**Proton Treatment Planning in the Presence of Uncertainties**

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AAPM 2018

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**Radiotherapy workflow**

- Patient info
  - Guidelines
- Info on system capabilities and limitations
- Plan evaluation
  - Plan
  - Criteria
- Delivery
  - Info acquired during delivery
- Treatment evaluation

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**Treatment plan robustness** is the ability to retain objectives under the influence of uncertainties

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**Proton range calculation uncertainties - Estimation**

- Proton range in tissue calculated with ambiguous HU – RPS translation

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![Calibration curve](image)
Proton range calculation uncertainties - Remedies

Robustness increase with
- Margins along each beam
- Multiple beams
- Beam orientation selection

Proton range calculation uncertainties – Remaining issues

Highly modulated beams
- No geometric margin can fix this
- Modulation reduction helps
  IMPT → limited modulation → SFUO

Intervening tissue variations

- Proton range depends on tissue composition and density
- Any tissue variation in proton path
  → range changes
  → dose distribution variation
- Setup errors
  Intra-fractional motions and deformations
  Inter-fractional anatomical changes
  range uncertainty
Intervening tissue variations - Estimation

- Setup errors – isocenter shifts

- Intra-fractional motion and deformation

- Inter-fractional anatomical variations
Intervening tissue variations - Remedies

Robustness increase with
- Margin along beam
- Multiple beams
- Beam orientation selection
Intervening tissue variations - Remedies

Robustness increase with

- Margin along beam
- Multiple beams
- Beam orientation selection
- Fractionation

Plan verification and adaptation schemes

Interplay - Estimation

- Interference of dynamic pencil beam delivery with the target motion results in local dose heterogeneities within the target
**Interplay - Remedies**

Do you use any of the following to reduce interplay effect?

- Fractionation
- Motion reduction
- Motion limits for PBS treatments
- Multiple fields
- Combinations of the above

Survey on PBS robustness: June/July 2018, answered by 11/20 US proton centers with PBS

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**RBE variability - Estimation**

- Clinically used proton RBE = 1.1 but

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**RBE variability - Remedies**

- Empirical methods to spare organs behind distal fall off
  - Multiple beams
  - Beam direction
  - Reduced physical dose limits

<table>
<thead>
<tr>
<th>Metric</th>
<th>Goal</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>D_{0.1cc}</td>
<td>56.6 Gy</td>
<td>58 Gy</td>
</tr>
<tr>
<td>D_{10cc}</td>
<td>55.4 Gy</td>
<td>56 Gy</td>
</tr>
<tr>
<td>D_{50cc}</td>
<td>52.4 Gy</td>
<td>54 Gy</td>
</tr>
</tbody>
</table>

- LET-weighted dose calculation and optimization
RBE variability - Remedies

- Empirical methods to spare organs behind distal fall off
  - Multiple beams
  - Beam direction
  - Reduced physical dose limits
  - Physiological motion

LET-weighted dose calculation and optimization

Clinical practice

Which uncertainties are usually accounted for in treatment planning at your clinic?

<table>
<thead>
<tr>
<th>ANSWER CHOICES</th>
<th>RESPONSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range calculation uncertainties</td>
<td>100.00%</td>
</tr>
<tr>
<td>Setup errors</td>
<td>100.00%</td>
</tr>
<tr>
<td>Intra-fractional anatomical variations (excluding interplay)</td>
<td>73.75%</td>
</tr>
<tr>
<td>Interplay effects between moving anatomy and scanning beam</td>
<td>36.36%</td>
</tr>
<tr>
<td>Inter-fractional anatomical variations (diluted to variation in target position relative to other tissues, not severe changes)</td>
<td>36.36%</td>
</tr>
<tr>
<td>Inter-fractional variations</td>
<td>96.36%</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>8.00%</td>
</tr>
<tr>
<td>Total Respondents:</td>
<td>11</td>
</tr>
</tbody>
</table>

Uncertainties and PTVs

Beam specific PTV
Reminder

- The goal is not to treat more but to treat better

Solution – Robust optimization

- Incorporation of error scenarios in optimization
- Common error scenarios:
  - range uncertainty
  - isocenter shifts
  - multiple CT sets
- Optimization approaches
  - Probabilistic
  - Worst-case
- Robust objectives and constraints for targets and OARs

Robust optimization

Target coverage
- static anatomy
- ±3.5% range uncertainty
- ±5 mm isocenter shifts (x, y or z)
- Inhale / Exhale / AVG
Robust optimization – Current limitations

- Worst-case of few uncertainties included
- Difficult implementation of probabilistic simulations
- No interplay included
- Difficult to distinguish between random and systematic errors
- Optimization is slow
- Difficult to evaluate

Robust optimization – Evaluation

Photon – Proton comparison

Equivalent scenarios
  - setup for photons
  - setup and range for protons
Calibration of old criteria with new for photons
Compare plans with the same metric
What is missing

- Robust optimization: fast MC, 4D, biological planning
- Robustness evaluation: Standard tools in commercial TPS
- Methods to score and compare plan quality that includes robustness to facilitate clinical decision making
11
Total Responses

Date Created: Monday, March 12, 2018
Complete Responses: 11

Q1: Institution

<table>
<thead>
<tr>
<th>ANSWER CHOICES</th>
<th>RESPONSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maryland Proton Treatment Center</td>
<td>9/10</td>
</tr>
<tr>
<td>Mayo Clinic Proton Beam Therapy AZ</td>
<td>9/10</td>
</tr>
<tr>
<td>Mayo Clinic Proton Beam Therapy WI</td>
<td>9/10</td>
</tr>
<tr>
<td>MD Anderson Proton Beam Therapy Center</td>
<td>9/10</td>
</tr>
<tr>
<td>Mount Sinai Cancer Institute</td>
<td>9/10</td>
</tr>
<tr>
<td>North Carolina Memorial Proton Center</td>
<td>9/10</td>
</tr>
<tr>
<td>Prince Proton Therapy Center AZ</td>
<td>9/10</td>
</tr>
<tr>
<td>Proton Therapy Center AZ</td>
<td>9/10</td>
</tr>
<tr>
<td>Texas Proton Therapy Institute</td>
<td>9/10</td>
</tr>
<tr>
<td>University of Florida Health Proton Therapy Institute</td>
<td>9/10</td>
</tr>
<tr>
<td>University of Pennsylvania Roberts Proton Therapy Center</td>
<td>9/10</td>
</tr>
</tbody>
</table>

Q4: Which uncertainties are usually accounted for in treatment planning at your clinic?

<table>
<thead>
<tr>
<th>ANSWER CHOICES</th>
<th>RESPONSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range calculation uncertainties</td>
<td>12/10</td>
</tr>
<tr>
<td>Edge areas</td>
<td>12/10</td>
</tr>
<tr>
<td>Interfractional anatomical changes including setup</td>
<td>12/10</td>
</tr>
<tr>
<td>Tumor motion and organ movement and organ motion</td>
<td>12/10</td>
</tr>
<tr>
<td>Setup error and organ motion</td>
<td>12/10</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>12/10</td>
</tr>
</tbody>
</table>

Other (please specify): We have introduced a 4D calculator, but at this time it is not widely used
Q5: How are these uncertainties usually accounted for?

Answered: 11    Skipped: 0

- Margins
- Dose reoptimisation
- Reprojection/track to field
- Variations in the areas
- Other (please specify)

Other (please specify): Intrinsic robustness of large spot size

Q6: Your approach for achieving and evaluating robustness is

Answered: 11    Skipped: 0

- SFUD
- Reduced IMPT
- Other (please specify)

Q7: Do you use SFUD or reduced modulation IMPT to increase plan robustness (eg specifying minimum isodose line for each field cover the target)?

Answered: 11    Skipped: 0

- Yes
- No
- Other (please specify)

Other (please specify): If SFU can be used then that is the first method.
Q8: What software do you use for robust optimization?

Other (please specify): We just introduced our in-house method that includes biologic and robustness along with Monte Carlo calc during optimization.

Q9: Do you use robust objectives/constraints for

Let me explain: Sometimes targets only, sometimes targets and OARs
Targets and select OARs, not all OARs
Usually, margins and SFUD are used, sometimes robust for targets and OARs

Q10: How do you evaluate plan robustness to uncertainties?

Other (please specify): PTV for prostate, CTV coverage in scenarios for other sites.
Q11: Are the error scenarios independent, i.e., +x, -x, etc.

Other (please specify): Each scenario is independent, i.e., +x, -x, etc.

Q12: For the error scenario calculation, which type of errors do you include?

Other (please specify): All get translation and range; for certain cases multiple CT sets are used, and certain cases we look at rotations. Interplay is just being introduced.

Q13: Is robustness performed and evaluated for every plan?

Let me explain Population-based For all PBS plans
Q14: Is robustness considered during plan evaluation and selection?

- Yes: 90.1%
- No: 0.0%
- No remarks or comments were made: 0.0%
- Not reported: 0.0%

Total Responses: 10

Q15: How do you present the results of robustness evaluation?

- Evaluated by physics, presented only on request: 60.0%
- Evaluated by physics, presented only on request for certain cases: 30.0%
- Other (please specify): 10.0%

Total Responses: 10

Other (please specify): Also look at the dose distribution of the robust scenarios for certain cases.

Q16: If your clinic also has conventional radiation, how do you deal with the uncertainties there?

- Yes: 90.0%
- Same approach as for photons: 0.0%
- Other (please specify): 10.0%

Total Responses: 10
Q17: How do you deal with uncertainties and robustness for inter-modality plan comparisons?

- No intermodality plans, proton only.

Q18: Do you compensate for range calculation errors with a margin?

- Sometimes
- Intrinsic robustness of large spot

Q19: Do you use a recipe for this margin?

- Formula/values used: 3.5% for PBS, 2.5% + 2mm for App/Comp based
  - 2.5% + 1.5mm
  - Variable: 3% + 1mm; 2.5% + 3mm H&N/Brain
  - Typically 3%, but depends on hardware and other factors; sometimes 5%
  - 2.5, 1
  - Uniform scanning, 2.5% + 2mm, PBS 3.5%
Q23: How do you compensate for setup errors?

- Other (please specify): not optimization, but verify plan on multiple images

Q24: How do you compensate for intra-fractional density variations?

Other (please specify): not optimization, but verify plan on multiple images

Q25: Do you calculate motion along the beams in WEPL (water equivalent pathlength)?

Other (please specify): I do not understand the question.

I meant the max difference in WEPL along the beam from the surface to the distal edge of the target during a breathing cycle. Stella
Q26: Do you have limits of the observed motion above which PBS is not used?

- **Yes**: 60.4% (10 responses)
- **No**:
  - 27.4% (4 responses)
  - (Please specify)
  - Total Responses: 10

Specify 0.5 cm of target motion:
- Less than 1.5 cm
- 1 cm limit
- 1 cm

Q27: How do you compensate for inter-fractional density variations? (for example relative prostate-to-bone position, not severe anatomical changes)

- **Yes**: 60.4% (10 responses)
- **No**:
  - 27.4% (4 responses)
  - (Please specify)
  - Total Responses: 10

Specify re CT and dose assessment

Robust evaluations

Q28: For PBS, do you use any of the following to reduce interplay effect?

- **No**: 60.4% (10 responses)
- **Yes**:
  - Multiple beam angles: 36.4% (6 responses)
  - Breath hold: 36.4% (6 responses)
  - Other (please specify):
    - We have a large spot but we do not treat moving targets yet
    - Multiple beam angles
    - Breath hold
  - Total Responses: 10
Q29: Do you have available tools to calculate interplay?

Answered: 11    Skipped: 0

- Yes
- Yes, interplay effects are calculated for patients with breathing motion
- Yes, interplay effects are calculated for specific target volumes or patient groups
- Yes, interplay effects are calculated automatically
- No
- Other (please specify)

Q30: Does lack of interplay calculation tools prevent you from treating patients?

Answered: 11    Skipped: 0

- Yes
- Other (please specify)

Other (please specify): If it is outside our comfort zone and if we did not have interplay calculation then yes it would prevent treatment of some patients

Q31: What image guidance do you use for treatment?

Answered: 11    Skipped: 0

- CT on Rails
- Other (please specify)

Other (please specify): CT on Rails
Q32: If you are using a target surrogate for registration, what is it? (ie fiducial markers, bone, etc)

**Responses:**
- For planer x-rays fiducials and bone depending the tx site
- Sometimes bones, sometimes markers
- Fiducial marker, surgical clips, calcifications
- Fiducial, bone
- Fiducial markers, wire on scars, bony anatomy
- Fiducials in prostate, bone elsewhere
- Implant marker, surgical clips, calcifications

**Answered:** 8  **Skipped:** 3

**Responses For planer x-rays fiducials and bone depending the tx site**
- Sometimes bones, sometimes markers
- Fiducial marker, surgical clips, calcifications
- Implant marker, surgical clips, calcifications
- Fiducial, bone

Q33: Do you monitor motion during irradiation?

**Answered:** 11  **Skipped:** 0

**Yes (please describe briefly your method)**
- Surface imaging
- Anzai laser interferometer, which functions like a RPM

Q34: Do you verify the dose distribution with QA CTs acquired throughout treatment?

**Answered:** 11  **Skipped:** 0

**Let me explain:** Population-based
Q35: Do you use CBCT-based virtual CTs to calculate dose and/or adapt plans?

<table>
<thead>
<tr>
<th>Answer</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respondents</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Let me explain: In research phase to calculate vCT

Q36: What percentage of your patients do you think have modifications to their plans?

<table>
<thead>
<tr>
<th>Responses</th>
<th>45</th>
<th>25</th>
<th>22%, 31% of non-prostate</th>
<th>40 to 50%</th>
<th>10</th>
<th>20</th>
<th>30%</th>
<th>5-15%</th>
</tr>
</thead>
</table>

Q37: What tools do you think you are missing for efficient robust treatment planning?

<table>
<thead>
<tr>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faster calculation and optimization times. Better tools to present robustness data to physicians.</td>
</tr>
<tr>
<td>Interplay calculator, fast error scenario calculator</td>
</tr>
<tr>
<td>Using worst case optimization is suboptimal, can miss certain things.</td>
</tr>
<tr>
<td>Multi-image and 4D optimization including robustness is needed.</td>
</tr>
<tr>
<td>Having robust biological planning is also needed.</td>
</tr>
<tr>
<td>RS7 is coming out with deformed target contour for robust optimization.</td>
</tr>
<tr>
<td>After that, I think we need an in-room proton CT to deal with uncertainty once and for all.</td>
</tr>
<tr>
<td>Currently, we evaluate scenarios independently after optimization. It would be ideal if dose information from robust optimization was saved and displayed. We look forward to using the new tools when we upgrade to RS8a.</td>
</tr>
<tr>
<td>Automated analysis</td>
</tr>
<tr>
<td>Fast Monte Carlo. Would like to avoid the &quot;garbage-in-garbage-out&quot; effect.</td>
</tr>
</tbody>
</table>
Q38: Do you have something to add?

Responses: It would be nice to see "PTV" concept totally gone from proton and photon therapy and use of robust optimization be mainstream.

These surveys are a great idea. This is the second one I have filled out so far. Have you published any results yet?

I like them too. I am afraid though that people are tired of them. I think it would be difficult to publish this with so few responses. Stella