Computational challenges in intensity modulated radiation therapy treatment planning

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SCHOOL OF MEDICINE
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- Cliff Chao, M.D.
- Angel Blanco, M.D.
- Andrew Hope, M.D.
- Jing Cui, PhD.

- Issam El Naqa, PhD
- Patricia Lindsay, PhD
- Jan Wilkens, PhD
- James Alaly, B.S.
- Eva Lee, PhD
- And many others…

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Preface: the current paradigm
A Pencil beam or *beamlet*

Fluence of *i*’th Beamlet, denoted \( b_i \)

Port or ‘beam’ of 8 beamlets
Optimization of beamlet fluence weights results in a ‘fluence map’ for each treatment head position

Fluence map example
(a map of the $b_i$’s)

(From: Chui et al., Medical Physics (2001) 28:2441-2449.)
An IMRT dose distribution is constructed from a superposition of open static fields of variable fluence.

(From: Kung and Chen, Medical Physics (2000) 27:1617-1622.)
Basic IMRTP approaches

- Optimize beamlet fluences
- Derive collimator sequences
- Select starting apertures, then modify them

(most common by far)
The ‘objective function’

• Typically, the objective function is a sum of terms, some of which represent normal tissue structures and one or more terms represents the target.
  – This is called a ‘linear sum objective function’
  – The different terms have different multiplying weights (constants) in front, representing relative importance
Linearly weighted objective functions

- Individual terms (or goal functions) are added to comprise the objective function.
- Typically, each anatomy structure of importance has one or more goal terms.
- Goals are evaluated for each voxel contained in a structure.

\[ F = w_{OAR} \sum_{i=1}^{n} (D_i - 0)^2 + w_{Target} \sum_{j=1}^{m} (D_j - 64)^2 \]

Objective for an OAR of \( n \) voxels

Objective for a target of \( m \) voxels

Graph of cost per voxel vs. dose
Iterative solution

- Start with a set of initial beamlet weights.
- Search along a series of directions in beamlet weight space.
- Stop when
  - cost is zero
  - cost not improved
  - fixed number of iterations exceeded
- When done, beamlet weights are ‘optimized.’

```
Start

Calculate Cost

Convergence Criterion Met?

Yes → Finish

No → Select Search Direction

Do Line Search
```
A ‘state of the art’ IMRT treatment planning system...

• Accepts constraints
  – Max dose
  – Min dose
  – Dose-volume constraints: no more than x% of an organ can receive y% dose (e.g., “V20 can be no larger than...”).

• Tries to match or exceed goal DVH parameters
  – for target volumes
  – for normal tissues
The CMS XiO Prescription Page

<table>
<thead>
<tr>
<th>Structure</th>
<th>Type</th>
<th>Rank</th>
<th>Objective</th>
<th>Dose (cGy)</th>
<th>Volume (%)</th>
<th>Weight</th>
<th>Power</th>
<th>Status</th>
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</table>
The weight paradox: hard-to-control tradeoffs and the lack of clear priorities

- Normal tissue weights should be large enough so the mathematical engine tries to reduce dose to those structures.
- Target weights should be much larger than normal tissue weights so that good target coverage is not compromised...but...
- There is no perfect compromise
  - Very high target weights: engine neglects normal tissues
  - Not very high target weights: engine does not preserve target dose characteristics
State-of-the-art workflow: “Are we finished yet?”

Physician: “Here is what I’d like.”

Later....Dosimetrist: “I tried it, and tried to fix it. Here it is.”

Physician thinks “Is that the best they can do?” Says: “How busy are you? Can you try to improve this part?”

Dosimetrist: “Pretty busy. But I’ll try if you want me to.”
Thus, current IMRT systems are highly inefficient, and lead to planning iterations with no clear guidelines for establishing that a ‘clinically superior’ plan cannot be achieved.
IMRT planning challenges

1. Lack of scientific comparisons
2. Incorporating accurate dose calculations
3. Mastering the ‘data-glut’
4. Controlling dose distribution characteristics & tradeoffs
5. Making tradeoffs responsive to outcomes models
Challenge #1: Lack of scientific comparisons
IMRT optimization and operations research: facilitating operations research approaches in IMRT

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(1) Washington Univ, Saint Louis, MO, (2) Georgia Inst Tech and Emory Univ, Atlanta, GA, (3) Indiana Univ, Indianapolis, IN, (4) Massachusetts General Hospital, Boston, MA, (5) Rice University, Houston, TX, (6) UT M.D. Anderson Cancer Center, Houston, TX, (7) University of Florida, Gainesville, FL, (8) Fox Chase Cancer Center, Philadelphia, PA, (9) Univ of North Carolina, Chapel Hill, NC, (10) Univ Michigan, Ann Arbor, MI, (11) Purdue Univ, W. Lafayette, IN,

(Deasy et al., Annals Op Res, In press)
Motivation I

- Many IMRT treatment planning algorithms, but...
- Few comparisons
- Tools for comparison and common data access are missing
- Common datasets are missing
- Few (no?) comparisons of techniques.
Motivation II

• Many optimization experts in the field of Operations Research
• No access to radiotherapy datasets
• Little interaction with the field of radiotherapy
ORART: Operations Research Applications in Radiation Therapy

• NCI/NSF jointly sponsored workshop, Feb. 2002
  – 10 physicians, 10 physicists, 10 optimization/operations research experts
  – Proceedings posted on the web.
• Optimization in Radiation Therapy meeting (Palta, Dempsey, Lee, Jan. 2003.)
• ORART Collaborative Working Group (NCI/NSF funded)
  – “ORART Toolbox” for sharing treatment planning data
  – ORART Test-suite data sets
Approach

• Construct common collaboratory framework: graphical and analytical plan review tools.

• Provide a common approach to generating test beamlet dosimetry data.

• Compile common benchmark suite of anonymized patient plans and IMRT prescription challenges.

• All publicly available and open-source.
Components

- CERR for plan review and analysis (common data format)
- Extensions to CERR to produce common beamlet dosimetry (ORART Toolbox)
- Treatment planning data exported in RTOG or DICOM format, converted to CERR format
**CERR: A Computational Environment for Radiotherapy Research**

- Matlab-based
  - Cross-platform
- RTOG format-based
  - Self-describing format
- Open-source
- Freely available via webpage: http://radium.wustl.edu/cerr
Successful imports from

- CMS Focus (RTOG)
- Pinnacle (RTOG)
- TMS Helax (RTOG)
- Helios (DICOM)
- …Many other systems
CERR: current major components

- Version 3 (in beta test)
- Can handle many CT sets
- Can import PET/MRI
- Transverse, coronal, sagittal slice viewers
- DVH calculation and display
- Contouring/re-contouring tools
- Plan metric comparison tools
- Dose comparison tools
- IMRT beamlet calculations
Computational Environment for Radiotherapy Research (CERR)

- 3-D plans exported from planning systems, archived, and converted to CERR format
- Matlab-based
- Freely available from http://radium.wustl.edu/cerr
Recomputed DVHs generally the same to within RMSE of 1%
CERR

- Has been downloaded nearly 1,000 times in the last year by users from 37 different countries
- Is used by clinical trial QA physicists in Sweden, UK, Japan, US, Netherlands.
- Is used by optimization researchers.
- E.g., PMH project by Tim Craig et al. to compute probabilistically desirable target volumes.
This figures shows the three target volumes: ‘CTV 1 3mm’, ‘CTV 2 3mm’, and ‘CTV 3 3mm’.
Prescription (Eisbruch)

• The prescription for this case was adapted from detailed suggestions by Avi Eisbruch:
  
  • 72 Gy to the CTV 1 3mm structure.
  
  • 64 Gy to the CTV 2 3mm structure,
  
  • 60 Gy to the CTV 3 3mm structure.
  
  • The mean dose to the parotid glands should be held as low as possible,
  
  • but not at the expense of an adequate target dose distribution. Preferably, one parotid gland at least should be held below 26 Gy.
  
  • The mean dose to the oral cavity should be held as low as possible, but not at the expense of an adequate target dose distribution.
• The mandible should receive no more than 70 Gy max dose.

• The max to the cord should be 45 Gy (hard constraint),

• The max to the cord_3mm should be 50 Gy (hard constraint),

• The max to the brainstem (brainstem) should be 54 Gy (hard constraint).

• The max to the brainstem expansion (brainstem_3mm) should be 58 Gy (hard constraint).

• An adequate target dose distribution will have:
  – Min 93% of prescribed dose
  – Max <115%

• Of course, it is impossible not to have heterogeneities near the integrated boost volume.
You can easily derive new structures using the structure fusion tool, under the structures menu (‘Derive new structure’).
IMRT beamlet generation: the ORART toolbox

- Software routines giving Matlab/CERR users access to beamlet dosimetry.
- Based on written CWG specification.
- Integrated with CERR.
- Generation of beamlet data
- Dosimetry data access within Matlab
- **Multiple output formats** (binary and ASCII-based).
Facilitating operations research activity in radiation therapy

- Operations researchers typically start with a matrix description of the problem.
- In our case:
  \[ d_i = \sum_{j=1}^{\text{Num beamlets}} A_{i,j} w_j. \]
- Much, much faster than iteratively recomputing dose
Access to beamlet data in Matlab

```matlab
>> doseNum = 1; structNum = 11; beamletNum = 1;
>> planC{12}(doseNum).IMDosimetry.beamlets(structNum,beamletNum)
ans =
    structureName: 'Target 1'
    format: 'uint8'
    influence: [1907x1 uint8]
    fullLength: 8054
    indexV: [1907x1 uint32]
    maxInfluenceVal: 0.0396
    sampleRate: 2
    beamNum: 1
```
The green target is the CTV 3 3mm. Other structures created included left and right parotids minus the CTV 3 3mm, as I gave the CTV priority.
Simple quadratic programming example of beam weights
Obviously there are some relatively hot regions outside the ‘CTV 3 3mm’ (the anchor zone weight perhaps could be increased). The max dose is 83.6 Gy.
Here are the DVHs. Not that great, but it’s something to beat up on. In particular the most spared parotid still gets about 28 Gy mean dose.
The ORART benchmark ‘paradigm’

1. Treatment planning example from the ORART test set (CERR)

2. Beamlet dosimetry (ORART Toolbox)

3. Optimization algorithm (third-party)

4. Comparisons and conclusions

Pooled results from other investigators/planning systems
Current weaknesses

- Lack of built-in leaf sequencing.
- Lack of ability to re-export CT and contour data into commercial treatment planning system. (But we almost have this capability now.)
The goal: “scientific” comparisons of IMRT optimization research results

That is, fair comparisons of IMRT treatment planning results, from multiple investigators, using standard realistic patient datasets
Challenge #2: Incorporating accurate dose calculations
The problem of scatter tails

- The scatter tails of beamlets take up most of the non-zero volume of the influence matrices
- But they contribute little to the ability to shape dose
- Yet it is important to factor in the influence of scatter…
- So how do we do it?
Beamlets are usually simplified for the optimization phase

Beamlet with 4 cm tail

Beamlet with 1 cm tail
The Iterative scatter correction method

- Estimate the scatter dose using full dose (primary plus scatter) beamlet matrices and best current estimate of beam weights.
- Adjust prescription dose, on a voxel by voxel basis, to reflect the expected scatter contribution.
- Solve for optimal beam weights using primary-only beamlet matrices.
- Recompute full dose using stored beamlets.
- If full dose is close enough to prescription, terminate; otherwise go to step 1.
- Typically, two iterations are sufficient.

(Zakarian et al., ASTRO 2004; also MSKCC)
Challenge #3: Mastering the ‘data-glut’
Approach: use adaptive gridding of dose points (El Naqa, et al., unpublished)
Key element is shortest distance to critical structures

Figure 1: Left: Treatment plan slice, showing target volumes and critical structure (brain stem) position. Right: the distance transform (lesser of distance to nearest target and critical structure).
Adaptive grid generation

• **STEP 1:** The contours are extracted. Gridding is more aggressive near the more significant structures. A weighted distance transform is used to generate the feature map.

• **STEP 2:** Generate mesh. Floyd-Steinberg error diffusion algorithm, modified to include dithering.

• **STEP 3:** Delaunay triangulation is used to generate the mesh structure.

• **STEP 4:** refinement by a regularized Laplacian (second derivative) smoothing.
2D error-diffused method
Extension to 3-D

Regularized 3d error diffused mesh
Other approaches

- Use coarse gridding on a regular grid for some structures
- Adaptive coalescing of voxels in old NOMOS planning system
- Aggressively cutoff beamlet low fluence contributions
- Randomly keep only some beamlet elements (DKFZ proposal)
Challenge #4: Controlling dose distribution characteristics & tradeoffs
Controlling dose falloff: the Anchor zone method
Hot spot outside target goes up to 80 Gy.

Hot spot outside target 74 Gy
The weight paradox: hard-to-control tradeoffs and the lack of clear priorities

- Normal tissue weights should be large enough so the mathematical engine tries to reduce dose to those structures.

- Target weights should be much larger than normal tissue weights so that good target coverage is not compromised...but...

- There is no perfect compromise
  - Very high target weights: engine neglects normal tissues
  - Not very high target weights: engine does not preserve target dose characteristics
Interim conclusion

• The efficient control and use of linearly weighted objective functions is problematic
• We need a new paradigm with more control over tradeoffs...
Approach: prioritize the prescription goals (‘Prioritized prescription goal planning’)
Current paradigm

Input algorithm parameters:
Hard constraints, objective function weights.

Solve an optimization problem

Review: is this the best plan possible? & is it clinically acceptable? If “no” to either, change input and re-run.

Prioritized prescription optimization

Input prioritized prescription planning objectives

Solve a series of optimization problems which add the next lower priority goal at each iteration. Higher priority goals are “constraints” in lower priority iterations.

Review: was the prescription statement appropriate? & is the resulting plan clinically acceptable? If “no” to either, change input and re-run.
<table>
<thead>
<tr>
<th>objectives</th>
<th>constraints</th>
</tr>
</thead>
</table>
| **step 1**
| target coverage, cardinal OARs | minimize $F_1 = \sum_{\text{all voxels}} (D_j - D_{\text{pres}})^2$ and maximize $D_{\text{min}}$ for all targets | $D_{\text{max}}$ for spinal cord, brainstem, cord+3mm, brainstem+3mm, mandible, and hotspot zone |
| **step 2**
| additional OARs | minimize $D_{\text{mean}}$ for parotid glands and oral cavity | as in step 1 and
| | | • max value for $F_1$ for all targets
| | | • min value for $D_{\text{min}}$ for all targets
| | | • max value for $D_{\text{max}}$ for all targets as achieved in step 1 |
| **step 3**
| dose falloff | minimize $D_{\text{mean}}$ in anchor zone, cord, brainstem, and mandible | as in step 2 and
| | | • max value for $D_{\text{mean}}$ for parotid glands and oral cavity
| | | as achieved in step 2 |

anchor zone = (Union of targets + 5cm) − (Union of targets + 0.5cm)
hotspot zone = skin − (Union of targets + 0.5cm)
prescription

• PTV1: 72 Gy
• PTV2: 54 Gy
• PTV3: 49.5 Gy

Maximum doses:
spinal cord 45 Gy
spinal cord + 3mm 50 Gy
brainstem 54 Gy
brainstem + 3mm 58 Gy
mandible – PTV1 70 Gy
hotspot zone 50 Gy
slip factor

no slip: then step 2 and step 3 yield the same solution as in step 1

introduce slip factor $1+s$ (here: $s=0.2$) for the dose variance in the targets (i.e. $\sim 10\%$ in standard deviation)

for all targets ($i=1..3$):

objective function: $F_i = \sum_{\text{all voxels}} j (D_j - D_{\text{pres}})^2 / \#\text{voxels}$

objective value after step 1: $F_i(1)$

constraint in step 2: $F_i \leq (1+s) F_i(1)$

constraint in step 3: $F_i \leq (1+s)^2 F_i(1)$

all other constraints: no slip
Challenge #5: Making tradeoffs responsive to outcomes models
But what do these simple equations have to do with outcomes?
Can we use prescription goals which are more likely to be related to outcomes?
**Endpoint type**

- **Inflammatory/ulcerative**
  - Acute
    - Mucositis
    - Diarrhea
    - Skin rash
    - Esophagitis
  - Late
    - Rectal bleeding
    - Sporadic pneumonitis
    - Skin rash
    - Brain necrosis

**Examples**

- Xerostomia
- Cognitive deficits
- Growth inhibition
- Chronic small bowel toxicity
- Rad. Induced liver disease
- Lung fibrosis

**Analysis methods**

- Function of hot spot absolute areas or volumes exceeding threshold doses (Bradley et al.; Thames et al.).

- Function of mean dose or fractional volume exceeding threshold doses.

**Local response endpoints**

**Collective response endpoints**
Elements of the “standard” NTCP volume effect model: EUD and LKB

- Sigmoidal dose response curve, parameters include
  - Slope parameter
  - TD50 parameter (tolerance dose for 50% response)
- Equivalent uniform dose equation. Typically a power-law (Lyman-Kutcher-Burman, Mohan, Niemierko, NKI)
Generalized Equivalent Uniform Dose is just a power-law weighted average of the dose

\[
gEUD(d; a) = \left( \frac{1}{N} \sum_{i=1}^{N} d_i^a \right)^{1/a}
\]

\[
= \left( \frac{1}{N} \sum_{i=1}^{N} d_i \left( d_i^{a-1} \right) \right)^{1/a}
\]

‘a’ is the localizing parameter.
Rapid loss of tolerance with volume when $a = 1$ (collective-response endpoints)

Small loss of tolerance with volume when $a = 10$ (local-response endpoints)

(From Moiseenko, Deasy, Van Dyk, 2005)
Can gEUD replace dose-volume metrics?
<table>
<thead>
<tr>
<th>Structure</th>
<th>Dose-volume endpoint</th>
<th>$a$ for highest correlation</th>
<th>Spearman correlation</th>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Prostate PTV</td>
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</tr>
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Table 1. Values of $a$ (gEUD variable parameter) that had the highest correlation with various dose-volume endpoints, along with the Spearman rank correlation coefficient. All associated p-values were negligible ($<10^{-6}$).

(Clark et al., unpublished)
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**Table 1.** Values of $a$ (gEUD variable parameter) that had the highest correlation with various dose-volume endpoints, along with the Spearman rank correlation coefficient. All associated p-values were negligible ($<10^{-6}$).

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The situation may be a bit better than that, because…

- Correlation between gEUD and outcome may be as good as for dose-volume constraints and outcome
- Example: gEUD(a = 3.2) has as good a Spearman’s correlation with severe acute esophagitis as do DV constraints (0.42).
gEUD used to drive treatment planning

- May often be useful for driving treatment planning for normal tissue or target objectives.
- Cannot completely replace the concept of tolerance based on a small, defined volume, irradiated to a high dose (ulcerative lesions).
- ‘Upper-mean-tail’ functions may be better for that.
  - Mean of the hottest x% of a volume.
  - Is a linear function
  - Cannot preserve linearity if we go to min of hottest x%
  - Idea needs to be tested against outcomes datasets
Concluding thoughts

- IMRTP planning can be made to be much more automated, responsive to clinical goals, and dosimetrically reliable.
- IMRTP research can benefit greatly by using shared benchmark test cases.