INTRODUCTION

This paper provides a general framework within which one may pose problems of scheduling for treatment regimes with particular reference to optimality. At present, schedules are derived in a purely heuristic fashion. Our mathematical formulation follows the work of Lions and Bensoussan (1) on stock control in which the system is described by a stochastic differential equation and the controls are of impulsive nature. Such controls change the state of the system at instants and by amounts which are available for choice. The minimization of a performance index leads to optimality criteria which can be formulated in terms of quasi-variational inequalities for which numerical methods of solutions have recently been developed. (Goursat and Maarek (2)).

In cancer radiotherapy the underlying dynamics are those of tumour growth, the tumour consisting of two types of cells with different growth rates and radiation sensitivities. The mathematical model is given in terms of differential equations representing the number of cells. Uncertainty in the dynamics is modelled by additive white noise. The performance index penalises the number of cancer cells at the end and during a treatment period. The controls are the levels and times at which radiation doses are given, and the performance index includes terms which limit the level and frequency of the doses.

Numerical computations have been carried out on a Sigma 5 computer using both the methods of Mosco and Scarpini (3) and dynamic programming approximation (2). The results justify and suggest improvements to treatments at present used by clinicians (Wheldon and Kirk)(4)).

THE DETERMINISTIC MODEL

The model of Fischer (5) describes the development and interplay among four different cell types: live oxygenated, dead oxygenated, live anoxic, and dead anoxic. These four cell types are emphasized because of their distinct responses.
to irradiation. The live oxygenated cells differ from the live anoxic cells in that they divide, hence causing tumour growth. Whereas the dead cells are those that have been damaged by radiation, and although they may metabolise, they no longer have the capacity to divide. It is possible for anoxic cells to become oxygenated and vice versa, and this interchange plays an important role in determining the effect of a treatment schedule.

We let $S_o$, $S_1$ be the surviving fraction of live oxygenated and live anoxic cells, respectively, after a radiation dose of $d$ rads, and assume

$$S_i(d) = 1 - (1 - e^{-D/D_i})^{n_i} \quad i=0,1$$

where $D_i$, $n_i$, $i = 0,1$ are constants derived from empirical data, the structure of this formula having been derived from a multi-target single list model of the effect of radiation.

We assume that doses of size $d_i$, $i = 1,2,...$ are given at times $t_i$, $i = 1,2,...$, and there is a constraint on this treatment schedule which is expressed by either

(a) directly placing bounds on the dose size, namely

$$d_i \in U \quad \text{for some compact } U,$$

(b) suitably modifying the form of the Cumulated Radiation Effect (CRE) due to Wheldon and Kirk (4).

Other authors (e.g. Alenquist and Banks (6) fix the times $t_i$ and penalise, through the cost functional, large doses (say, more than 500 rads). In the numerical results to be found in this paper, approach a) has been used.

In order to model the fact that as the tumour size increases the fraction of live oxygenated cells decreases, Fischer used

$$\frac{N_o(t)}{N(t)} = e^{-\beta N(t)}$$

where $N_o(t)$ and $N(t)$ are the number of live oxygenated and total number of tumour cells at time $t$, respectively, and $\beta$ is an empirically determined constant. Then since the growth of the tumour is determined by the number of live oxygenated cells, a simple law for an untreated tumour is

$$\frac{dN}{dt} = \alpha N_o \quad , \alpha \text{ constant}.$$  

From (2.3) we obtain

$$\frac{dN}{dt} = \alpha N e^{-\beta N}.$$  

The general features of (2.5) confirm with the observed behaviour of tumours.