Optimal Multi-Drug Chemotherapy Control Scheme for Cancer Treatment

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Optimal Multi-Drug Chemotherapy Control Scheme for Cancer Treatment

Design and development of a multi-drug feedback control scheme for optimal chemotherapy treatment for cancer. Evolutionary multi-objective optimisation algorithms were used to achieve the optimal parameters of the controller for effective treatment of cancer with minimum side effects.

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Table of Contents

List of Figures

List of Tables

Abbreviations

GA	Genetic Algorithm
PID	Proportional, Integrative and Derivative
I-PD	Integrative, Proportional and Derivative
MDR	Multi-Drug Resistance
DNA	Deoxyribonucleic Acid
G1	Growth
S	DNA synthesis
G2	Secondary Growth
M	Mitosis
G0	Quiescent
MOGA	Multi-Objective Genetic Algorithm
PSO	Particle Swarm Algorithm
MOPSO	Multi-Objective Particle Swarm Algorithm
MA	Memetic Algorithm
OCP	Optimal Control Problem
Rep	Repeated
Cont	Continue
SSD	Steady Size Distributions
AEGA	Iterative Dynamic Programming
IDP	Iterative Dynamic Programming

P-gp	P-glycoprotein
PK	Pharmacokinetics
ODE	Ordinary Differential Equation
AEGA	Adaptive Elitist- Genetic Algorithm

Abstract

Cancer is a generic term for a large group of diseases where cells of the body lose their normal mechanisms for growth so that they grow in an uncontrolled way. One of the most common treatments of cancer is chemotherapy that aims to kill abnormal proliferating cells; however normal cells and other organs of the patients are also adversely affected. In practice, it's often difficult to maintain optimum chemotherapy doses that can maximise the abnormal cell killing as well as reducing side effects. The most chemotherapy drugs used in cancer treatment are toxic agents and usually have narrow therapeutic indices, dose levels in which these drugs significantly kill the cancerous cells are close to the levels which sometime cause harmful toxic side effects.

To make the chemotherapeutic treatment effective, optimum drug scheduling is required to balance between the beneficial and toxic side effects of the cancer drugs. Conventional clinical methods very often fail to find drug doses that balance between these two due to their inherent conflicting nature. In this investigation, mathematical models for cancer chemotherapy are used to predict the number of tumour cells and control the tumour growth during treatment. A feedback control method is used so as to maintain certain level of drug concentrations at the tumour sites. Multi-objective Genetic Algorithm (MOGA) is then employed to find suitable solutions where drug resistances and drug concentrations are incorporated with cancer cell killing and toxic effects as design objectives. Several constraints and specific goal values were set for different design objectives in the optimisation process and a wide range of acceptable solutions were obtained trading off among different conflicting objectives.

In order to develop a multi-objective optimal control model, this study used proportional, integral and derivative (PID) and I-PD (modified PID with Integrator used as series) controllers based on Martin's growth model for optimum drug concentration to treat cancer. To the best of our knowledge, this is the first PID/I-PD based optimal chemotherapy control model used to investigate the cancer treatment. It has been observed that some solutions can reduce the cancer cells up to nearly 100% with much lower side effects and drug resistance during the whole period of treatment. The proposed strategy has been extended for more drugs and more design constraints and objectives.

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Publications

Chapters in Books

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- S. Alam, S. Algoul, A. Hossain and M. A. Majumder, (2010): "Multi-objective Particle Swarm Optimisation for Phase Specific Cancer Drug Scheduling", *Lecture Notes of Computer Science*, Springer Verlag, Berlin.

Journal Publications

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- S. Algoul, A. Hossain, and M. A. Majumder,(2009) Optimization an d Scheduling for Chemotherapy to Control Tumour Growth, IJMID, Medical and Engineering, Vol 4, abstract, Miami, USA .

Conference Contributions

- S. Algoul, A. Hossain, and M. A. Majumder, Multi-drug optimization and scheduling for chemotherapy to control tumour growth, 9th Informatics Workshop, University of Bradford, 2008, p. 33-35, Bradford, United Kingdom.

- S. Algoul, A. Hossain, and M. A. Majumder,(2009) Optimization and Scheduling for Chemotherapy to Control Tumour Growth, SBEC, Springer, Vol.24,p.371-376, Miami, USA.
- S. Algoul, S. Alam, M. Hossain, M. A. Majumder, (2010) ”Feedback Control of Chemotherapy Drug Scheduling for Phase Specific Cancer Treatment” *The IEEE Fifth International Conference on Bio-Inspired Computing: Theories and Applications (BIC-TA 2010),* IEEE xplore, Vol 2, p.1443-1457, Liverpool, United Kingdom.
- S. Alam, S. Algoul, A. Hossain and M. A. Majumder (2010) "Multi-objective Particle Swarm Optimisation for Phase Specific Cancer Drug Scheduling", The IEEE First International Conference on Computational Systems-Biology and Bioinformatics (CSBio), pp. 180-192, Bangkok, Thailand, (**CSBio 2010 Best Paper Award).**
- S. Algoul, S. Alam, M. Hossain, M. A. Majumder, (2010) “Multi-Objective Optimisation for Multi-Drug Chemotherapy Scheduling”. *The IEEE 13 International Conference on* Computer and Information Technology *(ICCIT - 2010),* pp. 464-469, Dhaka, Bangladesh.
- S. Algoul, M. Hossain, M. A. Majumder, S. Alam (2011) “Performances of the GA and PSO Algorithms for Phase Specific Optimal Treatment for Cancer”. *The IEEE 14 International Conference on* Computer and Information Technology *(ICCIT - 2011),* Dhaka, Bangladesh, 22- 24 December 2011 (to appear).

CHAPTER 1

Introduction

1.1 Background

Cancer is a generic term for a large group of diseases where cells of the body lose their normal mechanisms for growth so that they grow in an uncontrolled way (cancer research UK, 2011). (T. Kirkwood, 2005). Cancer is a leading cause of death worldwide – nearly 12.7 million new cancer cases and 7.6 million cancer deaths (around 13% of all deaths) occurred in 2008. According to World Health Organization (WHO, 2011), the main types of cancer are: lung cancer, stomach cancer, liver cancer, colorectal cancer and breast cancer. The most commonly diagnosed cancers worldwide are breast, lung, colorectal and prostrate cancers, which constitute over half of all new cases diagnosed as shows Figure 1.1 (A. Rachel, 2009). The most common causes of cancer death are lung, stomach and liver cancers (Cancer Research UK, 2011). More than 70% of all cancer deaths occurred in low- and middle-income countries. Deaths from cancer worldwide are projected to continue to rise to over 11 million in 2030 (WHO, 2011).

Every year, more than 285,000 people are diagnosed with cancer in the United Kingdom, and the current estimate is that more than one in three people will develop a form of cancer at some point in their lifetime (Rachel, 2009). Around 309,500 people were diagnosed with cancer in the UK in 2008; this equates to around 504 cases for every 100,000 people (Cancer Research UK, 2011).

Cancer is an abnormal growth of cells caused by multiple changes in gene expression leading to dys-regulated balance of cell proliferation and cell death, and ultimately into a population of cells that can invade tissues and metastasize to distant sites. Cancer refers to a set of disease where normal cells of the body lose their mechanisms which are responsible for controlling their growth and motility. Cancer cells typically proliferate in an exponential fashion, the size of the cancerous mass is measured experimentally as a volume, though this mass is often referred to in terms of the number of cells 10^9 (Martin and Teo, 1994).

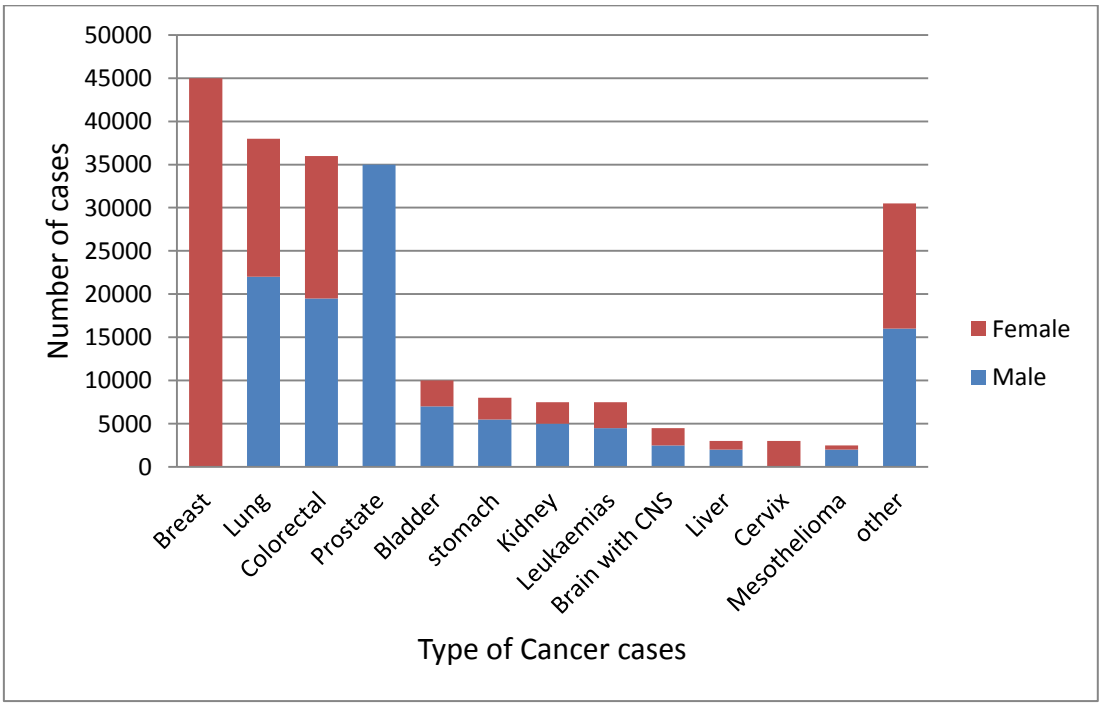

Fig. 1.1 The most commonly diagnosed cancers in the United Kingdom 2004 (Rachel, 2009).

The main treatment of cancer includes surgery, radiotherapy, chemotherapy, hormone therapy, bisphosphonates, bone marrow and stem cell transplants, and biological, therapies. Chemotherapy is one of the essential and common treatments methods for cancer, these drugs treatment (i.e. treatment with cell killing (cytotoxic) drugs). Patients may have just one chemotherapy drug or a combination of different chemotherapy drugs. There are many

different drugs currently available and new ones are being developed all the time. These drugs are often used as part of multimodality therapy that is along with surgery and/or radiotherapy to achieve and maintain remission. The process is likely to be long term where single agents or combination chemotherapy are given at intervals in pulsed doses or in cycles and are highly dependent upon the tumour type and characteristics. Monitoring of the patient takes place throughout the process, so that tumour response to therapy or incidences of tumour progression can be tracked and treatment aims adjusted accordingly.

The treatment given for cancer is highly variable and dependent on a number of factors including the type, location and amount of disease and the health status of the patient. The treatments are designed to either directly kill/remove the cancer cells or to lead to their eventual death by depriving them of signals needed for cell division. Other treatments work by stimulating the body's own defences. There are many cancer drugs existing and over 50 chemotherapy drugs that are commonly used (Robert, et al., 1998, Mahtani, 2010). Table 1.1 includes some of the examples of chemotherapy drugs, how they administrated, their usage of the drug and their various side effects. Side effects may occur just after treatment (days or weeks) or they may occur later (months or years) after the chemotherapy has been given (Richard, et al., 1996, Robert, et al., 1998, Michael, 2001, Mahtani, 2010).

Table: 1.1 Chemotherapy drugs used in cancer (M. Neal, 2005)

Group	Example	Mode of action
Alkylating agent	Chlormethine, cyclophosphamite, chlorambucil, cisplatin and busulphan	Act with the bases in DNA and prevent cell division by cross-linking the two stands of double helix.
Antimetabolite	Methotrexate and fluorouracil	Inhibits dihydrofolate reductase. Inhibits thymidylate synthetase.
Antibiotic	Doxorubin, dactinomycine and bleomucin	Intercalate between base pairs block RNA production. Degrades DNA by formation free radicals.
Vinca alkaloids	Vincristine, vinblastine and paclitaxel	Inhibit mitosis by binding to the micro-tubular proteins necessary for spindle formation.
Monoclonal ant-bodies	Trastuzumab and rituximab	Act with antigen specifically expressed on cancer cells.

The main aim of chemotherapy is to minimise/eliminate the number of cancer cells after a number of fixed treatment cycles with minimum toxic side effects. A cell is considered cancerous when it has lost its mechanism to divide normally. Traditionally one or more chemotherapy cancer drugs are infused to the body depends of the needs. The efficiency of the doses of the treatment is often measured as the interval of time from the start of therapy, until the end of treatment.

Chemotherapy creates a damaging range of side-effects as shows Table 1:2, and so it is normally given in cycles of treatment which alternate with rest periods, to allow the body to recover. Several cycles of treatment are needed, as chemotherapy only attacks cells that are actively dividing. At any one time, some cancer cells will be dormant, and may not be killed until a later round of drug treatment. The number and duration of these rounds depends on many factors including the type of cancer, how advanced it is, and the general health of the patient being treated (i. e, patient suffering from other diseases).

Table: 1.2 Effect of cytotoxic drugs (L. John, et al., 1993)

Drug	Mechanism	Specific adverse effects	Indications
Cyclophosphamide	Alkylating agent	Haematuria, cystitis	Haematological malignancy, solid tumour
Doxorubicin	Antibiotic	Alopecia, cardiac arrhythmia, local tissue necrosis	Wide range of Haematological
Cisplatin	Interacts with DNA	Neurotoxicity Nephrotoxicity Vomiting	Wide range of solid tumours, including lung, ovarian and testicular carcinoma
Bleomycin	Antibiotic	Pulmonory fibrosis, skin rashes	Lymphomas, testicular tetratoma, squamous cell carcinoma
Methotrexate	Antimetabolite	Mucositis	Leukaemia

The oldest documented in the world about the case of cancer disease was written in Egypt by ancient Egyptians, in 1500 b. c. The details about eight cases of the cancer disease occurring on the breast were recorded and treated by cauterization, a method to destroy tissue with a hot instrument called "the fire drill". (F. Lisa, 2009). There is evidence that the ancient Egyptians were able to tell the difference between malignant and benign tumours. According to inscriptions, surface tumours were surgically removed in a similar manner as they are removed today.

Recently, so much information is available about the human body. Hippocrates believed that the body was composed of four fluids: blood, phlegm, yellow bile and black bile. He believed that an excess of black bile in any given site in the body caused cancer. This was the general thought of the cause of cancer for the next 1400 years. In ancient Egypt, it was believed cancer was caused by the Gods (www.cancer.org, 2011, F. Lias, 2009).

Today, the human body has been described each organ separately and in very small details. The scientists now dealing with small part of the organ (called cell), the scientists are very lucky now because of the information which they got about the cancer disease, so many

researchers in different areas are working together side by side to find the best treatment of this disease. Many mathematical models created and developed for the tumour cells proliferating and their behaviours, before and after the period of treatment.

Researchers have designed optimal drug schedules of cancer chemotherapy and developed many mathematical models to predict tumour growth after the administration of chemotherapy. A number of models have been used to characterise the evolution and effects of treatment on cancer (Westman, et al., 2001; Liang, et al., 2006; Ochoa, et al., 2007) to reduce the side-effects. There are several reasons why a good mathematical model is very useful. For example, in animals the disease may take months to run its course, and in human, years also the clinical trials are costly and limited (R. Frank, 2011). It is often quicker and cheaper to formulate a mathematical model and simulate it on computer than perform a laboratory experiments or clinical trials (Martin and Teo, 1994). Martin (1992) proposed an optimal drug scheduling model and established numerical solution technique known as the control parameterisation and analytical gradients to construct a mathematical model with all constraints of cancer drug chemotherapy treatment.

Considering the complexity of designing a schedule that achieves certain goals whilst moderating the cancer drug's toxic side-effects, the idea of providing computer-based decision support system is appealing. The proposed Genetic algorithms (GAs) as a search tool in a decision support system for designing chemotherapy schedules. Using an underlying mathematical model that captures the essential qualitative features of a cancer tumour, the purpose is to use chemotherapy to control the system, and drive it into a desirable (minimal) tumour level after which the body could eliminate the remaining cancerous cells. This problem can be formulated as an optimisation problem and refers to a problem of finding a

control scheme for a given dynamic system, such that a certain optimality criterion is achieved.

In general, most chemotherapy drugs used in cancer treatment are toxic agents and usually have narrow therapeutic indices; dose levels in which these drugs significantly kill the cancerous cells are close to those levels which sometime cause harmful toxic side effects. Therefore, effective drug scheduling requires suitable balancing between the beneficial and toxic side effects.

Conventional clinical methods very often fail to find drug doses that balance between these two due to their inherent conflicting nature. The purpose is to design and implement a method of chemotherapy drug scheduling that can provide solutions trading-off between the cell killing and toxic side effects during the whole period of treatment. The model designed to control the drug to be infused to the patient's body using optimisation techniques to find suitable/acceptable drug concentration at tumour site and parameters of the controller.

1.2 Uncertainty in Optimal Treatment Model

The chemotherapy cancer drug treatment is very sensitive due to various uncertainty issues involve in the treatment process. Among these issues, the most important two are: *(i)* uncertainty due to the sensitivity of the patient and *(ii)* uncertainty associated with the drug administration process. This research focuses in chemotherapy cancer treatment through optimal drug administration in which risk could be stimulated due to optimisation through probability based Genetic Algorithm model. The Genetic Algorithm is used to tune the controller parameters to find the suitable value of each parameter for optimal solution. In this investigation, to avoid any uncertainty in the model, the optimisation process was run for

many generations in order to minimise all objectives simultaneously in an offline manner. Solutions not satisfying design constraints are penalised with very high values called penalty function. This penalty function reduces the probability of solutions yielding unacceptable values along any design objectives dominate the optimisation process, and on the contrary, favour acceptable solutions can be selected for reproduction that in turn may generate better solutions in subsequent generations. In optimisation process, non-dominated solutions called Pareto optimal set and corresponding decision variables are updated and preserved at the end of each generation. The parameters of the offline optimisation process are then applied to the proposed control model to test and validate the proposed scheme. Thus, the proposed scheme is considered to overcome the uncertainty factor for the treatment model. However, the uncertainty or risk associated with patient is beyond the scope of this research and is considered for future investigation.

1.3 Motivation

Cancer is a disease caused by normal cells, when start changing and growth in an uncontrolled way. The uncontrolled growth causes a lump called a tumour. There are over 200 different types of cancer; many people diagnosed that have one of these particular type of cancer disease every year. The survival time of the cancer patients is between 5 and 10 years time period after diagnosed initial diagnosis (cancerhelp.cancerreasechuk, 2011). There is no cure or perfect drug or treatment has been invented yet for cancer, so it is important to undertake research in this field to save lives of many people. There is a need to design, develop and implement the strategies of the cancer chemotherapy treatment in order to help the patients by balancing between the drug effectiveness and the side-effects. The idea is to

minimise the number of cancer cells of the patient, using a number of fixed of treatment cycles, and targeting minimum toxic side effects.

An automatic system of drug scheduling infused to the patient body can be reliable and safer than a manual one (Ronda and Blegen, 2008). This can be achieved by different approaches of treatments like single drug or multi-drug to increase the quality and the effectiveness of the chemotherapy treatment by decreasing the chance of the cancer cells resistance to the drug and eliminating any toxic side-effects of the treatment. Furthermore, the models for cancer chemotherapy treatment can be used to predict tumour growth and control the disease during the course of treatment by minimising the number of cancer cells and maximising the survival time of the patient. Control systems theory has been extended into many fields, medicine is not an exception, although the progress is slow in some cases due to particular challenges encountered by the inherent of the nature complexity of biological system (Ronda and Blegen, 2008). After more than three decades of research in this filed, still there is little points have been considered in the actual clinical environment. The main motivation of this research is to give this area another push towards this goal.

Current clinical practice involves manual regulation to infuse drugs into the patient's body. Programmable pumps are also used to either deliver the drugs at a constant rate or a variable rate to achieve a desired concentration. Control of such pumps is based on averaged pharmacokinetic data and is essentially open loop, requiring regular intervention by the attending physician or nurse to adjust the drug flow rates. It is desirable to have an automated system that closes the loop on primary variables, but monitor secondary variables and helps the physician to perform diagnosis. This would allow the physician to spend more time monitoring the patient conditions that are not easily measured and assure that the physician is

always “in the loop”. The physician would use his/her expertise to diagnose the patient, specify set points or ranges of values for the states to be regulated, close the drugs best suited to obtain the objective, and mandate permissible infusion rates, this information would then be explicitly used by the controller to automate the regulation of physiological states.

The close loop control system for the drug administration is the target in investigations as the drug is the main player in this work. Moreover, by applying optimal volumes of drug doses to the patients will meet the desired impact of cancer treatment. The main aim is to design mathematical models to control cancer chemotherapy treatment by scheduling the cancer drug during the whole period of treatment cycle. Therefore, the focus of this research will be in the area of drug scheduling to achieve the objectives by making the treatment more efficient in maximising the cancer cells killing and minimising the toxic side effect.

1.4 Aims and Objectives

The most important target of this investigation is to design and implement a model for optimal drug control scheme for cancer in order to meet the desired impact of cancer chemotherapy treatment. The development of optimal chemotherapy control model to minimise/eliminate the cancer cells after a number of fixed treatment cycles with minimum toxic side effects in order to improve the quality of life to the cancer patient. Moreover increases the effectiveness of greater cell kill by combining different type of cancer chemotherapy drug, decreases the chance of drug resistance by using drug combination and reduces any toxic side effects, also maximising the survival time of the patient life.

The cancer tumour model should be designed based on the cancer cells functions in order to show the effects of drug on different cell populations, drug concentration and toxic side effects. The using of multi-objective optimisation approach could generate a wide range of solutions that trade-off between cell killing and toxic side effects and satisfy associated goals of chemotherapy treatment. Depending on the physiological state of the patient and state of the cancer, the oncologist can pick the right solution suitable for the patient.

In order to achieve the aim, this study undertakes the following strategies to:

- Make the treatment more effective by balancing between the beneficial and the side-effect of the treatment. Understanding the system of the cancer cell (i. e, the function and life cycle) is required and a description of the effects of the chemotherapy treatment (i. e, maximising tumour cell killing, minimum toxicity and tolerable drug concentration) must be balanced to achieve the designing and implementing of the models.
- Design, develop and implement mathematical and computational models for cancer chemotherapy to predict the number of tumour cells and control the tumour growth during treatment. Developing these models and demonstrating the interactions between tumour and normal cells can affect the outcome of the treatment and the ability for a tumour to recur, which requires an understanding of the system in absence of treatment and a description of the treatment effects
- Develop controller to control the dosage of drug during the period of the treatment cycle to give the system more reliability by monitoring, and control the growth of tumour cells and the drug side-effect toxic.

- Optimise chemotherapy scheduling to increase the effectiveness of the cancer treatment chemotherapy and decrease the resistance of the treatment during the treatment cycle, in turn reduce the chance of the side-effect toxic.

1.5 Organisation of the Thesis

- Chapter 1 (Introduction) presents background and history about the cancer, motivation, the aims and objective of my work.
- Chapter 2 (literature review) introduces the literature review about the cancer disease including cancer growth modelling, optimal chemotherapy for cancer treatment, cells phase specific and non phase specific, combination of chemotherapy regime and drug resistance.
- Chapter 3 (Methodology) presents the proposed cancer treatment methodology, mathematical model for cancer drug scheduling, non phase specific, phase specific, four compartments, eight compartments, PID controller and optimisation techniques Multi-Objective Genetic algorithm (MOGA).
- Chapter 4 (Experiments and result) provides an overview and the results which have been implemented about non phase specific treatment, phase specific cancer cell treatment, four compartments model and proposed control sachem for eight compartments model.
- Chapter 5 (Comparative study) presents the comparisons of results produced by the systems implemented for non phase specific, phase specific with exist results, comparative between MOGA and Multi-Objective Particle swarm algorithm (MOPSO) phase specific model has been included as well, four compartment cancer cells model and eight compartment cancer cells model also covered in this Chapter.

- Finally, Chapter 6, includes the thesis conclusion, contributions and future direction of this research

CHAPTER 2

Literature Review

2.1 Introduction

Many mathematical models have been developed to describe the growth and control of tumours (Martin and Teo, 1994, Westman et al., 2002, Dua, 2008). These models considered the effect of the drug as well as the reactions of the cancer cells to chemotherapy treatment. These mathematical models are basically ordinary differential equations that describe the growth of the cancer cells along with the effects of chemotherapy treatment.

Mathematical models of cancer chemotherapy can demonstrate the interactions between tumour and normal cells, outcome of the cancer drug chemotherapy treatment and the ability for a tumour to recur (Panetta, 1996). The tumour cell population may be calculated from tumour volume measurements, since there is an approximately linear relationship between tumour volume and cell number (Stephens and Peacock, 1977).

A mathematical model can be used to model the growth of tumour cancer cells, provided that an initial tumour cell population is specified together with some general assumptions about the way in which the tumour grows. The purpose of using mathematical models of cancer chemotherapy is to predict and control the course of the disease when a given treatment is being used.

Also mathematical models are used to find the optimal cancer chemotherapy protocols which could minimise the number of the tumour cells to the minimum level with less side-effect by different optimisation methods. There are some numerical solution techniques that have been established to construct a mathematical model with all constraints (Martin and Teo, 1994).

The understanding of the system and a description of the effects of the treatment is required when designing and developing of the model which is desired to balance the benefits of the conflicts. The developing of the mathematical model in order to demonstrate the interactions between tumour and normal cells can affect the outcomes of the treatment and the ability for a tumour to recur. The main aspect of this review is to highlight the advantages which have been achieved, to avoid the weaknesses of the previous models identified and finally to propose new models to improve cancer treatment.

The aim of this Chapter is to conduct a literature review on cancer growth model, optimal chemotherapy for cancer model, phase specific and non-phase specific treatment models, combination of chemotherapy regimen, and mechanism and implications of drug resistance, related to the objectives of this study. The main aim is to predict the cancer cells populations and the growth rate of the cancer cells in order to estimate the treatment cycles. Some of the treatment models consider the cancer cells as a one compartment meaning that the behaviours of all cancer cells are similar. The balance between the benefits of the treatment in this case is to reduce the side-effects of the treatment. The proliferating cells at the tissue level are considered as active cancer cells and need to be treated by dividing them into two compartments (Proliferating and Quiescent cells) called cell phase specific model. The drug resistance has not been taken in account on the last two types of cancer

chemotherapy treatment models introduced by Martin and Liang (Martin and Teo, 1994, Liang et al, 2006). The multi-drug regimens models are designed to avoid the weaknesses of the previous cancer treatment models relating to the resistance of the cancer cells to the cancer drug. The cancer cells are divided into four and eight compartments and can be expended to more compartments based on the sensitivity of the cancer cell to drug.

2.2 Cancer Growth model

Cancer refers to a set of disease where normal cells of the body lose their mechanisms which are responsible for controlling their growth and motility. Cancer cells typically proliferate in an exponential fashion, the size of the cancerous mass is measured experimentally as a volume, though this mass is often referred to in terms of the number of cells 10^9 (Martin and Teo, 1994). The cancer cells growth as known in groups called tumours. A tumour is characterised by the number of cells or the size of tissue it contains, and the growth characteristics of individual normal cells within a tumour are influenced by the neighbouring cancer cells. The cell cycle is a sequence of phases that both normal and malignant cells undergo from their birth to death; consist of five stages as shown in Figure 1.2 in Chapter 1 (Liang, et, el, 2008). The tumour cell population may be calculated from tumour volume measurements, since there is an approximately linear relationship between tumour volume and cell number (Martin and Teo, 1994).

The tumour cell population may be calculated from tumour volume measurements, since there is an approximately linear relationship between tumour volume and cell number. A mathematical model used to predict and control the growth of tumour provide that an initial tumour cell population is specified together with some general assumptions about the way in which the tumour is growing which called a ordinary differential equation (ODE). The

mathematical models of cancer chemotherapy are to predict and control the course of the disease when a given treatment is being used. There are three growth models used to simulate and predict different type of tumour growth introduced by Martin, these include Gompertz, Logistic and exponential (Westman, et al., 2002). For all three models the initial tumour burden is 10^{10} cells and the initial tumour population doubling time is 4 weeks as shows Figure 2.1 (Martin and Teo, 1994).

$\acute{N}(t) = \lambda_E N$ *exponential* *(1)*

$\acute{N}(t) = \lambda_L N (1-N/\theta)$ *logistic* *(2)*

$\acute{N}(t) = \lambda_G N \ln(\theta/N)$ *Gompertz* *(3)*

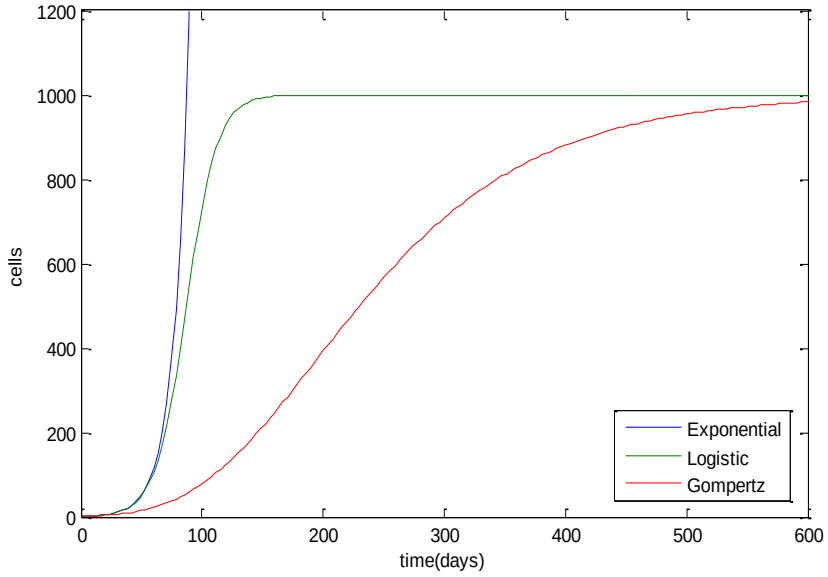

Fig. 2.1 Different models of calculating the cell populations

2.3 Optimal Chemotherapy for Cancer Treatment

Many studies proposed algorithms to design an optimal chemotherapy drug protocol for the treatment of cancer (Costa, et al., 1992, Martin and Teo, 1994, Bojkov, et al., 1993, Liang, et al., 2006). The target was to optimise the number of the treatment cycles and the drug doses. A mathematical model is employed in the form of ordinary differential equations controlling cancer tumour growth on a cell population level.

The most types of the cancer diseases are formulated for optimal control problems with a set of dynamic differential equations in the state space form (Neilan and Lenhart, 2010). The objectives functions are considered to minimise the tumour size as well as treatment side-effects under a set of constraints using optimisation techniques. Also, the drug resistant effect is considered on some models in the optimal treatment schedule (Westman, et al., 2002). The optimal cancer chemotherapy protocols are chosen to minimise the number of the tumour cells with less side-effect by different optimisation methods.

Alam and co-workers in (2010) developed a method of phase specific drug scheduling using a close-loop control method and multi-objective particle swarm optimisation algorithm (MOPSO) that can provide solutions for trading-off between the cell killing and toxic side effects. A close-loop control method, namely Integral-Proportional-Derivative (I-PD) is designed to control the drug to be infused to the patient's body and MOPSO is used to find suitable parameters of the controller. A phase specific cancer tumour model is used for this work to show the effects of drug on tumour.

An important target for cancer chemotherapy treatment is to maximise the cancer cells killing for a fixed treatment cycle. So, the drug scheduling of cancer chemotherapy treatment is essential for successful treatment. (Martin, 1992) proposed an optimal drug scheduling model and a numerical solution technique known as the control parameterisation and analytical gradients to construct a mathematical model with all constraints cells killing, side-effect and drug concentration of cancer drug chemotherapy treatment. Numerical solutions suggest that the best way of reducing the tumour burden after a fixed period of treatment is to keep the rate of decrease of the tumour size to a minimum initially, and then give high-intensity treatment towards the end of the treatment period.

The results were improved by Bojkov, et al., (1993), who used an intuitive approach coupled with the direct search procedure proposed in Luus (1998). Based on approaches of random numbers and search region contraction, a method of direct search optimisation was applied to solve the problem (Luus, 1995).

Carrasco and Banga (1998) proposed an adaptive stochastic algorithm to find the optimal control policy for cancer drug scheduling to maximise the killing of the tumour cells as measured at some particular time in the future. They suggested that drug concentration must be kept at the tolerable level throughout the treatment period and the cumulative toxicity effect of the drug must be kept below the ultimate tolerance level.

Swan in (1998) introduced two basic theoretical models, which demonstrated cancer growth under the action of a continuously delivered anticancer drug. The therapeutic objective is to obtain the nature of the control agent that can drive the tumour population to a desired level so as to decrease excessive usage of the drug and to keep deviations of the

tumour population from the desired level to a minimum. While the drug resistance which the key of the successful chemotherapy treatment did not consider.

Tan et al., (2001) presented an optimal control of drug scheduling in cancer chemotherapy using a distributed evolutionary computing software solutions called "Paladin-distributed evolutionary algorithm". The simulation result for the problem with and without point constraints confirmed the effectiveness of the proposed approach by producing control policies of the drug scheduling in cancer chemotherapy. The proposed evolutionary optimisation methodology is capable to automatically find near optimal solution for complex cancer chemotherapy problem. However, this solution does not take into all patients' situations as fixed parameters have been considered only.

Liang et al, (2005) demonstrated an anticancer drug scheduling model with different toxic elimination processes. The author also presented a sophisticated automating drug scheduling approach based on evolutionary computation and computer modelling. Also Liang et al, (2006) further introduced a customised optimal control model of drug scheduling in cancer chemotherapy and a new adaptive elitist population based genetic algorithm (AEGA) to solve it. These solutions did not consider the drug resistance which is key for a successful treatment. There are many researchers carried on the work to find the optimum solutions using different control techniques for example (Optimal Control Problem (OCP)) (Costa, 1992, Westman, et al., 2002, Basdevan, et al., 2004).

Optimal control is the standard method for solving dynamic optimisation problems, when these problems are expressed in continuous time. Treatment of cancer disease process can be interpreted as the optimal control of a dynamic system. Evolution of the disease is

characterised by a non-linear, ordinary differential equation that describes the stage of the disease, by predicting the number of tumour cancer cells.

Alexandru and Carmen (2003) presented an optimal control problem model of cancer chemotherapy drug scheduling, using a feedback adaptive neural network control. This method is valid for all classes of pharmacokinetical models. It has been proved that the feedback controller for drug scheduling approach is capable of automatically solving complex cancer chemotherapy problems in a realistic manner.

Hassani and Naghihi (2010) presented an optimal control problem of chemotherapy drug scheduling doses for patients with progressive cancer. The optimal control problem is used to design an effective drug schedule to reduce the size of the tumours in a time optimal fashion. Performance evaluation of the proposed algorithm has been performed by simulating the mathematical model of tumour cells interacting with immune system. Although the dynamic model of ordinary differential equations was implemented for the simulation of dynamic environment and reward signal, showing the ability of reinforcement learning (RL) algorithms in solving optimal control problems was the main purpose.

Even though there are many options of treatment for cancer patients such as surgery, chemotherapy, immunotherapy, radiotherapy and the combination of these options, all of them are not perfect treatments because cannot eliminate the cancer cells totally. The life expectancy of the cancer patients will be diminished due to the disease and quite possibly for the adverse effects of treatments as well. These treatment rules cannot in general provide a cure for cancer but may bring about remission that can later relapse (R. Webster, 2002). The effects of these treatments can vary from cancer to cancer and individual to individual, which

further complicates the situation for effective eradication of cancer in any given patient (Westman, et al, 2002). All these models did not consider the cell compartments that means all the cells will be affected by the cancer chemotherapy treatment even the normal cells, so the normal cells needs some rest after a period of treatment in order to recover from the drug toxic effect to start the next cycle of treatment.

The existing multi-drug cancer chemotherapy models are to control the growth of the tumour effectively and minimise drug resistance and toxicity. Using mathematical modelling helps us to design a model for tumour population to meet the requirements of the treatment, and to balance the benefits of the treatment. Different compartmental models based on the cells function are also existed and used to explore the effects of chemotherapy cancer drug throughout the period of treatment.

2.4 Phase specific and Non-phase specific Treatment Models

The most important challenge of cancer treatment is to maintain the normal physiological states of the patient's body system during the course of different treatment schedules. This can be achieved by optimising chemotherapy treatment in such a way as to reduce tumour burden to a minimum level with minimum/acceptable toxic side-effects. The other factors considered in chemotherapy include the stage of the diseases, scheduling of the therapy and interaction of the drugs (Martin and Teo, 1994).

The mathematical models of tumour responses for chemotherapy are widely used to predict the tumour responses and to design the drug dosages. The models are generally developed based on a set of differential equations. The purpose of using mathematical models

of cancer chemotherapy is to predict and control the course of the disease when a treatment is used.

Mathematical models of cancer chemotherapy treatment are designed and implemented to predict and control the growth of the cancer cells and demonstrate the interactions between tumour and normal cells which can affect the outcome of the treatment and the ability for a tumour to recur (Martin and Teo, 1994, Barbolosi and Iliadis, 2000). These mathematical models can be categorised by the number of compartments, for example, in one compartment models for the chemotherapy treatment, the various types of cancer cells are thought of as single types of cancer cells which are all included in the growth fraction.

Martin and Teo (1994) used control parameterisation and analytical gradients to find optimum drug schedules with all many constraints related to toxicity, drug concentration and tumour growth. Panetta (1999) developed a model to show how to determine an effective treatment, how combination of chemotherapy should be delivered and how this model may help to develop more effective cancer chemotherapeutic treatments. These models designed for limited number of drug combination which is made the chance of the drug resistance exist.

Barbolosi and Iliadis, (2000) considered the single compartment model for the cancer chemotherapy treatment and two compartments are used for the pharmacokinetics for the drug concentrations as well as a model that considers white blood cells to impose a toxicity constraint on the concentration of drugs administered. The model based on optimal drug doses in order to provide for greater cancer cell reduction, while limiting the risk of unacceptable toxicity.

Tes and co-workers (2005) further introduced a customised optimal control model of drug scheduling in cancer chemotherapy and they used genetic algorithm to solve it. The result of the first model shows that the drug should be injected towards the end of the chemotherapy period. In contrast, the second model shows that the quiescent cells are not remaining at the same level during the therapy and the rest of the cells do not directly affected by the drug.

An optimal control model of drug scheduling in cancer chemotherapy was introduced by Tes, et al, (2007) and it was optimised by using genetic algorithm (GA). Liang, et al, (2008) used a variant of GA, called adaptive elitist population based GA to design the chemotherapy drug scheduling for non-specific cancer treatment. In the aforementioned works, single objective evolutionary optimisation approaches were used, mainly to minimise the cancerous cells during the whole period of chemotherapy treatment.

In conventional single objective optimisation approaches, the individuals/solutions converge to a single point as the algorithms proceed. Optimal performance according to tumour eradication/cell reduction often yields unacceptably high doses or high toxic side effects.

As mentioned earlier, in chemotherapy drug scheduling problem, tumour eradication/reduction and toxic side-effects are always found in conflict to one another and it is never possible to minimise both the objectives simultaneously with conventional single objective optimisation techniques. Optimal performance according to one objective often yields unacceptably low performance in other objective domain, creating the need for compromise. To deal with multiple conflicting objectives and constraints, a relatively new set

of algorithms has emerged, commonly known as multi-objective evolutionary algorithms (MOEAs) (Deb, 2001).

McCall and Co-worker (2008) also utilised multi-objective evolutionary algorithms to design chemotherapy drug scheduling where drug doses and toxic side effect were set as constraints. A set of solutions were designed trading-off two design objectives; tumour eradication and patient survival time (PST). In their work, some important treatment parameters, such as, maximum cumulative drug doses, maximum allowable size of the tumour and toxic side-effects were used as constraints in the GA optimisation process that resulted an effective drug scheduling at the end.

In all preceding works, the chemotherapy drug scheduling was designed for non-specific tumour growth model and treatment where toxicity was set as constraint. Moreover, no control system/strategy was used to design the drug doses or scheduling. Motivated by the success and effectiveness of multi-objective optimisation in biomedical engineering and systems biology, the current researchers utilise its potential in designing chemotherapy drug scheduling for cell cycle specific cancer treatment as a first hand work.

The simplest mathematical models which are commonly used in research for optimal control of cancer chemotherapy assume the entire cell cycle as one compartment (Martin, 1992; Swierniak, 1994). In many cases, these single compartment models are proved to be inadequate and do not seem realistic due to the over simplified nature of the model compared to actual biological system. The actions of the chemotherapy treatment agents are based upon an understanding of the cell cycling mechanisms. The cell cycle is modelled in the form of multiple compartments which describe different cell phases or combine phases of the cell cycle into clusters. In general, the cell cycle comprises of five stages which should pass

thorough dependents of the type of the cell as shown in Figure 2. 2. A brief description of different stages is given below (Dua, et al, 2008; Martin and Teo, 1994):

- G1: Post mitotic gap, the cell prepares for DNA synthesis.
- S: DNA synthesis takes place in preparation for cell division (many anticancer drugs act by interfering with DNA at this stage, causing cell death).
- G2: Pre-mitotic gap, specialised proteins and RNA are synthesised in preparation for cell division.
- M: Mitotic phase, cell division takes place to produce two identical daughter cells.
- Go: Resting phase, cell is quiescent, viable but unable to divide. The cell cycle is a chain of phases that both normal and cancer cells undergo from their birth to death.

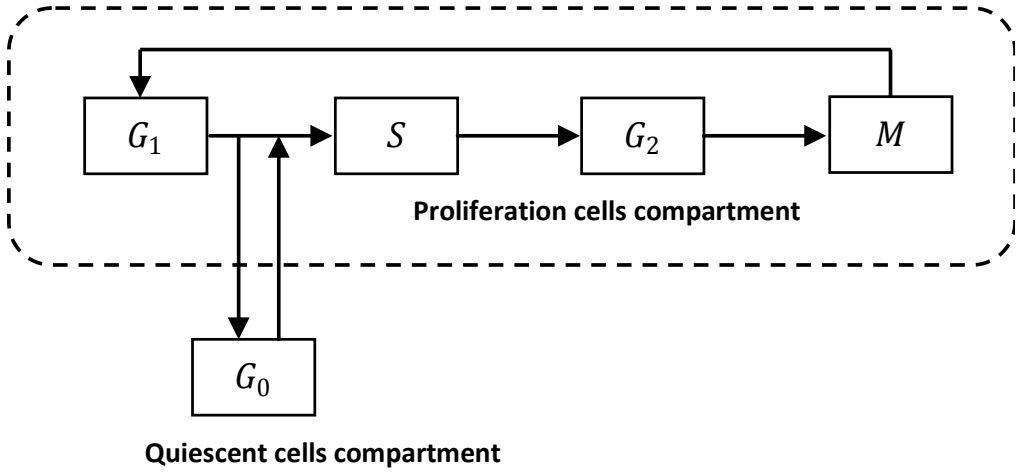

Fig. 2.2 Schematic diagrams of different phases of cell cycle

In all of these phases there are a number of checkpoints that the cell must pass through to insure the integrity of the DNA. If the cell fails to meet the necessary requirements at the various checkpoints, the cell either repairs or destroys itself, a process referred to as apoptosis or programmed cell death. Should one of these checkpoint mechanisms fail, the result can be

a malignant cell that has mutated from a normal cell and thus is a germ or initial proliferating cancerous cell which may potentially develop into cancer.

To explain tumour response more realistically, multi-compartment models have been proposed and used in optimal chemotherapy. Of the multi-compartment models, the simplest and at the same time most natural ones, are two/three sometime more compartment models; which divide the cell cycle into two/three compartments (Swierniak, et al., 1996).

In (2005), Swierniak considered a specific class of mathematical models based on cell cycle kinetics which are used to describe and improve cancer chemotherapy treatment protocols in phase-specific. This type of models contains a two compartmental model of single drug chemotherapy, three compartmental models of multi-drug therapy combining blocking and killing actions, and recruitment from quiescence together with killing action, as well as more general multi-compartmental model with many drugs. Moreover, this property is crucial for elimination of singular controls from candidates for optimality.

The study of Minaya Villasana (2010) extended a previous mathematical model of cancer cytotoxic chemotherapy, which considered cycling tumour cells and interactions with the immune system, by incorporating a different type of drug: a cytostatic agent. The effect of a cytostatic drug is to arrest cells in a phase of their cycle. In consequence, once tumour cells are arrested and synchronized, they can be targeted with a cytotoxic agent, thus maximizing cell kill fraction and minimising normal cell killing. The goal is to incorporate the new drug into the chemotherapy protocol and devise optimal delivery schedules. The author concluded that the approach can serve as a valuable decision support tool for the medical practitioner facing the complex problem of designing efficient combined chemotherapies

In these models the G_2 and M phases are combined into one compartment. In the two compartment model G_0, G_1 and S form another compartment while different three compartment models arise by separating the synthesis phase S or the dormant stage G_0 for the three-compartment model. The purpose of this division is to effectively model various drugs used in chemotherapy like killing agents, blocking agents or recruiting agents (Swierniak, et al., 2003a).

Two compartment models of cancer cells population have been considered in their work (Kozusko, et al., 2003) which includes transition rates between proliferating and quiescent cells as non-specified functions of the total population. The cancer cells in the first subpopulation are active and known as proliferating cells, while cells in the second group are mainly quiescent (inactive). In this dynamic system, proliferating and quiescent subpopulations can convert into each other; both subpopulations are affected by the natural death rate, and the proliferating subpopulation is also affected by the proliferating rate. Two cell population dynamics can be expressed in a mathematical model framework in terms of ordinary linear differential equations (Swierniak, et al., 1996, Dua, et al., 2008).

Kozusko and co-workers in (2003) has designed a model which predicts that the number of proliferating cells that increase with the total number of cells. The method which has been used to implement for obtaining the size of proliferating and quiescent subpopulation, based on postulated total cell population kinetics. The model has improved the effectiveness of the chemotherapy treatment but there are some weaknesses for this model such as the drug resistance.

Dua and co-workers in (2008) have presented two models for cancer chemotherapy. The first model describes the entire cell cycle as a uniform entity, where all the cells contained in a tumour are of the same type and consists of one compartment such that the effect of anticancer agents is at the same level within all the cells. The second model considers the cell cycle which consists of more than one compartment to take into account the type of cells that are affected by the drug.

The result of the first model shows that the drug should be injected towards the end of the chemotherapy period. In contrast, the second model shows that the quiescent cells are not remaining at the same level during the therapy and the rest of the cells do not directly affected by the drug. The tissue, in general, contains three different types of cells: the proliferating cells, the quiescent cells and the dead cells.

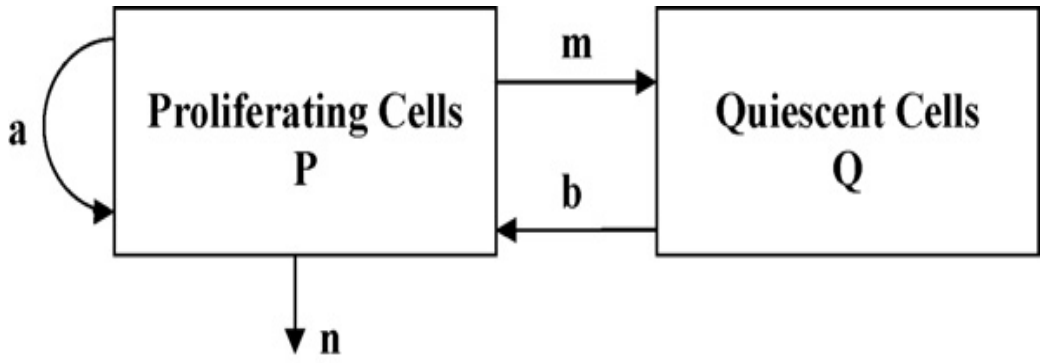

Fig. 2.3 The functional within tissue

So a cell compartment model containing aforementioned types of cells as shown in Figure 2. 3, is often considered to explain cancer tumour growth more clearly. The proliferating part contains actively dividing cells whereas quiescent part is inactive cells, but capable of dividing if a certain stimulus is given. The dead cells are unable to divide because they have completed their life cycle.

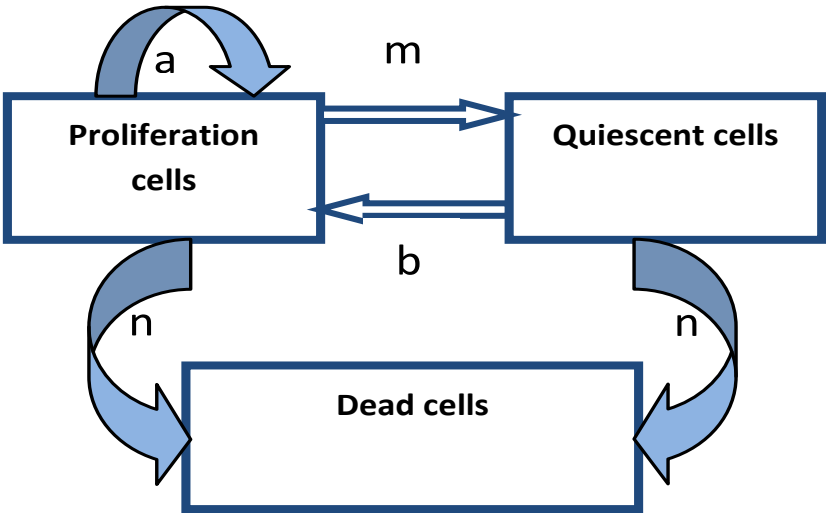

Fig. 2.4 Two compartments functional within tumour tissue

Figure 2.4, shows a two compartment model where P (Proliferating) presents the combination of the first four stages of the cell cycle as mentioned earlier (G_1, S, G_2 and M) and Q (Quiescent cells) indicates stage G_0. The parameters m and b express the immigrants between the proliferating cells and quiescent cells respectively. Here a is indicates to the growth rate of cycling cells and n is the natural decay of the cycling cells.

A number of models have been developed and used to characterise the evolution and effects of treatment on cancer by dividing the tumour into number of compartments (phase-specific) as considered in (Ochoa and Burke, 2007, Liang, et al., 2008). Evolutionary algorithms have been extensively applied to design the chemotherapy drug scheduling for cancer treatment. Single objective evolutionary optimisation approaches were used, mainly to minimise the cancerous cells throughout the whole period of chemotherapy treatment.

McCall, et al., (2008) designed chemotherapy drug scheduling using genetic algorithms where tumour eradication was used as the objective function, to be minimised. In their work, other important treatment parameters, such as, maximum drug doses, maximum cumulative drug doses, maximum allowable size of the tumour and toxic side effects were

used as constraints in the GA optimisation process that resulted an effective drug scheduling at the end.

In another work Petrovski, et al., (2004), used a relatively new bio-inspired algorithm, called particle swarm optimisation to design chemotherapy drug scheduling using aforementioned design objective and constraints.

A linear model presented by Adam and Panetta (1995) describes the administration of anticancer drug for cell cycling specific chemotherapy. Panetta (1999) developed a model to show how to determine an effective treatment, how combination of chemotherapy should be delivered and how this model may help to develop more effective cancer chemotherapeutic treatments. Two compartment models of cancer cells population have been considered in their work which includes transition rates between proliferating and quiescent cells as non-specified functions of the total population but the number of compartments was limited so that is made the combination of the drugs limited as well.

Kozusko (2003) designed a model which predicts that the number of proliferating cells that increase with the total number of cells. Basse et al., (2004) presented a method to model a population of cells and the effects of cancer therapy. The authors initially developed a theoretical one compartment size structured cell population model and investigated its asymptotic steady size distributions (SSDs), size was a generic term, but to obtain a realistic steady size distributions in one compartment model, the size was chosen to be DNA content and then devised a multi-compartment mathematical model for the cell division cycle where each compartment was related to a distinct phase of the cell cycle.

Swierniak in (2003b) demonstrated three models based in the cell cycle, those models considered the two compartment model during cell division constitutes. In all models the cumulative effect of the killing agent is used to model the negative effect of the treatment on healthy cells. Swierniak in (2005) combined models that so far have been analysed and implemented separately, taking into account both the partial sensitivity of the resistant subpopulation of gene amplification and drug specificity in chemotherapy in their different aspects.

Stengel and co-workers in (2002) introduced control histories that minimise a quadratic cost function are generated by numerical optimization over a fixed interval time. Tradeoffs between cost function weighting of pathogens, organ health, and use of therapeutics are evaluated. Optimal control solutions that defeat the pathogen and preserve organ health are demonstrated for four different approaches to therapy.

The chemotherapy treatments in these models either represent a continual kill where a fixed percentage of cells are killed at every cycle of treatment, or a reduced kill in which the fraction of cells is reduced dependent on the number of treatments cycle given. Monitoring the cancer cells can be done by tracking the total number of the cancer cells, while also tracking the subpopulations within it.

Many researchers have developed mathematical models of tumour growth and cell killing by considering the administration of drugs as well as drug resistance (Ledzewicz, et al., 2009; Tes, et al., 2007; Woderz, 2005). They have also developed mathematical models for drug scheduling and toxicity elimination based on ordinary differential equations. As

mentioned earlier, the optimal cancer chemotherapy protocols are chosen to minimise the number of the tumour cells with less toxic side-effects by different methods.

Recently, a model presented by Kozusko and Bajzer to accommodate the Gompertz function within the context of two compartment cell population dynamics and the study predicted an analytical solution for the evolution of two kinds of subpopulations within the tumour. They lately modified their model to include the presence of anti-mitotic drugs, when the drugs decrease the reproduction constant and increase the death rate of the proliferating subpopulation. The drug amount is considered to be constant in their study.

Kozusko, (2003) implemented his model which predicts that the number of proliferating cells increases along with the total number of cells, but the proliferating fraction appears to be a continuously decreasing function. Due, et al., (2008), presented, two models for cancer chemotherapy, the first model describes the entire cell cycle as a uniform entity, where all the cells contained in a tumour are of the same type and consists of one compartment such that the effect of anticancer agents is at the same level within all the cells, the second model considers the cell cycle which consists of more than one compartment to take into account the type of cells that are affected by the drug.

Mathematical models of tumour growth and response of tumour with anticancer drugs are crucial in the design and developments of new drugs and their scheduling. For example, the models in vivo and vitro may take months to run its course, and in some cases, years. It’s often quicker and cheaper to formulate a mathematical model and simulate it on silico than perform -laboratory experiments or clinical trials (Martin and Teo, 1994).

Finally, the first part of the analytical and modelling implementation shows that the all cell in the tissue considered as one compartment so when the drug be injected all the cells will effected by chemotherapy during the period of treatment. In contrast the second part of the analytical and modelling shows that the division of the tissue based on the cells behaviour does not directly affected all the cells by the drug. The quiescent cells are not remain same during the therapy that means the quiescent cells will be stimulate by the cancer drug chemotherapy and become active or proliferating cells and the normal cells will maintained.

2.5 Combination of Chemotherapy Regimen

The main aim of chemotherapy treatment, as motioned early in many places is to eradicate or minimise the cancer cells with minimum toxic side effects. Very often, cancer cells grow resistance to a drug if it continues for a long time and resistance to drug causes failure to treatment in most cases. When the chemotherapy treatment failure occurs, the drugs will need to be changed. The combinations of multiple drugs can decrease the drug resistance (Martin and Teo, 1994).

Toxic side-effects developed due to the infusion of chemotherapy drugs always pose a major challenge in drug scheduling. So drug doses and their cycles of intervals must be design in such a way as to make the treatment effective, i.e., eradicate the tumour with minimum/tolerable toxic side-effects. The actions of the chemotherapy drugs (agents) are based upon an understanding of the cell cycling mechanisms.

Researchers have developed mathematical models for drug scheduling and toxicity elimination based on ordinary differential equations (Martin, 1992). The optimal cancer

chemotherapy protocols are chosen to minimise the number of the tumour cells with less toxic side effects by different methods. Martin and Teo, (1994) used control parameterisation and analytical gradients to find optimum drug schedules with all many constraints related to toxicity, drug concentration and tumour growth.

The cancer chemotherapy treatment is used to minimise the number of cancer cells after a number of fixed treatment cycles with minimum toxic side-effects. Traditionally one or more drugs are infused to the body. The efficiency of the doses of the treatment is often measured as the interval of time from the start of therapy, until the end of treatment. Chemotherapy involving the use of cytotoxic anti-neoplastic agents remains an important strategy in the overall management of patients with malignant tumours.

Drug transporters and drug metabolising enzymes play key roles like most therapeutic agents in determining the pharmacokinetics and overall disposition of anti-neoplastic agents in the body. Drug transport and metabolism enzymes also influence the toxic effects of both anti-neoplastic agents in target tumour cells and normal host tissues (Kivisto, et al., 1995). Many characteristics of anti-neoplastic drugs make the metabolism of these agents particularly significant. Several anti-neoplastics display the doses response curves and low therapeutic indices, and the toxicity that they produce can be severe and life threatening.

In practice, multi-drug chemotherapy treatment is preferred to avoid or reduce the risks of resistance grown in cancer cells against the infused drug and thus make the treatment more effective. The development of drug resistance is one reason that drugs are often given in combination. Often, if a cancer becomes resistant to one drug or group of drugs, it is more likely that the cancer may be resistant to other drugs.

Multi-drug resistance is cross resistance to some structurally and functionally unrelated naturally derived drugs and is characterised by the occurrence of cross resistance to a broad range of structurally and functionally unrelated drugs. It is one of the most important causes of unsuccessful chemotherapy in cancer treatment. Some of tumours are initially resistant and never respond to drug treatment, where as others become resistant after a good initial response.

Use of multi-drug chemotherapy increases the effectiveness of greater cell kill, decreases the chance of drug resistance and reduces any toxic side-effects. Liang, et al., (2007), integrated the (AEGA) and Iterative Dynamic Programming (IDP) algorithms to form a new memetic algorithm (MA) approach. The new MA is developed to solve the multi-drug chemotherapy with a local search algorithm IDP. Ochoa, et al., (2007) investigated the employment of evolutionary algorithms as a search mechanism in a decision support system for designing chemotherapy scheduling.

Liang and co-workers in (2008) renewed two drug scheduling models with different toxicity metabolism according to kinetics of enzyme catalyzed chemical reactions. The different drug toxicity metabolism described according to kinetics of enzyme-catalyzed reaction. The combinations of drug has high efficiency of maximising killing the tumour of cells by decreasing the resistance of the cancer drug chemotherapy, but each drug has its own toxic so that is means the chance of increasing the toxicity will rising.

Multi-drug resistance (MDR) is one of the major factors in limiting the successful use of chemotherapy in cancer treatment Souslova, et al., (2004), Brandt, et al., (2006). A phenotype that is referred to as multidrug resistance was first described for chemotherapy resistant cancer cells that over expressed the drug efflux transporter P-glycoprotein (P-gp).

Abundo and Rossi in (1989) the proposed model to study the problem of the drug resistance by cancer cell populations when chemotherapeutic agents are used to control tumour growth. The differential equations are numerically integrated to simulate expected response to the chemotherapeutic strategies as a function of different parameters.

Westman, et al., (2002), presented a model to explores the role of drug resistance in the evolution of cancer subject to treatment with a single Cytotoxic agent. In (2004) Souslova proofed that some cells are more sensitive than other and hyperthermia is useful for eliminating MDR cells but the toxic bit high.

Brandt and co-workers in (2006) presented a model that allows selecting drug resistant and drug responsive by prolonged treatment with the antiepileptic drug Phenobarbital at maximum tolerated doses. Tes, et al., in (2007) integrated the AEGA and Iterative Dynamic Programming (IDP) algorithms to form a new mimetic algorithm (MA) approach. The new MA is developed to solve the multi-drug chemotherapy with a local search algorithm IDP.

Ochoa (2007) investigated the employment of evolutionary algorithms as a search mechanism in a decision support system for designing chemotherapy scheduling. Liang, et al., (2006) renewed two drug scheduling models with different toxicity metabolism according to kinetics of enzyme catalyzed chemical reactions. The different drug toxicity metabolism described according to kinetics of enzyme-catalyzed reaction.

In such case (multi-drug chemotherapy), the doses must be optimised to trade-off between the beneficial and adverse side-effects of the treatment. Since the beneficial and adverse side-effects are inherently found to be in conflict, conventional methods or single

objective optimisation techniques can hardly provide any suitable solution in multi-drug chemotherapy scheduling problem.

2.6 Drug Resistance: Mechanism and Implications

The chemotherapy drug resistance occurs when the cancer cells does not responding to a therapy, the cancer cells become resisting to the effects of the chemotherapy. This has been mentioned in many occasions as "cancer chemotherapy failed" (Martin and Teo, 1994). When this occurs, the drugs will need to be changed. There are several possible reasons for chemotherapy resistance (www.chemocare.com, 2011).

- Some of the cancer cells that are not killed by the chemotherapy mutate (change) and become resistant to the drug. Once they multiply, there may be more resistant cells than cells that are sensitive to the chemotherapy.
- Gene amplification: A cancer cell may produce hundreds of copies of a particular gene. This gene triggers an overproduction of protein that renders the anticancer drug ineffective.
- Cancer cells may pump the drug out of the cell as fast as it is going in using a molecule called p-glycoprotein.
- Cancer cells may stop taking in the drugs because the protein that transports the drug across the cell wall stops working.
- The cancer cells may learn how to repair the DNA breaks caused by some anti-cancer drugs.
- Cancer cells may develop a mechanism that inactivates the drug.

The development of cancer chemotherapy drug resistance is one reason that drugs are often given in combination. This reduces the incidence of developing resistance to any one drug. Often, if the cancer cells become resistant to one drug or group of drugs, it is more likely that the cancer cells may be resistant to other drugs.

A number of different mechanisms may contribute to chemotherapy resistance. The basic mechanism of drug resistance or transport mediated resistance is due to the decreased concentration of the active drug in target cells. Because of decrease drug uptake or increased drug efflux across tumour cell membranes, and is activation of cellular ant-apoptotic defence (Thomas, et al., 2002, Souslova, et al., 2004, Triller, et al., 2006).

Mechael and Gottesman in (2002) introduced a great knowledge about mechanisms of drug resistance in cancer cells, Figure 2.5. Regardless of the development of new targeted anticancer therapies, mechanisms that have evolved in mammals to protect cells against cytotoxic compounds in the environment will continue to act as obstacles to successful treatment of cancer. Even though, all these explorations about the cells mechanisms but still the behaviours of cancer cells not known as the research carrying on to discover more about it.

One of the most known mechanisms is the over expression of P-glycoprotein (P-gp), is a part of larger family of efflux transporters. P-glycoprotein is localised in numerous tissues throughout the body and plays an important role in the disposition of many xenobioutics. The contribution of P-glycoprotein mediated drug transport is being evaluated in early drug discovery stages, particularly for compounds targeted to the central nervous system.

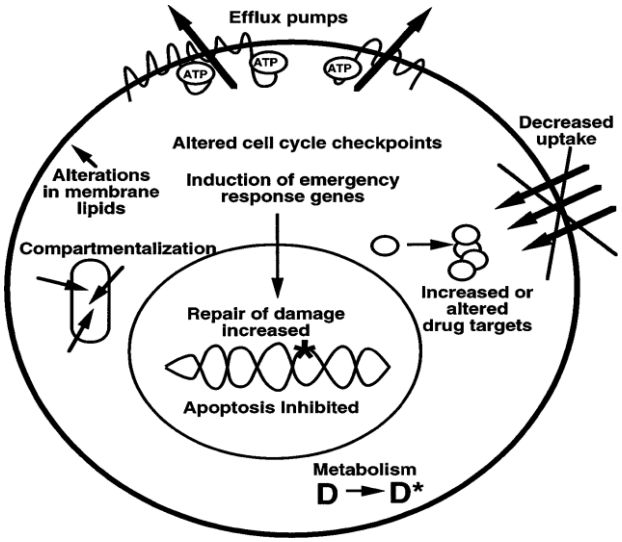

Fig. 2.5, Mechanisms of drug resistance in cancer cells, (Mechael and Gottesman, 2002).

A phenotype that is referred to as multi-drug resistance was first described for chemotherapy resistant cancer cells that over expressed the drug efflux transporters P-glycoprotein (P-gp). In Abundo (1989) proposed procedure to simulate different chemotherapeutic strategies. Westman, et al., (2002) presented a model to explore the role of drug resistance in the evolution of cancer subject to treatment with a single cytotoxic agent.

In Souslova, 2004, Souslova proofed that some cells are more sensitive than other and hyperthermia is useful for eliminating Multi-Drug Resistance MDR cells. Brandt, et al., (2006) presented a model that allows selecting drug resistance and drug responsive by prolonged treatment with the antiepileptic drug Phenobarbital at maximum tolerated doses.

Tes, et al., (2007), integrated the AEGA and Iterative Dynamic Programming (IDP) algorithms to form a new mimetic algorithm (MA) approach. The new MA is developed to solve the multi-drug chemotherapy with a local search algorithm IDP. The models referred above have investigated the multi-drug resistance problem with different way in order to find the desired salutation, but didn't consider the most effect factor which is the cell layers.

(Ledzewicz, et al., 2000) The resistant of cancer chemotherapy treatment is a universal problem and one of the main, although not the only obstacle to effective treatments. The hope is that the improvement in cancer chemotherapy drug scheduling sessions may delay the onset of drug resistance and thus give a higher life expectancy (Lobo and Balthasar, 2002). The authors presented a formulation and some preliminary analysis for two finite dimensional models using bang-bang controls for cancer chemotherapy taking into account drug resistance with respect to single and multiple killing agents.

2.7 Summary of the Reported Study

The cancer cells populations and the growth rate can be predicted by mathematical models to estimate the amount of the chemotherapy drug should be applied. One of the major aims of designing and implementing the chemotherapy drug scheduling models is to eradicate/minimise the tumour cells after a fixed treatment cycle with minimum side-effects. The understanding of the cell behaviours and division improves the treatment effectiveness. Some of the treatments models considered the cancer cells as one and many compartments which based on the mutations and behaviours of all cancer cells. The cancer cells divided for example; on four and eight compartments based on the sensitivity of the cancer cell to drug. The main challenges are to balance between the benefits and the side-effect of the chemotherapy cancer treatment. The proliferating cells at the tissue considered as active cancer cell and needs to be treated and divided to compartments called phase specific. The drug resistance has not been considered in some of the treatment models. The multi-drug regimen models are designed to overcome the limitations of the models which were designed to treat cancers.

2.8 Justification of this research

The investigation of the cancer diseases has raised many factors that should be considered in designing and implementing optimisation models, which would have significant impact on effective of the cancer chemotherapy treatment. Most of these factors have been investigated separately which has rise some limitations in the models developed earlier. Most of the cancer treatment models predict the cancer cells populations and the growth rate based on fixed rate (constant) which is may not applicable to all cases. However, the accuracy of the cancer cells prediction in the patient's body improves the impact of the treatment.

Some of the cancer treatments models considered the cancer cells as a one compartment which means that the behaviours of all cancer cells are same (non-phase specific) and all of them treated by chemotherapy, which is required high doses of the drug and increases the side-effect as well. Moreover, some of the chemotherapy cancer drug models designed depends on the behaviours and mutation of the cancer cell on the tissue. The balance between all conflicts and constraints of cancer treatment is to maximise the cancer cell killing and reduce the side-effect of the treatment. However, these constraints need to consider more factors such as type of the cancer cells, stage of the disease, age and gender of the patient.

Later on, many chemotherapy cancer drug models were designed and considered the proliferating cells on the tissue as active cancer cell and needs to be treated and divided to two compartments call phase specific. However, the division of the cancer cells based on their functions improves the chemotherapy treatment outcome. On the other hand, the drug resistance has not been taken in the account on these types of treatment models. The multi-drug regimen models are designed to avoid the weakness of the previous treatment models.

The cancer cells have been divided on four and eight compartments based upon the resistance of the cancer cell to one drug to another. Furthermore, the cancer cells killing have been maximised with reduction of the toxic (side-effect) by using multi-drug chemotherapy cancer drug scheduling models.

As motioned early, the main aim of chemotherapy treatment is to eradicate the tumour, if possible, or to reduce the tumour size to a minimum level with minimum toxic side-effects. But most chemotherapy drugs used in cancer treatment usually have narrow therapeutic indices, this means that the dose levels at which these drugs significantly kill the cancerous cells are close to those levels at which harmful toxic side-effects occur. Therefore, effective drug scheduling requires suitable balancing between the beneficial and toxic side-effects over a treatment period. Conventional clinical methods very often fail to find drug doses that balance between these two due to their inherent conflicting nature.

In conclusion, it is recommended that researchers should consider all these factors related to optimisation of cancer chemotherapy, which has reviewed in this Chapter in order to avoid the limitations of proposed models. In contrast, the advantages of these models should also be considered to help the new researchers to developed relevant models. These advantages, for example; cell compartments, drug combinations and multi-drug resistance would clearly improve the desired outcome of the cancer treatment and the quality of life and care of the cancer patients. In the next Chapters, more details will be discussed including the results.

CHAPTER 3

Methodology

3.1 Background

Many mathematical models have been developed to describe the growth and control of cancer cells. The main aspect of implementing those models is that they take into account the balance between the benefit and the side-effects of the treatment as well as the problems related to drug resistance. The mathematical model of such a system is generally represented by two or more ordinary differential equations which describe the growth of the cancer along with the effects of chemotherapy.

The problem is generally modelled with a set of defferential equations, aiming to minimise the tumour size by the drug chemotherapy scheduling treatment. The extensive course of chemotherapy drug scheduling is designed to treat the patient rapidly and effectively to reduce the tumour cell after a number of fixed treatment cycles, in order to maximise the survival time of the patient. The purpose of using optimised mathematical models of cancer chemotherapy is to predict and control the course of the disease when a given treatment is being used. Figure 3.1 shows the scheme diagram for the system model.

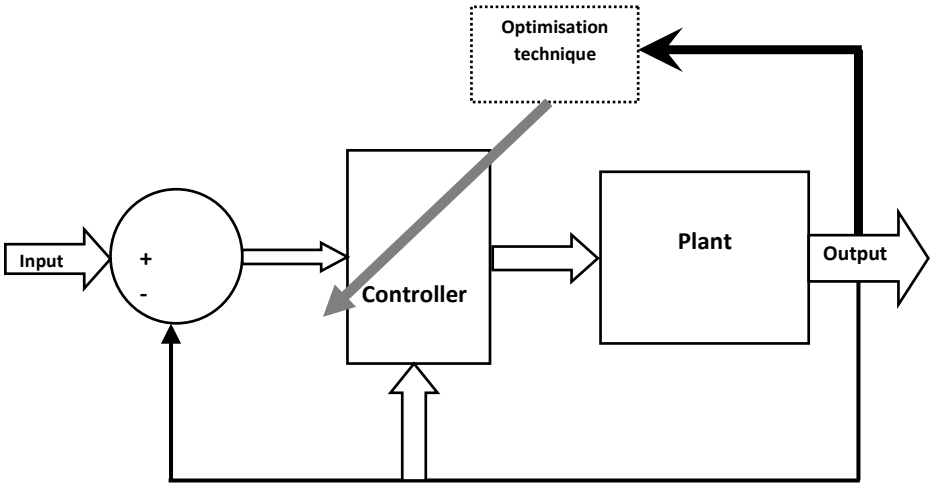

Fig. 3.1 Scheme diagram for the system model

3.2 Non Phase Specific

The greatest challenge of cancer chemotherapy treatment is to maintain the normal physiological states of the patient's body system during the period of treatment. This can be achieved by optimising chemotherapy treatment in such a way as to reduce/eliminate tumour burden to a minimum level with toxic side effects. The mathematical models are generally developed based on a set of defferential equations. The purpose of using mathematical models for cancer chemotherapy is to predict and control the course of the disease when a treatment is scheduled.

These mathematical models can be categorised by the number of compartments which has been considered. In one compartment models for the chemotherapy treatment, the various types of cancer cells are thought of as single types of cancer cells, which are all included in the growth fraction.

Martin (Martin and Teo, 1994) introduced the well known differential equation for tumour response with chemotherapy drug as follows:

$$\frac{dx_1}{dt} = -\lambda x_1 + \kappa(x_2 - \beta)H(x_2 - \beta) \tag{3.1}$$

$$H(x_2 - \beta) = \begin{cases} 1, & if\ x_2 \geq \beta \\ 0, & if\ x_2 \leq \beta \end{cases} \tag{3.2}$$

where x_1, λ, κ, x_2, β and H are transformed variables, growth speed of the cancer cells, cells killed per unit time per unit drug concentration, drug concentration at the tumour site, threshold level of drug concentration and Heaviside step function respectively. Equation (3.1) describes the net change in tumour cell population per unit time. The first term in the right-hand side of (3.1) describes the increase in cells due to cell proliferation and the second term describes the decrease in cells due to the drug. The parameter (λ) is a positive constant related to the growth speed of the cancer cells and (k) is the proportion of tumour cells killed per unit time per unit drug concentration, which is assumed to be a positive constant. Equation (3.2) is a Heaviside step function and the implication of it is that there is a threshold of the drug concentration level, β, below which the chemotherapy drug cannot kill the tumour cells (Due et al., 2008). A transformed variable x_1 is inversely related to the mass of the tumour, N as:

$$N = 10^{12} \exp(-x_1) \tag{3.3}$$

$$N(0) = N_0$$

where N_0 is the initial tumour cell population, which is assumed 10^{10} at the beginning of the treatment. The values of λ, κ and β used in this work are set at 9.9×10^{-4}, 8.4×10^{-3} and 10 respectively (Liang et al., 2008). The drug concentration is modelled using another differential equation as follows:

$$\frac{dx_2}{dt} = u - \gamma x_2 \tag{3.4}$$

where u is the rate drug delivery and γ is the biochemical character of the drug which is related to the half-life of the drug as: $\ln(2)/\gamma$. Equation (3.4) describes the net increase in the drug concentration at the cancer area. It is assumed that the drug is delivered by infusion, and there is an instantaneous mixing of the drug with plasma, as well as an immediate delivery of the drug to the cancer area. These assumptions represent approximations based on the relative amount of time it takes for the aforementioned activities to occur with respect to the total amount of time over which the treatment is administered. The value of γ is set at 0.27 (Due et al., 2008). In order to kill the cancerous cells, the chemotherapy drug concentration at tumour site should be more than 10. The cytotoxic chemotherapy drug may cause adverse toxic side effects if the doses are not controlled properly. In order to avoid unbearable toxic side effects, the drug concentration, during the whole period of treatment should not exceed 50. The limiting values of drug concentration as suggested by many researchers are as follows (Due et al., 2008):

$$10 < x_2(t) \leq 50 \tag{3.5}$$

Solving equation (3.4) gives:

$$x_2(t) = c_2 e^{-\gamma t} + \frac{\mu}{\gamma} \tag{3.6}$$

where c_2 is a constant, related to the increase of drug concentration at the tumour site.

Finally, the toxicity is modelled as:

$$\frac{dx_3}{dt} = x_2 - \eta x_3 \tag{3.7}$$

here η is a constant, set to 0.4 (Due et al., 2008). Equation (3.7) describes the level of toxicity inside the patient's body after applying the drug dosage, which relates the cumulative drug toxicity to the drug concentration. It is worth mentioning that the cumulative effect is the

integral of the drug concentration over the period of exposure. The maximum toxicity should not exceed 100 during the whole period of treatment, suggested by researchers as (Liang et al., 2008):

$$x_3(t) \leq 100 \tag{3.8}$$

Solving equation (3.7) and substituting $x_2(t)$ gives:

$$x_3(t) = \frac{1}{(-\gamma - \mu)}\, c_3 e^{-\gamma t} - \frac{u(t)}{\mu\gamma} \tag{3.9}$$

Where c_3 is a constant. Using equations (3.6), (3.9) and solving (3.1) gives:

$$x_1(t) = c_1 e^{\lambda t} - \left(\frac{ku(t)}{\gamma\lambda} - \frac{k\beta}{\lambda}\right) + \frac{kc_2 e^{-\gamma t}}{(-\gamma + \lambda)} \tag{3.10}$$

The first term of equation (3.9) shows the rate of tumour growth without treatment which appears to follow Gompartz growth model, as indicated by the parameter λ. The constant c_1 represents the time response of the cells reduction. So if c_1 is small, the response will be faster, otherwise the response will be relatively slower. The second term of equation (3.10) represents the drug doses $u(t)$, which affect the rate of cells killing where parameter β is threshold level of drug concentration. The last term also represents the cell reduction due to drug that becomes effective after some time as indicated by the parameter γ, which is drug decay.

3.3 Phase Specific

The tissue, in general, contains three different types of cells: the proliferating cells, the quiescent cells and the dead cells. So a cell compartment model containing the aforementioned types of cells, as shown in Figure 3.2, is often considered to explain cancer tumour growth more clearly. The proliferating part contains actively dividing cells whereas the quiescent part

is inactive cells, but ones capable of dividing if a certain stimulus is given. The dead cells are unable to divide because they have completed their life cycle. Figure 3.2 shows a two-compartment model where P (Proliferating) presents the combination of the first four stages of the cell cycle, as mentioned earlier (G_1, S, G_2 and M) and Q (Quiescent cells) indicates stage G_0.

The parameters m and b express the immigrants between the proliferating cells and quiescent cells respectively. Here a indicates the growth rate of cycling cells and n is the natural decay of the cycling cells. Based on clinical evidence, the population of proliferation and quiescent cells at the tumour site are assumed to be 10^{12} and 10^{9} at the time of diagnoses. For a two compartment model, it is assumed that 80% of the cell population is quiescent while the remaining 20% is active proliferating cells (Dua et al., 2008).

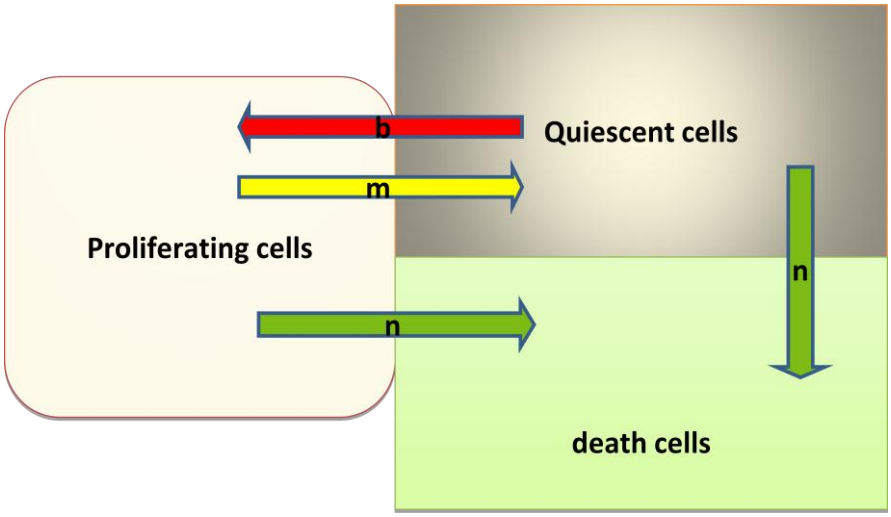

Fig. 3.2 Two functional compartments within tumour tissue

A number of differential equations used to build a two compartment model of cancer chemotherapy treatment are explained briefly. The first equation predicts the rate of change of

proliferation cells population at the tumour site during the treatment, as follows (Dua et al., 2008):

$$\frac{dP}{dt} = (a - m - n)P(t) + bQ(t) - g(t)P(t),$$

$$P(0) = P_0 \qquad (3.11)$$

where P and Q represent population of proliferating and quiescent cells. Here parameters $a, m, b \; and \; n$ indicate the rate of growth of proliferation cells, immigrant from cycling to quiescent cells, and natural death of cycling cells respectively. A variable $g(t)$ indicates the effects of the drug on the tumour cell, which is the rate of cell killing per unit drug. Equation (3.12) describes the rate of change of cell population in the quiescent compartment of the tumour site during the period of treatment.

$$\frac{dQ}{dt} = mP(t) - bQ(t), \quad Q(0) = Q_0 \qquad (3.12)$$

The anticancer drugs affect both tumour cells and normal cells. To reduce the toxic side effects of chemotherapy treatment, the population of normal cells should be maintained as high as possible during the whole treatment period. A logistic equation is used to describe the effect of chemotherapy drug on normal cells, as expressed by equation (3.13) below:

$$\frac{dY}{dt} = \delta y(t)\left(1 - \frac{Y(t)}{K}\right) - g(t)Y(t), \qquad (3.13)$$

$$Y(0) = Y_0$$

Here $Y(t)$ indicates the normal cells population whereas δ and K present the growth rate of the normal cells and the carrying capacity of normal cells respectively. $Y(0)$ is the initial

value of normal cell population at the beginning of the treatment. Equation (3.14) shows the rate of change of drug concentration at the tumour site during the treatment cycle.

$$\frac{dD}{dt} = u(t) - \gamma D(t), \qquad D(t) = D_0 \tag{3.14}$$

where $u(t)$ is the amount of drug doses to be infused to the patient's body and γ is drug decay, which is related to the metabolism of drug inside the patient's body. It is noted that the drug concentration $D(t)$ at the tumour site should remain within the limit as suggested by equation (3.15) in order to make the chemotherapy treatment effective (Martin and Teo, 1994).

$$10 < D(t) \leq 50 \tag{3.15}$$

Equation (3.16) shows the relationship between drug concentration at the tumour site and cell killing rate.

$$g(t) = k_1 D(t) \tag{3.16}$$

where k_1 is a constant related to the effect of drug concentration on cell killing. Equation (3.17) shows the relationship between the level of toxicity and drug concentration at the tumour site during the treatment period.

$$\frac{dT}{dt} = D(t) - \eta T(t) \tag{3.17}$$

$$T(t) \leq 100$$

where $T(t)$ is the level of toxicity developed inside the patient's body due to the chemotherapy drug and parameter η indicates the rate of elimination of toxicity. The level of toxicity should be controlled and kept within a tolerable range. The normal cells are

adversely affected by the drug. To limit the toxic effect, the number of normal cells should be maintained up to a certain value. Equation (3.18) expresses the limiting values of normal cell which should be maintained throughout the period of treatment.

$$Y_{\min} \leq Y(t) \leq K, \text{for all } t \in [0, T] \quad (3.18)$$

The parameter Y_{min} indicates the minimum number of the normal cells at the tumour site. Using the above equations, a Simulink (The Mathworks, Inc., 2008) model was developed with parameters and values as illustrated in Table 3. 1.

Table 3.1: Parameters of Patient Model (Dua et al., 2008)

Parameters		Values
a	The rate of growth Proliferating (cancer) cells	0.5 day^{-1}
m	The mutation rate of proliferating cells to quiescent cells	0.218 day^{-1}
n	The natural end of the cycling cells	0.477 day^{-1}
b	The mutation rate of quiescent cells to proliferating cells	0.05 day^{-1}
δ	The rate of normal (healthy) cell growth	0.1 day^{-1}
K	The carrying capacity of normal cell	10^9 cells
P	The proliferating cells population	$2x10^{11}$
Q	The quiescent (inactive cancer cells) cells population	$8x10^{11}$
Y	The normal cells population	10^9
Y_{min}	The limitation of normal cells	10^8

3.4 Four Compartments

This work focuses on multi-drug chemotherapy scheduling where two drugs are used and, for ease of discussion, those drugs are indicated by A and B, respectively. For two-drug chemotherapy treatment, a tumour model consisting of four compartments, as shown in Figure 3.3. The sub-population $S(t)$ presents the cells which are sensitive to both drugs A and B. The cells which are totally resistant to drug A are expressed by $N_A(t)$ while $N_B(t)$ indicates the number of cells resistant to drug B. $N_{AB}(t)$ presents the cells which are doubly resistant for all drugs (Martin and Teo, 1994). The chemotherapy drug A is effective on two sub-populations; $S(t)$ and $N_B(t)$ whereas the chemotherapy drug B is effective on the two sub-populations; $S(t)$ and $N_A(t)$. The sub-populations of cancer cells that are not resistant to drug A are killed only when the concentration of drug A, v_A is maintained above the threshold drug concentration v_{thA}. Similarly the drug concentration of drug B should be raised above the threshold drug concentration v_{thB} to kill cells which are not resistant to this drug. The two sub-populations $N_A and\ N_B$ increase by the constant rate, $\alpha_A\ and\ \alpha_B$, which are both less than 1. The total resistance cells for both drugs arise from two directions and two stages of process parallel, as illustrated in Figure 3. 2.

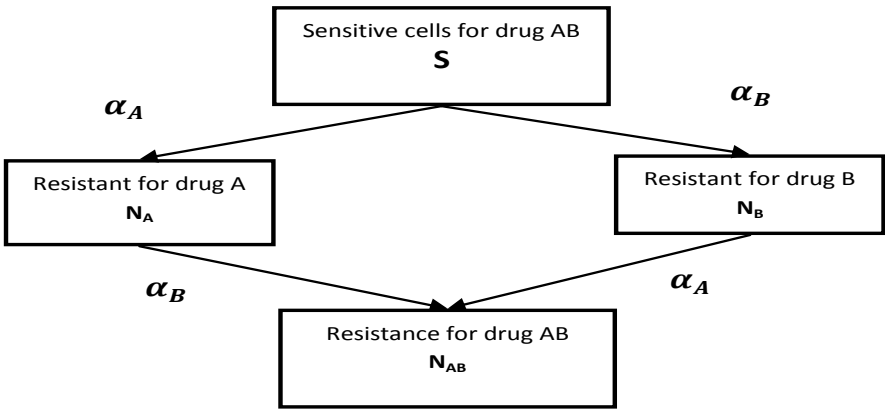

Fig. 3.3 Four compartments for multi-drug

The drugs A and B are assumed to be non-cross resistant. The proportions of cells killed by drug A from the sensitive and resistant sub-population S and N_B are the same. Similar things apply TO drug B (Martin and Teo, 1994).

$$\frac{dN}{dt} = \lambda N - k_A(v_A - v_{thA})H(v_A - v_{thA})(N - N_A - N_{AB}) - k_B(v_B - v_{thB})H(v_B - v_{thB})(N - N_B - N_{AB}) \quad (3.19)$$

where N represent population of the cancer cells. Here parameter λ relates to the rate of growth of cancer cells, k_A the rate of cancer cells killed by drug unit. Parameters $v_A, v_B, v_{thA}, v_{thB}$ relate to the drug concentration for drug A, drug B, threshold for drug A and threshold for drug B, respectively. The parameters $N_A, N_B \; and \; N_{AB}$ expressed the cells resistant to drug A, the cells resistant to drug B and doubly resistant cells respectively. Equation (3.20) describes the sensitive cell for all drugs (Martin and Teo, 1994).

$$\frac{dS}{dt} = \lambda S - k_A(v_A - v_{thA})H(v_A - v_{thA})S - k_B(v_B - v_{thB})H(v_B - v_{thB})S \quad (3.20)$$

Equation (3.21) describes the resistance cells for drug A, where Equation (3.22) represents the resistance cells for drug B and Equation (3.23) shows the cells which are doubly resistant.

$$\frac{dN_A}{dt} = \lambda[N_A - \alpha_A(N - N_B - N_{AB})] - k_B(v_B - v_{thB})H(v_B - v_{thB})N_A \quad (3.21)$$

$$\frac{dN_B}{dt} = \lambda[N_B - \alpha_B(N - N_A - N_{AB})] - k_A(v_A - v_{thA})H(v_A - v_{thA})N_B \quad (3.22)$$

$$\frac{dN_{AB}}{dt} = \lambda[(N_{AB} + \alpha_A N_B + \alpha_B N_A] \quad (3.23)$$

where $H(x)$ is the Heaviside step function defined as:

$$H(x) = \begin{cases} 1 & if \quad x \geq 0 \\ 0 & otherwise \end{cases} \quad (3.24)$$

The initial sizes of the cell sub-populations are:

$$(0) = N_0, S(0) = S_0, N_A(0) = N_{A0}, N_B(0) = N_{B0}, N_{AB} = N_{AB0} \quad (3.25)$$

The consequence of this model is that at every instant time

$$N(t) = S(t) + N_A(t) + N_B(t) + N_{AB}(t) \quad (3.26)$$

Equations (3.27) and 3.28) show the rate of change of drug concentration for both drugs at the tumour site during the treatment cycle.

$$\frac{\mathrm{dD_A}}{\mathrm{dt}} = \mathrm{u_A(t)} - \gamma_A \mathrm{D_A(t)}, \qquad \mathrm{D_A(t)} = \mathrm{D_{A0}} \quad (3.27)$$

$$\frac{\mathrm{dD_B}}{\mathrm{dt}} = \mathrm{u_B(t)} - \gamma_\mathrm{B} \mathrm{D_B(t)}, \qquad \mathrm{D_B(t)} = \mathrm{D_{B0}} \quad (3.28)$$

Where $u_A(t) and\ u_B(t)$ are the amounts of drug doses to be infused to the patient's body and γ is drug decay, which is related to the metabolism of drug inside the patient's body. It is noted that the drug concentration $D_A(t)\ and\ D_B(t)$ at the tumour site should not exceed the limit as suggested by equation (3.29) (Martin ad Teo, 1994).

$$\mathrm{D_A(t)} \leq 50 \qquad \mathrm{D_B(t)} \leq 50 \quad (3.29)$$

Equations (3.30) and (3.31) show the relationship between levels of toxicity and drug concentration at the tumour site during the treatment.

$$\frac{\mathrm{dT_A}}{\mathrm{dt}} = \mathrm{D_A(t)} - \eta_\mathrm{A} \mathrm{T_A(t)}\,, \qquad \mathrm{T_A(t)} \leq 100 \quad (3.30)$$

$$\frac{\mathrm{dT_B}}{\mathrm{dt}} = \mathrm{D_B(t)} - \eta_\mathrm{B} \mathrm{T_B(t)}\,, \qquad \mathrm{T_B(t)} \leq 100 \quad (3.31)$$

where $T_A(t) and\ T_B(t)$ are the level of toxicity for both drugs developed inside the patient's body due to chemotherapy drug, and parameter η indicates the rate of elimination of toxicity. Using the above equations, a Simulink model was developed with parameters and values as illustrated in Table 3.2 (Martin and Teo, 1994).

Table 3.2: The parameters of the simulink model (Liang, et al, 2008)

parameters	value	parameter	value
η_A	0.4 day^{-1}	N_{A0}	0
η_B	0.5 day^{-1}	N_{B0}	0
α_A	0.008	N_{AB0}	0
α_B	0.01	k_A	0.0084 day^{-1} D^{-1}
γ_A	0.32 day	k_B	0.0076 day^{-1} D^{-1}
γ_B	0.27 day	λ	-
v_{thA}	10 D	S_0	$4.60517X10^{11}$
v_{thB}	10 D		

3.5 Eight Compartment Model

For multi-drug chemotherapy treatment, three non-cross resistant drugs are denoted by A, B and C, in general, for ease of discussion. A tumour model consisting of eight compartments is considered, as shown in Figure 3.4, to examine the pharmacokinetic and pharmacodynamic effects of three drugs in the patient's body during the treatment. The sub-population $S(t)$ represents the cells which are sensitive to all drugs A, B and C. $N_A(t), N_B(t)\ and\ N_C(t)$ expressed the cells totally resistant to drugs A, B and C respectively. The $N_{AB}(t)$ presents the cells which are doubly resistant for drugs A and B. $N_{Ac}(t)$ and $N_{BC}(t)$ indicates the cells which are doubly resistant for drug A and C, and B and C respectively (Martin and Teo, 1994). The chemotherapy drug A is effective on four sub-populations: $S(t), N_B(t),\ N_C(t)$ and $N_{BC}(t)$. While the chemotherapy drug B is effective on the four sub-populations: $S(t), N_A(t),\ N_C(t)$ and $N_{AC}(t)$, and, on the other hand, the chemotherapy drug C is effective on the four sub-populations, $S(t), N_A(t),\ N_B(t)$ and

$N_{AB}(t)$. The sub-populations of cancer cells that are not resistant to drug A are killed only when the concentration of drug A, v_A is maintained above the drug concentration threshold v_{thA}. Similarly the drug concentration of drug B and C should be raised above the threshold drug concentration v_{thB} and v_{thC} to kill cells which are not resistant to these drugs. The three sub-populations $N_A, N_B \, and \, N_C$ increased by the constant rate $\alpha_{A,}\alpha_B \, and \, \alpha_C$, which are all less than 1 (Martin and Teo., 1994). The total resistance cells for all drugs arise from three directions in parallel, as illustrated in Figure 3.4.

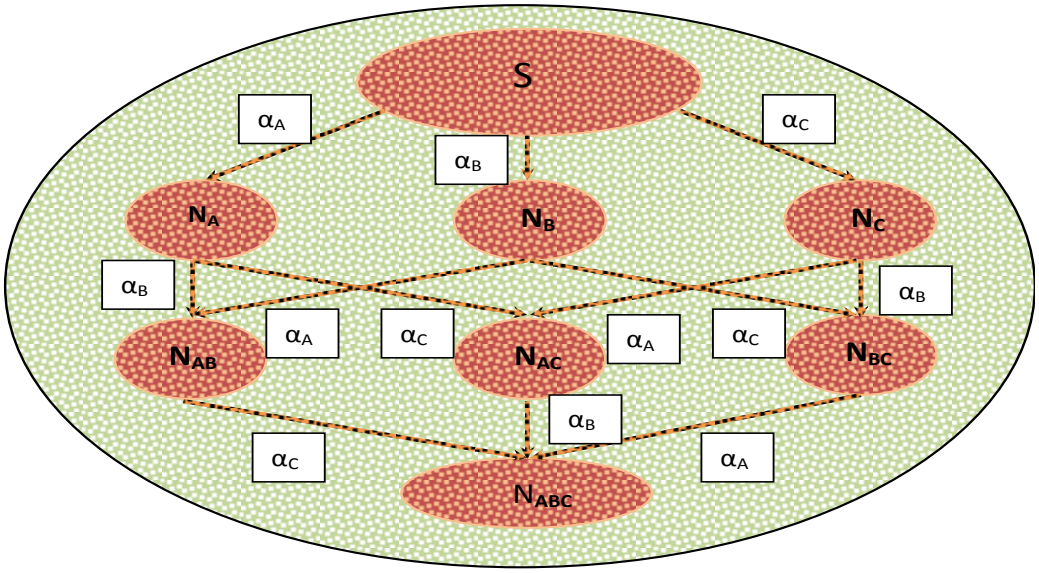

Fig. 3.4 Eight compartments for multi-drug

The proportions of cells killed by drug A from the sensitive and resistant sub-population S, N_B and N_C are the same, similar to drug B and C (Martin and Teo, 1994). If λ indicates the rate of growth of cancer cells and k_A, k_B and k_C are the rate of cancer cells killed by drug unit. Equation 1 describes the sensitive cell for all drugs, where $H(x) = \{1 : \text{if } x \geq 0, \text{otherwise } 0\}$ is the Heaviside step function.

$$\frac{\mathrm{dS}}{\mathrm{dt}} = \lambda[(1-\alpha_A-\alpha_B-\alpha_C)S] - k_A(v_A - v_{thA})H(v_A - v_{thA})S$$
$$- k_B(v_B - v_{thB})H(v_B - v_{thB})S - k_C(v_C - v_{thC})H(v_C - v_{thC})S \quad (3.32)$$

Equation (3.33) represents the resistance cells for drug A and can be calculated for drugs B and C similarly.

$$\frac{dN_A}{dt} = \lambda[(1-\alpha_B-\alpha_C)N_A + \alpha_A S] - k_B(v_B - v_{thB})H(v_B - v_{thB})$$
$$- k_C(v_C - v_{thC})H(v_C - v_{thC}) \quad (3.33)$$

Equations 3.34, 3.35 and 3.36 are for deriving the cells which are doubly resistant.

$$\frac{dN_{AB}}{dt} = \lambda[(1-\alpha_C)N_{AB} + \alpha_B N_A + \alpha_A N_B] - k_C(v_C - v_{thC})H(v_C - v_{thC}) \quad (3.34)$$

$$\frac{dN_{AC}}{dt} = \lambda[(1-\alpha_B)N_{AC} + \alpha_C N_A + \alpha_A N_C] - k_B(v_B - v_{thB})H(v_B - v_{thB}) \quad (3.35)$$

$$\frac{dN_{BC}}{dt} = \lambda[(1-\alpha_A)N_{BC} + \alpha_C N_B + \alpha_B N_C] - k_A(v_A - v_{thA})H(v_A - v_{thA}) \quad (3.36)$$

The initial sizes of the cell sub-populations are:

$$S(0) = S_0\ N_A(0) = N_{A0}, \qquad N_B(0) = N_{B0}, \qquad N_C(0) = N_{C0},$$
$$N_{AB}(0) = N_{AC0}, N_{AC}(0) = N_{AC0},\ N_{BC}(0) = N_{BC0},\ \ N_{ABC}(0)$$
$$= N_{ABC0} \quad (3.37)$$

The consequence of this model is shown in Equation 3.38

$$N(t) = S(t) + N_A(t) + N_B(t) + N_C(t) + N_{AB}(t) + N_{AC}(t) + N_{BC}(t) + N_{ABC}(t) \quad (3.38)$$

Now the rates of change of drug concentration $D_A(t), D_B(t)$ and $D_C(t)$ for drugs at the tumour site during the treatment cycle are shown, where $u_A(t), u_B(t)$ and $u_C(t)$ are the amounts of drug doses to be infused to the patient's body and λ is the drug decay which is related to the metabolism of drug inside patient's body. It should also be noted that all the

drug concentrations at the tumour site should not exceed the limit of 50, as suggested (Martin and Teo, 1994).

$$\frac{dD_Y}{dt} = u_Y(t) - \gamma_Y D_Y(t), D_Y(t) = D_{A0}\,, \text{where } Y = \{A \vdots B \vdots C\} \tag{3.39}$$

The following Equations show the relationship between level of toxicity and drug concentration at the tumour site during the treatment, where $T_A(t), T_B(t) and\ T_C(t)$ are the levels of toxicity for all drugs developed inside the patient's body due to chemotherapy drug and parameter η indicates the rate of elimination of toxicity.

$$\frac{dT_Y}{dt} = D_Y(t) - \eta_Y T_Y(t)\,, \qquad T_Y(t) \leq 100 \quad \text{where } Y = \{A \vdots B \vdots C\} \tag{3.40}$$

where $T_A(t), T_B(t) and\ T_C(t)$ are the levels of toxicity for both drugs developed inside the patient's body due to chemotherapy drug and parameter η indicates the rate of elimination of toxicity. Before the treatment starts, the number of cancer cells is set at 4.60517×10^{11}, as used by many researchers in cell cycle specific cancer treatment (Tes et al., 2007).

3.6 PID Controller

3.6.1 PID controller structure

The controllers are widely used in many different applications, such as industry sectors and it has been proved that the use of controllers enhances the performance of the system and eliminates errors which could affect the outcome of the system. The controllers provide more functions and features, which may require adding equipment, such as sensors, to the system. These additions can add to the expense of the controller. For example, there are many types of controllers which may be applicable in one application but not in another. We have used one of these controllers, a proportional (P), integrative (I) and derivative (D) celled PID controller; where details will be reviewed in the next section. The PID algorithm is the most popular feedback controller used within the process industries (M. Willis, 1999). It has been successfully used in the past for many years. It is a robust, easily understood algorithm that can provide excellent control performance despite the varied dynamic characteristics of process plant.

3.6.2 PID Integrated to the System

The proposed optimal control model and the close loop of treatment delivery in Figure 3.5 shows that the feedback of drug concentration is provided to the controller to correct the errors. The drug dosage (which is the input) will affect the three outputs: toxicity, drug concentration and the cell's population.

The mathematical models of tumour responses for chemotherapy are widely used to predict the tumour responses and to optimise the control parameters. The problem is generally modelled with a set of defferential equations, the aim being to minimise the tumour size by

the drug chemotherapy scheduling. The extensive course of chemotherapy is designed to treat the patient rapidly to reduce the tumour cell after a number of fixed treatment cycles, in order to maximise survival time of the patients.

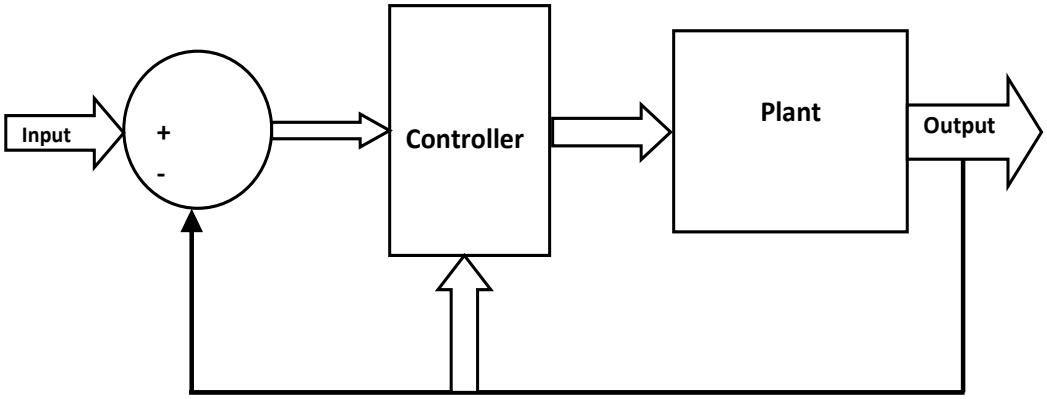

Fig. 3.5 The schematic diagram of the Control Scheme

The I-PD controller algorithm involves three separate parameters: the proportional, integral and derivate values. The proportional value gives a system control input (dosage of drug) proportional to the error, the integral value gives an addition from the sum of the previous errors to the system input (drug doses), and Derivative value gives an addition from the rate of change in the error to the system control input (drug doses). The weighted sum of these three actions is used to adjust the process via a control element, such as the position of a control value.

Three objective functions were considered for the cancer drug chemotherapy. These are discussed below(Martin, 1992):

$$\frac{dx_1}{dt} = \lambda * \kappa(x_2 - \beta)H(x_2 - \beta) \tag{3.41}$$

where χ_1 is a changed variable which is inversely related to the mass of the tumour. The tumour mass is given by $N = 10^{12}\ \exp(-x_1)$ cells, and the initial tumour cell population set at 10^{10} cells (Martin and Teo, 1994).

Equation (3.41) describes the net change in tumour cell population per unit time. The first term in the right- hand side of equation (3.41) describes the increase in cells payable to Cell proliferation and the second term describes the decrease in cells payable to the drug. The parameter (λ) is a positive constant related to the growth speed of the cancer cells and (κ) is the proportion of tumour cells killed per unit time per unit drug concentration, which is assumed to be a positive constant.

$$\frac{dx_2}{dt} = u - \eta * x_2 \tag{3.42}$$

Equation (3.42) describes the net increase in the drug concentration at the cancer site. The variable u is the rate of the delivery of the drug, and the half-life of the drug is $\ln(2)/\eta$. It is assumed that the drug is delivered by infusion, and there is an instantaneous mixing of the drug with plasma, as well as an immediate delivery of the drug to the cancer site. These assumptions represent approximations based on the relative amount of time it takes for the aforementioned activities to occur with respect to the total amount of time over which the treatment is administered.

$$\frac{dx_3}{dt} = x_2 - \eta * x_3 \tag{3.43}$$

Equation (3.43) describes the level of toxicity inside the patient's body after applying the drug dosage, which relates the cumulative drug toxicity to the drug concentration. It is worth

mentioning that the cumulative effect is the integral of the drug concentration over the period of exposure.

3.6.2.1 PID - Controller

Many application processes are nonlinear and thus to be described mathematically. However, it is known that many nonlinear processes can be satisfactorily controlled using PID controllers, providing that the controller parameters are tuned well. Practical experience shows that this type of control has a lot of value, since it is simple and based on three basic behaviour types: proportional (P), integrative (I) and derivative (D). Instead of using a small number of complex controllers, a larger number of simple PID controllers are used to control simpler processes in an assembly application in order to automate the certain more complex process (Vukic, 2002).

The PID controller is the most widely used controller and could be expected to be a backbone of many complex control systems (Astrom et al., 1993). Figure 3.6 shows a block diagram of the basic structure of PID controller, where the input is fed to the three gains of the controller. The input or set-point is added to the feedback of the system in order to eliminate the errors which may be generated during the initialisation of the system, to provide the suitable value to the system.

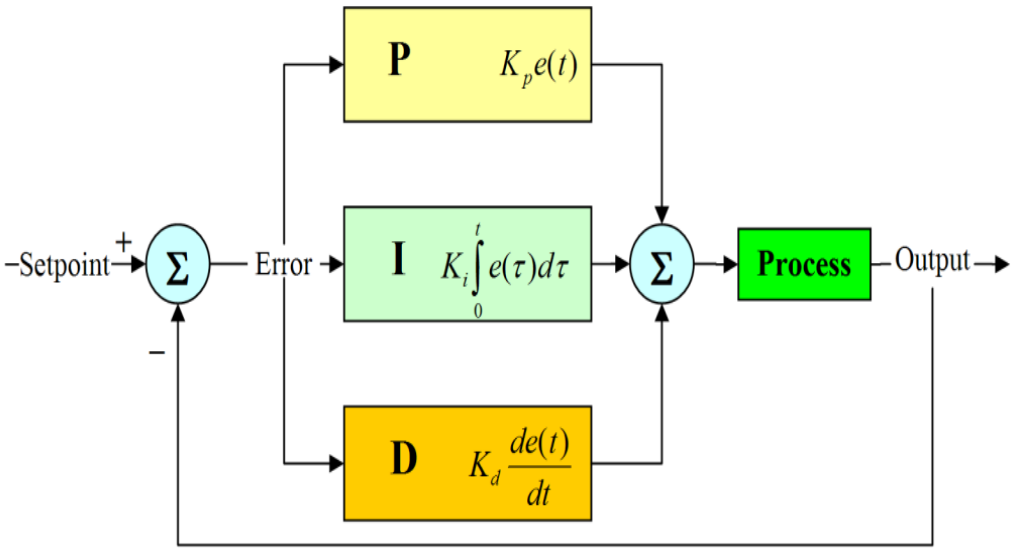

Fig. 3.6 Block diagram of PID controller

The PID controllers use three type of basic parameters or modes, which are P - proportional, I -integrative and D-derivative. While proportional and integrative modes are also used as single control modes, a derivative mode is rarely used on its own in control systems. Combinations such as PI and PD control are very often used in practical systems. It can also be shown that the PID controller is a natural generalization of the simplest possible controller, the On-off controller (Vukic, 2002). Table (3.3) shows the PID controller effects. The PID, as mentioned earlier, has three separate parameters; tuning the system is done by adjusting these three parameters, Kp, Ki and Kd, adding in various amounts of these functions to control how the system behaves.

Table 3.3: Shows the PID controller effects

Effects parameters				
Parameter	Rise time	Overshoot	Settling time	Error at equilibrium
K_p	Decrease	Increase	Small change	Decrease
K_i	Decrease	Increase	Increase	Eliminate
K_d	Indefinite (small decrease or increase)	Decrease	Decrease	None

This section presents an investigation into the development of a model for optimal chemotherapy scheduling to control tumour growth with the PID controller in different structures. This model is based on the cells functions which are used to predict and control the tumour growth and other effects of treatment. We used the Genetic Algorithm (GA) method to optimise the parameter of PID controllers, which are applied with Martin model of drug concentration in order to maximise the cells killing and to minimise the toxic effects to increase the survival time of the patient.

3.7 Genetic Algorithm (GA) for Optimisation

The term Genetic Algorithm or (GA) describes a set of optimisation methods. GAs are adaptive methods, which can be used to search for the optimal solutions and optimisation complex problems. They are based on the genetic processes of biological organisms. Over many generations, natural populations evolve according to the principles of natural selection and survival of the fittest. Genetic algorithms are able to evolve toward better solutions to real world problems, if they have been suitably encoded (Holland, 1975).

GA is started with a set of solutions (represented by chromosomes) called population. Solutions from one population are taken and used to form a new population. This is

motivated by a hope that the new population will be better than the old one. Solutions which are selected to form new solutions (offspring) are selected according to their fitness - the more suitable they are, the more chances they have to reproduce (Marek, 1998).

GAs works with a population of individuals, each representing a possible solution to a given problem. Each individual is assigned a fitness score according to how good a solution to the problem it is. The highly-fit individuals are given opportunities to reproduce by cross breeding with other individuals in the population. This produces new individuals as offspring, which share some features taken from each parent. The least fit members of the population are less likely to get selected for reproduction, and so die out (Chandy, 2006).

A whole new population of possible solutions is thus produced by selecting the best individuals from the current generation, and mating them to produce a new set of individuals. This new generation contains a higher proportion of the characteristics possessed by the good members of the previous generation. In this way, over many generations, good characteristics are spread throughout the population. By favouring the mating of the more fit individuals, the most promising areas of the search space are explored. If the GA has been designed well, the population will converge to an optimal solution to the problem. Genetic Algorithm and Direct Search Toolbox extends the optimization capabilities in MATLAB and optimisation toolbox with tools for using genetic algorithms, simulated annealing and direct search. It is possible to use these algorithms for problems that are difficult to solve with traditional optimisation techniques, including problems that are not well defined or are difficult to model mathematically. These can also be used when computation of the objective function is discontinuous, highly nonlinear, and stochastic or has unreliable or undefined derivatives (Busetti et al., 2001, Chandy, 2006).

3.7.1 Genetic Algorithms

GA as a stochastic optimisation algorithm is motivated by the mechanism of natural selection and evolutionary genetics (Holland, 1975). The basic element processed by a GA is a string formed by concatenating sub-strings, each of which is a numeric coding of a parameter. Each string represents a point in the search space. Selection, crossover and mutation are the main operations of a GA. Selection directs the search of GA towards the best individual. In the process, strings with high fitness receive multiple copies in the next generation, while strings with low fitness receive fewer copies or even none at all. Crossover can cause the exchange of properties of any two chromosomes via random decision in the mating pool and provides a mechanism to produce and match the desirable qualities. Although selection and crossover provide most of the power skills, the solution space will be limited. Mutation is a random alternation of a bit in the string and assists in keeping diversity in the population (Holland, 1975, Goldberg, 1989).

3.7.2 Multi-Objective Genetic Algorithm (MOGA)

Multi-objective optimisation is the search for feasible solutions to problems comprising multiple objectives, which are often in conflict with one other. It can be defined as the problem of finding a vector of decision variables which satisfies constraints and optimises a vector function whose elements represent the objective functions. A multi-objective optimisation problem can be expressed as:

Find the vector $x = [x_1, x_2, x_3 \ldots\ldots x_p]$ which satisfies the m inequality constraints: $g_i(x) \geq 0, i = 1, 2, 3, \ldots\ldots m$, the k equality constraints $h_i(x) = 0,\ i = 1, 2, \ldots\ldots, k,$ and optimises the vector function, $f(x) = [f_1(x),\ f_2(x), \ldots\ldots\ldots f_n(x)]$, where n is the number of objectives to

be considered, $x = [x_1, x_2, x_3 \ldots\ldots x_p]$ is the vector of decision variables, p is the number of decision variables that comprise the complete solution. Practical problems are often characterised by several competing objectives. The multi-objective optimisation problem is the problem of simultaneously minimising the n components $f_k, k = 1, \ldots\ldots, n$ of a possibly nonlinear vector function f of a general decision variable x in a universe U, where $f(x) = [f_1(x),\ f_2(x), \ldots\ldots\ldots f_n(x)]$. The problem usually has no unique, perfect solution, but a set of non-dominated solutions, known as the Pareto-optimal set (Deb, 2001).

3.7.2.1 Algorithm description

The MOGA optimisation process consists of a standard GA with multi-objective ranking, and with fitness sharing and mating restriction (Fonseca et al., 1993). A randomly selected population is generated within a specific range. Each individual of the population is evaluated with the objective functions. Then, each solution is checked for its domination in the population and a rank value is assigned to it. The ranking procedure can be explained through Figure 3. 7. For a two-objective minimisation problem, individuals that fall close to either the axes or origin of 2D objective space are better than those away from axes or origin. In the objective space some individuals may be found, such as, A, F, G, E etc., falling on the outer edge and close to the axes or origin and with one objective better than another, and form a set called the non-dominated solution set or Pareto optimal set. Individuals A, E, F, G etc. are called non-dominated because no other individuals provide better performance in the objective space. On the other hand, individuals falling away from the edges, such as, B, C, D etc., are called dominated solutions since many individuals provide better performance than these in terms of both objectives. For example, individual A dominates individual B, and similarly B dominates C and C dominates D in the objective space in terms of both

objectives. Each individual is ranked according to their degree of dominance, i.e., number of individuals that are better than that in terms of both objectives. An individual's ranking equals the number of individuals better than that in terms of both objectives plus one (See Figure 3. 7).

To a solution i, a rank r_i is assigned as: $r_i = 1 + n_i$ where n_i is the number of solutions that dominate the solution. In this way, non-dominated solutions are assigned a rank equal to 1, since no solution would dominate a non-dominated solution in a population. The maximum rank of any solution cannot be more than N (the population size). It is clear that the ranking procedure may not assign all possible ranks (between 1 and N) to any population. For example, ranks 5, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18 are missing in the population used in the Figure 3.7 Detail on ranking can be found in Fonseca, et al., (1995).

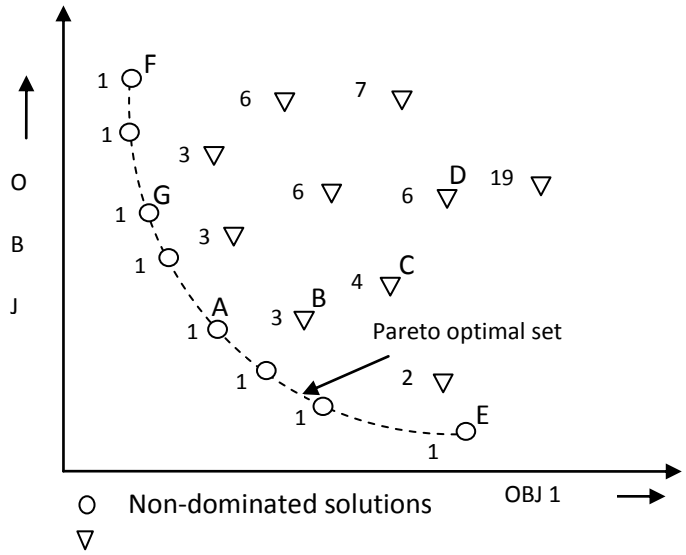

Fig. 3.7 Dominated and non-dominated solutions with rank values

Once the ranking is performed, a raw fitness to a solution is assigned based on its rank. To perform this, first the ranks are sorted in ascending order of magnitude. Then a raw fitness is

assigned to each solution by using a linear (or any other) mapping function. Usually, the mapping function is chosen so as to assign fitness between N (for the best-rank solution) and 1 (for the worst-rank solution). Thereafter, solutions of each rank are considered one at a time and their raw fitnesses are averaged. This average fitness is then called the assigned fitness to each solution of the rank. In this way, the total allocated raw fitness and total assigned fitness to each rank remain identical.

Moreover, the mapping and averaging procedure ensures that better ranked solutions have higher assigned fitnesses. In this way, non-dominated solutions are emphasised in a population. (Fonseca et al., 1993, Deb, 2001, Fonseca and Fleming, 1998). The rest of the algorithm is the same as that in a classical GA. Selection uses Baker's stochastic universal sampling algorithm (Baker, 1987), which is optimal in terms of bias and spread. GA operators, namely crossover and mutation, are employed on the selected individuals to form the next generation (Goldberg, 1989). Selected parents are paired up and recombined with high probability (0.8). Mating restriction is implemented by forming pairs of individuals within a distance of each other in the objective space, where possible. Reduced-surrogate shuffle crossover (Booker, 1987) is used for recombination. The mutation rate for this optimisation process was set at 0.01%. The algorithm flowchart is presented in Figure 3. 8.

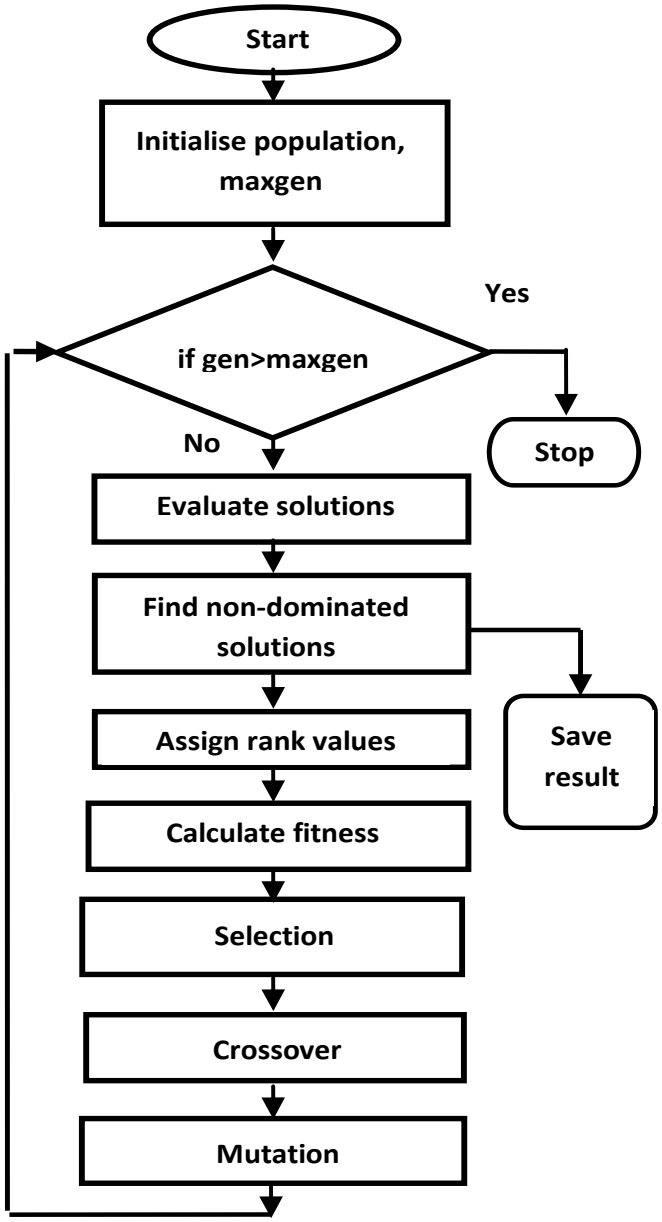

Fig. 3.8 Flowchart of MOGA optimisation

There are various flavours of MOGA in circulation, varying in implementation of these parameters, but in essence the algorithms all follow a standard procedure, described below.

Start with a randomly generated population of n l-bit strings, which initialise population. Maxgen, the number of gen will be compared with the limitation maxgen (if gen > maxgen)

that mean the processing will stop; if not will continue to evaluate the solutions or offer desired outputs.

- Calculate the fitness f(x) of each string in the population.
- Repeat the following steps until n new strings have been created:
    - Select a pair of parent strings from the current population, the probability of selection being an increasing function of fitness. Selection is done "with replacement" meaning that the same string can be selected more than once to become a parent.
    - With the crossover probability, cross over the pair at a randomly chosen point to form two new strings. If no crossover takes place, form two new strings that are exact copies of their respective parents.
    - Mutate the two new strings at each locus with the mutation probability, and place the resulting strings in the new population.

3.8 Summary

The most important challenge of cancer treatment is to maintain the normal physiological states of the patient's body system during the course of different treatment schedules. This can be achieved by optimising chemotherapy treatment in such a way as to reduce tumour burden to a minimum level with minimum/acceptable toxic side effects. The other factors considered in chemotherapy include the stage of the disease, scheduling of the therapy and interaction of the drugs. The mathematical models are generally developed based on a set of differential equations. The purpose of using mathematical models for cancer chemotherapy is to predict and control the course of the disease when a treatment is scheduled.

The multi-objective optimal chemotherapy control model aims to reduce the number of cancer cells after a number of fixed treatment cycles with minimum side effects. Close-loop control methods, namely I-PD and PID, are designed to control the drugs to be infused to the patient's body. In the proposed method, several design objectives, constraints and associated goal values are defined prior to the optimisation process and a wide range of solutions have been obtained satisfying all design goals and trading-off between two main but conflicting objectives of chemotherapy treatment; reducing cancerous cells and reducing toxic side effects. It is interesting to note that the design approach can offer flexibility in decision making and suitable solutions can be picked under different trade-off conditions. Many solutions may be found out of this method, as will be discussed in subsequent Chapters, and used to reduce the number of cancerous cells to a very low level, not achieved so far. Moreover, the average toxicity level and drug doses during the treatment are also found to be low.

One or more compartment models of cancer cells population have been considered as will in order to show the transition rates between proliferating and quiescent cells as non-specified functions of the total population. The understanding of the cell's behaviours and division improves the treatment effectiveness. Some of the treatment models considered the cancer cells as one and many compartments, based on the mutations and behaviours of all cancer cells. The big challenges are to balance the benefits and the side-effect of the chemotherapy cancer treatment. The proliferating cells at the tissue are considered as active cancer cell and need to be treated and divided to compartments called phase specific.

The single drug model has been designed for one compartment as a basic and standard cancer chemotherapy drug scheduling. The multi-drug regimen models are designed as well to avoid the weakness of the some chemotherapy cancer drug treatment models. The cancer cells

divided for example on four and eight compartments, based on the sensitivity of the cancer cell to the drug.

CHAPTER 4

The Experiments and Results

4.1. Non phase specific treatment

The simplest mathematical models which are commonly used in research for optimal control of cancer chemotherapy consider entire cell cycle as one compartment (Martin, 1992, Swierniak, 1994). In many cases, these single compartment models prove to be inadequate and do not seem realistic due to the over simplified nature of the model compared to actual biological system. The actions of chemotherapy agents are based upon an understanding of the cell cycling mechanisms. In general, the cell cycle comprises of five stages which should passes thorough dependents of the type of the cell as shown in Figure 2.2 in Chapter 2.

Matlab Simulink toolbox provides an interactive, graphical environment for modelling. The whole simulation is carried out in the Simulink environment with some m-files of Matlab (The Mathworks, Inc., 2010). The simulink model is chosen because it allows simple construction of control system with simple built-in components. Differential equations associated with relevant parameters were implemented in Simulink to develop a mathematical model of body metabolism, cell functions and their response to chemotherapy treatment to predict the number of tumour cells and to optimise the control parameters.

An automated close-loop control method is also developed to design the drug doses during the whole treatment period. Figure 4.2 shows the proposed chemotherapy drug scheduling scheme where drug concentration of the patient model is used as the feedback signal in order

to maintain a predefined level of drug concentration at the tumour site. In this investigation, a feedback control system was used including a Proportional-Integral-Derivative (PID) (Astrom, et el, 1993) and a variant of it (different structures of PID), namely Proportional-Integral-Derivative (PID) were designed to control the drugs to be infused to the patient's body. The proposed controllers; both PID and I-PD, involve three parameters: the proportional gain k_p, integral gain k_i, and derivative gain k_d. One of the outputs of the model $x_2(t)$ including the drug concentration is compared with a predefined reference level x_{r2} and an error signal $e(t)$ is generated by the difference between the reference input and drug concentration as follows:

$$e(t) = x_{r2} - x_2(t) \tag{4.1}$$

The error signal is used to generate the output of PID controller, $u(t)$ as:

$$\mathrm{u(t)} = \left[\mathrm{k_p e(t)} + \mathrm{k_i} \int_0^{\mathrm{t}} \mathrm{e(t)dt} + \mathrm{k_d} \frac{\mathrm{d}}{\mathrm{dt}} \mathrm{e(t)}\right] \tag{4.2}$$

Here, the first term of equation (4.2) gives a system control input (drug doses) proportional with the error $e(t)$, the second term (integral) gives an addition from the sum of the previous errors and last term gives an addition from the rate of change in the error to the system control input (drug doses).

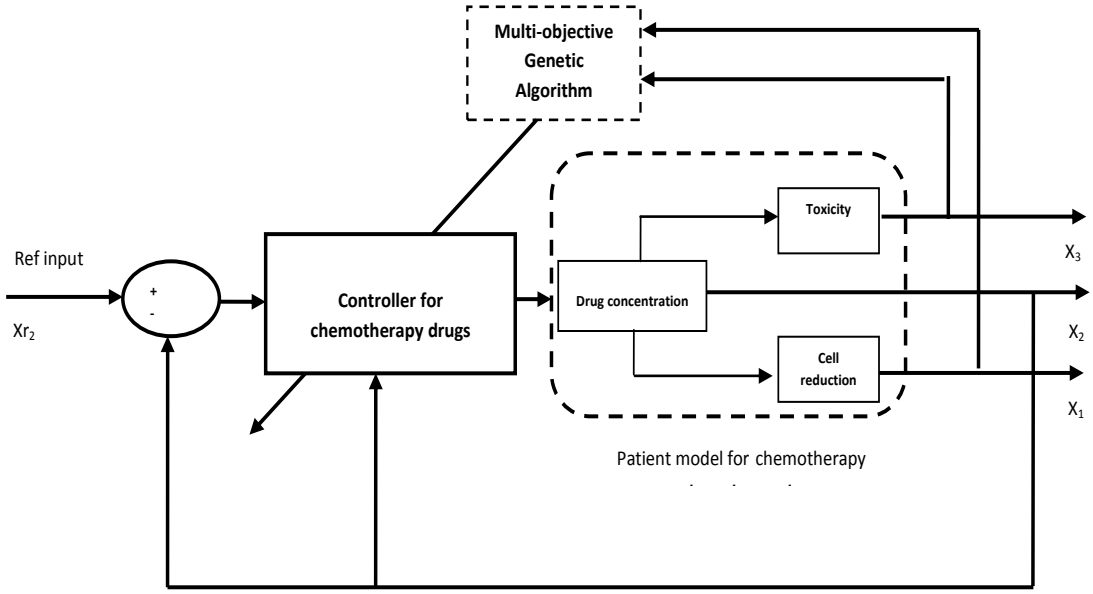

Fig. 4.1 Schematic diagram of proposed Control Scheme

In order to evaluate the effectiveness of MOGA in chemotherapy drug scheduling, several representative solutions are further assessed. To validate all solution sets, three solutions are selected on each Pareto front, one from each region. The solutions are selected in such a way that two fall on either extremes points of the two objectives, the other is at approximately in the middle of objective domain. Three selected solutions for PID with Rep & Cont (Repeated and Continuous), as shown in Figure 4.3(a) are denoted as PID-1, PID-2 and PID-3, for I-PD with Rep & Cont, see Figure 4.4(a) are denoted as I-PD-1 and I-PD-3 for the drug doses. Similarly three solutions are selected from each Pareto fonts of Figure 4. 3(b) where Rep is used as reference input with I-PD and PID controllers. These solutions are indicated as: PID-4, PID-5, PID-6, I-PD-4, I-PD-5 and I-PD-6 respectively.

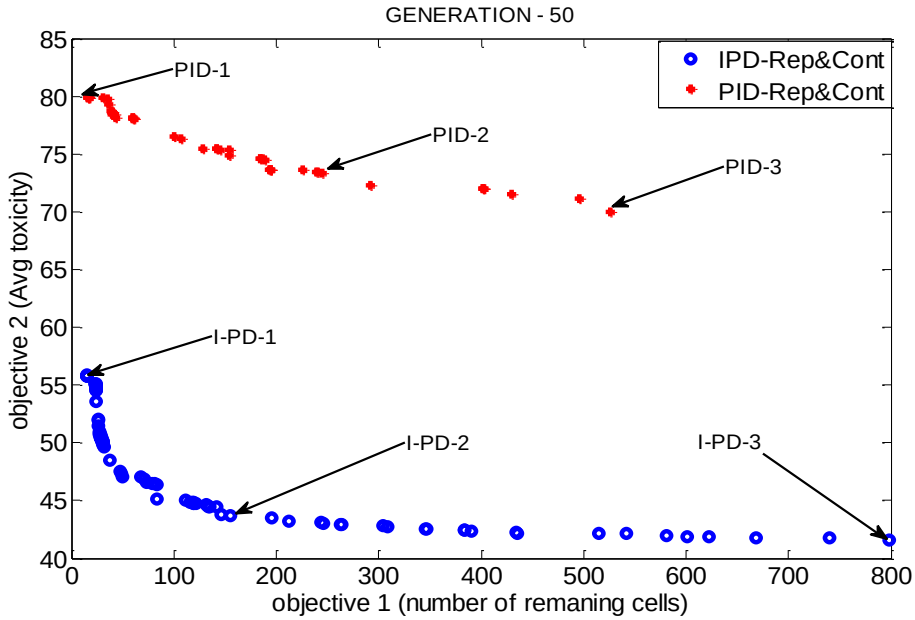

Fig. 4.2(a) Pareto optimal solution sets with Rep & Cont for PID and I-PD controllers

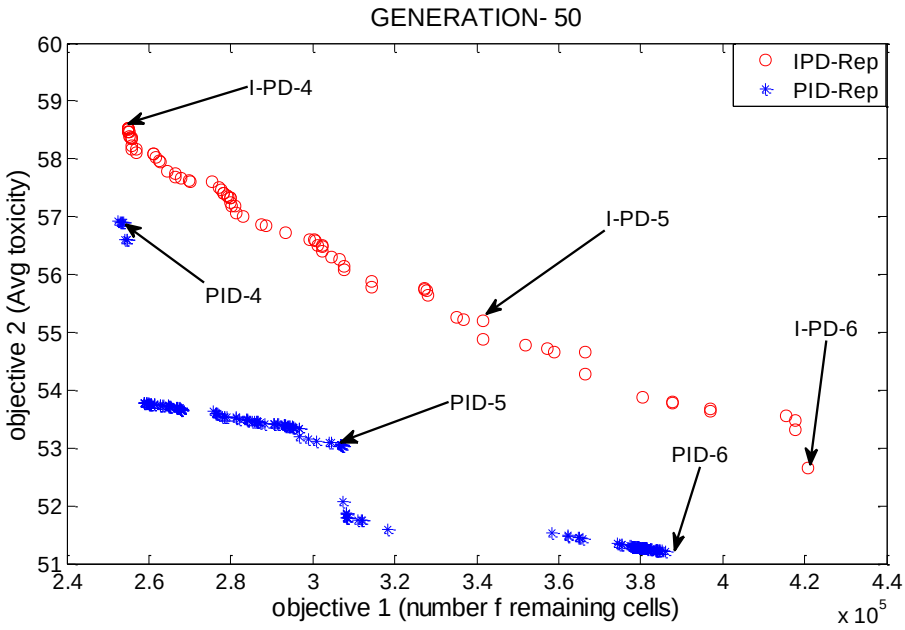

Fig. 4.2 (b) Pareto optimal solution sets with Rep for PID and I-PD controllers

4.1.1. Results

To obtain different performances, three decision variables, k_p, k_i and k_d corresponding to each aforementioned solution were fed to the I-PD and PID controllers and the whole system along with the patient model is simulated for 84 days. Then the output of the controller, $u(t)$, which is the desired chemotherapy drug scheduling and all outputs of the patient model, such as, drug concentration at the tumour site, toxicity and reduction in cancerous cells were recorded. For all solutions, average and maximum values of drug doses, drug concentration and toxicity during the whole period of treatment and number of remaining cells at the end of the treatment are shown in Table 4.1, where the minimum values considered as zero. It is important to note that, the selected solutions cover all solutions in the objective domain generated by MOGA optimisation process.

Table 4. 1 Performances of selected solutions

Controller type	Ref. Input to the controller	Selected Solutions	Drug Doses		Drug Concentration		Toxicity		Reduction of cancerous cells (at the end of 84 days)	
			Max	Avg	Max	Avg	Max	Avg	Cancer Cells remaining	% reduction
IPD	Rep & Cont	IPD-1	18.5	11.7	50	32.3	98.7	55.7	15	≈ 100%
		IPD-2	14.6	8	39.5	21.8	98.7	43.5	145	≈ 100%
		IPD-3	14.6	7.2	39.4	19.6	98.6	41.3	798	≈ 100%
	Repeated	IPD-4	18.4	9.4	49.6	25.4	67	58.5	$2.5x10^5$	> 99%
		IPD-5	11.8	8.9	32	24	66.4	55.3	$3.3x10^5$	> 99%
		IPD-6	10.7	8.4	28.8	22.8	66.4	52.7	$4.2x10^5$	> 99%
PID	Rep & Cont	PID-1	18.5	12.8	50	34.5	98.8	80.5	16	≈ 100%
		PID-2	14.6	11.7	39.5	31.6	98.8	76	193	≈ 100%
		PID-3	14.6	11.3	39.5	30.6	98.7	70	526	≈ 100%
	Repeated	PID-4	15.7	8.7	42.3	23.5	70	57	$2.5x10^5$	> 99%
		PID-5	12.6	8.4	34	22.6	63.3	53.2	$2.9x10^5$	> 99%
		PID-6	11.3	8	30.7	21.5	62.9	51.2	$3.8x10^5$	> 99%

4.1.1.1 Drug Scheduling

The reference input to the controller, x_{r2} is the desired drug concentration to be maintained at the tumour site while delivering drugs into patient's body. The reference input should be chosen in such a way that the drug concentration should remain within the limit as indicated by equation (3.5) in Chapter 3. This will not only enable the chemotherapy drugs kill cancerous cells but also limit the toxic side effects. Two types of reference inputs are designed and tested with both PID and IPD controllers in this work and these are: (i) Repeated and Continuous and (ii) Repeated. For ease of discussions, these two reference inputs will be indicated as Rep&Cont and Rep throughout the paper. The design of reference inputs is motivated by clinical evidences and some state of the art works in this field (Liang et al., 2008).

In case of Rep&Cont, the desired drug concentration is set to a maximum value of 50 for the first two days. This implies higher drug doses at the beginning of the treatment which has strong relevance in clinical practice (Liang et al., 2008). To avoid risks of toxic side effects, the desired reference level is reduced by 10% for the next couple of days and then reduced to almost zero next two days. For the remaining period of the treatment, the reference for drug concentration is set at 40 which is 20% less than the initial value. For clarity, Figure 4.3(a) shows the reference input Rep&Cont for the first two weeks. It is mentioned that the treatment is design for 12 weeks (84 days) as suggested by many researchers (Martin and Teo., 1994, Liang et al., 2008). The fixed level of reference from day 6 to the end implies stable drug concentration as well as drug doses for that period.

For reference input Rep, the desired drug concentration is set to maximum allowable value of 50 for one day followed by a minimum value of zero for next day and this pattern repeats

for 84 days of treatment. The close-loop control method results high doses with high reference and low doses with low reference level. The low reference level for alternate days may be attributed to rest days as observed in clinical doses. More importantly this will help reduce the toxic side effects during the treatment. Figure 4.3(b) shows the reference input Rep for the first two weeks, for clarity, and it repeats similar pattern for the remaining days of treatment.

The efficacy of the drug doses depends on three parameters K_i, K_p and K_d of PID and I-PD controllers. In this work, Rep&Cont and Rep are used as the reference inputs to the close-loop control system. For Rep&Cont as reference input with a specific value, as mentioned above will ensure approximately a constant level of drug concentration for most of the time of the treatment cycle. With reference input, Rep, although the drug concentration will fluctuate, it will remain below the maximum allowable value.

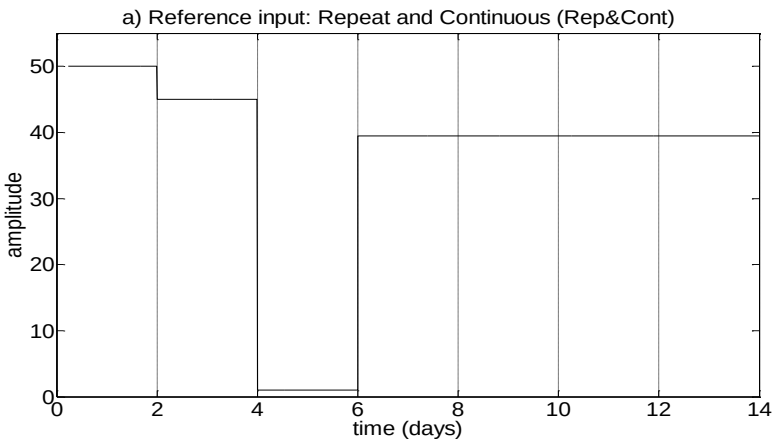

Fig. 4.3 (a) Reference input: Rep&Cont

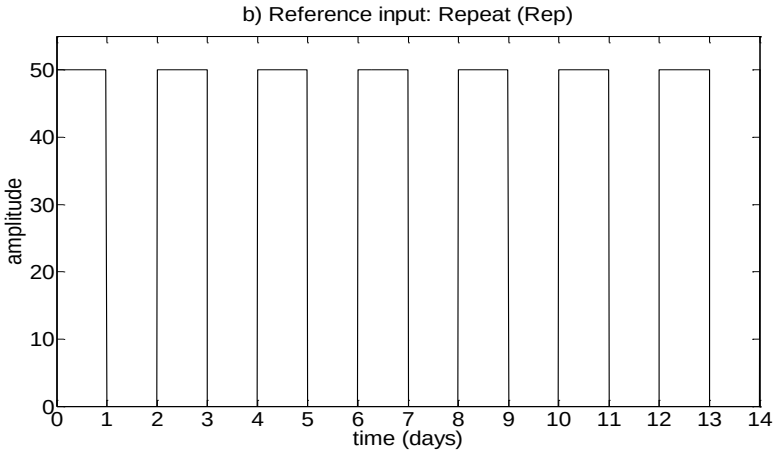

Fig. 4.3 (b) Reference input: Rep

Maximum drug doses during the whole period of treatment vary in the range of 10-19 while average of it remain within 8-13 for I-PD and PID, respectively. Figure 4.4(a) shows the chemotherapy drug scheduling for solutions; I-PD-1, I-PD-3, PID-1 and PID-3. For clarity, solutions lying on extreme ends of Pareto fonts are selected and responses of other solutions will remain within the limits of these solutions.

It is noted that, above four solutions use Rep & Cont as the reference input. For solutions I-PD-1 and PID-1, the drug doses sharply rise to a maximum value of 18.5 in first two days of treatment and then slightly reduce on days 3 and 4 followed by a sharp decrease on days 5 and 6. The drug doses then rise sharply to a level of nearly 14.5 and remain almost stable till the end of the treatment following the input reference (input dosage). The drug doses, for solutions, I-PD-3 and PID-3, rise slowly and steadily in first few weeks and then reach almost the same stable level in 8 weeks time. Figure 4.4(b) shows the chemotherapy drug scheduling for solutions; I-PD-4 and PID-4 where the reference input is Rep. In both cases, the drug doses increase sharply in first two days and then fluctuate within a range of 6-12 for the whole period of treatment to balance between the input and the feedback which

increase the effectiveness of the treatment. It is important to note that the drug doses are relatively lower for all solutions.

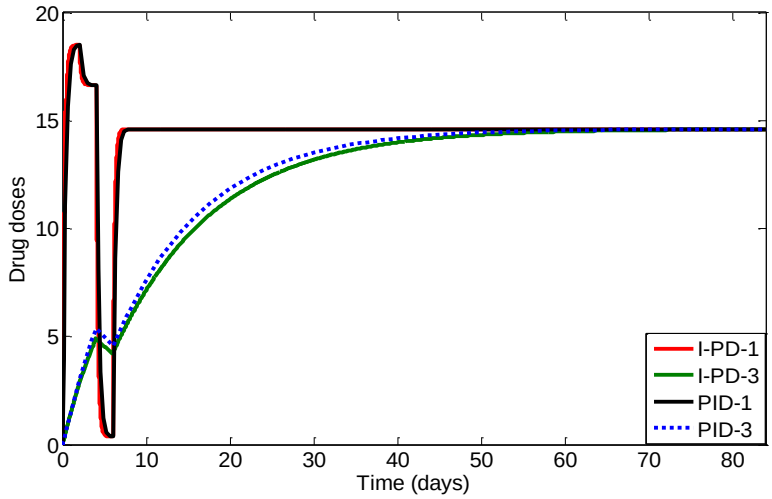

Fig. 4.4 (a), Drug doses throughout the whole period of treatment

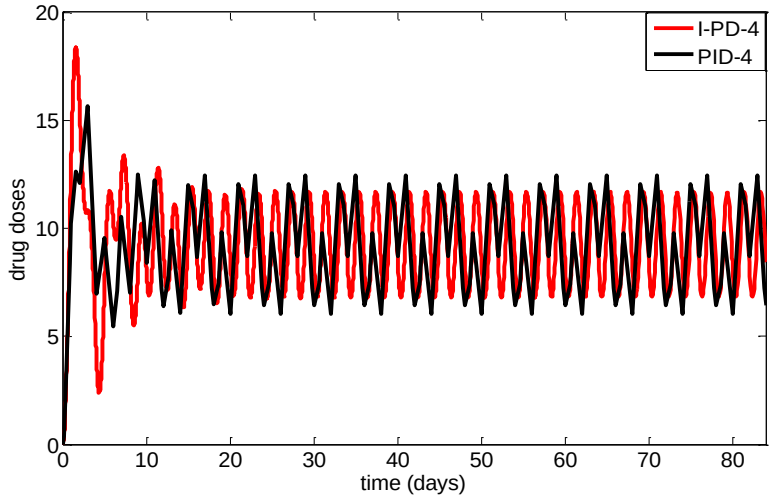

Fig. 4.4 (b) Drug doses throughout the whole period of treatment

4.1.1.2 Drug Concentration

The cancer drugs were infused to the patient body during the whole period of the treatment cycle. The drug flow with the blood stream depends of the metabolism of the patient body. Drug concentrations in the blood can be determined and a plotted against time. In most instances, the time course of a drug's concentration in the plasma correlates well with the onset, intensity, and duration of the pharmacologic effect (Laurence, et al., 2005). Thus, the measurement of sequential plasma concentration of drugs after their administration is used to establish dosage regimens that are likely to produce the desired therapeutic levels for appropriate periods of time, without the risk of drug failure or toxicity. Toxic drug levels may be observed when the body's normal mechanisms for metabolising and excreting drugs are impaired, as commonly occurs in patients with liver or kidney disorders and in infants with immature organs (P. Blackall, 2010).

In this work, the chemotherapy drug scheduling is obtained with PID and I-PD controllers and MOGA optimisation process throughout the whole period of treatment cycle. More importantly, the drug doses are much lower compared to conventional doses during 84 days of treatment. It is important to note that, the optimal doses of chemotherapy drugs are in general, and lower doses of these drugs can reduce the toxic side effects during the treatment cycle and thereby improve the quality of life of the cancer patient. Figure 4.5(a) shows the drug concentration against desired/reference input for solutions; I-PD-1, I-PD-3, PID-1 and PID-3 at the tumour site due to chemotherapy drug scheduling obtained for those cases. It is interesting to note that, the drug concentration increases and decreases with time in a similar manner as observed in case of drug scheduling. Figure 4.5(b) shows the drug concentration for solutions; I-PD-4 and PID-4 where the reference input is Rep and it also follows the corresponding drug scheduling as observed in Figure 4.5(b). It is important to note that, drug

concentrations for all solutions remain within the limits set by condition and average values are below 35 which are significantly lower compared to maximum allowable value 50.

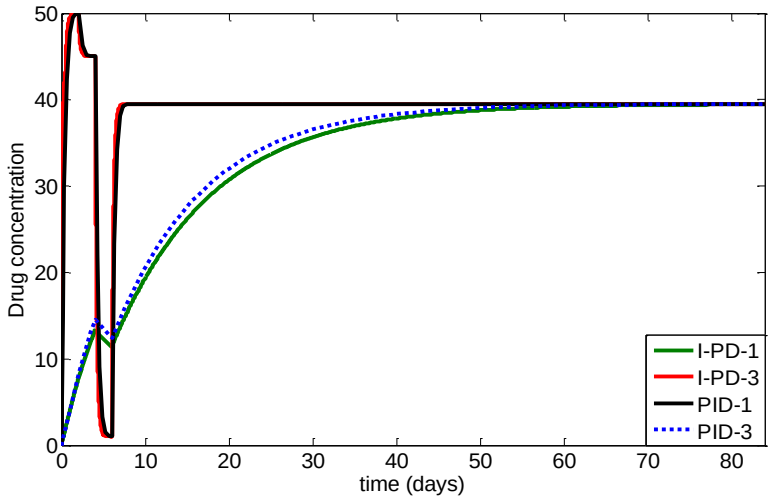

Fig. 4.5(a), Drug concentration throughout the whole period of treatment

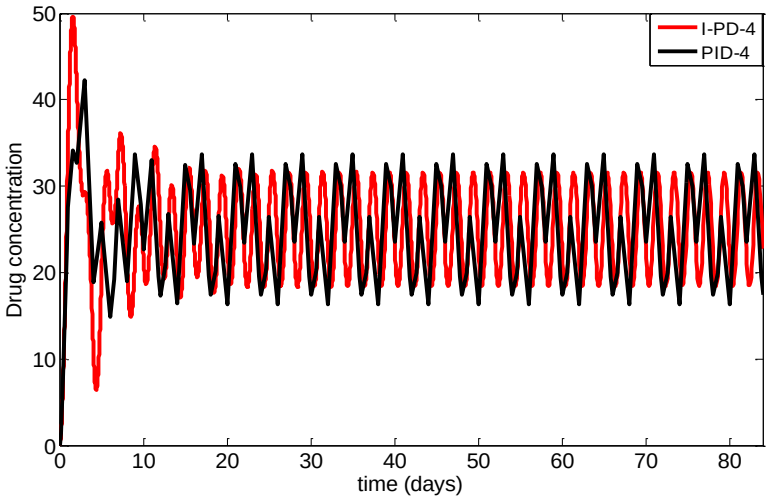

Fig. 4.5(b), Drug concentration throughout the whole period of treatment

4.1.1.3 Toxicity

The maximum and average toxicity of all selected solutions are determined during the whole period of treatment and shown in Table 4.1. It is important to note that the maximum

toxicity for all solutions are always lower than the maximum allowable value as mentioned in the conditions and average toxicity levels are far lower than this. The toxicities, for I-PD-1, I-PD-3, PID-1 and PID-3, developed due to the corresponding chemotherapy drug scheduling are shown in Figure 4.6(a). For I-PD-1 and PID-1, the toxicity sharply rises in first two days because of high drug doses infused to the patient. The toxicity then reduces and finally gets stable for the whole period at approximately a level of 98. For solutions I-PD-3 and PID-3, the toxicity gradually increases and becomes stable at nearly same value in 8/9 weeks time. Figure 4.6(b) shows the level of toxicity for solutions I-PD-4 and PID-4 where reference input is Rep. The toxicity sharply increases to a level of 60 in first week of treatment and then fluctuates between ranges of 58-68 for the remaining period. It is important to note that, toxicities in all cases remain under control and lower than the maximum limiting value set in design objective and constraint of the optimisation process.

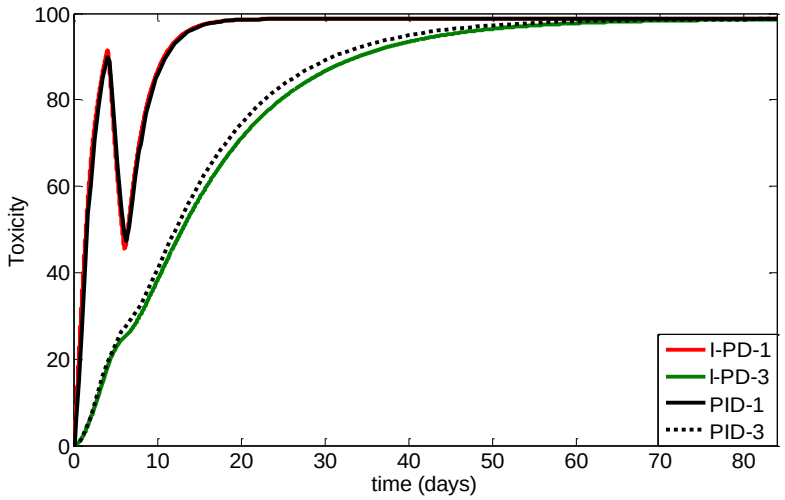

Fig. 4.6(a), Toxicity throughout the whole period of treatment

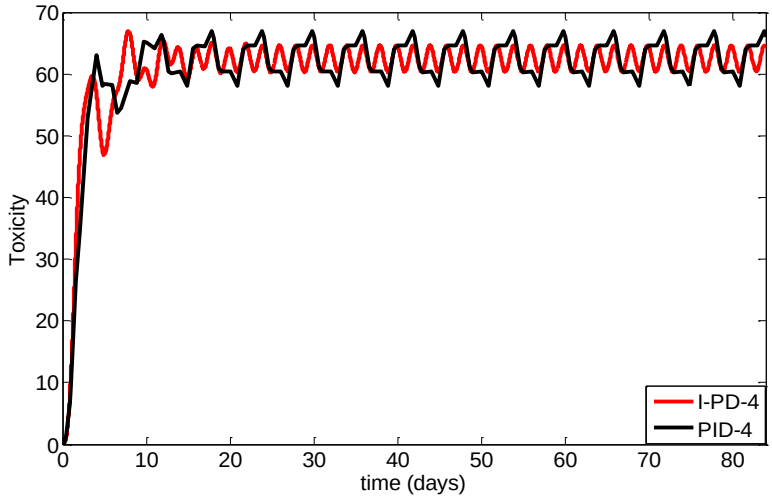

Fig. 4.6(b), Toxicity throughout the whole period of treatment

4.1.1.4 Reduction of cancerous cells

A reduction of the cancerous cell is considered as the main aim of chemotherapy treatment. Before the treatment starts, the number of proliferation cells is set at $1x10^9$, as used by many researchers (Martin and Teo, 1994, Liang et al, 2008) and the reduction of cancerous cells for all solutions are more than 99% with some approaching to 100%. The maximum cell reduction is obtained with a drug scheduling corresponds to solution I-PD-1, followed by PID-1 and I-PD-2. The number of remaining cells is much lower with reference (Rep & Cont) while this number is in the range of 10^5 with reference input Rep for both PID and I-PD controllers.

Figure 4.7(a) shows the reduction of cancerous cells during the whole period of treatment for solutions I-PD-1, I-PD-3, PID-1 and PID-4. For solutions I-PD-1and PID-1, at the first three days of the treatment the cancer cells look continuing growing until the drug dosages take place at the patient body, after that when drug becomes effective the rate of cell reduction is very high then further reduced remarkably in 3 weeks time. The numbers of cancer cells

remaining at the end of treatment for I-PD-1 and PID-1 were are 15 and 16 respectively. For solutions, I-PD-3 and PID-3, the rate of reduction was rather slow at the beginning but significant after 6 weeks. Figure 4.7(b) shows the reduction of cancerous cells for solutions I-PD-4 and PID-4. In both cases the rate of reduction is steady and reduces to a significant level within 6 weeks of the treatment.

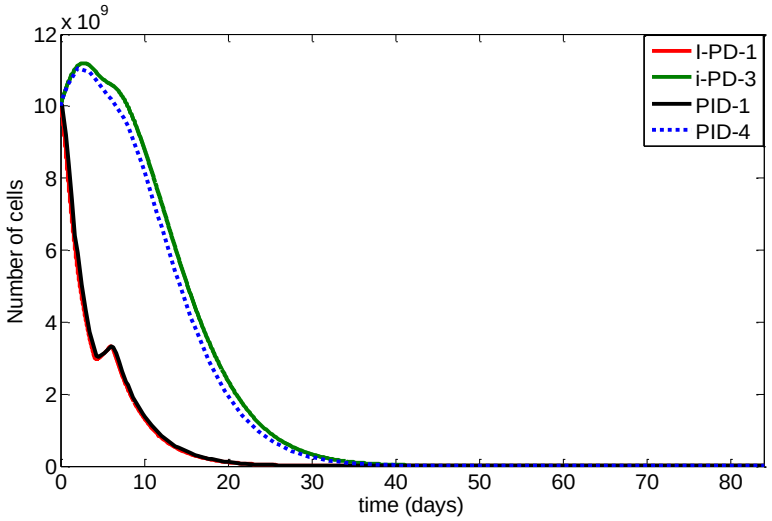

Fig. 4.7(a),Cells reduction throughout the whole period of treatment

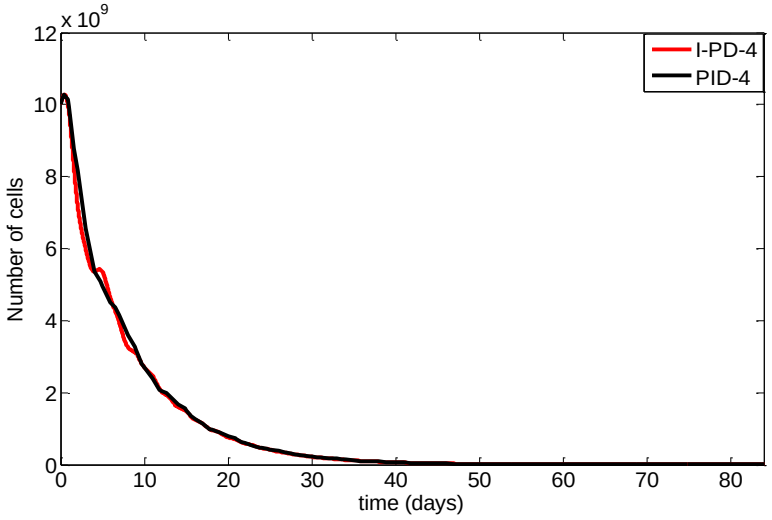

Fig. 4.7(b) Cells reduction throughout the whole period of treatment

4.2 Specific Cancer cells treatment

As mentioned earlier, the main aim of chemotherapy treatment is to eradicate/minimise the cancer cells at the tumour site with minimum toxic side effects produced by the drug throughout the whole period of the treatment. Very often, cancer cells grow resistance to a drug if it continues for a long time and resistance to drug causes failure to treatment in most cases. The combinations of multiple drugs can decrease the drug resistance (Martin and Teo, 1994). Toxic side effects developed due to the infusion of chemotherapy drugs always pose a major challenge in drug scheduling. So drug doses and their cycles of intervals must be designed in such a way as to make the treatment effective, i.e., eradicate the tumour with minimum/tolerable toxic side effects.

The actions of the cancer chemotherapy drugs are based upon an understanding of the cell cycling mechanisms in order to make the course of the treatment more effective. A number of models have been developed to study and analyse the effects of drugs on cancer cells by dividing the tumour into number of sub-populations (Tes, et, al, 2007, Martin and Teo, 1994, Panetta and Adam, 1995). In 1994, Martin introduced a model for two non-cross resistant agents who considered interaction between drug concentrations during the treatment within the patient body and the cells. A model has been developed for cancer chemotherapy drug scheduling to improve the performance throughout whole period of the treatment based on drug scheduling.

A schematic diagram of chemotherapy drug scheduling scheme for cancer treatment is shown in Figure 4.8. A feedback control method was developed in order to maintain a predefined level of drug concentration at tumour sites. A variant PID control, namely I-PD was used to control the drug to be infused to the patient's body. The proposed I-PD controller was used to

control the drug to be infused to the patient's body involving three parameters, the proportional gain k_p, integral gain k_i, and derivative gain k_d, Drug concentration at the tumour is used as the feedback signal to the controller which is compared with a predefined reference level. The difference between reference input and drug concentration at tumour site, output- $D(t)$, of the model is called the error which was used as input to the controller. The integral value gives an addition from the sum of the previous errors to the system input (drug doses).

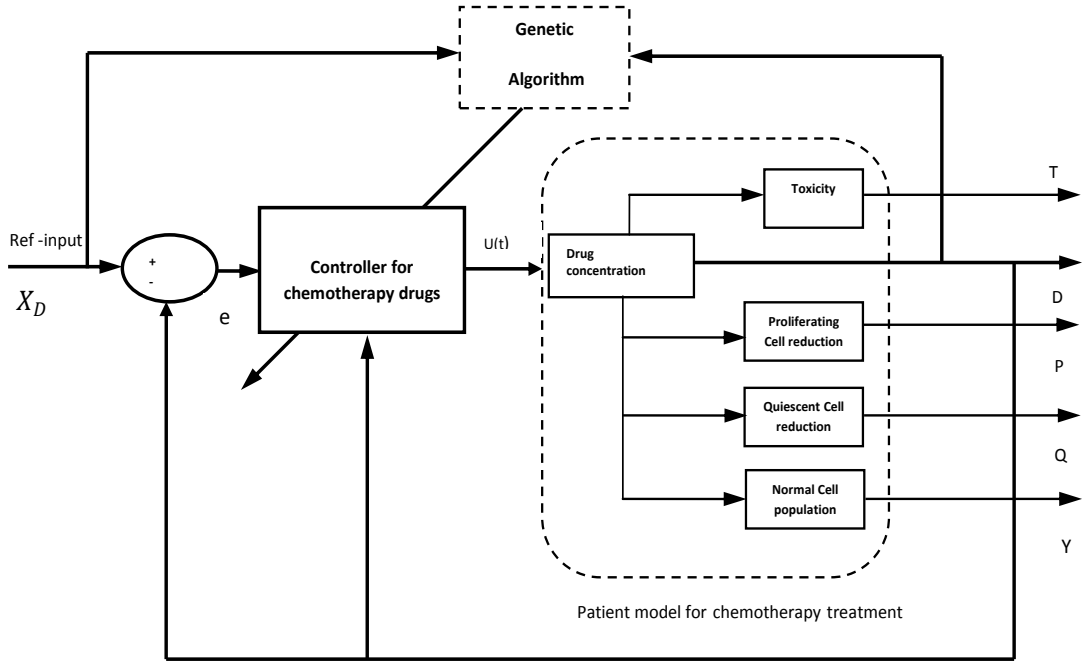

Fig. 4.8 Schematic diagram of the proposed drug scheduling scheme

In the control model, the 'Proportional' value gives a system control input (drug doses) proportional to the feedback signal $D(t)$ and 'Derivative' value gives an addition from the rate of change in the $D(t)$ to the system control input (drug doses). The output of the controller $u(t)$ as:

$$\mathrm{u(t)} = \mathrm{K_i} \int_0^t \mathrm{e(t)dt} - [\mathrm{K_d} \frac{\mathrm{d}}{\mathrm{dt}} \mathrm{D(t)} + \mathrm{K_p D(t)}] \qquad (4.3)$$

In order to evaluate the effectiveness of MOGA in chemotherapy drug scheduling, several representative solutions were further assessed. To validate the solution set, three solutions were selected on the Pareto front, one from each region. The solutions were selected in such a way that two fall on either extremes points of the two objectives, the other is at approximately in the middle of objective domain. Three selected solutions, as shown in Figure 4.9 which denoted as Case-1, Case-2 and Case-3 for further discussion. As mentioned earlier, an I-PD controller was developed to design the chemotherapy drug doses for cell cycle specific cancer treatment. The close-loop controller was designed in such a way that drug concentration, one of the outputs of the patient model can be maintained to the tolerable level which set by predefined level of the reference input to the controller.

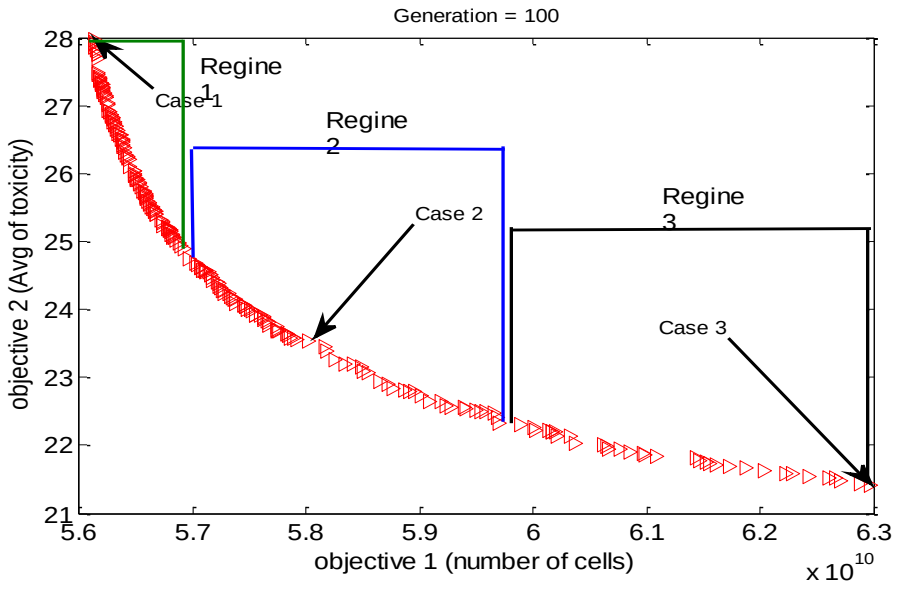

Fig.4.9 Shows three selected solutions, Case-1, Case-2 and Case-3

4.2.1. Results

At the beginning, when no drug was infused, the output was also zero where is considered as minimum value and the difference between the reference input and model output $D(t)$ is maximum. The difference gradually decreases with increasing time (days) and

after few weeks the difference becomes very small and then reduces to nearly zero. To make the chemotherapy drugs effective, the drug concentration at the tumour site should be maintained at a desired level for the whole period of treatment and this was implemented by using a fixed level of signal, called step input. In this work, the reference to the controller (desired drug concentration) was selected by the MOGA optimisation process and for different solutions the reference levels are different. For example, the reference levels for Case-1, Case-2 and Case-3 are 12.08, 12.17 and 11.66 respectively.

To obtain different performance measures in relation to chemotherapy treatment, three decision variables, k_p, k_i , k_d and reference input (desired drug concentration) corresponding to solution, Case-1, are feed to the I-PD controller and the feedback control system and the whole system along with the patient model was simulated for 84 days. Then the output of the I-PD controller,$\mathrm{u(t)}$, which is the desired chemotherapy drug scheduling for Case-1, was recorded. Several outputs of the patient model, such as, drug concentration at tumour site, toxicity, reduction of proliferating and quiescent cells and changes in normal cells were recorded due to the infusion of the designed chemotherapy doses. Similar procedure was repeated for Case-2 and Case-3 and similar parameters are recorded for the whole period of chemotherapy treatment.

Figure 4.10(a) shows the chemotherapy drug scheduling for Case-1, Case-2 and Case-3. The response of the patient model due to the infusion of these drug scheduling are shown in Figures 4.10(b) and (f). It is noted that, the response of the patient model are expressed in terms of several parameters such as, drug concentration, toxic side effects, reduction of proliferating and quiescent cells and changes in normal cells during the whole period of treatment. Moreover, the maximum and average levels of drug doses, toxicity and drug

concentrations for all three cases are calculated and presented in Table 4.2, where is the minimum value considered zero. Furthermore, percentage of reductions in proliferating and quiescent cells at the end of chemotherapy treatment were calculated and showed in Table 4.2 As mentioned earlier, in chemotherapy drug scheduling problem, number of normal cell population is often considered as an indication of toxic side effects developed in the patient's body. Since the normal cells are adversely affected by the chemotherapy drugs, the level of toxicity is assumed to be inversely proportional to the number of normal cells. Moreover, the number of normal cells remaining at the end of treatment is giving an indication about the physiological state of the patient. So this number was also calculated and displayed in Table 4.2.

Table 4.2: Performances of drug scheduling techniques

Example solutions	Value of Ref. input	For the whole period of treatment						At the end of 84 days treatment		
		Drug doses		Drug concentration		Toxicity		Reduction of Proliferating Cells	Reduction of Quiescent cells	No. of Normal cells
		Max	Avg	Max	Avg	Max	Avg			
Case-1	12.08	4.5	3.4	12	9.2	34.5	27.7	72.2%	60.4%	1.0002×10^8
Case-2	12.17	4.5	3	12	8.3	33.4	23.4	71.2%	58.9%	1.0024×10^8
Case-3	11.66	4.5	2.8	11.7	7.5	31.9	21.2	68.1%	55.1%	1.2815×10^8

4.2.1.1 Drug Scheduling

Figure 4.10 (a) shows the chemotherapy drug scheduling for Case-1, Case-2 and Case-3. In all cases, the drug doses increase from zero and finally become stable at a certain value. It is noted that the rate of increase is different for different cases. For Case-1, the doses reach maximum value of 4.5 within the first week of treatment and for the remaining periods

it becomes stable at that value. For Case-2, the chemotherapy drug scheduling takes slightly more than two weeks to reach the maximum and stable level of 4.5 whereas for Case-3, it takes nearly seven weeks to reach the fixed and stable level of 4.3. Although in all three cases the maximum chemotherapy drug doses are nearly same but the average levels of drug doses over the whole period of treatment are different. For Case-1, the average drug dose is maximum, which is 3.4 whereas this value is minimum (=2.8) for Case-3. For Case-2, the average drug dose is moderate (=3) relative to other two cases.

In this work, the chemotherapy drug scheduling obtained with I-PD controller and MOGA optimisation process was continuous throughout the whole period of treatment. More importantly, the drug doses were much lower compared to conventional doses during 84 days of treatment. It is important to note that, phase specific chemotherapy drugs, such as Vinca alkaloids, Hydroxyurea, Cytosine arabinoside, Methotrexate, 6-Mercaptopurin, 6-Thioguanine, Procarbazin, VM-26 and VP16-213 (Liang et al., 2008) are, in general, toxic agents and lower doses of these drugs can reduce the toxic side effects during the treatment cycle and thereby improve the quality of life of the patient.

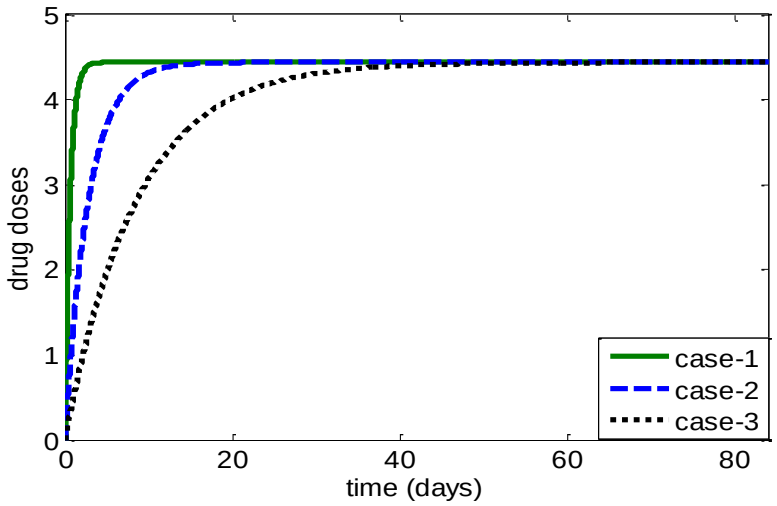

Fig. 4.10(a) Chemotherapy drug doses for whole period of treatment

4.2.1.2 Drug Concentration

Figure 4.10(b) shows the drug concentration against desired/reference input for Case-1, Case-2 and Case-3 at the tumour site due to chemotherapy drug scheduling obtained for those cases earlier in Figure 4.10(a). It is interesting to note that, the drug concentrations, for all three cases, increase gradually in similar manner as observed in case of corresponding drug scheduling and follow corresponding reference levels/desired levels. The drug concentrations at tumour site reach a maximum value as set by the corresponding reference/desired values.

It is also noted that, like average drug doses, the average drug concentrations also vary from case to case; Case-1 having maximum average value of 9.2 followed by Case-2 and Case-3, as listed in Table 4.2. More importantly, it is noted that, the average and maximum drug concentrations are always much lower than the allowable maximum value indicated in design objective and constraint for this particular parameter.

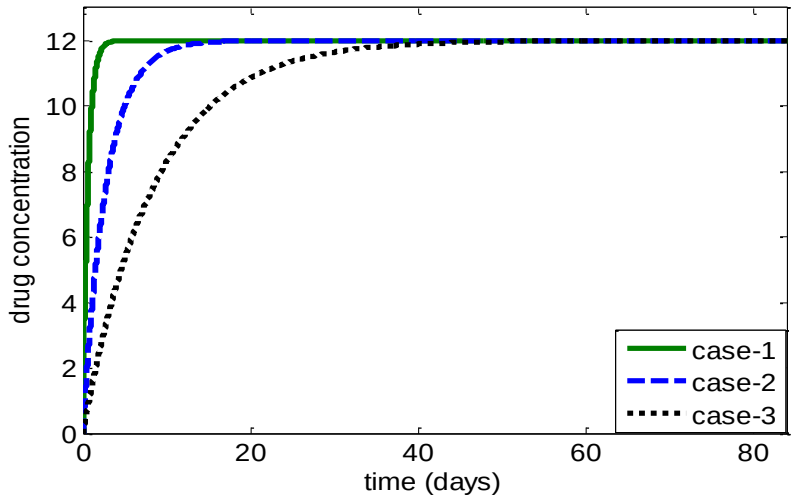

Fig. 4.10(b) drug concentration for whole period of treatment

4.2.1.3 Toxicity

The toxicities, for Case-1, Case-2 and Case-3, developed due to the corresponding chemotherapy drug scheduling are shown in Figure 4.10(c). For all three cases, the toxicities gradually increase from the first day of treatment and finally settle to a steady value after few weeks in a similar manner as observed in case of drug scheduling and drug concentration. The maximum level of toxicity is observed with the drug scheduling obtained with Case-1 and the value is 34.5 whereas the minimum toxicity is caused by Case-3.

The average toxicities for Case-1, Case-2 and Case-3 are 27.7, 23.4 and 21.2, respectively. Like maximum toxicity, the average toxicity is also maximum with Case-1, followed by Case-2 and Case-3. It is important to note that, toxicities in all cases remain under control and much lower than the maximum limiting value set in design objective and constraint of the optimisation process.

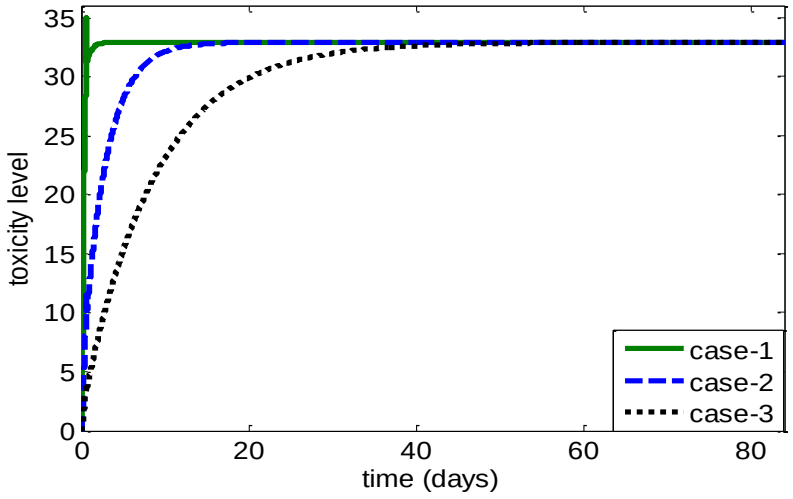

Fig. 4.10(c) Toxicity for whole period of treatment

4.2.1.4 Reduction of proliferating cells

The reduction of proliferating cells is the main target of chemotherapy treatment for cancer tumour. Before the treatment starts, the number of proliferation cells was set at $2x10^{11}$, as used by many researchers in cell cycle specific cancer treatment (Dua et al., 2008). Figure 4.10(d) shows the reduction of proliferating cells during the whole period of treatment. For Case-1, Case-2 and Case-3, the percentage of reductions obtained using the drugs scheduling shown in Figure 4. 10(a) is 72.2%, 71.2% and 68.1% respectively.

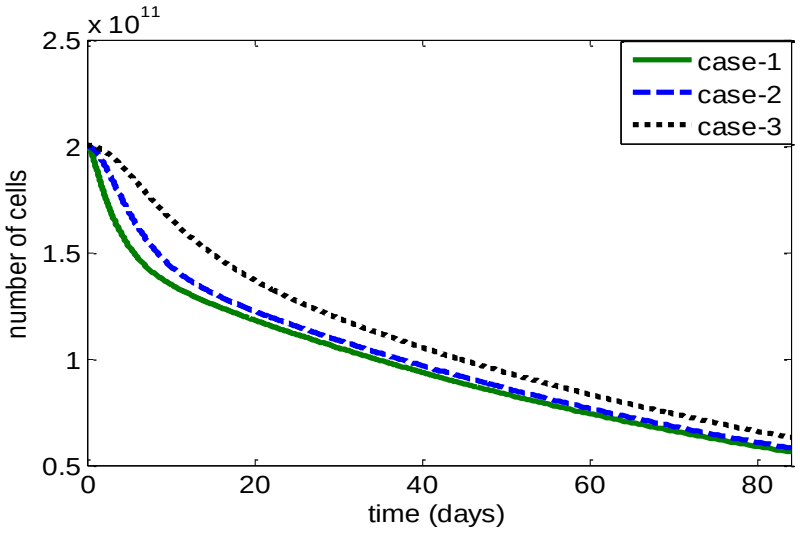

Fig. 4.10(d) Reduction of proliferation cell for whole period of treatment

4.2.1.5 Reduction of quiescent cells

Quiescent cells were also be reduced in cancer treatment as indicated in the design objectives. At the beginning the chemotherapy treatment, the total number of quiescent cell is assumed as $8x10^{11}$ (see Table 3. 1). During the treatment period, the number gradually decreases depending on chemotherapy drug doses and this is shown for all three cases in Figure 4.10(e). It is important to note 60.4%, 58.9% and 55.1% respectively.

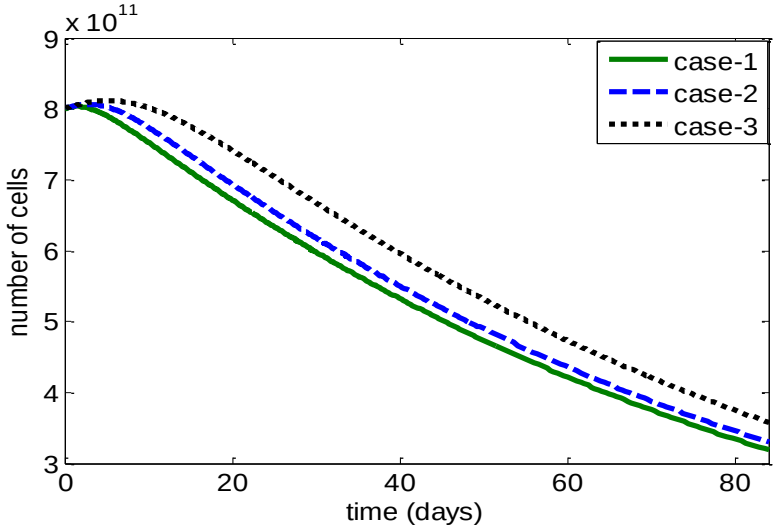

Fig. 4.10(e) Reduction of quiescent cell for whole period of treatment

4.2.1.6 Changes in normal cells

The chemotherapy drugs adversely affect the normal cells during the treatment. In the patient model used in this work, the number of normal cells was assumed $10x10^8$ before the administering the chemotherapy drugs into patient's body. Figure 4.10(f) shows the changes of normal cells during the whole period of treatment for all cases. For Case-1, Case-2 and Case-3, the number of normal cells remaining at the end of 84 days treatment are $1.03x10^8$, $1.0024x10^8$ and $1.2815x10^8$ respectively. It is important to note that, in all cases the number of remaining normal cells are more than the threshold value, $1x10^8$, as indicated in condition and in design constraint earlier. It is mentioned that these higher values of remaining normal cells are attributed to lower toxic side effects and better physiological conditions of patients.

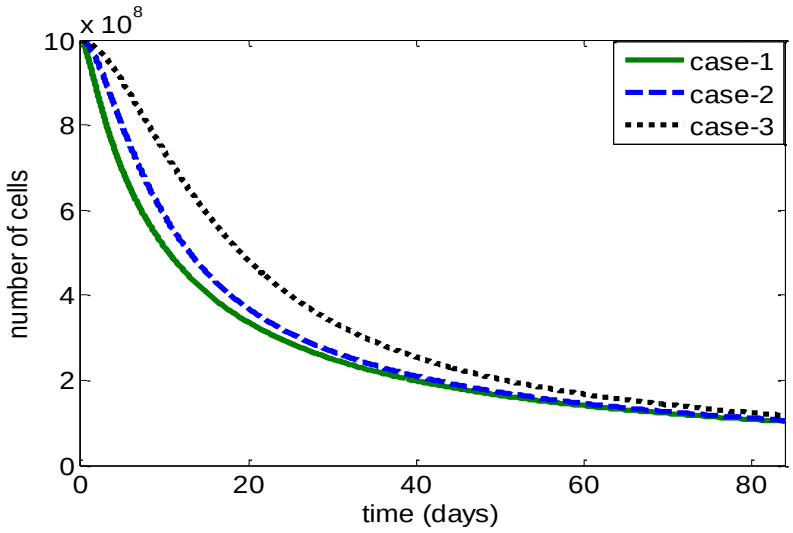

Fig.4.10(f) Number of the normal cells for whole period of treatment

4.3. Four Compartments Model

This section focuses on multi-drug chemotherapy scheduling where two drugs are used and, for ease of discussion, these drugs are indicated by A and B, respectively. To assess the effectiveness of two drugs in chemotherapy treatment, a tumour model consists of four compartments is considered. A schematic diagram of multi-drug scheduling scheme for chemotherapy treatment is shown in Figure 4.11. A feedback control method I-PD was developed to control the drug to be infused to the patient's body. The overall control structure contains two I-PDs controllers; one for drug A and another for drug B. Each I-PD controller involves three parameters, the proportional gains k_p integral gain k_i and derivative gains k_d. Drug concentration at the tumour is used as the feedback signal to the controller which is compared with a predefined references level. The difference between each two is called the error which is used as input to the controller. The output of the controller for drug A, $u_A(t)$ is formed as:

$$u_A(t) = K_{Ai} \int_0^t e(t)dt - [K_{Ad} \frac{d}{dt} D_A(t) + K_{Ap} D_A(t)] \quad (4.4)$$

While the output of the controller for drug B, $u_B(t)$ is:

$$u_B(t) = K_{Bi} \int_0^t e(t)dt - [K_{Bd} \frac{d}{dt} D_B(t) + K_{Bp} D_B(t)] \quad (4.5)$$

where, $e_A(t)\ and\ e_B(t)$ are the errors which are the differences between references $X_{DA}\ and\ X_{DB}$ and drugs concentrations $D_A(t)\ and\ D_B(t)$. These are expressed as:

$$\mathrm{e_A(t)} = \left(\mathrm{X_{DA}} - \mathrm{D_A(t)}\right) \quad (4.6)$$

$$e_B(t) = \left(X_{DB} - D_B(t)\right) \quad (4.7)$$

It is noted that $X_{DA}\ and\ X_{DB}$ indicate the reference signals to the controllers which can be depicted as the desired drugs concentrations to be maintained at the tumour site during the whole period of the treatment. It is the noted that when $e_A(t)\ and\ e_B(t)$ are zero, the drugs concentrations at tumour site will be equal to the desired drug concentrations. In such case, the cell killing will be maximum. If the differences between X_{DA} and $D_A(t)$ and X_{DB} and D_B are positive large or not stabile then the drugs concentrations will be lower than the desired level and in such case, the cell killing will be much lower than expected. It is required to tune the six parameters $k_{Ai},\ k_{Ap}, k_{Ad}, k_{Bi},\ k_{Bp},$ and k_{Ad} of I-PDs controllers to achieve the desired performance. In this work, MOGA is used to optimise these parameters of the I-PDs controllers and references to the controller. It is important to note that the whole control scheme and drugs scheduling is designed for a period of 84 days as recommended by many researchers (Tes, et al, 2007, Martin and Teo, 1994 and Ochoa and Burke, 2007).

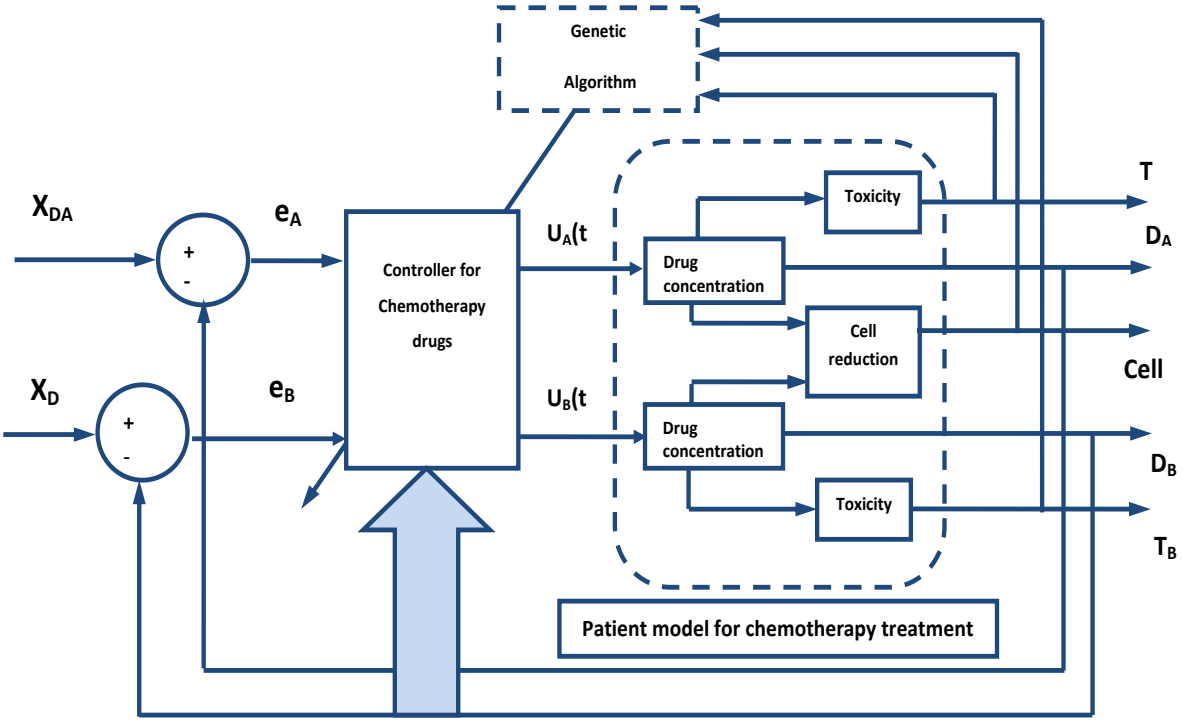

Fig. 4.11 Schematic diagram of the proposed multi-drug control scheme

The whole simulation was carried out in the Simulink environment with some .m-files of Matlab® (The Mathworks, Inc., 2010). The MOGA optimisation process started with a randomly generated population called chromosomes. A standard population size of 50 was chosen in this work. An initial population of dimension 50×8×12 was created where number of individuals and parameters in each individual were 50 and 8 respectively. Each parameter was encoded as 12 bit Gray code which is logarithmically mapped (Chipperfield et al, 1994) into real number within a range of [0, 2] for first six parameters and a range of [10, 50] for the remaining parameters. Each individual represents a solution where the first six elements were assigned to controller's parameters; k_{Ap}, $k_{Bp,}$ k_{Ad}, k_{Bd}, k_{Ai} and k_{Bi} respectively as indicated in the conditions. The seventh and eighth elements of each individual were assigned to the reference inputs, X_{DA} and X_{DB} to the close-loop control system.

The MOGA optimisation process was run for 200 generations in order to minimise the objectives simultaneously. It is worth mentioning that through the trial and error, 200 generations are found as the minimum number of generation to obtain highest level of convergence. Solutions not satisfying aforementioned design constraints are penalised with very high values, called penalty function. This penalty function will reduce the probability of solutions yielding unacceptable values along any design objectives dominate the optimisation process. On the other hand, favourable acceptable solutions to be selected for reproduction that in turn may generate better solutions in subsequent generations. In MOGA optimisation process, non-dominated solutions called Pareto optimal set and the corresponding decision variables were updated and preserved at the end of each generation. As the algorithm proceeds the number of preserved non-dominated solutions increases and more importantly, the solutions gradually get better and tend to move towards x-axis and origin of y-axis in the objective domain. A wide range of non-dominated solution satisfying all design constraints, objectives and associated goal values as were obtained at the end of maximum generation.

For a three-objective minimisation problem, a parallel line representation is shown in Figure 4.12 where x-axis is marked by three equidistant points representing design objectives to be minimised and y-axes at those points represent the values of corresponding objective functions. Moreover, three objective functions for each solution are connected by a line of specific style and colour. For clarity and ease of discussion, only few non-dominated solutions yielding value for objective-2 less than150 are shown in Figure 4.12. In such a case, individuals (solutions) that fall close to x-axis are better than those away from x-axis. Moreover, crossing-lines for two consecutive objectives indicate conflict between them whereas non-crossing lines indicate that objectives are not in conflict. It is observed that a solution giving minimum value along one objective yields relatively higher values along

other two objective domains. Similar nature is observed with other solutions. Although no solution can minimise all three design objective simultaneously to lowest possible values because of inherent conflict, each solution has equal potential as per as trade-off among different objectives are concerned.

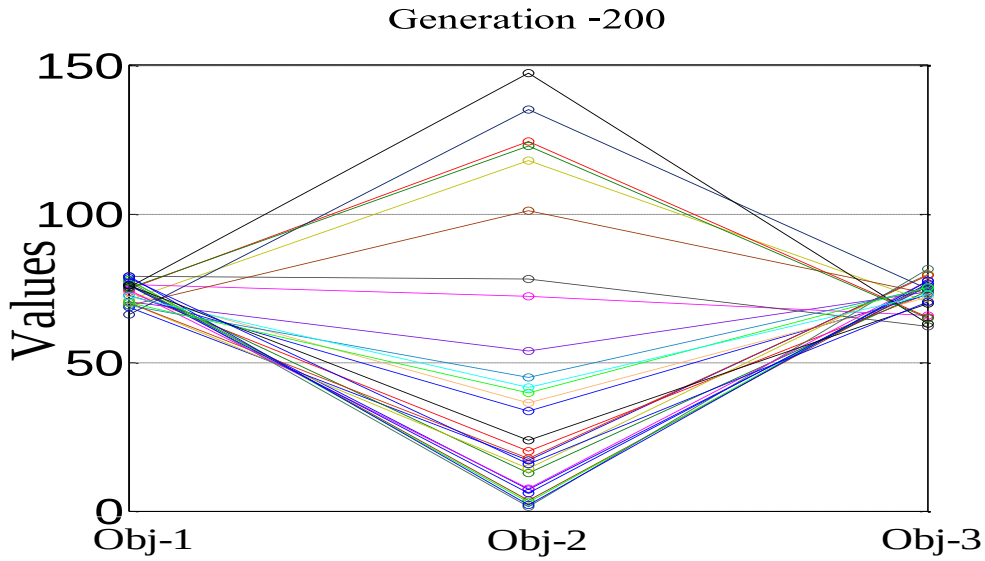

Fig. 4.12 Non-dominated solutions of MOGA optimisation at generation-200

4.3.1 Results

In order to evaluate the effectiveness of the proposed control strategy and MOGA optimisation process, an example solution yielding a minimum value for objective 2 is analysed in detail. To obtain different performance measures in relation to chemotherapy treatment, eight decision variables; 6 controller parameters (k_{Ap}, k_{Ai} , k_{Ad}, , k_{Bp}, k_{Bi} and k_{Bd}) and 2 reference inputs (X_{DA} and X_{DB}) were fed to the feedback control system and the whole system along with the patient model is simulated for 84 days. Then the outputs of two I-PD controllers, $u_A(\mathrm{t})$ and $u_B(\mathrm{t})$ are drug scheduling for drugs A and B were recorded.

Several outputs of the patient model, such as, drug concentration at tumour site, toxicity and reduction of cancer cells are recorded due to the infusion of the designed chemotherapy doses.

Figure 4.13(a) shows the chemotherapy drug scheduling for drug (A and B). In both drugs, the drug doses increase from zero and finally become stable at a certain value. It is noted that the level of increase is different for two drugs. It is worth to mention that the dosage of the multi-drug is lower as compared with single drug. Moreover the effectiveness of multi-drug by reducing the resistance of the chemotherapy cancer treatment increases the performance of the treatment. For drug A, the doses reach maximum value of 13.12 within the first week of treatment and for the remaining periods it becomes stable at that same value. For drug B, the drug dosage takes slightly more than one week to be to reach the maximum and Stable for rest of the period at 12.91.

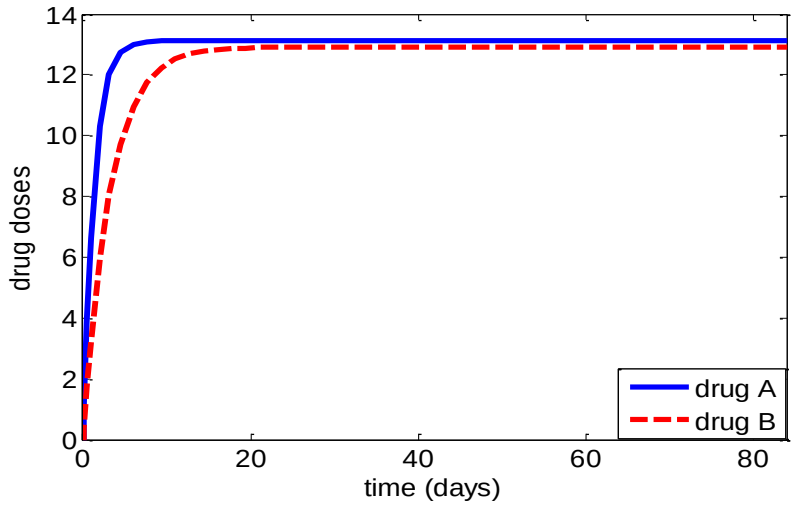

Fig. 4.13 (a) Chemotherapy drug doses for drugs A and B

4.3.2.1 Drug concentration

Figure 4.13(b) shows the drug concentration against desired/reference inputs for drug A and drug B at the tumour site due to chemotherapy drug scheduling obtained for both cases earlier in Figure 4.13(a). It is interesting to note that, the drug concentrations, for both drugs, increase gradually in similar manner as observed in case of corresponding drug scheduling and follow corresponding references levels/desired levels. The drug concentrations at tumour site reach a maximum value as set by the corresponding references/desired values. More importantly, it is noted that, the maximum drug concentrations are always much lower than the allowable maximum value indicated in design objective and constraint for this particular parameter. The toxicities, for drug A and drug B, developed due to the corresponding chemotherapy drug scheduling are shown in Figure 4.13(a).

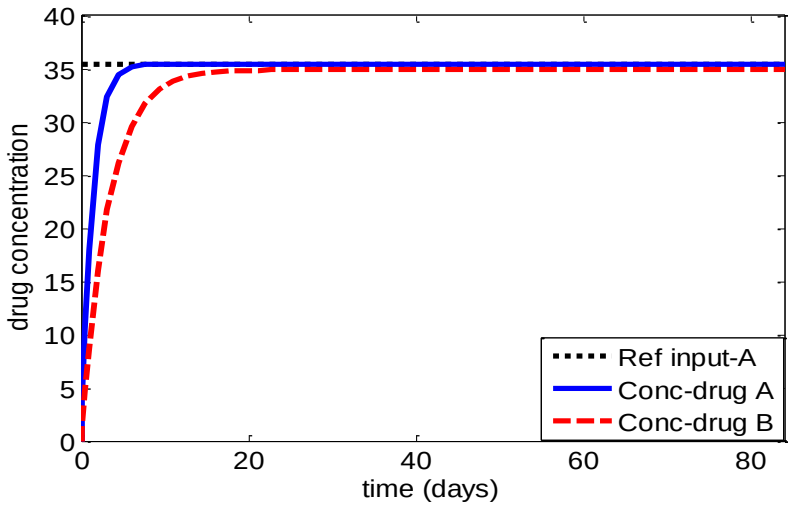

Fig. 4.13(b) Drug concentrating for drugs A and B for both throughout the treatment period

4.3.2.2 Toxicity

For both drugs, the toxicities gradually increase from the first day of treatment and finally settle to a steady value after few days in a similar manner as observed in case of drug scheduling and drug concentration as Figure 4.13(c) illustrated. It is noted that the level of toxicity for a multi-drug chemotherapy treatment is low compared with the single drug (Martin and Teo, 1994). The maximum level of toxicity is observed with the drug scheduling obtained with drug A and the value is 97.5 whereas the toxicity caused by drug B is at lower level of toxicity in comparison to drug A. The average toxicities for drug A and drug B are 81.7 and 77.5 respectively. It is important to note that, toxicities in all cases remain under control and much lower than the maximum limiting value set in design objective and constraint of the optimisation process. The main aim of chemotherapy treatment to eradicate or minimise the cancer resistance cells to the minimum level after a number of fixed treatment cycles. Before the treatment starts, the number of cancer cells was assumed 4.60517×10^{11}, as used by many researchers in cell cycle specific cancer treatment (Tes et al, 2007).

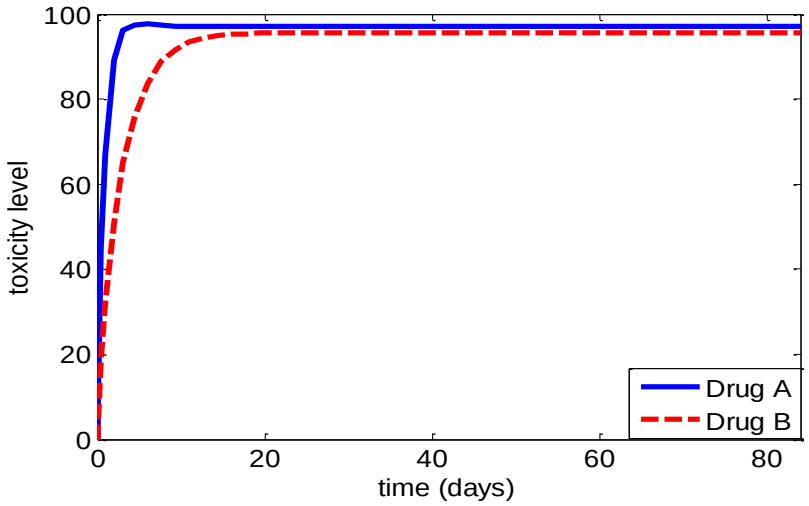

Fig. 4.13 (c) Toxicity for drugs A and B for both throughout the treatment period

4.3.2.3 Cell reduction

Figure 4.13(b) shows the effect of both drugs at the tumour site during the whole period of treatment. Figure 4.13(b) shows approximately 100% reduction of cancer cells during the whole period of treatment scheduling shown in Figure 4.13(a).

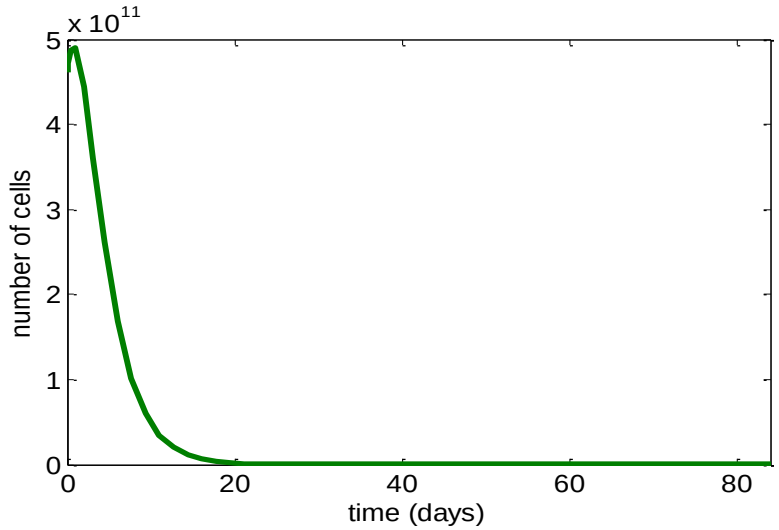

Fig. 4.13(d) The cell reduction for both throughout the treatment period

4.4 Proposed Control Scheme for Eight Compartments

A schematic diagram of multi-drug scheduling scheme for three chemotherapy treatment is shown in Figure 4.14. Feedback control methods using three I-PDs were developed to control the drugs to be infused to the patient's body. The overall control structure contains three I-PD controllers - one for each drug. Each I-PD controller involves three parameters, the proportional gains k_p, integral gain k_i and derivative gains k_d. Drug concentration at the tumour is used as the feedback signal to the controller which is compared with a predefined reference level. The difference between each two is called the error which is used as input to the controller. It is noteworthy that X_{DA}, X_{DB} and X_{DC} indicate reference

signals to the controllers which can be depicted as the desired drug concentrations to be maintained at the tumour site during the whole period of treatment. To achieve the desired performance, nine parameters of I-PDs such as k_{Ai}, k_{Ap}, k_{Ad}, k_{Bi}, k_{Bp}, k_{Bd}, k_{Ci}, k_{Cp}, k_{Cd} need to be tuned. In this research, MOGA is used to find suitable parameters for I-PD controllers and reference inputs (desired drug concentrations).

The mathematical model containing eight compartments stating the effects of three drugs as explained earlier is implemented in Matlab/Simulink (The Mathworks, Inc., 2010) environment with parameters and values as illustrated in Table 4.3 (Tes et al, 2007). Moreover, the I-PD feedback control scheme was also developed in Matlab/Simulink environment. The MOGA optimisation process begins with a randomly generated population called chromosome. An initial population of dimension 50X12X12 was created where number of individuals and parameters in each individual are 50 and 12 respectively. Each parameter was encoded as a 12 bit Gray code which is logarithmically mapped (Chipperfield, et al, 2007) into real number within the range of [0,2] for first nine parameters and a range of (10,50) for the last three parameters. Each individual represents a solution where the first nine elements are assigned to the controller parameters. The last three elements of each individual are assigned to the reference inputs to the close-loop control system. The whole control scheme and drug scheduling are designed for a period of 84 days as recommended by many researchers (Tes et al, 2007, Martine and Teo, 1994 and Ochoa and Burke, 2007).

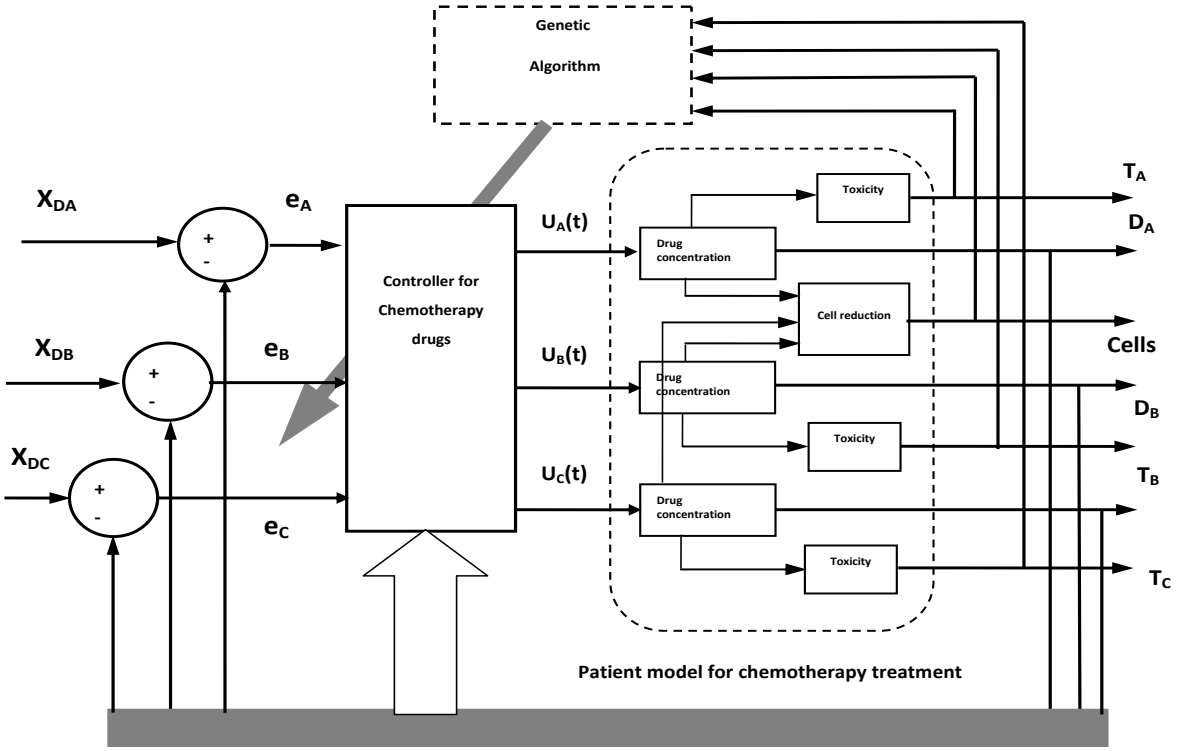

Fig. 4.14 Schematic diagram of the proposed multi-drug scheduling scheme

The MOGA optimisation process was run for 200 generations in order to minimise the all objectives simultaneously. It is worth mentioning that through trial and error, 200 generation was found as the minimum number of generation to obtain highest level of convergence. As the algorithm proceeds, number of preserved non-dominated solutions increases and more importantly, the solutions gradually get better and tend to move towards x-axis and origin of y-axis in the objective domain. A wide range of non-dominated solution satisfying all design constraints, objectives and associated goal values as were obtained at the end of maximum generation. A similar method has been followed for solutions not satisfying as mentioned above for three objectives. For a four-objective minimisation problem, a parallel line representation is shown in Figure 4.15 where x-axis is marked by four equidistant points representing design objectives to be minimised and y-axes at those points represent the values of corresponding objective functions. Moreover, four objective functions for each solution are connected by a line of specific style and colour. For clarity and ease of discussion, only

few non-dominated solutions yielding value for objective-2 is the number of the cells less than150. In such case, individuals (solutions) that fall close to x-axis are better than those away from x-axis. Moreover, crossing-lines for two consecutive objectives indicate conflict between them whereas non-crossing lines indicate that objectives are not in conflict. It is observed that a solution giving minimum value along one objective yields relatively higher values along other three objective domains. Similar nature is observed with other solutions. Although no solution can minimise all four design objective simultaneously to lowest possible values because of inherent conflict, each solution has equal potential as per as trade-off among different objectives are concerned.

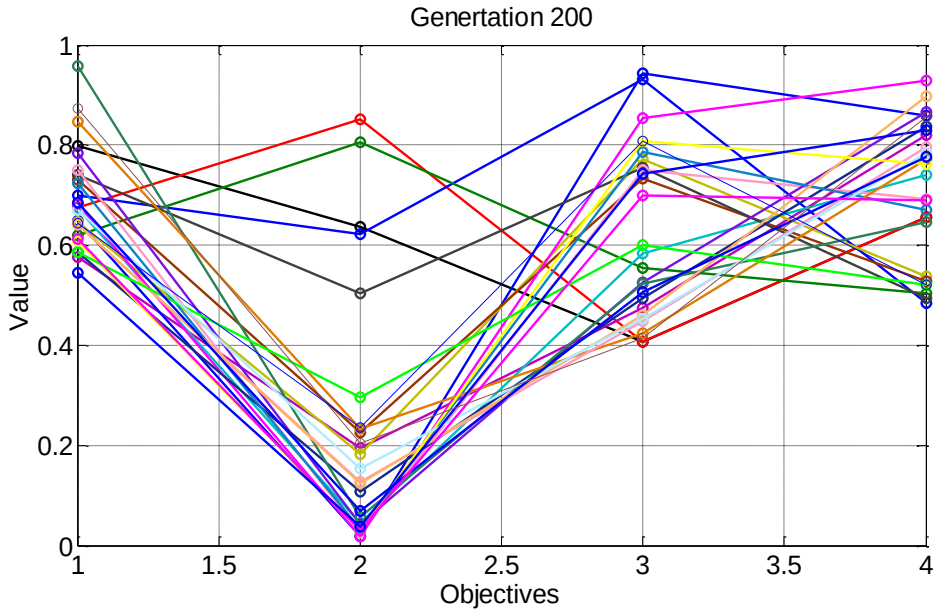

Fig. 4.15 Non-dominated solutions of MOGA optimisation at generation-200

4.4.1 Results

In order to evaluate the effectiveness of the proposed multi-drug scheduling scheme, an example solution yielding a minimum value alone objective 2 (i. e, the number of cells) is

performed. To obtain different performance measures in relation to chemotherapy treatment, twelve decision variables, which are the controller parameters $k_{Ai},\ k_{Ap}, k_{Ad}, k_{Bi},\ k_{Bp}, k_{Bd},\ k_{Ci}, k_{Cp}, k_{Cd},$ and three reference inputs (desired drug concentrations), of example solution were fed to the I-PDs controllers and the feedback control system along with the patient model is simulated for 84 days. Then the output of the I-PD controller, $u_A(t), u_B(t)$ and $u_C(t)$, and the desired chemotherapy drug scheduling were recorded. Several outputs of the patient model, such as, drug concentration at tumour site, toxicity and reduction of cancer cells were also recorded. Figure 4.16(a) shows the chemotherapy drug scheduling for drugs (A, B and C). The drug doses increase from zero and finally become stable at a certain value. It is noted that the rate of increase is different for different three drugs. For drug A, the doses took slightly more than one week to reach maximum value of 17.12 and for the remaining periods it became stable at that same value. For drug B, the chemotherapy drug scheduling took less than one week to reach the maximum and stable level of 15 and the doses of drug C got stable at the highest level which is 12.5 within one week.

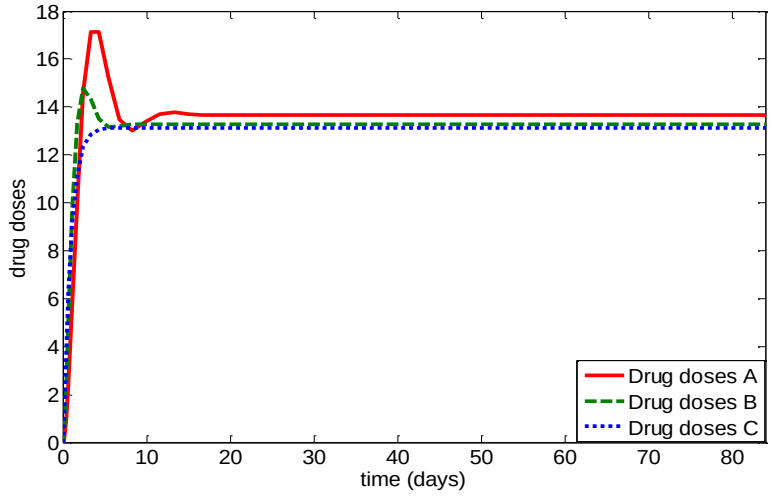

Fig. 4.16 (a) Chemotherapy drug doses for drugs A, B and C

4.4.1.1 Drug concentration

The second graph of Figure 4.16(b) shows the drug concentration at the tumour site due to chemotherapy drug scheduling obtained for all cases earlier in the first graph of Figure 4.16(a). It is interesting to note that the drug concentrations for all cases increase gradually in similar manner as observed with the corresponding drug dose scheduling and desired levels. The drug concentrations at tumour site reach a maximum value as set by the desired values. More importantly, it is noted that, the maximum drug concentrations are always much lower than the allowable maximum value indicated in design objective and constraint for this particular parameter.

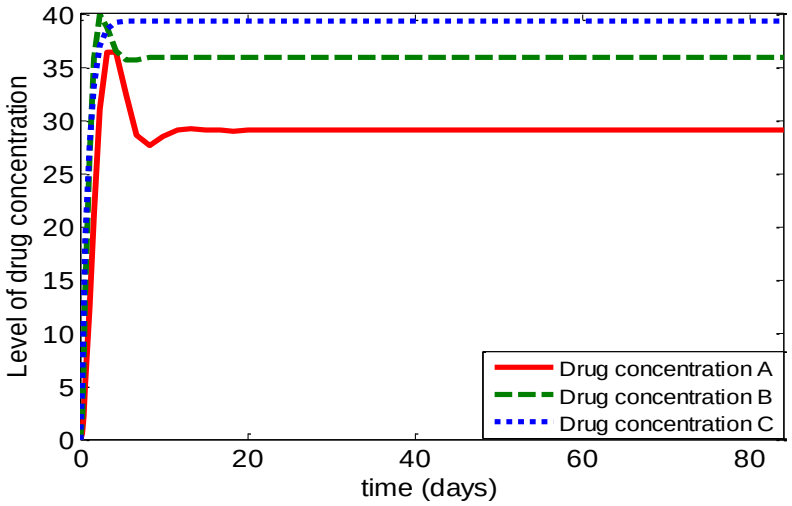

Fig. 4.16(b) Drug concentration for drugs A, B and C for the whole period of treatment

4.4.1.2 Toxicity

The toxicities, for drugs A, B and C, developed due to the chemotherapy drug scheduling are shown in Figure 4.16(a). For the three cases, the toxicities gradually increase from the first day of treatment and finally settle to a steady value after few days in a similar manner as observed in case of drug scheduling and drug concentration. The maximum level

of toxicity is observed with the drug scheduling obtained with drug A and the value is 92.3 whereas the minimum toxicity is caused by drug B is 71.7. Toxicities in all cases remain under control and much lower than the maximum limiting value set in design objective and constraint of the optimisation process.

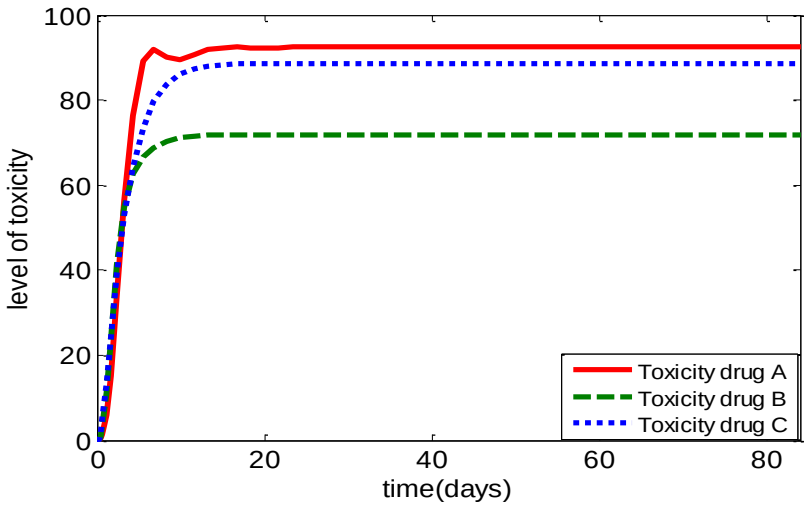

Fig. 4.16 (c) Level of toxicity for drugs A, B and C for whole period of treatment

4.4.1.3 Cells reduction

Figure 4.16(d) shows the reduction of cancer cells during the whole period of treatment. The percentage of reductions obtained using the drug scheduling shown in Figure 4.16 (a) is nearly 100% corresponds to the solution has been chosen.

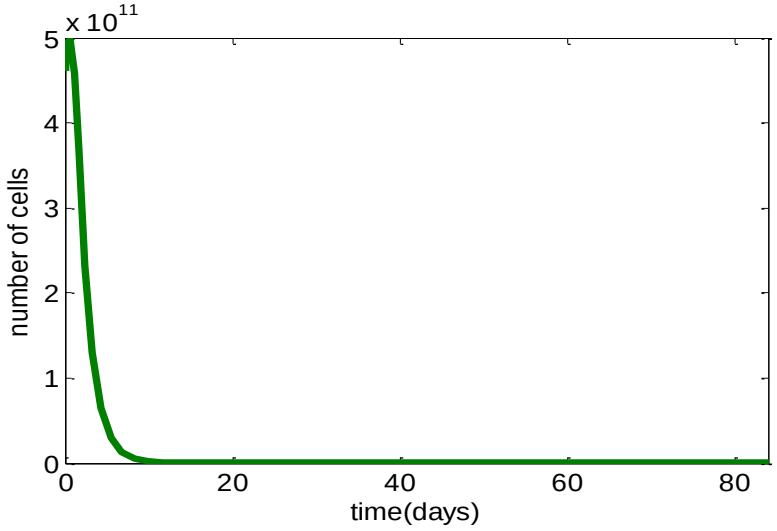

Fig. 4.16 (d) the cell reductions throughout the treatment period

4.5 Summary

This Chapter has presented an investigation into the development of multi-drug chemotherapy scheduling model using multi-objective optimisation technique. A novel close-loop control method was used to design drug doses by maintaining a suitable level of drug concentration at cancer sites. A multi-objective optimal chemotherapy control model used to reduce the number of cancer cells after a number of fixed treatment cycles with minimum side effects. In the proposed method, several design objectives, constraints and associated goal values were defined prior to the optimisation process and a wide range of solutions have been obtained satisfying all design goals and trading-off between two main but conflicting objectives of chemotherapy treatment; reducing cancerous cells and reducing toxic side effects.

It is interesting to note that the design approach can offer flexibility in decision making by the clinicians to pick suitable solution under different trade-off conditions by considering the patient's condition and tumour staging. Many solutions of the proposed drug scheduling

pattern have reduced the number of tumour cells more than 99% with the tolerable drug concentration and lower toxic side effects. The proposed model offered better performance as compared with existing models with regard to drug resistance and toxicity level.

The same control strategy and optimisation technique was used to extend for multidrug or combination chemotherapy regimen. The model was exploited to demonstrate the effect of different drug combinations, doses, and drug resistance. In conclusion, it may be mentioned that multi-objective optimisation can be a very useful computing tool to solve complex drug scheduling problems in cancers, and other deadly and infectious diseases.

CHAPTER 5

Comparative Performances of the Proposed Schemes

5.1 Introduction

This Chapter presents the comparative performances of the proposed models with some reported models for optimal drug scheduling for cancer chemotherapy. A close-loop control method was used with different structures of PID controller to control the chemotherapy dosages infused to the patient throughout the period of a treatment cycle. As mentioned in earlier Chapters, the main target of these studies is to achieve a balance between the constraints of cancer cell reduction and the side-effect of the treatment. The comparisons of these models' performance include different category (compartments) of cancer cells or base of number of drugs have been applied as followed in previous Chapters.

There are many multi-objectives techniques used to design chemotherapy drug scheduling, however, no optimal solution has been implemented yet, as mentioned in Chapter 2. The MOGA optimisation process was used to trade-off between the cell killing and toxic side effects during the whole period of treatment and to tune the parameters $k_p, k_i \; and \; k_d$ of the (PID) controller with different reference inputs. The process was used to find suitable/acceptable drug concentrations at the tumour site by tuning the parameters of the controller. A Phase specific and non-phase specific cancer tumour models were used for the present study to show the effects of drug in relation to different cell populations, drug concentration and toxic side effects. The comparisons show that the employed multi-

objective optimisation approach can generate a wide range of solutions that trade-off between cell killing and toxic side effects and satisfy the associated goals of chemotherapy treatment. Depending on the physiological state of the patient and state of the disease, the oncologist can pick the right drug schedule suitable for the patient. As mentioned earlier, the cancer chemotherapy treatment models have been classified dependent on the functionality of the cancer cells.

5.2 Non-Phase specific

This section presents a comparative performance analysis of the optimal chemotherapy cancer drug scheduling control model to reduce the number of cancer cells after a number of fixed treatment cycles with minimum side effects. Non-phase specific models have been designed and implemented. Close-loop control methods, namely IPD and PID, are designed to control the drugs doses to be infused to the patient's body. In the proposed method, several design objectives, constraints and associated goal values were defined prior to the optimisation process and a wide range of solutions have been obtained satisfying all design goals and trading-off between two main conflicting objectives of chemotherapy treatment; reducing cancerous cells and reducing toxic side effects.

As discussed in Chapters three and four, our proposed I-PD and PID control strategies have been used to control the drug infusion based on Martin's model (Martin and Teo, 1994) with two different references for desired drug concentration at the tumour site. This section also presents a comparative performance analysis of the proposed drug scheduling scheme with some reported works, as illustrated in Table 5. 1. Here, I-PD and PID controllers with Rep & Cont as the reference input have been considered since they offer the best performance in

terms of cell reduction among all strategies of chemotherapy drug scheduling investigated in this work. Table 5.1 shows the comparative performance of the proposed model with some mostly cited reported works in this field (Martin, 1994, Liang et al., 2008, Tan et al., 2002).

It is noted that the example solution IPD-1 of the proposed model has reduced the cancerous cells to a minimum value of 15, yielding highest index of 24.923 at the end of chemotherapy treatment. Another example solution of the proposed method, PID-1, has also reduced the number of cancerous cells to nearly the same value, giving a reduction index of 24.854. These two solutions have outperformed all the results reported so far in chemotherapy drug scheduling using Martin's model. Moreover, other solutions, such as IPD-2 and PID-2 have also recorded high index values; 22.654 and 22.368 as far as reduction is concerned. More importantly, it is worth mentioning that the proposed method does not generate single solution at the end; rather it gives a wide range of very good solutions trading off cell reduction and toxic side effect.

Table 5.1: The numbers of cells remain with different techniques

Techniques	Index (x_1)	Number of cells remain
R. Martin, 1994	16.836	$4.878X10^4$
Tan et al., 2002	17.993	$1.534X10^4$
Liang et al., 2008	20.158	$1.760X10^3$
Proposed technique: IPD-1	24.923	15
PID-1	24.854	16
IPD-2	22.654	145

This section has also presented a comparative performance analysis of the proposed best drug scheduling pattern for non-phase specific cancer cells with some reported works, as illustrated in Table 5.1. In order to demonstrate the merits and capabilities of the proposed model, we have considered I-PD 'Rep & Cont' pattern scheme as it offers the best performance among all the proposed patterns. We have compared our results with Liang et

al., 2008, who used optimal control techniques to control the drug infusion based on Martin's (1994) model, in order to reduce the number of cancerous cells with minimum toxicity level. As discussed earlier, our proposed optimal I-PD control strategy has been used to control the drug infusion in Martin's model with three different patterns of drug scheduling, as Liang et al., 2008. In order to demonstrate the merits and capabilities of the proposed model, we have compared the performance parameters with the best reported model by Liang's (2008).

Figure 5.1 shows a comparison of the toxicity level obtained for the different drug scheduling patterns. It is noted that the toxicity level of all patterns is within the tolerable limit and the 'Repeated' pattern is lowest among all the scheduling patterns. However, the toxicity level of our proposed model for the best cell reduction scheduling pattern (in this case, 'Rep & Cont') is familiar to the reported model (Liang et al., 2008) of the same pattern.

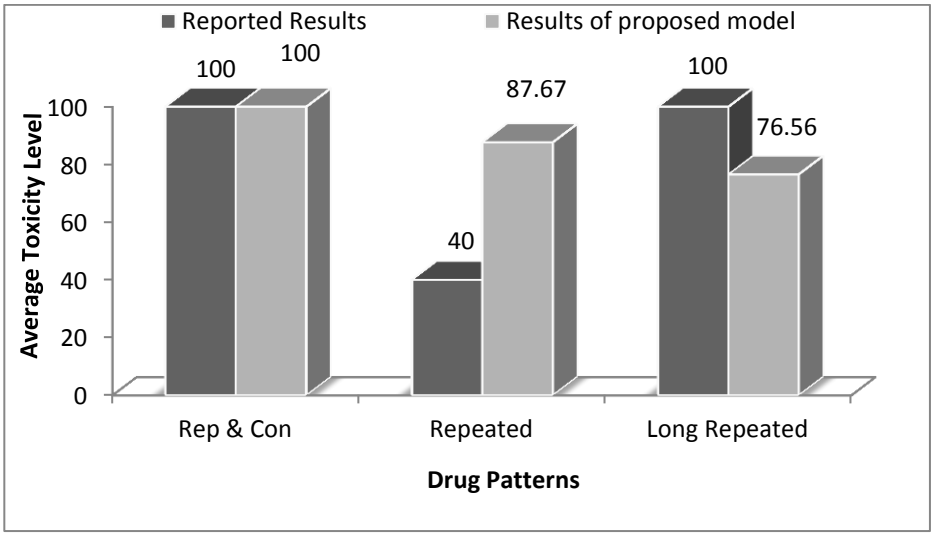

Fig. 5.1. Comparative level of final Toxicity for reported (Liang et al., 2008) and proposed model

Figure 5.2 show the drug concentration obtained for all proposed and reported patterns. It is observed that the final drug concentration levels of all patterns are within the tolerable limit.

Among these the 'Long Repeated' patterns of both the reported and proposed models achieved lowest level among all. In contrast, the 'Repeated' drug pattern of Liang et al., (2008) model offered the highest drug concentration level among all the patterns. On the other hand, the drug concentration level of our proposed best model ('Rep & Cont) is marginally higher as compared to Liang et al., 2008. It is noted that the drug concentration in the proposed method is still lower than the maximum value as indicated in the condition.

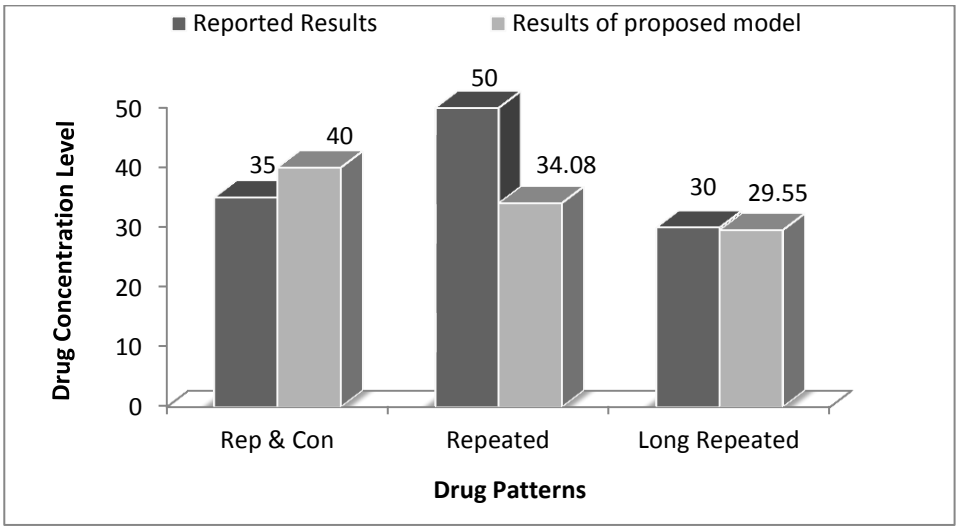

Fig. 5.2 Comparative level of final drug concentration into the body for reported (Liang et al., 2008) and proposed model

Figure 5.3 shows the number of remaining cells after the treatment cycle. It is noted that the 'Rep & Cont' of the proposed scheduling pattern offers best performance and 'Repeated' pattern of the Liang's (2008) offers the worst performance. It is worth mentioning that the proposed drug scheduling model for all three patterns performed better then all three patterns of the reported model. The performance (based on the remaining cells) of the best scheduling pattern 'Rep & Cont' of Liang is worse as compared to the proposed best scheduling pattern. Finally, the performance of the proposed model is also compared with other reported models for 84 days.

As mentioned earlier, Table 5.1 shows the comparative performance of the proposed model with three other best reported results (Martin and Teo, 1994, Liang et al., 2008, Tan et al., 2002). It is noted that the proposed model offers the best performance of all the reported results in terms of cancer cell reduction with highest index point. The model proposed by Tan et al., (2002) offers the best result compared with all other models which is the index(x_1) referred to 17.993 in terms of cancer cell reduction. In contrast, Martin's (1994) model offers the worst performance among all the models, which is the index(x_1) 16.836.

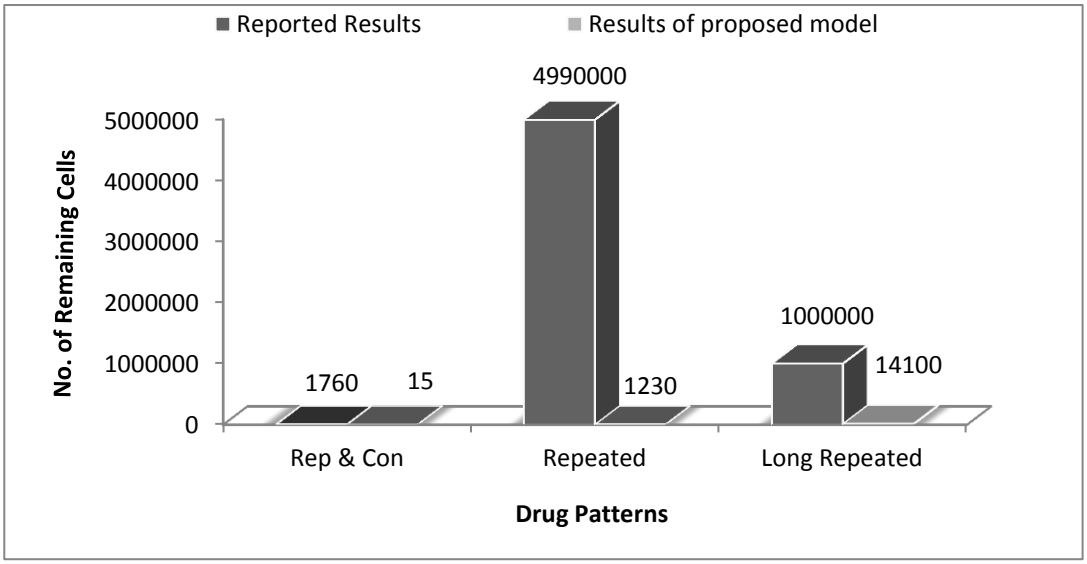

Fig. 5.3. Comparative performance for reported (Liang et al., 2008) and proposed model

Although all solutions on all Pareto fonts as shown in Figures 4.3 (a and b) satisfy design objectives by reducing cancerous cells by more than 99% with acceptable toxicity and drug concentration, the I-PD controller with Rep & Cont as the reference provides the best performances by minimising two conflicting design objectives simultaneously with significantly lower values. In order to choose a particular solution from this Pareto set, the solution set can be further divided into some regions., Solutions close to example solution I-PD-1 (see Figure 4.3(a) in Chapter 4) can be termed as high cells killing but high toxicity,

solutions around I-PD-2 as moderate cell killing and toxicity and solutions around I-PD-3 as low toxicity but low cell killing. Considering the physiological state of the patient and state of the cancer, an oncologist can choose a suitable solution from the objective space suitable for the patient. For patients having better physiological conditions and requiring faster response, chemotherapy drug scheduling resulting from solutions near I-PD-1 can be chosen. On the other hand, chemotherapy doses based on solutions residing close to I-PD-3 may be preferred for patients having relatively poor physiological conditions and vulnerable to toxic side effects. Patients not belonging to the aforementioned two categories may be recommended for chemotherapy doses based on example solution I-PD-2 or solutions residing close to it.

5.3 Phase specific

5.3.1. Comparative Performance between proposed and reported Model

This section presents a comparative performance analysis of the proposed drug scheduling pattern with some reported works using similar cancer tumour models. The outputs of the proposed drug scheduling scheme are compared with the results reported by (Dua et al. in 2008). The parameters chosen in this work are also used by other authors than Dua et al., (2008) as discussed in Chapter 4. Figure 5.4 shows a comparative analysis of the reduction in percentage of proliferating and quiescent cells at the end of treatment cycles with the proposed model and the reported one in Dua et al. in 2008.

It is noted in Figure 5.4 that the reduction of proliferating cells in the case of our proposed model is 72.5% compared to 70% in Dua et al., (2008) model. It is also noted that the reduction of quiescent cells is 61% whereas the reported model yields only 50%. It is clearly

evident that cell reductions for both proliferating and quiescent cells are marginally better in the case of the proposed model.

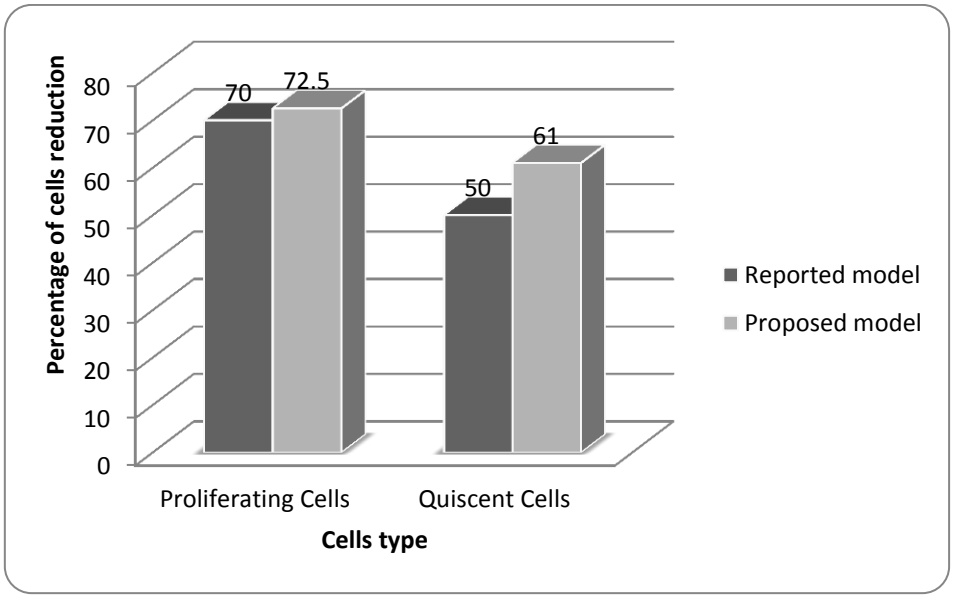

Fig. 5.4 Comparative performance for reported (Dua et al., 2008) and proposed model

Dua et al., (2008) designed chemotherapy drug scheduling for cell cycle specific model, as used in the present work, and reported reductions for proliferating and quiescent cells at the end of treatment, as mentioned earlier. In the present work, Case-1 and Case-2 result (as discussed in more details in Chapter 4) in a reduction of 72.5% and 71.2% for proliferating cells, which are marginally more than the reported one. More importantly, example solutions; Case-1, Case-2 and Case-3 of the proposed work can reduce the quiescent cells up to 60.4%, 58.9% and 55.1%, respectively, which are significantly higher than the reported result. Figure 5.5 shows the reductions of proliferating and quiescent cells for Case-1, Case-2, Case-3 and Reported work (Dua et al., 2008). It is clearly evident that cell reductions for both proliferating (except Case-3) and quiescent cells are better in the case of the proposed model.

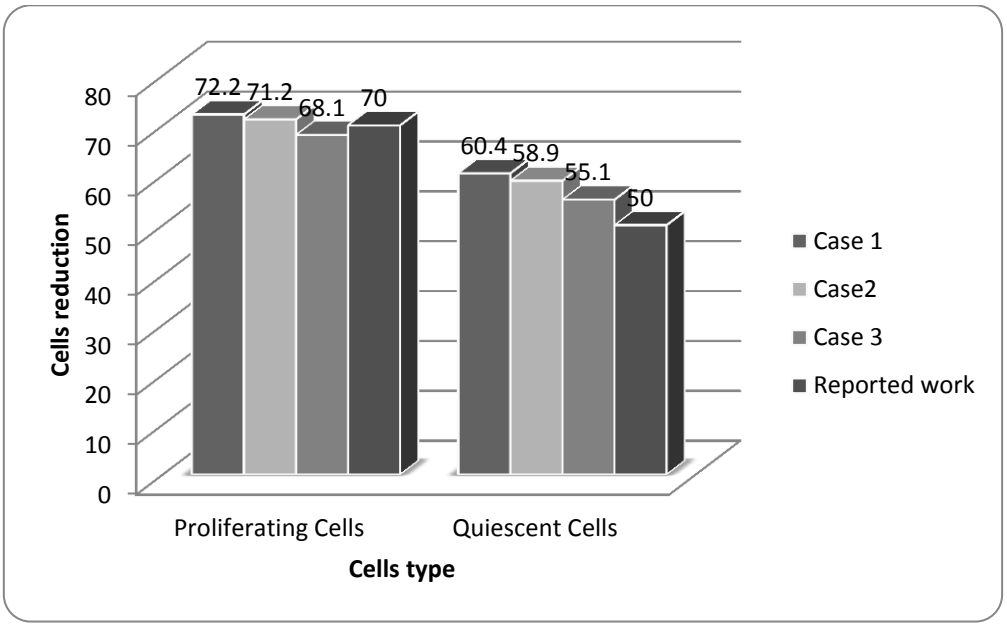

Fig. 5.5 Reductions of cells for Case-1, Case-2, Case-3 and Reported work (Dua et al., 2008)

5.3.2 Comparison between MOGA and MOPSO for Phase specific Model

This section presents a close-loop I-PD control method for optimal cancer drug scheduling using multi-objective algorithms such as MOGA and MOPSO (Alam, et al., 2010). The two main objectives of chemotherapy treatment, reducing cancerous cells and reducing toxic side effects, are always found in conflict. Both algorithms MOGA and MOPSO optimisations processes are used to design the drug scheduling that trade-off between these two. The proposed I-PD controller is designed to control the drug to be infused to the patient's body for a cell cycle specific treatment.

MOGA and MOPSO are used to tune the parameters for optimal control solution. In the proposed method, several design objectives, constraints and associated goal values are defined prior to the optimisation process and a wide range of non-dominated solutions have been obtained satisfying all design goals, known as Pareto-optimal set, which trade-off among

competing objectives. It is interesting to note that the design approach can offer flexibility in decision making and a suitable solution can be picked under different trade-off interventions for cancer treatment. It is noted that the drug scheduling pattern of the MOGA algorithm offers better performance as compared to the MOPSO algorithm.

Both MOGA and MOPSO optimisation processes were run for 100 generations in order to minimise both objectives simultaneously. Solutions not satisfying the aforementioned design constraints were penalised with very large numbers, called penalty function. This penalty function will reduce the probability of solutions yielding unacceptable values along any design objectives that dominate the optimisation process, and on the contrary, favour acceptable solutions to be selected for reproduction that in turn may generate better solutions in subsequent generations.

In MOGA and MOPSO optimisation processes, non-dominated solutions called Pareto optimal set and corresponding decision variables were updated and preserved at the end of each generation. At generation 1, each solution of the initial population was evaluated in the problem domain and depending on the values of two objective functions, non-dominated solutions and corresponding preserved decision variables. A wide range of non-dominated solution satisfying all design constraints, objectives and associated goal values were obtained at the end of maximum generation (=100). For decision making, (i.e., which solution to select or use from this wide range of acceptable solutions), the Pareto optimal set was redrawn, in a space of two objectives, namely number of proliferating cells and average toxicity, which were conflicting each other.

The objective space was divided into three regions, as shown in Figure 4.9 in Chapter 4, depending on the values of two objectives for each algorithm; number of proliferating cells

and average toxicity. The three solutions selected for MOGA and MOPSO are termed as, solution-1 (Sol-1, Case-1): high cells killing but high toxicity, solution-2 (Sol-2, Case-2): moderate cell killing and toxicity, and solution-3 (Sol-3, Case-3): low toxicity but low cell killing. The locations of solutions in the objectives space clearly indicate performances in terms of average toxicity and reduction of proliferating cells at the end of treatment. It is evident that solution-1, corresponds to higher cell (proliferating) killing at the cost of higher toxicity. The solutions-2 results for both cases show that the rates of the cell killing are reasonable with tolerable toxic side effects. It is noted that solution-3 causes minimum toxic side effects but the cell reduction is also lowest for these.

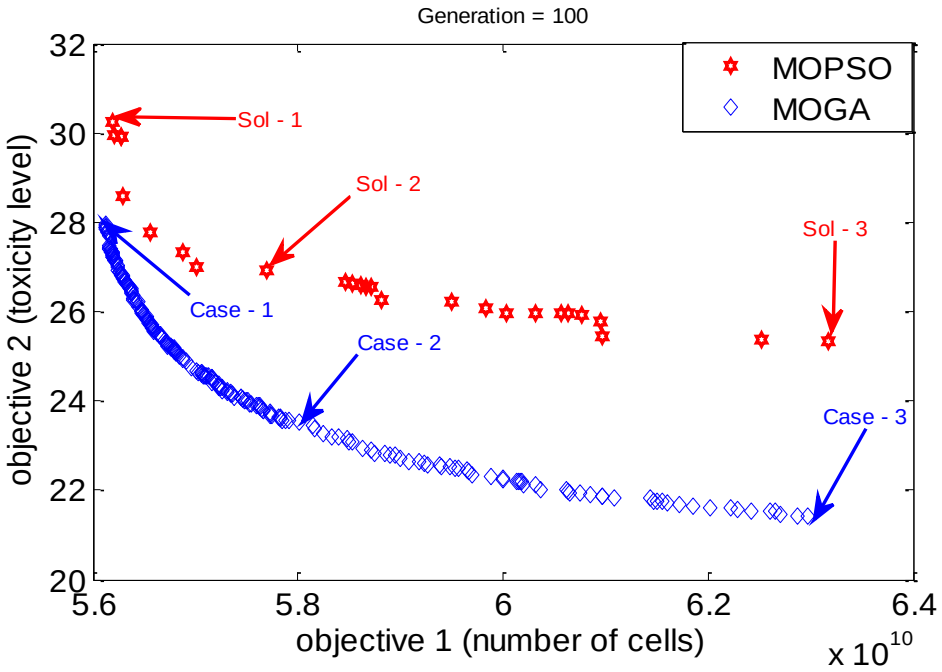

Fig. 5.6 Pareto optimal set of MOGA and MOPSO optimisation at generation 100

In order to evaluate the effectiveness of MOGA and MOPSO in chemotherapy drug scheduling, several representative solutions were further assessed. To validate the solution set, three solutions were selected on the Pareto front for each algorithm, one from each region. The solutions are selected in such a way that two falls on either extreme points of the

two objectives, and the other is approximately in the middle of the objective domain. Three selected solutions for MOGA, as shown in Figure 5.6, are denoted as case-1, case-2 and case-3. In the same manner MOPSO also has selected three solutions, Sol-1, Sol-2 and Sol-3 for further discussions. To make the chemotherapy drugs effective, the drug concentration at the tumour site should be maintained at a desired level for the whole period of treatment and this scheme was implemented by using a fixed level of signal, called step input.

Table 5. 2: Performance measures of drug scheduling techniques

Example solutions	For the whole period of treatment						At the end of 84 days treatment		
	Drug doses		Drug concentration		Toxicity		Reduction of Proliferating Cells	Reduction of Quiescent cells	No. of Normal cells
	Max	Avg	Max	Avg	Max	Avg			
Case-1	4.5	3.4	12	9.2	34.5	27.7	72.2%	60.4%	1.0002×10^8
Case-2	4.5	3	12	8.3	33.4	23.4	71.2%	58.9%	1.0024×10^8
Case-3	4.5	2.8	11.7	7.5	31.9	21.2	68.1%	55.1%	1.2815×10^8
Sol-1	4.4	3.9	12	10.6	34.4	30.2	72%	60%	1.03×10^8
Sol-2	4.4	3.5	12	9.5	32.9	26.9	71%	59%	1.05×10^8
Sol-3	4.4	3.4	12	9.1	32.8	25.3	68%	55%	1.17×10^8

In this work, the reference to the controller is selected by trial and error so that the maximum toxicity always remains below the maximum allowable value as indicated in design objective in Table 5.2, where the minimum value considered as zero. The fixed reference value is set at 12 in this work.

To obtain different performance measures in relation to chemotherapy treatment, decision variables, k_p, k_i and k_d corresponding to solutions; case-1, case-2, case-3, Sol-1, Sol-2 and Sol-3, were fed to the I-PD controller and the whole system along with the patient model was simulated for 84 days. Then the output of the I-PD controller, $\mathrm{u(t)}$, which is the chemotherapy drug scheduling was recorded in each case. Moreover, outputs of the patient

model, such as, drug concentration at tumour site, toxicity, reduction of proliferating and quiescent cells and changes in normal cells were also recorded due to the infusion of the chemotherapy doses. Figure 5.7 show the chemotherapy drug scheduling for Case-1, Case-2, Case-3, Sol-1, Sol-2 and Sol-3.

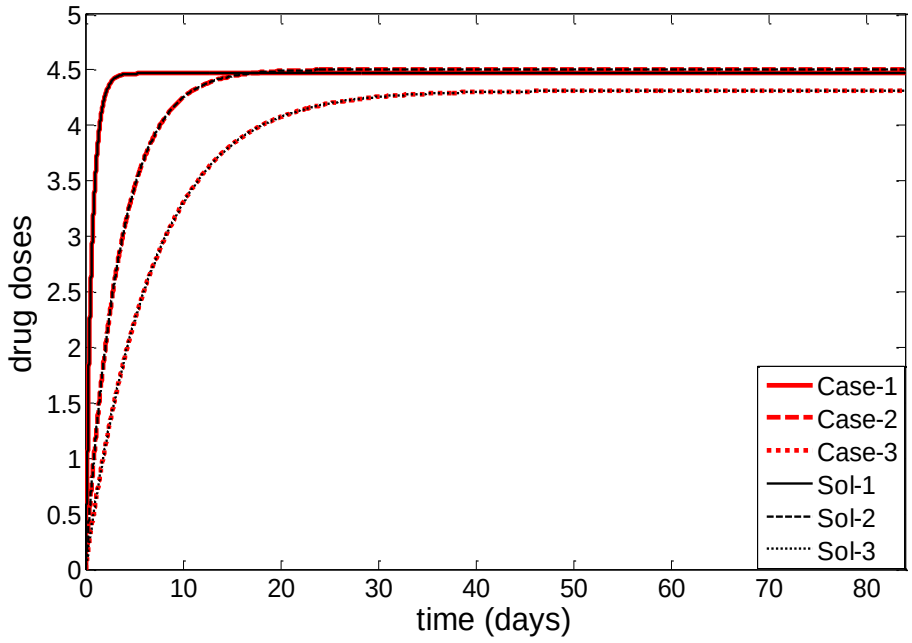

Fig. 5.7 Chemotherapy drug doses for solutions Case-1, Case-2 and Case-3, Sol-1, Sol-2 and Sol-3

Moreover, several performance measures of chemotherapy treatment, such as maximum and average levels of drug doses, toxicity and drug concentrations for all six solutions were recorded as shown in Table 5.2. Furthermore, percentage of the reductions in proliferating and quiescent cells at the end of chemotherapy treatment are also determined and shown in Table 5.2. The number of normal cells remaining at the end of treatment gives an indication of the physiological state of the patient. So this number was also calculated and displayed in the same Table.

5.3.2.1 Drug Concentrations

Figure 5.8 shows the drug concentration against the reference input for both algorithms Case-1, Case-2, Case-3, Sol-1, Sol-2 and Sol-3 at the tumour site due to chemotherapy drug scheduling. It is interesting to note that the drug concentrations for all cases (selected solutions), increase gradually in a similar manner as observed in the case of corresponding drug scheduling and follow the reference levels. The drug concentrations at the tumour site for the MOGA reach a maximum value as set by the corresponding reference values. It is also noted that, like average drug doses, the average drug concentrations also vary from case to case; Case-1 having maximum average value of 9.2 followed by Case-2 and Case-3, as listed in Table 5.2. While in the MOPSO, the average drug concentrations are different from case to case; Sol-1-1 having maximum average value of 10.6 followed by Sol-2 and Sol-3, which is slightly high compared to MOGA as listed in Table 5. 2. More importantly, the average and maximum drug concentrations are always much lower than the allowable maximum value indicated in design objective and constraint for this particular parameter.

It is important to mention that phase specific chemotherapy drugs, such as Vinca alkaloids, Hydroxyurea, Cytosine arabinoside, Methotrexate, 6-Mercaptopurin, 6-Thioguanine, Procarbazin, VM-26 and VP16-213 Liang et al., 2008, are, in general, toxic agents and lower doses of these drugs may reduce the toxic side effects during the treatment cycle and thereby improve the quality of life of the patient (Martin and Teo, 1994).

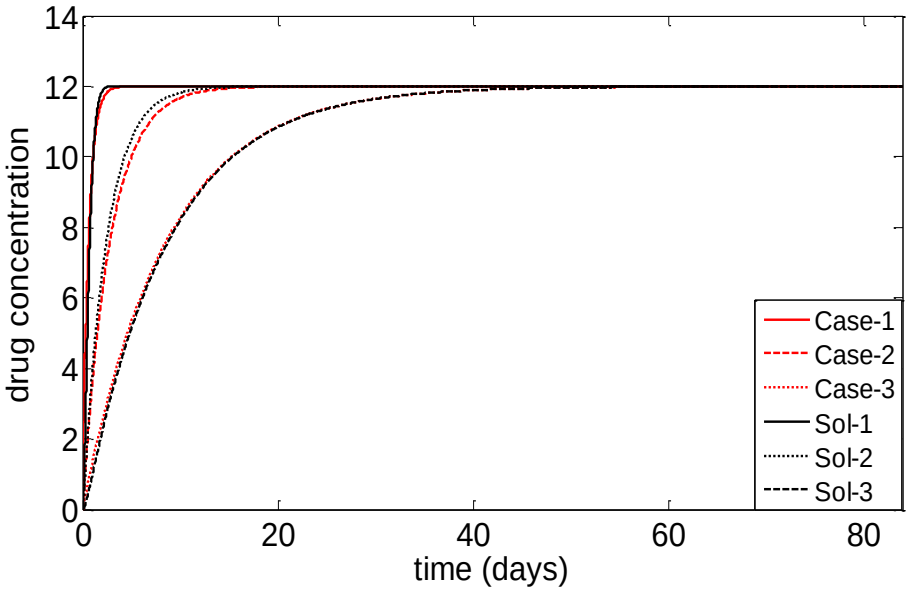

Fig. 5.8 Drug concentration for solutions Case-1, Case-2 and Case-3, Sol-1, Sol-2 and Sol-3

5.3.2.2 Toxicity

The toxicities for both algorithms MOGA and MOPSO, for Case-1, Case-2, Case-3, Sol-1, Sol-2 and Sol-3, developed due to the corresponding chemotherapy drug scheduling are shown in Figure 5.9. For all cases, the toxicities gradually increase from the first day of treatment and finally settle to a steady value after a few weeks, in a similar manner as observed in the case of drug scheduling and drug concentration. The maximum level of toxicity for MOGA is observed with the drug scheduling obtained with Case-1 and the value is 34.5, whereas the minimum toxicity is caused by Case-3. The average toxicities for Case-1, Case-2 and Case-3 are 27.7, 23.4 and 21.2, respectively. The maximum level of toxicity for MOPSO is observed with the drug scheduling obtained with Sol-1 and the value is 34.4, whereas the minimum toxicity is caused by Sol-3. The average toxicities for Sol-1, Sol-2 and Sol-3 are 30.2, 26.9 and 25.3, respectively; showing that the average toxicities for MOPSO

for are higher than MOGA. It is important to note that toxicities in all cases remain under control and much lower than the maximum limiting value set in design objective and constraint of the optimisation process.

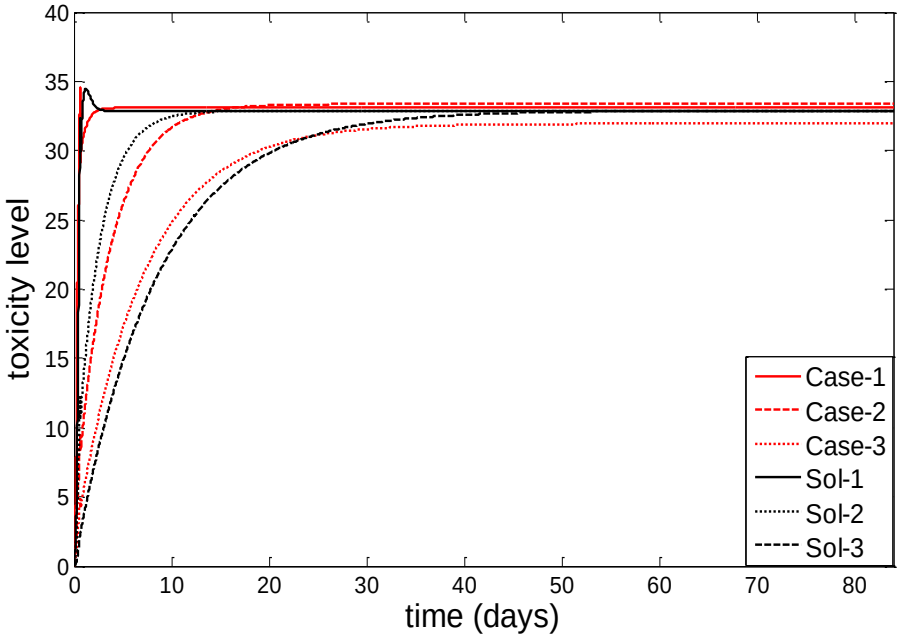

Fig. 5.9 Toxicity for all solutions Case-1, Case-2 and Case-3, Sol-1, Sol-2 and Sol-3

5.3.2.3 Reduction of cells

One of the aims of chemotherapy treatment is to reduce the proliferation and quiescent cells without affecting normal cells much during the treatment. Before the treatment starts, the numbers of all cells are listed in Table 5.1, and the number of proliferation cells is set at $2x10^{11}$, as used by many researchers in cell cycle specific cancer treatment (Dua et al., 2008). Figure 5.10 shows the reduction of proliferating cells during the whole period of treatment. For the MOGA Case-1, Case-2 and Case-3, the percentage of reductions obtained using the drug scheduling shown in Figure 5.7 are 72.5%, 71.2% and 68.1%, respectively. For the MOPSO Sol-1, Sol-2 and Sol-3, the percentage of reductions

obtained using the drug scheduling shown in Figure 5. 6 are 72%, 71% and 68%, respectively.

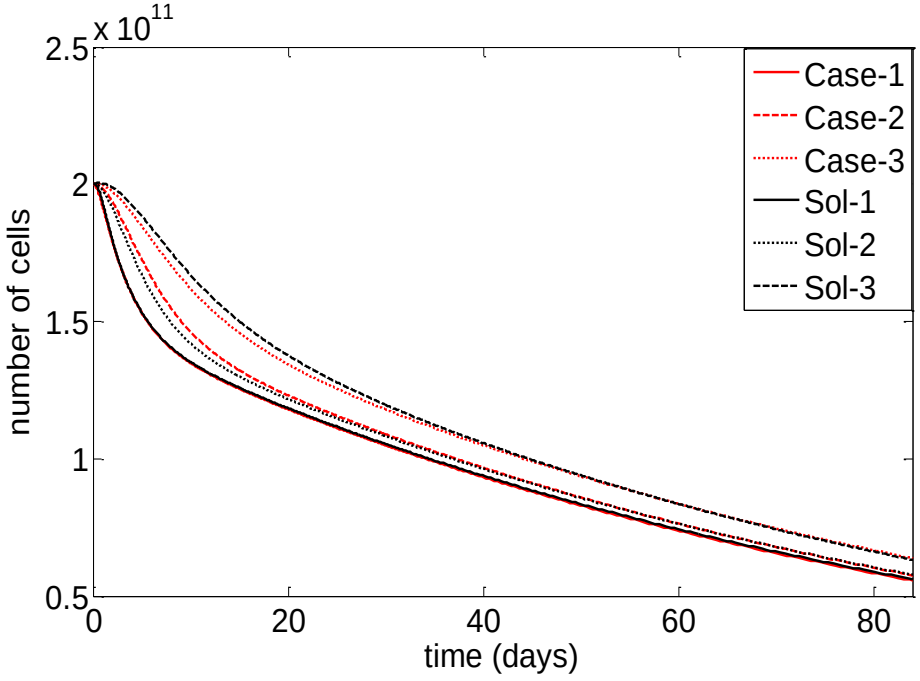

Fig. 5.10, Proliferating cells reduction for all solutions Case-1, Case-2 and Case-3, Sol-1, Sol-2 and Sol-3

It is noted that the MOGA performance of the cell reduction is better when compared to the MOPSO. During the treatment period, the number gradually decreases depending on chemotherapy drug doses and this is observed for all solutions in Figure 5.9. A similar trend is observed in the case of quiescent cells and it is shown in Figure 5.11. It is important to note that the reduction for all selected solutions are: Case-1, Case-2, Case-3, Sol-1, Sol-2 and Sol-3 are 61%, 58.9%, 55.1%, 60%, 59% and 55%, respectively. Figure 5.12 shows the changes of normal cells during the whole period of treatment for all solutions. It is mentioned that in all solutions, the number of normal cells is higher than the threshold value, as indicated in Table 5.2. Moreover, these higher values of remaining normal cells are attributed to lower toxic side effects and better physiological conditions of patients.

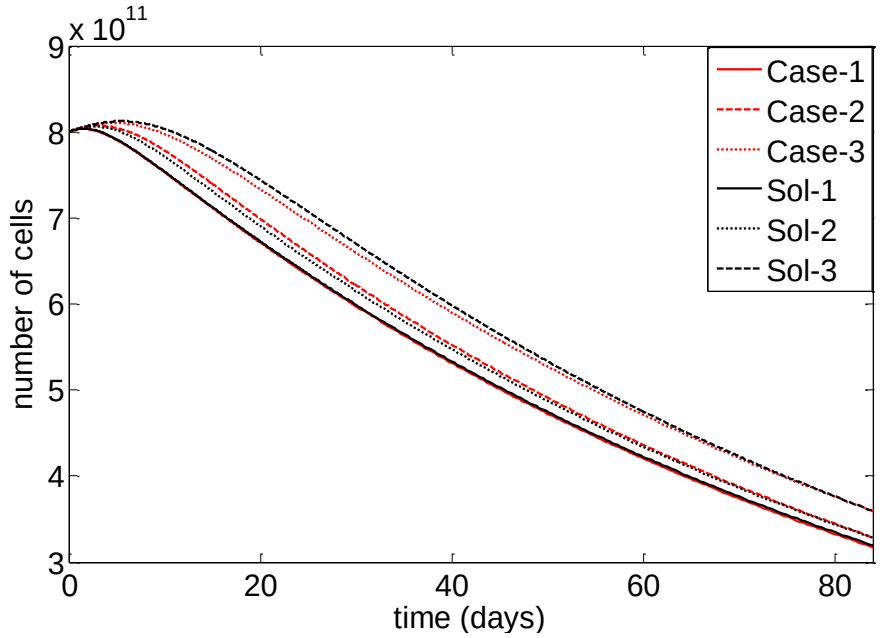

Fig. 5.11 Quiescent cells reduction for all solutions Case-1, Case-2 and Case-3, Sol-1, Sol-2 and Sol-3

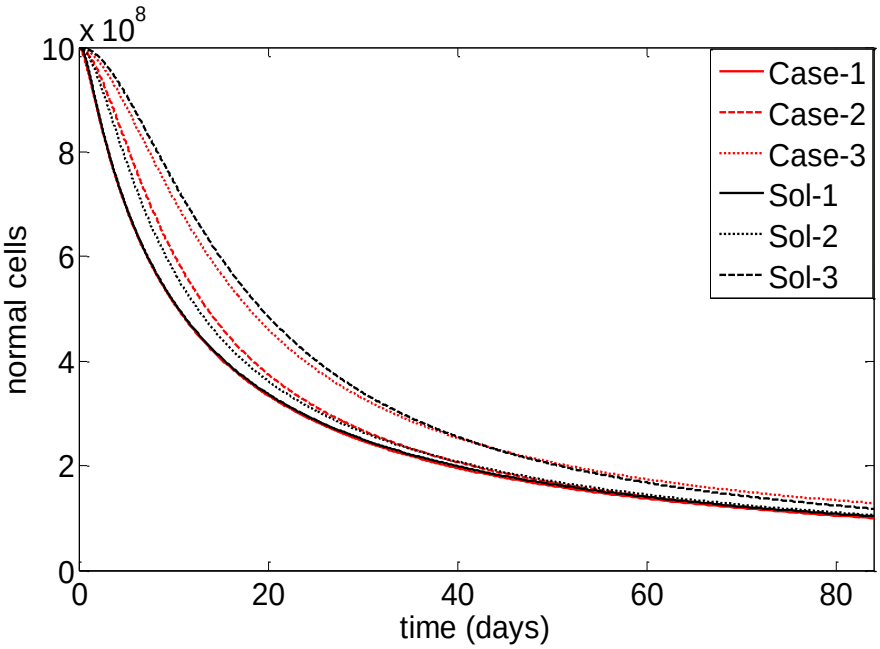

Fig. 5.12 Normal cells reduction for all solutions Case-1, Case-2 and Case-3, Sol-1, Sol-2 and Sol-3

5.4 Four compartments cancer cells model

This section presents an investigation into the comparison of a feedback I-PD controller for chemotherapy drug scheduling. To the best of our knowledge this is the I-PD based chemotherapy control model used to investigate the cell cycle specific treatment. MOGA has also been used to optimise the parameters of the controller. The main objective of the proposed control was to enhance the performance of the cancer drug treatment with minimum toxic side effects and drug resistance. Model based on the cells function has been used to analyse the effects of the drug scheduling designed by the controller. It is noted that the obtained drug schedule is continuous in nature having lower and nearly stable values throughout the whole period of treatment. The proposed drug scheduling pattern has reduced the number of tumour cells significantly with the tolerable drug concentration and toxicity level.

In order to evaluate the effectiveness of the proposed control strategy and MOGA optimisation process with cancer cells compartments, an example solution yielding minimum value was analysed in detail in Chapter 3. To obtain different performance measures in relation to chemotherapy treatment, eight decision variables; 6 controller parameters (k_{Ap}, k_{Ai} , k_{Ad}, , k_{Bp}, k_{Bi} and k_{Bd}) and 2 reference inputs (X_{DA} and X_{DB}) as shown in Figure 4. 11 in Chapter 4 were fed to the feedback control system and the whole system along with the patient model is simulated for 84 days. Then the outputs of two I-PD controllers, $u_A(\mathrm{t})$ and $u_B(\mathrm{t})$ which are scheduling for drugs A and B were recorded. Several outputs of the patient model, such as, drug concentration at tumour site, toxicity and reduction of cancer cells were recorded due to the infusion of the designed chemotherapy doses.

This compares the effectiveness of the cancer chemotherapy treatments based on drug scheduling between a single drug and combination of cancer drugs. Maximum drug doses found during the whole period of treatment vary in the range of 10-19, while the average remained within 8-13, as shown in Chapter 4, the chemotherapy drug scheduling for single drug. It is noted that, the use of Rep & Cont with single drug as the reference input, the drug doses sharply rise to a maximum value of 18.5 in the first two days of treatment and then slightly reduce on days 3 and 4 followed by a sharp decrease on days 5 and 6. The drug doses then rise sharply to a level of nearly 14.5 and remained almost stable till the end of the treatment.

In both drugs, the drug doses increase from zero and finally become stable at certain values of 12.91 and 13.12. It is noted that the level of increase is different for two drugs. It is worth mentioning that the dosage of the multi-drug is lower compared to the single drug. Moreover the effectiveness of the multi-drug by reducing the resistance of the chemotherapy cancer treatment increases the performance of the treatment. For drug A, the doses reach maximum value of 13.12 within the first week of treatment and for the remaining periods it becomes stable at that same value. For drug B, the drug dosage took slightly more than one week to reach the maximum and stabilised for the rest of the period at 12.91.

5.4.1 Drug concentration

Figure 5.13 shows that the drug concentration of the single chemotherapy cancer drug treatment increases and decreases with time in a similar manner as that observed in case of drug scheduling. Figure 4.(b) in Chapter 4 shows the drug concentration for the single drug, where the reference input is Rep & Con pattern and it also follows the corresponding drug scheduling; as observed the average values are below 35 and the maximum values 50.

It is interesting to note that the drug concentrations, for both drugs, increase gradually in similar manner as observed in the case of corresponding drug scheduling and follow corresponding references levels/desired levels. The drug concentrations at tumour site reach to a maximum value as set by the corresponding references/desired values. More importantly, it is noted that the maximum drug concentrations are always much lower than the allowable maximum value indicated in the design objective and constraint for this particular parameter.

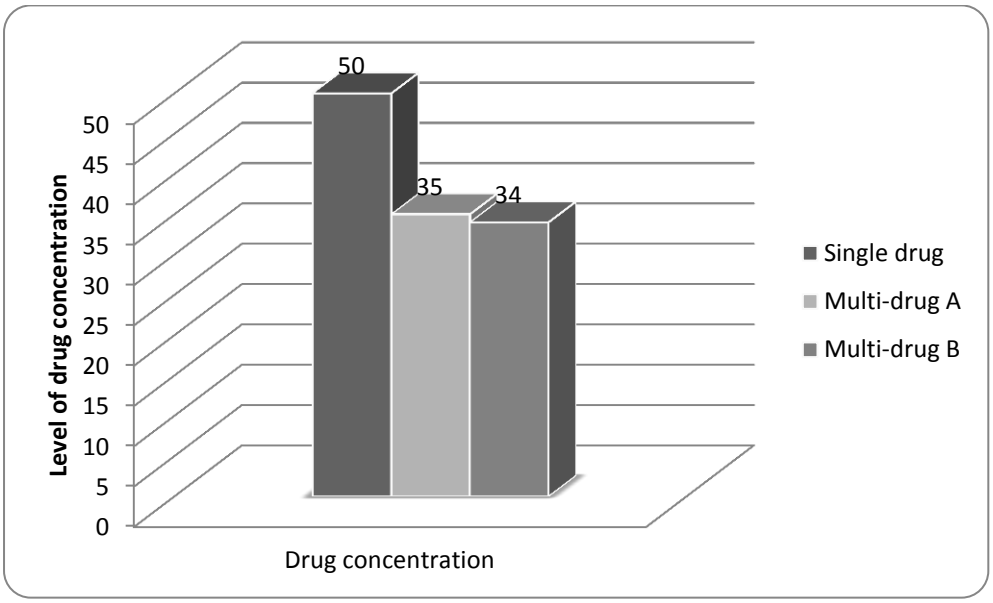

Fig. 5.13 Comparative level of final drug concentration for the single and multi-drugs

5.4.2 Toxicity

The maximum level of the toxicity of the single drug is determined during the whole period of treatment, as shown in Figure 5.14. The toxicity sharply rises in the first two days because of high drug doses infused to the patient, as shown in Figure 4.13(c) Chapter 4. The toxicity then reduces and finally gets stable for the whole period at an approximate level of 98.7. The toxicities is close to the edge of the critical point, while on the other hand it

remains under the maximum limiting value set in design objective and constraint of the optimisation process.

The toxicities, for drug A and drug B, developed due to the corresponding chemotherapy drug scheduling are shown in Figure 4.13(b) Chapter 4. For both drugs, the toxicities gradually increase from the first day of treatment and finally settle to a steady value after a few days in a similar manner as observed in case of drug scheduling and drug concentration. The maximum level of toxicity is observed with the drug scheduling obtained with drug A, and the value is 97.5 whereas the toxicity caused by drug B is at the lower level of toxicity in comparison to drug A. The level of toxicities for drug A and drug B are 81.7 and 77.5 respectively. It is noted that levels of toxicity for multi-drug chemotherapy treatment is low compared to the single drug. It is important to note that toxicities in all cases remain under control and much lower than the maximum limiting value set in the design objective and constraint of the optimisation process.

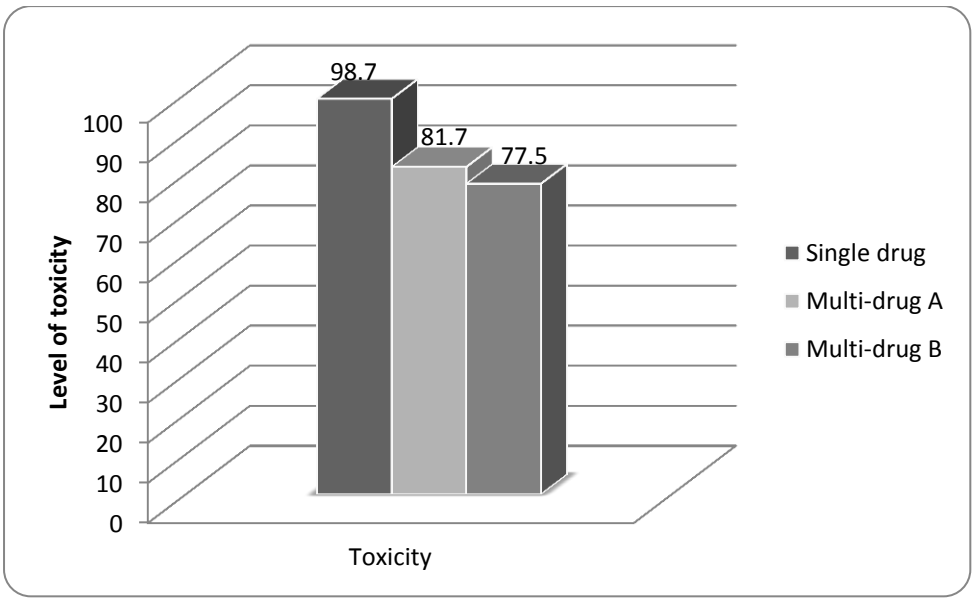

Fig. 5.14 Comparative level of final toxicity for the single and multi-drugs

5.4.3 Cells reductions

The main aim of chemotherapy combination regime treatment is to eradicate/minimise the cancer drug resistance to the minimum level after a number of fixed treatment cycles. Before the treatment starts for the single drug, the number of proliferation cells is set at $1x10^9$, as used by many researchers (Martin and Teo, 1994, Tes, et al, 2007) and reduction of cancerous cells for all solutions up to 99%. For the multi-drug the treatment starts, the number of cancer cells was assumed 4.60517×10^{11}, as used by many researchers in cell cycle specific cancer treatment (Dua et al., 2008) whereas the percentage of the reduction approximates nearly to 100%. Figure 5.15 shows the differences of the reduction between single and multi-drugs of cancer cells during the whole period of treatment. It is clear that the multi-drugs gives better performance than the single drug regarding the cancer cells reduction at the tumour site during the whole period of treatment.

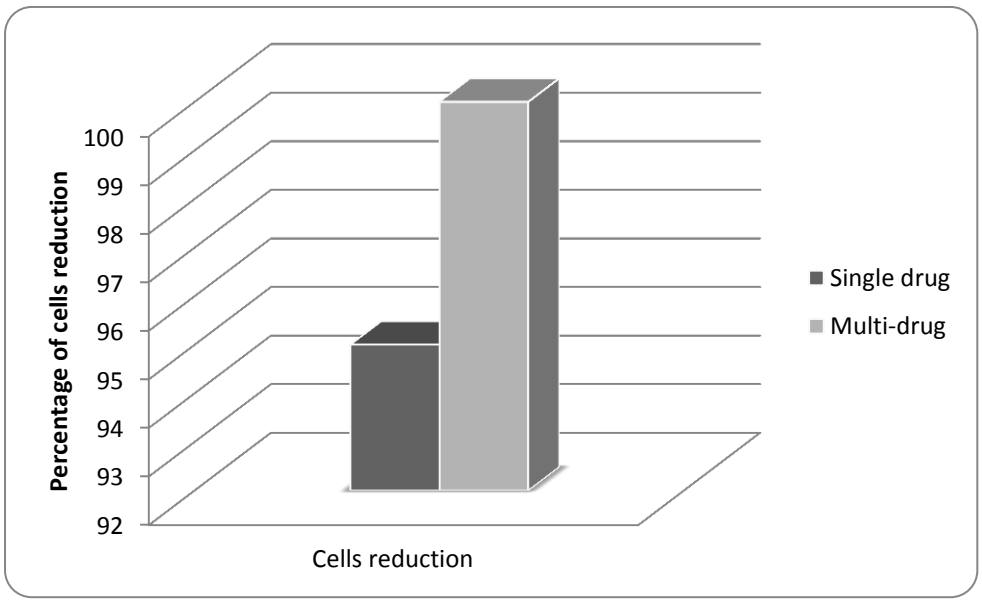

Fig. 5.15 Comparative percentage of the cells reduction for the single and multi-drugs

5.5 Eight compartments cancer cells model

This section presents a comparative investigation for the chemotherapy cancer drug scheduling between two algorithms, a proposed one multi-objective genetic algorithm (MOGA) and a reported algorithm called memetic algorithm (MA). A proposed novel method of multi-drug scheduling uses (MOGA) to find optimum dosages by trading-off between cell killing and toxic side-effects of chemotherapy treatment. A close-loop control method, namely Integral-Proportional-Derivative (IPD) was designed to control dosages of drugs to be infused to the patient's body and MOGA was used to find suitable parameters of the controller. A cell compartments model was developed and used to describe the effects of the drugs on different type of cells, plasma drug concentration and toxic side-effects. Results in Chapter 4 show that specific drug schedule obtained through the proposed method can reduce the tumour size nearly 100% with relatively fewer toxic side-effects.

The reported method was introduced by Liang and co-worker, 2007, called a new memetic algorithm (MA) to solve the Multi-drug chemotherapy optimization problem. A multi-drug chemotherapy cancer treatment model is implemented to simulate the possible response of the tumour cells under drugs administration. Optimization of the multiple chemotherapeutic agents' administration schedules was based on this tumour model. They formulate the optimization problem as an optimal control problem (OCP) with a set of dynamic equations. The objective was to design efficient schedules which minimise the tumour size under a set of constraints.

The proposed method investigated and analysed GA parameters and values that yielded very satisfactory results in similar applications; the details are described in Section 4.4 of Chapter 4. In this investigation a model based on the cells' function has been used to analyse

the effects of the drug scheduling designed by the controller. It is noted that the obtained drug schedule was continuous in nature and gives lower and stable values throughout the whole period of treatment.

Many solutions of the proposed drug scheduling pattern have reduced the number of tumour cells by more than 99% (eliminate the resistance cells) with the tolerable drug concentration and lower toxic side-effects. The proposed model offered better performance as compared to existing models with regard to drug resistance and toxicity levels. The drug effectiveness (cells reduction) (as shown in Figure 4.16(d) in Chapter 4) in the proposed model is nearly 100%, while in the existing it is about 99%. The maximum level of toxicity produced by drug A is 92.3 in the proposed model and 100 for all drugs in the existing one (Liang et al., 2007).

Figure 4.16(a) in Chapter 4 shows the chemotherapy drug scheduling for drug A, B and C. The drug doses increase from zero and finally become stable at a certain value. It is noted that the rate of increase is different for the three different drugs. For drug A, the doses take slightly more than one week to reach their maximum value of 17.12 and for the remaining periods it becomes stable at that same value. Drug B takes less than one week to reach the maximum and stable level of 15 and the doses of drug C get stable at the highest level, which are 12.5 within one week.

5.5.1 Drug Concentration

Figure 5.16 shows a comparison of the drug concentration between proposed and reported methods. The drug concentration at the tumour site due to chemotherapy drug scheduling obtained for all cases is shown earlier in Figure 4.16(b) in Chapter 4. It is interesting to note that the drug concentrations for all cases increase gradually in a similar

manner as observed in the case of corresponding drug dose scheduling. The drug concentrations at tumour site reach to maximum values, which are 29, 36 and 39 for drugs A, B and C respectively. More importantly, it is noted that the maximum drug concentrations are always much lower than the allowable maximum value indicated in the design objective and constraint for this particular parameter. In contrast, the MA (Tes et al, 2008), offered highest drug concentration level compare to the proposed model, whereas the levels of concentration for drugs A, B and C of the reported model are 40, 50 and 50 respectively. On the other hand, the drug concentration level of our proposed model is much lower as compared to Tes et al., (2008) as Figure 5.16 illustrated. It is noted that the drug concentration in the reported method is still lower than the maximum value of the drug concentration limit.

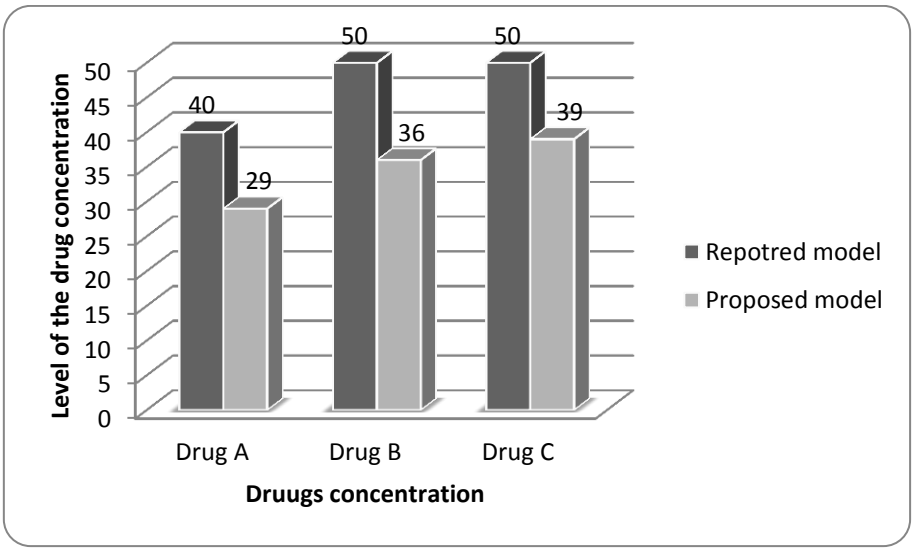

Fig. 5.16 Comparative level of final drug concentration for the reported and proposed model

5.5.2 Toxicity

This section presented a comparison of the toxicity for chemotherapy drug scheduling of the two algorithms mentioned earlier (MOGA and MA). The main objective of the proposed algorithm is to find solutions which enhance the performance of the cancer drug

treatment with minimum toxic side effects. A model based on the multi-drug has been used to analyse the effects of the drug scheduling designed by the controllers. It is noted that the obtained drug schedule is continuous in nature, having lower and nearly stable values throughout the whole period of treatment. The toxicities, 92.3, 90 and 71.1 for drugs A, B and C respectively, developed due to the corresponding chemotherapy drug scheduling, are shown in Figure 4.16(c) of Chapter 4.

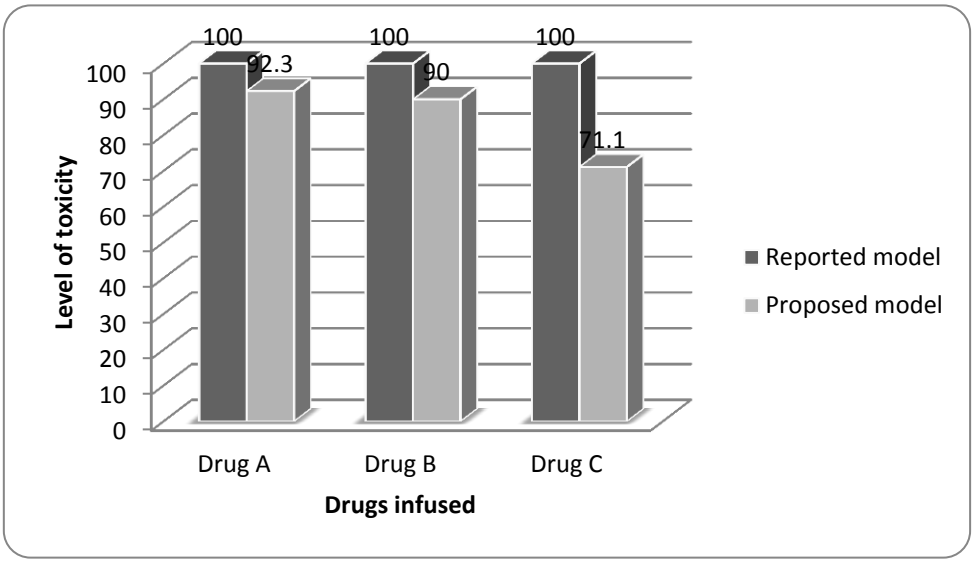

Fig. 5.17 Comparative level of final toxicity for the reported and proposed model

For three cases, the toxicities gradually increase from the first day of treatment and finally settle to a steady value after a few days in a similar manner as observed in the case of drug scheduling and drug concentration. The maximum level of toxicity was observed with the drug scheduling obtained with drug A and the value is 92.3, whereas the minimum toxicity, caused by drug B, is 71.7. Toxicities in all cases remain under control and much lower than the maximum limiting value set in the design objective and constraint of the optimisation process.

Figure 5.17 shows the level of the toxicity for both algorithms, whereas the levels of toxicity produced by the reported model Memetic Algorithm (MA) (Tes et al., 2008) are higher compared to the proposed algorithm. In all cases of the MA the toxicity levels reach 100, the maximum tolerable level which should not be exceeded.

5.5.3 Cell reduction

The main aim of chemotherapy treatment was to reduce the cancer cells without affecting normal cells in the tissue during the treatment. Figure 5.18 shows the percentage of reduction of cancer cells during the whole period of treatment for the two algorithms, proposed algorithm MOGA and the reported MA one. Before the treatment starts, the number of cancer cells is $4.60517X10^{11}$, as used by many researchers in cell cycle specific cancer treatment (Tes et al., 2008). The percentage of the cancer cells reduction for the proposed algorithm obtained using the drug scheduling is nearly 100%, which corresponds to the solution chosen. Moreover, this higher percentage of the cancer cells reduction is achieved with significantly lower toxic side effects and better physiological conditions of patients.

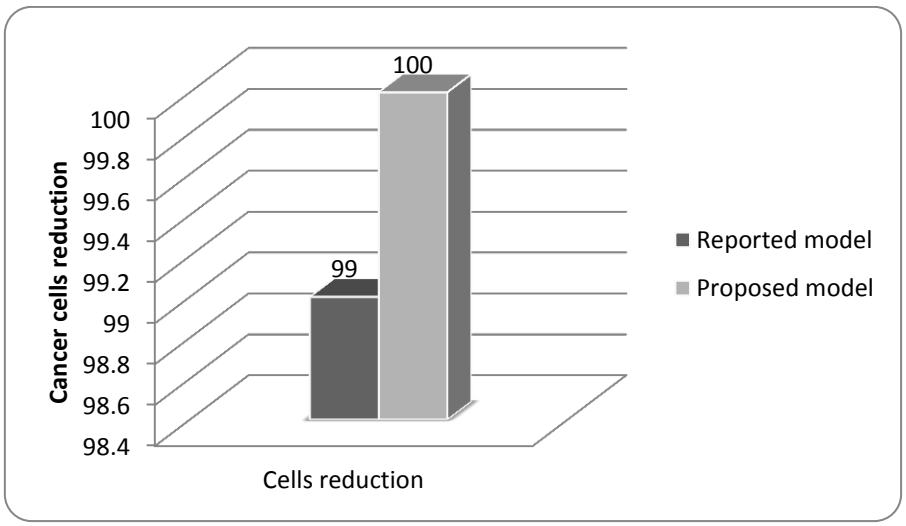

Fig. 5.18: Comparative percentage of the cells reduction for the reported and proposed model.

The rate of the cells' reduction of the memetic algorithm (MA) is lower than the proposed algorithm, which is about 99% with higher levels of toxicity as shown in the section above. It is important to note that the proposed algorithm MOGA gives better performance as compared to the MA Algorithm. In both cases the rate of reduction is steady and reduces to a significantly lower value throughout the period of the treatment.

5.6 Summary

This Chapter has presented a comparative study of all the different techniques that have been used in the earlier Chapters and the outcome for optimal cancer drug scheduling using multi-objective algorithms. Two main objectives of chemotherapy treatment, reducing cancerous cells and reducing toxic side effects are always found to be in conflict. In all techniques, optimisations process was used to design the drug scheduling that would trade-off between these conflicts. The proposed method was designed to control the drug to be infused to the patient's body for a cell cycle specific treatment.

A novel close-loop control method was used to design drug doses by maintaining a suitable level of drug concentration at tumour sites. Most used feedback control system; Proportional-Integral-Derivative (PID) (Astrom et al., 1993) and a variant of it (different structures of PID) were designed to control the drugs to be infused into the patient's body. A multi-objective optimal chemotherapy control model was used to reduce the number of cancer cells after a number of fixed treatment cycles with minimum side effects. MOGA and MOPSO were used to tune the parameters for optimal control solution. In the proposed method, several design objectives, constraints and associated goal values are defined prior to the optimisation process. The reported techniques are based on the optimisation process as

well, with different controllers to control the drug doses during the treatment cycle. These techniques were introduced by many researchers, as mentioned above.

A comparative study has been presented, based on the reduction of the cancer cells and the effectiveness of the treatment. Phase specific and non-phase specific cancer tumour models were used for this work to show the effects of drugs on different cell populations, drug concentration and toxic side effects. Comparisons show that the employed multi-objective optimisation approach can generate a wide range of solutions that trade-off between cell killing and toxic side effects and satisfy associated goals of chemotherapy treatment. As mentioned earlier, the cancer chemotherapy treatment models have been classified depending on the functional state of the cancer cells.

This Chapter has also presented an investigation into the development of multi-drug chemotherapy scheduling model using multi-objective optimisation techniques. An optimal control method was used to design drug doses by maintaining a suitable level of drug concentration at tumour sites. There were four design objectives: reducing cancer cells, reducing toxic side effects for two and three drugs (Four and eight compartments) and maintaining the concentration of all drugs at tolerable level. A model based on the cells' function has been used to analyse the effects of the drug scheduling designed by the controller. It is noted that the obtained drug schedule is continuous in nature and gives lower and stable values throughout the whole period of treatment. Many solutions of the proposed drug scheduling pattern have reduced the number of tumour cells by nearly 100% (eliminating the resistance cells) with tolerable drug concentration and lower toxic side effects.

It is interesting to note that the design approach can offer flexibility in decision making and a suitable solution can be picked up under different trade-off interventions for cancer treatment. It is noted that the drug scheduling pattern of the MOGA algorithm offers better performance as compared to the other algorithms.

CHAPTER 6

Conclusion and Future Work

6.1 Conclusion

This thesis has presented an investigation into the development of models for drug scheduling and optimisation for chemotherapy cancer treatment. The proposed models, based on the cells' functions, are used to predict and control the tumour growth and explore the other effects of treatment. In order to achieve multi-objective optimal control model, close-loop control methods using the proportional, integral and derivative (PID) are used. The Multi-objective Genetic Algorithm (MOGA) method was used to optimise the controller parameters, in order to maximise cell killing and minimise the toxic side effects to increase the survival time of the patient. The proposed method, several design objectives, constraints and associated goal values are defined prior to the optimisation process and a wide range of solutions have been obtained, satisfying all design goals and trading-off between two main conflicting objectives of chemotherapy treatment, reducing cancerous cells and reducing toxic side effects.

The results of the different optimal scheduling patterns of the proposed models are presented and discussed through a set of experiments. The observations are compared with the existing models in order to demonstrate the merits and capabilities of the proposed multi-objective optimisation models, which reduce the cancer cells by nearly 100% with tolerable levels of drug concentration and toxicity. It is noted that the proposed models offer best performance as compared to any models reported earlier.

6.2 List of Contributions

The main contributions of this research are as follows:

- Design and Development of a non-phase specific optimal PID and IPD control model for chemotherapy drug scheduling.
- MOGA based control model for phase specific cancer treatments using a single chemotherapy.
- MOGA based control models for cancer treatment using multiple chemotherapy drugs.

6.3 Future Work

Future research should focus on designing and implementing cancer treatment models with real clinical data and considering the biochemical behaviours of the cancer patients. The models should also be extended by incorporating the effect of different treatment combinations of doses, and different patterns of chemotherapy drug scheduling to generate applicable and reliable cancer treatment.

- The recommendation for the researchers in the next stage could focus specifically on the treatment combination and multi-drug scheduling using other strategies in order to get better performance. This type of research would increase the effectiveness of the treatment as compared to a single drug.
- Research should be carried out further by focusing on drug resistance as this is a one of the important factors for unsuccessful cancer treatment. The investigation can consider the cell proliferating cycle which divides the cell cycle in compartments

based on the stages of the cell cycling and treatment can be done for each cycle stage by different drugs.

- Finally, the different multi-objective optimisation technique with well as feedback control strategy could be used and extended further for any higher combination regimen to achieve better performance. Moreover, many design objectives and constraints can also be handled to design drug doses for more compartment models. The variety of multi-objective algorithms can be a very useful computing tool to solve complex chemotherapy cancer drug scheduling problems and other deadly and infectious diseases.

References

Abundo M and Rossi, C., (1989). "Numerical simulation of a stochastic model for cancerous cells submitted to chemotherapy," J. Math-Biol, vol. 27, pp. 81-90.

Adam, J. and Panetta, J, (1995)."A Mathematical Model of Cycle-Specific Chemotherapy." Math. Comput Modelling, 22(2), pp. 67-82.

Alam. S, Algoul. S, Hossain. A, Majumader. A, (2010). "Multi-objective Particle Swarm Optimisation for Phase Specific Cancer Drug Scheduling", First Int. Conf. CSBio, pp. 180-192.

Alexandru and Carmen, (2003). "Adaptive Neural Networks Control of Drug Dosage Regimens in Cancer Chemotherapy", IEEE conference, pp. 154-159.

Astrom, H., Hagglund, T., Hang, C and Ho, W., (1993). "Automatic tuning and adaptation for PID controller a survey," IFACJ Control Eng Practice, vol.1, no. 4, pp. 699-714.

Baker, E., (1987). "Reducing bias and inefficiency in the selection algorithm.", The Second International Conference on Genetic Algorithms, San Mateo, Morgan Kaufmann, Inc.

Barbolosi and Iliadis. (2000). "Optimizing Drug Regimens in Cancer chemotherapy by an Efficacy–Toxicity Mathematical Model" Computers and Biomedical Research 33, 211–226.

Basdevan, C., Clairambanlt, J and Levi, F., (2004). “Optimal drug Infusion Strategies for Cancer Chemotherapy”, Institute national de recherché informatique et automatique, INRIA.

Basse, B., Baguley, B., Marshall, E., Wake, G. and Wall, D., (2004). “Modelling cell population growth with applications to cancer therapy in human tumour cell lines”, Progress in Biophysics & Molecular Biology, 85, pp. 353–368.

Blackall, P. J. (ed.) 2010. The Merck veterinary manual. 10th ed. Merck and Co., Rahway, NJ. (www.merckbooks.com - access 2011).

Bojkov, B., Hansel, R and Luus, R., (1993). “Application of direct search optimization to Optimal control problems,” Hungarian J. Ind. Chem., vol. 21, pp. 177-185.

Booker, B, (1987). “Improving search in genetic algorithms, Genetic Algorithms and Simulated annealing”, Los Altos, Morgan Kaufmann.

Brandt, K., Gastens, A and Loscher, W., (2006)."The multidrug transporter hypothesis of Drug resistance in epilepsy: Proof-of-principle in a rat model of temporal lobe epilepsy", Neurobiology of diseases, vol. 24, pp. 202-211.

Busetti, F. (2001). "Genetic algorithms overview” (http://citeseer.nj.nec.com. - Accessed on 11/2009).

Cancer Research UK, 2011. Worldwide cancer statistics, (http://info.cancerresearchuk.org/cancerstats/world/ - accessed on 2011).

Care during Chemotherapy and Beyond – Chemotherapy Resistance, (http://www.chemocare.com – accessed 8/2011).

Carrasco, E and Banga, J., 1998. "Dynamic optimization of batch reactors using adaptive Stochastic algorithms,'' Ind. Eng. Chem. Res, vol. 36, pp. 2252-2261.

Chandy, D and Kumari V., (2006). "Genetic Algorithm Based Location of Optic Disc in Retinal Images", Academic Open Internet Journal, ISSN 1311-4360, (17).

Chemotherapy Medicines - Chemotherapy medications for breast cancer, (www.breastcancer.org. - accessed on 2011).

Chipperfield, A., Fleming, P., Pohlheim, H. and Fonseca, C., (1994). "Genetic algorithms toolbox user's guide", Research report no. 512, Dept. Automatic Control and Systems Engineering, The University of Sheffield, UK.

Chipperfield, A., Purshouse, R., Fleming, P., Thompson, H and Griffin, I., (2002). "Multi-objective optimisation in control system design: an evolutionary computing approach", IFAC World Congress, Barcelona.

Costa, L and Bassanezi, R., (1992)."Optimal Chemical Control of Populations Developing Drug Resistance," IMA Journal, vol. 9, pp. 215-226.

Deb, K., (2001). "Multi-objective optimisation using Evolutonary algorithms." New York, Willey.

Dua, P., Dua, V and Pistikopoulos, N., (2008)."Optimal delivery of chemotherapeutic agents In cancer," Computer and Chemical Engineering, vol. 32, pp. 99-107.

Fero Lab, Fred Hutchinson cancer research center, (http://labs.fhcrc.org/. - Accessed on 3/2010).

Fonseca, C and Fleming, P., (1998). "Multi-objective optimization and multiple constraint handling with evolutionary algorithms-part I: A unified formulation", IEEE Transaction on Systems, Man and Cybernetics- part A: Systems and Humans, 28(1), pp. 26-37.

Fonseca, C. and Fleming, P., (1993). "Genetic algorithms for multiobjective optimization: formulation, discussion and generalization". Genetic Algoritms: Proceeding of the Fifth International Conference, San Mateo, CA, pp. 416-423.

Fonseca, C., (1995). "Multi-objective genetic algorithms with application to Control Engineering problems", PhD thesis, Department of Automatic Control and Systems Engineering, The University of Sheffield, UK.

Frank, R., (2011). "Despite steep costs, payments for new cancer drugs make economic sense", nature medicine, Nature America, Inc (17), 244.

Goldberg, D. E. (1989). "Genetic algorithms in search, optimisation and machine learning", Addison Wesley Longman, Publishing Co. Inc., New York, ISBN:0201157675.

Handbook for Nurses", Ch-37, Agency for Healthcare Research and Quality, (US), (http://www.ncbi.nlm.nih.gov/books).

Hassani and Naghihi, (2010). "Reinforcement Learning Based Control of Tumour Growth with Chemotherapy" International Conference on System Science and Engineering, 185-189.

Hilary Thomas, H., (2002)."Overcoming Multidrug Resistance in Cancer: An Update on the Clinical Strategy of Inhibiting P-Glycoprotein." cancer control: 159-165.

Holland, H., (1975). "Adaptation in natural and artificial system." University of Michigan Press, USA, ISBN-10:0-262-58111-6.

Human body, "Histology and Cell Structure" (http://www.Ivy-rose.co.uk. - Accessed on 8/2010).

John, L., Peter, C and Brian, W., (1993), "Lecture notes on clinical pharmacology", fourth Edt, Blackwell Scientific, ch-13, pp.153-165.

Kirkwood, T, (2006). "Alzheimer's Disease", Mild Cognitive Impairment, and the Biology of Intrinsic Aging Philosophy, Psychiatry, & Psychology (13), pp. 79-82.

Kivisto, K., Kroemer, H and Eichelbaum, M., "The role of Human cytochrome P450 enzymes in metabolism of anticancer agents: implications for drug interactions." Br J Clin Parmacol 40, pp. 523-30, (1995).

Kozusko., F and Bajzer, Z., (2003)."Combining Gompertzian growth and cell population dynamics." Mathematical Biosciences, 185(**2**): pp. 153-167.

Laurence, M., Susan, C., MVetclinstud and Leigh, L., "Acute toxicity of local anesthetics: Underlying pharmacokinetic and pharmacodynamic concepts", Regional Anesthesia and Pain Medicine, Vol 30, No 6 (November–December), 2005: pp 553–566.

Learn about cancer, History of cancer, ACS, (http://www.cancer.org - Accessed on 10/20011).

Ledzewicz, U., Schatteler, U., and Marriott, J., (2009)."Piecewise Constant Suboptimal Controls for a System Describing Tumor Growth under Angiogenic Treatment." IEEE International Conference on Control Applications: 77-82.

Liang, Y, Leung, K and Mok, T, (2006). "A novel evolutionary drug scheduling model in Cancer Chemotherapy," IEEE Trans on Information Technology in Biomedicine, vol. 1, pp. 237-245.

Liang, Y, Leung, K and Mok, T, (2008). "Evolutionary drug scheduling models with Different toxicity metabolism in cancer chemotherapy," Applied soft computing, vol. 8, pp. 140-149.

Liang, Y., Leung, K., and Mok, T, (2004). "Evolutionary drug scheduling models for cancer Chemotherapy", Proc. of Int. Conf. GECCO, pp. 1126 – 1137.

Lisa, F., "The History of Cancer". (http://www.cancer.about.com. - Accessed on 2010).

Lobo E. D and Balthasar, J. P., (2002). "Pharmacodynamic Modelling of Chemotherapeutic Effects: Application of a Transit Compartment Model to Characterize Methotrexate Effects in Vitro", AAPS, PharmSci, 4 (4), pp. 1-11.

Luus, R., (1998). "Comments on "Dynamic Optimization of Batch Reactors Using Adaptive Stochastic Algorithms", Ind. Eng. Chem. Res, 37, 305.

Luus, R., Hartig, F and Keil, F, (1995). "Optimal drug scheduling of cancer chemotherapy by Direct search optimization,'' Hungarian J. Ind. Chem., vol. 23, pp. 55–58.

Mahtani R. L., ” Common Chemotherapy Drugs and Side Effects”, Caring4cancer, 2010. (http://www.caring4cancer.com/ - accessed 2011).

Marek, Obitko, (1998). "Introduction to Genetic Algorithms” (http://www.obitko.com. - Accessed on 2010).

Martin, R., (1992)."Optimal control drug scheduling of cancer chemotherapy." Automatica, ch-1, pp. 1113-1122.

Martin, R., and Teo, K., (1994). “Optimal control of drug administration in chemotherapy tumour Growth”, 1 ed. World Scientific, pp. 95-111.

McCall, J., Petrovski, A and Shakya, A., (2008)."Evolutionary Algorithms for Cancer Chemotherapy Optimization." Computational Intelligence in Bioinformatics: pp. 265-296.

Mechael and Gottesman, (2002). “Mechanisms of cancer drug resistance”, Annu, Rev. Med. 53: pp. 615–27.

Michael, C., (2001). “The chemotherapy source book”, Section II, Third ed, Lippincott Williams and Wlkkins.

Minaya Villasana, (2010). “Modeling and optimization of combined cytostatic and cytotoxic cancer chemotherapy” Artificial Intelligence in Medicine (50), pp. 163–173.

Mouth care during chemotherapy, http://www.macmillan.org.uk – accessed, 2011)

National cancer institute at the national institute of health, (http://www.cancer.gov/, accessed, 2011).

Neal, M., (2005), “Medical pharmacology at a glance”, Fifth Edt, Blackwell, ISBN-13: 978-1-4051-3360-9.

Neilan and Lenhart, (2010). “An Introduction to Optimal Control with an Application in Disease Modelling” DIMACS Series in Discrete Mathematics and Theoretical Computer Science, 75, pp. 67-81.

Nicola, C, Ferry, A and Khan, J, (2001). “Phase I and Pharmacological Study of the Oral Matrix Metalloproteinase Inhibitor, MMI270 (CGS27023A), in Patients with advanced Solid Cancer”, Clin-Cancer Res, 7: pp. 1912-1922.

Ochoa, M., and Burke, E., (2007)."An evolutionary approach to cancer chemotherapy scheduling." Springer science, 8, pp. 301-318.

Panetta, (1996). “A mathematical model for drug resistance heterogeneous tumours”, Elsevier science Inc. Mathematical Bioscience, 147, pp. 41-61.

Panetta, J. (1999). "A mathematical model of drug resistance: Heterogeneous tumour." Math. Biosci, 147, pp. 41-61.

Petrovski, A., Sudha, B., McCall, J., (2004). “Optimising cancer chemotherapy using particle swarm optimization and genetic algorithms”. Proceeding of the 8th International Conference on Parallel Problem Solving from Nature, Lecture Notes in Computer Science, Springer, Berlin, Heidelberg, 3242, pp. 633-41.

Phillips, R. M., (1998). “Prospects for bio-reductive drug development”, Pub Med, 7(6), pp. 905- 928.

Physiomics rational therapeutics, PLC (2010). (http://www.physiomics.co.uk. - Accessed on 5/2011).

Rachel, A., (2009). “Cancer Chemotherapy”, edition-1, Wiley-Black well, ch-1, 1-10.

Richard, E., Susan, A, Bonnie, K and Rex, Z., (1996). “Quick reference hand book of oncology drug”, W. B. Saunders company, ISBN:0-7216-6894-1.

Robert, J., Carol, S., Lloyd, E and Alan, V., (1998). “Cancer chemotherapy pocket guide”, Lippincott-Raven,ISBN:0-397-51521-9.

Ronda, G and Blegen, A., “Patient Safety and Quality: An Evidence-Based Handbook for Nurses”, Ch-37, Agency for Healthcare Research and Quality (US); 2008. http://www.ncbi.nlm.nih.gov/books/NBK2656.

Souslova, T and Averill-Bates, D., (2004)."Multidrug-resistant hela cells over-expressing MRP 1 exhibit sensitivity to cell killing by hyperthermia: Interactions with etoposide”,' International Journal of Radiation Oncology 'Biology' Physics, vol. 60, no. 5, pp. 1538-1551.

Stengel, F., Ghigliazza, R., Kulkarni N and Laplace, O., (2002). “Optimal control of innate immune response”, Optim, Control Appl. Meth. Wiley, 23: 91–104.

Stephens and Peacock, (1977). “Tumour volume response, initial cell kill and cellular repopulation in b16 melanoma treated with cyclophosphamide and 1-(2-chloroethyl)-3-cyclohexyl-1– nitrosourea” Br.J.Cancer, 36, pp. 313-321.

Swan, G. W., (1988). “General Applications of Optimal Control Theory in Cancer Chemotherapy”, IMA Journal of Mathematics Applied in Medicine & Biology, 5, 303 - 316.

Swierniak A., Polanski, A and Kimmel, M., (1996). “Optimalcontrol problems arising in cell-cycle-specific cancer chemotherapy”, Cell Prolif., 29(1), pp. 117–139.

Swierniak, A., (1994). “Some control problems for simplest differential models of proliferation cycle.” Appl. Math. Comp. Sci., 4(2), pp. 223–232.

Swierniak, A., (2005). “Positive dynamic systems resulting from modeling cancer chemotherapy” 44th IEEE Conference on Decision and Control, and the European Control Conference, Seville, Spain, December 12-15.

Swierniak, A., Ledzewicz, U and Schättler, H., (2003a). “Optimal control for a class of compartmental models in cancer chemotherapy”, Int. J. Appl. Math. Comput. Sci., 13(3), pp. 357–368.

Swierniak, A., Ledzewicz, U and Schättler, H., (2003b). “Optimal control for a class of compartmental models in cancer chemotherapy”, Int. J. Appl. Math. Comput. Sci., 13(3), pp. 357–368.

Tan, K., Khor, F., Cai, J., Heng, C. M and Lee, T. H., (2002). "Automating the drug Scheduling of cancer chemotherapy via: evolutionary computation," Artificial intelligent in Medicine, vol. (1), pp. 908-913.

Tangient LLC, (http://www.eapbiofield.wikispaces.com. - Accessed on 3/2011).

Tes, S., Liang, Y., Leung, K., Lee, K and Mok, T., (2007). "A Memetic Algorithm for Multiple-Drug Cancer Chemotherapy Scheduling Optimization," IEEE Trans on Systems, Man, and Cybernetics-part B, vol. 37, pp. 84-91.

The Mathworks, Inc., (2008) "Simulink Control Design User's Guide."

The Mathworks, Inc., (2010) "MATLAB Reference Guide."

Triller, N., Koroˇsec, P., Kern, I., Koˇsnik, M and Debeljak A., (2006). "Multidrug resistance in small cell lung cancer: Expression of P-glycoprotein, multidrug resistance protein 1 and lung resistance protein in chemo-naive patients and in relapsed disease", Elsevier Ireland Ltd.

Vahedi, G., Faryabi, B., Chamberland, J., and Datta, A., (2009). "Optimal intervention strategies for cyclic therapeutic methods". IEEE Transactions on Biomedical Eengineering, 56, pp. 281-291.

Vukic, O. K. (2002). "Lectures on PID Controllers." http://arri.uta.edu, (Accessed on 2010).

Webster, K, Kehr, (2002). "Natural Cancer Treatments", Independent Cancer Research Foundation, Inc, ch – 4.

Westman, J., (2003). "Cancer Treatment and Control" Proceedings of the 42nd IEEE Conference on Decision and Control, Maui, Hawaii USA, pp. 3030-3035.

Westman, J., Fabijonas, B, Kern, D., and Hanson, F., (2001)."Compartmental Model for Cancer Evolution: Chemotherapy and Drug Resistance." Citeulke: 2693574.

WHO, (2011). (http://www.who.int/mediacentre/factsheets/fs297/en/index.html - Accessed in 2011).

Willis, M. J., (1999). “Proportional-Integral-Derivative Control”, of Chemical and Process Engineering, University of Newcastle.

Woderz, N., (2005). “Computational Biology of Cancer Lecture Notes and Mathematical Modelling”, World Scientific, ISBN-10: 9789812560278.