Introduction to Proton Therapy

Lei Dong, Ph.D.
Scripps Proton Therapy Center
San Diego, California

Objectives
- Learn about the basic principle of proton therapy
- Introduce different delivery modes in proton therapy
- Understand the advantages and disadvantages of proton therapy

Outline
- A brief history
- Proton advantages
- Hardware: Cyclotron or Synchrotron?
- Delivery modes: PSPT; US; PBS
- Overall workflow comparison
- CT-Simulation
- IGRT
- Treatment planning
- Future development
A Condensed History

1904 Bragg & Kleeman report ion energy loss curves
1919 Rutherford proposes existence of the proton
1932 Lawrence & Livingston report 1st cyclotron
1946 Wilson proposes proton therapy
1954 Tobias et al treat patients w/ 340 MeV p at LBL
1990 First hospital-based proton treatment facility at Loma Linda University Medical Center
2006 Proton facilities open at MD Anderson and Univ. of Florida
2007 19 facilities worldwide (5 in US)
2012 10 operational + 12 being considered in US

Wilson proposes proton therapy

- In 1946 Harvard physicist Robert Wilson (1914-2000) suggested:
  - Protons can be used clinically
  - Accelerators are available
  - Maximum radiation dose can be placed into the tumor
  - Proton therapy provides sparing of normal tissues
  - Modulator wheels can spread narrow Bragg peak


Commissioned PT facilities (5)
- LLMUC (Optivus)
- MGH (IBA)
- MPRI (‘in house’)
- MD Anderson (Hitachi)
- UP PTI (IBA)

PT facilities to be commissioned (5+)
- St. Louis (StillRiver)
- Procure Oklahoma (IBA)
- ProCure Illinois (IBA)
- UPenn (IBA)
- SW (StillRiver)

Prototype (6-8)
Proton Advantages

A complete Bragg peak

From Newhauser, NPTC Internal Report
Why Protons are advantageous?

- Maximum dose at depth (Bragg peak)
- Relatively low entrance dose (plateau)
- Rapid distal dose fall-off
- RBE close to unity
- Comparable lateral penumbra
- Energy modulation

Clinical relevance of intensity-modulated therapy (protons vs photons)

- Complex anatomies/geometries (e.g., head & neck) with multiple critical structures
- Cases where Tx can be simplified, made faster
- Cases where integral dose is limiting (e.g., pediatric tumors)
- Cases where it may be possible to reduce side-effects (improve patient’s quality of life)

Medulloblastoma (3 y old boy)

- Photons (6 MV, 1 field)
- Photon IMRT (15 MV, 9 field)
- Protons (SOBP, 1 field)

Miralbell et al., IJROBP 2002
Dosimetric Comparison: 87.5 Gy in 35 fx

How to produce protons?
How to change the direction of a proton?

Magnetic Field (B)

Protons at relatively low energies are injected into the center of the cyclotron. The protons are accelerated each time they cross the gap between the dees until the radius of the path is large enough for the protons to be extracted from the cyclotron.

How Cyclotron Works?

Alternating Radio Frequency (RF) voltage accelerates protons when they go across the gap in each turn.

2/3 speed of light
• Dipoles: for bending the beam
• Quadrupoles: focusing the beam
• Vacuum pumps to keep beamline under very high level of vacuum (think about outer space)
• Beam profile monitors to measure beam along the central tube
Relativistic increase in mass

\[ E_T = m_0 c^2 \]  where \( m_0 \) is the proton rest mass

\[ E_T = E_0 + T \]  where \( T \) is the kinetic energy

\[ m = \gamma m_0 \]  where \( \gamma = \frac{m}{m_0} = \frac{E_T}{E_0} = \frac{(E_0 + T)}{E_0} \)

\[ m = m_0 \sqrt{1 - \beta^2}, \]  where \( \beta = \frac{v}{c} \)

For 230 MeV protons

- Beta is 0.596 (the protons are traveling at 59.6% of the speed of light, or 179,000 km/s).
- Gamma is 1.245 (the mass of the proton has increased 24.5% over the mass at rest).

Modern Hospital-Based Cyclotrons

**IBA C230**
- First commercially available cyclotron for PT
- 230 MeV protons
- Dedicated to therapy

**ACCEL/VARIAN K250**
- Compact 250 MeV superconducting cyclotron
- Higher magnetic field - less volume/mass
- High extraction efficiency and reproducible beam parameters

**THE FUTURE?**
- Energy: 250 MeV Protons
- Diameter: 1.7 m
- Magnetic field: 8.5 Tesla
- Beam structure: Pulsed, 1 kHz

The Principle of Synchrotrons

Hitachi and Siemens

**Synchrotrons:**
- Both designs use 7 MeV multi-turn injection for higher intensity: 1.2 x 10^11 protons per pulse (Hitachi).
- Both use RF driven extraction for turning beam on and off quickly (< 200 μsec) and for gated respiration.
- Both are strong focusing with similar magnet layout and beam optical.

**LLUMC Synchrotron:**
- Uses slow extraction with 0.2 – 0.5 sec every 2.2 sec weak focusing.
Proton beam delivery system at PTC-H

PROBEAT, Hitachi Ltd.

Accelerator Type: Slow-cycling Synchrotron
Injector: 7MV LINAC
Output Energy: 70-250MeV
Circumference: 23m
Repetition cycle: 2-7sec

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Cyclotron

Cyclotron works while: \( T = \text{const} \) independent from radius
(particles move in pace with V0)

However: at very strong magnetic fields:
Magnetic field decreases with radius

\( T \) increases with radius
\( \Rightarrow \) particles lose pace with frequency of V0 (RF).

\( \Rightarrow \) Smaller machines!!

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Synchro-Cyclotron

8-10 T 250 MeV Synchro-cyclotron on a gantry

MEVION

First beam extracted in May 2010
Cyclotron vs Synchrotron

Cyclotron
- Fixed output energy and "continuous" beam
- Energy variation requires post acceleration energy selector. Activation "problem"

Synchrotron
- Energy variable from pulse to pulse
- Pulsed beam (difficult for motion mgr)

Multi-Room Configuration

PTC-H
3 Rotating Gantry
1 Fixed Port
1 Eye Port
1 Experimental Port

Pencil Beam Scanning Port
Passive Scattering Port

Experimental Port
Large Fixed Port
Eye Port

Accelerator System (slow cycle synchrotron)
Multi-room Systems

- Hitachi 270 MeV proton synchrotron
- IBA 230 MeV cyclotron
- Mitsubishi 235 MeV proton synchrotron
- Mitsubishi* 320 MeV/u synchrotron (20 cm – $^{12}$C)
- Optivus 250 MeV proton synchrotron
- ProTom 330 MeV/u proton synchrotron
- Siemens * 430 MeV/u synchrotron (30 cm – $^{12}$C)
- Varian/Accel 250 MeV superconducting cyclotron

* Proton and $^{12}$C

Single Room Systems

- Mevion
  - 250 MeV gantry mounted compact superconducting synchrocyclotron. In production.

Proton Beam Delivery Mode

- Passive Scatter (PS)
  - Use scatter technique to create a large treatment field
  - Range modulation is required
- Pencil Beam Scanning (PBS)
  - Use magnetic field to scan the treatment field
  - Energy (range) can be changed spot-by-spot
- Uniform Scanning (US)
  - Pre-programmed PBS with beam aperture
**Comparisons**

<table>
<thead>
<tr>
<th></th>
<th>PS</th>
<th>US</th>
<th>PBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexibility in shaping the dose distribution</td>
<td>**</td>
<td>**</td>
<td>***</td>
</tr>
<tr>
<td>Dose conformity</td>
<td>**</td>
<td>**</td>
<td>***</td>
</tr>
<tr>
<td>No/reduced need for patient-specific hardware</td>
<td>*</td>
<td>*</td>
<td>***</td>
</tr>
<tr>
<td>Speed in energy changes</td>
<td>***</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Speed in overall dose delivery</td>
<td>***</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Ease of commissioning</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Maturity of the technique</td>
<td>***</td>
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<td>*</td>
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</tbody>
</table>

- **Comparisons**

**PS system**

**Passive Double Scattering System**

- The RMW rotates
- The beam is turned on at the thinnest part of the wheel
- The beam is then gated off at a predetermined modulator step
- The process is repeated 6 times for each revolution
- Sum of Bragg peaks (called "layers" in the TPS) = SOBP
Compensated (constant scattering for all thicknesses) bimaterial modulation wheel used for first scatterer
- 400 RPM
- 6 modulations per cycle
- Up to 16 cm modulation
- Beam gated for smaller modulation

Constant Range Modulation Width and Passive Range Compensation
- Usually use range modulator wheels
- 3-d range compensator (usually plastic or wax)
- Automatically designed and machined
- Very simple and clinically effective

Aperture and Compensating Bolus
- $800 / field

Lateral Field Edge Shaping
Distal Field Edge Shaping
Continuous scanning. Modulation in current and speed.

- Pencil beam spot width (\( \sigma \)) at the isocenter: ~4-10 mm
- Several identical paintings (frames) of the same target slice (layer)
- Max patient field (40x30) cm²

**Scattering vs Scanning**

- Scattering – no problem with organ motion.
- Scanning requires gating to overcome organ motion problems.
- Scanning – better conformation to target volume.
- Scanning - patient safety is a bigger problem than with scattering.
- Scanning – suitable for large volumes.
- Scanning – allows for IMPT

**Motivation for Pencil Beam Scanning**

- Fewer neutrons
- Sparing of healthy tissues proximal to the target
- Intensity modulated proton therapy (IMPT)
Step and shoot delivery of proton beam scanning

- Repeating many static irradiations
- Speedy beam switching with RF Driven Extraction technique

Dynamic scanning is achieved with discrete spot scanning method.

Proton Beam Characteristics

- Electromagnetic interaction with orbiting electrons - ionization and excitation
- Secondary electrons - short ranged and deposit energy locally
- Sharp increase in energy deposition as proton comes to rest
- Multiple Coulomb scattering, small angle
- Gaussian lateral spread-out, $\sigma = 5\%$ of the range
- Elastic nuclear collision, large angle scattering
- Nonelastic nuclear interactions, nuclear fragments deposit dose locally
- Statistical fluctuation in energy loss leads to range straggling-blurring of the peak ($1\%$ of range)
Energy Transfer Mechanisms

- Excitation
- Elastic scattering with nucleus
- Ionization
- Bremsstrahlung

Most energy loss is via coulombic interactions with atomic electrons. Small deflections are caused by coulombic interactions with nucleus. Nuclear reactions play only a small role.

Proton dose distribution in water

More Pristine Peaks
Generation of Spread-Out-Bragg-Peak (SOBP) with Energy Modulation of the Bragg Peak

PDD as a function of SOBP Widths

Note increase in entrance dose with increase in modulation.

Straggling from Multiple Particle Paths

10 MeV electrons 50 histories 80 MeV protons 50 histories 150 MeV/n carbon ions 500 histories
Protons vs Carbon

Alex Trofimov MGH

Workflow

Clinical Workflow

Patient Referral
New Patient Consultation
Diagnostic Imaging and Staging
Simulation
Treatment Planning
Treatment Delivery
Completion of Treatment Course

Networking/insurance
Initial clinical evaluation
Imaging, testing, and staging
Immobilization, CT scanning, scheduling
Designing treatment
1 – 40 treatments
Review and follow-up
CT number to SPR Conversion

- Degeneracy problem
  - $\text{HU}(\rho_1, Z_1) = \text{HU}(\rho_2, Z_2)$
  - $\text{SPR}(\rho_1, Z_1) \neq \text{SPR}(\rho_2, Z_2)$
Variations in Human Tissue Composition

Summary of CT# Variation

<table>
<thead>
<tr>
<th>Tissue Groups</th>
<th>Time and Scanner</th>
<th>Size</th>
<th>Position</th>
<th>Couch Position</th>
<th>Root-Sum-Square (RSS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT# Lung</td>
<td>1.0%</td>
<td>4.4%</td>
<td>2.2%</td>
<td>1.8%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Soft Lung</td>
<td>0.3%</td>
<td>0.5%</td>
<td>0.1%</td>
<td>0.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Bone Lung</td>
<td>0.6%</td>
<td>2.4%</td>
<td>1.3%</td>
<td>0.7%</td>
<td>2.9%</td>
</tr>
<tr>
<td>SPR Lung</td>
<td>1.0%</td>
<td>4.5%</td>
<td>2.2%</td>
<td>1.8%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Soft SPR</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.1%</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Bone SPR</td>
<td>0.4%</td>
<td>1.6%</td>
<td>0.9%</td>
<td>0.5%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

- Patient size is the dominating factor
- Uncertainty is a function of tissue types

Uncertainty Category | Uncertainty Source
--- | ---
CT Imaging uncertainties | The deviation of HU value from its calibrated value when imaging a patient.
Uncertainties in predicting theoretical CT numbers using tissue substitute phantoms | This includes the uncertainties in the definition and measurement using CT imaging for a tissue substitute phantom, including the parameterization of equation
Uncertainties to calculate SPRs of human tissues | The uncertainties caused by modeling SPR and variations of tissue composition in patient population.
Uncertainties in mean excitation energies | The value of mean excitation energy is critical in calculating SPR
Uncertainties caused by an assumption used in a dose calculation algorithm | For simplicity, some treatment planning systems ignored the SPR dependency on proton energy.

Comprehensive analysis of the stoichiometric calibration. Yang M. et al.
Mitigation of CT imaging uncertainties

- Distal and proximal margins
- Site-specific CT calibration (small phantom vs. large phantom)
- In patient calibration of CT numbers for known anatomy (Moyer et al. 2010)
- Avoiding couch or immobilization device outside CT scanner’s FOV

SPR uncertainties have a significant impact on proton dose distributions

Commonly it’s not visible on proton plans
IGRT

Hitachi gantry
two X-ray systems extended

Thoracic
CSI
Prostate

Patient Setup

Clinical Proton Therapy Physics
with Emphasis on Small Beam - 2012
Low Z fiducial markers

Impact of Organ Motion To Proton Dose Distributions
Free breathing treatment

Free breathing Treatment
Gated treated on exhale
Treatment Planning

(to minimize treatment uncertainties)

Treatment Planning System

- Varian Eclipse Planning System:
  - Pencil beam algorithm for dose calculation
  - Passive scatter and PBS
- Similar workflow in planning
  - Passive Scatter (PS): technique similar to 3DCRT
  - IMPT: similar to IMRT (inverse planning)
- Evaluation of a proton plan
- Including robustness in planning


PS vs. IMPT

(b) Conventional PT
(c) IMPT

Photons vs. Protons


Compensator Smearing and Aperture Expansion

PLANNED

AP margin: 7.5 mm
Setup error: 0 mm
Tumor motion: 0 mm

RC smear: 7.5 mm
AP margin: 7.5 mm
Setup error: 0 mm
Tumor motion: 0 mm

Courtesy of Martijn Engelsman (MGH)

Single PTV?

PTV A
PTV B
CTV
Field A
Field B

Beam specific PTV’s cannot easily be added and used for plan evaluation.

Single encompassing PTV is not appropriate

Addition of PTV’s not appropriate
Beam-specific PTV varies depending on beam angle and local heterogeneity

Proton Lateral Penumbra vs. Distal Falloff

95-50% ~ 10 mm
95-50% ~ 4 mm

Inter-fractional Variations

Planning contours mapped to 24 in-room CTs
Inter-fractional Variations

Simulation CT is a snapshot of patient's anatomy!

Planning contours mapped to 24 in-room CTs

Impact of Tumor Shrinkage on Proton Dose Distribution

Original Proton Plan
Dose recalculated on the new anatomy

Bucci/Dong et al. ASTRO Abstract, 2007
Smearing to Ensure Target Coverage

- The bolus thickness at point P, as calculated by the "simple" technique, is replaced by the thinnest bolus thickness calculated anywhere within ±d of the point P.


Typical proton dose distributions

An example of Robust IMPT planning
Conventional IMPT without Robust Planning

IMPT with Robust Planning

nominal range 5 mm undershoot 5 mm overshoot

Improving Proton Therapy

- Anatomy variations
  - IGRT/adaptive radiotherapy
  - Robust optimization
- Intra-fractional motion
  - Gating, coaching, tracking...
- Accurate stopping power ratios (CT number conversion)
- Scanning pencil beams (IMPT)

Main differences between photons and protons

<table>
<thead>
<tr>
<th>Factors</th>
<th>Photons</th>
<th>Photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT # and stopping powers</td>
<td>Sensitive - affect range, distal target coverage or distal normal tissue sparing</td>
<td>Not sensitive</td>
</tr>
<tr>
<td>Target motion normal to beam</td>
<td>Misses margin, may affect dose distribution distal to target</td>
<td>Affects margin</td>
</tr>
<tr>
<td>Normal structure motion parallel to beam</td>
<td>Affects range, dose distribution distal to structure</td>
<td>Minimal effect</td>
</tr>
<tr>
<td>Target motion along beam</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Normal structure motion along beam direction</td>
<td>Affects margin</td>
<td>Minimal effect</td>
</tr>
<tr>
<td>Organs</td>
<td>Not well characterized, partial dose distributions, degrade distal edge</td>
<td>Well understood, effect not strong</td>
</tr>
<tr>
<td>Radiation changes over course of RT</td>
<td>Affect dose distribution</td>
<td>Minimal effect</td>
</tr>
<tr>
<td>Plan Evaluation</td>
<td>Impact of uncertainties significant, PTV concept invalid, validity of initial nominal plan questionable</td>
<td>PTV concept valid, dose distributions relatively invariant to uncertainties, initial plan acceptable approximations</td>
</tr>
</tbody>
</table>
Summary of Proton Beam Properties

- Proton beams stop - no exit dose
- Although we don’t know exactly where they stop
- Proton beams are more sensitive to
  - CT number accuracy
  - Organ motion
  - Anatomy changes
- Proton plans are difficult to evaluate
- Proton demonstrated excellent low dose sparing
- IMPT shows additional benefits both in low dose sparing and high dose conformality
- IGRT and Adaptive RT will play an important role