Proton Treatment Planning: From Physics to Clinical Reality

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OUTLINE

• Background
• Proton beam delivery technologies and treatment techniques
• Treatment Planning
• Uncertainties in proton therapy.
• Summary

History of Proton therapy

• The existence of Proton was demonstrated by Rutherford in 1919.

• Robert Wilson proposed that:
  - accelerated protons and heavier ions be considered for RT of patients (1946).
  - developed the Harvard Cyclotron (160MeV) in 1949 / went clinical 1961
  - Europe, Upsala, 1957, 185 MeV Synchrocyclotron
The Proton

Hydrogen nucleus
Charge is +1, Atomic weight = 1.008 amu

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PROTONS

Particles with charge and mass:
- Defined range in tissue
- Proportional to energy
- Unmodulated: deposit dose in sharp Bragg Peak with no dose delivered beyond that point
- Bragg peak spread out toward surface to treat tumors

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PROTONS

Contrast with photons (x-rays)
- Photons continue to deposit dose beyond target in tissue.

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The Pristine Bragg Peak

- losses most of energy in the last few millimeters
- Property of charged particles
- Allows depth control of dose
- NO DOSE deeper
- Minimal scatter of bundle
- Consequence of particle "weight"
- Accuracy in "aiming" at target

Energy vs Depth (Range)
- Placement in (x,y) and (z)

Absorber changes depth
- Simple mechanical means
- Precise depth control by adjusting absorber thickness
- Intensity not affected

Tracks in Patient

 Courtesy of Hanne Kooy

Proton Technologies and Techniques

- Proton beam delivery technologies and treatment techniques

Technologies:
- SS  DS  US  PBS

Techniques:
- SOBP  SFUD  SFUDo  IMPT
- 3DCRT  IMRT
Delivery Methods: Passive Scattering

- Accelerated protons are near monochromatic and form a beam of small lateral dimension and angular divergence.
- There are two approaches to form a desired dose distribution:
  1. Passive Scattering and modulation (referring to the method of spreading the beam laterally and with method of spreading the beam in depth).

Physics of \( p \) is understood...

- Early use of PT was possible because the proton beam could be shaped and manipulated completely by mechanical means.
- Passage through an absorber means
  - Reduction in energy but NOT intensity (number)
  - Dispersion (scatter) of beam

The Tools of Scattering

- Degraders
  - Low-Z: Low Scatter per Large Energy Loss
  - High-Z: Large Scatter per Low Energy Loss
  - Order and combine for simultaneous control of energy loss and scatter

http://hubepl.harvard.edu/~gotschalk
The Tools of Scattering

- Beam Spreading
  - Highland’s Formula
    \[ n_i(x) = \sum \left( 1 + \frac{1}{2} \frac{d_i}{d_{i+1}} \right) H\left( 1 - \frac{1}{2} \frac{d_i}{d_{i+1}} \right) \]
  - For a stack of degraders:

Of course, the details of the calculations and formulas are not visible in the image. The paragraph continues:

Past & Present: SOBP Scattered Fields

Use of absorbers + intensity-modulation creates the SOBP dose distribution.

- Match target extent in depth
- Modulation wheel rotates in the beam, energy shift determined by height of step & weight determined by width of step
- Purely mechanical!
- SOBP encoded in modulator wheel construction
- Create flat dose distribution with Gaussian scatterers
- CT planning to construct field aperture and compensator
- 3D coverage of target

This, after 40 years, is still the dominant form of treatment!

Delivery Methods: Pencil Beam Scanning

- Dynamic Scanning of a pencil beam laterally and in depth
  - Involves scanning of a PB both laterally and in depth (by changing its energy) -> in a near arbitrary dose distribution laterally and dose sharpening in depth (Pedroni et al)
  - Lateral distribution determined by the lateral positions and weights of each pencil beam of a chosen energy
  - Distribution in depth is determined by weighting the pencil beam at each position within the field.

Note: Beam Scanning is the only practical technique which enables IMPT to be performed.

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Pencil-Beam Scanning – PBS

Magnetically scan p beam left / right (X,Y) and control depth with Energy (Z)

Fully electronic and no mechanical

A full set, with a homogenous dose conformed distally and proximally

Images courtesy of Eros Pedroni, PSI

MLC in Completed Proton Gantry

MLC in Completed Proton Gantry
Proton Therapy

- Ranges of 4-38 cm (70-250 MeV) are required to irradiate all possible target volumes in an adult patient.

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Proton Treatment Planning Commissioning

- The machine specific data are acquired, imported, modeled and validated in the TPS by the Physicist.

- The number of measurements performed for passive scattering commissioning is higher than PBS.
Proton Treatment Planning Commissioning

- The **options** are given by the combination of a range modulator and second scatterer used in a given span/energy.

- The **suboption** is a subspan of the option using its own beam current modulation.

- Each room has **8 double-scattering options**. Each **option** has **3 suboptions** that use a different beam current modulation.

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Planning of Proton Therapy

Dose calculation

Dose calculation algorithms comparison:

- Ray-tracing
- Pencil beam
- Monte Carlo


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Proton Treatment Planning Commissioning

- TPSs are predominantly based on a Pencil Beam Algorithm.
- For passive scattering Eclipse measurements at the thinnest and thickest part of the RMW are required. The data to be acquired for passive scattering are:

  **Measurements in water:**
  - Pristine peak, PDD/SOBP – in water

  **Measurements in air:**
  - Open field profiles measurements beam divergence => **Virtual SAD**
  - Fluence Along Beam Axis fitted based on inverse square law => **Effective SAD**
  - Half Beam Profiles Penumbra Width => **Effective Source Size**
Beam parameters/ TX length/width

[Gal et al. 1993]

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Proton treatment planning commissioning

For PBS Eclipse Treatment Planning Commissioning to determine:

- Integral pristine peaks in water measured throughout clinical range of energies

- Spot profiles in air measured as a function of elevation throughout clinical range of elevations and energies (with/without range-shifter)

Integral pristine peaks

- 27 peaks from 110 MeV to 226.7 MeV
- Longest range = 32.15 cm
- Shortest range = 7.72 cm
- Calibrated absolutely in Gy mm$^2$/MU so that Eclipse can calculate MU.
In-air X spot profiles at (iso)

In-air X spot profiles (-30 cm elevation)

In-air Y spot profiles (+33 cm elevation)
In-air Y spot profiles at (iso)

In-air Y spot profiles (-30 cm elevation)

In-air X spot size vs elevation (no RS)
**PBS Treatment Planning Commissioning**

*In-air X spot size vs elevation (with RS)*

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**Proton Treatment Planning Commissioning**

- Dose calculation has to be validated against measurements and MC:
  - In water phantom
  - Inhomogeneities
  - Oblique beams
  - Different geometries
- Integrity of the process to be verified:
  => CT/TPS/Comp/RV/Delivery

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**Eclipse model parameters affecting plan quality**

- Minimum MU/spot (fixed)
- Layer spacing between along beam direction
- Spot spacing perpendicular to beam direction (tunable)
- Elevation (SAD or SSD setup)
Proton Treatment Planning Beam Parameters

- Protons have a sharp lateral beam penumbra which decreases with increasing beam energy and, hence, depth of penetration.
- Proton beam penumbra is widest in the Bragg peak region where the proton energy is least.
- Penumbra is narrower for proton than photon beam for penetrations up to 17-18 cm.

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Proton Treatment Planning: Inhomogeneities

- The effect of tissue inhomogeneity is greater for protons than for photons (Gastie et al., Med. Phys. 5).
- Failure to allow for a higher density along the proton path may result in a near zero dose in a distal segment of the target due to the reduced range of the protons.
- Penumbra is minimally affected for the materials limited to the human body, but it changes significantly for other materials as it is caused by multiple scattering.
- Conversely neglecting to account for an air cavity upstream of the target => in high dose deposited in distal normal structures.

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Planning of Proton Therapy

- Illustration of the volume and margins relating to the definition of the target volume per ICRU 62.
Planning of Proton Therapy

Volumes and margins related to the OARs:

- Proton-specific issues related to the PTV
  - For photon beams the PTV is primarily used to delineate the lateral margin.
  - For protons in addition to lateral margins a margin in depth has to be left to allow for uncertainties in the knowledge where the distal 90% IDL would fall.
  - Proton Beam Energy should be selected in a way that the CTV is within the irradiated volume taking into account both motion and range uncertainties.
  - Since the lateral and the margins in depth solve different problems each beam orientation would need a different PTV.
  - Alternatively the beam parameters are determined based on the CTV adding the lateral and range margins to the TPS alg.

In practice the beam parameters are determined based on the CTV adding the lateral and range margins to the TPS alg for each beam.

For Scatter beam treatments, the lateral margins would be designed into the aperture in the BEV and depth in the compensator.

For scanned Beams and IMPT these margins would influence which pencil beam would be used and each one’s depth of penetration.

It is “required” that the dose distribution within the PTV is recorded and reported, therefore a PTV relative to CTV based on lateral uncertainties alone is proposed by ICRU 78.
Planning of Proton Therapy

- Individual proton beams can be shaped three dimensionally to the target:
  a. Perpendicular to the beam axis - aperture
  b. Along the beam axis - range and SOBP

Beam specific PTV margins MUST be related to the range uncertainties!

Lateral margins are set to ensure that the prescribed dose from each proton beam encompasses the CTV and takes into account IM, SM and penumbra margins. Distal and proximal margins are set from CTV calculated (Moyer, IROBP 49, 2001):

- DM = (0.035 x CTVdistal) + 3 mm
- PM = (0.035 x CTVproximal) + 3 mm

3.5% uncertainty in the CT and their conversion to relative proton linear stopping power
3 mm added to correct for range uncertainty due to compensator manufacturing, etc.

Planning of Proton Therapy
Patch Field

- Patched different from matching
- Targets wrapping around critical structures
- Spare OARS
- Each beam treats a part of the target
- No perfect match possible
- Hot & Cold regions possible
- Must know lateral and distal penumbra
- Clinical judgment required


Planning of Proton Therapy
Patch Field

- Patched beams should be selected:
  a. with short path lengths
  b. min. range uncertainties
  c. Qaed - very difficult

Unfortunately they are unavoidable for complex passive scattering plans.
Uncertainties in Proton Therapy

Sources of uncertainties:

- Patient related: Setup, motion, body contour, target definition, etc...
- Physics related: CT number conversion, dose calculation, etc...
- Machine related: Device tolerances, energy, delivery method, etc..
- Biology related: Relative biological effectiveness (RBE), etc..

Why are uncertainties dangerous in PT vs. XT?

- Protons STOP
- Protons are charged particle/scatter differently
- Their assessment is not trivial

“...If something goes wrong in the planning process it starts usually at the CT Simulator...”

Physics Issues:

- CT Calibration Curve:
  - Proton interaction ≠ Photon interaction
  - Multisegmental curves are in use
  - No unique SP values for soft tissue HU range
  - Tissue substitutes ≠ real tissues
  - Statistical and systematic variations in CT numbers
  - Image reconstruction artifacts (high Z materials)
**Uncertainties in Proton Therapy CT Calibration Curve Stoichiometric Method**

Step 1: Parameterization of H
Choose tissue substitutes
Obtain best-fitting parameters $A$, $B$, $C$

\[ H = N_{\text{rel}} \left( A \left(Z_{\text{pe}}\right)^{3.6} + B \left(Z_{\text{coh}}\right)^{1.9} + C \right) \]


Step 2: Define Calibration Curve
Select different standard tissues with known composition (e.g., ICRP)
Calculate H using parametric equation for each tissue
Calculate SP using Bethe Bloch equation fit linear segments through data points

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**Uncertainties in Proton Therapy CT Calibration Curve Stoichiometric Method • ICRU 78**

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**Uncertainties in Proton Therapy CT Calibration Curve Stoichiometric Method**

Is the 3.5% CTR correction for proton range uncertainty conservative?
Experimental evaluation of the relationship between the CTR and proton stopping power ratio was done at PSI using a stoichiometric method (Schaffner et al. 1998, PMB)

Conclusion: There is a 1.1% uncertainty in soft tissue and 1.8% in bone.

Reality...A decade later it is still **NOT** the current clinical practice! 3.5% standard...Further investigations needed.
Uncertainties in Proton Therapy

CT numbers

- HUs vary within 3% as a function of localization (Schneider 1996, PMB 41)
- HU for homogeneous materials vary between 1% to 2% (Schneider 1996, PMB 41)
- CBCT data cannot be used for plan calculations

Uncertainties in Proton Therapy CT

High Z artifacts

- Artifacts due to high Z materials (metal clips, markers, Calypso beacons, prosthesis, dental fillings, etc.) are common in RT and need to be identified at the beginning of the proton planning processes.

Advanced CT technology provides different phenomenological approaches for suppression of metal artifacts. For example:

a. Imaged base beam hardening corrections (corrected attenuation data by means of Fourier transformations)

b. Iterative correction of corrupt data (projected data through metal replaced by modified values)

c. Streak balancing (identify radial streaks and subtract them)
Uncertainties in Proton Therapy CT

High Z artifacts

Note: Image quality improvement for diagnostic purpose do not account for HU corrections at an accuracy level required for calculations in PT

Uncertainties in Proton Therapy

Motion and Setup uncertainties

• What happens if the beam is nearly tangential to the target?

Per ICRU 78

Correction through SMEARING

Compensator design based on radiological path = Unie et al., PMB 1984

Setup and motion corrected through smearing of the compensator based on:

\[(\text{Internal margin} + \text{Setup Margin})^2 + [0.03 \times (\text{distal CTV depth} + \text{bolus thickness})]^{0.5}\]

Corrects for Motion
Corrects for proton scattering

Moyers, et. al, IJROBP 49, 2001
Planning of Proton Therapy

- Motion management is critical.
  - Repainting/range comp, following the tumor site by site based-solution are different, strategies in photons don’t necessarily work in photons.

- The interplay effect just like in IMRT will be present for moving targets when IMPT is employed.

PBS & Motion

Scan Layer: 1

Scan Layer: 2
Uncertainties in Proton Therapy

Motion and Setup uncertainties

What do we know so far?

- Smearing improves dose distribution but increase the irradiated volume.
- Smearing degrades the distal end => increased range uncertainty.
- Smearing may increase dose heterogeneity.
- Repainting is an effective method to deal with IMPT motion uncertainty.
- Tangential beams to the surface may alter dose distribution and MUST be controlled carefully.
- It is desirable to avoid directions that bring the beam in line with large/variable heterogeneities or complex structure regions.
- Beams should not point towards critical structures (>2/3 of the PD).
- Imaging must be used for guidance.
Planning of Proton Therapy
RBE Uncertainties

• Clinical RBE: 1 Gy proton dose = 1.1 Gy Cobalt γ dose (RBE = 1.1 in the middle of SOBP)

• RBE weighted dose concept introduced by ICRU 73

• RBE vs. depth (LET) is not constant

• RBE also depends on
  – dose
  – biological system (cell type)
  – clinical endpoint (early response, late effect)

Planning of Proton Therapy
RBE Uncertainties

• Single RBE value of 1.1 may not be sufficient

• Biologically effective dose vs. physical dose

• Effect of proton nuclear interactions on RBE

Summary

• Photons and protons are different, however there are many similarities.

• Proton treatment planning commissioning and implementation process has to be developed based on the technology to be used and clinical applications.

• Uncertainties have a significant impact on dose distributions actually delivered and may affect outcome if not accounted for properly.

• It is essential to understand the impact of uncertainties and how we account for them in the planning process for different delivery technologies.

• PBS may be easier to commission and plan, however it is most difficult to manage uncertainties related to the actual treatment.
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Thank you.

The most conformal proton therapy techniques is:

1. Double scattering  
2. Wobbled beams  
3. Continuous scanned beams  
4. IMPT  
5. Single scattering

ICRU 78, Prescribing, Recording and reporting Proton-Beam Therapy, pg. 96, Journal of the ICRU Vol. 7 No2 2007, Oxford University Press.
In proton therapy the skin dose:

1. Increases comparative to megavoltage photon therapy
2. Is about the same like in IMRT
3. Decreases comparative to megavoltage photon therapy
4. Is not different from photon therapy
5. Is negligible

The PTV in proton therapy is dependent on beam orientation due to:

50% 1. The lateral penumbra of the beam
0% 2. The patient anatomy
45% 3. The range uncertainty
0% 4. The isocentricity of the proton machine
7% 5. The differences in directional target motion

The most straightforward approach to reduce the interplay effects in scanned beam therapy for a target moving in a heterogeneous media is:

51% 1. The use of an adequate PTV
57% 2. Dose repainting
4% 3. The use of PRVs
7% 4. To calculate the uncertainties
21% 5. To use multiple beam orientations
Measured lateral penumbra of a 200MeV proton beam compared to an 8 MV photon beam is:

- 1% narrower independent of depth
- 50% not always narrower
- 33% wider at any depth
- 4% identical
- 0% negligible

ICRU 78, Prescribing, Recording and Reporting Proton Beam Therapy, pg. 15, Journal of the ICRU vol 7 No2 2007, Oxford University Press.

Thank you.