Optimal Control for Cancer Chemotherapy using Genetic Algorithm

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Abstract: Chemotherapy is known as a useful method to reduce or eliminate the several residual diseases such as various types of cancers. In this way, the objective is to maximize the likelihood that the cancer will be eliminated. Classic optimization methods to determine the chemotherapy regime has been used for various types of cancers for many years ago. These methods usually use deterministic model for cancer and tumor growth provided chemotherapy protect. In recent year a new stochastic model of chemotherapy with cell sensitive to drugs include normal system growth functions has been proposed. This is cause to repaying new visits to chemotherapy and conventional treatment. An important result of this scheme is broken equivalent drug scenario treatment regime. In this paper, we solve an optimization problem using global optimization algorithm, GA (Genetic Algorithm) and compare this results with the previous optimization scheme, which has been referred in [4]. Non-equivalent drug delivery, which given from GA optimization has better effect on cure probability than equivalent drugs.

Key words and phrases: Stochastic optimal control, Chemotherapy, Genetic Algorithm (GA), Breast cancer.

1 Introduction

The addition of chemotherapy as an effective modality for the treatment of cancer over the past 30 years has had a significant impact upon the mortality and morbidity of the disease. Unfortunately, not all types of cancer are sensitive to one or more of the available anticancer drugs and those types show resistance too many of drugs. This senility is variant between individuals and over time. The characterization and causes of resistance has been an active area of oncologic research. Various diverse mechanisms of resistance have been identified which may relate to the architecture and location of the tumor, the pharmacokinetic characteristics of the host and the ability of the individual tumor cells to absorb, metabolism and excrete drugs. Research has shown that genetic changes may confer resistance to specific drugs by altering protein products necessary for the activation or effect of the drug or to classes of drugs by changing proteins associated with drug influx or efflux. Experiments show that random mutational changes as being the origin of these genetic changes. It is believed that the observed high frequency of these alterations is associated with genomic instability that is a characteristic of cancer and is a result of the nature of the steps that lead to cancer [1]. Several authors have attempted to quantitatively model the response of cancer to chemotherapy assuming that resistance can be present and that it is produced by random mutations. Typically they have used a birth and death model for tumor growth and assumed that resistant cells arise at a constant frequency in proportion to the division rate of the tumor cells.

Other authors, such as [3] are incorporated all treatments as instantaneous effects and the effect of different strategies are summarized in the probability of cure, which is the long term likelihood of the tumor being eliminated. The resulting models provide predictions that agree with results from a variety, but certainly not all, of experimental systems.

In [4] combine a dynamical model for the repopulation of the normal system with stochastic models of tumor growth, and developed this model to resistance and the likelihood of life threatening toxicity.
We use the presented model in [4] that simulate clinical data from the treatment of breast cancer, and re-analyze previous theoretical calculations to reach the result of optimal control then solve stochastic optimal problem using GA and introduce new control for anticancer drugs. In section two of the paper, stochastic model for malignant population and normal population proposed and in third section we solve the optimization problem uing stochastic method, then in section four, GA

will introduced and interested problem will be solved using Genetic Algorithms.

2 Modeling and Formulation:

1.1 The stochastic model for malignant population:

We consider a situation where two active drugs are available. Tumor cells may be in one of four mutually exclusive states defined by sensitivity to the drugs T_1 and T_2: R_0 (sensitive to both drugs), R_1 (resistant to T_1 and sensitive to T_2), R_2 (resistant to T_2 and sensitive to T_1) or R_3 (resistant to both drugs). Let $R_i(t)$ be the number of cells in the ith compartment at time t. Each compartment is assumed to grow with the kinetics of a pure birth process with compartment specific rates $b_i(t)R_i(t)$, $i = 0,1,2,3$. Transitions are assumed to occur between compartments with a constant probability per division, α_{ik} , where i is the index of the originator state and k is the destination state. Each tumor cell is assumed to obey the log-kill law in its response to drugs in which the log of the probability of cell survival P_D is proportional to the drug dose, i.e.,

$$\ln(P_D(d_k)) = \ln(P\{\text{tumor cell survival}\}) = -\rho_{ik} d_k \quad (1)$$

where d_k is the dose of drug T_k, $k = 1,2$ and ρ_{ik} is the parameter for drug T_k in cells of type i. In what follows, we will assume we have available treatment times, t_j , $j = 1,...,N$ on a scale where $t = 0$ represents the time the tumor developed (1 cell). The probability that the tumor is cured at time t is taken to be equivalent to the probability that there is no tumor cells alive, i.e. ,

$$P\{R_0(t) = 0,\ R_1(t) = 0, R_2(t) = 0, R_3(t) = 0\} = P\{R(t) = 0\}$$

If $\Psi_{R(t)}(s)$ is the probability generating function (PGF) of the process $R(t)$ then

$$P\{R(t) = 0\} = \Psi_{R(t)}(0) \quad (2)$$

Thus if we can calculate the PGF we can obtain the required probability by evaluating it at a particular point $s = 0$. We can obtain an expression for this PGF by using the well-known relationship that if Y_i , $i = 1,2,...$ are independent identically distributed integer valued stochastic processes and N is another independent integer valued process, then the process

$$Z = \sum_{n=1}^{N} Y_n \quad (3)$$

Y_n has PGF given by

$$\Psi_Z(s) = \Psi_N(\Psi_Y(s)) \quad (4)$$

where $\Psi_N(s)$ and $\Psi_Y(s)$ are the PGFs of N and Y. In particular we have that the PGF after treatment at time t, is given by the PGF prior to treatment at time t^- evaluated at a point given by the PGF of the effect of treatment on a single cell, i.e.,

$$\Psi_{R(t)}(s) = \Psi_{R(t^-)}(\Psi_s(s)) \quad (5)$$

where

$$\Psi_s(s) = 1 - P_D(d) + sP_D(d)$$

and $P_D(d)$ is given by Eq. (1). Similarly if we use G(t) to designate the process of growth and transformation (into resistant types) of a single cell present at t=0 then we have

$$\Psi_{R(t_2)}(s) = \Psi_{R(t_1)}(\Psi_{G(t_2-t_1)}(S)) \quad (6)$$

for a period $(t_1, t_2]$ when no treatments are given. The usual method for ending Ψ_G (use of forward and backward equations) results in a series of differential equations which have no obvious general solution for the process described although useful special solutions have been found. This result extended to apply to a larger class of birth processes that include filtered Poisson processes calculated Ψ_G which, growth is assumed to follow a stochastic Gompertzian process [5]. The following theorem shows this extension.

1.2 Theorem:

Let $B(t)$ be a birth process with rates $b_n(t) = nb(t)$, where $B(0) = 1$. At each birth (transition) a signal $Y_n(t, \tau_n)$ is generated where $\tau_n \in [0,t]$ is the time of

transition from n to $n+1$. Also a signal $Y_0(t)$ is generated regardless of the number of transitions (which may be viewed as associated with a transition from 0 to 1 at time $t=0$). $B(.)$ and $Y_n(.)$ are assumed mutually independent and the $Y_n(.)$ $(n \geq 0)$ are identically distributed. Define

$$Z(t) = \sum_{n=1}^{B(t)} Y_{n+1}(t, \tau_n) \tag{7}$$

then the PGF of $Z(t)$ is given by

$$\Psi_{Z(t)}(s) = E[s^{Y_0(t)}][\frac{P(t)}{1-I(s;t)}] \tag{8}$$

where

$$P(t) = \exp[-\int_0^t b(u)du] \tag{9}$$

and

$$I(s;t) = \int_0^t E[s^{Y(t,v)}]b(v)[\exp(-\int_v^t b(u)du)]dv \tag{10}$$

The proof of this theorem is in [4].

1.3 The stochastic model for normal population:

Both drugs are assumed to have unwanted dose dependent toxic effects on one or more normal systems. This will be summarized in a single variable X which is equal to the logarithm of the size of the critical normal population which is assumed to re-populate following a Gompertzian form of growth, i.e.,

$$x(t) = x_\infty - (x_\infty - x_s)e^{-k_1 t} \tag{11}$$

where x_s is the asymptotic size, k_1 a growth parameter and t is the elapsed time from when the system was of size x_∞. If the normal system is perturbed, then its re-growth is described by the same equation. The anticancer drugs T_k are assumed to perturb the normal system, indicated by Δx, following a log-kill law so that

$$\Delta x = -\rho_{xk} d_k \tag{12}$$

In attempting to model clinical cancer the important outcome associated with the effect of chemotherapy on the normal tissue is the occurrence of a toxic event. The toxic event can represent a variety of situations. As well as the most drastic, death of the patient, it can also typify a medical outcome such as kidney failure or neurological damage, that the therapist is trying to avoid. On a more basic level it denotes any outcome that causes the cessation of treatment. This variety of meanings can be affected by appropriate choices of the parameters in Eqs. (8) and (9).

A commonly used model for the probability of a specific binary toxic [17] (or therapeutic) effect, P_T, of single doses of a drug is the logistic function, i.e.,

$$P_T(d_k) = 1 - [1 + e^{\beta_0}][1 + e^{\beta_0 + \beta d_k}]^{-1} \tag{13}$$

where β_0 and $\beta > 0$ are constants. We may combine Eqs. (12) and (13) to provide a formula relating changes in the level of the normal system from its physiologic value to the probability of a toxic event, i.e.,

$$P_T(\Delta x) = 1 - [1 + e^{\beta_0}][1 + e^{\beta_0 - \beta \Delta x}]^{-1} \tag{14}$$

We assume in Eq. (14) that the determinant of the likelihood of toxicity is only influenced by the net kill on the normal system of the drug and not by which drug is used. One of the characteristics of cancer chemotherapy is that normal systems are being repeatedly perturbed by the ongoing sequential application of therapy and may not return to their physiologic values during the course of therapy. We may utilize the parameterization of Eq. (14) to model this situation as follows. If $x(t^-)$ is the size of the normal system prior to the administration of a drug dose at time t and $x(t)$ is the size after (as given in Eq. (11)), then the probability of a toxic event associated with this dose is given by

$$\begin{aligned} P_T(t) &= P_T(x(t) - x_\infty) - P_T(x(t^-) - x_\infty) / \\ &(1 - P_T(x(t^-) - x_\infty)) \\ &= 1 - (1 - \exp[\beta_0 + \beta(x_\infty - x(t^-))]) / \\ &(1 - \exp[\beta_0 + \beta(x_\infty - x(t))]) \end{aligned} \tag{15}$$

Eq. (15) provides an expression for the probability of toxicity conditional on no preceding toxic event. Using Bayes theorem we may simply calculate the

cumulative probability of a toxic event, $CUMP_T(t)$, from

$$CUMP_T(t_j) - CUMP_T(t_j^-) = P_T(t)\left[1 - CUMP_T(t_j^-)\right] \quad (16)$$

with the condition $CUMP_T(t_1^-) = 0$

In the next section stochastic models for malignant population and normal population are combined and an optimization problem with necessary condition for no toxicity will proposed.

1.4 Optimization problem:

Different objectives can be used that each combines the features of maximizing probability of cure while minimizing toxicity. Here we achieve this by maximizing the probability of uncomplicated control,

P(no toxicity) * P(tumor is cure) =

$$= (1 - CUMP_T(t_N) \times P\{R(t_N) = 0\}, \quad j = 1,...,N \quad (17)$$

The first term in Eq. (17) is determined from Eq. (16) with the change in the normal population Δx being given by

$$\Delta x(t_j) = -\rho_{x_1} d_1(t_j) - \rho_{x_2} d_2(t_j) \quad (18)$$

The second term in Eq. (17) is determined from Eq. (2) where the PGF Ψ_R is evaluated at $s = 0$ for $t = t_N$. The PGF Ψ_R, is calculated using repeated applications of Eq. (3) and combines the individual PGFs, Ψ_G Eq. (6)of growth and mutation between drug applications and Ψ_S at drug application, i.e.,

$$\Psi_{R(t_N)}(0) = \Psi_{G(t_1-0)}(\Psi_{S(t_1)}(\Psi_{G(t_2-t_1)}(...\Psi_{S(t_N)}(0))...) \quad (19)$$

Let D denote the vector of all drug choices for the fixed treatment times t_j, $j = 1,...,N$,

$$D = [d_1(t_1),...,d_1(t_N), d_2(t_1),...,d_2(t_N)] \quad (20)$$

Choosing the drug regimen that achieves the best response in terms of our objective, Eq. (17), is equivalent to the optimization problem:

$$\text{maximize } f_0(D) \quad \text{subject to } g_k(D) \le 0 \quad k = 1,...,K \quad (21)$$

where f_0 is the function in Eq. (17) and the g_k describe any explicit constraints on the drug regimen. For our problem we will restrict D so that

$$CUMP_T(t_N) \le C_{tox} \quad (22)$$

C_{tox} denotes any explicit limits on toxicity, apart from the implicit ones within the objective function Eq. (17), that the clinician may wish to impose. A large value for this parameter effectively removes this constraint and the objective becomes the maximization of uncomplicated control as described earlier. On the other hand the best regimen determined by maximization of Eq. (17) may prescribe a level of toxicity that is unacceptable for certain practical reasons. In this case a value of C_{tox} can be set that will ensure any regimen returned by the maximization of Equation (21) in conjunction with Equation (22) will satisfy any additional constraints.

1.5 Simulation 1:

The problem (17) was solved and optimized based on method which has been referred in [4] with medical information for optimal scheduling of two drugs.

Fig. 1 shows the optimal regimen for equivalent drugs, and expected cell component responses was shown in Fig. 2.

Tumor cell comportments are R_0, R_1, R_2 and R_3, The curve of R_0 was shown that sensitivity to both drugs, decrease, R_1 and R_2 curves were shown sensitivity to T_1 and T_2 was decrease. Another discussion in figure 2, fourth curve R_3 was increasing and resistant cells to both drugs will be raise. This chooses of parameters produced estimated probability of care of 0.45 with .025 probability toxicity.

3 Optimization with GA:

3.1 Introduce GA:

Genetic Algorithm (GA) emerged out of early attempts at modeling evolution on a computes. The use GA for solving optimization problems started around the end of the 1960, but grows dramatically

in popularity following the publication of adaptation on natural and artificial systems by john Holland [6]. GA is an important global optimization method for complex problems. This algorithm is a numerical searches algorithm. This algorithm produces similar natural live existent and genetic systems. For solving an optimization problem with GA at first generate a primary population, which selected randomly, and then introduce a fitness function as a performance function then minimization started that coming as follow.

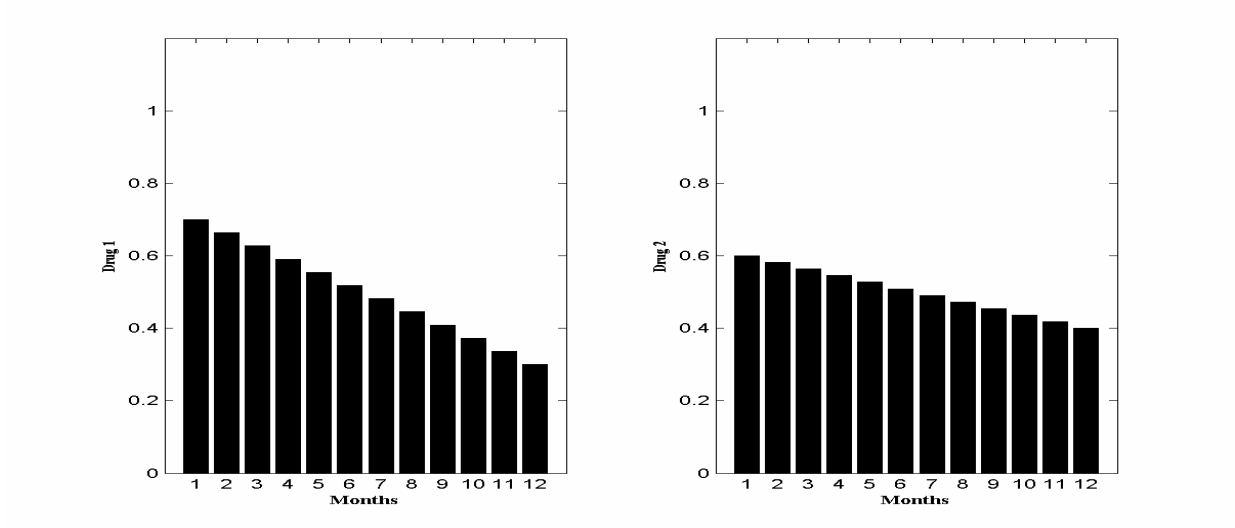

Figure 1- Optimal regimen for equivalent drugs (per month)

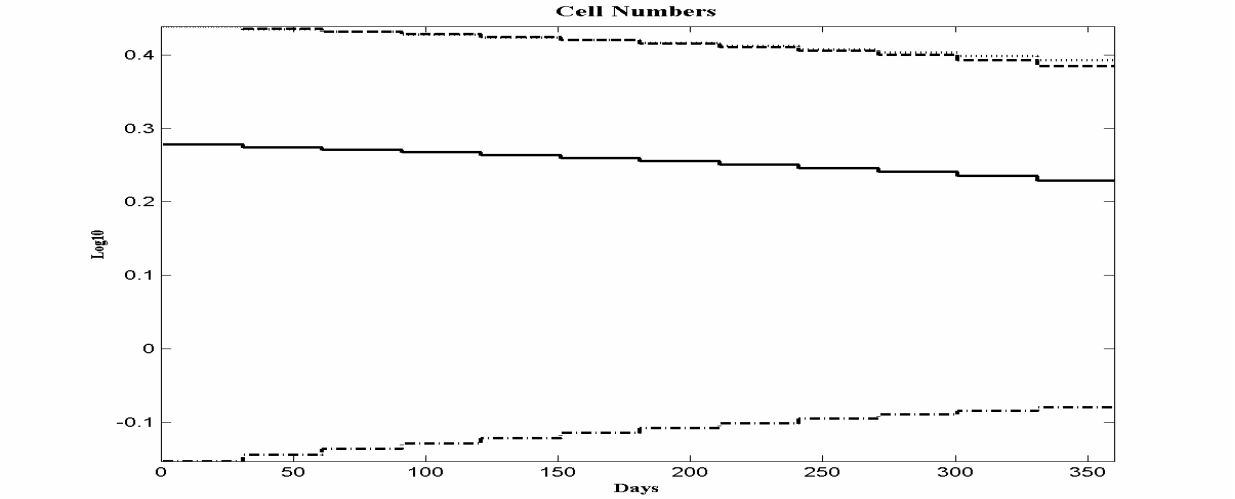

Figure 2- Expected cell component responses of tumor cell comportments $R_0 -$, $R_1 \cdots$, $R_2 --$ and $R_3 - \cdot$

3.2 GA operation and components:

GA including special operators and suitable and right working this is related to this operators and components which we referred to those in this subsection very compactly. The distinguishing feature GA as an optimization tool is that it introduces an additional move into the move-set, namely crossovers. This requires these to be a population. In the space of strings, it is a non-local move since the child need not be close to either of the parents' strings. Such non-local moves can significantly us reduce the problem of local-minima. Crossover does not make a large jump in search space.

Introducing a new move namely mutation in to the move-set will reduce the problems of local minima, However, if the probability of the move being beneficial is very small the move many be of little use. In the extreme limit a random move will removes all local minima but at the same time

reduces the search to a random search. Mutation makes a large jump in search space.

In the classic GA, a population is generated at random and acted upon iteratively by these evolution operators: selection, mutation and crossover. The algorithm is below:

1- start
2- creation initial population
3- fitness evaluation
4- selection of parents
5- generate new child from selected parents by crossover and mutation
6- termination condition evaluation
7- if yes terminate and go to step 8 otherwise if no go to step 3
8- stop

3.3 Simulation 2:

Another way for solving optimization problem (17) is using GA .The fitness function of this algorithm selected so that minimizes objective function with satiety toxicity conditions. We choose the fitness function as follow

fitness function
= f(no toxicity) * g(cure tumor) (2
$= (1 - CUMP_T(t_N)) \times P\{R(t_N) = 0\} \quad j = 1,...,N$ 3)

Chromosomes select similar (20) contains drugs values during chemotherapy pried. Primary population selected 50 and 1000 iteration for medical information [4].

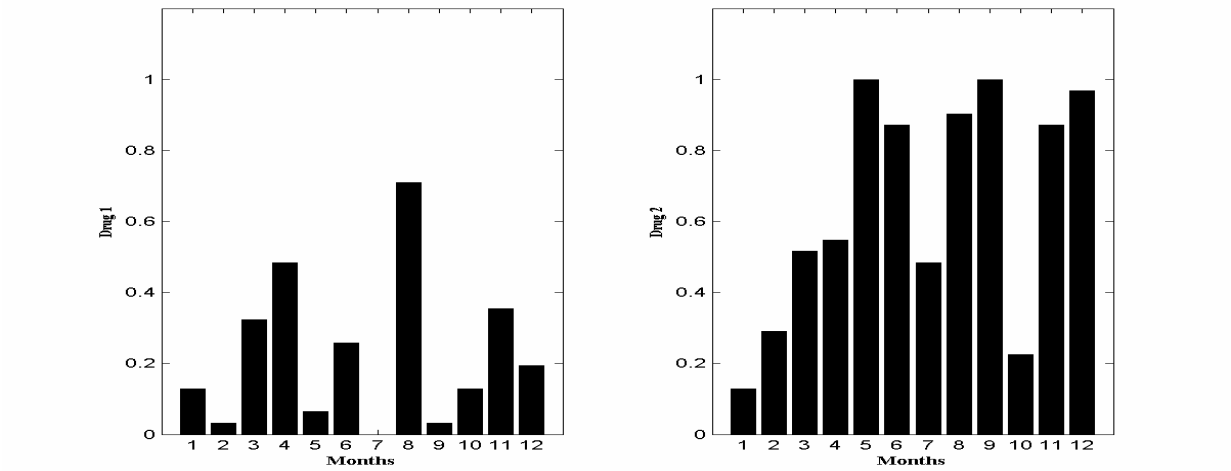

Figure 3- Drugs scheduling with GA optimization (per month)

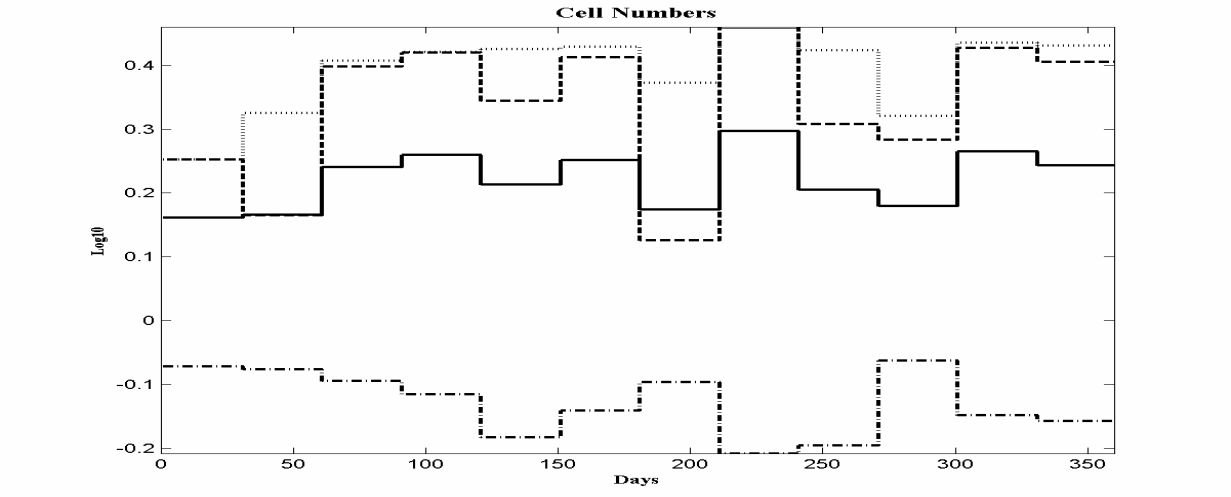

Figure 4- Expected cell component responses of tumor cell comportments $R_0 -$, $R_1 \cdots$, $R_2 --$ and $R_3 - \cdot$

Simulation results are shacked to Fig. 3 and Fig. 4. Fig. 3 shows drugs scheduling in each chemotherapy period, and expected response of different tumor cell components has been shown in Fig. 4. Tumor cell comportments are R_0 , R_1 , R_2 and R_3 , The important note in this figure comparing with figure 2 is curve R_3 , this response was almost constant every where and resistant cells to both drugs don't increase. Cure probability for this case is 0.64 and toxicity probability is 0.025.

3 Conclusion:

In this research, we re-analyzed proposed scheme in [4] for modeling and for mutation chemotherapy based on stochastic model. Then solve this problem for search optimal regimen of drugs scheduling by numerical methods. We used GA as a powerful tool in complex functions optimization. The GA optimization results compared with the results of reference [4]. Non-equivalent drug delivery has given from GA optimization. The simulation results show non-equivalent drug delivery has a better effect and a better performance on cure probability than equivalent drugs.

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