PROTON THERAPY
IN CLINICAL PRACTICE:
PAST, PRESENT AND FUTURE

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Synopsis

1. Physics
   interactions of protons with matter
treatment planning

2. Technology
   beam generation, shaping and delivery
   patient handling
   integration

3. Radiobiology
   RBE
   modelling and treatment strategy

4. Clinical Application
   clinical experience
   clinical trials
INTERACTIONS OF PROTONS WITH MATTER

proton penetration


multiple Coulomb scattering


and http://huhepl.harvard.edu/~gottschalk/

nuclear interactions

there is a vast literature

Based on a figure courtesy of Eros Pedroni, PSI
DOSIMETRY

• See ICRU report number 78
  - basically adopts IAEA’s prior protocol (TRS 398) (thus eliminating a 2% discrepancy)
  - proton dosimetry is based on X-ray calibration of ion chambers, with correction factors
  - however, the largest correction factor is in the w-value of protons in the ion chamber gas, and this value largely relies on Calorimetric determinations

• Stated standard error of from 2.0% to 2.3%

• Most important point:
  - Proton dosimetry is now standardized and the standard is (or will soon be) near-universally followed
INHOMOGENEITIES

A. Slab  
B. Thin Edge  
C. Sliver

and
interface effects are minor (few %)
– Koehler (unpublished)
SEMI–INFINITE SLAB (thin edge)

Goitein et al., Med Phys 5: 265 (1978)
Q. How wide a sliver can cause range shortening?

2mm wide Teflon “sliver”

A: pretty small (~ 1mm) – at the edge of available imaging and computation resolution!

Goitein & Sisterson
DISTAL EDGE DEGRADATION

Human skull (water-filled)

pristine Bragg Peak

spread-out Bragg Peak

Urie et al. Phys Med Biol 1986; 31: 1
lateral beam passing through inhomogeneities → distal dose degradation

"make up" beam to "fill in" the distal dose deficit

position C; SOBP

Dose (%)

Depth (cm)
PROTON CONSUMER’S REPORT SCHEMA

past  present  future

done / to do  current status

- almost nothing  as good as it gets
- very little  mostly understood
- some  glass half full
- quite a lot
- really a lot
- some work to be done, but not very critical  pretty ignorant
INTERACTION OF PROTONS – SUMMARY

past  present  future

proton penetration

multiple Coulomb scattering

nuclear interactions

dosimetry

inhomogeneities

awareness
TREATMENT PLANNING

- image-based geometric design
- dosimetric design (manual)
- uncertainty
- intensity-modulated proton therapy (IMPT)
- algorithmic plan design – optimization and robustness
**WHAT IS DIFFERENT ABOUT TREATMENT PLANNING FOR PROTON THERAPY?**

<table>
<thead>
<tr>
<th>step</th>
<th>proton vs. photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evaluate the patient using all relevant diagnostic tools, and decide whether to employ radiation therapy.</td>
<td>~same (but protons may affect choice of modality)</td>
</tr>
<tr>
<td>2. Obtain and inter-register imaging studies with the patient lying in the position to be used for therapy.</td>
<td>same</td>
</tr>
<tr>
<td>3. Delineate on the planning CT the target volumes (GTV, CTV and PTV) and normal tissues.</td>
<td>~same (but PTV has different interpretation)</td>
</tr>
<tr>
<td>4. Establish the planning aims for the treatment.</td>
<td>same</td>
</tr>
<tr>
<td>5. Design one or more sets of beams, together with their weights, each of which fulfills, to the extent possible, the requirements of the planning aims.</td>
<td>different</td>
</tr>
<tr>
<td>6. Evaluate these plan(s) and either select one of them for use or revise the planning aims and return to step 5.</td>
<td>need robust optimization more variables.</td>
</tr>
<tr>
<td>7. Finalize the prescription.</td>
<td>same</td>
</tr>
<tr>
<td>8. Simulate the selected plan to ensure it is deliverable.</td>
<td>same</td>
</tr>
<tr>
<td>9. Deliver the treatment, and verify that the delivery is correct.</td>
<td>~same (but QA harder)</td>
</tr>
<tr>
<td>10. Re-evaluate the patient during the course of treatment and, if necessary, return to step 5, or even 2, to re-plan the remainder of the treatment.</td>
<td>same</td>
</tr>
<tr>
<td>11. Document and archive the final treatment plan.</td>
<td>same</td>
</tr>
<tr>
<td>12. Review the treatment plan at the time of patient follow-up or possible recurrence.</td>
<td>same</td>
</tr>
</tbody>
</table>

adapted from
see also: ICRU report 78
GEOMETRIC DESIGN – image based

Beam’s-eye view aperture drawing virtual simulation

use of CT sagittal / coronal reconstructions contour definition

image registration (multi-modality imaging – “hat & head” technique Chen, Kessler, Pelizzari...)

DRRs reference for setup film

McShan et al. BJR 1979
**DOSIMETRIC DESIGN**

- **algorithms**
  - **broad beam** – radiological path length
  - **pencil beam** e.g. Hong et al. *A pencil beam algorithm for proton dose calculation. Phys Med Biol 41:1305–1330*
  - **Monte Carlo**
    - e.g. *GEANT, purpose-written code*

- **dose display**
  - color wash *(with scale!)*
  - side–by–side display
  - dose–difference displays

- **plan assessment and comparison**
  - **DVHs**
  - **score functions**

*Shipley et al. Proton radiation as boost therapy for localized prostatic carcinoma. JAMA 1979; 241:1912*
• Virtually all aspects of treatment planning are subject to significant (mainly systematic) uncertainties, such as:
  - definition of gross tumor, CTV, and normal anatomy
  - patient and organ localization and movement
  - dose estimation
  - treatment delivery
  - etc. etc.

• It is the job of the plan designer(s) to:
  - assess the uncertainties (at a given level of confidence)
  - take steps to minimize them to the extent practically possible
  - plan the treatment taking the residual uncertainties into account

COMPENSATION FOR MIS-REGISTRATION

Idealized compensation but, mis-registration can lead to undershoot:

solution, (if one gives priority to tumor coverage):
“open up” the compensator (at the price of certain overshoot)
At 15 cm depth, $\sigma \approx 3\text{mm}$

Based on a figure courtesy of Eros Pedroni, PSI
COMPENSATION FOR MULTIPLE SCATTERING

At 15cm depth, \( \sigma \approx 3\text{mm} \)

\[ \sigma \sim 2\% \text{ of range, } R \]

so, expand compensator

Based on a figure courtesy of Eros Pedroni, PSI

Michael Goitein, AAPM Symposium, Baltimore, May 2009
COMPENSATOR DESIGN (physical and virtual)

compensates for mis-registration 
and multiple scattering

COMPENSATING FOR REGISTRATION ERROR
- simple inhomogeneity

simple (nominal) bolus

“expanded” bolus

COMPENSATING FOR REGISTRATION ERROR – complex inhomogeneities

simple (nominal) bolus

“expanded” (by 3mm) bolus


Michael Goitein, AAPM Symposium, Baltimore, May 2009
• The greatest inhomogeneity is that which exists at the interface between the patient and the surrounding air.

• If the beam direction is near-tangent to a skin:tissue interface, the dose distribution can be very sensitive to patient motion or misalignment.
• Compute 3 dose distributions

- **nominal**
  - dose at a pixel computed using nominal values of all variables

- **lower bound**
  - dose at a pixel computed using the value of each variable that would tend to yield the lowest dose (but use the computed “upper bound” value, if lower)

- **upper bound**
  - dose at a pixel computed using the value of each variable that would tend to yield the highest dose (but use the computed “lower bound” value, if higher)
A MAJOR CONSEQUENCE OF UNCERTAINTY

• larger-than-desired safety margins
GEOMETRIC DESIGN, DOSE CALCULATION & UNCERTAINTY

- **image-based geometric design**
  - use of imaging
  - image registration
  - time variations (4D)

- **dosimetric design (manual)**
  - broad- & pencil-beams
  - Monte Carlo

- **uncertainty**
  - computation, and allowance for the uncertainties
TREATMENT PLANNING

- image-based geometric design
- dosimetric design (manual)
- uncertainty
- intensity-modulated proton therapy (IMPT)
- algorithmic plan design
  - optimization and robustness
OPTIMIZATION

• Why is the subject of optimization important?
  1. In IMPT, which presently requires pencil–beam scanning, there are so many variables that one needs a computer algorithm to set them perhaps 10,000 pencil beams or more, times the 3 variables of intensity, depth of penetration and transverse size for each pencil beam
  2. Even in uniform–beam irradiation, the choice of penetration (which can vary over the field, is difficult and can benefit from computer–based solutions (e.g. field–patching)

• Optimization requires a search algorithm to find the optimal set of variables, and a score function. Generally:
  a solution to the search problem is not hard to find, though it may be computationally demanding
  a clinically meaningful score function is extremely difficult to find

• In proton therapy, however
  due to the almost two orders of magnitude more variables, the search problem becomes even more demanding
  the score function is further complicated due to uncertainties in the penetration of each pencil beam
ROBUST OPTIMIZATION

• One simply has to deal with uncertainties.
• A robust plan is one which is not too negatively affected by the unavoidable or irreducible uncertainties.
• There are two ways of achieving robustness:
  • find the plan which has the least–bad “worst case”
    the worst case is the (unphysical) dose distribution for which, for a given level of uncertainty in the treatment variables in each voxel within the PTV the dose is set to the lowest possible dose; and in each voxel within an OAR the dose is set to the highest possible dose.
  • find the plan which on average has the best score – when averaging over all sources of uncertainty


these approaches have demonstrated very promising results
IMPT, OPTIMIZATION AND ROBUSTNESS

- **IMPT**
  - understanding of the problem
  - development of solutions

- **OPTIMIZATION**
  - search techniques
  - dose–based optimization
  - biological optimization

- **ROBUST PLANNING**
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There is a misapprehension that, since proton therapy has been developed over about half a century, the technology is mature.

It is not.

This is largely because:

- the early experience was in research environments in which less-than-efficient procedures were tolerated
- the current commercial offerings largely copied the existing technologies (with the addition of gantries)
- IMPT is a very recently-recognized possibility and has not had time to be satisfactorily commercially developed

But, don’t be too alarmed, because:

- proton therapy is currently being delivered with the existing technology to the benefit of large numbers of patients
- the developments are needed to allow protons to reach their full potential, and to be used in a clinically streamlined fashion.
• The technology of currently-used proton accelerators is pretty well developed
  synchrotrons cyclotrons both are adequate and reasonably reliable – except that:

• There is still an intensity problem – reflected in:
  low beam intensity at low energies (cyclotrons)
  too large pencil beam sizes (caused also by other factors)

• Cost remains a factor (we’re still waiting for true marketplace competition 15 years after MGH signed the first commercial contract for a proton facility)
NEW TECHNOLOGIES FOR PROTON GENERATION

- Good luck

- but, beware!
  remember the fate of d–T generators in neutron therapy

- and, don’t compromise performance – e.g.
  lowering the maximum energy failure to support IMPT etc.
• The technology has been very fully developed primarily by Andy Koehler, Bernie Gottschalk, and colleagues at the Harvard Cyclotron Laboratory

• Current commercial systems primarily use the “historic” technology, including double-scattering – with a few enhancements, e.g.
  - automatically selectable range modulator wheels
  - beam gating to vary the depth of the SOBP

• The depth characteristics are fairly satisfactory, using the current range modulator technology
  - except for low energies for which the Bragg peaks are too narrow to stack easily and a better method of spreading them (e.g. ridge filters) is needed
• But, beam penumbra in the current scattered beam implementations is very inadequate (worse than Cobalt-60 in many cases)

• For scattered beams, the historically achieved penumbras were OK due to their long throw, but in the current gantry implementations the penumbra is far from satisfactory.

This is because they use double-scattering with a relatively short throw (SAD)

large effective source size (a few cm)
BEAM SHAPING: SCANNED BEAMS
and intensity-modulated proton therapy (IMPT)

- IMPT requires the use of a pencil beam of protons whose Bragg peak is scanned throughout the target volume while its energy (penetration) and intensity are varied at will.
IMPT technology

• IMPT requires the use of a pencil beam of protons whose Bragg peak is scanned throughout the target volume while its energy (penetration) and intensity are varied.

• The only significant experience with IMPT to date has been at the Paul Scherrer Institute (PSI) in Switzerland where they developed, and have used since 1996, a prototype so-called spot-scanning gantry.

• PSI are now building a second gantry featuring isocentric rotation and faster scanning (due to start treating in 2010).

• Commercial scanning systems are just now in their infancy.
• In scanned beams, the beam penumbra is set by the diameter of the pencil beam near the end of range.

• This has two components:
  - scattering in the patient
    about which technology can do nothing
  - pencil beam size in the absence of the patient
    which is entirely due to the technology

• If one wants to at least match, at a depth of 10cm, typical linac penumbrae of about 7mm (80–20%), the pencil beam size at isocenter in the absence of the patient (i.e. due to the technology) needs to be no more than about:
  \[ \sigma \approx 3.5 \text{ mm} \quad \text{– i.e. a fwhm of no more than } \approx 8 \text{ mm} \]

• Current implementations fall short of this important goal.
The main downside of beam scanning is that, if there is motion of the patient and/or the tumor, so-called interplay effects can lead to up-and-down dose variations within the target (dose mottle).


Dose mottle is not just theoretical. It has been observed at about the 14% (SD) level in an animal experiment at PSI, caused merely by ~2mm movements of the mouse intestine irradiated in a scanned 10 mm pencil beam!

Gueulette et al. IJROBP 2005;62:838-845
CURRENT SOLUTION(S) TO THE INTERPLAY PROBLEM

• First, reduce the amount of motion to the extent possible
  □ respiratory gating
  □ abdominal compression
  □ tumor tracking

• Then, **repaint** the field **many times.** But...


• **In depth**
  - scattered beams
  - scanned beams

• **Laterally (penumbra)**
  - scattered beams
  - scanned beams
Proton therapy has, from its very beginning, emphasized accuracy of beam placement (relative to the target volume) and tight margins where possible and indicated.

This is for two reasons:

- Compensators need to be in accurate registration with the inhomogeneities and beam shapes they are intended to compensate for in order to avoid an unintended distribution of dose.
- A main goal of proton therapy is to minimize the volume of normal tissue outside the target volume which receives a high dose.

This has resulted in a number of developments which have found wide application.
PLANNING, IMMOBILIZATION AND LOCALIZATION

patient #1 at HCL (1974)

patient #2 at HCL (1974)

planning based on radiographs

planning based on smearing tomography

alignment based on radiographs
IMMOBILIZATION AND LOCALIZATION (contd.)

GATING & TARGET TRACKING (intra- & inter- fraction)

Gating & Target Tracking (intra- & inter- fraction)

- Implanted gold seeds
- Rectal probe & water-filled balloon

Respiratory gating (NIRS, Japan)

Shipley et al. Proton radiation as boost therapy for localized prostatic carcinoma. JAMA 1979; 241:1912


Ocular tumor tracking through real time video tracking of anterior eye position (HCL, PSI)

High-mag. image of anterior eye with the position of the pupil being outlined.

Picture courtesy J Vervey, PSI
HCL 6-degree of freedom patient supporter (Wagner)

Commercial 6 degree of freedom patient couch (IBA)

Orsay-Curie 6 degree of freedom patient couch (Mazal)

The additional degrees of freedom are required to adjust for small rotational misalignments of the patient.
• Currently it generally takes too long, and is too hard, to set up and treat a patient.
  
  this is hard on the patient
  
  this is hard on the staff
  
  it can degrade quality, and it tends to reduce accuracy
  
  reduces throughput and hence increases costs
  
• One partial solution is to perform the patient setup outside the treatment room and bring him or her into the treatment room when it becomes available without, in principle, the need for further localization, à la PSI.
  
• But, this does not get at the root of the problem which is: inadequate systems engineering – and inadequate specification of the needs
• Integration and Workflow are concepts which are more talked about than put into practice.
PATIENT HANDLING AND INTEGRATION

- **patient handling**
  - immobilization and motion management
  - patient support assembly
  - throughput

- **integration**
  - workflow
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RBE = 1.10 isn’t all that bad...

Paganetti et al.  
DOSE

100%

bio-effective dose
physical dose

DEPTH
But, proton RBE needs (some) refinement

1. RBE rises across SOBP
   - "blip" near end of SOBP
   - RBE rises to order of 1% / cm

2. RBE in entrance region a bit less (? 5%) than at SOBP center?

3. RBE ≈ 1.10 in center of SOBP

4. “blip” near end of SOBP
   - 5 - 10%

5. Elongation of range ~ 1-2 mm.

6. RBE depends on dose per fraction

7. RBE depends on tissue type & endpoint

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reduced tumor dose in the region in which the tumor is close to the brainstem

increased brainstem dose accepted in the small region in which it is close to the tumor
The development of biophysical models suggested that, for example, a partial boost to a tumor may increase the TCP.
BUT (as seen in IMRT and with interplay effects)...
BEWARE DOSE MOTTLE!

TCP (actual dose distribution < TCP (average tumor dose)
for a dose mottle of ±7.5%  ΔTCP ≈ − 4 %
for a dose mottle of ±10%  ΔTCP ≈ − 6.5 %

Brahme A. Acta Radiol Oncol
MODELLING NORMAL TISSUE COMPLICATION PROBABILITY (NTCP)

serial structure

parallel structure

Modelling supported the idea that organs could tolerate a higher dose if it was only delivered to part of the organ.
There are many important but unanswered questions
the answers to which are relevant for all radiations, but particularly to particles with which
one is attempting to spare normal tissues particularly effectively

Some of the unsolved issues are:
“bath-or-shower dilemma” (is it better to deliver
a lower dose to a larger volume of normal
tissue, or a higher dose to a smaller volume?)

- how does functional damage to an organ or tissue depend on the relative (or absolute) volume irradiated to high dose?

- how does functional damage to an organ or tissue depend on the (lower) dose delivered to the rest of the volume?

- how does the radiation damage of an organ or tissue depend on the radiation experience of nearby tissues and organs?

We need to resurrect whole-organ and whole-organism radiobiology

When we know the answers to some of these questions, we will need new biophysical models so we can use computers to optimize treatments
RBE, MODELLING AND TREATMENT STRATEGY

- RBE
- Radiation response of tissues
  - data
  - modelling
  - treatment strategies
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CLINICAL EXPERIENCE

- Some 61,000 patients have been treated with proton beam therapy as of Feb. 2009.
- The largest single group is comprised of ~17,000 patients with ocular melanomas.
  
  http://ptcog.web.psi.ch/patient_statistics.html

- There have been only a limited number of clinical trials of proton beam therapy, and only two randomized clinical trials of protons vs. conventional radiotherapy.
- The experience to date should perhaps be read as a confirmation that the theoretical arguments for proton beam therapy have been upheld in the limited number of situations in which they have been tested.

Chondrosarcoma - local control

Choroidal melanoma - local control

Paranasal sinus tumors

33 squamous cell carcinomas, 30 carcinomas with neuroendocrine differentiation
20 adenoid cystic carcinomas
13 soft tissue sarcomas, and 6 adenocarcinomas.
The median dose was 71.6 CGE.
THE RATIONALE FOR JUDGING THE CLINICAL SUPERIORITY OF PROTONS VIS-À-VIS X-RAYS

- For the same dose to the target volume, protons deliver a lower physical dose to the uninvolved normal tissues than do high-energy X-rays.
- There is very little difference in tissue response per unit dose between protons of therapeutic energies as compared with high-energy X-rays, so that the only relevant differences are physical.
- There is no medical reason to irradiate any tissue judged not to contain malignant cells.
- Radiation damages normal tissues and the severity of that damage increases with increasing dose.


Each of these 4 statements is established experimentally beyond reasonable doubt
There are two fundamental principles which govern whether a randomized clinical trial (RCT) is ethically appropriate:

The arms of the study must be in **equipoise**. That is to say, the arms must be judged to be substantially equivalent from a patient’s point of view.

When a doctor agrees to take care of a patient, he or she is entering into an **unwritten contract with the patient** to use his or her best efforts and judgment on behalf of that patient. There can be no unspoken reservation that societal interests may take priority over those of the patient, and the patient may expect to be fully informed regarding any facts that he or she might deem relevant.

These principles, together with the previous 4 statements, mean that many otherwise desirable RCTs can not be performed for ethical reasons - equipoise can not truthfully be said to obtain for them.
• It is a great pity that almost no case–controlled clinical studies have been planned or performed.

• It would seem that, in the absence of an ability in many cases to conduct randomized clinical trials, carefully designed prospective case–controlled comparisons between proton centers and institutions lacking a proton capacity would be desirable.

• clinical trials
  
  randomized
  
  case–controlled
File named “pbs.pdf” can be extracted from BGdocs.zip
See, also, PowerPoint lectures in BGtalks.zip

• ICRU report 78 “Prescribing, Recording and Reporting Proton Beam Therapy” Oxford U. Press. Journal of the ICRU 7(2); 2007

• T.F. Delaney and H.M. Kooy (eds) “Proton and Charged Particle Radiotherapy” Lippincott Williams and Wilkins, 2007

SUMMARY

INTERACTIONS OF PROTONS

proton penetration
Coulomb scattering
nuclear interactions
dosimetry
inhomogeneities

TECHNOLOGY

changes with time
broad- & pencil-beam algorithms
throughput, integration & workflow

current sources of protons
future sources of protons

Monte Carlo dose calculation
scattered beam technology & IMPT

uncertainties: calcn. and allowance for
scattered beam technology

IMPT: understanding
scattered beam: depth characteristics

IMPT: solutions
scattered beam: depth characteristics

optimization: search techniques
scattered beam: lateral penumbra

optimization: dose-based
scattered beam: lateral penumbra

optimization: biology-based
immobilization & motion management

radiobiology

RBE value(s)
tissue response: data
tissue response: models
treatment strategies based on biology

IMPT: understanding
scattered beam: depth characteristics

IMPT: solutions
scattered beam: depth characteristics

optimization: search techniques
scattered beam: lateral penumbra

optimization: dose-based
scattered beam: lateral penumbra

optimization: biology-based
immobilization & motion management

clinical trials

randomized protons vs. X-rays
case-controlled protons vs. X-rays

TREATMENT PLANNING

use of imaging
imaging registration

optimization: dose-based
optimization: biology-based

optimization: search techniques
immobilization & motion management

optimization: dose-based
immobilization & motion management

patient support systems

CLINICAL TRIALS

randomized protons vs. X-rays

Case-controlled protons vs. X-rays

Michael Goitein, AAPM Symposium, Baltimore, May 2009
CONCLUSIONS

• Much has been done.
• Much remains to be done.
• It is important that what has been learned in the past be incorporated into the clinical work of the future – and not simply regarded as being of purely historical interest and hardly worth learning about.
finis