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Multicriteria optinisatio in radiation therapy Juan Pardo Montero

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What is radiotherapy?

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- Treatment of cancer disease (mainly) with radiation.
- Radiation can kill cells mainly by damaging their DNA.
- Widely used with curative or palliative effects.



delivering a curative (palliative) radiation dose to the target, while sparing as much as possible nearby organs-at-risk (OARs) to preserve their function





Targets and OARs PTV CTV 24X OAR

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Typically, several OARs and PTVs.

<u>e.g.</u>

prostate cancer (bladder, rectum, femoral heads)

head-and-neck cancer (brainstem, eyes, cord, parotid + several targets)

Gross Tumour Volume + margins

Margin: microscopic disease + movement (prevent underdosage)







External radiotherapy: treatment with external beams, mainly photons/electrons, but also protons/light ions.

Typically beams coming from a few directions.

Also beams rotating 360⁰ around the patient.





-Fixed beams or -360⁰ rotation





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-developed at UW-Madison-rotating beam-51 irradiation directionsplanned





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-CNAO

-Synchrotron-based facility



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Conformal therapy



"Forward" planning:

- -Arrival directions
- -Weight of each beam
- -Constant fluence/simple shapes



Intensity Modulated Radiation Therapy (IMRT)



- Technological and methodological development in 90s.
- Multileaf collimators
- Inverse planning techniques







2D fluence map

beamlets/bixels: variables of our problem







MLC:

- leaf width ~mm
- leaf precision submillimetric





Optimisation in radiotherapy:

Three different problems:

- "1. The selection of the number of beams and the directions from which to focus radiation on the patient (*geometry problem or beam angle* optimization problem).
- The selection of intensity patterns or fluence maps for directions selected in Phase 1 (*intensity problem or fluence map optimization* problem).
- 3. The selection of a delivery sequence that efficiently administers the treatment (*realization problem or segmentation problem*)."

From Ehrgott et al, "Mathematical optimization in intensity modulated radiation therapy", 4OR (2008)



Direct Aperture Optimisation (DAO): -recently introduced (Shepard 2002) -avoids this step but has other problems



Intensity problem or fluence map optimization problem

Dose vs. beamlets weight

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The dose to each voxel can be expressed as linear combination of the weights of the beamlets, which are the variables to be optimised:

$$D_i(x) = \sum_{j=1}^n M_{ij} x_j \tag{4}$$

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M: dose matrix (M_{ij}= dose delivered by beamlet j to voxel i). Computed using a dose engine (pencil beam, convolution/superposition, Monte Carlo ...)

x: vector of weights

i=1,..., m voxels in the geometry

j=1, ..., n beamlets

beamlets ~ few thousand geometry voxels ~ several thousand LARGE SCALE PROBLEM!!^{o. 20th May 2010}





Intensity problem or fluence map optimization problem



s.t. $x \ge 0$

 $\min F(\boldsymbol{x})$

x

. . .

Basic problem:

F: objective function

non-negativity constraint



Convex functions are preferred

Dose functions:

$$F_{\rm PTV} = \frac{1}{N_{\rm PTV}} \sum_{i} (D_i - D_i^{\rm ref})^2 \quad \forall i \in \text{PTV} \qquad F_{\rm OAR} = \frac{1}{N_{\rm OAR}} \sum_{j} (D_j)^2 \quad \forall j \in \text{OAR}$$

$$F_{\rm PTV} = \frac{1}{N_{\rm PTV}} \sum_{j} \begin{cases} (D_j - D_j^{\rm ref})^2 & \text{if } D_j < D_j^{\rm ref} \\ 0 & \text{otherwise} \end{cases} \qquad F_{\rm OAR} = \frac{1}{N_{\rm OAR}} \sum_{j} D_j \quad \forall j \in \text{OAR}$$

$$F_{\rm PTV} = \frac{1}{N_{\rm PTV}} \sum_{i} |D_i - D_i^{\rm ref}| \quad \forall i \in \text{PTV} \qquad F_{\rm OAR} = \frac{1}{N_{\rm OAR}} \sum_{j} \begin{cases} (D_j - D_j^{\rm ref})^2 & \text{if } D_j > D_j^{\rm ref} \\ 0 & \text{otherwise} \end{cases}$$



Objective functions

Dose-volume functions

Minimise %V OAR receiving dose D Maximise %V target receiving dose D Minimise D received by at least %V OAR Maximise D received by at least %V target







Objective functions

Radiobiological functions

- Tumour Control Probability (TCP)
- Normal Tissue Complication Probability (NTCP)

NON CONVEX !!!





Objective functions

Weighted sum of different objectives

$$F(\mathbf{w}, \mathbf{x}) = \sum_{i=1}^{n} w_i F_i(\mathbf{x})$$





Deterministic

- gradient-based: steepest descent, conjugate gradient ...
- simplex method (linear programming)
- interior point
- integer programming methods (D-V functions)
- projection algorithms (feasibility problem)

Stochastic algorithms

- simulated annealing
- genetic algorithms





Multicriteria optimisation

"The process of optimizing systematically and simultaneously a collection of objective functions is called *multiobjective optimization* (MOO) or *vector optimization*." (from Marler and Arora 2003) ... or multicriteria optimization (MCO).

Widely used in engineering, economics ... and now in radiotherapy.

General formulation of the problem:

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Minimize F(**x**) = [F₁(**x**), F₂(**x**), ..., F_k(**x**)] subject to g_j(**x**)≤0 j=1,2,...,m $h_{l}(\mathbf{x})=0$ l=1,2,...,n







"Typically, there is no single global solution, and it is necessary to determine a set of points that all fit a predetermined definition of an optimum"

Pareto optimality

Vilfredo Pareto, "Manuale di economia politica" (1906)

"A point, $x^* \in X$, is Pareto optimal iff there does not exist another point, $x \in X$, such that $F(x) \le F(x^*)$, and $F_i(x) \le F_i(x^*)$ for at least one function."

" A point x is Pareto optimal if it is not possible to improve an objective without worsening at least one of the others"



All Pareto optimal points lie on the boundary of the objective space

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Figure 1. The set of Pareto optimal points (red curves) in parameter space (left) and objective space (right) and a population of approximate solutions.

Pareto front (surface, frontier): set of all Pareto optimal points (n-1) dimensional hypersurface.



MCO and radiotherapy

Several (conflicting) objectives ? ✓ kill tumour

spare OARS







Let's take a step back ...

Weighted sum of different objectives

$$F(\mathbf{w}, \mathbf{x}) = \sum_{i=1}^{n} w_i F_i(\mathbf{x})$$





<u>Class solutions</u> based on clinical experience are often used

VOI	On/ off	Overlap Priority	Organ Type	Max Dose	Weight	Min Dose	Weight	DVH Points
Target								
ΡΤν		< 3 ×		66.0	100.0	64.0	100.0	
GTV_70		1		74.0	10.0	68.0	50.0	
Organs at risk								
BLADDER		< 5 -	TOI	50.0	10.0	0.0	0.0	
RECTUM		4 -	TOI	40.0	30.0	0.0	0.0	
GRAD_PTV		- 6	TOI	45.0	10.0	0.0	0.0	

Not so effective for all sites/patients





- Selection of weights is arbitrary.
- The human-computer loop can be long.
- A good treatment will be obtained, but *better* (clinical) treatments lying on the neighbourhood could be missed.





It would be convenient to <u>obtain a set of solutions (Pareto</u> <u>front</u>) instead of a single one, so the planner/clinician could evaluate in real time several options, <u>making</u> <u>trade-off among objectives</u>, and selecting the <u>most</u> <u>adequate solution</u>.

MCO methods have been recently introduced in RT to do so and deal with single-solution limitations.





- late 90s, realisation and first developments

- after 2003, main developments

Work developed mainly at MGH, Boston (Bortfeld, Craft et al) and Germany (Küfer, Monz, Thieke at FI and DKFZ).



Papers on MCO in RT (ISI)





- "Pareto navigation-algorithmic foundation of interactive multi-criteria IMRT planning", Monz et al, PMB (2008)
- "An approach for practical multiobjective IMRT treatment planning", Craft et al, IJROBP (2008)
- "A multiobjective gradient-based dose optimization algorithm for external beam conformal radiotherapy", Cotrutz et al, PMB (2001)
- "A unifying framework for multi-criteria fluence map optimization models", Romeijn et al, PMB (2004)
- "Multiobjective decision theory for computational optimization in radiation therapy", Yu, MP (1997)
- "Exploration of tradeoffs in intensity-modulated radiotherapy", Craft et al, PMB (2005)
- "Dose-volume objectives in multi-criteria optimization", Halabi et al, PMB (2006)
- "How many plans are needed in an IMRT multi-objective plan database? " Craft and Bortfeld, PMB (2008)
- "Multicriteria optimization in intensity-modulated radiation therapy treatment planning for locally advanced cancer of the pancreatic head", Hong et al, IJROBP (2008)
- "How many plans are needed in an IMRT multi-objective plan database?", Craft and Bortfeld, PMB (2007)
- "Approximating convex Pareto surfaces in multiobjective radiotherapy planning", Craft et al, MP (2006)
- "Derivative-free generation and interpolation of convex Pareto optimal IMRT plans", Hoffmann et al, PMB (2006)
- "Multicriteria optimization in IMRT treatment planning for locally advanced cancer of the pancreatic head", Hong et al, IJROBP (2008)



Computing (approximating) the PF

- Scalarisation

obtaining Pareto optimal points

- Sandwiching

approximating the Pareto front





The MC problem is converted to a single or a series of single-objective optimisation problems

- weighted sum
- lexicographic method/priority list
- ε-constraint

More on "Survey of multi-objective optimization methods for engineering", Marler & Arora, Struct. Multidisc. Optim. (2004)


- The solution is a Pareto optimal point of the MCO problem.
- Simple method.
- Typically used in radiotherapy optimisation.







Lexicographic method (priority lists)

-Objectives ordered by importance

-Sequence of optimisations

$$\begin{array}{ll} \min_{\mathbf{x}} & F_{i}(\mathbf{x}) \\ \text{s.t.} & F_{j}(\mathbf{x}) \leq F_{j}(\mathbf{x}_{j}^{*}), \ j = 1, 2, \ ..., \ i - 1, \ i > 1 \\ i = 1, ..., \ n \end{array}$$



Optimum of jth objective found in the jth optimisation





Bounded objective function method (ε-constraint)

-One objective is minimised; n-1 constraints

min $F_i(\mathbf{x})$ X $F_{j}(\mathbf{x}) \leq \varepsilon_{j}, \quad j = 1, 2, \dots, n, \quad j \neq i$ s.t.

 $\mathcal{E} = (\mathcal{E}_1, ..., \mathcal{E}_{i-1}, \mathcal{E}_{i+1}, ..., \mathcal{E}_n)$ upper bounds





Sandwiching



- Hyperplanes (*P*,**w**) are <u>lower</u> <u>bounds</u> for the Pareto front (for weighted sum).

- A similar result can be obtained for ϵ -constraint.

Sanwiching

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improvement

F.,

- Some facets connecting Pareto optimal points are upper bounds for the Pareto front.

- Compute convex hull for the Pareto points (space containing all possible convex combinations of the set of points).

- Facets and normals (facets are defined by n-1 points: lines in 2D, triangles in 3D ...).

-Facets with a positive normal vector (depending on how we define the functions!!!) are the real upper bound!!!





Approximating the (convex) Pareto front

 δ = distance (upper bound, lower bound) gives approximation quality factor.

More points can be added (more optimisations can be done) in regions where δ is large, while this is not necessary where δ is small.





Approximating the (convex) Pareto front

- Despite efficient algorithms the pre-computation of the Pareto from is a lengthy process, requiring the inverse optimisation of a large number of plans.

N_{objectives}+1 for 15% error

<u>5% error</u>	Craft and Bortfeld, PMB, 2008
3D: 8-10	Craft, Phys. Med. 2010
4D: 20-25	
5D: 33-45	

- On the other hand, no human-computer iteration is necessary. The plans and the Pareto front are automatically computed.





Navigating the Pareto front

- When the Pareto front has been computed (approximated) the planner can navigate on it, interactively exploring different plans and making trade offs between objectives.
- Plans are computed not as combination of all Pareto optimal points, but as combination of the points defining an optimal facet!!!
- Navigation in "real time" is difficult for high-dimensional problems





Visualization







Visualization



Fig. 3. Graphic representation of navigation of the Pareto surface. For Patient 2, each move is shown on a three-dimensional surface representation of comparative dose trade-offs between stomach, kidney, and liver doses.

......n radiation therapy, Santiago, 20th May 2010





Visualization





Is all this of any utility??

-little clinical implementation

-just one article comparing "standard" and MCO optimisation (to my best knowledge)





Is all this of any utility??

PANCREAS CANCER (MGH)

Different results!!. Clinicians having access to the PF explored it and selected treatments delivering <u>significantly lower</u> <u>dose to the stomach</u>!!





- Non-convex Pareto-front not accessible by (most) scalarisation methods.
- Sandwiching algorithm requires convexity.

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"A unifying framework for multi-criteria fluence map optimization models"

Romeijn, Dempsey and Li, Phys. Med. Biol. (2004)

"transforming any or all of the criteria via increasing functions leads to equivalent Pareto fronts"

(h∘G)(**x**)

Theorem 2.2. The sets ∂B and ∂B^h are related through

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$$\partial B = \left\{ \left(h_1^{-1} \left(U_1^h \right), \dots, h_L^{-1} \left(U_L^h \right) \right) : \vec{U}^h \in \partial B^h \right\}$$

or, equivalently,

$$\partial B^h = \{(h_1(U_1), \ldots, h_L(U_L)) : \vec{U} \in \partial B\}.$$



	Parameter range	Criterion decomposition		
Criterion		$G(\vec{d})$	h(z)	
$\operatorname{TCP}(N, \alpha, \lambda, n, \Delta T)$	$N, \alpha > 0; n \ge 1; \lambda, \Delta T \ge 0$	$-\ln \text{TCP}(\vec{d}; N, \alpha, n, \Delta T, \lambda) -\text{EUD}(\vec{d}; \alpha)$	$-e^{-z}$ $-exp(-Ne^{\lambda(n-1)\Delta T+\alpha z})$	
$EUD(\alpha)$	$\alpha > 0$	$-\text{EUD}(\vec{d};\alpha)$ $F(\vec{d};\alpha)$	$\frac{z}{\frac{1}{\alpha}} \ln z$	
gEUD(a)	$-\infty \leq a \leq 0$ $-\infty < a < 0$ a = 0	$-gEUD(\vec{d}; a)$ $F^{g}(\vec{d}; a)$ $F^{g}(\vec{d}; 0)$	z $-z^{1/a}$ $-e^{-z}$	
$W(a, k, gEUD^0)$	$-\infty \leqslant a \leqslant 0; k, gEUD^0 > 0$	$W(\vec{d}; a, k, \text{gEUD}^0)$ -gEUD $(\vec{d}; a)$	$z \ln\left(1 + \left(-\frac{gEUD^0}{z}\right)^k\right)$	
$\breve{W}(a,\sigma,\mathrm{gEUD}^0)$	$-\infty \leqslant a \leqslant 0; \sigma, \text{gEUD}^0 > 0$	$\breve{W}(\vec{d}; a, \sigma, \text{gEUD}^0)$ -gEUD $(\vec{d}; a)$	$\frac{z}{-\ln\left(1 - \Phi\left(\frac{\text{gEUD}^0 + z}{\sigma \cdot \text{gEUD}^0}\right)\right)}$	
$F(\alpha)$	$\begin{array}{l} \alpha > 0 \\ \alpha > 0 \end{array}$	$F(\vec{d};\alpha)$ $-\text{EUD}(\vec{d};\alpha)$	z e ^z	
$F^{g}(a)$	$-\infty < a \leq 0$ $-\infty < a < 0$	$F^{g}(\vec{d}; a)$ -gEUD $(\vec{d}; a)$	$z (-z)^a$	

Table 1. Evaluation criteria for targets.



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Table 2. Evaluation criteria for critical structures.

Criterion	Parameter range	$G(\vec{d})$	h(z)
gEUD(a)	$1 \leqslant a \leqslant \infty$	$gEUD(\vec{d}; a)$	z
	$1 \leq a < \infty$	$F^{g}(\vec{d}; a)$	$z^{1/a}$
$W(a, k, gEUD^0)$	$1 \leq a \leq \infty; k, gEUD^0 > 0$	$\mathrm{gEUD}(\vec{d};a)$	$\ln\left(1 + \left(\frac{z}{gEUD^0}\right)^k\right)$
$\breve{W}(a,\sigma,\mathrm{gEUD^0})$	$1 \leqslant a \leqslant \infty; \sigma, \mathrm{gEUD}^0 > 0$	$\mathrm{gEUD}(\vec{d};a)$	$-\ln\left(1 - \Phi\left(\frac{z - gEUD^0}{\sigma \cdot gEUD^0}\right)\right)$
$\text{NTCP}^{L\&S}(a, m, D_{50})$	$1\leqslant a\leqslant\infty; m,D_{50}>0$	$\mathrm{gEUD}(\vec{d};a)$	$\Phi\left(\frac{z-D_{50}}{mD_{50}}\right)$
$NTCP^{A\&N}(a, \Delta)$	$1 \leq a < \infty, \Delta > 0$	$gEUD(\vec{d}; a)$	$1 - e^{-(z/\Delta)^{a}}$
$F^{g}(a)$	$1 \leqslant a \leqslant \infty$	$F^{g}(\vec{d}; a)$	τ
	$1 \leq a < \infty$	$gEUD(\vec{d}; a)$	z^a





Pareto optimisation

Advantages

- Computation of the whole Pareto front, not just a single solution.
- No human-computer interaction; PF automatically computed .

Problems

- A large # of plans are necessary.
- Dedicated computers (cluster) doing overnight calculations.

- Not implementable in most institutions (right not just MGH to my knowledge).



Fast approaches to RT MCO

Objective:

- To obtain a vast range of plans, with different trade-offs between objectives ...
- ... in shorter time than a rigorous Pareto optimisation.



"A method to dynamically balance intensity modulated radiotherapy dose between organs-at-risk", S.K. Das, Med. Phys. (2009)

- Fast non-Pareto approach
- Sequence of optimisations, sharing a starting point.
- N_{OAR}+2 optimisations.





- The optimisation sequence is computationally efficient because of the serial nature of the problem: each j optimisation is using a previous one as starting point.
- Few iterations are required to converge.
- Those N+2 solutions are linearly combined to obtain different treatments:

$$T_{\mathbf{w}} = \sum_{i} w_{i} T_{i}$$

Target coverage can be traded off for OARs sparing, and OARs doses traded off against each other by changing the respective weights in the combination.





"An approach to MCO of rotational therapy"

- Fast non rigorously Pareto optimal approach to MCO for arctherapy.
- Relying on the geometry of the slice and the rotational problem.

J. Pardo-Montero & J.D. Fenwick, Med. Phys. (2009) J.D. Fenwick & J. Pardo-Montero, Med. Phys. (2010) J. Pardo-Montero & J.D. Fenwick, Med. Phys. (2010)





<u>Arc therapy</u> - delivering dose with one or more arcs instead of a few fixed-fields

- Tomotherapy[™] (Mackie et al 1993)
 - Commercial since early 2000s (Tomotherapy Inc).
 - delivered helically using a purpose-built system which generates a beam collimated by a binary multileaf.
- Intensity Modulated Arc Therapy (IMAT) (Yu 1995)
 - Delivered with a normal LINAC.
 - Several unmodulated arc to obtain intensity modulation
 - Single arc techniques (Rapic-Arc, VMAT): intensity modulation achieved through speed a dose rate modulation.





Papers on arc-therapy





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- symmetry of rotational techniques makes simple geometry-based forward planning approaches appealing, e.g. SIMAT (Wong et al, IJROBP 2002), 2-Step IMAT (Bratengeier, Med. Phys. 2005).
- Those techniques rely on the use of blocked arcs and "compensatory arcs" when needed.



from Wong et al (2002)



(b)







- we further build on those geometrical-based techniques and introduce a simple approach to multiobjective planning for rotational therapy.
- a treatment basis of geometry-based arcs can be created, and the final treatment built as combination of the elements of the basis.







Treatment basis

- <u>A conformal arc</u>, which conforms to the PTV.
- <u>Single-blocked arcs</u>, which conform to the PTV but completely shield one OAR at a time.
- <u>Double-blocked arcs</u>, which shield two OARs at a time.

Each arc delivers as homogeneous as possible dose to the PTV while totally blocking the relevant structures!!





- Generalization of foundational work of Brahme, Roos and Lax "Solution of an integral equation encountered in rotation therapy", PMB (1982)
- Uniform dose can be delivered to an annular tumor whilst completely avoiding delivering dose to a circular structure located at the centre of the annulus.
- Generalization to OARs outside the target (Fenwick & Pardo-Montero, under review, Med. Phys.)







Construction of the arcs

- 2-step process
 - <u>Unmodulated arc</u>, conforming to the PTV and blocking the desired OARs (if any).
 - <u>Modulated arc</u> to compensate the dose inhomogeneity in the PTV due to the blocking.

- Fast computation!!



Modulated arcs: imaging-like approach



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Thus, for each iteration i (i > 0) the weight of a beamlet k is changed in three different ways, according to its geometry:

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• If $b_k \in \{\text{blocked beamlets}\},\$

$$x_k^i = 0. \tag{10}$$

• Else if $l_k \cap \text{target} \neq \emptyset$,

$$x_k^i = x_k^{i-1} + \frac{1}{N} \times \int_{l_k} (D_{\text{ref}}(l) - D_{i-1}(l)) dl.$$
 (11)

• Else (i.e., $l_k \cap \text{target margin} \neq \emptyset$)

$$x_{k}^{i} = x_{k}^{i-1} + \frac{1}{N} \times \int_{l_{k}} \frac{(D_{\text{ref}}(l^{*}) - D_{i-1}(l^{*}))}{d+1} dl,$$
 (12)

Modulated arcs

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Construction of modulated blocked arcs can easily be approached as an inverse problem, in which only nonblocked beamlets are included in the optimization and only objective functions regarding the PTV are minimized,

 $\min_{x_{\rm NB}} F_{\rm PTV},$

NB= non blocked

s.t. $x_{\rm NB} \ge 0$,

A gradient-descent method like Eq. (7) has been used to solve this problem. Computation is bound to be faster than for standard plan optimization

 The dimensionality of the problem is reduced, as blocked beamlets are not used in the optimization; and
 only one objective function (and its corresponding Jacobian) be evaluated





Pareto-optimal facets

Once a set of plans has been computed, the Pareto front can be approximately obtained by computing the convex hull of the plans in the space of objectives and selecting the proper facets of the convex hull according to their normal vector.⁹ If the normal vector is defined pointing outward, then with objective functions defined as in Sec. II A 1, Pareto optimal facets will have normal vectors with negative components.⁴⁹









The following 5 arcs have been included in the treatment *basis* for the prostate geometry:

- conformal (CA);
- blocked on both femoral heads (FHs);
- blocked on the segment of rectum not overlapping the PTVs (PR);
- blocked on the whole rectum (WR);
- double-blocked on the femoral heads and the rectal segment not overlapping the PTVs (PR+FHs).





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FIG. 5. Comparison between plans generated using the imagereconstruction-based algorithm (left panels) and inverse-based algorithm (right panels): (a) Conformal arc, (b) femoral heads block, and (c) block on the segment of rectum not overlapping the PTVs. Isodose levels of 7400, 6700, and 2000 cGy are shown as lighter lines.












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General conclusions

- Radiotherapy planning is a multicriteria problem, involving several conflicting objectives.
- This is not taken into account by available Treatment Planning Systems.
- MCO techniques are starting to be applied to radiotherapy optimisation, with good results.

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General conclusions

- Potential improvements:
 - Minimising or avoiding the human-computer interaction to find a suitable
 - Capability of creating a vast range of treatment that can be evaluated in real time selecting the most suitable.
- Pareto optimisation requires dedicated hardware to compute the large number of plans needed to approximate the Pareto front.



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General conclusions

- Serious limitation of this method: implementable only at large institutions with large resources.
- Fast approaches, even if less rigorous, are necessary to extend MCO in radiation therapy.
- We have focused only in the "dose problem". Some interesting work out there on the quality vs. complexity trade-off.





THANK YOU FOR YOUR ATTENTION!!!

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