CANCER CHEMOTHERAPY: OPTIMAL CONTROL USING THE VERHULST–PEARL EQUATION

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General (deterministic) ordinary differential equations for the representation of cancer growth are presented when the growth is perturbed due to the action of a chemotherapeutic agent. The Verhulst–Pearl equation is introduced as a particular example of a growth equation applicable to human tumors. An optimal control problem with general performance criterion and state equation is formulated and shown to possess a novel feedback control relationship. This relationship is used in two continuous drug delivery problems involving the Verhulst–Pearl equation.

Introduction. The work by Swan and Vincent (1977) used the Gompertz equation to represent the unperturbed growth of the human bone cancer multiple myeloma. To account for the perturbed growth of this tumor under the action of a chemotherapeutic agent, a loss term of saturation type is introduced. Parameters in the resulting mathematical model are obtained from real patient data. A typical melphalan, prednisone, cyclophosphamide (MCP) program of therapy given at the end of discrete time intervals is evaluated. Also considered is the therapy under a continuous delivery of anticancer drug. This novel approach is based on using the technique of engineering optimal control theory. A comparison of the discrete program with the continuous control program demonstrated the superiority of the latter.

This early theoretical belief that the continuous delivery of the anticancer drug would be a worthwhile therapeutic alternative to a regimen based on discrete drug dosages has received interesting confirmation in practice. First, progress was made in the development of reservoirs and pumps that could be used for the delivery of the anticancer drugs, e.g. Buckles (1978). Then Dorr et al. (1979), in perhaps the first paper to deal with clinical results using these extracorporeal pumps, showed how significant benefits accrued to the patients. Benefits of continuous chemotherapy include the significant lessening of the degree of systemic toxicity and the side effects of conventional therapy. Then McKinstry (1981) presented a review of the progress on implantable pumps for regional cancer chemotherapy. Progress in the clinical setting continues; Cohen et al. (1983) report on patients treated for the control of liver metastases via the continuous delivery of an anticancer drug from a totally implantable device: the drug is released into
the hepatic artery. Recently Shepard et al. (1985) report on the use of continuous chemotherapy for metastatic colo-rectal cancer.

Theoretical approaches to the solution of mathematical modeling problems involving the continuous chemotherapeutic control of cancer also continue. That applications of optimal control theory offered considerable promise in improvements for the radiotherapy and chemotherapy of cancer as well as for the therapy of other diseases is explored in Swan (1975, 1977, 1980, 1981a,b, 1982, 1984, 1985, 1986a–c).

One of the current approaches to the solution of optimal control problems in cancer chemotherapy is as follows. A mathematical model of the gross growth characteristics of the tumor is introduced with an appropriate control term. (This gives the state equation.) Then a performance criterion is constructed and the basic equations of the optimal control problem are derived and joined with the state equation. The analysis of these nonlinear, ordinary differential equations is complicated because the dependent variables are all jumbled up together.

In this paper, for a general class of optimal control problem arising in chemotherapy, it is shown how to obtain an exact first integral. This result is very beneficial for it provides a direct relationship between the control and the state variables. Also, it gives an equation for the determination of the initial value of the control.

The application of the Verhulst–Pearl equation to cancer growth appears to have been overlooked in favor of other mathematical models, such as the Gompertz equation. Here, the Verhulst–Pearl equation is introduced and support is given for its usage in human cancer chemotherapy problems. The analysis of several optimal control problems in cancer chemotherapy using this equation is presented. Throughout, attention is restricted to deterministic models. Data on human multiple myeloma are used in the models.

The quantity $u$ [see equation (5)] is a continuous time controller. This means that the models have possible applications in those situations where an anticancer drug is delivered to the subject on a continuous basis.

**Mathematical Models of Tumor Growth.** A general mathematical model that is assumed to represent the gross characteristics of a growing tumor is given by

$$\frac{dL(t)}{dt} = a_1 f_1(L), \quad L(0) = L_0$$  \hspace{1cm} (1)

where $a_1$ is a constant parameter with the dimensions of $(\text{time})^{-1}$. This is a deterministic ordinary differential equation. The quantity $L(t) \equiv L$, where $t$ is the time, is usually interpreted as the total number of tumor cells, or the level of tumor burden such as the volume of space occupied by the tumor. Equation (1) represents the situation for unperturbed growth. The growth