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Optimal Control in a Model of Chemotherapy-induced Radiosensilisation

Abstract In this work we consider a simple mathematical model of radiochemotherapy which includes a term responsible for radiosensilisation. We focus on finding theoretically optimal controls which maximise tumour cure probability for a finite, fixed therapeutic horizon. We prove that the optimal controls for both therapies are of 0-bang type, a result which is not altered by inclusion of the radiosensilisation term. By means of numerical simulations we show that optimal control offers a moderate increase in survival time over a sequential treatment. We then revisit in more detail a question of measuring the synergy between the therapies by means of isobolograms, a common experimental technique for measuring additivity of two treatments.

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1. Introduction The molecular mechanisms of interactions between radio- and chemotherapy have been thoroughly studied for decades, mainly due to the synergy between those two treatments when applied concurrently. That synergy (or supra-additivity) is attributed to chemotherapeutic radiosensilisation, i.e. the process in which chemotherapeutic agent renders the cells more susceptible to radiation. [4, 5]

Aside from biological experiments and clinical trials, these two therapies have been subject to mathematical modelling. Typically the process of radiosensilisation is omitted from those models [1, 2, 3], perhaps due to the underlying biological mechanism being relatively complex. Although in general such models provide insights into optimal therapy planning, the omission of radiosensilisation may impair their predictive capability.

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In this work we examine a mathematical model which includes a term responsible for radiosensilisation. We mostly focus on the theoretically optimal treatment which maximises the Tumour Cure Probability (TCP), but we also address a more general question of measuring the synergy effects in a pair of treatments. [6].

This work is a continuation of our previous study of optimal control in models of radiochemotherapy as described in [1] where we considered the following mathematical model:

$$\dot{N} = -\rho N \log \frac{N}{N_\infty} - cu(t)N - \left(\alpha v(t) + \beta v(t)^2\right) N, \tag{1}$$

where N denotes the tumour size, ρ is a proliferation rate, N_∞ is the carrying capacity for the tumour, c is the chemotherapy sensitivity parameter and α, β are the Linear-Quadratic (LQ) model parameters. The controls in the model are: $u(t)$, the chemotherapy dose at time t, and $v(t)$, the radiotherapy dose at time t. In [1] we have shown that if a goal is to minimise the tumour size at the end of a prescribed treatment horizon, then the optimal controls for both chemo- and radio-therapy are of 0-bang type. We have also concluded that introduction of pharmacokinetics and DNA repair does not alter the optimal controls in a significant manner.

2. Mathematical model One simplifying assumption we adopted in our previous work was that there was no interaction between the chemo- and radio-therapy, i.e. the process of radiosensilisation was not taken into account. The goal of this study is to explore how introducing radiosensilisation affects the optimal controls. As the exact molecular mechanism driving radiosensilisation is generally not known, we propose the following (purely behavioural) modification to our original model (1):

$$\dot{N} = -\rho N \log \frac{N}{N_\infty} - cu(t)N - \left(\alpha v(t) + \beta v(t)^2\right)\left(1 + ru(t)\right)\big)N, \tag{2}$$

where the parameter $r \geq 0$ measures the effect of synergy between radio- and chemotherapy.

The goal is to, for a prescribed therapy time T, maximise the Tumour Cure Probability (TCP) defined by $J\big(u(\cdot), v(\cdot)\big) = \exp(-N(T))$ while having upper bounds on the overall applied doses of chemotherapy and radiation, i.e. subject to: $\int_0^T u(t)dt \leq U$ and $\int_0^T v(t)dt \leq V$.

Before we proceed to the analysis of optimal control, let us perform a variable transformation to simplify the model. We introduce a new variable $x = \log \frac{N}{N_\infty}$ so that the model becomes:

$$\dot{x} = -\rho x - cu(t) - \left(\alpha v(t) + \beta v^2(t)\right)\left(1 + ru(t)\right). \tag{3}$$

We note that the change of variable was monotonously increasing, hence maximising TCP is equivalent to minimising $x(T)$.

3. Optimal Control. In this section we use Pontryagin Maximum Principle to examine the structure of the optimal control. We assume that the controls are bounded by some positive maximum doses u_{max} and v_{max}. In order to represent the dose constraints we introduce two auxiliary variables, so that the full problem becomes as follows: find measurable functions $u : [0,T] \to [0,u_{max}]$ and $v : [0,T] \to [0,v_{max}]$ such that $x(T)$ is minimised subject to

$$\begin{aligned} \dot{x} &= -\rho x - cu(t) - \big(\alpha v(t) + \beta v^2(t)\big)\big(1 + ru(t)\big), & x(0) &= x_0, \\ \dot{y} &= u(t), & y(0) &= 0, \\ \dot{z} &= v(t), & v(0) &= 0 \end{aligned} \tag{4}$$

with $y(T) \le U$ and $z(T) \le V$. We furthermore assume that $u_{max}T > U$ and $v_{max}T > V$, as otherwise the problem can be trivially solved by applying full dose throughout the whole treatment period.

The Hamiltonian of the above system is:

$$H(t,\mathbf{x},\mathbf{p},u,v) = -p_1\Big(\rho x + cu + \big(\alpha v + \beta v^2\big)\big(1 + ru(t)\big)\Big) + p_2 u + p_3 v, \tag{5}$$

where $\mathbf{x} = (x,y,z)$ is the state vector and $\mathbf{p} = (p_1,p_2,p_3)$ is the co-state (adjoint) vector. The adjoint variables satisfy the following system of differential equations:

$$\begin{aligned} \dot{p}_1 &= \rho p_1 & p_1(T) &= 1, \\ \dot{p}_2 &= 0, & p_2(T)\,(y(T) - U) &= 0, \\ \dot{p}_3 &= 0. & p_3(T)\,(z(T) - V) &= 0, \end{aligned} \tag{6}$$

with $p_2 \ge 0$ and $p_3 \ge 0$.

Note that from the first equation above we have:

$$p_1(t) = e^{\rho(t-T)} > 0. \tag{7}$$

We will now determine the structure of the optimal control using the minimising property of the Hamiltonian. Let $\mathbb{U} = [0,u_{max}] \times [0,v_{max}]$ denote the set of admissible controls. Then for almost all $t \in [0,T]$ it has to be that:

$$\begin{aligned} (u(t),v(t)) &= \operatorname*{arg\,min}_{(\eta,\xi)\in\mathbb{U}} H(t,\mathbf{x},\mathbf{p},\eta,\xi), \\ &= \operatorname*{arg\,min}_{(\eta,\xi)\in\mathbb{U}} \Big(-(1+r\eta)\beta p_1(t)\xi^2 + \big(p_3 - (1+r\eta)\alpha p_1(t)\big)\xi \\ &\qquad + (p_2 - cp_1(t))\eta - \rho p_1(t)x(t)\Big). \end{aligned} \tag{8}$$

From the functional form of the Hamiltonian we can deduce the following proposition:

PROPOSITION 3.1 *At any time t, if $(\eta, \xi) \in \mathbb{U}$ is the pair minimising the Hamiltonian, then $\xi = 0$ or $\xi = v_{max}$.*

PROOF Suppose not, i.e. that for some time $t \in [0,T]$ the minimum was attained for $(\eta, \xi) \in \mathbb{U}$ with $\xi \in (0, v_{max})$. But for t, $\mathbf{x}$, $\mathbf{p}$ and η fixed (i.e. as a function of ξ), the graph of the Hamiltonian is a parabola with arms facing downwards as the coefficient standing next to ξ^2 is negative. Therefore

$$\min\left(H(t,\mathbf{x},\mathbf{p},\eta,0), H(t,\mathbf{x},\mathbf{p},\eta,v_{max})\right) < H(t,\mathbf{x},\mathbf{p},\eta,\xi),$$

which is a contradiction. ∎

We therefore conclude that the optimal control v takes values 0 or v_{max} almost everywhere. Having established the above fact, we can formulate the following proposition regarding the control u:

PROPOSITION 3.2 *For almost all times $t \in [0,T]$ the control u is determined by the sign of the switching function*

$$\varphi(t) = \underline{H}u = p_2 - \big(c + r(\alpha v(t) + \beta v^2(t))\big)p_1(t).$$

with

$$u(t) = \begin{cases} 0 & \text{when } \varphi(t) > 0, \\ u_{max} & \text{when } \varphi(t) < 0. \end{cases}$$

PROOF If φ does not vanish over an interval, the above proposition is a direct consequence of the minimising property of the Hamiltonian, which is a linear function of u. But given that we established that the control v may only take values 0 or v_{max}, the function φ cannot possibly vanish identically on an interval, thus ending the proof. ∎

We have therefore established that at any given time t the optimal control may take one of the four possible pairs of values, namely:

$$\big(u(t), v(t)\big) \in \big\{(0,0), (u_{max},0), (0,v_{max}), (u_{max},v_{max})\big\}.$$

Which of these four values should be chosen may be determined directly from the Hamiltonian. Noting that the term involving the state variable is irrelevant as it does not depend on the controls, we define:

$$\begin{aligned}
H_{00}(t) &= H(t,\mathbf{0},\mathbf{p},0,0) &&= 0, \\
H_{10}(t) &= H(t,\mathbf{0},\mathbf{p},u_{max},0) &&= p_2 u_{max} - c u_{max} p_1(t), \\
H_{01}(t) &= H(t,\mathbf{0},\mathbf{p},0,v_{max}) &&= p_3 v_{max} - (\alpha v_{max} + \beta v_{max}^2) p_1(t), \\
H_{11}(t) &= H(t,\mathbf{0},\mathbf{p},u_{max},v_{max}) &&= H_{10} + H_{01} - r u_{max}(\alpha v_{max} + \beta v_{max}^2) p_1(t).
\end{aligned}$$

To determine the optimal control it is now enough to compute the four values above and pick the corresponding control. Of course the Hamiltonian depends on the two multipliers p_2 and p_3 which we do not know *a priori*, but based on the above we may still draw certain conclusions regarding the structure of the control.

PROPOSITION 3.3 *1. Control* $(0,0)$ *may be optimal only at the beginning of the treatment.*

2. Control $(u_{max},0)$ *cannot switch to control* $(0,v_{max})$.

3. Control $(0,v_{max})$ *cannot switch to control* $(u_{max},0)$.

4. If the control (u_{max},v_{max}) *becomes optimal, it remains optimal until the end of the treatment.*

PROOF 1. Control $(0,0)$ is optimal only if H_{10}, H_{01}, H_{11} are all positive. But since p_1 is increasing, they are all decreasing functions of t. Therefore once one of them becomes negative, it will remain negative for all subsequent times t and $H_{00}=0$ can never become the minimum of the four values of the Hamiltonian again.

2. Suppose that $(u_{max},0)$ is the optimal control at time τ. Then in particular $H_{10}(\tau) < H_{00}(\tau) = 0$ at time τ and for all subsequent times $t \geq \tau$. But then:

$$H_{11}(t) - H_{01}(t) = H_{10}(t) - ru(\alpha v_{max} + \beta v_{max}^2)p_1(t) < 0$$

for all $t \geq \tau$. Therefore $H_{11}(t) < H_{01}(t)$ and H_{01} will never be the minimum of the four values of the Hamiltonian.

3. Analogous as 2.

4. Suppose that the control (u_{max},v_{max}) is optimal at time τ. Then it has to be that

$$H_{11}(\tau) < H_{01}(\tau),\ H_{10}(\tau),\ H_{00}(\tau).$$

But we also have at all times t:

$$\dot{H}_{11} = \dot{H}_{10} + \dot{H}_{01} - ru_{max}(\alpha v_{max} + \beta v_{max}^2)\rho p_1(t) \leq \min\{\dot{H}_{10}, \dot{H}_{01}\},$$

so that H_{11} decreases more rapidly than H_{10} and H_{01} and therefore will remain the most negative of the four values of the Hamiltonian. ∎

Based on which switches are allowed, we therefore conclude that the only control which satisfies the Pontryagin Maximum Principle – i.e. the necessary conditions for optimality – is of the form 0-bang for both controls. As the

	Value	Unit	Role
N_0	3.0×10^3	mm^3	Initial volume
ρ	7.00×10^{-5} (mean), 7.23×10^{-3} (std)	$1/day$	Proliferation rate
N_∞	1.735×10^4	mm^3	Carrying capacity
c	1.4×10^{-2}	$1/ml$	Chemo sensitivity
α	3.98×10^{-2} (mean), 1.68×10^{-2} (std)	$1/Gy$	LQ parameter
β	$\alpha/10$	day/Gy^2	LQ parameter
r	0, 0.1 (see text)	-	Radiosensilisation
T	60	day	Therapy time
U	105	ml	Total chemo dose
u_{max}	15	ml/day	Max. chemo dose
V	60	Gy	Total radio dose
v_{max}	3	Gy/day	Max. radio dose

Table 1: Parameter values used in the simulations. Note that the proliferation rate ρ is correlated with the radiosensitivity parameter α with a coefficient 0.87. Truncated normal distributions were used for ρ and α to ensure that the parameters remain non-negative.

minimising solution exists due to the way the problem is formulated, the only one satisfying necessary conditions has to be optimal. Now, a treatment which does not use the full available dose cannot be optimal (as seen from terminal conditions in Equation (6)) thus fixing the switching times of the 0-bang switches. We therefore obtain:

THEOREM 3.4 *The optimal control strategy for the described problem the following:*

$$u(t) = \begin{cases} 0 & \text{if } t \in [0,\ T - \frac{U}{u_{max}}], \\ u_{max} & \text{if } t \in (T - \frac{U}{u_{max}},\ T], \end{cases} \quad v(t) = \begin{cases} 0 & \text{if } t \in [0,\ T - \frac{V}{v_{max}}], \\ v_{max} & \text{if } t \in (T - \frac{V}{v_{max}},\ T]. \end{cases}$$

4. Numerical simulations

Now that we have established how the optimal control looks like, we may examine how it performs in comparison with other possible strategies. Given that we introduced a radiosensilisation parameter r it is perhaps not surprising that the concurrent therapy performs better than any sequential one. To see how much better the performance is, we adapted the methodology used by Dolbniak et al. [2] where the survival curves are computed based on randomised "virtual" patients. Each patient is characterised by a random set of parameters ρ, α and β. Following [2] we assumed a 0.87 correlation between the proliferation rate ρ and the radiosensitivity parameter α. The parameter values used are summarised in Table 1 and were originally estimated by Geng et al. [3] from survival curves of patients with non-small cell lung carcinoma. The values of u_{max}, U, v_{max} and V could not have been used directly

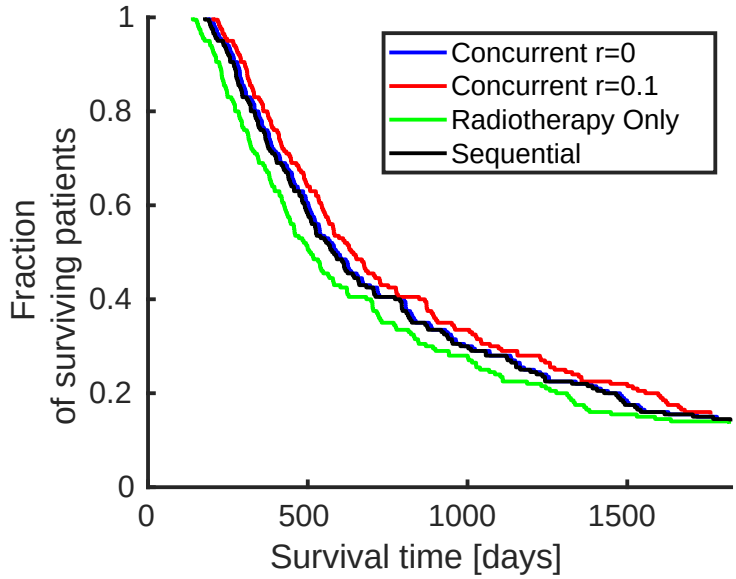

Figure 1: Survival curves for three treatment strategies. The optimal strategy is considered in a scenario with and without radiosensilisation.

due to a fixed treatment schedule used in [3], but clinically-realistic values were assumed.

4.1. Survival curves We computed survival curves for three treatment strategies, where the treatment was applied only over the first $T = 60$ days. The radiotherapy-only strategy is chosen as a reference point. We then considered a sequential strategy (chemotherapy first, then break, then radiotherapy) and the optimal strategy as computed in the previous section. The simulations for the latter were performed with two values of the radiosensilisation parameter: $r = 0$ and $r = 0.1$. Survival time is measured as the time needed to reach a critical volume of $12000mm^3$.

4.2. Presentation of the synergy effect

Although in this particular case the optimal chemotherapeutic strategy does not offer a tremendous improvement in survival time over the sequential strategy, an interesting question of measuring the effects of synergy between the two drugs emerges. In what follows, we apply the isobologram [6] framework to our mathematical model. Throughout this section we assume that the maximum instantaneous doses for chemo- and radiotherapies (u_{max} and v_{max}) remain constant and we vary the maximum total doses U and V. The applied treatment strategy is the optimal concurrent one.

The left plot in Figure 2 show the dose-response plots for the two treatments applied separately. The response of a given dose pair (U, V) is defined to be one minus the fraction of the number of cells after T days and the

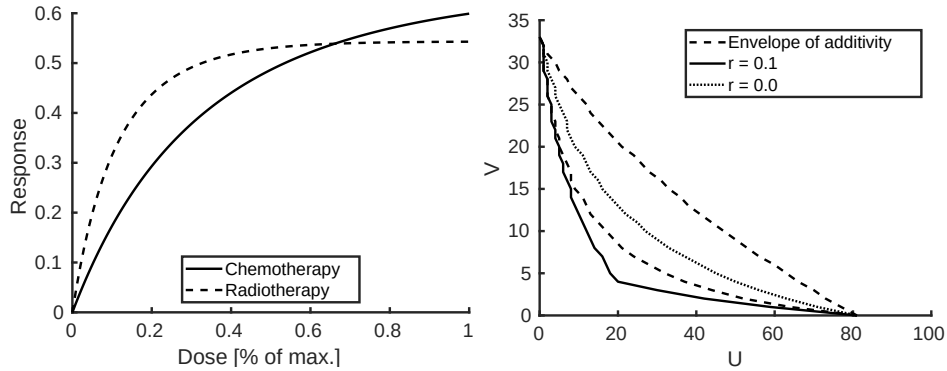

Figure 2: Left: dose-response plots for chemotherapy and radiotherapy. Right: Isobologram for the desired cytotoxic response of 50%.

number of cells after T days if no treatment is applied. The maximum total doses were chosen to be $U_{max} = 150$ for chemotherapy and $V_{max} = 100$ for radiotherapy. The right plot shows the so-called isobologram for a desired cytotoxic response of $R = 50\%$. The dashed curves constitute the boundary of the "envelope of additivity". They are constructed based on the isolated response curves (left plot). Let $R_u(U)$ and $R_v(V)$ denote the responses for a given total dose of chemotherapy and radiotherapy respectively. The Mode 1 and Mode 2 curves can be defined as follows (here with $R = 50\%$):

- Mode 1 (lower) curve is generated under the assumption that chemotherapy and radiotherapy act independently, i.e.:

$$M_1^R = \{(U, V) : U = R_u^{-1}\left(R - R_v(V)\right)\}$$

- Mode 2 (upper) curve is generated under the assumption that chemotherapy and radiotherapy have an identical mechanism of action, i.e.:

$$M_2^R = \{(U, V) : U = R_u^{-1}(R) - R_u^{-1}(R_v(V))\}$$

We also compute the actual doses (U, V) needed to achieve the 50% cytotoxic effect as predicted by the model. They are shown in the right plot of Figure 2 as a solid line ($r = 0.1$) and as a dotted line ($r = 0$). We note that, as expected, the $r = 0$ curve lies within the envelope of additivity (i.e. there is no synergy between treatments), while the $r = 0.1$ curve lies below the envelope, which indicates supra-additivity (synergy) of the two treatments.

5. Conclusions In this study we formulated a model of tumour response to radiochemotherapeutic treatment which includes the effects of radiosensitisation. We then showed that the optimal controls in this model are of type 0-bang for both radio- and chemotherapy. In Section 4.1 we showed that

optimal treatment offers a moderate improvement in survival over a sequential protocol. The improvement is unsurprisingly amplified by introducing radiosensilisation.

Section 4.2 consists of a brief discussion of how an experimental isobologram technique of assessing additivity between treatments may be used in the context of mathematical models. We formally define the “Mode 1" and “Mode 2" curves constituting the so-called envelope o additivity in an isobologram. We note that this technique may be useful when presenting model outcomes to experimentalists who may be used to isobolograms. In case of our particular model the treatment shows supra-additive behaviour (which is clear from the model construction).

The model we presented in this study treats radiosensilisation in a purely phenomenological manner and does not attempt to model the underlying biological mechanisms. Possible extensions of the model would involve subdivisions of the tumour population into compartments and analysis of the two treatments cross-interactions in a more biologically realistic manner.

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Optymalne sterowanie w modelu radiochemioterapii uwzględniającym uwrażliwienie

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Streszczenie W tej pracy rozważamy prosty model radiochemioterapii, w którym uwzględniamy składnik odpowiedzialny za uwrażliwienie komórek na radioterapię indukowane przez podaną chemioterapię. Skupiamy się na znalezieniu teoretycznie optymalnych strategii leczenia, które maksymalizują prawdopodobieństwo wyleczenia guza (tumour cure probability) w zadanym, skończonym horyzoncie terapeutycznym. Dowodzimy, że optymalne sterowania są postaci 0-bang i składnik odpowiedzialny za uwrażliwienie nie ma wpływu na strukturę tych sterowań. Przeprowadzamy symulacje numeryczne by pokazać, że optymalne sterowanie oferuje nieznaczny wzrost przeżycia pacjentów w porównaniu do terapii sekwencyjnej. Następnie, by zmierzyć synergię pomiędzy chemio- i radioterapią, korzystamy z metody izobologramu, techniki stosowanej w eksperymentach do oceny addytywności tych terapii.

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Słowa kluczowe: radiochemioterapia, optymalne sterowanie, krzywe przeżywalności, uwrażliwienie na radioterapię.

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