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fraction in the optimization of the  
radiotherapy scheduling**

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# Technical Report

## MINIMAL VALUE OF THE MAXIMAL DOSE FRACTION IN THE OPTIMIZATION OF THE RADIOTHERAPY SCHEDULING

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### Abstract

We report the analytical study of a constrained optimization problem which consists in finding the minimal value of the largest entry of a vector  $d$  in  $R^5$ , with constraints involving the entries sum and the squared entries sum. The solution of the problem studied in this paper provides the proof of a property needed to determine the admissible protocols of the radiotherapy scheduling optimization problem presented in [1], that includes constraints limiting the radiation damages to normal tissues. In particular, we find the minimal value of the maximal dose fraction of the protocols producing the maximal tolerable damage to both early and late responding tissues when there is not a prevalent normal tissue constraint. Then, we extend the property to all the protocols producing the maximal damage to the late responding tissue only.

*Keywords:* Nonlinear programming; Cancer radiotherapy.

# 1 Introduction

We address a rather general optimization problem arisen from the radiotherapy scheduling optimization reported in [1], which consists in determining the fractionated radiotherapy scheme that maximizes the overall tumour damage, keeping the damages to normal tissues, as well as the size of the daily dose fraction, within given admissible levels. In [1], some geometrical properties of the admissible domain, dependent on normal tissue parameter values, are also highlighted, in order to determine how the optimal solution changes when the normal tissue parameters change. The geometric characterization of the domain is shown in Table 2 of [1], while the details of the proof are reported in Appendix A of the same paper. In this report, we study an optimization problem that proves a property of the points of the admissible domain, in case of absence of a prevalent normal tissue constraint. In particular we determine the minimum value of the maximal entry of a 5-dimensional vector  $d$  belonging to the intersection between the boundaries of the normal tissue constrains. Then, we consider a second optimization problem and we extend the previous result to all the points belonging to the boundary of the “late” constraint satisfying also the “early” constraint. The study of the last problem proves Theorem 5.3 in [1]. Both the optimization problems are formulated as non-linear programming problems.

## 2 Minimum value of the maximal entry of vectors with fixed entries sum and fixed squared entries sum

In [1] the constraints on the admissible damage to normal tissues are given by

$$g_e(d) = \rho_e \sum_{k=1}^5 d_k + \sum_{k=1}^5 d_k^2 - k_e \leq 0, \quad (2.1)$$

$$g_l(d) = \rho_l \sum_{k=1}^5 d_k + \sum_{k=1}^5 d_k^2 - k_l \leq 0, \quad (2.2)$$

where  $\rho_e, \rho_l$  are the radiosensitivity parameter ratios and  $k_e, k_l$  are the maximal weekly damages of the “early” and “late” responding tissues respectively. In [1] it is also proved that points belonging to the intersections between the boundaries of normal tissue constrains, i.e. points satisfying  $g_e(d) = g_l(d) = 0, d \geq 0$ , are such that

$$\sum_{k=1}^5 d_k = \frac{k_e - k_l}{\rho_e - \rho_l} = S, \quad \sum_{k=1}^5 d_k^2 = \frac{\rho_e k_l - \rho_l k_e}{\rho_e - \rho_l} = \frac{S^2}{v}, \quad d_k \geq 0, \quad k = 1, \dots, 5, \quad (2.3)$$

where  $k_e - k_l > 0, \rho_e k_l - \rho_l k_e > 0$  and  $v \in [1, 5]$  (see Table 2 of [1] in absence of a prevalent constraint). Then, we formulate the constrained non-linear programming problem of finding the minimum value of the maximal entry of vectors  $d$  having fixed entries sum and fixed squared entries sum, according to (2.3). The admissible domain is the intersection between a hyperplane and a hypersphere in the region  $d \geq 0$  of  $R^5$  and, because of their symmetry with respect to the half-line  $\{d_5 = d_4 = d_3 = d_2 = d_1 \geq 0\}$ , we can choose an ordering of the entries of  $d$  without loss of generality. In particular, we choose the ordering  $d_5 \geq d_4 \geq d_3 \geq d_2 \geq d_1 \geq 0$ , leading to the following problem formulation.

**Problem 2.1** *Minimize the function:*

$$J(d) = d_5, \quad (2.4)$$

*on the admissible set:*

$$D = \{d \in R^5 \mid \sum_{k=1}^5 d_k = S, \sum_{k=1}^5 d_k^2 = \frac{S^2}{v}, d_5 \geq d_4 \geq d_3 \geq d_2 \geq d_1 \geq 0\}. \quad (2.5)$$

Firstly, we note that  $D$  is non-empty as  $v \in [1, 5]$  (see Appendix A in [1]). Secondly, Problem 2.1 certainly admits optimal solutions. Indeed, the admissible set (2.5) is compact and the cost function (2.4) is continuous on it, so that the Weierstrass theorem [2] guarantees the existence of optimal solutions. Moreover, 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 [2]. The Lagrangian function associated to the problem is

$$L(d, \lambda_0, \lambda_s, \lambda_q, \eta) = \lambda_0 d_5 + \lambda_s \left( \sum_{k=1}^5 d_k - S \right) + \lambda_q \left( \sum_{k=1}^5 d_k^2 - \frac{S^2}{v} \right) - \eta_1 d_1 + \sum_{k=1}^4 \eta_{k+1} (d_k - d_{k+1}), \quad (2.6)$$

where  $\lambda_0, \lambda_s, \lambda_q$  are scalar multipliers and  $\eta$  is the 5-dimensional vector of multipliers  $\eta_k$ ,  $k = 1, \dots, 5$ , related to the inequality constraints.

Let us now write the necessary and admissibility conditions

$$\frac{\partial L}{\partial d_k} = \lambda_s + 2\lambda_q d_k - \eta_k + \eta_{k+1} = 0, \quad k = 1, \dots, 4, \quad (2.7)$$

$$\frac{\partial L}{\partial d_5} = \lambda_0 + \lambda_s + 2\lambda_q d_5 - \eta_5 = 0, \quad (2.8)$$

$$\eta_1 d_1 = 0, \quad (2.9)$$

$$\eta_k (d_{k-1} - d_k) = 0, \quad k = 2, \dots, 5, \quad (2.10)$$

$$\sum_{k=1}^5 d_k = S, \quad (2.11)$$

$$\sum_{k=1}^5 d_k^2 = \frac{S^2}{v}, \quad (2.12)$$

$$\eta_k \geq 0, \quad k = 1, \dots, 5, \quad (2.13)$$

$$\lambda_0 \geq 0, \quad (2.14)$$

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 (2.7)-(2.14) are the extremals of Problem 2.1, that is all the possible candidates to the optimal solution. In particular, vectors  $d$  satisfying Eqs.(2.7)-(2.14) with  $\lambda_0 = 0$  are called ‘abnormal’ extremals, while vectors  $d$  satisfying Eqs.(2.7)-(2.14) with  $\lambda_0 \neq 0$  are called ‘normal’ extremals.

Taking into account Eqs. (2.9)-(2.12), let us multiply each equation  $\frac{\partial L}{\partial d_k} = 0$  in (2.7)-(2.8) by the corresponding  $d_k$ ,  $k = 1, \dots, 5$  adding the obtained equations. We get the relation

$$\lambda_0 d_5 + \lambda_s S + 2\lambda_q \frac{S^2}{v} = 0, \quad (2.15)$$

directly linking the multipliers  $\lambda_0, \lambda_s, \lambda_q$ , which turns out to be useful in the next sections where we separately study the cases  $\lambda_0 = 0$  and  $\lambda_0 \neq 0$ .

## 2.1 Existence and structure of abnormal extremals

By definition, the abnormal extremals satisfy the necessary and admissibility conditions with  $\lambda_0 = 0$ . Then Eq. (2.15) becomes

$$\lambda_s = -2\lambda_q \frac{S}{v} \quad (2.16)$$

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

- 1)  $\lambda_s = 0, \lambda_q = 0$ ,
  - 2)  $\lambda_s < 0, \lambda_q > 0$ ,
  - 3)  $\lambda_s > 0, \lambda_q < 0$ ,
- (2.17)

Let us verify if at least one of the three alternatives in (2.17) leads to solutions of the system (2.7)-(2.13).

Case 1) of (2.17) does not provide extremals as  $\lambda_0 = \lambda_s = \lambda_q = 0$  would imply  $\eta_k = 0, \forall k$  (see (2.7), (2.8)) and all the multipliers would be simultaneously equal to zero.

To study the last two cases of (2.17), it is convenient to exploit (2.16) rewriting (2.7), (2.8) (with  $\lambda_0 = 0$ ) in terms of  $\lambda_q$

$$\eta_k = \eta_{k+1} + 2\lambda_q \left( d_k - \frac{S}{v} \right), \quad k = 1, \dots, 4, \quad (2.18)$$

$$\eta_5 = 2\lambda_q \left( d_5 - \frac{S}{v} \right). \quad (2.19)$$

Consider case 2) of (2.17), i.e.  $\lambda_q > 0$ . If  $\eta_5 > 0$ , from (2.10) and (2.19), it results  $d_5 = d_4 > S/v$  and from (2.18), for  $k = 4$ , it is  $\eta_4 > \eta_5 > 0$ . Similarly,  $\eta_4 > 0$  implies  $\eta_3 > 0$  and so on until  $\eta_1 > 0$ . Then, from (2.9),(2.10), we have  $d_k = 0, k = 1, \dots, 5$ , that cannot be accepted as they do not satisfy Eqs. (2.11), (2.12). Conversely, if  $\eta_5 = 0$ , Eq.(2.19) implies  $d_5 = S/v$ . Because of the ordering of the entries of  $d$ , it must be  $d_k \leq S/v, k = 1, \dots, 4$ , and from (2.18) it is  $\eta_k \leq \eta_{k+1}, k = 1, \dots, 4$ . The latter condition can be verified if and only if all the multipliers  $\eta_k, k = 1, \dots, 5$ , are equal to zero (as  $\eta_5 = 0$ ) so that, from (2.18), we have  $d_k = S/v, k = 1, \dots, 5$ , while (2.11) imposes  $v = 5$ .

To analyze case 3) of (2.17) we follow a similar procedure. First consider  $\eta_5 > 0$  that gives  $d_5 = d_4 < S/v$  (see Eqs.(2.10),(2.19)) and consequently  $d_k < S/v, k = 1, \dots, 5$ , being  $d_5$  the maximal entry. Then, from (2.18), we have  $\eta_k > \eta_{k+1}, k = 1, \dots, 4$ , that implies  $d_k = 0, k = 1, \dots, 5$  (see (2.9),(2.10)). But, as already said, the vector  $d$  with all the entries equal to zero cannot be an extremal because it does not satisfy constraints (2.11), (2.12). Second consider  $\eta_5 = 0$  which gives  $d_5 = S/v$  from Eq.(2.19). As  $d_k \leq d_5 = S/v, k = 1, \dots, 4$ , and  $\lambda_q < 0$  by hypothesis, from (2.18) we obtain  $\eta_k \geq \eta_{k+1}, k = 1, \dots, 4$ . Taking into account  $\eta_k \geq 0, k = 1, \dots, 5$ , the following situations are possible:

- a)  $\eta_k = 0, k = 1, \dots, 5$  that implies  $d_k = S/v, k = 1, \dots, 5$ , (see Eqs. (2.19), (2.18)) and, in order to satisfy the constraint (2.11), the condition  $v = 5$ ;
- b)  $\exists \bar{k} = 1, \dots, 4 \mid \eta_k > 0, k = 1, \dots, \bar{k}$  and  $\eta_k = 0, k = \bar{k} + 1, \dots, 5$ . Recalling Eqs. (2.9), (2.10) and Eqs. (2.18), (2.19), it results  $d_k = 0, k = 1, \dots, \bar{k}$  and  $d_k = S/v, k = \bar{k} + 1, \dots, 5$ , respectively. Moreover, in order to satisfy the constraint (2.11), it must be  $v = 5 - \bar{k}$ .

In conclusion, if and only if the parameter  $v$  is integer Problem 2.1 admits abnormal extremals and in particular a unique extremal exists for each integer value of  $v$  in  $[1, 5]$ . The abnormal extremals are listed in Table 1.

$v$	$d$
1	(0 0 0 0 $S$ )
2	(0 0 0 $S/2$ $S/2$ )
3	(0 0 $S/3$ $S/3$ $S/3$ )
4	(0 $S/4$ $S/4$ $S/4$ $S/4$ )
5	( $S/5$ $S/5$ $S/5$ $S/5$ $S/5$ )

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 (2.7)–(2.14) with  $\lambda_0 = 1$  (we normalize the Lagrangian function with respect to  $\lambda_0$  when  $\lambda_0 > 0$ ). First of all, Eq. (2.15) can be rewritten as

$$d_5 = - \left( \lambda_s + 2\lambda_q \frac{S}{v} \right) S. \quad (2.20)$$

Since  $d_5$  must be positive ( $d_5 = 0$  is excluded implying  $d_k = 0, \forall k$ ),  $\lambda_s$  and  $\lambda_q$  can only take the following values:

- 1)  $\lambda_s = 0, \lambda_q < 0$ ,
  - 2)  $\lambda_s < 0, \lambda_q \leq 0$ ,
  - 3)  $\lambda_s < 0, \lambda_q > 0$ ,
  - 4)  $\lambda_s > 0, \lambda_q < 0$ ,
- (2.21)

Let us start from case 1) of (2.21) and rewrite Eqs. (2.7), (2.8) as

$$\eta_k = \eta_{k+1} + 2\lambda_q d_k, \quad k = 1, \dots, 4, \quad (2.22)$$

$$\eta_5 = 1 + 2\lambda_q d_5. \quad (2.23)$$

As  $\lambda_q < 0$  and  $d_k \geq 0$ , from Eqs. (2.22), (2.23), it results  $\eta_{k+1} \geq \eta_k, k = 1, \dots, 4$ , so that if  $\eta_k > 0$ , it necessarily is  $\eta_{k+1} > 0$ , too. Then, the following situations are possible:

- a)  $\eta_k > 0$ ,  $k = 1, \dots, 5$ , that, from Eqs. (2.9), (2.10), implies  $d_k = 0$ ,  $k = 1, \dots, 5$ , which is a non-admissible vector as it does not satisfy (2.11) or (2.12);
- b)  $\eta_k = 0$ ,  $k = 1, \dots, 5$ , that implies  $d_k = 0$ ,  $k = 1, \dots, 4$ , and  $d_5 = -1/2\lambda_q$  (see (2.22), (2.23)). Then, in order to satisfy constraints (2.11) and (2.12), it must be  $d_5 = S$  (because it results  $\lambda_q = -2/S$ ) and  $v = 1$ ;
- c)  $\exists \bar{k} = 1, \dots, 4 \mid \eta_k = 0$ ,  $k = 1, \dots, \bar{k}$ , and  $\eta_k > 0$ ,  $k = \bar{k} + 1, \dots, 5$ . First of all, from (2.10), it results  $d_k = d_{k-1}$ ,  $k = \bar{k} + 1, \dots, 5$ , and then it results  $d_k > 0$ ,  $k = \bar{k}, \dots, 5$ , because Eq.(2.22) 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  $d_k = 0$ ,  $k = 1, \dots, \bar{k} - 1$ , because Eq. (2.22) for  $k = \bar{k} - 1$  implies  $d_{\bar{k}-1} = 0$  ( $\eta_{\bar{k}} = \eta_{\bar{k}-1} = 0$  by definition) and consequently all the remaining components are zero too, taking into account the ordering of the components of  $d$ . So, we have a vector  $d$  with  $\bar{k} - 1$  components equal to zero and  $5 - \bar{k} + 1$  positive components equal to each other. These vectors are actually extremals if and only if  $v = 5 - \bar{k} + 1$  and  $d_k = S/v$ ,  $k = \bar{k}, \dots, 5$  (see constraints (2.11), (2.12)).

So, case 1) of (2.21) provides the extremals of the previous section.

Considering case 2) of (2.21), Eq. (2.7) implies  $\eta_{k+1} > \eta_k$ ,  $k = 1, \dots, 4$ , leading to the following situations:

- a)  $\eta_k > 0$ ,  $k = 1, \dots, 5$ , that implies  $d = 0$  (non-admissible);
- b)  $\eta_1 = 0$ ,  $\eta_k > 0$ ,  $k = 2, \dots, 5$ , which, taking into account (2.10), implies  $d_k = d_{k-1}$ ,  $k = 2, \dots, 5$ , all positive because  $d = 0$  has to be excluded. As already seen, the vector  $d$  with five components equal to each other satisfies the constraints (2.11), (2.12) if and only if  $d_k = S/v$ ,  $k = 1, \dots, 5$ , and provided that  $v = 5$ .

For the last two alternatives of (2.21), it is not possible to determine an a priori ordering for the multipliers  $\eta_k$ ,  $k = 1, \dots, 5$ , because  $\lambda_s \cdot \lambda_q < 0$ . Nevertheless, by exploiting the necessary conditions (2.7), (2.8), explicitly rewritten as

$$\eta_k = \eta_{k+1} + \lambda_s + 2\lambda_q d_k, \quad k = 1, \dots, 4, \quad (2.24)$$

$$\eta_5 = 1 + \lambda_s + 2\lambda_q d_5, \quad (2.25)$$

along with the complementary conditions (2.9), (2.10), it is possible to give some preliminary properties useful to characterize the structure of the extremal pairs  $\eta$ ,  $d$ , as well as to exclude some configurations of the vector  $\eta$ . The properties are listed in the following:

- i) if for an integer  $\bar{k} = 1, \dots, 4$  it is  $\eta_{\bar{k}} = 0$  and  $\eta_{\bar{k}+1} > 0$ , it follows  $\eta_k > 0$  for  $k = \bar{k} + 1, \dots, 5$  and then the last  $5 - \bar{k} + 1$  entries of  $d$  are positive and equal to each other;
- ii) if for an integer  $\bar{k} = 1, \dots, 4$  it is  $\eta_{\bar{k}} > 0$  and  $\eta_{\bar{k}+1} = 0$ , it follows  $\eta_k > 0$  for  $k = 1, \dots, \bar{k}$  and then the first  $\bar{k}$  entries of  $d$  are equal to zero;
- iii) if for an integer  $\bar{k} = 1, \dots, 4$  it is  $\eta_{\bar{k}} = \eta_{\bar{k}+1} = 0$ , it follows  $d_{\bar{k}} = -\lambda_s/(2\lambda_q) > 0$  and, if  $\bar{k} = 4$ , also  $d_5 = -(1 + \lambda_s)/(2\lambda_q) > 0$ .

Let us prove property i). Eq. (2.10) for  $k = \bar{k} + 1$  shows that  $\eta_{\bar{k}+1} > 0$  gives  $d_{\bar{k}+1} = d_{\bar{k}}$ , whereas Eq. (2.24) 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. (2.24), this time for  $k = \bar{k} + 1$  (if  $\bar{k} < 4$ ), 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  $k = \bar{k} + 1, \dots, 5$ . Then, as  $d_5$  is necessarily positive, it follows that the last  $5 - \bar{k}$  entries of  $d$  are positive and equal each other.

Property ii) can be proved similarly. Indeed, exploiting Eqs. (2.10), (2.24) 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. (2.24), 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. (2.9)).

Finally, property iii) comes directly from (2.24) with  $k = \bar{k}$ , and from (2.25) as well. The positivity of the doses is guaranteed by  $\lambda_s \lambda_q < 0$  and by the ordering of entries  $d_k$ .

Properties i) and ii) imply that only the following structures for  $\eta$  are possible:

- a)  $\eta_k > 0, k = 1, \dots, 5$ ;
- b)  $\eta_k = 0, k = 1, \dots, 5$ ;
- c)  $\eta_k = 0, k = 1, \dots, \tilde{k}$ , and  $\eta_k > 0, k = \tilde{k} + 1, \dots, 5$ , with  $\tilde{k} = 1, \dots, 4$ ;
- d)  $\eta_k > 0, k = 1, \dots, \tilde{k}$ , and  $\eta_k = 0, k = \tilde{k} + 1, \dots, 5$ , with  $\tilde{k} = 1, \dots, 4$ ;
- e)  $\eta_k > 0, k = 1, \dots, \tilde{k}$ ,  $\eta_k = 0, k = \tilde{k} + 1, \dots, \hat{k}$ , and  $\eta_k > 0, k = \hat{k} + 1, \dots, 5$ , with  $\tilde{k} = 1, \dots, 3$  and  $\hat{k} = \tilde{k} + 1, \dots, 4$ .

As it is shown in the following, the vector  $d$ , associated to each structure of  $\eta$  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)  $5 - j$  zeros or have the last  $j$  entries equal to  $y$ , the preceding  $i$  entries equal to  $x$  and (possibly) the first  $5 - i - j$  entries equal to zero. When  $d$  contains only positive entries equal to  $y$ , Eqs. (2.11), (2.12) lead to the system

$$\begin{cases} jy = S, \\ jy^2 = \frac{S^2}{v}, \end{cases} \quad (2.26)$$

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 (2.11), (2.12), it is necessary to solve the system

$$\begin{cases} ix + jy = S, \\ ix^2 + jy^2 = \frac{S^2}{v}. \end{cases} \quad (2.27)$$

As it must be  $y > x > 0$ , system (2.27) admits a unique real positive solution

$$x = R_{ji}^-, \quad (2.28)$$

$$y = R_{ij}^+, \quad (2.29)$$



where

$$R_{ji}^- = \frac{S}{i+j} \left( 1 - \sqrt{\frac{j(i+j-v)}{vi}} \right), \quad (2.30)$$

and

$$R_{ij}^+ = \frac{S}{i+j} \left( 1 + \sqrt{\frac{i(i+j-v)}{vj}} \right). \quad (2.31)$$

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

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

For the structures in a), Eqs. (2.9), (2.10) immediately imply  $d = 0$  which does not belong to  $D$ . For  $\eta$  in b), property iii) guarantees  $d_k = -\lambda_s/(2\lambda_q) > 0$ ,  $k = 1, \dots, 4$ , and  $d_5 = -(1 + \lambda_s)/(2\lambda_q) > 0$  (different for any  $\lambda_s, \lambda_q$ ) so that, solving (2.27) with  $i = 4$  and  $j = 1$ , we have  $d_k = x = R_{14}^-$ ,  $k = 1, \dots, 4$  and  $d_5 = y = R_{41}^+$  (see (2.28), (2.29)) if and only if  $v \in (1, 5)$ .

Concerning case c), property i) implies  $d_k = d_{k-1} > 0$ ,  $k = \tilde{k} + 1, \dots, 5$ . Then, for  $\tilde{k} = 1$  all the entries have the same value equal to  $S/v$  with  $v = 5$  (see solution of system (2.26)). For  $\tilde{k} > 1$ , from property iii), we have also  $d_k = -\lambda_s/(2\lambda_q) > 0$ ,  $k = 1, \dots, \tilde{k} - 1$  (different from the last entries in view of (2.24) for  $k = \tilde{k}$ ). Thus, solving system (2.27) with  $i = \tilde{k} - 1$  and  $j = 5 - \tilde{k} + 1$  we obtain the solution  $d_k = R_{ji}^-$ ,  $k = 1, \dots, \tilde{k} - 1$ ,  $d_k = R_{ij}^+$ ,  $k = \tilde{k}, \dots, 5$ , if and only if  $v \in (5 - \tilde{k} + 1, 5)$  (see (2.28), (2.29)).

For the structures d), property ii) guarantees that  $d_k = 0$ ,  $k = 1, \dots, \tilde{k}$ . Then, for  $\tilde{k} = 4$ , the vector  $d$  has only one positive entry  $d_5 = -(1 + \lambda_s)/(2\lambda_q) > 0$  (see (2.25)) which is equal to  $S/v$  with  $v = 1$ , solving (2.26) with  $j = 1$ . For  $\tilde{k} < 4$ , from property iii) we also have  $d_k = -\lambda_s/(2\lambda_q) > 0$ ,  $k = \tilde{k} + 1, \dots, 4$ , and  $d_5 = -(1 + \lambda_s)/(2\lambda_q) > 0$ . Thus, solving system (2.27) with  $i = 4 - \tilde{k}$  and  $j = 1$  we get  $d_k = R_{ji}^-$ ,  $k = \tilde{k} + 1, \dots, 4$ , and  $d_5 = R_{ij}^+$ , if and only if  $v \in (1, 5 - \tilde{k})$ .

In case e), property ii) implies  $d_k = 0$ ,  $k = 1, \dots, \tilde{k}$ , and property i) implies  $d_{k-1} = d_k > 0$ ,  $k = \hat{k} + 1, \dots, 5$ . Then, for  $\hat{k} = \tilde{k} + 1$ , the vector  $d$  contains  $\tilde{k}$  zeros and the last  $5 - \tilde{k}$  entries positive and equal. Solving system (2.26) with  $j = 5 - \tilde{k}$ , we obtain the solution  $d_k = S/v$ ,  $k = \tilde{k} + 1, \dots, 5$ , if and only if  $v = 5 - \tilde{k}$ . Conversely, for  $\hat{k} > \tilde{k} + 1$ , from property iii) it is  $d_k = -\lambda_s/(2\lambda_q) > 0$ ,  $k = \tilde{k} + 1, \dots, \hat{k} - 1$ . 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  $5 - \hat{k} + 1$  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  $d_k = R_{ji}^-$ ,  $k = \tilde{k} + 1, \dots, \hat{k} - 1$ , and  $d_k = R_{ij}^+$ ,  $k = \hat{k}, \dots, 5$ , with  $i = \hat{k} - \tilde{k} - 1$  and  $j = 5 - \hat{k} + 1$  if and only if  $v \in (5 - \hat{k} + 1, 5 - \tilde{k})$  (see (2.28), (2.29)).

It is simple to verify that for each extremal given above, at least one pair  $\lambda_s, \lambda_q$  of opposite sign exists. Thus, Problem 2.1 admits normal extremals for each value of  $v$  in  $[1, 5]$  but their structure depends on  $v$  itself. Note also that, if  $v = [v]$  it results  $R_{[v]i}^- = 0$ ,  $R_{i[v]}^+ = S/v$  so that extremals having two different positive entries coincide with the vector having  $[v]$  entries equal to  $S/v$  and  $5 - [v]$  zeroes.

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  $v = [v]$ .

$v$	$d$
$[1, 2)$	$(0 \ 0 \ 0 \ R_{11}^- \ R_{11}^+)$ $(0 \ 0 \ R_{12}^- \ R_{12}^- \ R_{21}^+)$ $(0 \ R_{13}^- \ R_{13}^- \ R_{13}^- \ R_{31}^+)$ $(R_{14}^- \ R_{14}^- \ R_{14}^- \ R_{14}^- \ R_{41}^+)$
$[2, 3)$	$(0 \ 0 \ R_{12}^- \ R_{12}^- \ R_{21}^+)$ $(0 \ 0 \ R_{21}^- \ R_{12}^+ \ R_{12}^+)$ $(0 \ R_{13}^- \ R_{13}^- \ R_{13}^- \ R_{31}^+)$ $(0 \ R_{22}^- \ R_{22}^- \ R_{22}^+ \ R_{22}^+)$ $(R_{14}^- \ R_{14}^- \ R_{14}^- \ R_{14}^- \ R_{41}^+)$ $(R_{23}^- \ R_{23}^- \ R_{23}^- \ R_{32}^+ \ R_{32}^+)$
$[3, 4)$	$(0 \ R_{13}^- \ R_{13}^- \ R_{13}^- \ R_{31}^+)$ $(0 \ R_{22}^- \ R_{22}^- \ R_{22}^+ \ R_{22}^+)$ $(0 \ R_{31}^- \ R_{13}^+ \ R_{13}^+ \ R_{13}^+)$ $(R_{14}^- \ R_{14}^- \ R_{14}^- \ R_{14}^- \ R_{41}^+)$ $(R_{23}^- \ R_{23}^- \ R_{23}^- \ R_{32}^+ \ R_{32}^+)$ $(R_{32}^- \ R_{32}^- \ R_{23}^+ \ R_{23}^+ \ R_{23}^+)$
$[4, 5)$	$(R_{14}^- \ R_{14}^- \ R_{14}^- \ R_{14}^- \ R_{41}^+)$ $(R_{23}^- \ R_{23}^- \ R_{23}^- \ R_{32}^+ \ R_{32}^+)$ $(R_{32}^- \ R_{32}^- \ R_{23}^+ \ R_{23}^+ \ R_{23}^+)$ $(R_{41}^- \ R_{14}^+ \ R_{14}^+ \ R_{14}^+ \ R_{14}^+)$
5	$(S/5 \ S/5 \ S/5 \ S/5 \ S/5)$

Table 2: Normal extremals of Problem 2.1.

### 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 (2.4) for all the extremals of the interval itself, identifying the minimum value of the  $J$ .

To this purpose we preliminary study the behaviour of  $R_{ij}^+$  defined in (2.31) keeping fixed the sum  $s = i + j$  but letting  $i$  vary and fixing the index  $j$  but letting  $s$  vary. Rewriting  $R_{ij}^+$  as a function  $R^+(i, s - i)$  and considering  $i, s$  as positive continuous variables, we have

$$\frac{\partial R^+(i, s - i)}{\partial i} = \frac{S}{2} \sqrt{\frac{s - v}{vi(s - i)^3}}, \quad (2.32)$$

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

$$\frac{\partial R^+(s - j, j)}{\partial s} = \frac{S \left( \sqrt{v(s - j)} - \sqrt{j(s - v)} \right)^2}{2s^2 \sqrt{vj(s - j)(s - v)}}, \quad (2.33)$$

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

Taking into account (2.32) and (2.33), 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 (2.1)

$v$	$d$
$[1, 2)$	$(0 \ 0 \ 0 \ R_{11}^- \ R_{11}^+)$
$[2, 3)$	$(0 \ 0 \ R_{21}^- \ R_{12}^+ \ R_{12}^+)$
$[3, 4)$	$(0 \ R_{31}^- \ R_{13}^+ \ R_{13}^+ \ R_{13}^+)$
$[4, 5)$	$(R_{41}^- \ R_{14}^+ \ R_{14}^+ \ R_{14}^+ \ R_{14}^+)$
$5$	$(S/5 \ S/5 \ S/5 \ S/5 \ S/5)$

Table 3: Optimal solutions of Problem 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  $v < 5$  (equal to zero if  $v = [v]$ ) and the remaining  $5 - [v] - 1$  entries equal to zero provided  $v < 4$ .

### 3 Minimum value of the maximal entry of vectors belonging to “late” constraint boundary and having a maximal entries sum

In [1] we proved that points satisfying  $g_l(d) = 0$ ,  $g_e(d) \leq 0$ ,  $d \geq 0$ , are such that

$$g_l(d) = \rho_l \sum_{k=1}^5 d_k + \sum_{k=1}^5 d_k^2 - k_l = 0, \quad \sum_{k=1}^5 d_k \leq S, \quad d_k \geq 0, \quad k = 1, \dots, 5. \quad (3.1)$$

So, in order to find the minimal value of the maximal entry of  $d$  in the new domain (3.1), we formulate the following non-linear programming problem whose domain clearly include the domain of Problem 2.1.

**Problem 3.1** *Minimize the function:*

$$J(d) = d_5, \quad (3.2)$$

*on the admissible set:*

$$D = \{d \in R^5 \mid g_l(d) = 0, \sum_{k=1}^5 d_k \leq S, d_5 \geq d_4 \geq d_3 \geq d_2 \geq d_1 \geq 0\}. \quad (3.3)$$

Clearly, Problem 3.1 admits optimal solutions ((3.3) is compact and (3.2) is a continuous function on it). The Lagrangian function associated to the problem is

$$L(d, \lambda_0, \lambda_s, \lambda_q, \eta) = \lambda_0 d_5 + \lambda \left( \rho_l \sum_{k=1}^5 d_k + \sum_{k=1}^5 d_k^2 - k_l \right) + \eta_s \left( \sum_{k=1}^5 d_k - S \right) - \eta_1 d_1 + \sum_{k=1}^4 \eta_{k+1} (d_k - d_{k+1}), \quad (3.4)$$

where  $\lambda_0, \eta_s, \lambda$  are scalar multipliers and  $\eta$  is the 5-dimensional vector of multipliers  $\eta_k, k = 1, \dots, 5$ .

The Kuhn-Tucker necessary and admissibility conditions are

$$\frac{\partial L}{\partial d_k} = \eta_s + \lambda (2d_k + \rho_l) - \eta_k + \eta_{k+1} = 0, \quad k = 1, \dots, 4, \quad (3.5)$$

$$\frac{\partial L}{\partial d_5} = \lambda_0 + \eta_s + \lambda (2d_5 + \rho_l) - \eta_5 = 0, \quad (3.6)$$

$$\eta_1 d_1 = 0, \quad (3.7)$$

$$\eta_k (d_{k-1} - d_k) = 0, \quad k = 2, \dots, 5, \quad (3.8)$$

$$\eta_s \left( \sum_{k=1}^5 d_k - S \right) = 0, \quad (3.9)$$

$$\rho_l \sum_{k=1}^5 d_k + \sum_{k=1}^5 d_k^2 - k_l = 0, \quad (3.10)$$

$$\eta_k \geq 0, \quad k = 1, \dots, 5, \quad (3.11)$$

$$\eta_s \geq 0, \quad (3.12)$$

$$\lambda_0 \geq 0, \quad (3.13)$$

with  $\lambda_0, \eta_s, \lambda, \eta$  never simultaneously equal to zero.

Following a similar procedure 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  $\sum_{k=1}^5 d_k = S$ , meaning that system (3.5)-(3.13) coincides with system (2.7)-(2.14), 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 (3.5)-(3.13) for  $\eta_s = 0$ .

- If  $\lambda_0 = 0$  it must be  $\lambda \geq 0$ , since  $\eta_5 \geq 0$ . However, if  $\lambda = 0$  it is  $\eta_k = 0, \forall k$  (see (3.5), (3.6)) and all the multipliers would be simultaneously equal to zero which is not admissible. If instead  $\lambda > 0$  it is  $\eta_5 > 0$  and  $\eta_k > \eta_{k+1}, k = 1, \dots, 4$  that imply  $d = 0$ , not satisfying  $g_l(d) = 0$ .
- Let us suppose  $\lambda_0 > 0$ . If  $\lambda \geq 0$  it is  $\eta_5 > 0$  and  $\eta_k \geq \eta_{k+1}, k = 1, \dots, 4$  that imply  $d = 0$ , not satisfying  $g_l(d) = 0$ . If  $\lambda < 0$  it is  $\eta_k < \eta_{k+1}, k = 1, \dots, 4$ , which means either  $\eta_k > 0, \forall k$ , or  $\eta_1 = 0, \eta_k > 0, k = 2, \dots, 5$ . The first case provides again  $d = 0$  whereas the second one implies  $d_k = d_{k+1}, k = 1, \dots, 4$ . For the latter case, in order to satisfies constraints

$g_l(d) = 0$  and  $\sum_{k=1}^5 d_k \leq S$ , it must be

$$d_k = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l}{5}} \leq \frac{S}{5}, \quad k = 1, \dots, 5,$$

or equivalently  $v \geq 5$  (see [1]). As  $v \in [1, 5]$ , only for  $v = 5$  we obtain a candidate, that is  $d_k = S/5, k = 1, \dots, 5$ , which coincides with the optimal solution of Table 3 for  $v = 5$ .

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

## 4 Concluding remarks

In this paper we prove a property valid for the admissible protocols of the optimization problem relevant to the radiotherapy scheduling presented in [1], when both early and late constraints act independently. In particular we find the minimal value of the maximal dose fraction of the protocols producing the maximal tolerable damage to both early and late responding tissues or to late tissues only (making the early constraint strictly satisfied). The minimum value is  $R_{1[v]}^+$ , given in (2.31) for  $i = 1$  and  $j = [v]$ , and the optimal protocol has  $[v]$  doses equal to  $R_{1[v]}^+$ , one dose equal to  $R_{[v]1}^-$  (provided  $v < 5$ ), and  $5 - [v] - 1$  doses equal to zero (provided  $v < 4$ ).

This result is significant for the radiotherapy problem studied in [1], where there is an upper bound  $d_M$  for the dose fraction. Indeed,  $R_{1[v]}^+$  acts as a threshold, in that when  $d_M < R_{1[v]}^+$  no points of the admissible region  $g_l(d) = 0, g_e(d) \leq 0, d \geq 0$  satisfy the upper bound and the optimum of the problem in [1] is given by a protocol producing a maximal damage to the “early” tissue.

## References

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