Periodic Chemotherapy Dose Schedule Optimization Using Genetic Algorithm

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Abstract. This paper presents a design method for optimal cancer chemotherapy schedules using genetic algorithm (GA). The main objective of chemotherapy is to reduce the number of cancer cells or eradicate completely, if possible, after a predefined time with minimum toxic side effects which is difficult to achieve using conventional clinical methods due to narrow therapeutic indices of chemotherapy drugs. Three drug scheduling schemes are proposed where GA is used to optimize the doses and schedules by satisfying several treatment constraints. Finally, a clinically relevant dose scheme with periodic nature is proposed. Here Martin's model is used to test the designed treatment schedules and observe cell population, drug concentration and toxicity during the treatment. The number of cancer cells is found zero at the end of the treatment for all three cases with acceptable toxicity. So the proposed design method clearly shows effectiveness in planning chemotherapy schedules.

Keywords: Cancer Chemotherapy, Drug Scheduling, Mathematical Model, Optimization, Genetic Algorithm.

1 Introduction

Cancer is a class of diseases characterized by an imbalance in the mechanisms of cellular proliferation and apoptosis [1-2]. There are four major approaches to cancer treatment: surgery and radiotherapy as local treatments, chemotherapy and the use of biological agents (such as hormones, antibodies and growth factors). Traditional chemotherapeutic agents act by killing cells that divide rapidly, one of the main properties of cancer cells. Chemotherapy also harms other cells that divide rapidly: cells in the bone marrow, digestive tract, hair follicles. This causes common side-effects: myelosuppression (decreased production of blood cells, hence

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also immunosuppression), mucostisitis (inflammation of the lining of the digestive tract), and alopecia (hair loss). Chemotherapy treatment schedule, defined as dose amount and frequency is needed to be conveniently chosen to reduce the number of cancer cells after a number of fixed treatment cycles with acceptable/minimum toxic side effects. Researchers have designed optimal drug schedules of cancer chemotherapy and developed mathematical models to predict tumor growth. Evolutionary algorithms have been employed to design the chemotherapy drug scheduling for cancer treatment [3-6]. Considering clinical limitations in maintaining continuous treatment and giving emphasis on clinical relevance and patient's comfort, this paper presents a design method of optimal cancer chemotherapy treatment schedules where genetic algorithm (GA) is used to optimize drug doses and intervals by minimizing treatment main objective (cancer cells) and satisfying other key objectives.

2 Mathematical Model, Design Objective and Constraints

Here we consider a mathematical model (Equations 1 –7), originally developed by Martin and Teo in [1] that accounts for a tumor proliferating in Gompertzian fashion along with therapeutic and toxicity effects of intravenous administration of drug.

$$\dot{C}(t)=D(t)-C(t) \tag{1}$$

$$\dot{N}(t)=\frac{1}{\tau_g}\left[\frac{\ln\left(\frac{\rho_g}{N_0}\right)}{\ln\left(\frac{\rho_g}{2N_0}\right)}\right]N(t)\ln\left(\frac{\rho_g}{N(t)}\right)-k_{eff}C_{eff}(t)N(t) \tag{2}$$

$$C_{eff}(t)=(C(t)-C_{th})H(C(t)-C_{th}) \tag{3}$$

$$H(C(t)-C_{th})=\begin{cases}1, & if\ C(t)\geq C_{th}\\ 0, & if\ C(t)<C_{th}\end{cases} \tag{4}$$

$$C(0)=C_0=0 \tag{5}$$

$$N(0)=N_0 \tag{6}$$

$$\dot{T}(t)=C(t)-\eta T(t) \tag{7}$$

Eqn 1 gives the pharmacokinetics of drug. The plasma drug concentration, $C(t)$ increases with intravenous infusions of the drug, $D(t)$, and decreases according to first–order elimination kinetics at a rate λ. Equation 2 gives the number of cancer cells proliferating in a Gompertzian fashion and the therapeutic effect of the drug on the tumor is represented by adding a negative bilinear kill term to the tumor growth equation. Here ρ_g is the asymptotic plateau population, N_0 is the initial number of tumor cells, τ_g is the first doubling time of the tumor during exponential growth [1]. The bilinear term is proportional to both the current size of the tumor, $N(t)$ and the effective drug plasma concentration, $C_{eff}(t)$ with constant of proportionality k_{eff} [1]. k_{eff} is called the fractional kill term per day of the drug. $C_{eff}(t)$ is the drug concentration above the minimum therapeutic concentration, C_{th}, as given in equation 3. Equation 4 is a Heaviside step function that implies drugs may not become effective until a therapeutic plasma concentration is reached (C_{th}). The initial drug concentration and number of cancer cells are given by C_0 and N_0, respectively. Equation 7 gives the toxicity level in body after infusion of drugs where is η a constant [8]. The values of λ, τ_g, ρ_g, N_0, k_{eff}, C_{th} and η are respectively considered to be 0.27 days^{-1}, 150 days, 10^{12}, 10^{10}, 2.7×10^{-2} days^{-1}[D]$^{-1}$, 10[D] and 0.4 days^{-1} [1],[8]. Here [D] is a unit of dose concentration/mass. The model is implemented in Matlab/Simulink environment and used in following sections.

Here we considered three types of toxicity constraints. The drug concentration in plasma should not exceed maximum allowable level C_{max} and the measurement of toxicity must not exceed an acute level T_{max} stated by following inequalities 8 and 9

$$C(t) \le C_{\max}; \qquad \forall t \in [0, t_f] \tag{8}$$

$$T(t) \le T_{\max}; \qquad \forall t \in [0, t_f] \tag{9}$$

Total exposure of drugs in plasma is commonly calculated by integrating drug plasma concentration over the treatment must not exceed a value C_{cum} as in 10

$$\int_0^{t_f} C(t)dt \le C_{cum} \tag{10}$$

The values of C_{max}, T_{max} and C_{cum} are taken to be 50[D], 100[D] and 4.1×10^3[D].days [7,8]. Finally, the efficacy constraint limits the number of cancer cells not to surpass the initial condition, N_0. Which gives

$$N(t) \le N_0; \qquad \forall t \in [0, t_f] \tag{11}$$

Here we have used the optimal control problem considered by Martin and Teo in [1] to minimize cancer cell no. at a final time. It can be expressed as:

$$MIN_{D(t)}N(tf)\ \ s.t.(1-11) \tag{12}$$

In words, we have to design a chemotherapy schedule for 1 year to minimize the final number of cancer cell. The drug concentration should range between 10 and 50 and cumulative plasma drug concentration at the end of the treatment should be lower than a value 4.1×10^3. Finally, the cancer cell number should never exceed 10^{12}.

3 Optimal Chemotherapy Schedule Using GA

Genetic Algorithm (GA) is a stochastic global search method that replicates the metaphor of natural biological evolution [8]. Selection, crossover and mutation are its main operators. The fundamental element processed is a string formed by concatenating sub-strings, each of which is a numeric coding of a parameter. Each string stands for a solution in the search space. Performance of each solution is assessed through an objective function imposed by the problem and used in the selection process to lead the search towards the best individual. Crossover can cause to swap the properties of any two chromosomes via random decision in the mating pool and provides a means to produce the desirable qualities. Mutation is a random alternation of a bit in the string to keep diversity in the population. Here we propose three drug scheduling schemes, all planned for 364 days and GA is employed to find doses and intervals throughout the period.

Dose Pattern 1: Variable Interval Variable Dose (VIVD): In VIVD scheme, chemotherapy treatment will be administered to patients only first two days of each week depending on decision variable. For each week, decision variable is encoded with one bit; '1' to indicate that a patient will receive treatment on that week and '0' to indicate rest week, i.e, no drugs will be administered on that week. Giving clinical relevance, same drug doses are administered to patient treatment for first two days of any treatment week and one variable is required for each week. So, two variables are defined for each week; one for dose and one for decision. For a year (364 days = 52 weeks) long treatment plan, 52×2=104 variables are required and GA is used find an optimum solution set.

Dose Pattern 2: Fixed Interval Variable Dose (FIVD): In FIVD, interval between two consecutive treatments is fixed throughout the whole treatment period. Drugs are administered to patients on first two days of every 4^{th} week following a rest period of 26 days. For any treatment week, same doses are administered on first two days. So, only one control variable is required to define the dose level of any treatment week. For a total period of one year, treatments are given only in 52/4=13 weeks and a total of 13 variables are required in designing this dose pattern. Aiming clinical relevance and to meet treatment efficacy, a high dose, called bowl (dose level of 50[D]) is administered to a patient at the beginning of the treatment.

Dose Pattern 3: Periodic Dose: Like FIVD, drugs are administered on first two days of every 4^{th} week followed by a rest period of 26 days in this case. Unlike dose pattern 2, in any treatment week, different drug doses are administered on first two days and similar doses are followed in subsequent treatment weeks. As a result only two control variables are required to design treatment schedules for a year.

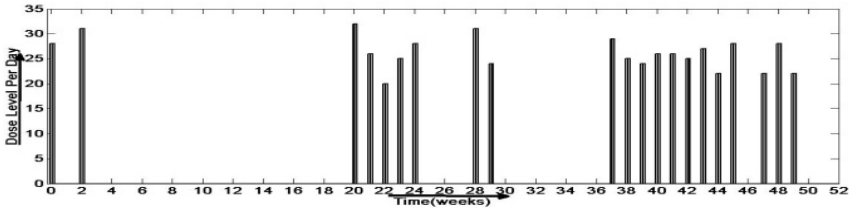
Encoding Scheme and GA Optimization Process: To design optimum dose pattern 1(VIVD), the GA optimization process begins with a randomly generated population called chromosome of size 50 × 676 where 50 is the number of individuals and 676((52×12)+(52×1)) is the length of the chromosome structure for 104 control variables. First 52 parameters are encoded as 12 bits binary strings which will define drug doses for each week while the remaining 52 parameters are encoded as 1 bit to define decision variables, i.e., whether treatment will be given to a patient. First 52 binary strings are converted into real numbers within a range of 10 to 50. Using each individual (solution), a chemotherapy drug schedule is designed for 1 year as discussed earlier and used as input $D(t)$ to the tumor model stated in Section 2. The model is simulated and several important output parameters: number of cells, drug concentration and toxicity are measured. The number of tumor cells at the end of treatment is used as objective function in GA optimization process. Before calculating fitness function, each individual is checked for constraints. If any of the constraint is not satisfied, that individual is penalized by adding a big penalty value so that it will have less chance to be selected for following generations. Once individuals are evaluated, fit individuals are selected through selection process to form the mating pool [8]. Genetic operators such as crossover, mutation and reinsertion are applied to form the new population for the next generation [8]. The crossover rate and mutation rate are set as 0.8 and 0.01 respectively. The maximum number of generations is set to 50. It is noted that, binary-coded GA is preferred and used in this optimization/design procedure because half of the control variable (=52) are binary-type decision variables represented by only single bit. GA with aforementioned parameters is run several times on the model. Table 1 gives a summary of the simulation results for five different runs.

Table 1 A summary of the simulation results of different runs for dose pattern 1

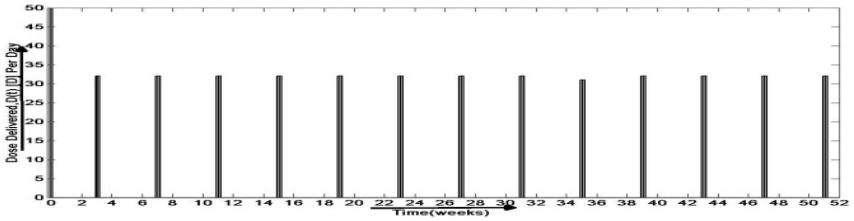
Run	Drug Dose		Drug Concentration		Toxicity		No. Cell at end	Cell Reduction
	Max	Avg	Max	Avg	Max	Avg		
1	32	10.7	49.4	11.2	83.4	27.7	≈ 0	≈ 100%
2	32	10.5	49.9	11.1	83.3	27.8	≈ 0	≈ 100%
3	32	10.6	49.5	11.2	81.3	27.9	≈ 0	≈ 100%
4	32	10.7	49.8	11.2	84.7	27.7	≈ 0	≈ 100%
5	32	10.7	49.9	11.2	82.2	27.7	≈ 0	≈ 100%

Table 2 Results of all three dose patterns

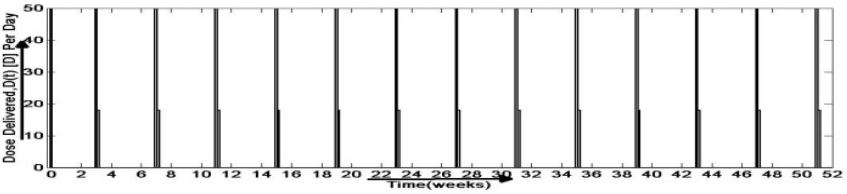
Scheme	Drug Dose		DrugConcentration		Toxicity		No. Cell at End	Cell Reduction
	Max	Avg	Max	Avg	Max	Avg		
VIVD (Run-1)	32	10.7	49.4	11.2	83.4	27.7	≈ 0	≈ 100%
FIVD	50	32.6	49.6	8.8	69.9	21.7	≈ 0	≈ 100%
Periodic	50	34.6	49.3	9.3	74.4	23	≈ 0	≈ 100%



(a) Dose pattern 1: Variable Interval Variable Dose Pattern.



(b) Dose pattern 2: Fixed Interval Variable Dose Pattern



(c) Dose pattern 3: Periodic dose pattern

Fig. 1 Different dose patterns

The minimum values of objective function out of the five runs are approximately same (see Table 1). Moreover, other performance measures, recorded and presented in Table 1, are also very close to one another. All these show repeatability and consistency of GA optimization process and the overall design procedure as well. Similar GA optimization process but with different number of control variables are used to design optimum treatment schedules for dose pattern 2 and dose pattern 3. Due to space constraints, like dose pattern 1, results of all runs for dose pattern 2 and dose pattern 3 are not shown here. Instead, results of best runs for dose pattern 2 and dose pattern 3 are provided against dose pattern 1(run-1) in

Table 2. The drug schedules obtained with corresponding runs for three dose patterns are shown in Figure 1.

For dose pattern 3 (see Figure 1(c)), a pre-decided constant dose concentration/mass of 50[D] on the 1st day of the treatment is applied to guarantee efficacy constraint. For every 4th week the dosing can be clearly seen to be periodic. Each 4th week is dosed with 50[D] on the 1st day followed by 18[D] on the 2nd day. The remaining days of a week are kept as rest period for the patient to recover from toxic side effects, if occur or tend to occur. Fig. 2 shows how the number of tumor cells reduces and finally reaches to approximately zero. Toxicity profile due to the dosing is displayed in Fig. 3 where it can be seen that the limiting value Tmax is never exceeded during the whole course of treatment.

It is relevant to mention that dose pattern 1: VIVD, highly lacks clinical and logical acceptability. We can call the solution mathematically optimal. But the plan requires too much information to record. As the dosing is at random weeks, a patient may forget to visit the clinic for administration. On the other hand, dose pattern 2: FIVD, leads towards logical and clinical relevance with its fixed dosing days (1st 2 days every 4th week), same level of doses for the two consecutive days of a week, an efficient resting period and a defined starting dose of 50[D] to meet efficacy constraint. 13 weekly dose levels/parameters calculated by applying GA in this scheme vary from 30 to 32 (Fig. 1(b)).

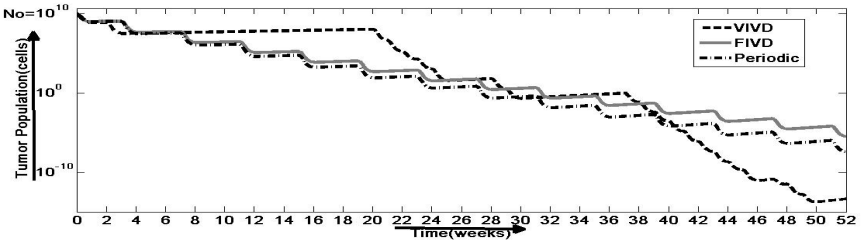


Fig. 2 Tumor cell population throughout the treatment period for all three dose patterns

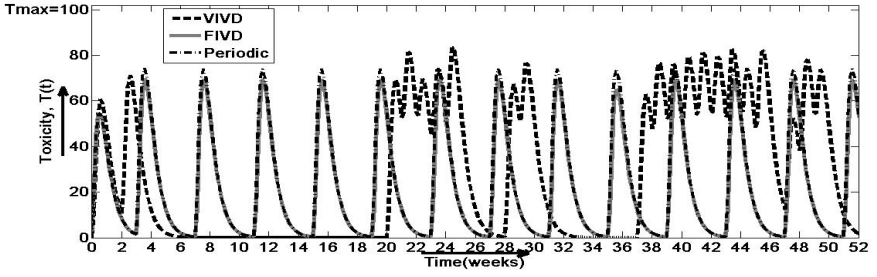


Fig. 3 Toxicity profile throughout the treatment period for all three dose patterns

If we compare FIVD and periodic pattern, both have same dosing days a, in the former, same level in two successive days are chosen, where in the latter we have used two separate levels. When FIVD is formulated, periodicity has not been imposed rather near periodicity is achieved from the 4^{th} week in the optimal result (negligible variation of dose levels). So for more simplification and clinical relevance, in our final step we have approached periodicity and proposed periodic dose pattern. Having two separate levels is just an additional variation to get a lower value of the objective function. The main feature of periodic pattern is it is highly simplified, clinically appropriate, but still effective.

4 Conclusion

This paper presents a optimal cancer chemotherapy schedule mothod using GA. All of the dose plans have successfully converged resulting in 100% elimination of cancer tumors without violating treatment constraints. More importantly, the maximum toxicity levels during the whole period of treatment remain lower than the maximum allowable value as indicated earlier and suggested by other researchers [1],[3],[8]. So the periodic dose plan can be preferred for clinical implementation. The proposed technique clearly demonstrates that 'GA with reliable tumor growth model' can help oncologists/clinicians in planning optimum chemotherapy drug scheduling besides conventional methods. Although multi-objective evolutionary algorithms can design different drug doses by trading of different conflicting treatment objectives, single-objective optimization process with efficient encoding and clearly defined constraints can also provide very satisfactory result. Moreover, personalized treatment schedules can also be obtained by adjusting model parameters depending on the physiological condition of the patient and state of the tumor. Furthermore, the same design method can be extended in planning multi-drug or combination chemotherapy regimen. Future work will include verification of the proposed scheduling with clinical data and efforts are underway in that direction.

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