A Novel Case-Based Reasoning Appraoch to Radiotherapy Dose Planning

by
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Abstract

In this thesis, novel Case-Based Reasoning (CBR) methods were developed to be included in CBRDP (**C**ase-**B**ased **R**easoning **D**ose **P**lanner) -an adaptive decision support system for radiotherapy dose planning. CBR is an artificial intelligence methodology which solves new problems by retrieving solutions to previously solved similar problems stored in a case base. The focus of this research is on dose planning for prostate cancer patients. The records of patients successfully treated in the Nottingham University Hospitals NHS Trust, City Hospital Campus, UK, were stored in a case base and were exploited using case-based reasoning for future decision making. After each successful run of the system, a group based Simulated Annealing (SA) algorithm automatically searches for an optimal/near optimal combination of feature weights to be used in the future retrieval process of CBR.

A number of research issues associated with the prostate cancer dose planning problem and the use of CBR are addressed including: (a) trade-off between the benefit of delivering a higher dose of radiation to cancer cells and the risk to damage surrounding organs, (b) deciding when and how much to violate the limitations of dose limits imposed to surrounding organs, (c) fusion of knowledge and experience gained over time in treating patients similar to the new one, (d) incorporation of the 5 years Progression Free Probability and success rate in the decision making process and (e) hybridisation of CBR with a novel group based simulated annealing algorithm to update knowledge/experience gained in treating patients over time.

The efficiency of the proposed system was validated using real data sets collected from the Nottingham University Hospitals. Experiments based on a leave-one-out strategy demonstrated that for most of the patients, the dose plans generated by our approach are coherent with the dose plans prescribed by an experienced oncologist or even better. This system may play a vital role to assist the oncologist in making a better decision in less time; it incorporates the success rate of previously treated similar patients in the dose planning for a new patient and it can also be used in teaching and training processes. In addition, the developed method is generic in nature and can be used to solve similar non-linear real world complex problems.

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Finally, I would like to thank my colleagues in the School of Computer Science, University of Nottingham for their support throughout the doctoral study.

Dedicated to

My dear mother, Smt. Shobha Mishra and father, Shri Bijay Kumar Mishra

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CHAPTER 1

Introduction

In this thesis, novel case-based reasoning approaches to radiotherapy dose planning problems are presented. The problem of dose planning for prostate cancer at the Nottingham University Hospitals NHS, City Hospital Campus, UK are investigated. The proposed case-based reasoning framework is generic in nature and can be used to solve similar complex non-linear real world problems. In this chapter, research background, motivation, research objectives and layout of the thesis are described.

1.1 Background

Cancer is a class of disease, caused by abnormal and uncontrolled proliferation of cells. It can spread to other parts of the body either directly or through the blood or the lymph. Lymph is a clear fluid that travels through the lymphatic system and one of its functions is to carry cells that defend the body against both infectious diseases and foreign materials. Cancer is an environmental disease with 90-95% of its cases attributed to environmental factors and 5-10% due to genetics [1]. The common environmental factors related to cancer deaths are: tobacco (25-30%), diet and obesity (30-35%), infections (15-20%), radiation (10%), stress and lack of physical activity (5-10%) [1]. There are more than 100 different types of cancers. It is generally named after the organ or the type of the cell in which it started. For example, cancer that begins in the prostate (a small gland of the male reproductive system) is called prostate cancer.

In a survey, it was found that 12.7 million new cases of cancer are diagnosed around the world every year and this number is expected to increase to 26 million by 2030 [2]. The UK has one of the highest cancer rates (22^{nd}), about 267 in 100,000 people in this country are diagnosed with cancer each year. One in four (27%) of all deaths in the UK are caused by cancer. There were 156,723 cancer deaths in the UK in the year 2008 [3]. The four most common cancers in the UK are breast cancer, colon cancer. prostate cancer and lung cancer. Prostate cancer is the most common form of cancer among the male population. In 2008, there were 37,051 new cases of prostate cancer diagnosed in the UK, which is around 101 men every day or one man every 15 minutes [4].

1.2 Motivation

Radiotherapy planning is a complex and time consuming process. In the earlier days, oncologists used to spend a large amount of time to generate a treatment plan using their past experience. A poorly constructed treatment plan may have an overdose to the normal cells and/or a under dose to the cancer cells. The planning process has drawn considerable attention from both practitioners and academics over the past few decades and led to the development of several software systems such as Helax-TMS, CMS Xio and Oncentra MasterPlan.

Most of the existing software systems are generic in their nature. However, different hospitals usually follow different ways of treatment while respecting the recommended guidelines of the UK standard. For example, in the Nottingham University Hospital oncologists usually use a fixed number of beams (i.e. four beams) in prostate cancer treatment. The radiotherapy problem

can be described as an optimisation problem. However, due to the large size of the search space of the problem it is difficult to achieve approximate global optimality using existing software. The main goal of all the developed optimisation methods is to attain a uniform tumoricidal dose and to minimise the side effects of the treatment. However, success rate of the treatment is often overlooked. It is very difficult to develop a mathematical model which would judge the success rate of the plan before the treatment. This can be predicted to some extent from the past experience of the oncologist.

Researchers investigated different knowledge based methods such as rule-based reasoning, case-based reasoning or hierarchical organisation of knowledge to capture the expertise and experience of oncologists in treating previous patients. They tried to mimic the way an oncologist plans the treatment. However, the developed knowledge-based methods are generally static in nature. In real life, oncologists cautiously learn from their past experience.

The lack of academic and industrial research in provision of adaptive methods for the radiotherapy planning problem which learn over time has inspired this PhD research. Radiotherapy dose planning process followed in the Nottingham University Hospital was investigated and various modeling issues were identified. In particular, the following issues were addressed:

–How to make a trade-off between the benefits of delivering a higher dose of radiation and the risk to surrounding organs.

–How to incorporate the experience of an oncologist to decide when and how much to violate limitations on the dose limits.

–How to fuse knowledge and experience in treating patients similar to new ones.

–How to include the 5 years Progression Free Probability and the success rate in the decision making process.

–How to update knowledge/ experience in treating patients over time.

1.3 Research Objectives

In this thesis, CBRDP (**C**ase-**B**ased **R**easoning **D**ose **P**lanner), an adaptive decision support system, was developed for radiotherapy dose planning problems. During its development the radiotherapy dose planning problem, as well as the methods which currently exist to solve them, were thoroughly investigated. The thesis aims to address the following research objectives:

(a) To investigate the complex radiotherapy dose planning problems, in particular focusing on the problem of determining the most appropriate dose plan for prostate cancer in the two stage treatment process.

(b) To explore the use of various existing methods in addressing the radiotherapy planning problems.

(c) To investigate the non-linear nature of the radiotherapy dose planning problem and to explore current 'state-of-the-art' case-based reasoning methods to resolve them.

(d) To model a complex radiotherapy dose planning problem followed in the Nottingham University Hospital, UK and to explore the relevance of this model to other problems in the literature.

(e) To study and investigate the oncologists' decision making process for radiotherapy dose planning. This will also include the trade-off between

(f) To develop an adaptive novel case-based reasoning method for radiotherapy dose planning problems which can also be used to solve a wide variety of similar non-linear optimisation problems.

In addition to the aforementioned objectives, the development of the CBRDP also addresses these additional objectives:

(a) To investigate the issues related to the dose planning problems and its representation and generalisation so that it can be applied to a wide range of similar future problems.

(b) To develop a novel method for case retrieval and adaptation to imitate the decision making process of the human expert.

(c) To integrate the CBR system with a meta-heuristic search method to develop an adaptive decision support system.

1.4 Layout of the Thesis

This thesis is organised into seven chapters including this introduction chapter. The entire thesis is divided into three parts as shown in Figure 1.1. In part I, 'state-of-the-art' case-based reasoning and radiotherapy planning problems are described. In part II, a Dempster-Shafer rule based CBR, a knowledge-light adaptation and an adaptive knowledge-light adaptation in CBR for radiotherapy planning are described. In part III, conclusions and future research work are described. Contribution of each chapter is highlighted in grey colour. The outline of the content of each chapter in this thesis is summarised below:

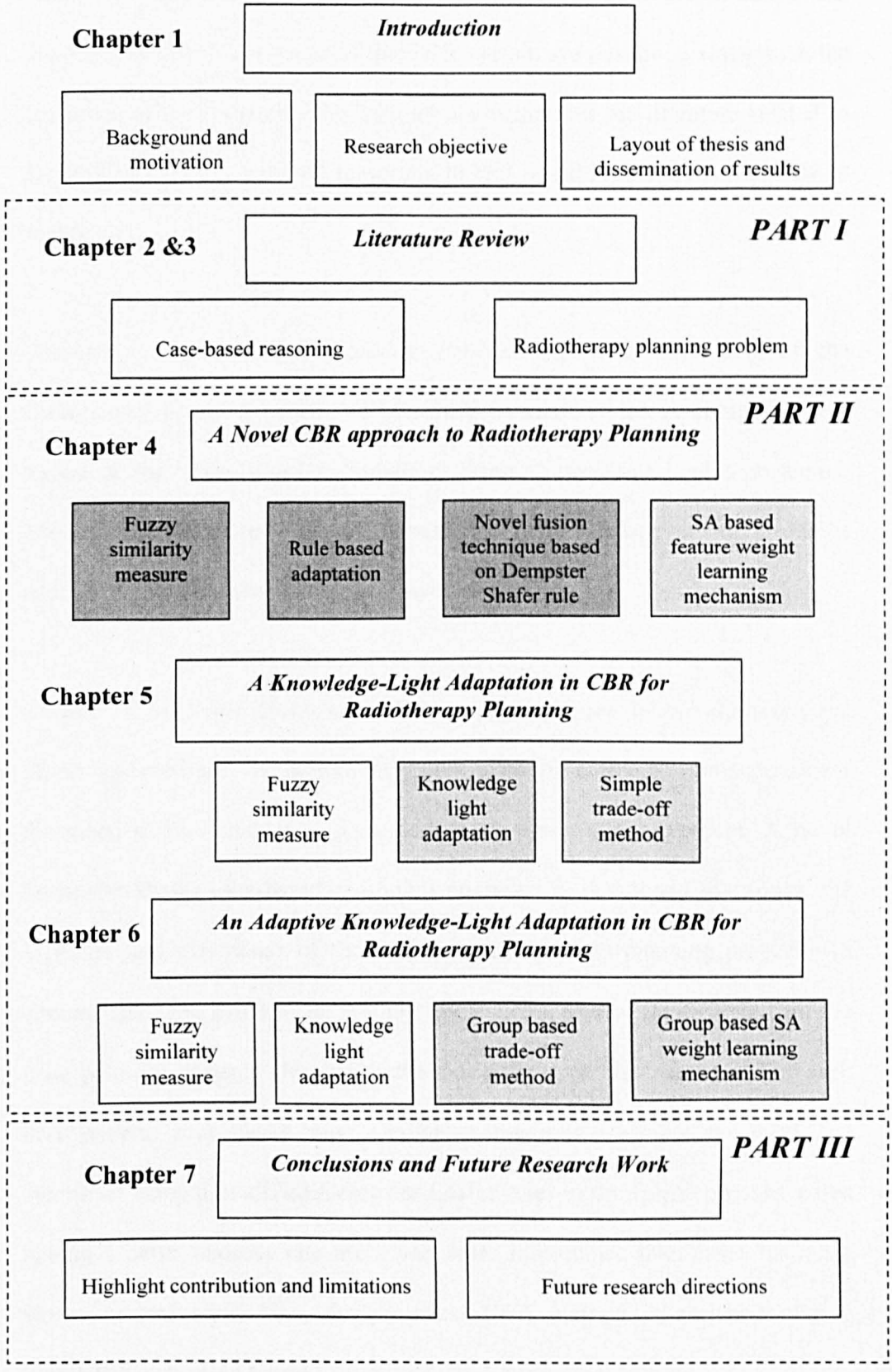


Figure 1.1 Structure of the thesis

Chapter 2 'Case-Based Reasoning': In this chapter, an overview of case-based reasoning is given. The steps of the CBR system are described along with the key areas of the research. This chapter also discusses the literature related to the application of case-based reasoning to real world problems, particularly in healthcare.

Chapter 3 'Radiotherapy Planning Problem': A brief overview of the radiotherapy planning process is presented in this chapter. A comprehensive review of the 'state-of-art' radiotherapy planning problems is also presented. The existing literature is classified based on two criteria: types of problems addressed and the methods used to solve them.

Chapter 4 'A Novel Case-Based Reasoning Approach to the Radiotherapy Planning Problem': The radiotherapy dose planning problem to prostate cancer discussed in this chapter is presented as an optimisation problem. A novel Dempster-Shafer case-based reasoning approach is developed to capture the expertise and experience of the oncologist in the dose planning process. An attempt has been made to incorporate the success rate of the treatment in the dose planning process along with the side effects of the treatment. For each new patient, four cases most similar to the new case are retrieved and combined using a modified Dempster-Shafer rule. In the fusion process, cases having a better success rate are given more importance than cases having a worse success rate. Also, the proposed CBR method is enriched with a Simulated Annealing based feature weights learning mechanism.

Chapter 5 'A Knowledge-Light Adaptation in Case-Based Reasoning for Radiotherapy Planning: In this chapter, firstly, the non-linear nature of the dose planning problem is discussed. Thereafter, a knowledge-light adaptation in case-based reasoning method is proposed to make a trade-off between the benefit and risk of the treatment. For each new patient, a case having a similar difference vector and gradient is retrieved as the new case and the dose limits of different volume percentages of the rectum, which surrounds the prostate, are calculated. Thereafter, based on calculated dose limits, the doses in phases I and II of the treatment are determined. The retrieval process is enriched by incorporating the 5 years Progression Free Probability and the success rate of the treatment in the similarity measure.

Chapter 6 'An Adaptive Knowledge-Light adaptation in case-based reasoning for Radiotherapy Planning': In this chapter, a novel group based trade-off method is proposed to ease the decision making process of the oncologist. The novel trade-off method makes a compromise between the benefit of the radiation and retrieves the case most similar to the new case. Firstly, cases are divided into different groups and trade-off is made by relaxing the constraints. Thereafter, knowledge-light adaptation is used to calculate the dose in phases I and II of the treatment. After each run of the system the feature weights are updated automatically using a group based Simulated Annealing approach.

Chapter 7 'Conclusions and Future Research Work': In this chapter, both a conclusion and a discussion about the effectiveness of the developed methods are presented. Firstly, an analysis of how the research objectives mentioned in

the introduction chapter were achieved is given. Secondly, some suggestions are given for continuation of the work presented in this thesis.

1.5 Dissemination of Results

The research described in this thesis has been disseminated through conferences, seminars and research publications in both medical and artificial intelligence fields. Below is a list of all the publications and the conferences/seminars which have been attended:

1.5.1 Journal Papers

[5] S. Petrovic. N. Mishra and S. Sundar. A novel case based reasoning approach to radiotherapy planning. *Expert Systems with Applications,* 38 (9), *10759-10769, 2011.*

This paper introduces a modified Dempster-Shafer rule which is used in the fusion of multiple cases retrieved in the retrieval process. The weights corresponding to each features used in the retrieval process are updated using a Simulated Annealing based weight leaning mechanism.

[6] N. Mishra, S. Petrovic, and S. Sundar. A Self-Adaptive Case-Based Reasoning System for Dose Planning in Prostate Cancer Radiotherapy, Accepted for publication in *Medical Physics Journal.*

In this paper, a novel trade-off method is addressed to make a compromise between the risk and the benefit of the radiation and to retrieve the case most similar to the new case. A group based Simulated Annealing approach to determine the importance (weights) of different clinical parameters used in the retrieval process is introduced.

1.5.2 Conference Papers

[7] A. Cox, N. Mishra, I. Sayers, S. Petrovic and S. Sundar, A decision aid for radiotherapy dose selection in prostate cancer based on non-linear Case Based Reasoning, *UK Radiation Oncology Conference, Manchester, UK* , 11th - 13th April, 2011

In this paper, the 5 years Progression Free Probability and success rate of the treatment in dose planning process is incorporated.

[8] N. Mishra, S. Petrovic and S. Sundar, A knowledge-light nonlinear case-based reasoning approach to radiotherapy planning, *in Proceedings of the 21st International Conference on Tools with Artificial Intelligence (ICTAI), Newark Liberty International Airport Marriott Newark (NYC Metropolitan Area), New Jersey, USA, 2-5 November,* 2009, pp. 776-783.

This paper introduces a knowledge-light adaptation in case-based reasoning to determine the dose limits of different volume percentages of the rectum.

[9] N. Mishra, S. Petrovic and S. Sundar, A non-linear case based reasoning approach to radiotherapy dose planning, *in Proceedings of the 35th annual Operational Research Applied to Health Services (ORAHS) Leuven, Belgium, 12-17 July,* 2009, 24, 2009

A case-based reasoning approach which takes into consideration the trade-off between risk and benefit of the proposed radiation is proposed in this paper.

[10] N. Mishra, S. Petrovic and S. Sundar, A Novel Case Based Reasoning Approach to Radiotherapy Planning, *in Proceedings of the 18th Triennial Conference of the International Federation of Operational Research Societies (IFORS'08), Sandton, South Africa, 13-18 July, 2008,* 66, 2008.

This article introduces a modified Dempster-Shafer rule based CBR approach to radiotherapy dose planning problems.

1.5.3 Book Chapters

[11] N. Mishra, S. Petrovic and S. Sundar, Self-adaptive case based reasoning for dose planning in radiotherapy, *in the book of the 36th annual Operational Research Applied to Health Services (ORAHS), 18-23 July, 2010*, 28-46, 2010.

In this article a group based Simulated Annealing approach is proposed to determine the weights corresponding to each feature used in the retrieval process.

1.5.4 Seminars and workshops

"A novel cased-based reasoning approach to radiotherapy treatment planning" presented at the workshop on LANCS Healthcare Modelling PhD Symposium, Cardiff University, 18th- 20th January, 2009.

"A non-linear case-based reasoning approach to radiotherapy dose planning" presented at the Automated Scheduling, Optimization and Planning Research

Group, School of Computer Science, University of Nottingham, 16th October, 2009.

"A case-based reasoning approach to dose planning in Radiotherapy" presented at the Automated Scheduling, Optimization and Planning Research Group, School of Computer Science, University of Nottingham, 3rd July, 2008.

"A novel case-based reasoning approach to radiotherapy planning" presented at the workshop on Radiotherapy Planning and Scheduling, Coventry University, 27th February, 2008.

CHAPTER 2

Case-Based Reasoning (CBR)

2.1 Introduction

Case-Based Reasoning is a knowledge based reasoning paradigm in which new problems are solved using the solutions of similar problems that have previously been resolved [12-13]. It is influenced by a cognitive model of human problem solving techniques. In the cognitive model, humans learn from their day-to-day experiences and store the empirical knowledge in the form of episodic memory. New problems are compared with the past experience based on psychological knowledge [14-15]. Thereafter, the most similar past experience is recalled and reused with small modifications according to the requirements of new problems.

2.2 What is Case-Based Reasoning?

In case-based reasoning, previously solved problems and their solutions are stored as cases in a data base known as a case base. For each new problem, cases similar to the new case are retrieved from the case base. If the new problem is the same as the extracted case, the solution of the new case is directly copied from it; otherwise it is revised using domain knowledge, so that the retrieved solution becomes relevant in the context of the new problem. Finally, if information gained from the new problem is useful for future reasoning then it is stored in the case base for future use. The aforementioned

steps make up the basic framework of a vast variety of different CBR approaches and are described in this chapter.

Case-based reasoning has a number of advantages as well as disadvantages over other problem solving techniques. The main advantages and disadvantages can be summarized as follows:

The main advantages of the CBR system are:

i. Case-based reasoning is easy to understand. During reasoning it cites actual cases solved in the past. Citing actual cases makes the explanation easier.

ii. Case-based reasoning helps to produce a solution to a new problem quickly by avoiding unnecessary time to derive the solution from scratch.

iii. It can capture ill-defined problems without a complete understanding of the complex system and can predict the solution for new problems, based on what has been worked in the past.

iv. Case-based reasoning increases competency over time. It helps the reasoner to avoid mistakes by remembering mistakes that have occurred in the similar scenarios.

v. Cases in the case base help the reasoner to focus on the important parts of a problem by pointing out important features of a problem.

vi. It can handle unexpected or missing inputs by assessing their similarity to stored cases or by reusing relevant cases.

vii. It is self-adaptive in nature. New knowledge in the form of new cases, faced in real operation, can be incorporated into the case base.

The main disadvantages of case-based reasoning are:

i. Case-based reasoning relies only on previously solved cases without validation in the new situations [12].

ii. Maintenance of the case base is a tedious task. Sometimes it is hard to design and develop a good quality case base.

iii. Knowledge acquisition (reasoning) is a problem when dealing with domains where cases are either unavailable or are only available in limited amounts.

iv. Sometimes it is hard to implement a CBR system in a dynamic problem domain.

v. In case-based reasoning, explanations of the solution are not always straightforward as in rule-based systems. Sometimes it is difficult to give explanations for all of the reasoning steps.

2.3 Methodology and Research Issues in CBR

In the literature, a large number of models have been suggested to address real world problems. The detailed description of the basic principle of case-based reasoning and its history could be found in the work of Kolonder (1993) [12]. This subject field is vast and in this chapter the author will attempt to focus on those models and research issues that are relevant only to the application of case-based reasoning in radiotherapy dose planning.

2.3.1 Case-Based Reasoning Framework

Based on their execution process, case-based reasoning systems can be divided into two categories: problem-solving CBR and interpretive CBR [12]. In the

problem solving CBR, the solution of the new problem is proposed based on the most similar retrieved case(s). It is generally used where solutions cannot be determined in advance, such as radiotherapy dose planning problems, whereas in interpretive CBR, the case base is used to justify the prescribed solution.

The overall framework of a CBR approach comprises four activities: Retrieve, Reuse, Revise and Retain [15]. In the retrieve stage, a case (or cases) which is (or are) most similar to the new case is (are) retrieved. In the reuse stage, the retrieved case is used to generate a solution for the new case. However, sometimes a solution generated by the reuse stage is incomplete or not fit for the new case. In this situation, the solution generated in the reuse step has to be revised to better fit the new problem and that is referred to as the revise stage. It compensates the differences between a retrieved case and a new case. Finally, in the retain stage, if the new solution is useful for future problem solving then it is stored in the case base for future use.

2.3.2. Case Representations

The performance of a CBR system, especially in a complex problem domain, depends heavily on case representation. In knowledge based reasoning, the decision is usually based on: problem features and how they are linked. However, in CBR, the decision is based on the problem features only [12].

A case usually consists of two major parts: problem parameters which describe the conditions under which similar case(s) should be retrieved and the solution to the problem. Each case describes knowledge relevant to a particular problem

instance. Cases can be classified according to their characteristics into three categories: *abstract/ concrete, partial/ complete* and *related/ isolated* [16].

Abstract/ Concrete: cases correspond to generalized or concentrated information.

Partial/Complete: is generally used where knowledge is inconsistent or suffers from stochastic interference. A case in the case base is divided into different sub-units and each sub-unit consists of different knowledge.

Related/Isolated: cases in the case base may be linked to each other in the form of a hierarchy or relationship network or are independent from each another.

The structure of the case affects the retrieval and revise steps of case-based reasoning. The accuracy and search time of the CBR system usually increases as the number of problem parameters increases. Cases normally contain all the necessary information so that the system performance is not degraded by the presence of erroneous, incomplete, or irrelevant information. It is argued by the researchers that the search time can be minimized by a good choice of case representation. A good case representation must be *Predictive, Abstract, Concrete,* and *Useful* [12, 17, 18].

Predictive: Cases should contain all the information that was taken into account in the decision (solution) making process.

Abstract: stored information should be generic and applicable to all possible future problems.

Concrete: the problem parameters should not be too abstract. A case cannot be recognized as being similar to the cases in the case base without extensive inference.

Useful: stored information must be relevant to the problem being solved.

Cases are usually represented as vectors of attribute value pairs. These attributes may have different measurement units with different scales. They can be numeric, symbolic, boolean, or object-based. The complexity of the structure increases as the complexity of the problem domain increases. Also, sometimes information/ knowledge collected from decision makers is imprecise. To manage the above difficulties in this thesis, a fuzzy membership function based representation method is used.

2.3.3 Retrieval

When a new problem arrives, a case based system first looks for a good case (or cases) in the case base [12]. A good case is the case most similar to the new problem and has the potential to make relevant predictions about the new problem. The retrieval process generally uses a similarity measure to rank the cases in the case base; often the highest ranked case is retrieved for further calculation. The success of a CBR system depends primarily on the similarity measure calculation. With an efficient similarity measure, we can obtain a good ordered list of similar cases. In the literature, many approaches such as Nearest Neighbour (NN), k Nearest Neighbour (k-NN), and Induction Algorithms based similarity measures have been developed. The choice depends heavily on the nature of the problem.

The Nearest Neighbour (NN) similarity measure is generally used for problems that can be characterized by feature vectors. Cases are represented as points in the feature space. One of the most common nearest neighbour distances used in the NN method is:

$$D(c_I, c_R) = \sum_{i=1}^{n} sim(f_i^I, f_i^R) \tag{1.1}$$

where,

$D(c_I, c_R)$ = distance between cases c_I and c_R

n = number of problem features in each case

sim = distance function

f_i^I = value of feature i in the input case c_I

f_i^R = value of feature i in the retrieved case c_R

The similarity is often calculated using the *Euclidian distance* between the points.

The NN methods can be extended by assigning weights to the problem features. Weights assigned to the problem features in the similarity measure represent their relative importance.

$$D(c_I, c_R) = \sum_{i=1}^{n} w_i sim(f_i^I, f_i^R) \tag{1.2}$$

where, w_i is the weight of feature i.

Sometimes, for a large data base it is very expensive to compare sequentially each and every case in the case base. Zhang et al. [19] proposed an indexing based NN method and restricted the search to a subset of the case base. However, this approach raises several problems. It usually does not give good results in constraint satisfaction problems that typically have a wide range of related constraints. In order to overcome the above limitation, Borner [20] proposed a structural similarity measure approach to assess the similarity between cases. Firstly, cases are represented by graphs, where problem features are represented by nodes and relations between them are denoted by edges.

Thereafter, similarity between the graphs is calculated and the most similar cases were retrieved.

For complex systems such as medical diagnosis, sometimes a single retrieved case is not sufficient to predict the solution of a new case. Wettschereck et al. [21] proposed the k Nearest Neighbour (k-NN) method, retrieved a set of nearest cases and used a voting system to determine which case will be passed on to the next steps.

Some CBR systems use induction algorithms such as ID family [22] and AQ family [23] for case retrieval. In the induction algorithm, cases in the case base are ranked using the decision tree method. The induction algorithm based retrieval process is faster but it needs to be adjusted when new cases are added to the case base and furthermore it is usually not suitable in dynamic domains.

Aamodat and Plaza [25] divided the case retrieval process into two categories: syntactical and semantical. In the syntactical method, the similarity measure is usually calculated based on the superficial knowledge of the system and is generally used in domains where explicit knowledge is difficult to elicit; whereas the retrieval process based on the semantic method employs deep and complex knowledge to compare feature values including their relative weights.

In the literature, usually a case most similar to the new case is retrieved for future decision making processes. However, sometimes the extraction of one similar case may lose important information contained in other similar cases [24]. Further, if the case base contains opinions of more than one decision maker, there may be a chance that different decision makers have different opinions about a solution for a similar situation. Moreover, the existing retrieval mechanisms extract a case taking into account the similarity measure.

In real life, decision makers sometimes make a trade-off between the different decision making parameters. Keeping the above criteria in mind, in this thesis a novel group based trade-off method is proposed in Chapter 6. In Chapter 3, four cases similar to the new case are retrieved and combined using a modified a Dempster-Shafer rule.

2.3.4 Adaptation

In case-based reasoning, old solutions are used as an inspiration for new problems. However, a new problem is rarely the same as the retrieved most similar case and its solution needs to be adapted to fit the new problem. Adaptation usually takes into account the prominent differences between a new case and the retrieved most similar case. It is the most difficult part of the CBR system. It is generally performed in two steps: figuring out what needs to be adapted and carrying out the adaptation.

In the simple problem domain where the difference between the past and the current problem is unimportant, adaptation focuses only on the parts of the solutions that can be reused for the new problem. In the complex domain, adaptation focuses not only on the parts of the solutions that can be reused for the new problem, but also on how the difference between the past and the current problems will affect this reuse [26].

In general, there are two types of adaptation [12]:

Structural adaptation: adaptation rules are applied directly to the retrieved similar cases.

Derivational adaptation: in this method, all the algorithms, methods and rules used in the past are stored in the memory along with the solution. The stored information is further explored in the context of the new problem.

For a complex problem, a CBR system may need both types of adaptation. Usually structural adaptation rules work well to adapt a poorly understood problem and derivational adaptation is applicable to problems that are well understood [12].

Watson and Marir [27] classified adaptation techniques in a more detailed way as follows:

Null Adaptation: A retrieved most similar solution is reused without any modification. It is useful for problems involving complex reasoning but having simple solutions [28].

Parameter Adjustment: is a structural adaptation technique where differences between the feature vectors of past and current problems are used to modify the retrieved the most similar solution [29].

Critic-Based adaptation: rules are generated to identify the problem features which are not compatible with the new problem or violate some domain constraints. Rules are generally elicited from the domain expert or learnt by using expert knowledge [30].

Reinstantiation: is used to instantiate features of an old solution with new features that must be present in the new solution because they are mentioned in the problem description [31].

Derivational Replay: is the process of implementing the previously derived methods or rules to generate the solution in the new problem instance [32].

Model-Guided Repair: is the process of using a casual model of the problem domain to guide the adaptation by repairing elements of the old solutions which are infeasible in the current problem [33].

Case Based Substitution: uses other cases to suggest appropriate adaptations to the current problem [34-36].

Adaptation is an important step of case-based reasoning and usually requires a lot of domain knowledge. In this thesis knowledge-light adaptation is proposed for the case-based reasoning system.

2.3.5 Maintenance

The success of a CBR also depends on the technologies used in the reasoning process and its maintenance. A good CBR system must be maintained intelligently, systematically and automatically. In the literature, most of the work in CBR maintenance refers to maintenance of the cases in the case base. However, retrieval and adaptation are important steps of the CBR system and must be taken into consideration while carrying out the maintenance.

Smyth [37] has divided CBR maintenance into two categories: efficiency directed maintenance and competence directed maintenance. The efficiency directed maintenance focuses on the minimisation of computational costs associated with retrieval, adaptation and storage of cases in the case base. The computational cost depends on the size of the case base. Addition of new case or new knowledge in the case base not only increases the success rate of the CBR system but also increases its computational cost. A number of methods have been developed to determine the saturation point [38-40]. It is the point where the addition of more knowledge into the knowledge base increases the

computational cost of the system only. The competence directed maintenance focuses on the reasoning outcomes and on the quality of the cases in the case base. In experiments, it has been found that the size of the case base does not provide accurate information about the distribution of cases in the case base in terms of features values [41]. The outcome and quality of the CBR system depends on the size, density and distribution of the cases in the case base. The density and distribution of the cases in the case base can be determined by a similarity measure. Some of the cases in the dense region may be redundant and have less influence on the reasoning process compared with those in spare regions [42]. If cases in the dense region have a large number of different solutions, outcomes of the CBR system will be inconsistent.

2.4 Case-Based Reasoning for Healthcare Systems

In recent years, CBR has emerged as a most vibrant and rapidly growing area for problem solving in the health domain. The earliest research in this area was focused on the modelling of medical expertise, particularly for diagnosis, treatment planning and follow up care. However, over the last decade it has been successfully implemented for all health sciences applications including nursing, human biology, genetics, proteomics and phylogenetics as shown in Table 2.1. There are over 250 research articles published in this area which focus on the CBR method. It has been observed that one third of the research articles were published in the last three to four years. This area is expected to grow continuously as healthcare research is growing.

Table 2.1 CBR in Medicine

Problem addressed	System name	Application domain	References
Diagnosis and decision support systems	SHRINK	Psychiatry	[43]
	CASEY	Heart failure	[44]
	MEDIC	Dyspnoes	[45]
	BOLERO	Pneumonia	[46]
	FLORENCE	Health care planning	[47]
	MNAOMIA	Psychiatry	[78]
	SCINA	Detection of coronary heart disease	[48] [49]
	CARE-PARTNER	Stem cell transplantation	[50]
	AUGUSTE	Alzheimer's disorders	[51]
	ExpressionCBR	Cancer diagnosis	[52]
	Fungi-PAD	Object recognition	[53]
	KASIMIR	Oncology	[54]
	Type-I diabetes	Breast cancer	[55]
	Dermatology	Diabetes treatment	[56]
	Bronchiolitis	Dermatology treatment	[57]
	SISAIH	Bronchiolitis	[58]
	RHENE	Fraud detection in healthcare	[59]
Classification systems	PROTOS	Audiological disorders	[60]
	MACRAD	Image analysis	[61]
	IMAGECREEK	Image analysis	[62]
	CTS	Image analysis	[63]
	PHYLSYST	Phylogenetic classification	[64]
	GeneCBR	Cancer classification	[65]
	Hep2-PAD	Image classification	[66-67]
	ADHD	Neuropsychiatric	[68]
Planning systems	ALEXIA	Hypertension	[69]
	ROENTGEN	Radiation therapy	[70]
	CAMP	Daily menu planning	[71-72]
	T-IDDM	Diabetes treatment	[73]
	SIDSTOU	Tourette syndrome	[74]
	Dempster-Shafer rule based CBR	Prostate cancer	[75]
Tutoring systems	ICONS	Antibiotics therapy for intensive care	[76]
	CADI	Cardiac auscultation diagnosis and instruction	[77]

Kolodner and Kolodner [43] proposed SHRINK, a case based system for psychiatric diagnosis and treatment. In the developed system, past solved psychiatric cases were stored in the case base and demonstrated how they could be used in teaching clinical reasoning. Later, Bichindaritz [78] extended the SHRINK idea and proposed MAHAOMIA, a CBR system for diagnosing and treating psychiatric eating disorders. In the developed system, an electronic data base was created to store the past patients' records such as: medical history of the patients, environment, symptoms, diseases, prescribed tests and treatments procedures. For each new patient or new disease episode, the system retrieved and displayed the most similar patients or disease episodes, degree of similarities and differences in relation to the current case and prescribed past successful treatments. Based on the extracted case it also recommended a diagnosis and treatment process for a new patient.

Bareiss et al. [79] built a CBR medical diagnosis software, PROTOS, to diagnose audiological or hearing disorders. The main task of the developed software was to classify a new patient into one of the 15 predefined categories based on 58 distinct diagnosis features. Koton [45] developed CASEY, case based medical diagnosis software to diagnose cardiac patients by comparing them with earlier cardiac patients stored in the case base. The similarity measure designed by him was based on both quantitative features (like heart rate) and qualitative features (like high or low arterial pressure or the presence or absence of a particular disease). Diagnosis of a new patient was presented by a graph showing the causality among the measures and states of the patient. It also demonstrated the comparison between the retrieved past most similar cases and the present case.

In real life, generally it takes up to two days in a laboratory to analyze the bacteria responsible for bacterial infections in a hospital Intensive Care Unit (ICU). In order to diagnose the problems quickly, Koton [44] and Heindl et al. [80] developed a case-based reasoning system ICONS. In the case base they stored all details of past ICU patients, who received antibiotic therapy. When a new infection arises, ICONS retrieved the most similar cases from the case base based on the following information: location of infection, way in which the infection was acquired, and condition of the patient. Based on the retrieved similar or prototypical case, it predicted the root cause of the problem and potential solution.

Petot et al. [71] developed CAMP, a CBR system for nutrition planning. The main objective of the system was to plan daily menus to meet individual nutrition requirements. They stored the list of all available repositories in the case base. Thereafter, integrated case-based reasoning and rule based reasoning methods were used to meet the multiple design constraints of the recipe.

Beddoe et al. [81] developed CABAROST for nurse rostering problems. The cases in the case base represent previous examples of constraint violations in schedules and the repair methods used in the past. The similarity between the constraint violations of the new problem and the cases in the case base was calculated based on the cases' structural and feature information. Firstly, they retrieved the cases identical to the current problem in terms of structural and feature information. Thereafter, a memetic algorithm was used to search for optimal sequences of repairs suggested by the retrieved cases.

Berger [70] proposed a CBR system to generate a radiotherapy treatment plan for a new patient using the past case (patient) that best matched the geometrical

similarity and the treatment constraints but no results were reported about the effectiveness of the developed system.

Song et al. [75] proposed a Dempster-Shafer rule based CBR approach for prostate cancer dose planning problems. In the developed CBR system, they retrieved four cases which were most similar to a new case and combined them using the Dempster-Shafer rule to suggest a dose for the treatment. However, if the dose limits imposed to the rectum are violated, then simple adaptation rules are used to rectify that. With this approach, the dose limits for different volume percentages of the rectum were assumed to be fixed.

Schlaefer and Dieterich [82] proposed a CBR approach to determine the beam configuration in robotic radiosurgery for prostate cancer. The role of case based reasoning was to propose a range of parameter values that determined the beam configuration based on previous treatments. These ranges of parameter values were passed to the optimisation technique to determine the beam configuration for a new treatment efficiently.

2.5 Conclusion

This chapter has described the general framework of case-based reasoning approaches. The key issues of the case-based reasoning approach namely case representation, retrieval adaptation and case based maintenance, have each been described in detail.

The application of CBR systems to a wider variety of healthcare problems was divided into four categories [228]: diagnosis problems, classification problems, planning problems and tutoring problems. A detailed description of developed decision support systems and their application domain has been given. The use

of a CBR system for the problem of radiotherapy dose planning is virtually unexplored. Two approaches, that of Berger [70] and Song et al. [75], have been cited in the literature. The authors drew positive conclusions about the success of the CBR system for dose planning problems but provided little insight into the applicability of this approach.

This thesis therefore attempts to apply many of the lessons learnt from the application of CBR approach to healthcare, law, management and finance related problems to dose planning in prostate cancer.

CHAPTER 3

The Radiotherapy Planning Problem

3.1 Introduction

Cancer is characterised by the abnormal and uncontrolled growth of cells. It is generally diagnosed by Computerized Tomography (CT) scans, Magnetic Resonance Imaging (MRI), nuclear medicine scans, biopsy and histopathology reports. A CT scan is a computerized (axial) tomography scan which uses a series of X-rays to create detailed images of the inside of the body. However, it cannot distinguish between normal and pathological cells. It can only be distinguished by the MRI. Sometimes, to judge the possible involvement of metastatic growth, nuclear medicine scans are prescribed by the oncologist. The aforementioned tests are diagnostic procedures and do not give conclusive evidence of malignant cancer. Biopsy and histopathology report are good ways to confirm this. Depending on the type, size, stage and location of the cancer, Chemotherapy, Hormonal Therapy, Surgery and Radiotherapy are usually used to treat the cancer. In chemotherapy, cancer is treated with drugs called antineoplastic drugs. In hormonal therapy, a special type of hormone is used to kill the cancer cells. The hormone is a special type of chemical released by one tissue to influence the physiology of another tissue. In surgery, cancer cells are physically removed. Radiotherapy uses X-rays or Gamma rays to kill the cancer cells. It is often used to treat all stages of the cancer, or in cases where surgery fails.

X-rays or Gamma rays used in radiotherapy treatment kill not only the cancer cells but also damage the cells through which they traverse. The cells do not die immediately, but after weeks or even months. Sometimes cells are reproduced before being eliminated from the organ. The rate of recovery of normal tissues is higher in comparison with cancer cells The radiation is generally delivered in a number of fractions (usually 1.8 to 2 Gy per day, five days in a week) over a period of one or several weeks. It allows normal tissues to regenerate during the treatment. In the early days of radiotherapy, X-rays were used. However, due to a lack of sufficient penetration they are generally used for skin cancer and other superficial lesions and avoided in the case of deep seated tumours such as prostate cancer. The introduction of megavoltage X-ray machines facilitate sufficient penetration to deal with seated tumours.

Radiotherapy treatment can be divided into three categories, namely external beam radiotherapy, brachytherapy or sealed source radiotherapy and systemic radioisotope therapy or unsealed source radiotherapy. The division is made based on the position of radiation sources used in the treatment. In external radiotherapy, radiation is delivered from a source located outside the body. In brachytherapy, sealed radioactive material is placed precisely in the area of the treatment. In the systemic radioisotope therapy, radioisotopes are placed inside the body by infusion or oral ingestion. Further, the external beam radiotherapy can be divided into three categories, namely conventional external beam radiotherapy, 3-Dimensional Conformal Radiotherapy (3DCRT) and Intensity-Modulated Radiotherapy Treatment (IMRT). In the conventional external beam radiotherapy, rays are delivered via a two-dimensional beam using linear accelerator machines. Firstly, a treatment plan is designed and calibrated using

a simulator. The simulator is a special type of calibrated diagnostic X-ray machine. Thereafter, prescribed radiation is delivered to the patient from different directions using a single beam. This technique is very simple and reliable. However, it is not applicable to the high-dose treatments that prostate cancer requires. The sensitivity of the surrounding organs limits the prescribed dose to such an extent that tumour control may not be easily achievable. The above-mentioned intricacy of conventional external beam radiotherapy can be overcome in the 3-Dimensional Conformal Radiotherapy, where multiple radiation beams are shaped to fit the profile of the target from the beam's eye view. It helps medical physicists to reduce the toxicity of the surrounding organs while allowing a higher dose of radiation to the cancer cells. Intensity-Modulated Radiotherapy (IMRT) is the next generation of 3DCRT, which enables a precise conformal radiation dose distribution to the cancer cells by controlling the intensity of radiation within a given area. In IMRT, multi-leaf collimators are used to modulate the beam, by uncovering specific parts of the beam and blocking the remaining parts. It can modulate and shape the beam in such a way that the prescribed dose can be delivered even in the concave target volumes whilst sparing the other healthy tissues near the cancer cells. The levels of this step function provide medical physicists different degrees of freedom to achieve the prescribed dose distributions in the body.

The treatment plans are generally designed by three groups of specialists: oncologists, medical physicists and computer scientists/operational researchers. Oncologists are doctors who outline the tumour volume and the organs at risk. Medical physicists model the deposition of radiation in the volume outlined by the oncologist. Operational researchers and computer scientists have an

important role in the treatment planning using optimisation and artificial intelligence techniques to help medical physicists and oncologists to achieve the desired goal.

A treatment plan can be generated by forward planning or by inverse planning. In forward planning, the medical physicist enters all treatment parameters such as the beam intensity, number of beams and direction of beams into the planning software and the dose distribution is calculated. If the dose distribution is unacceptable, the task is repeated until a desired dose distribution is achieved. This process is based on a trial-and-error process and there is no guarantee that the best possible dose distribution will be found. Hence, this process is not suitable for complicated anatomical situations. In inverse planning, the medical physicists know how much energy is to be deposited to tissues and they want to know the optimal/near-optimal combination of treatment parameters. IMRT is an inverse planning process which enables the oncologist to have better control of the radiation, i.e. limit the amount of radiation to be received by cancer cells and normal organs and determine the optimal combination of other planning parameters that adhere to the prescribed bounds.

3.2 Issues of Radiotherapy Planning Problems and Classification of Problems

The main goal of the planning process is to kill all the cancer cells without impairing the remaining body, particularly the organs lying close to the tumour cells. The treatment process includes imaging, treatment planning, plan confirmation and treatment. In imaging, the patient is scanned using a CT scan, nuclear scans or MRI scans. Thereafter, the oncologist outlines the tumour

volume, the Planning Target Volume (PTV) and Organs at Risk (OARs) on these images. PTV is an extension of the tumour volume containing tumours cells and the surrounding area to which the cancer has spread. Once the tumour volume is identified, the medical physicist and oncologist work together and produce a treatment plan. The treatment plan specifies the prescribed total amount of radiation dose, number, size and shape of radiation beams, number of wedges and the configuration and beam intensity profile for each beam. The suggested plan is reviewed and confirmed by viewing the Dose Volume Histogram (DVH). DVH presents the simulated radiation distribution within a volume of interest which would result from a proposed radiation treatment plan. The final prescribed plan is passed to the treatment department. The suggested radiation is delivered by a linear accelerator with a multi-leaf collimator equipped in the head of the treatment unit as shown in Figure 3.1. Beams of radiation are generated by a linear accelerator. Once beams are formed they travel through the gantry. The gantry of the linear accelerator can be rotated around the patient to deliver the radiation from different angles. The head of the gantry contains multiple metal leaves which can shape the radiation beam by blocking portions of the beam as shown in Figure 3.2. Shaping the beam helps to reduce the levels of radiation to the sensitive regions, while delivering a higher dose of radiation to the tumorous regions.

Figure 3.1 A linear accelerator [83]

Figure 3.2 A close-up view of multi-leaf collimator [83]

Many problems in the area of radiotherapy planning can be solved by using operational research techniques. A detailed summary of the radiotherapy planning problems as reported in the literature is given in Table 3.1.

Table 3.1 Issues of the radiotherapy planning problem raised in the literature

Problem addressed	Issues covered	References
Beams configuration	Determination of optimal number of beams, angle between the beams and their weights.	[84-107]
Beams weight and wedges configuration	Determination of optimal number of wedges and their configuration.	[108-112]
Outline of the treatment volume and movement of organs	Determination of planning target volume, organs at risk and margin, study of the movement of organs during a treatment and determination of the exact location of organs	[113-128]
Comparison of treatment methods	Comparative study of different types of radiotherapy treatments.	[129-137]
Dose planning	Determination of an optimal dose plan for different stages of a treatment.	[75,138-152]

3.2.1 Beams Configuration

The determination of beams configuration is an important step of the radiotherapy planning process. It might be possible to kill all the cancer cells with a single beam of radiation. However, the use of a single beam can damage the normal cells of the critical organs. It is always necessary to select the optimal/near-optimal number of beams and their orientation (angle between the beams) so that the prescribed dose can be delivered to the targeted cancer cells, while sparing the nearby organs. In traditional radiotherapy, a limited number of beams is used and fixed manually by the medical physicists based on their past experience. IMRT uses multiple beams, which increases the complexity of the treatment plan. Hence, the determination of the optimal beams configuration is a difficult and tedious task. A significant body of research to determine the optimal values of beams configuration has been described in the literature. Pugachev and Xing [86] suggested a Simulated Annealing (SA)

approach to determine beam orientation in IMRT planning. Firstly, the quality of each single beam of unit intensity in the absence of other beams is calculated and stored in beam's-eye-view metrics (BEVD). Thereafter, a SA algorithm was employed to search an optimal set of beam orientations, taking into account the BEVD scores of different incident beam directions. During the calculation of the quality of each possible beam orientation, they did not consider any interaction between the beams. Li et al. [84] suggested a Particle Swarm optimisation algorithm to determine the beam orientation while taking into account the interaction between the beams in IMRT planning for prostate and head-and-neck cancer. Mohan et al. [153] proposed a fast Simulated Annealing algorithm to determine the number of beams in IMRT for prostrate cancer. The aforementioned approaches optimise the number of beams and their orientation separately but they are related to each other. As the input of one problem is the output of another problem, the solution of one problem affects the solution of the other. In order to overcome the above intricacy, Schreibmann et al. [87] proposed a hybrid multi-objective evolutionary algorithm to determine the optimal number of beams and their orientations simultaneously.

3.2.2 Wedge Configuration

Wedges are wedge shaped blocks of metal that are used to make the dose more uniform over the planning target volume. They can replace missing tissues (e.g. air in the path of beam) or lower the dose received by tissues, which are in the path of two overlapping beams. The selection of the optimal number of wedges and their angles is a time consuming job and is usually determined by trial-and-error methods. The main objective behind this research is to find out the

optimal number of wedges and their configuration in a minimum amount of computational time. Jonathan et al. [154] proposed a Simulated Annealing based approach to find a better combination of the beam weights and the wedge filters in a minimum amount of computational time. In this approach, a dose based objective function was formulated for the 3D radiotherapy treatment planning process. To make the approach more realistic, Konard and Tabbert [155] investigated and developed a fast radiotherapy planning algorithm which determines the global optimal combination of wedges, leaf positions and the intensities of radiation simultaneously.

3.2.3 Movement of Organs and Outline of the Treatment Volume

Initially, the planning target volume (PTV) is outlined and thereafter decisions are taken on its margins, to take into account the three-dimensional (3D) intra-fractional motion of organs and tumours during the treatment. The margin depends on the organs near the tumour, the treatment process and information about the location of the tumour given in the image guided system. Pankis et al. [156] have performed an experiment to measure the effects of active breathing control on the internal margin within the Planning Target Volume (PTV). In the proposed approach a relationship between active breathing control and the internal margin was established by sequential studies of lung cancer patients suitable for radical radiotherapy treatment. Further, Jin et al. [157] investigated the selection of beam margins in the lung-cancer stereotactic body radiotherapy. They used a Monte Carlo simulation method for systematic and quantitative study of the beam margins for the lung cancer patient. However, sometime an oncologist is interested in knowing the exact location of the

tumour so that a high daily dose can be delivered effectively to the cancer cells. Timmerman et al. [158] studied the exact location of tumour, especially the tumour that moves with respiration. In the proposed approach, sophisticated image guidance and related treatment delivery technologies were developed to examine the tumour movement. However, the above approach requires a frequent change in the treatment setup. Li et al. [159] proposed a new lung IMRT planning algorithm to shape the dose distribution while taking into account the movement of the tumour over the breathing cycle.

3.2.4 Comparison of Treatment Methods

A radiotherapy treatment can be planned using different methods. Each treatment has its own pros and cons. Treatment methods vary from case to case. In the literature, a large amount of research has been carried out in comparison with different planning methods for different types of cancers. Underwood et al. [160] investigated the dosimetric advantages of inverse and forward planning in the intensity-modulated radiotherapy process of conventional 3D conformal radiotherapy (3D-CRT). Further, Varrkamp et al. [161] performed experiments to conduct a comparative study on the forward and inverse planning process of IMRT planning for prostate and pelvic nodes patients. The research has further been extended by Wu et al. [162] to compare the performance of forward and inverse planning in the 3DCRT and IMRT planning process.

3.2.5 The Dose Planning Problem

Determination of the radiation dose is an important step of the radiotherapy planning process. The medical physicist first defines the different planning parameters which include the number of beams to be used, the angle between beams, the number of wedges, the wedge angles and then generates a Distribution Volume Histogram (DVH). Thereafter, the oncologist prescribes the radiation dose so that the tumour cells can be killed without impairing the healthy organs, particularly the organs lying close to the tumour cells. The healthy organs close by should preferably not be impaired at all by the treatment. The oncologist usually looks for a compromise while distributing the inevitable dose among the organs. Romeijin *et al.* [163] proposed a linear programming approach to the radiotherapy dose planning problem. The main constraints of the developed model were hard bounds on the dose limits on the normal and cancer cells, namely a minimal prescribed dose to be irradiated to the cancer cells and a maximum tolerance dose to be irradiated to the normal cells. However, defining the dose limits of organs at risk a priori is not an easy task. Usually, the oncologist makes a trade-off between the risks and the benefits of radiation by varying (based on their past experience) the dose limits of organs at risk. Aubry et al. [149] proposed a modified Simulated Annealing algorithm to resolve a radiotherapy dose planning problem. First, a Pareto set of all non-dominated solutions was generated (using modified SA algorithm) and ranked by each objective. Thereafter, a Microsoft Excel graphical user interface was developed to help the decision maker to select an appropriate solution. The above approach can generate a good approximation of the Pareto front, but the selection of the best treatment plan is a challenging task. Meyer et

al. [147] used an influence diagram based on the Bayesian network to select the most appropriate solution from the set of non-dominated solutions of the Pareto front for prostate cancer.

3.3 Existing Approaches

The methodologies used for radiotherapy planning problems can be classified into two categories: optimisation methods and knowledge based methods as shown in Table 3.2. The optimisation methods explore a vast variety of approaches such as heuristics, meta heuristics, linear and non-linear programming, etc., while knowledge based methods include case-based reasoning, rule-based reasoning, hierarchical organization of knowledge, etc.

In experiments, it was found that the integral dose received by a cell is a linear function of the amount of energy transmitted along the sub-beams. Olafsson and Wright [164] proposed Linear Programming (LP) and Wang et al. [165] proposed a Mixed Integer Linear Programming (MILP) formulation of the radiotherapy beam configuration problem. However, these methods can generate one treatment plan at a time and this force the planners to launch a succession of experiments if they need multiple plans or if comparison are desired. To overcome the above, Hamacher et al. [166], Hamacher and Kufer [167] and Kufer et al. [168] proposed a multicriteria linear programming approach and generated Pareto optimal solutions. Each solution represents a treatment plan that is optimised with respect to the dose constraints of OARs. Thereafter, for each new patient, the oncologist can choose the most appropriate plan from set of Pareto optimal solutions. However, sometimes the radiation bounces off the cells and scatters into an area where it was not

intended and makes the problem non-linear. Cotrutz et al. [141] and Lahanas et al. [169] proposed a multi-objective non-linear programming approach to model the scattering effect of the radiation. The abovementioned linear or non-linear approaches need parameters to be fixed before the optimisation. Defining the parameters a priori is not an easy task since their value varies from case to case. Holder [170] proposed a novel linear model where constraints are flexible and which allowed the physician's desire to float during the optimisation process. The radiotherapy planning is itself a complex problem and the search space is very large. Hence, the aforementioned mathematical optimisation model required a large computational time. To reduce the computational time, the use of different meta-heuristics has been widely studied in the radiotherapy planning literature including Simulated Annealing, Genetic Algorithm and Particle Swarm optimisation, etc. A summary of the application of different meta-heuristics to the radiotherapy planning problem is given in Table 3.2. However, the main goal of all the developed optimisation methods is to attain a uniform tumoricidal dose and to minimise the side effects of the treatment. It is very hard to develop a mathematical model which would judge the success rate and side effects of the treatment plan before the treatment. It can only be predicted by the oncologists to some extent based on their past experiences.

Table 3.2 Methodologies developed in the literature to solve different aspect of radiotherapy planning problems

Methodologies	Problem addressed	References
Optimisation methods		
Linear and Non-linear Programming	Beam configuration	[173-177]
	Dose Planning	[178-179]
	Beam weight and wedge configuration	[180-181]
Quadratic programming	Beam weight and wedge configuration	[183-184]
Simulated Annealing	Beam configuration	[185-187]
	Dose Planning	[188-190]
	Beam weight and wedge configuration	[191-194]
Genetic Algorithm	Beam configuration	[195-198]
	Dose Planning	[199]
	Beam weight and wedge configuration	[200-201]
Ant colony optimisation	Beam configuration	[84]
Particle swarm optimisation	Beam configuration	[202]
Knowledge based methods		
Rule based system	Dose planning	[70,203-204]
Case-based reasoning	Dose planning	[75,171]
	Beam configuration	[172-205]

Knowledge based methods do not use mathematical algorithms, but determine the plan parameters on the basic of past experiences. They normally employ artificial intelligence methods such as rule-based reasoning, case-based reasoning or a hierarchical organization of the knowledge. Some knowledge based systems use rules to solve a new problem. These rules are designed by the decision makers based on their clinical knowledge. Lieber and Bresson [171] proposed two types of knowledge based decision support systems for breast cancer: a rule based reasoning system and a CBR system. In the first approach, decision rules were represented as a hierarchy of classes and for a new case appropriate rule was selected by nearest neighbour pattern classification technique. In the second approach, decision rules were stored in a

case base. For each new case, an appropriate rule was retrieved from the case base. If the retrieved rule was not suitable for the new case, knowledge (rules) were reformulated to generate a new rule. Berger [70] and Song et al. [75] proposed CBR based reasoning approach for radiotherapy planning problems. The detailed description of their approaches is given in section 2.4. Jagannathan et al. [172] suggested a fuzzy case-based reasoning approach to beam configuration problems for head and neck cancer.

Optimisation methods and knowledge based methods have both merits and demerits. To explore the amalgamated features of both methods, Schlaefer and Dieterich [205] proposed a novel case-based reasoning approach to determine the beam configuration in robotic radiosurgery for prostate cancer. The role of case-based reasoning was to propose a range of parameter values that determines the beam configuration based on previous treatments. These ranges of parameters were passed to the linear optimisation technique to efficiently determine the beam configuration for a new treatment.

3.4 Conclusion

This chapter has described different aspects of radiotherapy planning problems and the existing methods developed over the last 20 years. The literature review was divided into two parts: characteristics of the radiotherapy planning problems and developed methodologies.

The issues that were investigated in radiotherapy planning include dose planning, beams configuration, configuration of wedges, movement of organs, outlining of target volume and comparison of different treatment methods. To solve these problems both optimisation and knowledge based methods have been developed. However, the formulations of these problems have not taken

into account the success rate of the treatment and other real world constraints. Usually, based on the past experience, the oncologist or medical physicist modifies the plan generated by different methods, to make it more suitable for the treatment.

This thesis attempts to address the dose planning problem for prostate cancer while taking into account the experience gained in treating previous patients and the success rate of the treatment. The formulated dose planning problem and the developed decision support system are described in detail in the following chapters.

CHAPTER 4

A Novel Case-Based Reasoning Approach to Radiotherapy Planning

4.1 Introduction

Prostate cancer dose planning is a complex problem. Usually oncologists spend a large amount of time to determine the optimal combination of doses in phases I and II of the treatment. Using planning software, medical physicists first generate the optimal/ near-optimal combination of different planning parameters such as the number of beams to be used, the angle between beams, the number of wedges, the wedge angles, and a Distribution Volume Histogram (DVH) is then generated. Based on past experience, the oncologist then makes a trade-off between the risk and the benefit of the radiation, i.e. delivering a high dose to the cancer cells while minimizing the side effects of the treatment, and then prescribes a dose plan. The main goal of the existing software is to attain a uniform tumoricidal dose and to minimize the side effects of the treatment. However, existing software overlook the success rate of treatment. It is very difficult to develop a mathematical model which would judge the success rate of the plan before the treatment. However, this can be predicted to some extent from past experiences. 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 value of PSA, the better the long-term prospects of the patient remaining disease free. Also, clinical parameters used in the dose planning process are not equally

important. It is generally fixed by the system with the input from the oncologists based on their past experience.

In this chapter, a novel case-based reasoning approach is proposed to capture the expertise and experience of an oncologist encountered while treating pervious patients. In normal case-based reasoning a decision is generally made based on the retrieved case, most similar to the new case. This practice may lead to loss of important information contained in the other similar case. Oncologists usually combine two or more similar decisions while prescribing a dose plan to a new patient. Furthermore, sometimes the retrieved most similar case has a higher similarity value but lower success rate compared with the second most similar case in the case base. In this chapter, a modified Dempster-Shafer rule is used to make a trade-off between the similarity and the success rate of the treatment. Four most similar cases are retrieved from the case base and then fused to generate a combined decision. Furthermore, in order to mimic the continuous learning characteristic of oncologists, the weights corresponding to each feature used in the retrieval process are updated automatically using a Simulated Annealing algorithm.

4. 2 Prostate Cancer Dose Planning

The main aim of the prostate cancer treatment is to determine the optimal dose to be delivered while making a trade-off between the benefit and risk of the proposed radiation. It is beneficial to deliver a high enough dose to fight the cancer cells, while the risk refers to the side effects of the treatment. Prostate cancer is generally treated in two phases as shown in Figure 4.1. In phase I, both the prostate and the healthy surrounding tissues having microscopic (tiny) cancer cells are treated; while in phase II only the prostate is exposed to

radiation. The dose delivery in phases I and II of the treatment in the Nottingham City Hospital is usually an even number in the range of 46-64 Gy and 16-24 Gy, respectively. The total prescribed dose is in the range of 70-76 Gy and the dose is delivered in fractions, each fraction being 2 Gy usually.

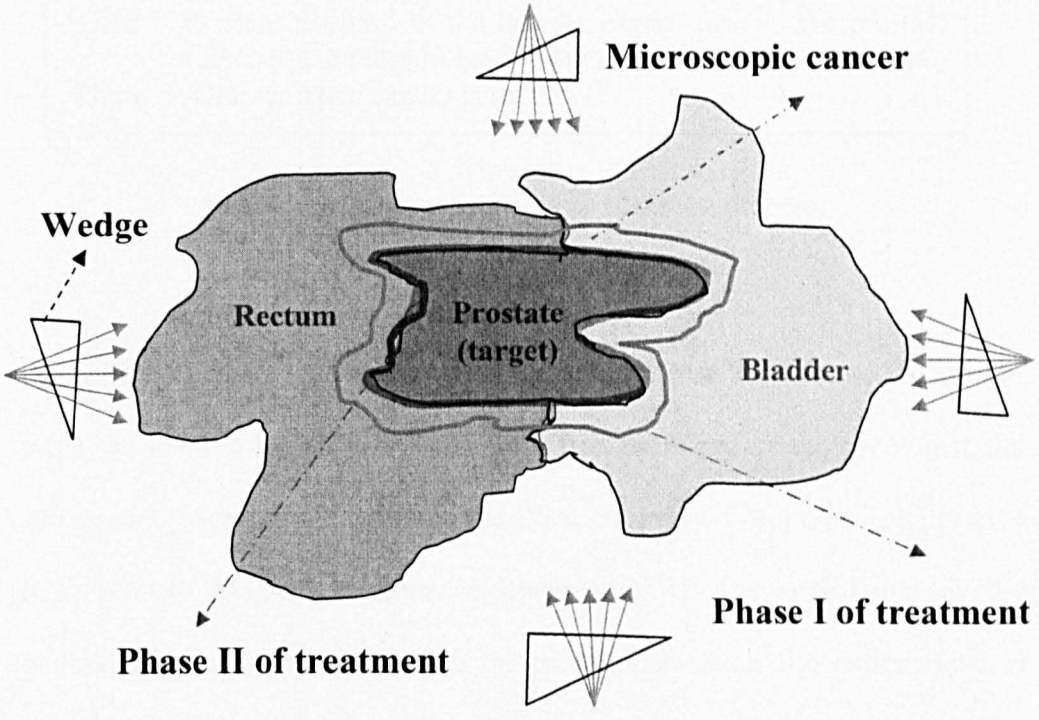


Figure 4.1 Prostate cancer dose planning

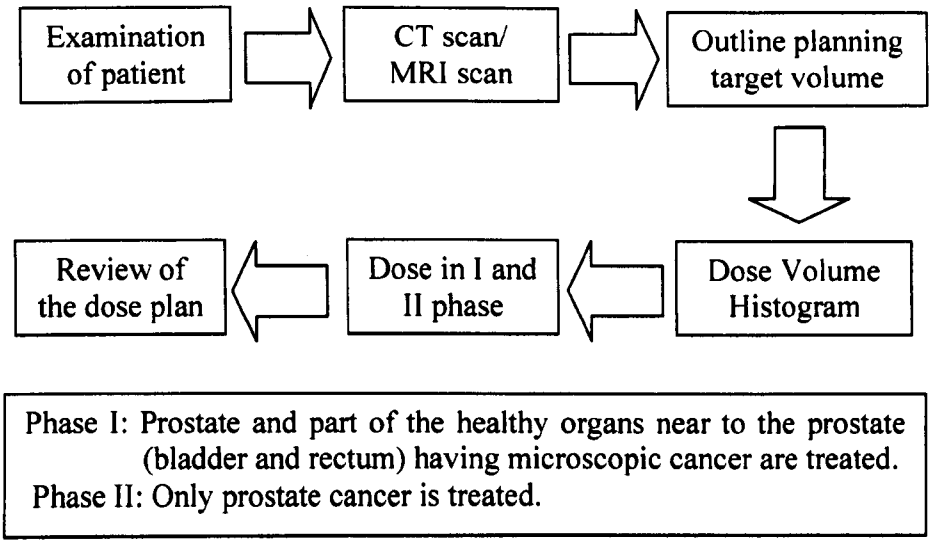


Figure 4.2 Prostate cancer dose planning process

In the Nottingham City Hospital, radiotherapy process is performed in several steps as shown in Figure 4.2. A patient is first examined by the oncologist and subsequently appropriate tests such as PSA, Biopsy, a Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) are carried out (by the pathologist) and a patient note is prepared. Thereafter, the patient note is passed on to the planning department. In the planning department, the cancer volume and the organs at risk are outlined by the oncologist so that the region that contains the cancer and microscopic cancer can be distinguished from other healthy organs near to the prostate. Afterward, the oncologist defines the following planning parameters: the number of beams, the angle between beams, the number of wedges and the wedge angles and generates a Distribution Volume Histogram (DVH) for phases I and phase II of the treatment. DVH is a simulated radiation distribution within a volume of interest of a patient which would result from a proposed radiation treatment plan. It is

related to the potential risk to the rectum. These parameters describe the degree of radiation received by different volume percentages of the rectum. For example, let us assume the DVH states that 66% of the rectum will receive 50% of radiation. This means that if the dose prescribed by the oncologist in phase I of the treatment is 60 Gy, then the amount of radiation received by 66% of the rectum will be 30 Gy. The next task is to decide the dose in phases I and II of the treatment so that the tumour cells can be killed without impairing the remaining healthy body, particularly the organs close to the tumour cells i.e. the rectum and the bladder. The healthy organs lying close by should preferably not be impaired at all by the treatment. However, the oncologist usually looks for a compromise of distributing the inevitable dose among the organs. The rectum is a more sensitive organ compared to the bladder and is the primary concern of oncologists while deciding the dose plan. The maximum dose limit for different volume percentages of the rectum, recommended by the UK standard, is shown in Table 4.1, and it has to be respected by oncologists when prescribing a dose plan. Ideally, the dose received by the different volume percentage of the rectum should be within the constraints as shown in Table 4.1. However, in some cases, this condition may be sacrificed to some extent so that an adequate dose can be imparted to the cancer cells. Oncologists generally use following five features: Clinical Stage, Gleason Score, Prostate Specific Antigen (PSA) value, and DVH in phases I and II of treatment to generate a good plan for each patient. The meaning of these parameters is given in the glossary in Appendix A.

Table 4.1 Total dose limits for the rectum

Rectum Volume	Total dose limits (Gy)
66%	45
50%	55
25%	65
10%	70

4.3 Solution Methodology

In the developed CBR system for dose planning the cases which are similar to the new case are retrieved using a fuzzy similarity measure. A modified Dempster-Shafer rule is applied to fuse the information from the retrieved cases and generate a solution as shown in Figure 4.3. A detailed description of the proposed methodology is given in the remaining part of this section.

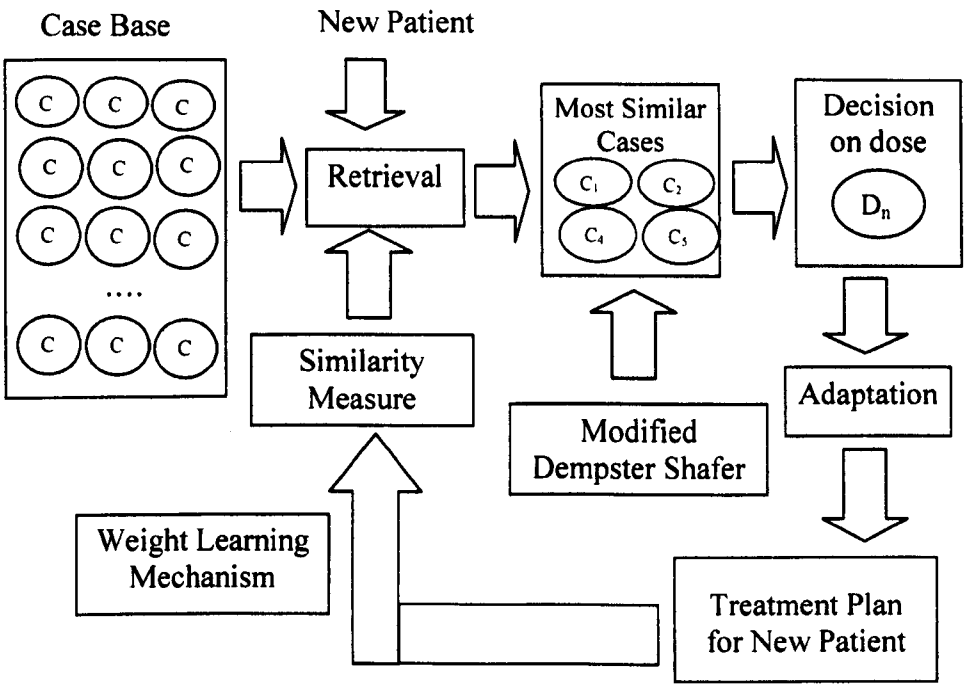


Figure 4.3 Architecture of the proposed CBR system

4.3.1 Representation of a Case

The five features described in the previous section related to the stage of the cancer (Clinical Stage ($l = 1$), Gleason score ($l = 2$), PSA ($l = 3$)) and geometry of the prostate (DVH in phase I ($l = 4$), and phase II ($l = 5$) of 66%, 50%, 25% and 10% of rectum volume) are generally used to retrieve the most similar cases from the case base. These features are given in different measurement units, which have different scales. The stage of the cancer is of an ordinal type and can be divided in seven different categories {T1a, T1b, T1c, T2a, T2b, T3a, T3b}, the value of the Gleason Score is an integer number from [1,10] interval, while PSA and DVH are real numbers from [1, 40] and [0,1] respectively. In order to use features of different data types and measurement units together in the similarity measure, we need to normalise them. However, it would not be easy to define a preferably linear mapping in the [0, 1] interval. Instead, we define fuzzy sets *low*, *medium* and *high* for each feature. They are normalised fuzzy sets whose membership functions take a value from the [0, 1] interval. In addition, fuzzy sets enable expression of the preference of the oncologist. An example of the membership functions of fuzzy sets *low*, *medium* and *high* Gleason score is given in Figure 4.4. The parameters of these membership functions were set in collaboration with the oncologist in the Nottingham City Hospital.

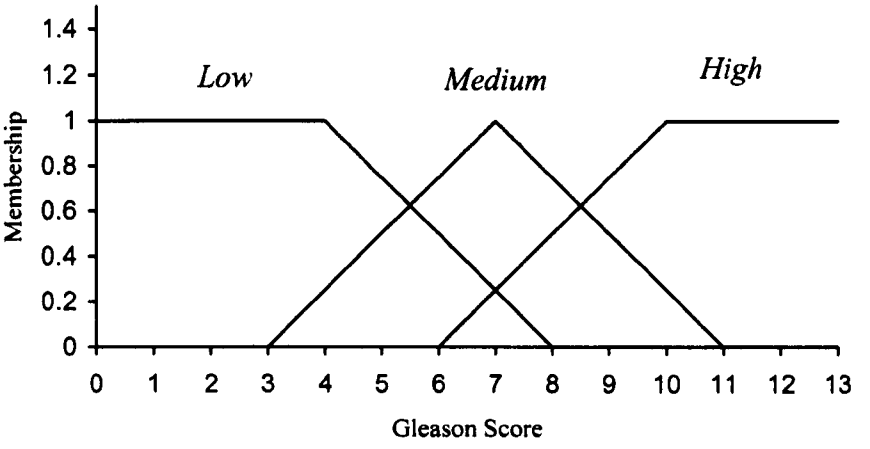


Figure 4.4 Membership function of fuzzy sets *low*, *medium* and *high* Gleason score.

Each attribute l (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 attribute l in the corresponding fuzzy sets *low* $(m = 1)$, *medium* $(m = 2)$ and *high* $(m = 3)$.

4.3.2 Retrieval Process

Only patients with similar clinical stage are relevant to the generation of the dose plan for a new patient. The case base is therefore first filtered based on the clinical stage of the cases. According to the stage of the cancer, the clinical stage can be sorted in the following order: {T1a, T1b, T1c, T2a, T2b, T3a, T3b}. The retrieval process first selects the cases whose value of the clinical stage is either the same as in the new case or the same as the adjacent element in the ordered list. Thereafter, four most similar cases are retrieved from the filtered case base using the nearest neighbour similarity measure.

Given two cases c_p and c_q, the distance between them, $d_1(c_p, c_q)$ which takes into consideration the fuzzy membership values of Gleason score ($l = 2$) and PSA ($l = 3$) is calculated using the formula:

$$d_1(c_p, c_q) = \left(\sum_{l=2}^{3} \left(w_l \left(\sum_{m=1}^{3} \left(v_{plm} - v_{qlm} \right)^2 \right) \right) \right)^{\frac{1}{2}} \tag{4.1}$$

where, w_l is the weight of attribute l and it is determined by using the Simulated Annealing method as described in section 4.4.

The distance between two cases c_p and c_q, which takes into consideration numerical values of the DVH, for phases I and II is $d_2(c_p, c_q)$, is defined as:

$$d_2(c_p, c_q) = \left(\sum_{l=4}^{5} \left(w_l \left(\sum_{k=1}^{4} \left(u_{pik} - u_{qik} \right)^2 \right) \right) \right)^{\frac{1}{2}} \tag{4.2}$$

where, u_{pik} and u_{qik} are the dose values received in phase I ($l = 4$), phase II ($l = 5$)), by 66% ($k = 1$), 50% ($k = 2$), 25% ($k = 3$) and 10% ($k = 4$) of the rectum volume in cases c_p and c_q, respectively, and w_l is the weight in phase l of the treatment and it is determined by using the Simulated Annealing method as described in section 4.4.

The similarity between cases c_p and c_q denoted by $s(c_p, c_q)$ is defined as:

$$s(c_p, c_q) = \frac{1}{d_1(c_p, c_q) + d_2(c_p, c_q)} \tag{4.3}$$

Thereafter, a modified Dempster-Shafer rule is applied to fuse the information from the retrieved cases and generate a unique dose plan.

4.3.3 A Novel Fusion Technique Based on the Dempster-Shafer rule

Usually, CBR systems retrieve only a single most similar case from the case base. However, this practice may lead to the loss of important information contained in other similar cases. Also, if the case base contains cases recommended by more than one oncologist, the suggested doses of radiation for similar patients may be different. Consequently, in this chapter, more than one similar case is retrieved from the case base and they are fused to generate a combined decision. Different fusion techniques such as the Dempster-Shafer rule [206-209] are reported in the literature for combining information obtained from different independent sources. We employ a modified Dempster-Shafer rule.

The Dempster-Shafer rule is based on the mathematical theory of evidence. The theory of evidence assigns a basic probability $m: 2^X \rightarrow [0,1]$ (X is the universal set) to the elements of the power set 2^X (contains all hypotheses). Basic probability is the probability that supports a particular hypothesis on the basis of all available evidences. For example, if $m(A)$ is the basic probability of hypothesis A, then $m(A)$ represents the probability that hypothesis A is true. The basic probability has two characteristics.

$$m(\varnothing) = 0$$

$$\sum m(A) = 1$$

The Dempster rule of combination aggregates basic probabilities based on independent evidences. The belief function, $m_{1,2}(C)$, supported by two independent events m_1 and m_2, is calculated using formula (4.4):

$$m_{1,2}(C) = \frac{\sum_{A \cap B = C} m_1(A)\, m_2(B)}{1 - \sum_{A \cap B = \varnothing} m_1(A)\, m_2(B)} \qquad (4.4)$$

where, $m_1(A)$ and $m_1(B)$ are the basic probabilities of hypothesis A and B, respectively. Belief function, $m_{1,2}(C)$, represents the degree of belief that supports hypothesis C. The combined belief function sums the products of the all basic probabilities of hypothesis which supports hypothesis C, while the denominator takes into consideration the conflict between them.

In the context of fusion of cases, the basic probability, denoted by $m_1(c_1)$, takes into consideration all relevant and available evidence that supports the selection of a particular case c_1. We define the basic probability as a similarity measure, $s(c_{new}, c_1)$. between case c_1 and the new case c_{new}. The necessary condition of applying the Dempster-Shafer rule is that the information to be fused should be obtained from independent sources. This condition is satisfied because in our case base, cases are independent. The outcome of the fusion process of cases c_1 and c_2 is either case c_1 or case c_2, or combination of cases c_1 and c_2 (i.e. $c_{1,2}$). In the fusion of cases c_1 and c_2, the power set (contains all possible outcome of the fusion) is $2^X = \{c_1, c_2, c_{1,2}\}$. The Dempster-Shafer rule combines two independent cases and calculates the agreement between them. The belief function, denoted by $m_{1,2}(C)$, (C being c_1, c_2 or $c_{1,2}$) takes

into consideration all sets of cases and the intersection of these cases is considered as decision C. It is calculated using the modified fusion rule:

$$m_{1,2}(C) = \frac{\sum_{A \cap B = C} w_A m_1(A)\, w_B m_2(B)}{1 - \sum_{A \cap B = \varnothing} w_A m_1(A)\, w_B m_2(B)} \tag{4.5}$$

where, w_A and w_B are weights assigned to hypotheses A and B, respectively. In the fusion of cases c_1 and c_2, weights w_A and w_B are defined to be the success rates of dose plans proposed in c_1 and c_2, respectively. The original Dempster-Shafer rule does not assign weights to decisions during the fusion process. In order to give cases a different importance in the fusion process, we assign weights to cases corresponding to their success rates, i.e. the PSA value, which is stored in the case base, measured 2 years after the treatment. During the fusion process, decisions having better success rates are given more importance than decisions having worse success rates. In order to have normalised weights, the PSA values are mapped into a [0, 1] interval as presented in Figure 4.5. The mapping is defined in consultation with the oncologist. The smaller the PSA value, the higher the weight assigned to the corresponding case.

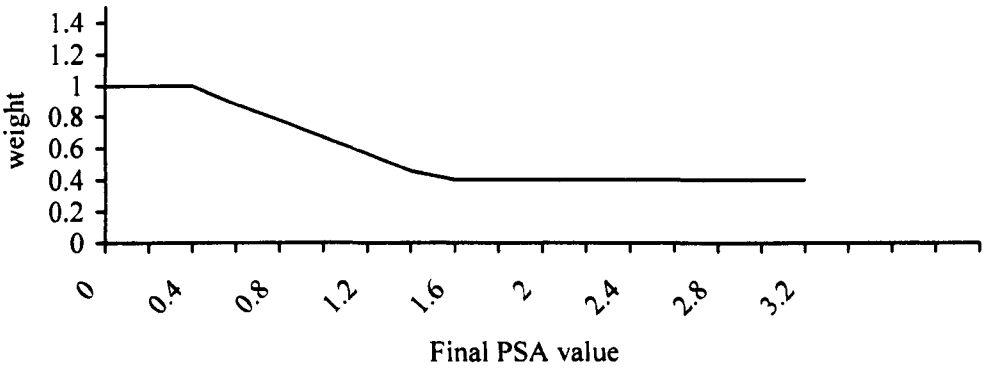


Figure 4.5 Mapping of PSA values to corresponding weights

The architecture of the proposed fusion technique is shown in Figure 4.6. As mentioned above, the outcome of the Dempster-Shafer rule (fusion of cases c_1 and c_2) is either case c_1, c_2 or combination of cases c_1 and c_2. If the outcome of the fusion process is a combination of two dose plans then the suggested dose plan will be the average of the recommended doses in these two plans.

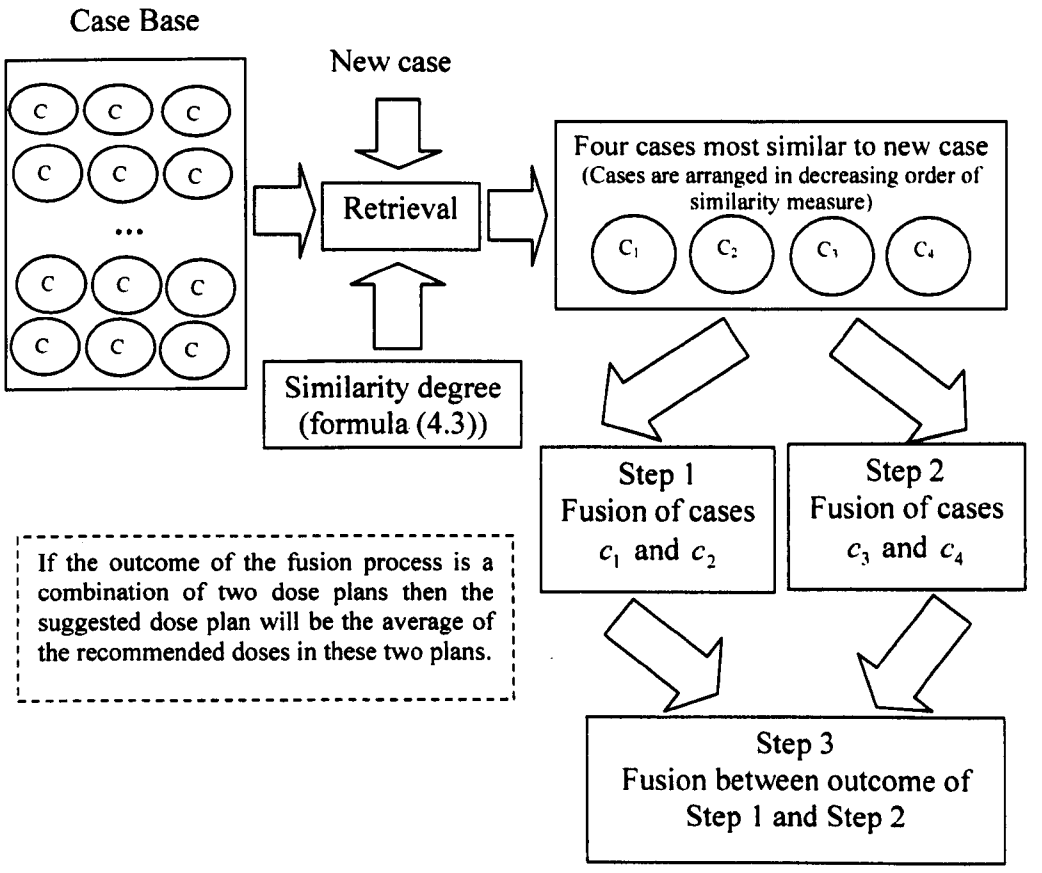


Figure 4.6 Architecture of the proposed fusion technique

An application of the Dempster-Shafer rule to radiotherapy dose planning problem is illustrated in Table 4.2 and Figure 4.7. In this example, c_1, c_2, c_3 and c_4 are the most similar four cases to c_{new} which are retrieved from the case base (using formula (4.3)), and are arranged in a decreasing order of their similarity to c_{new}. The value of similarity measures ($s(c_{new}, c_1)$, $s(c_{new}, c_2)$, $s(c_{new}, c_3)$ and $s(c_{new}, c_4)$) and the dose plans suggested by the cases are shown in the table. The order in which cases are fused is important and can affect the outcome of the fusion process. Hence, in this thesis, the fusion is performed in the following order. In the first step, two most

similar cases c_1 and c_2, are fused. In the second step, the second pair of cases c_3 and c_4, are fused. Finally, in the last step, the fusion is performed between the outcomes of step one and step two as shown in Figure 4.7. The fusion of the first pair of cases, c_1 and c_2, is shown in Table 4.3. Belief probability is calculated using expression (4.5). The belief probability of c_1, $m_{1,2}(c_1)$, is larger than both the belief probability of c_2, $m_{1,2}(c_2)$, and the belief probability of the combination of c_1 and c_2, $m_{1,2}(c_{1,2})$. Hence, the outcome of the fusion process is case c_1. Thereafter, the fusion of the second pair of cases c_3 and c_4 is performed. The outcome of the second fusion process is a combination of cases c_3 and c_4, because the values of the belief probability of c_3, $m_{1,2}(c_3)$ and c_4, $m_{1,2}(c_4)$, are equal, as shown in Table 4.4. Hence, in order to break the tie, the outcome of the fusion is considered as a combination of c_3 and c_4, which leads to a new dose plan denoted by c_d (as shown in Table 4.5). The Dempster-Shafer rule is applied again to fuse c_1 and c_d, as shown in Table 4.5. The final outcome is a dose plan with 62 Gy and 10 Gy of radiation in phases I and II of the treatment, respectively.

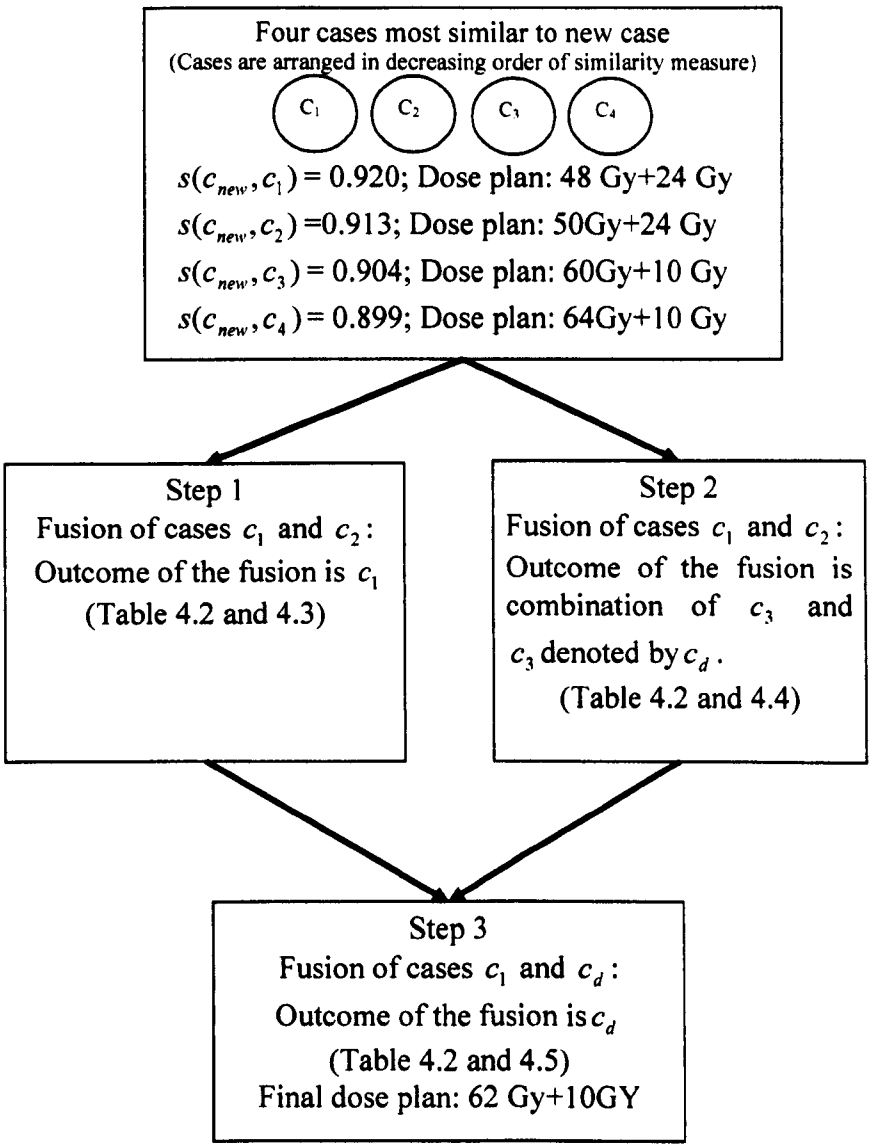


Figure 4.7 Flow chart of fusion of four cases

Table 4.2 Example of a fusion of four cases

<table>
<tr><td colspan="2">Fusion of cases c_1 and c_2</td><td colspan="2">Fusion of cases c_3 and c_4</td></tr>
<tr><td>c_1</td><td>c_2</td><td>c_3</td><td>c_4</td></tr>
<tr><td>$s(c_{new}, c_1) = 0.920$
Final PSA=0.92
we_1=0.71
Dose plan:
48 Gy+24 Gy</td><td>$s(c_{new}, c_2)$=0.913
Final PSA=0.851
we_2=0.75
Dose plan:
50Gy+24 Gy</td><td>$s(c_{new}, c_3) = 0.904$
Final PSA=0.5
we_3=0.94
Dose plan:
60Gy+10 Gy</td><td>$s(c_{new}, c_4) = 0.899$
Final PSA=0.3
we_4=1.00
Dose plan:
64Gy+10 Gy</td></tr>
<tr><td colspan="2">$m_{1,2}(c_1)$= 0.075
$m_{1,2}(c_2)$= 0.072
$m_{1,2}(c_1, c_2)$= 0.006
Outcome of the fusion is c_1.
$s(c_{new}, c_1) = 0.920$
Final PSA=0.92
we_1=0.71
Dose plan: 48 Gy+24 Gy</td><td colspan="2">$m_{1,2}(c_3)$=0.1089
$m_{1,2}(c_4)$=0.1089
$m_{1,2}(c_3, c_4)$=0.011
*Outcome of the fusion is a combination of c_3 and c_3 denoted by c_d.
$s(c_{new}, c_d)$=(0.904+0.899)/2=0.9015
Final PSA=(0.5+0.3)/2=0.4
we_d=1.00
Dose plan: {((60+64)/2=62 Gy), ((10+10)/2=10 Gy)
Dose plan: 62Gy+10Gy</td></tr>
<tr><td colspan="4">$m_{1,2}(c_1)$= 0.13378
$m_{1,2}(c_d)$=0.14995
$m_{1,2}(c_1, c_d)$= 0.01401
Final dose plan: 62 Gy+10 Gy</td></tr>
<tr><td colspan="4">Where, we_i = final PSA value of case c_i
*If the outcome of the fusion process is a combination of two dose plans then the suggested dose plan will be the average of the recommended doses in these two plans.</td></tr>
</table>

Table 4.3 Fusion of cases c_1 and c_2

		m_1	
		$m_1(c_1) = s(c_{new}, c_1)$ $= 0.92$ $we_1 = 0.71$	$m_1(c_1, c_2) = m_1(c_{1,2}) =$ $1 - s(c_{new}, c_1) = 0.08$ $we_{1,2} = \frac{we_1 + we_2}{2}$ $= 0.73$
m_2	$m_2(c_2) = s(c_{new}, c_2)$ $= 0.913$ $we_2 = 0.75$	$we_1 m_1(c_1) we_2 m_2(c_2)$ $=0.4472$	$we_{1,2} m_1(c_{1,2}) we_2 m_2(c_2)$ $=0.0399$
	$m_2(c_2, c_1) = m_2(c_{1,2})$ $= 1 - s(c_{new}, c_2)$ $=0.087$ $we_{1,2} = \frac{we_1 + we_2}{2}$ $= 0.73$	$we_1 m_1(c_1) we_{1,2} m_2(c_{1,2})$ $= 0.041484$	$we_{1,2} m_1(c_{1,2}) we_{1,2} m_2(c_{1,2})$ $=0.0037$

$$m_{1,2}(C) = \frac{\sum_{A \cap B = C} w_A m_1(A)\, w_B m_2(B)}{1 - \sum_{A \cap B_2 = \emptyset} w_A m_1(A)\, w_B m_2(B)}$$

$$m_{1,2}(c_1) = \frac{we_1 m_1(c_1) we_{1,2} m_2(c_{1,2})}{1 - we_1 m_1(c_1) we_2 m_2(c_2)} = \frac{0.041484}{1 - 0.4472} = 0.075$$

$$m_{1,2}(c_2) = \frac{we_2 m_2(c_2) we_{1,2} m_1(c_{1,2})}{1 - we_1 m_1(c_1) we_2 m_2(c_2)} = \frac{0.0399}{1 - 0.4472} = 0.072$$

$$m_{1,2}(c_{1,2}) = \frac{we_{1,2} m_1(c_{1,2}) we_{1,2} m_2(c_{1,2})}{1 - we_1 m_1(c_1) we_2 m_2(c_2)} = \frac{0.0037}{1 - 0.4472} = 0.006$$

The outcome of the fusion process is c_1.

Table 4.4 Fusion of cases c_3 and c_4

		m_1	
		$m_1(c_3) = s(c_{new}, c_3)$ = 0.90448 $we_3 = 0.904$	$m_1(c_3, c_4) = m_1(c_{3,4}) =$ $1 - s(c_{new}, c_3) = 0.09552$ $we_{3,4} = \frac{we_3 + we_4}{2} = 0.97$
m_2	$m_2(c_4) = s(c_{new}, c_4)$ $= 0.899$ $we_4 = 1.00$	$we_3 m_1(c_3) we_4 m_2(c_4)$ $=0.764338$	$we_{3,4} m_1(c_{3,4}) we_4 m_2(c_4)$ $=0.08329$
	$m_2(c_4, c_3) = m_2(c_{3,4})$ $= 1 - s(c_{new}, c_4) = 0.101$ $we_{3,4} = \frac{we_3 + we_4}{2}$ $= 0.97$	$we_3 m_1(c_3) we_{3,4} m_2(c_{3,4})$ $= 0.08329$	$we_{3,4} m_1(c_{3,4}) we_{3,4} m_2(c_{3,4})$ $=0.00908$

$$m_{1,2}(C) = \frac{\sum_{A \cap B = C} w_A m_1(A)\, w_B m_2(B)}{1 - \sum_{A \cap B = \varnothing} w_A m_1(A)\, w_B m_2(B)}$$

$$m_{1,2}(c_3) = \frac{we_3 m_1(c_3) we_{3,4} m_2(c_{3,4})}{1 - we_3 m_1(c_3) we_4 m_2(c_4)} = \frac{0.08329}{1 - 0.764338} = 0.1089$$

$$m_{1,2}(c_4) = \frac{we_4 m_2(c_4) we_{3,4} m_1(c_{3,4})}{1 - we_3 m_1(c_3) we_4 m_2(c_4)} = \frac{0.08329}{1 - 0.764338} = 0.1089$$

$$m_{1,2}(c_{3,4}) = \frac{we_{3,4} m_1(c_{3,4}) we_{3,4} m_2(c_{3,4})}{1 - we_3 m_1(c_3) we_4 m_2(c_4)} = \frac{0.009077}{1 - 0.764338} = 0.011$$

The outcome of the fusion process is a combination of c_3 and c_4.

Table 4.5 Fusion of c_1 and c_d

		m_1	
		$m_1(c_1) = s(c_{new}, c_1)$ =0.92 $we_1 = 0.71$	$m_1(c_1, c_d) = m_1(c_{1,d})$ $= 1 - s(c_{new}, c_1) = 0.08$ $we_{1,d} = \frac{we_1 + we_d}{2} = 0.855$
m_2	$m_2(c_d) = s(c_{new}, c_d)$ =0.9015 $we_d = 1.00$	$we_1 m_1(c_1) we_d m_2(c_d)$ =0.5889	$we_{1,d} m_1(c_{1,d}) we_d m_2(c_d)$ =0.06166
	$m_2(c_d, c_1) = m_2(c_{1,d})$ $= 1 - s(c_{new}, c_d)$ =0.0985 $we_{1,d} = \frac{we_1 + we_d}{2}$ $= 0.855$	$we_1 m_1(c_1) we_{1,d} m_2(c_{1,d})$ = 0.05501	$we_{1,d} m_1(c_{1,d}) we_{1,d} m_2(c_{1,d})$ =0.00576

where, c_d =outcome of a combination of c_3 and c_4.
we_d = combined weight of c_3 and c_4; $s(c_{new}, c_d)$ = combined similarity of c_3 and c_4.

$$m_{1,2}(C) = \frac{\sum_{A \cap B = C} w_A m_1(A)\, w_B m_2(B)}{1 - \sum_{A \cap B = \varnothing} w_A m_1(A)\, w_B m_2(B)}$$

$$m_{1,2}(c_1) = \frac{we_1 m_1(c_1) we_{1,d} m_2(c_{1,d})}{1 - we_1 m_1(c_1) we_d m_2(c_d)} = \frac{0.05501}{1 - 0.5889} = 0.13378$$

$$m_{1,2}(c_d) = \frac{we_d m_2(c_d) we_{1,d} m_1(c_{1,d})}{1 - we_1 m_1(c_1) we_2 m_2(c_d)} = \frac{0.06166}{1 - 0.5889} = 0.14995$$

$$m_{1,2}(c_{1,d}) = \frac{we_{1,d} m_1(c_{1,d}) we_{1,d} m_2(c_{1,d})}{1 - we_1 m_1(c_1) we_d m_2(c_d)} = \frac{0.00576}{1 - 0.5889} = 0.01401$$

The outcome of the fusion process is c_d.

4.3.4 Repair/ Adaptation Mechanism

The aim of the Dempster-Shafer rule is to generate a unique dose plan such that the dose received by different volume percentages of the rectum is within the recommended dose limits. Although the dose plans used in the Dempster-Shafer rule are feasible plans, sometimes the final dose plan generated by Dempster-Shafer rule is not suitable for the new patient, i.e. it exceeds some of the total dose limits set for the rectum. For example, cases c_1 and c_2 having dose plan (46 Gy and 24 Gy) and (50 Gy+20 Gy), respectively, are used in the fusion as shown in Table 4.6. If the outcome of the fusion process is a combination of cases c_1 and c_2, the dose plan prescribed by the Dempster-Shafer rule is 48 Gy and 22 Gy in phases I and II, respectively. The doses received by 66% of the rectum in cases c_1 and c_2 are 38.02 Gy and 36.1 Gy, respectively, while the dose received by 66 % of the rectum in the new case is 46.72 Gy, which is more than the recommended dose limit 45 Gy. If the dose plan suggested by the Dempster-Shafer rule is not fit for the new patient, a repair mechanism is applied to generate a feasible plan. The repair mechanism was designed using the criteria suggested by the oncologist. The proposed repair mechanism is carried out through the following steps:

Step 1: Decrease the dose of phase II by 2 Gy. If the dose plan is feasible go to step 7 else go to step 2.

Step 2: Increase the dose of phase II by 2 Gy and decrease the dose of phase I by 2 Gy . If the dose plan is feasible go to step 7 else go to step 3.

Step 3: Decrease the dose of phase II by 4 Gy and increase the dose of phase I by 2 Gy. If the dose plan is feasible go to step 7 else go to step 4.

Step 4: Increase the dose of phase II by 2 Gy and decrease the dose of phase I by 2 Gy. If the dose plan is feasible go to step 7 else go to step 5.

Step 5: Increase the current dose of phase II by 2 Gy and decrease the current dose of phase I by 2 Gy. If the dose plan is feasible go to step 7 else go to step 6.

Step 6: Consult the oncologist for a better dose plan.

Step 7: Recommend the dose plan suggested by the proposed repair mechanism.

The oncologist has to decide to store the new case in the case base or not for future use.

Table 4.6 An example of calculation of dose limit after the fusion

Case	DVH value of 66 % of the rectum		Dose Plan	
	Phase I	Phase II	Phase I	Phase II
c_1	0.55	0.53	46 Gy	24 Gy
c_2	0.53	0.48	50 Gy	20 Gy
c_{new}	0.68	0.64	(46+50)/2=48 Gy	(24+20)/2=22 Gy
Dose plan prescribed by the Dempster-Shafer rule: 48 Gy + 22 Gy				
Dose received by 66% of the rectum for case c_1: $0.55\times46+0.53\times24=38.02$ Gy				
Dose received by 66% of the rectum for case c_1: $0.53\times50+0.48\times20=36.1$ Gy				
Dose received by 66% of the rectum for case c_{new}: $0.68\times48+0.64\times22=46.72$ Gy				

The main aim of the oncologist is to maximise the total dose, but also to respect the total dose limits of the organs at risk. Dose plan having a higher dose in phase I of the treatment is considered to be better than the dose plan having a smaller dose. For example, dose plan 52 Gy +20 Gy is a better dose plan compared to the dose plan 50 Gy+22 Gy. Further, the amount of dose in each phase of the treatment must be an even integer number. That is why the repair mechanism tries first to decrease the dose in phase II by 2 Gy. However, if the new dose plan still violates some dose constraints given in Table 4.1 then the dose given in phase I of the treatment is decreased by 2 Gy. Also, in order to respect the decision of the oncologist, the dose corresponding to each phase of the treatment decreases by up to 4 Gy maximum. If the new dose plan generated after decreasing 4 Gy of radiation in each phase of the treatment is still an infeasible solution, a further decrease would modify the proposed decision too much. So, in that case, the oncologist is consulted to generate a better dose plan.

To demonstrate the proposed adaptation mechanism in a lucid way, an illustrative example is constructed and shown in Figure 4.8. In this example, the final outcome of the Dempster-Shafer rule is a dose plan having 62 Gy and 10 Gy of radiation in phases I and II of the treatment, respectively. This is not a feasible dose plan because the dose received by 10% of the rectum is 56.2 Gy which is larger than the prescribed maximum dose limit (55 Gy). Hence, in order to generate a feasible dose plan, the repair mechanism is performed. The dose corresponding to phase II of the treatment is decreased by 2 Gy, which leads to the new feasible dose plan 62 Gy and 8 Gy.

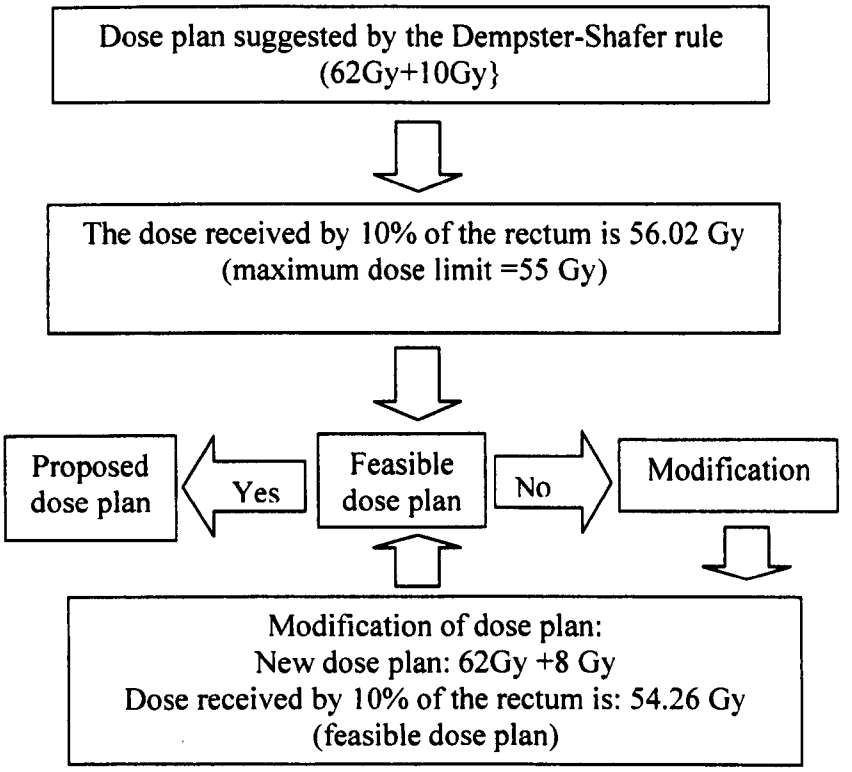


Figure 4.8 A demonstration of the repair mechanism

4.4 A Simulated Annealing Based Dynamic Feature Weight Learning Mechanism

The weights of different clinical parameters in dose planning are highly subjective, and are generally fixed by the system with input from the oncologists based on their past experience. However, manual selection of the weights is a difficult task and can cause unwanted bias in the retrieval process. In the literature a significant body of research has been carried out to investigate the weight setting in the k-NN method including Neural Network Approaches [212-213], Reinforcement Learning [214], a Genetic Algorithm [215], a Domain Knowledge from Experts [12], a Machine Learning Technique

[81], a Hybrid Genetic algorithm [217], a Data Compression and a Local Metrics [218], and a Decision Tree [219], etc. In this chapter, we investigate an automated weighting method based on a Simulated Annealing approach. After each run of the CBR system, the Simulated Annealing algorithm searches for such a combination of weights for which the difference between the doses suggested by the system and the doses recommended by the extracted similar cases are minimal.

Simulated Annealing (SA) is a stochastic search optimisation technique proposed by Kirkpatrick et al. [220]. In Simulated Annealing, solutions are iteratively generated by a random displacement of bits from feasible solutions. In order to avoid local optima, this process accepts not only those solutions which improve the objective function, but also the ones which do not, by using a transition probability. The transition probability depends on the change in the objective function value between the current and a new solution and the annealing temperature [221].

The main features of Simulated Annealing that affect its performance are: the definition of the neighbourhood of a solution, the annealing schedule and the transition probability. In this chapter, real encoding of solutions is used in which each bit represents the value of the corresponding feature weight. In each iteration, a solution from the neighbourhood of the current solution is generated by randomly choosing a bit in the string (i.e. a weight) and replacing it by a random number from [0.1,1] interval. The lower and upper limits of weights are designed following the guidance given by the oncologist. The weights are then normalised (each bit divided by the sum of all bits in the string), so that their sum is equal to 1. An annealing schedule controls the

initial temperature, the final temperature and the rate of cooling. The cooling schedule that is used is shown in formula (4.6).

$$T_r = \frac{T_0}{(1+\ln r)} \tag{4.6}$$

where, T_0 is the initial temperature, T_r is the temperature after r iterations and r is the allowed number of iterations. The proposed cooling schedule is initiated with a high temperature. This results in a high probability of acceptance of worse solutions and thus enables the exploration of a wide search space. However, as the search progresses and the temperature declines towards the end, it is less likely to move towards a worse neighbour solution.

The transition probability helps the algorithm to escape from local optima. For a candidate neighbour solution, which is inferior compared to the current solution, the transition probability, *TP*, is calculated by using formula (4.7):

$$TP = e^{\frac{-\Delta f}{T}} \tag{4.7}$$

where,

$\Delta f = |f(sol_{cand}) - f(sol_{curr})|$

$f(sol_{cand})$=objective function value of the candidate solution sol_{cand}.

$f(sol_{curr})$= objective function value of the current solution sol_{curr}.

The developed weights learning mechanism uses the leave-one-out strategy, namely, cases are taken out from the case base one by one. For each of them, similar cases are retrieved and the difference between the doses in these cases

is calculated in both phases I and II. The question arises as to how many cases one should retrieve from the case base in this learning process. We can set a threshold value and retrieve the cases with a similarity measure higher than that value or the retrieval process can retrieve a fixed number of cases. However, the determination of the threshold value is very difficult because it can be any real number from [0,1] and therefore we opt for the later option. The sum of the differences obtained for all retrieved cases presents the quality of a solution. Therefore, the objective function defined in Simulated Annealing, which has to be minimised, is:

$$f(sol) = f(w_1, w_2, ..., w_L) = \sum_{n=1}^{N} \sum_{s=1}^{S} \left| D_n^I - D_{sim\ s}^I \right| + \left| D_n^{II} - D_{sim\ s}^{II} \right| \qquad (4.8)$$

where,

$sol = (w_1, w_2, ..., w_L)$ is the list of weights w_l, $l = 1,2,...,L$ associated with L features which are used in the similarity measure, (i.e. the distance given in formula (1) and (2)), L=6,

D_n^I, D_n^{II} are the doses for phases I and II respectively prescribed by case c_n taken out from the case base.

$D_{sim\ s}^I, D_{sim\ s}^{II}$ are the doses for phases I and II, respectively, prescribed by the similar case c_s retrieved from the case base using the list of weights $(w_1, w_2, ..., w_L)$ in the similarity measure.

S is the number of cases similar to case c_n retrieved from the case base.

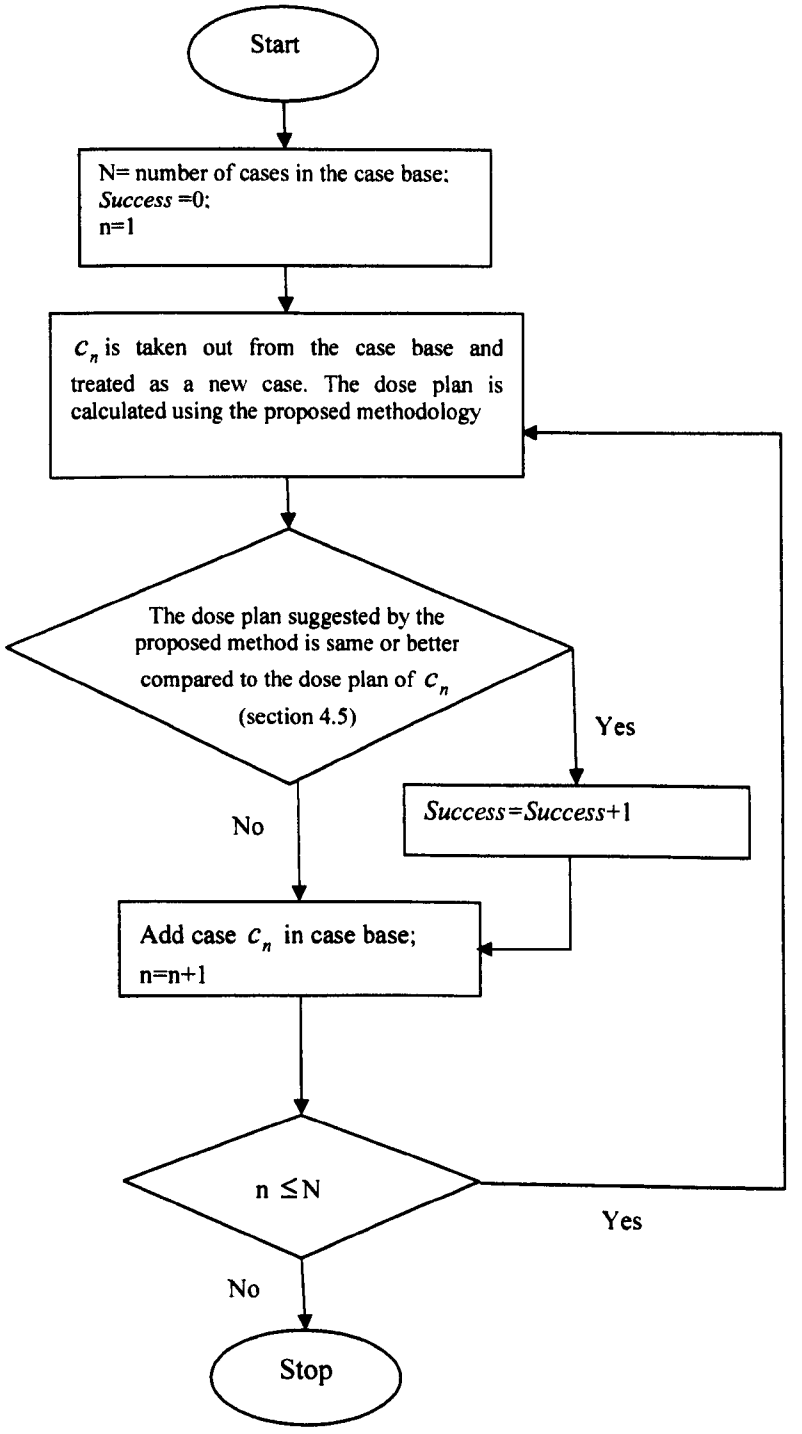
N is the number of cases in the case base.

4.5 Experimental Results

In order to demonstrate the effectiveness and robustness of the proposed methodology, we use the collected anonymised patient records obtained from Nottingham City Hospital. The software system was coded in Visual C++ and run on an Intel PC with Pentium IV CPU at 1.86 GHz.

At the present stage of the research, we have 71 different cases in our case base. The leave-one-out strategy is used to evaluate the performance of the system, flow chart given in Figure 4.9. Each one of the 71 cases is taken out from the case base and treated as a new case. Dose plan for the new case is calculated using the proposed methodology and compared with the dose plan suggested by the oncologists. The evaluation of the proposed plans is made by using criteria defined by the oncologist; namely if there is incongruity between the two plans (dose plan generated by the proposed method and dose plan prescribed by the oncologist), the decision which is better is made using the following two criteria:

(a) If the total sum of doses in phases I and II of the plans are different and the dose received by the different volume percentages of the rectum are within the limits in both plans or violated up to the same extent, then the quality of the plan is judged based on the 5 years Progression Free Probability value. The higher the dose, the higher the 5 years Progression Free Probability. The plan with a higher value of the 5 years Progression Free Probability is considered to be better. The 5 years Progression Free Probability is the probability of remaining disease free after 5 years of the treatment.



$$Success\ rate\ (\%) = \frac{Success}{N} \times 100$$

Figure 4.9 Flow chart of the leave-one-out strategy

(b) If the total sum of doses in phases I and II of the plans is the same and the dose received by different volume percentages of the rectum is (or doses are) within the limits in both plans or violated up to the same extent, then the quality of the plan is judged based on the dose in phase I of the treatment. The plan having a higher amount of dose in phase I is better. For example, a dose plan 54 Gy and 20 Gy in phase I and phase II, respectively, is a better than a dose plan 50 Gy and 24 Gy.

If the proposed dose plan violates the limits imposed on the rectum differently compared to the originally stored dose plan, then it is not considered to be a better plan.

First experiments are carried out to determine the appropriate number of cases to be retrieved and fused by using Dempster-Shafer rule. Using the described leave-one-out strategy it is found that the success rate of the proposed algorithm increases continuously up to four cases and thereafter it becomes constant as shown in Figure 4.10.

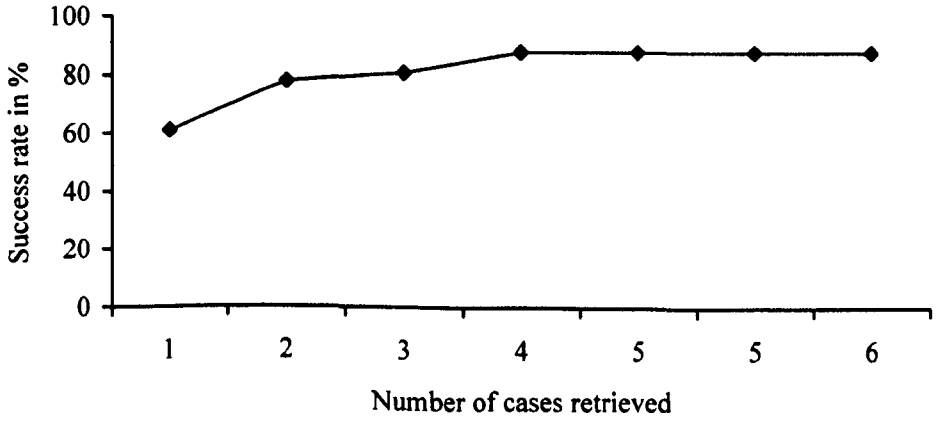


Figure 4.10 Success rate of the CBR system with different numbers of retrieved cases

Parameter setting is a time-consuming task which is crucial for any Simulated Annealing application. The parameters for Simulated Annealing are the maximum number of iterations (r), the initial temperature (T_0), the initial solution and stopping condition. Stopping condition describes the situation when solution is frozen i.e. the value has not changed for several iterations. It could be defined in different ways. For instance, a simple stopping condition can be a limited number of iterations or a limit set on the temperature [229]. In this thesis, the first condition is selected; Simulated Annealing will be stopped when there is no significant improvement during the last several iterations. Following the general guidelines available in the literature and combining them in the preliminary experiments, we have obtained the following configuration for Simulated Annealing: maximum number of iterations $r = 50$ (in experiments, it was found that there was no significant improvement after the 50^{th} iteration, as shown in Figure 4.11), initial temperature $T_0 = 300$ and the initial solution includes equal weights to each feature.

Using the leave-one-out strategy it is found that the success rate of the CBR system with the Simulated Annealing weight learning mechanism, 85.91 %, outperforms the CBR system with fixed equal weights, which is 83.09%. More precisely, the CBR system with the learning mechanism proposed in 52 out of 71 cases the same dose plan as suggested by the oncologist while in 9 cases, it was even better. In the rest of the 10 cases, dose plans suggested by the proposed method are different compared to the originally stored dose plan.

Further experiments are performed to investigate how many cases should be retrieved during the weight learning process (formula (4.8)). Note that in the

weight learning process the fusion process is not employed, and therefore we do not employ the Dempster-Shafer rule. Instead here the retrieved cases are used to define the weights of the features. In the experiments, it is also found that the success rate of the simulated annealing system which retrieves only one similar case (formula (4.8) S =1), 84.50 %, outperforms the approach in which four most similar cases (formula (4.8) S =4) are retrieved, which is 85.91 %. The final combination of weights (weight vector) obtained by the Simulated Annealing learning mechanism is given in Table 4.7.

Table 4.7 Weights obtained by the Simulated Annealing based weight learning mechanism

Clinical parameters	Weight obtained by Simulated Annealing
Gleason Score	0.27
PSA	0.10
DVH phase I	0.31
DVH phase II	0.32

The convergence trend of the Simulated Annealing based weight learning mechanism (with (S=1)) is shown in Figure 4.11. It is observed that Simulated Annealing converges towards a better combination of weights in 50 iterations.

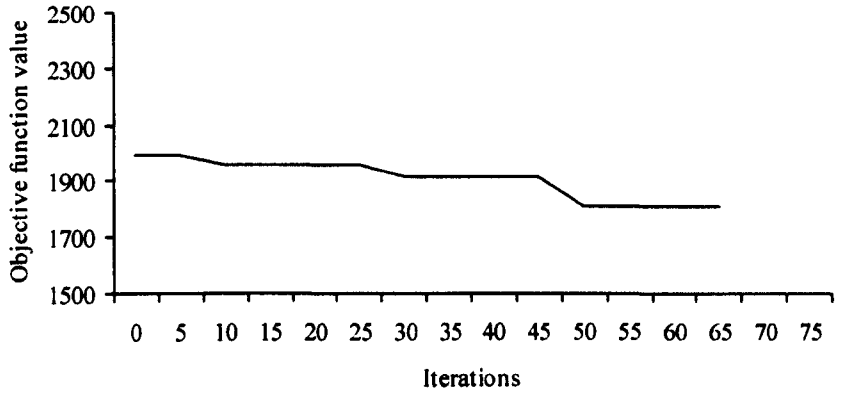


Figure 4.11 Convergence trend of the Simulated Annealing based weight learning mechanism

4.6 Conclusion

In this chapter, a novel case-based reasoning approach is proposed to radiotherapy dose planning for prostate cancer. Research carried out in radiotherapy dose planning usually focuses on the trade-off between the risk and the benefit of the radiation and overlooks the success rate of treatments ("make the patient well" criterion). In this chapter, an attempt has been made to incorporate the success rate of a treatment and trade-off between the risk and the benefit of radiation, simultaneously. The proposed CBR system is also enriched by a Simulated Annealing feature weights learning mechanism and a data fusion concept based on Dempster-Shafer rule.

For each new patient, four cases most similar to a new case are retrieved and combined using the modified Dempster-Shafer rule to suggest a dose for the treatment. In the standard Dempster-Shafer rule, cases are given equal

importance. In the modified Dempster-Shafer rule, weights are assigned to the cases according to their success rates. For prostate cancer the success rate of the treatment is determined by the Prostate Specific Antigen (PSA) value, measured two years after the treatment. During the fusion process cases having better success rates are given more importance than cases having worse success rates. In order to mimic the continuous learning process of oncologists, the weights corresponding to each feature used in the retrieval process are updated automatically each time after a treatment plan is generated for a new patient using the Simulated Annealing feature weight learning mechanism. Finally, if information gained from the new case is useful then it is stored in the case base for future use.

The developed algorithm was applied on data sets obtained from the Nottingham City Hospital. Computational experiments reveal the effectiveness of the proposed methodology. The algorithm not only captures the expertise and experience of the oncologist but also generates better solutions. Adaptation is an important step of CBR system and usually requires detailed knowledge of the problem domain. A Knowledge-Light adaptation is proposed in the next chapter.

CHAPTER 5

A Knowledge-Light Adaptation in Case-Based Reasoning for Radiotherapy Planning

5.1 Introduction

Radiotherapy dose planning is the process of determining the amount of dose to be delivered in the treatment. The main goal of the oncologist is to make a trade-off between the risk and the benefit of radiation i.e. to deliver a high tumoricidal dose to the cancerous region and low enough radiation to the surrounding healthy tissues so that they can maintain their functionality. In Chapter 4, a CBR system to determine the dose in phases I and II of the treatment is described. In the developed CBR system, four cases most similar to a new case are retrieved and combined using the Dempster-Shafer rule to suggest a dose for the treatment. If the dose limits imposed to the rectum are violated, then simple adaptation rules are used to rectify that. In that approach, the dose limits on different volume percentages of the rectum were assumed to be fixed. However, in the real world, in order to fight cancer cells better, the oncologist makes a trade-off between the risk and benefit of radiation and looks beyond the prescribed dose limits.

Adaptation of retrieved solution is a difficult process and it needs comprehensive knowledge of the problem domain and the task. Simple adaptation rule (as described in Chapter 4) works correctly in linear problem domains only i.e. for problems that can be represented by linear models.

Complexity of adaptation process increases with the complexity of problem domain. Highly complex non-linear problems require the addition of explicit adaptation knowledge. The effect of different planning parameters on the dose limits with different volume percentages of the rectum is not uniform; therefore it is considered to be a non-linear problem.

In addition, in Chapter 4, if there was an incongruity between the dose plans suggested by the CBR system and that prescribed by the oncologist, then the quality of a plan was judged by using the 5 years Progression Free Probability, which refers to the probability that a patient will not have cancer cells 5 years after the treatment (the patient is considered to be cured). However, in real life, the oncologist usually also takes into account the 5 years Progression Free Probability while making the trade-off between the benefit and risk of prescribed radiation. To address these issues, in this chapter a knowledge-light nonlinear case-based reasoning approach will be described.

Table 5.1 An example of the nonlinear nature of the radiotherapy planning problem

First pair of cases			
Gleason score	PSA	Dose in phase I	Dose in phase II
7	11.8	46	24
8	11.9	60	10
Second pair of cases			
6	9.7	46	24
7	9.8	46	24

5.2 Non-Linearity of the Dose Planning Problem

As mentioned in Chapter 4, oncologists generally use the following parameters to recommend the dose, to be delivered to the patient: clinical parameters, Dose Volume Histogram (DVH) and success rate of the treatment. The influence of each dose planning parameter on the solution is not linear throughout its range of values. For example, in Table 5.1, two cases are shown with Gleason Score and PSA values which correspond to real world patients. It can be seen that an increase of the Gleason Score by 1 from 7 to 8 and the Prostate Specific Antigen (PSA) by 0.1 from 11.8 to 11.9 affects the recommended dose differently than the same increase of the Gleason Score from 6 to 7 and the PSA from 9.7 to 9.8. Also, the rate of change of a solution is not uniform with the change in input parameters. For example, an increase in Gleason Score from 6 to 7 does not necessarily impact the dose in the same ratio as its increase from 6 to 8 as shown in Table 5.2. Furthermore, there may be interaction between different clinical parameters. For example, an effect of change in the Gleason Score may vary depending on the change in PSA.

Table 5.2 An example of the non-uniform gradient nature of the radiotherapy planning problem

First pair of cases			
Gleason score	PSA	Dose in phase I	Dose in phase II
6	11.8	46	24
7	11.8	46	24
Second pair of cases			
6	11.8	46	24
8	11.8	60	10

5.3 Knowledge-Light Adaptation in Case-Based Reasoning

In order to solve a new problem, a case most similar to the new case is retrieved from the case-base. If the new case is exactly the same as the extracted case, the proposed solution is directly copied from the similar case; otherwise it is adapted to match the requirements of the new case. Adaptation of a retrieved solution is a difficult task which takes into account the differences between the retrieved case and the new case and applies domain knowledge or rules to suggest a solution for the new case. The complexity of the adaptation process increases with the complexity of the problem domain. In recent years, an intensive research has been carried out to develop different types of adaptation methods.

Hanney and Keane [222] proposed a domain knowledge based adaptation method for house price problems. They first calculated the feature differences that exist between the cases in the case base. Thereafter, they examined how these dissimilarities are related to the differences in the case solutions. Based on this analysis they generated C-rules and F-rules. C-rules are the basic adaptation rules that associate the change in the case feature values with solution changes. For each C-rule, F rules were generated. F-rules calculate the frequency of groups of feature value differences. There may be a chance that two pair of cases having the same feature differences may have more than one consequent change in the solution. In this case, rules associated with the same feature difference were considered to be duplicates. To reduce the number of rules retrieved, a threshold value was set and the only rules with similarity value higher than the threshold value were retrieved for the adaptation process.

Craw *et al.* [223] created adaptation rules by considering feature difference vectors of the cases in the case base. They used a 'leave-one-out strategy' to generate the adaptation rules. Each one of the cases was taken out from the case base and treated as a new case. The case most similar to the new case was extracted. If there was incongruity between the solutions suggested by the extracted most similar case and the prescribed solution of the target case, then an adaptation rule was generated and arranged in the form of a decision tree. The top node of the decision tree represents the difference between the parameter values and the leaf nodes predict the adaptation rule. For each new case, a difference vector between the parameters of the new case and the most similar case was calculated and a suitable rule was selected for adaptation.

The positive aspects of the case difference based adaptation methods are that it utilises adaptation knowledge easily generated from the case base and is easily understood. However, it suffers from one major drawback: it will only work correctly in linear domains, i.e. domains that can be represented by a linear model. To resolve the problem caused by non-linearity within the problem domain, Jarmulak *et al.* [224] proposed a learning adaptation knowledge method. The method was based on the assumption of local linearity around the query and limited the search to this region of the domain space only. However, the restriction imposed to the search space does not take into account the individual characteristics of difference in the given domain. To overcome the difficulty caused by the above assumption, McDonnell and Cunningham [225] proposed three knowledge-light methods of adaptation: adaptation in which cases difference and gradients are considered separately; adaptation method where cases difference and gradients are combined and form a scalar; and case

difference based adaptation which is an adaptation method in which cases difference and gradients are considered as a vector. Here, the gradient is defined as the rate of change of the output with respect to the input parameters. The first method is a basic method which is based on local linear regression and the other three approaches are extensions of it. The method, in which cases difference and gradients are considered as a vector, was assessed to be the best general-purpose method and it works well in most problem domains. In this chapter, we explore two of the proposed methods in our radiotherapy planning problem: the basic adaptation method which is based on local linear regression and one of its extensions, the adaptation method, which combines case differences and gradients in a vector. In the next sub-sections, first we will describe the different components of knowledge-light adaptation approach i.e. similarity measure, case difference vector and gradient vector; thereafter we will investigate the basic steps of adaptation.

5.3.1 Similarity Measure

In Chapter 4, the similarity between cases c_p and c_q is measured in two steps. First, the distances between the fuzzy membership values of Clinical Stage ($l=1$), Gleason Score ($l=2$) and PSA ($l=3$) of cases c_p and c_q in the corresponding fuzzy sets is calculated using formula (4.1). Second, the distance, $d_2(c_p,c_q)$, between two cases c_p and c_q takes into consideration DVH of the rectum in phases I and II of the treatment is calculated using formula (4.2). Finally, the overall similarity $s(c_p,c_q)$ between cases c_p and c_q is calculated using formula (4.3).

As mentioned in the introduction section, in dose planning the oncologists takes into account not only the previously treated patients but also the 5 years Progression Free Probability of the proposed dose plans. It gives the probability for a patient to remain disease free after 5 years of treatment. It is calculated by using the values of the Clinical Stage, PSA, Gleason Score and the prescribed total dose. Higher the value of the 5 years Progression Free Probability, the lower the chance of reoccurrence of the cancer. In this chapter, similarity measure and the 5 years Progression Free Probability are combined as follows:

$$TF(c_p, c_q) = \frac{1}{1 + d_1(c_p, c_q) + d_2(c_p, c_q)} * pf_q \qquad (5.1)$$

where, pf_q is the 5 years Progression Free Probability of case c_q.

The overall trade-off function which takes into account the similarity measure, the 5 years Progression Free Probability and the success rate of the treatment between cases c_p and c_q is defined as:

$$OTF(c_p, c_q) = \frac{1}{1 + d_1(c_p, c_q) + d_2(c_p, c_q)} * pf_q * sr_q \qquad (5.2)$$

where, sr_q is the normalized value of the success rate of the treatment of case c_q measured 2 years after the treatment (explained in Section 4.3.3, Figure 4.3).

5.3.2 Cases Difference Vector

The case difference vector which takes into account the fuzzy membership values of feature l, Clinical Stage ($l=1$), Gleason Score ($l=2$) and PSA ($l=3$) of cases c_p and c_q, $\Delta_l(c_p,c_q)$, is defined as:

$$\Delta_l(c_p,c_q)=\frac{\sum_{m=1}^{3}\left(v_{plm}-v_{qlm}\right)}{3},\ l=1,2,3 \qquad (5.3)$$

where, v_{plm} and v_{qlm} are membership degrees of feature l in the fuzzy sets low ($m=1$), medium ($m=2$) and high ($m=3$) in cases c_p and c_q, respectively.

The case difference vector between cases c_p and c_q, $\Delta_{lk}(c_p,c_q)$, which takes into consideration DVH of phase I ($l=4$) and phase II ($l=5$) of 66% ($k=1$), 50% ($k=2$), 25% ($k=3$) and 10% ($k=4$) of the rectum volume is calculated using the following formula:

$$\Delta_{lk}(c_p,c_q)=\left(u_{plk}-u_{qlk}\right),\ l=4,5,\ k=1,2,3,4 \qquad (5.4)$$

where, u_{plk} and u_{qlk}, $k=1,2,3,4$ are DVH values of 66%, 50%, 25%, and 10% of the rectum volume in cases c_p and c_q, respectively.

Hence, difference vector of cases c_p and c_q is defined using formula (5.3) and (5.4)) as:

$$\Delta(c_p,c_q)=[\Delta_1(c_p,c_q),\Delta_2(c_p,c_q),\Delta_3(c_p,c_q),\Delta_{41}(c_p,c_q),\Delta_{42}(c_p,c_q),...,\Delta_{54}(c_p,c_q)] \qquad (5.5)$$

This vector consists of 11 elements.

5.3.3 Adaptation Method Based on Local Linear Regression

This case-based reasoning approach operates under the premise that similar cases also have similar solutions. The case base is searched for such a pair of cases which have similar difference between their feature values as that of the new case and the retrieved case similar to the new case. The case difference vector of the retrieved pair of cases is then used to set the dose limits for different volume percentages of rectum in the new case.

The steps of the local linear regression approach are given below:

Step 1: A case c_{newsim}, most similar to c_{new} with respect to the similarity measure given in formula (4.3) is retrieved from the case base. The cases difference vector $\Delta(c_{new}, c_{newsim})$ is calculated using formula (5.5).

Step 2: List all possible pairs of cases c_1 and c_2, where c_1 and c_2 are any two cases in the case base excluding c_{newsim} and calculate the difference between their features $\Delta(c_1, c_2)$ using formula (5.5) . Note that the order of cases in the pair is important, i.e. the pair c_1, c_2 is different from the pair c_2, c_1.

Step 3: Calculate similarity between vectors ($\Delta(c_1, c_2)$ and $\Delta(c_{newsim}, c_{new})$), sim_1, using formula (4.3), where $\Delta(c_1, c_2)$ and $\Delta(c_{newsim}, c_{new})$ are differences between the parameters of cases c_1 and c_2, and c_{newsim} and c_{new}, respectively, and are calculated using formula (5.5); Select such a pair of cases c_1 and c_2 from the list generated in Step 2 so that sim_1 is maximum.

Step 4: The dose limits to be set in the new case c_{new} are calculated based on the differences in the dose limits of cases c_1 and c_2 as shown in formula (5.6).

$$d_{new,k} = d_{newsim,k} - (d_{c_1,k} - d_{c_2,k}) \tag{5.6}$$

where, $d_{new,k}$, $d_{newsim,k}$, $d_{c_1,k}$, $d_{c_2,k}$, $k = 1,2,3,4$ are dose limits of 66%, 50%, 25%, and 10% of the rectum volume in cases c_{new}, c_{newsim}, c_1 and c_2, respectively.

For example, the calculated dose limits of 66%, 50%, 25% and 10% of the rectum volume of a new case using formula (5.6), are 45.7 Gy , 54.1 Gy, 65.7 Gy and 72.7 Gy, respectively, as shown in Table 5.3. However, the calculated dose limit of 50% of the rectum is smaller than the prescribed maximum dose limit (55 Gy). If the calculated dose limit of any percentage of the rectum volume is smaller than the prescribed maximum limit given in Table 4.1, it is modified and set to the prescribed corresponding maximum dose limit. Hence, the final suggested dose limits of the new case are 45.7 Gy , 55 Gy, 65.7 Gy, 72.7 Gy, as shown in Table 5.3.

Step 5: The recommended doses for phase I ($DP_{I\ \text{new}}$) and phase II ($DP_{II\ \text{new}}$) of the treatment are calculated by solving the linear inequalities shown in formula (5.7).

$$\left.\begin{array}{l} DP_{I\ \text{new}} \times u_{new\,I\,k} + DP_{II\ \text{new}} \times u_{new\,II\,k} \le d_{new\,k}, \\ 24 \le DP_I \le 64 \\ 8 \le DP_{II} \le 24 \\ DP_{I\ \text{new}} \text{ and } DP_{II\ \text{new}} \text{ must be even numbers} \end{array}\right\} \tag{5.7}$$

where, $u_{newI\,k}$, $u_{newII\,k}$, $k = 1,2,3,4$ are DVH values of 66%, 50%, 25% and 10% of the rectum volume in case c_{new} in phases I and

II of the treatment, respectively. This ensures that the dose limits suggested in step 4 are satisfied.

Finally, if the new problem is useful for future reasoning then it is stored in the case base for future use.

Table 5.3 An example of the calculation of dose limits $d_{new,k}$, $k = 1,2,3,4$

Case	66%	50%	25%	10%
c_{simnew}	45.0	55.3	65.8	72.3
c_1	45.5	56.3	65.4	70.9
c_2	46.2	55.1	65.3	71.3
$d_{new,1}$=45.0-(45.5-46.2)=45.7 Gy $d_{new,2}$=55.3-(55.3-55.1)=54.1 Gy $d_{new,3}$=65.8-(65.4-65.3)=65.7 Gy $d_{new,k}$ =72.3-(70.9-71.3)=72.7 Gy				
Suggested dose limit of 66 % of rectum= 45.7 Gy Suggested dose limit of 50 % of rectum= 55.0 Gy Suggested dose limit of 25 % of rectum= 65.7 Gy Suggested dose limit of 10 % of rectum= 72.7 Gy				

5.3.4 Adaptation Method Which Combines Cases Difference and Gradients in a Vector

Radiotherapy dose planning is a non-linear problem. As explained in Section 5.2, the influence of the dose planning parameters is not uniform on the output. In this section, an adaptation method, which takes into account case difference vector and gradients of the cases in the case base, is used (an extension to the previous described adaptation method based on local linear regression). It searches for a case in the case base that has the same gradient as the new case. The gradient is defined as the rate of change of output with respect to a problem feature. The gradient of a simple mathematical function

$Y = f(a_1, a_2, a_3, ..., a_L)$ is defined as:

$$g(f) = \nabla f = (\frac{\partial Y}{\partial a_1}, \frac{\partial Y}{\partial a_2}, ..., \frac{\partial Y}{\partial a_L}) \tag{5.8}$$

where, f is the mathematical relationship among features $a_1, a_2, a_3, ..., a_L$ and Y is the value of function f.

In the radiotherapy planning problem, features of interest are clinical stage, Gleason Score, PSA, and DVH values, but function f that will relate them to the dose limits set for different percentages of the rectum volume is not known. Hence, it is difficult to calculate the gradient. However, if we assume some degree of local linearity in the problem domain, it can be calculated as follows: The gradient of case c_p, $g_{pl}(c_p)$, which takes into consideration Clinical Stage $(l = 1)$, Gleason Score $(l = 2)$, and PSA $(l = 3)$ can be expressed as:

$$g_{pl}(c_p) = \frac{\left\{ \sum_{m=1}^{3} \sum_{k=1}^{4} \left(\frac{d_{pk} - d_{psimk}}{v_{plm} - v_{psimlm}} \right) \right\}}{12}, l = 1,2,3 \tag{5.9}$$

where, d_{pk}, d_{psimk}, k=1,2,3,4 are dose limits of $66\%(k = 1), 50\%(k = 2)$, $25\%(k = 3)$ *and* $10\%(k = 4)$ of the rectum volume in cases c_p and c_{psim}, respectively,

v_{plm}, v_{psimlm}, $m = 1,2,3$ are membership degrees of feature l in the corresponding fuzzy sets low $(m = 1)$, medium $(m = 2)$ and high $(m = 3)$ of cases c_p and c_{psim}, respectively.

The gradient of case c_p, $g_{plk}(c_p)$, which takes into consideration DVH of phase I ($l=4$) and phase II ($l=5$) of 66%($k=1$), 50%($k=2$), 25%($k=3$) *and* 10%($k=4$) of rectum is calculated using formula (5.10).

$$g_{plk}(c_p) = \frac{d_{pk} - d_{psimk}}{u_{plk} - u_{psimlk}} \tag{5.10}$$

where, d_{pk}, d_{psimk} are dose limits of 66%($k=1$), 50%($k=2$), 25%($k=3$) *and* 10%($k=4$) of the rectum volume in cases c_p and c_{psim}, respectively.

u_{plk}, u_{psimlk} are DVH values of phase I (l=4) and phase II (l=5) of the treatment of 66%($k=1$), 50%($k=2$), 25%($k=3$) *and* 10%($k=4$) of the rectum volume in cases c_p and c_{psim} respectively.

Hence, the gradient vector of case c_p is:

$$g(c_p) = \{g_{p1}(c_p), g_{p2}(c_p), g_{p3}(c_p), g_{p41}(c_p), g_{p42}(c_p), ..., g_{p54}(c_p)\} \tag{5.11}$$

For example, the gradient of case c_1 which takes into consideration the DVH value of phase I of the treatment is shown in Table 5.4.

Table 5.4 An example of the calculation of the gradient in phase I of the treatment

Case	DVH value in phase I of treatment				Dose Plan	
	66%	50%	25%	10%	Phase I	Phase II
c_1	0.55	0.70	0.99	0.92	46	24
c_{1sim}	0.64	0.88	0.90	1.00	54	16
Gradient of 66% of the rectum of case c_1 is: (46-54)/(0.55-0.64) = 88.88						
Gradient of 50% of the rectum of case c_1 is: (46-54)/(0.70-0.88) = 44.44						
Gradient of 25% of the rectum of case c_1 is: (46-54)/(0.99-90) = -88.88						
Gradient of 10% of the rectum of case c_1 is: (46-54)/(0.92-1.00) = 100						

The steps of the method which combines the cases difference and the gradient in a vector are given below and illustrated in Figure 5.1.

Step 1: Case c_{newsim}, the most similar to the new case, c_{new}, is retrieved from the case base, using formula (4.3). The cases difference vector $\Delta(c_{new}, c_{newsim})$ is calculated using formula (5.5).

Step 2: List all possible pairs of cases c_1 and c_2, where c_1 and c_2 are any two cases in the case base excluding c_{newsim} and calculate the difference between their features $\Delta(c_1, c_2)$ using formula (5.5) . Note that the order of cases in the pair is important, i.e. the pair c_1, c_2 is different from the pair c_2, c_1.

Step 3: Calculate similarity between vectors ($\Delta(c_1, c_2)$ and $\Delta(c_{newsim}, c_{new})$), sim_1, using formula (4.3), where $\Delta(c_1, c_2)$ and $\Delta(c_{newsim}, c_{new})$ are differences

between the parameters of cases c_1 and c_2, and c_{newsim} and c_{new}, respectively, and are calculated using formula (5.5);

Calculate similarity between vectors $g(c_{newsim})$ and $g(c_2)$, sim_2, where $g(c_{newsim})$ and $g(c_2)$ are gradients of cases c_{newsim} and c_2, respectively, and are calculated using formula (5.11).

Select such a pair of cases c_1 and c_2 from the list generated in Step 2 so that the sum of similarities sim_1 and sim_2 is maximum. Note that the order of cases is important, i.e. the pair c_1, c_2 is different from the pair c_2, c_1.

Step 4: A trade-off between the benefit and risk i.e. the extent of violation of the maximum prescribed dose limits, shown in Table 4.1, of the rectum for new case c_{new} is calculated using cases c_1, c_2 and c_{newsim} so that the difference in the dose limits of the extracted cases c_1 and c_2 is the same as of the c_{newsim} and c_{new} (formula (5.6)). If the calculated dose limits of any percentage of the rectum are smaller than the prescribed maximum dose limit given in Table 4.1, it will be modified and set to the prescribed corresponding maximum dose limit as explained in step 4 of section 5.3.3.

Step 5: Calculate the dose for phase I ($DP_{I\ new}$) and phase II ($DP_{II\ new}$) of the treatment as explained in step 5 of the method based on local linear regression in section 5.3.3.

Finally, the new case is stored in the case base if it is useful for future reasoning.

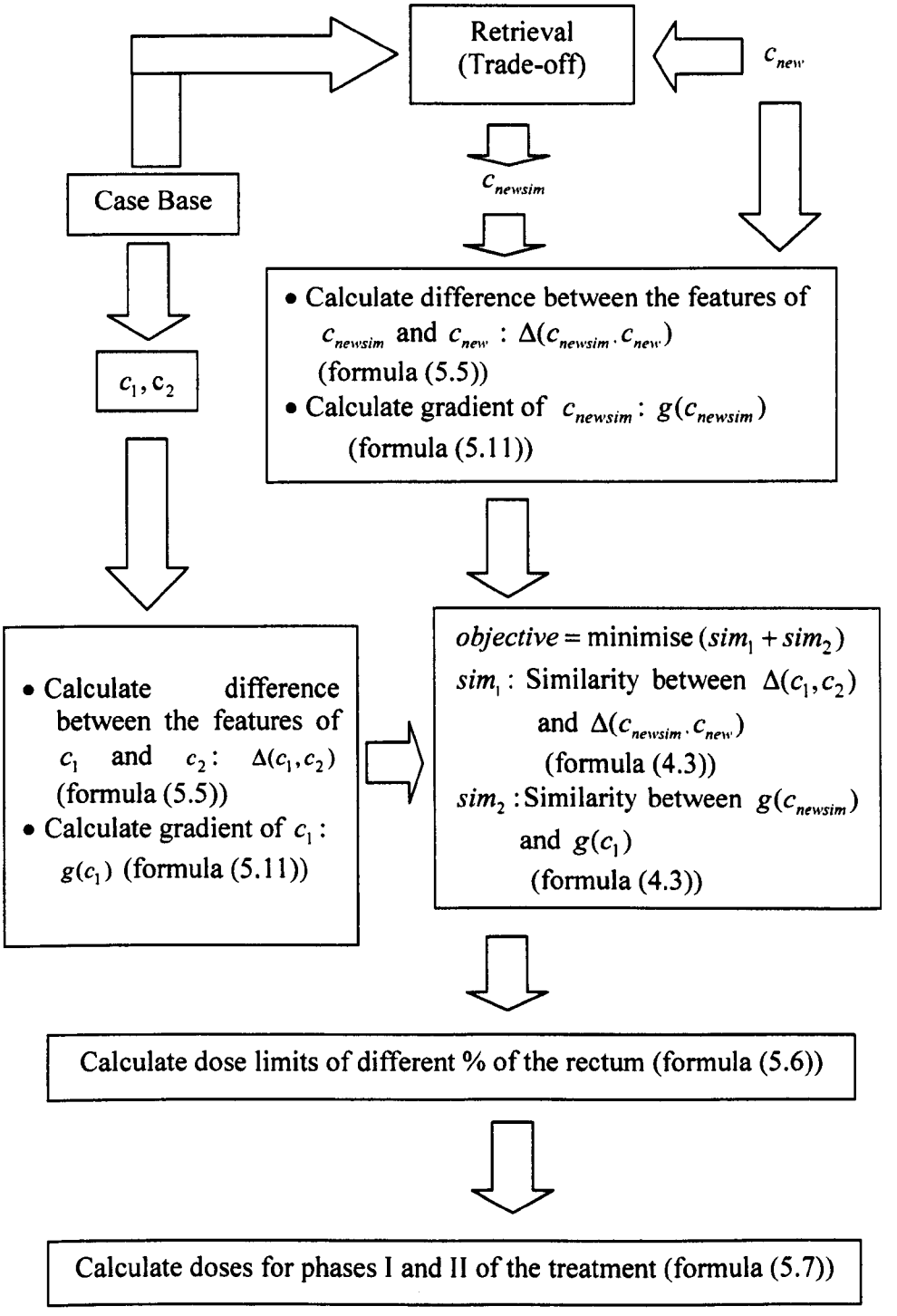


Figure 5.1 Flow chart of the adaptation method which combines differences case and the gradient in a vector

5.4 An Illustrative Example

To illustrate the execution process of the developed CBR system, a simple example is considered in this section. Table 5.5 presents a real patient record collected from the Nottingham City Hospital (some pieces of information are omitted because they do not play any role in the reasoning). The input data are: stage of the cancer, clinical stage, PSA value and DVH value in phases I and II of the treatment. A trade-off between the similarity measure, the 5 years Progression Free Probability and success rate of the treatment is made (formula (5.2)) and the case c_{newsim} the most similar to the new patient c_{new} is retrieved. The feature values of the retrieved similar case are given in Table 5.6 and the case difference $\Delta(c_{new}, c_{newsim})$ and gradient $g(c_{newsim})$ vectors are calculated using formula (5.5) and (5.11), respectively. Thereafter, two cases c_1 and c_2 presented in Table 5.7 and Table 5.8, respectively, are retrieved from the case base such that the sum of the similarity between the vectors $\Delta(c_1, c_2)$ and $\Delta(c_{new}, c_{newsim})$ and $g(c_{newsim})$ and $g(c_1)$ is minimum. A trade-off between benefit and risk is made and the dose limits for different volume percentages of the rectum are calculated based on the difference in dose limits of the selected cases c_{newsim}, c_1 and c_2. The calculated dose limits for different volume percentages of the rectum are shown in Table 5.9. The calculated dose limit of 10% of the rectum is 69.44 Gy which is smaller than the prescribed maximum dose limits which is 70 Gy. The modified dose limits of 66%, 50%, 25% and 10% of the rectum are 49.98 Gy, 55.06 Gy, 68.12 Gy, 70.00 Gy respectively. Subsequently, the doses for phases I and II of the treatment are calculated using formula (5.7). The calculated doses for phases I and II of the treatment are 46 Gy and 24 Gy, respectively.

Table 5.5. Case c_{new}

Clinical stage	Gleason score		PSA
T1c	8		16.0
DVH of phase I			
66%	50%	25%	10%
69	88	98	100
DVH of phase II			
66%	50%	25%	10%
51	60	96	100

Table 5.6. Case c_{newsim}

Clinical stage	Gleason score		PSA
T2b	9		25.7
DVH of phase I			
66%	50%	25%	10%
68	90	98	99
DVH of phase II			
66%	50%	25%	10%
51	53	95	98
(Dose Plan: 54Gy+16Gy) Dose limits of the rectum (Gy)			
66%	50%	25%	10%
45.00	57.08	68.12	70.00

Table 5.7. Case c_1

Clinical stage	Gleason score		PSA
T1c	7		17.3
DVH of phase I			
66%	50%	25%	10%
81	95	101	103
DVH of phase II			
66%	50%	25%	10%
53	62	98	102
(Dose Plan: 46Gy+24Gy) Dose limits of the rectum (Gy)			
66%	50%	25%	10%
45.00	58.58	69.98	71.86

Table 5.8. Case c_2

Clinical stage		Gleason score	PSA
T2a		6	18.2
DVH of phase I			
66%	50%	25%	10%
81	96	101	101
DVH of phase II			
66%	50%	25%	10%
53	60	98	99
(Dose Plan: 46Gy+24Gy) Dose limits of the rectum (Gy)			
66%	50%	25%	10%
49.98	58.56	69.98	70.20

Table 5.9. Calculation of dose limits $d_{new,k}$, $k = 1, 2, 3, 4$

Case	66%	50%	25%	10%
c_{simnew}	45.00	57.08	68.12	70.00
c_1	45.00	58.58	69.98	71.86
c_2	49.98	58.56	69.98	70.20
$d_{new,1}$=45.00-(45.00-49.98)=49.98 Gy $d_{new,2}$=57.08-(58.58-58.56)=55.06 Gy $d_{new,3}$=68.12-(69.98-69.98)=68.12 Gy $d_{new,4}$=70.00-(71.86-70.20)=68.34 Gy				
Suggested dose limit of 66 % of the rectum= 49.98 Gy Suggested dose limit of 50 % of the rectum= 55.06 Gy Suggested dose limit of 25 % of the rectum= 68.12 Gy Suggested dose limit of 10 % of the rectum= 70.00 Gy				

5.5 Experimental Results

To evaluate the performance of the developed CBR system and to compare it with the previously developed CBR systems (Chapter 4) extensive experiments were performed on the anonymised patient records collected (71 cases) in the

Nottingham City Hospital as mentioned in Chapter 4.

The leave-one-out strategy is used to evaluate the performance of the system as described in Chapter 4. The dose plan is calculated using the proposed methodology and compared with the dose plan suggested by the oncologists. The evaluation of the proposed plans is made by using criteria defined by the oncologist as described in Chapter 4.

The proposed algorithm is firstly compared with our previous approach (described in chapter 4) which does not take into consideration the success rate and the 5 years Progression Free Probability in the similarity measure. The comparative results are shown in Table 5.10. The new CBR system clearly outperforms the previous approach, namely its success rate is higher and it generates better plans (compared to the plan suggested by the oncologist) for a larger number of patients. Also it is compared with the local regression based case-based reasoning approach. The developed knowledge-light adaptation method which combines cases difference and gradients achieves the best results and will be used in the further experiments. The success rate of the system is 88.73 %; in 40 cases the dose plans suggested by the proposed methodology is the same as that of the oncologist, while in 23 cases it is even better. More precisely, in 8 among 23 cases it generates a dose plan having better the 5 years Progression Free Probability while still not violating the imposed dose limits of the rectum or violating up to the same extent as that of the plan prescribed by the oncologist. In the rest of the 8 cases, dose plans suggested by the proposed method are different compared to the originally stored dose plan.

Table 5.10 Results of the proposed methodology compared with the other methods

Methodology	CBR system based on Dempster-Shafer rule (chapter 4)	CBR based on local regression*	CBR combines cases difference and gradients in a vector*
Success rate (%)	81.69	80.28	88.73
Number of cases having better dose plan	6	16	23

*Takes into account the 5 years Progression Free Probability and success rate of the treatment in the trade-off

In order to investigate the importance of the 5 years Progression Free Probability and success rates in the dose planning process, additional experiments were performed. Using knowledge-light adaptation in case-based reasoning approach which does not take into account these two features in the retrieval process the success rate is 85.91%. If the 5 years Progression free probability and the success rate of the treatment are used in the retrieval process, the success rate is higher; it is 85.91 % and 87.32 % respectively. The results are shown in Table 5.11. We can conclude that the success rate and the 5 years Progression Free Probability are important decision making parameters. As expected, the 5 years Progression Free Probability based retrieval process

helps to generate dose plans having better 5 years Progression Probability. The success rate based trade-off function assists the retrieval process to increase the success rate of the treatment by increasing the dose in phase I of the treatment, while the combination of both decision making parameters explores the past experience of the oncologist in a better way and generates plans having a better 5 years Progression Free Probability and a better success rate.

Table 5.11 Comparative results of different types of trade-off functions

Retrieval	Similarity	Similarity + 5 years Progression Free Probability	Similarity + Success rate of the treatments	Similarity +5 years Progression Free Probability + Success rate of the treatments
Success rate (%)	85.91	85.91	87.32	88.73
Number of cases having same dose plan as that of oncologist	38	38	39	40
Number of cases having same amount of total dose but higher amount of dose in phase I of the treatment	16	15	16	15
Number of cases having better 5 years Progression Free Probability	7	8	7	8

5.6 Conclusion

This chapter has described a method to determine the dose limits of different volume percentages of the rectum and consequently the dose in phases I and II of the treatment. This is a non-linear problem. The influence of planning

parameters on the solution is not uniform through their range of values. A Knowledge-Light Adaptation in Case-Based Reasoning is proposed to retrieve the case which is the most appropriate for treating a new prostate cancer patient.

For each new case, a case in the case base that has a similar case difference vector and gradient as the new case is retrieved and dose limits for different volume percentages of the rectum are calculated. Thereafter, dose for phases I and II of treatment is prescribed. A trade-off between risk and benefit is made during the dose planning process. Success rate of the treatment measured 2 after years the treatment and the 5 years Progress Free Probability are taken into consideration, to overcome the drawback of optimisation methods (such as Genetic Algorithm, Simulated Annealing, Linear Programming, etc.) which cannot utilize this information.

The efficiency of the proposed methodology is validated using real data sets collected from the Nottingham University Hospitals. NHS, City Hospital Campus, UK. It is clear from the results shown in this chapter that the proposed Knowledge-Light adaptation in CBR not only increases the success rate of the CBR but also generates a better plan in larger number of cases compared with the methodology proposed in the previous chapter. In this chapter, in the retrieval process, equal weights were assigned to all the problem features and it is not always true. A novel group based Simulated Annealing feature weight learning mechanism is proposed in the next chapter.

CHAPTER 6

An Adaptive Knowledge-Light adaptation in case-based reasoning for Radiotherapy Planning

6.1 Introduction

In the knowledge-light adaptation in case-based reasoning, described in the previous chapter, equal weights were assigned to all features used in the retrieval process. However, equal weight assignment is not always appropriate in the real world prostate cancer dose planning problem. In Chapter 4, we proposed a Simulated Annealing based weight learning mechanism for the Dempster-Shafer rule based CBR system. The main aim of the SA algorithm was to minimize the sum of the differences obtained from all retrieved cases using the leave-one-out strategy. However, after analyzing the data, it is found that cases having different clinical parameters (case features) may have the same dose plan. Also, in the dose planning process, the oncologist makes a trade-off between the risk and the benefit of the radiation, i.e. the task is to deliver a high dose to the cancer cells and minimize the side effects of the treatment. In Chapter 5, a simple mathematical relationship (formula (5.2)), namely the product of similarity, the 5 years Progression Free Probability and the success rate of the treatment were used to make a balance between the risk and the benefit of the radiation. In this chapter, a novel trade-off mechanism and a group based Simulated Annealing feature weight learning algorithm will be described.

6.2 A Novel Trade-off Method for the Retrieval Process

Trade-off refers to a situation that involves compromising one objective in return for gaining other conflicting objectives. A decision is made with full comprehension of both the disadvantages and the advantages of all the objectives of a particular choice. The trade-off methods existing in the literature can be divided into three groups, namely a-priori, a-posteriori and interactive methods. In the a-priori methods the decision makers express their preference before the search starts. However, it is very difficult for a decision maker to quantify accurately the preference beforehand. In the a-posteriori methods, the search engine first generates a Pareto front i.e. set of non-dominated solutions. Thereafter, the decision maker selects the best solution. The drawback of this method is that it is very time consuming and computationally costly. In the interactive method, the decision maker continuously interacts with the search engine and drives the search with his/her preference towards the most preferred solution.

Multi-objective optimisation methods have been already applied to the radiotherapy planning problem. Lahanas *et al.* [169] proposed NSGA-II, a modified genetic multi-objective optimisation algorithm, to generate a Pareto front i.e. a set of non-dominated solutions (plans). Thereafter, the oncologists make a trade-off and select a treatment plan based on their past experience. The multi-objective optimisation method can generate a good approximation of the Pareto front, but the problem is to decide which treatment plan is the most appropriate for the patient.

Meyer et al. [147] used the influence diagram based on the Bayesian network which presented a probabilistic relation between the clinical input data and the

quality of the plan to select the most appropriate solution from the set of non-dominated solutions of the Pareto front for prostate cancer. The proposed approach generates different possible solutions by varying the weights of the planning target volume and organ-at-risk using Simulated Annealing (SA). Thereafter, solutions were ranked based upon the physicians' subjective judgements. This method was time consuming and also computationally costly.

Aubry *et al.* [138] proposed a modified Simulated Annealing algorithm to solve the radiotherapy dose planning problem. First, a Pareto set of all non-dominated solutions was generated and solutions were ranked by each objective. Thereafter, a Microsoft Excel graphical user interface was developed to help the decision maker to select an appropriate solution. However, as the number of real world constraints and/or objectives increases it becomes more difficult to understand their effects on the stochastic search, such as Simulated Annealing.

Singh and Dhillon [226] proposed a Fuzzy based Surrogate worth trade-off method for thermal power dispatch problems. Non-inferior solutions were generated by using the ε-constraint method. Equality and inequality constraints are clubbed with the objective function using Lagrangian multipliers and a penalty method respectively. A set of all non-dominated solutions was generated using Newton-Raphson. Thereafter, a Surrogate worth trade-off method is applied to identify the best solution from the set of non-dominated solutions.

Boman et al. [227] proposed a non-linear interactive multi-objective optimisation method for the radiotherapy dose planning problem. The decision maker divides the conflicting objectives in five different classes, namely,

functions whose values should be improved, functions whose values should be improved up to a desired aspiration level, function whose values are satisfactory, functions whose values can be impaired up to a given bound and functions whose values change freely. As the search proceeds based on the decision makers' preference, the search engine selects a solution from the solutions generated so far as a starting point for a new classification and generates a satisfactory solution.

6.2.1 Group Based Trade-off Method

In this research, we proposed a group based trade-off mechanism, which divides cases into different groups based on the similarity between the new case and the cases in the case base, the 5 years Progression Free Probability and the success rate of the treatment measured two years after the treatment. The trade-off gives the highest priority to the similarity between a case from the case base and the new case, then to the 5 years Progression Free Probability and finally to the success rate of the treatment. For each trade-off parameter a range of values is defined. Here, we define four ranges of values for each parameter as shown in Figure 6.1. The ranges are set empirically. Each case in the case base is assigned a triplet $c(s, p, sr)$, where s, p, sr denote the ordinal numbers of the range to which the values of the three trade-off parameters of the case belong.

It means that $(s, p, sr) \in \{(1,1,1),(1,1,2),(1,2,1),(1,2,2),(2,1,1),(2,1,2),...(4,4,4)\}$. To achieve the trade-off, the retrieval process searches first for the cases in the case base with triplet (1,1,1), then with triplets $(1,1,2),(1,2,1),(1,2,2),(2,1,1),(2,1,2),...(4,4,4)$ till a case is found. If more than

one case is selected from the case base, the conflict can be resolved using the following formula:

$$OTF(c_p, c_q) = \frac{1}{1 + d_1(c_p, c_q) + d_2(c_p, c_q)} \times pf_q \times sr_q \tag{6.1}$$

where,

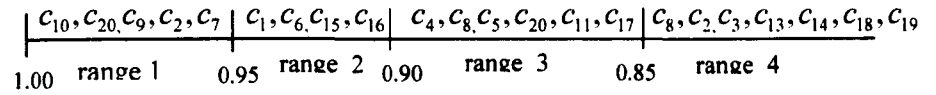
pf_q is the 5 years Progression Free Probability of case c_q.

sr_q is the normalized value of the success rate of the treatment of case c_q measured 2 years after the treatment (explained in section 4.3.3, Figure 4.3).

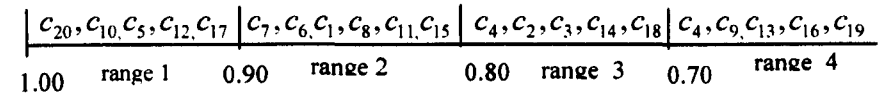
Following the illustration given in Figure 6.1, let us suppose that a case base consists of 20 cases. Based on the similarity between the new case and the cases in the case base, the 5 years Progression Free Probability and the success rate of the treatment, the cases are divided into four different groups. A triplet id is assigned to each case in the case base as shown in Table 6.1. Thereafter, the case base is searched, but there is no case in the case base with triplet (1,1,1) then the case base is searched for triplet (1,1,2) and case c_{10} is selected.

Table 6.1 Illustration of the triplet id of the cases in the case base

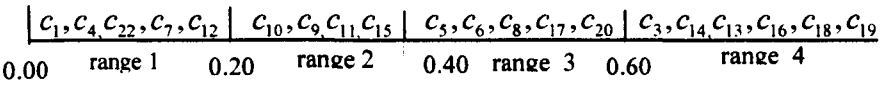
Case	Triplet id	Case	Triplet id	Case	Triplet id	Case	Triplet id
c_1	{2,2,1}	c_6	{2,2,3}	c_{11}	{3,2,2}	c_{16}	{2,4,4}
c_2	{4,3,1}	c_7	{1,2,1}	c_{12}	{4,1,1}	c_{17}	{3,1,3}
c_3	{4,3,4}	c_8	{3,2,3}	c_{13}	{4,4,4}	c_{18}	{4,3,4}
c_4	{3,3,4}	c_9	{1,4,2}	c_{14}	{4,3,4}	c_{19}	{4,4,4}
c_5	{3,1,3}	c_{10}	{1,1,2}	c_{15}	{2,2,2}	c_{20}	{1,1,3}



Similarity ranges



5 years Progression Free Probability



Success rate ranges

Figure 6.1 Illustration of range of values set for trade-off parameters

Once the case most similar to the new case is retrieved from the case base by using the trade-off mechanism, the CBR system finds two cases from the case base which have similar differences between their features values as the new case and the retrieved one, as explained in Chapter 5. These two cases and the gradient of one of them are used to set the dose limits for the rectum volumes in the new case. The architecture of the knowledge-light adaptation in case-based reasoning which uses the proposed trade-off in the retrieved process is shown in Figure 6.2. Based on the calculated dose limits, the dose in phases I and II of the treatment is determined.

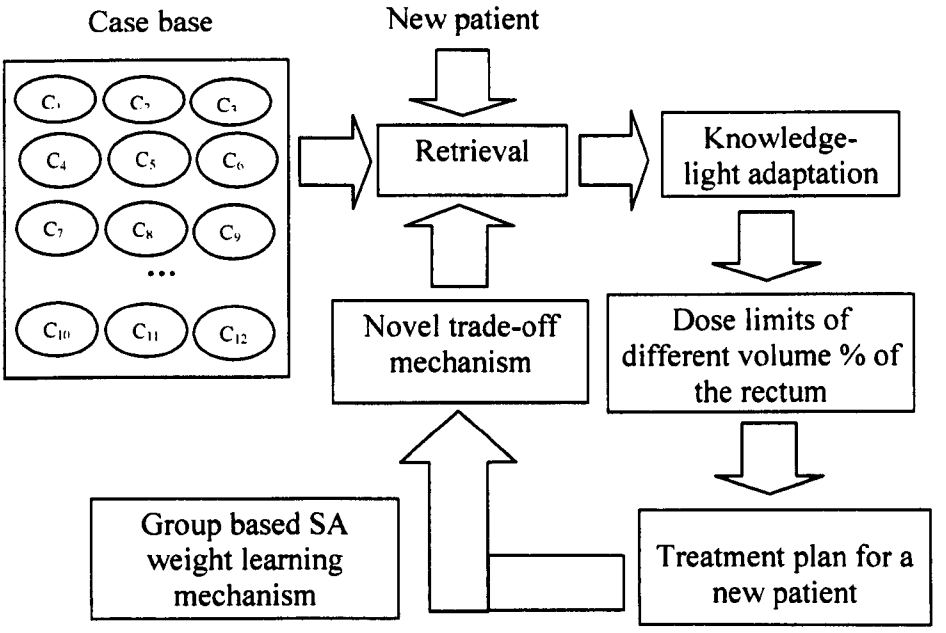


Figure 6.2 Architecture of the proposed knowledge-light adaptation in CBR

6.3 Group Based Simulated Annealing Feature Weight Learning Mechanism

Weights assigned to the features in the similarity measure represent their relative importance. In Chapter 4, we used simple Simulated Annealing (SA) to determine the weights of features. A leave-one-out strategy is used i.e. cases are taken out from the case base one-by-one and treated as a target case each. For each target case, the most similar case from the case base is retrieved and the differences in the doses between the target and retrieved case in both phases I and II are calculated. The sum of the differences obtained form all retrieved cases presents the objective function of Simulated Annealing. However, after analyzing the data it is found that cases having different clinical parameters (case features) may have the same dose plan. The main aim of the

retrieval process is to search for a case which recommends an appropriate dose plan for a new case. In the proposed approach, an attempt is made to push the new case toward the group of cases having the appropriate dose plan for a new case. In order to facilitate this, the cases in the case base are divided into different groups based on their dose plans. Each group holds the cases that have the same dose plan. The centre of a group is defined as a hypothetical case whose values of features are equal to the average values of the features of all the cases in the group. The execution process of the Group based Simulated Annealing is same as that of simple SA algorithm. The main difference is the organization of the case base.

Let a case base $C=\{c_1,c_2,c_3,...,c_N\}$ consist of N cases and each case is described by L problem features. A case $c_n=\{x_{n1},x_{n2},x_{n3},...,x_{NL}\}$, $n=1,2,3,...,N$, is composed of L features where x_{nl} is the value of feature l of case c_n. Let case base C be divided into R groups $G=\{g_1,g_2,g_3,...,g_R\}$ and $A=\{a_1,a_2,a_3,...,a_R\}$ is set of the group centres, where, $a_r=\{b_1,b_2,b_3,...,b_L\}$, $r=1,2,3...,R$, is the centre of group r and b_l is the value of feature l in a_r. Suppose further that group g_r consists of S cases. Then b_l is calculated using formula (6.2).

$$b_l=\frac{\sum_{i=1}^{S}x_{il}}{S},\ l=1,2,3,...,L \qquad (6.2)$$

where, x_{il} is the value of feature l of case i in group g_r.

In this chapter again, the learning mechanism uses a leave-one-out strategy. Namely, cases are taken out from the case base one-by-one, and their distances from the centre of each group are calculated. The closest group with its dose

plan is retrieved. Thereafter, the difference between the doses in phases I and II of the retrieved group and the taken out case is calculated. The sum of the differences obtained from all cases, using the leave-one-out strategy, presents the quality of a solution (solutions here are the weights assigned to features in the similarity measure). The objective function defined which has to be minimised is:

$$f(sol) = f(w_1, w_2, ..., w_L) = \sum_{n=1}^{N} \left| D_n^I - D_{sim\,j}^I \right| + \left| D_n^{II} - D_{sim\,j}^{II} \right| \tag{6.3}$$

where,

$sol = (w_1, w_2, ..., w_L)$ is list of weights w_l, $l = 1,2,...,L$ associated with L features which are used in the similarity measure.

N is the number of cases in the case base.

D_n^I, D_n^{II} are doses for phase I and II, respectively, prescribed by case c_n taken out from the case base.

$D_{sim\,j}^I, D_{sim\,j}^{II}$ are doses for phases I and II, respectively, of the group closest to case c_n using the list of weights $(w_1, w_2, ..., w_L)$ in the similarity measure.

6.4 Experimental Results

Extensive experiments have been carried out on the anonymised patient records collected in the Nottingham City Hospital to evaluate the performance of the developed CBR system. There are 71 cases in the case base. A leave-one-out cross-validation strategy is used to evaluate the performance of the system whereby a case is removed from the case-base and treated as a new case. The

dose plan is calculated and compared with the dose plan stored originally in the case. The evaluation of the proposed plans is made by using criteria defined by the oncologist as explained in Chapter 4.

In this chapter, the proposed CBR system was compared with the previously developed knowledge-light adaptation in CBR system (Chapter 5):

(a) With fixed weights of features in the similarity measure and a simple retrieval process which uses formula (6.1).

(b) With a group based SA weights learning mechanism and a simple retrieval process described in Chapter 5.

(c) With fixed weights and proposed trade-off in the retrieval process.

(d) With a simple SA weights learning mechanism and proposed trade-off in the retrieval process.

Following the general guidelines available in the literature and combining them in the preliminary experiments, the following configuration is used to run the Simulated Annealing (SA) algorithm: initial temperature $T_0 = 300$, initial solution assigns equal weights to each feature and termination condition is 34 iterations (set empirically). In experiments, it was found that there was no significant improvement in the solution after the 34^{th} iteration, as shown in Figure 6.3.

Table 6.2 Comparison of the proposed methodology and our earlier CBR approaches

Methodology	Simple CBR	Simple CBR+ trade-off using formula (5.2)	Simple CBR+ proposed trade-off method (Section 6.2.1)	knowledge-light adaptation in CBR	knowledge-light adaptation in CBR + trade-off using formula (5.2)	knowledge-light adaptation in CBR + proposed trade-off mechanism (Section 6.2.1)
Fixed Weights						
Success rate (%)	73.32	76.05	78.87	85.91	88.73	91.54
Number of cases having same dose plan as that of the oncologist	42	43	44	38	40	40
Number of cases having better dose plan	10	10	12	23	23	25
Number of cases having: (a) Better 5 years Progression Free Probability	1	2	3	7	8	9
(b) Same amount of total dose but higher amount of dose in phase I of the treatment	9	8	9	16	15	16
Simple SA weights learning mechanism						
Success rate (%)	77.46	78.87	81.69	88.79	90.14	92.95
Number of cases having same dose plan as that of the oncologist	42	44	45	40	40	39
Number of cases having better dose plan	13	12	13	23	24	27
Number of cases having: (a) Better 5 years Progress Free Probability	2	3	3	7	9	10
(b)Same amount of total dose but higher amount of dose in phase I of the treatment	11	9	10	16	15	17
Group based SA weights learning mechanism						
Success rate (%)	80.28	83.09	84.50	90.14	92.95	**94.36**
Number of cases having same dose plan as that of the oncologist	44	45	45	39	40	**39**
Number of cases having better dose plan	14	12	15	24	26	**28**
Number of cases having: (a) Better 5 years Progress Free Probability	2	2	3	8	10	**11**
(b)Same amount of total dose but higher amount of dose in phase I of the treatment	12	10	12	16	16	**17**

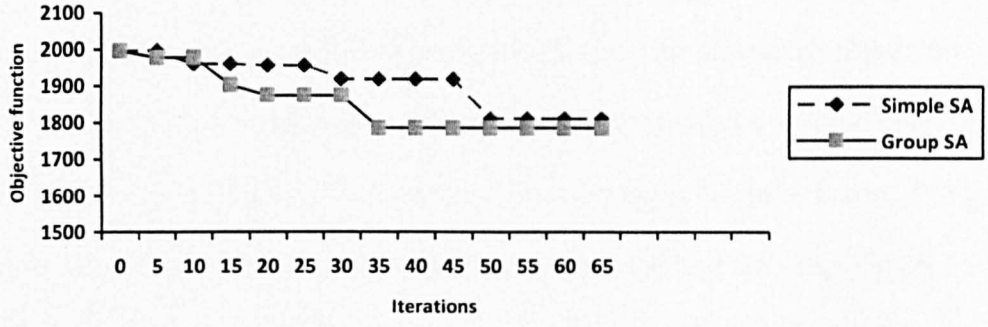


Figure 6.3 Convergence trend of the group based and simple SA weight learning algorithm.

The comparative results are shown in Table 6.2. From the table it can be concluded that the performance of knowledge-light adaptation in case-based reasoning is better than simple case-based reasoning system. The success rate of the knowledge-light adaptation in case-based reasoning approach, 88.73%, outperforms the success rate of the simple case-based reasoning approach, which is 73.32%.

We also compared the performance of the initial SA (described in Chapter 4) with the new one. Experiments show that the group based SA algorithm converges towards a better combination of weights more quickly than the simple SA weight learning algorithm. The convergence trends of both algorithms are shown in Figure 6.3.

Experiments also demonstrate that the performance of the group based SA weights learning mechanism is better than the simple SA based one. The success rate of the group based SA knowledge-light adaptation in case-based reasoning algorithm, 94.36%, outperforms the simple SA based knowledge-light adaptation in case-based reasoning algorithm which success rate is

92.95%. The proposed group based SA algorithm also helps both CBR systems in generating a better dose plan (i.e. better 5 years Progression Free Probability) in a higher number of cases compared to the simple SA algorithm. The final vector of weights obtained by the group based SA weight learning mechanism corresponding to features Clinical Stage, Gleason Score, PSA, DVH phase I and DVH phase II are 0.10, 0.12, 0.10, 0.33, 0.35, respectively.

We also investigated the stability of the weights suggested by both SA approaches. Both group based SA and simple SA were run 20 times using the same case-base. The ranges of weights of all features are shown in Figure 6.4. It can be noticed that the performance of the group based SA is more consistent than the simple SA weights learning mechanism, in the sense that the ranges of the obtained values are smaller, the only exception being DVH of phase I.

Further experiments are performed to investigate the impact of the number of cases in the case base on the performance of the system. In addition, the experiments are performed to investigate the benefit of the group weight learning mechanism. In the experiments two approaches of weights determination are used. The first approach refers to fixed weights. Weights are calculated based on 71 cases in the case base and weights will remain constant in all the experiments. The second approach uses a group based weight learning mechanism and the weight vector changes every time a new case is introduced. Each time a certain number of cases are removed randomly from the case base and the weights corresponding to each feature are updated using the group based SA mechanism. To avoid any bias, the experiments have been repeated 50 times with the same number of cases in the case base. For example, 6 cases are removed randomly 50 times and experiments have been performed

with the reaming 65 cases in the case base (row 6 in Table 6.3). The results of the experiments are shown in Table 6.3. From the table it can be concluded that the group based SA weights learning mechanism outperforms the fixed weights CBR system. The average success rate increases as the number of cases in the case base increases.

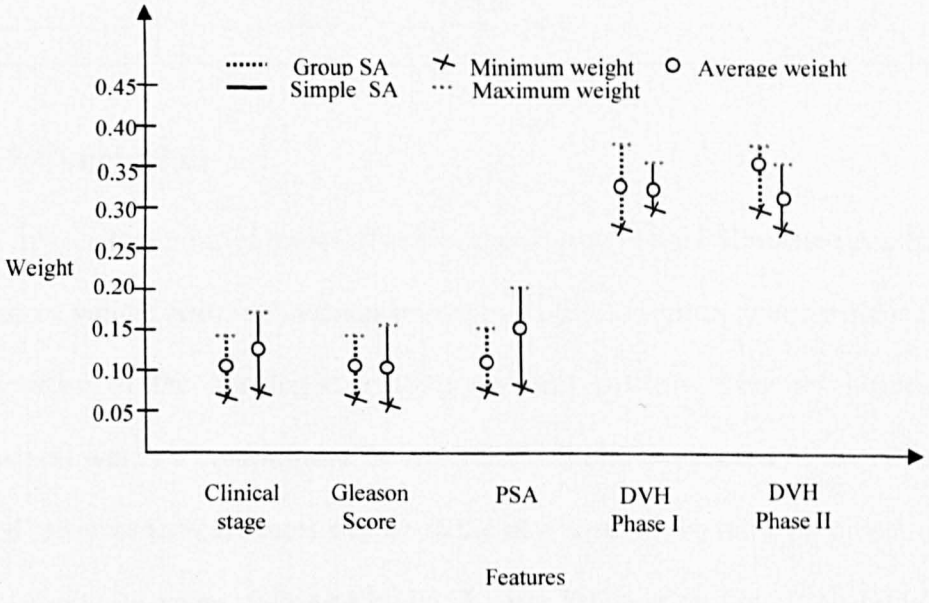


Figure 6.4 Convergence accuracy of group based SA and Simple SA

Table 6.3 Effect of cases in the case base

Number of cases in the case base	Average success rate (%) (Fixed weights)	Average success rate (%) (group based SA weights learning mechanism)
40	86.46	89.47
45	88.69	90.21
50	90.73	91.78
55	92.45	93.12
60	93.44	94.12
65	94.14	94.28
71	94.36	94.36

6.5 Conclusion

In this chapter a novel trade-off retrieval and group based Simulated Annealing feature weight learning mechanism are proposed to capture the experience and expertise of the oncologist treating pervious patients. The novel trade-off method makes a compromise between the risk and the benefit of the radiation and retrieves the case most similar to the new case. In the retrieval process first the similarity value, followed by the 5 years Progression Free Probability and then the success rate of the treatment are taken into account. A knowledge-light adaptation in case-based reasoning is performed and dose limits of different volume percentages of the rectum are calculated. Based on these, the doses in phases I and II of the treatment are prescribed.

In order to mimic the continuous learning mechanism of the oncologist, the group based Simulated Annealing weight learning mechanism is proposed. Cases are divided into different groups based on their dose plans. Thereafter, Simulated Annealing is performed to determine the weights of different clinical parameters used in the retrieval process. In the proposed weight learning

mechanism, an attempt is made to push the new case towards the group having the same dose plan as that of the new case, by updating the weights of the clinical parameters to be used in the similarity measure.

The results obtained using real-world data from Nottingham City Hospital, and evaluation of the generated plans suggested by the oncologists support the application of the new trade-off approach and group based features weights learning mechanism. The proposed approach not only increases the success rate of the system but also generates better plans in a higher number of cases.

CHAPTER 7

Conclusions and Future Research Work

The radiotherapy dose planning problem is a complex and ill-defined problem. The oncologist generally uses planning software to generate treatment plans for new patients. The existing software needs a large amount of knowledge to validate the generated solution. However, often the generated solution fails to meet the operational requirements of the oncologist, for example to decide when and how much to violate the limitations of dose limits imposed to surrounding organs. Also, due to the large size of the search space of the problem, it is difficult to cover all the treatment constraints in such models. Usually, the oncologist spends a large amount of time to select a better solution or to modify the solution generated by the software to meet the operational requirements.

In the dose planning process of prostate cancer treatment the oncologist makes a trade-off between the benefit of radiation, i.e. delivering a high enough dose to fight the cancer cells and the risk that refers to the side effects of the treatment. Usually, after looking at the clinical data, the oncologist looks for a compromise between fighting the prostate cancer cells with high enough radiation and irradiating an inevitable dose to the organs at risk (i.e. the rectum). Thereafter, they decide the extent to which the dose limits of different volume percentages of the rectum can be violated. There is no fixed rule; a decision is generally based on the past experience and is also very subjective. In addition, there may be a chance that for a particular patient different

oncologist may have different decisions. Therefore, it is useful to take them all into consideration while treating a new patient. Further, the influence (importance) of different clinical parameters on the dose planning is not fixed. It is at the discretion of the oncologist to consider them differently in the decision making process based on their past experience. The effect of a higher weight to a problem feature may alter the decision. It is very difficult for an operational research practitioner to translate the oncologist's experience (implicit knowledge) into a mathematical model and to implement different Operational Research (OR) methodologies.

Keeping the aforementioned difficulties in mind in this thesis, a CBRDP system is developed to represent the oncologists' knowledge using a novel case-based reasoning approach. The patients successfully treated in the Nottingham City Hospital were stored in a case base that was exploited using case-based reasoning for the future decision making process. Each case in the case base contains the following information: the problem parameters and the prescribed plan. A case-based reasoning method used in the CBRDP system when hybridised with meta-heuristic approaches becomes adaptive. After each run of the system or when a new case retained, the group based Simulated Annealing (SA) algorithm searches for an optimal/ near optimal combination of features weights. Finally, if information gained from the new problem is useful for future reasoning then it is stored in the case base for future use. In this way the system learns throughout its exploitation and updates its knowledge.

In experiments on the real data sets collected from the Nottingham City Hospital, it was observed that the developed CBRDP system successfully

imitates the decision making process of the oncologist. In most of the cases, the dose plans suggested by the proposed method were coherent with the dose plans prescribed by an experienced oncologist or even better. The oncology staff (both the oncologist and medical physicist) were impressed by the developed prototype of the CBRDP system. It is currently under evaluation in the Nottingham City Hospital. The manual of the software prototype is given in Appendix B. This system may play a vital role to assist the oncologist in making a better decision in smaller computational time; it can help in the prediction of the success rate before the treatment and it can also be used in teaching and training processes.

7.1 Contribution

The contribution of this thesis can be divided into two parts: contribution to radiotherapy planning, and contribution to the field of CBR.

The main contributions of the thesis are:

(a) This thesis provides a comprehensive literature review on radiotherapy planning and case-based reasoning. The literature discusses the key problem features, constraints and issues in radiotherapy planning problems. It also investigates the basic model of simple case-based reasoning and knowledge-light adaptation in case-based reasoning approaches to be used to solve the complex radiotherapy planning problem in the healthcare domain.

(b) The applicability of the CBR approach to radiotherapy dose planning problems was investigated. In the dose planning for prostate cancer treatment, the dose limits of different volume percentages of the rectum

are generally determined by the oncologists based on their past experience. In order to fight cancer cells better, the oncologist makes a trade-off between the risk and benefit of radiation and looks beyond the prescribed dose limits. Decision making knowledge is imprecise and it is hard to generate a precise mathematical model or 'IF-THEN' rules. In this thesis, the nature of oncologist's decision making process for prostate cancer dose planning has been studied. The CBR approach was investigated to overcome the difficulties in a traditional decision making process. The dose limit of different volume percentages of the rectum were calculated using a CBR approach; thereafter, the dose for phases I and II of the treatment are determined.

(c) In the literature, the radiotherapy dose planning problem is addressed as a linear optimisation problem. However, in our study it was found that it generally does not exhibit global linearity. The influence of each feature on the solution is not linear throughout its range of values. In this thesis, firstly, the non-linear nature of the radiotherapy dose planning was demonstrated. Thereafter, a novel knowledge-light adaptation in case-based reasoning approach was developed to capture the experience and the expertise of the oncologist in treating past patients.

(d) In this thesis, the 5 years Progression Free Probability has been taken into consideration in dose planning, which was neglected so far in the literature.

(e) The main aim of the oncologist is to prescribe a treatment plan having a better success rate. It is very difficult to develop a mathematical model

which would judge the success rate of the plan before the treatment. This can be predicted to some extent from the past experience of the oncologist. For prostate cancer, the success rate of the treatment is determined by the Prostate Specific Antigen (PSA) value, measured two years after the treatment. It is very difficult for the oncologist to recall the success rate of all the past treated plans. In this thesis, the success rates of the patients treated in the past were taken into consideration in the dose planning process. The success rate of all the past treated patients was stored in the case base along with other decision making parameters. Cases having better success rates are given more importance than others. In the experiments (based on a leave-one-out strategy), it was found that the incorporation of the success rate and the 5 years Progression Free Probability in the retrieval process increases the effectiveness of the CBR system, namely it helps in generating better dose plan (i.e. better 5 years Progression Free Probability) in a higher number of cases compared to the oncologists plans.

(f) A case representation is an important step of the CBR system development. In this thesis, knowledge stored in the case base was general enough and can be used to solve a wide range of dose planning problems for prostate cancer. The problem features used in this research were given in different measurement units, which have different scales. The stage of the cancer was ordinal type, the Gleason Score was an integer number and the PSA and DVH were real numbers. In order to use features of different data types, measurement units and scale

together, in this thesis, a fuzzy membership based similarity measure was proposed.

(g) Usually, case-based reasoning systems retrieve only one most similar case from the case base. However, this practice may lead to the loss of important information contained in other similar cases. In this thesis, four cases most similar to the new case were retrieved and combined using a modified Dempster-Shafer rule. Usually in the literature, the Dempster-Shafer rule gives equal importance to all pieces of evidence. In order to give cases different importance (based on their quality) a weight was assigned to each case in the case base corresponding to its success rate. In the fusion of cases, cases having better success rates were given more importance than cases having worse success rates.

(h) An adaptation is an important step of a CBR approach. Although the dose plans used in the modified Dempster-Shafer rule were feasible plans, sometimes the final dose plan generated by the Dempster-Shafer rule was not fit for a new patient i.e. it exceeds some of the total dose limits set for rectum volumes. If the dose plan suggested by the Dempster-Shafer rule was not fit for the new patient, a repair mechanism was applied to generate a feasible plan. The proposed adaptation mechanism was designed following the guidance given by the oncologist. It includes the knowledge/experience of the oncologist.

(i) Usually, in the dose planning process the oncologist makes a trade-off among the similarity measure (between previously treated patients and a new one), success rate and 5 years Progression Free Probability of the treatment. In this thesis, a new group based trade-off mechanism was

developed to mimic the decision making process of the oncologist. The trade-off gives the highest priority to the similarity, then to the 5 years Progression Free Probability and finally to the success rate of the treatment. Constraints were relaxed till a case was found.

(j) In the initial work on CBR for radiotherapy planning, equal weights were assigned to all clinical features used in the retrieval process. However, in real life the oncologist usually assigns different weights based on his past experience. In this thesis, weights were assigned dynamically to different parameters according to their importance using group based SA approach. After analysing the data it was found that cases having different clinical parameters (case features) may have the same dose plan. In the group based SA algorithm, cases in the case base were divided into different groups based on their dose plans. Each group holds the cases that have the same dose plan. Each time after a successful use of the CBRDP, the system, weights were updated automatically using a group based Simulated Annealing algorithm. In experiments it was found that the performance of the group based SA is better and more efficient in terms of CPU time than the simple SA algorithm.

7.2 Limitations

The developed CBRDP system is considerably different from the approaches existing in the literature. The developed software has been successfully tested on the data sets obtained from the Nottingham City Hospital. It was evident that the developed novel CBR approach was

capable in solving complex real-world dose planning problems for prostate cancer. Although the proposed system has many advantages and makes both theoretical and practical contributions, like any other research it also has certain limitations, some of them are discussed here:

(a) In CBRDP, a decision is based on five clinical parameters: Clinical Stage, Gleason Score, Prostate Specific Antigen (PSA), DVH value in phases I and II of 66%, 50%, 25%, and 10% of the rectum volume. However, sometimes the oncologist takes into account some other clinical features such as the volume of organs involved and the fitness of the patient in the decision making process, etc. Due to the unavailability of these data, this thesis does not take into account these clinical features.

(b) During the experiments, it was observed that in most of the cases, the dose plans generated by this system were coherent or better than the dose plans suggested by an experienced oncologist. However, in some cases, the dose plan was neither coherent nor better. No standardised method exists in the literature to review the quality of the plan. In the future, some methods need to be investigated to compare the quality of the plans generated by different methods.

(c) The content of the case-base, as in all CBR systems, affects the effectiveness of the system. The literature on case-base maintenance is still scarce. More research should be done to ensure the quality, consistency and coverage of the case base.

7.3 Applicability to other Domains

The basic principles used in the CBRDP system are generic in nature and can be used to solve similar non-linear real world complex problems. To facilitate the implementation of the developed system to other domains, the following key issues need to be addressed:

(a) *Problem parameters and constraints:* The problem parameters, which the decision maker generally takes into account in the decision making process need to be defined along with their scales and measurement units. The importance (weights) of different features could be determined by the group based SA weights learning mechanism proposed in Chapter 6. This algorithm is generic and would not need to be tailored to new problems; it could be used exactly as it is described in the thesis.

(b) *Retrieval operation*: In case-based reasoning, a new problem is solved by retrieving the most similar case from the case base. The success of the CBR system depends heavily on the retrieval mechanism. If the problem feature used in the retrieval process has different measurement units and scales, the fuzzy nearest neighborhood similarity measure described in Chapter 4 could be used. Decision makers can also build a trade-off between different factors, using the group based trade-off method described in Chapter 6. Furthermore, if they want to fuse more than one retrieved decision to generate a combined decision, the modified Dempster-Shafer rule based fusion method described in Chapter 4 can be used without any modification.

(c) *Adaptation operation*: In a CBR approach, a case retrieved from the case-base is usually adapted in the context of the new problem. Adaptation rules usually give guidelines on how to employ the difference between the new case and the retrieved most similar case in a sensible way to tailor the solution for the new problem. In Chapter 5, an adaptation method for the non-linear problem is suggested which could be used in the future.

7.4 Future Research Work

This thesis describes a novel CBR approach to radiotherapy planning for prostate cancer. Computational experiments revealed the effectiveness of the proposed methodology. This research has an adequate scope for further extension. Some suggestions and promising research directions related to radiotherapy dose planning problems and CBR methods are described.

In future research work, some more features could be incorporated in the decision making process such as the volume of organs involved, the age and the fitness of the patient, the movement of the organs, and additional parameters which may indicate the success of the treatment, etc. It is investigated that the addition of the aforementioned parameters will make the retrieval process more accurate.

In addition, more cases having different treatment plans should be added to the case base. The performance of the proposed method on the larger case base (for example on a case-base of thousands of cases) needs to be assessed. Different statistical tests could be performed to analyse the relationship between the clinical parameters and their effect on the dose plan. Further, the observed

analysis can be employed in the adaptation of weights, to search for a better combination of feature weights in minimum computational time, by restricting the search space.

One of the most promising directions for future research is the combination of case-based reasoning and meta-heuristic methods. The search space of the radiotherapy planning problem is huge (here by planning is meant the determination of parameter values of a radiotherapy plan, such as the number of beams, and the angle between them, etc.). Meta-heuristic optimisation methods usually take a large amount of time to generate an optimal / near optimal plan. Also, sometimes they do not meet the treatment requirements of oncologists. In the future, we can use the domain knowledge of the oncologist stored in the case base to restrict the search space and can generate a better clinically acceptable plan.

APPENDIX A

Medical Dictionary

Biological Therapy	:	Therapy that uses the body's own immune system to attack cancer cells. Biological therapy is sometimes called immunotherapy, biotherapy or biological response therapy.
Biopsy	:	Removal of a small portion of tissue to see whether it is cancerous.
Chemotherapy	:	Therapy that uses drugs to damage cancer cells and make it difficult for them to grow in number.
Clinical Stage	:	A labelling indicating the extent of the cancer. The clinical stage of prostate cancer depends on the size of cancer and the extent of the spread.
CT or CT scan	:	Computed tomography or computed axial tomography. In CT scan two-dimensional computer images can be reconstructed to produce three-dimensional images by some modern CT scanners.
Dose Volume Histogram (DVH)	:	Dose volume histogram, simulated radiation distribution within a volume (different volume %) of interest of a patient which would result from a proposed radiation treatment plan.
Follow-up	:	An appointment with your doctor after treatment to check the status of your cancer and overall health.
Gleason score	:	A system grading prostate cancer. The score is the sum of primary and secondary Gleason scores, used to help evaluate the prognosis of men with prostate cancer, Values: within the range [1, 10]
Gray (GY)	:	Patients are prescribed radiotherapy in numbers of Gray (GY) units. The number of units in determined by the amount of time the accelerator beam is switched on.
Helax-THM	:	Specialist radiotherapy planning software.
Linacs	:	Linear accelerator used for delivering of

radiation.

Lymph Node Involvement (LNI)	:	Lymph node involvement, used to indicate the spread of cancer. Values: within the range [0,1]
Malignant	:	Indicates that cancer cells are present and may be able to spread to other parts of the body.
Metastasis	:	The spread of cancer from one area of the body to another. For example, breast cancer may spread to the lymph nodes and lung cancer may spread to the brain.
Magnetic Resonance Imaging (MRI)	:	Magnetic resonance imaging, used to produce the picture of prostate gland.
Organs At Risk (OAR)	:	OAR are structures that neighbour the target volume.
Oncentra	:	Radiotherapy information management software.
Oncologist	:	A physician who specializes in cancer.
Pathologist	:	A doctor who identifies diseases (such as cancer) by studying cells under a microscope.
Planning	:	Decision on dose and angle and intensity of beams etc.
Prostate Nomogram	:	A computerised device to help patients and their physicians decides among the major treatment choices for early stage prostate cancer. Available for other sites.
Prostate Specific Antigen (PSA) Test	:	A test that measures the amount of a substance created by the prostate gland in the blood. An elevated amount could be the result of infection, prostate cancer or an enlarged prostate; Values: within the range [1, 40]
Planning Treatment Volume (PTV)	:	The planning treatment volume was defined as the gross tumor volume with no margin.
Reconstructive Surgery	:	Operation preformed to repair skin and muscles after surgery to treat cancer has been performed. Often used to reconstruct a breast after a mastectomy.
Recurrence	:	The development of cancerous cells in the same area or another area of the body after cancer

treatment.

Side Effects of Therapy	:	Problems caused by the damage of healthy cells along with cancerous cells during treatment. Some common side effects of cancer therapy include being tired, feeling sick to your stomach (nausea), throwing up, hair loss and mouth sores. Generally there are seven types of side effects (in case of prostate cancer) which a patient may have during or after the treatment. Side effect related to the rectum, Side effect related to the bladder/urethra, Side effect related to sexual dysfunction, Side effect related to small intestine/ colon, Side effect related to skin/subcutaneous tissue, Side effect related to mature bone (excluding mandible).
Simulation	:	Localisation of treatment fields using a CT scanner or simulator.
Stages of Cancer	:	The progression of cancer from mild to severe. Usually indicates whether it has spread to deeper tissues or other parts of the body. One method used by doctors to stage different types of cancer is the TNM classification system. In this system, doctors determine the presence and size of the tumor (T), how many (if any) lymph nodes are involved (N) and whether or not the cancer has metastasized (M). A number (usually 0-4) is assigned to each of the three categories to indicate its severity. The 1997 clinical stage include: T1a,T1b,T1c,T2a,T2b,T3a,T3b
Surgery	:	A procedure that removes repairs or allows for the further study of a specific body part.
Tumor	:	An abnormal mass of tissue that can be benign or malignant.
Verification	:	Verify a planning using simulator.
5 yr PFP:	:	5 years progression free probability shows the probability that the cancer will not appear again in 5 years time, depends on: clinical stage, Gleason score, PSA value, and total amount of does prescribed by the oncologist.

APPENDIX B

CBRDP Software Reference Manual

Software overview

Case-**B**ased **R**easoning System for **D**ose **P**lanning (CBRDP) is an adaptive radiotherapy dose planning software that helps to decide the dose in Phases I and II of the treatment for prostate cancer. In dose planning process, the oncologist has to makes a trade-off between the risk and benefit of the radiation i.e. the task is to deliver the high dose to the cancer cells and minimize the side effects of the treatment using Case-Based Reasoning (CBR) method. CBR is an artificial intelligence technique which memorises previously gained knowledge and experience, and utilises it in solving new problems. In dose planning process, CBRDP also takes into account 5 years Progress Free Probability and success rate measured after 2 years of the treatment. The cases having better 5 years Progress Free Probability and success rate of treatment are given more importance than having worse 5 years Progress Free Probability and worse success rates. In order to mimic the continuous learning characteristic of oncologists, the weights corresponding to each feature used in the retrieval process are updated automatically each time after generating a treatment plan for a new patient. Finally, if information gained from the new problem is useful for future reasoning then it is stored in the case base for future use.

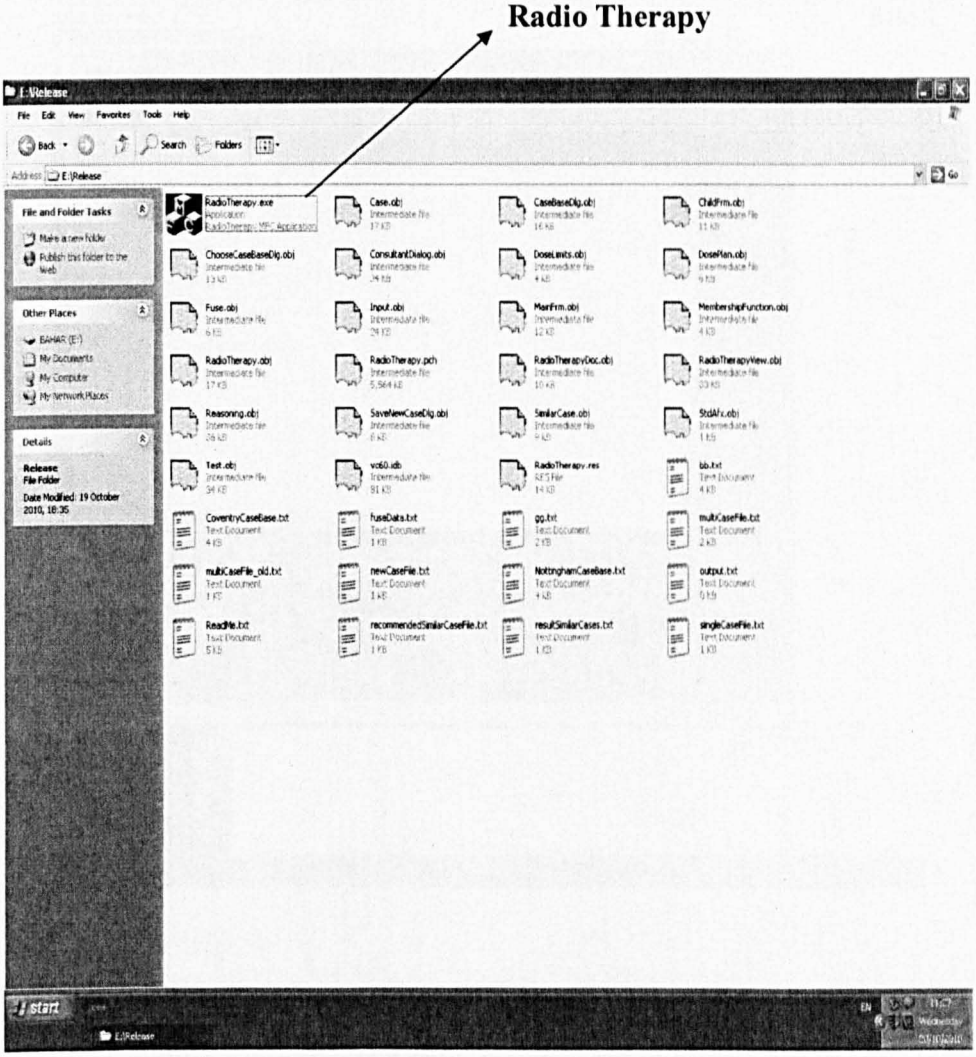
System Requirements

CBRD runs under Windows XP, Windows Server 2003 and Windows Vista. The program automatically adapts itself to the operating system on which it runs, eliminating the need for manual settings.

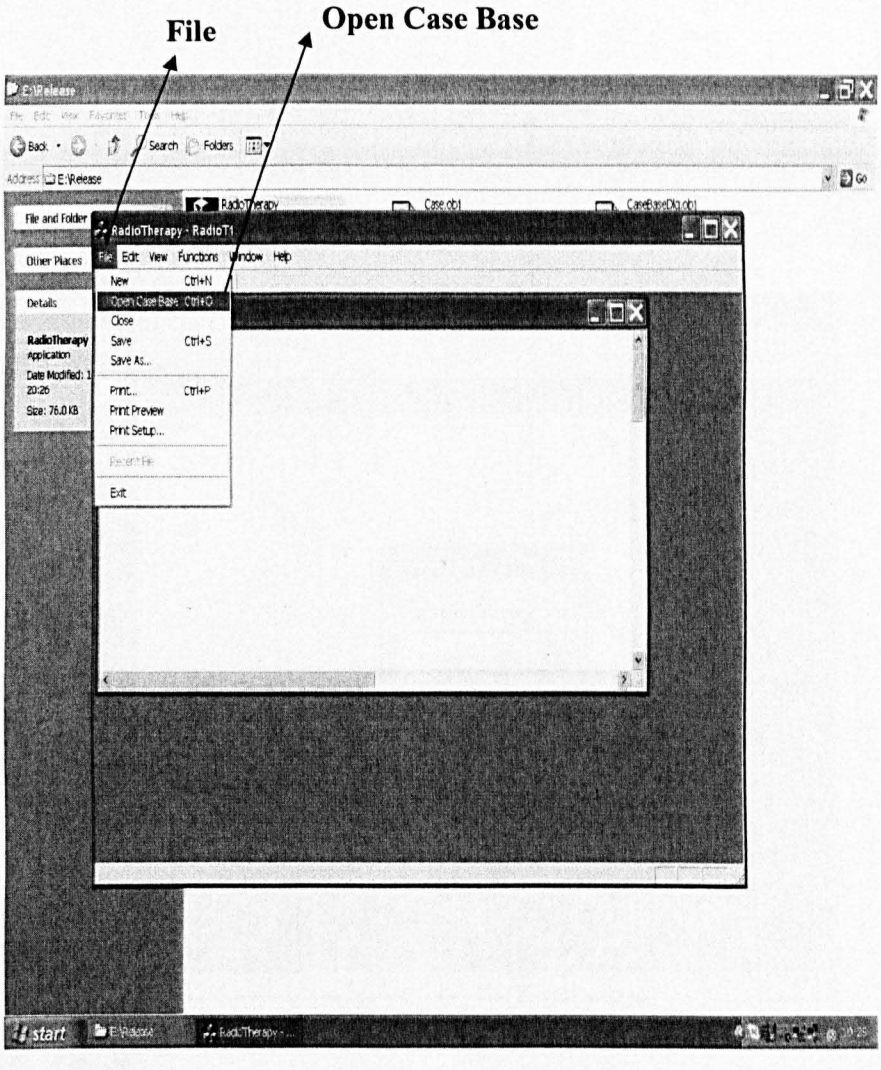
NOTICE You must have Administrative access to install CBRDP software.

Dose calculation procedure

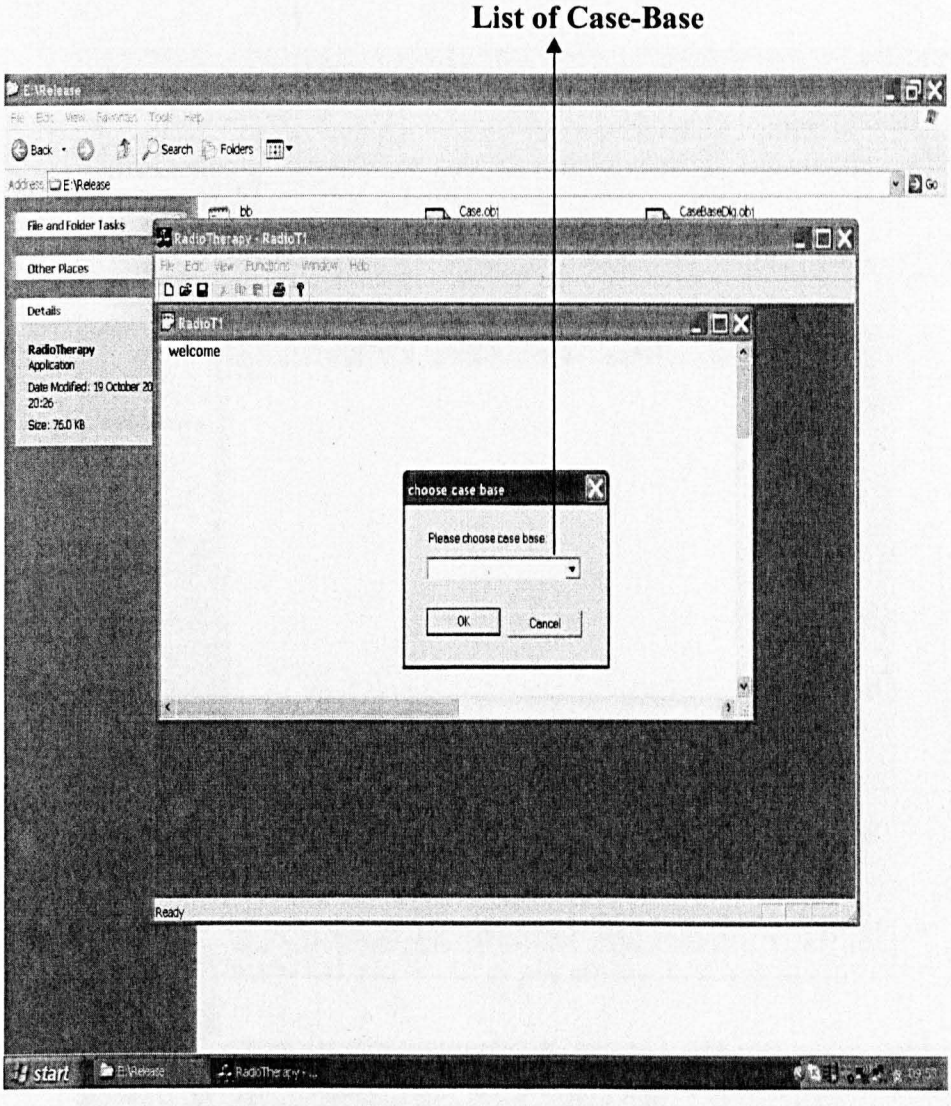
1. Click the "Radio Therapy" button to open the software.



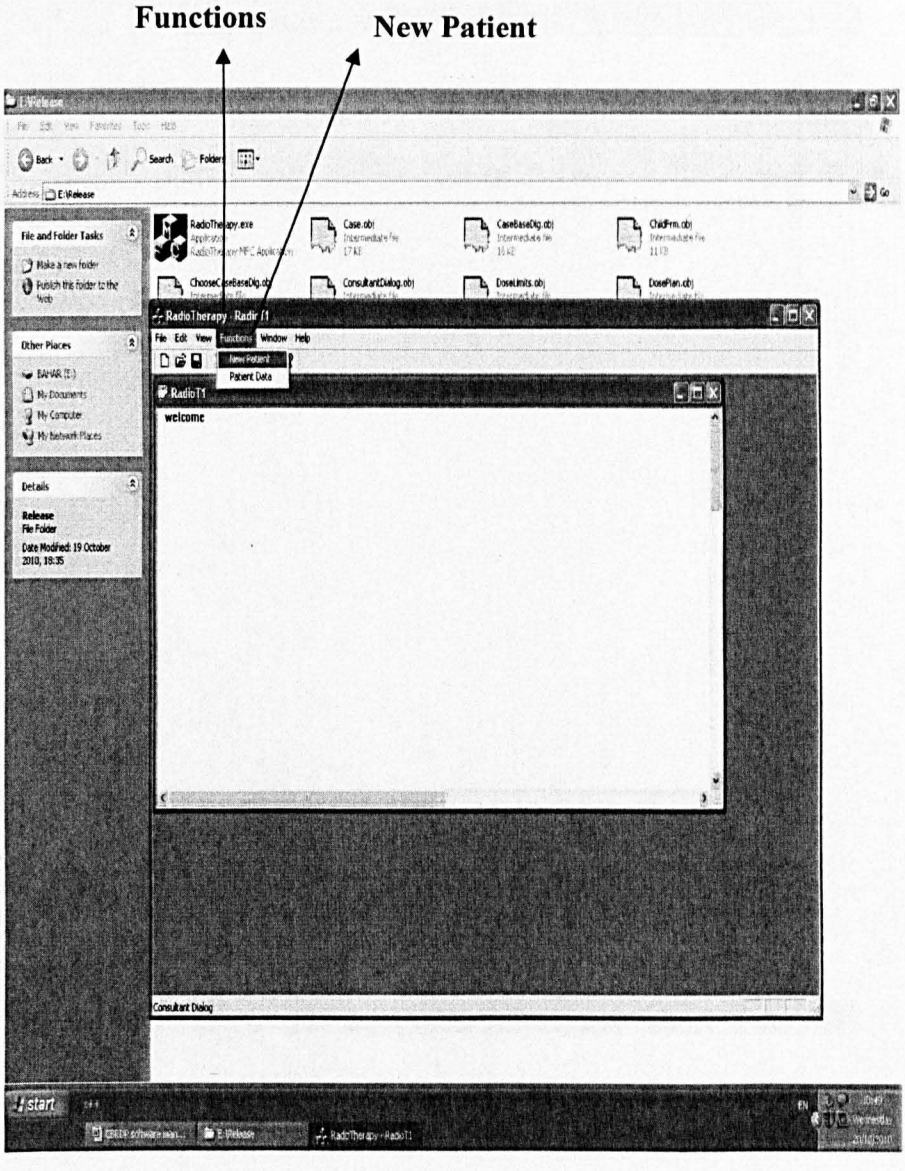
2. Click “File” and “Open Case Base” to select the case base.



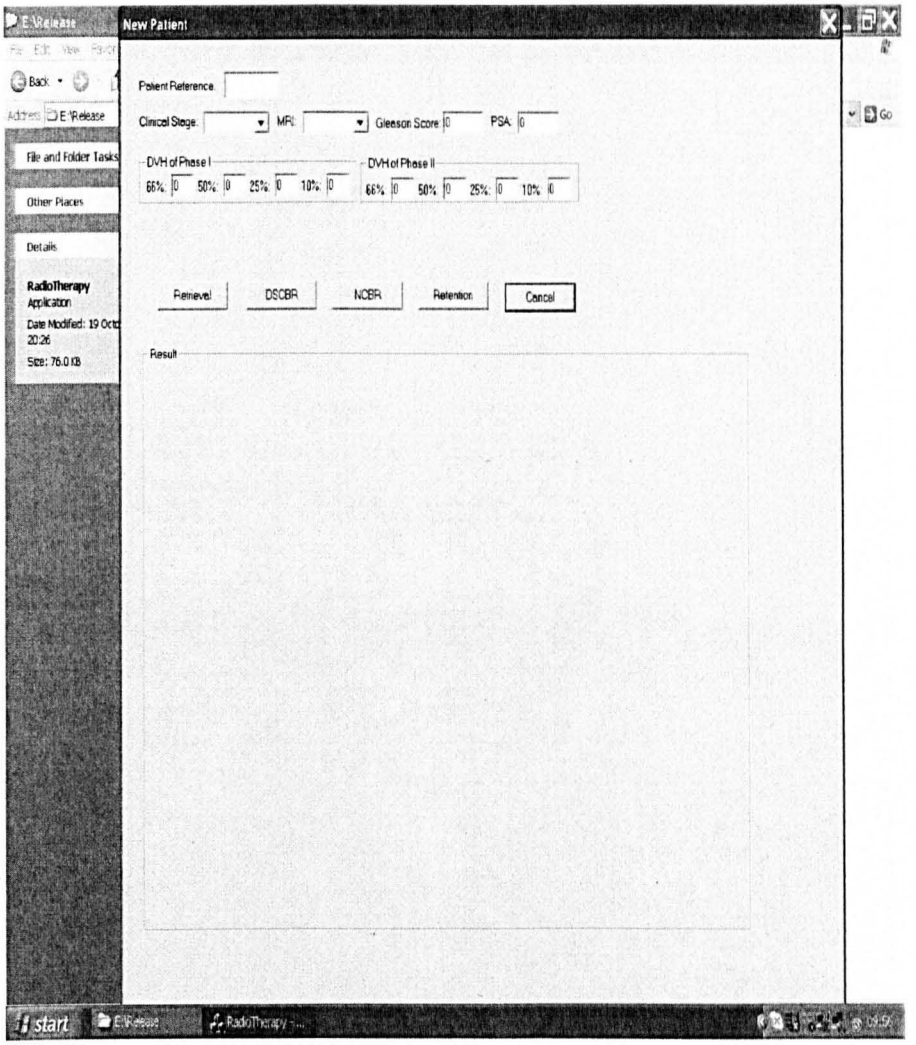
3. Select a case base from the list and click "OK".



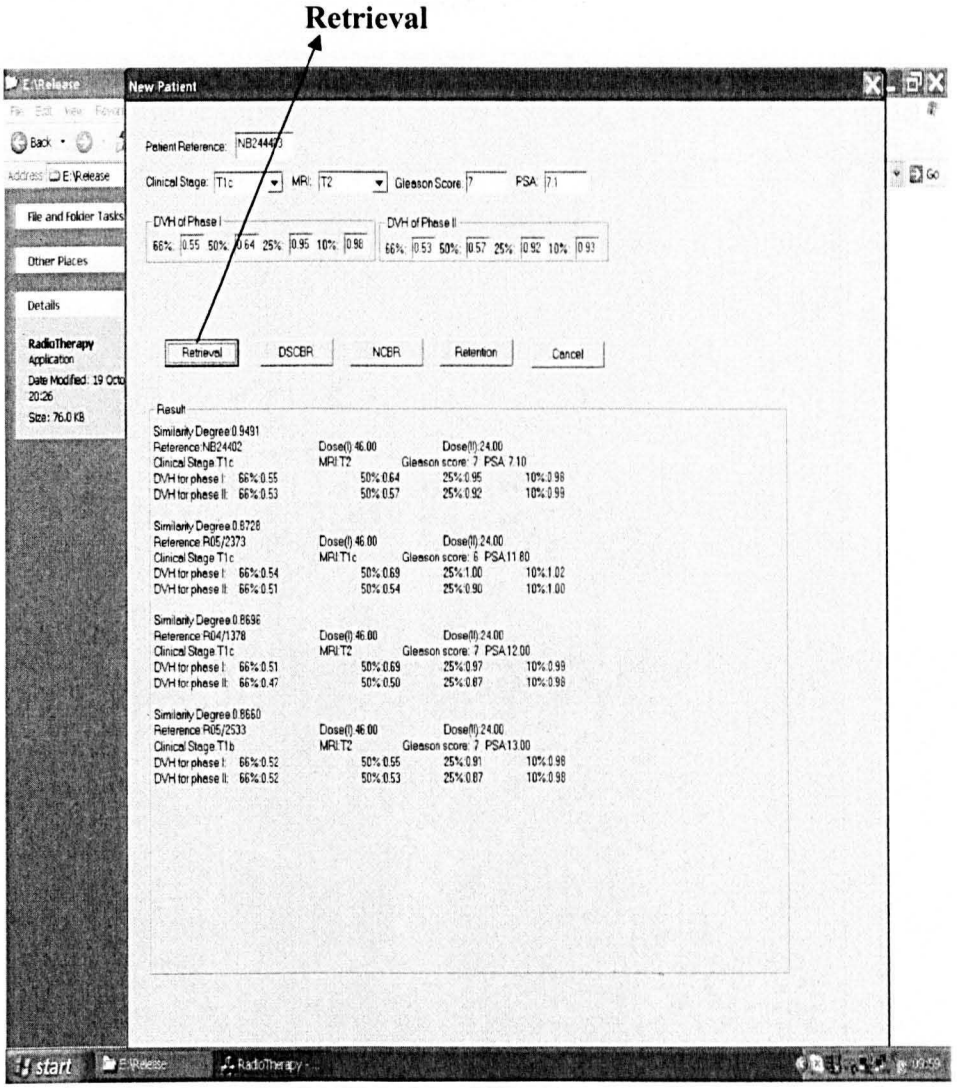
4. Click the "Functions" button and select "New Patient" button to enter the data of the new patient.



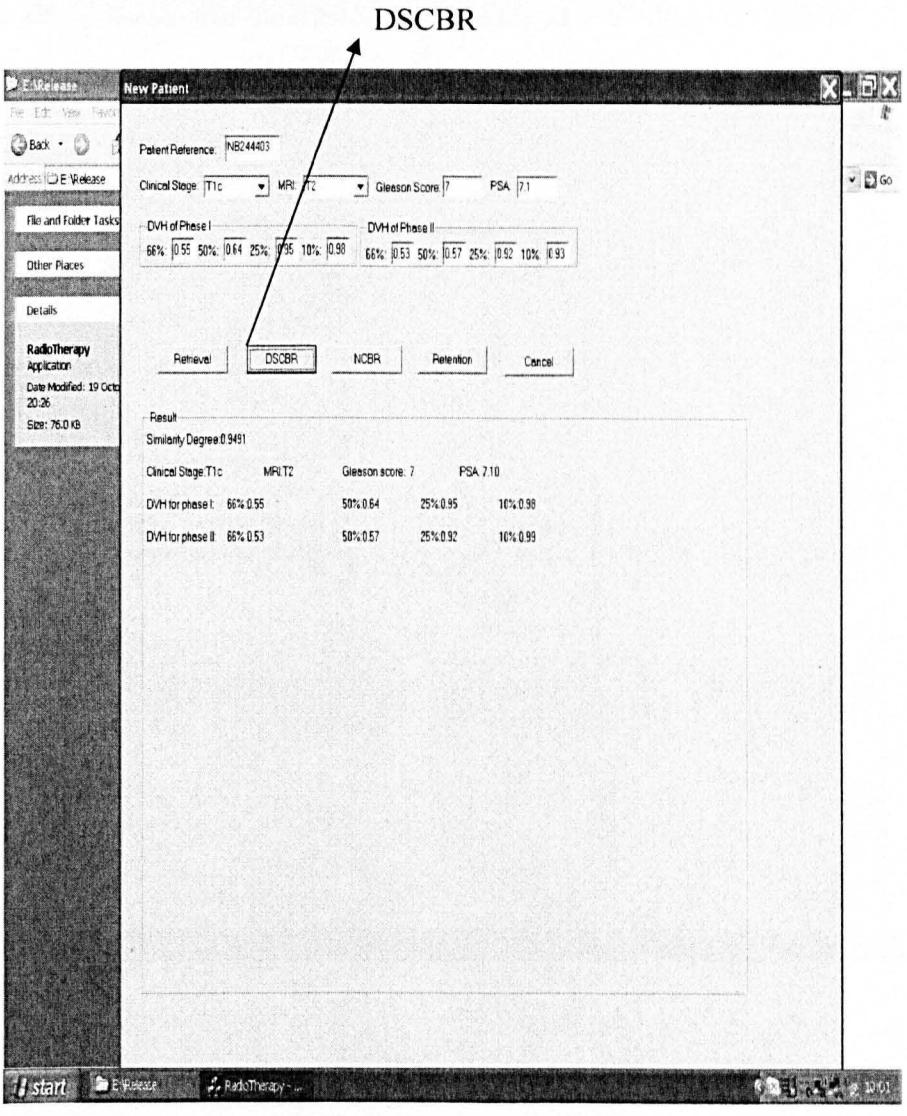
5. Please enter Patient Reference No, Clinical Stage, MRI, Gleason Score, DVH of phase I and DVH of phase II values in the appropriate boxes.



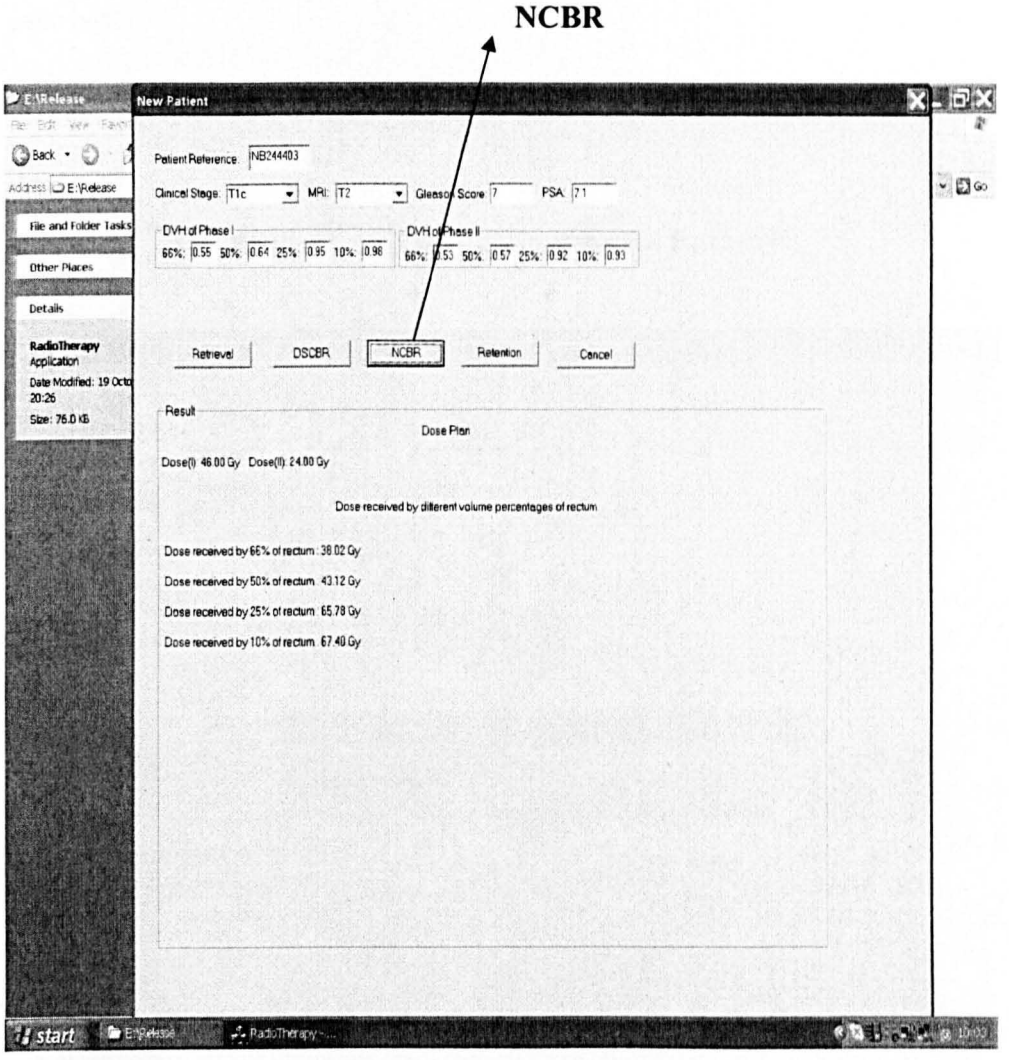
6. Click the "Retrieval" button to retrieve the cases similar to the new patient.



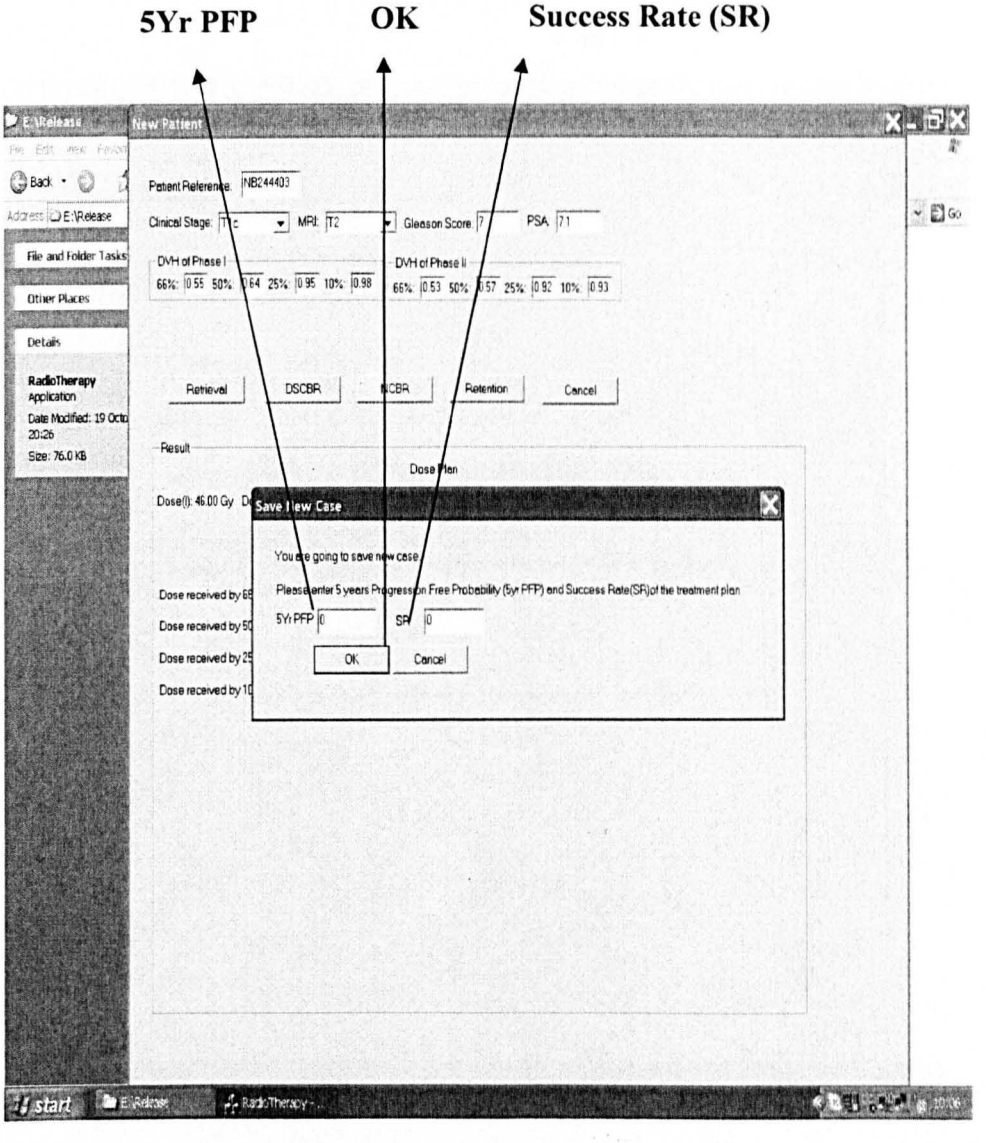
7. Click the "DSCBR" button to calculate the dose in Phases I and II using Dempster-Shafer rule based Case-Based reasoning method.



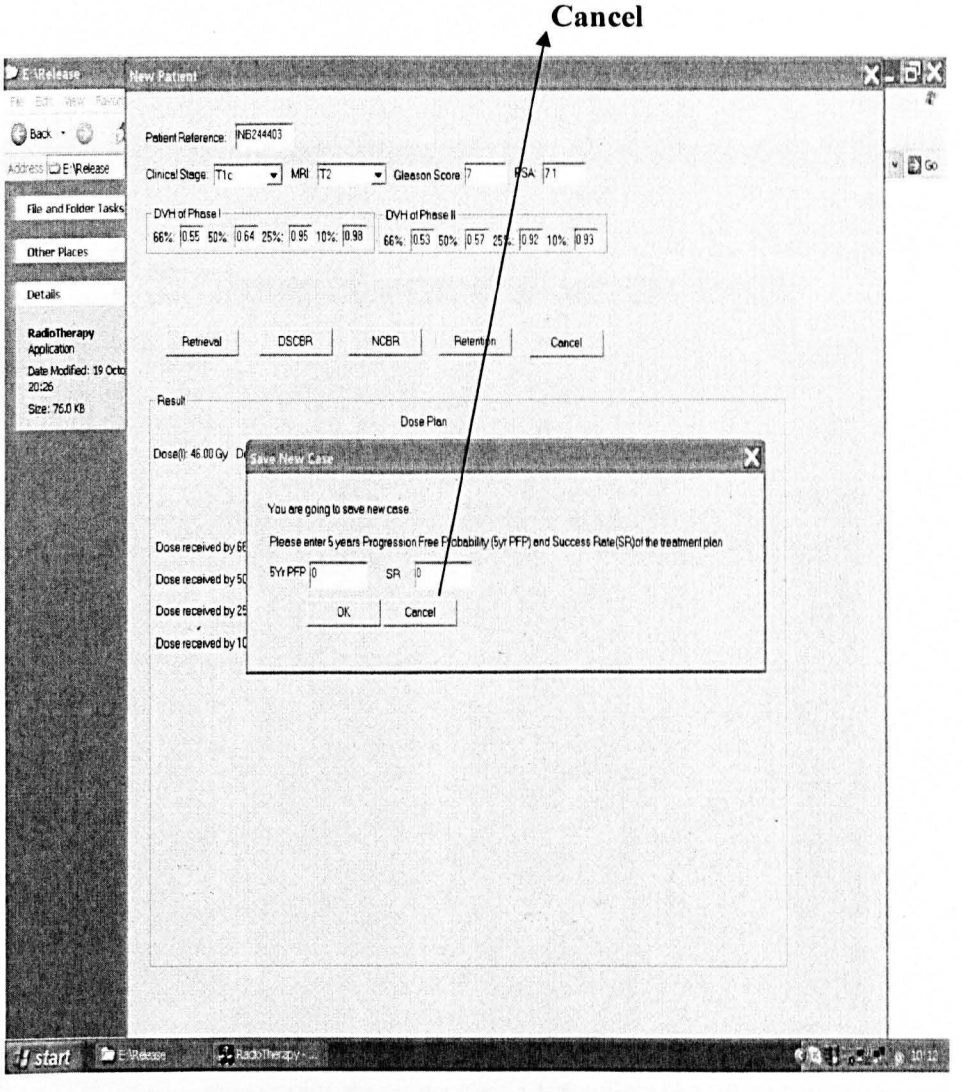
8. Click the "NCBR" button to calculate the dose plan using knowledge-light adaptation in case-based reasoning method.



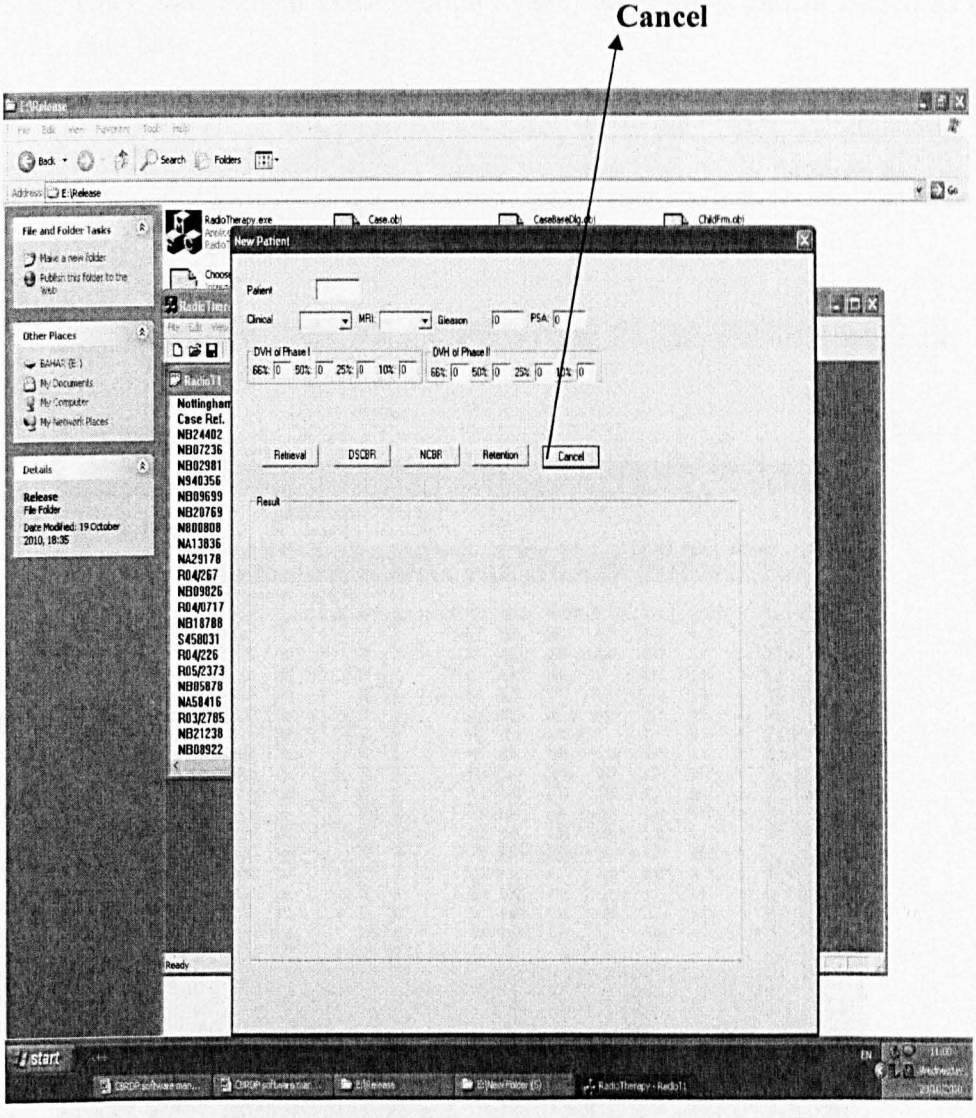
9. Click the "Retention" button and enter the values of 5yr PFP and Success Rate (SR) in the appropriate boxes and click OK to save the new case in the case base.



10. Click the "Cancel" button if you don't want to save the new case in the case base.

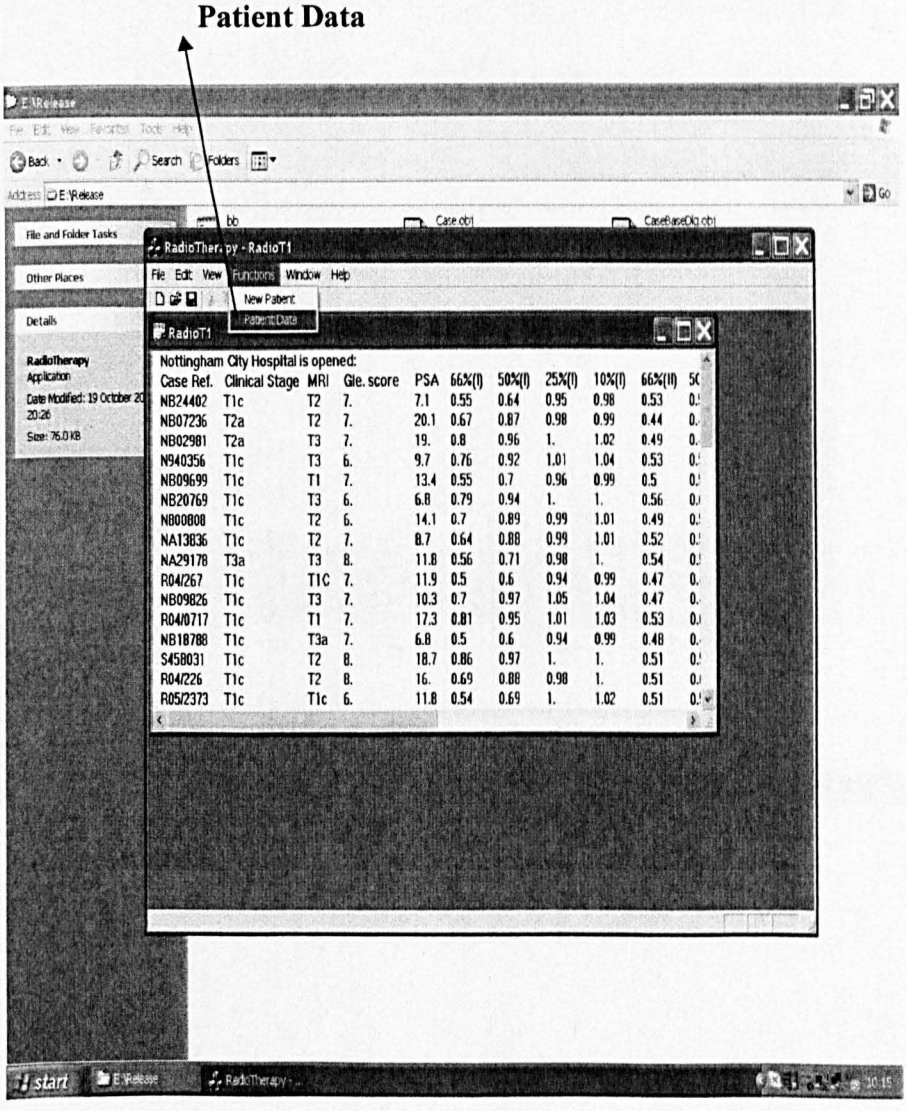


11. Click the "Cancel" button to close the software.

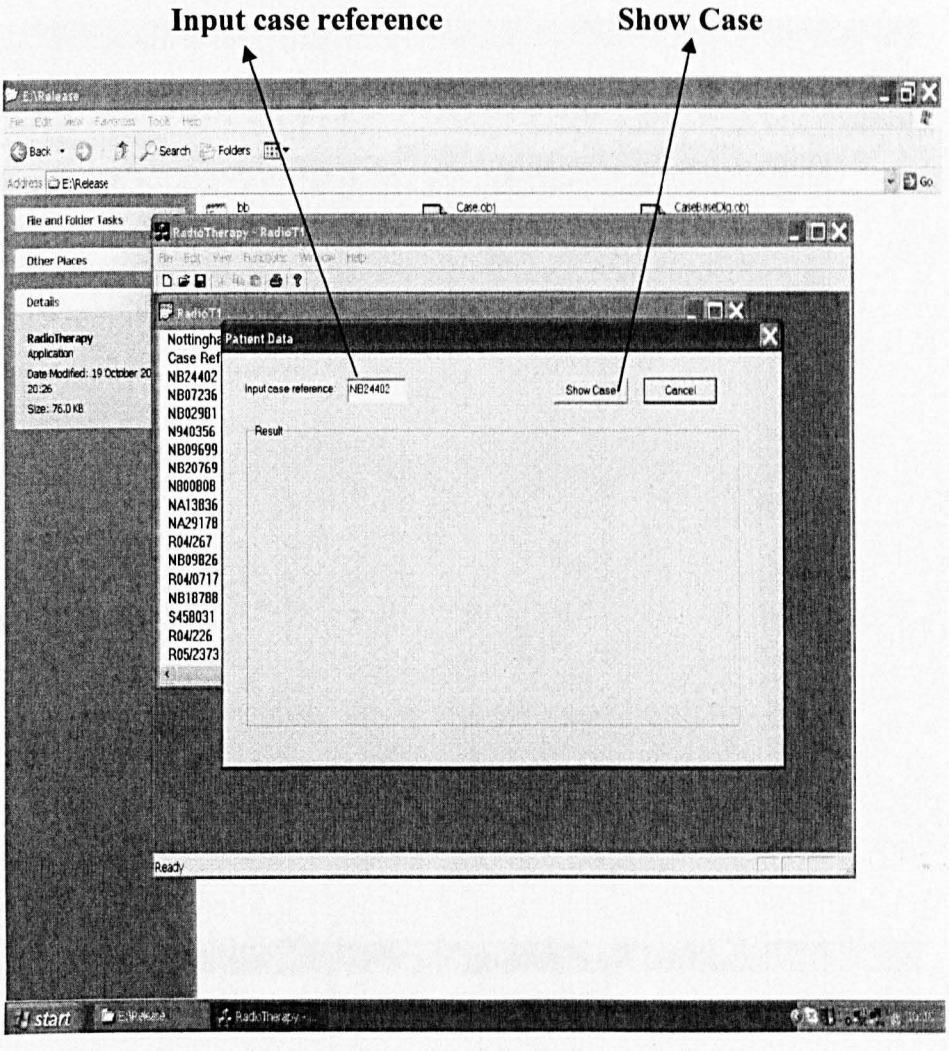


Procedure to see existing patient record

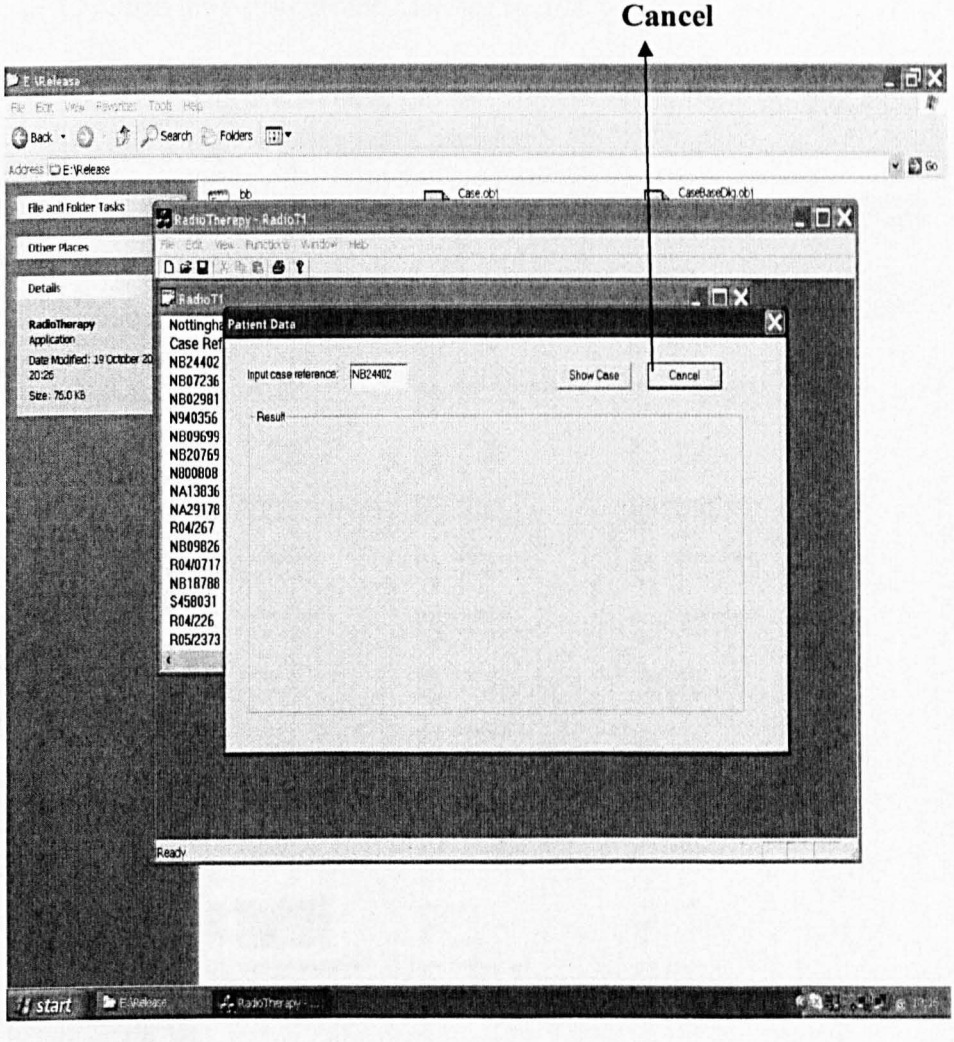
1. Click the "Patient Data" button to see the existing patient record in the data base.



2. Enter case reference number and click the “Show Case” button.

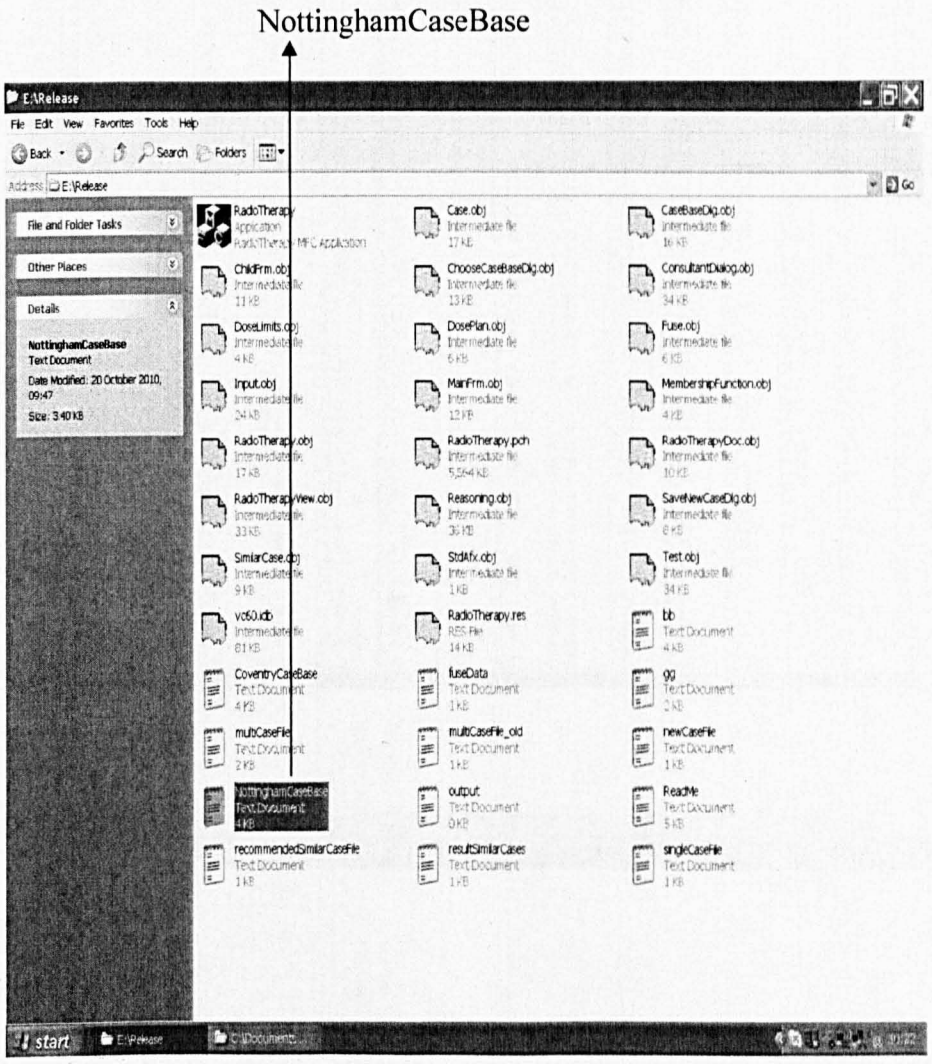


3. Click the “Cancel” to close patient data window.

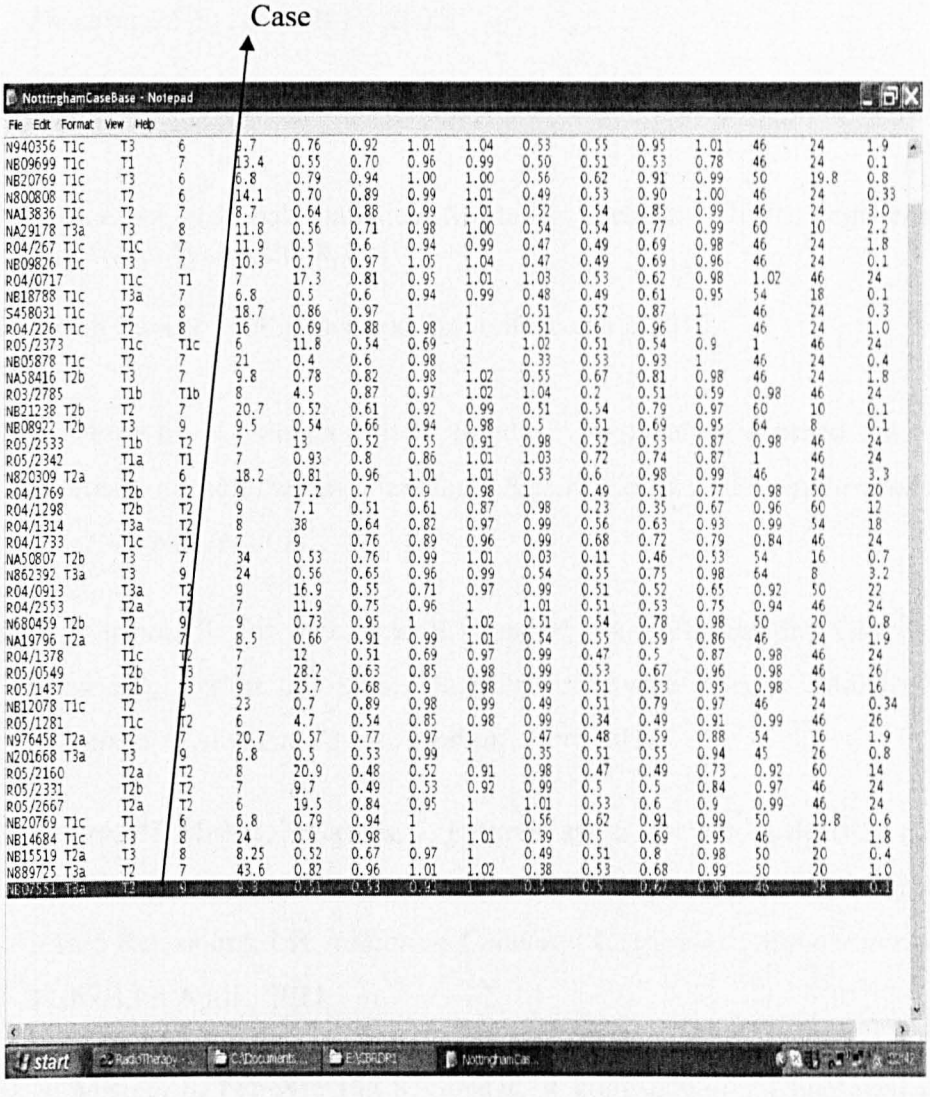


Procedure to delete stored patient record from the case base

1. Open the NottinghamCaseBase.txt file



2. Select the case and press delete button of the keyboard.



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