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MODELLING CANCER CHEMOTHERAPY WITH SIDE - EFFECTS

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ABSTRACT

Modelling and Analyzing chemotherapy treatment for cancer using mathematical framework is a complex optimization problem with huge number of constraints and variables. Previous researches have shown that several approaches can be applied to the cancer chemotherapy problem with various degree of success. In our previous work, we proposed a set of controlled stochastic differential equations to model the drug scheduling with quadratic cost criteria in cancer chemotherapy process. We developed a fast and efficient algorithm to solve such complex optimization problem. However, the obtained results did not take into account the toxicity or side-effects of the treatment. In this work, we present an extended version of the previous model, a parsimonious tradeoff between drug dose and toxic side - effects is carefully implemented. The ultimate goal here being optimizing drug scheduling to finding appropriate treatment design from many possibilities, we applied a novel version of *Adapted Genetic Algorithm* to reach optimal solution to the problem. Here we will present and discuss these new findings.

Keywords: Cancer model, nonlinear dynamic, modelling, complex systems, medical, applications, Adapted Genetic Algorithm.

1. Introduction

Cancer is viewed as one of the leading causes of death in many countries around the world. It is therefore not surprising that many researchers from various fields have been trying to model the disease and its treatment. The overall goal is to gain an understanding of the disease for a better design of its treatment. There is a vast literature on cancer models (see attached references) which contribute to solving the problem, albeit with some limitations. For example, most models consider a treatment with one drug whereas in medical practice it is common to use a mixture of drugs called a *drug cocktail*. Nevertheless, most models are sufficiently closed to the real situation and contribute to the understanding and advance in cancer research as a whole. From the biochemical and chemical engineering perspective, chemotherapy drugs work by attacking cells that are dividing rapidly, where normal cells divide at a rate that is tightly controlled by the body. However in cancer cells the division goes wrong, leading to the uncontrollable production of new cells and the formation of a tumor (Hardman *et. al.*, 1992). Chemotherapy drugs interfere with the division of these cells and may cause the cancer to recede completely. *A good treatment procedure should be able to reduce the number of cancerous cells to a minimum level and therefore we can see an increase in normal cell level until, hopefully, complete recovery*. In medical practice, there are standard protocols and approved maximum dosages for known commercial drugs; however it will often be the case that the oncologist would tailor a treatment according to the patient characteristics and disease progression, in a trial and error procedure. Recently, there have been previous evolutionary attempts to create optimized schedules of chemotherapy, based upon finding the optimal control to a system of ordinary differential equations ((Villasana et al., 2004) and (Ochoa et al., 2008)), or an estimation of distribution algorithm minimizing the cell response (modelled by Gompertz' equation) when a chemotherapy drug is injected ((Petrovski et al., 2006) and (Brownlee et al.2008)), or the actual solution of an ordinary differential equation (Leung *et al*., 2004). However, the methods above indicate an interest in the steady state and are deterministic.Chemotherapy itself consists of using anti-cancer drugs to help control or prevent the growth of cancerous tumors. *Anti-cancer drugs are chemical compounds which kill the cancer cells (and also normal cells) and a target for such therapy is to kill the maximum number of cancer cells while killing the minimum number of normal cells for some fixed treatment period*. As has been pointed out (Martin, 1992), drug scheduling is essential in cancer chemotherapy and finding a suitable treatment module for the large number of existing possibilities is a challenging problem from both a theoretical and practical point of view. Previous research has shown that a large range of algorithms, such as constrained optimization (Petrovski, 2006), the

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probabilistic approach (Matveev, 2002), and genetic algorithms (Villasana, 2004) can be applied to the chemotherapy problem, in conjunction with a steady state model of cells. In this work, we propose an extended version of our previous mode, taking in to account toxicity. As before this model relies on controlled stochastic difference equations with additional component for toxicity. In order to find optimal chemotherapy schedule, we convert the quadratic optimization problem to simple optimal control problem. The model has a control variable; we may restrict ourselves to the study of the related control in the model. This paper is organized as follows. Section 2 reviews the biochemical and biomedical background of the cancer chemotherapy problem. Section 3 formulates the mathematical model of the problem in a stochastic optimization framework. The design of an appropriate objective function based on the theory of optimal control is presented in Section 4. Our algorithm, experiments and discussion are presented in Section 5, with the conclusions given in Section 6.

2. Mathematical Model of Cancer Chemo-therapy with toxicity

It is now well established that chemotherapy treatment for cancer is a complex optimization problem involving many constraints (Brownlee et al., 2008). An important target for cancer chemotherapy is to maximally kill tumor cells and minimally affect normal cells over a fixed period of treatment. This implies that drug scheduling and periodic control are essential in such a process. Earlier models (Martin, 1992) considered a set of ordinary differential equations with a switch action control. In this work, we present an extension of the previous result. We model the toxicity in normal and cancer cells as functions that depends on cell concentration and threshold variable κ :

$$f_1\left(v_1, c_1(t)\right) = \sum_{t=1}^{T} v_1(t) e^{c_1(t)-\kappa}$$

$$f_2\left(v_2, c_2(t)\right) = \sum_{t=1}^{T} v_2(t) e^{C_2(t)-\kappa}$$

We also add noise to the dynamic and introduce a flexible control process to the system, obtaining a controlled stochastic model given by the following equations:

a. Normal cell dynamic with toxicity

$$x_1(t) = x_1(0) + \sum_{t=1}^{T} a_1 x_1(t-1) + \sum_{t=1}^{T} b_1 y_1(t-1) + \sum_{t=1}^{T} d_1 u(t-1) + \sum_{t=1}^{T} v_1(t) e^{\kappa - c_1(t)} + \varepsilon_1(t)$$

$$y_1(t) = C_1 + \varepsilon_1'(t)$$

$$\sigma_1^2(t) = k_1 + g_1 \sigma_1^2(t-1) + \alpha_1 \varepsilon_1''^2(t-1)$$

b. Cancer cell dynamic with toxicity

$$x_2(t) = x_2(0) + \sum_{t=1}^{T} a_2 x_2(t-1) + \sum_{t=1}^{T} b_2 y_2(t-1) + \sum_{t=1}^{T} d_2 u(t-1) + \sum_{t=1}^{T} v_2(t) e^{C_2(t)-\kappa} + \varepsilon_2(t)$$

$$y_2(t) = C_2 + \varepsilon_2'(t)$$

$$\sigma_2^2(t) = k_2 + g_2 \sigma_2^2(t-1) + \alpha_2 \varepsilon_2''^2(t-1)$$

X *:Cell concentration (physiological process)*

$u(t)$ *: Drug concentration (medication)*

$y_1(t), y_2(t)$ *: Internal disturbance (imperfection caused by chemical components of system)*

$X_1(t)$, $X_2(t)$ *: Population of normal / cancerous cells at time t*

$x_1(t)$, $x_2(t)$: *Logarithm of population of normal / cancer cells at time t*

$\sigma_1(t), \sigma_2(t)$ *: Spread of the medication in normal / cancerous cells*

$C_1, C_2, g_1, g_2, k_1, k_2, \alpha_1, \alpha_2$ *: Relatively stable parameters*

$a_1, a_2, b_1, b_2, d_1, d_2$ *: Vectors of coefficients*

$\varepsilon_1'(t) \sim N(0, \sigma_1^2), \varepsilon_2'(t) \sim N(0, \sigma_2^2)$ *:Normal noise vectors with each variance given by the quadratic regression shown in each case*

$\varepsilon_1''(t) \sim N(0,1), \varepsilon_2''(t) \sim N(2, 0.005)$ *Normal noise vectors and finally* v_1 *and* v_2 *are respectively normal and cancer cell volume and* c_1 *and* c_2 *are cell concentrations.*

The third equations of each model give the variances σ_1^2 *and* σ_2^2 *respectively. Each variance is a dynamic system, forming the changing variance related to* $y_1(t), y_2(t)$. *The dynamic* $u(t)$ *is a control process.* It can also be written as a matrix consisting solely of the values -1 and +1 where, columns represent the number of trials and rows represent the treatments. When a treatment works *well* it switches up and when it works *not well* it switches down. Additionally, if we label the rows of $u(t)$ as $u(1), u(2), \ldots, u(T)$ then $u(i)$ corresponds to the treatment at time $t = i$. So we may see the columns as vectors of the values -1 and +1, where +1 corresponds to increasing the drug administration and -1 corresponds to decreasing the drug administration for a fixed period of treatment which is then directly related to the state of recovery of the patient at fixed period of time. In summary, we claim that the dynamic of cell depends singularly on the initial concentration, along with previous cell concentration time series and inner disturbances or noise in cells (covering interactions and/or random processes between cells). This can be translated with coupled control dynamic and a Normal and/or Poisson noise. In fact, we shall observe later that the control process u is the main thrust of our investigation.

3. Parameter Estimation

In this paper, all relevant parameters are estimated using *garchtfit* toolbox in Matlab. The interested readers can find the related results in our earlier work (Jimbo and Craven 2012).

4. Objective Function

In to design of an effective chemotherapy with toxicity, two conflicting objectives are at play:

- The drug must destroy a minimum number of normal cells (Min J_1);
- The drug must destroy a maximum number of cancerous cells (Max J_2).

In our search for an effective cancer chemotherapy schedule, we convert our problem into an Optimal Control Problem; that is, given a dynamic system, we must find the optimal control. In this case we have two dynamic systems which form a coupled dynamic system with respect to control *u*, we must find the optimal control u^*. Below we give the objective functions we will use for finding u^*.

a. Objective function for the normal cells: $J_1 = J_1(u, c_1)$

From a quadratic programming standpoint, see for example (A.B, Lim et al. 2001), the objective functions J_1 and J_2 are measures that one must appropriate in order to technically control the variability in the number normal of cells x_1 and x_2. The objective function for normal cells is as follows:

$$J_1(u) = \frac{1}{T-1}\left(\frac{1}{2}x_1'(0)Hx_1(0) + \sum_{t=0}^{T} x_1'(t)Hx_1(t) + \sum_{t=0}^{T} y_1'(t)Ry_1(t) + \sum_{t=0}^{T} u'(t)Qu(t) + \sum_{1}^{T} v_1 c_1^{\kappa}(t)\right)$$

This also represents the number of normal cells killed for a fixed period of treatment T using a given drug schedule*u.*

b. Objective function for the cancerous cells: $J_2 = J_2(u, c_2)$

Similarly for cancer cells, we obtain the following.

$$J_2(u) = \frac{1}{T-1}\left(\frac{1}{2}x_2'(0)Hx_2(0) + \sum_{t=0}^{T} x_2'(t)Hx_2(t) + \sum_{t=0}^{T} y_2'(t)Ry_2(t) + \sum_{t=0}^{T} u'(t)(-Q)u(t) + \sum_{1}^{T} v_2 c_2^{\kappa}(t)\right)$$

In this case$J_2$is the number of cancer cells killed during a fixed period of treatment T using the drug scheduling *u.* In each case, optimizing $J_1(u)$ or $J_2(u)$ will lead to an amelioration of the condition of the patient. We begin with an '*unoptimised' u*, which we choose to contain the values -1 and +1 chosen uniformly at random. The matrices *H* and *R* are in line with the change in the system over time, and to be in accordance with experimental data they must take
small values; the matrix *Q* represents the effect of u upon the cells in each cell at each treatment period of time. In this spirit, the constants d_1, d_2 serve the same function as the matrix *Q*. The default values of the matrices in (a) and (b) were set to be $H = (0.01)$, $R = (0.02)$, $Q = (-0.5)$, in order to fulfill some stability condition.

5. Optimization problem

We are trying to minimize the number of normal cells killed while maximizing the number of cancer cells killed by the chemotherapy drug control. The problem can be set as follows:

$$\text{Solve:} \quad \min(J_1) \text{ or } \textit{(inclusive)} \max(J_2)$$

$$\text{subject to:} \quad u_1^* \le u^* \le u_2^*$$

$$c_1(t) < \kappa \quad \textit{and} \quad c_2(t) < \kappa$$

In other words, we wish to find the optimal value u^* that simultaneously minimizes J_1 and maximizes J_2 at each time $t < T$, based on the initial state $x(0)$. In our formulation, the goal is to design effective treatments *u* based on our stochastic models in section 2. In practice, we assume that the patient is as healthy as possible, so that the major factor remains the controller u. Recall that the controller u is a function of time and the rows are used to determine the scheduling of the drug. In the next section, we give our method of determining an optimal control, u^*.

5.1 Our method

In order to optimize *u*, or to produce at least an estimate u^*, we shall use a Random Mutation Hill Climbing algorithm (RMHC). This is justified, since the size of the matrix *u* is typically 100×100 (or larger), thus resulting in $2^{100\times100}$ possible matrices (a massive search space) through which we have to otherwise search in order to find an optimum u^* (this is known as *brute force search*).We begin with a randomly-chosen matrix *u* consisting of entries *-1* or *+1*, and *mutateu* a number, *q*, times, each time by multiplying an entry chosen uniformly at random by *-1*, to give the matrix *u'*. The values of J_1 and J_2 are then compared between u and its *q*-mutation u'. If the new value of J_1 is smaller and/or the new value of J_2 is larger than the previous values then we let

$u = u'$. The process then repeats until some maximum number of iterations has been reached (the termination criterion). The full algorithm is presented below.

5.2 RMHC Algorithm

Inputs: Matrices H, R, Q, initial data $x_1(0), x_2(0)$, *m:* maximum number of iterations, *T:* time to run dynamics, *q:* number of mutations.

Outputs: $u', J_1(u'), J_2(u')$

Let u be a matrix, as above, with each entry either -1 or +1 (chosen uniformly at random).

1. Let $u' \leftarrow u$.
2. Compute both dynamics up to $x_1(T), x_2(T)$ for some value of T, with control *u*.
3. Find the values $J_1(u), J_2(u)$. Let $j \leftarrow 1$.
4. While $j \leq m$ do
   a. *q*-Mutate: Choose an entry uniformly at random from u and multiply the entry by -1. Repeat a total of q times, to produce u'.
   b. Find the values $J_1(u'), J_2(u')$.
   c. If $J_1(u') < J_1(u)$ or $J_2(u') > J_2(u)$ then let $u \leftarrow u'$.
   d. $j \leftarrow j + 1$.

   End

5. Compute both dynamics up to $x_1(T), x_2(T)$ for some value of T, with control u'.

End

5.3 Comments on the Algorithm

Note that the appearance of 'or' in step 5c indicates an 'inclusive or', meaning that J_1, J_2 are not independent. We take typical values of the input constants to be $T = 1000, q = 100$ and $m = 1000$. Our algorithm begins by generating a random control u, followed by (via Step 3) the dynamics of the normal and cancer cells using that control (the base case). We then optimize u in the way specified (step 5), before generating (using Step 6) the dynamics of the normal and cancer cells again with respect to the now optimized control u (the optimal case). During this regeneration the same vectors $y_1, y_2, \sigma_1, \sigma_2$ and their associated noises are taken directly from the base case, providing a sensible comparison between the base and optimal case. The whole treatment last T periods and the performance index or objective function values at the optimum are $J_1(u^*)$ and $J_2(u^*)$. The cancerous cells will decrease with some variations reaching some minimum value, which may be the baseline for cancer-free cells. Usually the performance of hill climbing or evolutionary algorithms is judged according to some measure of the time taken to produce an acceptable solution (which may mean to within some tolerance). Of course, we cannot use this measure with the above algorithm, because by default the algorithm repeats for a given number of m iterations. Thus some other measure of performance might be required. In the next subsection we introduce such measures. In the next section we present our results and discussion.

6. Results

6.1 Experimental setup

Recall that we begin with u a random control matrix consisting of the values -1 and +1 (in our case, the dimensions of this matrix are Nx100), x1(0) and x2(0) are vectors of length 100. N is the number of iterations for which we run the models (1) and (2) to generate the dynamics of the normal and cancer cells. We took the sizes of our matrices H, Q and R to be 100x100. Following Section 3.2, the values of the constant parameters were experimentally set to be $a_1 = 0.03,\ a_2 = 0.04,$ $b_1 = 0.05,\ b_2 = 0.06,\ d_1 = -0.6, d_2 = -0.5.$ The absolute values of d_1, d_2 were comparatively larger than the other constants above because we wish changes to the control u to have a comparatively larger effect on the dynamics (1) and (2) than the effects implied by the values of a_1, a_2, b_1, b_2. As our algorithm computes an approximation to the optimal control u^* based upon a prior run of the stochastic models (1) and (2), the results will always be a little different and hence results derived from individual runs of the RMHC are not directly comparable.

6.2 Graphical plots

Our first figure (Fig. 1 below) depicts typical dynamics for x_1 (left) and x_2 (right). The top dynamic on each side in red represents the dynamic of x_1 and x_2 before u is optimized (that is, u is random), with the green dynamic representing the situation after optimization at Run-1

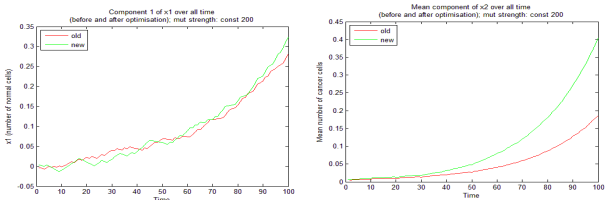

Fig 1: Plots of $x_1(t), x_2(t)$ before (red) and after green) after optimization. As expected, at this *earlier stage* the treatment is completely ineffective Run-1.

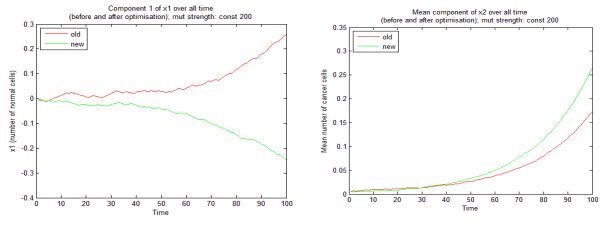

Fig 2. Plots of $x_1(t), x_2(t)$ before (red) and after green) after optimization. As expected, at this *late stage* the treatment is clearly ineffective over Run-5, except that the two dynamics cross in each case.

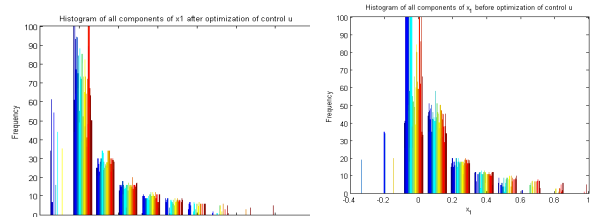

Fig 3. *Normal Cells.* The control u is optimized, we observe a redistribution in x_1 from left to right, more pronounced in size and peak. This increase frequency also traduces an increase in number over Run-1000.

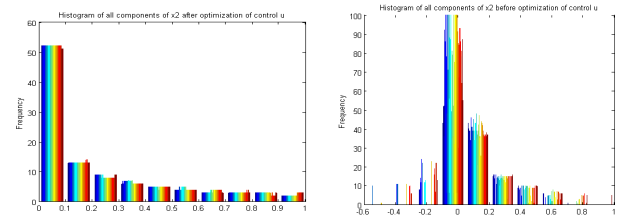

Fig 4. *Cancerous Cells.* The control u is optimized, we observe a *normalization* of x_2. The change from exponential to a normal distributed-like shape shows a good solution to the problem. This observation also traduces a considerable decrease in x_2 over Run-1000.

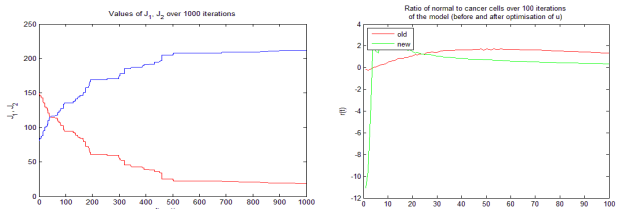

Fig 5. The above left subfigure depicts over Run-1000, the consistent decrease in J1 and increases in J2. The right subfigure depicts the *ratio of normal to cancerous cells* before (in red) and after optimization (in green). This ratio increases after optimization, indicating that the chemotherapy has a clear improvement on the ratio over Run-1000 (iterations) of the RMHC.

7. Discussion and Conclusion

From the existing experimental methods of cancer treatment, chemotherapy is often considered as inherently the most complex (Wheldon, 1988). It is extremely difficult to find effective chemotherapy treatments without a systemic approach. In order to solve the control problem, we need to find a set of treatment schedules which may also have some variations from one patient to another. In this respect, traditional optimization techniques alone will not be enough to solve the control problem. It has been however reported that Genetic Algorithms can improve the quality of the solution (A. Petrovski et al., 2005) for deterministic setups. But our work shows that for objective functions with noise-like disturbance on toxic chemotherapy scheduling, an appropriate GA with constant mutation will be limited and so the algorithm must be reformulated to search the optimal solution by random mutations. The optimum of the problem is, of course *unknown*, it is conceivable that better solutions exist than those found previously, which require a more sophisticated search (Brownlee, 2008). That is why we have considered the development and application of the RMHC algorithm to such chemotherapy problem with consideration of toxic side - effects. Although our results show reasonably good performance, improvements to lower risk of damaging other organs may be possible in future work. To the best of our knowledge, our model is the first stochastic model of this type for understanding such problem. Relaying on optimal control ingredients we were able to convert the quadratic optimization problem and use the powerful RMHC-type algorithm to find optimal solutions.

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