MATHEMATICAL APPROACHES TO OPTIMIZATION
OF CANCER CHEMOTHERAPY

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This paper uses optimal control theory in conjunction with a Gompertzian type model for cellular growth to determine the optimal method of administering cycle non-specific chemotherapy or more generally the optimal durations of treatment and rest periods during chemotherapy. The performance criteria employed to determine the relative merits of the therapy include not only the destruction of malignant cells, but also the sparing of a critical normal tissue. Since these criteria are at odds with one another, the solutions are found which satisfy the Pareto optimality conditions.

1. Introduction. Cancer is one of the most dreaded diseases of our time, killing approximately 350,000 individuals a year in the United States alone. One of the difficulties that we face in treating the wide variety of cancers is that almost all cancers metastasize. Metastasis is the process by which cells break away from the primary tumor site and spread through various pathways like the blood and lymph systems to distant sites of the body where they take up residence and form secondary growths. Once metastasis has occurred, treatment of cancer by localized methods like surgery and radiation therapy is no longer curative since these methods cannot destroy the multitude of microscopic metastatic growths, each of which have the capability of growing to life-threatening size.

Therefore, in such instances, systemic therapy must be undertaken. The most successful of such treatments to date is chemotherapy in which patients are given drugs which are supposed to destroy the tumor cells. However, these drugs also destroy normal cells, especially the fast growing regenerative tissues like the bone marrow and gut epithelium.

Thus, in administering chemotherapy the physician is dealing with a two-sided sword. In designing a chemotherapeutic protocol he must not only consider how well the drugs will destroy the malignant tissue, but also
how best he can protect vital normal tissue and minimize other toxic reactions of the treatment.

Often it is not obvious how "best" to administer chemotherapy in the face of conflicting criteria. Such treatment must always play off the benefits of treatment versus the risk of complications. Mathematical modeling of chemotherapy can help in exploring various strategies of treatment. In recent years various mathematical descriptions of cellular growth and the effect of chemotherapeutic agents on the growth have been developed (Aroesty et al., 1974; Nicolini et al., 1975, 1977; Zietz, 1977). Using the models it is possible to simulate therapy and to potentially make predictions of which protocol might be better than others.

However, using these models, it is also possible to try to optimize the treatments. That is, out of all possible treatments (with a confined group of possible strategies for treatment), predict the "best" one. Of course, the "best" must be made into a precise mathematical statement encompassing all the relevant criteria. Also, it is conceivable that the answers may be model dependent, that is, the models that seem to be equally plausible given our present biological knowledge might yield completely different answers. In this case we must go back to basic biology and do the critical experiments to distinguish between the models. However, if all plausible models give approximately the same answers, then we can feel a little safer that we have captured the essential aspects of the optimization problem.

Our approach to the optimization of cancer chemotherapy is to make judicious use of experiments, mathematical models and optimization techniques to explore optimal treatment strategies. Our modeling of chemotherapy takes place at many levels depending on the biological question under consideration. We feel that the mathematical complexity of the model to be considered must be directly related to the phenomena under consideration. Although a complex mathematical model might yield good quantitative predictions between experiment and theory often a less complex one will equally account for important experimental observations. Also, as the complexity of a model increases, the more intractable it becomes; and often the complexity causes great difficulty in trying to optimize for the best treatment.

There have been several mathematical attempts to apply optimal control theory to design of treatment protocols. Noteworthy in this respect are Almquist and Banks (1976) and Swan and Vincent (1977), which besides containing excellent work cite much of the relevant published literature.

In this work, we examine several simple cellular kinetic models of cell cycle non-specific chemotherapy* to determine the optimal method of

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*The models proposed more generally apply to the problem of how often to treat and how long to let a patient rest between treatment.