Evolutionary Drug Scheduling Model for Cancer Chemotherapy

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Abstract. This paper presents a modified optimal control model of drug scheduling in cancer chemotherapy and a new adaptive elitist-population based genetic algorithm (AEGA) to solve it. Working closely with an oncologist, we firstly modify the existing model, because the existing equation of the cumulative drug toxicity is not consistent with the clinical experience and the medicine knowledge. For exploring multiple efficient drug scheduling policies, we propose the novel variable representation – the cycle-wise representation; and adjust the elitist genetic search operators in the AEGA. The results obtained by the new model match well with the clinical treatment experience, and can provide much more realistic solutions than that by the previous model. Moreover, it has been shown that the evolutionary drug scheduling approach is simple and capable of solving complex cancer chemotherapy problems by adapting the suitable coding and the multimodal versions of EAs.

1 Introduction

An important target for cancer chemotherapy is to maximally kill tumor cells for a fixed treatment period. So drug scheduling is essential in cancer chemotherapy. Martin [6] have proposed the optimal drug scheduling model by the following differential equations:

$$\frac{dx_1}{dt} = -\lambda x_1 + k(x_2 - \beta)H(x_2 - \beta) \tag{1}$$

$$\frac{dx_2}{dt} = u - \gamma x_2 \tag{2}$$

$$\frac{dx_3}{dt} = x_2 \tag{3}$$

with the initial state $x^T(0) = [ln(100),\ 0,\ 0]$, the parameters $\lambda = 9.9 \times 10^{-4}$, $k = 8.4 \times 10^{-3}$, $\beta = 10$, $\gamma = 0.27$, $\eta = 0.4$, and:

$$H(x_2 - \beta) = \begin{cases} 1, & \text{if} \quad x_2 \geq \beta \\ 0, & \text{if} \quad x_2 \leq \beta \end{cases} \tag{4}$$

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where x_1 is a transformed variable that is inversely related to the mass of the tumor. The tumor mass is given by $N = 10^{12} \times exp(-x_1)$ cells, and the initial tumor cell population is set at 10^{10} cells [6]. The variable x_2 is the drug concentration in the body in drug units (D) and x_3 is the cumulative drug toxicity in the body. Equation (1) describes the net change in the tumor cell population per unit time. The first term on the right-hand side of Equation (1) describes the increase in cells due to cell proliferation and the second term describes the decrease in cells due to the drug. The parameter λ is a positive constant related to the growth speed of the cancer cells, and k is the proportion of tumor cells killed per unit time per unit drug concentration which is assumed to be a positive constant. The implication of the function described in Equation (4) is that there is a threshold drug concentration level, β below which the number of the killed tumor cells is smaller than the number of the reproduced tumor cells, and the drug is not efficient. Equation (2) describes the net increase in the drug concentration at the cancer site. The variable u is the rate of delivery of the drug, and the half-life of the drug is $ln(2)/\gamma$, where γ is the biochemical character parameter of the drug. It is assumed that the drug is delivered by infusion, and there is an instantaneous mixing of the drug with plasma, as well as an immediate delivery of the drug to the cancer site. These assumptions represent approximations based on the relative amount of time. It takes for the aforementioned activities to occur with respect to the total amount of time over which the treatment is administered. Equation (3) relates the cumulative drug toxicity to the drug concentration, e.g., the cumulative effect is the integral of the drug concentration over the period of exposure.

The performance index [6] to be maximized is:

$$I = x_1(t_f) \tag{5}$$

where the final time $t_f = 84$ days. The control optimization is performed subject to constraints on the drug delivery: $u \geq 0$, and on the state variables: $x_2 \leq 50$, $x_3 \leq 2.1 \times 10^3$.

Cancer chemotherapy is a systemic treatment, so the action of the chemotherapeutic agent is not restricted to the tumor site. Any of the body organs are liable to injury. This is on contrast to the localized treatments, such as surgery or radiotherapy. Therefore, the constraints on the drug concentration x_2 and the cumulative drug toxicity x_3 are to ensure that the patient can tolerate the toxic side effects of the drug. Drug resistance is considered to be a significant factor in chemotherapeutic failure [3] [7] [9] and it has been shown that the drug resistant cells are likely to increase as the tumor burden increases [2]. In order to reduce the likelihood of the emergence of drug resistant cells, the tumor size is forced to reduce by at least 50% every 3 weeks, so that: $x_1(21) \geq ln(200)$, $x_1(42) \geq ln(400)$, $x_1(63) \geq ln(800)$.

Many researchers have applied different optimization methods to improve the results of the drug scheduling model [1] [5] [6] [7] [10] [11]. Among of them, Tan et al. [10] have proposed the "Paladin-Distributed Evolutionary Algorithms" approach to solve this problem and got the best-known solutions.

Through analyzing the experimental results from the existing model, there are two obvious unreasonable outcomes in the optimal drug scheduling policies: (*i*) unreasonable timing for the first treatment; and (*ii*) three point constraints cannot improve the efficiency of the cancer treatment. We analyze the reasons causing these problems and modify the existing model. The newly modified model is consistent with the clinical experience. The drug scheduling models are multimodal optimization problems and their feasible solution spaces consist of several discontinuous subregions. Here we select our novel genetic algorithm (GA), called an adaptive elitist-population based genetic algorithm (AEGA) [4], which is an efficient algorithm for multimodal optimization problems, to solve the modified drug scheduling model. Simulation results obtained show that our multimodal optimization algorithm AEGA produces excellent drug scheduling policies in cancer chemotherapy, which match well with results from clinical treatment experience. The power of the AEGA in obtaining multimodal solutions for this problem is also demonstrated.

This paper is organized as follows. Section 2 analyzes the problems that exist in the best-known solutions obtained by the existing drug scheduling model. Section 3 presents the newly modified model of the drug scheduling for cancer chemotherapy. Section 4 introduces the automation of the drug scheduling for cancer chemotherapy through the AEGA. The adaptation and modelling of the modified model in the AEGA are detailed including the new chromosome representation and genetic operators. The experimental results and discussion are given in Section 4. The paper conclusion is drawn in Section 5.

2 Analysis of the Experimental Results of the Existing Model

Fig.1-(a) and (b) show the best-known drug scheduling policies without and with three point constraints respectively, which are explored by Tan et al. [10] using distributed evolutionary computing software. Through observing the experimental results obtained by the existing drug scheduling model, there are two obvious unreasonable problems:

- unreasonable timing for the first treatment; and
- three point constraints cannot improve the efficiency of the cancer treatment.

In the 84 days treatment, the two best-known control policies for the drug are that it first gives drug on the $41th$ day under the model without the three point constraints, and on the $18th$ day under the model with the three point constraints. This is the first unreasonable problem because these drug policies obviously do not correspond with the clinical experience. In the clinical treatment, the general policy for efficiently reducing the tumor cells is that we should give a multi-dose of the drug rather than a normal dose on the first day. Since in the early days of the treatment, the patient's body has the strongest metabolism capability of the drug, and also the drug resistance of the tumor cells is the weakest at this time. So giving the multi-dose drug at this time can get the best

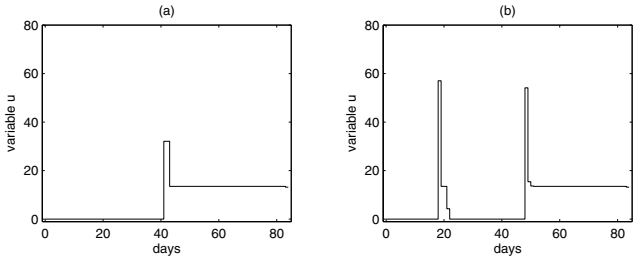

Fig. 1. The best-known solutions obtained by the existing drug scheduling model. (a): without the three point constrains; (b): with the three point constrains.

efficiency of the cancer treatment: to kill maximal tumor cells with minimal drug toxicity. According to this clinical experience, we can guess that an efficient drug scheduling policy should include the scheme that gives the multi-dose drug on the first day in the cancer treatment.

The second problem is that three point constraints cannot improve the efficiency of the cancer treatment. In the previous research works, the best-known performance index under the model with the three point constraints is 17.476 (corresponded to a final tumor size of $N = 2.57 \times 10^4$ cells). It is not better than the best-known performance index under the model without the three point constraints 17.993 (corresponded to a final tumor size of $N = 1.53 \times 10^4$ cells). This means that the three point constraints cannot improve the efficiency of the cancer treatment, but contrary to expectation, they reduce the overall efficiency of the drug chemotherapy. However, as described above, the aim of the three point constrains is to get more efficient drug scheduling policies. Because the drug resistance of the tumor cells increase with time and the emergence of drug resistant cells is thought to be a significant factor in chemotherapeutic failure [3] [7] [9]. In order to reduce the likelihood of the emergence of drug resistance cells, the tumor cells are forced to reduce by at least 50% every 3 weeks [5]. So these three point constraints should help to get more efficient drug scheduling policies for the cancer chemotherapy.

We believe the reason causing these problems is that the existing drug scheduling model is not consistent with the clinical experience. So we modify the existing model in the next section. The newly modified model can overcome the above two problems and its solutions are consistent with the clinical experience.

3 The Modified Model of the Drug Scheduling for Cancer Chemotherapy

The existing model [6] of cancer drug scheduling consists of three equations. Equation (1) can accurately describe the drug efficiency in the treatment period. Equation (2) also correctly describes the change process of the drug concentra-

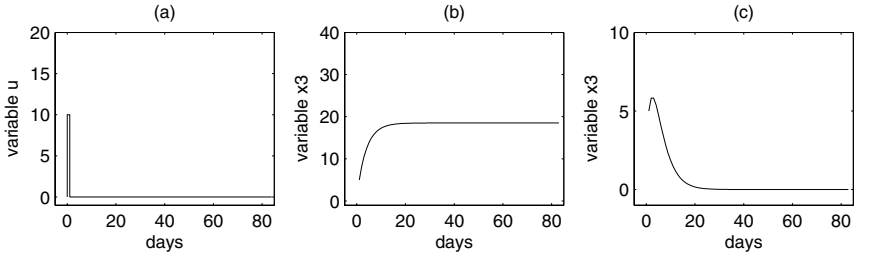

Fig. 2. The change processes of x_3 under the existing and modified models respectively.

tion in the body. But for Equation (3), the variable x_3 does not decrease in the whole cancer treatment, because on the right-side of Equation (3), the drug concentration x_2 is always not smaller than 0. Equation (3) may not be appropriate since it has not considered the metabolism process of the drug in the body. To clearly describe our analysis, we will use some experimental results to explain this problem.

In Fig.2-(a), we consider an additional test drug scheduling policy, which is giving $10D$ dose drug on the first day and not giving any drug in the later days. Fig.2-(b) shows the change process of the cumulative drug toxicity, x_3, in the fixed treatment period under the existing model. We can see that x_3 increases for the first few days due to the drug given on the first day, then x_3 almost remains constant in the later days. This means when the patient does not take the drug anymore, the drug toxicity still remains a constant value in the patient's body for the rest of the period. This does not correspond with the clinical experience. Because when the drug concentration x_2 decreased and tended to 0, generally the cumulative drug toxicity x_3 will be decreased through the metabolism and clearance by the liver and kidney in the body. To correct the above unreasonable model and accurately describe the change process of the cumulative drug toxicity x_3 in the body, with the help of an oncologist we have modified the third equation in the previous differential equation system as follows:

$$\frac{dx_3}{dt} = x_2 - \eta x_3 \tag{6}$$

Equation (6) describes the net change of the cumulative drug toxicity x_3 per unit time. In the right-hand side of this equation, the first term x_2 describes the increase of the cumulative drug toxicity x_3 due to the drug concentration x_2, and the second term $-\eta x_3$ describes the decrease in the drug toxicity due to the metabolism in the body. It is assumed that the metabolism speed of the drug is directly proportion to the amount of the current cumulative drug toxicity x_3. The parameter η is a positive constant related to the metabolism speed of the drug in the body.

Here we combine Equation (6) with Equations (1) and (2) to construct a new drug scheduling model. To demonstrate the difference of both models, we still use the additional test drug scheduling policy (Fig.2-(a)) to test the model and

analyze its results. The change processes of the variables x_1 and x_2 in the fixed treatment period (84 days) under the two models are the same. This means the new model also can correctly describe the change processes of the variables x_1 and x_2. Fig.2-(c) shows the change process of the cumulative drug toxicity x_3 in the fixed treatment period under the new model. The variable x_3 increases in the first few days after giving the drug on the first day, then it decreases to 0 along with the drug concentration x_2 decreasing to 0. The new drug scheduling model can correctly describe the metabolism process of the drug toxicity in the body.

Because we proposed the new Equation (6) to control the variable of the cumulative drug toxicity, x_3, the previous constraint $x_3 < 2100$ is not suitable. We use the two best-known solutions under the previous model without and with the three point constraints, to evaluate the new constraint about the variable x_3. Here we set the parameter $\eta = 0.4$ in Equation (6) and the maximal cumulative drug toxicity of these two best-known solutions are 99.851 and 99.999. These two maximal cumulative toxicities are too closed and all smaller than 100. According to this fact the new constraint for x_3 can be given as follows: $x_3 < 100$.

4 Evolutionary Drug Scheduling Model Via AEGA

In this section we use our adaptive elitist-population based genetic algorithm (AEGA), which is an efficient multimodal optimization algorithm [4], to implement the automation of the drug scheduling model for exploring multiply efficient drug scheduling policies. Why do we select a multimodal algorithm to solve this optimization problem? Because this problem includes some constraints, the feasible solution space consists of many subregions and these subregions are discontinuous. It is difficult for global optimization algorithms to search all subregions and explore a global optimum. We want to use a multimodal optimization algorithm to get multiple optima from all the subregions. On the other hand, in the clinical treatment, a doctor expects to select a different drug scheduling policy for a different patient. So we can use the multimodal optimization algorithm to solve the drug scheduling model, and get multiply efficient drug scheduling policies of the clinical treatment for the doctor to choose depending on the particular conditions of the patient under the treatment.

4.1 Variable Representation

For the drug scheduling problem in cancer chemotherapy as described in Section 1, there are 84 control variables to be optimized, which represent the dosage levels for the 84 days. The drug scheduling model is a high dimensional and multimodal optimization problem. Due to the large number of variables and fine accuracy involved, several representation schemes of variables in the evolutionary optimization were investigated. For example, some researchers used a pair-wise variable representation to reduce the complexity of variables. The information of dosage level and start-day are coded as variable pairs in such representation,

e.g., $(30.5, 28)$ meaning the starting of drug schedule from the $28th$ day with the dosage level of $30.5D$. However, the pair-wise variable representation is only useful when the given drug doses are not changed many times in the treatment period. For example, the best-known solution obtained by the previous model without the three point constraints is $\{(0, 0); (32.1, 41); (13.484, 43); (13.21, 83)\}$. The changes of the drug doses occur only 3 times in this solution. But in the clinical treatment, generally the drug schedule is a repeated policy (e.g., giving drug every two days). For such a case, the pair-wise variable representation will become more complex. Moreover, in EAs with the pair-wise variable representation, the existing evolutionary operators can only be implemented on the pair-wise variable representations, which consist of a constant number of variable pairs [10]. This will reduce the scheduling freedom and the efficiencies of EAs.

Here we propose a new variable representation—cycle-wise variable representation to accurately and efficiently describe the drug scheduling policy in a chromosome.

Definition 1: Due to the large number of variables and fine accuracy involved, the drug scheduling variable in the fixed treatment period defined by

$$\begin{aligned} \text{Variable Representation} &:= \{[C|D]^*|[D(DC)]^*\} \\ C &:= [c_i]^* \\ D &:= k_i \times \overline{d_i, \cdots, d_j} \end{aligned}$$

where

c_i is the drug dose on each day;
k_i is the number of cycles;
$\overline{d_i, \cdots, d_j}$ is the repetend;
$*$ represents the repetition of the structure that is located in the front square bracket, but the values can be different;

is called a cycle-wise variable representation of the drug scheduling model.

By Definition 1, the cycle-wise variable representation includes two parts: a front and a cyclic parts. The front part is $[C|D]^*$. It describes the drug doses in the initial treatment days. The cyclic part is $[D(DC)]^*$. It consists of the number of cycles k_i and the repetend $(\overline{d_i, \cdots, d_j})$. The cycle-wise variable representation is very suitable for the drug scheduling problem. Because in the first few days of the treatment period, the patient's body may not have adapted to the drug, but it is important to kill as much tumor cells as possible, the drug doses will be adjusted day by day. We use the front part to represent the drug doses in this initial period. Then when the patient's body gradually gets used to the drug, the drug administration schedule will follow a fixed cycle and a fixed dose pattern, which is suitably represented by the cycle-part.

Table 1. The multi-point crossover operator for the cycle-wise variable representation

Parents:
$\{94.92, \|_{r_1} \quad (8 \times \overline{10.8}), \quad \|_{r_2} \ (74 \times \overline{10.8})\}$
$\{136.98, \|_{r_1} \ (3 \times \overline{0}), 41.56, (3 \times \overline{0}), 35.85, \|_{r_2} \ (18 \times \overline{(3 \times \overline{0}), 39.58}), 0, 12.34\ \}$
Offspring:
$\{136.98, \|_{r_1} \quad (8 \times \overline{10.8}), \quad \|_{r_2} \ (74 \times \overline{10.8})\}$
$\{94.92, \|_{r_1} \ (3 \times \overline{0}), 41.56, (3 \times \overline{0}), 35.85, \|_{r_2} \ (74 \times \overline{10.8})\}$
$\{136.98, \|_{r_1} \ (3 \times \overline{0}), 41.56, (3 \times \overline{0}), 35.85, \|_{r_2} \ (74 \times \overline{10.8})\}$
$\{94.92, \|_{r_1} \quad (8 \times \overline{10.8}), \quad \|_{r_2} \ (18 \times \overline{(3 \times \overline{0}), 39.58}), 0, 12.34\ \}$
$\{136.98, \|_{r_1} \quad (8 \times \overline{10.8}), \quad \|_{r_2} \ (18 \times \overline{(3 \times \overline{0}), 39.58}), 0, 12.34\ \}$
$\{94.92, \|_{r_1} \ (3 \times \overline{0}), 41.56, (3 \times \overline{0}), 35.85, \|_{r_2} \ (18 \times \overline{(3 \times \overline{0}), 39.58}), 0, 12.34\ \}$

4.2 Elitist Crossover Operator for the Cycle-Wise Variable Representation

Here we combine the standard multi-point crossover operator with the adaptive elitist-population search techniques to construct the adaptive elitist-population based crossover operator for the cycle-wise variable representation. Let r_1 and r_2 be the crossover points in the front and the cyclic parts respectively of the two parents selected randomly from the population. The offspring are produced by taking all the combinations of the 3 segments (separated by r_1, r_2) of the parents' representations. In Table 1, the multi-point crossover operation generally can generate 6 offspring to improve the successful rate in the search process. Then two better solutions, which satisfy all the constraints, are selected from the parents and their offspring for the next generation.

Before we carry out the crossover operation, the adaptive elitist-population search technique incorporated in the crossover operator will delete the worse one from the two selected parents to reduce the population's redundancy, if they are located in the same optimal attraction. Of course, if this is carried out, no crossover will be performed. According to this principle, if the two parents have the same cyclic parts and similar front parts (smaller than the distance threshold σ_s), and the relative optimal directions of their front parts are face to face or one-way, the elitist operation will conserve the better one of these two parents for the next generation and delete the other one. Here we only use the front parts but not the whole cycle-wise representation to determine the relative optimal directions of both the parents to reduce the computation complexity of the algorithm.

4.3 Elitist Mutation Operator for the Cycle-Wise Variable Representation

In an elitist mutation operator, the basic mutation works as follows: for a randomly chosen position in the cycle-wise representation, replace its value with another randomly chosen value (not the same as the one to be replaced) with

Table 2. The one-point mutation operator for the cycle-wise variable representation

Parent:
$\{136.98, \boxed{(3 \times \overline{0})}, 41.56, (3 \times \overline{0}), 35.85, (18 \times \overline{(3 \times \overline{0}), 39.58})\};$
Offspring:
(1): $\{136.98, \boxed{(2 \times \overline{0}), 20.5}, 41.56, (3 \times \overline{0}), 35.85, (18 \times \overline{(3 \times \overline{0}), 39.58})\}$, or
(2): $\{136.98, (3 \times \overline{0}), 41.56, (3 \times \overline{0}), 35.85, (18 \times \overline{(3 \times \overline{0}), \boxed{27.64}})\}$, or
(3): $\{136.98, (3 \times \overline{0}), 41.56, (3 \times \overline{0}), 35.85, \boxed{(14 \times \overline{(4 \times \overline{0}), 39.58}), (2 \times \overline{0})}\}$.

certain mutation probability. For example, in Table 2, the fourth point of the parent is changed from 0 to 20.5 to generate its offspring (1); or the last value of the last cyclic part of the parent is changed form 39.58 to 27.64 to generate its offspring (2); or the number of cycles in the inner cycle of the last cyclic part is changed from 3 to 4 to generate its offspring (3).

The adaptive elitist-population search technique in mutation is that when the parent and its offspring are located in different optimal attractions, they are conserved together for the next generation to increase the population's diversity. For the cycle-wise representation, if the mutation operation is applied to its front part, and the relative optimal directions of the parent's and offspring's front parts is back to back, the elitist mutation operator will conserve the parent and its offspring together for the next generation. If the mutation operation is to apply the cyclic part, the elitist operation will not take place. As a general mutation operator, the elitist mutation operator conserves the best one of the parent and its offspring for the next generation.

4.4 The AEGA for the Drug Scheduling Model

In order to successfully explore multiple optimal solutions of the drug scheduling model, several rules for applying the AEGA are made as follows:

- Use the cycle-wise representation to keep the scheduling freedom and improve the efficiencies of EAs.
- Use the front part of the cycle-wise representation to check the dissimilarity of the individuals to reduce the computational complexity of the algorithm.
- Use the adaptive elitist-population search technique in the crossover operator to reduce the redundancy of the population.
- Use the adaptive elitist-population search technique in the mutation operator to increase the diversity of the population.
- Adaptively adjust the population size to optimally use the elitist individuals to explore multiple optima.

Following these rules, the AEGA for the drug scheduling model is implemented as follows:

1. Set $t = 0$ and initialize a chromosome population $P(t)$ (uniform random initialization within the bounds);
2. Evaluate $P(t)$ by using the fitness measure;
3. **While** (termination condition not satisfied) **Do**
   a) Elitist crossover operation to generate $P(t+1)$;
      i. check the dissimilarity of the randomly selected parents p_i and p_j;
      ii. **if** the parents p_i and p_j are similar, the elitist operation conserves the better one of them for the next generation; **else**, according to multi-point crossover operation, generates 6 offspring, and selects the better two from the parents and their offspring to the next generation;
   b) Elitist mutation operation to generate $P(t+1)$;
      i. according to the one-point mutation operation, generate the offspring c_i from the parent p_i;
      ii. **if** p_i and c_i are dissimilar, the elitist operation conserves p_i and c_i together for the next generation; **else**, selects the better one of them to the next generation;
4. Evaluate $P(t+1)$;
5. Stop if the termination condition is satisfied; otherwise, go to Step 3.

4.5 Experimental Results Under the New Model

The drug scheduling problem were simulated using the AEGA with the following parameters: initial population size=2000; maximal number of generations=20000; crossover rate=1.0; mutation rate=1.0 and the distance threshold σ_s=10. The drug scheduling model was simulated using numerical differentiation method of Runge-Kutta [8], with a small time interval of 0.1 day for good accuracy.

Automating the developed drug scheduling model via our multimodal optimization algorithm AEGA for 50 times can consistently obtain 6 most efficient drug scheduling policies. These results are listed in Table 3. For example, Fig. 3 and 4 show the control variable u, the best performance index x_1 (inversely related to the final mass of the tumor), the change processes of the drug concentration x_2 and the cumulative drug toxicity x_3 of the first and sixth optimal policies. The 6 best results all satisfy the three point constraints, and therefore it is not necessary to find the special solutions for the new model with the three point constraints separately.

The most efficient drug scheduling policies obtained by our new model are at least 8 times better than the best-known solution (corresponded to a final tumor size of $N = 1.53 \times 10^4$) under the previous model without the three point constraints and at least 13 times better than the best-known solution (corresponded to a final tumor size of $N = 2.57 \times 10^4$) under the previous model with the three point constraints. Since our modified dynamic model is more realistic, it has provided better drug administration scheduling solutions together with the AEGA approach used.

On the other hand, the multiple efficient drug scheduling policies under the new model match well with the clinical experience. In the clinical treatment, generally the drug scheduling policies include two kinds: continuous and repeated.

Table 3. The most efficient drug scheduling policies obtained by our new model

The most efficient drug scheduling policies	Tumor cells
(1): $\{94.92,(83 \times \overline{10.8})\}$	20
(2): $\{136.98, 0, 23.35, 0, 10.88, 0, 23.37, (38 \times \overline{0, 20.86}), 8.22\}$	34
(3): $\{136.98, (2 \times \overline{0}), 31.5, (2 \times \overline{0}), 24.5, (25 \times \overline{(2 \times \overline{0}), 30.41}), 0, 22.65\}$	76
(4): $\{136.98, (3 \times \overline{0}), 41.6, (3 \times \overline{0}), 35.9, (18 \times \overline{(3 \times \overline{0}), 39.6}), 0, 0, 25.6\}$	138
(5): $\{136.98, (4 \times \overline{0}), 50.1, (4 \times \overline{0}), 46.9, (14 \times \overline{(4 \times \overline{0}), 48.1}), 0, 21.3\}$	269
(6): $\{136.98, (13 \times \overline{(5 \times \overline{0}), 53.277}), 3 \times \overline{0}, 48.76\}$	1698

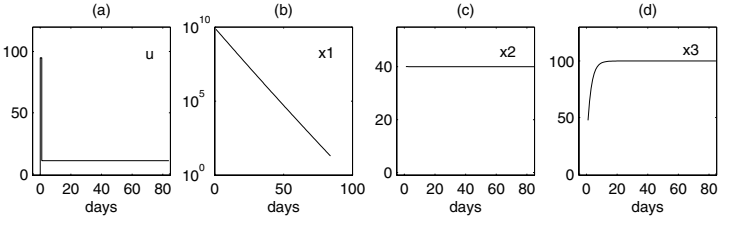

Fig. 3. The first efficient drug scheduling policy under our new model.

The drug scheduling policy (1) and the drug scheduling policies (2)-(6) represent these two kinds respectively. In some patients, the aim of treatment may be to reduce the tumor size with minimum toxicity and the drug scheduling policy (6) is suitable because its cumulative drug toxicity is low and often decreases to 60. For other patients, they may be cure despite higher toxicity, the drug scheduling policy (1) is suitable because this policy is most efficient but with high toxicity. So these multiple efficient drug scheduling policies obtained by the new model are more useful. According to the different conditions of the patients, the doctor can select the suitable drug scheduling policy to treat a cancer and get the best efficiency.

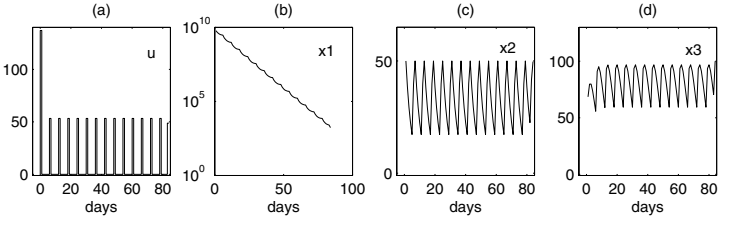

Fig. 4. The sixth efficient drug scheduling policy under our new model.

5 Conclusion

This paper has presented the modified optimal control model of drug scheduling in cancer chemotherapy and how to use our adaptive elitist-population based genetic algorithm (AEGA) to solve it. Working closely with an oncologist,we have firstly modified the existing model, because the existing equation, which control the cumulative drug toxicity x_3, is not consistent with the clinical experience and the medicine knowledge. For exploring multiple efficient drug scheduling policies, we have used our multimodal genetic algorithm (AEGA) to solve this complex multimodal optimization problem. We have proposed the novel variable representation – the cycle-wise representation, for the drug scheduling policy; and have adjusted the elitist genetic search operators in the AEGA to efficiently explore multiple efficient drug scheduling policies. The results obtained by the new model match well with the clinical treatment experience, and can provide much more realistic solutions than that by the previous model. Moreover, it has been shown that the evolutionary drug scheduling approach is simple and capable of solving complex cancer chemotherapy problems by adapting the suitable coding and the multimodal versions of EAs.

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