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1 Projections onto the Pareto surface in multicriteria
2 radiation therapy optimization

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4 August 2015

5 **Abstract**

6 **Purpose:** To eliminate or reduce the error to Pareto optimality that arises in
7 Pareto surface navigation when the Pareto surface is approximated by a small
8 number of plans.

9 **Methods:** We propose to project the navigated plan onto the Pareto surface
10 as a post-processing step to the navigation. The projection attempts to find
11 a Pareto optimal plan that is at least as good as or better than the initial
12 navigated plan with respect to all objective functions. An augmented form
13 of projection is also suggested where dose-volume histogram constraints are
14 used to prevent that the projection causes a violation of some clinical goal.
15 The projections were evaluated with respect to planning for intensity modu-
16 lated radiation therapy delivered by step-and-shoot and sliding window, and
17 spot-scanned intensity modulated proton therapy. Retrospective plans were
18 generated for a prostate and a head and neck case.

19 **Results:** The projections led to improved dose conformity and better sparing
20 of organs at risk (OARs) for all three delivery techniques and both patient cases.
21 The mean dose to OARs decreased by 3.1 Gy on average for the unconstrained
22 form of the projection and by 2.0 Gy on average when dose-volume histogram
23 constraints were used. No consistent improvements in target homogeneity were
24 observed.

25 **Conclusions:** There are situations when Pareto navigation leaves room for
26 improvement in OAR sparing and dose conformity, for example if the approx-
27 imation of the Pareto surface is coarse or the problem formulation has too
28 permissive constraints. A projection onto the Pareto surface can identify an
29 inaccurate Pareto surface representation and, if necessary, improve the quality
30 of the navigated plan.

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1 Introduction

Radiation therapy treatment planning is generally guided towards fulfilment of a set of physician-defined plan evaluation criteria. These criteria are sometimes incompatible, and the treatment planner is therefore asked to find a suitable tradeoff between the conflicting ones. The main tool that planners then have at their disposal are weights associated with the objective functions that drive the treatment plan optimization. These weights often need extensive tuning before the optimized plan meets approval [14,32], which can be time-consuming. Inefficient plan preparation is undesirable because it can cause a time lag between diagnosis and the first treatment fraction and poses a risk that plan quality is compromised in the interest of time.

Pareto surface navigation is an alternative planning technique that has recently entered clinical use, see, e.g., Craft [9] and references therein. This technique avoids a priori prioritization of the objectives. A representation of all the possible tradeoffs between the objectives is instead calculated, which the planner or physician can explore through linear interpolation of the precalculated plans' doses. Studies indicate that this form of navigation generally permits an acceptable plan to be identified within a time frame of tens of minutes or less [12,30]. The mathematical basis for Pareto surface navigation is multicriteria optimization, meaning optimization with multiple objectives where any feasible solution such that no objective can be improved without deteriorating at least one of the others is considered optimal (Pareto optimal), see, e.g., Miettinen [21].

The benefits of navigation are at the cost of that interpolation between precalculated plans introduces an error to Pareto optimality. Algorithms exist that can bound the magnitude of this error [4,5,27], but the number of plans that are required to maintain a given error bound increases exponentially with the number of objectives in the worst case (because hypervolume grows exponentially with increasing dimension). To some relief, studies report that the relation between the required number of plans and the number of objectives is more benign for radiation therapy optimization [8,10]. Nevertheless, Craft and Bortfeld [10] and Bokrantz [4] both observed approximation errors above 10% for representations with less than about 20 plans, and that up to about 75 plans are needed to reduce the error below 5%. These studies considered between five to ten objectives.

In view of these concerns, we present a technique that eliminates or reduces the error to Pareto optimality through the minimization of a projective distance between the navigated plan and the Pareto surface. We use a formulation of this projection as in Nakayama [23], which attempts to find a plan that is at least as good as or better than the navigated plan with respect to all objectives. We also suggest an augmented formulation where constraints are imposed on maintained dose-volume histogram (DVH) quality. We quantify the dosimetric benefit of the suggested technique by application to planning for step-and-shoot intensity-modulated radiation therapy (ss-IMRT), sliding window intensity-modulated radiation therapy (sw-IMRT), and spot-scanned intensity-modulated proton therapy (IMPT).

73 2 Methods

74 2.1 Pareto surface-based planning

75 We formulate treatment planning for radiation therapy as a multicriteria optimiza-
 76 tion problem with n objective functions f_1, \dots, f_n that are to be minimized with
 77 respect to the vector of variables x . The minimization occurs over a feasible set \mathcal{X}
 78 that represents the physical limitations of the delivery method and, possibly, con-
 79 straints on the planned dose, according to

$$\begin{aligned} & \underset{x}{\text{minimize}} && f(x) = [f_1(x) \cdots f_n(x)]^T \\ & \text{subject to} && x \in \mathcal{X}. \end{aligned} \tag{1}$$

80 We understand optimality to this formulation in a Pareto sense, meaning that a
 81 feasible x^* is Pareto optimal if there is no feasible x such that $f_i(x) \leq f_i(x^*)$ for
 82 $i = 1, \dots, n$, with a strict inequality for at least one index i . A feasible x^* is
 83 called weakly Pareto optimal if there is no feasible x such that $f_i(x) < f_i(x^*)$ for
 84 $i = 1, \dots, n$.

85 Formulation (1) has an infinite number of Pareto optimal solutions in general. To
 86 solve this problem from a practical perspective therefore entails to select the single,
 87 best preferred, Pareto optimal solution. We perform this selection by Pareto surface
 88 navigation, meaning that a representative set of Pareto optimal solutions x_1, \dots, x_m
 89 is first calculated and a convex combination $\bar{x} = \sum_{j=1}^m \lambda_j x_j$ of these solutions then
 90 selected, where the components of λ need to be nonnegative and sum to unity.
 91 The selection is guided by a navigation interface that permits the priorities of each
 92 objective to be continuously adjusted using associated slider bar controls. The sliders
 93 are coupled to an algorithm that updates λ accordingly, see, e.g., Craft et al. [11] and
 94 Monz et al. [22]. For the navigation to be valid, we assume that \mathcal{X} is a nonempty
 95 and convex set and that all functions f_1, \dots, f_n are convex and bounded on \mathcal{X} .

96 2.2 Projection onto the Pareto surface

97 The navigated plan \bar{x} is feasible thanks to the assumed convexity of formulation (1).
 98 It also has objective values that are bounded by Jensen's inequality for convex func-
 99 tions, i.e., $f_i(\sum_{j=1}^m \lambda_j x_j) \leq \sum_{j=1}^m \lambda_j f_i(x_j)$ for $i = 1, \dots, n$, as illustrated in Figure 1
 100 for the case $m = n = 2$. The figure also shows that the image of the Pareto opti-
 101 mal solutions in the objective space forms a connected surface in the boundary of a
 102 convex set [28, Proposition 2.3], but the surface is not convex itself, because convex
 103 surfaces are generally not convex sets. The navigated point $f(\bar{x})$ is therefore merely
 104 known to lie between the Pareto surface and the set of objective vectors that can be
 105 formed as convex combinations of the known points $f(x_1), \dots, f(x_m)$.

106 To mitigate that the navigated plan \bar{x} in general is not Pareto optimal, we pro-
 107 pose to convert this plan into a Pareto optimal plan with at least as good or better
 108 performance in all objectives. Specifically, we propose to solve the following opti-

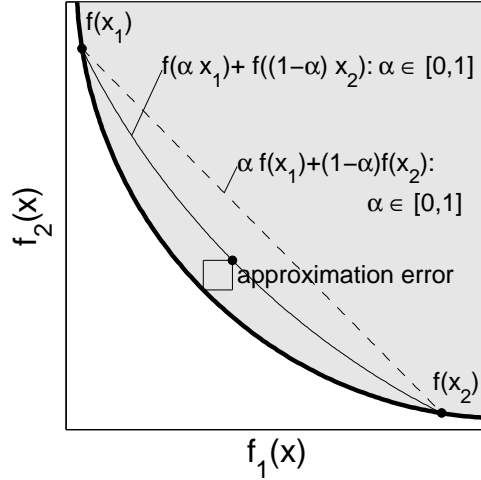


Figure 1: Continuous navigation between two Pareto optimal solutions x_1 and x_2 . The shaded area indicates the feasible objective space $f(\mathcal{X})$, the thick solid line indicates the set of Pareto optimal solutions, the thin solid line indicates the set of convex combinations of x_1 and x_2 , and the dashed line indicates the upper bound on the navigated objective values from Jensen's inequality. The componentwise error between a navigated plan and the Pareto surface is indicated by a square.

109 mization problem as a post-processing step to the navigation:

$$\begin{aligned} & \underset{x}{\text{minimize}} && \max_{i=1,\dots,n} \left\{ \frac{f_i(x) - f_i(\bar{x})}{f_i(\bar{x}) - z_i^*} \right\} \\ & \text{subject to} && x \in \mathcal{X}, \end{aligned} \quad (2)$$

110 where z^* is the ideal point, i.e., $z_i^* = \min_{j=1,\dots,m} f_i(x_j)$ for $i = 1, \dots, n$. This formu-
 111 lation is a variant of an achievement function suggested by Wierzbicki [31], which
 112 projects the navigated point $f(\bar{x})$ along a ray towards the ideal objective function
 113 vector z^* , see Figure 2. The particular achievement function that is used in (2) has
 114 been used previously by Nakayama [23]. Buchanan and Gardiner [7] observed that
 115 decision makers tend to prefer this form of minimization of the distance to the ideal
 116 point over maximization of the distance from the worst feasible point if the reference
 117 point is attainable, as is the case for $f(\bar{x})$.

118 The navigated plan \bar{x} is a feasible solution to (2) with an objective value of
 119 zero. An optimal solution x^* to (2) therefore satisfies $f_i(x^*) \leq f_i(\bar{x})$ for $i = 1, \dots, n$,
 120 meaning that x^* is at least as good as or better than the navigated plan with respect
 121 to all objectives. Further, x^* is weakly Pareto optimal because the achievement
 122 function in (2) is strictly increasing [21, Theorem 3.5.4]. If solutions that are weakly
 123 Pareto optimal but not Pareto optimal are to be avoided, it is possible to augment the
 124 objective function of (2) with the term $\rho \sum_{i=1}^n f_i(x) / (f_i(\bar{x}) - z_i^*)$ for some sufficiently
 125 small positive scalar ρ , as discussed in Miettinen [21, Section 5.8]. Addition of
 126 this term makes the objective function strongly increasing, which ensures Pareto
 127 optimality [21, Theorem 3.5.4]. With regard to numerical stability, observe that

128 the denominator in (2) can approach zero if the navigated point $f(\bar{x})$ becomes very
 129 close to the ideal point z^* in some component. The ideal point should therefore for
 130 numerical purposes be replaced with an utopian objective vector that is better by
 131 some small but numerically significant positive value [21, Definition 2.4.2].

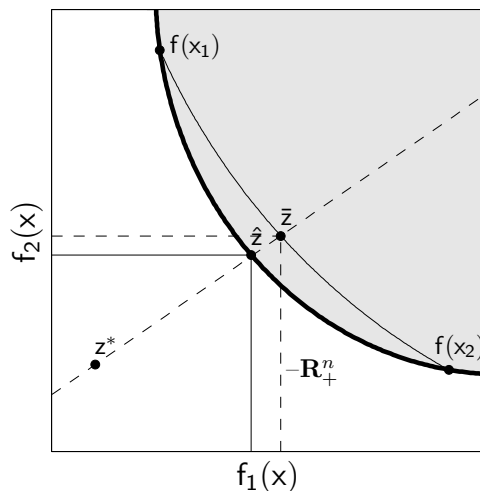


Figure 2: Projection of a navigated plan onto the Pareto surface. The point $\bar{z} = f(\bar{x})$ is shifted towards z^* along the dashed line until it intersects with the boundary of the feasible objective space. The projected point \hat{z} is nondominated, as illustrated by that no other point is contained in the cone $-\mathbb{R}_+^n$ that emanates from this point.

132 2.3 Dose-volume histogram constraints

133 A commonly used formulation for radiation therapy optimization is penalization of
 134 the deviation from the desired dose to each anatomical structure, see, e.g., Oelfke
 135 and Bortfeld [26]. Objective functions of this type cannot capture all aspects of
 136 plan quality, for instance, they do not take the three-dimensional shape of the dose
 137 into account nor the biological effect of the irradiation. It is therefore possible for
 138 a clinician to judge a plan obtained from formulation (1) as worse than the initial
 139 navigated plan even though it is better as measured by all objectives f_1, \dots, f_n . To
 140 mitigate any deterioration in plan quality not captured by the objectives, we consider
 141 an augmented version of formulation (2) that prevents deterioration with respect to
 142 clinical goals. We restrict ourselves to consider clinical goals that are related to the
 143 DVH distribution of the navigated plan. Consequently, we introduce constraints
 144 that require each DVH curve of the projected plan to lie between the corresponding
 145 DVH curve for the navigated plan and a vertical line that intersects the dose axis at
 146 the prescription level for targets and at zero for organs at risk (OARs), see Figure 3.
 147 These requirements ensure that a DVH criterion that is satisfied by the navigated
 148 plan cannot become violated after the projection.

149 The DVH requirements are implemented using functions that impose a one-sided
 150 penalty on the error between the DVH curves associated with the current dose d

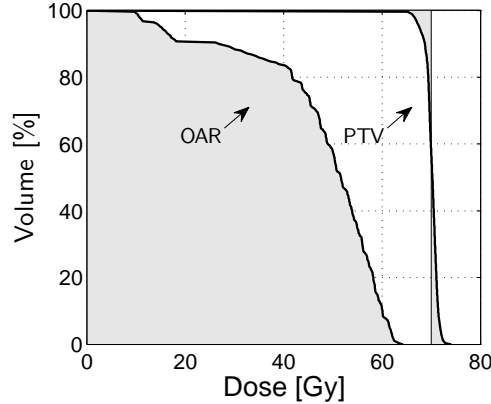


Figure 3: Feasible DVH region (shaded areas) for projection onto the Pareto surface under DVH constraints. The thick solid lines indicates the DVH of the navigated plan.

151 and the navigated dose \bar{d} . The one-sidedness prevents penalization of when d has
 152 better normal tissue sparing or target coverage than \bar{d} . To define the DVH functions
 153 mathematically, let $D(\cdot; d)$ be the function that parametrizes the DVH curve for
 154 some subvolume \mathcal{V} along the cumulative volume axis, i.e.,

$$D(v; d) = \max \left\{ d' \in \mathbb{R} : \frac{|q \in \mathcal{V} : d(q) \geq d'|}{|\mathcal{V}|} \geq v \right\},$$

where v denotes cumulative volume in percent, $d(q)$ is the dose to some point $q \in \mathcal{V}$, and $|\mathcal{V}|$ is the volume of \mathcal{V} . In other words, $D(v; d)$ is the DVH point associated with the some dose d and cumulative volume v . Let also \hat{d} denote the prescription level for targets and zero for OARs, \hat{v} denote the cumulative volume such that $\hat{d} = D(\hat{v}, \bar{d})$, and $(\cdot)_+$ denote the positive part operator $\max\{\cdot, 0\}$. Then, a min reference DVH constraint takes the form

$$\int_{\hat{v}}^1 (D(v; \bar{d}) - D(v; d))_+ dv \leq 0,$$

while a max reference DVH constraint takes the form

$$\int_0^{\hat{v}} (D(v; d) - D(v; \bar{d}))_+ dv \leq 0.$$

155 The requirements in Figure 3 are implemented by assignment of a max reference
 156 DVH constraint to each OAR, and assignment of a min reference DVH and max
 157 reference DVH constraint to each target. Similar reference DVH functions have
 158 been used previously in Bokrantz [3] and Fredriksson [13].

159 The use of DVH constraints leads to a nonconvex optimization formulation. An
 160 optimization solver can therefore not guarantee more than convergence to a locally
 161 optimal point. Some studies have, however, shown that the nonconvexity of DVH

162 functions does not lead to severe local optimality effects in practice [18, 20, 33], pos-
 163 sibly because the nonconvexities disappear or become negligible due to the physical
 164 properties of radiation delivery [9]. Regardless of convergence, the introduction of
 165 additional constraints implies that the projected solution in general lies in the interior
 166 of the feasible objective space and not on the Pareto surface itself.

167 2.4 Computational study

168 The projections were evaluated with respect to three delivery techniques: ss-IMRT,
 169 sw-IMRT, and IMPT; and two tumor sites: prostate and head and neck. We first
 170 outline our numerical implementation, then describe the studied patient cases and
 171 delivery techniques, and finally summarize our set of evaluation criteria.

172 2.4.1 Numerical optimization

173 The projections were implemented as an add-on to the multicriteria optimization
 174 module in RayStation v2.4 (RaySearch Laboratories, Stockholm, Sweden) [1]. This
 175 treatment planning system’s optimization solver (a quasi-Newton sequential quadratic
 176 programming method) requires a continuously differentiable objective and constraints.
 177 The nondifferentiability of the maximum in (2) was handled by the addition of $1 + \epsilon$,
 178 with ϵ being a positive infinitesimal value, to the arguments of the maximization
 179 (so that they become positive, see also Nakayama [24, Remark 3.1]), followed by a
 180 substitution a smooth power mean function for the maximum operator according to

$$\max_{i=1,\dots,n} \{x_i\} \approx \left(\frac{1}{n} \sum_{i=1}^n x_i^p \right)^{1/p}. \quad (3)$$

181 This approximation approaches the exact maximum of some positive x_1, \dots, x_n as
 182 $p \rightarrow \infty$. A parameter value of $p = 10$ was used for all numerical experiments in
 183 this paper, guided by the close relationship between (3) and an equivalent uniform
 184 dose (EUD) functions (the EUD is the power mean of the dose, with the power p
 185 determined by the EUD parameter a , cf. Niemerko [25]). An EUD function with
 186 an EUD parameter of about 10 is common for serial organs such as the spinal cord
 187 where the risk for complication highly depends on the maximum dose value, see,
 188 e.g., Thieke et al. [29].

The approximation (3) means that the results in Section 2.2 do not hold rig-
 orously for our numerical implementation. In particular, it is possible that the
 projection can lead to a mild degradation in objective function value compared to
 the navigated point for some objectives. Nevertheless, formulation (3) amounts to
 minimization of a strongly increasing achievement function, and it therefore finds
 Pareto optimal points [21, Theorem 3.5.4]. If it is critical to maintain objective
 function values exactly, then an everywhere differentiable epigraph reformulation

of (2) according to

$$\begin{aligned} & \underset{x,t}{\text{minimize}} && t \\ & \text{subject to} && \frac{f_i(x) - f_i(\bar{x})}{f_i(\bar{x}) - z_i^*} \leq t, \quad i = 1, \dots, n, \\ & && x \in \mathcal{X}, \end{aligned}$$

189 could be preferable to (3). The auxiliary nonlinear constraints of this formulation,
190 however, makes it more computationally expensive to solve than formulation (2)
191 combined with the approximation (3).

192 2.5 Patient data and machine model

193 Retrospective planning was performed with respect to the following two patient
194 cases:

- 195 • A prostate cancer patient with a prescribed dose of 59.2 Gy to the prostate
196 and seminal vesicles, with a simultaneous boost of 74 Gy to the prostate. Con-
197 sidered critical structures were the bladder and rectum.
- 198 • A head and neck cancer patient with a prescribed dose of 66 Gy, 60 Gy, and
199 50 Gy to the primary target, high risk nodal regions, and low risk nodal regions,
200 respectively. Considered critical structures were the brainstem, parotid glands,
201 and spinal cord.

202 Treatment planning for IMRT was performed with respect to a Varian 2100
203 linear accelerator (Varian Medical Systems, Palo Alto, California), with ten static
204 segments per field for ss-IMRT and 320 dynamic control points per field for sw-IMRT.
205 A coplanar five-field setup was used for the prostate case and a coplanar seven-field
206 setup used for the head and neck case. Planning for IMPT was for the prostate case
207 performed with respect to two coplanar and parallel-opposed fields and for the head
208 and neck case performed with respect to two coplanar fields with a perpendicular
209 setup. A dose grid resolution of $3 \times 3 \times 3 \text{ mm}^3$ was used for all calculations. The
210 optimizations were performed with respect to least-squares penalties on the deviation
211 in voxel dose or EUD from a scalar-valued reference level, see Appendix A for a
212 complete list functions and Bokrantz [3, Appendix C] for mathematical definitions.

213 2.6 Treatment plan generation

214 A total of $2n$ Pareto optimal plans was generated per delivery technique and pa-
215 tient case. RayStation uses the algorithm in Bokrantz and Forsgren [3] for this
216 calculation. A single plan was then selected by Pareto surface navigation, and the
217 projection finally applied with or without DVH constraints. Deliverable plans were
218 for comparative purposes generated without performing any projection. Minor dif-
219 ferences between the studied delivery techniques are elaborated in the following three
220 subsections.

2.6.1 Step-and-shoot IMRT

The plans in the Pareto surface representation were generated by fluence map optimization with respect to dose calculated using a singular value decomposition (SVD) of pencil beam kernels, similar to Bortfeld et al. [6]. The navigated plan was made deliverable by an optimization where the error in DVH due to the conversion was minimized, see Bokrantz [3]. This minimization was performed with leaf positions and segment weights as variables, see Hårdemark et al. [15], with the SVD dose augmented with intermediate and final dose calculations performed using a collapsed cone (CC) algorithm, see, e.g., Ahnesjö [2]. The projection was performed using the same set of variables and dose calculation algorithms.

2.6.2 Sliding window IMRT

The calculation of the Pareto surface representation and the projection were both performed with fluence as variables. The projected plan was converted to control points by sliding window conversion, see, e.g., Kamath [19]. All dose distributions were calculated by SVD.

2.6.3 IMPT

The calculation of the Pareto surface representation and the projection were both performed with spot weights as variables. All dose distributions were calculated using a pencil beam algorithm.

2.7 Evaluation criteria

Plan quality was assessed with respect to a selection of dose-volume statistics. The dose to OARs was assessed in terms of dose-to-volume levels V_x (the fractional volume of a structure that receives a dose greater than or equal to x Gy), volume-to-dose levels D_x (the minimum dose such that the associated isodose volume contains x % of the volume of a structure), and mean dose levels \bar{D} . The planned dose to target structures was assessed in terms of a homogeneity index (HI) [17] according to

$$\text{HI} = (D_2 - D_{98}) / D_{50},$$

and a conformity index (CI) [16] according to

$$\text{CI} = V_{95\%}^{\text{External}} / V^{\text{PTV}},$$

where $V_{95\%}$ is the volume contained within the isodose volume defined at 95 % of the prescription level and V^{PTV} the total volume of all targets with prescription level greater than or equal to the prescription level of the structure to which the index refers.

3 Results

Our numerical results are summarized by the DVHs in Figure 4 and the dose statistics in Tables 1 and 2. Results are shown for plans subject to no projection, subject to a projection without DVH constraints, and subject to a projection under DVH constraints. Planning target volumes (PTVs) are designated by their prescription level in subscript.

Table 1: Dose statistics for the prostate case. Values where the projection resulted in a relative improvement of 5% are indicated in bold.

Plan		PTV ₇₄		PTV _{59.2}		Bladder		Rectum	
		HI	CI	HI	CI	D ₁₀	D	D ₁₀	D
		[%]	[%]	[%]	[%]	[Gy]	[Gy]	[Gy]	[Gy]
ss-IMRT	No projection	8.2	117.6	27.9	111.1	55.6	26.6	56.1	31.9
	Projected	8.9	115.7	27.6	107.7	54.6	24.4	54.1	26.4
	DVH proj.	8.4	116.1	27.7	108.1	55.3	25.4	54.4	28.2
sw-IMRT	No projection	7.9	117.0	27.3	108.7	54.1	24.9	56.2	33.5
	Projected	9.2	117.0	27.3	109.0	54.7	23.6	54.7	25.5
	DVH proj.	7.8	116.3	27.1	108.0	54.1	24.2	55.7	28.6
IMPT	No projection	7.5	115.3	26.4	111.6	54.5	13.4	55.3	16.5
	Projected	8.6	114.1	27.0	103.8	53.7	12.3	55.9	14.8
	DVH proj.	7.7	115.1	26.8	104.8	54.1	13.0	55.2	14.2

Table 2: Dose statistics for the head and neck case. Values where the projection resulted in a relative improvement of 5% or more are indicated in bold.

Plan		PTV ₆₆		PTV ₆₀		PTV ₅₀		L Parotid		R Parotid	
		HI	CI	HI	CI	HI	CI	V ₃₀	D	V ₃₀	D
		[%]	[%]	[%]	[%]	[%]	[%]	[%]	[Gy]	[%]	[Gy]
ss-IMRT	No projection	6.8	132.4	12.0	160.1	18.6	152.7	52.1	34.2	29.1	22.4
	Projected	6.6	127.4	11.3	147.8	18.8	138.2	49.4	30.7	30.0	21.9
	DVH proj.	6.3	127.2	11.6	151.7	18.5	144.0	51.1	32.2	28.7	21.9
sw-IMRT	No projection	6.4	124.3	10.4	145.0	19.3	136.5	52.2	35.6	28.6	22.5
	Projected	6.8	124.1	10.1	141.9	18.8	134.4	46.9	30.1	29.6	21.9
	DVH proj.	6.9	123.5	10.0	141.8	19.1	133.5	47.4	30.3	28.0	21.5
IMPT	No projection	9.2	132.4	12.7	132.3	16.8	127.8	45.7	26.8	21.3	18.3
	Projected	8.4	126.8	11.2	127.5	16.9	117.5	38.2	22.5	20.0	15.2
	DVH proj.	8.4	129.9	12.3	128.5	16.8	120.8	44.1	25.6	20.8	17.9

The projection of a navigated plan onto the Pareto surface led to improved OAR sparing and better dose conformity for all three delivery techniques and both patient cases. The improved OAR sparing was most pronounced in the low and moderate dose regions whereas the high dose regions generally did not improve much, see, e.g., D₁₀ for the bladder and rectum of the prostate case in Table 1. The largest improvements in dose conformity occurred for low-dose targets, see, e.g., PTV_{59.2} of the IMPT plan for the prostate case and PTV₅₀ and PTV₆₀ of the ss-IMRT and IMPT plan for the head and neck case. The improvements in target homogeneity were very minor, except for PTV₆₆ of the IMPT plan of the head and neck case.

A projection without DVH constraints only in rare instances led to a deterioration in some dose statistics. Such occurrences are the reduced homogeneity for PTV₇₄ of the ss-IMRT and sw-IMRT plan for the prostate case, the increase of D₁₀ for the

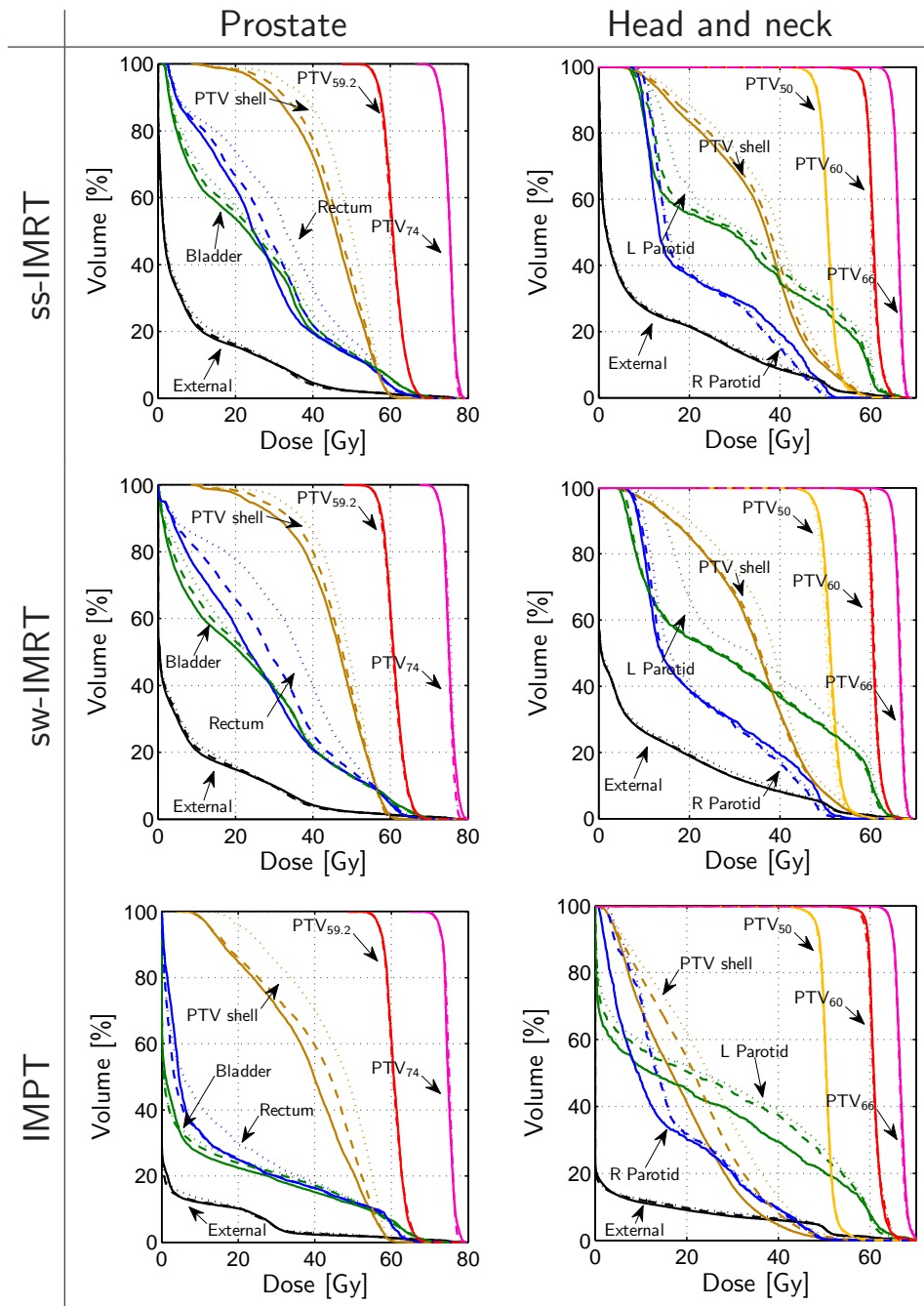


Figure 4: DVH results for projections onto Pareto surface. Plans projected without DVH constraints are indicated by solid lines, plans projected with DVH constraints indicated by dashed lines, and plans generated without performing the projection indicated by dotted lines.

263 rectum of the IMPT plan for the prostate case, and the decrease in homogeneity for
 264 PTV₆₆ of the sw-IMRT plan for the head and neck case. These deteriorations did
 265 not occur when DVH constraints were used; however, the improvements were then
 266 smaller overall.

267 Table 3 further quantifies the main observed effect of the projections, namely
 268 that the OAR sparing was improved but at a mild dose increase in the high dose
 269 regions of OARs unless DVH constraints were used. The improved sparing of OARs
 270 is in the tabulated data quantified by two-sided DVH curve differences while vio-
 271 lations of the navigated DVH are quantified by one-sided DVH curve differences.
 272 Clearly, a projection onto the Pareto surface poses a tradeoff between the degree
 273 of plan improvement and the acceptable violation of the navigated DVH. The aver-
 274 age decrease in dose to OARs and the average violation of the navigated DVH was
 275 3.13 Gy and 0.18 Gy, respectively. These figures should be contrasted to an average
 276 dose decrease for OARs at 1.98 Gy and a vanishing small violation of the navigated
 277 DVH for projection with DVH constraints.

Table 3: Mean two-sided and one-sided differences along the dose axis between DVH curves of projected plans and corresponding plans generated without performing any projection.

Patient		Prostate				Head and neck			
Plan		Bladder		Rectum		L Parotid		R Parotid	
		2-sided	1-sided	2-sided	1-sided	2-sided	1-sided	2-sided	1-sided
		[Gy]	[Gy]	[Gy]	[Gy]	[Gy]	[Gy]	[Gy]	[Gy]
ss-IMRT	Projected	-2.22	0.00	-5.52	0.00	-3.56	0.00	-0.56	0.65
	DVH proj.	-1.20	0.00	-3.70	0.00	-2.01	0.00	-0.48	0.00
sw-IMRT	Projected	-1.39	0.07	-8.04	0.00	-5.54	0.00	-0.55	0.45
	DVH proj.	-0.78	0.01	-4.93	0.00	-5.32	0.00	-0.95	0.00
IMPT	Projected	-1.03	0.16	-1.75	0.25	-4.26	0.05	-3.13	0.03
	DVH proj.	-0.42	0.00	-2.28	0.00	-1.21	0.00	-0.44	0.00

$$2\text{-sided} = \int_0^1 (D(v, d) - D(v, \bar{d})) dv, \quad 1\text{-sided} = \int_0^1 (D(v, d) - D(v, \bar{d}))_+ dv.$$

278 4 Discussion

279 Our results show that there exist situations when a projection onto the Pareto surface
 280 can improve OAR sparing and dose conformity of the navigated plan. This conclusion
 281 holds true both in the unconstrained case and if DVH constraints are used to preserve
 282 clinical goals. The DVH constraints were found effective for prevention of a dose
 283 increase in the high-dose region of OARs, but dampened the magnitude of the overall
 284 improvements. We therefore only recommend such constraints for structures where
 285 it is critical to maintain the navigated DVH exactly, e.g., if the dose to the structure
 286 only barely meets the clinical acceptance criteria. Another option is to first perform
 287 an unconstrained projection and then perform a second optimization that includes
 288 DVH constraints if necessary.

289 The observed dose improvement due to the projections was of the order of several
 290 Grays. This magnitude is, however, a function of the approximation error to Pareto
 291 optimality for the navigate plan, which depends on the number of objectives, the

292 number of plans used to represent the Pareto surface, and how large dose variations
 293 that the set of constraints permit. Our study only covers a narrow spectrum of the
 294 possible values for these parameters: 8–10 objectives, 16–20 plans in the representa-
 295 tions, and a single set of constraints per patient case. The results should therefore
 296 not be extrapolated to conclude that Pareto surface navigation yields plans that are
 297 sub-optimal in terms of OAR sparing in general. Rather, we envisage that the pro-
 298 jections can be used as a learning tool (for example in the training of practitioners),
 299 which can identify situations when Pareto surface representations are inaccurate.

300 Finally, note that the projections are unnecessary if it is possible to calculate such
 301 dense Pareto surface representations that the navigated plan is nearly error-free. If
 302 this is the case, however, then it is likely that the plan optimization times are so
 303 short that they are perceived as occurring in real time. The advance of real-time
 304 optimization would permit Pareto surface navigation where the navigated plan is
 305 generated on-the-fly instead of being interpolated from a set precalculated plans.

306 5 Conclusions

307 We have presented a method that eliminates or reduces the error to Pareto optimality
 308 that arises during Pareto surface navigation. The error is removed through mini-
 309 mization of a projective distance to the ideal point in the objective function space.
 310 An augmented form of the projection was also suggested where the DVH distribu-
 311 tion of the projected solution is required to be at least as good as that of the initial
 312 navigated plan. Empirical results with respect to two clinical cases and three de-
 313 livery techniques show that the projections can lead to improved OAR sparing and
 314 better dose conformity at maintained, or slightly improved, target coverage. The
 315 main mechanism behind the improvements observed in this study was a reduction
 316 of the low to moderate dose to healthy structures.

317 A Optimization problem formulations

318 The optimization formulations that were used in the numerical experiments are sum-
 319 marized in Tables 4 and 5.

Table 4: Optimization formulation for the prostate case. The reference dose level of a function is denoted \hat{d} . The constraints used during proton and photon therapy planning are indicated by “Pr” and “Ph” in subscript, respectively.

Objectives			Constraints			
Structure	Function	\hat{d} [Gy]	Structure	Function	\hat{d}_{Ph} [Gy]	\hat{d}_{Pr} [Gy]
PTV ₇₄	Min dose	74.00	PTV ₇₄	Min dose	66.60	68.00
	Uniform dose	74.00		Min 95 % DVH	71.78	72.52
PTV _{59.2}	Min dose	59.20	PTV _{59.2}	Max dose	81.04	79.92
PTV _{59.2} - PTV ₇₄	Uniform dose	59.20		Min dose	53.28	53.28
Bladder	Max EUD $a = 2$	0.00	PTV _{59.2} - PTV ₇₄	Min 95 % DVH	56.24	56.24
Rectum	Max EUD $a = 2$	0.00		Max 5 % DVH	66.50	65.71
PTV shell [5, 15] mm	Max EUD $a = 2$	0.00	External	Max dose	81.04	79.92
External	Dose fall-off 2 cm	74.00				

Table 5: Optimization formulation for the head and neck case. The reference dose level of a function is denoted \hat{d} . The constraints used during proton and photon therapy planning are indicated by “Pr” and “Ph” in subscript, respectively.

Objectives			Constraints			
Structure	Function	\hat{d} [Gy]	Structure	Function	\hat{d}_{Ph} [Gy]	\hat{d}_{Pr} [Gy]
PTV ₆₆	Min dose	66.00	PTV ₆₆	Min dose	59.40	60.72
	Uniform dose	66.00		Min 95 % DVH	62.70	63.36
PTV ₆₀	Min dose	60.00	PTV ₆₀	Max dose	72.60	72.60
	Uniform dose	60.00		Min dose	54.00	55.20
PTV ₅₀	Min dose	50.00	PTV ₅₀	Min 95 % DVH	57.00	57.60
	Uniform dose	50.00		Max 5 % DVH	66.00	66.00
L Parotid	Max EUD $a = 1$	0.00	PTV ₅₀	Min dose	45.00	45.00
R Parotid	Max EUD $a = 1$	0.00		Min 95 % DVH	47.50	47.50
PTV shell [5, 15] mm	Max EUD $a = 2$	0.00	Brainstem	Max 5 % DVH	57.50	55.00
External	Dose fall-off 2 cm	66.00		Max dose	52.00	52.00
				Spinal cord	Max dose	48.00
			External	Max dose	72.60	72.60

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