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Optimal Control Drug Scheduling of Cancer Chemotherapy*

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Anti-cancer drugs are delivered to minimize the size of a tumour. Analytical gradients of all constraints are constructed and the problem solved numerically. The optimal treatment is low intensity therapy followed by high intensity therapy.

Key Words—Biomedical; mathematical modeling; non-linear programming; optimal control.

Abstract—This optimal control model of cancer chemotherapy constructs drug schedules that most effectively reduce the size of a tumour after a fixed period of treatment has elapsed. A constraint is imposed so that the tumour size must decrease at or faster than a specified rate. The system is solved using an established numerical solution technique known as control parametrization, and analytical gradients are constructed of all the constraints so that the resulting non-linear programming problem is solvable using currently available software. An interesting feature of the constraints on the rate of decrease of the tumour size is that the corresponding co-state functions are discontinuous in time. 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.

1. INTRODUCTION

IN SEVERAL RECENT studies (Martin, 1991; Martin *et al.*, 1990; Murray, 1990a, b) cancer chemotherapy protocols were chosen to minimize the tumor burden after a fixed period of treatment. With this type of cost function, there is no reward for reducing the tumour burden earlier rather than later, since the efficacy of the drug protocol is measured solely in terms of the final tumour burden. However, there is evidence suggesting that drug regimens maintaining a low intermediate tumour size could decrease the likelihood of the emergence of drug resistant cells (Goldie and Coldman, 1979). The emergence of drug resistant cells is thought to be a significant factor in chemotherapeutic failure (Crowther, 1974; DeVita, 1985; Skipper, 1978).

The approach adopted in the current paper is to ensure that the tumour size decreases at, or faster than, a given rate over the whole treatment period. This type of constraint was also used in a recent multi-compartmental model of cancer chemotherapy (Sundareshan and Fundakowski, 1985). Here, the anti-cancer drug was delivered periodically at a constant dose to an exponentially growing tumour. The aim was to minimize the total amount of drug that was delivered, while ensuring that cancer cell population satisfied an exponential stability constraint. A further requirement was that the therapy lasted for some minimum length of time. In the current paper, however, the rate of delivery of the anti-cancer drug is described by a piecewise continuous function of time, rather than as a sequence of discrete doses. This increased flexibility may help to decide if continuous therapy is superior to treatments in which the drug is delivered at fixed time points. Also, the steady decrease in the tumour size is described by a set of constraints, each of which is dependent upon the state vector evaluated at two distinct time points. The resulting optimal control problem is solved using the control parametrization method developed by Teo and his co-workers (Goh and Teo, 1988; Jennings *et al.*, 1990; Teo and Goh, 1989). New theory has been developed so that the gradients of the state constraints with respect to the control parameters can be calculated analytically. After analytical gradients of all the system constraints have been constructed, the resulting non-linear programming problem is solved using currently available software.

2. OPTIMAL CONTROL MODEL

In a recent study, three models of simple logistical growth were used to describe volu-

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metric growth in heterogeneous tumours (Michelson *et al.*, 1987). In four of the five tumour cell populations, the Gompertz equation gave the best fit. The Gompertz equation is analytically tractable and has been used in the current study to describe the unperturbed growth of a population of cancer cells. Denote the number of tumour cells at time t by $N(t)$, and assume that $N(t)$ obeys the first-order differential equation

$$\begin{aligned} \dot{N} &= \lambda N \ln(\theta/N), \\ N(0) &= N_0. \end{aligned} \tag{2.1}$$

The treatment commences at $t = 0$ and ends at the fixed time $t = T$. The parameter λ is a positive constant. The Gompertz equation is a sigmoidal growth function, since as time increases the tumour mass asympotically approaches a stable level θ called the plateau population (also known as the carrying capacity). For human and animal tumours, the plateau population is above the level that is lethal to the host.

Tumour growth has also been modelled using an exponential growth function. However, it has been shown for some cancers that as the mass of a tumour increases, its growth slows due to a reduction in its growth fraction† (Simpson-Herren *et al.*, 1974). For example, a five-fold increase in mean tumour doubling times between early and late breast cancer has been observed (Shackney *et al.*, 1978). This cannot be reproduced using an exponential model.

The drug concentration at the cancer site is described by a model derived by Bellman (Bellman, 1983):

$$\begin{aligned} \dot{v}(t) &= u(t) - \gamma v(t), \\ v(0) &= v_0. \end{aligned} \tag{2.2}$$

The concentration at time t of the anti-cancer drug is denoted by $v(t)$, and the rate of delivery of the drug is $u(t)$. The function $u(t)$ is assumed to be piecewise continuous in time. The drug concentration at the instant before chemotherapy begins is denoted by v_0. This term is assumed to be zero in all future work. The half-life of the drug concentration is $\ln(2)/\gamma$. It is assumed that the drug is delivered by infusion, there is an instantaneous mixing of the drug with the plasma, and there is an immediate delivery of the drug to the cancer site. These assumptions represent approximations based on the relative amount of time it takes for the above activities to occur with respect to the total amount of time over which treatment is administered.

The relationship between the anti-cancer drug concentration and the growth of the tumour is now derived. It is assumed that the net change in the tumour cell population per unit time is the difference between the increase in cells due to cell proliferation, and the decrease in cells due to the drug, $L(\cdot)$:

$$\dot{N}(t) = \lambda N \ln(\theta/N) - L(N, v). \tag{2.3}$$

Anti-cancer drugs have been shown to kill cells by first-order kinetics (Skipper *et al.*, 1964). That is, the fraction of tumour cells killed by a drug of fixed concentration is not dependent upon the size of the tumour. However, for cycle-specific drugs, the proportion of cells killed depends upon the growth fraction of the tumour. The drugs modelled in the current study are assumed to be cycle-non-specific (e.g. alkylating agents), so that differences in growth fraction are unimportant. These results imply the cell-loss term $L(N, v)$ is linear in N. It is also known that if the drug concentration multiplied by the time of exposure to the drug is constant, the same degree of toxicity will result (DeVita, 1985). This is true over a wide range of drug concentrations. Furthermore, several studies have shown that there is a concentration v_{th} at which the drug ceases to have a therapeutic effect (DeVita, 1985). These results suggest that the cell-loss term $L(N, v)$ is an affine function of v. In summary, the cell-loss term has the form

$$L(N, v) = k(v - v_{\text{th}})H(v - v_{\text{th}})N. \tag{2.4}$$

The parameter k is the proportion of tumour cells killed per unit time per unit drug concentration, and is assumed to be a positive constant. In an exponentially growing tumour, equation (2.4) is equivalent to a linear relationship between the log of the number of cancer cells killed and the drug dose. For most anti-cancer drugs, this relationship breaks down at high dose levels, at which the number of cells killed begins to plateau. An exception to this is the agent cyclophosphamide, for which the cell kill is a linear function of the drug dose even at very high levels. As a result, cyclophosphamide is being used in therapies that employ very high drug doses followed by bone-marrow transplants.

Cancer chemotherapy is a systemic treatment, so the action of the chemotherapeutic agent is not restricted to the tumour site. Any of the body organs are liable to injury. This is in contrast to localized treatments such as surgery or radiotherapy. The drug concentration and the time of exposure to the drug determine the

† The fraction of cells that are replicating their DNA in preparation for division at a particular time (Mehnelsohn, 1960).

degree of toxicity that is sustained in both the normal organs and the tumour (DeVita, 1985; Wheldon, 1988).

In this paper, restrictions will be placed upon the way the anti-cancer drug is scheduled to ensure that the patient can tolerate its toxic side effects. Firstly, the drug concentration at the cancer site is bounded above by the positive parameter $v_{\max}$:

$$0 \leq v(t) \leq v_{\max} \quad \text{for all } t \in [0, T]. \tag{2.5}$$

A second measure of drug toxicity is the drug concentration multiplied by the time of exposure (DeVita, 1985). This can be quantified mathematically as the integral of the drug concentration over a specified period of time. When this period is the entire therapy, the constraint is upon the total cumulative toxicity:

$$\int_0^T v(s)\, ds \leq v_{\text{cum}}. \tag{2.6}$$

The parameter v_{cum} is a positive constant. Agents such as Adriamycin, cyclophosphamide, and doxorubicin require constraints on the amount of drug that is given over an interval of time. However, other agents may become ineffective before maximum cumulative toxicity is reached due to drug resistance.

Drug resistance is thought to be a significant factor in chemotherapeutic failure (Crowther, 1974; DeVita, 1985; Skipper, 1978) and it has been shown that drug resistant cells are more likely to emerge as the tumour burden increases (Goldie and Coldman, 1979). One way of achieving a low intermediate tumour burden is to force the tumour size to decrease at, or faster than, a given rate. Define a set of $M+1$ strictly increasing characteristic times $0 = \tau_0 < \tau_1 < \cdots < \tau_M \leq T$, and impose a minimum fractional reduction, ϵ, on the tumour size, as measured from one characteristic time to the next.

$$N(\tau_{i+1}) \leq \epsilon N(\tau_i), \quad \text{for } i = 0, 1, \ldots, M-1. \tag{2.7}$$

The parameter ϵ is a positive real number less than one. The constraint (2.7) will be referred to as a multiple characteristic time (MCT) constraint. This leads to the following optimal control problem.

Definition 1. Define Problem P as: minimize the final tumour population, $N(T)$, over all piecewise continuous controls, subject to the differential equations (2.2), (2.3), and (2.4) and the constraints (2.5), (2.6) and (2.7).

Bryson and Ho (1975) considered a similar class of optimal control problems and derived first order conditions necessary for a local minimum. The approach in the current paper is to convert the optimal control problem into an optimal parameter selection problem, using control parametrization (Teo and Goh, 1989). The co-state differential equations can be solved analytically to give the co-state functions, and the control parameter gradients can be calculated analytically. An explanation of the theory that achieves these goals is given in Appendix A. The resulting problem can be directly solved using existing non-linear programming software (Schittkowski, 1985), avoiding the necessity to use optimal control software such as MISER3 (Jennings *et al.*, 1990). This type of optimal control problem may also be solved using the gradient restoration technique developed by Gonzalez and Miele (1978) and Miele (1975).

3. CONTROL PARAMETRIZATION OF THE MODEL

Control parametrization is a method for solving general optimal control problems numerically (Goh and Teo, 1988; Jennings *et al.*, 1990; Teo and Goh, 1989). The technique generates a sequence of approximations to the control using piecewise constant functions with pre-assigned switching points. In this process, the heights of the piecewise constant functions are regarded as decision variables. They are called control parameters, and each one of the approximate problems is solvable as a non-linear programming problem.

The current model of cancer chemotherapy could have been posed as a discrete-time optimal control problem, and solved using dynamic programming (Bellman, 1957). There are several reasons why the current approach is superior. Firstly, the process being modelled—the growth of a tumour subject to the action of an anti-cancer drug—is fundamentally continuous in nature. This structure is exploited by using continuous variables and constraints. Secondly, in order to discretize the model, the tumour cell population and the drug concentration need to be evaluated at a set of discrete time points. It is not obvious how to choose these time points. Finally, a discrete-time version of this problem would include constraints upon the state variables. This type of problem is known to be difficult to solve numerically using dynamic programming.

The control parameter vector $\sigma = (\sigma_1, \ldots, \sigma_n)^T \in \mathbb{R}^n$ is introduced following the method outlined above. The control $u(t)$ is the piecewise-constant function of time described

below:

$$u(t) = \begin{cases} \sigma_1, & \text{if } 0 = t_0 \le t < t_1; \\ \sigma_2, & \text{if } t_1 \le t < t_2; \\ \vdots & \vdots \\ \sigma_n, & \text{if } t_{n-1} \le t \le t_n = T. \end{cases} \tag{3.1}$$

The switching times $\{t_i\}_{i=1}^n$ are fixed and evenly spaced over the treatment interval. That is, $t_i = iT/n$, for $i = 0, 1, \ldots, n$. By substituting equation (3.1) into the differential equation for the drug concentration (2.2), $v(t)$ may be expressed as a piecewise-linear function of the control parameters σ_i, for $i = 1, \ldots, n$. It is then possible to reduce the continuous inequality state constraint (2.5) to a finite number of inequality constraints on the control parameters. The results are summarized in Theorem 1.

Theorem 1. The constraint on the maximum drug concentration (2.5) is true throughout the treatment interval $[0, T]$ if and only if $v(t_i) \le v_{\max}$, for $i = 0, 1, \ldots, n$.

Proof. Consider the half-open sub-interval $[t_i, t_{i+1})$, for $i = 0, 1, \ldots, n-1$. Suppose that the drug concentration at time $t = t_i$ is $v(t_i)$. The control $u(t)$ is constant over $[t_i, t_{i+1})$, so after solving the differential equation (2.2), $v(t)$ can be expressed as a function of $v(t_i)$:

$$v(t) = v(t_i)\exp(-\gamma(t - t_i)) + \frac{\sigma_{i+1}}{\gamma}(1 - \exp(-\gamma(t - t_i))). \tag{3.2}$$

The drug concentration (3.2) is an infinitely differentiable function of t. Differentiating both sides once with respect to t gives:

$$\frac{dv(t)}{dt} = \exp(\gamma t_i)(\sigma_{i+1} - \gamma v(t_i))\exp(-\gamma t).$$

If $\sigma_{i+1} > \gamma v(t_i)$, $v(t)$ is monotonically increasing in t over $[t_i, t_{i+1})$. The function $v(t)$ is continuous in t over $[0, T]$, and therefore is maximized over $[t_i, t_{i+1}]$ at $t = t_{i+1}$. If $\sigma_{i+1} \le \gamma v(t_i)$, $v(t)$ is monotonically decreasing in t over $[t_i, t_{i+1})$, and is maximized at $t = t_i$. This completes the proof.

Theorem 1 enables Problem P to be transformed into a more numerically tractable problem. This is due to the reduction in computing effort required to satisfy the set of n interior point constraints to a given accuracy, compared with the computing effort required to satisfy the continuous inequality constraint (2.5) to the same accuracy.

The tumour size can be non-dimensionalized using the scaling $y = \ln(\theta/N)$. This affects the differential equation (2.1) and the MCT constraint (2.7). Once the control has been parametrized according to the equation (3.1), the toxicity constraints (2.5) and (2.6) become constraints on the parameter vector σ. The continuous inequality state constraint (2.5) can be reduced to a finite number of control parameter inequality constraints using Theorem 1. After combining these results, the problem may be transformed as follows

$$\text{minimize } J(\sigma) = -y(T), \tag{3.3}$$

over $\sigma = (\sigma_1, \ldots, \sigma_n)^T \in \mathbb{R}^n$, subject to the differential equation

$$\dot{y}(t) = -\lambda y(t) + k(v(t) - v_{\text{th}})H(v(t) - v_{\text{th}}),$$
$$y(0) = \ln(\theta/N_0), \tag{3.4}$$

the drug concentration

$$v(t) = \frac{1}{\gamma}\sum_{i=1}^{m-1}\sigma_i(\exp(-\gamma(t - t_i)) - \exp(-\gamma(t - t_{i-1}))) + \frac{\sigma_m}{\gamma}(1 - \exp(-\gamma(t - t_{m-1}))),$$
$$\text{where } t_{m-1} \le t < t_m, \text{ for m} = 1, \ldots, \text{n}; \tag{3.5}$$

the constraint on the maximum drug concentration

$$v_{\max} - \frac{1}{\gamma}\sum_{i=1}^{k}\sigma_i(\exp(-\gamma(t_k - t_i)) - \exp(-\gamma(t_k - t_{i-1}))) \ge 0, \quad \text{for } k = 1, \ldots, n; \tag{3.6}$$

the cumulative toxicity constraint

$$v_{\text{cum}} - \frac{\Delta t}{\gamma}\sum_{m=1}^{n}\sigma_m - \frac{1}{\gamma^2} \times \sum_{m=1}^{n}\sigma_m(\exp(-\gamma t_m) - \exp(-\gamma t_{m-1})) + \frac{1}{\gamma^2}(1 - \exp(-\gamma\Delta t)) \times \sum_{m=2}^{n}\sum_{i=1}^{m-1}\sigma_i(\exp(-\gamma(t_{m-1} - t_i)) - \exp(-\gamma(t_{m-1} - t_{i-1}))) \ge 0; \tag{3.7}$$

and the constraint on the tumour burden

$$y(\tau_i) - y(\tau_{i-1}) + \ln(\epsilon) \ge 0, \quad \text{for } i = 1, \ldots, M. \tag{3.8}$$

The term Δt is defined to be $\Delta t = T/n$. Problem P has now been reduced to its most numerically tractable form.

4. ESTIMATING GLOBAL OPTIMALITY

Non-linear programming software developed by Schittkowski (1985) was used to solve the optimal parameter selection model (3.3)–(3.8) numerically. This software requires the gradients of the objective function (3.3) and the constraints (3.6)–(3.8) with respect to the control parameters (see Appendix A). Firstly, note that the constraints (3.6) and (3.7) have gradients that are constant with respect to each control parameter. Note also, that the gradient of the objective function (3.3) can be formulated analytically (Martin *et al.*, 1990). An interesting feature of this problem is that the co-state functions that correspond to the constraints (3.8) are discontinuous at their characteristic times.

The NLPQL software developed by Schittkowski generates solutions that satisfy the first-order conditions necessary for a relative minimum. Numerical solutions of equations (3.3)–(3.8), using NLPQL, indicate that there are many such relative minima. A lower bound on the objective function (3.3) was constructed to measure this global optimality of any particular relative minimum. The construction of this lower bound is outlined below.

Define a function $v^*:[0, T]\rightarrow R$ that saturates the cumulative toxicity constraint (2.6)

$$\int_0^T v^*(s)\,ds = v_{cum}, \tag{4.1}$$

and which is piecewise constant over $[0, T]$

$$v^*(t) = \begin{cases} 0, & \text{if } 0 \le t < t^*; \\ v_{max}, & \text{if } t^* \le t \le T. \end{cases} \tag{4.2}$$

The parameter t^* is found by substituting equation (4.2) into equation (4.1):

$$t^* = T - \frac{v_{cum}}{v_{max}}. \tag{4.3}$$

Note that no piecewise continuous control can generate v^*, since it has a jump discontinuity at the time $t = t^*$. Consider the following solution of the differential equation (3.4):

$$y(t \mid \sigma) = y_0 \exp(-\lambda t) + k\int_0^t (v(s) - v_{th}) \times H(v(s) - v_{th}) \exp(-\lambda(t-s))\,ds. \tag{4.4}$$

Use equation (4.4) to define the parameter y^*:

$$y^* = y_0 \exp(-\lambda t) + k\int_0^t (v^*(s) - v_{th}) \times H(v^*(s) - v_{th}) \exp(-\lambda(t-s))\,ds. \tag{4.5}$$

Theorem 2 will prove that $-y^*$ is a lower bound on the objective function (3.3).

Theorem 2. Let $\sigma \in \mathbb{R}^n$ be any feasible vector of the non-linear programming problem (3.3)–(3.8). Then the parameter y^*, defined by equation (4.5), satisfies the inequality

$$y^* \ge y(T, \sigma). \tag{4.6}$$

Proof. Let v be the drug concentration function, defined by equation (3.5), that corresponds to the control parameter vector σ. Let v^* be the function defined by equations (4.1) and (4.2). It is readily shown that

$$\int_0^T (v^*(s) - v_{th})H(v^*(s) - v_{th}))\,ds \ge \int_0^T (v(s) - v_{th})H(v(s) - v_{th}))\,ds. \tag{4.7}$$

The notation is simplified by introducing the functions

$$\begin{aligned} f(t) &= (v(t) - v_{th})H(v(t) - v_{th}), \\ f^*(t) &= (v^*(t) - v_{th})H(v^*(t) - v_{th}). \end{aligned} \tag{4.8}$$

Since $v^*(t) = 0$ on $[0, t^*)$, equation (4.7) can be written as

$$\int_{t^*}^T f^*(s)\,ds \ge \int_0^T f(s)\,ds. \tag{4.9}$$

The result (4.6) is established by proving that equation (4.9) implies the following inequality

$$\int_{t^*}^T f^*(s) \exp(-\lambda(T-s))\,ds \ge \int_0^T f(s) \exp(-\lambda(T-s))\,ds. \tag{4.10}$$

The right-hand side of equation (4.9) can be expressed as

$$\int_0^T f(s)\,ds = \int_0^{t^*} f^*(s)\,ds + \int_{t^*}^T f(s)\,ds. \tag{4.11}$$

Substituting equation (4.11) into (4.9), and rearranging terms, leads to the inequality

$$\int_{t^*}^T f^*(s) - f(s)\,ds \ge \int_0^{t^*} f(s)\,ds. \tag{4.12}$$

After both sides of equation (4.12) are multiplied by $\exp(-\lambda(T-t^*))$, the following inequality is produced:

$$\exp(-\lambda(T-t^*))\int_{t^*}^T f^*(s) - f(s)\,ds \ge \exp(-\lambda(T-t^*))\int_0^{t^*} f(s)\,ds. \tag{4.13}$$

Equation (4.13) can be expressed as follows:

$$\int_{t^*}^{T} (f^*(s) - f(s)) \min_{[t^*,T]} \{\exp(-\lambda(T-s))\}\, ds \geq \int_0^{t^*} f(s) \max_{[0,t^*]} \{\exp -\lambda(T-s))\}\, ds. \quad (4.14)$$

The inequality (4.14) remains valid when the "min" and "max" functions are omitted:

$$\int_{t^*}^{T} (f^*(s) - f(s)) \exp(-\lambda(T-t^*))\, ds \geq \int_0^{t^*} f(s) \exp(-\lambda(T-t^*))\, ds, \quad (4.15)$$

and equation (4.15) can be rearranged to give equation (4.10). Equation (4.6) is established by multiplying equation (4.10) through by the positive constant k, and adding the term $y_0 \exp(-\lambda T)$ to both sides. This completes the proof.

Theorem 2 does not rely upon the control being parametrized. Hence, it can be used to construct a lower bound on the final tumour size, $N(T)$, that corresponds to any feasible control of Problem P:

$$N^* = \theta \exp(-y^*) \leq \theta \exp(-y(T)) = N(T). \quad (4.16)$$

5. RESULTS

The data used to solve the non-linear programming problem given by equations (3.3)–(3.8) are listed below. All values are accurate to two significant figures.

The treatment was assumed to last for 12 weeks ($T = 84$ days). The parameters λ, θ, γ, N_0, v_{th}, and v_{max} were given the same values as used by Martin and others (Martin, 1991; Martin *et al.*, 1990; Martin and Teo, 1991). It was assumed that a tumour of 10^{10} cells took five months to double in size. The growth parameter λ may be calculated from this value to be $\lambda = 9.9 \times 10^{-4}$ days^{-1} (Martin, 1991). The carrying capacity θ was set at 10^{12} cells, and the initial tumour cell population N_0 was set at 10^{10} cells. The half-life of the drug concentration was 2.5 days ($\gamma = 0.27$ days^{-1}), and the drug concentration below which no tumour cells were killed was $v_{th} = 10[D]$. Here $[D]$ is the unit of drug concentration. The maximum drug concentration was $50[D]$.

The parameter k was calculated following the method derived by Martin (Martin *et al.*, 1990). It was assumed that there was a 50% reduction in the population of a tumour of 10^{10} cells (i.e. a fractional kill of 50%), measured one week after a single maximal dose of drug was delivered. Thus, $k = 8.4 \times 10^{-3}$ days$^{-1}[D]^{-1}$. Two values were used for the cumulative drug toxicity parameter v_{cum}. The first was $v_{cum} = 2.1 \times 10^3[D]$ days, and was equal in cumulative toxicity to a regimen that satisfied $v(t) = v_{max}$ for exactly half of the treatment period, and $v(t) = 0$ for the remainder. The second was $v_{cum} = 1.1 \times 10^3[D]$ days, and was equal in cumulative toxicity to a regimen that satisfied $v(t) = v_{max}$ for exactly one quarter of the treatment period, and $v(t) = 0$ for the remainder.

Definition 2. Define P1 as the problem: minimize the objective function (3.3) over $\sigma = (\sigma_1, \ldots, \sigma_n)^T \in \mathbb{R}^n$, subject to equations (3.4)–(3.8), with $v_{cum} = 2.1 \times 10^3[D]$ days.

Definition 3. Define P2 as the problem: minimize the objective function (3.3) over $\sigma(\sigma_1, \ldots, \sigma_n)^T \in \mathbb{R}^n$, subject to equations (3.4)–(3.8), with $v_{cum} = 1.1 \times 10^3[D]$ days.

There were three multiple characteristic time constraints ($M = 3$), with characteristic times $\tau_i = iT/4$, for $i = 0, 1, 2, 3$. The minimum fractional reduction in tumour size over each three-weekly period was set to be 50%, so that $\epsilon = 1/2$.

Both non-linear programming problems P1 and P2 were solved in the following manner. A sequence of problems was solved, starting with a problem having 16 parameters ($n = 16$). The number of parameters was doubled at each iteration, using the solution from the previous iteration at the starting point for the next. This process continued until there was no improvement in the objective function (3.3). The method was repeated, starting from different initial points, and the best of these solutions was chosen as the solution to the problem. This solution was compared to the lower bound constructed in Theorem 2 to gauge its global optimality. The best solutions to problems P1 and P2 for each value of n are displayed in Table 1.

TABLE 1. TUMOUR CELL POPULATION AFTER 12 WEEKS OF THERAPY USING THE OPTIMAL SOLUTIONS TO PROBLEMS P1 AND P2. THE CORRESPONDING NUMBER OF CONTROL PARAMETERS IS DENOTED BY n. THE LOWER BOUND ON THE OBJECTIVE FUNCTION OF PROBLEM P1 IS $N^* = 1.5 \times 10^4$ CELLS, AND FOR PROBLEM P2, THE LOWER BOUND IS $N^* = 1.4 \times 10^7$ CELLS

n	$J_1(\sigma) = N(T)$	$J_2(\sigma) = N(T)$
16	6.396×10^4	6.424×10^7
32	5.611×10^4	5.808×10^7
64	4.976×10^4	5.808×10^7
128	4.878×10^4	—
256	4.878×10^4	—

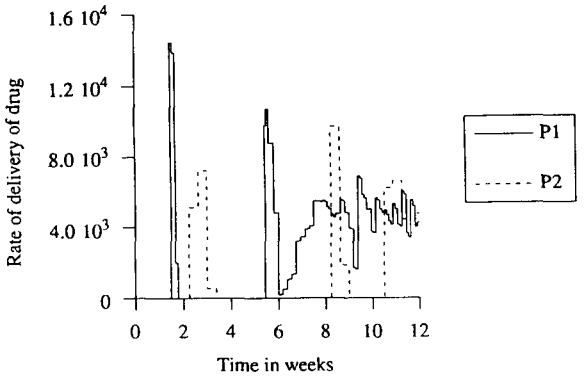

FIG. 1. Optimal treatment protocols for Problems P1 and P2. The units of the vertical axis are $[D]$ weeks^{-1}, $[D]$ being the units of drug concentration. The optimal solution to Problem P1 had 256 control parameters and is denoted by a solid line. The optimal solution to Problem P2 had 64 parameters and is denoted by a dashed line.

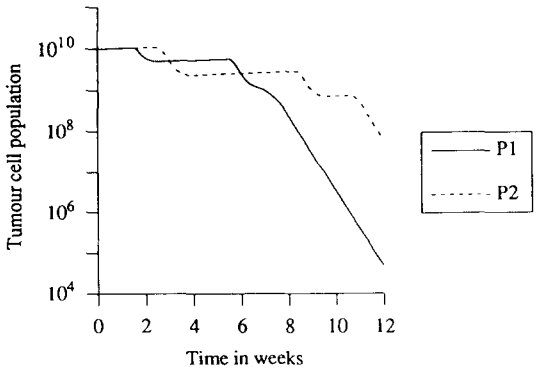

FIG. 3. Predicted tumour growth using the drug regimens of Fig. 1.

For Problem P2, the tumour burden after 12 weeks of optimal control treatment was three orders of magnitude greater than it was in Problem P1. This was due to the fact that the maximum allowable cumulative toxicity in Problem P2 was half that of Problem P1, so that less anti-cancer drug could be used.

The optimal control parameters for Problems P1 and P2 are plotted in Fig. 1. Most of the drug was delivered towards the end of the treatment interval in both drug regimens. For Problem P1, isolated doses of drug were given at weeks 2 and 6, while for Problem P2, isolated doses were given at weeks 3 and 9. Three of these times correspond to the characteristic times of the constraint (2.7). The extra drug available in Problem P1 (higher maximum cumulative toxicity) was distributed towards the end of the treatment interval. Both controls had a lot of fine structure, the reason for which is unknown. This could have been caused if the sequence of sub-optimal controls generated by the control parametrization technique did not converge. Recall that there is no guarantee that this sequence of controls will converge.

The drug concentration histories that correspond to the optimal control parameters of Fig. 1 are plotted in Fig. 2. The highest drug concentrations occurred near characteristic times and towards the end of the treatment interval.

Figure 3 displays the tumour growth that occurred when the treatment protocols of Fig. 1 were used. The optimal way to reduce the tumour size after three months of treatment was 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. This was true regardless of the maximum cumulative toxicity.

The co-state function that corresponded to the second of the MCT constraints is plotted in Fig. 4. This co-state was discontinuous at $t = 3$ weeks and at $t = 6$ weeks, which are the characteristic times of the constraint. This is of interest, since optimal control problems without MCT constraints usually have co-states that are continuous functions of time.

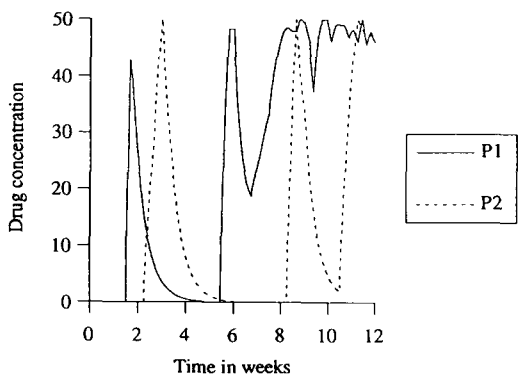

FIG. 2. Drug concentration functions that correspond to the controls of Fig. 1. The maximum cumulative toxicity of Problem P1 (area under the solid curve) was twice that of Problem P2 (area under the dashed curve).

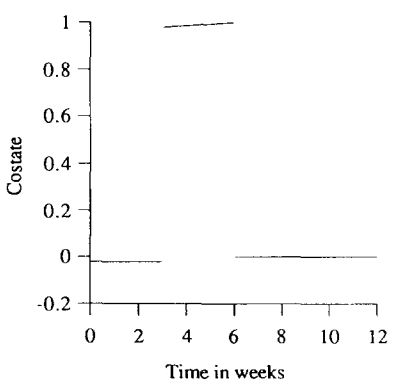

FIG. 4. Co-state function corresponding to the MCT constraint $N(t_6) \leq N(t_3)/2$. Jump discontinuities appeared at the third and sixth weeks, the characteristic times of the constraint.

6. CONCLUSIONS

A drug protocol was constructed in this paper to minimize the tumour burden after a fixed period of therapy. The protocol was chosen to force the tumour size to decrease at, or faster than, a specified rate over the whole treatment interval. The drug regimens most effective in reducing the final tumour size have kept the initial administration of drug to a minimum. This was followed by high intensity therapy near the end of the treatment interval. This finding was independent of the total amount of drug that could be delivered, measured in terms of total cumulative toxicity (cf. constraint (2.6)). There was no indication that the drug should be delivered continuously, since the optimal treatment protocols consisted of therapy separated by periods of rest.

The tumour size in the current model was forced to decrease at, or faster than, a certain rate to reduce the likelihood of the emergence of drug resistant cells, a suspected cause of chemotherapeutic failure (Crowther, 1974; DeVita, 1985; Skipper, 1978). However, the optimal treatment maintained a relatively high tumour burden during therapy. Hence, it may not be possible to minimize the final tumour burden and also reduce the risk of the development of drug resistance.

There are two advantages associated with low intensity therapy. Firstly, there should be an increased quality of life due to a relatively low drug toxicity. Secondly, down-regulation of the immune system should be minimized. This has the potential to contribute to the inhibition of tumour growth (Bast, 1985). On the other hand, a high tumour burden could be both uncomfortable and dangerous for the patient. Also, low intensity therapy may fail to destroy small tumour masses that could be eliminated using high intensity therapy.

The idea of extending the survival time by maintaining a high tumour burden has recently been supported by Prehn (Prehn, 1991). He suggests that a tumour behaves like a body organ in which the plateau population is too high for the host to survive. If an increase in the tumour cell population could be simulated, the growth of the tumour might be slowed or even stopped.

A major study published recently (Spiro *et al.*, 1989) has shown that, in patients with small cell lung cancer, the best two-year survival was seen using an initial short treatment cycle followed by additional chemotherapy at relapse. Spiro *et al.* (1989) found that withdrawal of patients from treatment was considerably less (29% vs 50%) in the group receiving delayed chemotherapy. It was clear from this study that delaying the administration of chemotherapeutic agents can have a significant clinical benefit. These observations are consistent with the findings in the present study. Adverse side-effects may be significantly decreased, since initial chemotherapy in the optimal control regimen is minimal compared to that of the conventional method of administration.

Further research has been conducted to optimize both single and multi-drug cancer chemotherapy when the tumour contains cells that are resistant to the anti-cancer drugs in use (Martin, 1991; Martin *et al.*, 1992a, b). The aim of these studies was to maximize the time during which the mass of a drug resistant tumour could be controlled to lie below a fixed level. This was an estimation of the survival time of the patient. The endpoint of the therapy was determined by either the destruction of the tumour or the overgrowth of cells that were totally resistant to anti-cancer drug(s). Low intensity therapy maximized the survival time for a tumour in Gompertz growth, and did not reduce the survival time when the tumour was in either exponential or logistic growth. This was true when the tumour contained cells that were resistant to all of the chemotherapeutic agents in use. The results support the hypothesis that low intensity chemotherapy may be more effective than conventional high-intensity chemotherapy in certain situations.

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APPENDIX A: CONSTRAINT GRADIENTS

The control parametrization technique was developed by Teo and his co-workers for solving optimal control problems numerically. For details see Teo *et al.* (1991). It involves the discretization of the control space by piecewise constant controls. Consider a process described by a system of differential equations.

$$\begin{aligned} \dot{x}(t) &= f(t, x(t), u(t)), \\ x(0) &= x_0, \end{aligned} \tag{A.1}$$

that are defined on the fixed time interval $[0, T]$, where $x = (x_1, \ldots, x_n)^T \in \mathbb{R}^n$ and $u = (u_1, \ldots, u_r)^T \in \mathbb{R}^r$ are the state and control vectors, respectively, and $f = (f_1, \ldots, f_n)^T \in \mathbb{R}^n$. The superscript ^{T} denotes vector transpose.

Consider an optimal control problem in which the cost functional

$$g_0(u) = \phi_0(x(\tau_1 \mid u), \ldots, x(\tau_M \mid u)) + \int_0^T L_0(t, x(t \mid u), u)\, \mathrm{d}t, \tag{A.2}$$

is to be minimized over all bounded measurable controls subject to the inequality constraints:

$$g_i(u) = \phi_i(x(\tau_1 \mid u), \ldots, x(\tau_M \mid u)) + \int_0^T L_i(t, x(t \mid u))\, \mathrm{d}t \geq 0, \tag{A.3}$$

for $i = 0, \ldots, N_c$, where ϕ_i and L_i are given real-valued functions. This problem will be called Problem P. The parameter N_c is the total number of constraints. There are no equality constraints, and the inequality constraints do not explicitly depend upon the control. Note also the fixed parameters $\tau_i \leq T$, for $i = 1, \ldots, M$, which are referred to as characteristic times. In standard optimal control theory, each canonical constraint depends upon only one such timepoint, but here there may be many of them. As a notational device, define $\tau_0 = 0$ and $\tau_{M+1} = T$.

Let $\{\mathcal{I}_p\}_{p=1}^{\infty}$ be a sequence of partitions of the interval $[0, T]$ such that $\mathcal{I}_p$ has $N_p + 1$ elements. The set $\mathcal{I}_{p+1}$ is a refinement of $\mathcal{I}_p$, and $\|\mathcal{I}_p\| \to 0$ as $p \to \infty$, where $\|\mathcal{I}_p\|$ is the length of the largest sub-interval of the partition $\mathcal{I}_p$. It is assumed that $\mathcal{I}_p$ is of the form

$$\mathcal{I}_p = \{I_j^p\}_{j=1}^{N_p},$$

where

$$I_j^p = [t_{j-1}^p, t_j^p), \quad \text{for } 0 = t_0^p < t_1^p < \cdots < t_{N_p}^p = T.$$

Let $\mathcal{U}^p$ be the subset of all bounded measurable controls that are piecewise constant on the sub-intervals of $\mathcal{I}_p$. Each $u^p \in \mathcal{U}^p$ can be written as

$$u^p(t) = \sum_{j=1}^{N_p} \sigma_j^p \chi_j^p(t), \quad \text{for } t \in [0, T], \tag{A.4}$$

where $\sigma_j^p \in \mathbb{R}^r$. The characteristic function of I_j^p, χ_j^p, is defined as

$$\chi_j^p(t) = \begin{cases} 1 & \text{if } t_{j-1}^p \leq t \leq t_j^p; \\ 0 & \text{otherwise.} \end{cases} \tag{A.5}$$

In the theory that follows, gradients are constructed of the canonical constraints (A.2) and (A.3) with respect to the control parameters. The Hamiltonian and co-state functions that correspond to these constraints may have jump discontinuities at the characteristic times. Therefore, it is convenient to define an index set S_j^p that specifies all of the characteristic times that fall between a consecutive pair of time partition points:

$$S_j^p = \{l \in \mathbb{Z}^+ \text{ such that } t_{j-1}^p < \tau_l < t_j^p\}. \tag{A.6}$$

Also, define τ_{l_1} as the smallest characteristic time such that $l_1 \in S_j^p$, and define τ_{l_2} as the largest characteristic time such that $l_2 \in S_j^p$. Note that l_1, l_2, and S_j^p are all dependent upon j and p.

Each control $u^p \in \mathcal{U}^p$ can be uniquely identified with a control parameter vector σ^p and vice versa, where

$$(\sigma^p)^T = [(\sigma_1^p)^T, \ldots, (\sigma_{N_p}^p)^T]. \tag{A.7}$$

The controls $u^p \in \mathcal{U}^p$ and $\sigma^p \in \mathcal{U}^p$ will be referred to interchangeably.

For each discretization of the control space, $\mathcal{U}^p$, an optimal parameter selection problem that approximates Problem P can be generated. A sequence of these problems is generated as p is increased. To solve each approximate problem as a non-linear programming problem, it is necessary to derive gradients of the canonical constraints with respect to the control parameters. This section describes how the gradients of the MCT constraints are constructed.

Define the Hamiltonian functions H_m and $\hat{H}_m$, $m = 0, 1, \ldots, N_c$, which correspond to the objective function (A.2) and the canonical constraints (A.3 (see Teo *et al.*, 1991):

$$H_m : \mathbb{R} \times \mathbb{R}^n \times \mathbb{R}^r \times \mathbb{R}^n \to \mathbb{R},$$

$$\hat{H}_m : \mathbb{R} \times \mathbb{R}^n \times \mathbb{R}^{rN_p} \times \mathbb{R}^n \to \mathbb{R},$$

$$H_0(t, x(t), \sigma_j^p, \lambda_0(t)) = L_0(t, x(t), \sigma_j^p) + \lambda_0^T(t) f(t, x(t), \sigma_j^p),$$

$$\hat{H}_0(t, x(t), \sigma^p, \lambda_0(t)) = \sum_{j=1}^{N_p} H_0(t, x(t), \sigma_j^p, \lambda_0(t)) \chi_j^p(t),$$

$$H_m(t, x(t), \sigma_j^p, \lambda_m(t)) = L_m(t, x(t)) + \lambda_m^T(t) f(t, x(t), \sigma_j^p) \quad \text{if } m \neq 0,$$

$$\hat{H}_m(t, x(t), \sigma^p, \lambda_m(t)) = \sum_{j=1}^{N_p} H_m(t, x(t), \sigma_j^p, \lambda_m(t)) \chi_j^p(t), \quad \text{if } m \neq 0,$$

where $\sigma_j^p \in \mathbb{R}^r$ for $j = 1, \ldots, N_p$. The mth canonical constraint, for $m = 0, 1, \ldots, N_c$, may be expressed as follows:

$$\hat{g}_m(\sigma^p) = \phi_m(x(\tau_1 \mid \sigma^p), \ldots, x(\tau_M \mid \sigma^p)) + \int_0^T \hat{H}_m(t, x(t), \sigma^p, \lambda_m(t)) - \lambda_m^T(t) \hat{f}(t, x(t), \sigma^p)\, dt. \quad \text{(A.8)}$$

The following theorem constructs the gradients of the canonical constraints (A.8) with respect to the components of the control parameters $\sigma_j^{p,i}$, for $i = 1, \ldots, r$, where

$$(\sigma_j^{p,i})^T = [\sigma_j^{p,1}, \ldots, \sigma_j^{p,r}].$$

Theorem A1. Consider the mth constraint (A.8). Its gradient is

$$\nabla_{\sigma_j^{p,i}} \hat{g}_m(\sigma^p) = \int_{t_{j-1}^p}^{\tau_{l_1}} \frac{\partial H_m}{\partial \sigma_j^{p,i}}\, dt + \sum_{l \text{ and } l+1 \in S_j^p} \int_{\tau_l}^{\tau_{l+1}} \frac{\partial H_m}{\partial \sigma_j^{p,i}}\, dt + \int_{\tau_{l_2}}^{t_j^p} \frac{\partial H_m}{\partial \sigma_j^{p,i}}, \quad \text{(A.9)}$$

where $0 \leq m \leq N_c$, $j = 1, \ldots, N_p$, $i = 1, \ldots, r$, and τ_{l_1}, τ_{l_2}, and S_j^p are defined by equation (A.6.)

Proof. To allow the Hamiltonian and co-state functions $\hat{H}_m$ and λ_m to have time discontinuities at the characteristic times τ_i, $i = 1, \ldots, M$, express the mth canonical constraint (A.8) as follows:

$$\hat{g}_m(\sigma^p) = \phi_m(x(\tau_1 \mid \sigma^p), \ldots, x(\tau_M \mid \sigma^p)) + \sum_{k=1}^{M+1} \int_{\tau_{k-1}}^{\tau_k} [\hat{H}_m(t, x(t), \sigma^p, \lambda_m(t)) - \lambda_m^T(t) \hat{f}(t, x(t), \sigma^p)]\, dt. \quad \text{(A.10)}$$

The solution of the system of differential equations

$$\dot{x}(t) = \hat{f}(t, x, \sigma^p), \qquad x(0) = x_0,$$

is given by

$$x \equiv x(t \mid \sigma^p) = x(0) + \int_0^t \hat{f}(s, x(s \mid \sigma^p), \sigma^p)\, ds. \quad \text{(A.11)}$$

The partial derivative of $x(t \mid \sigma^p)$ with respect to the scalar $\sigma_j^{p,i}$, where $i = 1, \ldots, r$, and $j = 1, \ldots, N_p$, is given by

$$\frac{\partial x}{\partial \sigma_j^{p,i}} = \int_0^t \left[\frac{\partial \hat{f}}{\partial x} \frac{\partial x}{\partial \sigma_j^{p,i}} + \frac{\partial \hat{f}}{\partial \sigma_j^{p,i}} \right] ds. \quad \text{(A.12)}$$

Equation (A.12) may be differentiated with respect to time:

$$\frac{\partial \dot{x}}{\partial \sigma_j^{p,i}} = \frac{\partial \hat{f}}{\partial x} \frac{\partial x}{\partial \sigma_j^{p,i}} + \frac{\partial \hat{f}}{\partial \sigma_j^{p,i}}. \quad \text{(A.13)}$$

The gradient of the mth canonical constraint (A.10) is as follows:

$$\nabla_{\sigma_j^{p,i}} \hat{g}_m(\sigma^p) \sum_{l=1}^{M} \frac{\partial \phi_m(x(\tau_1), \ldots, x(\tau_M))}{\partial x(\tau_l)} \frac{\partial x(\tau_l)}{\partial \sigma_j^{p,i}} + \sum_{k=1}^{M+1} \int_{\tau_{k-1}}^{\tau_k} \left[\frac{\partial \hat{H}_m}{\partial x} \frac{\partial x}{\partial \sigma_j^{p,i}} + \frac{\partial \hat{H}_m}{\partial \sigma_j^{p,i}} + \frac{\partial \hat{H}_m}{\partial \lambda_m} \frac{\partial \lambda_m^T}{\partial \sigma_j^{p,i}} - \frac{\partial \lambda_m^T}{\partial \sigma_j^{p,i}} \hat{f}(t, x, \sigma^p) - \lambda_m^T \left(\frac{\partial \hat{f}}{\partial x} \frac{\partial x}{\partial \sigma_j^{p,i}} + \frac{\partial \hat{f}}{\partial \sigma_j^{p,i}} \right) \right] dt.$$

Hence,

$$\nabla_{\sigma_j^{p,i}} \hat{g}(m)(\sigma^p) = \sum_{l=1}^{M} \frac{\partial \phi_m(x(\tau_1), \ldots, x(\tau_M))}{\partial x(\tau_l)} \frac{\partial x(\tau_l)}{\partial \sigma_j^{p,i}} + \sum_{k=1}^{M+1} \int_{\tau_{k-1}}^{\tau_k} \left[\left(\frac{\partial \hat{H}_m}{\partial x} \frac{\partial x}{\partial \sigma_j^{p,i}} + \frac{\partial \hat{H}_m}{\partial \sigma_j^{p,i}} \chi_j^p(t) - \lambda_m^T \frac{\partial \dot{x}}{\partial \sigma_j^{p,i}} \right] dt. \quad \text{(A.14)}$$

If the last term in equation (A.14) is integrated by parts, the result is

$$\nabla_{\sigma_j^{p,i}} \hat{g}(m)(\sigma^p) = \sum_{l=1}^{M} \frac{\partial \phi_m(x(\tau_1), \ldots, x(\tau_M))}{\partial x(\tau_l)} \frac{\partial x(\tau_l)}{\partial \sigma_j^{p,i}} - \sum_{k=1}^{M+1} \lambda_m^T \frac{\partial x}{\partial \sigma_j^{p,i}} \Bigg|_{t=\tau_{k-1}^+}^{t=\tau_k^-} + \sum_{k=1}^{M+1} \int_{\tau_{k-1}}^{\tau_k} \left[\left(\frac{\partial \hat{H}_m}{\partial x} + \dot{\lambda}_m^T \right) \frac{\partial x}{\partial \sigma_j^{p,i}} + \frac{\partial \hat{H}_m}{\partial \sigma_j^{p,i}} \chi_j^p(t) \right] dt. \quad \text{(A.15)}$$

Since the state is continuous in t on $[0, T]$ (cf. Teo *et al.*, 1991), $x(\tau_k^-) = x(\tau_k^-)$, for $k = 1, \ldots, M$. The second summation appearing in equation (A.15) can be expanded:

$$\sum_{k=1}^{M+1} \lambda_m^T \frac{\partial x}{\partial \sigma_j^{p,i}} \Bigg|_{t=\tau_{k-1}^+}^{t=\tau_k^-} = \sum_{k=1}^{M} (\lambda_m^T(\tau_k^-) - \lambda_m^T(\tau_k^+)) \frac{\partial x(\tau_k)}{\partial \sigma_j^{p,i}} - \lambda_m^T(\tau_0^+) \frac{\partial x(\tau_0^+)}{\partial \sigma_j^{p,i}} + \lambda_m^T(\tau_{m+1}^-) \frac{\partial x(\tau_{M+1}^-)}{\partial \sigma_j^{p,i}} = \sum_{k=1}^{M} (\lambda_m^T(\tau_k^-) - \lambda_m^T(\tau_k^+)) \frac{\partial x(\tau_k)}{\partial \sigma_j^{p,i}} + \lambda_m^T(T) \frac{\partial x(T)}{\partial \sigma_j^{p,i}}. \quad \text{(A.16)}$$

Here, $x(\tau_0^+) = x(0) = x_0$, which is a fixed vector in $\mathbb{R}^n$. The gradient equation (A.15) becomes

$$\nabla_{\sigma_j^{p,i}} \hat{g}(m)(\sigma^p) = \sum_{k=1}^{M} \left(\frac{\partial \phi_m(x(\tau_1), \ldots, x(\tau_M))}{\partial x(\tau_k)} - \lambda_m^T(\tau_k^-) + \lambda_m^T(\tau_k^+) \right) \times \frac{\partial x(\tau_k)}{\partial \sigma_j^{p,i}} - \lambda_m^T(T) \frac{\partial x(T)}{\partial \sigma_j^{p,i}} + \sum_{k=1}^{M+1} \int_{\tau_{k-1}}^{\tau_k} \left[\frac{\partial \hat{H}_m}{\partial x} + \dot{\lambda}_m^T \right) \frac{\partial x}{\partial \sigma_j^{p,i}} + \frac{\partial H_m}{\partial \sigma_j^{p,i}} \chi_j^p(t) \Bigg] dt. \quad \text{(A.17)}$$

Define a co-state system corresponding to the mth canonical constraint. The differential equation for $\lambda_{(m)}^T(t)$ is

$$\dot{\lambda}_m^T(t) = -\frac{\partial \hat{H}_m(t, x(t \mid \sigma^p), \sigma^p, \lambda_m(t))}{\partial x(t \mid \sigma^p)}, \quad \text{where } t \in (\tau_{k-1}, \tau_k), \text{ for } k = 1, \ldots, M+1, \quad \text{(A.18)}$$

with the jump conditions

$$\lambda_m^T(\tau_k^+) - \lambda_m^T(\tau_k^-) = -\frac{\partial \phi_m(x(\tau_1), \ldots, x(\tau_M))}{\partial x(\tau_k)} \quad \text{for } k = 1, \ldots, M,$$
$$\lambda_m^T(T) = 0. \tag{A.19}$$

Notice that these interior conditions give co-states that are discontinuous at the characteristic times. In view of the co-state system of equations (A.18) and (A.19), the gradient of the mth canonical constraint may be simplified:

$$\nabla_{\sigma_j^{p,i}} \hat{g}(m)(\sigma^p) = \sum_{k=1}^{M+1} \int_{\tau_{k-1}}^{\tau_k} \frac{\partial H_m}{\partial \sigma_j^{p,i}} \chi_j^p(t)\, dt. \tag{A.20}$$

The final form of the gradient is derived using the definitions of $\chi_j^p(t)$, τ_{l_1}, and τ_{l_2}, and S_j^p as given in equations (A.5) and (A.6):

$$\nabla_{\sigma_j^{p,i}} \hat{g}(m)(\sigma^p) = \int_{t_{j-1}^p}^{\tau_{l_1}} \frac{\partial H_m}{\partial \sigma_j^{p,i}} dt + \sum_{l \text{ and } l+1 \in S_j^p} \int_{\tau_l}^{\tau_{l+1}} \frac{\partial H_m}{\partial \sigma_j^{p,i}} dt + \int_{\tau_{l_2}}^{t_j^p} \frac{\partial H_m}{\partial \sigma_j^{p,i}} dt. \tag{A.21}$$

This completes the proof.