Multi-objective multi-drug scheduling schemes for cell cycle specific cancer treatment

M.S. Alam\textsuperscript{a}, M.A. Hossain\textsuperscript{a,∗}, S. Algoul\textsuperscript{a}, M.A.A. Majumader\textsuperscript{b}, M.A. Al-Mamun\textsuperscript{a}, G. Sexton\textsuperscript{a}, R. Phillips\textsuperscript{c}

\textsuperscript{a}Computational Intelligence Research Group, School of Computing, Engineering and Information Science, University of Northumbria at Newcastle, UK
\textsuperscript{b}Clinical Science, University of Bradford, UK
\textsuperscript{c}Institute of Cancer Therapeutics, University of Bradford, UK

\textbf{A B S T R A C T}

This paper presents an investigation into the development of an optimal chemotherapy drug(s) scheduling scheme to control the drug doses to be infused to the patient’s body. The current standard of practice of treatment is based on empirical evidence gathered from preclinical and clinical trials carried out during the drug development process. In general, most chemotherapy drugs used in cancer treatments are toxic agents and usually have narrow therapeutic indices; dose levels at which these drugs significantly kill the cancerous cells are close to those levels at which harmful toxic side effects occur. Therefore, an effective chemotherapy treatment protocol requires advanced automation and treatment design tools for use in clinical practice and the challenges inherent to complex biomedical systems and clinical deployment of technology (Parker, 2009). An optimum but effective drug scheduling requires suitable balancing between the beneficial and toxic side effects. Conventional clinical methods very often fail to find right drug doses that balance between these two constraints due to their inherent conflicting nature. A Multi-objective Genetic Algorithm Optimization (MOGA) process is employed to find the desired drug concentration at tumour sites that trade-off between the conflicting objectives. 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 MOGA is used to find suitable/acceptable drug concentration at tumour site and parameters of the controller. Cell cycle specific cancer tumour models have been used in this work to show the effects of drug(s) on different cell populations, drug concentrations and toxic side effects. Results show that the applied multi-objective optimization approach can produce 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. The chemotherapy drug schedules obtained by the proposed treatment protocols appears to be continuous on the time (day) scale, i.e., specific amount of drugs to be administered to the patient on daily basis which can be termed as Metronomics in nature. The dose duration and the interval period between dose applications can be adjusted in the proposed scheme either by setting the sampling time of closed-loop I-PD controller to any value depending on the state of the patient and disease (model parameters) or by using genetic optimization process aiming to minimize/maximize treatment objectives and satisfying treatment constraints. Regarding the total duration of the treatment, clinical knowledge can be utilized giving emphasis on physiological state of the patient, state of the tumour and disease. Moreover, the total duration of the treatment can also be found/determined for specific values of model parameters describing physiological state of the patient, state of the tumour and disease through multi-objective optimization process. It is noted that the proposed scheme offered the best treatment performance as compared to the reported work available so far. Moreover, robustness analysis shows that the control scheme is highly stable and robust despite the model uncertainties; from small to wide range, and the percentage of proliferating cell reduction is almost same as it is found with optimum model parameters without having any uncertainty.

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* Corresponding author at: School of Computing, Engineering and Information Sciences, Northumbria University, Newcastle upon Tyne NE1 8ST, UK. Tel.: +4401912437449.
E-mail addresses: msalam@univdhaaka.edu (M.S. Alam), alamgr.hossain@northumbria.ac.uk (M.A. Hossain), m.a.majumder@bradford.ac.uk (M.A.A. Majumader), mohammed.al-mamun@northumbria.ac.uk (M.A. Al-Mamun), g.sexton@northumbria.ac.uk (G. Sexton), r.m.phillips@bradford.ac.uk (R. Phillips).

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1. Introduction

Cancer informatics that include but not limited to mathematical modelling of tumour growth, designing of optimum treatment protocols and treatment management and decision support systems are a complex collection of case studies where the principles of automation, optimization and control theory are seen increased application. This interdisciplinary growing interest has a twofold motivation: the need for advanced automation and treatment design tools for use in medical practice and the challenges inherent to biomedical systems and clinical deployment of technology (Parker, 2009). Cancer is a collective term that depicts a group of diseases specified by uncontrolled growth of cells leading to invasion of surrounding tissues and metastasis. The Office for National Statistics (ONS) reveals that during 2008–2010 nearly 320,000 people were diagnosed each year and out of that about 156,000 people died each year (www.nhs.uk, accessed 12 December). Moreover research indicates that 42% of people who die in the UK will have had a cancer diagnosis at some point in their lives. At the same time, the number of people in the UK living with cancer has increased by approximately one third in the last decade (Mistry, Parkin, Ahmad, Sasiemi, 2011). 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 in terms of the number of cells (Martin & Teo, 1994). There are three main phases of tumour expansion in a patient’s body, namely avascular, vascular and metastasis (Folkman, 1974, 1990). Avascular phase is that stage, where the cells must acquire nutrients through diffusion from outside the tumour. In other words, a normal cell undergoes mutation process and transformed into a cancer cell, it starts proliferating in an uncontrolled manner. As a result, the uncontrolled growth continues and it quickly reaches up to a maximum value of $10^6$ cells. The tumour, in general, does not grow beyond this size due to inadequate supply of nutrients required for growth and reaches a stage classified as avascular tumour. There are a number of models that have been proposed to model the tumour growth and in particular exponential, Gompertz and logistic equations are most commonly used (Kozusko, Chen, Grant, Day, & Panetta, 2001; Martin & Teo, 1994; Norton, 1988). An extensive literature review on tumour growth model can be found in (Araujo & Mcelwain, 2004; Byrne, Alarcon, Owen, Webb, & Maini, 2006; Materi and David, 2007). The tumour grows exponentially at the beginning and then gradually slows down as it reaches to limiting value. For growing beyond the diffusion-limited state, tumours require blood supply. This is accomplished by secreting tumour angiogenesis factors (TAF) like vascular endothelial growth factor (VEGF), etc. The TAF diffuses across the tissue between the tumour and blood vessel and activates angiogenesis, new blood vessel formation. This phase is called vasculature stage. The third stage is the metastasis phase, in which cells breaks off and is transported to other parts of the body. The tumour must undergo metastasis in order to be clinically recognized as cancer. In this phase it is the very difficult to treat because cancer cells are now circulating inside the body and can lodge anywhere, set up a new cancer colony and start the whole process over and over (Folkman, 1974, 2002; Weinberg & Allan, 2007).

There are four major cancer treatment approaches: surgery and radiotherapy as local treatments, chemotherapy and the use of biological agents (such as hormones, antibodies and growth factors) (Miller, Hogestraeten, Staquet, & Winkler, 1981; WHO handbook, 1979). The aim of surgery is to eliminate as much of the cancer as is possible; in some cases the oncologist suggests further treatment. This could be radiotherapy, chemotherapy or a combination of the two. In radiotherapy, radiation is used to destroy cells in the region of treatment. Traditional chemotherapeutic agents act by killing cells that divide rapidly, one of the main properties of cancer cells. Being unable to distinguish normal cells from cancerous cells, chemotherapy also harms other cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract, hair follicles, etc. As a result, this causes common side-effects: myelosuppression (decreased production of blood cells, hence also immunosuppression), mucositis (inflammation of the lining of the digestive tract), and alopecia (hair loss). It allows oncologists to administer the patients through vein, injected into a body cavity, or delivered orally in the form of a pill. As a result, chemotherapy is considered a systemic treatment (www.cancer.gov, accessed September 17, 2012; Holleb et al., 1991; Ignoffo & Rosenbaum, 2008). Finding an optimal chemotherapy treatment is a very complex, multiparametric issue, due to the different types of cancer, patient variability and specific state of the disease. Traditionally one or more drugs are infused to the body. The efficiency of the dosages during the treatment is often measured as the interval of time from the start of therapy, until the end of treatment. Drug transport and metabolism enzymes also influence the toxic effects of both anti-neoplastic agents in target tumour cells and normal host tissues (Mistry et al., 2011). The most important challenge of cancer treatment is to retain/maintain the normal physiological states of the patient’s body during the course of different treatment schedules. This can be achieved by optimizing the scheduling of chemotherapy drug(s) in such a way as to reduce tumour burden to a minimum level with acceptable toxic side effects. Currently this is determined empirically in the clinic by clinical trials which are an expensive and time consuming process (Citron et al., 2003; Hryniuk & Bush, 1984; Miller, 1981; WHO handbook, 1979; www.nhs.uk, accessed on March 15, 2013).

Chemotherapy is commonly employed as a treatment by clinicians, who must deliver the agent on a schedule that balances treatment efficacy with the toxic side effects. The current standard of practice of treatment is based on empirical evidence gathered from preclinical and clinical trials carried out during the drug development process. Research is underway to improve/optimize the treatment objectives with new drugs, doses and their schedules (Jinghua, Oguzhan, Fatih, & Qiang, 2011). Engineers have considered the development of drug administration schedules for simulated cancer patients constrained by pharmacokinetic (PK) and pharmacodynamic (PD) models (Harrold & Parker, 2009; Harrold, 2005). The actions of the chemotherapy treatment agents are based upon an understanding of the cell cycling mechanisms. To model untreated tumour growth, exponential, Gompertz and logistic growth models (Martin & Teo, 1994) are commonly used whereas cell-cycle models provide more insight into cell behaviour (Florian et al., 2004; Panetta & Adam, 1995). The Gompertz model is capable of capturing clinically observed tumour dynamics (Norton, 1988), but it does not capture information regarding the progression of cells through the individual phases of the cell-cycle. Cell cycle information is vital from a treatment perspective because cycle-specific anti-cancer compounds such as curacin A, Taxol, and tamoxifen can be modelled in a biologically meaningful manner (Florian et al., 2004). The cell cycle is a chain of phases that both normal and cancer cells undergo from their birth to death. 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 cycle comprises of five stages as show in Fig. 1. A brief description of different stages is given below (Dua, Dua, & Pistikopoulos, 2008; Holleb et al., 1991; Martin & Teo, 1994).

Go: Resting phase, cell is quiescent, viable but unable to divide. The cell has not yet started to divide. Cells spend much of their lives in this phase. Depending on the type of cell, Go can last from a few hours to a few years. When the cell gets a signal to reproduce, it moves into the G1 phase.

G1: Post mitotic gap, the cell prepares for DNA synthesis. During this phase, the cell starts making more proteins and growing.
larger, so the new cells will be of normal size. This phase lasts about 18–30 h.

S: DNA synthesis takes place in preparation for cell division (many anticancer drugs act by interfering with DNA at this stage, causing cell death). In the S phase, the chromosomes containing the genetic code (DNA) are copied so that both of the new cells formed will have matching strands of DNA. The S phase lasts about 18–20 h.

G2: Pre-mitotic gap, specialized proteins and RNA are synthesized in preparation for cell division. In the G2 phase, the cell checks the DNA and gets ready to start splitting into 2 cells. This phase lasts from 2 to 10 h.

M: Mitotic phase, cell division takes place to produce two identical daughter cells. In this phase, which lasts only 30–60 min, the cell actually splits into 2 new cells.

The ability of chemotherapy to kill cancer cells depends on its ability to halt cell division. Usually, cancer drugs work by damaging the RNA or DNA that tells the cell how to copy itself in division. If the cancer cells are unable to divide, they die. The faster that cancer cells divide, the more likely it is that chemotherapy will kill the cells, causing the tumour to shrink. They also induce cell suicide (self-death or apoptosis) (Holleb et al., 1991). Chemotherapy drugs that kill cancer cells when they are at rest are called cell-cycle non-specific. On the other hand, chemotherapy drugs that kill cancer cells only when they are dividing are called cell-cycle specific. Some drugs specifically attack cells in a particular phase of the cell cycle (the M or S phases, for example). Understanding how these drugs work helps oncologists predict which drugs are likely to work well together. Doctors can also plan how often doses of each drug should be given based on the timing of the cell phases (Florian et al., 2004).

Anti-metabolites masquerade as purines (azathioprine, mercaptopurine) or pyrimidines, which become the building-blocks of DNA. They prevent these substances from becoming incorporated into DNA during the “S” phase of the cell cycle, stopping normal development and division. They also affect RNA synthesis. Due to their efficiency, these drugs are the most widely used cytostatics (WHO handbook, 1979; Miller, 1981). Vinca alkaloids bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules (M phase of the cell cycle). The vinca alkaloids include: Vincristine, Vinblastine, Vinorelbine and Vindesine (WHO handbook, 1979; Miller, 1981). Podophyllotoxin is a plant-derived compound that is said to help with digestion as well as used to produce two other cytostatic drugs, etoposide and teniposide. They prevent the cell from entering the G1 phase (the start of DNA replication) and the replication of DNA (the S phase) (Miller, 1981; WHO handbook, 1979).

A number of attempts have been taken by many researchers to characterize the evolution and effects of treatment on cancer by dividing the cell cycle into a number of compartments (phase-specific) as considered in (Liang, Leung, & Mok, 2008; Ochoa & Burke, 2007). Evolutionary algorithms have been extensively applied to design the chemotherapy drug scheduling for cancer treatment. In McCall, Petrovski, and Shakya (2008) designed chemotherapy drug scheduling using genetic algorithm (GA) where tumour eradication was used as the objective function, to be minimized. 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 optimization process that resulted in an effective drug scheduling at the end. In Petrovski, Sudha, and McCall (2004), the researchers used a relatively new bio-inspired algorithm, called particle swarm optimization to design chemotherapy drug scheduling using the aforementioned design objective and constraints. An optimal control model of drug scheduling in cancer chemotherapy was introduced and optimized by using GA in (Tes, Leung, Lee, & Mok, 2007). In 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 optimization approaches were used, mainly to minimize the cancerous cells during the whole period of chemotherapy treatment. In conventional single objective optimization approaches, the individuals/solutions converge to a single point as the algorithms proceed and the solution obtained at the end of the optimization process may yield high toxic side effects or may not be relevant to clinical doses. In such case, the whole optimization needs to run time and again until a near-clinical-relevant dose is obtained. 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 minimize both the objectives simultaneously with conventional single objective optimization 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 set of algorithms, commonly known as multi-objective evolutionary algorithms (MOEAs) was used in Deb (2001). McCall and co-workers also utilized 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) (McCall et al., 2008).

Motivated by the success and effectiveness of multi-objective optimization in biomedical engineering and systems biology, the current study utilize its potential in designing chemotherapy drug scheduling for cell cycle specific cancer treatment. This paper presents an investigation into the development of an optimal chemotherapy drug(s) scheduling scheme using a close-loop control method and multi-objective genetic algorithm (MOGA) that can provide solutions trading-off between the cell killing and toxic side effects during the whole period of treatment. Earlier the current researchers reported the Multi Objective Particle Swarm Optimization (MOPSO) based drug scheduling scheme for two

![Fig. 1. Schematic diagram of different phases of cell cycle.](image1)

![Fig. 2. Two compartments functional within tumour tissue.](image2)
compartments (Proliferation and Quiescent) based model in (Alam et al., 2010). This paper particularly focuses on MOGA based single and multi-drug scheduling schemes for two, four and eight compartments based optimal control models to demonstrate the merits and effectiveness through a set of experiments. A control strategy, namely Integral-Derivative-Proportional (I-PD) is used to control the drug doses to be infused to the patient’s body. MOGA optimization process is employed to find desired drug concentration at tumour site and acceptable parameters of the controller that trade-off between two conflicting objectives; reducing cancerous cells and toxic side effects simultaneously.

2. Proposed methods

2.1. Mathematical model

The tissue, in general, contains three different types of cells: the proliferating cells, the quiescent cells and the dead cells as shown in Fig. 2. So a two-compartment model containing the aforementioned types of cells is often considered to explain cancer tumour growth. The proliferating part contains actively dividing cells whereas quiescent part contains 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. In Fig. 2, proliferating cells show the combination of the first four stages of the cell cycle as mentioned earlier (G1, S, G2 and M) and Q (Quiescent cells) indicates stage G0. 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 evidences, 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 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).

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).

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

where \( P \) and \( Q \) represent the proliferating and quiescent cells population. Here parameters \( a, m, b \) and \( n \) indicate the rate of growth of proliferation cells, immigrant from cycling to quiescent cells, immigrant from quiescent cells to cycling cells and natural death of cycling cells respectively. Parameter \( g(t) \) represents the rate of cell killing per unit drug. Eq. (2) describes the rate of change of cell population in the quiescent compartment of the tumour site during the period of treatment and Eq. (3) indicates the effect of chemotherapy.

\[
\frac{dQ}{dt} = mP(t) - bQ(t), \quad Q(0) = Q_0
\]

The anticancer drugs affect tumour cells and normal cells as well. A logistic equation is used to describe the effect of chemotherapy drug on normal cells, as expressed by Eq. (3) below:

\[
\frac{dY}{dt} = \delta Y(t) \left( 1 - \frac{Y(t)}{K} \right) - g(t)Y(t), \quad Y(0) = Y_0
\]

Here \( Y(t) \) indicates the normal cells population whereas \( \delta \) 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. Eq. (4) shows the rate of change of drug concentration at the tumour site during the treatment cycle.

\[
\frac{dD}{dt} = u(t) - \gamma D(t), \quad D(t) = D_0
\]

where \( u(t) \) is the amount of drug doses to be infused to patient’s body and \( \gamma \) 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 the condition below in order to make the chemotherapy treatment effective (Martin & Teo, 1994).

\[
10 < D(t) \leq 50
\]

Eq. (5) shows the relationship between drug concentration at the tumour site and cell killing rate.

\[
g(t) = k_1D(t)
\]

where \( k_1 \) is a constant related to the effect of drug concentration on cell killing. Eq. (6) shows the relationship between level of toxicity and drug concentration at the tumour site during the treatment period.

\[
\frac{dT}{dt} = D(t) - \eta T(t)
\]

\[
T(t) \leq 100
\]

where \( T(t) \) is the level of toxicity developed inside the patient’s body due to chemotherapy drug and parameter \( \eta \) indicates the rate of elimination of toxicity. The level of toxicity should be controlled and kept below the maximum allowable range of \( T(t) \leq 100 \) as suggested by many researchers working on optimum dose scheduling with similar models based on empirical data (Dua et al., 2006, 2008; Liang, Leung, & M, 2006; Liang et al., 2008; Martin & Teo, 1994; Tan, Khor, Cai, Heng, & L, 2002; Tes et al., 2007). 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. The condition below expresses the limiting values of normal cell which should be maintained throughout the period of treatment.

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

The parameter \( Y_{\text{min}} \) indicates the minimum number of the normal cells at tumour site. Using the above equations, a Simulink (MATLAB, 2010) model was developed with parameters and values as illustrated in Table 1. It is to be noted that the models and their parameters used in this work are initially derived empirically by Martin and co-workers in (Dua et al., 2008; Martin, 1992) for lung cancer & breast cancer and are widely used by other researchers in similar investigations as listed in the reference.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
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</thead>
<tbody>
<tr>
<td>( a )</td>
<td>0.5 day^{-1}</td>
</tr>
<tr>
<td>( m )</td>
<td>0.218 day^{-1}</td>
</tr>
<tr>
<td>( n )</td>
<td>0.477 day^{-1}</td>
</tr>
<tr>
<td>( b )</td>
<td>0.05 day^{-1}</td>
</tr>
<tr>
<td>( \delta )</td>
<td>0.1 day^{-1}</td>
</tr>
<tr>
<td>( K )</td>
<td>10^9 cells</td>
</tr>
<tr>
<td>( p )</td>
<td>2 \times 10^{11}</td>
</tr>
<tr>
<td>( Q )</td>
<td>8 \times 10^{11}</td>
</tr>
<tr>
<td>( Y )</td>
<td>10^9</td>
</tr>
<tr>
<td>( Y_{\text{min}} )</td>
<td>10^9</td>
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</tbody>
</table>
2.2. Proposed control schema

A schematic diagram of chemotherapy drug scheduling scheme for cancer treatment is shown in Fig. 3. A control method is developed in order to maintain a predefined level of drug concentration at tumour sites. A variant of Proportional-Integral-Derivative (PID) control, namely I-PD, is used to control the drug to be infused to the patient’s body. The proposed I-PD controller involves 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 is used as input to the controller.

The output of the controller \( u(t) \) as:

\[
 u(t) = K_p \int_0^t e(t)dt - \left[ K_d \frac{d}{dt}D(t) + K_p D(t) \right] 
\]

where \( e(t) \) is the error which is the difference between reference \( X_0 \) and drug concentration \( D(t) \) as:

\[
 e(t) = (X_0 - D(t)) 
\]

It is noted that \( X_0 \) indicates reference signal to the controller which can be depicted as the desired drug concentration to be maintained at the tumour site during the whole period of treatment. The reference input, both magnitude and pattern, is very crucial in the proposed drug scheduling scheme since reduction of cancerous cells largely depends on drug concentration developed in plasma and at the tumour site. Using Eqs. (4), (5) and (8) in Eq. (1), \( P(t) \) gives:

\[
P(t) = (a - m - n)P(t) + bQ(t) \\
- k_1 \left( K_i \int_0^t e(t)dt - \left[ K_d \frac{d}{dt}D(t) + K_p D(t) \right] - \gamma D(t) \right) P(t) 
\]

Eq. (10) shows the interaction between the parameters of I-PD controller and the cells reduction. The third term of (10) expresses how the parameters of the controller affect the rate of cells reduction.

It is noted that when \( e(t) = 0 \); the drug concentration at tumour site will be equal to the desired drug concentration. In such case, the cell killing will be maximum. If the difference between \( X_0 \) and \( D(t) \) is non-zero, the cell killing will be relatively lower. The output of the I-PD control, which is chemotherapy drug dose, is applied to the model to observe its effects. The efficacy of the drug doses depends on three parameters \( K_i, K_p \) and \( K_d \) of I-PD controller. In this work, step input signal is chosen as the reference input to the close-loop control system. The step input with a specific value will ensure approximately a constant level of drug concentration for most of the time of the treatment cycle. A multi-objective evolutionary algorithm, called MOGA is used to find suitable reference level (value of the step input to the controller) and three parameters of the I-PD and thereby design a wide range of the drug doses that trade-off cell killing and toxic side effects. It is important to note that the chemotherapy drug scheduling is design for a period of 84 days as recommended by many researchers (Dua et al., 2006, 2008; Liang et al., 2006, 2008; Martin & Teo, 1994; Tan et al., 2002; Tes et al., 2007). The duration of the proposed drug scheduling/treatment scheme may appear to be a bit long as far as the practical treatment/survival period is concerned but research is underway to improve/optimize the treatment objectives with new drugs, doses and their schedules. Following this thread, researchers have also attempted to explore the potential of ‘relatively lower doses with longer period’, called Metronomics (Gasparini, 2001) as alternatives to conventional ‘relatively higher doses for shorter period’ in cancer treatment. At the same time, research is underway to find/design optimal chemotherapy schedules based on tumour growth models for phase-specific and non-phase-specific cancer treatment schemes where treatment period has been assigned as 12 weeks (84 days) or more as reported in (Dua et al., 2006, 2008; Liang et al., 2006, 2008; Martin & Teo, 1994; Tan et al., 2002; Tes et al., 2007). To conduct comparative assessments and to show the effectiveness of the proposed drug scheduling technique, the treatment period is also assigned as 84 days in present work.

2.3. Design objectives and goal values

The design objectives and goal values of different performance measures of chemotherapy drug scheduling are as follows:

(a) Number of proliferating cells: This is required to be minimum or as small as possible at the end of the treatment. The number of proliferating cells, without chemotherapy treatment, is assumed \( 2 \times 10^{11} \), as used by other researcher and reduction, so far achieved with chemotherapy treatment is approximately 70% (Dua et al., 2008). While designing the drug scheduling in this work, the acceptable goal value for reduction of proliferating cell is approximately set at 65% in the multi-objective optimization process.

(b) Number of quiescent cells: This is also required to be minimum at the end of the treatment. At the beginning of the treatment, the number is assumed \( 8 \times 10^{11} \) as used in (Dua et al., 2008). With Chemotherapy treatment, the number will reduce and the reduction is set at 55% as minimum acceptable value in this work. It is to be noted that this goal value is chosen based on existing literature that reported a reduction of nearly 50% or more of quiescent cell using similar model but different optimum scheduling technique in (Dua et al., 2008; Tes et al., 2007).

(c) Number of normal cells: The number of normal cells is required to be as high as possible throughout the whole treatment period. In this work, the minimum acceptable value of normal cells is set as \( 1 \times 10^8 \) as suggested by other researchers (Dua et al., 2008).

(d) Level of toxicity: The level of toxicity should be as low as possible during the whole period of treatment. The maximum toxicity should not exceed 100 as indicated in Eq. (6). It is to be noted that the highest permissible value of 100 is suggested by many researchers working with similar models based on empirical data (Dua et al., 2006, 2008; Liang et al., 2006, 2008; Martin & Teo, 1994; Ochoa & Burke, 2007; Tan et al., 2002; Tes et al., 2007).

(e) Drug doses: Due to risk of toxic side effects, the drug doses infused to the patient’s body should be optimum. Based on
clinical trials, there are two limiting factors for each chemotherapy drugs set by the drug designer. These are called (i) maximum dose and (ii) maximum cumulative dose. The drug dose infused at any particular time must not exceed the maximum dose and cumulative sum of all doses of a drug used administered at different cycles of whole treatment period should remain within the maximum cumulative dose (Dua et al., 2008; Liang et al., 2008; McCall et al., 2008; Ochoa & Burke, 2007; Petrovska et al., 2004; Tes et al., 2007).

(f) Drug concentration: It depends on the amount of the drug doses infused and status of the metabolic functions of the patient. The drug concentration should be low but meet the threshold value, as the condition mentioned early.

(g) Stability of the drug delivery scheme: Since a close-loop control strategy has been used to control the drug scheduling, stability of the whole drug delivery system is very crucial. As mentioned earlier, drug concentration is used as the feedback in the control scheme, settling of this parameter within a range of ±2% of the reference signal (desired drug concentration) has been used as a constraint, to be met, in the optimization process to ensure the overall stability of the system. Design objectives and goal values of chemotherapy drug scheduling for cancer treatment are listed in Table 2.

### Table 2

<table>
<thead>
<tr>
<th>Notations</th>
<th>Design objectives</th>
<th>Accepted goal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{C_{p}}$</td>
<td>% of reduction of proliferating cells</td>
<td>$R_{C_{p}} &gt; 65%$</td>
</tr>
<tr>
<td>$R_{C_{q}}$</td>
<td>% of reduction of quiescent cells</td>
<td>$R_{C_{q}} &gt; 55%$</td>
</tr>
<tr>
<td>$Y_{N}(t)$</td>
<td>Number of normal cells</td>
<td>$Y_{N}(t) &gt; 1 \times 10^8$</td>
</tr>
<tr>
<td>$T(i)$</td>
<td>Toxicity</td>
<td>$T(i) \leq 100$</td>
</tr>
<tr>
<td>$D(t)$</td>
<td>Drug concentration</td>
<td>$10 &lt; D(t) \leq 50$</td>
</tr>
</tbody>
</table>

2.4. Genetic algorithms

Over the last two decades, GAs have been extensively used as search and optimization tools in various control system optimization problems (Madkour, Hossain, Dahal, & Yu, 2007). The GA as a stochastic optimization 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 to exchange the properties of any two chromosomes via random decision in the mating pool and provides a mechanism to produce and match the desirable qualities through crossover. 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).

2.5. Multi-objective optimization

Multi-objective optimization is a search technique for feasible solutions to that problems comprising of 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 optimizes a vector function whose elements represent the objective functions. A multi-objective optimization problem can be expressed as: Find the vector $x = [x_1, x_2, \ldots, x_p]$ which satisfies the $m$ inequality constraints: $g_i(x) \geq 0, i = 1, 2, \ldots, m$, the $k$ equality constraints $h_i(x) = 0, i = 1, 2, \ldots, k$, and optimizes the vector function, $f(x) = [f_1(x), f_2(x), \ldots, f_n(x)]$, where $n$ is the number of objectives to be considered, $x = [x_1, x_2, \ldots, x_p]$ is the vector of decision variables, $p$ is the number of decision variables that comprise the complete solution. The problem usually has no unique, perfect solution, but a set of non-dominated solutions, known as the Pareto-optimal set (Chipperfield, Purhouse, Fleming, Thompson, & Griffin, 2002; Deb, 2001).

2.6. Algorithm description

The MOGA optimization process consists of a standard GA with multi-objective ranking, and with fitness sharing and mating restriction (Fonseca & Fleming, 1993). A randomly selected population is generated within a specific range. Each individual of the population is evaluated with the objective functions. The MOGA differs from the standard GA in the way fitness is assigned to each solution in the population. For a two-objective minimization problem, individuals that fall close to either axes or origin of 2-dimensional 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 and E in Fig. 4, falling on outer edge and close to axes or origin and having one objective better than another, and form a set called non-dominated solution set or Pareto optimal set.

Individuals A, E, F and G are called non-dominated because no other individuals provide better performance in the objective space. On the other hand, individuals, falling away from edges, such as, B, C and D, are called dominated solutions since many individuals provide better performance than these in terms of both objectives. For example, individual A dominates individual B, similarly B dominates C and C dominates D in the objective space in terms of both objectives. After evaluating different objective functions, multi-objective ranks are computed according to the current preferences and the population sorted. Each individual is ranked according to their degree of dominance. Details of this method can be found in (Deb, 2001; Fonseca & Fleming, 1993).

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 is used for recombination (Booker, 1987). The mutation rate for this optimization process was set at 0.01%.
3. Results and discussion

The simulation work has been carried out in the simulink environment with some .m-files of Matlab\textsuperscript{8} (MATLAB, 2010). The GA optimization process begins with a randomly generated population called chromosome. An initial population of dimension $50 \times 4 \times 12$ is created where number of individuals and parameters in each individual are 50 and 4 respectively. Each parameter is encoded as 12 bit Grey code which is logarithmically mapped (Chipperfield et al., 1994) into real number within a range of $[0, 2]$ for first three parameters and a range of $(10, 50)$ for the fourth parameter. Each individual represents a solution where the first three elements are assigned to controller parameters; proportional gain $k_p$, integral gain $k_i$ and derivative gain $k_d$ respectively as indicated in Eq. (8). The fourth element of each individual is assigned to the reference input to the control system.

3.1. Two-objective optimization solutions

At first, MOGA has been used to design chemotherapy drug scheduling which find trade-off between two competing objectives; (i) number of proliferating cells at the end of the treatment and (ii) average level of toxicity over the whole period of treatment. The objectives are formulated as follows

$$f_1(x) = P(t_f)$$

$$f_2(x) = \frac{1}{t_f} \int_0^{t_f} T(t)dt$$

where $P(t_f)$ number of is proliferating cells at the end of the treatment. $T(t)$ is the toxicity and $t_f$ is the total period of chemotherapy treatment, which is 84 days (12 weeks). Stability of the close-loop system and design objectives, as listed in Table 2 are used as constraints in the optimization process in order to obtain solutions satisfying all design objectives.

The MOGA optimization process was designed and run for large number of generations in order to generate a wide range of solutions aiming to minimize both objectives simultaneously. Solutions not satisfying aforementioned design constraints are penalized with very large numbers, called penalty function. This penalty function will reduce the probability of solutions yielding unacceptable values along any design objectives dominate the optimization 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 optimization process, non-dominated solutions called Pareto optimal set and corresponding decision variables are updated and preserved at the end of each generation.

At generation 1, each solution of the initial population is evaluated in the problem domain and depending on the values of two objective functions, as indicated by Eqs. (11) and (12), non-dominated solutions are and corresponding decision variables are preserved. For following generations, non-dominated solutions of current generation are compared with preserved non-dominated solutions, found so far and preserved non-dominated solutions and corresponding decision variables are updated. As the algorithm proceeds, number of preserved non-dominated solutions increases and more importantly, the solutions gradually get better and tend to move towards $X$ and $Y$ axes in the objective domain. Non-dominated solutions are recorded at the end of generations 10, 20, 30, 50 and 100 and are shown in Fig. 5. It is worth mentioning that, a wide range of non-dominated solutions satisfying all design objectives and constraints as set initially was generated and the solution set converged to the lowest level in the objective domain after 100 generations. In Fig. 5, objective-1 is represented on the X-axis and objective-2 on the Y-axis. It is observed that, number of solutions increases with increasing generation and the non-dominated solution set gradually appears to take a concave shape towards both axes indicating lower values along both objectives.

3.2. Decision making

A wide range of non-dominated solution satisfying all design constraints, objectives and associated goal values as are obtained at the end of 100 generations. For decision making, i.e., which solution to select or use from this wide range of acceptable solutions, the approximate near-Pareto optimal set is redrawn, as shown in Fig. 6, in a space of two objectives, namely number of proliferating cells and average toxicity, which are conflicting each other. The objective space is divided into three regions depending on the values of two objectives; number of proliferating cells and average toxicity.

The three regions are termed as, region-1: high cells killing but high toxicity, region-2: moderate cell killing and toxicity, and region-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 from Fig. 6, solutions reside in region-1, correspond to higher cell (proliferating) killing at the cost of higher toxicity. The solutions in region-2 result moderate cell killing with moderate toxic side effects. It is noted that, solutions, fall in region-3, cause minimum toxic side effects but the cell reduction is also lowest for these.

![Fig. 6. Non-dominated solution set at generation 100. Region-1: High cells killing but high toxicity. Region-2: Moderate cell killing and toxicity. Region-3: Low toxicity but low cell killing.](image-url)
Remarks. It is worth noting that chemotherapy drug scheduling resulting from solutions within region-2 may be preferred unless there are some specific reasons. However an oncologist can choose a suitable solution from the objective space suitable for the patient based on the physiological state of the patient and state of the cancer. For patients, having better physiological conditions and requiring faster response, chemotherapy drug scheduling resulting from region-1 can be chosen. In contrast, patients having relatively poor physiological conditions and vulnerable to toxic side effects may be given chemotherapy doses based on solutions residing in region-3.

In order to evaluate the effectiveness of MOGA in chemotherapy drug scheduling, several representative solutions are further assessed. To validate the solution set, three solutions are selected on the Pareto front, one from each region. Solutions are selected in such a way that two solutions fall on either extreme point of the two objectives and the other is at approximately in the middle of the objective domain. Three selected solutions, as shown in Fig. 6 will be denoted as Case-1, Case-2 and Case-3 for further discussion. As mentioned earlier, an I-PD controller is developed to design the chemotherapy drug doses for cell cycle specific cancer treatment. The controller is designed in such a way that drug concentration, one of the outputs of the patient model can be maintained to a predefined level set by the reference input to the controller.

At the beginning, when no drug is infused, the output is also zero 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 is implemented by using a fixed level of signal, called step input. In this work, the reference to the controller (desired drug concentration) is selected by the MOGA optimization 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, \( k_p \), \( k_i \) and \( k_d \) and desired drug concentration, which is corresponded to solution Case-1, are fed to the I-PD controller. The control system and the whole system along with the patient model are simulated for 84 days. Then the output of the I-PD controller, \( u(t) \), which is the desired chemotherapy drug scheduling for Case-1, is 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 are recorded due to the infusion of the designed chemotherapy doses. Similar procedure is repeated for Case-2 and Case-3 and similar parameters are recorded for the whole period of chemotherapy treatment. Fig. 7(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 Fig. 7(b)–(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, maximum and average levels of drug doses, toxicity and drug concentrations for all three cases are calculated and presented in Table 3. Furthermore, percentage of reductions in proliferating and quiescent cells at the end of chemotherapy treatment are calculated and showed in Table 3. 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 is also calculated and displayed in Table 3.

3.3. Drug scheduling

The chemotherapy doses for Case-1, Case-2 and Case-3 (Fig. 7), increase from zero and finally become stable at a certain value and 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, it takes more than 2 weeks to reach 4.5 and 7 weeks for Case-3, 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 (3.4) and it is minimum (2.8) for Case-3. In contrast, for Case-2, the dose is moderate (3).

3.3.1. Drug concentration

Fig. 7(b) shows the drug concentration against reference input for Case-1, Case-2 and Case-3 at the tumour site due to chemotherapy drug scheduling. 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 the reference levels. The drug concentrations at tumour site reach to 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 3. 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.

3.3.2. Toxicity

The toxicities, for Case-1, Case-2 and Case-3, developed due to the corresponding chemotherapy drug scheduling are shown in Fig. 7(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. 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 optimization process.

3.3.3. Reduction of proliferating cells

Reduction of proliferating cells is taken as the main aim of chemotherapy treatment because of these cells, cancer can spreads to the other parts of the body. Before the treatment starts, the number of proliferation cells is set at \( 2 \times 10^{11} \), as used by many researchers in cell cycle specific cancer treatment (Dua et al., 2008). Fig. 7(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 drug scheduling shown in Fig. 7(a) are 72.2%, 71.2% and 68.1%, respectively.

Many attempts have been taken to design similar drug optimization techniques reported earlier. Alam et al. (2010) used Practical Swarm Algorithm (PSO) to achieve optimal drug scheduling. The authors reported that Solution-1, Solution-2 and
Solution-3 reduced the proliferating cells by 72%, 71% and 68%, respectively at the end of treatment. In present work, Case-1 and Case-2 result a reduction of 72.2% and 71.2% for proliferating cells which are slightly better than the reported results of Alam et al. (2010). It is also worth noting that the average drug concentration and toxicity using MOGA are 8.3 and 24.1 respectively, which are lower than the MPSO performance 9.7 and 27.4. However reduction of proliferating cells in Case-3 is same as the Solution-3. Considering the physiological and clinical state of the patient and the cancer status, the oncologist can choose a suitable solution for a patient.

Table 3
Performance measures of drug scheduling techniques.

<table>
<thead>
<tr>
<th>Example solutions</th>
<th>Value of Ref. input</th>
<th>For the whole period of treatment</th>
<th>At the end of 84 days treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug doses</td>
<td>Drug concentration</td>
<td>Toxicity</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>Avg</td>
<td>Max</td>
</tr>
<tr>
<td>Case-1</td>
<td>12.08</td>
<td>4.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Case-2</td>
<td>12.17</td>
<td>4.5</td>
<td>3</td>
</tr>
<tr>
<td>Case-3</td>
<td>11.66</td>
<td>4.5</td>
<td>2.8</td>
</tr>
</tbody>
</table>
3.3.4. Reduction of quiescent cells

Quiescent cells are also to be reduced in cancer treatment as indicated in design objectives. At the beginning the chemotherapy treatment, the total number of quiescent cell is assumed as $8 \times 10^{11}$ (see Table 1). During the treatment period, the number gradually decreases depending on chemotherapy drug doses and this is shown for all three cases in Fig. 7(e). It is important to note 60.4%, 58.9% and 55.1%, respectively.

Remarks. It is worth noting that Dua and co-workers designed chemotherapy drug scheduling for cell cycle specific model, as used in the present work, and reported reductions of 70% and 50% for proliferating and quiescent cells at the end of treatment (Martin & Teo, 1994). In this investigation, Case-1 and Case-2 result a reduction of 72.2% and 71.2% for proliferating cells which are slightly better than the reported one. More importantly to note that, example solutions; Case-1, Case-2 and Case-3 of present work can reduce the quiescent cells up to 60.4%, 58.9% and 55.1%, respectively which are significantly higher than the reported result. Fig. 8 shows the reductions of proliferating and quiescent cells for Case-1, Case-2, Case-3 and reported work (Martin & Teo, 1994). It is noted that cell reductions for both proliferating (except Case-3) and quiescent cells are better in case of proposed optimal scheme.

3.3.5. 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 is assumed 10x10^8 before the treatment. Fig. 7(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 1.03 x 10^6, 1.0024 x 10^6 and 1.2815 x 10^6 respectively. It is important to note that, in all cases the number of remaining normal cells are more than the threshold value, 1 x 10^6, as indicated in the 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. The input parameters used in this work were also used by Dua et al. (2008) to compare the performance of the proposed and reported models. It is noted that the reduction of the proliferating cells in case of proposed model is 72.2% compared to 70% in reported one. It is also noted that the reduction of quiescent cells is 60.4% whereas the reported model yields only 50%. It is clearly evident that the proposed optimal model offers better outcomes for both proliferating and quiescent cell reductions.

As the cancer chemotherapy treatment models have classified depending on the functional state of the cancer cells, the purpose of using mathematical models of cancer chemotherapy is to predict and control the course of the disease during treatment cycle. Occasionally, after few cycles of treatment, single drug treatment does not work due to resistance developed by cancer cells. Moreover, cancer tumour, in general, contains different types of cells and single drug treatment becomes ineffective against those cells. To counteract the drug resistance developed by cell, multi-drug chemotherapy has emerged and is being recommended as an alternative but very effective treatment plan. Depending on state/intensity of the tumour, especially types/volumes of cells and physiological state of the patient, several multi-drug treatments, such as, two-drugs, three-drugs etc. are recommended and administered to patients. In order to design chemotherapy drug scheduling for multi-drug treatments and to observe/assess their effectiveness on tumour cells, several multi-compartments models are suggested and extensively used by researchers as reported in literatures (Panetta, 1999; Westman, Fabijonas, Kern, & Hanson, 2001). To be specific, four compartment tumour models are used to design chemotherapy scheduling for two-drugs and its response on different cell population whereas eight compartment tumour models are used for three-drugs treatment plan. Considering the limited success of single drug chemotherapy treatment, we extended our new drug scheduling schemes for two and three different drugs during the whole course of chemotherapy treatment. To assess/analyze the effectiveness of the proposed multi-drug scheduling schemes, four compartments and eight compartments models are implemented and utilized in following sections of this work. It is to be noted that, treatment objectives and constraints to be met are also more in case of multi-drug treatment compared to that of single drug chemotherapy. Considering this fact, design objectives and constraints are also increased in control design & multi-objective optimization process in following sections. In general, four design objectives were considered for the schemes; reducing cancer cells, reducing toxic side effects for two and three drugs (Four and eight compartments) and maintain the concentration of all drugs at tolerable level.

3.4. Four compartments based multi-drug model

To explore further, the investigation was extended further for multi-drug (here assuming two drugs) where a four compartmental model is used which is based on the theoretical basis provided by (Martin & Teo, 1994). For simplicity and to avoid repetition, this paper only shows the MOGA based optimal control scheme and the performance of the scheme in cell reduction for four compartmental models. This focuses on multi-drug chemotherapy scheduling where two drugs were used and, for ease of discussion, those drugs are indicated by A and B respectively. A schematic diagram of multi-drug scheduling scheme for chemotherapy treatment is shown in Fig. 9. Similar control method was developed to control the drugs 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 was used as the feedback signal to the controller to compare with a predefined references level. The difference between each of the two schemes is called the error which was used as input to the controller. The output of the controller for drug A, $u_A(t)$ is formed as:

$$ u_A(t) = K_M \int_0^t e(t) \, dt - \left[ K_{AD} \frac{d}{dt} D_A(t) + K_{BP} D_B(t) \right] $$

(13)

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

$$ u_B(t) = K_M \int_0^t e(t) \, dt - \left[ K_{BD} \frac{d}{dt} D_B(t) + K_{BP} D_B(t) \right] $$

(14)

where $e_A(t)$ and $e_B(t)$ are the errors which are the differences between references $X_{DAM}$ and $X_{DB}$ and drugs concentrations.
$D_A(t)$ and $D_B(t)$. These can be expressed as: Use $e_A(t)$ and $e_B(t)$ in Eqs. (13) and (14)

$$e_A(t) = (X_{DA} - D_A(t))$$

$$e_B(t) = (X_{DB} - D_B(t))$$

It is noted that $X_{DA}$ and $X_{DB}$ indicate references 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 treatment. It is 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 stabilie that means 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 find six parameters $k_A, k_B, k_{Ap}, k_{Ad}, k_{Bi}, k_{Bb}$ and $k_{AD}$ of I-PDs controllers to achieve desired performance. In this investigation, MOGA was used to find a wide range of parameters of the I-PDs controllers by minimizing three objectives simultaneously to design two-drugs chemotherapy scheduling. The objectives are formulated as follows (Algoul, Alam, Hossain, Majumder, 2010).

(i) Average level of toxicity for drug

$$f_1(x) = \frac{1}{t_f} \int_0^{t_f} T_A(t) \, dt$$

(ii) Number of cancer cells at the end of the treatment

$$f_2(x) = N(t_f)$$

(iii) Average level of toxicity for drug B

$$f_3(x) = \frac{1}{t_f} \int_0^{t_f} T_B(t) \, dt$$

Like two compartments model, the whole simulation was carried out in the Simulink environment with some .m-files of Matlab. The MOGA optimization process was allowed to run for larger number of generations in order to minimize all objectives simultaneously. Solutions not satisfying aforementioned design constraints are penalized with very high values, called penalty function. The MOGA optimization process started with a randomly generated population called chromosome. A population size of 50 was chosen in this investigation as it was found as minimum number of population for best convergence. An initial population of dimension $50 \times 8 \times 12$ was created where number of individuals and parameters in each individual were 50 and 8 respectively. Each parameter was encoded as 12 bit Grey code which is logarithmically mapped 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; $k_A$, $k_B$, $k_{Ap}$, $k_{Ad}$, $k_{Bi}$ and $k_{Ad}$, 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.

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. A wide range of non-dominated solutions satisfying all design constraints, objectives and associated goal values as were obtained at the end of maximum generation (see Fig. 10). For clarity and ease of discussion, only few non-dominated solutions yielding lower values for objective-2, i.e., the number of cells less than 150, are shown in Fig. 10. Figs. 11–13 show

![Fig. 9. Schematic diagram of the proposed multi-drug (two-drugs) control scheme.](image)

![Fig. 10. Non-dominated solutions of MOGA optimization at generation-200.](image)
the performance of the proposed multi-drugs control model for four compartments. It is noted that the proposed model offered 100% cell reduction of proliferating cells as compared to 99% of the reported best work (Tes et al., 2007). Overall toxicity and drug concentration of two drugs are within the tolerable limit but combined effect could be higher as compared to single drug.

3.5. Eight compartments based multi-drug control model

The investigation has been extended further to explore the issues of drug concentration and toxicity as compared to reported eight compartmental models. A schematic diagram of multi-drug scheduling scheme for chemotherapy treatment is shown in Fig. 14. For simplicity and to avoid repetition, this paper only shows the MOGA based optimal control scheme and the performance of the scheme in cell reduction. This focuses on multi-drug chemotherapy scheduling where three drugs were used and, for ease of discussion, those drugs are indicated by A–C, respectively.

A similar control method I-PD was developed to control the drug 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 gain $k_p$, 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 $k_A$, $k_B$, $k_A$, $k_B$, $k_B$, $k_B$, $k_C$, $k_D$, $k_D$ need to be tuned. In this research, MOGA is used to find suitable optimal parameters for I-PD controllers. The mathematical model containing eight compartments stating the effects of three drugs as explained in Tes et al. (2007) is implemented in Matlab/Simulink environment. Moreover, the I-PD feedback control scheme was also developed in Matlab/Simulink environment.

At first, MOGA has been used to design chemotherapy drug scheduling for three drugs which finds the trade-off between competing objectives, (i) number of cancer cells at the end of the treatment and (ii) average level of toxicity for three drugs (A–C) over the whole period of treatment. The four objective functions are formulated as follows:

$$f_1(x) = \frac{1}{T_f} \int_0^{T_f} A(t)dt,$$

$$f_2(x) = N(t_f)(T_f)$$

$$f_3(x) = \frac{1}{T_f} \int_0^{T_f} B(t)dt,$$

$$f_4(x) = \frac{1}{T_f} \int_0^{T_f} C(t)dt,$$

where $T_A(t), T_B(t)$ and $T_C(t)$ are the toxicity for three drugs and $T_f$ is the total period of chemotherapy treatment, i.e., 84 days (12 weeks). The stability of the close-loop system and design objectives are used as constraints in the optimization process in order to obtain solutions satisfying all objectives. The constraints are (Algoul et al., 2011).

1. Stability of drug delivery control system.
2. Minimum reduction of cancer cells at the end of treatment: $N(t) < S_0.$
3. Maximum level of toxicity during the treatment: $T_f(t) < 100,$ where $Y = A, B$ or $C$
4. Drug concentration at the tumour site during the treatment: $10 < D(t) < 50,$ where $Y = A, B$, or $C$

The MOGA optimization process begins with a randomly generated population called chromosome. An initial population of dimension $50 \times 12 \times 12$ was created where number of individuals and parameters in each individual are 50 and 12 respectively. Each parameter was encoded as a 12 bit Grey code which is logarithmically mapped into real number within the range of $[0,2]$ for first nine parameters and a range of $(10,50)$ for the last three parameter. Each individual represents a solution where the first nine elements were assigned to controller parameters. The last three elements of each individual were assigned to the reference inputs to the close-loop control system. The whole control scheme and drug scheduling were designed for a period of 84 days as recommended by many.
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 minimization problem, a parallel line representation is shown in Fig. 15 where X-axis is marked by four equidistant points representing design objectives to be minimized 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, only few non-dominated solutions, yielding lower number of cells at the end of treatment, are shown in Fig. 15. 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 lower value along one objective yields relatively higher values along other three objective domains. Similar nature is observed with other solutions. Although no solution can minimize 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. 16 shows the drug concentration at the tumour site due to chemotherapy drug scheduling obtained for the whole period. It is interesting to note that the drug concentrations for all cases increase gradually in similar manner as observed in case of corresponding drug dose scheduling and desired levels. The drug concentrations at tumour site reach to 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.

The toxicities, for drugs A–C, developed due to the corresponding chemotherapy drug scheduling are shown in Fig. 17. For 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 optimization process. Fig. 18 shows the reduction of cancer cells during the whole period of treatment. The percentage of reductions obtained using the drug scheduling shown in Fig. 17 is nearly 100% corresponds to the solution has been chosen.

3.6. Robustness analysis of the proposed closed-loop drug scheduling scheme

To be applicable/effective in real-world applications, any closed-loop control system must be robust, i.e., the control system is required to exhibit the desired performance despite the presence of significant model/plant uncertainty. So a closed-loop control system is said to be robust when it is stable over the range of parameter variations and the performance continues to meet the specifications in the presence of a set of changes in the system parameters. To test the robustness of the proposed closed-loop drug scheduling scheme, MOGA-based IPD controller using two-compartment tumour growth model is investigated/assessed. For ease of discussion, simple schematic diagram of drug scheduling scheme used to test the robustness is given below (Fig. 19) where important parameters of tumour growth and response model are assumed to have uncertainties of different ranges around their optimum values. The model parameters those are assumed to have uncertainty are listed in Table 4 along with their optimum values as used in (Dua et al., 2008; Liang et al., 2008).

As discussed earlier, MOGA has been used to find parameters of I-PD controller by trading-off several conflicting objectives and satisfying several design constraints. It is to be mentioned that, as many as 136 solutions; both non-dominated and satisfying all design constraints and objectives were found in two-objective optimization drug scheduling scheme covering a wide range of objective domain (see Fig. 5). Controller parameters correspond to solution Case 2, as marked in Fig. 5, are used for robustness analysis in the following discussions.

The drug scheduling system was run several times each with different level (percentage) of model uncertainty around optimum values. At first, the model parameters, as listed in Table 4 are assigned to have an uncertainty of 5% and the whole close-loop scheduling scheme is run with controller parameters, as indicated above. The treatment outcomes/model outputs; changes in different cell population and toxicity are observed and recorded along with the infused drug doses. Similar procedure was repeated for model parameters given an uncertainty of 10%, followed by 15% and finally an uncertainty of 20%. The output response is compared against the same drug scheduling scheme having optimum values of model parameters. Some important quantitative performance measures in relation to chemotherapy during and end of 12 weeks treatment scheduling schemes; with and without model uncertainty, are presented in Table 5. The prime treatment objective is to reduce the number of proliferating cells during and at the end of treatment. Table 5 shows that despite the model uncertainties; from small to wide range, the percentage of reduction is almost same as it was found with optimum model parameters without having any uncertainty.

Fig. 20 shows the changes of proliferating cells during the treatment period for all closed-loop drug scheduling schemes; models with optimum parameters and models having parameter uncertainty of four different percentages. It is observed that proliferating cell profiles for models having uncertainties almost fully coincide with that of model with optimum parameters. This figure clearly exhibits that the closed-loop control scheme is highly robust as far as the proliferating cell response is concerned.

The number of quiescent cell is also required to reduce during the chemotherapy treatment. Table 5 shows that the reduction in quiescent cell is almost same despite the uncertainties in model parameters. Fig. 21 shows the response of quiescent cells for all

![Fig. 17. Level of toxicity for drugs A–C for whole period of treatment.](image1)

![Fig. 18. The cell reductions throughout the treatment period.](image2)

![Fig. 19. Schematic diagram of drug scheduling scheme used to test the robustness.](image3)

![Fig. 20. Changes of proliferating cells during the treatment period for all closed-loop drug scheduling schemes.](image4)

![Fig. 21. The response of quiescent cells for all cases.](image5)

**Table 4**

Parameters of cancer tumour model (two-compartment) assumed to have uncertainties and used in robustness analysis.

<table>
<thead>
<tr>
<th>Model parameters</th>
<th>Optimum values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a )</td>
<td>The rate of growth proliferating cells</td>
</tr>
<tr>
<td>( m )</td>
<td>The mutation rate of proliferating cells to quiescent cells</td>
</tr>
<tr>
<td>( y' )</td>
<td>Drug decay</td>
</tr>
<tr>
<td>( \eta )</td>
<td>Rate of toxicity elimination</td>
</tr>
<tr>
<td>( k )</td>
<td>Cell killed per unit time per unit drug concentration</td>
</tr>
</tbody>
</table>
Table 5
Robustness analysis of the closed-loop chemotherapy drug scheduling scheme in time domain.

<table>
<thead>
<tr>
<th>Model parameters</th>
<th>Treatment outcomes during and end of 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average drug dose</td>
</tr>
<tr>
<td>Optimum values²</td>
<td>3.05</td>
</tr>
<tr>
<td>Parameters vary by ±5%</td>
<td>4.27</td>
</tr>
<tr>
<td>Parameters vary by ±10%</td>
<td>4.27</td>
</tr>
<tr>
<td>Parameters vary by ±15%</td>
<td>4.27</td>
</tr>
<tr>
<td>Parameters vary by ±20%</td>
<td>4.28</td>
</tr>
</tbody>
</table>

Fig. 20. Change of proliferating cell population during the treatment period.

models; having optimum model parameters and having parameter with different percentages of uncertainties. It is clearly evident that quiescent cell profile changes in the same manner despite model uncertainties which also exhibits a higher degree of robustness of the proposed control scheme.

The number of normal cells shows the physiological state of the patient which is required to remain as close as it was at the beginning of the chemotherapy treatment. It is evident from Table 5 and Fig. 22 that the control scheme is highly stable and robust despite the changes in model parameters due to its closed-loop/feedback mechanism.

Toxicity is always regarded as second most important performance measures after the reduction of proliferating cancerous cells. Table 5 shows that average and maximum toxicity gradually increase with increasing level of uncertainty in model parameters but in all cases those values are within the acceptable/tolerable
range as far as the physiological condition of the patient and treatment constraint are concerned. Fig. 23 shows the toxicity profile developed for all cases under investigation here. For clarity, changes in toxicity profile (for two days) with different percentage of model uncertainty are shown in enlarged form within a window in the same figure. Although the toxicity varies with degree of model uncertainty, it is always less than nearly half of the highest permissible value of 100 as used by other researcher in (Dua et al., 2008; Liang et al., 2008; Martin & Teo, 1994) for similar tumour growth model.

Fig. 24 shows the drug doses for 12 weeks obtained with the proposed closed-loop schemes for the models; both having optimum parameters and model uncertainties of different degrees. For clarity, changes in drug doses (for five days) with different percentage of model uncertainty are shown in enlarged form within a window in the same figure. Table 5 shows the average and maximum drug doses infused to the patient during the 12 weeks treatment period. Like the toxicity, the average and maximum drug doses increases with the percentage of model uncertainty. In fact, relatively higher level of drug doses causes higher toxicity during the treatment. The drug doses, as shown in Fig. 24, are still low but effective for all runs. It is to be noted that the uncertainty/variation in model parameter during the treatment period is compensated by different dose levels due to the feedback/closed-loop nature of the scheduling scheme. It can also be said that drug doses are adapted/adjusted looking at the variations of the model parameters. Although the input (drug dose) of the control scheme fluctuates around average value, the outputs of the model; i.e., responses of different cell populations are highly stable and almost coincides with the response of model using optimum value and having no uncertainty at all.

All the preceding facts, figures and discussion clearly assure that the proposed control scheme for chemotherapy is highly robust and stable. Moreover, it is noted that the application of MOGA in finding parameters of I-PD controller also add more robustness in overall design scheme since huge number of acceptable solutions are generated out of a single run of the optimization process.

This section presents the comparative investigations for the chemotherapy cancer drug scheduling between two algorithms, proposed multi-objective genetic algorithm (MOGA) and reported method. The reported method introduced by Liang et al. (2008),
called a new memetic algorithm (MA) to solve the Multi-drug chemotherapy optimization problem. The authors formulate the optimization problem as an optimal control problem (OCP) with a set of dynamic equations. The objective was to design efficient schedules which minimize the tumour size under a set of constraints.

Many solutions of the proposed drug scheduling pattern have reduced the number of tumour cells more than 99% (elminate 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 level.

Drug concentration: Table 6 shows the comparative performance of the drug concentration between proposed and reported methods. It is interesting to note that, the drug concentrations at tumour site reach to maximum values which are 29, 36 and 39 for drugs A–C respectively. More importantly, the maximum drug concentrations are always much lower than the allowable maximum value indicated in design objective and constraint for this particular parameter. In contrast, the MA algorithm (Tes et al., 2007) offered higher drug concentration level as compared to the proposed model. These are 40, 50 and 50 respectively.

Toxicity: Fig. 25 shows a comparison of the toxicity for chemotherapy drug scheduling of the two algorithms mentioned early (MOGA and MA). It is noted that the obtained drug schedule is continuous in nature having lower and nearly stable value throughout the whole period of treatment. 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 was 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 optimization process. It is also noted that the levels of toxicity produced by the reported model memetic algorithm (MA) are higher as compared to the proposed algorithm (Tes et al., 2007). In all cases, the toxicity level of the MA reach to the maximum tolerable level 100.

Cell reduction: Before the treatment starts, the numbers of cancer cells are $4.80517 	imes 10^{11}$, as used by many researchers in cell cycle specific cancer treatment (Tes et al., 2007). The percentage of the cancer cells reduction for the proposed algorithm obtained using the drug scheduling is nearly 100%. Moreover, this higher percentage of the cancer cells reduction is achieved with significantly lower toxic side effects and better physiological conditions of patients. The rate of the cells reduction of the memetic algorithm (MA) is lower than the proposed algorithm which is about 99% with higher level of toxicity as shown in the section above. Overall, the proposed algorithm MOGA offered 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.

<table>
<thead>
<tr>
<th>Table 6</th>
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<tbody>
<tr>
<td>Comparative level of final drug concentration for the reported and proposed model.</td>
</tr>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>Reported model</td>
</tr>
<tr>
<td>Proposed model</td>
</tr>
</tbody>
</table>

4. Conclusions

This paper has presented a novel method of chemotherapy drug(s) scheduling for cell cycle specific cancer treatment by using a control method. Based on the cells functions, the proposed models predicted and controlled the tumour growth to demonstrate the merits and capabilities for cancer treatment. An I-PD controller has been developed to design drug doses and MOGA has been employed
to find a wide range of acceptable solutions for controller parameters by trading-off conflicting treatment objectives and satisfying important treatment constraints. To the best of our knowledge, this is the first multi-objective based chemotherapy I-PD control model used to investigate the cell cycle specific treatment.

In the proposed method, several design objectives, constraints and associated goal values are defined prior to the optimization process and a wide range of non-dominated solutions, known as near Pareto-optimal set, have been obtained. It is interesting to note that the design approach can offer flexibility in decision making and suitable solution can be picked under different trade-off interventions for cancer treatment. To assess the effectiveness of the design procedures, several solutions on the non-dominated solution set have been evaluated on the problem domain and corresponding responses have been presented. Significant reduction in cancerous cells has been achieved with a very low level of toxicity and other performance measures such as, lower drug doses, lower drug concentration and higher number of normal cells at the end of treatment. The unique feature of the proposed models is that the design approach can offer flexibility in decision making and suitable solution can be picked under different trade-off conditions. Considering the state of the physiological condition of the patient and state of the tumour, clinicians can choose a particular solution from this set as required by treatment.

It is mentioned that the obtained drug schedule is continuous in nature having lower and nearly stable value throughout the whole period of treatment. The proposed controlled drug(s) scheduling pattern has reduced the number of tumour cells significantly with low drug doses. More importantly, the maximum toxicity levels during the whole period of treatment remain much lower than the maximum allowable value as indicated earlier and suggested by other researchers (Liang et al., 2008; Martin & Teo, 1994).

It is worth mentioning that this paper also demonstrates the robustness of the proposed drug scheduling scheme which has not been reported earlier. Majority of the model parameters are related to physiological conditions of patients, internal drug absorption/clearance/metabolic actions, drugs to be used in treatments, state of the disease/tumour population when it was detected etc. So model parameters, in principle and realistically vary from patient to patient and also dependent on drugs to be used, state of the disease etc. Moreover, values of majority of the parameters may also vary in-vivo or in-silico experiments conducted under same environment but at different instances. So to develop more accurate/realistic models for specific cancer, existing/commonly used parameters are modified/adjusted with empirical data or new parameters are added to existing model with proper justification and this has been an active research area all the time. The authors would like to clarify that modelling/parameter tuning for a specific type of cancer is not the scope of the present work rather an optimum drug scheduling method is presented, emphasized and discussed in detail with different compartmental models for phase specific treatment of cancer. It is also to be noted that, the values of the parameters of the models used in this research are optimum and were obtained through statistical analysis on in-vivo/in-silico experiments as reported in (Dua et al., 2008; Liang et al. 2006; Liang et al., 2008; Martin & Teo, 1994; Martin, 1992; Tan et al., 2002).

To test the robustness of the proposed drug scheduling scheme, two-compartment tumour growth model has been investigated further with important parameters are assumed to have uncertainties of different ranges around their optimum values. Then the drug scheduling system was run several times each with different level (percentage) of model uncertainty around optimum values. Results showed that despite the model uncertainties; from small to wide range, the percentage of cell reduction was almost same as it was found with optimum model parameters without having any uncertainty. Moreover, it is important to note that the control scheme is highly stable and effective despite the model uncertainties up to a large range. The same control strategy and optimization technique have been extended to develop multi-drug or combination chemotherapy regimen for two and three drugs where four compartments and eight compartments models have been used to observe the response. Many design objectives and constraints were also handled to design drug doses for the four and eight compartments based models. The proposed scheme offered a solution for 100% reduction of proliferating cell. Finally, it is worth noting that the drug scheduling pattern of the proposed models (two, four and eight compartments) offered better performance as compared to the reported models available till date.

The proposed closed-loop fashion drug scheduling control relies on frequent measurements of tumour response due to drugs administered at earlier instant. Although chemotherapy is given in cycles with periodic updates (every two weeks to two months) with treatment alterations based on evaluations of toxicity and patient response, researchers have also attempted to explore the potential of ‘relatively lower doses with longer period’, as alternatives to conventional ‘relatively higher doses for shorter period’ in cancer treatment. Moreover, the dose duration and the interval period between dose applications have also been investigated and adjusted to obtain better treatment schedules as reported in (Alam, Sultana, Alam, Al-Mamun, & Hossain, 2013). The chemotherapy drug schedules obtained by the proposed treatment protocols appears to be continuous on the time (day) scale, i.e., specific amount of drugs to be administered to the patient on daily basis which can be termed as Metronomics in nature. It is important to note that the dose duration and the interval period between dose applications can be adjusted in the proposed scheme by setting the sampling time of closed-loop I-PD controller to an agreed pre-defined value. Moreover these two important parameters can also be adjusted/optimized through multi-objective genetic optimization process aiming to trading-off conflicting treatment objectives and satisfying associated treatment constraints. Clinical knowledge can be utilized to define the total duration of the treatment, giving emphasis on physiological state of the patient, state of the tumour and disease. Moreover, the total duration of the treatment can also be determined for specific values of model parameters describing physiological state of the patient, state of the tumour and disease through multi-objective optimization process. In such case, the total duration of simulation/run-time should be considered as a variable in the genetic optimization process. So the scheme may result various drug schedules spanning a range of days and oncologists can choose suitable one for a particular patient.

In conclusion, it may be mentioned that multi-objective algorithm can be a very useful computing tool to solve complex drug scheduling problems in other deadly and infectious diseases. However, validation of the proposed optimal drug(s) administration model is required in vivo before this approach can be applied in the clinic. So in order to achieve that, as future work, we consider to extend this research by incorporating cellular automaton model reported earlier (Nabila, Hossain, Phillips, Al-Mamun, & Bass, 2012) with further in-vitro experiments in tissue culture lab.

Authors’ contributions

All the authors equally contributed.

References
