MOGA-based Multi-drug Optimisation for Cancer Chemotherapy

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Abstract This paper presents a novel method of multi-drug scheduling using multi-objective genetic algorithm (MOGA) that can find suitable/optimum dosages by trading-off between cell killing and toxic side-effects of chemotherapy treatment. A close-loop control method, namely Integral-Proportional-Derivative (I-PD) is designed to control dosages of drugs to be infused to the patient's body and MOGA is used to find suitable parameters of the controller. A cell compartments model is developed and used to describe the effects of the drugs on different type of cells, plasma drug concentration and toxic side-effects. Results show that specific drug schedule obtained through the proposed method can reduce the tumour size nearly 100% with relatively lower toxic side-effects.

1 Introduction

Cancer refers to a set of malignant disorder where normal cells of the body lose their control mechanisms and grow in an uncontrolled way. Cancer cells typically proliferate in an exponential fashion and the size of the cancerous mass is measured experimentally as a volume, though this mass is often referred to in terms of the number of cells 4.60517×10^{11} [1]. The main aim of chemotherapy treatment is to eradicate or minimise the cancer cells with minimum toxic side-effects. Very often, cancer cells grow resistance to Add: drugs that causes failure to treatment in most cases. The combination of multiple drugs can decrease the drug resistance. Toxic side-effects developed due to the infusion of chemotherapy drugs always pose a major challenge in drug scheduling. So drug doses and their cycles of intervals must be designed in such a way that it eradicates the tumour with minimum/tolerable toxic side-effects. The actions of the chemotherapy drugs (agents) are based upon an understanding of the cell cycling mechanisms. A number of models have been developed to study and analyse the effects of drugs on cancer cells by dividing the tumour into number of sub-populations [1-3]. Martin introduced a model for two non-cross resistant agents, which are considered interaction between drug concentrations during the treatment within patient body and cells

[2]. Tes et.al. have presented a model to simulate the effects of multi-drug administration to the cancer cells [1]. Earlier, to explore the potential of classical closed-loop control strategy, researchers developed two controllers, namely Proportional-Integral-Derivative (PID) and Integral-Proportional-Derivative (IPD) [4, 5]. The controllers were designed to administer a single chemotherapy drug for non-phase-specific and phase-specific treatments and genetic algorithm (GA) was used to optimise the controller parameters by minimising a single design objective; mean squared error between the desired drug concentration and actual concentration. Although the drug scheduling obtained with IPD controller could significantly reduce the size of the tumour, other important design objectives such as drug resistance and toxic side-effects were ignored in the process [5, 6]. In practice, multi-drug chemotherapy treatment is preferred to avoid or reduce the risks of resistance grown in cancer cells against the infused drug and thus make the treatment more effective. In such case, the doses must be optimised to trade off between the beneficial and adverse side-effects. Since those are inherently found to be in conflict, conventional methods or single objective optimisation techniques can hardly provide any suitable solution in multi-drug chemotherapy scheduling problem. This paper presents a novel method of multi-drug scheduling using Multi-Objective GA (MOGA). Being motivated by the success of IPD controller in single drug scheduling problem [6], this research also explores its potential in multi-drug scheduling.

2 Mathematical Model

For multi-drug chemotherapy treatment, three non-cross resistant drugs are denoted by A, B and C, in general, for ease of discussion. A tumour model consists of eight compartments are considered as shown in Figure 1 to show the pharmacokinetic and pharmacodynamic effects of three drugs in patients' body during the treatment. The sub-population $S(t)$ represents the cells which are sensitive to all drugs A, B and C. $N_A(t), N_B(t)\ and\ N_C(t)$ expressed the cells totally resistant to drugs A, B and C respectively. The $N_{AB}(t)$ presents the cells which are doubly resistance for drugs A and B. $N_{Ac}(t)$ and $N_{BC}(t)$ indicates to cells which are doubly resistance for drug A and C, and B and C respectively [2]. The chemotherapy drug A is effective on four sub-populations, $S(t)$, $N_B(t)$, $N_C(t)$ and $N_{BC}(t)$. While the chemotherapy drug B is effective on the four sub-populations, $S(t)$, $N_A(t)$, $N_C(t)$ and $N_{AC}(t)$, on the other hand, the chemotherapy drug C is effective on the four sub-populations, $S(t)$, $N_A(t)$, $N_B(t)$ and $N_{AB}(t)$. The sub-populations of cancer cells that are not resistant to drug A are killed only when the concentration of drug A, v_A is maintained above the drug concentration threshold v_{thA}. Similarly the drug concentration of drug B and C should be raised above the threshold drug concentration v_{thB} and v_{thC} to kill cells which are not resistant to these drugs.

The three sub-populations N_A, N_B *and* N_C increased by the constant rate $\alpha_{A,}\alpha_B$ *and* α_C which are all less than 1[2]. The total resistance cells for all drugs arise from three directions in parallel, as illustrated in Figure 1.

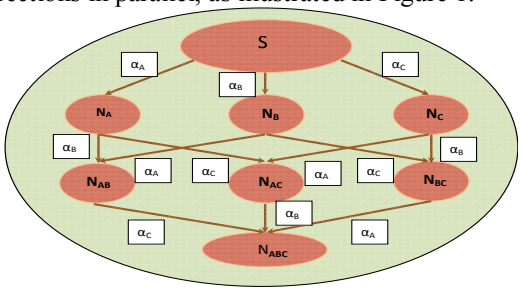


Fig. 1. Eight compartments for multi-drug

The proportions of cells killed by drug A from the sensitive and resistant sub-population S, N_B and N_C are the same, similar to drug B and C [2]. If λ indicates the rate of growth of cancer cells and k_A, k_B and k_C are the rate of cancer cells killed by drug unit, Equation 1describes the sensitive cell for all drugs, where $H(x) = \{1 : \text{if } x \geq 0, \text{otherwise } 0\}$ is the Heaviside tep function.

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

Equation (2) represents the resistance cells for drug A and can be calculated for drugs B and C similarly.

$$\frac{dN_A}{dt} = \lambda[(1-\alpha_B-\alpha_C)N_A + \alpha_A S] - k_B(v_B - v_{thB})H(v_B - v_{thB}) - k_C(v_C - v_{thC})H(v_C - v_{thC}) \quad (2)$$

Equations 3, 4 and 5 are deriving the cells which are doubly resistance.

$$\frac{dN_{AB}}{dt} = \lambda[(1-\alpha_C)N_{AB} + \alpha_B N_A + \alpha_A N_B] - k_C(v_C - v_{thC})H(v_C - v_{thC}) \quad (3)$$

$$\frac{dN_{AC}}{dt} = \lambda[(1-\alpha_B)N_{AC} + \alpha_C N_A + \alpha_A N_C] - k_B(v_B - v_{thB})H(v_B - v_{thB}) \quad (4)$$

$$\frac{dN_{BC}}{dt} = \lambda[(1-\alpha_A)N_{BC} + \alpha_C N_B + \alpha_B N_C] - k_A(v_A - v_{thA})H(v_A - v_{thA}) \quad (5)$$

The initial sizes of the cell sub-populations are:

$$S(0) = S_0\ N_A(0) = N_{A0},\ N_B(0) = N_{B0},\ N_C(0) = N_{C0},$$
$$N_{AB}(0) = N_{AC0}, N_{AC}(0) = N_{AC0},\ N_{BC}(0) = N_{BC0},\ N_{ABC}(0) = N_{ABC0} \quad (6)$$

The consequence of this model is shown in Equation 7

$$N(t) = S(t) + N_A(t) + N_B(t) + N_C(t) + N_{AB}(t) + N_{AC}(t) + N_{BC}(t) + N_{ABC}(t) \quad (7)$$

Now the rates of change of drug concentration $D_A(t), D_B(t)$ and $D_C(t)$ for drugs at the tumour site during the treatment cycle are shown, where $u_A(t), u_B(t)$ and $u_C(t)$ are the amounts of drug doses to be infused to the patient's body and λ is the drug decay which is related to the metabolism of drug inside patient's body. It should also be noted that all the drug concentrations at the tumour site should not exceed the limit of 50 as suggested [2].

$$\frac{dD_Y}{dt} = u_Y(t) - \gamma_Y D_Y(t), D_Y(t) = D_{A0}\text{ , where } Y = \{A : B : C\} \quad (8)$$

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

$$\frac{dT_Y}{dt} = D_Y(t) - \eta_Y T_Y(t), \qquad T_Y(t) \leq 100 \quad \text{where } Y = \{A : B : C\} \tag{9}$$

Where $T_A(t), T_B(t) and\ T_C(t)$ are the level of toxicity for both drugs developed inside the patient's body due to chemotherapy drug and parameter η indicates the rate of elimination of toxicity. Before the treatment starts, the number of cancer cells is set at 4.60517×10^{11}, as used by many researchers in cell cycle specific cancer treatment [1].

3 Implementation

A schematic diagram of multi-drug scheduling scheme for chemotherapy treatment is shown in Figure 2. A feedback control method I-PD is 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 gains k_p, integral gain k_i and derivative gains k_d. Drug concentration at the tumour is used as the feedback signal to the controller which is compared with a predefined reference level. The difference between each two is called the error which is used as input to the controller. It is noteworthy that X_{DA}, X_{DB} and X_{DC} indicate reference signals to the controllers which can be depicted as the desired drug concentrations to be maintained at the tumour site during the whole period of treatment. To achieve the desired performance, nine parameters of I-PDs such as $k_{Ai}, k_{Ap}, k_{Ad}, k_{Bi}, k_{Bp}, k_{Bd}, k_{Ci}, k_{Cp}, k_{Cd}$ need to be tuned. In this research, MOGA is used to find suitable parameters for I-PD controllers and reference inputs (desired drug concentrations).

The mathematical model containing eight compartments stating the effects of three drugs as explained earlier is implemented in Matlab/Simulink [8] environment with parameters and values as illustrated in Table 1 [1]. Moreover, the I-PD feedback control scheme is also developed in Matlab/Simulink environment The MOGA optimisation process begins with a randomly generated population called chromosome. An initial population of dimension 50X12X12 is created where number of individuals and parameters in each individual are 50 and 12 respectively. Each parameter is encoded as a 12 bit Gray code which is logarithmically mapped [9] 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 are assigned to controller parameters. The last three elements of each individual are assigned to the reference inputs to the close-loop control system. The whole control scheme and drug scheduling are designed for a period of 84 days as recommended by many researchers [1, 2, 7,10].

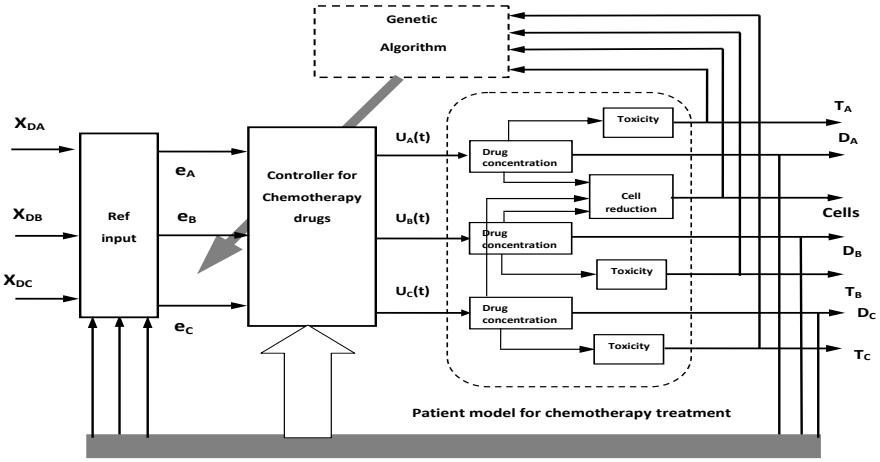


Fig. 2. Schematic diagram of the proposed multi-drug scheduling scheme

TABLE I THE PARAMETERS OF THE SIMULINK MODEL [1]

parameters	Value	parameters	value	parameters	value	parameters	value
η_A	0.4 day^{-1}	γ_A	0.32 day	N_{A0}	0	N_{ABC0}	0
η_B	0.5 day^{-1}	γ_B	0.27 day	N_{B0}	0	k_A	0.0084 day^{-1} D^{-1}
η_C	0.45 day^{-1}	γ_C	0.25 day	N_{B0}	0	k_B	0.0076 day^{-1} D^{-1}
α_A	0.008	v_{thA}	10 D	N_{AB0}	0	k_C	0.0092 day^{-1} D^{-1}
α_B	0.01	v_{thB}	10 D	N_{AC0}	0	λ	0.0099
α_C	0.014	v_{thC}	10 D	N_{BC0}	0	S_0	4.60517X10^{11}

At first, MOGA has been used to design drug scheduling 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, B and C) over the whole period of treatment. The four objective functions are formulated as follows:

$$f_{iY}(x) = \frac{1}{t_f}\int_0^{t_f} T_Y(t)dt,\ where\ i = \{1 : 2 : 3\} and\ Y = \{A : B : C\} \quad (10)$$

$$f_4(x) = N(t)(t_f) \quad (11)$$

$T_A(t), T_B(t) and\ T_C(t)$ 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 optimisation process in order to obtain solutions satisfying all objectives. The constraints are:

1. Stability of close-loop system
2. Minimum reduction of cancer cells at the end of treatment: $N(t) < S_0$
3. Maximum level of toxicity during the treatment:
$T_Y(t) < 100, where\ Y = A, B\ or\ C$
4. Drug concentration at the tumour site during the treatment:
$10 < D_Y(t) \leq 50, where\ Y = A, B\ or\ C$

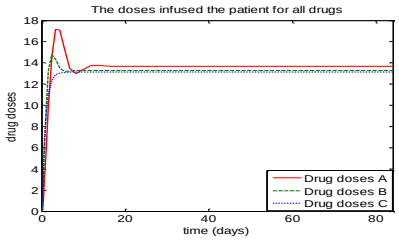
After evaluating the fitness function of each individual, as discussed in [11, 12], GA operators, namely selection, crossover and mutation are employed on current individuals to form individuals of next generation [11, 12]. Selection uses Baker's stochastic universal sampling algorithm [9], which is optimal in terms of bias and spread. Solutions not satisfying aforementioned design constraints are penalised

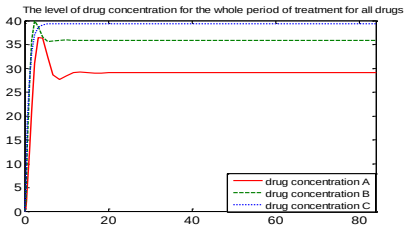
with very high values, called penalty function. This penalty function will reduce the probability of solutions yielding unacceptable values along any design objectives dominate the optimisation process, and on the contrary, favour acceptable solutions to be selected for reproduction that in turn may generate better solutions in subsequent generations. 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 [9]. The mutation rate for this optimisation process was set at 0.01%. In MOGA, non-dominated solutions called Pareto optimal set and corresponding decision variables are updated and preserved at the end of each generation. The MOGA optimisation process was run for 200 generations in order to minimise four design objectives, simultaneously and the non-dominated solutions recorded at the end.

5 Experimental Evaluations

To obtain different performance measures in relation to treatment, twelve decision variables, k_{Ai}, k_{Ap}, k_{Ad}, k_{Bi}, k_{Bp}, k_{Bd}, k_{Ci}, k_{Cp}, k_{Cd}, and three reference inputs (desired drug concentrations), of example solution are fed to the I-PDs controllers and the feedback control system along with the patient model is simulated for 84 days (12 weeks). Then the output of the I-PD controller, $u_A(t), u_B(t)$ and $u_C(t)$, the desired chemotherapy drug scheduling, are recorded. Several outputs of the patient model, such as, drug concentration at tumour site, toxicity and reduction of cancer cells are recorded. Figure 4(a) shows the chemotherapy drug scheduling for drug (A, B and C). The drug doses increase from zero and finally become stable at a certain value. It is noted that the rate of increase is different for different three drugs. For drug A, the doses take slightly more than one week to reach maximum value of 17.12 and for the remaining periods it becomes stable at that same value. Drug B takes less than one week to reach the maximum and stable level of 15 and the doses of drug C get stable at the highest level which is 12.5 within one week.

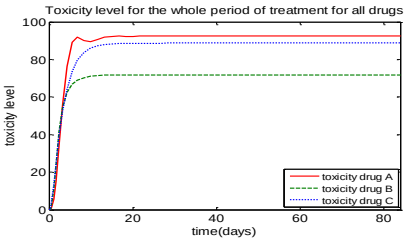
The second graph of Figure 4(b) shows the drug concentration at the tumour site due to chemotherapy drug scheduling obtained for all cases earlier in the first graph of Figure 4(a). It is interesting to note that, the drug concentrations, for all cases, increase gradually in similar manner as observed in case of corresponding drug dose scheduling. 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.

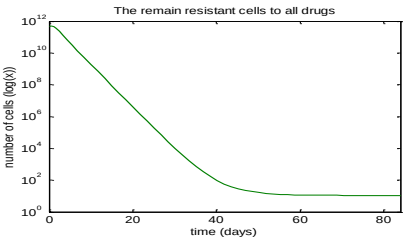




(b) Drug concentration for drugs A, B and C

Fig. 4. (a) Chemotherapy drug doses for drugs A, B and C





(b) The cell reduction throughout the treatment period

Fig. 5. (a) Level of toxicity for drugs A, B and C

The toxicities, for drugs A, B and C, developed due to the corresponding chemotherapy drug scheduling are shown in Figure 5(a). 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 optimisation process. Figure 5(b) shows the reduction of cancer cells during the whole period of treatment. The percentage of reductions obtained using the drug scheduling shown in Figure 4(a) is nearly 100% corresponds to the solution has been chosen.

6 Conclusion

The authors investigated and analyzed GA parameters and values that yielded very satisfactory results in similar application; the details are described in authors' earlier works [5, 13]. In this investigation model based on the cells function has been used to analyse the effects of the drug scheduling designed by the controller. It is noted that the obtained drug schedule is continuous in nature and gives lower and stable value throughout the whole period of treatment. Many solutions of the proposed drug scheduling pattern have reduced the number of tumour cells more than

99% (eliminate the resistance cells) with the tolerable drug concentration and lower toxic side-effects. The proposed model offered better performance as compared to existing models with regard to drug resistance and toxicity level. The drug effectiveness (cells reduction) as shown in Figure 5(b) in proposed model is nearly 100% while in the existing is about 99%. Where is the maximum level of the toxicity 92.3 which produced by drug A in proposed model and 100 for all drugs in the existing one [1]. Finally, the same multi-objective optimisation technique and feedback control strategy can be extended for any higher combination regimen. Future work will include verification of the proposed method with clinical data and experiments.

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