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Model-based control of tumor progression

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Abstract—**This paper presents our work on the application of mathematical modeling and optimal control techniques in the modeling of tumor progression and optimal treatment planning. We present a pharmacokinetic-pharmacodynamic approach to the modeling of tumor progression in mice. Specifically, we describe colon cancer progression in both untreated mice as well as mice treated with anti-cancer agents. We also a present pharmacokinetic model to describe the drug kinetics in the body as well as toxicity models to describe the severity of side-effects. Lastly, we propose a promising methodology by which cancer progression in mice with drug-resistance can be controlled. By using optimal control, we demonstrate that the optimal planning of the frequency and magnitude of treatment breaks is key to cancer control in subjects with resistance and should be further investigated in an experimental setting, which is currently underway.**

Keywords—cancer chemotherapy; mathematical modeling; optimal control; toxicity; drug-resistance.

I. INTRODUCTION

Cancer is a leading cause of death worldwide. Many management options exist for cancer, including: chemotherapy, radiation therapy, immunotherapy, and surgery. Issues faced during therapy include: metastasis, drug toxicity, inter-individual variability, and drug-resistance.

Numerous mathematical models of cancer and healthy tissue growth at different levels, from gene expression to the phenomenological description of macroscopic tumour development, have been formulated. These models have employed concepts from several fields such as systems theory, signal processing and probability theory and include spatially structured models, physiologically structured, continuous and agent-based, deterministic and stochastic, phenomenological and mechanistic. The type of modeling methodology to be employed clearly depends on the process to be modelled and the point of view of the modeller.

Many studies have utilized ordinary differential equations (ODEs), which typically involve cancer dynamics alone. Gompertzian growth has been widely used [1], which, unlike exponential growth, also considers the reduced growth rate of the tumor as its size increases. Other ODE models have also been used (e.g., proliferation quiescence models; [2,3]).

Models of cancer treatment have also been considered: chemotherapy [2], immunotherapy [4], as well as a combination of the above [5]. In most of this work, the reported findings have been based on models which, to begin with, were not validated with real data, thus their ability to provide results which can be of clinical value is yet to be demonstrated. Some models included pharmacokinetics [2], however no particular drug was examined through real data of effectiveness/ toxicity. One previous study [6] used mice data and toxicity was accounted for based on weight loss. This is an improved approach; nevertheless, their model ignored that in colon cancer, which was addressed, weight loss is not only a result of drugs, but also of cancer itself [7].

Clearly, modeling and optimization work needs to account for drug-resistance being one of the most important reasons for treatment failure. Some fraction of the cancer population may develop drug-resistance and thus evade eradication. Despite the numerous mechanisms to circumvent this problem, currently no holistic solution exists [8]. Resistance is unavoidable and may lead to a halt of treatment, hence the problem is not to eliminate the cancerous tumor, but to prolong the patient's life-expectancy [9]. Both stochastic [9,10] as well as deterministic models have been developed [11] to describe drug-resistance. In [12] tumor size is analyzed as a stochastic process and the probability of having no resistant cells appearing is examined. Two-compartment models distinguishing drug-resistant and sensitive cells were developed. [13] considered infinitely many levels of partial resistance and the corresponding deterministic models were formulated and analyzed by [14]. Due to their high dimensionality, these often only allow for a limited analysis. Others studied drug-resistance in a cell-cycle specific context [10]. Models under evolving drug-resistance with several killing agents acting separately have also been considered [9]. Most of the resistance work found in the literature used no real data for model development, which is important if the goal is to promote modeling and optimal control as a therapy planning tool in the clinic.

II. MATHERMATICAL MODELING

A. Model of cancer progression in mice-subjects

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 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 designed was the exponential model. Assuming there is no limitation to growth, each cell dividing at a rate λ, (constant doubling time, $T_d = \ln 2/\lambda$), cell population evolution with unlimited growth is simply:

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$$\frac{dx}{dt} = \lambda x \qquad (1)$$

Gompertz-type growth models have also been proposed [15] to describe experimental consensus that as the tumor size increases, growth slows as the mass approaches a plateau population. This type of model is very popular amongst clinicians dealing with chemotherapy and radiotherapy. The tumor dynamics in the body as predicted by this type of models is depicted in Fig. 1 with model equations as in (2).

$$\frac{dN(t)}{dt} = \frac{1}{\tau_g} \ln\left[\frac{\ln[\theta_g / N_0]}{\ln[\theta_g / 2N_0]}\right] N(t) \ln\left[\frac{\theta_g}{N(t)}\right] - L(N(t), C_2(t)) \qquad (2a)$$

where N(t): tumor volume (mm^3), θ_g: plateau size (mm^3), τ_g: tumor doubling time (d), and N_0: initial tumor size. The first term represents the increase in cells due to proliferation and *L* is a function describing killing of cells due to drugs. When *L* is 0, then (2) is the untreated model. *L* is linear in N(t), since most drugs kill cells by first-order kinetics, i.e. the fraction of cells killed by a drug of fixed concentration is not dependent upon tumor size. *L* is an affine function of drug concentration:

$$L(N(t), C_2(t)) = k_{eff}(C_2(t) - C_{2thr}) H(C_2(t) - C_{2thr}) N(t) \qquad (2b)$$

where C_{2thr} (ng ml^{-1}) is a therapeutic threshold, k_{eff} (d ng ml^{-1}) is the drug kill rate, and *H* is the Heaviside function: if $C_2(t) - C_{2thr} < 0$, *H*=0, if $C_2(t) - C_{2thr} \geq 0$, *H*=1. The drug will only be effective if it reaches a threshold. Below this, the drug has no effect on tumor but still adds to toxicity (Fig. 2).

In Fig. 1 [16], our model results are plotted with experimental data from [17]. There, both untreated and treated mice with colon cancer were involved. One group received 5-FU, the other received CPT-11. It can be seen that the model results in a good fit to untreated and treated tumor dynamics.

B. Pharmacokinetic Modeling

Drug administration can be described using pharmacokinetic models. Perhaps the most straightforward method is to assume that the body can be approximated as a well-mixed tank. The advantage of this approach is the small number of parameters that can often be quantitated using data. The low-order model is an adequate approximation for compounds with rapid distribution/metabolism characteristics. While this is sufficient for drugs whose action is based on plasma concentration, or whose treatment objective is PK-driven, a more detailed description of drug distribution is of interest when the site of action or toxicological effect is remote to the plasma. Near the other extreme in complexity lie physiologically- based (PB) models [18] (Fig. 3 left). Here differential

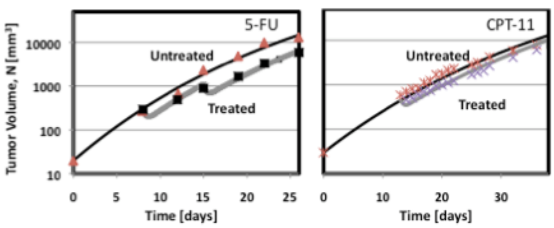

Figure 1. Tumor growth plotted alongside mice data [16]. Data from untreated mice (✱, ▲) and from mice that received treatment (■, ×).

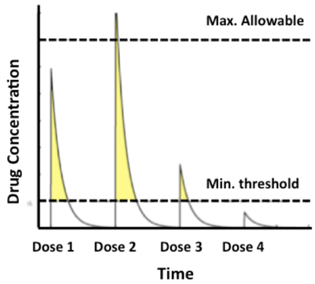

Figure 2. Drug concentrations in the body.

equations are used to describe concentrations in organs where organs are subdivided into compartments. This is [19]:

$$V_{vi}\frac{dC_{vi}}{dt} = F_i(C_c - C_{vi}) + (k_{tv}C_{ti} - k_{vt}C_{vi}) \qquad (3)$$

$$V_{ti}\frac{dC_{ti}}{dt} = -k_{tv}C_{ti} + k_{vt}C_{vi} - r_r \qquad (4)$$

where v: vascular and t: tissue spaces of tissue i, respectively. Drug distribution volumes are given by V_t, C is concentration, and F is the blood flow rate. The number of parameters in a PBPK model is significantly greater than a compartmental PK description, and the information necessary to inform these parameters is often tissue-specific. When available, these data and model structure can provide markedly increased insight into the kinetics and any toxicity effects [20], however, due to the detailed information needed these are not commonly used. In between the two extremes lie low-order compartmental models, which we present next. A 3-compartmental pharmacokinetic model is given by (Fig. 3 right):

$$\frac{dC_1(t)}{dt} = k_{21}C_2(t)\frac{V_2}{V_1} + k_{31}C_3(t)\frac{V_3}{V_1} - (k_{12} + k_{13})C_1(t) - k_{10}C_1(t) + \frac{d(t)}{V_1} \qquad (5)$$

$$\frac{dC_2(t)}{dt} = k_{12}C_1(t)\frac{V_1}{V_2} - k_{21}C_2(t) \qquad (6$$

$$\frac{dC_3(t)}{dt} = k_{13}C_1(t)\frac{V_1}{V_3} - k_{31}C_3(t) \qquad (7$$

where $C_1(t)$, $C_2(t)$, $C_3(t)$ denote drug concentration in the plasma, tumor site, and other slowly diffused tissues, respectively, V_i denote volumes of distribution, and *d* is drug dosage. Rate constants k_{12},k_{21},k_{13},k_{31} express the link process between the central and the other compartments and k_{10} denotes other elimination processes.

Fig. 4 [21] depicts the concentration profile of anti-cancer agent docetaxel against data [22] in tumor-bearing mice receiving a single dose of a 20 mg kg-1 i.v. bolus. This drug has been shown experimentally to exhibit this type of kinetics [23] as opposed to other drugs (5-FU, CPT-11), which have been shown to exhibit kinetics best described using 2-compartment models. The model parameters used are from [24] and represent the kinetics as estimated in an experiment involving tumor bearing mice treated with docetaxel.

C. Toxicity modeling

The main objective of optimal therapy planning is successful disease control. However, neglecting drug-related toxicity, might prove fatal to the patient.

Many studies [2,3] considered toxicity, but based this on the magnitude of drug concentration only and no specific drug

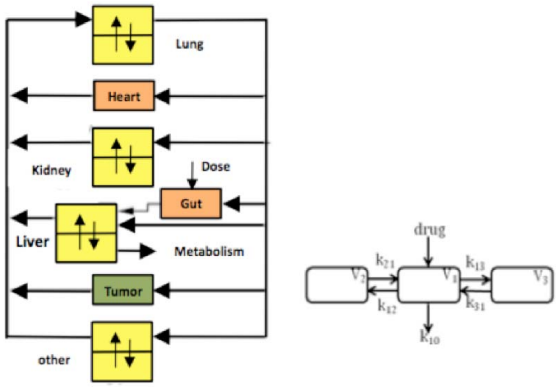

Figure 3. Left: Physiologically based pharmacokinetic model. Right: 3-compartmental pharmacokinetic model.

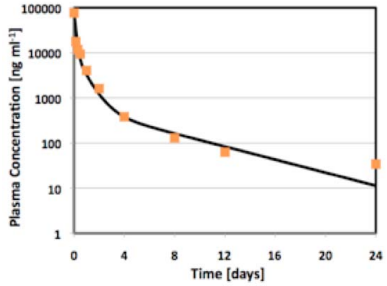

Figure 4. Model predictions for plasma concentration with experimental data following i.v. bolus administration of docetaxel (20 mg kg^{-1}).

was involved. Because of inter–patient and drug-variability, variations can occur across a population, hence average exposure (of a generic or even specific drug) as a metric for approximating toxicity may provide little utility. As a more quantitative and experimentally accessible metric, reductions in body weight are often considered. By modeling this, a constraint on the maximum allowable weight loss can be included in the treatment design algorithm. Therefore, it is advantageous to quantify toxicity effects on bodyweight.

A weight loss model includes terms for weight loss due to toxicity but also due to cancer itself.

$$\frac{dW_{net}(t)}{dt} = k_g W_{net}(t) - k_{l1} C_2(t) - k_{l2} N(t) \qquad (8)$$

The body weight, W(t), is the total mass of the animal which includes the mass of the tumor. The body weight for toxicity purposes, W_{net}, is calculated using $W_{net}=W(t)-\rho N(t)$. This corrects body weight as the tumor burden changes by removing the mass from that of the animal [25]). Body mass grows at a rate k_g and decreases with the drug at a rate constant k_{l1}. The effect of colon cancer on weight is accounted for by k_{l2} N(t).

Fig. 5. [16] depicts body weight dynamics using the model above of both untreated and treated mice with colon cancer (data from [26]). The tumor dynamics for the same mice are also presented. Note the effect of the tumor on the weight of untreated mice. These experience a reduction in weight as the tumor grows, even though therapy has not been given. Certain types of cancer, including colon cancer may cause this weight loss, and the model captures this important phenomenon.

D. Mathematical modeling with drug-resistance

Drug-resistance is one of the major drawbacks of chemotherapy. Despite an increasing number of clinical studies as well as theoretical work on treatment interruptions as a means to fight resistance in HIV [27-28], these have not been studied extensively in cancer. In HIV, treatment breaks have been studied to reduce toxicity and facilitate the interplay between the drug-sensitive and drug-resistant HIV strains to control their growth. The interplay arises as a result of the reduced fitness of the resistant strain; this has been studied experimentally for the case of resistant cancer cells [20]. Although the two cancer populations are not in direct competition with each other, the fight for nutrients leads to dynamics that are in principle the same as those observed in competition. Next, we present our work on drug-resistance and treatment interruptions as a treatment strategy [21].

Experimental data from drug-resistance studies [30] were used in model development. Two compartments consisting of drug-sensitive and resistant cells were considered (T_S and T_R, respectively). Total cancer load is denoted by T_T. Once a sensitive cell undergoes cell division (Fig. 6), the mother cell dies and one of the daughters remains sensitive. The other changes into a resistant cell with probability μ_{SR}, where $0<\mu_{SR}<1$. Similarly, when a resistant cell undergoes cell division, the mother cell dies, and one of the daughters remains resistant. It has been shown experimentally [31] that a resistant cell may mutate back into sensitive with μ_{RS}. Denoting the inverses of the transit times of cells through the sensitive and resistant populations by α, then:

$$\frac{dT_S(t)}{dt} = -aT_s(t) + (1-u(t))(2-\mu_{SR})aT_S(t) + \mu_{RS}a\phi T_R(t) - r_1 T_S T_R \qquad (9)$$

$$\frac{dT_R(t)}{dt} = -a\phi T_s(t) + (2-\mu_{RS})a\phi T_R(t) + (1-u(t))\mu_{SR}aT_S(t) - r_2 T_R T_S \qquad (10)$$

$$T_T(t) = T_S(t) + T_R(t) \qquad (11)$$

where the first terms on the right hand sides represent mother cell death, the second terms describe the return flows into the compartments, the third terms correspond to the cross-over flows, and φ is a relative fitness factor for the drug-resistant population. The model is based on [9] and a good explanation of the mechanisms involved can be found in that study. The above model includes improvements to that work. Specifically, it has been show n experimentally [29] that the cancer cells, which have undergone mutations and developed resistance to drugs, are less "fit" compared to the drug-sensitive strain in terms of their growth rate given ample natural resources (oxygen, glucose, etc). This phenomenon is well-documented where T_R will decrease in a drug free medium. These

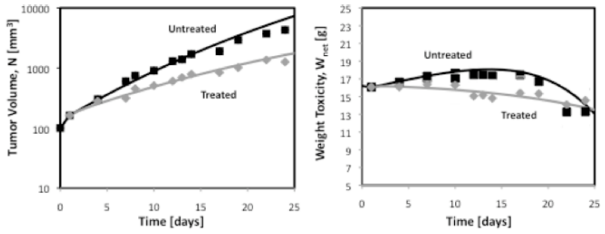

Fig. 5. Left panel: Tumor growth with mice data Hattori et al. (2009). Data from untreated mice (■) and mice receiving CPT-11 (♦). Right panel: Net body weight with mice data from the same study.

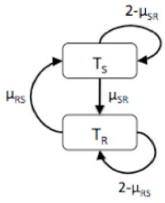

Figure 6. Mechanism of drug-resistance.

considerations are included in the model through the fitness and competition constants φ and r_1, r_2, where $r_1<r_2$.

In the model above, drug therapy is denoted by u(t) which presents the drug efficacy ([0, 1], with 0 and 1 indicating no treatment and full treatment, respectively). It is assumed that the drug has no effect on resistant cells. Drug efficacies are often used in mathematical modeling and are a function of the concentration and effectiveness of the drug. The drug efficacy of an anti-cancer agent is:

$$u(t) = \frac{C(t)}{C(t) + \omega IC_{50}} \tag{12}$$

where C(t) denotes drug concentration at the tumor site and IC_{50} represents the median inhibitory concentration of the drug. Although IC_{50} can be measured by phenotype assays in vitro, it may not be equivalent to the IC_{50} in vivo [33] and the parameter ω indicates a conversion factor between the two (ω = 1 in this work) IC_{50} for drug docetaxel (see Fig. 5) is 4.12 ng ml^{-1}, following [34]'s study and the concentration is predicted using the pharmacokinetic model in (5)-(7). The results of the model above are plotted against experimental data for tumor-bearing mice developing resistance to a 25mg once weekly schedule of docetaxel. Fig. 7 (top) shows the results for the case of mouse T10. Note the response to treatment during the initial stages of therapy; however, it is evident that following the first two doses, drug-resistant tumor emerges and prevails over sensitive tumor resulting in total cancer load rapid growth. Resistance to docetaxel was also verified experimentally in that study. Model results replicate the response to treatment during initial therapy and the emergence of resistance following successive drug dosages. It can be seen that whereas the sensitive strain is controlled by drugs, the resistant one grows uncontrollably hence fast tumor growth. If this mouse were to continue receiving the same treatment schedule, cancer numbers would reach the maximum allowable size for mice in experiments short after that, hence treatment failure would occur (4000 m^3; [34]). This is depicted in Fig. 7 (Bottom).

The proposed model captures a number of important phenomena during resistance emergence and replicates data. One such model could be utilized in the investigation of treatment interruptions through optimal control techniques to highlight avenues of attack to cancer.

III. Optimal Control

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 re-

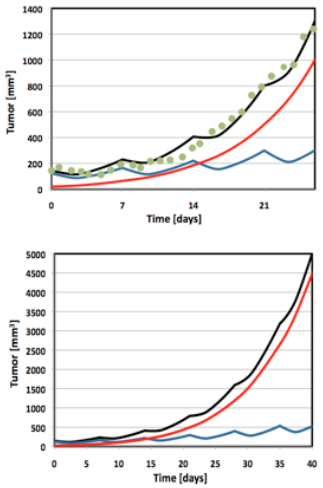

Fig. 7. Top panel: Model predictions for tumor volume with experimental data (●) for mice receiving docetaxel once weekly. Bottom panel: Long-term model predictions for tumor volume according to the schedule in the top panel.

cast as an optimization problem targeting a desired tumor volume trajectory subject to drug dosing constraints [19].

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 [2], immunotherapy as a way to boost the immune system, as well as a combination of the above treatments [5]. Most of these studies designed optimal treatments using models, which were neither developed nor validated with real data. Moreover, they 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 behavior [2], however no particular drug was examined through real data of effectiveness/ toxicity. Lastly, many studies [3] formulated optimal control problems to obtain a schedule that minimizes the final tumor size, which while an intuitive objective, is not necessarily clinically relevant.

An optimal control algorithm that can be used in treatment design is:

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

where $d\mathbf{x}/dt = f(t,\mathbf{x},d)$ is the model, $t \in [t_0, t_f]$ sets the finite horizon, $d_{min} \le d \le d_{max}$ sets bounds on the maximum tolerated dose (MTD), and $N(t_f) \le N_{target}$ sets an end-point constraint for tumor size. A path-constraint in the form of $N(t) \le N_{max} = 4{,}000$ mm^3 prevents tumor growth in excess of a maximum allowable size before the mice is euthanized [34]. Similarly, $W_{net}(t) \ge W_{net}^{min} = 12.8$g marks the maximum weight loss as set in experimental protocols [35]. Weighting values a_1 and a_2 penalise extended use of drugs. Unlike other studies solving for minimum tumor burden at a final t only, we minimize tumor

throughout therapy. Moreover, the path and end-point formulations add further constraints to the tumor and weight trajectories both throughout and at the end of therapy. This considers a more clinically relevant to therapy design.

The results for the optimal treatment of the case study presented in Fig. 5 are depicted in Fig. 8. It can be seen that the optimal control is successful in maintaining tumor at reduced sizes throughout therapy, driving the final volume to desired levels at the end of treatment. The latter is considerably lower than the size obtained using the therapy in the original study (1270 mm3), thus the schedule controls tumor growth within the same horizon more efficiently. In doing this, the dosages administered do not exceed the MTD for drug CPT-11 and the inevitable weight loss is within acceptable limits.

Next, we present optimal control work on the treatment of mice with resistance described earlier (Fig. 7). In a similar manner to the optimal control problem formulation above, the treatment benefit is based on the minimization of the total tumor size while penalizing extended use of the drug. The administered dosage was fixed to the Maximum Tolerated Dose of the drug as found experimentally [30] and treatment intervals were allowed to vary. The treatment levels were fixed during the optimization, since administration of fixed drug dosages over treatment intervals makes sense as it helps compliance from clinicians and patients.

The results of the optimal control are depicted in Fig. 9 and it can be seen that the optimal management of the magnitude and frequency of the treatment breaks during chemotherapy is key in the control of the progression, hence treatment success. Specifically, the optimal management of the treatment breaks facilitates the interplay between the drug-sensitive and drug-resistant strains, thus neither the sensitive nor the resistant strain grows in an uncontrollable manner, and as a result the total cancer load remains at all times below the maximum allowable size before euthanasia of the animal. In doing this, the dosages administered do not exceed the maximum tolerated doses for docetaxel administration in mice. This result may be explained as follows: when therapy is administered, it is clear that the resistant strain has an advantage over the sensitive one and will grow faster; the reverse is true in the absence of therapy due to the reduced fitness of the former in terms of its ability to compete for nutrients and grow, hence the sensitive strain will prevail in this case. Taking advantage of the competitive nature of the two strains so as to prevent their uncontrolled growth using optimized treatment interruption schedules has, in our opinion, great potential and should be explored further with experimental studies.

IV. Discussion and Conclusions

Despite a long history of theoretical work in modeling cancer and optimizing chemotherapy, its practical application has been arguably negligible. This stems to a great extent from the lack of collaboration with experimentalists/ clinicians. Most studies to date have based their findings on models which were never developed alongside data or validated and, hence, are often paid little attention by clinicians.

As a result, the primary aim in our work is to utilise, to the extent possible, all information and data available from clinical

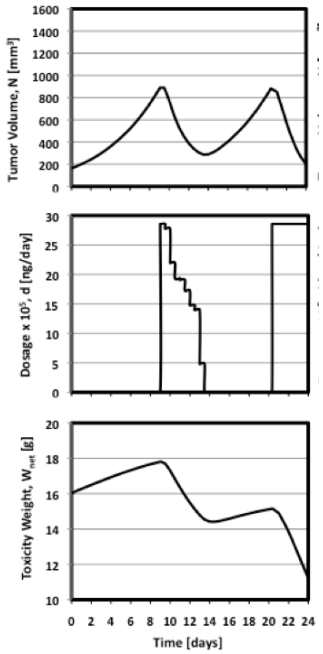

Figure 8. Optimal control in tumor bearing mice with colon cancer

practice and experiments to construct mathematical models which represent reality more closely and which may be used in optimal treatment design. Specifically, herein we presented models & control algorithms alongside experimental data from mice. Each of these models is very important in an optimal design framework. Specifically, we presented models for:

Mice not receiving any therapy in order to model the cancer dynamics in the absence of drugs. The exponential growth of cancer cells during the first stages of the disease when nutrients are available as well as the slowing down of growth as the tumor size increases is shown in the model results.

Mice receiving CPT-11 and 5-FU. The killing effect of each drug was explicitly included in the model and its magnitude was estimated from the respective data. In both cases results successfully represent cancer dynamics during this period.

Mice receiving treatment with docetaxel and developing resistance to this drug. Model results successfully predict drug-resistance following repeated cycles of docetaxel treatment. The model for drug-resistance also takes into consideration the reduced fitness of the drug-resistant cancer population in terms of its ability to compete for natural nutrients with the «fit» drug-sensitive strain.

Drug-specific pharmacokinetics and toxicity. In other formulations to-date, the toxicity was generally an inferred or generalized toxicity handled by constraining drug dosage rather than the measurable toxic effect validated with real data that may be specific to a particular drug-tumor pair. The use of body weight, which is most often proportional to toxicity in an experimental setting, to develop a toxicity model based on data is believed to be an improved approach.

Use in control algorithms with (i) dosage constraints, (ii) path and end–point tumor constraints as a way to minimize the tumor burden, and (iii) weight loss constraints as a way to

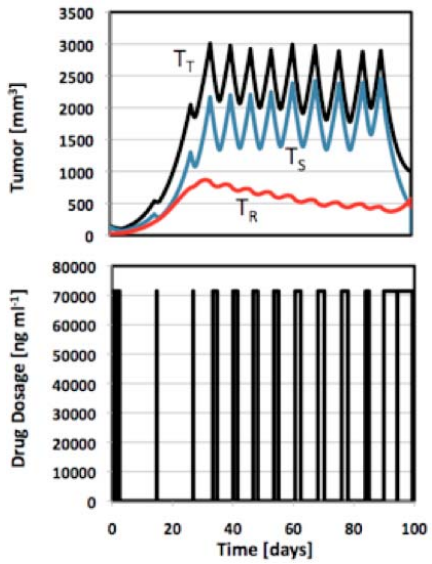

Figure 9. Top: Total, drug-sensitive, and drug-restistant tumor trajectories with optimal control. Bottom: Optimal administration of docetaxel.

minimize body weight loss which is a result of both toxicity as well as cancer itself. An optimal control case was presented for mice with and without drug-resistance.

An important result was shown. Drug-resistance is one of the most important reasons behind treatment failure, and a solution to this problem has not yet been demonstrated. The results show that the key to overcoming resistance and controlling progression is by facilitating the interplay between the drug-sensitive and resistant cells through optimized therapy interruptions. We believe this approach has great potential and we are already exploring this through mice experiments.

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