Analysis and Optimization of Cell-Cycle Specific Cancer Chemotherapy

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Introduction

Cell-cycle specific chemotherapy is a common procedure for treating cancer, administered by using drugs that attack cells in particular phases of the cell-cycle. The phases of the cell-cycle that are relevant for chemotherapy differ for each drug, for instance, Cyclophosphamide acts on cells in the DNA replication phase, while Taxol targets cells in the division phase (Fister et. al., 2000). The common link between all cell-cycle specific chemotherapy drugs is their ability to affect cells that are proliferating, while leaving quiescent (resting) cells unharmed. This is the fundamental basis of chemotherapy.

Current treatment practice involves multiple chemotherapy regimens. In a single regimen, the patient is dosed with a fixed concentration of the drug for a time period (the active period), and allowed to rest for another period of time (the resting period). An active period of 24 h and a resting period of 20 days is typical (Panetta, 1997), but in clinical trials involving Taxol, active periods ranging from 1 to 96 h, drug doses from 75 to 300 mg/m^3, and total periods (active plus resting) from 7 to 21 days have been reported (Huinink et. al., 1993, Hainsworth et. al., 1994, Klaassen et. al., 1996, Riondel et. al., 1986). The implication of the vast differences between these trial conditions is that there is still no clear optimal treatment strategy (Panetta, 1997).

A major obstacle to the effectiveness of chemotherapy is that during the active period of a regimen, both healthy and cancerous cells are damaged, since the drug does not differentiate between healthy and cancer cells, just between proliferative and quiescent cells. For most types of healthy cells, this is not a problem, since they are not rapidly proliferating. However, for rapidly proliferating healthy cells, such as hair, and especially bone marrow, the effect is significant, and this is the limiting factor in a chemotherapy regimen. Thus, chemotherapy involves a delicate balance between destroying cancer cells and minimizing collateral damage to normal cells. Determining an optimal treatment strategy that comprehensively addresses both of these competing objectives remains an important problem. In previous work, different mathematical models have been used to investigate the effects of chemotherapy regimens on cell populations. Age-structured and probabilistic models have been used to investigate the effects on bone marrow (Agur, 1986, Agur et. al., 1988, Cojocaru et. al., 1992), while deterministic ODE models have been used to investigate effects on breast and ovarian cancer (Panetta, 1997), and bone marrow (Fister et. al., 2000). The fundamental problem of chemotherapy, the delicate balance between destruction of cancer cells and minimization of collateral damage to normal cells, however, has not been addressed comprehensively. The present work approaches this problem through a physiological model-based analytical methodology that considers the dynamic behavior of cancer and healthy cells simultaneously in determining optimal chemotherapy regimens.

Approach

An existing model by Panetta (1997) was used as the starting point for this work. The original model is a set of ODEs describing the dynamics of proliferating (P) and quiescent (Q) cell populations. By introducing new variables, Y=P+Q, and Θ=P/Y, the original model is transformed into one that is more tractable analytically, revealing many interesting features that will be discussed in the presentation.

Results

For purposes of optimization, the typical chemotherapy regimen involves three decision variables: the active period (A), the drug strength (C), and the resting period (R). By specifying appropriate objectives in the active period (maximize $\Phi=Y_N-Y_C$), and in the resting period (maximize selectivity $\Theta_C-\Theta_N$), where the subscripts denote normal and cancer cell populations, respectively, the transformed model is used to derive optimum values for A, R, and a piece-wise constant C. The procedure and its application are illustrated with three case studies, the results of which will be discussed in the presentation.

Future Work

Future work will include making the model more realistic and reformulating the chemotherapy problem such that dosage application can be determined using model predictive control (MPC) techniques. Concerning model improvements, issues to consider include enhanced prediction (including interaction) of the model parameters, spatial and transport effects, and the important phenomenon of drug resistance (Luebeck et. al., 1995, Alacorn et. al., 2003, Cui et. al., 2000, Ward et. al., 2003, Jackson et. al., 2000, Swierniak et. al., 2003). MPC allows us the flexibility of applying varying drug doses over smaller, regular intervals of time rather than the fixed amount over a predetermined active period.

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