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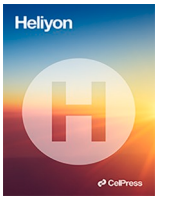

Optimization of drug scheduling for cancer chemotherapy with considering reducing cumulative drug toxicity

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ABSTRACT

An improved optimal drug scheduling model with considering two control drugs is proposed and the Gauss pseudospectral-based optimization method is studied to decrease the tumor size and drug toxicity in this work. Firstly, the Dexrazoxane drug, which has significant clinical effect to reduce the toxicity of the anticancer drug, is introduced. By analyzing the growth kinetics model of cancer chemotherapy, the toxicity reduction drug is regarded as the second input in the cancer dynamic equations. Correspondingly, the drug scheduling optimization problem with particular optimization goal and necessary constraints is established. Next, a model transformation technique is proposed to reduce the complexity of dynamic equations. With deriving the Gaussian time grid discretization detailly, the Gauss pseudospectral method (GPM)-based cancer chemotherapy drug scheduling algorithm is presented to test the performance of the proposed model within different rates. Finally, the implementation structure of drug scheduling optimization is given in detail. To test and validate the performance of proposed chemotherapy model, extensive simulation results and comparative evaluation are carried out on a specific mathematical model. Simulation results show that the improved optimization model is superior to other literature studies, resulting in the average improvement of performance index by 66.54% and revealing the significant guiding property for cancer chemotherapy.

1. Introduction

Cancer is the general term for a group of more than 100 diseases. Although there are many types of cancer, all of them start when abnormal cells are grown and reproduced uncontrollably. The cancerous cells may invade surrounding tissue and metastasize to the whole body. Untreated cancers can cause serious illness and even death. A significant portion of cancers can be cured by surgery, radiotherapy or chemotherapy, especially if they are detected in early stages (American Cancer Society 2016; World Health Organization 2016). Chemotherapy is a commonly used and powerful treatment method. Anti-cancer drugs are usually used to destroy

Abbreviations: GPM, Gauss pseudospectral method; NLP, Nonlinear programming; LG, Legendre–Gauss; OCP, Optimal control problem; SQP, Sequential quadratic programming; CCDSOM, Cancer chemotherapy drug scheduling optimization model; IWO, Invasive weed optimization; CPAG, Control parametrization and analytical gradients; DSO-RNRC, Direct search optimization based on random numbers and region contraction; AH-CVP, Alternative stochastic and hybrid techniques based on the control vector parameterization; TS-CVP, Control vector parameterization and time-scaling transformation; IFS-IWO, Intuitionistic fuzzy sets and invasive weed optimization.

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cancerous cells. Depending upon the type of cancer, the patient can also be treated with a single medicine (monotherapy) or a combination of medicines (combination therapy) [1]. Many clinically significant anticancer drugs, for instance, anthracyclines, have been widely used and have played a very important role for cancer chemotherapy [2]. However, this kind of anticancer drugs have an obvious side effect, which will lead to cardiac toxicity in patients and this issue has attracted much attention in recent years [3]. In the past cancer treatment process, drug delivery is basically relied on experience of doctors. With the development of computation science, some optimized treatments have been established through mathematical modeling and corresponding optimizations have been proposed. In 1992, Martin et al. [4] proposed an optimal drug scheduling model for cancer chemotherapy to optimize drug delivery and minimize tumor. Then, this model was solved by using an established numerical solution technique known as control parametrization optimization method.

Currently, plenty of scholars have proposed many optimization methods to solve the model of cancer chemotherapy [4] and improve the optimization results. For instance, Luus et al. [5] employed direct search optimization to solve this model and obtained scheduling strategy; Banga et al. [6] used stochastic techniques to obtain better optimization results; Liang et al. [7] proposed a fast drug scheduling optimization approach based on cycle-wise genetic algorithm to enhance the solving efficiency; Li et al. [8] employed the smoothed penalty function method to further improve the chemotherapy effect under theoretically analysis. The above researches have effectively improved the drug scheduling strategies for cancer chemotherapy in theoretical. However, the previous literature basically retained the original model established by Martin to solve and did not involve the treatment of reducing cardiotoxicity, which would have great effect on the chemotherapy in the process of cancer chemotherapy. Therefore, more factors should be considered in the chemotherapy model. In the part of cumulative drug toxicity, only certain restrictions on the drug toxicity are made in previous models, that is, an upper limit on the cumulative drug toxicity in the model is set, but the reduction of drug toxicity was not considered, which limits the research to a certain extent. In view of this situation, Martin's model [4] is further studied in this work and the drug toxicity is taken into account. Meanwhile, on the basis of previous literatures, it is found that anthracycline is one of the most commonly used anticancer drugs in clinic with high efficiency [9], and the anthracycline anticancer drug is therefore employed in this work for cancer chemotherapy model. Furthermore, with the development of pharmacology, Dexrazoxane has been clinically recognized as the most efficient drug for the prevention of anthracycline cardiotoxicity [10]. On this basis, it is necessary to consider the control of drug toxicity in drug scheduling optimization model. Furthermore, uncertainty and sensitivity are also the hotspots of drug scheduling, many researchers have paid much attention on these issues. For example, Pachauri et al. [11] designed the modified fractional order internal model control for cancer treatment; Panjwani et al. [12] focused on multi-objective optimization of a multi-drug chemotherapy schedule for cell-cycle-specific cancer treatment under the influence of drug resistance, where the parametric uncertainty was considered by the proposed method.

Combined with the above reasons, it can be seen that reducing tumor cells and inhibiting cumulative drug toxicity simultaneously is extremely important for cancer chemotherapy. An improved drug scheduling optimal control model, which employs two control variables to decrease the tumor size and drug toxicity simultaneously, is thereby established in this work. In terms of solving algorithm, Gauss pseudospectral method was rarely used to solve the cancer chemotherapy scheduling model in previous studies. However, it can be found that Gauss pseudospectral method has the advantages of high accuracy and fast speed. Therefore, based on the improvement of the model, this paper uses the Gauss pseudospectral method to solve the corresponding problem, and the optimal effect of tumor cells obtained is better than the results of previous studies, and the cardiotoxicity caused by the anticancer drug has been significantly reduced. To further verify the therapeutic effect of Dexrazoxane for drug toxicity prevention and tumor reduction in cancer chemotherapy, different Dexrazoxane drug efficiency effects are considered in this improved model so as to analyze the influence. Simulation tests are carried out to verify the efficiency of the proposed model and the corresponding optimization method, where some literature results [4–6,8,13] are employed to make comparisons.

2. Improved drug scheduling model of cancer chemotherapy

2.1. Growth kinetics model of cancer chemotherapy

Based on the model of Ref. [4], it is known that the single chemotherapeutic agent is widely used to treat a tumor, and the anticancer drug concentration at the cancer site is always described by differential equation (1):

$$\begin{aligned} &\dot{v}(t) = u(t) - \gamma v(t) \\ &v(0) = v_0 \end{aligned} \tag{1}$$

where $v(t)$ is the anticancer drug concentration at time t, $u(t)$ is the corresponding injection rate of anticancer drug at time t, γ is the half-life parameter and the half-life is denoted as $\ln(2/\gamma)$. $v(0)$ is the initial drug concentration at start time and is defined as v_0.

Meanwhile, the treatment is delivered over the fixed interval $[0, \mathrm{T}]$ in this work. Therefore, the Gompertz growth model [4], which has been widely used in tumor growth, is employed to describe the growth of cancer tumor as equation (2):

$$\begin{aligned} &\dot{N}(t) = \lambda N(t) \ln[\rho / N(t)] - \zeta[v(t) - \alpha] H[v(t) - \alpha] N(t) \\ &N(0) = N_0 \end{aligned} \tag{2}$$

where $N(t)$ is the tumor cell population at time t, and N_0 is the initial tumor size at $t = 0$; the parameter λ is a positive constant to describe the rate of tumor growth; ρ is the plateau population (also known as the carrying capacity), which reflects the maximum value that the tumor can grow naturally under the Gompertz growth model. Besides, ζ is the killing fraction, describing the killing effect of

drugs on tumor; α is a positive constant to reflect the minimum concentration at which the anticancer drug can work; $H[v(t)-\alpha]$ is the Heaviside step function defined as equation (3):

$$H(v(t)-\alpha)=\begin{cases}1, \text{if } v(t)\geq\alpha\\ 0, \text{if } v(t)<\alpha\end{cases} \tag{3}$$

Furthermore, in the process of cancer chemotherapy, Ref. [4] also considered the cardiotoxicity caused by anticancer drugs. The cardiotoxicity is described as equation (4) by the integral method and is limited by v_{cum} for safety reason:

$$\int_0^{\mathrm{T}} v(t)\mathrm{d}t \leq v_{cum} \tag{4}$$

During the treatment, the cardiotoxicity is measured in the drug concentration multiplied by the time of exposure, which can be quantified mathematically as the integral of the drug concentration $v(t)$ over the entire therapy interval [0, T].

2.2. Improved drug scheduling optimization model

As it is studied in Ref. [4], it is found that cardiotoxicity always exists in the form of integral and has not been eliminated or reduced, which greatly affects the effect of drug scheduling of cancer chemotherapy. However, in the previous literatures [5,6,8], cardiotoxicity is only limited in a certain threshold, control strategies are rarely taken to reduce this parameter value. With the development of pharmacology in recent decades, lots of drugs, such as Dexrazoxane [10], have been proved very effective to reduce cardiotoxicity, which provides a good basis for further improving cancer chemotherapy. Therefore, this paper reconsiders the modeling of drug-induced cardiotoxicity and introduces the following work to control cardiotoxicity.

Firstly, an additional state variable $\mu(t)$ is introduced to describe the cardiotoxicity as equation (5):

$$\mu(t)=\int_0^{\mathrm{T}} v(t)\mathrm{d}t \tag{5}$$

Since there are many existing drugs, such as Dexrazoxane, which can be used to reduce cardiotoxicity, the cardiotoxicity can be controlled. On this basis, the following treatment model (6) is introduced for cardiotoxicity control:

$$\overline{\mu}(t)=\int_0^{\mathrm{T}} [v(t)-\theta\omega(t)]\mathrm{d}t \tag{6}$$

where $\omega(t)$ is the injection rate of Dexrazoxane, and θ is the efficacy parameter of Dexrazoxane.

The addition of Dexrazoxane can reduce the cardiotoxicity of the anticancer drug in the process of chemotherapy, and the parameter θ can reflect the reducing effect of the anticancer drug with different efficacy on cardiotoxicity, which is helpful for the analysis of other possible cardiotoxicity reducing drugs. Since there is no precedent in the previous studies to add Dexrazoxane to the model proposed by Martin, the efficacy of Dexrazoxane after adding the model cannot be determined temporarily. In current work, its value range is set between 0% and 100%. Correspondingly, seven groups of efficacy values (0%, 5%, 10%, 25%, 50%, 75% and 100% respectively) are selected for simulation test to verify the reduction of cumulative drug toxicity and tumor cells after the addition of Dexrazoxane. On the basis of clinical experience, the value of cardiotoxicity is expressed as the integral expression of the whole treatment cycle.

With introducing anticancer drug and cardiotoxicity control drug, the growth and treatment kinetics model of cancer chemotherapy can be described by differential equation (7):

$$\begin{aligned}&\dot{N}(t)=\lambda N(t)\ln[\rho/N(t)]-\zeta[v(t)-\alpha]H[v(t)-\alpha]N(t)\\ &\dot{v}(t)=u(t)-\gamma v(t)\\ &\dot{\overline{\mu}}(t)=v(t)-\theta\omega(t)\\ &v(0)=v_0, N(0)=N_0, \overline{\mu}(0)=\overline{\mu}_0\end{aligned} \tag{7}$$

While, during the treatment process of cancer chemotherapy, Ref. [4] has pointed out that the drug should be controlled within limited concentrations for safety reasons. Thus, during the treatment process, growth constraints should be considered in the optimization model. In this work, the concentration constraint of the anticancer drug and cardiotoxicity limitation are studied as equation (8):

$$\begin{aligned}&0\leq v(t)\leq v_{\max} \quad \text{for} \quad \text{all} \quad t\in[0,\mathrm{T}]\\ &0\leq \overline{\mu}(t)\leq \overline{\mu}_{\max} \quad \text{for} \quad \text{all} \quad t\in[0,\mathrm{T}]\end{aligned} \tag{8}$$

where $v_{\max}$ is the maximal limit of the anticancer drug concentration and $\overline{\mu}_{\max}$ is the maximal cardiotoxicity that the patient can accept during the therapy [4].

Meanwhile, it has been studied in Ref. [14] that drug-resistance was a frequent cause of chemotherapeutic failure in human cancers. Correspondingly, it has been shown that the probability of having drug resistant lines and the proportion of drug resistant cells increases with increasing tumor size [15]. Therefore, to limit the tumor size during treatment, the continuous state constraint (9) is imposed in the optimization model.

$$N(t) \le N_{\max} \quad \text{for} \quad \text{all} \quad t \in [0, \mathrm{T}] \tag{9}$$

where $N_{\max}$ denotes the upper bound of tumor cell population.

Furthermore, reducing the likelihood of the emergence of drug resistant cells in the course of treatment is necessary, the tumor size should be forced to reduce by at least 50% every 3 weeks [4]. That is, during the three time periods (t_1, t_2, t_3), the mass of cancer cells must be lower than a certain value (η_1, η_2, η_3). Accordingly, the tumor size constraints at different time points are introduced as equation (10):

$$N(t_1) \le \eta_1, N(t_2) \le \eta_2, N(t_3) \le \eta_3. \tag{10}$$

Typically, various objective functions can be considered in cancer chemotherapy. Combining with the clinical treatment requirements, the following performance index (11), which is mainly employed for reducing the number of cancer cells, is studied in this work as the optimization goal:

$$\text{minimize } J_1(u(t), \omega(t)) = N(\mathrm{T}) \tag{11}$$

Finally, the improved drug scheduling optimization model for cancer chemotherapy can be stated below:

Problem 1: ***Giving the continuous growth and treatment kinetics system Eq.* (7) *and initial conditions of system, optimize the drug injection rates of*** $u(t)$ ***and*** $\omega(t)$ ***under certain boundaries to obtain the minimum cancer cells of*** $N(\mathrm{T})$ ***within the limited treating period, where the constraints* (8)∼(10) *are satisfied simultaneously during the whole treatment domain.***

For ease of description, let $x_1(t) = N(t)$, which represents the mass of tumors, $x_2(t) = v(t)$ denotes the anticancer drug concentration in the body in drug units [D], and $x_3(t) = \overline{\mu}(t)$ expresses the cumulative drug toxicity. Meanwhile, denote $u_1(t) = u(t)$ and $u_2(t) = \omega(t)$ as the control variables. Therefore, Problem 1 can be stated by the dynamic optimization mathematical model as equation (12):

$$\begin{aligned}
&\min \ J_1(u_1(t), u_2(t)) = x_1(\mathrm{T}) \\
&\text{s.t.} \quad \dot{x}_1(t) = \lambda x_1(t) \ln[\rho / x_1(t)] - \zeta(x_2(t) - \alpha) H(x_2(t) - \alpha) x_1(t) \\
&\qquad \dot{x}_2(t) = u_1(t) - \beta x_2(t) \\
&\qquad \dot{x}_3(t) = x_2(t) - \theta u_2(t) \\
&\qquad x_1(0) = N_0, x_2(0) = v_0, x_3(0) = \overline{\mu}_0 \\
&\qquad x_1(t_1) \le \eta_1, x_1(t_2) \le \eta_2, x_1(t_3) \le \eta_3 \\
&\qquad 0 \le x_2(t) \le v_{\max}, 0 \le x_3(t) \le \overline{\mu}_{\max} \quad \text{for} \quad \text{all} \quad t \in [0, \mathrm{T}] \\
&\qquad 0 \le u_1(t) \le u_{1,\max}, 0 \le u_2(t) \le u_{2,\max} \quad \text{for} \quad \text{all} \quad t \in [0, \mathrm{T}]
\end{aligned} \tag{12}$$

It can be seen that Problem 1 is a complex infinite dimensional dynamic optimization problem containing three state variables $\boldsymbol{x}(t) = [x_1(t) \quad x_2(t) \quad x_3(t)]^{\mathrm{T}}$, two control variables $\boldsymbol{u}(t) = [u_1(t) \quad u_2(t)]^{\mathrm{T}}$ and several complex constraints of state and control vector.

3. Gauss pseudospectral optimization-based drug scheduling

Usually, it is difficult to solve the infinite optimization problem. Recent years, with the development of numerical optimization theory, plenty of methods have been proposed for solving this kind of problem [16–18]. To sum up, these methods can be divided into three categories [19–21]: indirect methods, direct methods and intelligent algorithms. As one of the most efficient direct methods, Gauss pseudospectral method (GPM) converges faster and has larger convergence domain when compared with other optimization methods, it is therefore employed for solving Problem 1 in this work. The main idea of GPM is to discretize a continuous optimal control problem into a nonlinear programming (NLP) problem [22,23] by using the theory of orthogonal collocation where the collocation points are the Legendre–Gauss (LG) points. The purpose of this method is to approximate the continuous solution to a set of differential equations using polynomial interpolation through discrete LG points or nodes [24].

3.1. Optimization model transformation

As it is discussed in Ref. [4] that the mass of tumors $x_1(t) = N(t)$ would be a very big value, which would affect the solving performance of optimization methods. According to previous research [4,7], $N(t)$ can be expressed by the function of $10^{12} \times \exp(\cdot)$. To reduce the complexity of dynamic equations, the transform equation (13) is introduced:

$$N(t) = x_1(t) = 10^{12} \times \exp(-\overline{x}_1(t)) \tag{13}$$

Then, equation (14) can be obtained:

$$\dot{N}(t) = \dot{x}_1(t) = -10^{12} \times \exp(-\overline{x}_1(t)) \dot{\overline{x}}_1(t) \tag{14}$$

Accordingly, the objective function of problem (12) can be restated as function (15):

$$\text{minimize } J_1(\boldsymbol{u}(t)) = 10^{12} \times \exp(-\overline{x}_1(t)) \tag{15}$$

For ease of calculation, objective function (14) can be represented by the function (16):

$$\text{minimize } J_2(\boldsymbol{u}(t)) = -\overline{x}_1(t) \tag{16}$$

Meanwhile, the growth kinetic of $\dot{N}(t)$ can be stated as equation (17):

$$\begin{aligned}\dot{N}(t)=\dot{x}_1(t)=&-10^{12}\times\exp(-\bar{x}_1(t))\dot{\bar{x}}_1(t)\\ =&-\lambda\times10^{12}\times\exp(-\bar{x}_1(t))\ln\big[\rho \quad /\left(10^{12}\times\exp(-\bar{x}_1(t))\right)\big]\\ &-\zeta(x_2(t)-\alpha)H(x_2(t)-\alpha)\times10^{12}\times\exp(-\bar{x}_1(t))\end{aligned} \tag{17}$$

By arranging Eq. (17), equation (18) can be obtained:

$$\dot{\bar{x}}_1(t)=-\lambda\times\left(\bar{x}_1(t)+\ln\left(\rho/10^{12}\right)\right)+\zeta(x_2(t)-\alpha)H(x_2(t)-\alpha) \tag{18}$$

Since $\rho=10^{12}$ is employed in Ref. [4], $\ln(\rho/10^{12})=0$ can be calculated. Sequentially, optimization model (12) is transformed into the optimal control problem (19):

$$\begin{aligned}&\min\ J_2(\boldsymbol{u}(t))=-\bar{x}_1(\mathrm{T})\\ &\text{s.t.}\quad \dot{\bar{x}}_1(t)=-\lambda\times\bar{x}_1(t)+\zeta(x_2(t)-\alpha)H(x_2(t)-\alpha)\\ &\qquad \dot{x}_2(t)=u_1(t)-\beta x_2(t)\\ &\qquad \dot{x}_3(t)=x_2(t)-\theta u_2(t)\\ &\qquad \bar{x}_1(0)=\bar{N}_0,x_2(0)=v_0,x_3(0)=\bar{\mu}_0\\ &\qquad \bar{x}_1(t_1)\geq\bar{\eta}_1,\bar{x}_1(t_2)\geq\bar{\eta}_2,\bar{x}_1(t_3)\geq\bar{\eta}_3\\ &\qquad 0\leq x_2(t)\leq v_{\max},0\leq x_3(t)\leq\bar{\mu}_{\max}\quad \text{for all}\quad t\in[0,\mathrm{T}]\\ &\qquad 0\leq u_1(t)\leq u_{1,\max},0\leq u_2(t)\leq u_{2,\max}\quad \text{for all}\quad t\in[0,\mathrm{T}]\end{aligned} \tag{19}$$

3.2. Gaussian time grid discretization

Without loss of generality, the cancer chemotherapy optimization problem (19) is formulated into the unified form optimal control problem (OCP) (20):

$$\begin{aligned}&\min J_2(\boldsymbol{u}(t))=\varphi(\boldsymbol{x}(\mathrm{T}),\mathrm{T})\\ &\text{s.t.}\begin{bmatrix}\dot{\bar{x}}_1(t)\\ \dot{x}_2(t)\\ \dot{x}_3(t)\end{bmatrix}=\frac{\mathrm{d}\boldsymbol{x}(t)}{\mathrm{d}t}=f(\boldsymbol{x}(t),\boldsymbol{u}(t),t),t\in[0,\mathrm{T}]\\ &\varphi(\boldsymbol{x}(t_0),t_0)=\boldsymbol{x}_0\\ &C(\boldsymbol{x}(t),\boldsymbol{u}(t),t_0,t_i,\mathrm{T})\leq0,i=1,2,3\\ &\boldsymbol{x}_{\mathrm{L}}\leq\boldsymbol{x}(t)\leq\boldsymbol{x}_U,\boldsymbol{u}_{\mathrm{L}}\leq\boldsymbol{u}(t)\leq\boldsymbol{u}_U\end{aligned} \tag{20}$$

Firstly, by introducing the time scale transformation strategy [25], which is shown as equation (21), the original time interval $t\in[t_0,\mathrm{T}]$ is transformed into time interval [−1,1].

$$\tau=\frac{2t}{\mathrm{T}-t_0}-\frac{\mathrm{T}+t_0}{\mathrm{T}-t_0} \tag{21}$$

Next, the Gaussian distribution nodes (named Gauss points) are obtained by solving the zero point of the Legendre polynomial in time domain $(-1,1)$. According to the properties of orthogonal polynomials, all zeros are single real roots in the open time domain. Therefore, the distribution nodes can be obtained by solving the *N*-order Legendre polynomial as equation (22) and equation (23) adopted in Ref. [26].

$$P_{n+1}(\tau)=(\tau-\alpha_n)P_n(\tau)-\beta_n^2P_{n-1}(\tau),n=0,1,\cdots \tag{22}$$

$$P_0(\tau)=1,P_{-1}(\tau)=0 \tag{23}$$

To solve Eq. (22), the following inference is employed in this work.

Inference 1. ***The root of N-order Legendre polynomial is the eigenvalue of the matrix*** H ***as follows.***

$$\mathrm{H}=\begin{pmatrix}\alpha_0 & \beta_1 & & & \\ \beta_1 & \alpha_1 & \beta_2 & & \\ & \ddots & & & \\ & & \alpha_{n-2} & \beta_{n-1} & \\ & & \beta_{n-1} & \alpha_{n-1} & \end{pmatrix}$$

ProofBased on the definition of Legendre polynomial, the root of the *N*-order Legendre polynomial is the solution of equation (24):

$$P_{n+1}(\tau)=(\tau-\alpha_n)P_n(\tau)-\beta_n^2P_{n-1}(\tau)=0 \tag{24}$$

When $n=0$, equation (25) can be obtained:

$$P_1(\tau) = (\tau - \alpha_0)P_0(\tau) - \beta_0^2 P_{-1}(\tau) \tag{25}$$

Since $P_{-1}(\tau) = 0$, $P_1(\tau) = (\tau - \alpha_0)\tau$ can be obtained.
When $n = 1$, equation (26) can be obtained:

$$P_2(\tau) = (\tau - \alpha_1)P_1(\tau) - \beta_1^2 P_0(\tau) \tag{26}$$

Since $P_0(\tau) = 1$, it can be found that $P_2(\tau) = (\tau - \alpha_1)P_1(\tau) - \beta_1^2$.
Let equation (27):

$$A_0 = \alpha_0, A_1 = \begin{bmatrix} A_0 & \beta_1 \\ \beta_1 & \alpha_1 \end{bmatrix} \tag{27}$$

It can be found that the root of $P_2(\tau) = 0$ is the solution of $(\tau - \alpha_1)(\tau - \alpha_0) - \beta_1^2 = 0$. Furthermore, the eigenvalue of A_1 is in the form (28):

$$|\bar{\lambda} I - A_1| = (\bar{\lambda} - A_0)(\bar{\lambda} - \alpha_1) - \beta_1^2 = 0 \tag{28}$$

By comparing Eq. (26) with Eq. (28), it can be seen that the root of $P_2(\tau) = 0$ is the eigenvalue of matrix A_1.
Similarly, let equation (29):

$$A_2 = \begin{bmatrix} A_1 & \beta_2 \\ \beta_2 & \alpha_2 \end{bmatrix} \tag{29}$$

Then, the root of $P_3(\tau) = 0$ is as equation (30):

$$(\tau - \alpha_2)|\tau I - A_1| - \beta_2^2 |\tau I - A_0| = 0 \tag{30}$$

The eigenvalue of $A_2 = \begin{bmatrix} A_1 & \beta_2 \\ \beta_2 & \alpha_2 \end{bmatrix}$ is as equation (31):

$$\begin{aligned} |\bar{\lambda} I - A_2| &= \begin{vmatrix} \bar{\lambda} I - A_1 & -\beta_2 \\ -\beta_2 & \bar{\lambda} - \alpha_2 \end{vmatrix} = \begin{vmatrix} \bar{\lambda} - \alpha_0 - \beta_1 & -\beta_1 \bar{\lambda} - \alpha_1 & -\beta_2 \\ & -\beta_2 & \bar{\lambda} - \alpha_2 \end{vmatrix} \\ &= (\bar{\lambda} - \alpha_2)|\bar{\lambda} I - A_1| + \beta_2(-\beta_2)|\bar{\lambda} I - A_0| = 0 \end{aligned} \tag{31}$$

Therefore, the root of $P_3(\tau) = 0$ is the eigenvalue of matrix A_2. By using the recursive method, it can be seen that the root of N-order Legendre polynomial is the eigenvalue of matrix H.

Finally, by solving Eq. (22), these N discrete points will be obtained. On this basis, control vector and state vector are further simultaneously approximated by Lagrange polynomials [27] as equation (32):

$$\begin{aligned} \boldsymbol{x}(\tau) &\approx \boldsymbol{X}(\tau) = \sum_{i=0}^{N} L_i(\tau)\boldsymbol{X}(\tau_i) = \sum_{i=0}^{N} L_i(\tau)\boldsymbol{X}_i \\ \boldsymbol{u}(\tau) &\approx \boldsymbol{U}(\tau) = \sum_{i=0}^{N} L_i(\tau)\boldsymbol{U}(\tau_i) = \sum_{i=0}^{N} L_i(\tau)\boldsymbol{U}_i \end{aligned} \tag{32}$$

where $\boldsymbol{X}_i$ and $\boldsymbol{U}_i$ are the value of state vector and control vector at discrete point τ_i respectively. Meanwhile, Lagrange interpolation functions are stated as equation (33):

$$\begin{aligned} L_i(\tau) &= \prod_{j=0, j\neq i}^{N} \frac{\tau - \tau_j}{\tau_i - \tau_j} = \frac{b(\tau)}{(\tau - \tau_i)\dot{b}(\tau_i)} \\ b(\tau) &= \prod_{i=0}^{N} (\tau - \tau_i) \end{aligned} \tag{33}$$

3.3. Optimal control problem discretization

Consequently, it is easy to calculate the derivation of state vector as equation (34):

$$\dot{\boldsymbol{x}}(\tau) \approx \dot{\boldsymbol{X}}(\tau) = \sum_{i=0}^{N} \dot{L}_i(\tau)\boldsymbol{X}_i \tag{34}$$

Let $D_{k,i} = \dot{L}_i(\tau_k)$ at each discrete points, the discretization of state equations can be replaced by the constraints (35):

$$\dot{\boldsymbol{x}}(\tau) \approx \dot{\boldsymbol{X}}(\tau) = \sum_{i=0}^{N} D_{k,i}\boldsymbol{X}_i = \frac{\mathrm{T} - t_0}{2} f\left(\boldsymbol{X}_k, \boldsymbol{U}_k, \tau_k; t_0, t_f\right), k = 1, 2, \ldots, N \tag{35}$$

Correspondingly, terminal state can be calculated by using equation (36):

$$\boldsymbol{x}(1) = \boldsymbol{x}(\tau_0) + \int_{-1}^{1} f(\boldsymbol{x}(\tau), \boldsymbol{u}(\tau), \tau)\mathrm{d}\tau \tag{36}$$

With employing the discrete integral formula [28], Eq. (36) can be expressed as equation (37):

$$\boldsymbol{X}_{\mathrm{T}} = \boldsymbol{X}_0 + \sum_{i=0}^{N} \boldsymbol{X}_i \sum_{k=1}^{N} w_i D_{k,i} \tag{37}$$

where w_i is the integral weight in Gauss integral formula and the calculation function please see Ref. [28].

Furthermore, during the treatment processing, the mass of cancer cells must be lower than certain values in three time periods. In this work, the corresponding three times nodes are transformed into three discrete state points. Finally, the optimal control problem is transformed into the general nonlinear programming (NLP) problem (38).

$$\begin{aligned}
&\min J_2 = \varphi(\boldsymbol{X}_{\mathrm{T}}, 1) \\
&\text{s.t.} \sum_{i=0}^{N} D_{k,i}\boldsymbol{X}_i - \frac{\mathrm{T} - t_0}{2} f(\boldsymbol{X}_k, \boldsymbol{U}_k, \tau_k; -1, 1) = 0 \\
&\boldsymbol{C}(\boldsymbol{X}_k, \boldsymbol{U}_k, \tau_k; -1, 1) \le 0 \\
&\boldsymbol{X}_{\mathrm{T}} = \boldsymbol{X}_0 + \sum_{i=0}^{N} \boldsymbol{X}_i \sum_{k=1}^{N} w_i D_{k,i} \\
&\boldsymbol{x}_{\mathrm{L}} \le \boldsymbol{X}_k \le \boldsymbol{x}_U, \boldsymbol{u}_{\mathrm{L}} \le \boldsymbol{U}_k \le \boldsymbol{u}_U, k = 1, 2, ..., N
\end{aligned} \tag{38}$$

It is obvious that the goal of Problem (38) is to find a set of variables $(\boldsymbol{X}_k, \boldsymbol{U}_k)$ to minimize the performance index. Typically, many effective methods, such as gradient-based NLP solvers, can be used to solve the transformed Problem (38) with high precision [29]. In this work, sequential quadratic programming (SQP) method [30,31] is recommended. Briefly, the steps are stated as follows:

Step 1: Use time scale conversion method to convert the original time interval into a new time domain [−1,1];

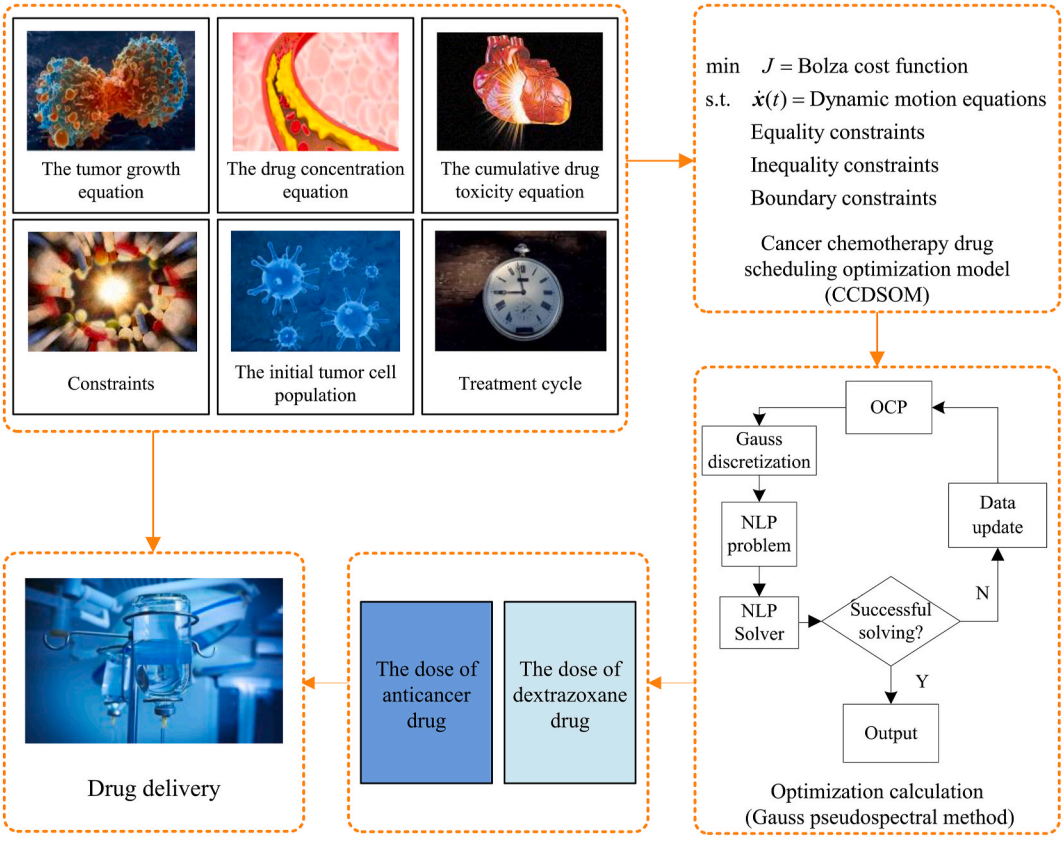

Fig. 1. Structure of optimization implementation.

Step 2: Solve the zero point of Legendre polynomial in the new time domain to obtain the Gaussian distribution nodes;
Step 3: Use Lagrange interpolation polynomial to discrete control variables and state variables;
Step 4: Select the terminal constraint calculation strategy to calculate the terminal point;
Step 5: Convert the original OCP problem into NLP problem;
Step 6: Calculate the gradient of the NLP problem relative to the optimization parameters;
Step 7: Use the gradient-based NLP solver to solve the transformed problem.

4. Drug scheduling optimization implementation

Based on the specific details of proposed improved optimization model, with combining with the GPM method, the implementation structure of drug scheduling optimization for cancer chemotherapy is given in Fig. 1.

To obtain the drugs delivery strategies for cancer chemotherapy, the tumor growth model, drug and toxicity concentration equations, treatment constraints will be analyzed at first; the dynamic cancer chemotherapy drug scheduling dynamic optimization model are then established; the corresponding optimal control problem is subsequently solved by employing the GPM ; finally, the outputs of the optimization processing are the dose curves of anticancer drug and Dexrazoxane drug. Specifically, the implementation steps of drug scheduling computation are given as follows:

Algorithm.

Step 1: INPUT division number N and initial state variable $\mathbf{X}_0$, set initial parameters $\overline{\mathbf{X}}_0$ and $\mathbf{U}_0$, set NLP solver tolerance ς, state and control boundaries $\boldsymbol{x}_{\mathrm{L}}$, $\boldsymbol{x}_{\mathrm{U}}$, $\boldsymbol{u}_{\mathrm{L}}$, $\boldsymbol{u}_{\mathrm{U}}$.

Step 2: Using optimization model transformation strategy to transform problem (12) into problem (19).

Step 3: Calculating the Gauss distribution points by using **Inference 1.**

Step 4: Arranging the Gaussian time grid nodes and transform them into corresponding discrete points in time interval $(-1, 1)$.

Step 5: Using the obtained N Gauss discretization points to discrete state and control variables.

Step 6: Choosing terminal constraints computation strategy to calculate the terminal points.

Step 7: Employing the Lagrange interpolation functions to discrete the OCP problem (19) into an NLP problem. **THEN GO TO** Step 8;

Step 8: Calculating the gradients of NLP problem with respect to optimization parameters.

Step 9: Using the gradient-based NLP solver to solve NLP problem.

Step 10: OUTPUT the drug scheduling optimization results.

5. Simulation studies of cancer chemotherapy

To verify the performance of improved cancer chemotherapy optimization model for drug scheduling, the model parameters, which has been widely studied in Refs. [4,6–8] are employed in this work for testing. Meanwhile, the limitation of $u_{2,\max}$ is chosen as 10 times of $u_{1,\max}$ based on Ref. [32]. Furthermore, the presented Gauss pseudospectral method (GPM) are used for solving the improved OCP problems and some literature results are adopted to make comparison. Correspondingly, the parameter values, initial values and constraint parameters are given in Table 1. All simulation studies are carried out on a personal computer in MATLAB 2018a platform with a 1.0 GHz Intel Core i5-1035G1 processor and 16 GB 3200 MHz SK Hynix DDR4 memory.

As it is discussed section 2.2, θ is the efficacy parameter of Dexrazoxane in improved optimization model, the specific efficacy of the newly added input amount of Dexrazoxane in the improved model is uncertain, while its efficiency range can be roughly determined, 7 groups of efficacy assumptions are therefore employed for testing, and the treatment optimization results under different efficacy are analyzed. The simulation results are shown in Table 2.

It can be seen in Table 2 that without using the toxicity reduction drug, the performance index of J_2 is 16.79641, while by employing the Dexrazoxane to reduce toxicity, the average performance index of J_2 is 31.16389, which improves the index by 85.54%. With using the transformation Eq. (13) to calculate the tumor cells, it can be obtained that N(T) is reduced from 50,747 to 0.0292, showing the effectiveness of toxicity reduction for treatment. Furthermore, results in Table 2 reveal that the efficacy rate parameter (> 0%) does not influence the performance indexes, while it will affect the drug values of $u_2(t)$ so as to change the values of $x_3(t)$. Table 3 gives the average values of control and state variables in cancer chemotherapy optimization under different efficacy rates. It is obvious that the introduction of toxicity reduction drug for cancer chemotherapy is significative, which provides a good reference for further exploring the toxicity reduction efficiency of Dexrazoxane in treatment process.

Table 1
Parameters of cancer chemotherapy model.

Symbol	Value	Symbol	Value	Symbol	Value
λ	9.9×10^{-4}	$\overline{\mu}_0$	0	$\overline{\eta}_3$	ln(800)
ζ	8.4×10^{-3}	t_1	21	$\nu_{\max}$	50
α	10	t_2	42	$\overline{\mu}_{\max}$	2100
β	0.27	t_3	63	T	84
$\overline{N}_0$	ln(100)	$\overline{\eta}_1$	ln(200)	$u_{1,\max}$	120
ν_0	0	$\overline{\eta}_2$	ln(400)	$u_{2,\max}$	1200

Table 2
Test results of different efficacy parameters.

Toxicity reduction drug	Efficacy rate (θ)	J_2 (max)	Average value	Improvement
None	0%	16.79641	16.79641	0
Dexrazoxane	5%	31.16389	31.16389	85.54%
	10%	31.16389		
	25%	31.16389		
	50%	31.16389		
	75%	31.16389		
	100%	31.16389		

Table 3
Average values of control and state variables in cancer chemotherapy optimization under different efficacy rates.

Efficacy rate (θ)	Average value of $u_1(t)$	Average value of $u_2(t)$	Average value of $\bar{x}_1(t)$	Average value of $x_2(t)$	Average value of $x_3(t)$	J_2 (max)
0%	8.747	0	10.98	22.3	1064	16.79641
5%	15.78	657	17.31	46.32	256.1	31.16389
10%	15.78	391.6	17.31	46.32	125.6	31.16389
25%	15.78	167.4	17.31	46.32	44.75	31.16389
50%	15.78	89.55	17.31	46.32	29.55	31.16389
75%	15.78	60.98	17.31	46.32	16.52	31.16389
100%	15.78	45.67	17.31	46.32	13.07	31.16389

To further verify the improvement property of proposed cancer chemotherapy model, the literature results of previous optimization methods are also concluded in this work and are listed in Table 4. By analyzing these results, it is found that Martin et al. [4] employed the control parameterization method to solve the traditional cancer chemotherapy optimization problem and obtained a performance index of 16.836. Later, Luss et al. [5] reported a performance value of 17.4760, while Banga et al. [6] pointed out the path constraint on $x_2(t)$ was slightly violated. Accordingly, they proposed the two-phase hybrid approach to solve this optimization model and presented a value of 17.4811. To further improve the efficiency of control vector parameterization method for solving this cancer chemotherapy optimal control problem with incomplete and different integral time domains, Li et al. [8] proposed an efficient computational method and obtained the performance index of 17.4852. Recently, Karar et al. [13] introduced a new closed loop fuzzy logic controller based on intuitionistic fuzzy sets and invasive weed optimization (IWO) algorithm for regulating intravenous anti-cancer drug delivery, simulation results shown that the remaining cancer cells of 27.63 was obtained. Compared with the reported results, it can be seen that when efficacy rate parameter $\theta = 0$ (no toxicity reduction), the performance index value of this work is 16.79641, which is similar with the literature result of Ref. [4]. However, when the toxicity reduction drug works, better treatment effect can be achieved, resulting the minimum number of remaining cancer cells of 31.16389 and 0.0292. The comparison with previous literature results in Table 4 shows the improvement of proposed optimization model is excellent.

By arranging the variable values of cancer chemotherapy optimization under different efficacy rates, the control curves and state curves are shown in Fig. 2~Fig. 6. In Fig. 2, the numbers in parentheses represent different efficacy of Dexrazoxane, and it is obvious that when efficacy rate $\theta = 0$, the days of using the anticancer drug and not using the anticancer drug are almost the same, accounting for half of the treatment course, and the time of administration is mainly concentrated in the first three weeks and the last four weeks, which is similar to the results of Ref. [4]. While, when Dexrazoxane works, the law of administration is the same: in the first week, a large dose was administered, and the latter is almost uniform, with the dosage being maintained below 20 [D]. It can be seen from the above that the dose of each given anticancer drug does not vary greatly when the Dexrazoxane takes effect during the chemotherapy process, which will be more convenient for the administration process of clinical treatment.

Correspondingly, Fig. 3 shows the Dexrazoxane drug delivery curves, and the numbers in parentheses represent different efficacy of Dexrazoxane. The curves show a large trend of increasing first and then decreasing in the dosage of Dexrazoxane with the increase of time when $\theta \leq 0.25$. And when $0.25 < \theta \leq 1$, the dosage of Dexrazoxane is less than 200 [D], and is basically uniform. With the

Table 4
Results comparison of different cancer chemotherapy optimization methods.

Author	Journal	Year	Method	J_2 (max)	N(T)
Martin et al. [4]	*Automatica*	1992	CPAG	16.836	48,777
Luus et al. [5]	*Hungarian Journal of Industrial Chemistry*	1994	DSO-RNRC	17.4760	25,720
Banga et al. [6]	*Journal of Biotechnology*	2005	AH-CVP	17.4811	25,589
Li et al. [8]	*Nonlinear Dynamics*	2014	TS-CVP	17.4852	25,484
Karar et al. [13]	*Biomedical Signal Processing and Control*	2020	IFS-IWO	27.63	0.806
Current work	–	2023	GPM	31.16389	0.0292

Notes: CPAG—Control parametrization and analytical gradients; DSO-RNRC—Direct search optimization based on random numbers and region contraction; AH-CVP—Alternative stochastic and hybrid techniques based on the control vector parameterization; TS-CVP—Control vector parameterization and time-scaling transformation; IFS-IWO—Intuitionistic fuzzy sets and invasive weed optimization; GPM—Gauss pseudospectral method.

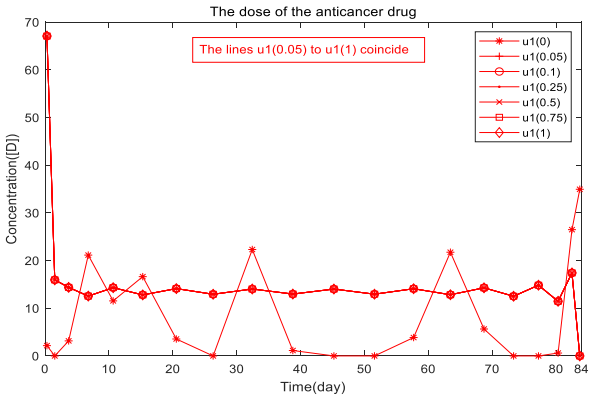

Fig. 2. Anticancer drug curves of cancer chemotherapy optimization under different efficacy rates.

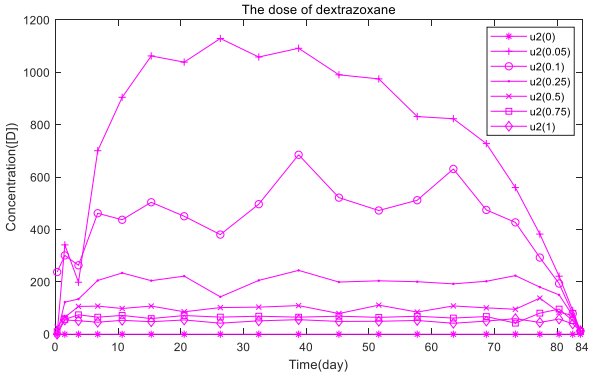

Fig. 3. Dexrazoxane drug curves of cancer chemotherapy optimization under different efficacy rates.

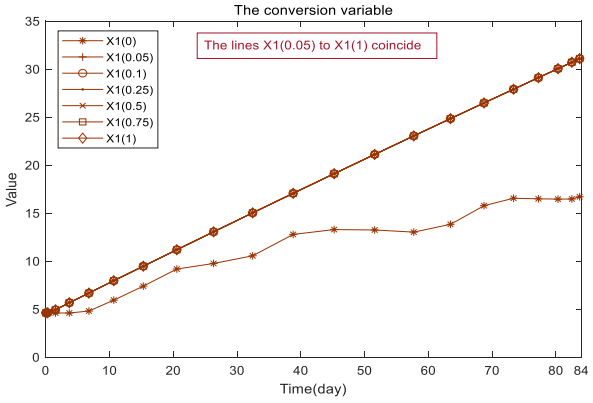

Fig. 4. Conversion variable curves of cancer chemotherapy optimization under different efficacy rates (Due to the limitation of input symbols, replace $\bar{x}_1$ with $\times 1$).

increasing of θ, the overall dosage of Dexrazoxane decreases gradually. Therefore, in clinical practice, the efficacy of Dexrazoxane can determine its dosage in the process of chemotherapy, which will greatly affect the cost of chemotherapy. Besides, as it can be seen in Fig. 4, under the work of the anticancer drug, tumor cells will be gradually killed by the input drug. Since the value of $\bar{x}_1$ is negatively correlated with the number of tumor cells, the value of the conversion variable $\bar{x}_1$ will gradually increase with the decreasing of tumor cells. And when Dexrazoxane is not used, the value of $\bar{x}_1$ increases step by step and changes relatively slowly. But when Dexrazoxane is used, the value of $\bar{x}_1$ increases in the same straight-line trend no matter how effective Dexrazoxane is. It can be seen from the above that as long as there is the effect of Dexrazoxane in the process of chemotherapy, tumor cells can be reduced to a greater extent regardless of its efficacy.

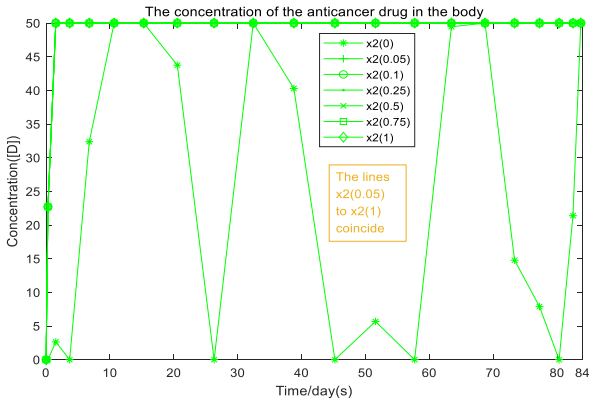

Fig. 5. Concentration curves of the anticancer drug in cancer chemotherapy optimization under different efficacy rates.

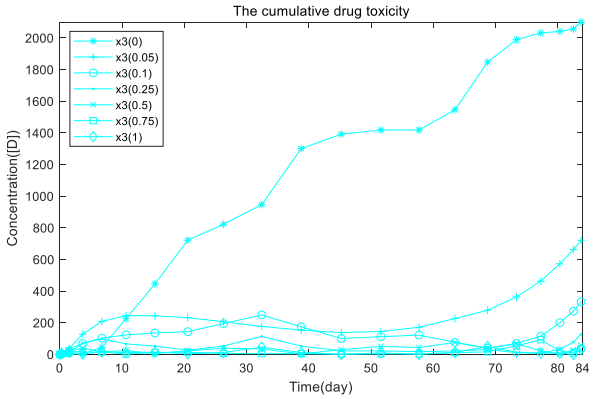

Fig. 6. Concentration curves of the cumulative drug toxicity in cancer chemotherapy optimization under different efficacy rates.

Meanwhile, results in Fig. 5 reveal that when Dexrazoxane works, the concentration of the anticancer drug in the body is basically maintained at about 50 [D], while without the work of Dexrazoxane, the overall concentration of the anticancer drug in the body is less than 50 [D], which indicates that the effect of Dexrazoxane will increase the overall concentration of anticancer drugs in the body.

Furthermore, as it can be seen from Fig. 6, the cumulative drug toxicity increases rapidly with the increase of time and reaches 2100 [D] at the end of treatment when $\theta = 0$. While, with introducing Dexrazoxane, a relatively stable change trends of toxicity occur with the increase of time, and no matter how effective Dexrazoxane is, the final cardiotoxicity is less than 800 [D]. Based on above findings, even a weak efficacy rate of the toxicity reduction drug can still result better cancer chemotherapy property, revealing that the improved model has a very significant effect on reducing the tumor size and inhibiting drug toxicity. Numerical simulation of this work has a very positive effect on the development of cancer chemotherapy in the future.

6. Conclusion

In this work, an improved optimal drug scheduling model with considering the anticancer drug scheduling and toxicity reducing. Gauss pseudospectral method is employed for cancer chemotherapy to achieve the least cancer cell and the least drug toxicity simultaneously after chemotherapy by changing the dosage of the anticancer drug and the toxicity-reducing drug. There are two main novel concepts contributed by this work: 1) an improved optimal drug scheduling model of cancer chemotherapy is proposed, where the Dexrazoxane drug is introduced as the second input in the improved model to reduce cancer cell and drug toxicity simultaneously; 2) optimization treatment strategies of drugs under 7 different toxicity reduction efficiency rates are studied to verify the performance of the proposed model by employing Gauss pseudospectral optimization method. Numerical test results reveal that 66.54% improvement of performance index is achieved when compared with the traditional model and drug toxicity that have not been dealt with by predecessors are greatly reduced. This is a great progress for the optimal drug scheduling of cancer chemotherapy, and plays a great positive role for the future cancer chemotherapy. Meanwhile, the research finding provides a good reference for further study of the toxicity reduction efficiency of Dexrazoxane in the treatment. The current limitations of this study include the temporary lack of clinical trials to verify the clinical effectiveness of the drug delivery strategy proposed in this study. In addition, the precise pharmacodynamic value of Dexrazoxane in the model also needs to be determined by the clinical experiment combined with the simulation results in the study. Therefore, conducting preclinical experiments of the developed model to verify the drug delivery strategy will be

the further work. Also, using specific efficacy rate of Dexrazoxane with clinical complex conditions in the improved optimization model will be considered in the future studies. Besides, the uncertainty analysis and sensitivity analysis of the proposed drug scheduling model will be conducted in our further research.

Author contribution statement

Ping Liu: Conceived and designed the experiments; Wrote the paper.
Qi Xiao: Performed the experiments; Wrote the paper.
Shidong Zhai; Hongchun Qu: Analyzed and interpreted the data.
Fei Guo; Jun Deng: Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] N. Bazrafshan, M.M. Lotfi, A finite-horizon Markov decision process model for cancer chemotherapy treatment planning: an application to sequential treatment decision making in clinical trials, Ann. Oper. Res. 295 (1) (2020) 483–502.
[2] W. Nan, L. Rong, J. Juan, S. Xi, Response and prognosis of taxanes and anthracyclines neoadjuvant chemotherapy in patients with triple-negative breast cancer, J. Cancer Res. Clin. Oncol. 137 (10) (2011) 1505–1510.
[3] I. Hrynchak, E. Sousa, M. Pinto, V.M. Costa, The importance of drug metabolites synthesis: the case-study of cardiotoxic anticancer drugs, Drug Metabol. Rev. 49 (2) (2017) 158–196.
[4] R.B. Martin, Optimal control drug scheduling of cancer chemotherapy, Automatica 28 (6) (1992) 1113–1123.
[5] R. Luus, F. Hartig, F.J. Keil, Optimal drug scheduling of cancer chemotherapy by direct search optimization, Hung. J. Ind. Chem. 23 (1) (1995) 55–58.
[6] J.R. Banga, E. Balsa-Canto, C.G. Moles, A.A. Alonso, Dynamic optimization of bioprocesses: efficient and robust numerical strategies, J. Biotechnol. 117 (4) (2005) 407–419.
[7] Y. Liang, K.S. Leung, T.S.K. Mok, Fast drug scheduling optimization approach for cancer chemotherapy, in: Computational Science – ICCS 2007, Lecture Notes in Computer Science), 2007, pp. 1099–1107.
[8] L. Dong, L. Gao, Optimal control problems with incomplete and different integral time domains in the objective and constraints, Nonlinear Dynam. 78 (4) (2014) 2883–2895.
[9] R. Danesi, S. Fogli, A. Gennari, P. Conte, M.D. Tacca, Pharmacokinetic-pharmacodynamic relationships of the anthracycline anticancer drugs, Clin. Pharmacokinet. 41 (6) (2002) 431–444.
[10] S. Fu, C. Wei, W. Zheng, S. Bo, H. Ning, L. Jun, et al., Protection effect of Dexrazoxane on anthracycline induced cardiotoxicity in rats, Med. J. Wuhan Univ. 37 (5) (2016) 730–733.
[11] N. Pachauri, J. Yadav, A. Rani A, V. Singh, Modified fractional order IMC design based drug scheduling for cancer treatment, Comput. Biol. Med. 109 (2019) 121–137.
[12] B. Panjwani, V. Singh, A. Rani, V. Mohan, Optimum multi-drug regime for compartment model of tumour: cell-cycle-specific dynamics in the presence of resistance, J. Pharmacokinet. Pharmacodyn. 48 (4) (2021) 543–562.
[13] M.E. Karar, A.H. El-Garawany, M. El-Brawany, Optimal adaptive intuitionistic fuzzy logic control of anti-cancer drug delivery systems, Biomed. Signal Process Control 58 (2020), 101861.
[14] C. Swanton, M. Marani, O. Pardo, P.H. Warne, G. Kelly, E. Sahai, et al., Regulators of mitotic arrest and ceramide metabolism are determinants of sensitivity to paclitaxel and other chemotherapeutic drugs, Cancer Cell 11 (6) (2007) 498–512.
[15] J.H. Goldie, A.J. Coldman, A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate, Cancer Treat Rep. 63 (11–12) (1979) 1727.
[16] Y.M. Agamawi, A.V. Rao, CGPOPS, A C++ software for solving multiple-phase optimal control problems using adaptive Gaussian quadrature collocation and sparse nonlinear programming, ACM Trans. Math Software 46 (3) (2020) 1–38.
[17] M. Nategh, B. Vaferi, M. Riazi, Orthogonal collocation method for solving the diffusivity equation: application on dual porosity reservoirs with constant pressure outer boundary, J. Energy Resour. Technol. 141 (4) (2019), 042001, 1-042001.9.
[18] M.K. Oshagh, M. Shamsi, Direct pseudo-spectral method for optimal control of obstacle problem – an optimal control problem governed by elliptic variational inequality(Article), Math. Methods Appl. Sci. 13 (2017) 4993–5004.
[19] B.A. Conway, Survey of methods available for the numerical optimization of continuous dynamic systems, J. Optim. Theor. Appl. 152 (2) (2012) 271–306.
[20] L. Ping, L. Gao, W. Ping, L. Dong, X. Long, Y. Jie, et al., Control variable parameterisation with penalty approach for hypersonic vehicle reentry optimisation, Int. J. Control 92 (3) (2018) 1–25.
[21] L. Gao, H. Ting, G. Zhi, X. Peng, Z. Yin, W. Hai, et al., A robust cutting pattern recognition method for shearer based on least square support vector machine equipped with chaos modified particle swarm optimization and online correcting strategy, ISA (Instrum. Soc. Am.) Trans. 99 (2020) 199–209.
[22] W. Kang, Rate of convergence for the Legendre pseudospectral optimal control of feedback linearizable systems, J. Control Theor. Appl. 8 (4) (2010) 391–405.
[23] G.T. Huntington, A.V. Rao, Optimal reconfiguration of spacecraft formations using the Gauss pseudospectral method, J. Guid. Control Dynam. 31 (3) (2008) 689–698.
[24] L. Zhang, H. Gao, Z. Chen, S. Lin, Z. Hui, Multi-objective global optimal parafoil homing trajectory optimization via Gauss pseudospectral method, Nonlinear Dynam. 72 (1) (2012) 1–8.
[25] L. Ping, L. Yu, L. Gao, H. Qing, An improved smoothing technique-based control vector parameterization method for optimal control problems with inequality path constraints, Optim. Control Appl. Methods 38 (4) (2017) 586–600.
[26] L. Ping, H. Qing, L. Jun, F. Li, L. Yu, L. Gao, Optimization operation of electric locomotive based on two-stage adaptive Gauss re-collocation pseudospectral approach, Acta Autom. Sin. 45 (12) (2019) 2344–2354.
[27] L. Xiao, J. Ying, L. Gao, L. Ma, An effective simultaneous approach with variable time nodes for dynamic optimization problems, Eng. Optim. 49 (10) (2017) 1761–1776.

[28] F. Li, L. Ping, H. Teng, Q. Qing, P. Jing, Design of LQR tracking controller combined with orthogonal collocation state planning for process optimal control, IEEE Access 8 (2020) 223905–223917.
[29] R. Loxton, K.L. Teo, V. Rehbock, Robust suboptimal control of nonlinear systems, Appl. Math. Comput. 217 (14) (2011) 6566–6576.
[30] M. Heinkenschloss, D. Ridzal, A matrix-free trust-region SQP method for equality constrained optimization, SIAM J. Optim. 24 (3) (2014) 1507–1541.
[31] K.F. Bloss, L.T. Biegler, W.E. Schiesser, Dynamic process optimization through adjoint formulations and constraint aggregation, Ind.eng.chem.res. 38 (2) (1999) 421–432.
[32] K. In-Ho, L.J. Eun, Y. Ho-Joong, B.J. Song, C.B. Joo, Cardioprotective, Effect of Dexrazoxane in patients with HER2-positive breast cancer who receive anthracycline based adjuvant chemotherapy followed by trastuzumab, J.Breast Cancer 20 (1) (2017) 82–90.