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Model Based Design of Cancer Chemotherapy Drug Scheduling: A Particle Swarm Optimization Approach

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ABSTRACT

This paper presents an investigation into the development of a cancer model for chemotherapy drug scheduling using Particle Swarm Optimization (PSO) algorithm. PSO is a population-based search method whose mechanics are inspired by the ability of flocks of birds, schools of fish, and herds of animals to adapt to their environment and find rich sources of food by implementing "information sharing" approaches. The main aim of chemotherapy treatment is to reduce the tumor size to a desired minimum level so that cannot be detected in vivo clinically. 'Mouse' and 'Human' models developed by de Pillis and co-workers in 2006 are used to design chemotherapy drug doses and observe its effects on different cell populations. Besides chemotherapy, these models are also used to study the effects of immunotherapy, anti-angiogenic therapy or combinations of these. Chemotherapy drug scheduling is designed as optimal control problem based on these models and PSO is used to find drug doses for specific intervals and periods relevant to clinical practice. Results show that the employed method can generate a wide range of solutions that trade-off between cell killing and toxic side effects and satisfy associated goals of chemotherapy treatment.

Keywords: Cancer, Chemotherapy, Control, Drug Scheduling, Particle Swarm Optimization.

1. Introduction

Cancer is a group of disease characterized by abnormal proliferation of cells, usually in a random, disorderly manner. This uncontrolled growth results a malignancy and tumors are formed. These affect healthy tissues and organs and interfere with the proper functioning of the affected organs (Pecorino, 2012). Chemotherapy takes the advantage of the rapidly proliferating nature of cancer cells. However healthy tissues, such as white blood cells, intestinal mucosa etc. also proliferate sufficiently and are affected by chemotherapeutic treatment and produce a negative side effect which must be kept under control. Such therapies may be combined with the other therapies like anti-angiogenesis and immunotherapy. The dose and frequency of drug admission is the most crucial part of the cancer treatment (Chabner and Longo, 2011).

The purpose of a mathematical model of cancer chemotherapy (Bellomo, et al., 2008) is to predict and control the disease using a drug. The reasons why a good mathematical model is very useful are many. It is often faster and cheaper to develop a mathematical model and simulate it on a computer than perform a laboratory work or make clinical trial. Once a mathematical model is found that fulfills requirements, then one may focus on the design of an improved treatment protocol. The goal of chemotherapy is to destroy the tumor cells, while maintaining healthy tissues. Therefore, the development of a chemotherapy protocol can be phrased as an optimal control problem with constraints: for a fixed time interval, find the points within that interval at which the drug should be administered so that the number of tumor cells has been minimized, while the number of healthy cells has been kept above a prescribed threshold (Algoul, et al., 2011, Nadia, et al., 2013).

2. Mathematical Modeling of Cancer and Tumor

de Pillis and co-workers (2006, 2009) used empirical data to develop cancer tumor growth models with chemotherapy and immunotherapy drugs for mouse and human. A set of differential equations have been derived, where each equation gives the rate of change of the particular cell population in terms of growth and death, cell-cell kill, cell recruitment, and cell inactivation. For simplicity, we omit the time dependency of states and controls equations are (Engelhart et al., 2011):

$$\dot{x_0} = ax_0\,(1 - bx_0) - cx_1x_0 - Dx_0 - K_T\,(1 - e^{-x_4})x_0, \quad (1)$$

$$\dot{x_1} = ex_3 - fx_1 + g\frac{x_0^2}{h + x_0^2}x_1 - px_1x_0 - K_N\,(1 - e^{-x_4})x_1, \quad (2)$$

$$\dot{x_2} = -mx_2 + j\frac{D^2x_0^2}{k + D^2x_0^2}x_2 - qx_2x_0 + (r_1x_1 + r_2x_3)x_0 - ux_1x_2^2 - K_L(1 - e^{-x_4})x_2 + \frac{p_1x_2x_5}{g_1 + x_5} + u_2, \quad (3)$$

$$\dot{x_3} = \alpha - \beta x_3 - K_c(1 - e^{-x_4})x_3, \quad (4)$$

$$\dot{x_4} = -\gamma x_4 + u_0, \quad (5)$$

$$\dot{x_5} = -\mu_1 x_5 + u_1, \quad (6)$$

$$D = d\frac{(x_2/x_0)^t}{s + (x_2/x_0)^t}, \quad 0 \le x_0, x_1, x_2, x_3, x_4, x_5, \quad 0 \le u_0, u_1, u_2, \quad t \epsilon [t_0, t_f]$$

Models consist of six states, three controls and 29 parameters in three parameter sets. The models also contain a combination of chemotherapy and immunotherapy. The six different states of models are: (i) Tumor volume x_0 - tumor population measured in absolute cell count, (ii) NK

cells x_1 – unspecific immune cells which are also present in a healthy body, "natural killer" cells. Measured in cells/L, (iii) CD8+T cells x_2 – tumor specific immune cells (cells/L), (iv) Circulating lymphocytes x_3 – white blood cells (cells/L), (v) x_4- chemotherapeutic drug concentration (mg/L) and (vi) x_5- interleukin-2 concentration(IU/liter). IL-2, a naturally produced molecule, is a widely administered immunotherapy drug, particularly for cancer. The activity of this molecule is often included in immunological models of cancer treatment. IL-2 is a cytokine that stimulates CD8+T activation cells and is used to boost immune system function. Although IL-2 promotes the proliferation of T-cells, it also shortens their lifespan (Moore, 2007). In addition, there is a control for a classic cytostatic drug u_0 and one for a tumor infiltrating lymphocyte injection (TIL) u_2. The latter means an injection of CD8+ T cells that have been stimulated against tumor cells outside the body.

3. Particle Swarm Optimization (PSO) Algorithm

The PSO algorithm is simple in concept, easy to implement and computationally efficient. The original version of PSO can be implemented as follows (Eberhart and Kennedy, 1995):

1. Initialize a population of particles with random positions and velocities on d-dimensions.
2. For each particle, evaluate the desired optimization fitness function in d variables.
3. Compare particle's fitness evaluation with its *pbest*. If current value is better than *pbest*, then set *pbest* equal to the current value, and P_i equals to the current location X_i .
4. Identify the particle in the neighborhood with the best success so far, and assign its index to the variable *gbest*. Compare this *gbest* with the populations overall previous best. If the current value is better than *gbest*, then reset *gbest* to the current particle's array index.
5. Change the velocity and position of the particle.
6. Loop to step 2) until a criterion is met, usually a sufficiently good fitness or a maximum number of iterations. The velocity and position of the particle in step (5) are changed according to the following equation respectively:

$$V_{id} = V_{id} + c_1 rand()(P_{id} - X_{id}) + c_2 Rand()(P_{gd} - X_{id}) \quad (7)$$

$$X_{id} = X_{id} + V_{id} \quad (8)$$

Where, c_1 and c_2 are cognitive and social parameters, rand() and Rand() are two random functions in the range [0,1], g is the index of the best particle among all the particles in the population, $X_i = (X_{i1}, X_{i2}, \ldots\ldots, X_{id})$ represents the ith particle position, $P_i = (P_{i1}, P_{i2}, \ldots\ldots\ldots, P_{id})$ represents the best previous position of the ith particle and $Vi = (V_{i1}, V_{i2}, \ldots\ldots\ldots, V_{id})$ represents the rate of the position change (velocity) for ith particle. It has been demonstrated that the optimal solution can be improved by varying the value of w from 0.9 at the beginning of the search to 0.4 at the end of the search for most problems. If the sum of the three parts on the right side of eq.(7) exceeds a value specified by user, then the velocity on that dimension is assigned to be $\pm V_{max}$, that is, particles' velocities on each dimension is clamped to a maximum velocity V_{max}, and it is the only parameter required to be adjusted by users. A well designed dynamically changing V_{max} might improve the performance of a PSO.

4. Chemotherapy Drug Scheduling Using PSO

Model–based control is currently considered the state–of–the–art in the field of process control and it is an active research field for drug scheduling of different chronic diseases including cancer (Harrold and Parker, 2009). In this paper, first tumor growth models developed by de Pillis and co-workers (2006) are implemented then based on models chemotherapy drug scheduler designed using PSO that would produce an improved outcome by reducing final tumor size without causing large losses in the normal cell population. Figure 1 shows the schematic diagram of drug scheduling design.

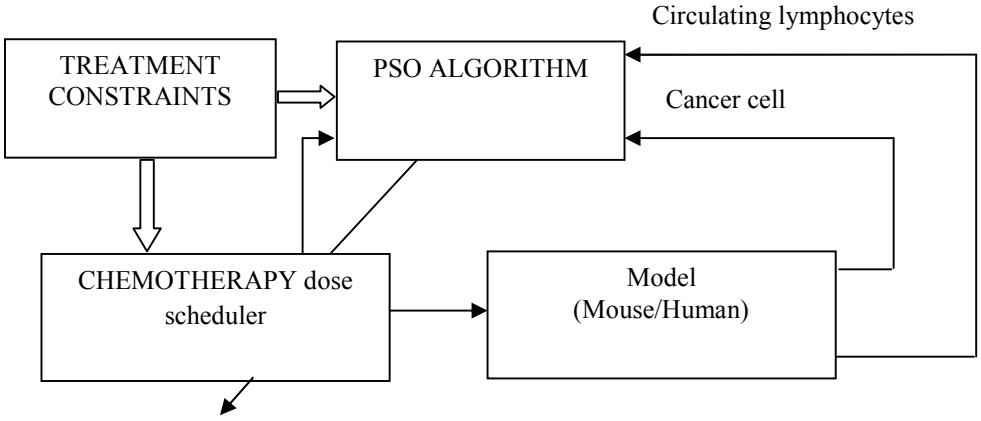

Figure 1: Schematic diagram of drug scheduling scheme

Implementation

PSO algorithm works on the social behavior of the swarm. PSO optimization process begins with randomly generated candidate solutions called particles. In this research work, MATLAB & SIMULINK (The Mathworks, Inc., 2015) have been used to encode and implement the desired drug dose and optimization process. For the optimization of the process the maximum number of generation is set at 300. Then this designed dose obtained is applied to the model and the number of different types of cells are counted at the end of the each treatment cycle to see the effect of various dose and to determine the effectiveness of the dose schedule designed by PSO algorithm.

5. Results

In this paper, chemotherapy drug schedules are designed for 'mouse' and 'human 10' models and results are shown and discussed in following sections. It is noted that, values of parameters for 'mouse' and 'human 10' models used in this paper were collected by Engelhart and co-workers (2011) from various sources treating different types of cancer and different types of mice.

Mouse Scenario

For the treatment of mouse only the chemotherapy is applied mouse model with maximum dose of 1. The chemotherapy drug is applied for 42 days i.e. for 6 weeks in a cycle of 7 days. In this method PSO is designed to take the decision to apply/not apply the drug. If it decides to apply drug then also controls the amount of drug. It is designed to administer drug for cumulative 4 days of a week and the remaining three days is considered as rest period for the balance of healthy cells. With this technique of drug schedule to assess the reproducibility of the PSO the same model is run 10 times and at the end of the each treatment period the number of different cells are counted. Table 1 shows the percentage of cell change due to the effect of chemotherapy.

Table 1 shows that for most of the run the cancer cell population changes in between 37% and 39%. Whereas maximum reduction of cancer cell population occurs in run 5 and it is 38.75% and minimum cancer cell reduction occurs in run 7 which is 12.35%. Except run 7 all the run shows the average result for reduction of tumor cells. Figure 2 graphically shows the reduction of cancer cells for different drug doses generated by the program of the PSO.

Table 1: Percentage of cell population changes due to the effect of chemotherapy

Run no	Tumor cells reduction	NK cells increment	Cir. lymphocyte reduction
Run1	33.15%	88.77%	39.55%
Run2	38.23%	78.32%	42.13%
Run3	37.93%	78.87%	41.97%
Run4	38.15%	78.48%	42.08%
Run5	38.75%	77.41%	42.41%
Run6	38.34%	78.14%	42.19%
Run7	12.35%	112.24%	28.13%
Run8	37.67%	79.35%	41.83%
Run9	37.82%	79.07%	41.91%
Run10	38.61%	77.66%	42.33%

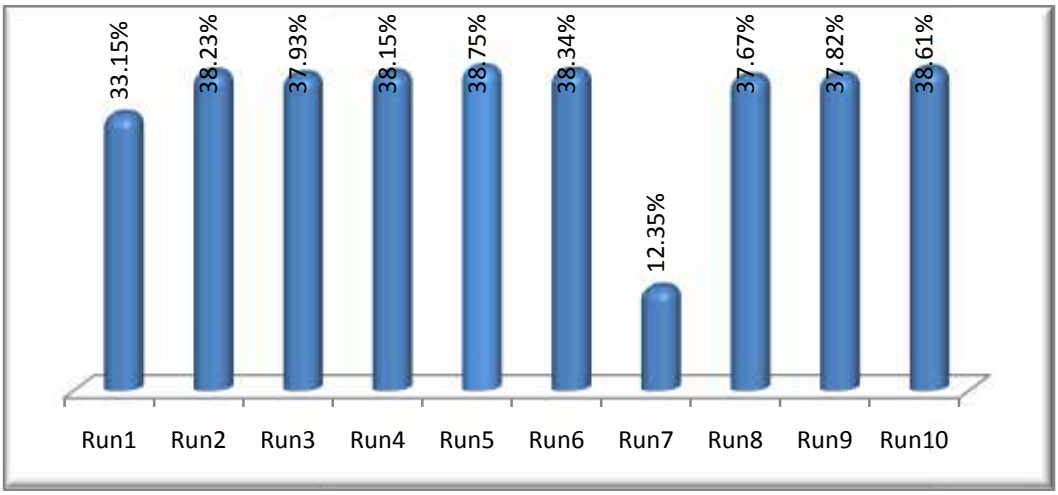

Fig. 2: Cancer cell reduction for different run

The main objective of the chemotherapy is to reduce the cancer cells with minimum side effects i.e. to reduce the cancer cells while the other healthy cells remain above a certain minimum level. The maximum reduction of cancer cells occurs in run 5 and in this case NK cells are increased by 77.41% and reduction of circulating lymphocytes is 42.41%. This shows that with the maximum reduction of cancer cells the other cells remain on the average level. Compared with other runs this run shows the better solution with maximum cancerous cells destruction and tolerable minimization of the circulating lymphocytes. So this dose of chemotherapy can be considered as a best dose for chemotherapy treatment. The chemotherapy drug dose and the corresponding response of the cell populations to this drug dose are shown in figure 3. This figure shows that the maximum dose applied at first week is 1.0 and the minimum applied dose is 0.6. With this applied dose cancer cells reduces from initial value 10^6 to 6.1251×10^5 at the end of the 42 days treatment period. Circulating lymphocytes cells which are the important cells for healthy body are also decrease with the reduction of cancer cells. Initial value of the circ. lymphocytes for mouse is 1.1×10^7 while at the end of the treatment period it reaches 6.3343×10^6. Reduction of circ. lymphocytes is one of the side effects of chemotherapy which must be controlled to reduce toxicity level.

Human Scenario

For the drug scheduling, the chemotherapy dose generated by PSO algorithm is applied to the to the 'human 10' model. In this case the maximum dose of chemotherapy applied is limited to 5.0. 'Human 10' model contains chemotherapy as well as immunotherapy. In this drug scheduling process immunotherapy is considered as almost zero and only the chemotherapy is applied. The chemotherapy is applied for a treatment period of 40 days. Like the mouse model PSO algorithm is used here to take the decision to apply or not apply the therapy. If the decision is taken to apply the drug then amount of drug to be applied is also adjusted by the program of PSO. In this case it decided to apply the drug for cumulative four days of a week. The remaining three days are considered as rest period for the recovery of the healthy cells so that toxicity of chemotherapy to the body organs is reduced. To obtain the useful drug the 'human 10' model is run 10 times. At the end of the each treatment the number of cell for different cell types are counted to observe the effectiveness of the drug dose generated by PSO. Table 2 shows the percentage of cell number change that makes easy to understand the activity of the drug. It is observed that for most of the runs, percentage of cancer cell changes vary from 39% to 40%. It proves the repeatability of the PSO algorithm. The maximum cancer cell changes occur in run 6 which is 40.05% and minimum cancer cell changes occur is 37.70% and it occurs in run 7. For NK cell, maximum number of cell changes occurs in run 6 which is 41.93% and minimum cell number changes is 40.54% and occurs in run 7.

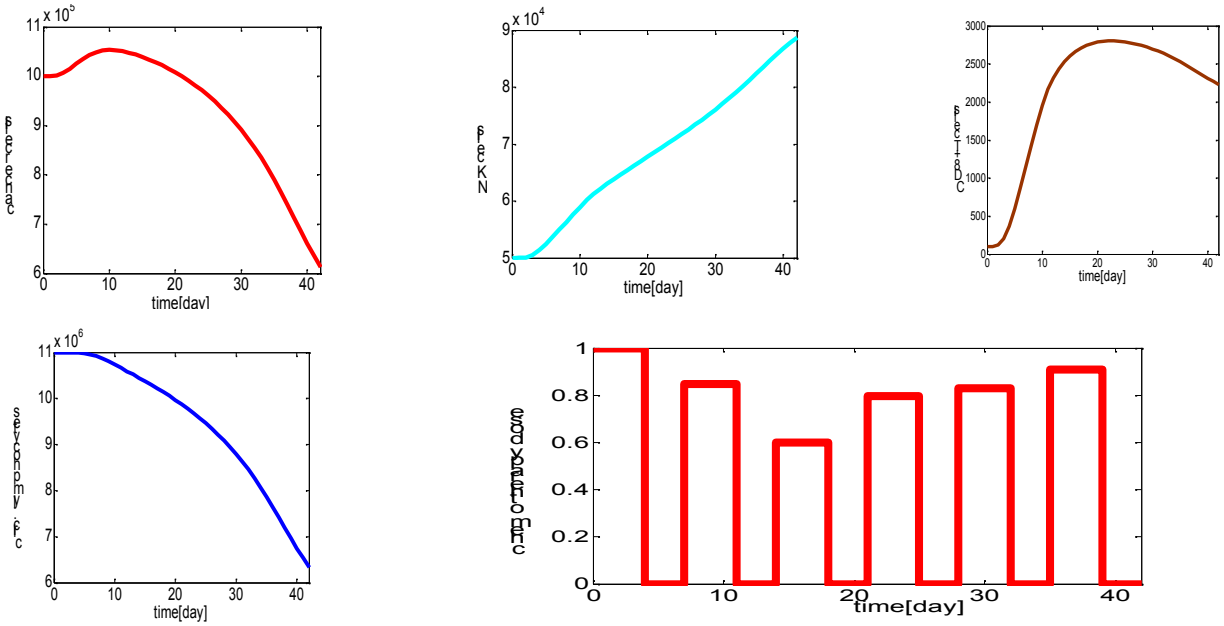

Fig. 3: Response of different types of cells due to chemotherapy applied to mouse model

For all cases the difference in number of cell changes is very small. In case of circulating lymphocytes maximum number of cell changes occurs in run 6 which is 31.44% and minimum number of cell changes 29.49% occur in run 7. Now the result obtained from Table 2 represents that the percentage of cell number changes for different run is very small. So it is to be noted that the dose generated by PSO is very similar and effect of these dose in different cell population is also similar. As run 6 gives the maximum changes in cancer cells, the drug schedule generated by this run and the response of different types of cells to this drug schedule is shown in figure 4. Figure 5 shows that as chemotherapy is applied to the 'human 10' model the cancer cells decrease with time and in 40 days treatment period it reduced from initial value of 1×10^5 to 5.9953×10^4 i.e. it reduced about 40% from its initial value. The chemotherapy has maximum dose of about 5.0 and is applied in first, fourth and fifth week. The minimum dose applied is 4.0 and it happens in third week. Circulating lymphocytes the most important cells in human is also reduced due to the application of chemotherapy. Its initial value in 'human 10' is 6×10^{10} and due to the chemotherapy it reduces to 4.1134×10^{10} at the end of 40 days treatment.

Table 2: Percentage of cell population changes in 'human 10' due to chemotherapy.

Run no.	Reduction of cancer cells at the end of treatment	Reduction of NK cells at the end of the treatment	Reduction of Circ. Lymphocytes at the end of treatment
Run 1	39.36%	41.53%	30.88%
Run 2	39.34%	41.54%	30.87%
Run 3	39.28%	41.48%	30.79%
Run 4	39.94%	41.87%	31.35%
Run 5	39.68%	41.71%	31.13%
Run 6	40.05%	41.93%	31.44%
Run 7	37.70%	40.54%	29.49%
Run 8	38.78%	41.20%	30.38%
Run 9	39.97%	41.88%	31.38%
Run 10	39.69%	41.72%	31.14%

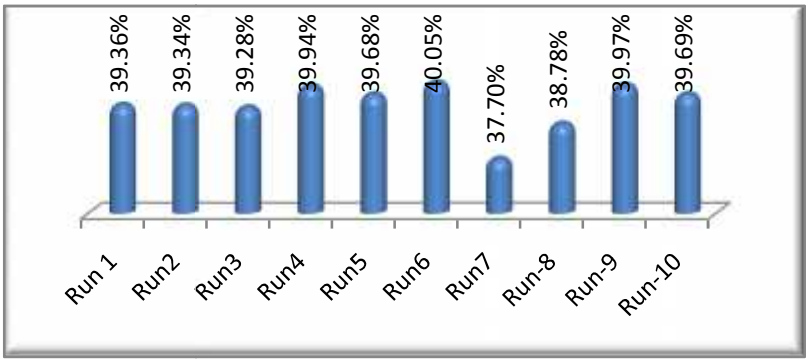

Fig. 4: Cancer cell reductions for different run

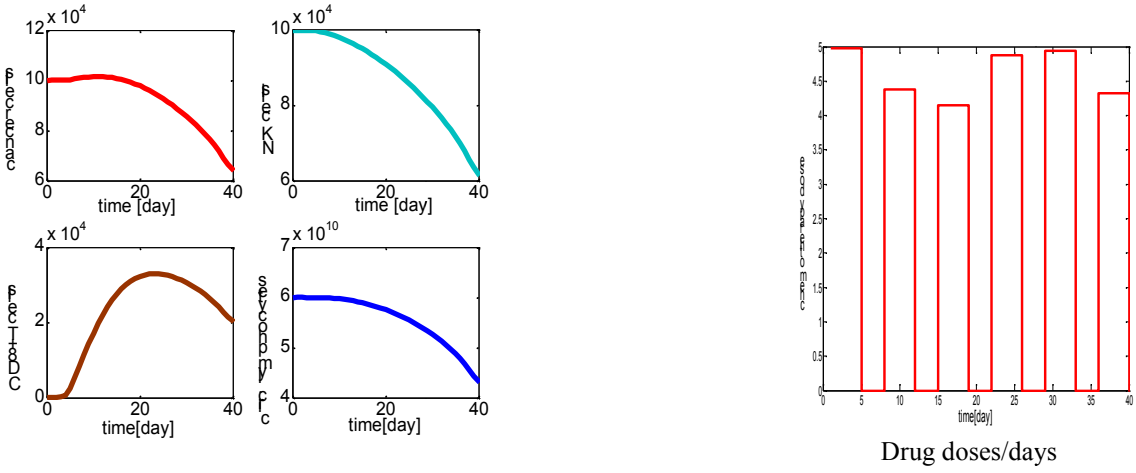

Fig. 5: Response of the different types of cells to the chemotherapy generated by run 6

6. Conclusions

In this work particle swarm optimization is used as a control to develop a drug schedule process. The main objective of this proposed drug schedule procedure is to develop an effective cancer treatment drug schedule technique to reduce the cancer cell in a biological system. The treatment schedule produced using PSO has been used to analyze the effect of the chemotherapy on different cell population. Genetic Algorithms have some limitations such as complexity in algorithm, huge parameter estimation, large computation time, slow convergence. But PSO is a relatively new evolutionary algorithm and it has small parameter to be estimated, faster convergence, lower computational cost and easier to implement. So PSO can be used as very efficient tool for drug dose scheduling as reported in recent literature (Alam et al., 2010, 2013). It is to be noted that the obtained drug schedule is square wave in nature having ups and downs to control the tumor population cells on a minimized level and to keep the others cells above a threshold value. Furthermore, the same control strategy can be extended for multidrug or combination chemotherapy scheduling for more efficient cancer treatment.

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