Genetic Algorithm Based Optimized Radiotherapy Patient Scheduling

By

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Declaration

I, the undersigned, declare that this MSc thesis is my original work, has not been presented for fulfillment of a degree in this or any other University, and all sources and materials used for the thesis have been acknowledged.

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Date: _____

This MSc. Thesis has been submitted for examination with my approval as an advisor.

_____

Dawit Assefa Haile (PhD)

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Abstract

Radiotherapy is the major means to treat cancer patients. Radiotherapy comprises two phases: pretreatment and treatment on radiation machines. This thesis work focuses on the treatment phase. Treatment consists of multiple, almost daily irradiation appointments, followed by optional imaging and control assignments. The scheduling of radiotherapy appointments is a complex problem due to various medical and scheduling constraints, such as patient category, machine availability, waiting time targets and also due to the size of the problem (i.e., number of machines, facilities and patients). The objective of this thesis is to minimize waiting time and maximize device utilization in) patient's appointment scheduling. Thus, this thesis presents an optimization algorithm for scheduling of radiotherapy treatments for categorized cancer patients. In order to manage patient information effectively in digital data format a web application is built. This web application registers users (professionals) that are responsible to register patients and includes a database to store patient's information. Following this, custom genetic algorithm (GA) is developed considering constraints primarily patient category and the rest constraints such as patient in date and time, number of fractions, number of machine and also working days and working hour. Moreover, for the GA to be user friendly a desktop application with graphical user interface (GUI) is developed. The GUI supports the medical professionals to easily manipulate the GA parameters such as number of populations, crossover probability, and mutation probability and also change the dynamic resources or attributes like number of machines, number of patients treated per single machine and number of working days. As a result, the medical professional can schedule patients dynamically. In this thesis best GA performances (i.e., fitness value of 88% - 96.67% accuracy) are obtained for probability crossover (Pc) values between 60% - 80% and probability of mutation (Pm) between 20% - 40%. This means if the health professional sets the cross-over and mutation probability in these ranges, the scheduling will have better optimization, i.e. prioritize high-risk patients, minimize high risk patient waiting time, thus better care for patients. From the resuls, emergency patients are able to get early treatment than radical patients. Compared to traditional manual scheduling, where scheduling is done based on patients arrival date, GA based scheduling enables to prioritize higher risk patients.

Keywords: Radiotherapy scheduling, genetic algorithm, optimize patient schedule

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List of Abbreviations

ASR	**A**ge-**S**tandardized **R**ate
CIM	**C**entre **I**nverse **M**utation
DNA	**D**eoxyribo**n**ucleic **A**cid
FLM	**F**lip **M**utation
IVM	**I**nversion **M**utation
GA	**G**enetic **A**lgorithm
JCCO	**J**oint **C**ouncil for **C**linical **O**ncology
KeV	**K**illo **E**lectron **V**olt
Linac	**L**inear **A**ccelerator
MeV	**M**ega **E**lectron **V**olt
MPC	**M**ulti **P**oint **C**rossover
RT	**R**adio**t**herapy
RTP	**R**adiation **T**reatment **P**lanning
RNS	**R**andom **S**election
RKS	**R**ank **S**election
RWS	**R**oulette **W**heel **S**election
SM	**S**cramble **M**utation
SPC	**S**ingle **P**oint Crossover
SWM	**S**wap **M**utation
TASH	**T**ikur **A**nbessa **S**pecialized **H**ospital
TBq	**T**era **B**ecquerel
TS	**T**ournament **S**election
UC	**U**niform **C**rossover
WHO	**W**orld **H**ealth **O**rganization

Chapter 1 Introduction

1.1 Background

Cancer is one of the leading causes of death in the World. According to world health organization (WHO), approximately 8.2 million people die each year from cancer [1]. Cancer is a class of diseases characterized by an imbalance in the mechanisms of cellular proliferation and apoptosis leading to a solid mass of cells known as tumor [1]. There are four major approaches to cancer treatment: surgery and radiotherapy as local treatments, chemotherapy and the use of biological agents (such as hormones, antibodies and growth factors). However, death is mostly due to spread of the primary tumor to one or more other sites in the body (by a process called metastasis), which makes surgical intervention impracticable [2]. Thus, radiotherapy is often used as an essential means to treat cancer patients. Its application has grown worldwide. According to Delaney et al [3], an estimated 52% of cancer patients received radiotherapy at least once in their regimen.

Like most other Sub-Saharan African countries, Ethiopia, just had doesn't have cancer registry recently. An organized oncology service in Ethiopia started in Tikur Anbessa Specialized Hospital (TASH) in 2005/2006 G.C. [4]. An age-standardized rate (ASR) of cancer incidence, mortality profile and statistics of both sexes in Ethiopia are shown in Fig. 1.1, Fig. 1.2, and Table 1.1 respectively, as reported by the WHO.

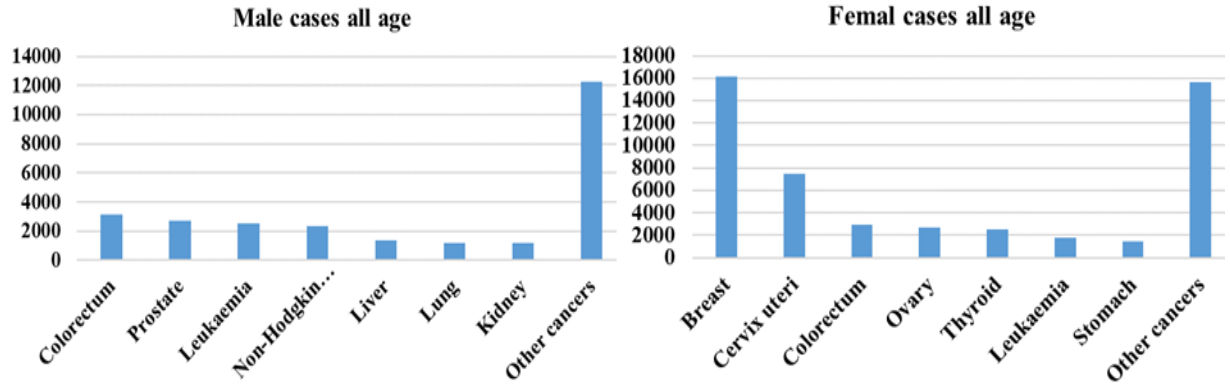


Figure 1.1: Cancer incidence profile in Ethiopia (114,963,583 total population; adapted from World Health Organization – Global Cancer observatory, https://gco.iarc.fr/, 2020).

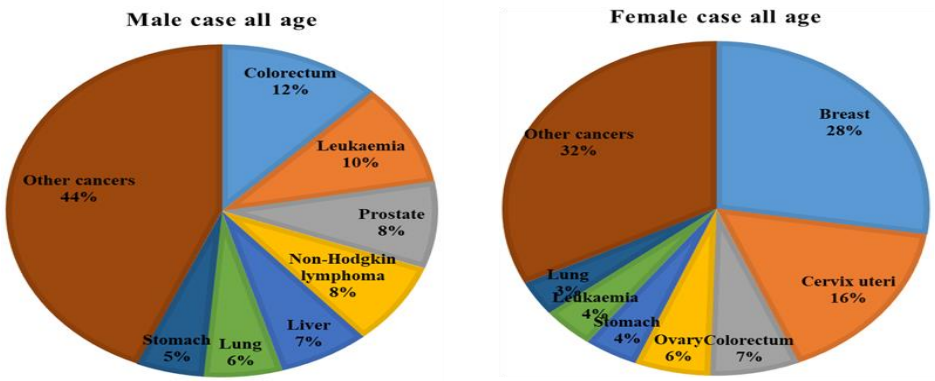


Figure 1.2: Cancer mortality profile in Ethiopia (114,963,583 total population; adapted from World Health Organization - Cancer Country Profiles, Global Cancer Observatory, https://gco.iarc.fr/, 2020).

Table 1.1: Cancer incidence profile in Ethiopia summary statistics both sexes, all ages, (114,963,583 total population; adapted from World Health Organization - Global Cancer Observatory, https://gco.iarc.fr/, 2020).

	Males	Females	Both sexes
Population	57 516 835	57 446 748	114 963 583
Number of new cancer cases	26 754	50 598	77 352
Age-standardized incidence rate (World)	77.9	134.2	106.7
Risk of developing cancer before the age of 75 years (%)	8.2	13.5	11.0
Number of cancer deaths	18 895	32 970	51 865
Age-standardized mortality rate (World)	58.0	91.7	75.3
Risk of dying from cancer before the age of 75 years (%)	6.2	9.8	8.1
5-year prevalent cases	43 705	87 153	130 858
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	Colorectum Prostate Leukaemia Non-Hodgkin lymphoma Liver	Breast Cervix uteri Colorectum Ovary Thyroid	Breast Cervix uteri Colorectum Leukaemia Non-Hodgkin lymphoma

Radiotherapy represents an important phase of treatment for a large number of cancer patients. In general, the radiotherapy processes encompass planning, administration of external or internal radiation therapy (brachytherapy), attention to side effects, and follow up after treatment. The focus of the current study is on external radiation treatment and workflows at the radiotherapy center using TASH as an example.

The scheduling of radiotherapy pretreatment and treatment appointments is a complex problem due to various medical and scheduling constraints, such as patient category, availability of treatment machine and required health professionals, waiting time targets (i.e., the time when a patient should receive the first radiotherapy fraction, etc.) and also the size of the problem (i.e., number of machines and facilities required as well as the number of patients in the cue). The

scheduling requires consideration of different objectives including minimization of the number of patients who do not meet their waiting time targets, minimization of usage of overtime slots and minimization of machines problems. Hence, the aim of this thesis is to develop an optimized radiotherapy scheduling system considering different constraints such as patient category, number of machines etc. As a result patients with high risk will be treated as early as possible.

1.2 Statement of the problem

The scheduling of radiotherapy appointments is a complex problem due to various medical and scheduling constraints, such as patient category, machine availability, waiting time targets (i.e., the time when a patient should receive the first radiotherapy fraction, etc.), and also the size of the problem (i.e., number of machines, facilities and patients). The objective of this thesis is to minimize any penalties arising from violations of scheduling constraints by optimizing (minimize waiting time and maximize device utilization) patient's appointment schedule. Hence, the aim of this thesis is to develop an optimization scheme for scheduling of radiotherapy treatments for categorized cancer patients considering more constraints.

1.3 Objective of the thesis

1.4 General objective

The main objective of this thesis is to investigate and develop an optimization scheme to schedule radio therapy patients based on genetic algorithm.

1.5 Specific objectives

The specific objectives of this thesis are to:

- To assess impacts of paper-based system and lack of timely scheduling of patients in radiotherapy center;
- Develop web application to effectively register patient data;
- Identify objective function and pinpoint the main optimization constraints;
- Develop Genetic Algorithm based scheduling system considering urgency and priority;
- Analyze the scheduled accuracy.

1.6 Significance of the thesis

Health care systems have been confronted in recent years to provide high quality care with restricted resources. Hence, an effective radiotherapy patient scheduling, within radiotherapy departments, plays a vital role in order to warrant the delivery of treatment at the right time. There is an appointment scheduling problem in radiotherapy. Emergency cancer patients with high risk of mortality should not have long waiting time rather should be treated as early as possible regardless of the patient in date and time. Therefore, developing schedule optimization that minimizes waiting time and maximizes device utilization is crucial. Thus, optimizing cancer patients' schedule for radiotherapy services ensures proper, continuous, timely and safe treatment of radiation.

1.7 Scope and delimitations of the thesis

The thesis focusses on optimizing radiotherapy scheduling system. Constraints such as availability of medical professional/s, adjusting skipping of treatment day by the patient and the performance of the radiation machine are not considered during optimization. In addition, holy days are considered as working days. In principle the system might be applicable on other health information system modalities and different types of cancer treatments while investigation of such is beyond the scope of the current study.

1.8 Organization of the thesis

The rest of the thesis is organized into the following chapters. Chapter 2 presents a general introduction about radiation treatment and cancer patient radiation treatment scheduling for external beam therapy. It also includes brief description on timely treatment of cancer patients and patients' quality of life related with the treatment. Chapter 3 explains the methods and materials that have been used in this thesis. Observation on available resources, interviewing of selected professionals and quantitative and qualitative data were collected through questionnaire. Chapter 4 presents selected results obtained by the proposed methodology accompanied by discussions. Graphical presentations are used to express the results obtained on the assessment of radiation treatment in radiotherapy center. Chapter 5 concludes the thesis and provides insights into future avenues of research with proposed recommendations for future work.

Chapter 2 Radiotherapy Treatment

2.1 Introduction

This chapter offers a brief overview of radiation therapy. The topics to be discussed include the physical aspects of how radiation works (ionization radiation interactions) and how it is conveyed (treatment and treatment planning). These topics are not enclosed in great technical detail, and no effort is made to discuss the radiobiological effects of radiation therapy. It is hoped that a fundamental understanding of radiation treatment will benefit those practicing in other disciplines of cancer management.

2.2 Radiotherapy

Radiotherapy (RT), also known as radiation therapy, is a treatment for cancer and, less commonly, thyroid diseases, blood disorders, and noncancerous growths. RT has advanced in both methodological and biological aspects over the past few decades. Though RT is a momentous adjuvant noninvasive technique, it leaves behind some unsympathetic effects [5].

2.2.1 Principles of Radiotherapy

Radiation therapy is a therapeutic use of ionizing radiation. Ionizing radiation is energy sufficiently strong to remove an orbital electron from an atom. This radiation can assume an electromagnetic form, such as a high-energy photon, or a particulate form, such as an electron, proton, neutron, or alpha particle. Radiation is energy that is carried by waves or a stream of particles. It damages the genes, deoxyribonucleic acid (DNA) and some of the molecules of a cell. Genes control how cells grow and divide. Radiation damages the genes of a cancer cell so that it cannot grow and divide any more. This means radiation can be used to kill cancer cells and shrink tumors [6].

Cancer cells tend to divide quickly and grow out of control. Radiation therapy kills cancer cells that are dividing, but it also affects dividing cells of normal tissues. The damage to normal cells causes unwanted side effects. Each time radiation therapy is given, it requires balancing between destroying the cancer cells and minimizing damage to the normal cells.

Radiation does not always kill cancer cells or normal cells right away. It might take days or even weeks of treatment for cells to begin dying, and they may continue to die off for months after treatment ends. Tissues that grow quickly, such as skin, bone marrow, and the lining of the intestines are often affected right away. In contrast, nerve, breast, and bone tissue show later effects. For this reason, radiation treatment can have long-term side effects that might not be seen until long after treatment is over.

2.2.2 Types of Radiation

Radiation used for cancer treatment is called ionizing radiation because it forms ions (electrically charged particles) in the cells of the tissues it passes through. This can kill cells or change genes so the cells cannot grow. Other forms of radiation such as radio waves, microwaves, and light waves are called non-ionizing. They don't have as much energy and are not able to form ions.

Ionizing radiation can be sorted into two major types: Photons (x-rays and gamma rays), which are most widely used and Particle radiation (electrons, protons, neutrons, alpha particles, and beta particles) [6]. Some types of ionizing radiation have more energy than others. The higher the energy, the more deeply the radiation can penetrate (get into) the tissues. The way a certain type of radiation behaves is important in planning radiation treatments. The radiation oncologist (a doctor specially trained to treat cancer patients with radiation) selects the type and energy of radiation that is most suitable for each patient's cancer.

2.3 Radiotherapy Machines

2.3.1 Cobalt 60

The basis of cobalt-60 machine is a high activity sealed source producing 1.17 MeV and 1.33 MeV gamma rays. The source activity on delivery can be from 185 to 555 Tera Becquerel (TBq). The source is driven to an open position and collimation is used to limit the beam to the treatment target. Its advantages over other machines are that cobalt therapy machines have less maintenance costs and less infrastructure requirements [7], [8]. Typical cobalt 60 machine is shown in Fig. 2.1.

Figure 2.1: Cobalt 60 radiotherapy machine at TASH.

2.3.2 Linear Accelerators

In linear accelerator (Linac) (see Fig. 2.2) electronically generated high-energy radiation is provided to tumors by means of a linear accelerator. A beam of electrons is produced and accelerated through a waveguide that enhances their energy to the keV to MeV range. These electrons hit a tungsten target and produce x-rays. X-rays generated in the 10–30-keV range are known as grenz rays, whereas the energy range for superficial units is about 30–125 keV. Orthovoltage units generate x-rays from 125–500 keV. In effect, the linac components of the klystron or magnetron, waveguide, electron gun, target, monitor chamber, steering coils and ancillary control electronics replace the radioactive source of the cobalt-60 machine, and here-in lies the complexity of the linac over the cobalt-60 machine [6], [9], [10].

Figure 2.2: Linac machine at TASH.

2.3.3 Cobalt 60 versus Linear Accelerators

Both cobalt 60 and linear accelerators are mature technologies for external beam radiotherapy. However, there are some differences in that cobalt 60 uses Co-60 produced by irradiating ordinary stable Co-59 with neutrons in a reactor and LINAC uses high frequency electromagnetic waves to accelerate charged particles to high energies through a linear tube. Detailed comparison is presented described in Table 2.1.

Table 2.1: Cobalt-60 versus linear accelerator comparison.

Cobalt-60		**Linear Accelerator**	
Advantage	**Disadvantage**	**Advantage**	**Disadvantage**
Cheaper: Reduced maintenance, running costs and downtime	Lower % depth dose, Less penetrating	Ability of delivering complex treatments	Expensive: Preventive maintenance is essential, higher life cycle cost
More simple mechanical, electrical components and operation	Poor field flatness, Greater penumbra	Edges of the beams are sharp	Complex electro-magnetic componentry
Relative constancy of beam output	Lower dose rate	Better dose distribution, modulated dose rate, Higher beam energy	
Predictability of decay		Decreased skin dose	

2.4 Advantages of Radiotherapy

More than half of the cases of cancer in the world arise in people in low-income and middle income countries. This proportion was forecasted to rise to 70% by 2020. Radiotherapy is an essential part of the treatment of cancer. It can cure tumors alone and when used in conjunction with surgery or chemotherapy. Furthermore, it can relieve symptoms in patients with incurable cancer (palliation) [9]. Radiotherapy is used in at least two-thirds of cancer treatment regimens in Western countries, and remains an important curative treatment modality for uncomplicated locoregional tumors [11].

2.5 Radiotherapy Planning

The radiation treatment planning (RTP) process comprises a series of patient-related work tasks that eventually result in a custom plan of the external beam treatment and will enable the radiation dose prescription to be applied. Radiotherapy includes two phases: pre-treatment, and treatment. The goal of the pre-treatment is to outline the exact area to be treated with radiotherapy, and to minimize radiation to the surrounding healthy tissues and organs [5], [7].

The first step of planning is the positioning of the patient. The aim of such positioning is to immobilize the treated area and get the best expose and warrant reproducibility. The next step is a simulation which imitates the real treatment delivery and is hence important for proper delivery of radiation. Having completed the simulation process, the radiation oncologist decides on the treatment volumes, beam positions, and beam parameters and along with the physicists, creates treatment plans and verifies if the plans produced to cover the targeted volume. Finally targeted radiation is delivered to the patient [12], [13]. The treatment planning is shown in Fig. 2.3.

2.6 Radiotherapy Scheduling

In radiotherapy, radiation is given as a series of small doses, referred to as fractions, over a period of days or weeks, although it can also be given as a single fraction [7]. It is usually given in a set of (daily) irradiation sessions, administered by an RT machine [3], [14]. The scheduling depends on the type of patient. Patients are categorized according to treatment intent and a waiting list status. The treatment intention can be to remove symptoms (palliative) or cure (radical) treatment. There are three waiting list ranks: emergency, urgent, and routine. The waiting list status is determined by the location and growth of cancer. The waiting time target determines the date by which pre-treatment has to finish [15]. Table 2.2 shows the Joint Council for Clinical Oncology (JCCO) good practice and maximum acceptable waiting time targets given in days.

Table 2.2: Joint Council of Clinical Oncology (JCCO) waiting time targets.

Standard	**JCCO targets (in days)**		
	Emergency	**Palliative**	**Radical**
Good practice	1	2	14
Maximum acceptable	2	14	28

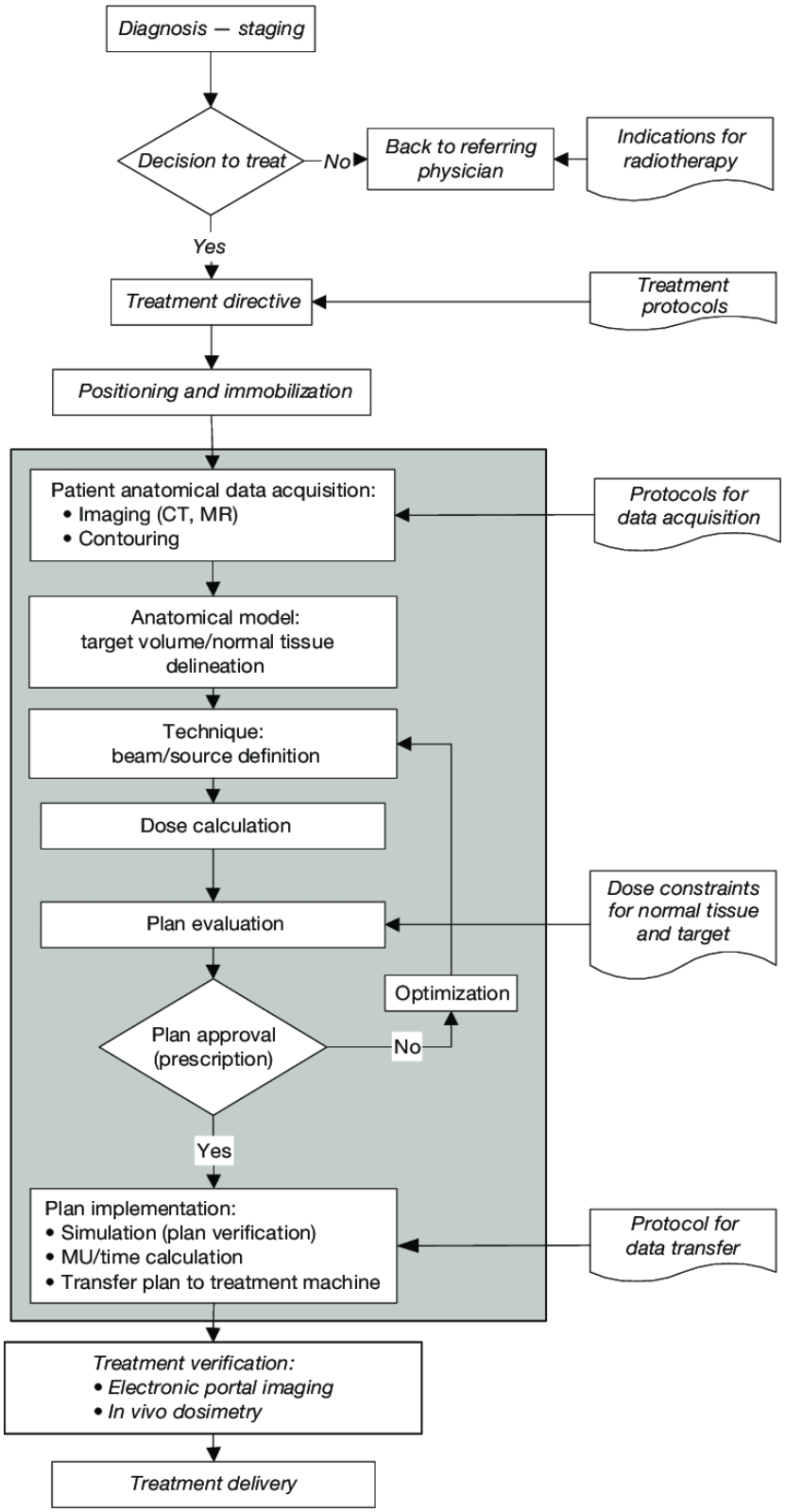


Figure 2.3: Steps in the radiation therapy planning process. Note: process parts in italics are not included in this report [16].

Chapter 3 Genetic Algorithm Based Optimization

3.1 Introduction

In the previous chapter, radiotherapy treatment principles, planning and scheduling were discussed. The current chapter discusses the fundamentals of genetic algorithm (GA) with the aim of giving insight about GA based optimization and its applications in optimizing radiotherapy treatment schedule.

3.2 Genetic Algorithm

A genetic algorithm is a search heuristic inspired by Charles Darwin's theory of natural selection. It is generally used to resolve optimization and search problems. It merges survival of the fittest among solutions with a structured as well as a randomized information exchange to form a search algorithm. This algorithm reveals the process of natural selection where the fittest offspring's are selected for reproduction so that it produces offspring of the next generation. Their elasticity makes them attractive for various optimization problems in the real world [17], [18].

The process of natural selection starts with the selection of fittest individuals from a population. They produce offspring which inherit the characteristics of the parents and will be added to the next generation. If parents have better fitness, their offspring will be better than parents and have a better chance at surviving. This process keeps on iterating and at the end, a generation with the fittest individuals will be found [19], [20]. The general flow of GA is shown in Fig. 3.1.

3.3 Advantages of Genetic Algorithm

In this study genetic algorithm is used because of several advantages that GA has for multi-objective optimization problem like scheduling [17]. GA is robust in in finding local minima or maxima, searches from population of points rather than from a point which makes it easier to find solution out of many candidate scheduling. GA also, and supports multi objective optimization which is good for radiotherapy scheduling.

3.4 Genetic Algorithm: Basic Terminologies

There are different terms used in GA including population, chromosome, gene, allele, genotype, phenotype, encoding and decoding. These terms are shown in Fig. 3.1.

3.4.1 Population

The population is a set of chromosomes that is a subset of all the likely encoded solutions to a given problem. Often the first generation is usually generated randomly.

3.4.2 Chromosomes and Gene

A chromosome is a series of genes. It is one such solution to a given problem. Whereas gene is a single element location of a chromosome. It is a bit string of arbitrary lengths [21].

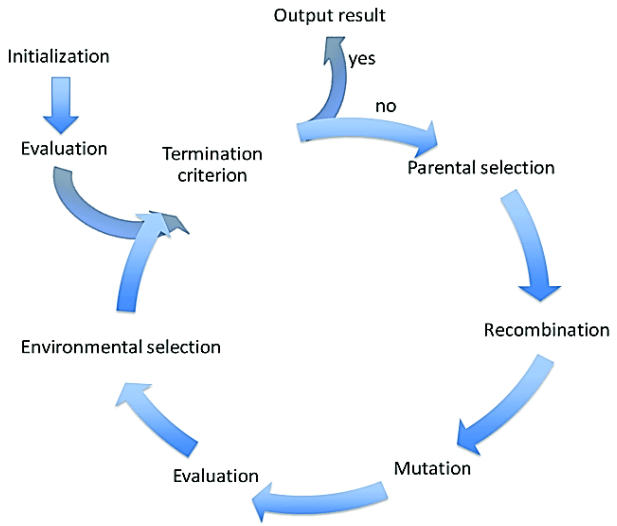


Figure 3.1: Genetic algorithm general flow diagram.

3.4.3 Allele and Genotype

An allele is a value a gene takes for a specific chromosome (see Fig. 3.2). Whereas genotype is the population in the computation space. In the computation space, the solutions are denoted in a way that can be easily understood and manipulated using a computing system [22], [23].

3.4.4 Phenotype

The phenotype represents the actual physical (outward) representation of the chromosome in the real-world solution space [22].

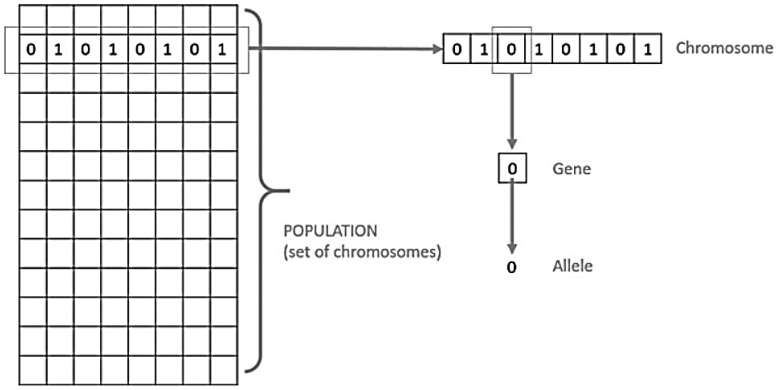


Figure 3.2: Terms used in genetic algorithm.

3.4.5 Encoding and Decoding

Encoding of chromosomes is the first step in solving GA problems and it greatly depends on the problem at hand. Basically, encoding is a process of converting from the phenotype space to genotype space. That is a representation of the solution in the form of a string of bits that expresses the crucial information. Similar to chromosomes, each gene represents a particular feature of the individual, likewise, each bit in the string symbolizes a behavior of the solution [24]–[27].

On the other hand, decoding is the transformation of a solution from the genotype space to the phenotype space. However, for trivial problems, the genotype and phenotype spaces are both the same. Nevertheless, in most of the cases, the genotype and phenotype spaces are not the same. Moreover, since decoding is carried out repeatedly in a GA during the fitness value calculation, it should be fast in computation. The concept of encoding and decoding is shown in Fig. 3.3.

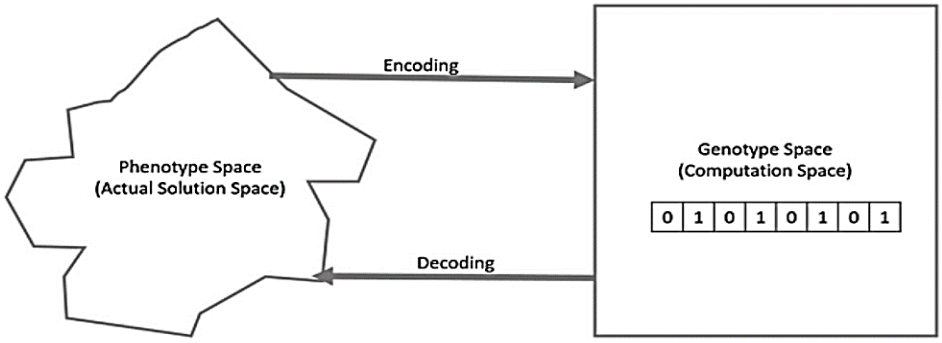


Figure 3.3: Concept of encoding and decoding.

3.4.6 Encoding Methods

Binary Encoding

This is one of the easiest and is the most commonly used encoding method. In this type of representation, the genotype consists string of 1s and 0s and each location in the chromosome represents specific features of the problem (see Fig. 3.4) [20], [21].

Chromosome A	10110010110011100101
Chromosome B	11111110000000011111

Figure 3.4: Example of chromosomes with binary encoding.

Permutation Encoding

Is widely used in sequencing problems, such as a traveling salesman (TSP) problem or task ordering problem. In permutation encoding, each chromosome is a string of numbers, which represents numbers in a sequence. For instance in TSP, each chromosome is a string of numbers or vectors representing a city to be visited. An example of permutation encoding is shown in Fig. 3.5 [21], [26].

Chromosome A	1 5 3 2 6 4 7 9 8
Chromosome B	8 5 6 7 2 3 1 4 9

Figure 3.5: Example of chromosomes with permutation encoding.

Value Encoding

Value coding is used when binary encoding is not sufficient. For instance, it is used for problems where we want to define the genes using some complicated value, real numbers, continuous rather than discrete variables (see Fig. 3.6). Values could be whatsoever connected to problems, form numbers, real numbers, or characters to some complicated objects [20], [21], [26].

Chromosome A	1.235 5.323 0.454 2.321 2.454
Chromosome B	(left), (back), (left), (right), (forward)

Figure 3.6: Example of chromosomes with permutation encoding.

3.5 Stages in Genetic Algorithm

A genetic algorithm commences with guessing the set of solutions represented by chromosomes, and this stage is known as population initialization. Next, new solutions (offspring) are selected out of the initial population-based of fitness evaluation. The more the new solution fits, the more chances they have to reproduce or move to the next population. This cycle (i.e. generate population and selection) is repeated until some criteria is met. For instance, the criteria could be the maximum number of generation or the accuracy of the fittest solution. Nevertheless, the detailed steps include population initialization, fitness computation, selection, crossover and mutation [21], [28].

3.5.1 Initialize Population

The initial population (population seeding) is an entire range of possible search space (the solutions) when the GA starts, also known as a set of chromosomes. When a population is initialized, there are two things to consider: the diversity of the population and the size of the population. If the diversity of the population is not maintained, the GA may converge prematurely. As a result, the best solution is not achieved. The population size also plays a great role. The population size depends on the nature of the problem and the greater the number of population, the more variety of solutions it produces. Thus, it increases the probability of obtaining the best solution. In addition, increasing the population size also causes GA to reach suitable solutions faster (i.e. reduce the computational costs) [17], [21], [29].

There are two main methods to initialize a population in a GA. These are random initialization and heuristic initialization. From observation, heuristic initialization may result in less diversity of population hence, premature convergence is possible. In contrast, random initialization is preferred because it generates a variety of candidate solutions as a result, it drives the population to optimality [30].

3.5.2 Fitness Computation

Faintness is evaluated using a fitness function (also known as the evaluation function) which takes a candidate solution to the problem as input and produces an output. The measure of the output how fit or how good the solution is with respect to the problem in consideration is known as fitness. It essentially measures the quality of the solutions the GA has produced [17], [21].

A fitness function should have the following characteristics:

a. It should be clear how the fitness score is computed;
b. It must measure quantitatively how fit a given solution is;
c. Since it is done repeatedly in a GA and it should be sufficiently fast, and
d. The result candidates should have best/worst score values.

3.5.3 Selection

Selection is the process of selecting parents (individual genomes) from a population, which are used to breed and recombine to produce offspring's for the new generation. Parent selection is very vital step to the convergence rate of the GA. In order to progress towards the optimum solutions, the fittest offspring solutions have to be selected to be parents in the next parental population. The new generation is selected based on the fitness values in the population. In case of maximization problems, the high fitness values are preferred and vice versa in case of minimization problems [17], [21].

Although, as selecting good parents leads to better and fitter solutions, care should be taken. If an extremely fit solution is selected it may over take the entire population in a few generations. Thus, this leads to premature convergence of solutions leading to a loss of diversity and is an unwanted condition in a GA. Therefore, maintaining good diversity in the population is very essential for the success of GA [29], [31], [32].

3.5.4 Selection Methods

There are various ways of selecting parent chromosomes. The most common ones include random selection, tournament selection, rank selection, and Roulette wheel selection.

Random Selection

Random selection (RNS) is a trivial way of randomly selecting pairs of chromosomes from parents without the use of fitness values. Merely, it uses randomly generated index values to select the parent chromosome.

Tournament Selection

Tournament selection (TS) makes a selection based on fitness values. It involves running several tournaments among a few individuals or chromosomes and then the winner of each tournament is selected based on the fitness value. The tournament starts by selecting *n* individuals from a large population. Then those *n* individuals compete against each other. The number of individuals competing against each other is known as tournament size. Out of the individual competitions, the one with the highest fitness wins and participates in the crossover [21], [33]. The winner is then added to the breeding pool. The mating pool consists of tournament winners, which have higher average fitness than the average population fitness. This fitness change provides the selection pressure, which provokes the GA to increase the fitness of each following generation. Increasing the tournament size n increases selection pressure, as the winner from a bigger tournament, will, on average, have higher fitness than the winner of a lesser tournament [33].

Because tournament selection provides an equal probability to all the individuals to compete, therefore, diversity is preserved. However, this also leads to a reduction of convergence speed. The probability of an individual i being selected for reproduction is given by [34].

$$p(i) = \begin{cases} \dfrac{C(k-1, n-1)}{C(k,n)} & \text{if } i \in [1, n-k-1] \\ 0 & \text{if } i \in [n-k, n] \end{cases} \qquad Eq.(3.1)$$

Where C is set of population, n is tournament size and k is set of individuals selected.

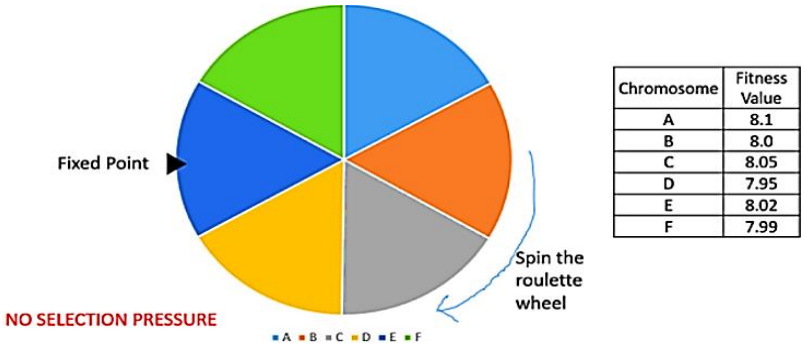
Rank Selection

In rank selection (RKS), first ranks the population and then every chromosome receives fitness from this ranking. The best individual i gets highest rank N and the worst individual gets rank 1. Thus, every chromosome is allocated selection probability with respect to its rank (Eq. 3.2). Individuals are selected as per their selection probability and the selection probability of an individual i for population size n is given by [16], [34].

$$p(i) = \frac{rank(i)}{n \times (n-1)} \qquad Eq.(3.2)$$

Rank selection works with negative fitness values and prevents too quick convergence of GA solution. Usually it is used when the individuals in the population have very close fitness values

(i.e. at the end of GA run). Consequently, each individual will have an almost equal share of the pie as shown in Fig. 3.7. As a result, each individual has an approximately same probability of getting selected as a parent. Rank selection avoids too rapid convergence and differs from roulette wheel selection in terms of selection pressure [35], [36].

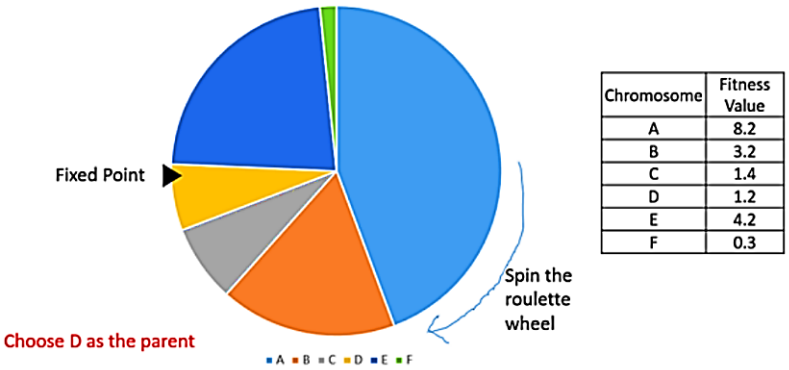


Chromosome	Fitness Value
A	8.1
B	8.0
C	8.05
D	7.95
E	8.02
F	7.99

Figure 3.7: Rank selection characteristics.

Roulette Wheel Selection

In the Roulette Wheel Selection (RWS) method, all the probability of choosing an individual (chromosomes) for breeding of the next generation individuals in the population are placed on the roulette wheel according to their fitness value [18], [35], [37]. The better the fitness is, the higher chance for that individual to be selected. The principle of roulette selection follows a linear search through a roulette wheel with the slots in the wheel weighted in proportion to the individual's fitness values. Then, the virtual roulette wheel is spun as shown in Fig. 3.8. The individual corresponding to the segment on which roulette wheel stops are then selected. The process is repeated until the desired number of individuals is selected. RWS selection uses exploitation technique in its approach [34], [35].



Chromosome	Fitness Value
A	8.2
B	3.2
C	1.4
D	1.2
E	4.2
F	0.3

Figure 3.8: Example of roulette wheel selection, each section pie chart represents the fitness values.

The average fitness (Eq. 3.3) of the population for i^{th} generation in roulette wheel selection is calculated as:

$$\overline{FRW_{i,j}} = \frac{\sum_{j=1}^{N} FRW_j}{N} \qquad Eq.(3.3)$$

where FRW_j is fitness of individual chromosome j in RWS, i varies from 1 to total number of generations and j varies from 1 to N and N is the population size.

Therefore, the probability of a j^{th} individual (chromosomes) being selected (Eq. 3.4) as a parent for crossover is given by:

$$PRW_j = \frac{FRW_j}{\sum_{j=1}^{N} FRW_j} \qquad Eq.(3.4)$$

where N is the population size and FRW_j is the fitness of individual j.

3.5.5 Crossover

Crossover is the stage of GA after selection where a new chromosome is generated by combining two or more parent chromosomes. When these two chromosomes are combined, it is hoped that new and efficient chromosomes are generated. It helps to exchange genetic material (information) between two or more parents to form two new (child) offspring. Consequently, these children become next-generation parent chromosomes. There are different methods of exchanging alleles between two selected parent chromosomes in order to get a new solution space. The commonly used methods include one-point crossover, two-point crossover, multi-point crossover, and uniform crossover [19], [38]–[40].

Single and Two Point Crossover

In this single-point crossover (SPC), two parents are each cut at a randomly selected crossover point and the tails of this individuals are swapped to get new off-springs (see Fig. 3.9) [38]–[40]. The sequence of steps is:

i. Select a cut point randomly between any two genes.
ii. Copy first substring from Parent 1 and insert as it is in the Offspring 1.

iii. Then, copy one by one gene from the Parent 2 and insert them in the Offspring 1 by omitting the repeated values to avoid duplicity.

The roles of parents are interchanged in order to get offspring 2.

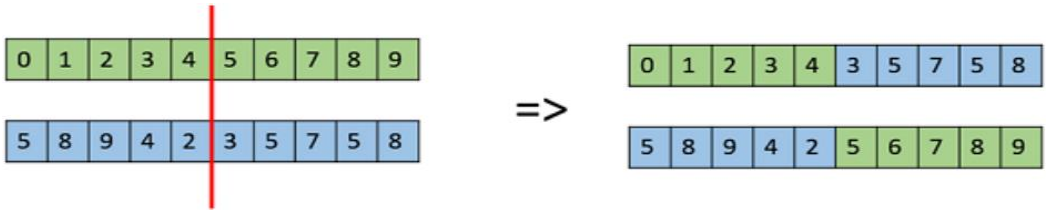


Figure 3.9: Diagram representation of one-point crossover.

Unlike one point crossover, in a two-point crossover, chromosomes are cut at two randomly chosen crossover points. The two cut points are selected at the same positions in two parents and then two offspring are formed. Compared to single point crossover, two-point crossover gives a better probability to parents in exchanging the primary genes of their chromosomal strings [38], [39]. Implementation for a two point crossover is shown in Fig. 3.10. The steps for the two-point crossover are:

i. Select two cut points randomly between genes of each parent.
ii. Select the substring between the two cut points from Parent 2 and copy it to the Offspring 1 as shown in Fig. 3.10.

Remaining values are copied from first parent and placed as it is in Offspring 1 omitting repeated values.

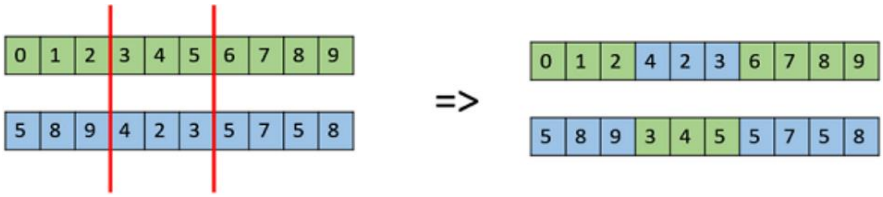


Figure 3.10: Two-point crossover implementation.

Multi Point Crossover

Multi point crossover (MPC) generalizes one-point crossover, where by alternating sections are interchanged to get a new off-springs [21]. It provides a more dispersed exchange by taking a large number of crossover points. Its implementation is shown in Fig. 3.11. The step are as follows:

i. Crossover points ($n_c \geq 3$) are randomly chosen.

ii. Individuals are cut at these sites to be separated into $n_c + 1$.

iii. Complete the process exchanging either one of the two groups of portions as a whole.

The first group consist of the set of $\{1st, 3rd, .., (2k-1)th,$ where $k = 1, 2, \dots, int(n_c/2+1)\}$ portions, and the second group involves those portions which are not included in the first group, i.e., $\{2nd, 4th, .., (2k)th,$ where $k = 1, 2, \dots, int[(n_c+1)/2]\}$ [38].

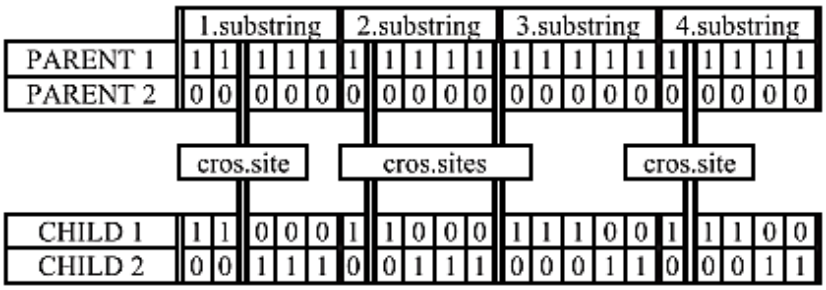


Figure 3.11: Multi-(4)-point crossover implementation.

Uniform Crossover

The Uniform crossover (UC) technique is different from previous methods (see Fig. 3.12). In this method, instead of segmenting the chromosomes into sections, each gene is treated separately. Its implementation is shown in Fig. 3.12 [21], [38], [41]. The implementation steps are as follows:

i. Create random crossover mask.

ii. Copy genes of child individual from the parents according to this mask.

iii. If the site mask is 1, carry genes from parent 1; if site mask is 0, carry genes from parent 2.

Complement the mask to get second child or repeat the above step forming new mask to get second child.

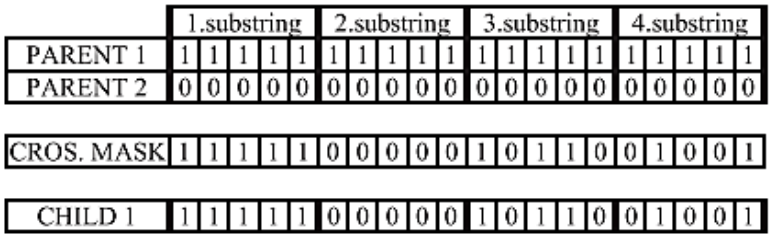


Figure 3.12: Uniform crossover implementation.

3.5.6 Mutation

After next generations are generated, the new chromosomes are subjected to mutation. Mutation modifies gene values so that a new population with new characteristics (i.e. nonexistent in the population pool) is added. It helps to recover lost genetic materials as well as for arbitrarily disturbing genetic information. As a result, it helps to maintain genetic diversity in the population by randomly varying some of its child genes. In addition, it is useful for preventing the GA from being trapped in a local minimum. However, the importance of mutation depends on mutation rate, maximum percent change made in the value of any gene. High mutation rate makes the individuals explore in search of the optima by continuously changing the gene values. Hence, no convergence to solution. On the contrary, very low mutation rate won't have any effect hence, very slow convergence. Therefore, care should be taken when selecting mutation rate. It should not be high to cause too much randomness and should not be too small having no effect [21], [28], [40], [42]. There are various types of mutation for the different kinds of representations.

Flip Mutation

Flip mutation (FM) is often used for binary encoded GAs. It involves flipping of a bit from 0 to 1 and vice versa. A child chromosome is produced by flipping (0 to 1 and 1 to 0) the randomly selected bit in parent chromosome (see Fig. 3.13) [21], [43].

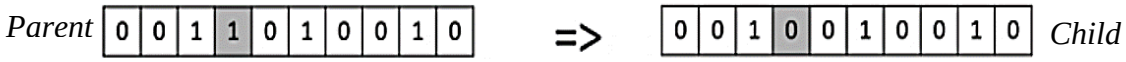


Figure 3.13: Flip mutation implementation.

Swap Mutation

In swap mutation (SWM), two positions on the chromosome are randomly selected and their values (alleles) are interchanged. Its implementation is shown in Fig. 3.14. This is commonly used in permutation based encodings. It conserves most of the adjacency information but links broken disrupts order more [21], [43].

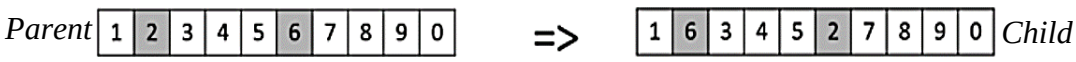


Figure 3.14: Swap mutation implementation.

Scramble Mutation

The scramble mutation (SM) operator selects a random subset of genes and then randomly shuffles or scrambles the alleles in those positions (see Fig. 3.15). This method is also often used in permutation representation [43], [44].

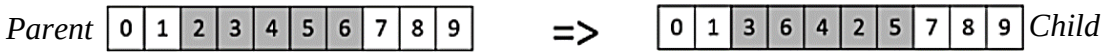


Figure 3.15: Scramble mutation implementation.

Inversion Mutation

Similar to scramble mutation, inversion mutation (*IVM*) randomly selects subsets of genes. However, instead of scrambling the subset, it removes it and inserts the entire string in reversed order (see Fig. 3.16) [43], [44].

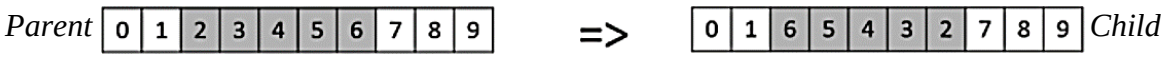


Figure 3.16: Inversion mutation implementation.

Centre Inverse Mutation

In center inverse mutation (CIM), parent chromosome is divided into two sections. All genes in each section are copied and then inversely placed in the same section of a child [42]. Its implementation is shown in Fig. 3.17.

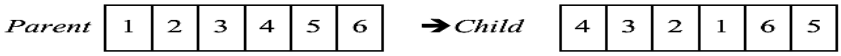


Figure 3.17: Center inverse mutation implementation.

Chapter 4 Literature Review

In the past two decades, radiotherapy scheduling has got interest of researchers. Kapamara et al. [45] were the first to present a literature review about scheduling and then radiotherapy treatment booking proposed by Petrovic et al. [46]. Other authors focus on the pre-treatment phase and use linear programming, simple dispatching rules, and GAs to optimize scheduling problem (Petrovic and Castro) [47], [48]. In addition Leite-Rocha [49] Ph.D. thesis summarizes research on radiotherapy scheduling prior to 2011 and proposes various extensions to their mathematical models.

The genetic algorithm developed by Petrovic, sanja, et al. for patient scheduling evolves priority rules for operations of radiotherapy pre-treatment [3]. The fitness function takes into consideration the waiting time targets of patients and also the early idle time on resources and concludes that the GA reduced waiting idle time. Also, a GA is applied to generate schedules by Petrovic, d., Morshed et al. for radiotherapy patients at Arden Cancer Centre and the GA performed well for radical and palliative patients, but badly for emergency patients [50]. Moreover, radiotherapy patient scheduling, within oncology departments is developed by Conforti, d., Guerriero, F. et al. and their study concluded that results were encouraging because it allowed overcoming the performance of human experts [51].

Furthermore, GA is proposed by Vogl, p., Braune, R. Et al. to minimize the operation time of the bottleneck resource, the particle beam, while simultaneously minimizing any penalties arising from violations of time window constraints and concluded that it performed well on both small and large problem instances [52]. They also concluded that future research could incorporate other additional constraints besides waiting time and early idle time on resources.

Thus, the current thesis research aims to add other constraints affecting radiotherapy scheduling, such as the number of machines, number of fractions, and number of working days.

Chapter 5 Methodology

5.1 Introduction

In this chapter, the methodology adopted for scheduling of external beam therapy patients will be discussed. First, web application is developed in order to register and view patients that are going to be scheduled. Secondly, GA based optimized scheduling, which includes priority rules for procedures of radiotherapy desktop application is developed. The web application integrates with desktop application using excel file. Real world data from Black Lion hospital is used in experiments.

5.2 Radiotherapy Patient Management System (RTPMS)

The web application is known as radiotherapy patient management system (RTPMS). The application is developed in order to manage users that are registering patients and to register patients that are going to be scheduled. The following interfaces were implemented:

- An admin interface to create users;
- An admin interface to view and update users account;
- An interface to register new patients;
- An interface to view and update patients' information, and
- An interface to export patients' information to excel.

5.3 Development Environments

The web application is developed on a desktop running Windows 10 operating system (OS). Apart from the personal computer (PC) and OS, the implementation required a development environment to be set up. The development environment consists of different software programs and tools to work with them.

5.3.1 Visual Studio Code

Visual Studio Code is a lightweight but powerful free source-code editor made by Microsoft. It combines the simplicity of a source code editor with powerful developer tooling, like IntelliSense code completion and debugging. Features include support for debugging, syntax highlighting, intelligent code completion, snippets and code refactoring. Because of its wide use and its

advanced features, Visual Studio Code was chosen to develop the web application in the current work.

5.3.2 XAMPP Server

In order to develop a web based application, it requires server to store the application and serve for users from different network. XAMPP is a web server application stack and XAMPP stands for Cross-Platform (X), Apache (A), MySQL (M), PHP (P) and Perl (P). It is a simple, lightweight Apache distribution that makes it extremely easy for developers to create a local web server for testing and deployment purposes. The major components it includes are Apache HTTP server, MySQL database server, Perl and PHP scripting language modules for Apache HTTP. XAMPP Control Panel Application included in the release allows for an easy administration of the various server software packages. For the above reason XAMPP web server application is chosen in the current study. Figure 5.1 shows the XAMPP control panel.

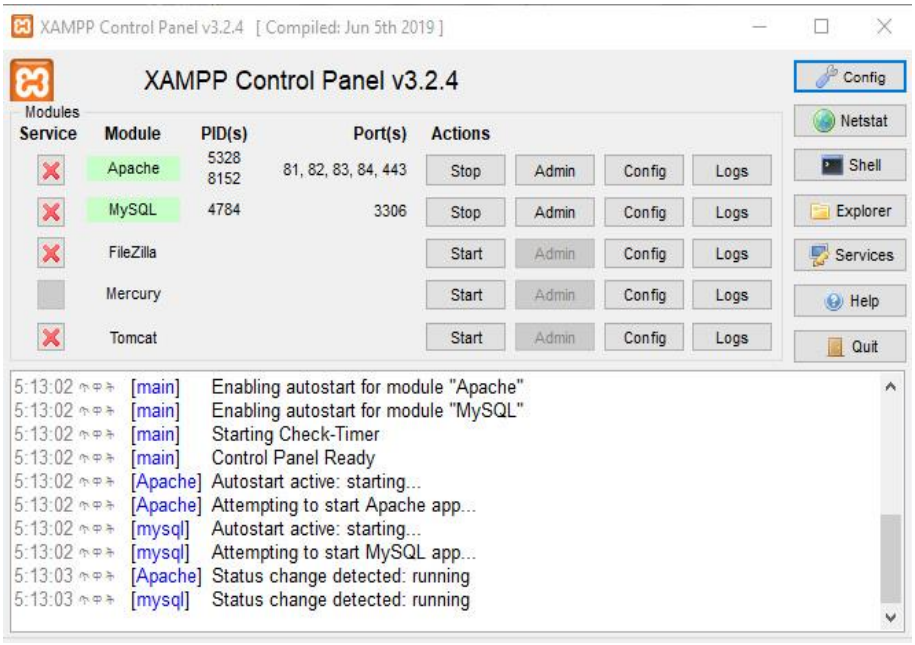


Figure 5.1: XAMPP web server control panel.

Database

Database is the second most important part of the web development environment because the application requires a database to store and query various data. In this thesis, My Structured Query Language (MySQL) is used. MySQL is the most popular relational database management system

(RDMS) widely used by huge sites such as Google or Amazon. In addition, it works well together with PHP, which is used to develop the web application, as well as other languages to manage. The database schema is shown in Fig. 5.2.

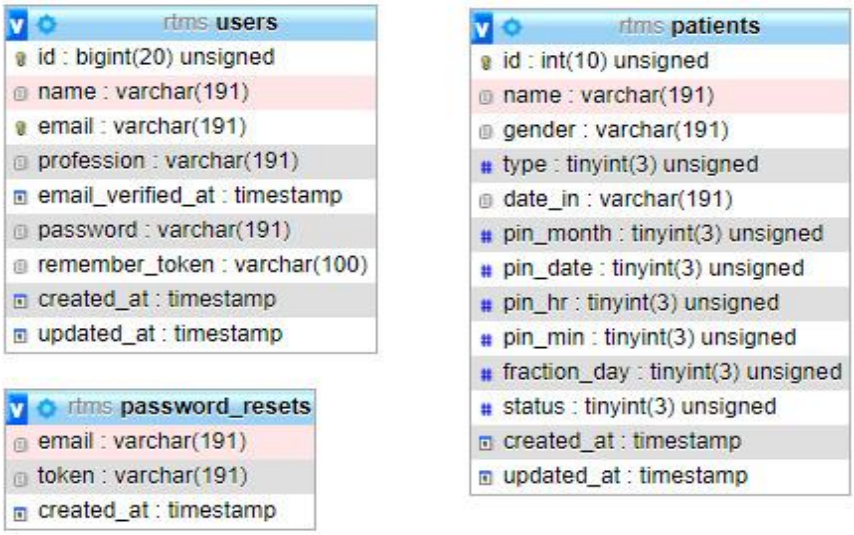


Figure 5.2: Web application database schema.

5.4 Pages in the Web Application

There are four main pages as seen in Fig. 5.3 in the web application: manage user, manage patient, GA-Schedule and patient statistics.

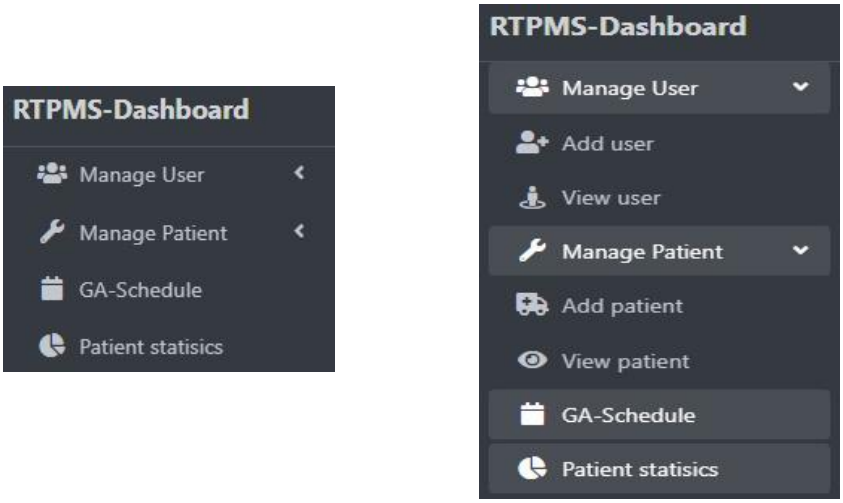


Figure 5.3: Web application sidebar menus.

5.4.1 Manage User Page

The Manage User page contains other sub-web pages. First is an add user page which is used to register professionals who manage and register patients. The second is a view user page which is used to view list of professional users and contains action links to edit and update user info. The third is an update page where user's info such as name or profession are edited and updated.

5.4.2 Manage Patient Page

Similar to the manage user page, manage patient page has also three functions. The first is to add patients with their respective information. Second function is to view patients' page which allows professionals to view list of patients in table format and edit patients' information if needed. The last page is update page. Incase patients' information needs to be changed, this page allows to edit and update patients' information such as name, age or even its radio therapy fractions.

5.4.3 GA-Patient Schedule Page

In this page, patients to be scheduled using the GA optimization are selected from the database. This page allows the professionals to select patients to be scheduled using a calendar. Patients could be selected within one month or more.

5.5 Genetic Algorithm Based Scheduler

The scheduling of radiotherapy treatment appointments is a complex problem due to various medical and scheduling constraints, such as patient category, machine availability, waiting time targets (i.e., the time when a patient should receive the first radiotherapy fraction, etc.), and, also, due to the size of the problem (i.e., number of machines, and patients). Hence, an automated scheduling technique (GA-Scheduling) is important. The algorithm is implemented using MATLAB 2019 on a windows platform, core i3 Intel processor and 6GB RAM.

5.5.1 Problem Formulation

This thesis research is concerned with a radiotherapy scheduling problem which is essentially a complex real-world problem. The radiotherapy scheduling considers newly arriving patients to be scheduled. The size of the patient list is uncertain and also type of patients arriving within the

scheduling horizon is uncertain. The following are the symbols used in the formulation of the problem.

Notation

- : scheduling horizon given in days
- nd: total number of new patients arriving on day d, d = 1, 2, . . . , H
- Npt : total number of patients for a given horizon H (see Eq. 5.1)

$$Npt = \sum_{d=1}^{H} nd \qquad \text{Eq.(5.1)}$$

- j : patient for $j = 1, 2, \ldots, Npt$
- Nm : set of machines and facilities
- k : machine or facility, $k \in M$
- E : emergency patient category
- P : palliative patient category
- R : radical patient category
- C_j : category of patient j
- $Tpsm$: treated patients with single machine per day
- Tpd : total treated patients per day
- $Dwrk$: work days
- Nf_j : number of fractions prescribed by a doctor for patient j
- Phr_j : arrival time for patient j
- Pdy_j : arrival day for patient j

5.5.2 Assumptions, Constraints and Objectives

The following assumptions, constraints and objectives of the radiotherapy scheduling problem were derived based on the insight from the TASH radiotherapy department.

Assumptions

- All appointments are scheduled weekly.
- Treatment working hour is between 8:00am and 5:00pm
- Average time between patients is taken 7 minutes.
- The processing times (i.e. for each operation) for each machine considered are shown in Table 4.1. These processing times were suggested based on the averages obtained from the data collected.
- The waiting time in days is shown in Table 4.2. These times were suggested by the radiotherapy professionals.

- Number of fractions given to patients is shown in Table 4.3. These fractions were suggested by the radiotherapy professionals.
- Each doctor is available in the radiotherapy unit at specified time periods per week.

Machines and/or facilities are continuously available from Monday through Friday from 8.00am to 5.00pm except for weekends, holidays and days when overtime is considered.

Table 5.1: Size of slots for the machines and facilities.

Unit		Slot size (in minute)
Planning	Simulators	30
	CT scanners	20
	Mold rooms	20
Treatment	High energy	15
	Low energy	12

Table 5.2: Average number of fraction/s delivered per patient category at TASH Radiotherapy department (based on type and stage of cancer).

Patient Category	Average Number of fractions delivered
Emergency	1-5
Palliative	7-10
Radical	23-40

Table 5.3: Waiting times of Cancer patients at TASH radiotherapy department.

Patient Category	Waiting Time in days
Emergency	1-2
Palliative	2-14
Radical	455-545

5.5.3 Objectives and Constraints

Objectives:

The main objective is to create schedules of appointments for the treatment of N patients received within the period H. The created schedules of appointments should aim:

- To minimize the average waiting time of emergency patients, and
- To minimize the average percentage of patients that do not meet their JCCO due dates.

Constraints:

- Number of patients treated per-week
- Patient type: emergency, palliative and radical
- Patient arrival hour
- Patient arrival day
- Number of working days
- Working hours
- Number of fractions
- Number of machines
- During the maintenance period, the machines cannot be used for either planning or treatment
- A patient's schedule of appointment for a given procedure cannot be altered once scheduled.

Two consecutive fractions for a patient must be separated by up to one day, apart for cases when the treatment machine has been scheduled for service and maintenance.

5.5.4 Chromosome and Genotype Representation

Chromosome

Chromosome represents in this GA one possible solution (i.e. schedule sequence). In this thesis, vector representation holding sequence of patients is used, which indirectly represents a schedule. For example, in the case of five patients, the vector can have the following form [1 4 3 5 2], where all patients are named using the patient-id. For this instance, patient-id 1 is scheduled first while patient-id 4 is scheduled second and so forth.

Genotype

Genotype refers to the elements contained in chromosomes (i.e., type of representation used). In this case natural numbers i.e., $N = \{1, 2, 3, 4, 5, 6, 7, 8, 9, 10 \ldots\}$ are used to represent each patient.

Fitness Function

Fitness function takes a candidate solution (i.e., schedule) to the problem as input and produces as output how "fit" or how "good" the solution is with respect to the problem in consideration. In this thesis, the fitness function considers patient type, arrival time (hour and minute) of patient, arrival day of patient, number of fraction and number of machines. Moreover, constraints are assigned weights based on the objective function. Weights assigned for different constraints are shown in Table 5.4. Hence the fitness is given by:

$$Fitness = W_{pt} + W_{hr} + W_{dy} + N_m + Dwrk \quad \text{Eq.(5.2)}$$

Where W_{pt}, W_{hr}, W_{dy} are weights of patient type, patient arrival time and patient arrival day, respectively.

Table 5.4: Constraints and their descriptions.

Constraint	**Description**	**Weight**
Patient type	Emergency, palliative, radical	[1, 2, 3]
Patient arrival minute	1min - 60min	[1, 2, 3…, 60]
Patient arrival hour	8:00am, - 5:00pm	[1, 2, 3…, 9]
Patient arrival day	Monday, Tuesday, Wednesday, Thursday, Friday, Saturday, Sunday	[1, 2, 3…7]

In addition to these constraints, the GA-schedule also considers number of machines available, number of days of work and number of fractions prescribed by the doctor for the patient.

5.6 Genetic Algorithm

Genetic algorithm commences with initial population (which was generated at random). Next, the selection of parents from this population of patient schedule is done by the Roulette Wheel Selection method. Following this, crossover and mutation are applied. In order to reduce computation time, one point crossover technique is utilized. Moreover, a popular mutation technique, swamp mutation, is used to mutate genotypes. Finally, termination is based on two criteria combined. The first is faintness criteria. In case the first stopping criterion is not satisfied, the second stopping criterion is number of generations used. The overall flow of the proposed GA-based scheduling is shown in the flowchart shown in Fig. 5.4.

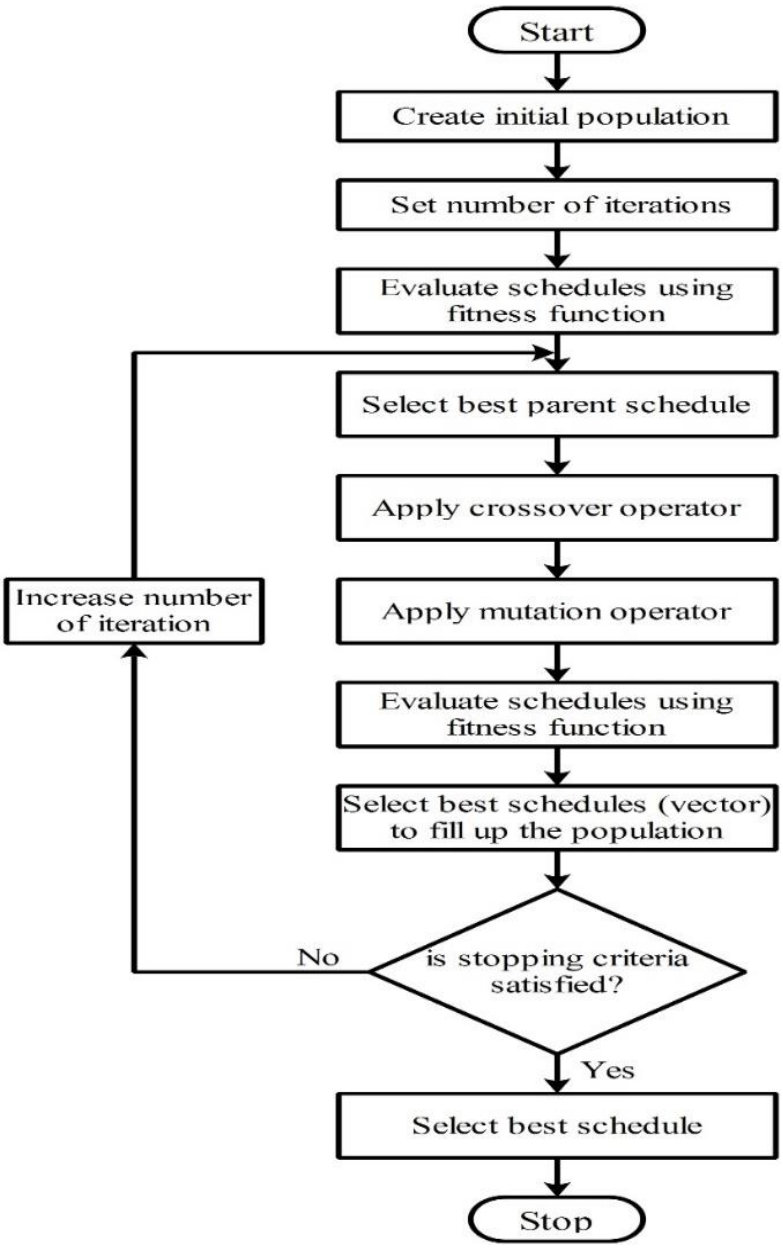


Figure 5.4: Flow chart for the proposed scheduling genetic algorithm.

Chapter 6 Result and Discussion

6.1 Patients Data Set

According to TASH radiotherapy treatment center, on average 30 patients are treated per day, implying 150 patients are treated per week. Therefore, in this study 150 patients are scheduled using the proposed GA based scheduler. A sample of 60 patients to be scheduled is presented in Table 6.1 out of 150 total number of patients. The columns of the table show the constraints for the GA scheduling and the row indicates patient's number.

Table 6.1: Patients data set

ID	*Type*	*Day*	*Hour*	*Minute*	*Fractions*	*ID*	*Type*	*Day*	*Hour*	*Minute*	*Fractions*
1	1	2	11	53	4	31	2	2	2	35	7
2	2	5	4	41	8	32	1	2	6	4	5
3	2	5	4	55	7	33	1	4	4	30	1
4	3	5	8	5	32	34	1	4	3	49	4
5	1	4	8	39	1	35	3	1	7	27	24
6	1	5	4	35	3	36	3	4	3	8	37
7	2	5	8	28	7	37	2	4	5	38	8
8	3	4	9	34	33	38	2	2	5	39	9
9	2	2	3	16	9	39	1	1	6	43	2
10	2	1	7	34	9	40	1	1	11	59	5
11	3	3	4	52	25	41	1	3	2	49	4
12	1	2	6	59	2	42	2	1	10	2	9
13	2	3	10	46	10	43	3	4	2	13	30
14	2	3	3	38	9	44	1	5	11	41	1
15	1	5	5	1	1	45	1	4	3	1	3
16	1	4	8	17	4	46	2	4	11	21	7
17	2	5	3	13	10	47	1	1	11	18	1
18	1	1	2	40	1	48	3	4	9	31	40
19	1	5	5	37	3	49	1	1	2	32	4
20	1	4	4	33	4	50	1	2	11	33	2
21	3	2	5	16	26	51	3	3	5	45	32
22	2	1	3	35	7	52	2	4	4	37	8
23	3	1	11	57	40	53	2	5	2	34	8
24	2	2	3	47	10	54	3	4	5	37	31

25	3	5	2	25	32	55	2	2	9	20	10
26	2	1	2	9	10	56	2	5	7	47	7
27	1	5	8	31	5	57	3	5	7	55	36
28	3	3	6	17	23	58	1	4	10	30	3
29	1	1	3	24	1	59	1	3	9	54	3
30	1	2	9	57	3	60	2	3	4	22	10

6.2 Effect of Constraints on Scheduling

Constraints considered in this study include the patient type, arrival date, number of machines, and number of working days. In the case of the patient type, according to the Joint Council of Clinical Oncology (JCCO), emergency patients, should be treated within a day. Therefore, they are given priority before palliative and radical patients. On the other hand, because radical patients can wait up to 14 days, thus they are treated at the end after palliative patients. After the patient type constraint is considered on the GA schedule, next arrival date constraint is considered, which includes the arrival date and time (hours and minutes). If two patients are the same patient types, their schedule is differentiated by the arrival date constraint. Moreover, the GA scheduler also considers the number of machines available. If more machines are available, more patients will be treated within a day thus, the GA scheduler assigns patients to each machine available accordingly and the GA application enables health care professionals to dynamically change the number of machines in order to adjust the schedule. The last constraint to consider is the number of working days. In this thesis, based on TASH working schedule, patients are treated on government working days and patients are not scheduled on weekends.

6.3 GA Optimized Schedule

The number of days to treat all GA scheduled patients depends on the constraints of the specific patient information. In this study, 150 patients are scheduled using the GA optimizer. The sample result of the schedule for one month is shown in Table. 6.2. On the optimized schedule, the column indicates treatment sessions (S1, S2, S3 …), the row indicates the five weekdays (Monday through Friday), and the cell indicates the patient (patient id) treated on that specific day.

Table 6.2: Sample 4-week optimized schedule of 150 patients.

Date																														
	Week - 1																													
	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17	S18	S19	S20	S21	S22	S23	S24	S25	S26	S27	S28	S29	S30
D1	49	81	18	120	29	47	84	128	39	116	66	144	59	50	1	101	94	19	12	102	15	86	90	27	30	98	40	16	33	32
D2	49	81	120	84	128	39	116	66	144	59	50	1	101	94	19	12	102	86	27	30	98	40	16	32	20	5	6	45	34	41
D3	49	81	120	84	128	116	144	59	1	101	94	19	102	86	27	30	98	40	16	32	20	6	45	34	41	44	58	72	82	79
D4	49	81	84	116	1	101	94	102	86	27	98	40	16	32	20	6	45	34	41	58	72	80	62	111	105	139	140	103	123	26
D5	102	27	40	32	20	34	41	58	72	80	62	105	140	103	123	26	125	22	2	148	114	124	104	136	109	55	126	69	113	31
	Week - 2																													
D1	72	62	105	103	123	26	125	22	2	148	114	124	104	136	109	55	126	69	113	31	60	65	9	97	10	52	89	68	13	17
D2	105	103	123	26	125	22	2	148	114	124	104	136	109	55	126	69	113	31	60	65	9	97	10	52	89	68	13	17	117	112
D3	123	26	125	22	2	148	114	124	104	136	109	55	126	69	113	31	60	65	9	97	10	52	89	68	13	17	117	112	7	77
D4	123	26	125	22	2	148	114	124	104	136	109	55	126	69	113	31	60	65	9	97	10	52	89	68	13	17	117	112	7	77
D5	123	26	125	22	2	148	114	124	104	136	109	55	126	69	113	31	60	65	9	97	10	52	89	68	13	17	117	112	7	77
	Week - 3																													
D1	123	26	125	22	2	148	114	124	104	136	109	55	126	69	113	31	60	65	9	97	10	52	89	68	13	17	117	112	7	77
D2	26	125	2	148	114	124	136	109	55	126	113	60	65	9	97	10	52	89	68	13	17	117	112	7	77	3	14	24	135	133
D3	26	148	114	124	109	55	126	113	60	65	9	97	10	52	68	13	17	117	112	7	77	3	14	24	135	133	118	37	46	38
D4	148	124	109	55	126	60	65	9	10	68	13	17	117	7	77	3	14	24	135	133	118	37	46	38	53	42	74	147	61	93
D5	60	13	17	117	3	14	24	135	133	118	37	46	38	53	42	74	147	61	93	64	87	108	130	56	91	110	134	145	119	142
	Week - 4																													
D1	3	14	24	135	133	118	37	46	38	53	42	74	147	61	93	64	87	108	130	56	91	110	134	145	119	142	143	35	76	75
D2	3	14	24	135	133	118	37	46	38	53	42	74	147	61	93	64	87	108	130	56	91	110	134	145	119	142	143	35	76	75
D3	3	14	24	135	133	118	37	46	38	53	42	74	147	61	93	64	87	108	130	56	91	110	134	145	119	142	143	35	76	75
D4	14	24	118	37	46	38	53	42	74	147	61	93	64	87	108	130	56	91	110	134	145	119	142	143	35	76	75	107	122	23
D5	14	24	118	37	38	53	42	74	147	61	93	64	87	108	130	56	91	110	134	145	119	142	143	35	76	75	107	122	23	63

6.4 Schedule Validation

Based on the capacity of TASH radiotherapy treatment center, on average 30 patients are treated hence, 30 patients are scheduled for the first day as shown in Table 6.3. As stated on the objective statement, the aim of this thesis was to minimize waiting time of patients and prioritize the emergency patients, hence better health care for cancer patients could be guaranteed. For the normal way of radiotherapy scheduling (i.e. without using GA optimization), all types of patients (emergency, palliative, radical) are scheduled according to arrival date, first come first serve approach.

Table 6.3: Comparison of patient scheduling with and without GA optimization.

Schedule Without GA Optimization							Schedule With GA Optimization					
Patient ID	Type	Day	Hour	Minute	Fractions		Patient ID	Type	Day	Hour	Minute	Fractions
26	2	1	2	9	10		49	1	1	2	32	4
49	1	1	2	32	4		81	1	3	3	28	4
18	1	1	2	40	1		18	1	1	2	40	1
120	1	1	3	13	3		120	1	1	3	13	3
63	3	1	3	19	34		29	1	1	3	24	1
29	1	1	3	24	1		47	1	1	11	18	1
22	2	1	3	35	7		84	1	1	5	5	4

76	3	1	3	56	26		128	1	1	6	42	3
139	1	1	4	2	1		39	1	1	6	43	2
148	2	1	4	12	10		116	1	1	9	37	4
149	3	1	4	18	36		66	1	1	10	60	2
84	1	1	5	5	4		144	1	1	10	11	3
143	3	1	5	25	34		59	1	3	9	54	3
136	2	1	5	31	8		50	1	2	11	33	2
125	2	1	5	42	8		1	1	2	11	53	4
123	2	1	6	5	8		101	1	2	3	11	4
128	1	1	6	42	3		94	1	2	3	5	4
39	1	1	6	43	2		19	1	5	5	37	3
35	3	1	7	27	24		12	1	2	6	59	2
10	2	1	7	34	9		102	1	2	6	5	5
70	3	1	8	37	37		15	1	5	5	1	1
130	2	1	8	42	8		86	1	2	8	19	4
122	3	1	9	29	31		90	1	2	9	2	1
116	1	1	9	37	4		27	1	5	8	31	5
42	2	1	10	2	9		30	1	2	9	57	3
144	1	1	10	11	3		98	1	3	9	36	4
66	1	1	10	60	2		40	1	1	11	59	5
47	1	1	11	18	1		16	1	4	8	17	4
114	2	1	11	52	9		33	1	4	4	30	1
23	3	1	11	57	40		32	1	2	6	4	5

However, with GA scheduling all constraints are considered for a better treatment plan minimizing waiting time of high-risk emergency patients. Based on the GA schedule, patient 49, 81, 18, 120, 29, 47, 84, 128, 39, 116, 66, 144, 59, 50, 1, 101, 94, 19, 12, 102, 15, 86, 90, 27, 30, 98, 40, 16, 33 32 are treated on the first week first day. For a valid schedule, their constraints should be fulfilled by the GA scheduler. The effect of constraints on the sequence of the GA schedule can clearly be seen in Table 6.3. From the result, it can be observed that the GA scheduler scheduled the patients prioritizing patient type before considering the arrival date. This is crucial because according to JACCO, emergency patients should be treated within one day, followed by palliative patients and radical patients later.

6.5 Accuracy Measurement

Accuracy measurement is done by comparing GA schedule with manually optimized schedule as a reference. Manually optimized schedule is done by manually picking each patient constraints and satisfy each constraint. Although, it gives an ideal schedule, it is very time consuming and as

the number of patients increase, it becomes more difficult to apply. Thus, the accuracy is the measurement of similarity of GA based schedule and manual schedule. The similarity is computed by calculating Euclidean distance (Eq. 6.1) between the GA schedule (g_s) and the reference manual schedule (m_s).

$$d(m_s, g_s) = \sqrt{\sum_{i=1}^{N_s}(m_i - g_i)^2} \tag{6.1}$$

Where, N_s is number of schedule sessions.

The computed similarity is shown in Fig. 6.2. From the figure we can observe that GA schedule has better similarity with manual schedule than normal way of scheduling.

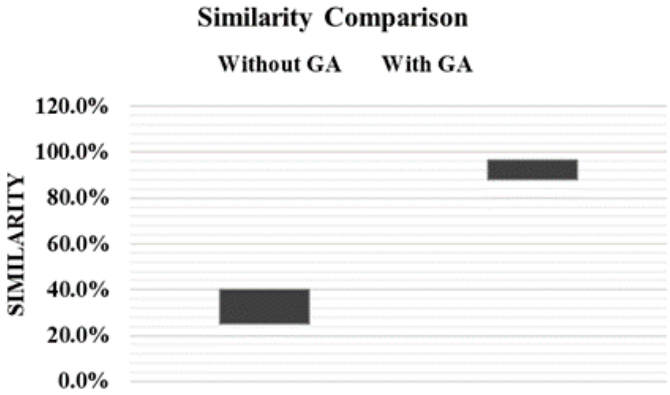


Figure 6.1: Comparison of similarity measurement of accuracy.

6.6 Effect of Number of Population on Schedule Fitness

In order to investigate the effect of population size on the performance of optimization, different population sizes (Np = 12, 24, 36, 48) were tested. From the results, it is observed that when the number of population is decreased, scheduling fitness starts to saturate at a lower accuracy value. On the contrary, as the population size increases, the fitness score increases and that results in better fitness. In addition, increasing population size reduces the number of iterations to reach maximum accuracy. Fitness versus number of iterations for different values of population size is shown in Fig. 6.3.

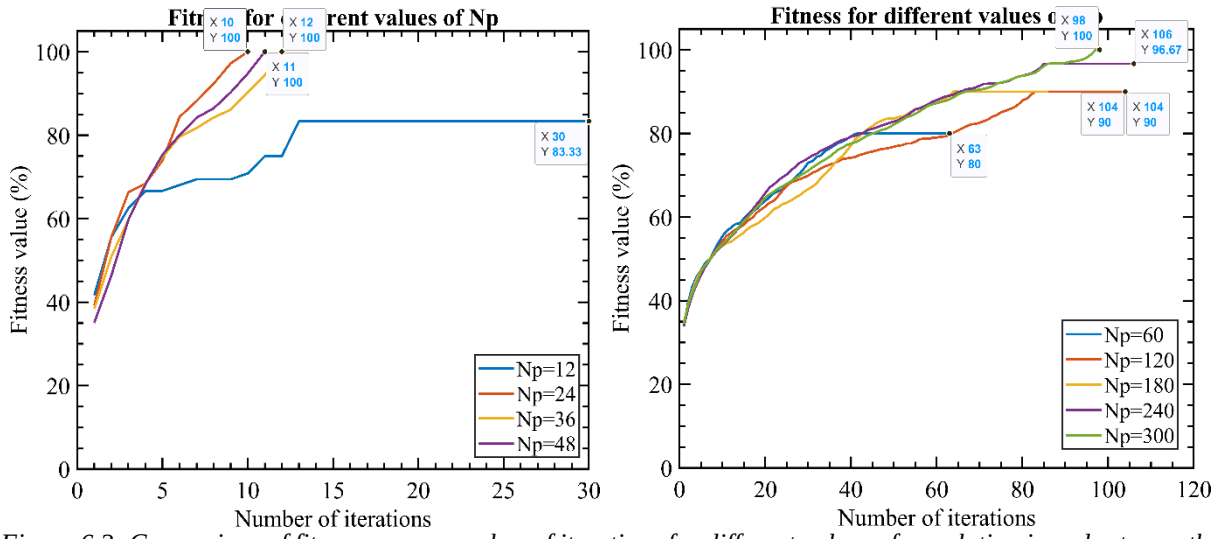


Figure 6.2: Comparison of fitness versus number of iterations for different values of population in order to see the progress of the fitness score.

6.7 Effect of Crossover on Schedule Fitness

The effect of crossover is investigated by using different values of cross-over probabilities (20%, 40%, 60%, 80%, 100%). The impact of the crossover probability value on scheduling fitness (accuracy) can be seen clearly in Fig. 6.4. The result has shown that as the crossover probability increases, the fitness value also increases. However, it is also noted that increasing crossover probability above 80% results in a quick increment of fitness value. Nevertheless, because the crossover probability is too much, fitness goes down after reaching maximum fitness value. In addition, increasing crossover probability also increases the time it takes to optimize the scheduling process. Moreover, lower crossover probability saturates to a specific fitness value after a few iterations. Hence, the crossover probability value should not be increased indefinitely and its value should be wisely chosen. For this thesis, best fitness is achieved for crossover probability (Pc) values between 60% - 80% depending on the number of populations to be scheduled. The higher the population, the higher the crossover probability.

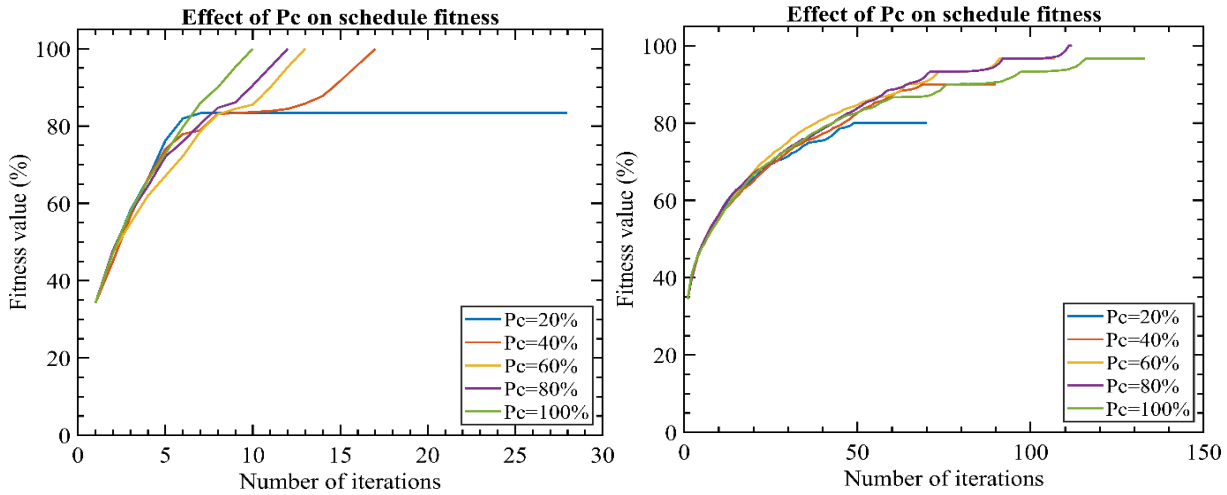


Figure 6.3: Effect of crossover probability on scheduling of patients of 12 (left) and 60 (right).

6.8 Effect of Mutation on Schedule Fitness

In this thesis, different values of probability mutation (Pm = 20%, 40%, 60%, 80%, 100%) were used to examine its effect on the scheduling algorithm. The effect of the probability of mutation is shown in Fig. 6.5. From the figure it can be seen that the higher the mutation probability the lower the convergence probability is. Hence, the longer computation time or the number of iterations it takes to reach maximum fitness value (slower scheduling). On the contrary, lowering the mutation probability increases the convergence probability of fitness value to the maximum, hence, speeds up the scheduling process. However, very low mutation probability (<20%) also results in a longer convergence time, i.e. more number of iterations. Thus Pm value should be taken accordingly. For this thesis, best fitness results were obtained for values of Pm between 20% and 40%.

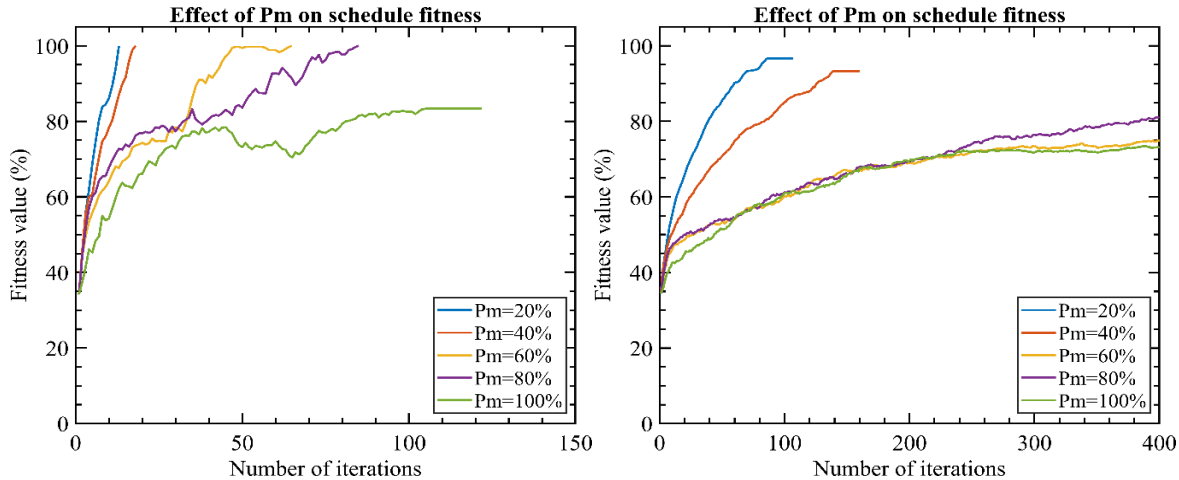


Figure 6.4: Effect of probability of mutation on scheduling of patients of 12 (left) and 60 (right).

6.9 Schedule Process

In this thesis, a user-friendly GA-based application is developed. The user can change different values of the parameters accordingly for scheduling various population sizes, i.e. number of patients. After the patient's data is loaded and the user enters the appropriate GA parameters on the GA-based application form as shown in Fig. 6.6 and Fig 6.7, the scheduling process starts. The scheduling process time mainly depends on the number of patients that are scheduled, the diversity of the randomly generated population, the value of the probability of mutation and crossover. The higher the population size entered on the application form at a startup, the faster the scheduling process is.

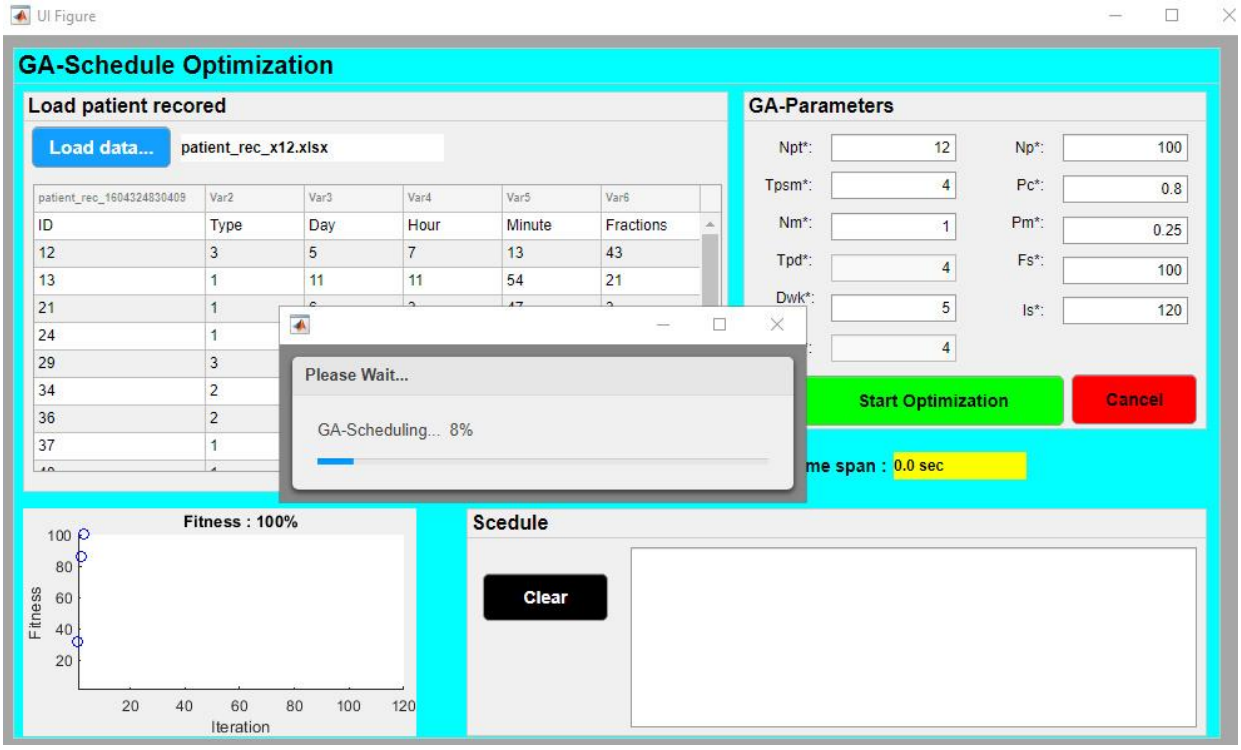


Figure 6.5: GA-Scheduling after fitness values are computed.

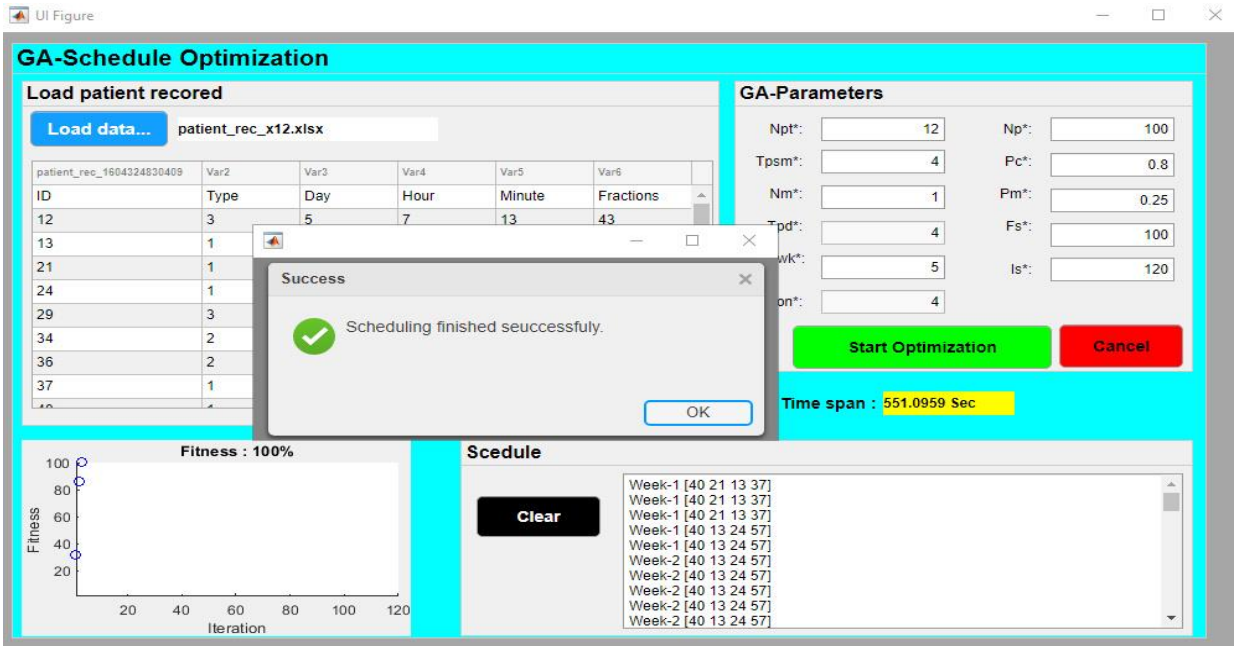


Figure 6.6: Success message after optimized scheduling is done.

6.9.1 Optimized Schedule

The scheduling application generates an excel spreadsheet with the schedule, where the column indicates the number of patients (P1, P2, P3, ...), the row indicates the week (week-1, week-2, week-3, ...), and the cell indicates the patient (patient id) treated on that day. For instance, assuming only 12 patients are treated per week and assuming 4 patients are treated in one day, the first row week-1 shows patients with id (40, 21, 13, 37) are treated in week-1. Patients 40 and 21 are treated in the morning session and patients 13 and 37 are treated in the afternoon session. The results of the GA schedule for a different number of machines and number of patients are shown in Table 6.4 and Table 6.5 respectively. From the results it can be seen that when the availability of machines increases, the time it takes to finish patient treatment decreases. Hence, the GA scheduler adjusts according to the number of machines minimizing patients waiting time.

Table 6.4: GA-schedule result of week-1 to week-5 schedule for the GA-parameters Npt = 12, Tpsm = 4, Nm = 1, Dwk = 5, Np = 100, Pc = 0.8, Pm = 0.25, Fs = 100, Is = 120.

	p1	p2	p3	p4
Week-1	40	21	13	37
Week-1	40	21	13	37
Week-1	40	21	13	37
Week-1	40	13	24	57
Week-1	40	13	24	57
	p1	p2	p3	p4
Week-2	40	13	24	57
Week-2	40	13	24	57
Week-2	40	13	24	57
Week-2	40	13	24	57
Week-2	40	13	24	57
	p1	p2	p3	p4
Week-3	40	13	24	57
Week-3	40	13	24	57
Week-3	40	13	24	57
Week-3	40	13	24	57
Week-3	40	13	24	57
	p1	p2	p3	p4
Week-4	40	13	24	57
Week-4	40	13	24	57
Week-4	40	13	24	52
Week-4	40	13	24	52
Week-4	40	13	24	52
	p1	p2	p3	p4
Week-5	40	13	24	52
Week-5	40	24	52	36
Week-5	24	52	36	34
Week-5	24	52	36	34
Week-5	24	52	36	34

	p1	p2	p3	p4
Week-6	24	52	36	34
Week-6	24	52	36	34
Week-6	24	52	36	34
Week-6	24	52	34	12
Week-6	24	52	12	43
	p1	p2	p3	p4
Week-7	24	52	12	43
Week-7	24	52	12	43
Week-7	24	52	12	43
Week-7	24	52	12	43
Week-7	24	52	12	43
	p1	p2	p3	p4
Week-8	24	52	12	43
Week-8	24	52	12	43
Week-8	24	52	12	43
Week-8	24	52	12	43
Week-8	24	52	12	43
	p1	p2	p3	p4
Week-9	24	52	12	43
Week-9	24	52	12	43
Week-9	24	52	12	43
Week-9	24	12	43	29
Week-9	24	12	43	29
	p1	p2	p3	p4
Week-10	24	12	43	
Week-10	12	43	29	
Week-10	12	43		
Week-10	12			
Week-10	12			

	p1	p2	p3	p4
Week-11	12			
Week-11	12			
Week-11	12			
Week-11	12			
Week-11	12			
	p1	p2	p3	p4
Week-12	12			
Week-12	12			
Week-12	12			
Week-12	12			
Week-12	12			
	p1	p2	p3	p4
Week-13	12			
Week-13	12			
Week-13	12			
Week-13	12			
Week-13	12			
	p1	p2	p3	p4
Week-14	12			
Week-14	12			
Week-14	12			
Week-14	12			
Week-14	12			
	p1	p2	p3	p4
Week-15	12			
Week-15				
Week-15				
Week-15				
Week-15				

Table 6.5: GA-schedule result of week-1 to week-5 schedule for the GA-parameters Npt = 12, Tpsm = 4, Nm = 5, Dwk = 5, Np = 100, Pc = 0.8, Pm = 0.25, Fs = 100, Is = 120.

	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12
Week-1	40	21	13	37	24	57	52	36	34	12	43	29
Week-1	40	21	13	37	24	57	52	36	34	12	43	29
Week-1	40	21	13	37	24	57	52	36	34	12		
Week-1	40	13	24	57	52	36	34	12	43	29		
Week-1	40	13	24	57	52	36	34	12	43			
	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12
Week-2	40	13	24	57	52	36	34	12	43			
Week-2	40	13	24	57	52	36	34					
Week-2	40	13	24	57	52	12	43					
Week-2	40	13	24	57	52	12	43					
Week-2	40	13	24	57	52	12	43					
	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12
Week-3	40	13	24	57	52	12	43					
Week-3	40	13	24	57	52	12	43					
Week-3	40	13	24	57	52	12	43					
Week-3	40	13	24	57	52	12						
Week-3	40	13	24	52	12	43						
	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12
Week-4	40	13	24	52	12	43						
Week-4	40	13	24	52	12	43						
Week-4	40	13	24	52	12	43						
Week-4	40	13	24	52	12	43						
Week-4	40	13	24	52	12	43						
	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12
Week-5	40	13	24	52	12							
Week-5	40	24	52	12								
Week-5	24	52	12	43								
Week-5	24	52	12	43								
Week-5	24	52	12									
	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12
Week-6	24	52										
Week-6	24	12										
Week-6	24	12										
Week-6	24	12										
Week-6	24	12										
	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12
Week-7	24	12										
Week-7	24	12										
Week-7	24	12										
Week-7	24	12										
Week-7	24	12										
	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12
Week-8	24	12										
Week-8	24	12										
Week-8	24	12										
Week-8	24	12										
Week-8	24	12										
	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12
Week-9	24	12										
Week-9	24	12										
Week-9	24											
Week-9	12											
Week-9	12											
	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12
Week-10	12											
Week-10												
Week-10												
Week-10												
Week-10												

Chapter 7 Conclusion and Recommendation

In this thesis, a specific radiotherapy targeted patient schedule optimization web and desktop app hybrid application is developed. The web application is useful for registering user and patient data and the desktop application is used to implement the proposed genetic algorithm and provide optimized schedule. The developed application alleviates the problem of scheduling with multiple constraints. In addition, it reduces the time it takes to schedule patients. The optimization prioritizes emergency patients and hence it reduces inconvenience of manual scheduling. Moreover, because the application is flexible according to the number of patients, number of machines and number of days of work, it is an ideal tool to use in radiotherapy departments in hospitals. In this thesis, best GA performances (i.e. fitness value of 88% -96.67% accuracy) were obtained for probability crossover (Pc) value between 60-80% and probability of mutation (Pm) between 20%-40%. This means if the health professional sets the cross-over and mutation probability in these ranges the scheduling will have better optimization i.e. prioritize high-risk patients, minimize high risk patient waiting time. Thus, better care for patients. From the result of GA scheduling emergency patients are able to get early treatment than radical patients, which can wait longer time for treatment. Compared to traditional manual scheduling, where scheduling is done based on patients arrival date GA based scheduling enables to prioritize higher risk patients.

The research that has been undertaken in this thesis has highlighted a number of matters on which further research would be helpful. Some areas where information is lacking were highlighted in the different chapters. Here are few ideas to consider for future works. The number of physicians, availability, machine maintenance period, and holydays are not considered. Adding these constraints may make the scheduling application more generic. Moreover, further research can be made for more objective functions and large number of constraints such as the performance of the radiotherapy machine. These and similar other issues await further investigations.

Chapter 8 References

[1] I. F. Tannock, R. P. Hill, R. G. Bristow, L. Harrington, and others, *The basic science of oncology*. Pergamon press New York:, 1987.

[2] D. E. Thurston, *Chemistry and pharmacology of anticancer drugs*. CRC press, 2006.

[3] D. Petrovic, E. Castro, S. Petrovic, and T. Kapamara, "Radiotherapy scheduling," in *Automated Scheduling and Planning*, Springer, 2013, pp. 155–189.

[4] W. Tigeneh, A. Molla, A. Abreha, and M. Assefa, "Pattern of cancer in Tikur Anbessa specialized hospital oncology center in Ethiopia from 1998 to 2010," *Int J Cancer Res Mol Mech*, vol. 1, no. 1, 2015.

[5] G. Mohan, A. H. TP, A. J. Jijo, S. D. KM, A. Narayanasamy, and B. Vellingiri, "Recent advances in radiotherapy and its associated side effects in cancer—a review," *J. Basic Appl. Zool.*, vol. 80, no. 1, pp. 1–10, 2019.

[6] K. A. Camphausen and L. R. Coia, "Principles of radiation therapy," *Brachytherapy*, 2009.

[7] C. K. Bomford, J. Walter, H. Miller, I. H. Kunkler, and S. B. Sherriff, *Walter and Miller's textbook of radiotherapy: radiation physics, therapy, and oncology*, no. Sirsi) i9780443028731. 1993.

[8] R. Ravichandran, "Radioactive Cobalt-60 Teletherapy Machine--Estimates of Personnel Dose in Mock Emergency in Patient Release during 'Source Stuck Situation,'" *J. Med. Phys.*, vol. 42, no. 2, p. 96, 2017.

[9] B. J. Healy, D. van der Merwe, K. E. Christaki, and A. Meghzifene, "Cobalt-60 machines and medical linear accelerators: competing technologies for external beam radiotherapy," *Clin. Oncol.*, vol. 29, no. 2, pp. 110–115, 2017.

[10] D. I. Thwaites and J. B. Tuohy, "Back to the future: the history and development of the clinical linear accelerator," *Phys. Med. Biol.*, vol. 51, no. 13, p. R343, 2006.

[11] H. H. W. Chen and M. T. Kuo, "Improving radiotherapy in cancer treatment: Promises and

challenges," *Oncotarget*, vol. 8, no. 37, pp. 62742–62758, 2017, doi: 10.18632/oncotarget.18409.

[12] *Basics of Planning and Management of Patients during Radiation Therapy*. .

[13] G. Delaney, S. Jacob, C. Featherstone, and M. Barton, "The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines," *Cancer Interdiscip. Int. J. Am. Cancer Soc.*, vol. 104, no. 6, pp. 1129–1137, 2005.

[14] B. Vieira *et al.*, "Radiotherapy treatment scheduling considering time window preferences," *Health Care Manag. Sci.*, vol. 23, no. 4, pp. 520–534, 2020.

[15] S. Petrovic and E. Castro, "A genetic algorithm for radiotherapy pre-treatment scheduling," *Lect. Notes Comput. Sci. (including Subser. Lect. Notes Artif. Intell. Lect. Notes Bioinformatics)*, vol. 6625 LNCS, no. PART 2, pp. 454–463, 2011, doi: 10.1007/978-3-642-20520-0_46.

[16] *Commissioning and Quality Assurance of Computerized Planning Systems for Radiation Treatment of Cancer*, no. 430. Vienna: INTERNATIONAL ATOMIC ENERGY AGENCY, 2004.

[17] O. Kramer, *Genetic algorithm essentials*, vol. 679. Springer, 2017.

[18] D. E. Goldenberg, "Genetic algorithms in search, optimization and machine learning." Addison Wesley, Reading: MA, 1989.

[19] B. W. Wah, *Wiley encyclopedia of computer science and engineering*. John Wiley, 2009.

[20] S. Katoch, S. S. Chauhan, and V. Kumar, "A review on genetic algorithm: past, present, and future," *Multimed. Tools Appl.*, pp. 1–36, 2020.

[21] Sivanandam S. N. and S. N. Deepa, *Introduction to Genetic Algorithms*. Springer, 2008.

[22] C. Meli, "Using a GA to Determine Genotype and Phenotype Relationships."

[23] N. Ariff, N. Elaiza, A. Khalid, and R. Hashim, "Selfish Gene Algorithm Vs Genetic

Algorithm : A Review Selfish Gene Algorithm Vs Genetic Algorithm : A Review," 2016, doi: 10.1088/1757-899X/160/1/012098.

[24] J.-Y. Lee, M.-S. Kim, C.-T. Kim, and J.-J. Lee, "Study on encoding schemes in compact genetic algorithm for the continuous numerical problems," in *SICE Annual Conference 2007*, 2007, pp. 2694–2699.

[25] G. Shi, H. Iima, and N. Sannomiya, "A new encoding scheme for solving job shop problems by genetic algorithm," in *Proceedings of 35th IEEE Conference on Decision and Control*, 1996, vol. 4, pp. 4395–4400.

[26] A. Kumar, "Encoding schemes in genetic algorithm," *Int. J. Adv. Res. IT Eng.*, vol. 2, no. 3, pp. 1–7, 2013.

[27] A. Costa, G. Celano, S. Fichera, and E. Trovato, "A new efficient encoding/decoding procedure for the design of a supply chain network with genetic algorithms," *Comput. Ind. Eng.*, vol. 59, no. 4, pp. 986–999, 2010.

[28] L. Zhang, *Repetitive project scheduling: Theory and methods*. Elsevier, 2015.

[29] B. Kazimipour, X. Li, and A. K. Qin, "A review of population initialization techniques for evolutionary algorithms," in *2014 IEEE Congress on Evolutionary Computation (CEC)*, 2014, pp. 2585–2592.

[30] Y. Deng, Y. Liu, and D. Zhou, "An improved genetic algorithm with initial population strategy for symmetric TSP," *Math. Probl. Eng.*, vol. 2015, 2015.

[31] Y.-W. Leung and Y. Wang, "An orthogonal genetic algorithm with quantization for global numerical optimization," *IEEE Trans. Evol. Comput.*, vol. 5, no. 1, pp. 41–53, 2001.

[32] M. Gong, L. Jiao, F. Liu, and W. Ma, "Immune algorithm with orthogonal design based initialization, cloning, and selection for global optimization," *Knowl. Inf. Syst.*, vol. 25, no. 3, pp. 523–549, 2010.

[33] B. L. Miller, D. E. Goldberg, and others, "Genetic algorithms, tournament selection, and the effects of noise," *Complex Syst.*, vol. 9, no. 3, pp. 193–212, 1995.

[34] N. Saini, “Review of selection methods in genetic algorithms,” *Int. J. Eng. Comput. Sci.*, vol. 6, no. 12, pp. 22261–22263, 2017.

[35] R. Kumar and others, “Blending roulette wheel selection & rank selection in genetic algorithms,” *Int. J. Mach. Learn. Comput.*, vol. 2, no. 4, pp. 365–370, 2012.

[36] L. D. Whitley and others, “The GENITOR algorithm and selection pressure: why rank-based allocation of reproductive trials is best.,” in *Icga*, 1989, vol. 89, pp. 116–123.

[37] K. A. De Jong, “Analysis of the behavior of a class of genetic adaptive systems,” 1975.

[38] O. Hasançebi and F. Erbatur, “Evaluation of crossover techniques in genetic algorithm based optimum structural design,” *Comput. Struct.*, vol. 78, no. 1–3, pp. 435–448, 2000.

[39] S. G. Varun Kumar and R. Panneerselvam, “A study of crossover operators for genetic algorithms to solve VRP and its variants and new sinusoidal motion crossover operator,” *Int. J. Comput. Intell. Res.*, vol. 13, no. 7, pp. 1717–1733, 2017.

[40] R. Kala, *On-road intelligent vehicles: Motion planning for intelligent transportation systems*. Butterworth-Heinemann, 2016.

[41] D. Beasley, D. R. Bull, and R. R. Martin, “An overview of genetic algorithms: Part 2, research topics,” *Univ. Comput.*, vol. 15, no. 4, pp. 170–181, 1993.

[42] O. Abdoun, J. Abouchabaka, and C. Tajani, “Analyzing the performance of mutation operators to solve the travelling salesman problem,” *arXiv Prepr. arXiv1203.3099*, 2012.

[43] N. Soni and T. Kumar, “Study of various mutation operators in genetic algorithms,” *Int. J. Comput. Sci. Inf. Technol.*, vol. 5, no. 3, pp. 4519–4521, 2014.

[44] P. Larranaga, C. M. H. Kuijpers, R. H. Murga, I. Inza, and S. Dizdarevic, “Genetic algorithms for the travelling salesman problem: A review of representations and operators,” *Artif. Intell. Rev.*, vol. 13, no. 2, pp. 129–170, 1999.

[45] T. Kapamara, K. Sheibani, O. C. L. Haas, C. R. Reeves, and D. Petrovic, “A review of scheduling problems in radiotherapy,” in *Proceedings of the Eighteenth International Conference on Systems Engineering (ICSE2006), Coventry University, UK*, 2006, pp. 201–

207.

[46] S. Petrovic, W. Leung, X. Song, and S. Sundar, “Algorithms for radiotherapy treatment booking,” in *25th Workshop of the {UK} planning and scheduling special interest group*, 2006, pp. 105–112.

[47] P. P. Bruyant, “Analytic and iterative reconstruction algorithms in SPECT,” *J. Nucl. Med.*, vol. 43, no. 10, pp. 1343–1358, 2002.

[48] E. Castro and S. Petrovic, “Combined mathematical programming and heuristics for a radiotherapy pre-treatment scheduling problem,” *J. Sched.*, vol. 15, no. 3, pp. 333–346, 2012.

[49] E. K. Burke, P. Leite-Rocha, and S. Petrovic, “An integer linear programming model for the radiotherapy treatment scheduling problem,” *arXiv Prepr. arXiv1103.3391*, 2011.

[50] D. Petrovic, M. Morshed, and S. Petrovic, “Multi-objective genetic algorithms for scheduling of radiotherapy treatments for categorised cancer patients,” *Expert Syst. Appl.*, vol. 38, no. 6, pp. 6994–7002, 2011.

[51] D. Conforti, F. Guerriero, and R. Guido, “Optimization models for radiotherapy patient scheduling,” *4OR*, vol. 6, no. 3, pp. 263–278, 2008.

[52] P. Vogl, R. Braune, and K. F. Doerner, “Scheduling recurring radiotherapy appointments in an ion beam facility,” *J. Sched.*, vol. 22, no. 2, pp. 137–154, 2019.