Optimal control of drug administration in cancer chemotherapy

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To my mother Peggy and my fiancé Renata

RBM

To my mother, Lyanne, James, Thomas, Cheryl

KLT

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PREFACE

This monograph is a study of optimal control applied to cancer chemotherapy, the treatment of cancer using drugs that kill cancer cells. The aim is to determine whether current methods for the administration of chemotherapy are optimal, and if alternative regimens should be considered.

The research utilizes the mathematical theory of optimal control, an active research area for many mathematicians, scientists, and engineers. It is of multi-disciplinary nature, having been applied to areas ranging from engineering to biomedicine. The aim in optimal control is to achieve a given objective at minimum cost. A set of differential equations is used to describe the evolution in time of the process being modelled, and constraints limit the policies that can be used to attain the objective.

In this monograph, mathematical models are used to construct optimal drug schedules. These are timetables specifying which drug to deliver, when, and at what dose. Many current drug schedules have been derived empirically, based upon 'rules of thumb'.

The monograph has been structured so that most of the high-level mathematics is introduced in a special appendix. In this way, a scientist can skip the more subtle aspects of the theory and still understand the biomedical applications that follow. However, the text is self-contained so that a deeper understanding of the mathematics of optimal control can be gained from the mathematical appendix.

Two classes of mathematical model are used. The first describes chemotherapy as a series of discrete drug doses, and is referred to as an optimal parameter selection problem (Chapters 5, 6, and 9). In the second class of model, a continuous function of time called a control is chosen to optimize treatment. The model is formulated as an optimal control problem, and the control may represent the rate of delivery of the drug (Chapter 7) or the total tumour cell population (Chapter 8). Two types of chemotherapy are considered in this study: those in which the toxic side-effects of the anti-cancer drugs force the treatment to end, and those in which the period of treatment is limited by drug resistance.

Chapter 1 derives the elements that are common to the models used in this text. It is shown how differential equations can be used to model tumour growth and to calculate tumour doubling times. A model of the effect of the anti-cancer drug

on the tumour is proposed. Also, several measures of the toxic side-effects of the anti-cancer drugs on normal tissue are examined.

The introduction presented in Chapter 2 explains concepts that are fundamental to optimal control theory, and some examples are given of how optimal control has been applied to biomedicine. Chapter 2 describes some of the mathematical models that have been used to optimize cancer chemotherapy. A brief literature survey of optimal control applied to cancer chemotherapy is included. At the beginning of each subsequent chapter, more detailed reviews are presented of the literature relevant to that chapter.

In Chapter 3 a general class of combined optimal parameter and control problems is considered that has general constraints on the state and control variables. The control parametrization technique, a unified computational method, is reviewed briefly. This includes the construction of gradients of the objective functional and the constraint functionals. Various important classes of optimal controls are then shown to be transformable to special cases of the problem under consideration.

In Chapter 4, a class of optimal control problems is considered in which the objective function and constraints depend upon two or more discrete time-points. These time-points are referred to as characteristic times. In standard optimal control theory, at most one such characteristic time exists (for the objective function it is normally the terminal time). One way in which multiple characteristic time systems arise is when a large number of constraints is reduced to a single equivalent constraint using the constraint transcription technique (see Chapter 9 for an example of such a system). The control parametrization technique is used to develop a numerical scheme for solving this class of problem. This includes constructing gradients of the canonical constraint functionals with respect to the control parameters. An unusual feature of the corresponding costate functions is that they have jump discontinuities at the characteristic times.

A fundamental model of cancer chemotherapy is presented in Chapter 5. The aim is to minimize the tumour size at the end of a fixed period of therapy by scheduling a fixed number of doses of drug. The tumour growth is modelled by the Gompertz differential equation. Throughout therapy, the drug concentration and tumour burden are bounded above, and the total cumulative drug toxicity is also constrained. To make the problem numerically tractable, the constraints that are continuously parametrized by time are transformed to sets of interior-point state constraints that are not time dependent. Numerical solutions show that an optimal drug regimen withholds the bulk of the doses until the end of the treatment period. This is in contrast to conventional treatments, which begin with high intensity therapy.

Many of the parameters that influence the scheduling of anti-cancer drugs cannot be precisely determined at the start of chemotherapy. These may include the initial

tumour burden and the proportion (if any) of drug resistant cells, the rate of tumour growth, and the effectiveness of the anti-cancer drugs. These parameters are crucial to the design of effective therapy.

Parameter uncertainty is explicitly taken into account in the model explored in Chapter 6. Its structure is similar to the model in Chapter 5, except that the only information about certain ‘unknown’ parameters is they lie in a known set. The system constraints must be satisfied for any values the parameters take in this set. The drug is scheduled so that the final tumour burden is minimized when the parameters assume their most unfavourable values (a worst-case scenario).

The optimal control model in Chapter 7 is a development of the basic model presented in Chapter 5. The tumour size is constrained to decrease at or faster than a given rate (this is a multiple characteristic time constraint). Numerical solutions suggest that the best way of reducing the tumour burden after a fixed period of treatment is to keep the rate of decrease of the tumour size to a minimum initially, and then give high intensity treatment towards the end of the treatment period.

Chapters 8 and 9 deal with cancer chemotherapy in which some tumour cells are totally resistant to the anti-cancer drug(s). The high failure rates encountered in chemotherapy suggest that this is a very common occurrence.

Since the tumour cannot be destroyed, the endpoint of the treatment occurs when the tumour is totally drug resistant and exceeds a given size. This point in time is termed the survival time of the patient. These chapters question whether aggressive therapy, which maximizes the probability of destroying a cancerous tumour, is the best choice for drug resistant tumours.

In the optimal control model considered in Chapter 8, the tumour burden during therapy is used to slow the growth of the drug resistant cells. Three models of tumour growth are considered: Gompertz, logistic, and exponential.

It is shown that the policy maximizing survival time—maximize the tumour burden at all times—does not depend upon the particular growth model.

In Chapter 9, a model of multiple drug chemotherapy is investigated. Two non-cross-resistant drugs are used to treat a drug resistant tumour. The system is described as an optimal parameter selection problem in which the terminal time is free to vary. New theory is developed so that the optimal parameter selection problem can be solved as a sequence of fixed terminal time problems using existing optimal control software. Simulations show that low intensive therapy with non-curative intent increases patient survival time by 200–300% compared with the more traditional aggressive therapy.

Chapter 10 is a conclusion chapter.

The Appendix contains elements of mathematical analysis that were used to develop the research in this book. This material has been drawn together into the one easy-to-refer-to section for the benefit of scientists who are not familiar with these results. However, scientists who are not interested in mathematical details can skip the theorem proofs and still understand the biomedical material in the main body of the book.

This book is highly interdisciplinary in nature. The authors believe that it will be useful to applied mathematicians, biomedical engineers, and scientists working in the areas of operations research, cancer research, and medicine.

It is our pleasure to acknowledge the contribution of Dr Mike Fisher and Dr Rod Minchin. Many of the results contained in the book were obtained jointly with them. The first author thanks Dr Michael Byrne, an oncologist at the QEII Medical Centre, Perth, Western Australia for a number of challenging discussions in the clinical aspects of cancer chemotherapy. Dr Les Jennings helped re-write sections of the MISER3 optimal control software to suit the optimal parameter selection problems in the book, for which we are grateful. We are grateful to Professor R. Doraiswami of the University of New Brunswick, and Dr Z.Q. Zang for their useful suggestions and comments about drafts of this book. Our thanks also go to the Defence Science and Technology Organisation at Salisbury, South Australia, and the Department of Mathematics at the University of Western Australia. Partial financial support came from a research grant from the Australian Research Committee.

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