2012 American Control Conference
Fairmont Queen Elizabeth, Montréal, Canada
June 27-June 29, 2012

Towards tumor growth control subject to reduced toxicity

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Abstract—**This study examines the application of mathematical modeling and optimal control in the investigation of optimal cancer therapy. We present models to predict cancer dynamics in mice with colon cancer as well as pharmacokinetic and drug-related toxicity models to study the effect of anti-cancer agents irinotecan and 5-fluorouracil. We present two methodologies which can be used to design optimal therapies subject to reduced toxicity. The first methodology employs a toxicity model based on body weight loss as is usually the case in an experimental setting whilst the other utilises a well-documented side-effect chart to quantify overall toxicity. These drug-specific formulations are proved to be especially useful when formulating multidrug therapies. Our models replicate both tumor and toxicity data successfully and can be used in treatment planning. The optimal control results suggest that optimal therapy is a balance between minimum toxicity and minimum tumor growth. Whilst in the original experimental studies from which the data was extracted, treatment was not succesful in controlling tumor growth, our schedules successfully control growth while at the same time preventing undesirable toxicity beyond the tolerated limits set by experimental guidelines. The control study on the combination 5-FU/CPT-11 favours 5-FU administration, the main reason being that this drug has been shown experimentally to be less toxic. Lastly, we show that combination therapy is more effective than monotherapy.**

I. Introduction

Cancer can be described as an evolutionary disease, where a population of cells shows inefficient control of its proliferation. Many management options exist for cancer with chemotherapy and surgery being the most widely used. Sometimes, chemotherapy is used as the only treatment however it is often possible that the patient will also receive other treatments. Synergistic effects have also been exploitted in the case of different drugs during combination therapy (e.g. 5-Fluoronancil and Irinotecan in colon cancer) to increase treatment efficacy and reduce drug-related resistance.

Mathematical models describing the biological phenomena underlying cancer can synthesize existing knowledge and can be used as a powerful tool in therapy planning. Numerous models of cancer at different levels have been formulated over many years of active research. In this study, we focus on models in the form of ordinary differential equations (ODEs) governing cancer growth on a cell population level. [4], [5], [6] studied cancer growth by using Gompertzian growth, which, unlike exponential models also considers the fact that as tumor increases, tumor growth slows down due to limit supply of nutrients [3]. Other ODE models have also been used, such as simple proliferation quiescence models, which describe exchanges between proliferating and quiescence cell populations [4]. Others, have considered some form of tumour–immune interaction [7], [8]. Normal cells have also been modelled in many forms (e.g. white blood cells) [4], [9] in an attempt to model toxicity drawbacks.

Cancer treatment design is a field that could benefit from the contributions of researchers in the field of optimal control. Classical feedback principles in control are not directly applicable to most chemotherapy regimens due to the scheduled nature of therapy and the shortage of available measurements. Therefore, the control problem is generally recast as an optimization problem targeting a desired tumour volume trajectory subject to drug dosing constraints [10]. A number of studies have examined schedules of cancer treatment via optimal control techniques. Various treatment types have been used, including chemotherapy as means to deplete cancer cells [4], [11], immunotherapy as a way to boost the immune system [12], as well as a combination of the above treatments [7], [13]. Most of these studies based their optimal treatment results on models which to begin with were not validated with real data, thus their ability to predict real phenomena and provide treatment schedules which are of clinical value is yet to be demonstrated. Furthermore, the therapeutic investigation did not include the pharmacokinetic behaviour of drugs involved, but instead generic drug efficacy terms were used to represent the percentage effectiveness of the drugs following administration. Some studies did make use of this behaviour [4], however no particular drug was examined through real data of effectiveness/ toxicity. Lastly, many studies [9] formulated optimal control problems to obtain a schedule that minimizes the final tumour size, which while an intuitive objective, is not necessarily clinically relevant. These clearly present important limitations which need to be remedied.

In an improved work, [3] solved cancer treatment problems using data, which is more clinically relevant than other work. Toxicity was accounted for based on mouse body weight loss. This is an improved approach when compared to other studies which formulated reduced-toxicity optimal treatments based solely on the magnitude of drug concentration, thus ignoring the severity of the associated side-effects (planning multi-drug therapies or evaluating various monotherapy regimes using only the magnitude of concentration as a toxicity criterion can clearly lead to results which are less accurate). Nevertheless, [3] ignored the fact that in many types of cancer, including colon cancer which their study dealt with, weight loss is not only a as result of drugs, but also of the

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978-1-4577-1094-0/12/$26.00 ©2012 AACC

cancer itself [14]. Clearly, this important fact, which to our knowledge has not been considered by other studies in the literature, affects the profile of the schedule and needs to be examined.

II. Mathematical modeling

A. PK-PD model

Modeling for cancer systems requires two components. The first is an understanding of the system in the absence of treatment and the second is a description of the effects of treatment. A nominal understanding of how cancer progresses is necessary for model construction in the case of the untreated system. Initially, cancer cells typically proliferate in an exponential fashion. The simplest model, firstly designed to describe tumour growth, is the exponential model, or linear model, if one refers to the ODE rather than to its solution. Assuming that there is no limitation to growth, each cell dividing at a constant rate λ, i.e., with constant doubling time of the cell population given by the relation $T_d = \ln 2/\lambda$, the model describing tumor size evolution with unlimited growth is simply $\frac{\mathrm{d}N}{\mathrm{d}t} = \lambda N$, where N denotes the volume of tumor at time t in mm^3. The size of the cancerous mass is measured experimentally as a volume, hence in this work we will model tumor growth in terms of volume in mm^3. Naturally such a simple model can only describe very early stages of tumour growth, when no limitation by nutrient supply or mechanical constraint is present. To take account of these natural limitations, herein we will use a Gompertz-type growth equation which confirms experimental consensus that as the tumor size increases, the tumor growth slows as the mass approaches a plateau population [15]:

$$\frac{\mathrm{d}N(t)}{\mathrm{dt}} = \frac{1}{\tau_g}\ln[\frac{\ln[\theta_g/N_0]}{\ln[\theta_g/2N_0]}]N(t)\ \ln(\frac{\theta_g}{N(t)}) - L(N(t),C_2(t)) \quad (1)$$

where parameter θ_g represents the plateau tumor size, parameter τ_g represents the doubling time of the tumor during exponential growth, and quantity N_0 denotes the initial size of the tumor at time $t = 0$. L is a function used to describe the decrease in tumor cells (and hence volume) due to the action of anticancer drugs. L is assumed to be linear in N, due to the fact that most anticancer agents have been shown to kill cells by first-order kinetics. The cell-loss term is an affine function of drug concentration and has the form:

$$L(N(t),C_2(t)) = k_{eff}(C_2(\mathrm{t})\text{-}C_{2-thr})\mathcal{H}(C_2(\mathrm{t})\text{-}C_{2-thr})N(t) \quad (2)$$

where C_{2-th} is the therapeutic threshold level, k_{eff} is the kill rate of drug, and $\mathcal{H}$ is the Heaviside function: if $C_2(t) - C_{2-thr} < 0,\ \mathcal{H} = 0$, if $C_2(t) - C_{2-thr} \geq 0,\ \mathcal{H} = 1$. This suggests that the drug will only be effective if its concentration reaches a threshold value. Below this, the drug has no effect on tumor, however it still adds to the drug-related toxicity.

The dynamic relationship between the kinetic behavior of the drug and its concentration profile is modelled in the form of a 2-compartmental PK model, which is given below:

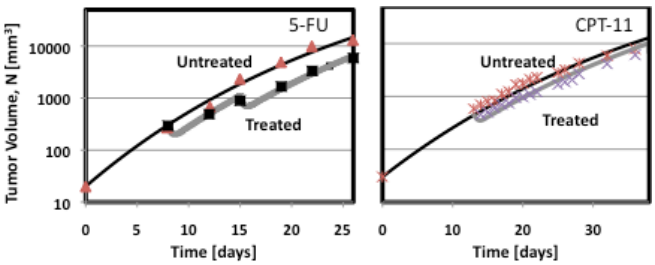

Figure 1. Tumor growth plotted alongside mice data [16]. Data from untreated mice (▲, ✳) and from mice which received treatment (■, ×).

$$\frac{\mathrm{d}C_1(t)}{\mathrm{dt}} = k_{21}C_2(t)\frac{V_2}{V_1} - k_{12}C_1(t) - k_{10}C_1(t) + \frac{d(t)}{V_1} \quad (3)$$

$$\frac{\mathrm{d}C_2(t)}{\mathrm{dt}} = k_{12}C_1(t)\frac{V_1}{V_2} - k_{21}C_2(t) \quad (4)$$

where $C_1(t)$ and $C_2(t)$ represent plasma drug concentration and the tumour site, respectively, V_1 and V_2 represent volumes of distribution, and $d(t)$ is drug dosage. Rate constants k_{12} and k_{21} express the link process between the plasma compartment where the drug is introduced and the compartment of drug action at the cell level, and k_{10} denotes other elimination processes.

To evaluate the above models, we have used data for both untreated and treated mice from the study in [16]. In order to obtain the subject-specific tumor model for the untreated mice, we formulated a Maximum Likelihood Parameter Estimation problem *(gPROMS ModelBuilder 3.3.1* [17]) to estimate the doubling time of the tumor during exponential growth, τ_g. The model predictions alongside data [16] are depicted in Fig. 1 (*untreated*) and it can be concluded that the Gompertzian model can provide a good fit to the data of disease progression in real-subjects (see Table I).

We also evaluated the treatment model using data from the treated mice. Two types of therapies were considered: (a) 5-FU was given as an i.v. bolus at a dose level of 50 mg/kg once weekly from Day 8 for 2 weeks and (b) CPT-11 (i.v. bolus) was given as a single dose at 45 mg/kg on Day 13. The parameters used in the PK model are consistent with [16]'s recommendations ($k_{10}^{CPT} = 13.27, k_{10}^{5FU} = 151.2$, $k_{12}^{CPT} = 0.276$, $k_{12}^{5FU} = 5.62$, $k_{21}^{CPT} = 1.48$, $k_{21}^{5FU} = 2.31\ \mathrm{d}^{-1}, V_1^{CPT} = 4.85\mathrm{x}10^3, V_1^{5FU} = 0.71\mathrm{x}10^3, V_2^{CPT} = 8\mathrm{x}10^3, V_2^{5FU} = 0.1\mathrm{x}10^3$ ml) and the model results show very good agreement with the data for both drugs (Fig. 1 (*treated*) and 2). It can be concluded that the PK-PD model used in this study is able to predict (to the extent possible) real biological phenomena adequately and as a result this could be used to investigate treatment strategies using optimal control techniques.

B. Toxicity model

Optimal treatment planning involves the successful control of the disease. Another parameter which has to be considered in treatment planning, however, is the intensity of drug toxicity. Neglecting this might prove fatal to the patient. As

Table I
PARAMETER VALUES AND STATISTICAL MEASURES FOLLOWING ESTIMATION USING TUMOR [16], [18] AND WEIGHT LOSS DATA [18], WHERE S.D. (STANDARD DEVIATION), CI 95%: 95% CONFIDENCE INTERVAL, AND WR: WEIGHTED RESIDUAL.

Parameter	Value	s.d.	CI 95%	WR
Tumor *				
$\tau_{g_{(5FU)}}$	1.88 d	0.045	0.125	6.61
$\tau_{g_{(CPT)}}$	3.00 d	0.253	0.538	0.96
$k_{eff(5FU)}$	$1.20\ 10^{-4}\ \frac{\text{d ng}}{\text{ml}}$	$1.52\ 10^{-5}$	$4.83\ 10^{-5}$	6.58
$k_{eff(CPT)}$	$1.27\ 10^{-3}\ \frac{\text{d ng}}{\text{ml}}$	$1.72\ 10^{-4}$	$3.71\ 10^{-4}$	16.8
Tumor **				
$\tau_{g_{(CPT)}}$	3.27 d	0.423	0.9301	1.26
$k_{eff(CPT)}$	$3.06\ 10^{-3}\ \frac{\text{d ng}}{\text{ml}}$	0.0001116	0.0002328	22.319
Weight **				
k_g	0.0163	0.00204	0.00431	21.72
k_{l1}	0.00598	0.000395	0.00083	20.05
k_{l2}	0.000183	$2.65\ 10^{-5}$	$5.59\ 10^{-5}$	21.72

* estimated from the data sets in [16]; **estimated from the CPT-11 data set in [18].

a more quantitative and experimentally accessible metric for assessing toxicity, we will consider two methodologies in this section.

1) Weight loss: By modeling body weight, a constraint specifying the minimum allowable weight during treatment can be included in the control formulation. The experimental protocol specifies that animals with weight below a prescribed value (20% of initial weight [19]) will have treatment withheld until the animal recovers, therefore, it is advantageous to quantify the effects of drug administration on bodyweight. It is a widely appreciated fact that not only drugs may lead to weight loss, but also cancer itself can cause this undesirable condition. This has not been accounted in the weight loss models to-date, nevertheless including this in our work will help us produce results which represent reality more closely.

$$\frac{\mathrm{d}W_{net}(t)}{\mathrm{dt}} = k_g W_{net}(t) - k_{l1} C_2(t) - k_{l2} N(t) \qquad (5)$$

In (5), $W_{net}(t) = W(t) - \rho N(t)$ where $W(t)$ is the total mass of the animal which includes the mass of the tumor

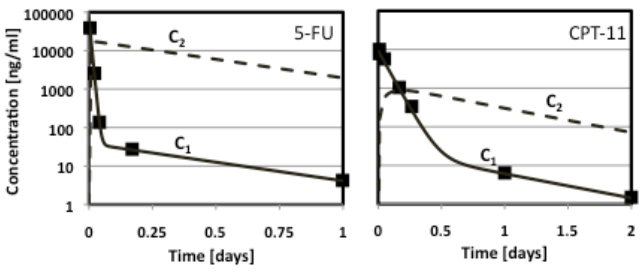

Figure 2. Plasma concentrations of 5-FU and CPT-11 with mice data (■; [16]) following a single dose of 50 mg/kg and 45 mg/kg, respectively (iv. bolus).

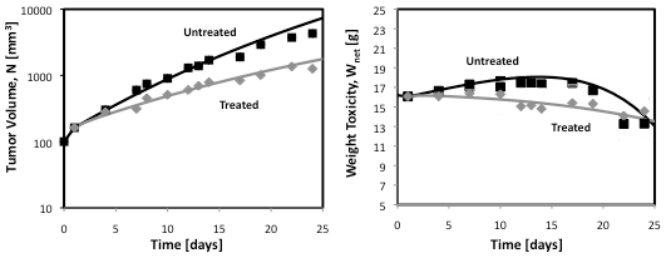

Figure 3. *Left panel:* Tumor growth with mice data [18]. Data from untreated mice (■) and mice which received 60 mg/kg of CPT-11 starting on Day 1 (⧫). *Right panel:* Net body weight with mice data from the same study. Net body weight following correction of the actual tumor mass.

($\rho = 0.001$ g mm^{-3} is the density of the tumor [20]). This corrects body weight as the tumor burden changes by removing the mass from that of the animal. The body mass is assumed to grow at a rate k_g and its rate of decrease is first order in respect to the concentration of the drug with a rate constant k_{l1}. The effect of colon cancer on weight loss is accounted for in the model by the term $k_{l2}N$. In order to evaluate the weight loss model we used data from [18]. In that study, tumor volume and weight loss data for untreated as well as treated (a total of 60 mg/kg CPT-11 were used) mice with colon cancer were presented. We used these to estimate our weight loss model and the fitting results are presented on Table I. Note that k_g and k_{l2} were estimated using untreated data whereas k_{l1} was estimated using treated data. Model predictions alongside data are depicted in Fig. 3 and we can conclude that the model is able to predict the loss in body weight following cancer adequately. It is important to note the effect of the tumor on the weight of untreated mice. These experience a reduction in weight as the tumor grows, even though toxic treatment has not been administered. Certain types of cancer, including colon cancer which we are dealing with in this study, may cause this reduction in body weight, and our model, unlike other work is able to capture this important phenomenon.

2) Side-effect index: Here, we will introduce another methodology for quantifying toxicity. This is based on the severity and frequency of appearance within a population of the individual side-effects of each drug as found by clinical studies. This methodology has been previously proposed [21] for HIV. Table II presents the observed side-effects at standard dosage with CPT-11 and 5-FU [23], [24]. Note that the actual algorithm employed in this work uses a total of 57 side-effects; due to space constaints only a selection is presented here. Severity is clearly subjective, *e.g.*, "chills" should be less undesirable than "diarrhoea". The total side-effect of a drug regime at a given time is given as a function drug concentrations, the relative magnitude of the side-effect, and its observed frequency within a population. This is given below [25]:

$$S_e(t) = \sum_{i=1}^{N} \bar{e_i} \frac{C_2^i(t)}{\overline{C_2^i}} \qquad (6)$$

Table II
FREQUENCIES AND RELATIVE MAGNITUDE OF SELECTED CPT-11 AND 5-FU SIDE EFFECTS [23], [24]. REPORTED IN >15% OF PATIENTS (×), 5-15% (□), <5% (+), 0% (-) AND IS STRONGLY (***), MODERATELY (**), OR WEAKLY (*) UNDESIRABLE.

SIDE EFFECT	CPT-11	5-FU
**Diarrhea (1/2)	×	×
**Nausea (1/2)	×	×
***Leukopenia (3/4)	×	□
*Cutaneous (1/2)	□	□
**Vasodilation (flushing)	□	-

$$e_i = \sum_{j \in J_i} (q_j \cdot h_{i,\,j}) \qquad i \in N \tag{7}$$

$$\bar{e_i} = \frac{e_i}{\max(e_i)} \qquad i \in N \tag{8}$$

In (6)-(8), $S_e(t)$, represents the magnitude of the side-effect of a drug regime at time t. $i(i = 1, 2, ..., N)$ denotes drugs, J_i is the set of side-effects related to drug i, $C_2^i(t)$ is the concentration of drug i at time t in the peripheral compartment, $\overline{C_i}$ is the mean concentration of drug i at steady-state at standard dosage, $e_i(\bar{e_i})$ is the magnitude (normalised magnitude) of the side-effect caused by drug i at standard dosage, $h_{i,\,j}$ is the frequency of individuals that present side-effect j when subject to drug i at standard regime, and q_j is the relative magnitude of side-effect j, *i.e.*, "undesirability". This model is based on the additivity of the observed frequencies and magnitudes of side-effects, and considers that the magnitude of the side-effect index is proportional to the amount of drug administered. The observed frequencies of side-effects are modelled using their actual values as found in the clinical studies (e.g. 29% for ↓Body weight). Evaluating the above formulation for CPT-11 and 5-FU at standard dosage we conclude that CPT-11 presents a more toxic drug when compared to 5-FU. As a result, we would expect optimization studies which utilise this information when formulating a combination therapy for 5-FU/CPT-11 to present schedules which administer more 5-FU than CPT-11 throughout treatment duration given that both drugs present a close to similar anti-cancer effect. We will examine this point in Section III. The total side-effect index of a drug regime, S_e^T, initiated at time t_0 up until time t_f is given as the integral of the side-effect index during this time interval.

III. OPTIMAL CONTROL

In this section, we investigate optimal treatments for the mice subjects presented in [16] (Fig. 1) and [18] (Fig. 3). Specifically, in a similar manner to the original experiments, we administer CPT-11 by using schedules which are determined by our optimal control study. The benefit of treatment is based on the depletion of cancer cells subject to reduced toxicity.

For the case of the mouse subject in [18], an optimal control problem was formulated using a Control Vector Parameterisation Single Shooting algorithm *(gPROMS* [17]) in order to obtain an optimal profile of drug dosage for CPT-11 in the form of continuous infusion. This is referred to as **OCP1**:

$$\begin{aligned} &\min\ J(t_f, \mathbf{d}) \\ \text{s. t.} \quad &J(t_f,\ \mathbf{d}) = \textstyle\int_{t_0}^{t_f} [a_1 N(t) - a_2 W_{net}(t)]\ \mathrm{dt} \\ &\dot{\mathbf{x}} = \ f(t,\ \mathbf{x},\ \mathbf{d}), \\ &N(t) \le N_{max},\ N(t_f) \le N_{target} \\ &W_{net}(t) \ge W_{net}^{min},\ d_{min} \le \mathbf{d} \le d_{max},\ t \in [t_0,\ t_f] \end{aligned} \tag{9}$$

where $\dot{\mathbf{x}} = \ f(t, \mathbf{x}, \mathbf{d})$ represents equations (1)-(5), $t \in [t_0 = 1, t_f = 24]$ sets the finite horizon of the optimization, d_{min}= $0 \le \mathbf{d} \le d_{max} = 2.86\ 10^5$ng g^{-1} sets bounds on the maximum tolerated dose (MTD) for the drug as identified experimentally [26], and $N(t_f) \le\ N_{target} = 200$ mm^3 sets an end-point constraint for tumor size. A path-constraint in the form of $N(t) \le\ N_{max} = 4,000$ mm^3 is added in order to prevent tumor growth in excess of a maximum allowable size before the mouse is euthanised in accordance to experiment guidelines [27]. In a similar manner, the path-constraint $W_{net}(t) \ge W_{net}^{min} = 12.8$ g marks the maximum allowable weight reduction as set in experimental protocols [19]. Weighting values a_1 and a_2 were set to 1 and 1x10^3, respectively, thus penalising extended use of the drug. Note that unlike many other similar studies [9] which solved for the minimisation of the tumor burden at a future final time only, our objective function includes tumor minimisation throughout the treatment horizon. Furthermore, the path and end-point formulations used add further constraints to the tumor and body weight trajectories both throughout and at the end of the treatment cycle. We consider such a methodology to be more clinically relevant [19], [27]. Here, piecewise-constant control profiles are considered with a total of 23 control intervals.

The optimization results for the treatment of the subjects involved in the experimental study presented in [18] are depicted in Fig. 4 (*left panel*). It can be seen that the optimal control is successful in maintaining tumor at reduced sizes throughout treatment, driving the final volume to less than 200 mm^3. This is considerably lower than the volume using the drug schedule given in the original study (1270 mm^3), which suggests that our treatment is able to control growth within the same horizon more efficiently. In doing this, the dosages do not exceed the MTD for CPT-11 in mice and the inevitable reduction in body weight, as a result of toxicity and of the cancer itself, is within the acceptable limits set in experimental protocols. Note the optimal profile of the dosage; the drug is only administered half way into treatment, a drug-free period then follows in an attempt to maintain toxicity levels within limits, and finally more drug is given towards the end in order to inhibit tumor growth and reduce it under the desirable size. The produced profile mimics a treatment methodology which has been investigated widely in HIV/AIDS and lately in cancer as well as cancer, specifically

Structured Treatment Interruptions[21], [22].

Having investigated the use of the weight loss model in the quest for minimal toxicity, we will now examine the use of the side-effect index formulation. The optimal control problem is formulated for the case study in [16] (Fig. 1 (*right panel*)) and is referred to as **OCP2**:

$$\begin{aligned} &\min\ J(t_f, \mathbf{d}) \\ \text{s. t.} \quad &J(t_f,\ \mathbf{d}) = \int_{t_0}^{t_f} [a_1 N(t) + a_2 S_e(t)]\ \mathrm{dt} \\ &\dot{\mathbf{x}} = \ f(t,\ \mathbf{x},\ \mathbf{d}), \\ &N(t) \leq N_{max},\ N(t_f) \leq N_{target} \\ &d_{min} \leq \mathbf{d} \leq d_{max},\ t \in [t_0,\ t_f] \end{aligned} \tag{10}$$

where $\dot{\mathbf{x}} = \ f(t, \mathbf{x}, \mathbf{d})$ represents (1)-(4) and (6)-(8), $t \in [t_0 = 13, t_f = 39]$, d_{min}= $0 \leq \mathbf{d} \leq d_{max} = 2.86\ 10^5$ ng g^{-1}, and $N_{target} = 100$ mm^3. Weighting values a_1 and a_2 were set to 1 and 1x10^7. The optimization results for the treatment of the subjects involved in [16] are depicted in Fig. 4 (*right panel-single*). It can be seen that the optimal control is successful in maintaining tumor at reduced sizes throughout treatment, driving tumor volume to less than 100 mm^{-3}. This is considerably lower than the original tumor at treatment initiation. In doing this, the drug is only administered half way into treatment at dosages which do not exceed the MTD for CPT-11. In fact, the total side effect index achieved was 13.5, as opposed to 22.2 which is the index found when the drug is given at its MTD throughout treatment.

Please note that using either toxicity model in the optimization, the result is schedules of treatment which successfully control tumor growth while at the same time keeping toxicity levels at acceptable levels. In the weight loss model, this is verified by the fact that the weight loss is within the tolerated limits set by experimental guidelines whereas in the side-effect index case, the index achieved is considerably less than the one achieved at MTD. Both methods utilise real data and are drug-specific, hence present an improved approach to methodologies employed to-date. Nevertheless, the side-effect index method might be considered more advantageous in that it takes into consideration side-effects other than just weight loss; this is usually the case in humans treated for cancer, hence we consider this methodology to be more useful in a clinical setting.

To examine further the methodology for formulating optimal schedules which utilise information on the behaviour of specific drugs as well as their toxicity, we revisit OCP2 above, however this time we consider both 5-FU/CPT-11. Combination therapies are widely used in clinical practice to increase treatment efficacy through synergistic effects, reduce drug-resistance, and other. The combination 5-FU/CPT-11 is common in clinical practice for the case of colon cancer [26]. The formulation is similar to OCP2 with the only difference being the value of $d_{max} = 1.43$x10^5ng d^{-1}. Experimental results [26] suggest that the MTD for drugs in combination differs from the MTD of the drug when administered alone.

The results for the combination treatment are depicted

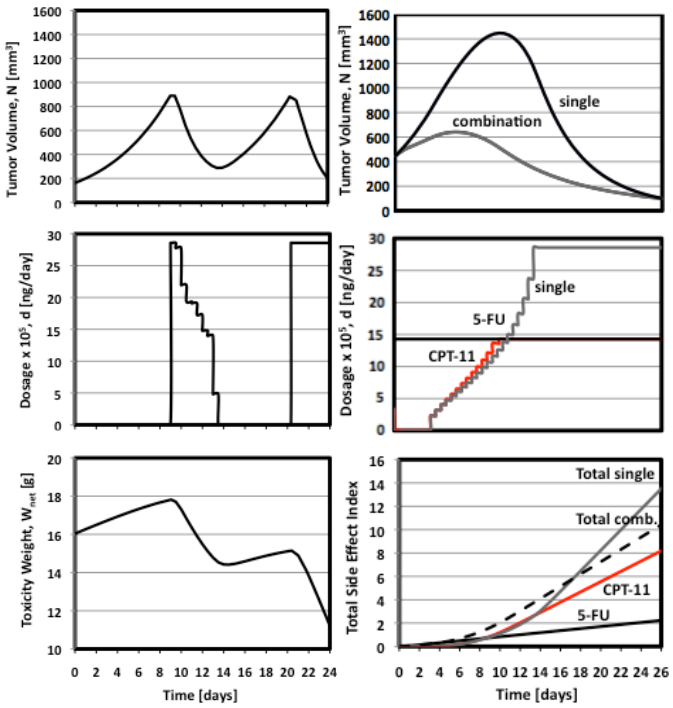

Figure 4. Optimal control profile of cancer chemotherapy using the (i) weight loss model for monotherapy with CPT-11 (OCP1; *left panel*), (ii) side-effect index for (a) monotherapy with CPT-11 (*grey line*) and (b) combination therapy with 5-FU (*black line*) and CPT-11 (*red line*) (OCP2; *right panel*).

in Fig. 4 (*right panel-combination*). In a similar manner to monotherapy above, tumor growth is inhibited considerably resulting in reduction in its size. In doing this, the optimal schedule administers more 5-FU than CPT-11. This is expected because as found in Section II, the latter is associated with higher degree of toxicity at standard dosage and the two drugs share a close to similar anti-cancer effect as seen by the parameter values above. This result could not have been possible if the drug-specific side-effects were not considered (note that 5-FU and CPT-11 also share the same MTD as suggested by experimental studies), hence the real value of our work. In fact, ignoring the toxicity parameter ($\alpha_2 = 0$), yields a treatment which administers both drugs at high dosages. Moreover, the total toxicity for this treatment was 10.4, which is lower than the one achieved at MTD (13.3), but also considerably lower than the CPT-11 monotherapy schedule above (13.5). This is a result of the administration of 5-FU, which as suggested is associated with lower toxicity. Lastly, as can be seen in Fig. 4 (*right panel*) combination therapy also appears to be more effective in terms of tumor depletion inhibiting growth by a greater degree when compared to monotherapy, thus verifying experimental results [26] which support use of combination therapies. We consider these results promising and encouraging for further mathematical modeling and optimization attempts, which utilise experimental and/ or clinical information and data in an attempt to obtain clinically

relevant results.

IV. Discussion and conclusions

Despite a long history of theoretical work in optimizing chemotherapy, its practical application has been arguably negligible. This stems to a great extent from the lack of collaboration between the theoretical groups developing cancer models and clinicians. Most studies to date have based their optimal treatments on models which have not been validated with real data and, as a result, are often paid little attention by clinicians. Another reason for the minimal application of modeling in clinical practice is the questionable suitability of the former to individuals. One regime may be very effective in one patient but might fail in another. Moreover, most studies to date also ignore the individual characteristics of drugs, including varied efficacy in the body as well as toxicity. In these formulations the toxicity was generally an inferred or generalized toxicity handled by constraining input magnitude or rate rather than the measurable and specific toxic effect that may be specific to a particular drug-tumour pair. It is clear that penalizing the administration of a highly toxic drug in the same way as penalizing another drug with milder side-effects is not desirable.

The use of toxicity models based on real data, which describe the varied side-effects associated with different drugs, can lead to improved predictions, especially in the case of combination therapy, where one drug may be chosen to be administered at a higher dose (or more frequently) as a result of mlider toxicity (5-FU in this study). Our aim has been to utilise, to the extend possible, all information and data available from animal experiments in the form of mathematical models and investigate via optimal control cancer chemotherapy. Our approach to model weight loss not only as a result of drug toxicity but also as a result of the cancer itself, has been the first attempt to incorporate this important phenomenon. For the mice investigated, tumor and weight loss data were replicated and objective functions which control tumor growth throughout treatment and maintain drug dosages below toxic levels and weight reduction above the acceptable threshold set in experimental protocols, were solved with encouraging results.

Clearly, the models produced in this study are a simplified description of reality, as are all such modeling attempts at present. As a closing remark, we are convinced that the only route forward is one which involves a collaboration with clinical/ experimental practicioners. Mathematical and clinical optimality are not necessarily equivalent, and the eventual use of a treatment profile is in the clinical setting.

References

[1] A. Asachenkov, G. Marchuk, R. Mohler, *et al.*, Disease Dynamics, Birkhauser, Boston; 1994.

[2] R. Martin and K.L. Teo, Optimal Control of Drug Administration in Cancer Chemotherapy, World Scientific, River Edge, NJ; 1994.

[3] J.M. Harrold and R.S. Parker, Clinically relevant cancer chemotherapy dose scheduling via mixed-integer optimisation, Comp & Chem Eng, vol. 4, 2009, pp 2042-2054.

[4] P. Dua, V. Dua, and E.N. Pistikopoulos, Optimal delivery of chemotherapeutic agents in cancer, Comp & Chem Eng, vol. 32, 2009, pp 99-107.

[5] F. Kozusko and Z. Bajzer, Combining Gompertzian growth and cell population dynamics, Math. Biosci., 185, 2003, pp 153–67.

[6] M. Gyllenberg and G. Webb, Quiescence as an explanation of Gompertzian tumour growth, Growth Dev. Aging, vol. 153, 1989, pp 25–33.

[7] L.G. de Pillis, W. Gu, and A.E. Radunskaya, Mixed immunotherapy and chemotherapy of tumours: modelling, applications and biological interpretations, J. Theor. Biol., vol. 238, 2006, pp 841.

[8] N. Bellomo, A. Bellouquid and M. Delitala, Mathematical topics on the modelling of multicellular systems in competition between tumour and immune cells, Math. Mod. Meth. Appl. Sci., vol. 14, 2004, pp 1683.

[9] D. Barbolosi and A. Iliadis, Optimizing drug regimens in cancer chemotherapy: a simulation study using a PK-PD model, Comp. Biol. Med., vol. 31, 2001, pp 157-172.

[10] F. Doyle, L. Jovanovic, D. Seborg, *et al.*, A tutorial on biomedical process control, J. Proc. Control, vol. 17, 2007, pp 571–594.

[11] K. R. Fister and J.C. Panetta, Optimal control applied to cell-cycle-specific cancer chemotherapy, SIAM J. Appl. Math., vol. 60, 2000, pp 1059–1072.

[12] F. Castiglione and B. Piccoli, Cancer immunotherapy, mathematical modelling and optimal control, J. Theor. Biol., vol. 247, 2007, pp 723–732.

[13] A. d' Onofrio, U. Ledzewicz, H. Maurer, *et al.*, On optimal delivery of combination therapy for tumours, Math. Biosci., vol. 222, 2009, pp 13-26.

[14] Mayo Clinic, Colon Cancer: Signs and Symptoms, 2007.

[15] L. Norton. A Gompertzian model of human breast cancer growth, Cancer Res., vol. 48, 1988, pp 7067– 7071.

[16] M. Simeoni, P. Magni, C. Cammia, *et al.*, Predictive pharmacokinetic-pharmacodynamic modelling of tumour growth kinetics in xenograft models after administration of anticancer agents, Cancer Res., vol. 64, 2004, 1094–1101.

[17] gPROMS, Process System Enterprise Ltd, UK; 2004.

[18] Y. Hattori, L. Shi, W. Ding, *et al.*, Novel irinotecan-loaded liposome using phytic acid with high therapeutic efficacy for colon tumors, J. Contr. Release 136, 2009, pp 30–37.

[19] Netherlands Inspectorate for Health Protection, "Animal experiments in cancer research", Zutphen/The Hague; 1999.

[20] J.M. Harrold, Model-based design of cancer chemotherapy treatment schedules, Ph.D. thesis, University of Pittsburgh, PA; 2005.

[21] M.M. Hadjiandreou, R. Conejeros, D.I. Wilson, Long-term HIV dynamics subject to continuous therapy and structured treatment interruptions, Chem. Eng. Sci., vol. 64, 2009, pp 1400-1417.

[22] M.M. Hadjiandreou, G.D. Mitsis, "Model-based control of cancer progression subject to drug- resistance" in Proc of the 51st IEEE Conf. on Decision and Control, Hawaii, USA, 2012, Submitted.

[23] J.M. Joulia, F. Pinguet, M. Ychou, *et al.*, Plasma and Salivary Pharmacokinetics of 5-FU in Patients with Metastatic Colorectal Cancer Receiving 5-FU Bolus Plus Continuous Infusion with High-dose Folinic Acid, EJC, vol. 35, 1999, pp 296-301.

[24] Drugs.com, Irinotecan Side Effects - for the Professional, 2011.

[25] M. Joly, J.M. Pinto, Role of Mathematical Modeling on the Optimal Control of HIV-1 Pathogenesis. AIChE J., vol. 52, 2006, pp 856-885.

[26] S. Cao, F.A. Durrani, Y.M. Rustum, Synergistic antitumor activity of capecitabine in combination with irinotecan, Clin. Color. Cancer, vol. 4, 2005, pp 336-343.

[27] OECD, "Recognition, Assessment, and Use of Clinical Signs as Humane, Endpoints for Experimental Animals Used in Safety Evaluation", 2000.