ISTITUTO DI ANALISI DEI SISTEMI ED INFORMATICA
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CONSIGLIO NAZIONALE DELLE RICERCHE

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Minimum value of the maximal entry of n-dimensional vectors with constant sum of the entries and of the squared entries

R. 10, 2015

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Abstract

We present the analytical study of a constrained non-linear optimization problem relevant to the optimization of fractionated radiotherapy protocols of length n. The admissible set considered here is derived from the imposition of constraints, mandatory in radiotherapy, to guarantee that the damages caused to healthy tissues by the radiation do not exceed assigned tolerable levels. Radiation damages are evaluated by means of the well-known LQ model and, for suitable values of the normal tissue parameters, the constraints are written as a linear constraint and a quadratic constraint. In this report, we prove a property satisfied by the value of the maximal entry of vectors in the mentioned feasible region, and precisely we determine the minimal value of the maximal entry of such vectors. This result is significant for the problem of radiotherapy optimization when an upper bound is set on the size of the daily fraction doses in addition to the normal tissue constraints [3]. Indeed, the optimum of the present problem acts as a threshold with regard to the dose upper bound influencing the type of solution of the radiotherapy optimization problem.

1. Introduction

We present the analytical study of a constrained non-linear optimization problem in the positive subspace of the Euclidean space $\mathbb{R}^n$. The problem originated midstream the study of the optimization problem of radiotherapy schedules. In short, with reference to fractionated radiotherapy protocols of fixed length, the original problem consists in determining the daily fraction doses so to maximize the overall tumour damage while keeping the damages to normal tissues within given admissible levels, and it is based on mathematical models of the radiation response of tumours and normal tissues. So, to get to the formulation of the problem considered here, let us introduce the notations relevant to the original optimization problem, referring to radiotherapy schedules of the kind one fraction/day, five fractions/week, having a *fixed* number n of fraction doses, with $n \in \{1, \dots, n_M\}$, which are the problem decision variables.

Consider a homogeneous cell population subject to fractionated radiotherapy and let $d_k \geq 0$, $k = 1, \dots, n$, represent the sizes of the daily fraction doses (measurement unit Gy) constituting the protocol. The cell population response to radiation can be evaluated by means of the well-known LQ model that expresses the fraction Φ of cells surviving irradiation [1],[7],[2]. According to the LQ model, the logarithm of such surviving fraction is given by

$$\ln(\Phi) = -\alpha \sum_{k=1}^{n} d_k - \beta \sum_{k=1}^{n} d_k^2 + \frac{\ln(2)}{T_P}(T - T_K)H(T - T_K). \tag{1}$$

where $\alpha, \beta > 0$ are the LQ radiosensitivity parameters of the population, accounting for non-repairable lesions to DNA and, respectively, for the lethal misrepair events occurring in the repair process of DNA double strand breaks [7]. In (1), the two negative terms represent the cumulated effect of instantaneous lethal damages, whereas the positive term accounts for cell repopulation, with T_P the repopulation doubling time, T_K the kick-off time of compensatory proliferation, T the (fixed) overall treatment length, and H the Heaviside function. We notice that while (1) represents a *survival*, the same expression with opposite sign represents the *damage* induced by the radiation to cells.

The LQ model is used to represent the tumour response to radiation, but as it suitably represents also the response of normal tissues surrounding the tumour ([8, 6]), it is used here to define the admissibility constraints, necessary to guarantee that the damage to healthy tissues is kept below assigned levels of tolerability. Based on their different reaction velocity and sensitivity to radiation, it is usual to distinguish early responding normal tissues (complications arise hours or days after irradiation) and late responding normal tissues (complications after months or even years). Therefore, attributing the subscripts "e" and "l" to the radiosensitivity parameters referring to the early and, respectively, late tissue, we write the following constraints:

$$\alpha_e \sum_{k=1}^{n} d_k + \beta_e \sum_{k=1}^{n} d_k^2 - \frac{\ln(2)}{T_{Pe}}(T - T_{Ke})H(T - T_{Ke}) \leq C_e, \tag{2}$$

$$\alpha_l \sum_{k=1}^{n} d_k + \beta_l \sum_{k=1}^{n} d_k^2 \leq C_l, \tag{3}$$

where $C_e, C_l > 0$ are the maximal damage levels, respectively tolerable for early and late responding normal tissues. The cell repopulation term is absent in constraint (3) as, being typical values of T_{Kl} much larger than T, it is negligible for late responding tissues [6].

4.

Dividing (2), (3) respectively by β_e, β_l, the constraints can be rewritten in a more compact form as

$$g_e(d) = \rho_e \sum_{k=1}^{n} d_k + \sum_{k=1}^{n} d_k^2 - k_e \leq 0 \,, \tag{4}$$

$$g_l(d) = \rho_l \sum_{k=1}^{n} d_k + \sum_{k=1}^{n} d_k^2 - k_l \leq 0 \,, \tag{5}$$

where $\rho_e = \alpha_e/\beta_e$, $\rho_l = \alpha_l/\beta_l$ are the normal tissue radiosensitivity ratios, with $\rho_e > \rho_l$, and the constant terms k_e, k_l group together all the terms independent of the doses. Clearly, the doses d_k are subject to physically meaningful constraints of non negativity. Moreover, as done in [4, 3], additional precautionary constraints may be set to limit the size of the daily fraction doses.

As proved in [4, 3], an interesting set in the optimization of radiotherapy protocols, is the set defined by the intersection of the constraint boundaries $I = \{g_e(d) = 0, \ g_l(d) = 0, d_k \geq 0, k = 1, \ldots, n\}$. Indeed, the set I is made by protocols simultaneously providing the maximal permitted damage to both the early and late normal tissue. For particular tumour classes, this set of possibly infinite cardinality coincides with the set of optimal solutions.

In this report, we intend to study a property of I, and in particular to determine the minimum value of the maximal entry of the vectors describing its points. To this aim, we suppose the normal tissue parameters are such that the set I is non empty. As shown in [3], that means to assume: i) $k_e(n) - k_l > 0$, and $\rho_e k_l - \rho_l k_e(n) > 0$; ii) $v \in [1, n]$, where v is defined as

$$v \triangleq \frac{(k_e(n) - k_l)^2}{(\rho_e - \rho_l)(\rho_e k_l - \rho_l k_e(n))}. \tag{6}$$

The minimum value of the maximal entry of vectors belonging to I represents a threshold value for the dose size of radiotherapy protocol. Indeed, if a daily dose upper bound is set below this threshold, no points of the intersection set I satisfy the chosen upper bound, and then no point of I is admissible.

Recalling the expressions (4), (5), it is easy to see that points belonging to the intersection set I are such that

$$\sum_{k=1}^{n} d_k = \frac{k_e - k_l}{\rho_e - \rho_l} \triangleq S \,, \qquad \sum_{k=1}^{n} d_k^2 = \frac{\rho_e k_l - \rho_l k_e}{\rho_e - \rho_l} = \frac{S^2}{v} \,, \qquad d_k \geq 0 \,, \ \ k = 1, \ldots, n \,. \tag{7}$$

Note that under the assumptions i), ii), the quantities S, S^2/v are positive and well defined [3]. Next, we formulate the constrained non-linear programming problem of finding the minimum value of the maximal entry of vectors d having fixed sum of the entries and of the squared entries, according to (7). The admissible domain is the intersection between a hyperplane and a hypersphere in the region $d \geq 0$ of $\mathbb{R}^n$ and, because of their symmetry with respect to the half-line $\{d_n = d_{n-1} = \ldots = d_2 = d_1 \geq 0\}$, we can reduce the admissible set choosing one of the $n!$ possible ordering of the entries of d without loss of generality.

2. Problem formulation

Let us assume $S > 0$, $v \in [1, n]$ and consider the vectors with entry ordering $d_n \geq d_{n-1} \geq \ldots \geq d_2 \geq d_1 \geq 0$. We formulate the optimization problem as follows.

Problem 2.1. *Minimize the function:*

$$J(d) = d_n, \tag{8}$$

on the admissible set:

$$D = \{d \in R^n| \quad \sum_{k=1}^{n} d_k = S, \ \sum_{k=1}^{n} d_k^2 = \frac{S^2}{v}, \ d_n \geq d_{n-1} \geq \ldots \geq d_2 \geq d_1 \geq 0, \ v \in [1, n]\}. \tag{9}$$

As seen above, D is non-empty for $v \in [1, n]$ (see [3]). Moreover, Problem 2.1 certainly admits an optimal solution as the admissible set (9) is compact and the cost function (8) is continuous on it (Weierstrass theorem [5]). It is evident that the Problem 2.1 is not convex so that we can only use the optimal necessary conditions provided by the Kuhn Tucker Theorem [5]. The Lagrangian function associated to the problem is

$$L(d, \lambda_0, \lambda_s, \lambda_q, \eta) = \lambda_0 d_n + \lambda_s \left(\sum_{k=1}^{n} d_k - S \right) + \lambda_q \left(\sum_{k=1}^{n} d_k^2 - \frac{S^2}{v} \right) - \eta_1 d_1 + \sum_{k=1}^{n-1} \eta_{k+1} \left(d_k - d_{k+1} \right), \tag{10}$$

where $\lambda_0, \lambda_s, \lambda_q$ are scalar multipliers and η is the n-dimensional vector of multipliers η_k, $k = 1, \ldots, n$, related to the inequality constraints.

Let us now write the necessary and admissibility conditions

$$\frac{\partial L}{\partial d_k} = \lambda_s + 2\lambda_q d_k - \eta_k + \eta_{k+1} = 0, \qquad k = 1, \ldots, n-1, \tag{11}$$

$$\frac{\partial L}{\partial d_n} = \lambda_0 + \lambda_s + 2\lambda_q d_n - \eta_n = 0, \tag{12}$$

$$\eta_1 d_1 = 0, \tag{13}$$

$$\eta_k(d_{k-1} - d_k) = 0, \qquad k = 2, \ldots, n, \tag{14}$$

$$\sum_{k=1}^{n} d_k = S, \tag{15}$$

$$\sum_{k=1}^{n} d_k^2 = \frac{S^2}{v}, \tag{16}$$

$$\eta_k \geq 0, \qquad k = 1, \ldots, n, \tag{17}$$

$$\lambda_0 \geq 0, \tag{18}$$

with $\lambda_0, \lambda_s, \lambda_q, \eta$ never simultaneously equal to zero.

The vectors d and the related multipliers $\lambda_0, \lambda_s, \lambda_q, \eta$ that satisfy the system (11)-(18) are the extremals of Problem 2.1, that is all the possible candidates to the optimal solution. In particular, vectors d satisfying Eqs.(11)-(18) with $\lambda_0 = 0$ are called 'abnormal' extremals, while vectors d satisfing Eqs.(11)-(18) with $\lambda_0 \neq 0$ are called 'normal' extremals.

6.

Taking into account Eqs. (13)-(16), let us multiply each equation $\dfrac{\partial L}{\partial d_k} = 0$ in (11)-(12) by the corresponding d_k, $k = 1, \ldots, n$, then adding together the obtained n equations. We get the relation

$$\lambda_0 d_n + \lambda_s S + 2\lambda_q \frac{S^2}{v} = 0 \,, \tag{19}$$

linking directly the multipliers $\lambda_0, \lambda_s, \lambda_q$ so to turn out to be useful to separately study the cases $\lambda_0 = 0$ and $\lambda_0 \neq 0$.

2.1. Existence and structure of abnormal extremals

The abnormal extremals satisfy the necessary and admissibility conditions with $\lambda_0 = 0$ by definition. Then Eq. (19) becomes

$$\lambda_s = -2\lambda_q \frac{S}{v} \tag{20}$$

so that, (as $S/v > 0$), only the following alternatives for the sign of λ_s and λ_q are possible:

1) $\lambda_s = 0, \lambda_q = 0$,
2) $\lambda_s < 0, \lambda_q > 0$, $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad$ (21)
3) $\lambda_s > 0, \lambda_q < 0$.

Let us verify if at least one of the three alternatives in (21) leads to solutions of the system (11)-(17).

Case 1) of (21) does not provide extremals as $\lambda_0 = \lambda_s = \lambda_q = 0$ would imply $\eta_k = 0$, $\forall\, k$ (see (11), (12)) and all the multipliers would be simultaneously equal to zero.

To study the last two cases of (21), it is convenient to exploit (20) rewriting (11), (12) (with $\lambda_0 = 0$) in terms of λ_q

$$\eta_k = \eta_{k+1} + 2\lambda_q \left(d_k - \frac{S}{v} \right), \quad k = 1, \ldots, n-1, \tag{22}$$

$$\eta_n = 2\lambda_q \left(d_n - \frac{S}{v} \right). \tag{23}$$

Consider case 2) of (21), i.e. $\lambda_q > 0$. If $\eta_n > 0$, from (14) and (23), we deduce $d_n = d_{n-1} > S/v$ and from (22), for $k = n-1$, it is $\eta_{n-1} > \eta_n > 0$. Similarly, $\eta_{n-1} > 0$ implies $\eta_{n-2} > 0$ and so on until $\eta_1 > 0$. Then, from (13),(14), we have $d_k = 0$, $k = 1, \ldots, n$, that cannot be accepted as they do not satisfy Eqs. (15), (16). Conversely, if $\eta_n = 0$, Eq.(23) implies $d_n = S/v$. Because of the ordering of the entries of d, it must be $d_k \leq S/v$, $k = 1, \ldots, n-1$, and from (22) it is $\eta_k \leq \eta_{k+1}$, $k = 1, \ldots, n-1$. The latter condition can be verified if and only if all the multipliers η_k, $k = 1, \ldots, n$, are equal to zero (as $\eta_n = 0$) so that, from (22), we have $d_k = S/v$, $k = 1, \ldots, n$, while (15) imposes $v = n$.

To analyze case 3) of (21) we follow a similar procedure. First consider $\eta_n > 0$ that gives $d_n = d_{n-1} < S/v$ (see Eqs.(14),(23)) and consequently $d_k < S/v$, $k = 1, \ldots, n$, being d_n the maximal entry. Then, from (22), we have $\eta_k > \eta_{k+1}$, $k = 1, \ldots, n-1$, that implies $d_k = 0$, $k = 1, \ldots, n$ (see (13),(14)). But, as already said, the vector d with all the entries equal to zero cannot be an extremal because it does not satisfy constraints (15), (16). Second consider $\eta_n = 0$ which gives $d_n = S/v$ from Eq.(23). As $d_k \leq d_n = S/v$, $k = 1, \ldots, n-1$, and $\lambda_q < 0$ by hypothesis, from (22) we obtain $\eta_k \geq \eta_{k+1}$, $k = 1, \ldots, n-1$. Taking into account $\eta_k \geq 0$, $k = 1, \ldots, n$, the following situations are possible:

a) $\eta_k = 0$, $k = 1, \ldots, n$ that implies $d_k = S/v$, $k = 1, \ldots, n$, (see Eqs. (23), (22)) and, in order to satisfy the constraint (15), the condition $v = n$;

b) $\exists \ \bar{k} = 1 \ldots, n - 1 \mid \eta_k > 0$, $k = 1, \ldots, \bar{k}$ and $\eta_k = 0$, $k = \bar{k} + 1, \ldots, n$. Recalling Eqs. (13),(14) and Eqs. (22),(23), it is $d_k = 0$, $k = 1, \ldots, \bar{k}$ and $d_k = S/v$, $k = \bar{k} + 1, \ldots, n$, respectively. Moreover, in order to satisfy the constraint (15), it must be $v = n - \bar{k}$.

In conclusion, if and only if the parameter v is integer Problem 2.1 admits abnormal extremals. In particular, a unique abnormal extremal exists for each integer value of v, $v \in [1, n]$, which is the vector $d \in R^n$ such that $d_k = 0$, $k = 1, \ldots, n - v$ and $d_k = S/v$, $k = n - v + 1, \ldots, n$, when $v \neq n$, or such that $d_k = S/n$, $\forall k$, when $v = n$. The list of the abnormal extremals is reported in Table 1, for all the integer values of v.

v	d
1	$(0 \ \ 0 \ \ \ldots \ \ 0 \ \ 0 \ \ S)$
2	$(0 \ \ 0 \ \ \ldots \ \ 0 \ \ S/2 \ \ S/2)$
3	$(0 \ \ 0 \ \ \ldots \ \ S/3 \ \ S/3 \ \ S/3)$
$\vdots$	$\vdots$
$n-1$	$(0 \ \ S/(n-1) \ \ \ldots \ \ S/(n-1) \ \ S/(n-1) \ \ S/(n-1))$
n	$(S/n \ \ S/n \ \ \ldots \ \ S/n \ \ S/n \ \ S/n)$

Table 1: Abnormal extremals of Problem 2.1.

2.2. Existence and structure of normal extremals

In order to find the normal extremals, let us consider the necessary and admissibility conditions (11)–(18) with $\lambda_0 = 1$ (we normalize the Lagrangian function with respect to λ_0 when $\lambda_0 > 0$). First of all, Eq. (19) can be rewritten as

$$d_n = -\left(\lambda_s + 2\lambda_q \frac{S}{v}\right) S. \tag{24}$$

Since d_n must be positive ($d_n = 0$ is excluded implying $d_k = 0$, $\forall k$), λ_s and λ_q can only take the following values:

$$
\begin{aligned}
&1) \quad \lambda_s = 0, \lambda_q < 0, \\
&2) \quad \lambda_s < 0, \lambda_q \leq 0, \\
&3) \quad \lambda_s < 0, \lambda_q > 0, \\
&4) \quad \lambda_s > 0, \lambda_q < 0.
\end{aligned}
\tag{25}
$$

Let us start from case 1) of (25) and rewrite Eqs. (11), (12) as

$$
\begin{aligned}
\eta_k &= \eta_{k+1} + 2\lambda_q d_k, \quad k = 1, \ldots, n-1, \tag{26} \\
\eta_n &= 1 + 2\lambda_q d_n. \tag{27}
\end{aligned}
$$

As $\lambda_q < 0$ and $d_k \geq 0$, from Eqs. (26), (27), we have $\eta_{k+1} \geq \eta_k$, $k = 1, \ldots, n-1$, so that if $\eta_k > 0$, it necessarily is $\eta_{k+1} > 0$. Then, the following situations are possible:

8.

a) $\eta_k > 0$, $k = 1, \ldots, n$, that, from Eqs. (13), (14), implies $d_k = 0$, $k = 1, \ldots, n$, which is a non-admissible vector as it does not satisfy (15) or (16);

b) $\eta_k = 0$, $k = 1, \ldots, n$, that implies $d_k = 0$, $k = 1, \ldots, n-1$, and $d_n = -1/2\lambda_q$ (see (26), (27)). Then, in order to satisfy constraints (15) and (16), it must be $d_n = S$ (because $\lambda_q = -2/S$) and $v = 1$;

c) $\exists\ \bar{k} = 1, \ldots, n-1 \mid \eta_k = 0$, $k = 1, \ldots, \bar{k}$, and $\eta_k > 0$, $k = \bar{k}+1, \ldots, n$. First of all, from (14), we see that $d_k = d_{k-1}$, $k = \bar{k}+1, \ldots, n$, and then we have $d_k > 0$, $k = \bar{k}, \ldots, n$, because Eq.(26) for $k = \bar{k}$, implies $d_{\bar{k}} > 0$ ($\eta_{\bar{k}} = 0$, $\eta_{\bar{k}+1} > 0$ by definition and $\lambda_q < 0$). Note that, if $\bar{k} = 1$ we have a vector d with all the components equal to each other and positive, while if $\bar{k} > 1$ we have $d_k = 0$, $k = 1, \ldots, \bar{k}-1$, because Eq. (26) for $k = \bar{k}-1$ implies $d_{\bar{k}-1} = 0$ ($\eta_{\bar{k}} = \eta_{\bar{k}-1} = 0$ by definition) and consequently, because of the ordering of the components of d, all the remaining components are zero too. So, we have a vector d with $\bar{k} - 1$ components equal to zero and $n - \bar{k} + 1$ equal positive components. These vectors are actually extremals if and only if $v = n - \bar{k} + 1$ and $d_k = S/v$, $k = \bar{k}, \ldots, n$ (see constraints (15), (16)).

So, case 1) of (25) provides the extremals of the previous section.

Considering case 2) of (25), Eq. (11) implies $\eta_{k+1} > \eta_k$, $k = 1, \ldots, n-1$, leading to the following situations:

a) $\eta_k > 0$, $k = 1, \ldots, n$, that implies $d = 0$ (non-admissible);

b) $\eta_1 = 0$, $\eta_k > 0$, $k = 2, \ldots, n$, which, taking into account (14), implies $d_k = d_{k-1}$, $k = 2, \ldots, n$, all positive because $d = 0$ has to be excluded. As already seen, the vector d with five equal components the constraints (15), (16) if and only if $d_k = S/v$, $k = 1, \ldots, n$, and provided that $v = n$.

For the last two alternatives of (25), it is not possible to determine an a priori ordering for the multipliers η_k, $k = 1, \ldots, n$, because $\lambda_s \cdot \lambda_q < 0$. Nevertheless, by exploiting the necessary conditions (11), (12), explicitly rewritten as

$$\eta_k = \eta_{k+1} + \lambda_s + 2\lambda_q d_k, \qquad k = 1, \ldots, n-1, \tag{28}$$
$$\eta_n = 1 + \lambda_s + 2\lambda_q d_n, \tag{29}$$

along with the complementary conditions (13), (14), it is possible to give some preliminary properties useful to characterize the structure of the extremal pairs η, d, as well as to exclude some configurations of the vector η. The properties are listed in the following:

i) if for an integer $\bar{k} = 1, \ldots, n-1$ it is $\eta_{\bar{k}} = 0$ and $\eta_{\bar{k}+1} > 0$, it follows $\eta_k > 0$ for $k = \bar{k}+1, \ldots, n$ and then the last $n - \bar{k} + 1$ entries of d are positive and equal;

ii) if for an integer $\bar{k} = 1, \ldots, n-1$ it is $\eta_{\bar{k}} > 0$ and $\eta_{\bar{k}+1} = 0$, it follows $\eta_k > 0$ for $k = 1, \ldots, \bar{k}$ and then the first $\bar{k}$ entries of d are equal to zero;

iii) if for an integer $\bar{k} = 1, \ldots, n-1$ it is $\eta_{\bar{k}} = \eta_{\bar{k}+1} = 0$, it follows $d_{\bar{k}} = -\lambda_s/(2\lambda_q) > 0$; for the case $\bar{k} = n-1$ it is also $d_n = -(1 + \lambda_s)/(2\lambda_q) > 0$.

Let us prove property i). Eq. (14) for $k = \bar{k} + 1$ shows that $\eta_{\bar{k}+1} > 0$ gives $d_{\bar{k}+1} = d_{\bar{k}}$, whereas Eq. (28) for $k = \bar{k}$ shows that the pair of conditions $\eta_{\bar{k}} = 0$ and $\eta_{\bar{k}+1} > 0$ imply $\lambda_s + 2\lambda_q d_{\bar{k}} < 0$. Exploiting again Eq. (28), this time for $k = \bar{k} + 1$ (if $\bar{k} < n - 1$), it is $\eta_{\bar{k}+2} > 0$ because $\eta_{\bar{k}+1} > 0$ and $\lambda_s + 2\lambda_q d_{\bar{k}+1} < 0$ ($d_{\bar{k}+1} = d_{\bar{k}}$). Proceeding for k increasing over $\bar{k}$, it is easy to obtain $\eta_k > 0$, and consequently $d_k = d_{k-1}$, for $k = \bar{k} + 1, \dots, n$. Then, as d_n is necessarily positive, it follows that the last $n - \bar{k}$ entries of d are equal and positive.

Property ii) can be proved similarly. Indeed, exploiting Eqs. (14), (28) for $k = \bar{k}$, we have $d_{\bar{k}} = d_{\bar{k}-1}$ (if $\bar{k} > 1$) and $\lambda_s + 2\lambda_q d_{\bar{k}} > 0$ respectively. Eq. (28), for $k = \bar{k} - 1$ (if $\bar{k} > 1$), implies also $\eta_{\bar{k}-1} > 0$ and then, proceeding for k decreasing from $\bar{k}$, we have $\eta_k > 0$, for $k = 1, \dots, \bar{k}$. Consequently, the first $\bar{k}$ entries of d have the same value which must be zero because $\eta_1 > 0$ implies $d_1 = 0$ (see Eq. (13)).

Finally, property iii) comes directly from (28) with $k = \bar{k}$, and from (29) as well. The positivity of the doses is guaranteed by $\lambda_s \cdot \lambda_q < 0$ and by the ordering of entries d_k.

Properties i) and ii) imply that only the following structures for η are possible:

a) $\eta_k > 0$, $k = 1, \dots, n$;

b) $\eta_k = 0$, $k = 1, \dots, n$;

c) $\eta_k = 0$, $k = 1, \dots, \tilde{k}$, and $\eta_k > 0$, $k = \tilde{k} + 1, \dots, n$, with $\tilde{k} = 1, \dots, n - 1$;

d) $\eta_k > 0$, $k = 1, \dots, \tilde{k}$, and $\eta_k = 0$, $k = \tilde{k} + 1, \dots, n$, with $\tilde{k} = 1, \dots, n - 1$;

e) $\eta_k > 0$, $k = 1, \dots, \tilde{k}$, $\eta_k = 0$, $k = \tilde{k} + 1, \dots, \hat{k}$, and $\eta_k > 0$, $k = \hat{k} + 1, \dots, n$, with $\tilde{k} = 1, \dots, n - 2$ and $\hat{k} = \tilde{k} + 1 \dots, n - 1$.

As it is shown in the following, the vector d, associated to each structure of η in a)-e), contains at most two different positive entries. So, denoting these entries by x, y and assuming $y > x > 0$, the vector d can either have the last j entries equal to y and (possibly) $n - j$ zeros or have the last j entries equal to y, the preceding i entries equal to x and (possibly) the first $n - i - j$ entries equal to zero. When d contains only positive entries equal to y, Eqs. (15), (16) lead to the system

$$\begin{cases} jy = S, \\ jy^2 = \dfrac{S^2}{v}, \end{cases} \tag{30}$$

which admits the real positive solution $y = S/v$ only for v integer and equal to j. Conversely, when d contains two different positive values x, y, in order to satisfy the constraints (15), (16), it is necessary to solve the system

$$\begin{cases} ix + jy = S, \\ ix^2 + jy^2 = \dfrac{S^2}{v}. \end{cases} \tag{31}$$

As it must be $y > x > 0$, system (31) admits a unique real positive solution

$$x = R^-_{j,i}, \tag{32}$$

$$y = R^+_{i,j}, \tag{33}$$

where

$$R^-_{j,i} = \frac{S}{i+j}\left(1 - \sqrt{\frac{j(i+j-v)}{vi}}\right), \tag{34}$$

and

$$R_{i,j}^+ = \frac{S}{i+j}\left(1 + \sqrt{\frac{i(i+j-v)}{vj}}\right).\qquad(35)$$

Indeed, it is easy to verify that the quantities $R_{j,i}^-$, $R_{i,j}^+$ are real and positive, with $R_{i,j}^+ > R_{j,i}^-$, if and only if $j < v < i + j$.

Let us now show what vectors d are actually associated to the structures of η in a)-e).

For the structures in a), Eqs. (13), (14) immediately imply $d = 0$ which does not belong to D. For η in b), property iii) guarantees $d_k = -\lambda_s/(2\lambda_q) > 0$, $k = 1,\ldots,n-1$, and $d_n = -(1+\lambda_s)/(2\lambda_q) > 0$ (different for any λ_s,λ_q) so that, solving (31) with $i = n-1$ and $j = 1$, we have $d_k = x = R_{1,n-1}^-$, $k = 1,\ldots,n-1$ and $d_n = y = R_{n-1,1}^+$ (see (32), (33)) if and only if $v \in (1,n)$.

Concerning case c), property i) implies $d_k = d_{k-1} > 0$, $k = \tilde{k}+1,\ldots,n$. Then, for $\tilde{k} = 1$ all the entries have the same value equal to S/v with $v = n$ (see solution of system (30)). For $\tilde{k} > 1$, from property iii), we have also $d_k = -\lambda_s/(2\lambda_q) > 0$, $k = 1,\ldots,\tilde{k}-1$ (different from the last entries in view of (28) for $k = \tilde{k}$). Thus, the solution of the system (31) is $d_k = R_{j,i}^-$, $k = 1,\ldots,\tilde{k}-1$, $d_k = R_{i,j}^+$, $k = \tilde{k},\ldots,n$, with $i = \tilde{k}-1$ and $j = n-\tilde{k}+1$, if and only if $v \in (n-\tilde{k}+1,n)$ (see (32), (33)).

For the structures d), property ii) guarantees that $d_k = 0$, $k = 1,\ldots,\tilde{k}$. Then, for $\tilde{k} = n-1$, the vector d has only one positive entry $d_n = -(1+\lambda_s)/(2\lambda_q) > 0$ (see (29)) which is equal to S/v with $v = 1$, solving (30) with $j = 1$. For $\tilde{k} < n-1$, from property iii) we also have $d_k = -\lambda_s/(2\lambda_q) > 0$, $k = \tilde{k}+1,\ldots,n-1$, and $d_n = -(1+\lambda_s)/(2\lambda_q) > 0$. Thus, from system (31), we get $d_k = R_{j,i}^-$, $k = \tilde{k}+1,\ldots,n-1$ and $d_n = R_{i,j}^+$, with $i = n-1-\tilde{k}$ and $j = 1$, if and only if $v \in (1,n-\tilde{k})$.

In case e), property ii) implies $d_k = 0$, $k = 1,\ldots,\tilde{k}$, and property i) implies $d_{k-1} = d_k > 0$, $k = \hat{k}+1,\ldots,n$. Then, for $\hat{k} = \tilde{k}+1$, the vector d contains $\tilde{k}$ zeros and the last $n-\tilde{k}$ entries positive and equal. Solving system (30) with $j = n-\tilde{k}$, we obtain the solution $d_k = S/v$, $k = \tilde{k}+1,\ldots,n$, if and only if $v = n-\tilde{k}$. Conversely, for $\hat{k} > \tilde{k}+1$, from property iii) it is $d_k = -\lambda_s/(2\lambda_q) > 0$, $k = \tilde{k}+1,\ldots,\hat{k}-1$. Then, d contains the first $\tilde{k}$ components equal to zero, the next $\hat{k}-\tilde{k}-1$ components equal to $-\lambda_s/(2\lambda_q)$ and the last $n-\hat{k}+1$ components equal to each other (and greater than $-\lambda_s/(2\lambda_q)$). In particular, the values of the entries of d are given by $d_k = R_{j,i}^-$, $k = \tilde{k}+1,\ldots,\hat{k}-1$, and $d_k = R_{i,j}^+$, $k = \hat{k},\ldots,n$, with $i = \hat{k}-\tilde{k}-1$ and $j = n-\hat{k}+1$, if and only if $v \in (n-\hat{k}+1,n-\tilde{k})$ (see (32), (33)).

It is simple to verify that for each extremal given above, at least one pair λ_s, λ_q of opposite sign exists. Thus, Problem 2.1 admits normal extremals for each value of v in $[1,n]$ but their structure depends on v itself. Note also that, if $v = [v]$ it is $R_{[v],i}^- = 0$, $R_{i,[v]}^+ = S/v$, so that extremals coming from system (31) coincide with the vector having $[v]$ entries equal to S/v and $n-[v]$ zeroes, that is the solution of system (30).

Summarizing, the normal extremals of Problem 2.1 are listed in Table 2 for each v interval. Note that a unique normal extremal exists for each value of v and that the abnormal extremals, given in Table 1, are also included in Table 2 for $v = [v]$.

2.3. Optimal solution

In order to actually determine the optimal solution in each interval of v, we need to evaluate the cost function J in (8) for all the extremals of the interval itself, identifying the minimum of the J.

v	d
$[1,2)$	$(0 \;\; 0 \;\; \ldots \;\; 0 \;\; 0 \;\; R_{1,1}^- \;\; R_{1,1}^+)$ $(0 \;\; 0 \;\; \ldots \;\; 0 \;\; R_{1,2}^- \;\; R_{1,2}^- \;\; R_{2,1}^+)$ $\vdots$ $(0 \;\; R_{1,n-2}^- \;\; \ldots \;\; R_{1,n-2}^- \;\; R_{1,n-2}^- \;\; R_{n-2,1}^+)$ $(R_{1,n-1}^- \;\; R_{1,n-1}^- \;\; \ldots \;\; R_{1,n-1}^- \;\; R_{1,n-1}^- \;\; R_{n-1,1}^+)$
$[2,3)$	$(0 \;\; 0 \;\; \ldots \;\; 0 \;\; R_{1,2}^- \;\; R_{1,2}^- \;\; R_{2,1}^+)$ $(0 \;\; 0 \;\; \ldots \;\; 0 \;\; R_{2,1}^- \;\; R_{1,2}^+ \;\; R_{1,2}^+)$ $(0 \;\; 0 \;\; \ldots \;\; 0 \;\; R_{1,3}^- \;\; R_{1,3}^- \;\; R_{1,3}^- \;\; R_{3,1}^+)$ $(0 \;\; 0 \;\; \ldots \;\; 0 \;\; R_{2,2}^- \;\; R_{2,2}^- \;\; R_{2,2}^+ \;\; R_{2,2}^+)$ $\vdots$ $(R_{1,n-1}^- \;\; R_{1,n-1}^- \;\; R_{1,n-1}^- \;\; R_{1,n-1}^- \;\; R_{n-1,1}^+)$ $(R_{2,n-2}^- \;\; R_{2,n-2}^- \;\; R_{2,n-2}^- \;\; R_{n-2,2}^+ \;\; R_{n-2,2}^+)$
$\vdots$	$\vdots$
$[n-2,n-1)$	$(0 \;\; R_{1,n-2}^- \;\; \ldots \;\; R_{1,n-2}^- \;\; R_{1,n-2}^- \;\; R_{n-2,1}^+)$ $(0 \;\; R_{2,n-3}^- \;\; \ldots \;\; R_{2,n-3}^- \;\; R_{n-3,2}^+ \;\; R_{n-3,2}^+)$ $\vdots$ $(0 \;\; R_{n-2,1}^- \;\; R_{1,n-2}^+ \;\; \ldots \;\; R_{1,n-2}^+ \;\; R_{1,n-2}^+)$ $(R_{1,n-1}^- \;\; R_{1,n-1}^- \;\; \ldots \;\; R_{1,n-1}^- \;\; R_{1,n-1}^- \;\; R_{n-1,1}^+)$ $(R_{2,n-2}^- \;\; R_{2,n-2}^- \;\; \ldots \;\; R_{2,n-2}^- \;\; R_{n-2,2}^+ \;\; R_{n-2,2}^+)$ $\vdots$ $(R_{n-2,2}^- \;\; R_{n-2,2}^- \;\; R_{2,n-2}^+ \;\; \ldots \;\; R_{2,n-2}^+ \;\; R_{2,n-2}^+)$
$[n-1,n)$	$(R_{1,n-1}^- \;\; R_{1,n-1}^- \;\; \ldots \;\; R_{1,n-1}^- \;\; R_{1,n-1}^- \;\; R_{n-1,1}^+)$ $(R_{2,n-2}^- \;\; R_{2,n-2}^- \;\; \ldots \;\; R_{2,n-2}^+ \;\; R_{n-2,2}^+ \;\; R_{n-2,2}^+)$ $(R_{3,n-3}^- \;\; \ldots \;\; R_{3,n-3}^- \;\; R_{n-3,3}^+ \;\; R_{n-3,3}^+ \;\; R_{n-3,3}^+)$ $\vdots$ $(R_{n-1,1}^- \;\; R_{1,n-1}^+ \;\; \ldots \;\; R_{1,n-1}^+ \;\; R_{1,n-1}^+ \;\; R_{1,n-1}^+)$
n	$(S/n \;\; S/n \;\; \ldots \;\; S/n \;\; S/n \;\; S/n)$

Table 2: Normal extremals of Problem 2.1.

12.

To this purpose we preliminary study the behaviour of $R_{i,j}^+$ defined in (35) keeping fixed the sum $s = i + j$ but letting i vary, and then fixing the index j but letting s vary. Rewriting $R_{i,j}^+$ as a function $R^+(i, s - i)$ and considering i, s as positive continuous variables, we have

$$\frac{\partial R^+(i, s - i)}{\partial i} = \frac{S}{2} \sqrt{\frac{s - v}{vi(s - i)^3}}, \tag{36}$$

which is strictly positive since $v < s$. On the other hand, rewriting $R_{i,j}^+$ as a function $R^+(s - j, j)$ and considering s, j as positive continuous variables, we have

$$\frac{\partial R^+(s - j, j)}{\partial s} = \frac{S \left(\sqrt{v(s - j)} - \sqrt{j(s - v)} \right)^2}{2s^2 \sqrt{vj(s - j)(s - v)}}, \tag{37}$$

which is strictly positive as $v > j$. Therefore, for a fixed sum $i + j$, $R_{i,j}^+$ increases as i increases, while for a fixed j, $R_{i,j}^+$ increases as the sum $i + j$ increases.

Taking into account (36) and (37), it is easy to determine, in each interval of v, the optimal solutions of Problem (2.1) which are listed Table 3. In conclusion, the optimum of Problem

v	d
$[1, 2)$	$(0 \quad \ldots \quad 0 \quad 0 \quad R_{1,1}^- \quad R_{1,1}^+)$
$[2, 3)$	$(0 \quad \ldots \quad 0 \quad R_{2,1}^- \quad R_{1,2}^+ \quad R_{1,2}^+)$
$\vdots$	$\vdots$
$[n - 2, n - 1)$	$(0 \quad R_{n-2,1}^- \quad R_{1,n-2}^+ \quad \ldots \quad R_{1,n-2}^+ \quad R_{1,n-2}^+)$
$[n - 1, n)$	$(R_{n-1,1}^- \quad R_{1,n-1}^+ \quad R_{1,n-1}^+ \quad \ldots \quad R_{1,n-1}^+ \quad R_{1,n-1}^+)$
n	$(S/n \quad S/n \quad \ldots \quad S/n \quad S/n \quad S/n)$

Table 3: Optimal solutions of Problem 2.1.

(2.1) is the vector d having the last $[v]$ entries equal to $R_{1,[v]}^+$ (equal to S/v if $v = [v]$), one entry equal to $R_{[v],1}^-$ provided $v < n$ (equal to zero if $v = [v]$) and the remaining $n - [v] - 1$ entries equal to zero provided $v < n - 1$.

3. Minimum value of the maximal entry of vectors belonging to the "late" constraint boundary and having limited entry sum

It is easy to see that the constraints $g_l(d) = 0$, $g_e(d) \leq 0$, $d \geq 0$ can be rewritten as

$$g_l(d) = \rho_l \sum_{k=1}^{n} d_k + \sum_{k=1}^{n} d_k^2 - k_l = 0, \qquad \sum_{k=1}^{n} d_k \leq S, \qquad d_k \geq 0, \ k = 1, \ldots, n. \tag{38}$$

So, in order to find the minimal value of the maximal entry of d in the domain (38), we formulate the following non-linear programming problem whose admissible set clearly include the admissible set of Problem 2.1.

Problem 3.1. *Minimize the function:*

$$J(d) = d_n, \tag{39}$$

on the admissible set:

$$D = \{d \in R^n | \ g_l(d) = 0, \ \sum_{k=1}^{n} d_k \leq S, \ d_n \geq d_{n-1} \geq d_3 \geq d_2 \geq d_1 \geq 0\}. \tag{40}$$

Clearly, Problem 3.1 admits optimal solutions ((40) is compact and (39) is a continuous function on it). The Lagrangian function associated to the problem is

$$L(d, \lambda_0, \lambda_s, \lambda_q, \eta) = \lambda_0 d_n + \lambda \left(\rho_l \sum_{k=1}^{n} d_k + \sum_{k=1}^{n} d_k^2 - k_l \right) + \eta_s \left(\sum_{k=1}^{n} d_k - S \right) - \eta_1 d_1 + \sum_{k=1}^{n-1} \eta_{k+1} (d_k - d_{k+1}), \tag{41}$$

where λ_0, η_s, λ are scalar multipliers and η is the n-dimensional vector of multipliers η_k, $k = 1, \ldots, n$.

The Kuhn-Tucker necessary and admissibility conditions are

$$\frac{\partial L}{\partial d_k} = \eta_s + \lambda (2d_k + \rho_l) - \eta_k + \eta_{k+1} = 0, \qquad k = 1, \ldots, n-1, \tag{42}$$

$$\frac{\partial L}{\partial d_n} = \lambda_0 + \eta_s + \lambda (2d_n + \rho_l) - \eta_n = 0, \tag{43}$$

$$\eta_1 d_1 = 0, \tag{44}$$

$$\eta_k (d_{k-1} - d_k) = 0, \qquad k = 2, \ldots, n, \tag{45}$$

$$\eta_s \left(\sum_{k=1}^{n} d_k - S \right) = 0, \tag{46}$$

$$\rho_l \sum_{k=1}^{n} d_k + \sum_{k=1}^{n} d_k^2 - k_l = 0, \tag{47}$$

$$\eta_k \geq 0, \qquad k = 1, \ldots, n, \tag{48}$$

$$\eta_s \geq 0, \tag{49}$$

$$\lambda_0 \geq 0, \tag{50}$$

with λ_0, η_s, λ, η never simultaneously equal to zero.

Following a procedure similar to that used for Problem 2.1, we obtain that the optimum of Problem 3.1 coincides with the optimum of Problem 2.1. Indeed, if $\eta_s > 0$ it follows $\sum_{k=1}^{n} d_k = S$, meaning that system (42)-(50) coincides with system (11)-(18), by replacing $\lambda_s = \eta_s + \lambda \rho_l$ and $\lambda_q = \lambda$. Then, we obtain the same set of candidates of Problem 2.1, obviously containing the vectors of Table 3, reporting for each value of v the "best" candidate of the set. Conversely, when $\eta_s = 0$ we prove that no additional candidates exist. This is briefly shown in the following items obtained taking into account (42)-(50) for $\eta_s = 0$.

- If $\lambda_0 = 0$ it must be $\lambda \geq 0$, since $\eta_n \geq 0$. However, if $\lambda = 0$ it is $\eta_k = 0$, $\forall k$ (see (42), (43)) and all the multipliers would be simultaneously equal to zero which is not admissible. If instead $\lambda > 0$ it is $\eta_n > 0$ and $\eta_k > \eta_{k+1}$, $k = 1, \ldots, n-1$ that imply $d = 0$, not satisfying $g_l(d) = 0$.

14.

- Let us suppose $\lambda_0 > 0$. If $\lambda \geq 0$ it is $\eta_n > 0$ and $\eta_k \geq \eta_{k+1}$, $k = 1, \ldots, n-1$ that imply $d = 0$, not satisfying $g_l(d) = 0$. If $\lambda < 0$ it is $\eta_k < \eta_{k+1}$, $k = 1, \ldots, n-1$, which means either $\eta_k > 0$, $\forall k$, or $\eta_1 = 0$, $\eta_k > 0$, $k = 2, \ldots, n$. The first case provides again $d = 0$ whereas the second one implies $d_k = d_{k+1}$, $k = 1, \ldots, n-1$. For the latter case, in order to satisfies constraints $g_l(d) = 0$ and $\sum_{k=1}^{n} d_k \leq S$, it must be

$$d_k = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l}{n}} \leq \frac{S}{n}, \quad k = 1, \ldots, n,$$

  or equivalently $v \geq n$ (see [4]). As $v \in [1, n]$, only for $v = n$ we obtain a candidate, that is $d_k = S/n$, $k = 1, \ldots, n$, which coincides with the optimal solution of Table 3 for $v = n$.

To sum up, as $\eta_s = 0$ does not provide additional candidates, the optimal solution of Problem 3.1 is given again by Table 3 for each value of v.

4. Concluding remarks

We addressed a costrained optimization problem arisen in the context of cancer radiotherapy optimization. The admissible sets considered here derived from the imposition of constraints limiting the radiation damage to the early and late normal tissues, and they actually are formed by protocols producing the maximal tolerable damage: i) to both the early and late responding tissues (Problem 2.1); ii) to the late tissue only (Problem 3.1). Clearly, the second admissible set includes the first one.

This paper reports the proof of a property satisfied by the value of the maximal entry of vectors belonging to the admissible regions i) and ii). Precisely, we find that there exists a minimal value of the maximal dose fraction, which is given by the quantity $R_{1[v]}^{+}$ defined in (35) for $i = 1$ and $j = [v]$. The corresponding (unique) optimal vector is composed by $[v]$ doses equal to $R_{1[v]}^{+}$, one dose equal to $R_{[v]1}^{-}$ (provided $v < n$), and $n - [v] - 1$ doses equal to zero (provided $v < n - 1$).

This result is significant for the problem of radiotherapy optimization studied in [3], where, besides the early and late constraints, the fraction dose sizes are constrained to satisfy an upper bound d_M. Then, the value $R_{1[v]}^{+}$ acts as a threshold with regard to d_M, making the optimal solution switch from solutions lying on the *late* constraint boundary to solutions on the *early* constraint boundary. Indeed, when $d_M < R_{1[v]}^{+}$ no points of the region $g_l(d) = 0$, $g_e(d) \leq 0$, $d \geq 0$ satisfy the upper bound (then none of these points is admissible) and the optimum of the problem in [3] is given by a protocol producing the maximal damage to the "early" tissue.

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