optimization and knowledge-based approaches. Typically the optimization methods consist of obtaining the optimal value (minimum or maximum) of a real function by systematically choosing input values from within an allowed set, which is called the constraints and computing the value of the function. However, this function can be of a linear, non-linear, fractional, continuous or discrete type. Furthermore, multiple objective functions can be considered in a problem to reach a compromising solution between various available goals and factors. In order to solve

an optimization problem, depending on the nature of the problem, linear programming, non-linear programming, integer programming, heuristics and evolutionary algorithms, stochastic or robust optimization techniques may be applied. Knowledge-based approaches usually rely on the existing knowledge and utilize the past solutions found for a problem in order to suggest a new one for the problem at hand. Cased-Based Reasoning (CBR) and rule-based reasoning are two major methodologies applied within the knowledge-based approaches.

Craft (138) proposed a gradient-based optimization model which used linear programming duality theory to optimize the beam angle in IMRT planning. It was able to produce a set of local optima for the treatment plan; however, it was not able to deal with the non-linearity which is the result of a 3-D imaging and target volumes. Still, the gradient-based optimization follows the basics of local search methods. Zhang et al. (139) argued that the use of heuristics and local search approaches, such as SA, GA and gradient-based optimization, despite the high speed in handling the large-spaced and timely expensive IMRT planning, has some particular disadvantages. They could be stuck in the local optima and not obtaining a global optimal answer. Thus, in IMRT planning where a feasible and bound problem can be formulated the use of exact approaches can be more attractive. They modified the traditional two-stage IMRT optimization process by augmenting the second stage via an accurate Monte Carlo-based kernel superposition dose calculation corresponding to beam apertures. After that, they combined the calculations with a sequential optimization approach based on exact linear mathematical programming. Finally, they calculated the dose plan for IMRT more efficiently than previous existing approaches and was able to obtain a global optimal solution.

Taskin et al. (140) developed a mixed integer programming model for IMRT intensity matrix calculation and provided an upper and lower bound for a set of acceptable solutions in the optimal Pareto. However, comparing the derived solutions and choosing the optimal for a specific patient in IMRT task is still missing in this research. Fiege et al. (141) proposed a multi-objective GA in order to improve the results obtained by a single-objective fluence optimizer commercial pack and simultaneously calculate the beam angles and fluence patterns in IMRT treatment planning. In their approach, a set of the non-dominated solution, as the Pareto frontier was obtained by applying the algorithm to a real patient dataset and the results were showing good correlation with the actual treatment prescribed.

The Pareto frontier or non-dominated Pareto set of solutions in multi-objective optimization is highly dependent on the weights selected for different objectives and this task is usually done by the planning team, manually adjusting the objective weights using a trial-and-error procedure. Yang et al. (142) developed a new particle swarm optimization (PSO) method which can adjust the weighting factors automatically to contribute to the development of a fully automated planning process. A perturbation strategy – the crossover and mutation operator hybrid approach – is employed to enhance the population diversity in each iteration. The treatment plans designed by this approach were promising.

A summary of different optimization techniques applications in radiotherapy for cancer treatment is shown in table 2.3.

Table 2.3 Optimization techniques in radiotherapy planning problem

Methodology	Main problem focus	reference
Linear Programming and Mixed Integer Programming	Beam configuration	(143-151)
	Dose planning	(152,153)
Non-linear programming	Beam configuration	(154,155)
	Dose planning	(156,158)
	Wedges configuration	(159)
Quadratic programming	Dose planning	(160-162)
Genetic Algorithm (GA)	Beam configuration	(163-167)
	Dose planning	(168-170)
Particle Swarm Optimization (PSO)	Beam Configuration	(171)
Simulated Annealing (SA)	Beam configuration	(172,177)
	Dose planning	(178-180)

Advancements in Artificial Intelligence (AI) has led to a set of approaches called knowledge-based methods. These approaches do not use optimization techniques and instead, they are based on the assumption that the solution to a new problem can be found based on the searches done in the similar problems already solved. The rule-based reasoning is an approach in which the decision makers come up with a hierarchy of rules which can be applied to a new problem based on their previous experiences and practical observations. While the Cased-Based Reasoning is based on the similarity between a new case and past successful cases. Generally, the solution of the most similar past successful case is prescribed or suggested for the new case (8).

Rossille et al. (181) applied both the rule-based and Cased-Based Reasoning to model a decision support system in order to find the treatment plans for new cancer cases. In this research firstly, a rule-based system depending on the type of cancer selects the most critical attributes for the case. Thereafter a Cased-Based Reasoning approach based on the selected attribute extracts the most similar case to the new case. Teodorovic et al. (124) used Cased-Based Reasoning approach for dose planning in thyroid cancer. Bee Colony Optimization (BCO) was used to assign weights to various attributes of the cases to measure the similarity between a new case and cases in the case pool.

Ping et al. (182) proposed a multiple measurements Cased-Based Reasoning (MMCBR) method for liver cancer recurrence predictive models. This approach used pairing method through time series and dynamically determined matching pairs among cases and paired all cases in the database with the new case. In above method, various similarity measures were considered but results were not outstanding. Learning from past experiences can be a lucrative approach in particular for the sensitive tasks. In radiotherapy for cancer determining the volume targets, OARs and DVH values are examples of such sensitive tasks which can be penalized if being done with errors. Deshpande et al. (183) designed a decision support system by coupling a database of retrospective DICOM RT for neck and head cancer radiotherapy to a Cased-Based Reasoning model. This decision support system indicated cases within the database that are anatomically similar to a new case of cancer. The dose profiles of these database cases can assist physicians to modify their estimations more accurately for dose distributions in the surrounding organs based on similar cases and empirical data available for their treatment. Also, the large size of data enabled the system to compare the new cases with a high variety of previous cases in order to find the most similar

case. A summary of the application of knowledge-based approaches is illustrated in table 2.4.

Table 2.4 Knowledge-based approaches in radiotherapy planning problem

Methodology	Main problem focus	reference
Knowledge-based reasoning	Dose Planning	(184-186)
Cased-based reasoning (CBR)	Beam Configuration	(187-190)
	Dose planning	(6,7,191-194)

2.4 Conclusion

Within this chapter, we have explained the nature of the cancer disease and provided an introduction to its different types and the various treatment measures which can be applied to confront it. Moreover, different types of radiotherapy and the treatment planning process have been reviewed. The body of literature consists of two main parts. Firstly, the different characteristics and actions needed for the radiotherapy planning and secondly, the methodologies which have been used to overcome the problems, barriers and gaps existing in decision making and optimization process to design an optimal treatment plan.

Beam configuration, wedges configuration, segmentation problem, determining outline of the treatment volumes and movement of organs as well as finding the optimal dose plan are the main issues covered by the operational research techniques in the literature and two categories of optimization techniques including linear, non-linear and quadratic programming, heuristic algorithms and knowledge-based approaches including case-based and rule-based reasoning are the most commonly applied approaches. However, in the models developed in the literature many criteria have not been considered in the process of planning the treatment and in final evaluations, the

multi-criteria nature of the problem, as well as some significant limitations and compromising actions that usually are done by real world oncologists, have been neglected. Furthermore, in knowledge-based approaches, the uncertainties involved in human judgment have not been considered in the process of reusing human past experiences.

In this research with the help of multi-attribute and multi-objective decision-making techniques the gaps mentioned will be addressed for dose planning in prostate cancer radiotherapy. The multi-criteria nature of the problem is considered, introducing compromises and uncertainty in human judgment that reflect those required by oncologists and medical treatment teams to improve the efficiency of a Cased-Based Reasoning system for radiotherapy prostate cancer.

Chapter 3

A novel hybrid TOPSIS and CBR approach for radiotherapy in prostate cancer

3.1 Introduction

Prostate cancer is the most common cancer among male population in the UK (13) and the second most common cancer in all male population around the world with a share of 15% of all patients diagnosed with cancer (3). In 2011, about 42,000 of cases of prostate cancer were reported in the UK and it has caused approximately 11,000 deaths in 2012. In 2014, there were an estimated 3,085,209 men living with prostate cancer in the United States. Treatment of choice for prostate cancer is radiotherapy with X-rays or Gamma rays. However, complementary treatments such as surgery in combination with radiotherapy are common depending on the size of a tumour and stage of cancer. Oncologists and medical physicists dedicate a lot of time to produce an optimal treatment plan for each patient. They also get aid from planning software in determining the initial, near optimal values for different parameters of radiotherapy like the number of the beams, beam angles, position and angle of the wedges. Thereafter they create DVHs related to various organs and volume targets involved in the treatment. Based on their past experiences and a trade-off between the possibility of killing cancer cells and the risk of threatening sensitive organs, they prescribe a dose plan.

It is almost impossible for a medical team to predict the outcome of a treatment and mathematically it is a highly complex task to set a model to anticipate the expected success rate of a treatment. However, similar previous cases and the experiences gained through them can be an elucidative guide for the medical team as they have already been done and the results due to the treatment plan prescribed to them are available. Moreover, oncologists may need to consider several factors in order to make a decision and efficiently use their past experiences while human brain has limited capacity to consider a high number of factors simultaneously and evaluate multiple options effectively.

In this chapter, a hybrid approach of Cased-Based Reasoning (CBR) and multi-criteria decision-making technique is proposed. That is the Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS), in order to suggest the most appropriate dose plan for prostate cancer radiotherapy based on the previous experiences and patients treated. Through applying CBR the most similar cases to a new case can be extracted and thus the experience gained through their treatment can be applied to the new cases. However, not all the time the most similar case is the most appropriate scenario to be suggested and so based on various criteria the most similar cases with a minimum limitation on similarity rate have competed with each other in TOPSIS evaluations. Furthermore, oncologists in real life scenarios do not rely only on one successful past scenario and usually, they combine the solutions of some equally successful cases together. To do so we have provided a rule-based system that performs the same kind of case combinations is provided and makes this system as close as possible to the real life medical decision-making process. The rest of this chapter is structured as follows: in section 2 the Cased-Based Reasoning (CBR) approach and its different steps are being explained and a summary of the literature related to CBR application in cancer

treatment is given. In section 3, TOPSIS methodology is presented and thereafter in section 4 radiotherapy process for prostate cancer and its features is explained in detail. Our proposed methodology for developing a more realistic and successful treatment planning based on TOPSIS and CBR is explained in section 5, followed by a numerical example provided in section 6 to better illustrate the efficiency of the proposed methodology and the results are being discussed. Finally, section 7 is the conclusion of this chapter.

3.2 Cased-Based Reasoning

In order to deal with a new problem, past solutions that were developed to solve similar problems are good indicators of which solutions have been successful and which of them have led to failure. Furthermore, these past experiences could teach us about the factors essential to success and also those that cause failure. Cased-Based Reasoning is a general paradigm for reasoning from experience. It uses a memory model for representing, indexing, and organizing past cases and a process model for retrieving and modifying old cases and assimilating new ones (195,196). Case-based reasoning, a knowledge-based system is a problem-solving approach that relies on past similar cases to find out solutions to new problems (8,197,198).

In Cased-Based Reasoning, cases are similar events or problems consisting of two main parts; several features which define a case and a solution part. Case pool is a place where these cases are stored to be used by the system. Figure 3.1 shows the main procedure of a Cased-Based Reasoning system. There are four main stages in Cased-Based Reasoning: retrieval, reusing, adaptation or revising and retaining.

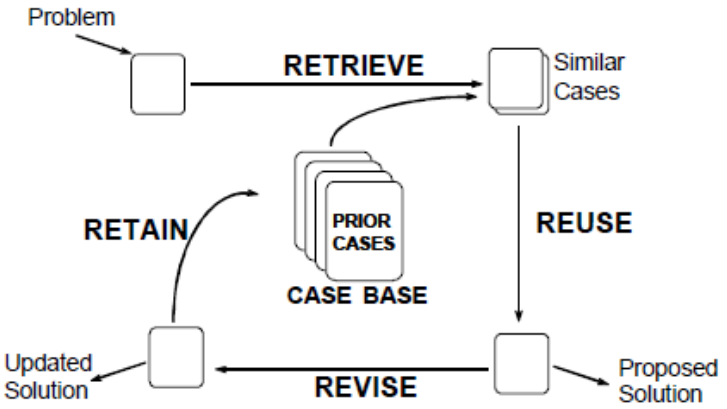

Figure 3.1 Case Based Reasoning process (adopted from Aamodt & Plaza (199))

3.2.1 Retrieval:

Case retrieval is often seen as the most important step of a CBR problem and due to its pivotal role in CBR, it has gained the attention of many researchers in the field. The first thing that must be done in a CBR system, as soon as a case enters the system, is to search for an appropriate match for the new case. An appropriate match often refers to a case highly similar to the new case. Thus, the adopted similarity measure of the system has a significant influence on its performance and success of a CBR is directly depended on the strategy adopted for the similarity measure.

K nearest neighbour or simply *K-NN* is the most popular retrieval approach in the literature. The similarity between two cases in this approach is usually a number belonging to $[0, 1]$ and is calculated based on the distance between the feature vector of the two cases. The most common distance applied is based on the location of the vector features in Euclidean space. The Euclidean distance is able to deal with negative and proportionate numbers and is sensitive to small differences between two vectors (200). The geometrical distance between any to point in the space is obtainable with Euclidean distance. The Euclidean distance is easily transferable to various forms of similarity measure (201) and the low complexities in assigning weights to different

features of the vector and calculation process make it an attractive option to be used in problems with a high number of variables (202).

We can calculate the Euclidean distance of two cases by equation 1 and 2:

$$d(C_1, C_2) = \sqrt{\sum_{k=1}^{K} (w_k \times d_k(C_1, C_2))^2} \quad (1)$$

$$d_k(C_1, C_2) = |x_{1k} - x_{2k}| \quad (2)$$

Where $d(C_1, C_2)$ is the Euclidian distance between two cases of C_1 and C_2. k is the number of features for each case and w_k is the relative importance of feature k compared to other features. x_{1k} and x_{2k} are the values of k^{th} feature in cases 1 and 2 respectively. After the distance between two cases has been calculated, we can obtain the similarity between the pair of cases based on equations 3 or 4.

$$SIM(C_1, C_2) = \frac{1}{1 + d(C_1, C_2)} \quad (3)$$

$$SIM(C_1, C_2) = 1 - d(C_1, C_2) \quad (4)$$

3.2.2 Reusing and Revision:

Reuse is the step of CBR process when a solution of a retrieved case is being used for a new case. In some situations, reusing would be easily done by just assigning the old solution as the new solution. An example of such a situation is classification problems where the cases in one class are usually so similar in nature that just the most similar case can contain the solution for a new case. However, in some situations when the new case and retrieved case differ significantly from each other, another process (3rd step) revising or adaptation for the retrieved solution is needed. Medical decision

making is one domain in which adaptation is commonly required. Adaptation becomes particularly relevant when CBR is used for constructive problem-solving tasks such as design, configuration, and planning (203). In revisions, the goal is to investigate the applicability of the solution proposed for the new case and if required altering parts of the solutions in order to make it compatible with the new case.

3.2.3 Retaining:

When a solution has been assigned to a new case (by using the solution of the most similar case, the reusing step) through a revising process (if the assigned solution requires changes to better adapt the problem), a completely new case has been generated and this new case needs to be stored in order to update the case pool. The case retention or maintenance should be managed intelligently and systematically. Maintenance issues appear when the effectiveness of the system is being discussed regarding the nature of the problem in focus. In some cases, the new (learned) case may not be retained as its solution is provided by Artificial Intelligence (AI) and some researchers believe that knowledge should only be gained by real-life experiences in CBR. However, some researchers believe that learned knowledge through AI could be helpful to increase the frequency of the cases in the case pool and subsequently to increase the alternatives available for a new case.

We can summarize the CBR steps as, firstly, each case is divided into 2 parts of the case features and case solutions. Then the similarity between a new case and the cases in the case pool is being calculated so we can retrieve the most similar case. After that, the solution of the most similar case is being reused for the new case. Depending on the circumstances of the problem, the solution can be revised in the revision step to better fit the new case. Finally, in the last step, the retaining step, the new case features

and solution are being merged to form a new case and is being added to the case pool to be utilized in the future.

The efficiency of CBR approaches in the healthcare domain and medical decision making, and in particular in different stages of the cancer treatment has been proved by its widely used applications. An initial stage for many treatment planning problems is classification. Achieving a well-suited classification can reduce the prediction errors in treatment planning. Thus, many researchers have applied CBR individually or in combination with other techniques to solve the classification problem. De Paz et al. (204) proposed a hybrid CBR and decision tree approach that classified the leukaemia patients from data obtained from microarray profiles. Huang et al. (205) applying logistic regression model, compared three different methods of Particle Swarm Optimization (PSO) based on neural networks (ANNs), the adaptive neuro-fuzzy inference system (ANFIS) and CBR classifier for breast cancer diagnosis problem. However, they showed that application of individual CBR could lead to lower accuracy in comparison to other methodologies.

In addition to classification of the patients by CBR, pairing patients and prescribing the treatment solution of a treated patient to a new one, which is the main application of CBR, has been abundant in the literature. Petrovic et al. (7) combined Cased-Based Reasoning and Dempster–Shafer theory to combine the solution of the most similar cases retrieved by CBR to apply in radiotherapy dose planning for prostate cancer, however, they consider the similarity measure as the only factor for retrieving a solution. Mishra et al. (125) applied non-linear programming to radiotherapy dose planning for prostate cancer and used two different success rates as other criteria for retrieving a solution. Although they did not apply an MCDM approach despite the existence of several criteria and simply used criteria as filters with different priorities.

Gu et al. (194) applied CBR with a new distance measure named weighted heterogeneous value distance metric and GA to set the weights for the feature attributes in breast cancer diagnosis and reported increased efficiency compared to previous CBR with other distance types.

3.3 TOPSIS

TOPSIS (Technique for Order Preference by Similarity to an Ideal Solution) is an MCDM method developed by Hwang and Yoon (206). The main purpose of this technique is to rank different alternatives based on their distances from ideal positive and negative solutions. TOPSIS can be performed using the following steps:

At the beginning of the process, a decision Matrix *DM* is constructed. The row of each matrix represents alternative solutions, while columns represent different criteria.

$$DM = [y_{ij}] = \begin{bmatrix} y_{11} & \cdots & y_{1r} \\ \vdots & \ddots & \vdots \\ y_{n1} & \cdots & y_{nr} \end{bmatrix} \quad (5)$$

Where y_{ij} $(i = 1, \cdots, n\,; j = 1, \cdots, r)$ are the elements of the decision matrix *DM*.

After that, the following steps are performed to select the best alternative:

Step 1- Decision Matrix is normalized using equation 6:

$$R_{ij} = \frac{y_{ij}}{\sqrt{\sum_{j=1}^{j} y_{ij}}} \quad (6)$$

R_{ij} is the normalized value of the element y_{ij} in decision matrix.

Step 2- Weighted normalized decision matrix is calculated using equation 7.

$$v_{ij} = w_i R_{ij} \tag{7}$$

Step 3-Positive and negative ideal solutions are specified using equations 8 and 9 respectively:

$$PIS = \{v_1^*, \cdots, v_r^*\} = \begin{cases} \max\limits_j v_{ij} \Big| i \in benefit \\ \min\limits_j v_{ij} \Big| i \in \quad cost \end{cases} \tag{8}$$

$$NIS = \{v_1^-, \cdots, v_r^-\} = \begin{cases} \min\limits_j v_{ij} \Big| i \in benefit \\ \max\limits_j v_{ij} \Big| i \in \quad cost \end{cases} \tag{9}$$

Step 4- Distance of each alternative from Positive Ideal Solutions (PIS) and Negative Ideal Solutions (NIS) are calculated using equations 10 and 11 respectively.

$$D_j^+ = \sqrt{\sum_{i=1}^{n} \left(v_{ij} - v_i^*\right)^2} \tag{10}$$

$$D_j^- = \sqrt{\sum_{i=1}^{n} \left(v_{ij} - v_i^-\right)^2} \tag{11}$$

Step 5- Finally, relative closeness coefficient is calculated using equation 12 and the alternative with the highest coefficient is ranked as the best alternative.

$$C_j^* = \frac{D_j^-}{D_j^- + D_j^+} \tag{12}$$

TOPSIS is one of the most widely used MCDM techniques in health-care decision making and medical decision support systems. Ferrari et al. (207) applied TOPSIS to evaluate Triptan treatment options in a migraine. In the proposed method trade-offs between conflicting criteria are made and seven available Triptan used in the treatment

process are ranked using the TOPSIS methodology. Rahimi et al. (208) applied TOPSIS and fuzzy logic to develop a diagnosis system. They considered a set of diseases as alternatives and the most similar case (highest ranked in being similar to the new patients' symptoms) in symptoms is being diagnosed as the condition that the patient is dealing with. Using TOPSIS method, La Scalia et al. (209) developed a decision support system for pancreatic islet transplantation. The proposed system can help doctors calculate the probability of transplant success in relation to four classes of identified variables (donor, organ, isolation and recipient).

3.4 Prostate cancer radiotherapy formulation

Radiotherapy planning for prostate cancer problem is a complex and time-consuming process. The treatment is usually performed in two stages, phase I and phase II. In phase, I, prostate and surrounding organs where cancer has spread are treated. While in the second phase only prostate will be the focus of radiation. Figure 3.2 shows a prostate tumour and surrounding area in a schematic picture.

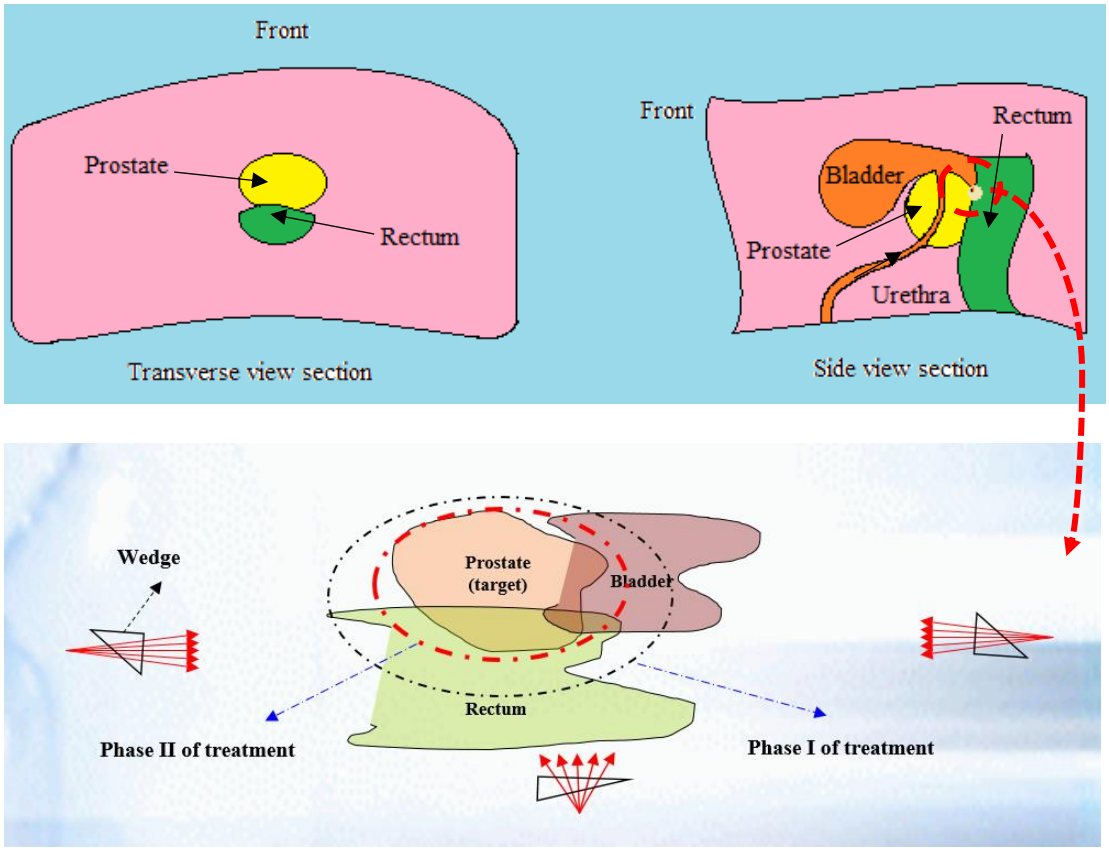

Figure 3.2 Phase I and II of the radiotherapy for prostate cancer and organs involved

The main objective of treatment is to kill the cancerous cells without affecting the functionality of surrounding organs. In Nottingham City Hospital usually, doses are prescribed in the range of 46-64Gy and 16-24Gy in Phase I and II of the treatment respectively. The prescribed total dose of 70 to 76 Gy is usually delivered in fractions, and each fraction approximately accounts for 2 Gy. The overall process of radiotherapy treatment is explained in figure 3.3.

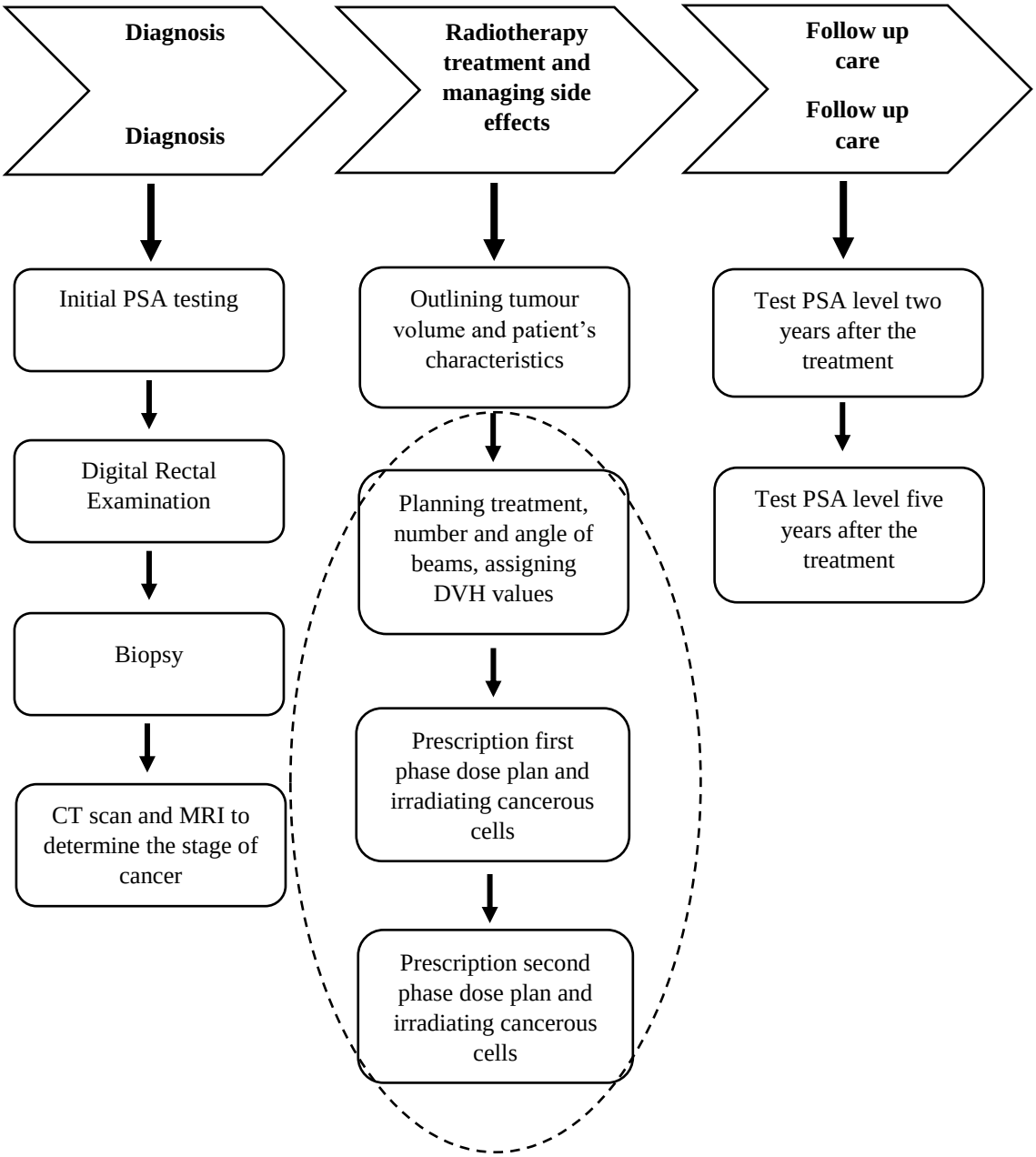

Figure 3.3 Radiotherapy dose planning process

Radiotherapy planning process is generally performed in several steps. The Oncologist examines the new patient and tests the level of PSA (Prostate Specific Antigen). Prostate cancer can increase the production of PSA, and so a PSA test looks for raised levels in the blood that may be a sign of the condition in its early stages. Through PSA test, Digital Rectal Examination (DRE) and biopsy the oncologists can detect prostate cancer and prescribe different clinical tests such as Computed Tomography (CT) scan

and Magnetic Resonance Imaging (MRI) to determine the stage of cancer. After that, medical physicists in the planning department, sketch the tumour volume and determine the organs at risks, considering the scans. Throughout this process areas involved crucially within cancerous cells and areas containing only microscopic tumour cells can be segregated.

Based on the sketched volume and characteristics of the patient, different planning parameters and Dose Volume Histogram (DVH) for both phases of treatment are set by the oncologists and medical physicist. DVH is a graphical representation of the dose that is received by normal tissues and target volumes within a 3-D radiation therapy plan. It allows oncologists to calculate the amount of radiation that would be received by different volume percentage of the rectum. For example, if DVH value of 66 % of the rectum in phase II of treatment is 0.7 and prescribed dose in phase II of treatment is 20 GY than the dose received by 66 % of the rectum will be 14 GY (0.7×20 GY=14GY).

Based on calculated DVH value and Clinical stage, Gleason Score and Prostate Specific Antigen (PSA) value oncologists perform several successive experiments to determine doses in Phase I and II of the treatment so that cancerous cells can be killed effectively without impairing the normal organs near to the cancerous cells, particularly bladder and rectum. Compared to the bladder, the rectum is a very sensitive organ. In a feasible dose plan dose received by different volume percentage of rectum must be within the constraints. The recommended dose limits of different volume percentages of the rectum are given in table 3.1. In some cases, these dose limits can be overlooked to some extent so that sufficient dose can be delivered to the cancerous cells.

Table 3.1 Dose limits for different volume percentage of the rectum

Rectal volume %	Total dose limits
66	45
50	55
25	65
10	70

In order design, a condign treatment plan, oncologists and medical physicists usually consider five features of Clinical Stage, Gleason Score, Prostate Specific Antigen (PSA) value, and DVH values in phases I and II of treatment. Table 3.2 describes these features in detail.

Table 3.2 Features of interest in prostate cancer radiotherapy

Features	**Description**
Clinical stage	A labelling system that indicates the local extent of a prostate tumour and its spread to surrounding organs. It includes T1a, T1b, T1c, T2a, T2b, T3a and T3b categories.
DVH	A graphical representation of the dose that is received by normal tissues and target volumes within a 3-D radiation therapy plan. They provide information on the volume of a structure receiving a given dose over a range of doses. In Prostate cancer radiotherapy, rectum's volumes of interest are 66, 50, 25 and 10 percent.
Gleason Score	A classification of prostate cancer grade on the basis of histology with predictive value for progression. The values are in the range of 1 to 10. Cancers with a higher Gleason score are more aggressive and have a worse prognosis.
PSA	Prostate Specific Antigen. The PSA test measures the level of PSA in a man's blood. Elevated amounts of PSA could be the result of inflammation of the prostate, infection or prostate cancer. The values are within the range of 1 to 40.

3.5 Proposed method for dose plan suggestion

In real life, to prescribe a dose plan, oncologists not only take into consideration the clinical attributes of a patient but also recall previous cases they have treated to utilize

their past experiences. Based on above-mentioned facts, Cased-Based Reasoning (CBR), a knowledge-based technique is an appropriate approach to deal with this healthcare problem. A case usually consists of two major parts: problem features which describe the conditions under which similar case(s) should be retrieved and the solution to the problem (195). Based on the extracted most similar case a solution for the new case is suggested. The advantage of this method is its capacity to consider more cases than a doctor can recall and that it shares the experiences of other oncologists and provides a more comprehensive base to make decisions. The solution, second aspect of a retrieved case, is usually suggested to a new case. However, extracting the most similar case and prescribing solution based on that may not provide a thorough answer. As previously mentioned, a solution is prescribed by means of extracting several most similar cases and evaluating them by TOPSIS in comparison to an ideal solution and prescribe the final solution based on the obtained results.

3.5.1 Representation of the case

In the radiotherapy treatment of prostate cancer usually, the clinical stage of cancer and the geometry of prostate are taken into consideration. Attributes related to both the factors are listed in table 3.3.

Table 3.3 Range of values and their type for features of prostate cancer radiotherapy

Feature	Values	Type of values
Stage of the cancer	T1a, T1b, T1c, T2a, T2b, T3a, T3b	Ordinal
Gleason Score	[1, 10]	Integer number
PSA	[1, 40]	Real number
DVH	[0, 1]	Real number

The data type, measurement unit and scale of the aforementioned parameters vary. To develop a comprehensive similarity measure, clinical stage, Gleason score and PSA are represented by fuzzy sets. Normalized fuzzy sets low, medium, and high, whose membership functions take values from [0, 1] interval are defined for each feature. Parameters of these membership functions are set in collaboration with an expert oncologist in Nottingham City Hospital. Each, features *l* (clinical stage (*l* =1), Gleason Score (*l* =2), PSA (*l* =3)) of case $C_p$is represented by a triplet ($v_{pl1}, v_{pl2}, v_{pl3}$), where v_{plm} , m = 1, 2, 3 are membership degrees of feature *l* to fuzzy sets low (*m = 1*), medium (*m = 2*) and high (*m = 3*). The membership functions of sets applied for Gleason Score and PSA are shown in Figures 3.4 and 3.5.

Figure 3.4 Membership function for Gleason score

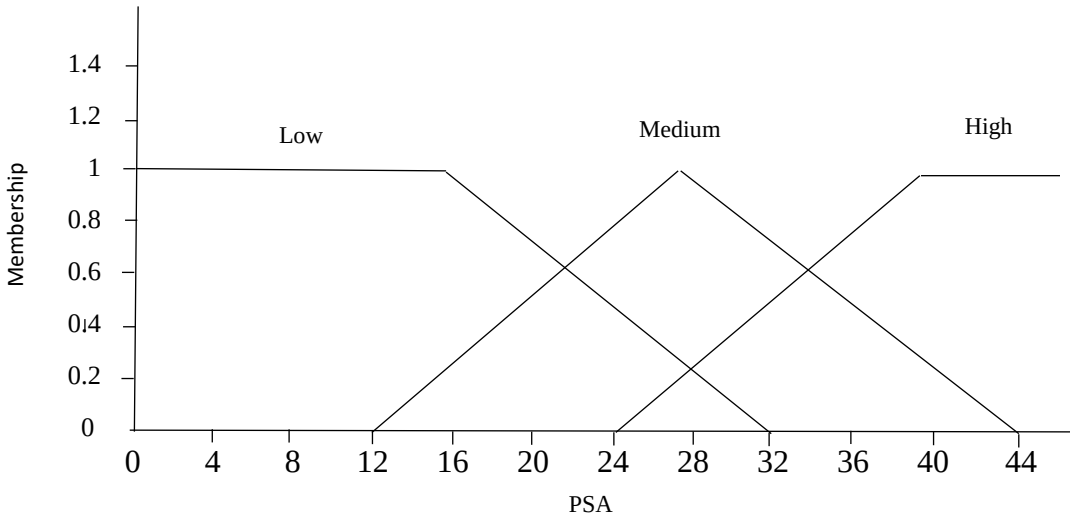

Figure 3.5 Membership function for Gleason score

3.5.2 Retrieval process of similar cases

Clinical stage is an important decision-making criterion; cases having the same clinical stage are relevant to the prescribed dose plan for a new patient. According to the stage of cancer, the clinical stage can be sorted in the following order: {T1a, T1b, T1c, T2a, T2b, T3a, T3b}. At first, cases presenting the same clinical stage or adjacent to the new case in the ordered list are filtered. Thereafter, from the filtered list cases similar to the new case are retrieved.

The distance between new case C_p and case in the database C_q is calculated using equation 13. It takes into consideration fuzzy membership values of Gleason Score (*l = 1)* and PSA (*l = 2).*

$$d_1(C_p, C_q) = \left(\sum_{l=1}^{2} \sum_{m=1}^{3} \left(v_{plm} - v_{qlm} \right)^2 \right)^{\frac{1}{2}} \tag{13}$$

Taking into account numerical values of different DVH volume percentage of rectum 66%, 50%, 25% and 10% represented by $m = 1, 2, 3, 4$ respectively distance between

two cases of C_p and C_q is calculated using equation 14. In this equation (i *=1, 2*) represents the phase of treatment.

$$d_2(C_p, C_q) = \left(\sum_{i=1}^{2} \sum_{m=1}^{4} (u_{pim} - u_{qim})^2 \right)^{\frac{1}{2}} \quad (14)$$

The overall similarity measure between cases C_p and C_q is measured by equation 15.

$$S(C_p, C_q) = \frac{1}{1 + d_1(C_p, C_q) + d_2(C_p, C_q)} \quad (15)$$

3.5.3 Solution methodology which improves CBR

In a simple CBR usually, decisions are based on the extracted most similar case. However, in radiotherapy dose planning the most similar case may not be the most appropriate one to base decisions on. In addition to the similarity measure, there are other criteria, which have an influence on the preference of a case over others. It was found experimentally that in some instances, the case having the highest similarity measure was not convincing to base a decision on. Sometimes they have low success rate or DVH level has exceeded the recommended restrictions. For this study, the MCDM method is used to overcome the problem above. Firstly, cases most similar to the new case are retrieved from the database. Thereafter, an MCDM technique called TOPSIS is used to compare them based on the similarity measure, quality of dose plan, success rate and side efferent of treatment. Figure 3.6 shows the architecture of the proposed method.

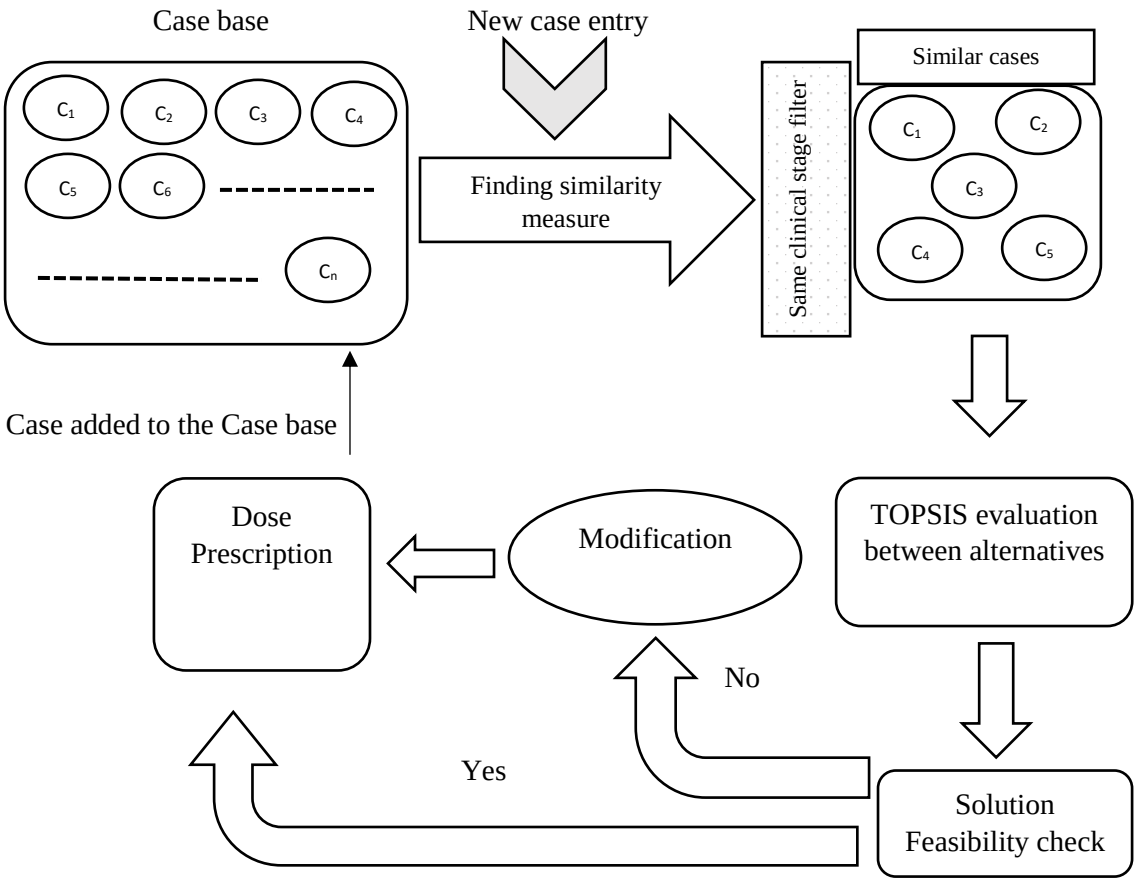

Figure 3.6 Process of proposed CBR/TOPSIS approach

3.5.4 Radiotherapy dose planning criteria

In this study, the following criteria have been selected to evaluate the extracted most similar cases using TOPSIS method: dose plan in phases I and II of the treatment; similarity measure; and the distance of each DVH values to the standard dose limitation in respected volume percentage. These parameters are set in collaboration with oncologists working at Nottingham City Hospital. It supports the proposed method to prescribe a dose plan that provides higher accuracy and fewer treatment side effects to patients.

In the decision matrix, the dose plan having a higher dose in the first phase of the treatment is considered as an added advantage. It will annihilate the cancer cells to the maximum because in the first phase of the treatment cancer cells and the surrounding

organs where cancer has spread are treated. Although in the second phase of radiotherapy treatment the beams only target the prostate gland and the purpose is to concentrate on the prostate rather than affecting the surrounding area which has already gone through removal process in phase I. In the decision matrix the plan with higher share of the total dose is considered to be a better dose plan. In case the total dose plans for two related treatment plans are equal, the priority is with the dose plan with a higher dose in the first phase of the treatment (7). In order to minimize the side effects of the treatment, the dose received by the rectum should be as low as possible. Cases, where the dose received by different volume percentage of the rectum in phase I and phase II of treatment are far from maximum specified value, is considered as a better dose plan. In the evaluation process firstly, the distance between actual dose received by different volume percentage of the rectum and specified maximum value for all extracted cases is calculated. The higher the distance is, the better possibility of keeping other organs out of risk. As an example, the dose received with different volumes of a patient in the treatment and their distance from the maximum standard values in Table 3.1 is given in Table 3.4.

Table 3.4 An example of correspondence distance value based on the dose received by each percentage of the rectum volume

Rectum Volume	66%	50%	25%	10%
Dose received	36.18	46.98	52.92	53.46
Distance value	8.82	8.02	12.08	16.54

3.6 An example of the case base reasoning combined with TOPSIS

To demonstrate the step-by-step execution process of the proposed method in a lucid way an illustrative example is constructed. In this example, a case is extracted from the

case base and treated as a new case. Dose planning parameters of the new case are given in Table 3.5. Firstly, cases presenting the same or adjacent clinical stage to the new case are extracted from the case base. Thereafter, from the filtered list the five cases most similar to the new case are retrieved. The detailed description of the extracted cases similar to our new case depicted in Table 3.5 and the related criteria values for running the evaluation process are shown in Table 3.6. As can be seen dose plan in phase I and II of the treatment, distance to the different volume level, recommended by standards and similarity measures are the considered criteria.

Table 3.5: Values for numerical example cases

	PSA	GS	DVH_1 66%	DVH_1 50%	DVH_1 25%	DVH_1 10%	DVH_2 66%	DVH_2 50%	DVH_2 25%	DVH_2 10%
C_{new}	7	11.90	0.50	0.60	0.94	0.99	0.47	0.49	0.69	0.98
C1	7	6.80	0.50	0.60	0.94	0.99	0.48	0.49	0.61	0.95
C2	7	6.40	0.50	0.58	0.92	0.97	0.50	0.53	0.86	0.90
C3	7	12	0.51	0.69	0.97	0.99	0.47	0.50	0.87	0.98
C4	7	7.10	0.55	0.64	0.95	0.98	0.53	0.57	0.92	0.99
C5	7	13	0.52	0.55	0.91	0.98	0.52	0.53	0.87	0.98

Table 3.6 Decision Matrix applied for TOPSIS evaluation of the numerical example

Alternative	Criteria						
	Dose plan in phase I	Dose plan in phase II	Dis to $R_{66\%}$	Dis to $R_{50\%}$	Dis to $R_{25\%}$	Dis to $R_{10\%}$	Similarity Measure
C1	54	18	9.36	13.78	3.26	0.56	92.08
C2	46	24	10.00	15.60	2.04	3.78	83.51
C3	46	24	10.26	11.26	0.5	0.94	83.06
C4	46	24	6.98	11.88	0.78	1.16	79.40
C5	46	24	8.60	16.98	2.26	1.40	79.15

Thereafter, extracted cases are evaluated based on the similarity measure, success rate and side effect of treatment. With the use of TOPSIS technique, the relative closeness

coefficient is calculated for each case (Table 3.7). Among all the extracted cases, case number 5 is found to be the best possible option due to its greater relative coefficient despite relatively lower similarity measures. The doses prescribed by the treatment alternative 4 are 46 and 24 Gy in the first and second phase of treatment respectively.

Table 3.7 Final ranking of alternatives through TOPSIS

Alternative treatment	Relative closeness	Rank
5	0.7923	1
4	0.7132	2
2	0.5893	3
3	0.4142	4
1	0.4131	5

In the final step it is necessary to check the feasibility of the suggested doses by the best alternative solution through the following restriction:

1- The suggested dose in Phase I should be more than that suggested for Phase II.

2- All the doses received by different volumes of the rectum must be lower than the recommended standards in Table 3.1.

3.6.1 Modification and repair mechanism of treatments

In some instances, the prescribed dose by the retrieved case does not fit in the limitations of recommended dose as mentioned in Table 3.1. To overcome this situation a modification process has been proposed. In this process, the prescribed dose plan is modified by the next best alternative. The modification will be done based on the alternative distances with positive ideal solutions. The modification process will be performed based on these rules:

Step 1: First the second-best alternative will be checked. If the dose plan corresponding to second-best alternative satisfies the restrictions, then it will be selected.

Step 2: Next if the second option is not feasible, a combination of first and second-best alternatives will be elicited with the help of equations 16 - 18.

Step 3: If the outcome of Step 2 is not a feasible plan, a combination of the first, second and third option will be considered.

Assume the doses prescribed by the first alternative (P) are P_1 and P_2 and the doses of the second-best alternative with a lower amount of doses (E) are E_1 and E_2 respectively in the first and second phase of treatment. The distance of each alternative from the ideal solution is:

$$Dis(A_p) = \sqrt{\sum_{i=1}^{n} \left(v_{ij} - v_i^*\right)^2} \tag{16}$$

v_{ij} are the normalized vector elements for each alternative and v_i^* is the best performance in criterion j which consist the ideal solution. If the distance of alternatives P and E from the ideal solution is Dis_p and Dis_e the outcome dose plan of this modification iteration is as follows:

$$Dose\ plan\ in\ phase\ I \ = \ \frac{Dis_p . P_1 + Dis_e . E_1}{Dis_p + Dis_e} \tag{17}$$

$$Dose\ plan\ in\ phase\ II \ = \ \frac{Dis_p . P_2 + Dis_e . E_2}{Dis_p + Dis_e} \tag{18}$$

In the above equation, $P_{1,2}$ and $E_{1,2}$ are dose plans in phase I and II of alternative P and E respectively.

3.6.2 Results accuracy and methodology effectiveness

To test the effectiveness and robustness of the proposed method, the leave-one-out strategy has been employed. In leave-one-out strategy, each case stored in case base is taken out one by one as is treated as a new case. The dose plan for each extracted case is estimated using proposed methodology. Thereafter, the estimated dose plan is compared with the dose plan prescribed by the expert oncologist. The dataset used in this research is based on anonymized data collected from Nottingham City Hospital which are stored in a database. This data collection provided 69 different cases.

If there is any inconsistency between the dose plan estimated by the used method and that prescribed by the oncologist, then firstly the received dose is calculated by different volume percentage of the rectum and if it is within the constraint then the quality of the plan is judged on the basis of the total dose prescribed. When a dose plan has a higher amount of the total dose it is considered better because it will help to kill more cancerous cells without affecting surrounding organs. However, if two dose plans have the same amount of total dose then the quality of the plan is judged based on the amount of dose prescribed in Phase I of the treatment. Since in Phase I of the treatment both cancer and its surrounding organs where cancer has spread is treated, the dose plan having higher amount of dose in phase I of treatment is considered as better dose plan compared to other dose plans which have less amount of dose in phase I. In Leave-one-out strategy the dose plan suggested by our method is considered to be successful if it is same or better (based on the abovementioned criteria) then the plan prescribed by the expert oncologist.

During the experiment, the success rate of the proposed method is 86.88%. More precisely in 53 out of 61 cases, the dose suggested by the method has been the same or higher than that prescribed by oncologists. In 33 cases dose plan suggested by the

method was the same as that of oncologists while in 20 cases was higher than the prescribed dose. To demonstrate the suitability of case-base reasoning with TOPSIS we have compared it with the success rate of normal case base reasoning as shown in Table 3.8. The success rate of normal case base reasoning is 73.43% while the success rate of case-base reasoning with TOPSIS is 83.6%. The use of TOPSIS also helped case-base reasoning to generate a better plan in a higher number of cases. It is increased from 15 to 18. Further to investigate the relevance of modification rule experiment has been conducted where it was found that success rate has increased to 86.88% from 83.6%. The proposed modification rule also helped case base reasoning with TOPSIS method to generate more number of better dose plan. It has increased from 18 to 20.

Table 3.8 Comparative success rate for different approaches applied in this chapter

	Success rate	Number of cases with better dose plan than the original one
Simple CBR	73.43%	15
CBR+TOPSIS	83.6%	18
CBR+TOPSIS + Modification rule	86.88%	20

3.7 Conclusion

In this chapter, a novel approach to radiotherapy dose planning for prostate cancer has been developed by combining TOPSIS, an MCDM technique with Cased-Based Reasoning, a knowledge-based approach. Previously, as was reviewed in the literature, the extent of similarity between two cases has been the singular feature that the researchers have focused on. Only one study has applied other factors in addition to similarity; however, still, the first filter was the similarity measure and thus played the most important role. In this chapter, the problem has been structured as a multi-criteria

problem and a wide range of attributes have been included to ensure close similarity to real-life scenarios, where oncologists rely on several factors to decide on dose planning for a patient.

Firstly, with the help of CBR approach, the case similarity measures between a new case and cases in the case pool were calculated. Thereafter, the cases, satisfying a certain minimum amount of similarity measure, were selected as potential final solutions to the new case. Retrieved cases are evaluated using multi-criteria evaluation method. Due to the nature of medical problems, the proposed solution should be the nearest to the most ideal solution and the furthest from the worst scenario. It will enhance the advantages and avoid potential damages as far as possible by minimising the treatment side effects. In order to achieve this target, we have used TOPSIS as our chosen method for multi-criteria decision making. The highest ranked retrieved case is then prescribed for the new case. Although if the prescribed doses are not within the DVH's maximum limitations, then the modification rules try to modify the doses and finalize the dose plan. This approach has been applied to a real data set obtained from Nottingham University Hospital and shows significant improvements compared to simple CBR which only considers similarity measure. However, there is still place for improving the dose plans toward more optimized values and a multi-objective optimization method to optimize the dose plans is being explained in the next chapter.

Chapter 4

A Goal Programming-CBR model to optimize the dose planning for radiotherapy

4.1 Introduction

Treatment planning can be referred to as the heart of radiotherapy planning and its precision results in better outcomes for patients. An important step in designing a treatment plan is radiotherapy dose planning. The primary goal of oncologists and medical physicists is to deliver an effective amount of radiation dose to the patient, which should be concomitant with two principal features. Firstly, the dose should be high enough to eradicate the main tumour and cancer cells within the main organ involved as well as spreading microscopic tumours in surrounding organs. Secondly, the dose plan should be prescribed and shaped in such a value to allow the organs imposed by radiation to maintain their functionality. While an endeavour by treatment plan team is made to a trade-off between the two features, sometimes sacrifices are inevitable and require that healthy organs are exposed to some extent of radiation, in order to kill the cancer cells effectively(210).

In chapter 3, an approach to determine the dose plan for radiotherapy in prostate cancer was introduced. As radiotherapy in prostate cancer is done in two phases, the developed system suggested the dose plan for each of the phases. In this approach, a hybrid TOPSIS-CBR method is developed to consider multiple criteria for prescribing a dose

plan rather than just the similarity measure which is the only feature used by simple CBR to find a solution to the problem. In the experiment, it was found that the case which has a high similarity measure is not always the most appropriate to base a decision on, because sometimes they have low success rate or dose received by different volume percentages of rectum surpass the restrictions as shown in table 4.1. In the developed method, initially, the similarities between a new case and the existing cases in the case pool are calculated through Euclidean CBR. Thereafter, the most similar cases to the new case, which satisfy a minimum similarity measure, are being evaluated by TOPSIS in respect of criteria related to dose planning. If the highest ranked case does not satisfy the dose limits regarding the rectum volumes, in the next step with a rule based-system, the solution will be modified by the second highest ranked case and the modified dose plan solution will be finally suggested to be prescribed for the new patient.

The aforementioned approach achieved success rate improvements were demonstrated in the experiments and in comparisons of the doses with original dose plans with consideration of the DVH values of different percentages of the rectum. However, we find that the dose plans prescribed by TOPSIS-CBR are not optimal and there is scope for improvement. In some cases, the dose plan can increase without deviating the standard limitations and thus kill the cancer cells more effectively. Such an example is provided in table 4.1.

Table 4.1 An example of a non-optimal solution

Case number	Dose in phase 1	Dose in phase 2	Distance to 66% limitation	Distance to 50% limitation	Distance to 25% limitation	Distance to 10% limitation
Case 37	54	10	5.68	2.4	2.48	6.74

In Table 4.1, the dose plan in phase I and II of the treatment provided by TOPSIS-CBR is 54 and 10 Gy respectively. However, this dose plan results in positive dose distances (detailed explanation about how to calculate these is provided in section 3) from limitations regarding different volumes of the rectum. These positive distances indicate that the dose plan is increasable without causing any considerable damages to OARs if necessary.

In some other cases simply, the dose prescribed by the system is violating the limitations and thus is considered as a failure due to its hazardous effects on OARs. Such an example is provided in Table 4.2.

Table 4.2 An example of non-feasible solution

Case number	Dose in phase 1	Dose in phase 2	Distance to 66% limitation	Distance to 50% limitation	Distance to 25% limitation	Distance to 10% limitation
Case 38	64	8	-2.6	-6.48	-5.32	-1.2

In Table 4.2, the dose plan prescribed by TOPSIS-CBR is 64 and 8 Gy in phases I and II of the treatment respectively. Despite the fact that it provides with a more effective dose plan, compared to the original dose plan, all the standard limitations have been violated due to negative values of the distances.

The aforementioned problems provided the motivation to develop an approach that prevents them happening as much as possible. To achieve more optimal dose plans, in this chapter Goal Programming is used to calculate the optimal dose plans for the treatment by endeavouring to achieve nearest dose plans to oncologists' ideal dose plans while considering the side effects of the treatment and avoiding risks endangering patients.

4.2 Goal Programming

Goal programming (GP) is basically a multi-objective linear optimization tool, which assists a solution to move towards an ideal goal. In some situations, conflict of interests or incompleteness of information makes it challenging to formulate a reliable mathematical model that captures the preferences of decision makers (211). Moreover, there are problems that the decision makers are already aware of regarding their desired final goals or targets for variables of the model and they demand an answer as close as possible to their goals. In such an environment GP is the perfect tool to deal with the multi-objective optimization problem.

Goal programming consists of the following attributes: an objective function, a set of limitations related to goals and systematic constraints related to the geometry of the problem. The aim of the objective function is to minimize deviations from the given goals. The deviation in the objective function is usually weighted to define the priority of some objectives over others. Mathematical formulation of the Goal Programming is as follows:

$$min\, Z = \sum_{j=1}^{n} (w_k d_k^+ + w_k d_k^-) \tag{1}$$

s.t.

$$f(x_1, \cdots, x_i)_k - d_k^+ + d_k^- = g_k \qquad k = 1,2, \cdots, n;\ and\ i = 1,2, \cdots, M; \tag{2}$$

$$AX \leq or \geq B \tag{3}$$

Where, X is a set of variables, that is, $X = \{x_1, x_2, \cdots, x_M\}$, A is a matrix consisting of coefficients for variables in our systematic constraints, B is a matrix for right side

values of systematic constraints and g_k represents the goal corresponding to constraint *k*.

$d_k^+$and d_k^- are the auxiliary variables that demonstrate the upper and lower deviations from the goal g_k. In GP we try to minimize the undesirable deviations (211). When the objective is reaching a certain goal (exactly equal to the number which is considered as our goal), we try to minimize both upper and lower deviations from the goal as they are both undesirable for us. While the goal is to achieving equal or less than a certain value, then only the upper deviation (d_k^+) is minimized as higher values than our goal is considered to be undesirable. On the other hand, when the goal is to achieving equal or more than a value, then only the lower deviation (d_k^-) is minimized. In the objective function, we try to minimize the deviations based on our goals to satisfy the goals and w_k is the importance of the k^{th} goal compared to other goals.

The application of these equations which converts the multi-objective optimization problem into single objective linear programming and can be solved by Simplex methods is available in numerous mathematical modelling packages such as LINGO and MATLAB.

Application of GP is wide-ranging in different health-care domains of scheduling and outpatient prioritizing (212-216), healthcare planning (217,218) and waste management (219, 220). However, application of GP in healthcare interventions and medical decision making is scarce. The reason for this could be uncertainty and problems in determining the values of goals required. In this chapter, the real dataset case pool (used previously) is used again to provide an effective scenario to determine the ideal dynamic goals for the radiotherapy doses objectives which are explained in detail in section 3.1. Dynamic goals refer to the feature that goals for the objective

function can change and improve themselves based on the cases created in the pool (finding new solutions for cases) or by adding other real-life data.

4.3 Solution methodology for improving CBR and optimizing the final dose plan

During the study, it was found that sometimes the dose plan suggested by TOPSIS-CBR is not optimal dose plan and there is a scope for improvement. Moreover, sometimes the calculated dose plan is not suitable for a new case as it may violate the recommended dose limits associated with different volume percentages of the rectum. To solve the above problem optimization of dose planning is performed using integer goal programming mathematical model, where the deviation from DVH recommended values is calculated with the help of best similar case suggested by CBR-TOPSIS. Thereafter, deviations corresponding to different volume percentages of the rectum are calculated using equation 4:

$$S_v^p = d_{q1} DVH_{1p}^v + d_{q2} DVH_{2p}^v - Recommended\ standard \quad (4)$$

S_v^p represents devthe iation of a new case p corresponding to the different volume percentage of rectum v (v = 66%, 50%, 25%, 10%) that we consider for this new case-based on the extracted case assigned to it from TOPSIS. Where d_{q1} and d_{q2} represent the dose of the extracted case in phases I and II of treatment respectively. This value shows how much the case, as determined by CBR-TOPSIS as the most appropriate for a new case, has either violated the recommended standard dose limits or kept its distance from them, based on the dose received by different volume percentage of the rectum.

To treat cancerous cells, in real life sometimes oncologists overlook the recommended dose limit. The amount of deviation from the recommended limit is usually based on oncologist's past experience. To employ the oncologist's knowledge and expertise,

deviations are calculated based on the extracted past treated patients' information stored in the database. The overall decision-making process applied in this chapter is shown in figure 4.1.

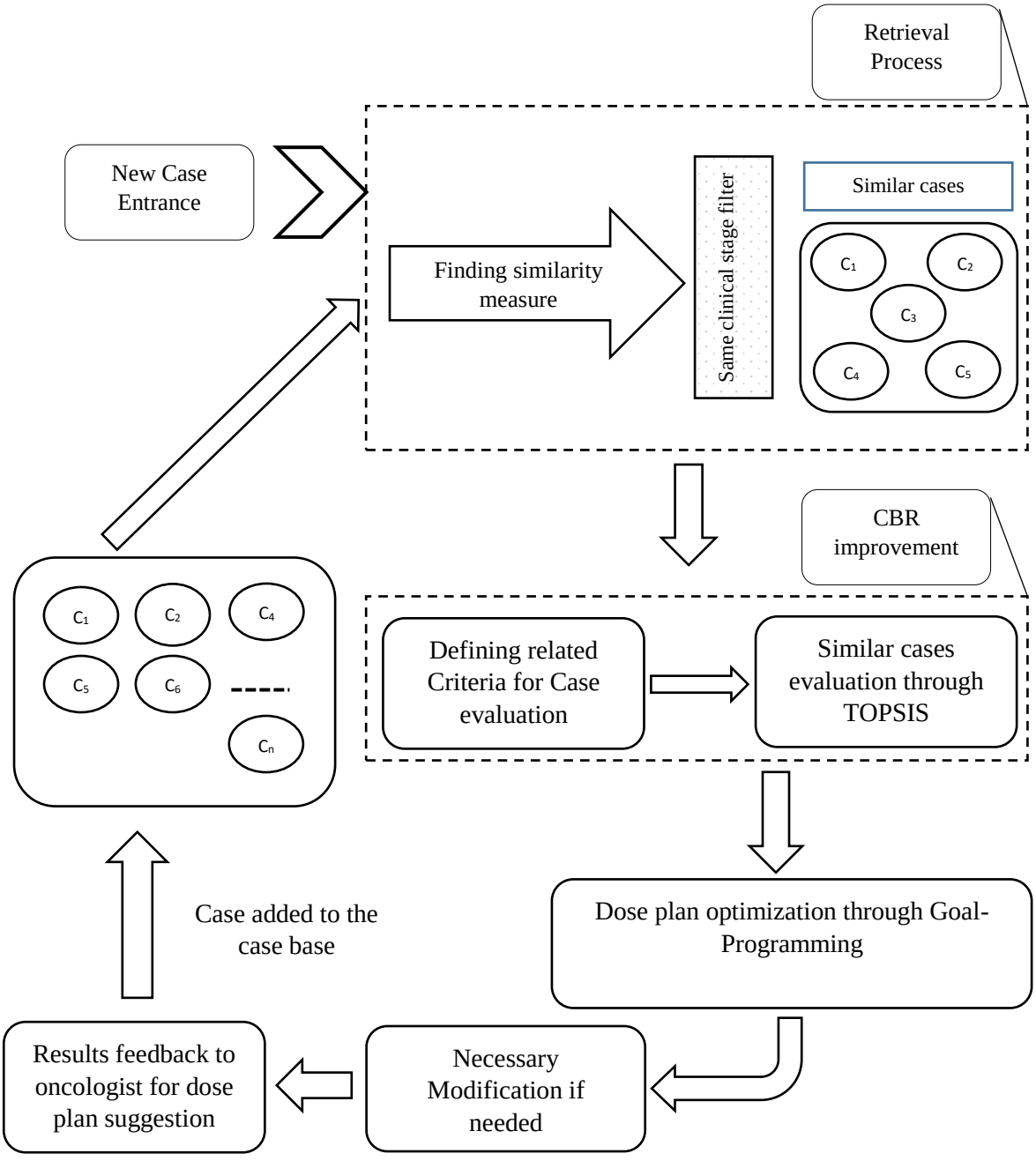

Figure 4.1 Overview of the decision-making system in CBR-TOPSIS-GP

4.3.1 Determining the goals for Goal Programming

During discussions with oncologists, it was found that the main objective of dose planning process is to maximize overall total dose while respecting the dose corresponding to the different volume percentage of the rectum. If two-dose plans have the same value of total dose and the dose received by different volume percentage of the rectum is within the constraint then the dose plan having the higher amount of dose in phase I is considered as a preferable dose plan. In this chapter, goals are set based on the abovementioned criteria. Goal objectives are as follows:

Objective 1: Goal objective of the total dose plan is to assign the maximum amount of recommended dose in our case pool.

Objective 2: Goal objective of the dose in Phase I is to deliver the maximum amount of dose prescribed in Phase I in the case pool.

Objective 3: Goal objective of the dose plan in Phase II is to assign the maximum amount of dose prescribed in Phase II in the case pool.

Figure 4.2 shows the process of modelling the GP problem.

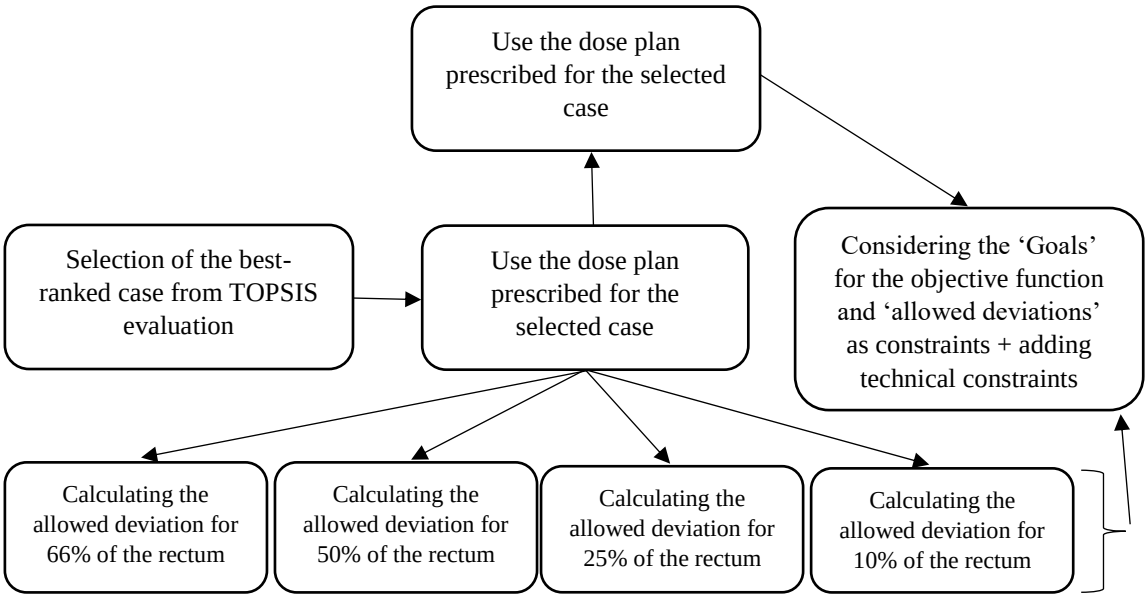

Figure 4.2 The process of modelling GP problem by using CBR and TOPSIS results

The mathematical formulation for integer goal programming related to prostate cancer dose planning process is as follows:

$$Min\ Z = \sum_{j=1}^{3} (w_k d_k^+ + w_k d_k^-) \quad (5)$$

$$x_1 + x_2 - d_1^+ + d_1^- = g_1 \quad (6)$$

$$x_1 - d_2^+ + d_2^- = g_2 \quad (7)$$

$$x_2 - d_3^+ + d_3^- = g_3 \quad (8)$$

$$DVH_{66\%}^{1p} x_1 + DVH_{66\%}^{2p} x_2 + S_{66\%}^{p} \leq 45; \quad (9)$$

$$DVH_{50\%}^{1p} x_1 + DVH_{50\%}^{2p} x_2 + S_{50\%}^{p} \leq 55; \quad (10)$$

$$DVH_{25\%}^{1p} x_1 + DVH_{25\%}^{2p} x_2 + S_{25\%}^{p} \leq 65; \quad (11)$$

$$DVH_{10\%}^{1p} x_1 + DVH_{10\%}^{2p} x_2 + S_{10\%}^{p} \leq 70; \quad (12)$$

$x_1, x_2 \geq 0$ and integer; (13)

$d_1^{+,-}, d_2^{+,-}, d_3^{+,-} \geq 0$; (14)

Where,

$k = 1,2,3$ The goals

x_1 Dose plan in Phase 1 of the treatment

x_2 Dose plan in Phase II of the treatment

w_j Weight of k^{th} goal

g_1, g_2 and g_3 Goal objectives

$DVH_{66,50,25,10\%}^{1p}$ DVH values of case *p*, in the first phase of treatment corresponding to 66, 50, 25 and 10 percent of the rectum volume

$DVH_{66,50,25,10\%}^{2p}$ DVH values of case *p*, in the first phase of treatment corresponding to 66, 50, 25 and 10 percent of the rectum volume

$S_{66,50,25,10\%}^{p}$ The amount of deviation oncologists committed corresponding to different volume percentage of rethe ctum for the new case p.

Equation 5 is the objective function for minimizing the deviations from our goals. Equations 9 to 14 are our goal related constraints, which determine deviations from total dose plan, dose plan in Phase I and II of the treatment respectively. Equations 6

to 8 are the systematic goals which restrict the optimization process to find solutions without violating the recommended doses based on oncologist's suggestions and pre-prescribed standards. Equation 13 achieves positive integer values for the dose plan.

In above GP model, we try to optimize the total amount of dose plan, the dose in Phases I and II of the treatment so that they are as close as possible to the ideal dose amounts which are obtained from the dataset and in collaboration with oncologists' suggestions. To do that we consider the deviations, gained from the best case selected for a new case by CBR-TOPSIS, from recommended standards (equation 4) as our constraints and the optimized dose is calculated to be as much as possible close to our goals.

4.3.2. Maximization of dose plan within the safe risk zone

If the dose received by different volume percentages of the rectum is within the constraint the dose plan is acceptable. The higher total dose increases the probability to kill the cancerous cells. So, in cases where there are positive S_v^n, this means that a higher dose can be received and tolerated by the rectum without causing any significant damage. In the final step, modification is performed to minimize the deviation from recommended standards as described in equation 15.

$$S_v^p = \begin{cases} S_v^p & if \quad \geq 0 \\ 0 & if \quad \leq 0 \end{cases} \tag{15}$$

In real life sometimes, oncologists overlook the recommended dose limit associated with a different volume percentage of the rectum. Similarly, in our proposed model the system will retrieve the past similar cases and it will decide the dose limit associated with a different volume percentage of the rectum. The proposed model will overlook the recommended dose limit if oncologists have taken similar decisions in the past.

Once the dose limit is set, goal programming method will search for the optimal dose plan.

4.3.3. Modification rule for integer programming

Usually, the dose is delivered in 2Gy packs. Hence, the dose in phase I and II of the treatment must be an even number. In order to solve the problem of odd numbers the following conditions are incorporated in programming:

1- If calculated dose in Phases I or II is an odd number, then:

a. Increase the dose by 1Gy. If dose received by different volume percentages of rectum violate the constraint, then decrease the dose by 1Gy.

2- If dose plan in both Phases is an odd number, then:

a. Increase the dose plan in both Phases of the treatment by 1Gy and check the limitation suggested by oncologists; if violated go to step b.

b. Increase the dose plan in Phase I by 1Gy and decrease dose plan in Phase II by 1Gy. Check the limitation suggested by oncologists; if violated go to step c.

c. Decrease the dose plan in Phase I by 1Gy and increase dose plan in Phase II by 1Gy. Check the limitation suggested by oncologists; if violated go to step d.

d. Decrease the dose in Phase I and II by 1 GY.

4.4 Numerical example

In this section, a numerical example is considered to illustrate the execution process of the proposed method. In this example, a case is extracted from the database and assumed as a new case. Firstly, cases having the same clinical stage or adjacent to the new case are extracted from the database. After that, from the extracted cases the five most similar cases are retrieved and evaluated using TOPSIS method. The features values of five selected cases are depicted in Table 4.3. Corresponding to every five cases the numerical values of different evaluation criteria used in TOPSIS, are shown

in Table 4.4 Subsequently, the distance from PIS and NIS are calculated to find closeness coefficients as shown in Table 4.5. In the given example, case 4 has higher closeness coefficient compared to other cases and thus is selected as our guide (as an oncologist opinion) to calculate deviations from the recommended standard. Thereafter, with equation (4) the deviations from recommended dose limit are calculated (Table 4.6).

Table 4.3: Features values of five retrieved cases

	PSA	GS	DVH Phase I 66%	DVH Phase I 50%	DVH Phase I 25%	DVH Phase I 10%	DVH Phase II 66%	DVH Phase II 50%	DVH Phase II 25%	DVH Phase II 10%
C_{new}	7	11.9	0.50	0.60	0.94	0.99	0.47	0.49	0.69	0.98
Case 1	7	6.8	0.50	0.60	0.94	0.99	0.48	0.49	0.61	0.95
Case 2	7	6.4	0.50	0.58	0.92	0.97	0.50	0.53	0.86	0.90
Case 3	7	12	0.51	0.69	0.97	0.99	0.47	0.50	0.87	0.98
Case 4	7	7.1	0.55	0.64	0.95	0.98	0.53	0.57	0.92	0.99
Case 5	7	13	0.52	0.55	0.91	0.98	0.52	0.53	0.87	0.98

Table 4.4 Numerical value of evaluation criteria used in TOPSIS

Criteria / Alternatives	Dose plan in Phase I	Dose plan in Phase II	Deviation $S_{66\%}$	Deviation $S_{50\%}$	Deviation $S_{25\%}$	Deviation $S_{10\%}$	Similarity Measure (%)
Case1	54	18	9.36	13.78	3.26	0.56	92.08
Case2	46	24	10	15.6	2.04	3.78	83.51
Case3	46	24	10.26	11.26	0.5	0.94	83.06
Case4	46	24	6.98	11.88	0.78	1.16	79.4
Case5	46	24	8.6	16.98	2.26	1.4	79.15

Table 4.5 Distance from positive and negative ideal solution

	NIS	PIS	CC	Rank
Case1	0.01200	0.00780	0.60311	3
Case2	0.00151	0.01486	0.09260	5
Case3	0.01693	0.00112	0.93760	2
Case4	0.01456	0.00096	0.93791	1
Case5	0.00727	0.00510	0.58735	4

Table 4.6 Deviations from recommended dose limit

Rectum volume	66% of rectum	50% of rectum	25% of rectum	10% of rectum
Allowed deviations	-10.7200	-15.6400	-5.2000	-0.9400

The initial number of similar cases is limited (i.e. five in this paper) based on an average similarity measure between a new case and cases in the case database. All the cases have been chosen as a new case and average similarity measure between $t = 3, 4, 5, 6\ and\ 7$ most similar cases to them was calculated (Table 4.7). As can be seen by moving forward from 5 to 6 similar cases the average similarity measure of *t* cases with the new case significantly reduces from 81.1 to 70.5 percent and some outliers with less than 50% similarity to a new case were found. So, we chose 5 most similar cases as our initial number for the dose planning process.

Table 4.7 Average similarity measure between first *t* similar case and a new case

Number of similar cases	t = 3	t = 4	t = 5	t = 6	t = 7
Average similarity measures	85.2%	83.6%	81.1%	70.5%	63.2%

To optimize the dose plan goal programming is formulated. The importance of each of the goals needed to be assigned prior to execution of the model. In this research, the weight associated with total dose, the dose in Phases I and II are set as 0.70, 0.25 and 0.05 respectively. Following weights have been assigned based on consultations and discussions with an oncologist in Nottingham City Hospital which reflect his expertise and experience gained regarding the importance of each phase of the treatment. It should be considered that there is a difference between each oncologist's opinion regarding the importance of each stage of the treatment and there could not find a global optimal set of weights and as an advantage of a DSS, each oncologist can enter his desirable opinion as weight inputs.

Here, higher weight is assigned to the total dose of treatment to maximize the overall recommended dose. When the maximum total dose is achieved the next goal is to

maximize the dose in Phase I. In Nottingham City Hospital maximum total dose, highest dose in Phases I and II are prescribed as 74Gy, 64Gy and 14Gy respectively. Hence, in this model, the constraint related to maximum total dose, the dose in Phases I and II is set as 74Gy, 64Gy and 14Gy respectively.

The overall goal programming for the selected case is as follows:

$$Min\ Z = 0.7{d_1}_{-}^{+} + 0.7d_1^- + 0.25d_2^- + 0.05d_3^-$$

$$x_1 + x_2 - d_1^+ + d_1^- = 74$$

$$x_1 - d_2^+ + d_2^- = 64$$

$$x_2 - d_3^+ + d_3^- = 14$$

$$DVH_{66\%}^1 x_1 + DVH_{66\%}^2 x_2 + 10.72 \leq 45;$$

$$DVH_{50\%}^1 x_1 + DVH_{50\%}^2 x_2 + 15.64 \leq 55;$$

$$DVH_{25\%}^1 x_1 + DVH_{25\%}^2 x_2 + 5.2 \leq 65;$$

$$DVH_{10\%}^1 x_1 + DVH_{10\%}^2 x_2 + 0.94 \leq 70;$$

$x_1, x_2 \geq 0$ and integer;

$d_1^{+,-}, d_2^{+,-}, d_3^{+,-} \geq 0;$

Due to positive values of DVH violation ($S^p \geq 0$), there is a scope for improvement. To determine the dose limit of different volume percentage of the rectum we eliminated all the S^k based on what we described in section 3.2. After solving the linear integer goal programming, the value of dose in Phases I and II is 56 GY and 14 GY respectively, which is within the safe recommended limit.

4.5 Experimental Results

In order to examine the effectiveness of the proposed methodology, the leave one out strategy was employed. Anonymous records of previously treated patients were collected from Nottingham City Hospital and stored in the database forming a collection of 69 cases. In leave-one-out approach, cases stored in our case base are

extracted one-by-one and considered as a new case. The dose plan related to each of the taken out cases is calculated through the proposed methodology and the result is compared with the dose plan prescribed by the oncologist. If there is any discrepancy between the dose plan computed by the proposed methodology and that prescribed by the oncologists' then firstly the dose received by different volume percentage of the rectum is calculated. If dose received by the different volume percentages of the rectum is less than or equal to the recommended limit then the quality of dose plan is judged based on the following conditions.

The dose plan having a higher amount of total dose is considered preferable because while radiation received by rectum is in the safe zone (lower than recommended standards) the probability of killing cancerous cells without damaging surrounding organs, especially rectum, is higher (125). However, if two plans have the same amount of total dose then the quality of the plan is judged based on the amount of dose prescribed in Phase I. In Phase I both cancer cells and the surrounding organs where cancer has spread are treated and the dose plan having the higher amount of dose in Phase I is preferable. If the dose plan generated by the proposed system is equal or better (based on abovementioned criteria) compared with the oncologist prescription then it is considered as a successful case.

The success rate of the proposed method is 87.6%. In 57 cases (out of 65 cases) the dose plan suggested by the proposed method is the same as prescribed by the oncologists or better. More precisely, in 29 cases it generates a better dose plan. Further, in order to demonstrate the suitability of TOPSIS and goal programming method, it is compared with CBR and CBR-TOPSIS (Table 4.8 and Figure 4.3). The

performance of CBR-TOPSIS Goal programming is better than that of other approaches.

Table 4.8 Comparison of the proposed methodology with other approaches

	Simple CBR	CBR+TOPSIS	CBR+TOPSIS + Modification rule	CBR+TOPSIS + GP
Success rate (%)	73.43	83.6	86.88	87.6
Number of cases with better dose plan	15	18	20	29

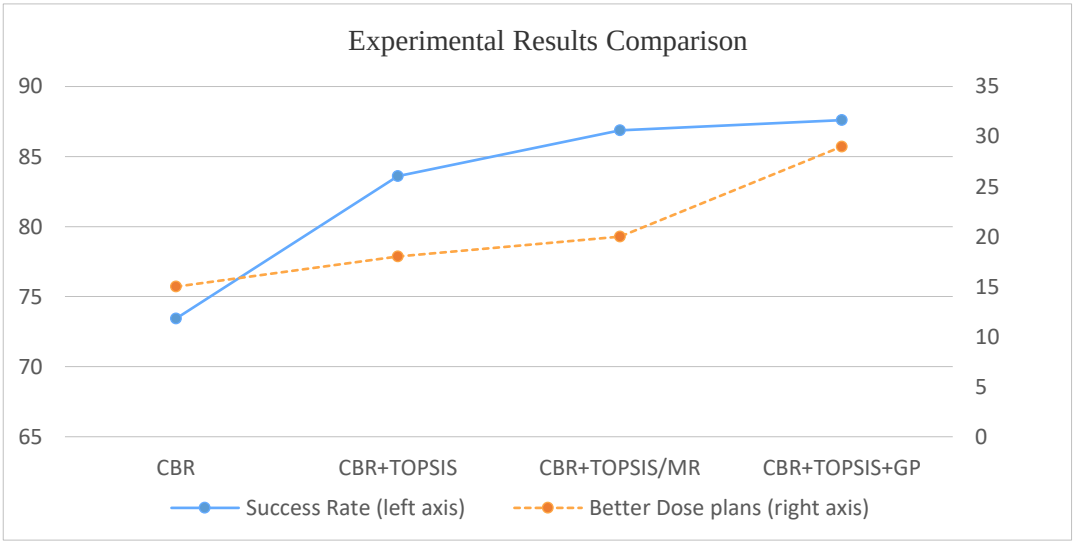

Figure 4.3 Graphical representation of success rate

Also in order to further consider the number of retrieved most similar cases for consideration in TOPSIS evaluation, the whole experiment has been done for $t = 3, 4, 5, 6, and\ 7$ most similar case to a new case (Table 4.9). Increasing the number of most similar cases from 4 to 5, the success rate of the process increased by 7.6%. Increasing the number of cases from 5 to 6 and 7 cases did not have an effect on the outcome of the process simply because the extra similar cases due to their low

similarity to the new case were not evaluated positively by TOPSIS to be considered as the reference case for GP optimization.

Table 4.9 Success rate of the approach by considering different number of similar cases

Number of cases / Success rate	t = 3	t = 4	t = 5	t = 6	t = 7
Success rate (%) with CBR+TOPSIS+GP approach	75.3	80	87.6	87.6	87.6
Number of cases with better dose plan	17	21	29	29	29

4.6 Conclusion

In this chapter a novel hybrid approach of TOPSIS, CBR and goal programming is proposed to help oncologists with decision making in radiotherapy dose planning for prostate cancer. Previously, in order to improve the simple CBR, an MCDM approach of TOPSIS has been merged with CBR to solve the radiotherapy dose planning problem and to include more factors in the process. However, through investigating all the cases solved through the TOPSIS-CBR approach and their prescribed solutions two main problems with cases counted as failures were found; ability to increase the dose plans without violating the recommended standards (non-optimality of some solutions) and trespassing of the standard limitation and putting surrounding organs at risk (solutions out of the feasible area of interest).

To optimize the solutions (obviating the first issue) within the feasible area considered by oncologists' experiences (obviating the second issue) and propel the solutions towards desirable dose plans goal programming was used. Firstly, the similar process of choosing the most similar cases through CBR and evaluation of the extracted cases through TOPSIS was performed. Then based on deviations from the highest ranked case by TOPSIS the constraints of the goal programming model were determined.

Thereafter, the goal regarding the doses was formulated with respect to the values in the case pool and finally by solving the goal programming model the optimized doses for the new case were prescribed. The robustness of the proposed method was tested on real datasets collected from Nottingham City Hospital using leave-one-out strategy. In experiments, it was found that the proposed system helped oncologists to make a trade-off between different decision-making criteria and to decide on the optimal dose plan for the treatment.

The success rate of the treatment can be considered as an output of the radiotherapy dose planning and it is measured by years of cancer-free probability determined by PSA values 2 years and 5 years after the treatment. Developing a model that is able to differentiate success rate with other factors involved in radiotherapy dose planning in evaluations can significantly improve the oncologist's ability to determine the extent of each solution’s efficiency. Furthermore, the uncertainty involved in oncologists’ judgments and scales in real life scenarios is an unavoidable aspect of the decision-making process. The two mentioned problems will be the focus of further development of a model for radiotherapy dose planning in the next chapter.

Chapter 5

Interval-valued Factor Analysis for unnecessary data reduction in DEA and its application in radiotherapy for prostate cancer

5.1 Introduction

Finding the appropriate amount of radiation dose is an important step in radiotherapy for prostate cancer. Use of intelligence systems, which is also known as, Artificial Intelligence (AI) is popular within the healthcare domain, and in particular, Cased-Based Reasoning has been used extensively in order to help oncologists with decisions in radiotherapy planning. The application of CBR has been successful in dealing with simple diseases. However, when it comes to complex healthcare problems with multiple domains and several factors to be considered, CBR suffers lack of accuracy and may not provide a comprehensive solution (221).

Dose planning is a complex problem and requires the consideration of many aspects of the process of planning. Thus, CBR may suffer from the same issue mentioned before subsequently. In order to improve the CBR results, in previous chapters, we applied MCDM methods to consider the multiple criteria nature of the problem. Furthermore, to direct the solutions toward optimized dose plans we used multi-objective optimization. By applying TOPSIS and defining various criteria, we considered not only the similarity between two cases but also took into account the values for other

dose planning characteristics and safe distance to the standard limitations. The obtained answers benefit from multi-aspect evaluations and have been filtered through various criteria. Their suitability to real-world decision-making scenarios dealt with by oncologists has been proven by their higher success rate compared to simple CBR.

Moreover, these solutions made of a larger number of experiences, provided by CBR and TOPSIS, than a human brain can utilize. To obtain even more efficient answers, we applied a Goal Programming model using goals from the case pool of data and setting hard constraints regarding the DVH values to prevent the optimized solutions from violating the harmful dose amounts for OARs. The solutions provided not only exceed the success rate of previous approaches but also improved the number of dose plans with better solutions.

For prostate cancer, the success rate of the treatment is determined by the Prostate Specific Antigen (PSA) value, measured two years after the treatment. The lower the level of the PSA, the higher is the possibility of cancer cells being eradicated effectively and the lower the probability of a cancer tumour reappearing. Accommodating this criterion in evaluations of cases can benefit patients significantly, as it gives higher importance weight to cases with better treatment results.

While TOPSIS evaluates alternatives, and ranks them based on a distance approach, in the presence of criteria, which are dividable into sets of inputs and outputs as a result of the inputs, Data Envelopment Analysis (DEA) is a more reasonable method to calculate the efficiency of each of the alternatives. DEA is an efficient and relatively common approach to compare the performance of a set of competing Units called Decision Making Units (DMUs). DEA has been applied on various forms of DMUs i.e. to evaluate the performance of countries from different perspectives [(222), (223)],

regions (224), hospitals (225), business firms (226), etc. However, due to very few assumptions required, DEA has also opened opportunities to evaluate the performance of cases which are difficult to investigate because of the complex relations between inputs and outputs of each DMU (227).

Applying DEA to obtain the efficiency of the cases retrieved from CBR can equip us with a valuable tool to separate the criteria in our evaluations based on their essence and perform a better assessment. DEA does not come without limitations, the most important of which is a limitation on the number of inputs and outputs. Through increasing the number of inputs and outputs we can investigate the performance of a DMU from multiple points of view and increase the precision of the assessment. However, DEA in the presence of a high aggregative number of inputs and outputs in comparison to the number of DMUs can be unreliable and results in incorrect efficiency predictions.

Furthermore, in recent years with massive data generation in various fields decision makers and managers are not dealing with small-scale problems and the massive number of alternatives and criteria can affect the calculation's precision and computational time. In our problem, we are also dealing with a considerable number of criteria, as we used 7 criteria for TOPSIS evaluations. These criteria are dose plan in phase I and II of the treatment, similarity measure (indicates the similarity between a new case and the most similar cases) and the distance between the standard dose limitations and dose received by different volumes of the rectum (10%, 25%, 50% and 66% of the rectum volume) which indicates the risk of the treatment (the higher the distance, the lower the risk of prescribed treatment is).

Adding up the success rate of the treatment is going to increase the number of criteria to 8. Thus, applying a methodology to decrease the dimensions of the problem, and reduce the unnecessary information and variables would be helpful. Adler and Golany (228,229), suggested using Principal Component Analysis (PCA), a methodology that produces uncorrelated linear combinations of original inputs and outputs, to improve discrimination in DEA with minimal loss of information. In this approach, it is assumed that removal of the Principal Components (PCs) with less exploratory ability has a venial effect on discrimination of our DMUs efficiency scores. Thus, a higher number of criteria are waved in the calculations and only principal components, which account for most of the variance of the observed variables, are considered.

Although PCA is a reliable variable reduction method it is different in several aspects with Factor Analysis (230). Principal Components in PCA retained account for a maximum amount of variance of observed variables. The main goal in PCA is to create a few index variables out of a large set of measured variables in an optimal way. The number of the components, existing variables in each component and the weight of the variables in the components are calculated in an optimal way. FA is a method to measure a latent variable which cannot be measured with a single variable and must be seen through the relationship it creates between a set of other variables (231).

In FA, factors account for common variance in the data. In PCA, Component scores are a linear combination of the observed variables weighted by eigenvectors while in FA observed variables are linear combinations of the underlying and unique factors. Identification and interpretation of inputs and outputs, which decrease or improve the efficiency is important to us in DEA. Therefore, applying FA and exploratory factors as the source of DEA inputs and outputs entry can be helpful in post-analysis discussions.

In real life scenarios, oncologists, in order to make a decision about a dose plan, do not treat all the parameters involved with exact precision based on crisp numbers and there is some level of uncertainty in their judgment. To reflect this uncertainty in our dose plan calculation and approach the way oncologists take decisions we found applying grey numbers associated with opinions of oncologists in real life scenarios, an advantageous method. Grey theory and consequently grey numbers application are suitable to handle the incomplete and uncertain interval-valued data within the preferences of decision makers. Thus, the main aim of this research is to develop a solution to apply Data Envelopment Analysis (DEA) in the presence of numerous interval data inputs and outputs and obtain as much as possible precise efficiency scores for the Decision-Making Units (DMUs) to calculate the appropriate dose plan for radiotherapy dose planning. In order to do so, we apply FA based on PCA to reduce the dimension of our data.

In this chapter, the interval-valued PCA for grey numbers is synchronised and the exploratory factors (EFs) for a set of inputs and outputs are obtained. The purpose is to illustrate the proposed MCDM approach of Data Envelopment Analysis combined with Factor Analysis for interval grey numbers and demonstrate its efficiency in solving the issues faced in radiotherapy dose planning. The EFs and PCs will be used as variables separately to be fed into DEA and results of efficiency scores based on interval-valued DEA will be carried out for them. In order to closely reflect a real-life scenario, where the oncologists expressed their preferences about one criterion by approximated linguistic terms, the data acquired from real cases will be transformed to grey intervals of $G = [\underline{G}, \overline{G}]$ where it is appropriate and matches reality. The benefits of applying variable reduction techniques by performing FA-PCA-DEA on grey type data are demonstrated and the analysis is extended by interpreting the factors and

highlighting the important inputs and outputs for the evaluation of this certain problem. The main contributions of this chapter can lie on:

- Firstly, the introduction of a platform to perform more inclusive and accurate evaluation. This is achieved by considering more input and output attributes in presence of uncertainty preference of DM about an alternative, applying PCA and FA on grey data and preparing the obtained variables to be used in MCDM methods, specifically in this approach, the DEA method.
- Secondly, to provide a better solution for radiotherapy dose planning problem for prostate cancer by considering uncertainty involved in human judgments and a detailed step by step approach (Figure 5.1).

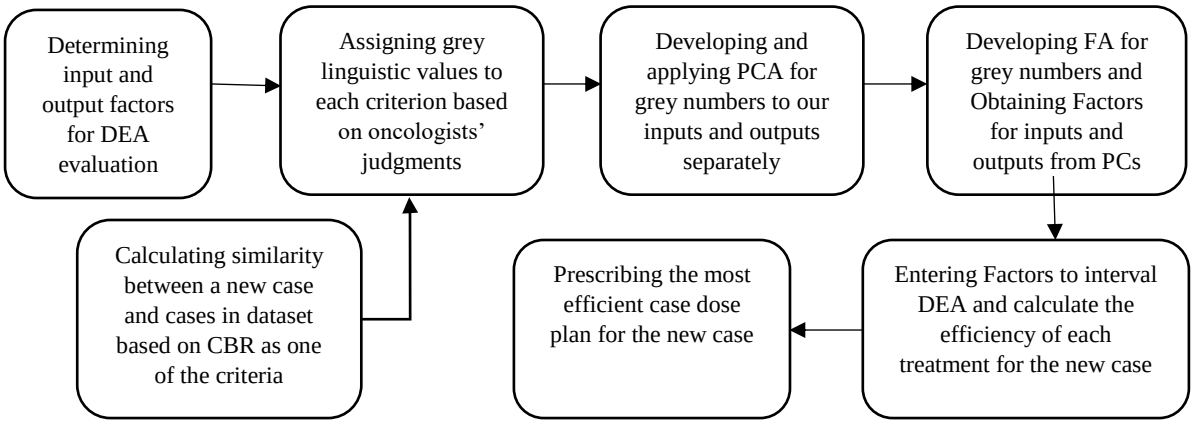

Figure 5.1 Overview of PCA-FA-DEA based on CBR solution to radiotherapy dose planning problem

Application of PCA as an approach, which produces data with lower complexity in order to be used by other methods, has drawn the attention of many researchers. Lam et al. (232) applied ANP to principal components obtained from a fuzzy decision matrix of judgments by decision-makers in the construction industry to evaluate their material suppliers. However, before applying PCA, they defuzzified their fuzzy data and thus did not develop any method to perform PCA on fuzzy data. Doukas et al. (233) applied PCA to produce sustainable energy performance indicators for different

communities in the EU. The authors never tried to present an approach that can actually evaluate these communities and sufficed to just prepare the background for future research. As previous research in the direction of utilizing PCA for data reduction to be used in DEA is concerned, Adler and Golany (228), for the first time evaluated the efficiency of deregulated airline networks in European Union by the means of DEA and in order to overcome the excessive amount of inputs and outputs, applied PCA.

Jenkins and Anderson (234) argued that omitting even highly correlated variables can extensively impact the efficiency score results and Dyson (235) pointed out that only analysing simple variances is in some levels insufficient to distinguishing unimportant variables. Poldaru and Roots (236) used the same combination of PCA and DEA to compare the quality of life in Estonian counties and through comparison of PCA-DEA with simple DEA demonstrated the valuable distinction improvement that PCA can add to DEA. All the aforementioned examples applied crisp values and datasets, while the uncertainty in real life scenarios necessitates the application of interval data in evaluations.

Cazes et al. (237) introduced two methods of Centralized PCA (CPCA) and vertex PCA (VCPA) to deal with applying PCA of interval-data and Wang et al. (238) extend their method to Complete Information PCA (CIPCA) by introducing a new squared norm of an interval-valued variable. Liu et al. (239) developed the PCA method for intuitionistic fuzzy numbers and introduced new operators to deal with them in order to apply them in group decision-making problems over a large set of data. After that, they obtained each alternative's overall evaluation value by utilizing conventional information aggregation operators. An extensive literature review has not revealed any research in which PCA for grey data has been considered and furthermore the application of FA in DEA has been investigated.

5.2 Methodology

In this section, different methodologies applied within this chapter are presented. Following an initial review of the interval grey numbers the method enabling PCA in the presence of grey numbers is introduced. After that, the Factor Analysis is described by using components of PCA and explanatory comments about why and how to rotate the final factors for simpler structure. Finally, Interval DEA is illustrated and discussed.

5.2.1. Interval Grey Numbers

Deng (240), through combining System theory, Space theory and Control theory introduced a new type of expressing data called grey theory and grey sets. A grey system is defined as a system capable of covering uncertain information presented by a grey number and a grey variable. For defining a grey number let *X* be the universal set and $x \in X$. Then a grey set *G* of *X* is defined by its two mappings in equation 1 and 2:

$$\bar{\mu}_G(x): x \to [0,1] \tag{1}$$

$$\underline{\mu}_G(x): x \to [0,1] \tag{2}$$

In above equations, $\bar{\mu}_G(x)$ and $\underline{\mu}_G(x)$ are upper and lower membership functions respectively. Generally, Grey numbers are expressed as:

$$\otimes G = G|_{\underline{\mu}}^{\bar{\mu}} \tag{3}$$

While the lower and upper memberships can be estimated and an interval-valued grey number with lower and upper bound can be defined as:

$$\otimes G = [\underline{G}, \overline{G}] \tag{4}$$

If we assume$\otimes G_1 = [\underline{G_1}, \overline{G_1}]$ and $\otimes G_2 = [\underline{G_2}, \overline{G_2}]$ two Grey interval numbers then, the main operations on grey numbers is done through following:

$$\otimes G1 + \otimes G2 = [\underline{G1} + \underline{G2}\,, \overline{G1} + \overline{G2}] \quad (5)$$

$$\otimes G1 - \otimes G2 = [\underline{G}1 - \overline{G2}, \overline{G1} - \underline{G2}] \quad (6)$$

$$\otimes G1 \times \otimes G2 = [\min(\underline{G1}\ \underline{G2}, \underline{G1}\ \overline{G2}, \overline{G1}\ \underline{G2}, \overline{G2}\ \overline{G1}),$$

$$\max(\underline{G1}\ \underline{G2}, \underline{G1}\ \overline{G2}, \overline{G1}\ \underline{G2}, \overline{G2}\ \overline{G1})] \quad (7)$$

$$\otimes G1 \div \otimes G2 = [\underline{G1}\,, \overline{G1}] \times [\tfrac{1}{\underline{G2}}\,, \tfrac{1}{\underline{G2}}] \quad (8)$$

Also, the lengths of a grey number can be calculated as follow:

$$L(\otimes G) = \left|\overline{G} - \underline{G}\right| \quad (9)$$

Application of grey system theory has been common in medical treatment literature as it can perfectly deal with the ambiguity of medical data. Xuerui and Yuguang (241) applied Grey Relational Analysis (GRA) on several experimental and trial medical data set to analyse and evaluate them. Icer at al. (242) applied grey data and GRA to assess the values for fatty liver and developed an approach based on GRA and ultrasonography, which eliminated the visual evaluation of radiologists and improved the diagnosis results. Li et al. (243) applied GRA in combination with Dempster–Shafer theory of evidence to find an appropriate level of soft sets for fuzzy soft sets and demonstrated its effectiveness in medical diagnosis where the final diagnosis of medical experts comes along with levels of uncertainty and improved the precision of diagnosis.

5.2.2. PCA

There are two main viewpoints of algebraic and geometrical approaches to drive Principal Components (PCs). The main goal of PCA is to describe variations in a set of relatively correlated variables $X' = (x_1, x_2, \cdots, x_m)$, due to a new set of uncorrelated variables of $Z' = (z_1, z_2, \cdots, z_k)$. Each of the PCs is a linear combination of variables of X array. The PCs are driven out in such a way that the first PC accounts for the most variations among others and there is a decreasing order of importance (fewer variations) between first and last PC. Given *m* random variables $x_1, x_2, \cdots, x_m$, we can express the PCs as $Z_k = \sum_{j=1}^{m} L_{jk} X_j$. Initially, the variances of Z_k should be maximized subject to $L_k' L_q = 0$ for all the $l \neq q$ and $L_k' L_k = 1$. If we define *H* as the known covariance matrix of the x variables, then we can demonstrate through Lagrange multiplier technique that vector of coefficients related to the *k*th Component of Z is eigenvectors of the H matrix respected to the *k*th largest eigenvalue. So as if we denote the p biggest eigenvalues of the H by $\lambda_i \; and \; i = (1, 2, \cdots, p)$ then the variance of the *i*th PC is described by λ_i.

5.2.2.1 PCA for Grey data:

Each grey number is an interval-valued number, in the form of a uniform distributed variable in the $\underline{G}$ and $\overline{G}$ intervals as lower and upper boundaries respectively. Furthermore, grey numbers are regarded with infinitely density over their boundaries. So, some of the basic operators have been commonly used for interval uniformly distributed and infinite dense numbers, variance-covariance matrix for interval valued data (237) and the process of extracting principal components for interval valued data [(238), (239)] has been reviewed and made compatible with Grey numbers as follow.

Definition 1. The mean of a grey number is calculated based on the following equation:

$$E(\otimes G) = \frac{\int_{\underline{G}}^{\overline{G}} A.dA}{\overline{G} - \underline{G}} = \frac{1}{2}\left(\overline{G} - \underline{G}\right) \tag{10}$$

So if we have a variable $G_j' = \left(\left[\underline{G_{1j}}, \overline{G_{1j}}\right], \left[\underline{G_{2j}}, \overline{G_{2j}}\right], \cdots, \left[\underline{G_{mj}}, \overline{G_{mj}}\right]\right)$ then the mean of such a variable is given by

$$E\left(G_j'\right) = 1/m \sum_{i=1}^{n} E\left(G_{ij}\right) \tag{11}$$

Thus, a centralized matrix of x_{ij} is based on following formula:

$$G_{ij} - E\left(G_j'\right) = \left[\underline{G}_{jj} - E\left(X_j'\right), \overline{G}_{ij} - E\left(X_j'\right)\right] \tag{12}$$

Definition 2. Where $(l \neq m)$, for any two grey interval variables of X_l' and X_m' the inner product of these two numbers, denoted by (X_l', X_m') is calculated based on summation the of inner product of G_{il} and G_{im}.

$$(X_l', X_m') = \sum_{i=1}^{n} (G_{il}, G_{im}) \tag{13}$$

The term (G_{il}, G_{im}) is calculated based on following:

$$(G_{il}, G_{im}) = \frac{\int_{\underline{G}_{il}}^{\overline{G}_{il}} \int_{\underline{G}_{im}}^{\overline{G}_{im}} AT.dAdT}{\left(\overline{G}_{il} - \underline{G}_{il}\right)\left(\overline{G}_{im} - \underline{G}_{im}\right)} = \frac{1}{4}\left(\underline{G}_{jl} + \overline{G}_{il}\right)\left(\underline{G}_{jm} + \overline{G}_{im}\right) \tag{14}$$

While the inner product operator defined in definition 2 is only applicable for two different variables, we cannot drive the squared norm of a variable X_j as $\left\|X_j\right\|^2$ and equal it by $\left(X_j, X_j\right)$. Instead, we add a new definition based on Wang et al. [238] and calculate the mentioned value through it.

Definition 3. The squared norm of an interval variable of X_j is obtained by

$$\|X_j\|^2 = \sum_{i=1}^{n} \|G_{ij}\|^2 \tag{15}$$

Where the term $\|G_{ij}\|^2$ is given by following integral

$$\|G_{ij}\|^2 = \int_{\underline{G}_{ij}}^{\overline{G}_{ij}} A^2 . \frac{1}{\overline{G_{ij}} - \underline{G_{ij}}} dA = \frac{1}{3}\left(\underline{G}_{ij}^2 + \underline{G}_{ij}\overline{G}_{ij} + \overline{G}_{ij}^2\right) \tag{16}$$

The most important operator for conducting PCA is how to calculate the covariance matrix. So, the terms $Cov(X_l', X_m')$ and $Var(X_j')$ is given by

$$Cov(X_l', X_m') = \frac{1}{n}(X_l', X_m') \tag{17}$$

$$Var(X_j') = \frac{1}{n}\|X_l\|^2 \tag{18}$$

In order to demonstrate the covariance matrix of $X_{n\times p}$ all the variables G_{ij} have to be centralized based on equation 12 and after that, the covariance matrix is computed based on the following:

$$\begin{pmatrix} Var\,X_1 & Cov(X_1,X_2) & \cdots & Cov(X_1,X_p) \\ Cov(X_2,X_1) & VarX_2 & \cdots & Cov(X_2,X_p) \\ \vdots & \vdots & \ddots & \vdots \\ Cov(X_p,X_1) & Cov(X_p,X_2) & \cdots & VarX_p \end{pmatrix} = \begin{pmatrix} \frac{1}{n}(X_1,X_1) & \frac{1}{n}(X_1,X_2) & \cdots & \frac{1}{n}(X_1,X_p) \\ \frac{1}{n}(X_2,X_1) & \frac{1}{n}(X_2,X_2) & \cdots & \frac{1}{n}(X_2,X_p) \\ \vdots & \vdots & \ddots & \vdots \\ \frac{1}{n}(X_p,X_1) & \frac{1}{n}(X_p,X_2) & \cdots & \frac{1}{n}(X_p,X_p) \end{pmatrix}$$

$$= \begin{pmatrix} \frac{1}{3}\left(\underline{G}_{i1}^2 + \underline{G}_{i1}\overline{G}_{i1} + \overline{G}_{i1}^2\right) & \frac{1}{4}(\underline{G}_{i1} + \overline{G}_{i1})(\underline{G}_{i2} + \overline{G}_{i2}) & \cdots & \frac{1}{4}(\underline{G}_{i1} + \overline{G}_{i1})(\underline{G}_{ip} + \overline{G}_{ip}) \\ \frac{1}{4}(\underline{G}_{i2} + \overline{G}_{i2})(\underline{G}_{i1} + \overline{G}_{i1}) & \frac{1}{3}\left(\underline{G}_{i2}^2 + \underline{G}_{i2}\overline{G}_{i2} + \overline{G}_{i2}^2\right) & \cdots & \frac{1}{4}(\underline{G}_{i2} + \overline{G}_{i2})(\underline{G}_{ip} + \overline{G}_{ip}) \\ \vdots & \vdots & \ddots & \vdots \\ \frac{1}{4}(\underline{G}_{ip} + \overline{G}_{ip})(\underline{G}_{i1} + \overline{G}_{i1}) & \frac{1}{4}(\underline{G}_{ip} + \overline{G}_{ip})(\underline{G}_{i2} + \overline{G}_{i2}) & \cdots & \frac{1}{3}\left(\underline{G}_{ip}^2 + \underline{G}_{ip}\overline{G}_{ip} + \overline{G}_{ip}^2\right) \end{pmatrix} \tag{19}$$

5.2.3 Linear Combination of Interval Value Data

Based on Moore's work (244) each interval-valued data unit of $G_i = [\underline{G_i}, \overline{G_i}]$ and $i = 1,2,\cdots,n$ the data can also be indicated as a continuous numeric set with lower and upper boundaries i.e. $G_i = \{s|s\epsilon[\underline{G_i}, \overline{G_i}]\}$. Thus, if we have a function of various G we can say:

$$f(G_1, G_2, \cdots, G_n) = \{f(s_1, s_2, \cdots, s_n)|s_i\epsilon G_i\} \tag{20}$$

The fact that *f* is a continuous function of Moore's linear combination algorithm for interval value data is based on:

$$Y = \sum_{j=1}^{n} u_j X_j = \left(\left[\underline{y}_1, \overline{y}_1\right], \left[\underline{y}_2, \overline{y}_2\right], \cdots, \left[\underline{y}_n, \overline{y}_n\right]\right) \tag{21}$$

Assuming X_j as an interval valued variable with *n* interval value data, for $u_j\epsilon R$, $j = 1,2,\cdots,m$ we are able to define a new variable Y like above which is a linear combination of our primary X_j variables in which lower and upper boundaries of y_i are given by:

$$\underline{y}_i = \sum_{j=m}^{p} u_j\left(\mu\underline{G}_{ij} + (1-\mu)\overline{G}_{ij}\right) \qquad for\ 1 \le i \le n \tag{22}$$

$$\overline{y}_i = \sum_{j=m}^{p} u_j\left((1-\mu)\underline{G}_{ij} + \mu\overline{G}_{ij}\right) \qquad for\ 1 \le i \le n \tag{23}$$

And respect to the fact that $\mu = \begin{cases} 0 & if \quad u_j \le 0 \\ 1 & if \quad u_j > 0 \end{cases}$ (24)

5.2.4 Eigen Vector and Eigen values computation in Grey Principal Components Analysis

Similar to previous sections, all the interval value grey numbers have been centralized through equation (12). Given p grey variables of $X_1, X_2, \cdots, X_p$, the kth PC Y_k ($k = 1,2, \cdots, p$) is a linear combination of grey variables, i.e. $Y_k = Xe_k = \sum_{j=1}^{p} e_{jk}X_j$ where we can define $e_{jk} = (e_{1k}, e_{2k}, \cdots, e_{mk})^T$ which is subject to $e_k^T e_k = 1$ and $e_k^T e_l = 0$, $\forall\, l \neq k$. The variance of Y_k can be defined as

$$Var(Y_k) = Cov(Y_k, Y_k) = \frac{1}{n}(Y_k, Y_k) \tag{25}$$

Where

$$\frac{1}{n}(Y_k, Y_k) = e_k^T C e_k \tag{26}$$

In equation (26), C represents for the covariance matrix of grey variables of $X_1, X_2, \cdots, X_p$.

The following derivation is the same one for a classical PCA in which we are looking after the m orthonormalized vectors of $e_1, e_2, \cdots, e_m$ that maximize the total variance term of $\sum_{k=1}^{m} Var(Y_k)$ subject to $Var(Y_1), Var(Y_2), \cdots, Var(Y_m)$ by solving the following optimization problem:

$$Max \sum_{k=1}^{m} e_k^T C e_k, \tag{27}$$

$$s.t. \begin{cases} e_k^T e_k = 1, \\ e_k^T e_k = 0, \\ e_1^T C e_1 \geq e_2^T C e_2 \geq \cdots \geq e_m^T C e_m \\ l = 1,2, \cdots, m \; and \; l \neq k. \end{cases} \tag{28}$$

The optimal solution of above problem, $e_1, e_2, \cdots, e_m$ are the eigenvectors of C corresponding to eigenvalues of $\lambda_1, \lambda_2, \cdots, \lambda_m$. By means of such an eigendecomposition of covariance matrix C, the derivation of PC coefficients is converted to a simple eigendecomposition problem. Through obtaining $e_1, e_2, \cdots, e_m$ we can finally have the kth PCs of $Y_1, Y_2, \cdots, Y_m$.

5.2.5 Inclusion of data by PCs

As eigenvectors of each PC (λ_i) are equal to the variance of that component, this could be interpreted as the amount of the total variance of the data which is being included in the component. If we chose the first kth PCs then the amount of total variance included by them can be calculated through the following:

$$Variance\ inclusion\ amount = \frac{\sum_{i=1}^{k} \lambda_i}{\sum_{i=1}^{m} \lambda_i} \tag{29}$$

5.2.6 Factor Analysis

Factor Analysis (FA) pursues the same goals as PCA. The most important of them are describing p variables in a a lower number of factors to decrease the complexity of further calculations and understanding the relying relation between the variables. One way to calculate the Factors in FA is first obtaining the PCs of the data and apply them as the primary un-rotated Factors. Given the p variables of $X_1, X_2, \cdots, X_p$, we have p Principal Components we calculated in previous sections as follow:

$$Y_1 = e_{11}X_1 + e_{12}X_2 + \cdots + e_{1p}X_p$$
$$Y_2 = e_{21}X_1 + e_{22}X_2 + \cdots + e_{2p}X_p$$
. Step(1)
.

$$Y_p = e_{p1}X_1 + e_{p2}X_2 + \cdots + e_{pp}X_p$$

This transformation of X is orthogonal to Y so that the following equations are simply acquired

$$X_1 = e_{11}Y_1 + e_{12}Y_2 + \cdots + e_{1p}Y_p$$
$$X_2 = e_{21}Y_1 + e_{22}Y_2 + \cdots + e_{2p}Y_p$$
. Step(2)
.
$$X_p = e_{p1}Y_1 + e_{p2}Y_2 + \cdots + e_{pp}Y_p$$

Regarding section 2.3 about the inclusion of PCs only the first m PCs are being selected which include the majority of information and so the model 2 is being transformed to following to model 3:

$$X_1 = e_{11}Y_1 + e_{12}Y_2 + \cdots + e_{1m}Y_m + E_1$$
$$X_2 = e_{21}Y_1 + e_{22}Y_2 + \cdots + e_{2m}Y_m + E_2$$
. Step(3)
.
$$X_p = e_{p1}Y_1 + e_{p2}Y_2 + \cdots + e_{pm}Y_m + E_p$$

Elimination of some PCs will cause errors. E_ps are residuals with zero means and correlations of zero with the factors. Now by standardization of the PCs should be done so that they have unit variance and can be transformed into appropriate Factors. To do so each PC of Y_m is being divided by its standard deviation $\sqrt{\lambda_m}$ which is the root of the related eigenvalue in covariance matrix for Y_m and thus the equations above become as follow:

$$X_1 = a_{11}F_1 + a_{12}F_2 + \cdots + a_{1m}F_m + E_1$$
$$X_2 = a_{21}F_1 + a_{22}F_2 + \cdots + a_{2m}F_m + E_2$$
. Step(4)

.

$$X_p = a_{p1}F_1 + a_{p2}F_2 + \cdots + a_{pm}F_m + E_p$$

In model 4 F_m and a_m are based on follow

$$F_m = \frac{Y_m}{\sqrt{\lambda_m}} \tag{30}$$

$$a_{pm} = \sqrt{\lambda_m} \times e_{pm} \tag{31}$$

So, the p variables of $X_1, X_2, \cdots, X_p$ are being described through m Factors of $F_1, F_2, \cdots, F_m$.

In order to obtain the factors, we rely on matrix algebra relations by Harman (245). The final equations calculated above can be described in Matrix form based on equation 32.

$$X_{m\times p} = A^T_{p\times m} F_{p\times m} \tag{32}$$

F can be obtained by the following calculations:

$$F = A^{-1T} X = (A.A^T)^{-1} A.X \tag{33}$$

5.2.7 Varimax Rotation

Factors rotation is performing an arithmetic operation to obtain a new set of factor loadings which explain the structure of the original factors simpler and more interpretable. This operation is done through rotating axis or dimensions of the factor loadings (246-248). For correlated factors oblique rotation and for uncorrelated factors, orthogonal rotation are the best options. While after the rotation the partition of variances explained by axes is changed, but the part of variance explained by the total

subspace after rotation is the same as it was before rotation. Assuming we have only two dimensions of X and Y in an exemplary problem, figure 5.2 shows what happens during a rotation.

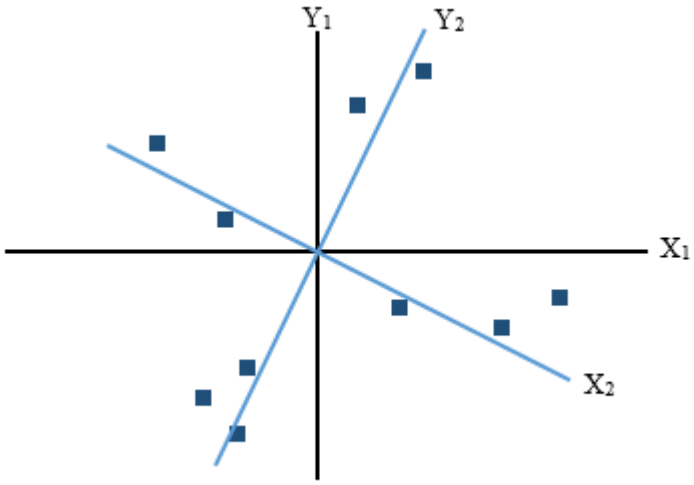

Figure 5.2 visualization of factor rotation

In figure 5.2 the original X and Y axes, are X_1 and Y_1 in black and factor loadings are the dots. Following axes rotation, the factor loadings are better explained by new X or Y axes (X_2 and Y_2). While the factor loadings are same before just the axes have been rotated to better explain the situation. In this research, because our exploratory factors have been obtained from Uncorrelated PCS, we have selected the Varimax rotation by Kaiser criterion which is the most common orthogonal rotation. The process will be done through MATLAB software and statistical toolbox.

5.2.8 Interval DEA

Data Envelopment Analysis (DEA) is a data-oriented approach to evaluate the performance of a set of peer entities called Decision Making Units (DMUs). As a linear programming technique, DEA measure the efficiency of the aforementioned DMUs on the basis of multiple weighted inputs and multiple weighted outputs (227). The weights are estimated in such a way to maximize the efficiency of the unit under evaluation. In

recent years a variety of DEA applications in different fields involving various types of DMU have been developed. Furthermore, because of few assumption requirements in DEA, it has become the preferable method for a range of fields to handle the complex relation between inputs and outputs of a problem. A common use of DEA is in finding the efficiency of hospitals and healthcare deliveries. Nayar and Ozcan (249), evaluated the efficiency of Virginia hospitals and classified the efficient and inefficient hospitals regarding both technical and quality efficiencies and remedied suggestions for inefficient hospitals to improve their performance. Kawaguchi et al. (250) applied a dynamic network DEA to calculate the efficiency of the municipal hospitals in Japan. They used network DEA to calculate the efficiency of two types of departments within the hospital, medical and administrative, simultaneously with the overall efficiency of the hospital. They applied the dynamic model to calculate the results for a series of years. Thanassoulis et al. (251) applied DEA on Chronic obstructive pulmonary disease patients and obtained the most efficient length of stay for each of them in terms of savings for the hospital. Some of the literature above highlight the fact that in some occasions different types of DEA model need to be applied to the problem in order to deal with the problem and data type appropriately.

While including uncertain opinions and judgments of a medical team requires us to use grey numbers, we have to use a model of DEA that is able to deal with interval data. As the classical DEA methodologies have been fully addressed in Molinero and Woracker (252) and Cooper et al. (253), here we discuss the preliminaries and methodology for performing DEA on interval values to include grey data in our evaluations. Assume there are *n* DMUs, denoted by $j(j = 1,2,\cdots,n)$, and each of them are producing *k* outputs from *m* inputs. y_{rj} and x_{ij} stand for the level of *r*th output ($r = 1,2,\cdots k$) and *i*th input ($i = 1,2,\cdots,m$) in *j*th DMU respectively. Despite the classical

DEA in which the y_{rj} and x_{ij} are crisp values, in our approach, within this chapter they are grey numbers and based on following:

$$y_{rj} = [\underline{G}_{rj}, \overline{G}_{rj}] \quad \text{and} \quad x_{ij} = [\underline{G}_{ij}, \overline{G}_{ij}]$$

As far as each of our output and input levels are grey numbers which make it probable each of our variables related to a unit lies within their lower and upper bounds, the classical points in the frontier diagram are transformed into quadrangles. So, units are allowed to assign any values within the quadrangle to maximize its efficiency. Figure 5.3 elucidate the differences between classical and Grey DEA frontier shapes.

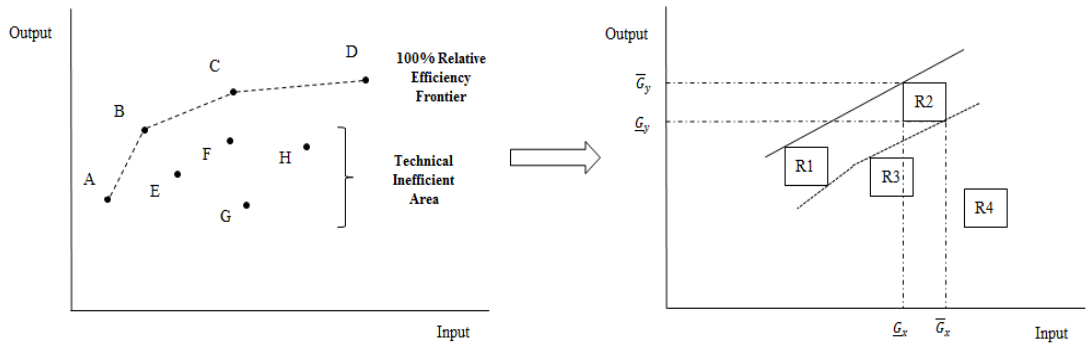

Figure 5.3 Classical and grey Frontiers of efficient units in DEA

The left diagram in figure 5.3 shows the efficiency frontier for eight DMUs of A to H in respect of one input and one output in a classical crisp value problem. The units on the efficiency frontier are considered as efficient units by using the lowest possible level of resources, they are producing the highest possible amount of output. The units E, F, G and H are inefficient units as they can produce more outcome by using current amount of resources or by using current amount of resources they can increase their output levels. In the right diagram through the output and input are defined by interval grey values. If a DMU selects the upper left corner of its quadrangle due to the production of maximum output by consuming a minimum amount of input it could have the maximum efficiency, while on the contrary, the lower right corner will cause

a DMU to perform in its lowest possible efficiency. There are two probable frontier lines for the interval grey diagram in figure 3. While units R1 and R2 are efficient and unit R4 is inefficient in the probable selection of both frontiers, according to the selection of line 1 the R3 unit will be inefficient while designation of line 2 will result in efficiency of the unit R3.

Application of grey data instead of traditional crisp data will transform a linear CCR input-oriented DEA model to a non-linear model as in addition to $u_1, u_2, \cdots, u_s$ and $v_1, v_2, \cdots, v_m$ which are outputs and inputs weights respectively, the level of variables $x_{ij}$and y_{rj} should be also estimated in order to evaluate the efficiency level of unit j.

$$\max D_{j0} = \sum_{r=1}^{s} u_i y_{rj0}$$

$$s.t. \sum_{i=1}^{m} v_r x_{ij0} = 1 \qquad Model(1)$$

$$\sum_{i=1}^{m} v_i x_{ij} - \sum_{r=1}^{s} u_r y_{rj} \geq 0 \ , j = 1,2, \cdots, n$$

$$u_r \ and \ v_i \geq \varepsilon \quad \forall \mathrm{r, i}$$

In this research based on following, we apply the Despotis and Smilris (254) transformation to convert the non-linear DEA to the linear formulation.

$$x_{ij} = x_{ij}^L + s_{ij}\left(x_{ij}^U - x_{ij}^L\right), \ \ i = 1,2, \cdots, m; \ j = 1,2, \cdots, n \ \ with \ 0 \leq s_{ij} \leq 1 \qquad (34)$$

$$y_{rj} = y_{rj}^L + t_{rj}\left(y_{rj}^U - y_{rj}^L\right), \ \ r = 1,2, \cdots, s; \ j = 1,2, \cdots, n \ \ with \ 0 \leq t_{rj} \leq 1 \qquad (35)$$

Variables s_{ij} and t_{rj} are introduced in above transformation, which locate the levels of inputs and outputs within the bounded intervals of $[x_{ij}^L, x_{rj}^U]$ and $[y_{rj}^L, y_{rj}^U]$

respectively, to be superseded with variables x_{ij} and y_{rj} in model 1. Although due to products of $v_i s_{ij}$ for inputs and $u_r t_{rj}$ for outputs, model one still remains non-linear. Writing the $v_i x_{ij}$ and $u_r y_{rj}$ based on s_{ij} and t_{rj} results in the following equations.

$$v_i x_{ij} = v_i x_{ij}^L + v_i s_{ij}\left(x_{ij}^U - x_{ij}^L\right) \tag{36}$$

$$u_r y_{rj} = u_r y_{rj}^L + u_r t_{rj}\left(y_{rj}^U - y_{rj}^L\right) \tag{37}$$

Then in the process of linearization, we replace $v_i s_{ij}$ by q_{ij} and $u_r y_{rj}$ by p_{rj}. So, the weighted sum composite for inputs will transform into equation 38.

$$\sum_{i=1}^{m} v_i x_{ij} = \sum_{i=1}^{m} v_i x_{ij}^L + q_{ij}\left(x_{ij}^U - x_{ij}^L\right) \tag{38}$$

Where $0 \le q_{ij} \le v_i$; $s_{ij} = \frac{q_{ij}}{v_i}$, $v_i \ge 0$ and $0 \le s_{ij} \le 1 \ \ \forall i, j$ (39)

Similarly, the weighted sum composite for outputs will transform to equation 40.

$$\sum_{r=1}^{s} u_r y_{rj} = \sum_{r=1}^{s} u_r y_{rj}^L + p_{rj}\left(y_{ij}^U - y_{ij}^L\right) \tag{40}$$

Where $0 \le p_{rj} \le u_r$; $t_{rj} = \frac{p_{ij}}{u_r}$, $u_r \ge 0$ and $0 \le t_{rj} \le 1 \ \ \forall r, j$

By applying the abovementioned equation and substituting the transformations, model 1 can be elucidated as following linear programming:

$$\max D_{j0} = \sum_{r=1}^{s} u_r y_{rj}^L + p_{rj0}\left(y_{ij0}^U - y_{ij0}^L\right)$$

$$s.t. \ \sum_{i=1}^{m} v_i x_{ij0}^L + q_{ij0}\left(x_{ij0}^U - x_{ij0}^L\right) = 1 \qquad Model\ (2)$$

$$\sum_{r=1}^{s} u_r y_{rj}^{L} + \sum_{r=1}^{s} p_{rj}\left(y_{ij}^{U} - y_{ij}^{L}\right) - \sum_{i=1}^{m} v_i x_{ij}^{L} + \sum_{i=1}^{m} q_{ij}\left(x_{ij}^{U} - x_{ij}^{L}\right) \leq 0 \ , j = 1,2,\cdots,n$$

$$p_{rj} - u_r \geq 0\,, r = 1,2,\cdots,s; j = 1,2,\cdots,n$$

$$q_{ij} - v_i \geq 0\,, i = 1,2,\cdots,m; j = 1,2,\cdots,n$$

$$u_r \; and \; v_i \geq \varepsilon \quad \forall \mathrm{r, i}$$

In the above model, if the lower and upper bounds of an interval number are equal, i.e. a crisp value, the model will transform again to a normal CCR model. So, if we set the level of outputs and inputs in favour of the under-evaluation unit of j_0, which means we consider all the outputs in their highest level and inputs in their lowest level then through model 3 we can obtain the upper bounds of our efficiency scores.

$$\max \quad D_{j0}^{U} = \sum_{r=1}^{s} u_r y_{rj}^{u}$$

$$s.t. \ \sum_{i=1}^{m} v_i x_{ij0}^{L} = 1$$

$$\sum_{r=1}^{s} u_r y_{rj0}^{U} - \sum_{i=1}^{m} v_i x_{ij0}^{L} \leq 0 \ , \qquad Model\ (3)$$

$$\sum_{r=1}^{s} u_r y_{rj}^{L} - \sum_{i=1}^{m} v_i x_{ij}^{U} \leq 0 \ , \qquad j = 1,2,\cdots,n \ and \ j \neq j_0$$

$$u_r \; and \; v_i \geq \varepsilon \quad \forall \mathrm{r, i}$$

Similarly, if we set the level of outputs and inputs extremely against the under-evaluation unit of j_0, which means we consider all the outputs in their lowest level and all the inputs in their highest, then through model 4 we can obtain the lower bound of our efficiency scores.

$$\max \quad D_{j0}^{L} = \sum_{r=1}^{s} u_r y_{rj}^{l}$$

$$s.t. \sum_{i=1}^{m} v_i x_{ij0}^{U} = 1$$

$$\sum_{r=1}^{s} u_r y_{rj0}^{L} - \sum_{i=1}^{m} v_i x_{ij0}^{U} \leq 0 \ , \qquad Model\ (4)$$

$$\sum_{r=1}^{s} u_r y_{rj}^{U} - \sum_{i=1}^{m} v_i x_{ij}^{L} \leq 0 \ , \qquad j = 1,2,\cdots,n \ and \ j \neq j_0$$

$$u_r \ and \ v_i \geq \varepsilon \quad \forall \mathrm{r, i}$$

By calculating the above boundaries of efficiency, we can confirm that efficiency scores higher than D_{j0}^{U} or lower than D_{j0}^{L} for unit j_0 cannot be obtained regardless of the variable values assigned.

5.3 Numerical Example

One detailed application of the proposed FA-PCA-DEA methodology that has been described in previous sections is presented in this section to demonstrate the approach and deal with nuances in different steps of this approach. Firstly, a new case enters and in order to suggest a dose plan prescription to oncologists, all the other existing cases in our case pool compete with each other. The most efficient case evaluated by the FA-DEA approach is the winner to be prescribed as the solution to the new case. Our data set consists of 49 real case scenarios and information about prostate cancer patients, treated by Gamma-ray radiotherapy at Nottingham University Hospital. In order to choose a new case, we select one of these cases as a new case and the other 48 cases remain the case pool. This way we can compare the final result obtained from FA-DEA with the actual prescription of the case and measure the precision and success rate of

the system. Every one of the cases in the case pool has been considered as a DMU in this research. Based on the nature of the attributes in the data set they were divided into input and output criteria. Table 5.1 shows the features and criteria used in the suggested solution for selecting the best radiotherapy dose plan.

Table 5.1 Input and output criteria used for efficiency evaluation

Criteria	**Explanation**	**Input/Output**
Gleason Score	A parameter which defines the grade of cancer, lower the amount, the lower risk of cancer is	Input
PSA-B	Prostate Specific Antigen before the treatment, this protein is elevated in men's blood if the prostate is cancerous	Input
D1	The distance of radiation dose received by 66% of the rectum to standard limitation based on DVH values	Input
D2	The distance of radiation dose received by 50% of the rectum to standard limitation based on DVH values	Input
D3	The distance of radiation dose received by 25% of the rectum to standard limitation based on DVH values	Input
D4	The distance of radiation dose received by 10% of the rectum to standard limitation based on DVH values	Input
Similarity Measure	The similarity of the new case with previous cases in the data set, calculated through Cased-Based Reasoning	Input
Dose I	Dose plan applied to a case in the first phase of the treatment	Output
Dose II	Dose plan applied to a case in the first phase of the treatment	Output
Success rate	How successful the treatment is, based on PSA measurement 2 years after the treatment	Output

In above table Gleason Score (GS) and PSA values before the treatment are parameters regarding the stage of cancer and D1, D2, D3 and D4 are parameters regarding risk assessment of the treatment. As previously mentioned rays also damage surrounding organs, among all rectum, is the most vulnerable one and thus, is a priority to control for side effect damage. DVH values determined how much of the radiation is being absorbed by the 66, 50, 25 and 10% of the rectum. As an example, if the DVH value in phase I of the treatment states that 66% of the rectum will receive 55% and 45% of

the radiation in phase I and II of the treatment respectively and dose plan is 46Gy in first and 24Gy in second phase of the treatment then based on follow D1 is calculated:

$$D1 = Standard\ limitation\ for\ 66\% - [(55\% \times 46) + (45\% \times 24)]$$

As previously explained (section 1) oncologists are not so precise about the amounts of various criteria when they make a decision about a dose plan. For example, similarities above 90% between two cases is acceptably high or in case of distance to standard recommendations, there is not a meaningful difference between 0.2 and 0.5 Gy. Therefore, in this research, the crisp criteria are transformed into grey numbers to reflect the uncertainty of oncologists' judgments.

The transformation of data into interval grey numbers is based on table 5.2 where the original amount, linguistic terms and interval grey numbers allocated to them are elucidated based on consultation with experts.

Table 5.2 Linguistic terms and values respect to original amounts of data

Criteria	Original value	Linguistic term	Grey number
Similarity	≥ 90%	Very High (VH)	[8 9]
	[80 to 90) %	High (H)	[7 8]
	[75 to 80) %	Medium High (MH)	[6 7]
	[70 to 75) %	Medium (M)	[5 6]
	[60 to 70) %	Low Medium (LM)	[3 5]
	< 60%	Low (L)	[1 3]
PSA-B	> 30	Very High (VH)	[8 9]
	[22 to 30)	High (H)	[7 8]
	[15 to 22)	Medium High (MH)	[5 7]
	[9 to 15)	Medium (M)	[3 5]
	[0 to 9)	Low (L)	[1 3]
Distances to recommended standard limitations	[0 to 1]	Excellent (EX)	[8 9]
	[1 to 3.5)	Very Good (VG)	[7 8]
	[3.5 to 5.5)	Good (G)	[5 7]
	[5.5 to 9.5)	Fair (F)	[3 5]
	> 9.5	Poor (L)	[1 3]
Success rate (PSA value after 2 years)	[0 to 0.4]	Excellent (EX)	[8 9]
	[0.4 to 0.8)	Very Good (VG)	[7 8]
	[0.8 to 1.6)	Good (G)	[5 7]
	[1.6 to 2.4)	Fair (F)	[3 5]
	> 2.4	Poor (L)	[1 3]

5.3.2 Procedure for FA-DEA

In this research, the importance level of criteria is not the same. Through oncologist opinions about the inputs and outputs, the importance weight of each criterion in linguistic terms, the grey number assigned to it and normalized amount of it is shown in table 5.3. The importance of these criteria is relative to each other. In order to normalize them, they will be divided by the maximum amount existing in each criteria type.

Table 5.3 importance weights of criteria

Type of criteria	Criteria	Linguistic term	Grey value	Normalized weight
Input				
	Similarity	High Importance	[8, 9]	[0.88, 1]
	Distances	Medium High Importance	[6, 7]	[0.66, 0.77]
	G.S	Low Importance	[1, 3]	[0.11, 0.33]
	PSA	Low Importance	[1, 3]	[0.11, 0.33]
Output				
	Dose in Phase I	Medium Importance	[3, 5]	[033, 0.55]
	Dose In phase II	Low Importance	[1, 3]	[0.11, 0.33]
	Success Rate	High Importance	[8, 9]	[0.88, 1]

After that, the normalized weights are being multiplied by decision matrix to obtain the weighted decision matrix. With weighted inputs and outputs, the following 4 steps are required:

(1) Standardizing and normalizing the decision matrix; preparing it for PCA.

(2) Applying PCA on the decision matrix of inputs and outputs separately. Computing the PCs and eigenvalues corresponding to them.

(3) Selecting the sufficient PCs, account for the inclusion of data more than 75 percent, and calculating factor loadings and factor values of each case by use of PCs.

(4) Normalizing the factors, and calculating upper bound and lower bound of each case (unit) efficiency by interval DEA.

5.3.3 Principal Components

Noting that the decision matrix we have for both input and output criteria are in different scales and belonging to different types of benefit (the higher the better) and cost (the lower the better) criteria, first we need to standardize and normalize the data

set before starting the PCA procedure. First, by using the equation 41 cost criteria (i.e. PSA-B and G.S) are inverted into benefit criteria.

$$G_{ij}^{s} = [Max\overline{G}_j - \overline{G}_{ij}\,, Max\overline{G}_j - \underline{G}_{ij}]\,; \quad \text{for} \quad i = 1,2,\cdots,n \quad \text{and} \quad j = 1,2,\cdots,p \qquad (41)$$

Where G_{ij}^{n} is the standardized element in the standard decision matrix and $Max\overline{G}_j$ is the maximum upper bound of the criterion j.

After that, there is need to normalize the decision matrix so that each criterion has mean and variance equal to zero and 1 respectively. The decision matrix is being normalized through equation 42.

$$G^{n} = \left[G_{ij}^{n}\right] = \frac{G_{ij}^{s} - E(G_j)}{\sqrt{Var(G_j^{s})}} = \left[\frac{\underline{G}_{ij}^{s} - E(G_j^{s})}{Var(G_j^{s})} - \frac{\overline{G}_{ij}^{s} - E(G_j^{s})}{Var(G_j^{s})}\right] : \text{for } i = 1,2,\cdots,n \;\&\; j = 1,2,\cdots,p \qquad (42)$$

Where G_{ij}^{n} is the normalized element in our final normalized decision matrix which the PCA procedure will be applied on. Through equation 19 we compute the covariance matrix from G^{n}, which here due to normalization is also the correlation matrix between our grey variables. By eigendecomposition of the correlation matrix, we finally have the PCs and the corresponding eigenvalues for input and output variables separately, determining how much of information representing by original variables is being summarized by each of them, which are shown in tables 5.4 and 5.5.

Table 5.4 Input PC variances and inclusion percentages

PCs, Input	PC variences	Cumulative Inclusion%
PC1	1.9784	28.26
PC2	1.3077	46.95
PC3	1.1413	63.24
PC4	0.9515	76.85
PC5	0.8125	88.46
PC6	0.5828	96.78
PC7	0.2256	99.99

Table 5.5 Output PC variances and inclusion percentages

PCs, Output	PC variences	Cumulative Inclusion%
PC1	1.3281	44.27
PC2	0.9854	77.12
PC3	0.6865	100

The first four PCs of the input variables can be accounted for more than 76 percent of the input information and respectively the first two PCs of the output variables include more than 77 percent of the output information. So hereby, they are chosen to form the factors.

5.3.4 Factor Analysis

Selecting the first four and two PCs for inputs and outputs respectively to compute the factors and by having PC coefficients and variances (eigenvectors and eigenvalues obtained from the eigen decomposition of the correlation matrix), the model 1 to 4 was

applied to calculate the un-rotated factors. The Factor Analysis model for input variables is based on:

$$G_1^{In} = -0.1976F_1^{in} - 0.5193F_2^{In} - 0.1543F_3^{In} + 0.3875F_4^{In}$$
$$G_2^{In} = -0.1203F_1^{in} + 0.4597F_2^{In} - 0.1544F_3^{In} + 0.6696F_4^{In}$$
$$G_3^{In} = 0.2541F_1^{in} - 0.4801F_2^{In} + 0.0183F_3^{In} + 0.2773F_4^{In}$$
$$G_4^{In} = -0.4297F_1^{in} + 0.0550F_2^{In} - 0.0666F_3^{In} - 0.0723F_4^{In}$$
$$G_5^{In} = -0.4379F_1^{in} - 0.2223F_2^{In} - 0.0173F_3^{In} - 0.2079F_4^{In}$$
$$G_6^{In} = -0.0915F_1^{in} - 0.0219F_2^{In} + 0.5978F_3^{In} + 0.5207F_4^{In}$$
$$G_7^{In} = -0.0515F_1^{in} + 0.0184F_2^{In} + 0.6828F_3^{In} - 0.2366F_4^{In}$$

In the above equations, G_p^{In} is the Grey input variable described by four input Factors of. $F_{1,2,3,4}^{In}$ The Factor Analysis model for output variables is also based on follow:

$$G_1^{Out} = -0.1794F_1^{Out} + 0.9854F_2^{Out}$$
$$G_2^{Out} = -0.6014F_1^{Out} - 0.1340F_2^{Out}$$
$$G_3^{Out} = 0.5992F_1^{Out} + 0.1606F_2^{Out}$$

In the above equations, G_e^{Out} is the Grey output variable described by two output Factors of F_1^{Out}.

To obtain simpler and more interpretable Factors, by using Varimax rotation with Kaiser normalization criterion (section 2.7), the rotated factors were calculated for input variables as following:

$$G_1^{In} = -0.1812F_1^{in} - 0.6622F_2^{In} - 0.035F_3^{In} + 0.0978F_4^{In}$$
$$G_2^{In} = 0.0501F_1^{in} + 0.0056F_2^{In} - 0.0123F_3^{In} + 0.8339F_4^{In}$$
$$G_3^{In} = 0.2551F_1^{in} - 0.5444F_2^{In} + 0.0437F_3^{In} - 0.0943F_4^{In}$$
$$G_4^{In} = -0.432F_1^{in} + 0.0716F_2^{In} - 0.0196F_3^{In} + 0.0723F_4^{In}$$
$$G_5^{In} = -0.4906F_1^{in} - 0.0816F_2^{In} + 0.0004F_3^{In} - 0.1931F_4^{In}$$
$$G_6^{In} = 0.0716F_1^{in} - 0.2229F_2^{In} + 0.7037F_3^{In} + 0.2953F_4^{In}$$
$$G_7^{In} = -0.0299F_1^{in} + 0.2266F_2^{In} + 0.6150F_3^{In} - 0.3077F_4^{In}$$

As can be seen, before rotation most of the variables were depended on more than two factors by having factor coefficients higher than 0.1, while after rotation other factors can be described by one or two factors. In the final step of Factor analysis by applying formula 33, the Final factors are computed based on variables to apply them within interval DEA and calculate the efficiency score for each of the cases. The Factors which are shown below and in table 5.6 show the results after multiplication of variable coefficients by the normalized interval grey variable values.

Input Factors:

$$F_1^{In*} = -0.3906G_1^{In} - 0.0583G_2^{In} + 0.4787G_3^{In} - 0.8380G_4^{In} - 0.9110G_5^{In} - 0.0127G_6^{In} - 0.0665G_7^{In}$$

$$F_2^{In*} = -0.7909G_1^{In} + 0.1372G_2^{In} - 0.6576G_3^{In} + 0.0781G_4^{In} - 0.1491G_5^{In} - 0.2055G_6^{In} + 0.2367G_7^{In}$$

$$F_3^{In*} = -0.0324G_1^{In} + 0.0004G_2^{In} + 0.0087G_3^{In} + 0.0314G_4^{In} + 0.0609G_5^{In} + 0.7924G_6^{In} + 0.7178G_7^{In}$$

$$F_4^{In*} = 0.0400G_1^{In} + 0.9126G_2^{In} - 0.2351G_3^{In} + 0.1705G_4^{In} - 0.1356G_5^{In} + 0.2723G_6^{In} - 0.3053G_7^{In}$$

Output Factors:

$$F_1^{Out} = -0.2383G_1^{Out} - 0.7988G_2^{Out} + 0.7958G_3^{Out}$$

$$F_2^{Out} = 0.9711G_1^{Out} - 0.1321G_2^{Out} + 0.1583G_3^{Out}$$

Table 5.6 Final factors values respect to each case

	F_1^{In*}	F_2^{In*}	F_3^{In*}	F_4^{In*}	F_1^{out}	F_2^{out}
C1	[0.080,2.534]	[-2.207,-0.12]	[-2.335,2.482]	[-0.064,0.159]	[0.21,0.25]	[0.411,1.33]
C2	[0.570,2.905]	[-0.381, 1.332]	[-3.765,-1.084]	[-0.126,-0.119]	[0.21,0.25]	[0.411,1.33]
C3	[-2.932,-0.329]	[-1.923, 0.007]	[-2.059,3.017]	[-0.110,0.057]	[0.826,0.85]	[-2.099,-1.114]
C4	[-0.432,1.903]	[-0.474, 1.574]	[-2.272,2.545]	[-2.131,-1.76]	[-3.143,-1.058]	[-1.688,-0.998]
C5	[-3.072, -1.07]	[-0.306, 1.763]	[-1.992,3.08]	[0.220,0.220]	[0.21,0.25]	[0.411,1.33]
C6	[0.566, 2.967]	[-2.683, -0.649]	[-2.335,2.468]	[-0.398,-0.383]	[-1.613,-0.664]	[0.256,0.991]
C7	[-0.511, 1.835]	[0.971, 2.814]	[-2.319,2.491]	[2.099,2.373]	[0.21,0.25]	[0.411,1.33]
C6	[-2.331, 0.199]	[-0.705, 1.079]	[-2.015,3.066]	[-0.164,-0.004]	[0.6508,0.6509]	[-1.381,-0.299]
C9	[0.222, 2.477]	[1.887, 3.618]	[-2.275,2.54]	[0.238,0.268]	[-3.543,-1.498]	[0.104,0.631]
C10	[0.688, 3.065]	[-0.884, 0.986]	[-2.428,2.123]	[-0.165,-0.042]	[0.298,0.35]	[0.052,0.922]
C11	[-2.182, 0.070]	[-1.68, 0.53]	[-2.363,2.181]	[-0.054,0.011]	[0.6508,0.6509]	[-1.381,-0.299]
C12	[-2.146, 0.094]	[-1.807, 0.445]	[-2.62,1.795]	[0.055,0.17]	[0.298,0.35]	[0.052,0.922]
C13	[-3.072, -1.07]	[-0.306, 1.763]	[-1.992,3.08]	[0.220,0.220]	[0.826,0.85]	[-2.099,-1.114]
C14	[-3.459, -1.218]	[-2.204, -0.204]	[-2.542,1.859]	[-0.181,-0.139]	[0.6508,0.6509]	[-2.099,-1.114]
C15	[1.869, 4.1]	[-1.307, 0.612]	[-2.19,2.886]	[-0.45,-0.389]	[0.21,0.25]	[0.411,1.33]
C16	[-4.285, -2.143]	[-0.63, 1.524]	[-2.172,2.636]	[2.324,2.773]	[0.6508,0.6509]	[-1.381,-0.299]
C17	[1.905, 4.112]	[-1.434, 0.57]	[-2.319,2.5]	[-0.395,-0.225]	[0.21,0.25]	[0.411,1.33]
C18	[-2.085, 0.172]	[-1.864, 0.306]	[-2.235,2.566]	[-2.226,-1.886]	[-0.833,-0.277]	[0.323,1.13]

5.3.5 Interval DEA

To evaluate the efficiency of each treatment plan we have applied CCR-DEA model (section 2.8). Due to the inability of CCR-DEA models to handle negative values which we have in the factors, a normalization has been done based on the following formula:

$$F_{ij}^{n} = F_{ij}^{in*or\ out} - MinF_{j}^{in*/out} + 0.5$$

In above normalization, each element in one factor is subtracted by the minimum value existing in the factor *j* and then to avoid zero amounts in each factor a constant value of 0.5 is added to each of them. Such a normalization has been applied in several research projects dealing with negative values in DEA (255). By applying models 7and 8, (section 2.8), for upper and lower bound of the DMUs efficiency scores the efficiency results were calculated (table 5.7). As can be seen when the outputs and inputs are set in favour of each treatment plan all treatment plans are completely efficient. When the situation is critical and all the uncertain decisions made by oncologists are against the treatment plans, only case 18 with dose plan of 50Gy in the first and 20Gy in the second phase is efficient and thus the case 18 will be suggested to oncologist as the best treatment plan.

Table 5.7 Lower and upper bounds of efficiency scores

DMUs (treatment plans)	Lower bound of efficiency	Upper bound of efficiency
C1	0.4142	1
C2	0.5876	1
C3	0.5584	1
C4	0.1256	1
C5	0.5334	1
C6	0.3609	1
C7	0.3025	1
C6	0.5066	1
C9	0.2425	1
C10	0.3469	1
C11	0.5147	1
C12	0.4661	1
C13	0.6036	1
C14	0.6732	1
C15	0.3637	1
C16	0.4976	1
C17	0.3627	1
C18	1	1

5.4 Discussion

In this section, we try to analyse the factors and determine their characteristics. At first, we investigate the communalities described by each variable and overall FA model for input and output variables. Commonality can be interpreted as the proportion of variance accounted for by each variable. In order to compute the commonality of a variable, we need to sum the squared factor loadings of the variable. In the un-rotated model (9) for input variables the commonalities are 0.482, 0.695, 0.372, 0.197, 0.285, 0.6373 and 0.525 respectively for the 7 input variables. Also, large and moderate factor

loadings can indicate how a factor is related to a variable and factors which are related at least to one and maximum two variables are our desirable factors and loading factors more than 0.5 can be interpreted as moderate or large. So higher loading factors related to a variable is favourable. As can be seen in model 9 and 11, after Varimax rotation the balance of loadings has become in favour of some factors in most of the variables and provided for a better solution to interpret each factor. Also, the amount of communalities remained the same as it should be. The diagrams depicted in figure 5.4 show the differences between loadings before and after Kaiser Varimax rotation.

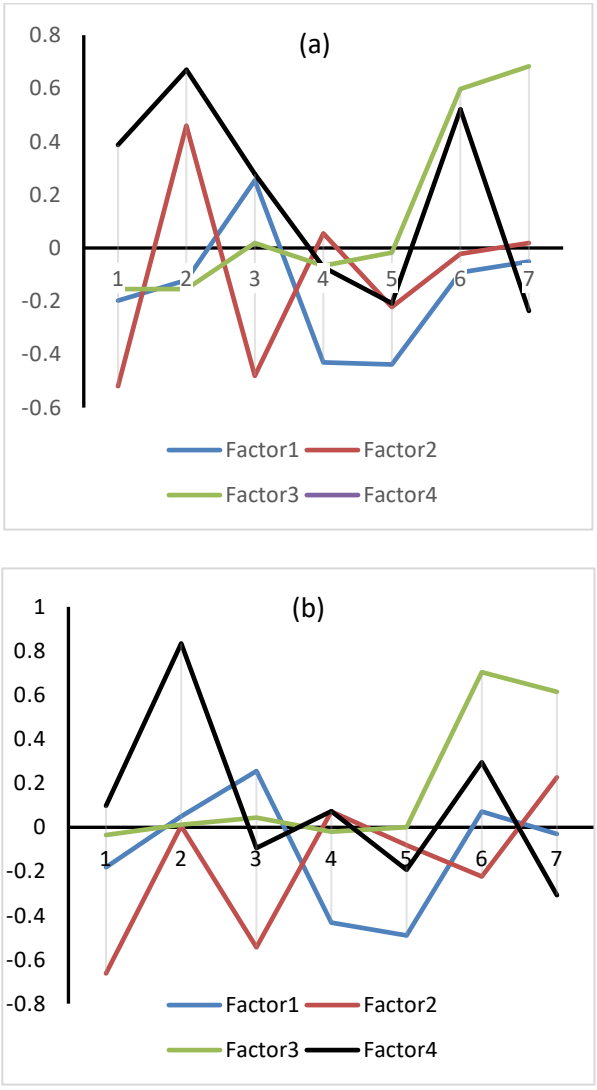

Figure 5.4 Factor loadings before (a) and after (b) the rotation

Figure 4(a) is showing the factor loadings before and figure 4(b) after the rotation where the number of loadings with amounts of more than 0.5 are reduced as a result of rotation and the amounts of remaining loadings more than 0.5 are increased which can help us by relating the factors to variables.

To determine the characteristics of factors applied in DEA, we use model 10 and 11 for output and input variables respectively. Starting with output factors, the first factor has big loadings on the second and third variable, dose plan in second phase and success rate. Due to the approximately equal positive value of success rate and negative value of second phase dose plan loadings, it can be said that this factor is associated with success rate and is in contrast with amount of dose plan in the second phase. The second factor is only highly associated with the dose plan in the first phase of the treatment. As the dose plan in the first phase of the treatment increases, oncologists apply lower amounts of radiation in the second plan and the success rate in these scenarios is usually higher due to more effective treatment; the factor analysis supports this observation.

Regarding our input factors, the first factor has only relatively low moderate loading in fourth and fifth variables, distances to standard recommendations for 50% and 66% of the rectum. Because of their negative values, this factor can be labelled as slightly opposite of the Distances to standard recommendations for 50% and 66% of the rectum. Similarly, the second factor can be labelled as the moderate opposite of similarity measure and distance to 25% of the rectum with slightly more importance of similarity measure. The third factor has a strong association with G.S and PSA before the treatment. The fourth factor only has high loading in the second variable, distance to standard recommendations for 10% of the rectum. Also by summation of individual commonalities, the total commonality can be estimated and it indicates how much of

the variation in original data is explained by the factor model. For output variables, this summation is 1.7577 out of 3 (the overall variance of output data). So factor model describes 58.59% of the variances in output data.

5.5 Overall results and success rate of the approach

In order to assess the approach of interval FA-DEA, the same leave-one-out strategy which was used in previous chapters was applied. A case was pulled out of the dataset and was treated like a new case. The result obtained was compared with the original result that was prescribed by oncologists. However, the success rates of the treatment (PSA values 5 years after the radiotherapy) were available for only 49 cases of our case pool; thus, the result comparison of different approaches was performed considering these 49 cases (table 5.8).

Table 5.8 Comparison of the proposed methodology of interval FA-DEA with other approaches

	Simple CBR	CBR+TOPSIS	CBR+TOPSIS + GP	Interval FA+DEA
Number of successful obtained cases	34 out of 49	38 out of 49	43 out of 49	43 cases out of 49
Number of cases with better dose plan	9	12	21	16
Success rate (%)	69.38	77.55	87.75	87.75

The application of interval FA-DEA results in 43 successful dose plan prescriptions which is higher than CBR and CBR-TOPSIS methods and equal to CBR-TOPSIS-GP approach. However, the number of cases with better dose plans is less than CBR-

TOPSIS-GP which is due to not performing the optimization process in this approach and using only evaluation of cases. The obtained results are demonstrating the effectiveness of the proposed approach.

5.6 Conclusion

This chapter has presented a hybrid approach of FA with the help of PCA and DEA to help oncologists with dose planning in radiotherapy for prostate cancer. In previous chapters, in the process of MCDM approach in order to assess different cases, all criteria were treated in the same way. This chapter demonstrates that classifying them in two categories of input and output delivers improved results. Thus, DEA was chosen to evaluate the cases as it is a non-parametric method based on multiple inputs and outputs to obtain the efficiency of available options. Moreover, in order to capture the uncertainty that oncologists have in their judgments in real life scenarios while dealing with values of different factors (human imprecise evaluation), we used grey numbers and adjusted our system as close as possible to real life oncologists' way of thinking.

Applying more criteria, inputs and outputs, in DEA makes the methodology to consider more dimensions of the problem and thus result in more comprehensive answers, however, due to characteristics of DEA, while the accumulative number of inputs and outputs increase in comparison to DMUs, it can be problematic because of weak discrimination among DMUs. We initially used 7 inputs including the similarity measure obtained from CBR and 3 outputs including a new criterion of the success rate of the treatment. To solve the problem, we applied FA based on Principal Components to reduce the dimensions of the problem. Because of using grey numbers, we developed the FA for grey numbers and we presented the novel hybrid approach of interval FA-DEA. The approach was tested on a real dataset collected from Nottingham University Hospital consisting of 49 cases and the results were compared with previous

approaches applied in chapters three and four. The results show the effectiveness of the proposed approach and demonstrate its applicability for prostate cancer dose planning. The detailed numerical example presented can be a guide for other researchers to apply the interval FA-DEA in other domains.

Chapter 6

New similarity measures and mechanism for feature weight assigning

6.1 Introduction

In previous chapters, CBR in collaboration with MCDM techniques has been applied to present a solution to radiotherapy dose planning problem. However, the weights applied for each feature of the case-base reasoning, to calculate the similarity measure, have been considered equally. In real-life problems, the decision makers can take into account different weights for each feature of the problem. Moreover, in various situations based on the circumstances, some features play a more significant role than others. Prostate cancer dose planning in a similar way to the other real-life problems can benefit from different weight features.

On the other hand, the similarity between a new case and an existing case in the case pool has been calculated through CBR with Euclidean distances. When researchers are confronted with the problem of low predictive rate of CBR, the common approaches to increase the accuracy of the case retrieval are assigning weights to features or changing the features selection strategy (256). However, in addition to feature weight optimization, application of different types of distances for similarity calculation other than Euclidean distance has also been suggested through literature (257-261). The Euclidean distance is independent of the data distribution (262), in presence multiple dimensions may cause a poor performance for CBR and as it uses square root to

measure a geometrical distance, its performance is only reliable in a linear domain where the attributes of the problem have linear or near linear relation to each other. Moreover, in CBR many researchers have found the fact that due to characteristics of the data set some methods may perform with better precision or can provide a better explanation for a part of the search space (263). Thus, using other similarity methods or a combination of them may improve the accuracy of the predictions in complex systems (264).

To this end, to cover the two mentioned problems in this chapter, we present two new similarity calculation approaches i.e. similarity measure based on Grey Relational Analysis (GRA) and Gaussian CBR. Also, to find the most appropriate set of weights for each feature and increase the precision of the system a Genetic Algorithm (GA) based feature weight selection is being performed for each new distance. GRA is a mathematical approach that is distinguished with excellent performance while the number of variables is high in comparison to the data and can efficiently describe the relationship between two series of information as well as avoiding the subjective setting of parameters within the model (257).

Also, when the problem space shows non-linear characteristics, non-linear Gaussian transformation can transform the space into linearly separable space and therefore enhance the effectiveness of finding similar neighbours (265). The radiotherapy dose planning problem suffers from both of the aforementioned issues i.e. a high number of variables and non-linearity among different features. In our problem and similarity measuring operation we have 14 different features and usually, the number of cases in the dataset is not sufficient for this quantity of features. The relation among the features is also not linear, e.g. there is no specific global linear relation between the increase in PSA value and Gleason Score in various cases.

Application of a heuristic model in order to determine the optimal weights for features of the CBR has been successfully applied throughout the literature in medical and other domains. Ahn and Kim (266) used GA for weight assigning of the features in a CBR problem of bankruptcy prediction n and obtained successful results and improvement in the precision of the predictions. Wu et al. (258) developed a hybrid model of CBR system for estimation of software effort failure by applying a different type of distances for CBR and obtaining the optimal weights of the features by Particle Swarm Optimization (PSO) technique. Inbarani et al. (267) applied PSO on a feature retrieval model regarding a diagnosis data set to improve the efficiency of the retrieval process. A complete literature of the recent body of research regarding the hybrid application of heuristic algorithms and CBR in radiotherapy treatment has been provided in chapter 2, sections 2.2 and 2.3.

GA has received remarkable attention among researchers due to its unique characteristics and advantages. GA is an adaptable technique and does not require a heavy mathematical computational load for the optimization of a model. GA will search for the optimal matter with no regards of the specific problem function and can be applied to a wide range of linear or non-linear, discrete or continuous and defined or mixed search spaces (268). Evolutionary nature of GA makes it effective to run a better global search than many other heuristics as well as reducing the computational effort. Also, GA has the ability to deal with complex systems and large objective functions and provide a great flexibility to solve hybridized and domain-specific problems (269).

6.2 Methodology

In this section, the applied methodologies, i.e. Grey Relational Analysis, Gaussian distance CBR and Genetic Algorithm are explained in detailed for use in radiotherapy dose planning problem.

6.2.1 Grey Relational Analysis

Grey system theory has been introduced by Deng (240) in 1982 and has the capability to deal with both known and unknown information. GRA is part of the grey system theory which is distinguished by the ability to deliver excellent performance in presence of problems with a high number of variables. The main goal in GRA is to undertake a comparison between two sequences to measure the similarity or difference between them (270).

Assuming two objective and reference sequences as:

Objective sequence: $X_0(k) = \{X_0(1), X_0(2), \cdots, X_0(k)\} \quad k = 1,2, \cdots, n;$

Reference sequence: $X_i(k) = \{X_i(1), X_i(2), \cdots, X_i(k)\} \quad k = 1,2, \cdots, n; \quad and\ i = 1,2, \cdots, m;$

To obtain the grey similarity between two series, the following steps should be followed.

Step 1: Normalization of the objective and reference sequences based on the features nature, if the feature belongs to cost or benefit criteria (the lower or higher values are more desirable respectively) or values closer to the Desired Amount (DA) are more favourable:

$$R_i(k) = \frac{X_i(k) - \min(X_i(k), i = 1,2, \cdots, m)}{\max(X_i(k), i = 1,2, \cdots, m) - \min(X_i(k), i = 1,2, \cdots, m)} \qquad (1)$$

$$R_i(k) = \frac{ma\,x(X_i(k), i = 1,2,\cdots,m) - X_i(k)}{\max(X_i(k), i = 1,2,\cdots,m) - \min(X_i(k), i = 1,2,\cdots,m)} \quad (2)$$

$$R_i(k) = 1 - \frac{|X_i(k) - DA|}{\max\{\max(X_i(k), i = 1,2,\cdots,m) - DA, DA - \min(X_i(k), i = 1,2,\cdots,m)\}} \quad (3)$$

Step 2: Calculating the grey coefficient between the objective sequence and the reference sequence applying equation 4.

$$\gamma = \frac{\min\limits_i \min\limits_k \Delta_{0i} + \zeta \max\limits_i \max\limits_k \Delta_{0i}}{\Delta_{0i} + \zeta \max\limits_i \max\limits_k \Delta_{0i}} \quad (4)$$

Where $\Delta_{0i} = |R_0(k) - R_i(k)|$, and ζ is the distinguished coefficient ($\zeta \in [0,1]$). Adopting different values for distinguishing coefficient results in compressing or expanding the range of grey relational coefficient and usually $\zeta = 0.5$ is being used by researchers.

Step 3: Calculating the grey relational degree between a reference sequence and the objective sequence based on equation 5:

$$\Gamma_i = \sum_{k=1}^{n} w_k \gamma(R_0(k), R_i(k)) \quad for\ i = 1,2,\cdots,m. \quad (5)$$

The full comparison between the objective sequence and all the reference sequences provides us with a set of similarity measures. The highest grey relational degree indicates the most similar sequence to the objective sequence.

6.2.2 Gaussian similarity measure

In Gaussian distance Cased-Based Reasoning, the Gaussian distance which is a non-linear transformation of Euclidean distance is applied to compute the similarity between a new case and cases in the case pool. This Gaussian transformation indicates

the similarity of the two cases based on each feature. Assuming two cases of C_a and C_b consisting of k features, Equation 6 shows the non-linear Gaussian transformation between them on each feature:

$$g_k(C_a, C_b) = \exp\left[-\left(\frac{d_k(C_a, C_b)}{\sqrt{2} \times \sigma_k}\right)^2\right] \quad (6)$$

Where $g_k(C_a, C_b)$ is the Gaussian indicator between two cases on the *k*th feature, $d_k(C_a, C_b)$ is the distance between the *k*th feature of cases *a* and *b* and is calculated by equation 7 and σ_k is the flexure point and is obtained through equation 8.

$$d_k(C_a, C_b) = |c_{ak} - c_{bk}| \quad (7)$$

$$\sigma_k = \sigma \times (\max c_k - \min c_k) \quad (8)$$

c_{ak} and c_{bk} are the values of cases *a* and *b* over the *k*th feature and $\sigma \in [0, 1]$ is the parameter of flexure point.

Finally, the Gaussian similarity measure between cases *a* and *b* is obtained by integration of the Gaussian indicators based on equation 9.

$$GSIM(C_a, C_b) = \sum_{k=1}^{n} w_k \, g_k(C_a, C_b) \quad (9)$$

Where w_k indicates the importance weight for each Gaussian indicator or case feature.

6.2.3 Genetic algorithm

Genetic algorithms (GA) are stochastic random search techniques providing us with near to optimum solutions for the objective functions of an optimization problem. They are part of the heuristic methods which follow the natural pattern of evolution theory

and were introduced by Barricelli (271). GA functions as an iterative search method, where a new answer is created out of the combination of previously developed answers. There are certain terms in GA which refer to different operations and components of the methodology. *Chromosomes* are candidates for solutions and a feasible set of them creates a *population*. In each iteration of GA, each chromosome is evaluated based on the objective function value and is accordingly assigned with a *survival probability*. The better the solution provided with the chromosome the higher the survival probability assigned to the chromosome. Each of these iterations is called a *generation* and through two operations of *cross over* and *mutation,* the next population is generated. Selection process through survival probability filters the poor chromosomes and increase the probability of participation of fittest members of each generation in the next generation.; simultaneously the cross over and mutation guarantee the development of new chromosomes avoiding the possibility of GA to be trapped in local optima loop (figure 6.1). A typical GA can be executed through the following steps:

Step 0: Generating the initial population based on the population size fitting the problem.

Step 1: Evaluation of each chromosome by obtaining its objective function value. Updating the best solution, maximum or minimum value for objective function according to the problem.

Step 2: Check for the stopping criteria, whether the number of iterations reached a pre-defined maximum or the threshold for fitness function improvement has not been satisfied. If the stopping criteria have been met then stop and return the best value for fitness function as the solution.

Step 3: Define the cross over and mutation process and probability.

Step 4: Create a new generation of parents based on the survival probability mutation, and cross over operations. Go to step 1.

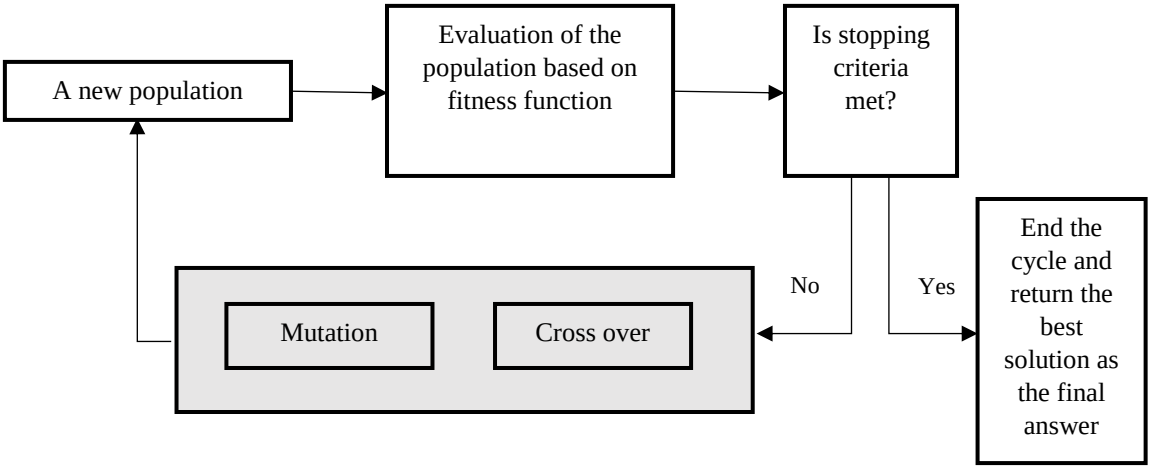

Figure 6.1 Genetic Algorithm procedures

GA operations, namely cross over and mutation provide the situation for the birth of new chromosomes in each generation. Cross over is being done on two chromosomes at the same time and two other chromosomes are being born by the confusion of two parent chromosomes. Cross over probability is a defining factor in this operation which defines the proportion of newly born children with respect to original population. Larger cross over probability allows a wider part of solution space to be searched for a solution; however, it may result in a more time-consuming search. A common type of cross over being performed by many researchers is traditional random point cross over. Assuming there are two parents based on binary coding with 9 genes in each chromosome (figure 6.2). A point of cross over is randomly chosen and the two parents are separated into two parts from there and these two parts are exchanged among the parents two give birth to the new chromosomes.

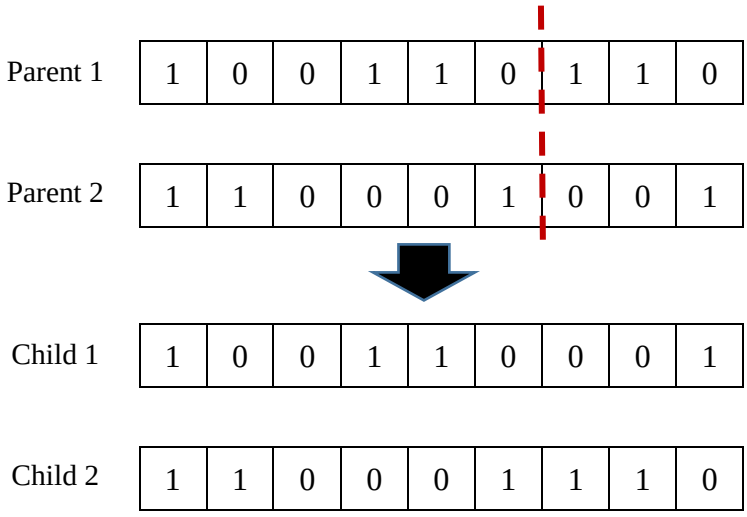

Figure 6.2 Cross Over operation in GA

Mutation operation causes random flips in the value of some genes and inserts the new chromosomes which did not previously exist in the population. The mutation probability determines the proportion of mutated chromosomes in respect of the original population size. Mutation operation is an effective tool to prevent the problem to be trapped in a local optima. The uniform mutation introduced by Michalewicz (272) is a common mutation approach applied by many researchers. Assuming a chromosome with 9 genes has been chosen for the mutation process. A random number *Rand* in the [1, *L*] range, in which L is the length of the chromosome, is extracted and then the gene associated with that number is exchanged (figure 6.3).

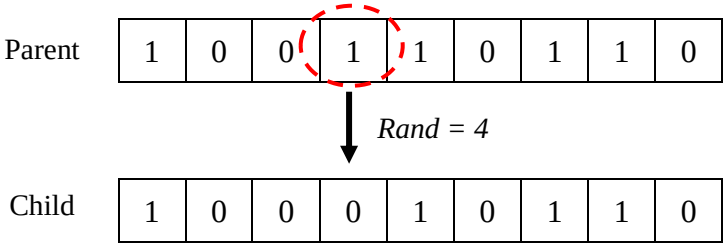

Figure 6.3 Mutation operation in GA

6.3 Problem formulation

In this chapter, in order to improve the efficiency of the CBR system in extracting a better dose plan prescription, firstly a case from the case pool is selected and the similarity measures based on GRA and Gaussian distance CBR with the cases in the case pool are calculated. Thereafter, through a GA optimization problem, the weights for the features involved in calculating the similarity is selected to guide the system towards better answers with higher precision. The similarity measures are computed with the new feature weights and finally, the final prescription is suggested. The overall implementation of the GA in combination with GRA and Gaussian distance CBR (figure 6.4).

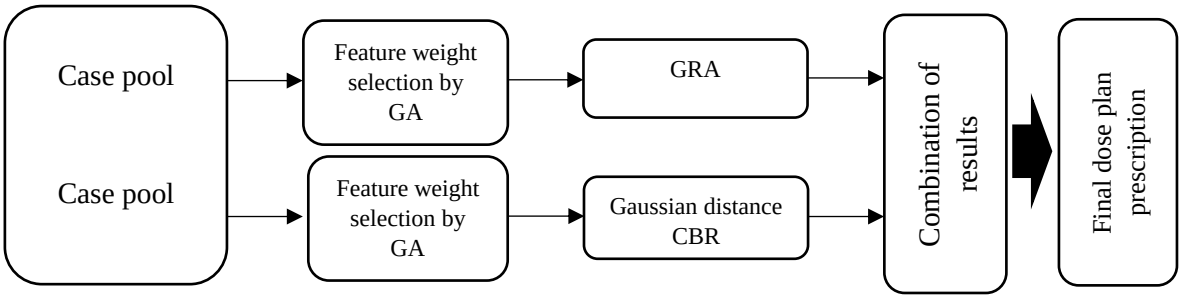

Figure 6.4 Hybrid GA-GRA, GA-Gaussian CBR approach

The feature weight selection mechanism developed for this research is based on the total dose differences of the system. Initially, as the first iteration of the GA, a random weight value is assigned to each feature. Then through GRA or Gaussian distance CBR, the most similar case to each of the cases in the case pool is extracted and the difference between the original dose plan prescribed for the case and the dose plan obtained by the system is calculated. The goal of the GA is to minimize the dose difference between extracted dose plan and the original dose plan for each case in each iteration. The objective function of the GA is defined as equation 10.

$$\min f(w_1, w_2, \cdots, w_n) = \sum_{i=1}^{m} \left(Dose_i^{o,1} + Dose_i^{o,2}\right) - \left(Dose_i^1 + Dose_i^2\right) \quad (10)$$

Where $Dose_i^{o,1}$ and $Dose_i^{o,2}$ are the original dose plan of the case *i* for phase I and II of the treatment respectively. $Dose_i^1$ and $Dose_i^2$ are the obtained dose plans through GRA or Gaussian distance CBR in phase I and II of the treatment respectively and their values is a function of $(w_1, w_2, \cdots, w_n)$ i.e. the weights for each feature of the CBR. The total number of cases in the case pool is *m*.

6.4 Results

In order to demonstrate the efficiency of the proposed methodology, it has been applied on a real dataset from the Nottingham University Hospital. To find the similarity measures among a new case and cases in the case pool 14 features have been applied i.e. fuzzy memberships of low, medium and high regarding the Prostate Specific Antigen (PSA) and Gleason Score, which consists in total 6 of features, the DVH levels in the first and second phase of the treatment for 66%, 50%, 25% and 10% of the rectum which create the rest of the 8 features of the CBR problem. A detailed explanation of each of the features can be found in chapter 3 section 4. The GA procedure has been performed by MATLAB Global Optimization Toolbox GA function on a core i7 3.2 GHz CPU. The efficacy has been measured by leave-one-out strategy in which after calculation of the features weight, a case is being chosen as a new case out of the case base. Then after, the chosen case for the new case based on the similarity measure is being evaluated regarding its dose plan to investigate the succession of the case extraction. The flowchart of the leave-one-out strategy further illustrates the success rate calculation (figure 6.5).

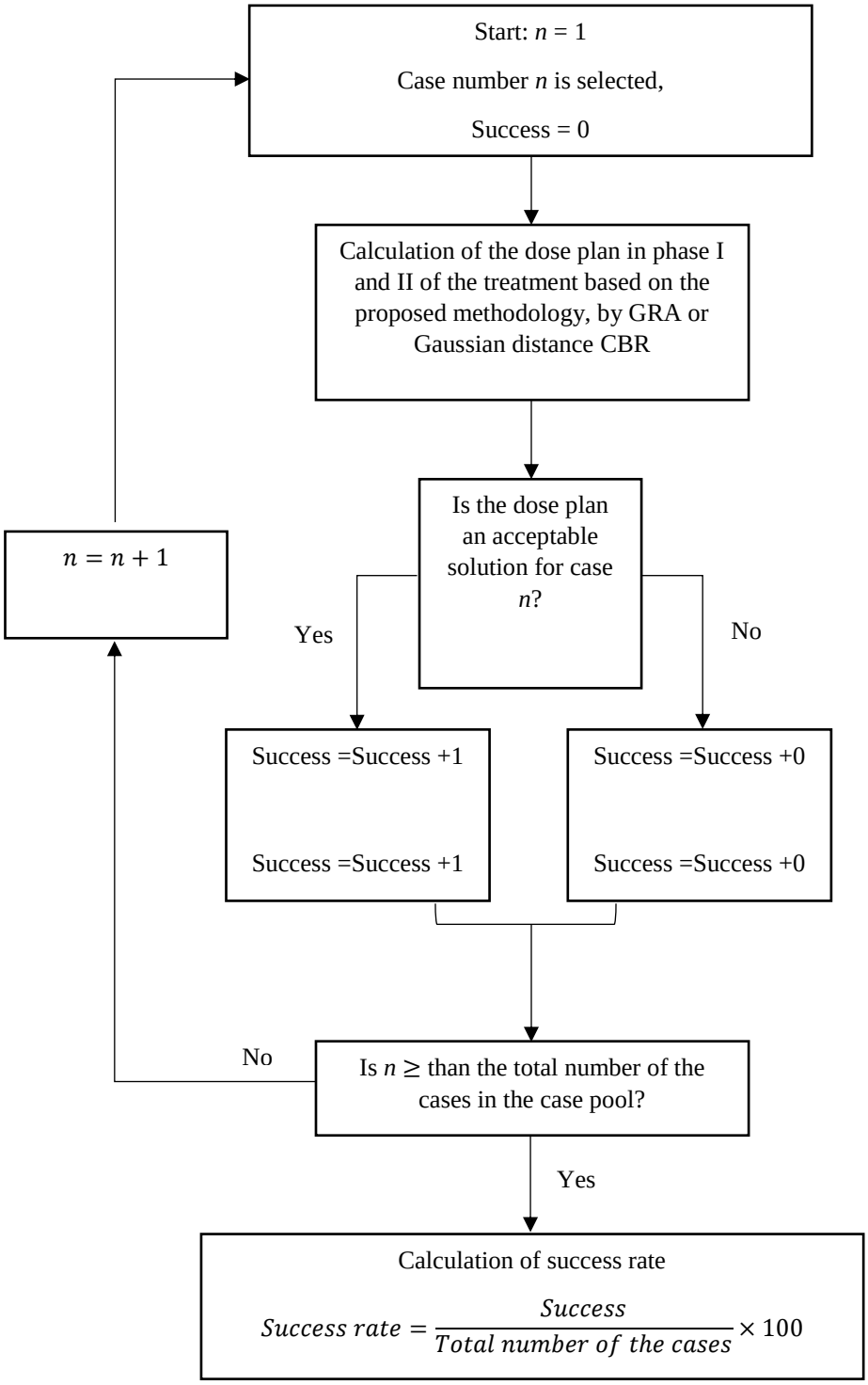

Figure 6.5 Success rate calculation flowchart

There are 69 cases in the database and the experiment has been carried out for all the cases to determine the success rate of the proposed approach. The obtained dose plan of the treatment is considered as a successful result if:

a. The dose plan does not violate the recommended standard dose limit received by each volume of the rectum
b. The total dose plan in phase I and II of the treatment is higher or equal to the dose plan originally prescribed by the oncologists.
c. In situations where the obtained total dose plan is equal to the original dose plan, obtained dose plan in Phase I of the treatment has to be equal or higher than the original dose plan in phase I of the treatment.

Firstly, we have obtained the success rate for each of the FRA and Gaussian distance CBR with equal weights for each feature (table 6.1).

Table 6.1 Success rate of the approaches with equal weights for features

CBR approach	Simple CBR	GRA	Gaussian CBR
Success Rate (%)	73.43	78.26	79.71

As can be seen the application of GRA and Gaussian distance CBR even without any weight selection of the features have improved the results in comparison to Simple CBR by use of Euclidean distance. Through applying GRA, dose plan prescription for 54 out of 69 cases have been done successfully. By applying Gaussian distance CBR, the number of successfully predicted dose plans has been increased to 55 out 69 cases.

The GA with 14 variables, $w_1, w_2, \cdots, w_{14}$ has been implemented by MATLAB 17a version. The initial number of chromosomes in each generation has been chosen as 20 and the stopping criterion has been chosen as if there was no significant improvement in dose difference of the current generation and the previous generation, i.e. 10 for this threshold or the running time exceeds 6 hours. The initial starting point for the GA has been selected as equal weights for all the features i.e. 1/14 (~0.071). The following

weights have been selected as the weight features for each of the GRA and Gaussian distance CBR approaches (table 6.2).

Table 6.2 Features weights obtained by GA

Feature	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}
GRA	0.055	0.035	0.052	0.056	0.059	0.057	0.087	0.05	0.035	0.092	0.02	0.071	0.277	0.056
Gaussian	0.022	0.034	0.035	0.028	0.102	0.043	0.03	0.032	0.032	0.052	0.021	0.03	0.039	0.03

F_k shows each feature of the problem. PSA membership functions of low, medium and high are indexed with k = 1,2,3; Gleason Score membership functions of low, medium and high are indexed with k = 4,5,6; The DVH values in the first and second phase of the treatment for 66%, 50%, 25% and 10% of the rectum are indexed with k = 7,8,9,10 and k =11,12,13,14 respectively.

Using the features' weights calculated by the GA to compute the success rate of the GRA and Gaussian distance CBR has resulted in new success rates (table 6.3).

Table 6.3 Success rate of the approaches with optimal feature weights

CBR approach	GRA	Gaussian CBR	Average similarity of GRA and Gaussian CBR
Success Rate (%)	81.15	82.6	82.6

Applying the feature weight selection mechanism has improved the results of both the CBR approaches and their combination. The average similarity measure for a case obtained from two approaches has been calculated and based on the most similar case the dose plan was assigned to the test case. However, as can be seen the number of successful cases has been similar to Gaussian distance CBR approach.

6.5 Conclusion

In this chapter, an approach based on GRA and Gaussian distance CBR has been developed to help a better case extraction by applying methods which can result in higher precision similarity measures in presence of high number of features for CBR and the non-linear relationships among the parameters of the problem. Additionally, to make the problem more similar to a real-life scenario, different features of the CBR problem have been assigned an importance weight for each of the similarity measuring techniques of GRA and Gaussian CBR. In order to avoid the objective weight assignment by the decision makers, medical planning team, and enabling the system to update the feature weights based on the existing cases in the case pool a GA weight selection mechanism has been proposed. The leave-one-out strategy has been applied on a real data set of the successful prostate cancer cases treated by radiotherapy to measure the success rate of the proposed approaches. Firstly, the results for GRA and Gaussian distance CBR has been carried out with equal weights of the features. The results showed a significant improvement in comparison with Euclidian distance based CBR. Furthermore, the GA features weight assigning mechanism has been adapted to the problem and the success rates have been calculated based on the weighted features. Both of the new CBR approaches showed a better performance in integration with GA and newly obtained weights in the prescription of the successful dose plans. However, the performance of the Gaussian distance CBR was slightly superior to GRA. Finally, the average similarity measures of both approaches have been tested and the efficiency of this approach has shown more promising performance compared to GRA. The results clarify the advantages of a hybrid approach of GA with GRA and Gaussian CBR in providing a better platform for measuring the similarity between the cases and

performing CBR in order to achieve better solutions for radiotherapy dose planning problem.

Chapter 7

7.1 Conclusion

The problem of radiotherapy dose planning involves intricacies and significant complexities, which make it hard to define. A common approach for most oncologists is to rely on radiotherapy planning software to generate an initial dose plan for treatment. These software applications require a considerable amount of information from different teams of radiotherapy departments to generate a useful output. However, while the plans created by software may seem clinically acceptable, in practice they often fail. Moreover, different software may generate different plans which are far too distant from each other (273); thus, software credibility is questionable. In some cases, even the proposed solutions are not acceptable by oncologists due to errors in satisfying their expectations, i.e. prescribing a low dose to respect OARs, while violating dose limit in that case seems necessary to oncologists due to exceptional situation of the patient, or otherwise, prescribing a high dose resulting in a hazardous situation for the patient. Large solution space of the problem, different clinical and environmental conditions of the patients and necessity of trade-offs between risks and benefits of the high radiation in exceptional circumstances are among the factors contributing to the failure of software generated plans.

In real life scenarios, the oncologists make trade-offs between the risks of a high radiative dose plan and the benefits it may cause to effectively eradicate the cancerous cells. Therefore, sometimes the oncologists prescribe a high dose plan, which can even be harmful to other surrounding sensitive organs, such as the rectum in case of the prostate cancer, in order to fight cancer which can be fatal to the patient. This compromising balance among the unavoidable risks is based on oncologists' experiences and cannot be formulated by any mathematical model or operational research technique. There is no common rule about the violation of dose limits in different volumes of the rectum or other surrounding organs. Thus, there is a good chance that subjective decisions of different oncologists also lead to distinctive plans of treatment even about the same patient. Furthermore, various oncologists may consider different weights to different attributes related to clinical and operational factors and this can make the reliable formulation of the radiotherapy dose planning problem even more complicated. Moreover, while oncologists take into account different factors related to operational and clinical criteria of the problem, their judgments about the values of the criteria are not crisp, fixed or certain. There is a certain ambiguity within all human judgment and to follow their true judgment, their perception of a value may be better categorized into a range definable with qualitative words. Grasping the experiences of oncologists dealing with judgment uncertainty is one more problem that needs to be addressed.

Taking into consideration the aforementioned complexities and obstacles, a number of research objectives have been defined in this thesis and throughout the chapters of this research, an effort has been made to accomplish the research objectives. Achieving the defined research objectives can assist oncologists to develop the quality of decisions they are making regarding dose planning and deal with complexities and obstacles.

Investigating the radiotherapy treatment planning problem as well as reviewing the state-of-the-art literature of radiotherapy dose planning with a particular focus on operational researches approaches have been considered as the first objective of this thesis. To achieve this objective, we proceeded to review the radiotherapy planning problem and related research works with operational research background. This provided us with a valuable understanding of the problem, the critical features and parameters involved and the gaps in the previously done researches.

Firstly, an overview of the importance of cancer and its fatality rate both globally and in the UK through recent statistical data has been provided to emphasize the significance of this research. After that, the treatment options have been explained and out of treatment options, the different types of radiotherapy have been introduced. The process of the radiotherapy treatment and different steps necessary for radiotherapy have been described further. Moreover, a comprehensive literature review of the studies based on the type of the problem they focused on and problem description has been presented. Finally, a review of the operational research methodologies which has been applied throughout the literature based on the main problem of their focus has been provided. The operational research methodologies have been divided into two categories optimization techniques and knowledge-based approaches to better distinguish the application of different methodologies.

Exploring the decision-making principles based on which oncologists decide in real-life scenarios and multi-criteria nature of the problem and incorporate them in a Decision Support System (DSS) to assists oncologists with their decisions has been introduced as the second objective of this thesis. Cased-Based Reasoning, a knowledge-based approach which can apply the previous experiences of the oncologists to solve the complex problem of the radiotherapy dose planning has been

selected to prescribe the dose plans. In chapter 3, the problem parameters are used to find the most similar case to a new case and then the dose plan of the exploited case is suggested as the final solution. However, in real-life scenarios, the similarity between two cases cannot be the only determining factor in matching two cases. In order to include other contributing factors, which are taken into account by oncologists in real life, an evaluation process based on TOPSIS has been designed to assess the most similar cases with respect to the multiple criteria and obtained the dose plan of the most appropriate case for the new case.

In chapter 5, to improve the evaluation process of the treatment alternatives (cases in the case pool), the contributing criteria have been divided into two categories of inputs and outputs and DEA has been applied to obtain the efficiency of each of the alternatives. Furthermore, in DEA, in addition to criteria that were used in TOPSIS, the success rate of the treatment has been considered among the outputs to improve the assessment. Chapter 6, provides a better base for calculating the similarity measures and case extraction by testing different similarity measures. Two similarity measures of GRA and Gaussian distance have been introduced in this chapter to incorporate the non-linear relation between different parameters of the problem and enhancing the calculation of similarity in presence of a large number of criteria.

Designing a mathematical programming model which is capable of directing the final doses towards optimal dose plans considered by oncologists and increase the efficiency of the dose plans while simultaneously looking after the risks of the treatment was considered as the fourth objective of this research. Thus, to optimize the final solutions generated by TOPSIS-CBR, a Goal Programming mathematical model has been proposed in chapter 4 of this thesis. The aim of the GP model is to optimize the final dose plan towards the ideal goal of the oncologists by considering the DVH level

associated with each volume of the rectum. The objective function of this GP model is to reduce the difference between each prescribed dose and the oncologists' ideal goals and the constraint are in charge of considering the dose received by different volumes of the rectum based on DVH levels. At the same time, a rule-based process in assigning the right-hand side of the constraint was accommodated to consider the necessity of violating the standard limitations when it is vital to eradicate cancer effectively. This rule-based approach is also making the problem more similar to the real-life decision-making process of oncologists and is a contributor to second objective research.

In order to achieve the fourth research objective, incorporating the existing uncertainties in oncologists' judgments about the values of different criteria and factors in dose planning, in chapter 5 we presented grey DEA. In this chapter and evaluation process, the values for inputs and outputs have been considered as grey numbers to better cover the uncertainty of the oncologists' judgments regarding the crisp values to make the problem closer to real-life decision-making process. FA based on principal components have been applied to reduce the number of attributes for inputs and outputs and assist with the better performance of grey interval DEA.

The fifth research objective of the thesis is to develop a mechanism to assign optimal non-objective importance weight to each feature of the radiotherapy dose planning problem. The importance of different features of the CBR can be assigned based on oncologists' opinions, however, this would be objective as it depends on the singular preference of oncologists. Also, the opinions of the oncologists change throughout the time with gaining new experiences. To add the automatic capability of features weight assignment to our dose planning prescriptions, an optimal weight calculation model has been developed in chapter 6. The optimal weight for each feature is being calculated through GA and minimization of a dose difference function as the fitness

function for the GA. Thus, every time a case is added to the case pool, the optimal weights of each feature is calculated so that the total dose difference between the prescribed doses for each case and the original doses in the case pool is minimized.

The success rate of the approaches throughout the whole process has been examined with a strategy called leave-one-out. In this strategy every time one case is selected from the case pool and is treated as a new case. After calculation of the dose plan for the case, a comparison has been made between the obtained and original dose plan and after performing this strategy for all the cases in the pool, the total success rate of the approach has determined. The results for approaches that were applied based on different necessities have shown better coherence with the oncologists' original dose plans compared to simple CBR, confirming in this way the effectiveness and robustness of the proposed methods.

7.2 Contributions

The contributions of this research can be divided into two categories of theoretical implications or methodological contributions and practical implication or contributions to practice.

Decision making is a necessary procedure which plays a significant practical role in many areas of human activities. There are basic principles and methodologies developed in this thesis, the application of which can solve real-world problems and assist with making decisions in other domains rather than radiotherapy dose planning problem as demonstrated in this thesis. These can be considered as theoretical implications.

1- PCA and FA are two useful means of variable or dimension reduction with minimum loss of information and thus are very popular where the problem at

hand consists of multiple dimensions or the complexity of the system under investigation is extremely high. The application of PCA and FA is not limited to MCDM techniques and is extended to other operational research and statistical approaches. Also, the grey numbers are widely used in dealing with uncertainty and interval-valued parameters. Thus, the presented PCA and FA for grey numbers can be helpful to reduce complexity and dimensions essential to providing acceptable inputs to continue with other methods.

2- DEA is a well-known method to measure the efficiency of multiple units with consideration of several inputs and outputs at the same time without considering the distribution of the data. The integrated FA-DEA approach proposed in this thesis is generic in nature and is able to increase the accuracy and discrimination ability of DEA regarding the efficiency measuring problems in presence of interval data type and high numbers of inputs and outputs in comparison to the number of decision-making units. Following the detailed procedural steps provided and the normalization nuances, the approach is generalizable to other domains.

3- Successful application of CBR with TOPSIS shows the promising benefits of this approach, which can be further, applied in other research with knowledge-based methods. Although the criteria and decision makers' opinions about each criterion's importance should be modified and utilized depending on the target domain.

Throughout this thesis, a number of contributions to improve the efficiency of the dose plan prescriptions for radiotherapy dose planning have been made. Following the practical implications of this thesis is listed.

1- An extensive literature review on radiotherapy and dose planning stage of the radiotherapy has been represented. An overview of the radiotherapy treatment approaches, problem features, crucial barriers in the treatment planning and essential constraints for radiotherapy have been discussed. Moreover, the operational research techniques and mathematical applied model have been investigated and the application of them as well as a knowledge-based model, in particular, CBR, within different phases and problems of radiotherapy planning have been provided.

2- Through a combination of a number of MCDM techniques such as TOPSIS and DEA, the multi-criteria nature of the problem has been considered in this thesis. In previous researches where CBR was used to prescribe the dose plans in radiotherapy, it was only based on a similarity measure between different cases. While in real life scenarios, the oncologists' decisions depend on many other factors. Relying only on similarity measure can result in loss of information that can be provided by other cases with lower similarity measure but more appropriate for the problem at hand. By application of TOPSIS in combination with CBR, the risks of each treatment and the amount of dose plans in addition to the similarity between two cases have been considered. To improve the evaluations by TOPSIS, DEA was applied to assess the efficiency of prescribed cases based on an input-output approach and be able to better utilize the success rate of the previously done treatments.

3- Investigation and testing multiple types of similarity measures which have not been applied in radiotherapy planning is among the practical contributions of this research. The Euclidean similarity measure that has been applied in previous research has some main problems. Being independent of the data

distribution, weak performance in presence of multiple dimensions and inability to adapt the non-linear relation among different features of the problem can lead to non-satisfactory results. To improve the similarity measure calculation, GRA and Gaussian distance CBR have been applied in this thesis and the singular and combinatorial performances of them have achieved a higher success rate than simple Euclidean CBR.

4- In real life scenarios, the importance weight for each feature of the problem, i.e. clinical features regarding finding similarity measures, is assigned based on experience and preference of the decision makers, i.e. oncologists. Different oncologists might have varying opinions about the significance of various features and consider their preference may result in subjective weight assigning of the features that can affect the success rate and coherence of the dose planning. In this thesis, an automatic weight assigning strategy based on GA and minimization of a total dose difference function has been proposed. The robustness and effectiveness of the proposed algorithm have been demonstrated through a success rate calculation test.

5- The dose plans obtained based on the original prescription of the oncologists may not be the optimal dose plan. There are situations when the dose plan can be increased without compromising the safe limits for different percentages of the rectum. Also in some exceptional situations, the oncologists overlook the dose limit, do a trade-off between risks of the treatment and the benefits of deviating the sensitive limits by applying higher than standard doses to kill the cancerous cells effectively. To generalize the two aforementioned points into the dose plan suggestion and optimize the dose plans towards the preferable

dose goals suggested by oncologists. The developed GP model optimises the CBR-TOPSIS dose plans.

7.3 Limitations

While the performance of the developed approaches has been evaluated successfully and the practical, as well as methodological contributions, have been explained, like any other researches this PhD has certain limitations.

In the calculation of the similarity between two cases a set of clinical parameters including the PSA values, Gleason score and DVH values of different volumes of the rectum. However, the general condition of the patient e.g. age, fitness level and other physical characteristics could influence the decision-making process of the medical planning team. Given the availability of the aforementioned parameters in the dataset and by developing approaches to consider and properly incorporating them into the problem, the precision of results can be improved. Due to current lack of availability of these parameters in the accessible dataset, this has not happened for this thesis.

The success of the approaches has been evaluated based on the final obtained doses and whether those were coherent or provided a better dose plan compared to the original dose plan prescribed by the oncologists. The research at current stage suffers from the fact that there is no ascertained method of determining the quality of a dose plan in the literature.

The variety of the dose plans in the dataset is not very high and in some occasions, the most similar cases to the new case did not have adequate similarity measure; thus, some

cases had to be omitted completely. A larger dataset with more cases and variety of dose plans may lead to better results in terms of reliability and practical success rate.

7.4 Future research work

The novel hybrid approaches to support oncologists' decisions on dose planning for radiotherapy presented in this thesis have shown robustness and effectiveness through computational experiments. Moreover, the research done in this thesis provides an appropriate context for further extension. In this section will follow suggestions for future quality improvements and directions to better fill the gaps.

Incorporation of more clinically related features, such as age, fitness level and physical attributes of the patient as well as information on additional radiation effects on other sensitive surrounding organs rather than just the rectum can lead to a better similarity measure calculation and better experience on retrieval process. The availability of data on mentioned features and attributes makes the problem more similar to a real-life scenario where oncologists take into account more aspects of the problem.

The performance of the approaches with regards to larger datasets should be examined. Larger datasets with more cases can provide a better variety of the cases. In addition, integration of the datasets collected from different treatment centres can increase the flow of experiences by different oncologists into the system and lead to a more global decision support system. However, the increase in the number of the cases can result in an increase in required time for computational operations. In particular, for the feature weights operation done by GA, this problem can be more serious due to high time-consuming nature of the operation. In order to solve the problems associated with larger data sets, feature selection and feature categorization as well as case classification approaches to divide and restrict the solution space can be introduced to

the problem. Also, a research on more effective and faster-converging heuristics to reduce the computational time and effort can be an important direction for further research.

Appendix 1: Medical terminology

Biopsy:	Is a medical procedure in which a small sample of body tissue is taken out for further tests.
CT scan:	Also called as CAT scan, Computed Axial Tomography, is a technology that utilized two-dimensional images to build three-dimensional images that shows inside a body part in medical imaging.
Fluence:	The fluence of a beam is the number of photons that enter to an imaginary sphere with a cross-sectional area of A in m^2.
Gastrointestinal:	Any issues related to stomach and digesting organs.
Gray (Gy):	The unit for radiation dose which is expressed in terms of absorbed energy per unit of tissue mass in international system (SI). i.e. 1 Gy is 1 joule per kilogram.
Gynecologic malignancies:	Cancers related to female reproductive systems such as ovarian cancer, uterine cancer, vaginal cancer, cervical cancer, and vulvar cancer.
Isodose:	Isodose curves are the lines joining the points of equal Percentage Depth Dose (PDD). The curves are usually drawn at regular intervals of absorbed dose and expressed as a percentage of the dose at a reference point (274).
Multi-leaf collimators:	Is an important part of equipment for a radiotherapy dose delivery system that is consisted of individual leaves made of a material with high atomic numbers e.g. tungsten. These leaves can move independently and block the radiation.
MRI:	Magnetic Resonance Imaging, an imaging technology in radiology which uses radio waves and magnetic fields to form pictures of healthy and diseased body parts.
Pediatric malignancies:	Cancers related to infants and children.
Sarcomas:	Is cancer that arises from transformed cells of mesenchymal origin i.e. bone, fat, muscle and vascular cells.

Therapeutic ratio:	Is the ratio of therapeutic agents that causes the beneficial effects in a treatment to the amount that causes toxicity.

References

1. Hejmadi M. *Introduction to cancer biology*. 2nd ed. Bookboon.com. Ventus Publishing ApS; 2009.

2. *Comprehensive Cancer Information* - National Cancer Institute [Internet]. [cited 2018 May 4]. Available from: https://www.cancer.gov/

3. Cancer Research UK. Available from: https://www.cancerresearchuk.org/

4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer*. 2015 Mar 1;136(5):E359–86.

5. Malicki J. The importance of accurate treatment planning, delivery, and dose verification. *Reports of Practical Oncology and Radiotherapy*. 2012;17(2).

6. Jagannathan R, Petrovic S, McKenna A, Newton L. *A fuzzy non-linear similarity measure for Cased-Based Reasoning systems for radiotherapy treatment planning*. In IFIP International Conference on Artificial Intelligence Applications and Innovations. 2010. p. 112–9.

7. Petrovic S, Mishra N, Sundar S. A novel Cased-Based Reasoning approach to radiotherapy planning. *Expert Systems with Application*. 2011;38(9):10759–69.

8. Kolodner J. *Cased-Based Reasoning*. San Mateo CA 94403: Morgan Kaufmann Publishers; 2014.

9. Thokala P, Devlin N, Marsh K, Baltussen R, Boysen M, Kalo Z, et al. Multiple criteria decision analysis for health care decision making; an introduction: report 1 of the ISPOR MCDA Emerging Good Practices Task Force. *Value in Health Journal*. 2016;19(1):1–13.

10. Kang Y., Krishnaswamy S, Zaslavsky A. A retrieval strategy for Cased-Based Reasoning using similarity and association knowledge. *IEEE Transactions on Cybernetics*. 2014;44(4):437–87.

11. Cooper WW, Seiford LM, Zhu J. *Data Envelopment Analysis: history, models, and interpretations*. International Series in Operations Research & Management Science 2011. p. 1–39. Available from: http://link.springer.com/10.1007/978-1-4419-6151-8_1

12. Cancer statistics | World Cancer Research Fund UK. 2014. Available from: https://www.wcrf-uk.org/uk/preventing-cancer/cancer-preventability-statistics

13. Worldwide data | World Cancer Research Fund International [Internet]. [cited

2018 May 4]. Available from: https://www.wcrf.org/int/cancer-facts-figures/worldwide-data

14. Cancer statistics - Statistics Explained. Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Cancer_statistics

15. Beyer T, Townsend D., Burn T, Kinhan P. A combined PET/CT scanner for clinical oncology. The Journal of Nuclear Medicine. 2000;41(8):1369–79.

16. Radiotherapy treatments | NUH [Internet]. [cited 2018 May 4]. Available from: https://www.nuh.nhs.uk/radiotherapy-treatments

17. Biopsy overview [Internet]. [cited 2018 May 5]. Available from: https://www.radiologyinfo.org/en/info.cfm?pg=biopgen

18. *Types of hormonal therapy*. Canadian Cancer Society [Internet]. [cited 2018 May 4]. Available from: http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/chemotherapy-and-other-drug-therapies/hormonal-therapy/types-of-hormonal-therapy/?region=on

19. Seco J, Clasie B, Biology MP-P in M&, 2014 U. Review on the characteristics of radiation detectors for dosimetry and imaging. iopscience.iop.org. 2014;59(20). Available from: http://iopscience.iop.org/article/10.1088/0031-9155/59/20/R303/meta

20. Barrett A, Dobbs J, Roques T. Practical radiotherapy planning. 4th ed. London: Holder Arnold; 2009. Available from : https://books.google.co.uk/books?hl=en&lr=&id=EyTSBQAAQBAJ&oi=fnd&pg=PP1&dq=.+Practical+Radiotherapy+Planning+Fourth+Editio&ots=6j-6jqKMxP&sig=2QtBkTv2onmohGDM363NgeIP5ZQ

21. *Systemic Radiation Therapy*. Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/radiation/systemic-radiation-therapy.html

22. Mijnheer B, Beddar S, Izewska J, Reft C. In vivo dosimetry in external beam radiotherapy. *Medical Physics*. 2013;40(7).

23. Morgan-Fletcher SL. Prescribing, recording and reporting Photon Beam Therapy (Supplement to ICRU Report 50), ICRU Report 62 . [Internet]. Vol. 74, *The British Journal of Radiology*. 2001 Mar [cited 2018 May 4]. Available from: http://www.birpublications.org/doi/10.1259/bjr.74.879.740294

24. Feng F, Kim H, Lyden T, Maxer M. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose–effect relationships for the swallowing structures. *International Journal of Radiation Oncology Biology*

Physics. 2007;68(5):1289–98.

25. Wang-Chesebro A, Xia P, Coleman J, Akazawa C, Roach M. Intensity-modulated radiotherapy improves lymph node coverage and dose to critical structures compared with three-dimensional conformal radiation therapy .*International Journal of Radiation Oncology Biology Physics*. 2007;68(5):1289–98.

26. Mundt A, Lujan A, Rotmensch J, Waggoner S, Yamada S, Fleming G, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies1.*International Journal of Radiation Oncology Biology Physics*. 2006;66(3):654–62.

27. Baskar R, Lee KA, Yeo R, Yeoh K-W. Cancer and radiation therapy: current advances and future directions. *International Journal of Medical Sciences*. 2012;9(3):193–9.

28. Holder A, Salter B. *A tutorial on radiation oncology and optimization [Internet]*. Springer. 2005 [cited 2018 May 3]. 1-4 p. Available from: https://link.springer.com/chapter/10.1007/0-387-22827-6_4

29. Ehrgott M, Güler Ç, Hamacher HW, Shao L. Mathematical optimization in intensity modulated radiation therapy. *Annals of Operations Research*. 2010;175(1):309–65.

30. Morris K AL. Pelvic radiation therapy: Between delight and disaster. *World Journal of Gastrointestinal Surgery* [Internet]. 2015;7(11):279. Available from: http://www.wjgnet.com/1948-9366/full/v7/i11/279.htm

31. *Modern Radiotherapy [Internet]*. [cited 2018 May 4]. Available from: https://www.slideshare.net/OmarHashim/modern-radiotherapy

32. Yaeger TE, Montemaggi P, Trombetta M, Pignol J-P, Brady L. Introduction. In: *Medical Radiology*. Springer Link; 2017. Available from: http://link.springer.com/10.1007/174_2017_92

33. Li Y, Yao D, Yao J, Chen W. A particle swarm optimization algorithm for beam angle selection in intensity-modulated radiotherapy planning. *Physics in Medicine and Biology* . 2005 Aug 7;50(15):3491–514.

34. Schreibmann E, Lahanas M, Uricchio R, Theodorou K, Kappas C, Baltas D. A geometry-based optimization algorithm for conformal external beam radiotherapy. *Physics in Medicine and Biology* . 2003 Jun 21;48(12):1825–41.

35. Yang R, Dai J, Yang Y, Hu Y. Beam orientation optimization for intensity-modulated radiation therapy using mixed integer programming. *Physics in*

Medicine and Biology . 2006 Aug 7;51(15):3653–66.

36. Li Y, Lei J. A feasible solution to the beam-angle-optimization problem in radiotherapy planning with a DNA-based genetic algorithm. *IEEE Transactions on Biomedical Engineering*. 2010;57(3):499–508.

37. Pugachev A. Incorporating prior knowledge into beam orientation optimization in IMRT. *International Journal of Radiation Oncology Biology Physics*. 2001;50(2):551–60.

38. Pugachev A, Li J, Boyer A, Hancock S, Le Q, Xing L. Role of beam orientation optimization in intensity-modulated radiation therapy. *International Journal of Radiation Oncology Biology Physics*. 2005;50(15):3491.

39. Li Y, Yao D, Yao J, Chen W. A particle swarm optimization algorithm for beam angle selection in intensity-modulated radiotherapy planning. *Physics in Medicine and Biology*. 2005;50(15):3491–514.

40. Vaitheeswaran R, Sathiya Narayanan VK, Bhangle JR, Nirhali A, Kumar N, Basu S, et al. An algorithm for fast beam angle selection in intensity modulated radiotherapy. *Medical Physics*. 2010 Nov 30;37(12):6443–52.

41. Bortfeld T. The number of beams in IMRT—theoretical investigations and implications for single-arc IMRT. *Physics in Medicine and Biology*. 2010 Jan 7;55(1):83–97.

42. Guckenberger M, Krieger T, Richter A, Baier K, Wilbert J, Sweeney R, et al. Potential of image-guidance, gating and real-time tracking to improve accuracy in pulmonary stereotactic body radiotherapy. *Radiotherapy and Oncology*. 2009;91(3):288–95.

43. Bedford JL, Webb S. Elimination of importance factors for clinically accurate selection of beam orientations, beam weights and wedge angles in conformal radiation therapy. *Medical Physics*. 2003 Jun 25;30(7):1788–804.

44. Haas OCL, Burnham KJ, Mills JA. Optimization of beam orientation in radiotherapy using planar geometry. *Physics in Medicine and Biology*. 1998 Aug 1;43(8):2179–93.

45. Lahanas M, Schreibmann E, Milickovic N, Baltas D. Intensity Modulated Beam Radiation Therapy dose optimization with multiobjective evolutionary algorithms. *In: Evolutionary Multi-Criterion Optimization*. Springer Link; 2003. p. 648–61.

46. Meedt G, Alber M, N sslin F. Non-coplanar beam direction optimization for intensity-modulated radiotherapy. *Physics in Medicine and Biology*. 2003 Sep

21;48(18):2999–3019.

47. Pugachev A, Xing L. Computer-assisted selection of coplanar beam orientations in intensity-modulated radiation therapy. *Physics in Medicine and Biology*. 2001 Sep 1;46(9):2467–76.

48. Rowbottom CG, Khoo VS, Webb S. Simultaneous optimization of beam orientations and beam weights in conformal radiotherapy. *Medical Physics*. 2001 Aug;28(8):1696–702.

49. Schreibmann E, Lahanas M, Uricchio R, Theodorou K, Kappas C, Baltas D. A geometry-based optimization algorithm for conformal external beam radiotherapy. *Physics in Medicine and Biology*. 2003 Jun 21;48(12):1825–41.

50. Stein J, Mohan R, Wang X-H, Bortfeld T, Wu Q, Preiser K, et al. Number and orientations of beams in intensity-modulated radiation treatments. *Medical Physics*. 1997 Feb;24(2):149–60.

51. Wu X, Zhu Y. An optimization method for importance factors and beam weights based on genetic algorithms for radiotherapy treatment planning. *Physics in Medicine and Biology*. 2001 Apr 1;46(4):1085–99.

52. Braunstein M, Levine RY. Optimum beam configurations in tomographic intensity modulated radiation therapy. *Physics in Medicine and Biology*. 2000;45(2):305–28.

53. Crooks SM, Xing L. Linear algebraic methods applied to intensity modulated radiation therapy. *Physics in Medicine and Biology*. 2001;46(10):2587–606.

54. Das S, Cullip T, Tracton G, Chang S, Marks L, Anscher M, et al. Beam orientation selection for intensity-modulated radiation therapy based on target equivalent uniform dose maximization. *International Journal of Radiation Oncology Biology Physics*. 2003;55(1):215–24.

55. Schreibmann E, Lahanas M, Xing L, Baltas D. Multiobjective evolutionary optimization of the number of beams, their orientations and weights for intensity-modulated radiation therapy. *Physics in Medicine and Biology*. 2004;49(5):747–70.

56. Breedveld S, Storchi PRM, Voet PWJ, Heijmen BJM. ICycle: Integrated, multicriterial beam angle, and profile optimization for generation of coplanar and noncoplanar IMRT plans. *Medical Physics*. 2012;39(2):951–63.

57. Jia X, Men C, Lou Y, Jiang SB. Beam orientation optimization for intensity modulated radiation therapy using adaptive l2,1-minimization. *Physics in Medicine and Biology*. 2011;56(19):6205–22.

58. Zhu X, Ge Y, Li T, Thongphiew D, Yin FF, Wu QJ. A planning quality evaluation tool for prostate adaptive IMRT based on machine learning. *Medical Physics*. 2011;38(2):719–26.

59. Voet PWJ, Breedveld S, Dirkx MLP, Levendag PC, Heijmen BJM. Integrated multicriterial optimization of beam angles and intensity profiles for coplanar and noncoplanar head and neck IMRT and implications for VMAT. *Medical Physics*. 2012;39(8):4858–65.

60. Lim GJ, Cao W. A two-phase method for selecting IMRT treatment beam angles: Branch-and-Prune and local neighborhood search. *European Journal of Operational Research*. 2012;217(3):609–18.

61. Rocha H, Dias JM, Ferreira BC, Lopes MC. Selection of intensity modulated radiation therapy treatment beam directions using radial basis functions within a pattern search methods framework. J*ournal of Global Optimization*. 2013;57(4):1065–89.

62. Lee CHJ, Aleman DM, Sharpe MB. A set cover approach to fast beam orientation optimization in intensity modulated radiation therapy for total marrow irradiation. *Physics in Medicine and Biology*. 2011;56(17):5679–95.

63. Van De Schoot AJAJ, Visser J, Van Kesteren Z, Janssen TM, Rasch CRN, Bel A. Beam configuration selection for robust intensity modulated proton therapy in cervical cancer using Pareto front comparison. *Physics in Medicine and Biology*. 2016;61(4):1780–94.

64. Koger B, Kirkby C. Optimization of photon beam energies in gold nanoparticle enhanced arc radiation therapy using Monte Carlo methods. *Physics in Medicine and Biology*. 2016;61(24):8839–53.

65. Ranganathan V, Das KJM. Determination of optimal number of beams in direct machine parameter optimization-based intensity-modulated radiotherapy for head and neck cases. *Journal of Medical Physics*. 2016;41(2):129–34.

66. Dias J, Rocha H, Ferreira B, Do Carmo Lopez M. Simulated annealing applied to IMRT beam angle optimization: A computational study. *Physica Medica*. 2015;31(7):746–56.

67. Lim GJ, Kardar L, Cao W. A hybrid framework for optimizing beam angles in radiation therapy planning. *Annals of Operations Research*. 2014;217(1):357–83.

68. Mišić V V., Aleman DM, Sharpe MB. Neighborhood search approaches to non-coplanar beam orientation optimization for total marrow irradiation using IMRT. *European Journal of Operational Research*. 2010;205(3):522–7.

69. Oskoorouchi MR, Ghaffari HR, Terlaky T, Aleman DM. An interior point constraint generation algorithm for semi-infinite optimization with healthcare application. *Operations Research*. 2011;59(5):1184–97.

70. Cabrera G. G, Ehrgott M, Mason AJ, Raith A. A metaheuristic approach to solve the multiobjective beam angle optimization problem in intensity-modulated radiation therapy. *International Transactions in Operational Research*. 2018;25(1):243–68.

71. Engel K, Tabbert E. Fast simultaneous angle, wedge, and beam intensity optimization in inverse radiotherapy planning. *Optimization and Engineering*. 2005;6(4):393–419.

72. Oldham M, Neal AJ, Webb S. The optimisation of wedge filters in radiotherapy of the prostate. *Radiotherapy and Oncology*. 1995;37(3):209–20.

73. Thomas SJ, Foster KR. Radiotherapy treatment planning with dynamic wedges - An algorithm for generating wedge factors and beam data. *Physics in Medicine and Biology*. 1995;40(9):1421–33.

74. Beaulieu F, Beaulieu L, Tremblay D, Roy R. Simultaneous optimization of beam orientations, wedge filters and field weights for inverse planning with anatomy-based MLC fields. *Medical Physics*. 2004;31(6):1546–57.

75. Xing L, Pelizzari C, Kuchnir FT, Chen GTY. Optimization of relative weights and wedge angles in treatment planning. *Medical Physics*. 1997;24(2):215–21.

76. Casesnoves F. Geometrical determinations of IMRT photon pencil-beam path in radiotherapy wedges and limit divergence angle with the Anisotropic Analytic Algorithm (AAA). *International Journal of Cancer Therapy and Oncology*. 2014;18(2).

77. Treutwein M, Hipp M, Kölbl O, Bogner L. IMRT of prostate cancer. *Strahlentherapie und Onkologie*. 2009 Jun 9;185(6):379–83.

78. Arráns R, Gallardo MI, Roselló J, Sánchez-Doblado F. Computer optimization of class solutions designed on a beam segmentation basis. *Radiotherapy and Oncology*. 2003;69(3):315–21.

79. Qiu W, Yuan J, Ukwatta E, Sun Y, Rajchl M, Fenster A. Dual optimization based prostate zonal segmentation in 3D MR images. *Medical Image Analysis*. 2014;18(4):660–73.

80. Hamacher HW, Ufer K-HK. Inverse radiation therapy planning; a multiple objective optimization approach. *Discrete Applied Mathematics*. 2002;118:145–61.

81. Baatar D, Hamacher HW, Ehrgott M, Woeginger GJ. Decomposition of integer matrices and multileaf collimator sequencing. *Discrete Applied Mathematics*. 2005;152(1–3):6–34.

82. Baatar D, Boland N, Johnston R, Hamacher HW. A new sequential extraction heuristic for optimizing the delivery of cancer radiation treatment using multileaf collimators. *INFORMS Journal on Computing*. 2009;21(2):224–41.

83. Engelbeen C, Fiorini S. Constrained decompositions of integer matrices and their applications to intensity modulated radiation therapy. *Networks*. 2010;55(2):138–48.

84. Bussels B, Goethals L, Feron M, Bielen D, Dymarkowski S, Suetens P, et al. Respiration-induced movement of the upper abdominal organs: a pitfall for the three-dimensional conformal radiation treatment of pancreatic cancer. *Radiotherapy and Oncology*. 2003;68(1):69–74.

85. McCarthy C, Davies J, Stratford J, Duffy M, Gattamaneni HR. X-ray volumetric imaging in paediatric radiotherapy - a case study. *Clinical Oncology*. 2007;19(3):194–6.

86. Stroom JC, De Boer HCJ, Huizenga H, Visser AG. Inclusion of geometrical uncertainties in radiotherapy treatment planning by means of coverage probability.*International Journal of Radiation Oncology Biology Physics*. 1999;43(4):905–19.

87. Stroom JC, Heijmen BJM. Geometrical uncertainties, radiotherapy planning margins, and the ICRU-62 report. *Radiotherapy and Oncology*. 2002;64(1):75–83.

88. Yamamoto M, Nagata Y, Okajima K, Ishigaki T, Murata R, Mizowaki T, et al. Differences in target outline delineation from CT scans of brain tumours using different methods and different observers. *Radiotherapy and Oncology*. 1999;50(2):151–6.

89. McNair HA, Brock J, Symonds-Tayler JRN, Ashley S, Eagle S, Evans PM, et al. Feasibility of the use of the Active Breathing Co ordinator^{TM} (ABC) in patients receiving radical radiotherapy for non-small cell lung cancer (NSCLC). *Radiotherapy and Oncology*. 2009;93(3):424–9.

90. Murphy MJ. Tracking moving organs in real time. Vol. 14, *Seminars in Radiation Oncology*. 2004. p. 91–100.

91. Ford EC, Mageras GS, Yorke E, Rosenzweig KE, Wagman R, Ling CC. Evaluation of respiratory movement during gated radiotherapy using film and electronic portal imaging.*International Journal of Radiation Oncology Biology*

Physics. 2002;52(2):522–31.

92. Vedam SS, Kini VR, Keall PJ, Ramakrishnan V, Mostafavi H, Mohan R. Quantifying the predictability of diaphragm motion during respiration with a noninvasive external marker. *Medical Physics*. 2003;30(4):505–13.

93. Pevsner A, Nehmeh SA, Humm JL, Mageras GS, Erdi YE. Effect of motion on tracer activity determination in CT attenuation-corrected PET images: A lung phantom study. *Medical Physics*. 2005;32(7):2358–62.

94. Sharp GC, Jiang SB, Shimizu S, Shirato H. Prediction of respiratory tumour motion for real-time image-guided radiotherapy. *Physics in Medicine and Biology*. 2004;49(3):425–40.

95. Berbeco R, Neicu T, Rietzel E, Chen G, Jiang S. WE-D-I-6B-05: A technique for respiratory-gated radiotherapy treatment verification with an EPID in cine mode. *Medical Physics*. 2005;32(6):2132.

96. Stroom JC, Storchi PRM. Automatic calculation of three-dimensional margins around treatment volumes in radiotherapy planning. *Physics in Medicine and Biology*. 1997;42(4):745–55.

97. Orton NP, Tomé WA. The impact of daily shifts on prostate IMRT dose distributions. *Medical Physics*. 2004;31(10):2845–8.

98. Zeng R, Fessler JA, Balter JM. Respiratory motion estimation from slowly rotating x-ray projections: Theory and simulation. *Medical Physics*. 2005;32(4):984–91.

99. Blonigen BJ, Steinmetz RD, Levin L, Lamba MA, Warnick RE, Breneman JC. Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. *International Journal of Radiation Oncology Biology Physics*. 2010;77(4):996–1001.

100. Iyengar S, Li X, Xu H, Mukhopadhyay S, Balakrishnan N, Sawant A, et al. Toward more precise radiotherapy treatment of lung tumors. Vol. 45, *Computer*. 2012. p. 59–65.

101. Marquet F, Aubry JF, Pernot M, Fink M, Tanter M. Optimal transcostal high-intensity focused ultrasound with combined real-time 3D movement tracking and correction. *Physics in Medicine and Biology*. 2011;56(22):7061–80.

102. Khan A, Jensen LG, Sun S, Song WY, Yashar CM, Mundt AJ, et al. Optimized planning target volume for intact cervical cancer. *International Journal of Radiation Oncology Biology Physics*. 2012;83(5):1500–5.

103. Pella A, Cambria R, Riboldi M, Jereczek-Fossa BA, Fodor C, Zerini D, et al.

Use of machine learning methods for prediction of acute toxicity in organs at risk following prostate radiotherapy. *Medical Physics*. 2011;38(6):2859–67.

104. Chen W, Unkelbach J, Trofimov A, Madden T, Kooy H, Bortfeld T, et al. Including robustness in multi-criteria optimization for intensity-modulated proton therapy. *Physics in Medicine and Biology*. 2012;57(3):591–608.

105. Valdagni R, Rancati T. Reducing rectal injury during external beam radiotherapy for prostate cancer. Vol. 10, *Nature Reviews Urology*. 2013. p. 345–57.

106. Saka B, Rardin RL, Langer MP, Dink D. Adaptive intensity modulated radiation therapy planning optimization with changing tumor geometry and fraction size limits. *IIE Transactions on Healthcare Systems Engineering*. 2011;1(4):247–63.

107. Tsang HS, Kamerling CP, Ziegenhein P, Nill S, Oelfke U. A novel probabilistic approach to generating PTV with partial voxel contributions. *Physics in Medicine and Biology*. 2017;62(12):4917–28.

108. Sir MY, Epelman MA, Pollock SM. Stochastic programming for off-line adaptive radiotherapy. *Annals of Operations Research*. 2012;196(1):767–97.

109. Lens E, Kotte ANTJ, Patel A, Heerkens HD, Bal M, van Tienhoven G, et al. Probabilistic treatment planning for pancreatic cancer treatment: prospective incorporation of respiratory motion shows only limited dosimetric benefit. *Acta Oncologica (Madr)*. 2017;56(3):398–404.

110. Li Y, Niemela P, Liao L, Jiang S, Li H, Poenisch F, et al. Selective robust optimization: A new intensity-modulated proton therapy optimization strategy. *Medical Physics*. 2015;42(8):4840–7.

111. Aubry J-F, Beaulieu F, Sevigny C, Beaulieu L, Tremblay D. Multiobjective optimization with a modified simulated annealing algorithm for external beam radiotherapy treatment planning. *Medical Physics*. 2006;33(12):4718–29.

112. Alterovitz R, Lessard E, Pouliot J, Hsu I-CJ, O'Brien JF, Goldberg K. Optimization of HDR brachytherapy dose distributions using linear programming with penalty costs. *Medical Physics*. 2006;33(11):4012–9.

113. Chen Z, Ma C-M, Paskalev K, Li J, Yang J, Richardson T, et al. Investigation of MR image distortion for radiotherapy treatment planning of prostate cancer. *Physics in Medicine and Biology*. 2006;51(6):1393–403.

114. Cotrutz C, Lahanas M, Kappas C, Baltas D. A multiobjective gradient-based dose optimization algorithm for external beam conformal radiotherapy. *Physics in Medicine and Biology*. 2001;46(8):2161–75.

115. Lahanas M, Baltas D, Zamboglou N. A hybrid evolutionary algorithm for multi-objective anatomy-based dose optimization in high-dose-rate brachytherapy. *Physics in Medicine and Biology*. 2003;48(3):399–415.

116. Lahanas M, Baltas D, Zamboglou N. Anatomy-based three-dimensional dose optimization in brachytherapy using multiobjective genetic algorithms. *Medical Physics*. 1999;26(9):1904–18.

117. Martel MK, Ten Haken RK, Hazuka MB, Kessler ML, Strawderman M, Turrisi a T, et al. Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients. *Lung Cancer*. 1999;24(1):31–7.

118. Meyer J, Phillips MH, Cho PS, Kalet I, Doctor JN. Application of influence diagrams to prostate intensity-modulated radiation therapy plan selection. *Physics in Medicine and Biology*. 2004;49(9):1637–53.

119. Monz M, Küfer KH, Bortfeld TR, Thieke C. Pareto navigation - Algorithmic foundation of interactive multi-criteria IMRT planning. *Physics in Medicine and Biology*. 2008;53(4):985–98.

120. Aubry J-F, Beaulieu F, Sévigny C, Beaulieu L, Tremblay D. Multiobjective optimization with a modified simulated annealing algorithm for external beam radiotherapy treatment planning. *Medical Physics*. 2006 Nov 28;33(12):4718–29.

121. Wu Q, Djajaputra D, Lauterbach M, Wu Y, Mohan R. A fast dose calculation method based on table lookup for IMRT optimization. *Physics in Medicine and Biology*. 2003;48(12).

122. Yu Y, Zhang JB, Cheng G, Schell MC, Okunieff P. Multi-objective optimization in radiotherapy: Applications to stereotactic radiosurgery and prostate brachytherapy. *Artificial Intelligence in Medicine*. 2000;19(1):39–51.

123. Gu X, Choi D, Men C, Pan H, Majumdar A, Jiang SB. GPU-based ultra-fast dose calculation using a finite size pencil beam model. *Physics in Medicine and Biology*. 2009;54(20):6287–97.

124. Teodorović D, Šelmić M, Mijatović-Teodorović L. Combining Cased-Based Reasoning with Bee Colony Optimization for dose planning in well-differentiated thyroid cancer treatment. *Expert Systems with Application*. 2013;40(6):2147–55.

125. Mishra N, Petrovic S, Sundar S. A self-adaptive Cased-Based Reasoning system for dose planning in prostate cancer radiotherapy. *Medical Physics*. 2011;38(12):6528–38.

126. Zarepisheh M, Long T, Li N, Tian Z, Romeijn HE, Jia X, et al. A DVH-guided IMRT optimization algorithm for automatic treatment planning and adaptive radiotherapy replanning. *Medical Physics*. 2014;41(6).

127. Inaniwa T, Kanematsu N, Noda K, Kamada T. Treatment planning of intensity modulated composite particle therapy with dose and linear energy transfer optimization. *Physics in Medicine and Biology*. 2017;62(12):5180–97.

128. Jalalimanesh A, Haghighi H, Ahmadi A, Soltani M. Simulation-based optimization of radiotherapy: Agent-based modeling and reinforcement learning. *Mathematics and Computers in Simultion*. 2017;133:235–48.

129. Zhang Y, Merritt M. Dose-volume-based IMRT fluence optimization: A fast least-squares approach with differentiability. *Linear Algebra and Its Applications*. 2008;428(5–6):1365–87.

130. Modiri A, Gu X, Hagan AM, Sawant A. Radiotherapy planning using an improved search strategy in particle swarm optimization. *IEEE Transactions on Biomedical Engineering*. 2017;64(5):980–9.

131. Pugachev AB, Boyer AL, Xing L. Beam orientation optimization in intensity-modulated radiation treatment planning. *Medical Physics*. 2000;27(6):1238–45.

132. Yang R, Dai J, Yang Y, Hu Y. Beam orientation optimization for intensity-modulated radiation therapy using mixed integer programming. Physics in *Medicine and Biology*. 2006;51(15):3653–66.

133. Hou Q, Wang J, Chen Y, Galvin JM. Beam orientation optimization for IMRT by a hybrid method of the genetic algorithm and the simulated dynamics. *Medical Physics*. 2003;30(9):2360–7.

134. Li Y, Yao J, Yao D. Automatic beam angle selection in IMRT planning using genetic algorithm. *Physics in Medicine and Biology* . 2004;49(10):1915–32.

135. Buzdar S, Khan M, Nazir A, Gandhi M, Nizamani A, Saleem H. Effect of change in orientation of enhanced dynamic wedges on radiotherapy treatment dose. *International Journal of Applied Research and Technology*. 2013;2:496–500.

136. Albertini F, Hug EB, Lomax AJ. The influence of the optimization starting conditions on the robustness of intensity-modulated proton therapy plans. *Physics in Medicine and Biology*. 2010;55(10):2863–78.

137. Romeijn HE, Ahuja RK, Dempsey JF, Kumar A. A new linear programming approach to radiation therapy treatment planning problems. *Operational Research*. 2006 Apr;54(2):201–16.

138. Craft D. Local beam angle optimization with linear programming and gradient search. *Physics in Medicine and Biology*. 2007;52(7).

139. Zhang HH, Shi L, Meyer R, Nazareth D, D'souza W. Solving beam-angle selection and dose optimization simultaneously via high-throughput computing. *INFORMS Journal on Computing*. 2009;21(3):427–44.

140. Taşkin ZC, Smith JC, Romeijn HE. Mixed-integer programming techniques for decomposing IMRT fluence maps using rectangular apertures. *Annals of Operations Research*. 2012;196(1):799–818.

141. Fiege J, McCurdy B, Potrebko P, Champion H, Cull A. PARETO: A novel evolutionary optimization approach to multiobjective IMRT planning. *Medical Physics*. 2011;38(9):5217–29.

142. Yang J, Zhang P, Zhang L, Shu H, Li B, Gui Z. Particle swarm optimizer for weighting factor selection in intensity-modulated radiation therapy optimization algorithms. *Physica Medica*. 2017;33:136–45.

143. Shao L, Ehrgott M. Approximately solving multiobjective linear programmes in objective space and an application in radiotherapy treatment planning. *Mathematical Methods of Operations Research*. 2008;68(2):257–76.

144. Bangert M, Ziegenhein P, Oelfke U. Comparison of beam angle selection strategies for intracranial IMRT. *Medical Physics*. 2013;40(1).

145. Ureba A, Salguero FJ, Barbeiro AR, Jimenez-Ortega E, Baeza JA, Miras H, et al. MCTP system model based on linear programming optimization of apertures obtained from sequencing patient image data maps. *Medical Physics*. 2014;41(8).

146. Zaghian M, Lim G, Liu W, Mohan R. An automatic approach for satisfying dose-volume constraints in linear fluence map optimization for IMPT. *Journal of Cancer Therapy*. 2014;5(2):198–207.

147. Gorissen BL, Den Hertog D, Hoffmann AL. Mixed integer programming improves comprehensibility and plan quality in inverse optimization of prostate HDR brachytherapy. *Physics in Medicine and Biology*. 2013;58(4):1041–57.

148. Akartunali K, Mak-Hau V, Tran T. A unified mixed-integer programming model for simultaneous fluence weight and aperture optimization in VMAT, Tomotherapy, and Cyberknife. *Computers and Operations Research*. 2015;56:134–50.

149. Zhang P, Fan N, Shan J, Schild SE, Bues M, Liu W. Mixed integer programming with dose-volume constraints in intensity-modulated proton therapy. *Journal of*

Applied Clinical Medical Physics. 2017;18(5):29–35.

150. Cao W, Lim G. *Beam angle selection in Intensity Modulated Proton Therapy treatment planning for prostate cancer*. In: IIE Annual Conference Institute of Industrial and Systems Engineers. 2011. p. 1.

151. Cao W, Lim GJ, Lee A, Li Y, Liu W, Ronald Zhu X, et al. Uncertainty incorporated beam angle optimization for IMPT treatment planning. *Medical Physics*. 2012;39(8):5248–56.

152. Siauw T, Cunha A, Atamtürk A, Hsu IC, Pouliot J, Goldberg K. IPIP: A new approach to inverse planning for HDR brachytherapy by directly optimizing dosimetric indices. *Medical Physics*. 2011;38(7):4045–51.

153. Holm Å, Larsson T, Tedgren ÅC. A linear programming model for optimizing HDR brachytherapy dose distributions with respect to mean dose in the DVH-tail. *Medical Physics*. 2013;40(8).

154. Bertsimas D, Cacchiani V, Craft D, Nohadani O. A hybrid approach to beam angle optimization in intensity-modulated radiation therapy. *Computers and Operations Research*. 2013;40(9):2187–97.

155. Wu VW, Epelman MA, Wang H, Edwin Romeijn H, Feng M, Cao Y, et al. Optimizing global liver function in radiation therapy treatment planning. *Physics in Medicine and Biology*. 2016 Sep 7;61(17):6465–84.

156. Badri H, Pitter K, Holland EC, Michor F, Leder K. Optimization of radiation dosing schedules for proneural glioblastoma. *Journal of Mathematical Biology*. 2016;72(5):1301–36.

157. Zaghian M, Cao W, Liu W, Kardar L, Randeniya S, Mohan R, et al. Comparison of linear and nonlinear programming approaches for "worst case dose" and "minmax" robust optimization of intensity-modulated proton therapy dose distributions. *Journal of Applied Clinical Medical Physics*. 2017;18(2):15–25.

158. Bruni C, Conte F, Papa F, Sinisgalli C. Optimal weekly scheduling in fractionated radiotherapy: effect of an upper bound on the dose fraction size. *Journal of Mathematical Biology*. 2015 Aug 29;71(2):361–98.

159. Casesnoves F. Exact integral equation determination with 3D wedge filter convolution factor solution in radiotherapy. Series of Computational-Programming 2D-3D. *International Journal of Scientific Research in Science, Engineering and Technology*. 2016;

160. Meyer RR, Zhang HH, Goadrich L, Nazareth DP, Shi L, D'Souza WD. A Multiplan Treatment-Planning Framework: A Paradigm Shift for Intensity-

Modulated Radiotherapy. *International Journal of Radiation Oncology Biology Physics*. 2007;68(4):1178–89.

161. Hoegele W, Loeschel R, Merkle N, Zygmanski P. An efficient inverse radiotherapy planning method for VMAT using quadratic programming optimization. *Medical Physics*. 2012;39(1):444–54.

162. Liu X, Belcher AH, Grelewicz Z, Wiersma RD. *Constrained quadratic optimization for radiation treatment planning by use of graph form ADMM*. In: Proceedings of the American Control Conference. 2016. p. 5599–604.

163. Goldbarg M., Goldbarg E., Mendez C. *Selecting beam directions in radiotherapy with an evolutionary algorithm*. In: Proceedings of 2008 ACM Symposium on Applied Computing. 2008;1420–1.

164. Nazareth D, Brunner S, Jones M, Malhorta H. Optimization of beam angles for intensity modulated radiation therapy treatment planning using genetic algorithm on a distributed computing platform. *Journal of Medical Physics*. 2009;34(3).

165. Ahmad SU, Bergen SWA. A genetic algorithm approach to the inverse problem of treatment planning for intensity-modulated radiotherapy. *Biomedical Signal Processing and Control*. 2010;5(3):189–95.

166. Dias J, Rocha H, Ferreira B, Lopes M do C. A genetic algorithm with neural network fitness function evaluation for IMRT beam angle optimization. *Central European Journal of Operational Research*. 2014;22(3):431–55.

167. Smith WP, Kim M, Holdsworth C, Liao J, Phillips MH. Personalized treatment planning with a model of radiation therapy outcomes for use in multiobjective optimization of IMRT plans for prostate cancer. *Radiation Oncology*. 2016 Dec 11;11(1):38.

168. McGeachy P, Madamesila J, Beauchamp A, Khan R. An open-source genetic algorithm for determining optimal seed distributions for low-dose-rate prostate brachytherapy. *Brachytherapy*. 2015;14(5):692–702.

169. Altomare C, Guglielmann R, Riboldi M, Bellazzi R, Baroni G. Optimal marker placement in hadrontherapy: Intelligent optimization strategies with augmented Lagrangian pattern search. *Journal of Biomedical Informatics*. 2015;53:65–72.

170. Ibáñez P, Vidal M, García-Marcos R, Guerra P, Udías JM. PD-0571: New genetic algorithm-based procedure to determine phase space for intraoperative radiation therapy. *Radiotherapy and Oncology*. 2015;115:S278–9.

171. Li YLY, Yao DYD, Chen WCW. *Adaptive particle swarm optimizer for beam*

angle selection in radiotherapy planning. IEEE International Conference Mechatronics and Automation 2005. 2005;1(July):421–5.

172. Lee EK, Fox T, Crocker I. *Simultaneous beam geometry and intensity map optimization in intensity-modulated radiation therapy*. In: International Journal of Radiation Oncology Biology Physics. 2006. p. 301–20.

173. Hartmann M, Bogner L. Investigation of intensity-modulated radiotherapy optimization with gEUD-based objectives by means of simulated annealing. *Medical Physics*. 2008 Apr 25;35(5):2041–9.

174. Robini MC, Smekens F, Sixou B. Optimal inverse treatment planning by stochastic continuation. *In: Proceedings - International Symposium on Biomedical Imaging*. 2011. p. 1792–6.

175. Bangert M, Ziegenhein P, Oelfke U. Characterizing the combinatorial beam angle selection problem. *Physics in Medicine and Biology*. 2012;57(20):6707–23.

176. Rocha H, Dias JM, Ferreira BC, Lopes MC. *Noncoplanar beam angle optimization in IMRT treatment planning using pattern search methods*. Journal of Physics: Conference Series. 2015 May 22;616:012014.

177. Kim DH, Wang-Chesebro A, Weinberg V, Pouliot J, Chen LM, Speight J, et al. High-dose-rate brachytherapy using inverse planning simulated annealing for locoregionally advanced cervical cancer: A clinical report with 2-year follow-up. *International Journal of Radiation Oncology Biology Physics*. 2009;75(5):1329–34.

178. Cunha JAM, Pouliot J, Weinberg V, Wang-Chesebro A, Roach M, Hsu IC. Urethra low-dose tunnels: Validation of and class solution for generating urethra-sparing dose plans using inverse planning simulated annealing for prostate high-dose-rate brachytherapy. *Brachytherapy*. 2012;11(5):348–53.

179. Yao R, Templeton AK, Liao Y, Turian J V., Kiel KD, Chu JCH. Optimization for high-dose-rate brachytherapy of cervical cancer with adaptive simulated annealing and gradient descent. *Brachytherapy*. 2014;13(4):352–60.

180. Pelagade S, Maddirala HR, Misra R, Suryanarayan U, Neema JP. Dosimetric comparison of volume-based and inverse planning simulated annealing-based dose optimizations for high-dose-rate brachytherapy. *Medical Dosimetry*. 2015;40(3):235–9.

181. Rossille D, Laurent JF, Burgun A. Modelling a decision-support system for oncology using rule-based and Cased-Based Reasoning methodologies. Vol. 74, *International Journal of Medical Informatics*. 2005. p. 299–306.

182. Ping XO, Tseng YJ, Lin YP, Chiu HJ, Lai F, Liang J Der, et al. A multiple measurements Cased-Based Reasoning method for predicting recurrent status of liver cancer patients. *Computers in Industry*. 2015;69:12–21.

183. Deshpande RR, DeMarco J, Sayre JW, Liu BJ. Knowledge-driven decision support for assessing dose distributions in radiation therapy of head and neck cancer. *International Journal of Computer Assisted Radiology and Surgery*. 2016;11(11):2071–83.

184. d'Aquin M, Lieber J, Napoli A. Adaptation knowledge acquisition: a case study for Cased-Based decision support in oncology. *Computational Intelligence*. 2006 Aug;22(3–4):161–76.

185. Salmeron JL, Papageorgiou EI. A fuzzy grey cognitive maps-based decision support system for radiotherapy treatment planning. *Knowledge-Based Systems*. 2012;30:151–60.

186. Good D, Lo J, Lee WR, Wu QJ, Yin FF, Das SK. A knowledge-based approach to improving and homogenizing intensity modulated radiation therapy planning quality among treatment centers: An example application to prostate cancer planning. *International Journal of Radiation Oncology Biology Physics*. 2013;87(1):176–81.

187. Schlaefer A, Dieterich S. Feasibility of case-based beam generation for robotic radiosurgery. *Artificial Intelligence in Medicine*. 2011;52(2):67–75.

188. Magome T, Arimura H, Shioyama Y, Nakamura K, Honda H, Hirata H. Similar-case-based optimization of beam arrangements in stereotactic body radiotherapy for assisting treatment planners. *BioMed Research International*. 2013;2013.

189. Khussainova G, Petrovic S, Jagannathan R. *Retrieval with clustering in a Cased-Based Reasoning system for radiotherapy treatment planning*. Journal of Physics: Conference Series. 2015 May 22;616:012013.

190. Petrovic S, Khussainova G, Jagannathan R. Knowledge-light adaptation approaches in Cased-Based Reasoning for radiotherapy treatment planning. *Artificial Intelligence in Medicine*. 2016;68:17–28.

191. Song X, Petrovic S, Sunder S. *A Cased-Based Reasoning approach to dose planning in radiotherapy*. In: The 7th International Conference on Cased-Based Reasoning. 2007. p. 13–6.

192. Lieber J, D'Aquin M, Badra F, Napoli A. Modeling adaptation of breast cancer treatment decision protocols in the Kasimir project. *Applied Intelligence*. 2008;28(3):261–74.

193. Cox A, Mishra N, Sayers I, Petrovic S, Sundar S. A decision aid for radiotherapy dose selection in prostate cancer based on non-linear Cased-Based Reasoning. *Clinical Oncology*. 2011;23(3):19–20.

194. Gu D, Liang C, Zhao H. A Cased-Based Reasoning system based on weighted heterogeneous value distance metric for breast cancer diagnosis. *Artificial Intelligence in Medicine*. 2017;77:31–47.

195. Slade S, Henry P. Cased-Based Reasoning : A research paradigm. *AI Magazine*. 1991;12(1):41–55.

196. Yin Z, Dong Z, Lu X, Yu S, Chen X, Duan H. A clinical decision support system for the diagnosis of probable migraine and probable tension-type headache based on Cased-Based Reasoning. *Journal of Headache and Pain*. 2015;16(1).

197. Begum S, Ahmed MU, Funk P, Xiong N, Folke M. Cased-Based Reasoning systems in the health sciences: A survey of recent trends and developments. Vol. 41, *IEEE Transactions on Systems, Man and Cybernetics Part C: Applications and Reviews*. 2011. p. 421–34.

198. Ayeldeen H, Shaker O, Hegazy O, Hassanien AE. *Cased-Based Reasoning: a knowledge extraction tool to use*. In: Information System Design and Intelligent Applications. Springer Link; 2015. p. 369–78.

199. Aamodt A, Plaza N. Case-Based Reasoning: Foundational issues, methodological variations and system approaches. *AI Communications*. 1994;7(1):39–59

200. Qian G, Sural S, Gu Y, Pramanik S. *Similarity between Euclidean and cosine angle distance for nearest neighbor queries*. In: Proceedings of the 2004 ACM symposium on Applied computing - SAC ’04. 2004. p. 1232.

201. Kumar KA, Singh Y, Sanyal S. Hybrid approach using Cased-Based Reasoning and rule-based reasoning for domain independent clinical decision support in ICU. *Expert Systems with Application*. 2009;36(1):65–71.

202. Weinberger K, Blitzer J, Saul L. Distance metric learning for large margin nearest neighbor classification. *Advances in neural information processing systems*. 2006;18:1473.

203. De Mantaras RL, Mcsherry D, Bridge D, Leake D, Smyth B, Craw S, et al. Retrieval, reuse, revision and retention in Cased-Based Reasoning. Vol. 20, *Knowledge Engineering Review*. 2005;20:215-40.

204. De Paz JF, Rodriguez S, Bajo J, Corchado JM. Cased-Based Reasoning as a decision support system for cancer diagnosis: A case study. *International Journal of Hybrid Intelligent Systems*. 2009;6(2):97–110.

205. Huang F, Jiang Z, Zhang S, Gao S. *Reliability evaluation of wireless sensor networks using logistic regression*. In: Communication and Mobile Computing, 2010 International Conference. 2010. p. 334–8.

206. Hwang C-L, Yoon K. *Concluding remarks*. In: Multiple Attribute Decision Making. 1981. p. 207–25.

207. Ferrari MD, Goadsby PJ, Lipton RB, Dodick DW, Cutrer FM, McCrory D, et al. The use of multiattribute decision models in evaluating triptan treatment options in migraine. *Journal of Neurology*. 2005;252(9):1026–32.

208. Rahimi S, Jamshidi A, Ait-Kadi D, Bartolome A. Risk-based decision making framework for prioritizing patients' access to healthcare services by considering uncertainties. *In: Industrial Engineering and Systems Management (IESM)*. 2015. p. 291–7.

209. Scalia G La, Aiello G, Rastellini C, Micale R, Cicalese L. Multi-criteria decision making support system for pancreatic islet transplantation. *Expert Systems with Application*. 2011;38(4):3091–7.

210. Lim GJ, Cao W. A two-phase method for selecting IMRT treatment beam angles: Branch-and-Prune and local neighborhood search. *European Journal of Operational Research*. 2012;217(3):609–18.

211. Tamiz M, Jones D, Romero C. Goal programming for decision making: An overview of the current state-of-the-art. *European Journal of Operational Research*. 1998;111(3):569–81.

212. Güler MG. A hierarchical goal programming model for scheduling the outpatient clinics. *Expert Systems with Application*. 2013;40(12):4906–14.

213. Güler MG, Idin K, Yilmaz Güler E. A goal programming model for scheduling residents in an anesthesia and reanimation department. *Expert Systems with Application*. 2013;40(6):2117–26.

214. Maenhout B, Vanhoucke M. An integrated nurse staffing and scheduling analysis for longer-term nursing staff allocation problems. *Omega*. 2013;41(2):485–99.

215. Wang SP, Hsieh YK, Zhuang ZY, Ou NC. Solving an outpatient nurse scheduling problem by binary goal programming. *Journal of Industrial and Production Engineering*. 2014;31(1):41–50.

216. Cappanera P, Visintin F, Banditori C. Addressing conflicting stakeholders' priorities in surgical scheduling by goal programming. *Flexible Services and Manufacturing Journal*. 2016;1–20.

217. Oddoye JP, Jones DF, Tamiz M, Schmidt P. Combining simulation and goal programming for healthcare planning in a medical assessment unit. *European Journal of Operational Research*. 2009;193(1):250–61.

218. Turgay S, Taşkin H. Fuzzy goal programming for health-care organization. *Computers and Industrial Engineering*. 2015;86:14–21.

219. Chaerul M, Tanaka M, Shekdar A V. Resolving complexities in healthcare waste management: A goal programming approach. *Waste Management and Research*. 2008;26(3):217–32.

220. Özkan A. Evaluation of healthcare waste treatment/disposal alternatives by using multi-criteria decision-making techniques. *Waste Management and Research*. 2013 Feb 11;31(2):141–9.

221. Chattopadhyay S, Banerjee S, Rabhi FA, Acharya UR. A Cased-Based Reasoning system for complex medical diagnosis. *Expert Systems*. 2013;30(1):12–20.

222. Wu P-C, Huang T-H, Pan S-C. Country performance evaluation: the DEA model approach. *Social Indicators Research*. 2014;118(2).

223. Berenguer G, Iyer A V., Yadav P. Disentangling the efficiency drivers in country-level global health programs: an empirical study. *Journal of Operations Management*. 2016;45:30–43.

224. Wang K, Yu S, Zhang W. China's regional energy and environmental efficiency: A DEA window analysis based dynamic evaluation. *Mathematical and Computer Modeling*. 2013;58(5–6):1117–27.

225. Du J, Wang J, Chen Y, Chou S-Y, Zhu J. Incorporating health outcomes in Pennsylvania hospital efficiency: an additive super-efficiency DEA approach. *Annals of Operations Research*. 2014 Oct 3;221(1):161–72.

226. Chen Y, Chiu Y, Huang C, Tu C. The analysis of bank business performance and market risk—Applying Fuzzy DEA. *Economic Modelling*. 2013;32:225–32.

227. Cooper W, Seiford L, Tone K. *Introduction to data envelopment analysis and its uses: with DEA-solver software and references*. 2006.

228. Adler N, Golany B. Evaluation of deregulated airline networks using data envelopment analysis combined with principal component analysis with an application to Western Europe. *European Journal of Operational Research*. 2001;132(2):260–73.

229. Adler N, Golany B. Including principal component weights to improve

discrimination in data envelopment analysis. *Journal of the Operational Research Society*. 2002 Sep 21;53(9):985–91.

230. Manly B, Alberto J. *Multivariate statistical methods: a primer*. 4th ed. Boca Raton Florida: CRC Press; 2016.

231. Suhr D. *Principal component analysis vs. exploratory factor analysis*. pdfs.semanticscholar.org [Internet]. [cited 2018 May 3]; Available from: https://pdfs.semanticscholar.org/936e/76d8f2203cb534a3952d3ea7032fc57f8ad0.pdf

232. Lam K, Tao R, Lam M. A material supplier selection model for property developers using fuzzy principal component analysis. *Automation in Construction*. 2010;19(5):608–18.

233. Doukas H, Papadopoulou A, Savvakis N, Tsoutsos T, Psarras J. Assessing energy sustainability of rural communities using Principal Component Analysis. *Renewable and Sustainable Energy Reviews*. 2012;16(4):1949–57.

234. Jenkins L, Anderson M. A multivariate statistical approach to reducing the number of variables in data envelopment analysis. *European Journal of Operational Research*. 2003;147(1):51–61.

235. Dyson RG, Allen R, Camanho AS, Podinovski V V., Sarrico CS, Shale EA. Pitfalls and protocols in DEA. *European Journal of Operational Research*. 2001;132(2):245–59.

236. Põldaru R, Roots J. A PCA–DEA approach to measure the quality of life in Estonian counties. *Socio-Economic Planning Sciences*. 2014;48(1):65–73.

237. Cazes P, Chouakria A, Diday E. Extension de l'analyse en composantes principales à des données de type intervalle. eudml.org; Available from: https://eudml.org/doc/106421

238. Wang H, Guan R, Wu J. CIPCA: Complete-Information-based Principal Component Analysis for interval-valued data. *Neurocomputing*. 2012;86:158–69.

239. Liu B, Shen Y, Zhang W, Chen X, Wang X. An interval-valued intuitionistic fuzzy principal component analysis model-based method for complex multi-attribute large-group decision-making. *European Journal of Operational Research*. 2015;245(1):209–25.

240. Julong D. *Introduction to Grey System Theory*. [cited 2018 May 4]; Available from: http://www.researchinformation.co.uk/grey/IntroGreySysTheory.pdf

241. Xuerui T, Yuguang L. Using grey relational analysis to analyze the medical data.

Kybernetes. 2004 Feb;33(2):355–62.

242. İçer S, Coşkun A, İkizceli T. Quantitative grading using Grey Relational Analysis on ultrasonographic images of a fatty liver. *Journal of Medical Systems*. 2012 Aug 28;36(4):2521–8.

243. Li Z, Wen G, Xie N. An approach to fuzzy soft sets in decision making based on grey relational analysis and Dempster–Shafer theory of evidence: An application in medical diagnosis. *Artificial Intelligence in Medicine*. 2015;64(3):161–71.

244. Moore RE, Society for Industrial and Applied Mathematics. *Methods and applications of interval analysis*. Society for Industrial and Applied Mathematics (SIAM, 3600 Market Street, Floor 6, Philadelphia, PA 19104); 1979. 190 p.

245. Harman H. *Modern factor analysis*. University of chicago Press; 1976. Available from: https://books.google.co.uk/books?hl=en&lr=&id=e-vMN68C3M4C&oi=fnd&pg=PR11&dq=%5D+Harman+HH.+Modern+factor+analysis.+University+of+Chicago+Press%3B+1976+Apr+1&ots=t5JoJvbX-A&sig=oDWzhV6sKbVEcgaBjjZNVXRt-5w

246. Bryant F, Yarnold P. *Principal-components analysis and exploratory and confirmatory factor analysis*. 1995 [cited 2018 May 3]; Available from: http://psycnet.apa.org/record/1995-97110-004

247. Vogt W, Johnson R. *Dictionary of statistics and methodology: a nontechnical guide for the social sciences*. 4th ed. Los Angeles: SAGE; 2011.

248. McDonald R. *Factor analysis and related methods*. New Jeresey: Lawrence Erlbaum Associates; 2014.

249. Nayar P, Ozcan YA. Data Envelopment Analysis comparison of hospital efficiency and quality. *Journal of Medical Systems*. 2008 Jun 22;32(3):193–9.

250. Kawaguchi H, Tone K, Tsutsui M. Estimation of the efficiency of Japanese hospitals using a dynamic and network data envelopment analysis model. *Health Care Management Science*. 2014 Jun 13;17(2):101–12.

251. Thanassoulis E, Portela M, Graveney M. Identifying the scope for savings at inpatient episode level: An illustration applying DEA to chronic obstructive pulmonary disease. *European Journal of Operational Research*. 2016;255(2):570–82.

252. Molinero CM, Woracker D. Data Envelopment Analysis: OR Insight [Internet]. 1996 Oct 1 [cited 2018 May 4];9(4):22–8. Available from:

http://link.springer.com/10.1057/ori.1996.21

253. Cooper WW, Seiford LM, Zhu J. Chapter 1:Data Envelopment Analysis. In: Handbook on Data Envelopment Analysis. *International series in operations research and management science*. 2nd ed. Springer; 2011;1–39.

254. Despotis D, Smirlis Y. Data envelopment analysis with imprecise data. *European Journal of Operational Research*. 2002;140(1):24–36.

255. Adler N, Golany B. Pca-Dea. *Modeling Data Irregularities and Structural Complexities in Data Envelopment Analysis*. 2007. 139-153 p.

256. Yip AYN. *Predicting business failure with a Cased-Based Reasoning approach*. In International Conference on Knowledge-Based and Intelligent Information and Engineering Systems 2004. p. 665–71.

257. Chuang C-L. Application of hybrid Cased-Based Reasoning for enhanced performance in bankruptcy prediction. *Information Sciences*. 2013;236:174–85.

258. Wu D, Li J, Liang Y. Linear combination of multiple Cased-Based Reasoning with optimized weight for software effort estimation. *The Journal of Supercomputing*. 2013;64(3):898–918.

259. Twala B, Verner J. *Toward accurate software effort prediction using multiple classifier systems*. Computational Intelligence and Quantitative Software Engineering 2016 (pp. 135-151). Springer, Cham.

260. Wang H, Sun B, Shen X. Hybrid similarity measure for retrieval in Cased-Based Reasoning systems and its applications for computer numerical control turret design. *Proceedings of the Institution of Mechanical Engineers, Part B: Journal of Engineering Manufacture*. 2018 Apr 27;232(5):918–27.

261. Biswas SK, Chakraborty M, Singh HR, Devi D, Purkayastha B, Das AK. Hybrid Cased-Based Reasoning system by cost-sensitive neural network for classification. *Soft Computing*. 2017;21(24):7579–96.

262. Li X, King I. Gaussian mixture distance for information retrieval. *In: Neural Networks*. 1999. p. 2544–9.

263. MacDonell S, Shepperd M. Combining techniques to optimize effort predictions in software project management. *Journal of Systems and Software*. 2003;66(2):91–8.

264. Clemen R. Combining forecasts: A review and annotated bibliography. *International Journal of Forecasting*. 1989;5(4):559–83.

265. Pan R, Yang Q, Pan S. Mining competent case bases for Cased-Based

Reasoning. *Artificial Intelligence*. 2007;171(16):1039–68.

266. Ahn H, Kim K. Bankruptcy prediction modeling with hybrid Cased-Based Reasoning and genetic algorithms approach. *Applied Soft Computing*. 2009;9(2):599–607.

267. Inbarani H, Azar A, Jothi G. Supervised hybrid feature selection based on PSO and rough sets for medical diagnosis. *Computer Methods and Programs Biomedicine*. 2014;113(1):175–85.

268. Man K, Tang K, Kwong S. *Genetic Algorithms: Concepts and Designs*. 2nd ed. London: Springer; 1999.

269. Gen M, Cheng R, Lin L. *Network models and optimization: Multiobjective genetic algorithm approach*. London: Springer; 2008.

270. Julong D. Introduction to Grey System Theory. *Journal of Grey Systems*. 1989;1:1–24.

271. Barricelli NA. Numerical testing of evolution theories - Part II preliminary tests of performance. symbiogenesis and terrestrial life. *Acta Biotheoretica*. 1963;16(3–4):99–126.

272. Michalewicz Z, Janikow CZ, Krawczyk JB. A modified genetic algorithm for optimal control problems. *Computers & Mathematics with Applications*. 1992;23(12):83–94.

273. Lee Y, Leavens C, Ruschin M. *Evaluation of Monaco treatment planning system for hypofractionated stereotactic volumetric arc radiotherapy of multiple brain metastases*. Available from: https://www.elekta.com/dam/jcr:3788a607-f1b5-441b-8ae3-ba86eefd91ac/Odette Cancer Centre case study.pdf

274. *Isodose curves radiation oncology*. Available from: https://www.slideshare.net/paulpampz04/isodose-curves-26644276