Optimization of radiation therapy

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2014 Southern California Optimization Day
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Outline

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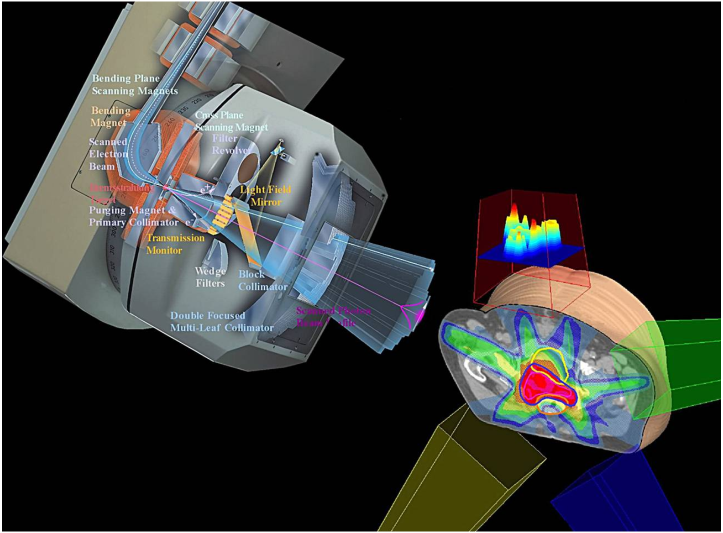
Radiation therapy

- Treatment of cancer by radiation therapy means that the patient is subject to radiation by a particle beam (photon beam or proton beam in our case).
- The main parts of a treatment unit are:
  - the particle accelerator, which creates the beam;
  - beam optical components, which direct the beam;
  - the supporting gantry, which gives the beam angle of incidence;
  - the treatment head, which modulates the intensity of the beam.

Radiation treatment unit



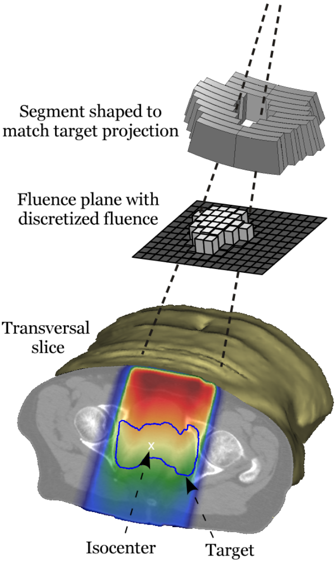
Radiation therapy

- Closely related optimization problem

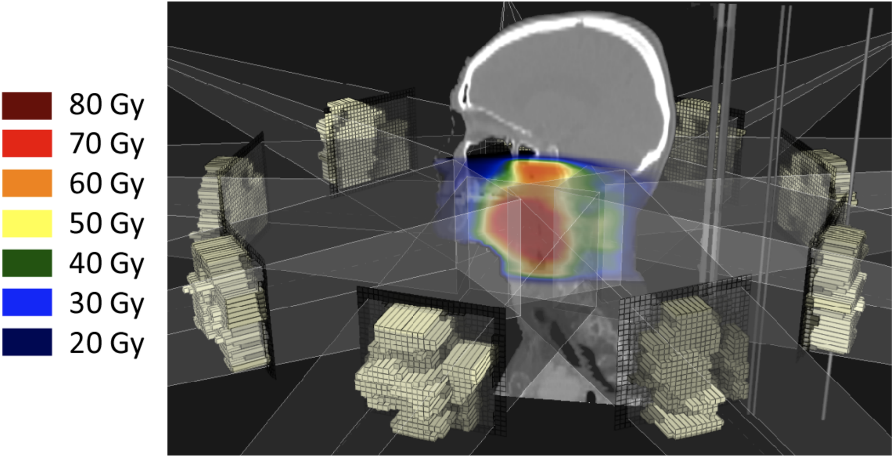
$$\begin{array}{ll} \text{minimize} & f(x) \\ \text{subject to} & x \in R^n, \end{array}$$

  where f is a smooth convex function.
- Optimal solution x^* given by $\nabla f(x^*) = 0$.
- Problem structure highly important.

Radiation treatment



Radiation treatment, cont.



Aim of radiation therapy

- The aim of radiation therapy is typically to give a treatment that leads to a desirable dose distribution in the patient.
- Typically, high dose is desired in the tumor cells, and low dose in the other cells.
- In particular, certain organs are very sensitive to radiation and must have a low dose level, e.g., the spine.
- Hence, requirements on the desired dose distribution can be specified, and the question is how to achieve this distribution.
- This is an inverse problem in that the desired result of the radiation is known, but the treatment plan has to be designed.

Formulation of optimization problem

- A radiation treatment is typically given as a series of radiations.
- For an individual treatment, the performance depends on
  - the beam angle of incidence, which is governed by the supporting gantry; and
  - the intensity modulation of the beam, which is governed by the treatment head.
- One may now formulate an optimization problem, where the variables are the beam angles of incidence and the intensity modulations of the beams.
- Referred to as intensity-modulated radiation therapy (IMRT).
- In this talk, we assume that the beam angles of incidence are fixed.

Characteristics of the optimization problem

- The resulting optimization problem is a large-scale nonlinear optimization problem, typically with a large number of degrees of freedom at the solution.
- Many different objective functions have been proposed. The above problem characteristics hold.
- Many conflicting goals. May form a weighted sum of different optimization functions, e.g., quadratic penalties of dose deviations.

Choice of optimization problem

Fundamental optimization problem.

- Fluence map optimization.
  - Variables given by the beam intensities.
  - Requires a post-processing step to obtain machine parameter settings.
- Direct machine-parameter optimization.
  - Outcome of optimization problem is a deliverable plan.
  - Increased complexity of optimization problem.

More advanced aspects.

- Handling of conflicting treatment goals.
- Handling of uncertainty.

Outline

Solution method for fluence map optimization problem

Related to the fluence map optimization problem, a simplified bound-constrained problem may be posed as

$$\begin{array}{ll} \underset{x \in \mathbb{R}^n}{\text{minimize}} & f(x) \\ \text{subject to} & l \le x \le u. \end{array}$$

- Large-scale problem solved in few ($\sim$20) iterations using a quasi-Newton SQP method.
- Difficulty: “Jagged” solutions for more accurate plans.
- Idea: Use second-derivatives and an interior method to obtain fast convergence and smooth solutions.
  - Good news: Faster convergence.
  - Bad news: Increased jaggedness.
- Not following the folklore.
- Better idea: Utilize problem structure.

Radiation therapy and the conjugate-gradient method

- Why does a quasi-Newton sequential quadratic programming method do so well on these problems?
- The answer lies in the problem structure.
- Related to the conjugate-gradient method.
- The conjugate-gradient method minimizes in directions corresponding to large eigenvalues first.
- Our simplified problem has few large eigenvalues, corresponding to smooth solutions.
- Many small eigenvalues that correspond to jagged solutions.
- The conjugate-gradient method takes a desirable path to the solution. Known as iterative regularization.
- Additional properties of the solution, not seen in the formulation, are important.

Outline

Direct machine parameter optimization

Characteristics of direct machine parameter optimization.

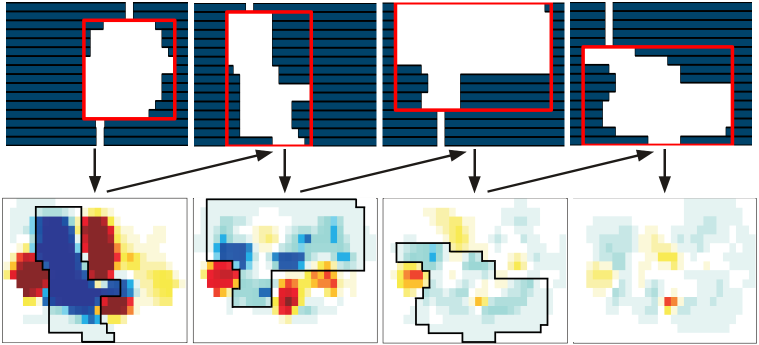
- Solution to optimization problem is a deliverable plan.
- The optimization problem is harder to solve.

A dynamic approach is one option.

- Discretize the set of leaf positions.
- Generate plans “as needed” in a column generation framework.

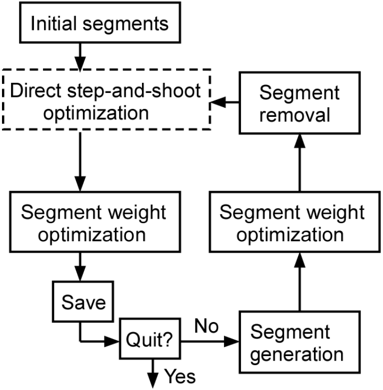
Segment generation

Segments are generated in a dynamic fashion.



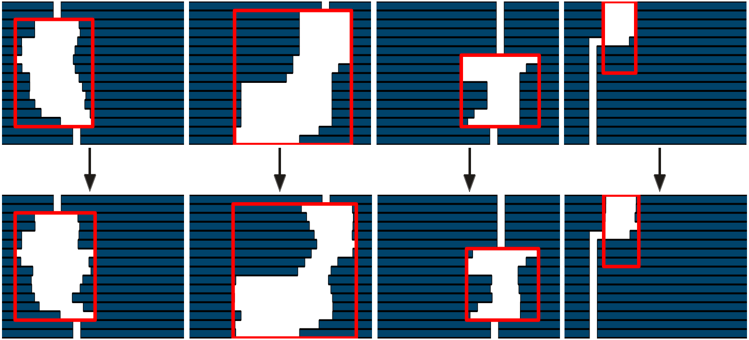
Adjustable leaves approach

In the adjustable leaves approach, direct step-and-shoot optimization is included.



Adjustable leaves approach

Change of segment shapes by direct step-and-shoot optimization.



Adjustable leaves approach

- The dynamic approach gives a sequence of plans of improving quality.
- The number of segments is adjusted dynamically.
- Allows tradeoff between delivery time and plan quality.
- Column generation covers “big changes”, direct step-and-shoot optimization gives “fine tuning”.

Outline

Intensity modulated radiation therapy (IMRT)

- Delivery. Ionizing radiation field generated by a linear accelerator equipped with a rotating gantry.
- Fluence modulation. Superposition in time of collimated fields with uniform intensity.
- Treatment goal. Deliver a highly conformal dose to the tumor volume while sparing surrounding healthy tissues.

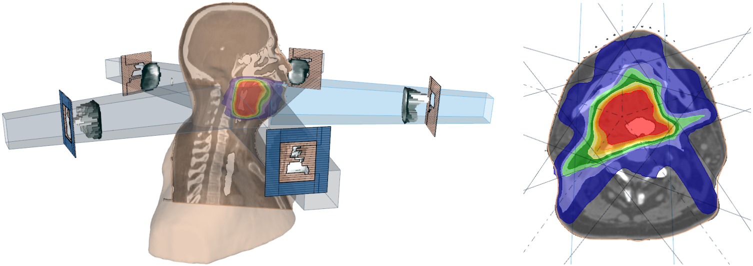


Figure : Five-field treatment of head-and-neck cancer case.

The inverse treatment planning problem

Find the machine parameters that best achieve the treatment goals within the limitations of the delivery method.

Multi-objective programming formulation

$$
(MOP) \qquad \begin{array}{ll} \underset{x}{\text{minimize}} & f(x) = (f_1(x), \dots, f_n(x))^T \\ \text{subject to} & x \in X = \{x : c(x) \le 0\}, \end{array}
$$

where

- $f : R^m \to R^n$ vector of treatment objectives.
- $c : R^m \to R^k$ vector of planning and delivery constraints.
- $x \in R^m$ incident energy fluence.

Assumptions

- X nonempty.
- f, c convex and bounded on X.
- $n \sim 3$–15.

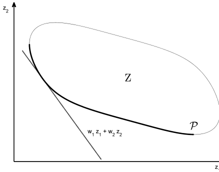
Solving the treatment planning problem

Conventional approach

1. Assign vector of weights $w \in R^n_+$ and solve

$$(SUM(w)) \quad \begin{array}{ll} \underset{x}{\text{minimize}} & \sum_{i=1}^{n} w_i f_i(x) \\ \text{subject to} & x \in X. \end{array}$$

2. Refine problem formulation and re-optimize until satisfactory solution has been found.

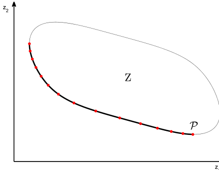


Multi-criteria approach

1. Generate discrete representation of the Pareto optimal set $\mathcal{P}$ by solving $SUM(w)$ for varying w.

$$x^* \text{ Pareto optimal} \Leftrightarrow (f(x^*) - R^n_+ \setminus \{0\}) \cap Z = \emptyset$$

2. Evaluate possible treatment options by forming convex combinations between the pre-computed Pareto optimal solutions.

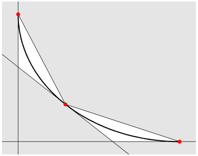


Sandwich algorithm for approximating convex sets

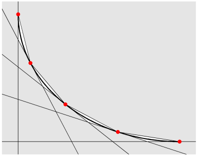
- (MOP) convex $\Rightarrow Z_+ = f(X) + R^n_+$ convex, $\mathcal{P}$ connected.

An iteration in the algorithm

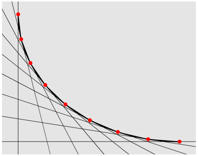
1. Construct inner and outer polyhedral approximations of the Pareto optimal set.
2. Calculate the maximum distance between the inner and outer approximations.
3. Take w to be normal to the inner approximation at the point where the maximum distance is attained.



(a) Iteration 1



(b) Iteration 3



(c) Iteration 7

Figure : Approximation of a convex function generated by the sandwich algorithm.

Polyhedral approximations of the Pareto optimal set

Let P be a discrete set of Pareto optimal points generated by a set of weighting vectors W.

Inner approximation ($Z_{\text{in}} \subseteq Z_+$)
Setwise sum between convex hull of P and R_+^n, i.e.,

$$Z_{\text{in}} = \left\{ P^T\lambda + \mu : \lambda, \mu \geq 0, e^T\lambda = 1 \right\}.$$

Outer approximation ($Z_{\text{out}} \supseteq Z_+$)

Intersection of positive halfspaces associated with supporting hyperplanes to $\mathcal{P}$ at points in P, i.e.,

$$Z_{\text{out}} = \{z : Wz \geq r\},$$

where r is the vector of pairwise scalar products between elements in P and W.

Quantifying the approximation error

Approximation error

Minimum ε such that for any $z^* \in \mathcal{P}$, $\exists\, z \in Z_{\text{in}} : z^* \in z + (R^n_+ - \varepsilon e)$.

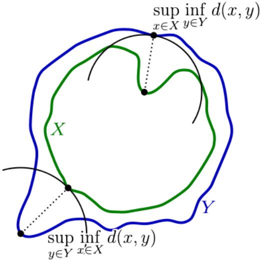
Upper bound on the approximation error

Hausdorff distance

$$h(Z_{\text{in}}, Z_{\text{out}}) = \max_{z \in Z_{\text{out}}} \min_{z' \in Z_{\text{in}}} d(z, z'),$$

with respect to the one-sided distance function

$$d(z, z') = \max_{i \in \{1,\dots,n\}} (z'_i - z_i)_+.$$



Calculating the upper bound

The distance $h(Z_{\text{in}}, Z_{\text{out}})$ can be calculated by solving the linear-bilevel program

$$\begin{array}{ll} \underset{z}{\text{maximize}} & \left\{ \begin{array}{ll} \underset{\eta,\ \lambda,\ \mu}{\text{minimize}} & \eta \\ \text{subject to} & \eta e \geq P^T\lambda + \mu - z, \\ & e^T\lambda = 1, \\ & \eta,\ \lambda,\ \mu \geq 0, \end{array} \right\} \\ \text{subject to} & Wz \geq r, \end{array}$$

which amounts to maximizing a convex function over a polyhedral set, i.e., a nonconvex optimization problem.

Proposition

At least one vertex of the feasible set is an optimal solution.

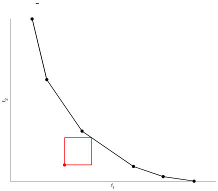
Solution by vertex enume

Solve the primal-dual pair of linear programs

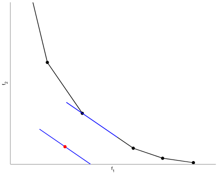
$$
(PLP(v)) \qquad \begin{array}{ll} \underset{\eta,\ \lambda,\ \mu}{\text{minimize}} & \eta \\ \text{subject to} & \eta e \geq P^T \lambda + \mu - v, \\ & e^T \lambda = 1, \\ & \eta,\ \lambda,\ \mu \geq 0, \end{array}
$$

$$
(DLP(v)) \qquad \begin{array}{ll} \underset{\pi,\ \rho}{\text{maximize}} & \rho - v^T \pi \\ \text{subject to} & P\pi \geq \rho e, \\ & e^T \pi \leq 1, \\ & \pi \geq 0. \end{array}
$$

over all vertices v of the feasible set.



(a) Primal



(b) Dual

Proposition

Let $(\eta, \lambda, \mu, \pi, \rho)$ be a primal-dual optimal solution to $PLP(v)$ and $DLP(v)$. Then $\{z : \pi^T z = \rho\}$ is a supporting hyperplane to Z_{in} at $P^T \lambda + \mu$ with normal vector $\pi \in R^n_+$.

Reducing the number of subproblems to be solved

The number of linear programming problems that needs to be solved can be reduced by upper-bounding the optimal value of some of the subproblems.

Proposition

Let V denote the vertex set of Z_{out} in a given iteration and let the corresponding notation with superscript "$+$" apply to the subsequent iteration. Then, for any v in V^+, it holds that

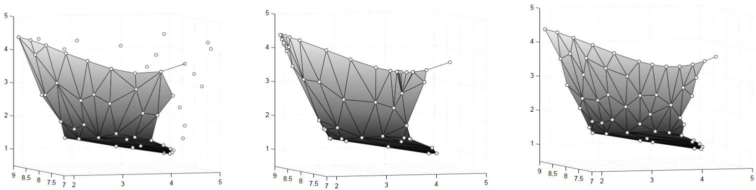
$$\text{optval}(PLP^+(v)) \le \begin{cases} \text{optval}(PLP(v)) & \text{if} \quad v \in V^+ \\ \max_{\bar{v} \in E} \text{optval}(PLP(\bar{v})) & \text{otherwise} \end{cases},$$

where E denotes the extreme point set of the edge of Z_{out} that contains v.

Comparison with algorithms in the literature

Related algorithms

- Solanki et al. (1993) Approximating the noninferior set in multiobjective linear programming problems. *European Journal of Operational Research* **68(3)**, 356–373.
- Craft et al. (2006) Approximating convex Pareto surfaces in multiobjective radiotherapy planning. *Medical Physics* **33(9)**, 3399–3407.
- Rennen et al. (2011) Enhancement of Sandwich Algorithms for Approximating Higher-Dimensional Convex Pareto Sets. *INFORMS Journal on Computing* **23(4)**, 493–517.



(a) Solanki et al. (b) Craft et al. (c) Rennen et al.

Figure : Pareto surface approximations generated by sandwich algorithms in the literature. Adapted from Rennen et al. (2011).

Computational complexity

McMullen's Upper-Bound Theorem gives

Vertex enumeration	Facet enumeration
$\mathcal{O}(p\varphi(2n+p+1,n))$	$\mathcal{O}(p\varphi((p+1)(n+1),n))$

where p is the total number of iterations and

$$\varphi(k,n) = \binom{k - \lfloor \frac{n+1}{2} \rfloor}{k-n} + \binom{k - \lfloor \frac{n+2}{2} \rfloor}{k-n}.$$

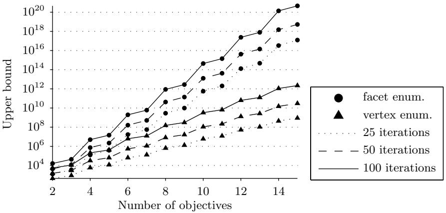


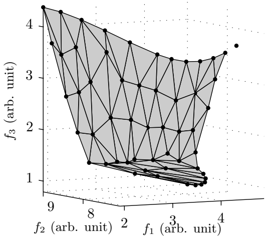
Figure : Upper bound on number of linear programming solves as a function of number of objectives and total number of iterations.

Computational study

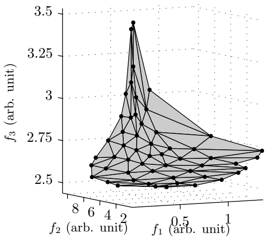
- The vertex enumerative algorithm and the facet enumerative algorithm were interfaced to CPLEX and SNOPT.

Test problems (scalable in the number of objectives *n*)

1. Test problem from Rennen et al. (2011) (QCLP).
2. IMRT problem for head-and-neck cancer case (QP).



(a) Problem 1

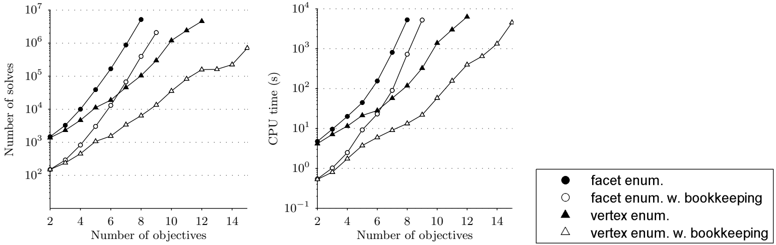


(b) Problem 2

Figure : Pareto surface representation at $n = 3$ and $p = 50$.

Numerical results (Problem 2)

- Vertex enumeration + bookkeeping reduces number of linear programming solves by ~ 10 for $n \geq 2$ and by $\sim 10^2$ for $n \geq 5$.
- Maximum problem dimension tractable at times in the order of minutes increases from about six to eleven.



(a) Linear programming solves

(b) CPU time

(c) Legend

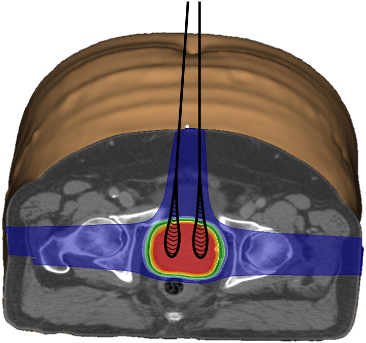
Figure : Numerical results of applying 50 sandwich algorithm iterations to Problem 2. All depicted quantities are summed over 50 iterations.

Summary and conclusion

- The vertex enumerative approach generates equivalent output to the facet enumerative approach while solving fewer subproblems.
- Both the vertex and the facet enumerative approach can be enhanced with an upper bounding procedure for reducing the number of subproblems.
- The combined effect of the proposed enhancement increases the number of tractable problem dimensions from about six to eleven.

Outline

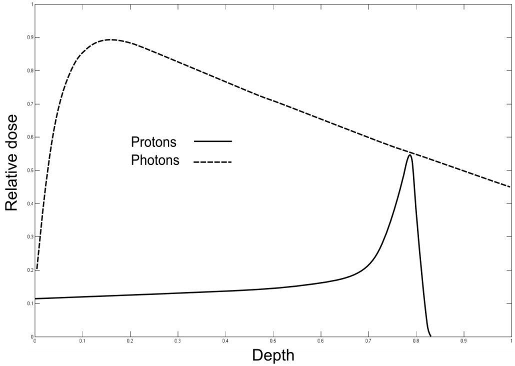
Intensity modulated proton therapy (IMPT)



- The patient is irradiated with proton beams.
- Variable energy and fluence over the beam cross-sections are used to conform the dose to the shape of the target.
- The treatment is divided into a number of treatment fractions.
- Goal: eradicate all clonogenic tumor cells while sparing healthy tissues.

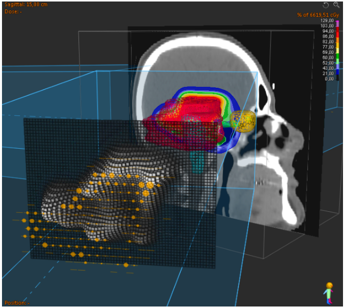
Intensity modulated proton therapy (IMPT)

- Protons interact with impeding particles.
- The dose depositions increase as the protons slow down.
- Bragg peaks and depth modulation allow for conformal dose.
- Steep beam dose gradients and stopping power sensitivity make IMPT sensitive to errors.



Optimization problem

Objective: minimize the difference between delivered dose d and the reference dose d^{ref}.



- The patient volume is discretized into m cubic voxels.
- The beams are discretized into n spots.
- The dose is given by $d(x) = Px$ where $x \in R^n$ is the spot weight vector and $P \in R^{m \times n}$ is a matrix mapping spot weights to dose.
- Typically, $m \sim 10^6$ and $n \sim 10^4$.

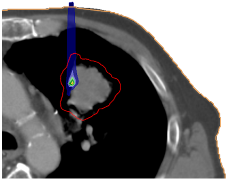
Considered uncertainties

Three influencial uncertainties are considered:

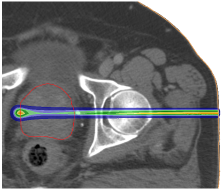
- Range of beams
- Setup of patient
- Organ motion

When the density of the treatment volume is heterogeneous, the resulting errors distort the dose distribution heavily.

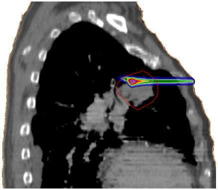
Effects of the errors



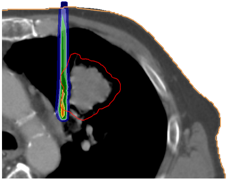
(a) Nominal setup



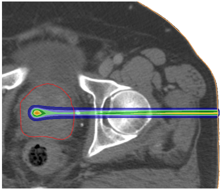
(b) Nominal density



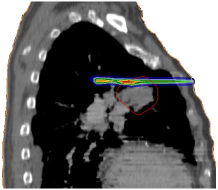
(c) Nominal tumor position



(d) Shifted setup



(e) Scaled density



(f) Shifted organ position

Figure : Dose distributions of a single spot in nominal plans and plans after setup error, density error, and organ motion realizations.

Conventional methods for handling uncertainties

IMPT + margin

- Sensitive to errors due to interplay effects between beams
- No protection against steep dose gradients close to OARs
- A margin in a low density volume (e.g., lung) amounts to just a slight margin in radiological depth

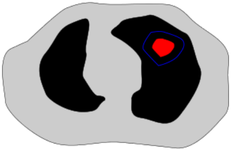
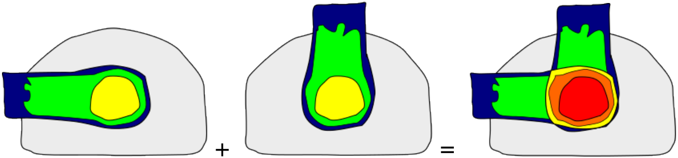


Figure : Conventional margin (blue)

Conventional methods for handling uncertainties

Single field uniform dose (SFUD) + margin

- Enforce uniform beam doses



(a) Beam 1 (b) Beam 2 (c) Total dose

SFUD + material override (MO) + margin

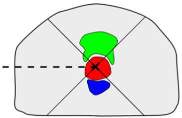
- Plan as if margin in low density volume were of tumor tissue

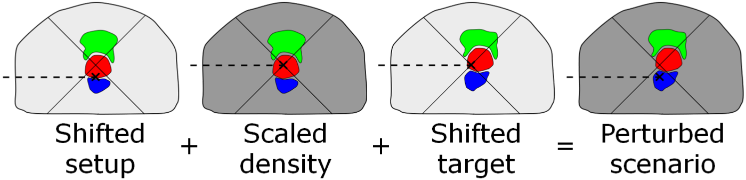
(d) Margin (e) Material override

Robust method

Conventional methods $\Rightarrow$ heuristic restrictions.
Instead: Utilize more information.

- Instead of margins, specify uncertainties
- The optimizer locates where to deposit dose
- "Inverse planning of margins"
- Error realizations are discretized into a number of scenarios





Robust method

Minimax optimization

$$\underset{x \geq 0}{\text{minimize}} \quad \max_{s \in \mathcal{S}} f(d_s(x)).$$

- $\mathcal{S}$ – scenarios
- x – spot weights
- d_s – dose in scenario $s \in \mathcal{S}$
- f – objective function

Scenarios are selected to cover 95% of the realizations of errors.

The problems are solved using an in-house quasi-Newton SQP method.

Scenario dose computation

During the optimization, approximate scenario doses by shifting spot weights in spot grid:

- Setup shifts: lateral interpolation
- Density scalings: longitudinal interpolation
- Organ motion: lateral and longitudinal interpolation (or using multiple images)

Approximate scenario dose $d_s(x) = PT_s x$, where T_s is a transformation matrix for scenario $s \in \mathcal{S}$.

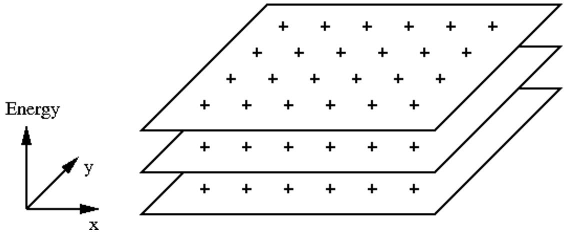


Figure : The spot grid

Evaluation of robustness

To evaluate the methods, scenario doses are calculated as exactly as possible.

- Shift beam isocenters
- Scale patient density
- Move organs using deformable registration (or using multiple images)

The evaluation scenarios are selected randomly from the ellipsoids corresponding to the accounted for errors.

Lung case

The conventional and robust method is applied to a lung case.

- Setup uncertainty: 3 mm isotropically
- Density uncertainty: 3 %
- Organ motion: 5 mm inferiorly-superiorly, 2 mm in the other directions.

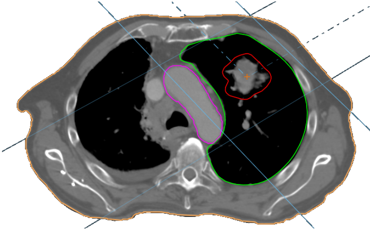
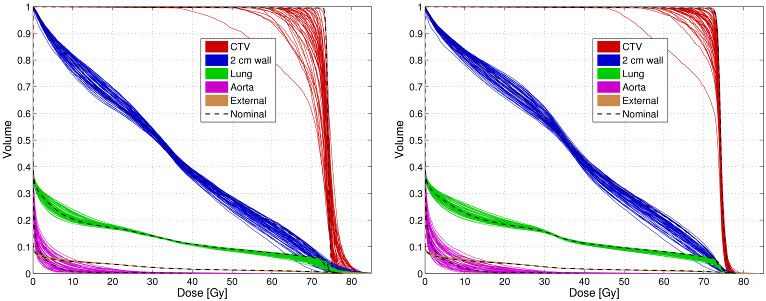


Figure : The lung case

The margin used for conventional planning is 8 mm inferiorly-superiorly and 5 mm in the other directions.

Results – lung case

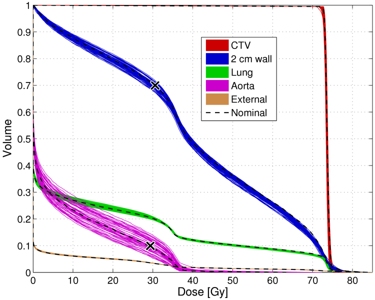
Margin or SFUD with margin are insufficient for robust target coverage.



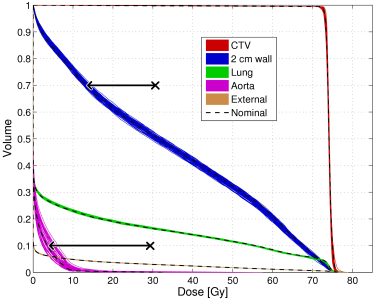
(a) Nominal with margin (b) SFUD with margin

Figure : IMPT plan in 50 scenarios

Results – lung case



(a) SFUD with MO and margin



(b) Robust method

Figure : DVHs for 50 randomly sampled scenarios.

Conclusion

- For complicated cases, conventional margins may be insufficient for providing robust target coverage.
- Material override and robust optimization can yield robust target coverage.
- By utilizing more information in the optimization, the dose to healthy tissues can be reduced.

Outline

Summary

- Optimization is an indispensible part of radiation therapy.
- Good knowledge of methods is not sufficient.
- Close interaction with experts in the field is vital.
- Increased level of sophistication through the projects.
- Very rewarding application and environment.
- Close connection to fundamental methodological questions.

Two new graduate students started in September 2013:
Michelle Böck and Lovisa Engberg.

References related to talk

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Thank you for your attention!