MULTIOBJECTIVE APPROACHES BASED ON VARIABLE ORDERING STRUCTURES FOR INTENSITY PROBLEMS IN RADIOTHERAPY TREATMENT

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ABSTRACT
Recently, in many papers intensity modulated radiotherapy treatment problems are studied as multicriteria optimization problems with respect to a constant ordering cone. In these problems, the goal is to maximize the dose delivered to cancer tumor as well as to reduce side effects. However, from a practical perspective, it is more convenient to consider such problems with respect to a variable ordering structure. In this paper, we introduce an appropriate cone-valued mapping based on the goal of cancer treatment. We consider a mathematical formulation of beam intensity optimization equipped with this ordering structure. In addition, we investigate necessary optimality conditions for solutions of a vector-valued approximation problem with respect to a general ordering cone and the proposed variable ordering structure as well. Finally, we calculate in detail necessary optimality conditions for solutions of the mathematical model of beam intensity optimization in radiotherapy treatment.

KEYWORDS: coderivative, dose response curve, intensity modulated radiotherapy treatment, normal cone, threshold dose, variable ordering structure, vector-valued norm.

MSC: 90C26, 90C29, 90C30, 90C46.

RESUMEN
Recientemente, en muchos artículos los problemas relacionados con determinar tratamientos de radioterapia con intensidad modulada se estudian como problemas de optimización multicriterio con respecto a un orden dado por un cono constante. En estos problemas, el objetivo es maximizar la dosis para tratar el tumor mientras se reducen los efectos secundarios. Sin embargo, desde un punto de vista práctico , es mejor considerar estructuras de orden variable. Ene ste trabajo se introduce una aplicación cono evaluada para este problema. Se considera la formulacón matemática del problema. Además, se investigan condiciones necesarias de optimalidad con respecto al cono que da el orden en el caso constante y la estructura variable. Finalmente se analiza el caso particular correspondiente al modelo de optimizar la intensidad en la radioterapia.

PALABRAS CLAVE: co-derivadas, cono normal, curva de dosis d respuesta, dosis umbral, estructura de orden variable, norma vectorial, tratamiento de radioterapia de intensidad modulada,

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1. MOTIVATION

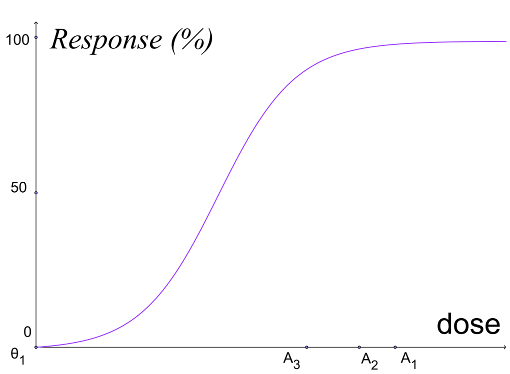
Intensity Modulated Radiotherapy Treatment (IMRT) is an advancement in radiotherapy that allows modulating radiation intensity across a beam. Currently, it is being used to treat cancers of the prostate, head and neck, breast, lung as well as certain types of sarcomas. The basic idea of IMRT is to reduce the intensity of rays going through particularly sensitive critical structures and to increase the intensity of those rays seeing primarily the target volume.

The problem of calculating those intensities based on dose prescription in the target volume and the surrounding critical structures is called inverse planning. This problem is modeled as a multicriteria optimization problem with an objective function depending on the specific goal that the treatment planner wants to achieve. In general, a level dose of radiation in the cancer organ should be closed to desired dose while it is absolutely necessary to avoid radiation in the organs outside the tumor (the critical organs) as much as possible. This inverse problem with respect to (w.r.t.) a constant cone is studied by several authors and can be divided into two categories, multiobjective nonlinear programming and multiobjective linear programming. For a general survey we refer the reader to [4]. However, from a practical perspective, it may seem more appropriate to concern this inverse problem as a multicriteria optimization problem w.r.t. a variable ordering structure, see [5]. This will be illustrated for a special problem in radiotherapy treatment in the following.

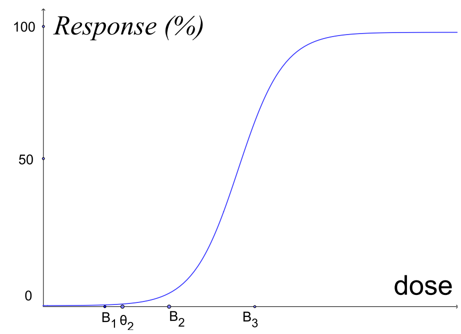
We consider the treatment of a lung cancer, lung is the most sensitive organ to radiotherapy damage. The dose delivered to lung is limited by spinal cord and heart (critical organs). Thus, to reduce side effects, the doses delivered to spinal cord and heart have to be minimized. A dose response curve describes the change in effect on an organ caused by differing levels of doses delivered to it. We suppose that the dose response curves for lung, spinal cord and heart in lung cancer treatment are illustrated in Fig1.

These curves can be used to estimate a threshold dose for each organ. The threshold dose is defined as the dose of radiation, below which the organism does not suffer from any effect. In mathematical point of view, it is the dose, below which the response is zero and above which it is nonzero, see [7, 12]. In this case, we assume that θ_1, θ_2 and θ_3 are respectively the threshold doses of lung, spinal cord and heart. We now have a look at three treatment plans $(A_1, B_1, C_1), (A_2, B_2, C_2),$ and (A_3, B_3, C_3) where A_i, B_i, C_i are the doses delivered to lung, spinal cord and heart respectively, $i = 1, 2, 3$. From a practical point of view, if the response of the organ on dose variations is relatively small, a rise of the dose delivered to that organ in favor of an improvement of the value for another organ is preferred, see [5]. In more detail, we would not only prefer an improvement of the dose level in lung, spinal cord and heart but also to rise the dose delivered to spinal cord from B_1 to B_2 for reducing the dose amount in heart, for instance, from C_1 to C_2. The reason is that a large improvement in the effect on heart is reached by changing the dose to C_2 while the effects on lung and spinal cord are changed mildly.

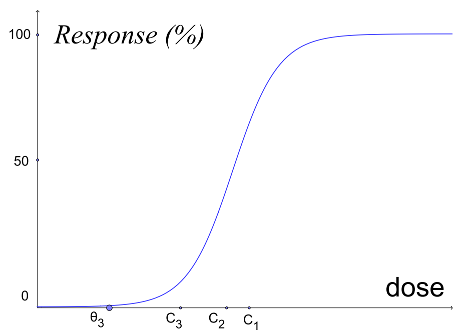
We assume that all treatment plans is a subset of $\mathbb{R}^3$ and consider a closed convex cone $\mathcal{C} \subset \mathbb{R}^3$. Suppose that we derive a mathematical model for this problem w.r.t $\mathcal{C}$. We denote $(A_2, B_2, C_2) \leq_{\mathcal{C}} (A_1, B_1, C_1)$ if $d := (A_1, B_1, C_1) - (A_2, B_2, C_2) \in \mathcal{C}$. Since $\mathcal{C}$ is a cone, $\lambda d \in \mathcal{C}$ for all $\lambda > 0$ and therefore if (A_3, B_3, C_3) satisfies $(A_2, B_2, C_2) - (A_3, B_3, C_3) = \beta d$ with $\beta > 0$ we have $(A_3, B_3, C_3) \leq_{\mathcal{C}}$



(a) Dose response curve for lung



(b) Dose response curve for spinal cord



(c) Dose response curve for heart

Figure 1: Dose response curves in lung cancer treatment

(A_2, B_2, C_2) i.e., (A_3, B_3, C_3) is "better" than (A_2, B_2, C_2).
On the other hand, having a look at the dose response curve of spinal cord, the increase in the effect for spinal cord is large by changing the dose from B_2 to B_3. Therefore, (A_3, B_3, C_3) might not be a preferred solution from a practical point of view. Thus, the choice of variable ordering cone depending on the actual doses in this circumstance seems to be more appropriate. Note that this illustration has the same idea as that in [5] for the case of prostate cancer treatment.
The rest of this paper is organized as follows: In Section 2, we recall some preliminaries which will be used in this work. In Section 3, we construct a variable ordering structure based on the goal of cancer treatment and formulate a mathematical problem for IMRT beam intensity optimization. Many important properties of this ordering structure are also investigated in this part. Section 4 introduces a multiobjective approximation problem equipped with the proposed structure as well as a general cone-valued mapping. This section is also concerned with providing optimality conditions for nondominated solutions and minimal solutions of this problem. In Section 5, we present an application in radiotherapy treatment by giving specific conditions for solutions of the mathematical formulation

introduced in Section 3.

2. PRELIMINARIES

2.1. Some notions related to variable ordering structures

In this part, we consider some notions related to variable ordering structures in $\mathbb{R}^n$, which will be used in the next sections. A set $Q \subset \mathbb{R}^n$ is a cone if for every $q \in Q$ and for all $\lambda \geq 0, \lambda q \in Q$ holds true. A cone Q is called convex if $Q + Q \subseteq Q$. In addition, a cone Q is called pointed if $Q \cap (-Q) = \{0\}$ and Q is proper if $Q \neq \mathbb{R}^n$ and $Q \neq \{0\}$. For a cone $Q \subset \mathbb{R}^n$ we set $Q^+ := \{y^* \in \mathbb{R}^n | \; \forall \, y \in Q : y^*(y) \geq 0\}$ for the positive dual cone of Q. For a nonempty set $A \subseteq \mathbb{R}^n$ we define

$$\operatorname{cone} A := \{ta : t \in \mathbb{R}_+, a \in A\} \text{ where } \mathbb{R}_+ = [0, \infty).$$

Recall that the affine hull of A is defined as

$$\operatorname{aff} A := \{\sum_{i=1}^{l} \lambda_i x_i | \; x_i \in A, \lambda_i \in \mathbb{R}, \sum_{i=1}^{l} \lambda_i = 1, l \in \mathbb{N}\},$$

which is the smallest affine set containing A. The closure of $\operatorname{aff} A$ in $\mathbb{R}^n$ is called the closed affine hull of A and is denoted by $\overline{\operatorname{aff}} A$. The relative interior $\operatorname{rint} A$ of A is the interior of A w.r.t. $\overline{\operatorname{aff}} A$.
In this paper, we are concerning a model of beam intensity optimization equipped with variable ordering structures. For an introduction to variable ordering structures and some recent results in this area, we refer the reader to [1, 2, 3, 5, 16, 17].

Definition 2.1. *(Variable ordering structure, [5]) Let $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$ be a set-valued map such that for every $y \in \mathbb{R}^n$, $\mathcal{K}(y)$ is a proper convex cone. Then, for every $y_1, y_2 \in \mathbb{R}^n$, we define*

$$y_1 \leq_{N,\mathcal{K}} y_2 \text{ if } \; y_2 \in y_1 + \mathcal{K}(y_1), \tag{2.1}$$

and

$$y_1 \leq_{P,\mathcal{K}} y_2 \text{ if } \; y_2 \in y_1 + \mathcal{K}(y_2). \tag{2.2}$$

If elements in the space $\mathbb{R}^n$ are compared using the binary relation (2.1) or (2.2), then it is said that $\mathcal{K}$ defines a variable ordering structure on Y.

For convenience, from now on we write the notations $\leq_{N,\mathcal{K}}$, $\leq_{P,\mathcal{K}}$ by relaxed forms $\leq_N$ and $\leq_P$.
Before deriving the definitions for efficient solutions of a vector optimization problem w.r.t. a variable ordering structure, it is necessary to concern the definition of nondominated elements and minimal elements of sets w.r.t. variable ordering structures.

Definition 2.2. *Let A be a nonempty subset of $\mathbb{R}^n$, $\bar{a} \in A$, and $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$ be a cone-valued map. We say that:*

(i) $\bar{a}$ is a nondominated element of A w.r.t. $\mathcal{K}(\cdot)$ if there is no $a \in A \setminus \{\bar{a}\}$ such that $a \leq_N \bar{a}$, i.e., $\bar{a} \in a + \mathcal{K}(a)$ or equivalently $\bar{a} \notin \bigcup_{a \in A} (\{a\} + \mathcal{K}(a) \setminus \{0_{\mathbb{R}^n}\})$. The set of all nondominated elements of A w.r.t. $\mathcal{K}(\cdot)$ is denoted by $\operatorname{ND}(A, \mathcal{K}(\cdot))$.

(ii) $\bar{a}$ *is a minimal element of* A *w.r.t.* $\mathcal{K}(\cdot)$ *if there is no* $a \in A \setminus \{\bar{a}\}$ *such that* $a \leq_P \bar{a}$*, i.e.,* $\bar{a} \in a + \mathcal{K}(\bar{a})$*, or equivalently* $(\{\bar{a}\} - \mathcal{K}(\bar{a})) \cap A = \{\bar{a}\}$*. The set of all minimal elements of* A *w.r.t.* $\mathcal{K}(\cdot)$ *is denoted by* $\mathrm{Min}(A, \mathcal{K}(\cdot))$*.*

Remark 2.1.

(i) Obviously, when $\mathcal{K}(\cdot) = C$ *where* C *is a closed, convex and pointed cone of* $\mathbb{R}^n$*, the concepts of nondominated elements and minimal elements are identical. It this case, we called them Pareto efficient elements of the set* A *in* $\mathbb{R}^n$ *w.r.t. the cone* C*.*

(ii) [5, Lemma 2.15] An element $\bar{a}$ *is a minimal element of* A *w.r.t.* $\mathcal{K}(\cdot)$ *if and only if it is an efficient element of* A *in* $\mathbb{R}^n$ *w.r.t. the cone* $\mathcal{K}(\bar{a})$*.*

We now consider a vector optimization problem w.r.t. a variable ordering structure and some concepts of its solution in the preimage space.

Let $f : \mathbb{R}^m \to \mathbb{R}^n$ be a continuous mapping, $\Omega \subseteq \mathbb{R}^m$ be a nonempty closed set and $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$ be a cone-valued ordering map. Let $f(\Omega) := \{f(x) |\ x \in \Omega\}$. We consider the following problem:

$$\mathcal{K} - \min_{x \in \Omega} f(x). \tag{$P_{\mathcal{K}}$}$$

Definition 2.3. *(Nondominated solutions and minimal solutions of a vector optimization problem w.r.t. a variable ordering structure)*
Consider the vector optimization problem $(P_{\mathcal{K}})$ *and* $\bar{x} \in \Omega$*. We say that:*

(i) $\bar{x}$ *is a nondominated solution of problem* $(P_{\mathcal{K}})$ *if* $f(\bar{x})$ *is a nondominated element of the set* $f(\Omega)$*.*

(ii) $\bar{x}$ *is a minimal solution of problem* $(P_{\mathcal{K}})$ *if* $f(\bar{x})$ *is a minimal element of the set* $f(\Omega)$*.*

Remark 2.2.

(i) When $\mathcal{K}(\cdot) = C$ *where* C *is a closed, convex and pointed cone of* $\mathbb{R}^n$*, the concepts of nondominated solutions and minimal solutions are identical. It this case, we called them Pareto efficient solutions of the problem* $C - \mathrm{Min}_{x \in \Omega} f(x)$*.*

(ii) If $\bar{x} \in \Omega$ *is a minimal solution of problem* $(P_{\mathcal{K}})$*, then it is also a Pareto efficient solution of the problem* $\mathcal{K}(f(\bar{x})) - \mathrm{Min}_{x \in \Omega} f(x)$*.*

2.2. Normal cones and Coderivatives

In this section, we present some definitions of normal cones and coderivatives which will be used to derive optimal conditions for vector optimization problems w.r.t. variable ordering structures. We begin with recalling notions of limits for set-valued mappings. Let $F : \mathbb{R}^m \rightrightarrows \mathbb{R}^n$ be a set-valued mapping with the domain and the graph respectively defined by

$$\mathrm{dom}\, F := \{x \in \mathbb{R}^m |\ F(x) \neq \emptyset\},$$

and

$$\mathrm{gph}\, F := \{(u, v) \in \mathbb{R}^m \times \mathbb{R}^n |\ v \in F(u)\}.$$

We denote the upper limits and lower limits of F as $x \to \bar{x}$ by $\limsup_{x\to\bar{x}} F(x)$ and $\liminf_{x\to\bar{x}} F(x)$ which are defined by, respectively,

$$\limsup_{x\to\bar{x}} F(x) := \{y \in \mathbb{R}^n |\ \exists\ \{x_k\} \to \bar{x} \text{ and } y_k \to y \text{ with } y_k \in F(x_k) \text{ for all } k \in \mathbb{N}\},$$

and

$$\liminf_{x\to\bar{x}} F(x) := \{y \in \mathbb{R}^n |\ \forall\ \{x_k\} \to \bar{x},\ \exists\ y_k \in F(x_k) \text{ with } k \in \mathbb{N} : y_k \to y \text{ as } k \to \infty\}.$$

Definition 2.4. *(Normal cones, [11])*
Let S be a nonempty subset of $\mathbb{R}^n$, and let $x \in S$, $\epsilon > 0$. We define the set of $\epsilon-$normals to S at x as:

$$\hat{N}_\epsilon(S, x) := \{x^* \in \mathbb{R}^n |\ \limsup_{v \xrightarrow{S} x} \frac{x^*(v - x)}{\|v - x\|} \le \epsilon\}. \tag{2.3}$$

When $\epsilon = 0$, the elements in the right hand side of (2.3) are called Fréchet normals and their collection, denoted by $\hat{N}(S, x)$ is the Fréchet normal cone to S at x.
Let $\bar{x} \in S$. The (basic, limiting, Mordukhovich) normal cone to S at $\bar{x}$ is defined by

$$N(S, \bar{x}) := \{x^* \in \mathbb{R}^n |\ \exists\ x_k \xrightarrow{S} \bar{x}, x_k^* \xrightarrow{w^*} x^*, x_k^* \in \hat{N}(S, x_k),\ \forall k \in \mathbb{N}\}.$$

Now we introduce the definition of coderivative of a general set-valued mapping $F : \mathbb{R}^m \rightrightarrows \mathbb{R}^n$. This definition will be used in Section 4. for two special mappings: a vector-valued mapping $f : \mathbb{R}^m \to \mathbb{R}^n$ and a cone-valued mapping $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$.

Definition 2.5. *(Fréchet coderivative and normal coderivative, [11])*
Let $F : \mathbb{R}^m \rightrightarrows \mathbb{R}^n$ be a set-valued mapping and $(\bar{x}, \bar{y}) \in \operatorname{gph} F$. The Fréchet coderivative of F at $(\bar{x}, \bar{y})$ is the set-valued map $\hat{D}^*F(\bar{x}, \bar{y}) : \mathbb{R}^n \rightrightarrows \mathbb{R}^m$ defined by:

$$\hat{D}^*F(\bar{x}, \bar{y})(y^*) := \{x^* \in \mathbb{R}^m |\ (x^*, -y^*) \in \hat{N}(\operatorname{gph} F, (\bar{x}, \bar{y}))\}.$$

The normal coderivative of F at $(\bar{x}, \bar{y})$ is the set-valued map $D^*F(\bar{x}, \bar{y}) : \mathbb{R}^n \rightrightarrows \mathbb{R}^m$ given by:

$$D^*F(\bar{x}, \bar{y})(y^*) := \{x^* \in \mathbb{R}^m |\ (x^*, -y^*) \in N(\operatorname{gph} F, (\bar{x}, \bar{y}))\}.$$

In order to provide specific optimality conditions for solutions of our problems, we recall some results of normal cone to some special sets in $\mathbb{R}^n$. These results are given by Rockafellar and Wets [15], so we omit their proofs in this paper.

Proposition 2.1. *(Normal cones to product sets, [15, Theorem 6.41])*
Let C_i be closed subsets of $\mathbb{R}^{n_i}, i = 1, \ldots, k$ and $\mathbb{R}^n = \mathbb{R}^{n_1} \times \ldots \times \mathbb{R}^{n_k}$. If $C = C_1 \times \ldots \times C_k$, then at any $\bar{x} = (\bar{x}_1, \ldots, \bar{x}_k)$ with $\bar{x}_i \in C_i$, it holds that

$$N(C, \bar{x}) = N(C_1, \bar{x}_1) \times \ldots \times N(C_k, \bar{x}_k).$$

Proposition 2.2. *(Normal cones to boxes, [15, Example 6.10])*
Assume that $C = C_1 \times \ldots \times C_n$ in which C_i is a closed interval in $\mathbb{R}$, $i = 1, \ldots, n$. Then, at any $\bar{x} = (\bar{x}_1, \bar{x}_2, \ldots, \bar{x}_n)$ with $\bar{x}_i \in C_i$, one has

$$N(C, \bar{x}) = N(C_1, \bar{x}_1) \times \ldots \times N(C_n, \bar{x}_n), \text{ where}$$

$$N(C_i, \bar{x}_i) = \begin{cases} [0, \infty) & \text{if } \bar{x}_i \text{ is (only) the right end point of } C_i, \\ (-\infty, 0] & \text{if } \bar{x}_i \text{ is (only) the left end point of } C_i, \\ \{0\} & \text{if } \bar{x}_i \text{ is an interior point of } C_i, \\ (-\infty, \infty) & \text{if } C_i \text{ is a one-point interval.} \end{cases}$$

In order to provide necessary conditions for our problems in the next section, we present in the following a result concerning nondomination conditions for vector optimization problem w.r.t. a cone-valued mapping. This result is given by Bao [2] for Asplund spaces, i.e. a Banach space X such that any convex continuous function $\varphi : U \to \mathbb{R}$ defined on an open convex subset U of X is Fréchet differentiable on a dense subset of U, see [13, Definition 1.22]. However, since we do not consider infinite dimensional spaces in this paper, we present this result for the case finite dimensional spaces. For the proof, we refer to [2, Theorem 4.2].

Theorem 2.1. *[2, Theorem 4.2] Let $f : \mathbb{R}^m \to \mathbb{R}^n$, $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$ and a nonempty closed subset $\Omega \subset \mathbb{R}^m$. Let $\bar{x}$ be a nondominated solution of problem $(P_{\mathcal{K}})$. Set $\bar{y} := f(\bar{x})$ and suppose that $\mathcal{K}(\cdot)$ satisfies the following conditions:*

(a) For all $y \in \mathbb{R}^n$, $\mathcal{K}(y)$ is a nonempty convex cone;

(b) There exists $e \in \mathbb{R}^n, e \neq 0$ such that $e \in \bigcap_{y \in \mathbb{R}^n} \mathcal{K}(y) \setminus (-\mathcal{K}(\bar{y}))$;

(c) There is a unique point y^* satisfying $-y^* \in D^*\mathcal{K}(\bar{y}, 0)(y^*)$.

Moreover, assume that $D^*f(\bar{x})(0) \cap (-N(\Omega, \bar{x})) = \{0\}$. Then, there is $y^* \in \mathbb{R}^n \setminus \{0\}$ such that

$$0 \in D^*f(\bar{x})(y^* + D^*\mathcal{K}(f(\bar{x}), 0)(y^*)) + N(\Omega, \bar{x}).$$

2.3. Vector-valued norm and its subdifferential

In this part, we denote the linear space of the continuous linear maps from $\mathbb{R}^m$ to $\mathbb{R}^n$ by $L(\mathbb{R}^m, \mathbb{R}^n)$. We begin this section by recalling the definition of the vectorial norm and the subdifferential of a vector-valued function.

Definition 2.6. *(Vectorial norm, [8]) Let C be a convex cone in $\mathbb{R}^n$. A map $\| \cdot \| : \mathbb{R}^m \to C$ is called a vectorial norm if for all $x, x_1, x_2 \in \mathbb{R}^n$ and all $\lambda \in \mathbb{R}$ the following conditions hold:*

(i) $\|x\| = 0_{\mathbb{R}^n} \iff x = 0_{\mathbb{R}^m}$;

(ii) $\|\lambda x\| = |\lambda| \, \|x\|$;

(iii) $\|x_1 + x_2\| \in \|x_1\| + \|x_2\| - C$.

Definition 2.7. *(Subdiferential of vector-valued function, [8]) Let $C \subset \mathbb{R}^n$ be a convex cone, and $f : \mathbb{R}^m \to \mathbb{R}^n$ be a given map. For an arbitrary $\bar{x} \in \mathbb{R}^m$, the set*

$$\partial f(\bar{x}) := \{T \in L(\mathbb{R}^m, \mathbb{R}^n) | \ \forall h \in \mathbb{R}^m : f(\bar{x} + h) - f(\bar{x}) - T(h) \in C\}$$

is called the subdifferential of f at $\bar{x}$.

Remark 2.3. *We present in the following the subdifferential of some special kinds of vector-valued function.*

(i) [8, Example 2.22] For the vector-valued norm function $\| \cdot \| : \mathbb{R}^m \to \mathbb{R}^n$, $\bar{x} \in \mathbb{R}^m$, we have that

$$\partial \|\bar{x}\| = \{T \in L(\mathbb{R}^m, \mathbb{R}^n) | \ T(\bar{x}) = \|\bar{x}\| \text{ and for all } x \in \mathbb{R}^m : T(x) \in \|\bar{x}\| - C\},$$

where C is a pointed convex cone in $\mathbb{R}^n$.

(ii) [6, Theorem 4.1.12] Let $A \in L(\mathbb{R}^m, \mathbb{R}^n)$ and A^* denotes the adjoint operator to A, $a \in \mathbb{R}^n$, $x^0 \in \mathbb{R}^m$. Then,

$$\partial \|A(\cdot) - a\|(x^0) = \{A^* T | \ T \in L(\mathbb{R}^n, \mathbb{R}), \ T(Ax^0 - a) = \|Ax^0 - a\| \text{ and } \|T\|_* \leq 1\},$$

where $\| \cdot \|$ is a norm in $\mathbb{R}^n$.

In order to derive the relationship between coderivative of a vector function and subdifferential of its scalarization, we need the Lipschitz properties of a mapping which are defined in the following.

Definition 2.8. *([11]) Let $f : \mathbb{R}^m \to \mathbb{R}^n$ be a vector-valued mapping.*

(i) f is Lipschitz on $U \subset \mathbb{R}^m$ if $U \subset \operatorname{dom} f$, and there exists $\ell \geq 0$ such that

$$\|f(x) - f(x')\|_{\mathbb{R}^n} \leq \ell \|x - x'\|_{\mathbb{R}^m}, \ \forall x, x' \in U.$$

(ii) f is said to be locally Lipschitz at $x \in \mathbb{R}^m$ if there is a neighbourhood U_x of x such that f is Lipschitz on U_x.

(iii) f is locally Lipschitz on a nonempty subset D of $\mathbb{R}^m$ if f is Lipschitz around every point $x \in D$.

It is known that a proper convex function $f : \mathbb{R}^m \to \mathbb{R}$ is locally Lipschitz at any interior point of its domain [14, Theorem 10.4]. In addition, in [10], the authors proved that a convex vector function from a convex subset D of $\mathbb{R}^m$ to $\mathbb{R}^n$ is locally Lipschitz on $\operatorname{rint} D$.

Proposition 2.3. *[11, Theorem 3.28] Let $f : \mathbb{R}^m \to \mathbb{R}^n$. Then, for all $y^* \in \mathbb{R}^n$, it holds that*

$$D^* f(\bar{x})(y^*) = \partial (y^* \circ f)(\bar{x}) \neq \emptyset,$$

provided that f is locally Lipschitz at $\bar{x}$.

3. BEAM INTENSITY PROBLEM WITH VARIABLE ORDERING STRUCTURES

3.1. A variable ordering cone relevant to radiotherapy treatment

As illustrated in [4], in order to derive a mathematical model for beam intensity optimization, the beam is discretized into p bixels or beamlets. The $3D$ volume of patient is divided into l voxels which include l_T tumor voxels, l_C critical organ voxels ($l = l_T + l_C$) in which T represents the tumor, C represents critical organs. The dose deposited in voxel i at unit intensity for bixel j is denoted by $a_{ij} \in \mathbb{R}$. We assume that the dose deposition matrix $A = (a_{ij}) \in \mathbb{R}^{l\times p}$ is given. We denote the beam intensity by $x \in \mathbb{R}^p$. Then, the beam intensity and the dose have the following relationship

$$d = Ax,$$

where $d \in \mathbb{R}^l$ is a dose vector and its element d_i correspond to the dose deposited in voxel i. We assume that A can be partitioned and reordered into sub-matrices $A_T \in \mathbb{R}^{l_T\times p}$ and $A_C \in \mathbb{R}^{l_N\times p}$ whose rows corresponding to tumor and normal voxels. It is obvious that the dose delivered to tumor and critical

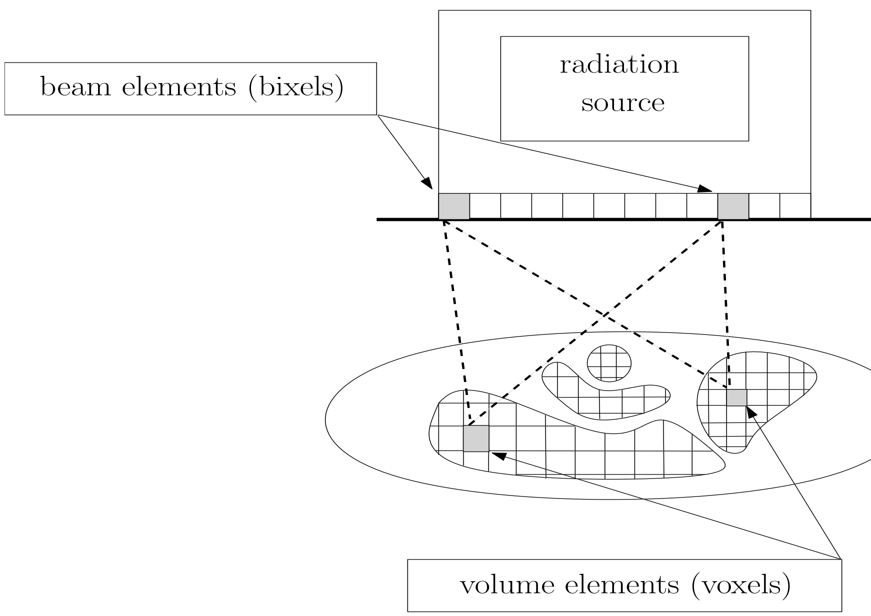


Figure 2: Discretization of patient into voxels and of beam into bixels ([4])

organ voxels are A_Tx and A_Cx respectively. A_Cx can be partitioned into $A_{C_1}x, \ldots, A_{C_k}x$ according to the doses delivered to k different organs $C_1, \ldots, C_k$. Because different tissues can tolerate different amounts of radiation, the radiation oncologist need to determine a "prescription dose" which consists of the target dose for the tumor $TG \in \mathbb{R}^{l_T}$, the lower bounds and upper bounds on the dose to tumor voxels $TLB, TUB \in \mathbb{R}^{l_T}$, the upper bounds on the dose to normal voxels CUB. CUB can be divided into $C_1UB, C_2UB, \ldots, C_kUB$ according to the voxels corresponding to different critical organs. In radiation treatment, threshold dose is defined as the amount of radiation that is required to cause a specific tissue effect.

As has been outlined before, a vector optimization w.r.t. a variable ordering cone modeling for radiotherapy treatment is more appropriate than that one w.r.t. a constant cone. Therefore, it is necessary to construct a suitable ordering structure in order to find the desired dose for our beam intensity optimization problem. From a practical perspective, a dose delivered to a critical organ should be reduced when it exceeds the threshold dose of that organ. If not, we can increase this dose in favor of an improvement in the value of another critical organ. This leads us to a variable ordering structure in the space $\mathbb{R}^n$ determined as follows:
Given $\theta \in \mathbb{R}^n$, for every $y = (y_1, y_2, \ldots, y_n) \in \mathbb{R}^n$ we set

$$I^{>}(y) := \{i \in \{1, 2, \ldots, n\} |\ y_i > \theta_i\},$$

and

$$I_{\leq}(y) := \{i \in \{1, 2, \ldots, n\} |\ y_i \leq \theta_i\}.$$

Obviously, for each $y \in \mathbb{R}^n$, it holds that $I^{>}(y) \cup I_{\leq}(y) = \{1, 2, \ldots, n\}$.
We define the variable ordering map $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$ as follows:

$$y \in \mathbb{R}^n,\ \mathcal{K}(y) := \{d \in \mathbb{R}^n |\ d_i \geq 0 \text{ for } i \in I^{>}(y)\}. \tag{3.1}$$

This set-valued mapping will be used in the following section to construct a formulation of the intensity problem in radiotherapy treatment when θ is chosen appropriately .

3.2. A formulation for beam intensity optimization in radiotherapy treatment

We begin this section by presenting a mathematical formulation of beam intensity optimization which is discussed in the previous parts. Assume that θ_{C_i} is given threshold dose of critical organ i, where $i \in \{1, \ldots, k\}$. Since the deviation from the dose delivered to tumor organ to the target dose is always nonnegative and should be minimized, we set $\theta := (0, \theta_{C_1}, \ldots, \theta_{C_k}) \in \mathbb{R}^{k+1}$. The set of bound conditions for beam intensity is given by

$$\Omega := \{x \in \mathbb{R}^p |\ 0 \leq x, TLB \leq A_T x \leq TUB, A_{C_i} x \leq C_i UB \text{ for } i = 1, \ldots, k\}.$$

By using the variable ordering mapping $\mathcal{K}(\cdot)$ given by (3.1) with $n := k + 1$, the problem of finding beam intensity in radiotherapy treatment can now be formulated as a special case of $(P_{\mathcal{K}})$ introduced in Section 2.1..

$$\text{Minimize } f(x) \text{ subject to } x \in \Omega \text{ w.r.t. } \mathcal{K}(\cdot), \tag{P_1}$$

where

$$f : \mathbb{R}^p \to \mathbb{R}^{k+1}$$

$$f(x) := \begin{pmatrix} \|A_T x - TG\|_\infty \\ \|A_{C_1} x\|_\infty \\ \cdots \\ \|A_{C_k} x\|_\infty \end{pmatrix}.$$

The first criterion can be interpreted as the deviation from the prescribed dose to the tumor. $\|A_{C_i}x\|_\infty$ is the dose to the critical organ i $(i = 1, \dots, k)$. The objective function can be constructed by using Euclidean norm, see [9]. However, this norm allows the averaging out of large deviations on a small tissue by small or no deviation on a large tissue. Therefore, it seems to be more reasonable to use the maximum norm.

In the following, we present some properties of the proposed variable ordering cone $\mathcal{K}(\cdot)$ given by (3.1).

Proposition 3.1. *Consider the variable ordering structure $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$ determined by (3.1) and let Ω be a subset of $\mathbb{R}^n$. Then, the following assertions hold true*

(i) For each $y \in \mathbb{R}^n$, $\mathcal{K}(y)$ is a closed and convex cone and $\mathbb{R}^n_+ \subseteq \mathcal{K}(y)$. In addition, $\mathcal{K}(y)$ is pointed if and only if $y_i > \theta_i, \ \forall\ i = 1, 2, \dots, n$.

(ii) For all $y^1, y^2 \in \mathbb{R}^n$, $y^1 - y^2 \in \mathbb{R}^n_+$ implies $\mathcal{K}(y^1) \subseteq \mathcal{K}(y^2)$.

(iii) If $\bar{y} \in \Omega$ satifies $I^>(\bar{y}) \neq \emptyset$, then there exists $e \neq 0$ such that

$$e \in \bigcap_{y\in\Omega} \mathcal{K}(y) \setminus (-\mathcal{K}(\bar{y})).$$

(iv) $\operatorname{gph}\mathcal{K}$ is a closed subset of $\mathbb{R}^n \times \mathbb{R}^n$.

Proof.

(i) Obviously, for all $y \in \mathbb{R}^n$ we have that $\mathcal{K}(y)$ is a closed and convex cone. $\mathcal{K}(y)$ is pointed if and only if $\mathcal{K}(y) \cap (-\mathcal{K}(y)) = \{0\}$. By the definition of $\mathcal{K}(\cdot)$, it holds that

$$\mathcal{K}(y) \cap (-\mathcal{K}(y)) = \{d \in \mathbb{R}^n |\ d_i = 0 \text{ with } i \in I^>(y)\}.$$

Thus, $\mathcal{K}(y)$ is pointed if and only if $I^>(y) = \{1, 2, \dots, n\}$. This condition also means that $y_i > \theta_i, \ \forall\ i = 1, 2, \dots, n$.

(ii) It follows from $y^1 - y^2 \in \mathbb{R}^n_+$ that $y^1_i \geq y^2_i$ for all $i = 1, 2, \dots, n$. Therefore, for all $i \in I^>(y^2)$ we have $y^1_i \geq y^2_i > \theta_i$, i.e., $i \in I^>(y^1)$. Thus, $I^>(y^2) \subseteq I^>(y^1)$ and $\mathcal{K}(y^1) \subseteq \mathcal{K}(y^2)$ holds true.

(iii) Assume that $i_0 \in I^>(\bar{y})$ i.e., $\bar{y}_{i_0} > \theta_{i_0}$. It follows from the definition of $\mathcal{K}(\cdot)$ that if $d = (d_1, \dots, d_n) \in (-\mathcal{K}(\bar{y}))$ then $d_{i_0} \leq 0$. Take $e := (e_1, \dots, e_n)$, where $e_i > 0$ for all $i = 1, 2, \dots, n$, i.e., $e \in \mathbb{R}^n_+$. Since $\mathbb{R}^n_+ \subseteq \bigcap_{y\in\Omega} \mathcal{K}(y)$, $e \in \bigcap_{y\in\Omega} \mathcal{K}(y)$. Because $e_{i_0} > 0$, we have that $e \notin (-\mathcal{K}(\bar{y}))$. Therefore, $e \in \bigcap_{y\in\Omega} \mathcal{K}(y) \setminus (-\mathcal{K}(\bar{y}))$.

(iv) Consider a consequence $\{(y^k, d^k)\} \subset \operatorname{gph}\mathcal{K}$ which convergences to (y, d) when $k \to \infty$. We need to show that $(y, d) \in \operatorname{gph}\mathcal{K}$.

Suppose that

$$(y^k, d^k) = (y^k_1, y^k_2, \dots, y^k_n, d^k_1, d^k_2, \dots, d^k_n),$$

and

$$(y, d) = (y_1, y_2, \dots, y_n, d_1, d_2, \dots, d_n).$$

To proceed, we consider the following cases.
Case 1: $I^{>}(y) \neq \emptyset$. Let $i \in I^{>}(y)$ be arbitrary. We will prove that $d_i \geq 0$.
Because

$$y_i > \theta_i \text{ and } \{y_i^k\} \to y_i \text{ when } k \to \infty,$$

it holds that

$$\exists\, k_0 \in \mathbb{N}^* \text{ such that for all } k \geq k_0 : y_i^k > \theta_i.$$

Taking into account $(y_1^k, y_2^k, \ldots, y_n^k, d_1^k, \ldots, d_n^k) \in \operatorname{gph} \mathcal{K}$, we get that

$$d_i^k \geq 0,\ \forall\, k \geq k_0.$$

Since $d_i^k \to d_i$ when $k \to \infty$, it yields $d_i \geq 0$ for all $i \in I^{>}(y)$. Thus, $(y, d) \in \operatorname{gph} \mathcal{K}$.
Case 2: $I^{>}(y) = \emptyset$, i.e., $y_i \leq \theta_i,\ \forall\, i = 1, 2, \ldots, n$. It follows directly from the definition of $\mathcal{K}(\cdot)$ that $(y, d) \in \operatorname{gph} \mathcal{K}$. The proof is complete. □

4. OPTIMALITY CONDITIONS FOR SOLUTIONS OF MULTIOBJECTIVE APPROXIMATION PROBLEMS

4.1. Optimality conditions for nondominated solutions of approximation problems w.r.t. a general ordering structure

We begin this section by introducing in the following a vector approximation problem which is considered as a general problem of the problem (P_1).
Let A_i be linear mappings from $\mathbb{R}^m$ to $\mathbb{R}^{m_i}$, $a_i \in \mathbb{R}^{m_i}, i = 1, 2, \ldots, n$, $\|\cdot\|_i$ be norms in $\mathbb{R}^{m_i}$. Given a nonempty closed set $\Omega \subseteq \mathbb{R}^m$ and a set-valued map $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$ satisfying $\mathcal{K}(y)$ is a closed and convex cone for each $y \in \mathbb{R}^n$. We consider the following problem:

$$\text{Minimize } f(x) \text{ subject to } x \in \Omega \text{ w.r.t. } \mathcal{K}(\cdot), \tag{P_2}$$

where

$$f : \mathbb{R}^m \to \mathbb{R}^n$$

$$f(x) := \begin{pmatrix} \|A_1 x - a_1\|_1 \\ \|A_2 x - a_2\|_2 \\ \cdots \\ \|A_n x - a_n\|_n \end{pmatrix}.$$

In Section 4.2., we will discuss the problem (P_2) for the case $\mathcal{K}(\cdot)$ is given by (3.1). Now, we present a necessary optimality condition for nondominated solutions of the vector approximation problem (P_2).

Theorem 4.1. *We consider the problem (P_2) w.r.t. a cone-valued mapping $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$. Suppose that $\bar{x} \in \Omega$ is a nondominated solution of (P_2) and let $\bar{y} := f(\bar{x})$. We assume that the following conditions hold:*

(i) $\forall\, y \in \mathbb{R}^n$, $\mathcal{K}(y)$ is a nonempty convex cone.

(ii) *There exists* $e \in \mathbb{R}^n$, $e \neq 0$ *with* $e \in \bigcap_{y \in \mathbb{R}^n} \mathcal{K}(y) \setminus (-\mathcal{K}(\bar{y}))$.

(iii) *There is a unique point* y^* *satisfying* $-y^* \in D^*\mathcal{K}(\bar{y}, 0)(y^*)$.

Then, there are $y^* \in \mathbb{R}^n \setminus \{0\}$ *and corresponding* $z^* \in (y^* + D^*\mathcal{K}(\bar{y}; 0)(y^*))$ *and* $T_i \in L(\mathbb{R}^{m_i}, \mathbb{R})$ *satisfying* $T_i(A_i(\bar{x}) - a^i) = \|A_i(\bar{x}) - a^i\|_i$ *and* $\|T_i\|_{i^*} \leq 1$ *such that*

$$0 \in \sum_{i=1}^{n} A_i^* z^* T_i + N(\Omega, \bar{x}).$$

Proof. Since f is Lipschitz and by using the relationship between coderivative of a vector function with subdiferential of its scalarization (Proposition 2.3.), we get the following assertion:

$$\forall\, y^* \in \mathbb{R}^n,\ \forall\, \bar{x} \in \Omega : D^*f(\bar{x})(y^*) = \partial(y^* \circ f)(\bar{x}).$$

This implies that $D^*f(\bar{x})(0) = \{0\}$ and thus $D^*f(\bar{x})(0) \cap (-N(\Omega, \bar{x})) = \{0\}$.
Applying Theorem 2.1., there exists $y^* \in \mathbb{R}^n \setminus \{0\}$ such that

$$0 \in D^*f(\bar{x})(y^* + D^*\mathcal{K}(\bar{y}, 0)(y^*)) + N(\Omega, \bar{x}).$$

This means that there is $z^* \in (y^* + D^*\mathcal{K}(\bar{y}, 0)(y^*))$ satisfying

$$\begin{aligned} & 0 \in D^*f(\bar{x})(z^*) + N(\Omega, \bar{x}) \\ \Longleftrightarrow\ & 0 \in \partial(z^* \circ f)(\bar{x}) + N(\Omega, \bar{x}). \end{aligned}$$

Taking into account the formulation of coderivative of a vector-valued norm function in Remark 2.3., we have that

$$\exists\, T_i \in L(\mathbb{R}^{m_i}, \mathbb{R}), T_i(A_i(\bar{x}) - a^i) = \|A_i(\bar{x}) - a^i\|_i \text{ and } \|T_i\|_{i^*} \leq 1, (i = 1, \ldots, n)$$

such that

$$0 \in \sum_{i=1}^{n} A_i^* z^* T_i + N(\Omega, \bar{x}).$$

The proof is complete. □

In the following, we present a corollary of Theorem 4.1. concerning a necessary optimality condition for Pareto efficient solutions of problem (P_2) w.r.t. a constant cone.

Corollary 4.1. *We consider the problem* (P_2) *w.r.t. a fixed valued mapping* $\mathcal{K}(\cdot) = Q$, *where* Q *is a closed, convex and pointed cone in* $\mathbb{R}^n$. *Suppose that* $\bar{x} \in \Omega$ *is a Pareto efficient solution of* (P_2) *and let* $\bar{y} := f(\bar{x})$. *In addition, suppose that there exists* $e \in \mathbb{R}^n$, $e \neq 0$ *with* $e \in Q \setminus (-Q)$. *Then, there are* $y^* \in -N(Q, 0) \setminus \{0\}$ *and* $T_i \in L(\mathbb{R}^{m_i}, \mathbb{R})$ *satisfying* $T_i(A_i(\bar{x}) - a^i) = \|A_i(\bar{x}) - a^i\|_i$ *and* $\|T_i\|_{i^*} \leq 1$ *such that*

$$0 \in \sum_{i=1}^{n} A_i^* y^* T_i + N(\Omega, \bar{x}).$$

4.2. Optimality conditions for solutions of vector approximation problems w.r.t. the proposed ordering structure

This section is concerned with deriving optimality conditions for solutions of the following problem which is a special case of (P_2) when the ordering $\mathcal{K}(\cdot)$ is given by (3.1):

$$\text{Minimize } f(x) \text{ subject to } x \in \Omega \text{ w.r.t. } \mathcal{K}(\cdot), \tag{P_3}$$

where

$$f : \mathbb{R}^m \to \mathbb{R}^n$$

$$f(x) := \begin{pmatrix} \|A_1x - a_1\|_1 \\ \|A_2x - a_2\|_2 \\ \dots \\ \|A_nx - a_n\|_n \end{pmatrix},$$

and $\mathcal{K}(\cdot)$ is determined by (3.1).

Notice that (P_3) reduces to the problem (P_1) when we choose $\theta := (0, \theta_1, \dots, \theta_k)$, $a_1 = TG$, $a_2 = ... = a_n = 0$, $m := p, n := k+1, A_1 := A_T, A_{j+1} := A_{C_j},\ j = 1, \dots, k$ and $\|\cdot\|_i := \|\cdot\|_\infty$, $\forall\ i = 1, \dots, n$. It is necessary to determine $D^*\mathcal{K}(\bar{y}, 0)(y^*)$ in order to derive a specific optimality conditions for nondominated solutions as well as minimal solutions of the problem (P_3). For this aim, we will calculate the normal cone $N(\operatorname{gph}\mathcal{K}, (\bar{y}, 0))$. First, we suppose that Ω is a subset of $\mathbb{R}^n$. We consider the associated distance function

$$\operatorname{dist}(x, \Omega) := \inf_{u \in \Omega} \|x - u\|,$$

and define the Euclidean projector of x to Ω by

$$P(x, \Omega) := \{\omega \in \Omega |\ \|x - \omega\| = \operatorname{dist}(x, \Omega)\}, \tag{4.1}$$

where $\|\cdot\|$ is Euclidean norm in $\mathbb{R}^n$. The following theorem describes the formulation of the basic normal cone to a subset $\Omega \subseteq \mathbb{R}^n$ which is locally closed around $\bar{x} \in \Omega$.

Theorem 4.2. *[11, Theorem 1.6] Let $\Omega \subseteq \mathbb{R}^n$ be locally closed around $\bar{x} \in \Omega$. Then, it holds that*

$$N(\Omega, \bar{x}) = \limsup_{x \to \bar{x}} \hat{N}(\Omega, x),$$

and

$$N(\Omega, \bar{x}) = \limsup_{x \to \bar{x}} [\operatorname{cone}(x - P(x; \Omega))].$$

In order to compute $N(\operatorname{gph}\mathcal{K}, (\bar{y}, 0))$, we rewrite the graph of mapping $\mathcal{K}(\cdot)$ as follows:

For each $I \subseteq \{1, 2, \dots, n\}$, we set:

$$U_I := \{y \in \mathbb{R}^n |\ I^>(y) = I\},$$

and

$$\mathbb{R}^n_I := \{d \in \mathbb{R}^n |\ d_i \geq 0,\ \forall\ i \in I\}.$$

Obviously, if $y \in U_I$ then $\mathcal{K}(y) = \mathbb{R}^n_I$. Therefore, we obtain

$$\operatorname{gph} \mathcal{K} = \bigcup_{I \subseteq \{1,2,\ldots,n\}} U_I \times \mathbb{R}^n_I.$$

Since $\operatorname{gph} \mathcal{K}$ is closed (Proposition 3.1.) and taking into account Theorem 4.2., we have that

$$N(\operatorname{gph} \mathcal{K}, (\bar{y}, 0)) = \limsup_{(y,d) \to (\bar{y},0)} [\operatorname{cone}((y,d) - P((y,d); \bigcup_{I \subseteq \{1,2,\ldots,n\}} U_I \times \mathbb{R}^n_I))].$$

This analysis leads to the question if we can provide the results of Euclidean projector to graph of $\mathcal{K}(\cdot)$ which gives the formulation of the normal cone to its graph by using Theorem 4.2.. This is discussed in the following theorem.

Theorem 4.3. *Given a point $\theta = (\theta_1, \ldots, \theta_n) \in \mathbb{R}^n$ and the set-valued mapping $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$ determined by (3.1). For each element $(y, d) \in \mathbb{R}^n \times \mathbb{R}^n$ we set*

$$J^{\geq}(d) := \{i \in \{1, 2, \ldots, n\} |\ d_i \geq 0\},$$

and

$$I^{>}(y) := \{i \in \{1, 2, \ldots, n\} |\ y_i > \theta_i\}.$$

Then, it holds for the Euclidean projector given by (4.1) that

(i) If $I \not\subseteq I^{>}(y)$ then $P((y, d); U_I \times \mathbb{R}^n_I) = \emptyset$.

(ii) If $I \subseteq I^{>}(y)$ then

(a)

$$P((y, d); U_I \times \mathbb{R}^n_I) = \{(y^I, d^I) \in U_I \times \mathbb{R}^n_I\},$$

where $(y^I, d^I) := (y^I_1, \ldots, y^I_n, d^I_1, \ldots, d^I_n)$ determined by:

$$\begin{aligned}
d^I_i =& d_i, \forall\ i \in (\{1, 2, \ldots, n\} \setminus I) \bigcup J^{\geq}(d);\\
d^I =& 0,\ \forall\ i \in I \setminus J^{\geq}(d);\\
y^I_i =& \theta_i,\ \forall\ i \in I^{>}(y) \setminus I;\\
y^I_i =& y_i,\ \forall\ i \in (\{1, 2, \ldots, n\} \setminus I^{>}(y)) \cup I.
\end{aligned}$$

(b) $\operatorname{dist}((y, d), U_I \times \mathbb{R}^n_I) = \sqrt{\sum_{i \in I^{>}(y) \setminus I} (y_i - \theta_i)^2 + \sum_{i \in I \setminus J^{\geq}(d)} (d_i)^2}$*;*

(iii) $P((y, d); \operatorname{gph} \mathcal{K}) = \bigcup_I P((y, d); U_I \times \mathbb{R}^n_I)$,
where $I = \operatorname{argmin}_{I \subseteq I^{>}(y)} dist((y, d), U_I \times \mathbb{R}^n_I)$.

Proof. Let I and I' be two arbitrary subsets of $\{1, 2, \ldots, n\}$. We have that

$$(U_I \times \mathbb{R}^n_I) \bigcap (U_{I'} \times \mathbb{R}^n_{I'}) = \emptyset \text{ with } I \neq I'.$$

Therefore,

$$P((y, d); \cup_{I \subseteq \{1,2,\ldots,n\}} U_I \times \mathbb{R}^n_I) = \operatorname{argmin}_{(y^I, d^I) \in U_I \times \mathbb{R}^n_I} (\|(y, d) - (y^I, d^I)\|^2).$$

Thus, for each $I \subset \{1, 2, \ldots, n\}$, we need to find $P((y, d); U_I \times \mathbb{R}^n_I)$.

(i) $I \not\subseteq I^>(y)$ i.e., $\exists\, i_0 \in I$ but $i_0 \notin I^>(y)$. We will prove that

$$P((y, d); U_I \times \mathbb{R}^n_I) = \emptyset.$$

Indeed, suppose that there is an element $(y^I, d^I) \in U_I \times \mathbb{R}^n_I$ such that

$$\|(y^I, d^I) - (y, d)\|^2 = \inf_{(\omega,\gamma) \in U_I \times \mathbb{R}^n_I} \|(\omega, \gamma) - (y, d)\|^2.$$

Since $y^I \in U_I$ and $i_0 \in I$, we assume that

$$(y^I, d^I) = (y^I_1, y^I_2, \ldots, y^I_n, d^I_1, d^I_2, \ldots, d^I_n),$$

and $y^I_{i_0} = \theta_{i_0} + \epsilon$ with $\epsilon > 0$. We consider the point

$$(y^*, d^*) := (y^*_1, y^*_2, \ldots, y^*_n, d^*_1, d^*_2, \ldots, d^*_n),$$

determined by

$$y^*_{i_0} = \theta_{i_0} + \frac{\epsilon}{2}, y^*_i = y^I_i \text{ for } i \in \{1, 2, \ldots, n\} \setminus \{i_0\},$$

and

$$d^*_k = d^I_k, k = 1, 2, \ldots, n.$$

Obviously, $(y^*, d^*) \in U_I \times \mathbb{R}^n_I$. Now we get

$$\begin{aligned}
\|(y^*, d^*) - (y, d)\|^2 &= \sum_{i=1}^{n} ((y^*_i - y_i)^2 + (d^*_i - d_i)^2) \\
&= \sum_{i \in \{1,2,\ldots,n\} \setminus \{i_0\}} (y^*_i - y_i)^2 + (y^*_{i_0} - y_{i_0})^2 + \sum_{i=1}^{n} (d^*_i - d_i)^2 \\
&= \sum_{i \in \{1,2,\ldots,n\} \setminus \{i_0\}} (y^I_i - y_i)^2 + (\theta_{i_0} + \frac{\epsilon}{2} - y_{i_0})^2 + \sum_{i=1}^{n} (d^I_i - d_i)^2 \\
&< \sum_{i \in \{1,2,\ldots,n\} \setminus \{i_0\}} (y^I_i - y_i)^2 + (\theta_{i_0} + \epsilon - y_{i_0})^2 + \sum_{i=1}^{n} (d^I_i - d_i)^2 \\
&\quad (y^I_{i_0} = \theta_{i_0} + \epsilon) \\
&= \sum_{i \in \{1,2,\ldots,n\} \setminus \{i_0\}} (y^I_i - y_i)^2 + (y^I_{i_0} - y_{i_0})^2 + \sum_{i=1}^{n} (d^I_i - d_i)^2 \\
&= \sum_{i=1}^{n} ((y^I_i - y_i)^2 + (d^I_i - d_i)^2) \\
&= \|(y^I, d^I) - (y, d)\|^2
\end{aligned}$$

Thus, $(y^*, d^*) \in U_I \times \mathbb{R}^n_I$ and $\|(y^*, d^*) - (y, d)\|^2 < \|(y^I, d^I) - (y, d)\|^2$, this is a contradiction with the definition of (y^I, d^I):

$$\|(y^I, d^I) - (y, d)\|^2 = \inf_{(\omega,\gamma)\in U_I\times\mathbb{R}^n_I} \|(\omega, \gamma) - (y, d)\|^2.$$

(ii)

(a) Let $I \subseteq I^>(y)$ and take an arbitrary element $(y^I, d^I) \in U_I \times \mathbb{R}^n_I$. It holds that

$$\begin{aligned}
\|(y^I, d^I) - (y, d)\|^2 &= \sum_{i=1}^{n}(y_i^I - y_i)^2 + \sum_{i=1}^{n}(d_i^I - d_i)^2 \\
&= \sum_{i\in I}(y_i^I - y_i)^2 + \sum_{i\in I^>(y)\setminus I}(y_i^I - y_i)^2 + \sum_{i\in\{1,2,\ldots,n\}\setminus I^>(y)}(y_i^I - y_i)^2 \\
&+ \sum_{i\in(\{1,2,\ldots,n\}\setminus\{I\cup J^\geq(d)\})}(d_i^I - d_i)^2 + \sum_{i\in I\setminus J^\geq(d)}(d_i^I - d_i)^2 \\
&+ \sum_{i\in J^\geq(d)\setminus I}(d_i^I - d_i)^2 + \sum_{I\cap J^\geq(d)}(d_i^I - d_i)^2 \\
&\geq \sum_{i\in I^>(y)\setminus I}(y_i^I - y_i)^2 + \sum_{i\in I\setminus J^\geq(d)}(0 - d_i)^2 \\
&\geq \sum_{i\in I^>(y)\setminus I}(\theta_i - y_i)^2 + \sum_{i\in I\setminus J^\geq(d)}(0 - d_i)^2.
\end{aligned}$$

The last conclusion is obtained since: $\begin{cases} \forall\ i \in I^>(y) \setminus I : y_i > \theta_i \text{ and } y_i^I \leq \theta_i, \\ \forall\ i \in I \setminus J^\geq(d) : d_i^I \geq 0 \text{ and } d_i < 0. \end{cases}$

Therefore, $\|(y^I, d^I) - (y, d)\|^2 \geq \sum_{i\in I^>(y)\setminus I}(\theta_i - y_i)^2 + \sum_{i\in I\setminus J^\geq(d)}(0 - d_i)^2$,

and the equation holds true if we choose

$$\begin{aligned}
d_i^I &= d_i,\ \forall\ i \in (\{1, 2, \ldots, n\} \setminus I) \cup J^\geq(d); \\
d^I &= 0,\ \forall\ i \in I \setminus J^\geq(d); \\
y_i^I &= \theta_i,\ \forall\ i \in I^>(y) \setminus I; \\
y_i^I &= y_i,\ \forall\ i \in (\{1, 2, \ldots, n\} \setminus I^>(y)) \cup I.
\end{aligned}$$

(b) It is obviously that if $I \subseteq I^>(y)$ then

$$\operatorname{dist}((y, d), U_I \times \mathbb{R}^n_I) = \sqrt{\sum_{i\in I^>(y)\setminus I}(y_i - \theta_i)^2 + \sum_{i\in I\setminus J^\geq(d)}(d_i)^2}.$$

(iii) Since $\operatorname{gph}\mathcal{K}$ is a closed set, $P((y, d), \operatorname{gph}\mathcal{K}) \neq \emptyset$ [15, Example 1.20]. Suppose that

$$(\hat{y}, \hat{d}) \in P((y, d), \operatorname{gph}\mathcal{K}),$$

then

$$\exists\ J \subset \{1, 2, \ldots, n\} \text{ such that } (\hat{y}, \hat{d}) \in U_J \times \mathbb{R}^n_J.$$

It holds that

$$\begin{aligned} d((y,d),(\hat{y},\hat{d}) &= d((y,d),\operatorname{gph}\mathcal{K}) \\ &\le d((y,d),U_J\times\mathbb{R}^n_J) \\ &\le d((y,d),(\hat{y},\hat{d})). \end{aligned}$$

The equation holds true if $(\hat{y},\hat{d}) = P((y,d),U_J\times\mathbb{R}^n_J)$. Taking into account (i) and (ii), we get $J\subseteq I^>(y)$ and this completes the proof. □

The following remark shows how one obtains the Euclidean projector of an arbitrary point in $\mathbb{R}^n\times\mathbb{R}^n$ to the graph of the mapping $\mathcal{K}(\cdot)$, the normal cone to its graph as well as its coderivative.

Remark 4.1.

(i) *We can get the projection of* (y,d) *to* $\operatorname{gph}\mathcal{K}$ *through these following steps:*
Step 1: Determine $I^>(y)$.
Step 2: For each $I\subseteq I^>(y)$, *calculate* $d((y,d),U_I\times\mathbb{R}^n_I)=\sigma_I$ *and*

$$P((y,d);U_I\times\mathbb{R}^n_I)=\{(y^I,d^I)\in U_I\times\mathbb{R}^I : d((y^I,d^I),U_I\times\mathbb{R}^n_I)=\sigma_I\}.$$

Step 3: Find $\sigma := min_{I\subseteq\{1,2,\dots,n\}}\{\sigma_I\}$ *and*

$$P((y,d),\operatorname{gph}\mathcal{K})=\cup_I P((y,d);U_I\times\mathbb{R}^n_I),$$

where I satisfies $I\subseteq I^>(y)$ *and* $d((y,d),U_I\times\mathbb{R}^n_I)=\sigma$.

(ii) *From the Theorem 4.3. above we obtain that*

$$N(\operatorname{gph}\mathcal{K},(\bar{y},0)) = \limsup_{(y,d)\to(\bar{y},0)} \operatorname{cone}((y,d)-P((y,d),\operatorname{gph}\mathcal{K}), \tag{4.2}$$

where $P((y,d),\operatorname{gph}\mathcal{K})$ *is determined in Theorem 4.3.* (iii). *In addition, it holds that*

$$D^*\mathcal{K}(\bar{y},0)(y^*)=\{x^*\in\mathbb{R}^n|\ (x^*,-y^*)\in N(\operatorname{gph}\mathcal{K},(\bar{y},0))\}, \tag{4.3}$$

where $N(\operatorname{gph}\mathcal{K},(\bar{y},0))$ *given by (4.2).*

Now we are ready to derive the optimality condition for nondominated solutions of the problem (P_3).

Theorem 4.4. *Let* $\mathcal{K}:\mathbb{R}^n\rightrightarrows\mathbb{R}^n$ *be a set-valued map given by (3.1). Suppose that* $\bar{x}\in\Omega$ *is a nondominated solution of the problem* (P_3), $\bar{y}:=f(\bar{x})$ *and the following assertions hold true*

(i) $I^>(\bar{y})\neq\emptyset$.

(ii) *There is a unique point* y^* *such that* $-y^*\in D^*\mathcal{K}(\bar{y},0)(y^*)$.

Then, there exist $y^* \in \mathbb{R}^n \setminus \{0\}$ and corresponding $z^* \in (y^* + D^*\mathcal{K}(\bar{y};0)(y^*))$ and $T_i \in L(\mathbb{R}^{m_i}, \mathbb{R})$ satisfying

$$T_i(A_i(\bar{x}) - a^i) = \|A_i(\bar{x}) - a^i\|_i \text{ and } \|T_i\|_{i^*} \leq 1 (i = 1, 2, \ldots, n) \text{ such that}$$

$$0 \in \sum_{i=1}^{n} A_i^* z^* T_i + N(\Omega, \bar{x}),$$

where $D^*\mathcal{K}(\bar{y},0)(y^*)$ is determined by (4.3).

Proof. For every $y \in \mathbb{R}^n$, $\mathcal{K}(y)$ is a closed convex cone (Proposition 3.1. (i)). Taking into account $I^>(\bar{y}) \neq \emptyset$ and Proposition 3.1.(iii), it holds that

$$\exists\, e \in \mathbb{R}^n,\ e \neq 0 :\ e \in \bigcap_{y \in \mathbb{R}^n} \mathcal{K}(y) \setminus (-\mathcal{K}(\bar{y})).$$

Applying directly Theorem 4.1. and the formulation of $D^*\mathcal{K}(\bar{y},0)(y^*)$ given in Remark 4.1.(ii), we obtain the desired conclusion. □

The following result provides a specific optimality condition for minimal solutions of (P_3) by calculating the normal cone to $\mathcal{K}(\bar{y})$ at 0.

Theorem 4.5. *Let $\mathcal{K} : \mathbb{R}^n \rightrightarrows \mathbb{R}^n$ be a set-valued map given by (3.1).*

(i) Let $\bar{x} \in \Omega$ and $\bar{y} := f(\bar{x})$. Then, the normal cone to $\mathcal{K}(\bar{y})$ at 0 is given by:

$$N(\mathcal{K}(\bar{y}), 0) = N_1 \times \ldots \times N_n,$$

where for $i = 1, 2, \ldots, n$:

$$\begin{cases} N_i := (-\infty, 0] & \text{with } i \in I^>(\bar{y}), \\ N_i := \{0\} & \text{with } i \notin I^>(\bar{y}). \end{cases}$$

(ii) Suppose that $\bar{x}$ is a minimal solution of (P_3) w.r.t. $\mathcal{K}(\cdot)$. In addition, assume that $I^>(\bar{y}) \neq \emptyset$, then there exist $y^* \in \mathcal{K}(\bar{y})^+ \setminus \{0\}$ and $T_i \in L(\mathbb{R}^{m_i}, \mathbb{R})$ satisfying

$$T_i(A_i(\bar{x}) - a^i) = \|A_i(\bar{x}) - a^i\|_i \text{ and } \|T_i\|_{i^*} \leq 1 \text{ such that}$$

$$0 \in \sum_{i=1}^{n} A_i^* y^* T_i + N(\Omega, \bar{x}).$$

Proof.
(i) By the definition of $\mathcal{K}(\cdot)$, we get that

$$\mathcal{K}(\bar{y}) = K_1 \times \ldots \times K_n,$$

where for $i = 1, 2, \ldots, n$:

$$\begin{cases} K_i := [0, +\infty) & \text{with } i \in I^>(\bar{y}), \\ K_i := \mathbb{R} & \text{with } i \notin I^>(\bar{y}). \end{cases} \tag{4.4}$$

Taking into account Proposition 2.2. and the formula of K_i in (4.4), it holds that

$$N(\mathcal{K}(\bar{y}),0) = N(K_1,0) \times N(K_2,0) \times \ldots \times N(K_n,0) = N_1 \times \ldots \times N_n,$$

where for $i = 1, 2, \ldots, n$:

$$\begin{cases} N_i := (-\infty, 0] & \text{if } K_i = [0, +\infty), \\ N_i := \{0\} & \text{if } K_i = \mathbb{R}. \end{cases} \tag{4.5}$$

Thus, from (4.4) and (4.5) it yields:

$$N(\mathcal{K}(\bar{y}),0) = N_1 \times \ldots \times N_n,$$

where for $i = 1, 2, \ldots, n$:

$$\begin{cases} N_i := (-\infty, 0] & \text{with } i \in I^>(\bar{y}), \\ N_i := \{0\} & \text{with } i \notin I^>(\bar{y}). \end{cases} \tag{4.6}$$

(ii) Suppose that $\bar{x}$ is a minimal solution of the problem (P_3) w.r.t. $\mathcal{K}(\cdot)$. Then, $\bar{x}$ is a Pareto efficient solution of (P_3) w.r.t the closed and convex cone $\mathcal{K}(\bar{y})$. In addition, since $I^>(\bar{y}) \neq \emptyset$, it holds from Proposition 3.1.(iii) that there is $e \in \mathbb{R}^n \setminus \{0\}$ such that

$$e \in \bigcap_{y \in \mathbb{R}^n} \mathcal{K}(y) \setminus (-\mathcal{K}(\bar{y})) \subseteq \mathcal{K}(\bar{y}) \setminus (-\mathcal{K}(\bar{y})).$$

Applying Corollary 4.1. for the constant cone $Q := \mathcal{K}(\bar{y})$, we have that there exist $y^* \in -N(\mathcal{K}(\bar{y}),0)) \setminus \{0\}$ and $T_i \in L(\mathbb{R}^{m_i}, \mathbb{R})$ satisfying

$$T_i(A_i(\bar{x}) - a^i) = \|A_i(\bar{x}) - a^i\|_i \text{ and } \|T_i\|_{i^*} \leq 1 (i = 1, 2, \ldots, n) \text{ such that}$$

$$0 \in \sum_{i=1}^{n} A_i^* y^* T_i + N(\Omega, \bar{x}).$$

To obtain the desired conclusion, it is sufficient to prove that $-N(\mathcal{K}(\bar{y}),0) = \mathcal{K}(\bar{y})^+$. Indeed, taking $d \in \mathcal{K}(\bar{y})$, we have that

$$d_i \geq 0, \ \forall\ i \in I^>(\bar{y}) \text{ and } d_i \in \mathbb{R}, \ \forall\ i \notin I^>(\bar{y}). \tag{4.7}$$

Let $t^* \in -N(\mathcal{K}(\bar{y}),0)$ arbitrary and taking into account (4.6), it holds for $i = 1, 2, \ldots, n$ that

$$\begin{cases} t_i^* \geq 0, & \forall\ i \in I^>(\bar{y}) \\ t_i^* = 0, & \forall\ i \notin I^>(\bar{y}). \end{cases} \tag{4.8}$$

(4.7) and (4.8) imply that for all $d \in \mathcal{K}(\bar{y})$, it holds that $t^*(d) \geq 0$.
Therefore,

$$-N(\mathcal{K}(\bar{y},0)) = \{t^* \in \mathbb{R}^n |\ t^*(d) \geq 0, \forall d \in \mathcal{K}(\bar{y})\},$$

i.e., $-N(\mathcal{K}(\bar{y}),0) = \mathcal{K}(\bar{y})^+$. This completes our proof. □

5. APPLICATION IN RADIOTHERAPY TREATMENT

Now we concern the problem (P_1) which is a mathematical model of beam intensity optimization in radiotherapy treatment. Suppose that $\theta_T := 0$ and $\theta_{C_i} \geq 0$, $i = 1, \ldots, k$ are threshold doses of k critical organs. We propose here two methods to get a desired beam intensity $\bar{x}$. As for the first one, the doctor looks for $\bar{x} \in \Omega$, $\bar{y} := f(\bar{x})$ such that there is no $y \in f(\Omega) \setminus \{\bar{y}\}$ satisfying $y \in \bar{y} - \mathcal{K}(\bar{y})$, where $\mathcal{K}(\cdot)$ is given by (3.1). This means that $\bar{x}$ is a minimal solution of (P_1) w.r.t. $\mathcal{K}(\cdot)$ in the sense that there is no $y \in f(\Omega) \setminus \{\bar{y}\}$ being 'better' than $\bar{y}$. On the other hand, if there is no $y \in f(\Omega) \setminus \{\bar{y}\}$ satisfying $\bar{y} \in y + \mathcal{K}(y)$ i.e., $\bar{y}$ is not 'worse' than any $y \neq \bar{y}$. This means that the doctor seeks for a nondominated solution of our problem. The following remark shows that if $\bar{x}$ is a desired beam intensity then $I^{>}(\bar{y}) \neq \emptyset$.

Remark 5.1. *From the practical point of view, we can see that if $\bar{x}$ is a desired beam intensity, $\bar{y} := f(\bar{x})$ then $I^{>}(\bar{y}) \neq \emptyset$. Indeed, suppose that $I^{>}(\bar{y}) = \emptyset$, i.e., $\bar{y}_1 \leq 0$ and $\bar{y}_i \leq \theta_{C_i}$, $\forall\, i = 1, 2, \ldots, k$. Since $\bar{y}_1 = \|A_T\bar{x} - TG\| \geq 0$, it yields $\bar{y}_1 = 0$. This condition means that the dose $A_T\bar{x}$ delivered to the tumor is equal to TG. Because of this large dose, some other critical organs will suffer from some effects. From this circumstance, there exists $i \in \{1, 2, \ldots, k\}$ such that $\bar{y}_i > \theta_{C_i}$. Thus, we arrive at a contradiction to $I^{>}(\bar{y}) = \emptyset$.*

To this end, we present the following a corollary about the conditions for the beam intensity which we search when dealing with the inverse problem in IMRT. It is concerned as a direct consequence of Theorem 4.5. (ii). Since the proof is mostly similar to that of Theorem 4.5.(ii) with the only exception being the condition $I^{>}(\bar{y}) \neq \emptyset$ is relaxed, the proof is omitted. For the sake of the shortness, we only present in this paper an optimality condition for a desired beam intensity which is considered as a minimal solution of problem (P_1). The case of nondominated solutions of problem (P_1) can be derived similarly by using Theorem 4.4..

Corollary 5.1. *Let $\theta = (0, \theta_{C_1}, \ldots, \theta_{C_k}) \in \mathbb{R}^{k+1}$ is given and suppose that $\bar{x} \in \Omega$ is a minimal solution of the problem (P_1) w.r.t. the ordering cone $\mathcal{K}(\cdot)$ determined by (3.1). Let $\bar{y} := f(\bar{x})$, then there exist $y^* \in \mathcal{K}(\bar{y})^+ \setminus \{0\}$ and $T_1 \in L(\mathbb{R}^{l_T}, \mathbb{R})$, $T_i \in L(\mathbb{R}^{l_{C_{i-1}}}, \mathbb{R})$, $i = 2, \ldots, k+1$ satisfying*

$$T_1(A_T\bar{x} - TG) = \|A_T\bar{x} - TG\|_\infty, T_i(A_{C_{i-1}}\bar{x}) = \|A_{C_{i-1}}\bar{x}\|_\infty, i = 2, \ldots, k+1$$

and

$$\|T_j\|_\infty \leq 1 \text{ for all } j = 1, \ldots, k+1$$

such that

$$0 \in \sum_{j=1}^{k+1} A_j^* y^* T_j + N(\Omega, \bar{x}).$$

6. CONCLUSION

This paper investigated a mathematical model of beam intensity optimization in radiotherapy treatment and introduced an appropriate variable order depending on the value of the objective function which relates to the doses delivered to the tumor organ as well as the critical organs. A vector approximation problem is also considered as a generation for the formulation for the inverse beam intensity optimization problem. We derived the optimal conditions for solutions of the vector approximation problem w.r.t. a general cone-valued mapping as well as the proposed variable order. The beam intensity we look for in IMRT is concerned as a minimal solution (or a nondominated solution) of this problem equipped with our ordering structure. In this work, we also calculated and obtained a specific formulation of optimality conditions for these solutions. Our future research is deriving numerical methods and applying these presented results in practical problems.

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