A Dynamical Model of Cancer Chemotherapy with Disturbance

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ABSTRACT

This work proposes a controlled stochastic difference equation model of scheduling, with quadratic cost criteria, for cancer chemotherapy. By reducing the problem to quadratic control optimization and introducing a random search algorithm, we seek an optimal chemotherapy schedule. Our ultimate goal is to provide more realistic solutions than previous models. To reach this goal, our model ideally kills the maximum number of cancer cells to eradicate the disease while preserving the number of normal cells. Our results show the proposed model works well for cancer chemotherapy. Our algorithm is fast and helps produce practical schedules.

Categories and Subject Descriptors

G.1.6 [**Optimization**]: Quadratic programming methods; G.3 [**Probability and Statistics**]: Stochastic processes; J.3 [**Life and Medical Sciences**]: Biology and genetics

Keywords

Nonlinear dynamics, chemotherapy, cancer model, optimal control, algorithm, controlled stochastic difference equation.

1. INTRODUCTION AND BACKGROUND

It is well known that cancer chemotherapy treatment is a complex optimization problem involving many constraints [1]. Chemotherapy consists of using anti-cancer drugs to control or prevent growth of cancerous tumors. Anti-cancer drugs are chemical compounds that kill cancer cells (and also non-cancerous cells). A target is to kill a maximal number of cancer cells while killing a minimal number of "normal" cells for some fixed treatment period. This implies drug scheduling and periodic control are essential in such a process [2].

Chemotherapy drugs attack rapidly dividing cells. Normal cells divide at a rate controlled by the body; in cancer cells this division goes awry, leading to uncontrollable production of new cells and formation of tumors. Chemotherapy drugs interfere with this cell division and may cause the cancer to recede, whereupon we hope to observe an increase in normal cells until recovery. In practice, there are protocols and approved doses for known drugs, but often oncologists tailor a treatment by patient characteristics and disease progression, by trial and error. There also exist evolutionary attempts to optimize chemotherapy schedules, based upon solving or finding an optimal control to a system of ODEs [3], or an EDA minimizing cell response (modeled by Gompertz' equation) when a drug is applied [1]. However, these methods are steady state based and non-stochastic.

We propose a new model based on controlled stochastic difference equations to capture dynamics of cancer and normal cells over time. To find an optimal schedule, we reduce this task to solving a quadratic optimization problem (QOP), and apply a random search algorithm to solve QOP instances. The model has a control variable; thus we restrict study to the related control in the objective functions of the algorithm. We use this approach since we view the system not as growing (as in Gompertz' model) but as a controlled environment. Our model respects random fluctuations at the concentration level inside cells (and their intra-cellular dynamics) and the cell-cell interactions due to concentration variability over time, and is an applicable dynamical system.

2. OUR MODEL

The work of [2] considers a set of ODEs with a switch action control. We extend this, adding noise to the dynamics and a control process, obtaining the stochastic model below. The cancer dynamic (2) follows the normal cells dynamic (1).

$$\begin{aligned} x_1(t) &= x_1(0) + \sum_{t=1}^{T} a_1 x_1(t-1) + \sum_{t=1}^{T} b_1 y_1(t-1) \\ &\quad + \sum_{t=1}^{T} d_1 u(t-1) + \varepsilon_1(t) \\ y_1(t) &= C_1 + \varepsilon_1'(t) \\ \sigma_1^2(t) &= k_1 + g_1\sigma_1^2(t-1) + \alpha_1 \varepsilon_1''^2(t-1) \end{aligned} \quad (1)$$

$$\begin{aligned} x_2(t) &= x_2(0) + \sum_{t=1}^{T} a_2 x_2(t-1) + \sum_{t=1}^{T} b_2 y_2(t-1) \\ &\quad + \sum_{t=1}^{T} d_2 u(t-1) + \varepsilon_2(t) \\ y_2(t) &= C_2 + \varepsilon_2'(t) \\ \sigma_2^2(t) &= k_2 + g_2\sigma_2^2(t-1) + \alpha_2 \varepsilon_2''^2(t-1) \end{aligned} \quad (2)$$

For time t, $u(t)$ represents the schedule, $y_1(t), y_2(t)$ the internal disturbances, $x_1(t), x_2(t)$ the logarithms of numbers of normal/cancer cells, and $\sigma_1(t), \sigma_2(t)$ the spread of medication in normal/cancer cells. Parameters a_1, a_2, b_1, b_2, d_1, d_2 are vectors of small numbers, with the remaining parameters estimated. The disturbance noises are $\varepsilon_1'(t) \sim N(0, \sigma_1^2)$, $\varepsilon_2'(t) \sim N(0, \sigma_2^2)$. The control dynamic $u(t)$ is a $T \times T$

GECCO'12 Companion, July 7–11, 2012, Philadelphia, PA, USA.
ACM 978-1-4503-1178-6/12/07.

$(-1, 1)$-matrix, whose columns represent components and rows treatments at times $1, \ldots, T$, and 1/-1 means to increase/decrease the drug dose at the applicable time. Assume each cell has a measured concentration over time, and that we may follow changes in number of cells via changes in their concentrations. The model implies the dynamic of each type of cell depends on all previous cell concentrations, disturbances in chemical interactions, control and external noise. We set the initial dynamics $x_1(0)$, $x_2(0)$ by experimental cell concentration data [4] and $\sigma_1(0) = \sigma_2(0) = 0$.

3. THE ALGORITHM

Designing an effective chemotherapy schedule, two objectives J_1, J_2 conflict: the drug must destroy a minimum number of normal cells (minimize J_1) and a maximum number of cancer cells (maximize J_2). In search of such a schedule, we convert our problem into one of optimal control: given the coupled dynamical system (1)–(2) with control u, find the optimal control u^* producing the best desired behavior of the system. From a quadratic programming standpoint, the objective functions J_1, J_2 are measures we must optimize to control variability in the numbers x_1, x_2 of normal/cancer cells. The objective function for normal cells is

$$J_1(u) = \frac{1}{T-1}\left(\begin{array}{c} \frac{1}{2}x_1'(0)Hx_1(0) + \sum_{t=0}^{T} x_1'(t)Hx_1(t) \\ + \sum_{t=0}^{T} y_1'(t)Ry_1(t) + \sum_{t=0}^{T} u'(t)Qu(t) \end{array}\right), \tag{3}$$

representing the number of normal cells killed for a fixed treatment period, T, with schedule u. Similarly we obtain the following objective function for cancer cells.

$$J_2(u) = \frac{1}{T-1}\left(\begin{array}{c} \frac{1}{2}x_2'(0)Hx_2(0) + \sum_{t=0}^{T} x_2'(t)Hx_2(t) \\ + \sum_{t=0}^{T} y_2'(t)Ry_2(t) + \sum_{t=0}^{T} u'(t)(-Q)u(t) \end{array}\right) \tag{4}$$

Conforming to experimental data, matrices H, R have small entries. The matrix Q represents the effect of u on cells at each time. Constants d_1, d_2 serve the same function as Q. The matrix entries in (3)–(4) are in line with the constants in (1)–(2) (we wish all eigenvalues of the above matrices to be inside the unit disc, to ensure stability of the problem).

To optimize u, we use a Random Mutation Hill Climb (RMHC). This is justified, as the number of possible matrices u is typically $2^{100\times100}$. We begin with a random matrix u with entries -1 or +1, and mutate u a number, q, times, each time multiplying an entry chosen u.a.r. by -1, to give a matrix $\lambda^q(u)$. The values of J_1, J_2 are then compared for u and $\lambda^q(u)$. If $J_1\left(\lambda^q(u)\right) < J_1\left(u\right)$ and/or $J_2\left(\lambda^q(u)\right) > J_2\left(u\right)$ then we let $u \leftarrow \lambda^q(u)$. The process repeats for a given number (m) of iterations. We then compute both dynamics x_1, x_2 with control u^*, and vectors y_1, y_2, σ_1, σ_2 and all noises are as with u. This enables comparison of the dynamics computed for u with those computed for u^*.

4. RESULTS AND CONCLUSION

We ran the model (1)–(2) for 1000 iterations to generate the dynamics of the normal and cancer cells, and took the size of matrices H, Q, R to be 100×100. Fig. 1 depicts typical dynamics for x_1 (top) and x_2 (bottom). The red dynamic on each represents the dynamic before u is optimized (random u), with the green dynamic that after optimization. Plots (omitted) of J_1, J_2 show that over subsequent iterations the value of J_1 decreases and that of J_2 increases, with the durations of local optima generally increasing. The algorithm runtime is linear in the number of model iterations and the number of steps in each mutation (q), and dependent on the lengths of initial vectors $x_1(0)$, $x_2(0)$. In practice the algorithm is consistent and stable (proof omitted).

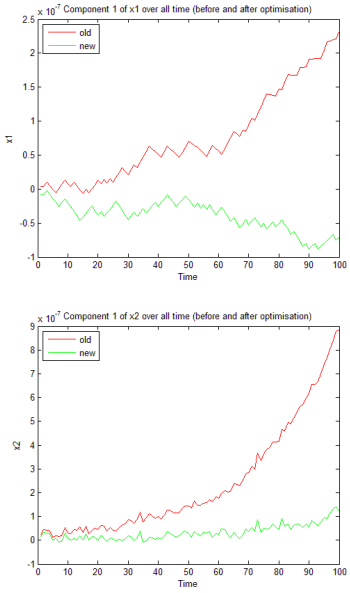

Figure 1: Typical components of x_1, x_2 before (red) and after (green) optimization. The random treatment is ineffective; in particular, the number of cancer cells increases exponentially over time. After optimization the number of cancer cells increases more slowly, implying improvement in the schedule u.

Although the results show good performance, improvements to lower the risk of damaging other organs may be possible in future work via improved models, a more sophisticated algorithm, or by using operators more suited to the problem. To our knowledge, our approach is the first stochastic model of this type employing reduction to a QOP followed by an RMHC to find optimal solutions. Finally, we believe our model will produce good results for other initial datasets (the initial condition of the patient) besides [4]. An extended version of this work is available from the authors.

5. REFERENCES

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