Proceedings of the 17th World Congress
The International Federation of Automatic Control
Seoul, Korea, July 6-11, 2008

CHEMOTHERAPY USING LINEAR ANALYSIS AND SWARM INTELLIGENCE

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Abstract: In this paper, a linear analysis of Gompertz equation will be introduced. By applying the analysis and the Least Square Error (LSE) method, the estimation of nonlinear relation between the drug dosage and the initial and final number of cancer cells, after a specified treatment gap, is possible. The new method is applied in combination with swarm intelligence, to find an estimation of optimal treatment program for chemotherapy with various cost functions. The main advantage of the analysis is that it reduces the corresponding search space of the swarm.

Keywords: Drug delivery, Optimal control, Linear systems, Sum-of-squares, Swarm behavior, Artificial intelligence.

1. INTRODUCTION

The treatment of the tumoural diseases has a long history; usually a combination of various treatments is used. Chemotherapy is one of the important and effective medical treatments for patients (DeVita, *et al.*, 2005). The successfulness of a chemotherapy treatment depends on how the grade and the stage of the tumour is, type and the dosage of the drug and the duration of treatment gaps (DeVita, *et al.*, 2005, Ribba, *et al.*, 2005, Martin, 1992, Floares, *et al.*, 2003, Tarnawski, *et al.*, 2002). To improve the effect of the chemotherapy, simulating the growth and the response of a solid tumour to a specific treatment by mathematical models (Preziosi, 2003, Byrne, *et al.*, 2006a, b, Martin, 1992) and finding the best treatment program using optimal control methods, may have an important role (Martin, 1992, Floares, *et al.*, 2003, Swierniak, *et al.*, 2003).

The practicability of a suggested treatment, total drug dosage and total number of cancer cells during and at the end of the treatment, are important factors to evaluate a suggestion. It has been investigated that low intensity and distributed chemotherapy drug causes resistance of cells to the drug in compare with high intensity dosage in the same time (DeVita, *et al.*, 2005, Martin, 1992, Floares, *et al.*, 2003). In addition, it has been showed that long lasted treatment gaps, affected on the repopulation of cancer cells (Ribba, *et al.*, 2005, Tarnawski, *et al.*, 2002). Another important factor is side effect of the drugs. Because of toxic side effect of the dugs, the usual treatments are arranged corresponding to the necessary time for recovery of bone marrow (DeVita, *et al.*, 2005).

Although toxic constraints are considered by Martin (1992) and Floares, *et al.* (2003), the drug dosage regimens do not seem applicable. The constraints are considered only in the 84 days of treatment. However, the cytotoxic agents will be still active after the 84 days. Therefore, the corresponding constraint may not be satisfied after 84 days. As a result high-continues drug dosage at the end of 84 days, is not practicable. In order to ensure the recovery of the bone marrow, it might be better to schedule the treatment program with floating treatment gaps in which the minimum duration of the gap, depends on the type of the drug and lasts one week or more.

Because of discrete nature (Martin, 1992) and exponential explosion of dynamic programming approach, applying this method to find the best treatment program with floating treatment gaps, is impossible. To solve such problems, swarm intelligence might be a reliable choice (Zomaya, 2006).

For each particle of the swarm a reference trajectory of cancer cells, in 84 days of the treatment program, will be created randomly. In each trajectory, the duration of treatment gaps, the initial and final number of cancer cells of that duration are predetermined. To improve the performance of the swarm intelligence and make some reduction in its iterations, the final number of cancer cells at the end of the gap will be chosen less than the initial ones. A drug dosage which is needed to reach the final number of cancer cells in the specified time, should be calculated. This goal could be achieved using some linear analysis and algebraic methods. By using a linear analysis, the nonlinear relation between the drug dosage, and the initial size and final size of the tumour after a specified treatment gap is expressed. The Least Square Error (LSE) method optimizes the result of the analysis. Therefore, the search space of the particles of the swarm will be reduced considerably.

In Section 2, the Gompertz model and a brief history of some optimal methods will be reviewed. The analysis by which the

drug dosage will be calculable, is presented in Section 3. Optimal control, via swarm intelligence, will be explained in section 4. The accuracy of the presented analysis, the results of the swarm optimization and the effect of the cost function on optimal treatment program will be discussed in Section 5. Finally in Section 6 the conclusion will be presented.

2. GOMPERTZ EQUATION AND OPTIMAL CONTROL

The Gompertz equation (1) is one of the mathematical models which is used to simulate the tumour growth (Preziosi, 2003, Martin, 1992, Floares, *et al.*, 2003). Although the effect of angiogenesis is not addressed directly by avasculr models, the corresponding affect is shown by Gompertz equation indirectly (Preziosi, 2003).

$$\begin{cases} \dot{N} = \lambda N \ln(\theta / N) - k(v - v_{th})H(v - v_{th})N & , N(0) = N_0 \\ \dot{v} = u - \gamma v & , v(0) = 0 \end{cases} \quad (1)$$

In the Gompertz equation (1), $N(t)$ is the number of cancer cells at the time t, $v(t)$ is the drug concentration, $u(t)$ is the drug which is delivered to the system, λ and k are positive constants corresponding to the cell growth rate and cell death rate, θ is the maximum cancer cells number that tumour can reach, γ is a positive constant which is related to the half life of the drug (i.e. $\gamma = \ln(2)/HLD$, HLD is the drug half life), H is the heaviside function and v_{th} is the minimum drug concentration which should be exist to affect the drug. v_{max} is the maximum allowable drug dosage (2). The values of all constants are given in table 1.

$$0 \le v(t) \le v_{\max} \quad (2)$$

The i^{th} treatment gap ($1 \le i \le M$) is defined by the time interval $[\tau_i^+, \tau_{i+1}^-]$ in which M is the final treatment gap and $0 = \tau_1 < \tau_2 < \cdots < \tau_M \le T = 84 * 24(hour)$. Treatment program lasted 84 days (i.e. 84*24 (hour)). The drug dosage σ_i will be delivered to the system using (3) in which $\delta(.)$ is dirac function. The remainder of the drug from the last drug delivery ($v(\tau_i^-)$) is also added to the current dosage.

$$u(t) = \begin{cases} \sigma_1.\delta(t - \tau_1^+) & t \in [\tau_1^+, \tau_2^-] \\ (\sigma_2 + v(\tau_2^-)).\delta(t - \tau_2^+) & t \in [\tau_2^+, \tau_3^-] \\ \vdots & \vdots \\ (\sigma_M + v(\tau_M^-)).\delta(t - \tau_M^+) & t \in [\tau_M^+, T] \end{cases} \quad (3)$$

The constraint on toxic side effect of the drug is presented in (4) in which v_{cum} is maximum cumulative toxicicity (Martin, 1992).

$$\int_0^T v(s)ds \le v_{cum} \quad (4)$$

Based on (1)-(4), Martin (1992) introduced an optimal treatment program, which is based on "control parameterization" and "is a method for solving general optimal control problems numerically". In this way, the solution of an optimal control problem will be approximated via non liner programming techniques (for more details, one may see (Martin, 1992)).

In practice the drug injection for chemotherapy has a discrete nature (DeVita, *et al.*, 2005). Because of problematic state space of discrete treatment gaps to apply methods such as dynamic programming, the continuous injections are suggested by (Martin, 1992). However, a high-continuous drug dosage especially at the end of the 84 days of treatment program is harmful for patients.

In (Floares, *et al.,* 2003) the treatment program and the recommended drug dosages are not given directly in the paper. However, for a treatment gap which lasts one week and the maximum drug dosage per each week, total number of cancer cells will decrease into $2.6*10^6$. As a result, the cancer cells could not reduce enough to reach the reported goals in that paper, unless by using a high-continues drug dosage similar to Martin (1992) which has not a guaranty to recovery bone marrow after 84 days.

Therefore, the treatment gap in a practicable treatment program, seems better to have a floating nature which lasts minimally 1-2 weeks, depends on the type of the drug.

Table 1. The value of parameters of Gompertz equation, which are taken from (Martin, 1992)

Parameter	Value	Description
λ	$9.9*10^{-4}$ (day^{-1})	In this paper, the converted values to ($hour^{-1}$) and (hour) are used.
k	$8.4*10^{-3}$ (day^{-1})	
γ	0.27 (day^{-1})	
HLD	2.5 (day)	
θ	10^{12}	
N_0	10^{10}	
T	84 (day)	
v_{th}	10 (D)	(D) is the unit of drug concentration (Martin, 1992)
v_{max}	50 (D)	
v_{cum}	$2.1*10^3$ (D)	

3. ANALYSIS OF DRUG DOSAGE

3.1.State of the Problem

In this section, a linear analysis in order to find a relation between drug dosage and initial and final number of cancer cells after a specified treatment gap, will be presented. In order to ensure the recovery of the bone marrow, it's assumed that for a given drug with a half life of 2.5(day), the treatment gap lasts at least 1 week. Therefore, the time interval for drug delivery is rewritten as (5). This means that the treatment gap should last minimally 7 days and maximally 21 days, like ordinary treatments.

$$\begin{aligned} &0 = \tau_1 < \tau_2 < \cdots < \tau_M \le \tau_{M+1} = T \\ &\tau_{i+1} - \tau_i \in [7,21](day) \qquad 1 \le i \le M \end{aligned} \quad (5)$$

Forward this point, to make appearance of equations simple, it will be assumed that i^{th} treatment gap has the following time interval; $[0, t_f]$ ($7 \le t_f \le 21$).

3.2. Linear Analysis

As simulation results shows, the drug will be ineffective before 168 hours (7 days). The repopulation phase begins when the drug concentration becomes less effective in compare with natural cancer cells increment (in Fig. 1 is showed by $t_{regrowth}$). When the drug concentration equals to the concentration v_{th}, the drug will be totally ineffective (in Fig. 1, The Ineffective Drug time is showed by t_{ID}). At this time, only the growth term of Gompertz equation will be remain, without affecting dynamics of the drug (6).

$$\dot{N} = \lambda.N.\ln(\theta / N) \quad for \quad 0 < t_{ID} < t < t_f \tag{6}$$

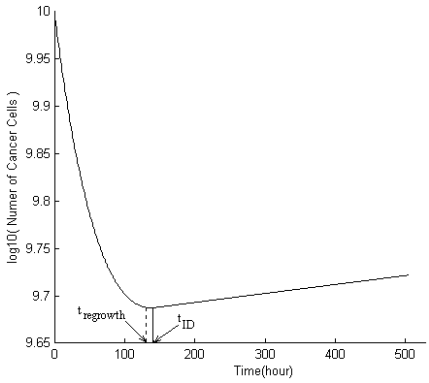


Fig. 1. The repopulation phase begins at time $t_{regrowth}$ when the drug concentration becomes less effective in compare with natural cancer cells increment. When the drug concentration equals to the concentration v_{th}, at time t_{ID}, the drug will be totally ineffective.

By replacing (7) instead of N in Gomperz equation (Martin, 1992, Floares, *et al.*, 2003), it may be rewritten as (8) :

$$N = \theta \exp(-y) \tag{7}$$

$$\begin{cases} \dot{y} = -\lambda y + k(v - v_{th})H(v - v_{th}) & , y(0) = \ln(\theta / N_0) \\ \dot{v} = u - \gamma v & , v(0) = v_0 \end{cases} \tag{8}$$

t_{ID} separates (8) into two linear systems as follows:

$$\begin{cases} \dot{y} = -\lambda y + k(v - v_{th}) & for \quad 0 \le t \le t_{ID} \\ \dot{v} = -\gamma v \end{cases} \tag{9}$$

$$\begin{cases} \dot{y} = -\lambda y & for \quad t_{ID} < t \le t_f \\ \dot{v} = -\gamma v \end{cases} \tag{10}$$

In (9) the initial value of $v(t)$ at the beginning time of i^{th} gap is same as value of $u(t)$ in the same time (3). According to the fact that dynamic of the drug can not be affected by cancer cells, in i^{th} gap dynamic of the drug concentration will be solvable (11).

$$v(t) = v_0 \exp(-\gamma.t) \quad \text{with } v_0 = v(\tau_i^-) + \sigma_i \tag{11}$$

By replacing t_{ID} in (11) and recalling that the concentration of the drug will become v_{th} at t_{ID}, v_0 will be related to v_{th} as follows:

$$v_{th} = v_0 \exp(-\gamma.t_{ID}) \tag{12}$$

The initial value of $y(t)$ in (9) will be calculated from last treatment gap (i.e. $N_0 = N(\tau_i^-)$) . With initial values of y_0 and v_0 and according to (11), (9) has the following solution:

$$y(t) = y_0 \exp(-\lambda.t) + k.\int_0^t [\exp(-\lambda.(t-s))(v_0 \exp(-\gamma.s) - v_{th})]ds \tag{13}$$

By replacing v_0 (v_0 is calculable from (12)) in (13) and some algebraic calculations, $y(t_{ID})$ will be:

$$y(t_{ID}) = [k.\gamma.v_{th} / (\lambda^2 - \lambda.\gamma)] + \exp(-\lambda.t_{ID}).[y_0 - (k.v_{th}.\exp(\gamma.t_{ID})/(\lambda - \gamma)) + (k.v_{th}/\lambda)] \tag{14}$$

$y(t_{ID})$ is the initial value of (10). As a result, the response of (10) at t_f will be calculated as:

$$y(t_f) = y(t_{ID}).\exp(-\lambda.(t_f - t_{ID})) \tag{15}$$

$$\Rightarrow y(t_{ID}) = y(t_f).\exp(\lambda.(t_f - t_{ID})) \tag{16}$$

$y(t_{ID})$ in (14) and (16) is the same. The result of equality of (14) and (16) is:

$$M = (\gamma.\exp(\lambda.t_{ID})/\lambda) - \exp(\gamma.t_{ID}) \quad \text{with}$$
$$M = [(\lambda - \gamma)/(k.v_{th})].[y(t_f).\exp(\lambda.t_f) - y_0 - k.v_{th}/\lambda] \tag{17}$$

With determined value of y_0 and desired values of t_f and $y(t_f)$, in order to solve (17), *exp* function should be estimated as follows:

$$\exp(\alpha.x) = 1 + \alpha.x + \alpha^2.x^2/2 \tag{18}$$

By replacing the estimation of *exp(.)* in (17) and some simplifications, $\tilde{t}_{ID}$ which is the estimation of t_{ID}, will be:

$$\tilde{t}_{ID} = \sqrt{2\left(y(t_f)\exp(\lambda.t_f) - y_0\right) \Big/ (k.\gamma.v_{th})} \tag{19}$$

3.3. Least Square Error Estimation

The estimation (19) can be optimized by using LSE method. Suppose that:

$$t_{ID} = a_3.\tilde{t}_{ID}^3 + a_2.\tilde{t}_{ID}^2 + a_1.\tilde{t}_{ID} + a_0 \tag{20}$$

Simulating the response of (8) on a random set, consisting of y_0, t_f and v_0, will result in $y(t_f)$ and t_{ID} (say $t_{ID\text{-}i}$ for i^{th} sample). The values of $\tilde{t}_{ID-i}$ on the given sample set, consists of y_0, t_f and $y(t_f)$, are calculable via (19). By applying LSE method and (21) and (22), the best value to estimate coefficient vector $\underline{a} = [a_3 \quad a_2 \quad a_1 \quad a_0]^T$ can be calculated via (23).

$$\begin{bmatrix} \widetilde{t}_{ID-1}^{3} & \widetilde{t}_{ID-1}^{2} & \widetilde{t}_{ID-1} & 1 \\ \widetilde{t}_{ID-2}^{3} & \widetilde{t}_{ID-2}^{2} & \widetilde{t}_{ID-2} & 1 \\ \vdots & \vdots & \vdots & \vdots \\ \widetilde{t}_{ID-n}^{3} & \widetilde{t}_{ID-n}^{2} & \widetilde{t}_{ID-n} & 1 \end{bmatrix} \begin{bmatrix} a_3 \\ a_2 \\ a_1 \\ a_0 \end{bmatrix} = \begin{bmatrix} t_{ID-1} \\ t_{ID-2} \\ \vdots \\ t_{ID-n} \end{bmatrix} \quad (21)$$

$$\widetilde{T}_{ID} = \begin{bmatrix} \widetilde{t}_{ID-1}^{3} & \widetilde{t}_{ID-1}^{2} & \widetilde{t}_{ID-1} & 1 \\ \widetilde{t}_{ID-2}^{3} & \widetilde{t}_{ID-2}^{2} & \widetilde{t}_{ID-2} & 1 \\ \vdots & \vdots & \vdots & \vdots \\ \widetilde{t}_{ID-n}^{3} & \widetilde{t}_{ID-n}^{2} & \widetilde{t}_{ID-n} & 1 \end{bmatrix} \quad (22)$$

$$\xrightarrow[LSE]{} \underline{a} = \begin{bmatrix} a_3 \\ a_2 \\ a_1 \\ a_0 \end{bmatrix} = (\widetilde{T}_{ID}{}^{T}.\widetilde{T}_{ID})^{-1}.\widetilde{T}_{ID}{}^{T} \begin{bmatrix} t_{ID-1} \\ t_{ID-2} \\ \vdots \\ t_{ID-3} \end{bmatrix} \quad (23)$$

In (23), the superscript $.^{T}$ stands for transpose operator. The coefficient vector $\underline{a}$ can be calculated just once in an offline manner. In this paper in order to gain better results, the sample sets has been created for 8 intervals of N_0 (i.e. $i \le \log_{10}(N_0) < i+1$ for i = 3, 4,…, 10) and the calculated coefficient vectors ($\underline{a}$) are stored in a 8*4 table (Table 2). Although the memory needed to store the table is not worthy, it will increase the accuracy of the results.

Table 2. The value of coefficient vector $\underline{a}$ for 8 different intervals of N_0

$\lfloor \log_{10}(N_0) \rfloor$*	a_0	a_1	a_2	a_3
3	2.0936	0.9861	-0.0016	0.1676*10^{-5}
4	2.1356	0.9851	-0.0016	0.1659*10^{-5}
5	2.1721	0.9843	-0.0016	0.1643*10^{-5}
6	2.2031	0.9836	-0.0016	0.1630*10^{-5}
7	2.2286	0.9830	-0.0016	0.1619*10^{-5}
8	2.2486	0.9825	-0.0016	0.1611*10^{-5}
9	2.2630	0.9821	-0.0016	0.1604*10^{-5}
10	2.2719	0.9819	-0.0016	0.1601*10^{-5}

* the notation $\lfloor . \rfloor$ stands for floor operation

In (20), a_1 (the coefficient of $\widetilde{t}_{ID}$) equals, approximately, to one. Additionally, the values of a_2 and a_3 are around zero. The value of a_0 shows that the estimation of t_{ID} is usually about 2(hour) less than the actual value. The coefficient vector $\underline{a}$ varies finely in 8 intervals. Considering these facts, (19) is a powerful estimation of t_{ID} which can be optimized in combination with (20).

3.4. Drug Estimation

After estimation of t_{ID} by applying (12), the initial value of $v(t)$ in the i^{th} treatment gap (v_0) will be determined. As $v_0 = \sigma_i + v(\tau_i^-)$ in which $v(\tau_i^-)$ is the remainder of the drug from the last drug delivery, for i^{th} treatment gap the drug dosage (σ_i) can be calculated by (24).

$$\sigma_i = v_{th}.\exp(\gamma.t_{ID}) - v(\tau_i^-) \quad (24)$$

4. OPTIMAL CONTROL

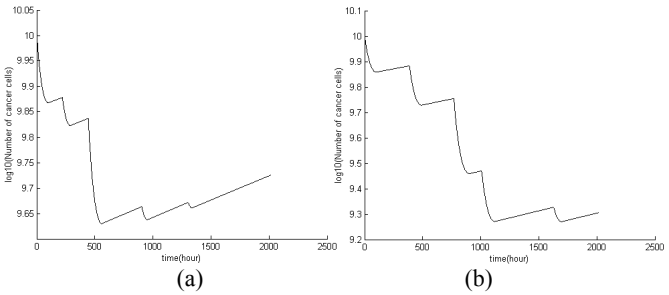
As mentioned in Section 2, the treatment gap in a practicable treatment program, seems better to have a floating nature which lasts minimally one week in this paper. However, because of discrete nature (Martin, 1992) and exponential explosion of dynamic programming approach, applying this method to find the best treatment program with floating treatment gaps, is impossible. To solve such problems, swarm intelligence might be a reliable choice (Zomaya, 2006).

For each particle of the swarm, a reference trajectory of cancer cells, in 84 days of the treatment program, will be created randomly. In each iteration based on the cost of trajectories, the best particles will be selected. The next generation of the swarm will be created by the selected population.

4.1. Acceptable Trajectories

A trajectory begins with an initial number of cancer cells (N_0) and follows with random drug dosages ($v_0 \in [v_{th}, v_{\max}](D)$) and random duration of treatment gaps ($t_f \in [7,21](day)$). The goal of chemotherapy is reduction of cancer cells. As a result, a trajectory will be called unacceptable, if it has a treatment gap which has less initial number of cancer cells in compare with the final one at the end of that gap (Fig. 2.a). If there is not any acceptable trajectory, chemotherapy will not be a desirable candidate to choose, while tumour size has not a decreasing behavior during the treatment. In order to filter unacceptable trajectories by considering a random set of drug dosages and treatment gaps, the numerical algorithm corresponding to (1) should run.

Another way to create trajectories is, to suggest the drug dosage randomly such that it could be guidance to an acceptable trajectory. An acceptable trajectory (Fig. 2.a) begins from an initial number of cancer cells (N_0) and follows with random treatment durations ($t_f \in [7,21](day)$) and random values for final number of cancer cell at t_f such that $N(t_f) \in [\alpha.N_0, N_0)$ $(0 \ne \alpha << 1)$. The appropriate drug dosages which leads to desired $N(t_f)$, could be suggested by (19) and (20).



(a) (b)

Fig. 2. (a) In some treatment gaps of unacceptable trajectories, the initial number of cancer cells is less than the final one, at the end of that gap.
(b) Using the presented analysis, only acceptable trajectories will be created.

4.2. Finding the Optimal Trajectory

4.2.1. Cost Function

In order to find the optimal trajectory, a cost function should be determined to evaluate each particle. The final number of cancer cells at the end of 84 days is one of the choices (Martin, 1992, Floares, *et al.*, 2003); however, in some special cases such as old patients or for whom normal dosages may be harmful, total drug dosage might be considered, in addition to final cells (Swierniak, *et al.*, 2003).

For swarm optimization, two different cost functions will be tested. One of the cost functions is the final number of cancer cells at the end of 84 days (25). The other one is based on final number of cancer cells and total drug dosage (26).

$$J_1 = \log_{10}(N(T)) \tag{25}$$

$$J_2 = C_N.\log_{10}(N(T)) + C_D.\sum_{i=1}^{M}\sigma_i \tag{26}$$

In (26), C_N and C_D are positive constants, related to the special conditions of the patient.

4.2.2. Swarm Algorithm

At first step of the swarm algorithm, the initial population of the particles will be generated. Each particle presents a random-acceptable trajectory. In each iteration, the best particles will be selected. Based on the selected population, the next generation of the population will be created.

To generate a new particle, a cut point will be chosen randomly from the parent. The cut point determines that the new treatment program would be a combination of which first-steps of the parent's trajectory and a new-acceptable trajectory. As the cut point is chosen randomly, both chances for creating new trajectories or maintaining the parent's path with some verifications will be exists (Fig. 3).

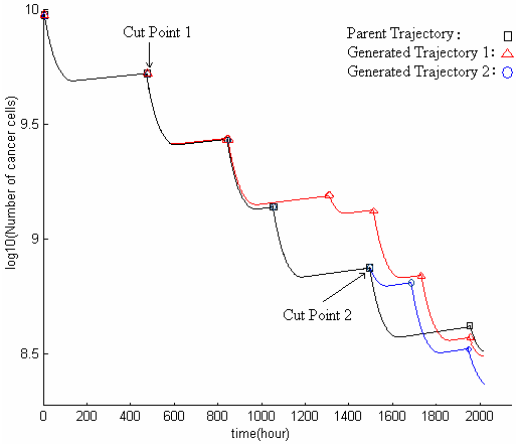


Fig. 3. The Parent Trajectory (black path with square) and two cut points are shown. As the cut point is chosen randomly, both chances of creating new trajectories (red path with triangle) or maintain the parent's path with some modifications (blue one with circle) will be exists.

In the first iterations, the best-selection sets (parent's sets) are greater than the sets in the next iterations. It increases the chance that the search space will be discovered by a coarse view. After determining the scope of the solution, by reduction in the size of parent's sets, new trajectories will be generating in the corresponding scope. More details of the algorithm are given in Fig. 4.

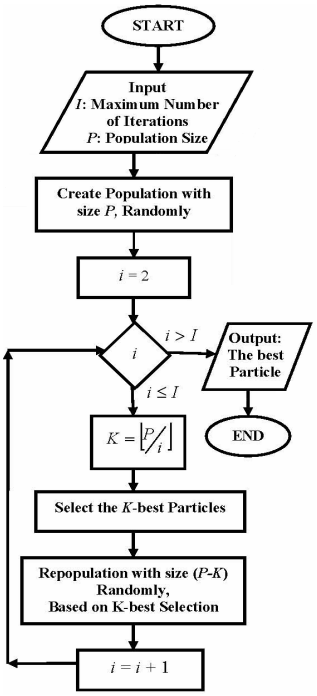


Fig. 4. The Flowchart of the swarm optimization algorithm. After some tests, the value of the swarm parameters are adjusted as follows: P= 600 and I= 60. In this way, the best results of the swarm will be changed rarely at the last iterations of the algorithm.

5. RESULTS

In Section 3.3 an estimation of t_{ID} (20) to optimize (19), is presented. Equation (20) has been introduces with a polynomial with degree 3. Additionally, the verification has been done with other polynomials with degree 1, 2, 4. Each polynomial has been tested for 8 intervals of N_0 (i.e. $i \le \log_{10}(N_0) < i+1$ for i = 3, 4,…, 10). In each interval 14,560 samples has been tested. In compare with other degrees, (20) has the minimum mean square error for drug estimation (Fig. 5).

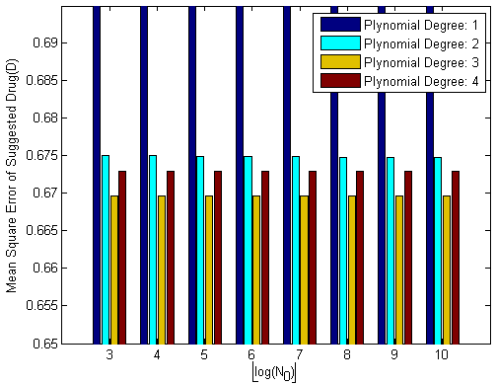


Fig. 5. The bar chart of the least square error of estimated drug for various number of initial cancer cells and polynomials with various degrees. The error of the polynomial with degree 1 is more than 1.2. The polynomial with degree 3 has the minimum error.

In order to find optimal treatment program, the cost functions (25) and (26) has been presented. According to the fact, that the minimum time interval of a treatment gap and the maximum drug dosage (v_{max}) are determined; the best treatment to reach minimum final number of cells (i.e. the result of (25)), is maximum drug dosage for each week. This could be a good reference to evaluate the accuracy of the swarm method.

Because of using the acceptable trajectories and the best-selection sets with variable size, the algorithm finds an estimation of the optimal trajectory with 60 iterations on a 600 member population. After 60th iteration, there would be rarely changes in the best trajectories. In Fig. 6 the best trajectory to reach minimum final number of cancer cells and two estimations of optimal trajectory which swarm determines, are shown. The estimation of the optimal trajectory is usually between specified trajectories in Fig. 6. Although the number of iterations is low, the result is an acceptable estimation of the best.

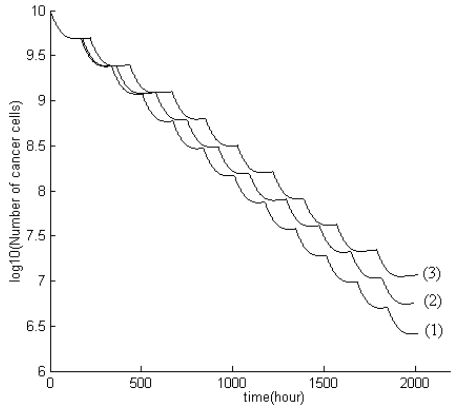


Fig. 6. (1) The best trajectory to reach minimum number of cancer cells.
(2), (3) Two estimations of optimal trajectory which swarm determines. The estimations of the swarm are usually between these trajectories.

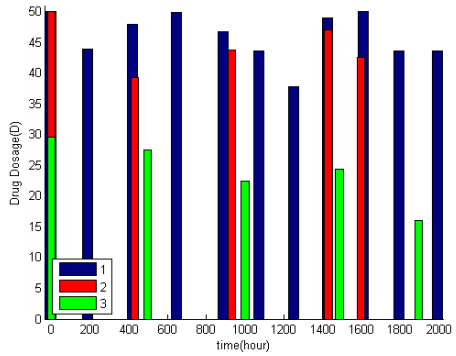


Fig. 7. Three optimal treatment programs with different values of C_N and C_D:
(1) C_N=1, C_D=0; the goal of treatment is the minimum number of cancer cells.
(2) C_N=100, C_D=1; the treatment gaps last more than case (1).
(3) C_N=0, C_D=1; the treatment gaps last more than cases (1),(2) and the drug dosages reduce in compare with them.

By applying cost function (26) with three different values for C_N and C_D, some treatment programs are achieved (Fig. 7). Increasing in value C_N/C_D causes that the optimal trajectory of (26) approximates the best treatment of (25). Although, these suggestions reduces the number of cancer cells; they may not be applicable. These treatment programs could not guaranty recovery of the bone marrow (DeVita, *et al.*, 2005). Lower values of C_N/C_D cause that the treatment gaps last more than the other case. Additionally, more reduction in the value of C_N/C_D causes more reduction in drug dosage. Considering the conditions of the patient, parameters C_N and C_D should be determined.

6. CONCLUSION

By using a combination of linear analysis and LSE method, it is possible to estimate the drug dosage in a specified treatment gap with initial and final number of cancer cells. The main advantage of the presented analysis is that it is to avoid unacceptable trajectories without applying numerical algorithms or artificial methods such as neural networks. By decreasing the search space of the swarm, the required number of iterations to approximate the optimal treatment program will be reduced.

The suggested treatment programs may be used in combination with complex simulation methods such as multiscale cancer modelling (Byrne, *et al.*, 2006a, b).

ACKNOWLEDGEMENT

The first author wishes to thank Dr. A. Bavafa and Mr. A. Harati for their encouragement and suggestions.

REFERENCES

Byrne, H. M. Owen, M. R. (2006a). Modelling the Response of Vascular Tumors to Chemotherapy: a Multiscale approach, *Mathematical Models and Methods in Applied Sciences*, **vol. 16**, pp. 1219-1241.

Byrne, H. M. Alarcon, T. Owen, M. R. Webb, S. D. Maini, P. K. (2006b). Modelling aspects of cancer dynamics: a review, *Philosophical Transactions on the Royal Society A*, **vol. 364**, pp. 1563–1578.

DeVita,V.T. Hellman, S. Rosenberg, S. (2005). *Cancer: Principles and practice of Oncology*, 7th Ed, Lippincott Williams.

Floares, A. Floares, C. Cucu, M. Lazar, L. (2003). Neural Networks Control of Drug Dosage Regimens in Cancer Chemotherapy, *Proceedings of IJCNN2003*, **vol. 1**, pp. 154-159.

Martin, R. B. (1992). Optimal Control Drug Scheduling of Cancer Chemotherapy, *Automatica,***vol. 6**, pp. 1113-1123.

Preziosi, L. (2003). *Cancer Modelling and Simulation*, CRC Press, London.

Ribba, B. Marron, K. Agur, Z. Alarcon, T. Maini, P. K. (2005). A mathematical model of Doxorubicin treatment efficacy for non-Hodgkin's lymphoma: investigation of the current protocol through theoretical modeling results, *Bulletin of Mathematical Biology*, **vol. 67**, pp. 79-99.

Swierniak, A. Ledzewicz, U. Schättler, H. (2003). Optimal Control for a Class of Compartmental Models in Cancer Chemotherapy, *International Journal on Applied Mathematics and Computer Science*, **vol. 13**, pp. 357-368.

Tarnawski, R. Fowler, J. Skladowski, K. Swierniak, A. Swinski, R. Maciejewski, B. Wygoda, A. (2002). How fast is repopulation of tumor cells during the treatment gap, *Int. J. Radiation Oncology Biol. Phys.*, **vol. 54**, pp. 229-236.

Zomaya, A. Y. (2006). *Handbook of Nature-Inspired and Innovative Computing: Integrating Classical Models with Emerging Technologies*, chapter 6, Springer.