Development and delivery of biologically optimized treatment plans in proton radiotherapy

Alejandro Carabe-Fernandez
Department of Radiation Oncology
University of Pennsylvania
Elements of Radiobiological Optimization

- Microdosimetry
- Biophysical Modeling
- Innovative Treatment Planning
- Experimental Radiobiology
Elements of Radiobiological Optimization

- Microdosimetry
- Biophysical Modeling
- Innovative Treatment Planning
- Experimental Radiobiology
Biophysical aspects of current proton treatment planning approaches
Standard treatment LET$_d$ distributions

Dose averaged contribution

RT - Lateral

LT - Lateral

Disease control uniquely depends on dose

Wasted LET effect on normal tissue

LET$_d$ [keV/µm]

0

5

10
Biophysical aspects of current proton treatment planning approaches

Figure 13: Axial CT image with color-wash dose display resulting from thru-field which irradiates the anterior portion of the target while avoiding the brainstem and patch-field which treats the remaining portion of the target while avoiding the brainstem. The lower figure shows the combined thru/patch field combination. All doses are given in percent. (Bussiere and Adams, 2003)

Biophysical aspects of current proton treatment planning approaches

Axial CT image with color-wash dose display resulting from thru-field which irradiates the anterior portion of the target while avoiding the brainstem and patch-field which treats the remaining portion of the target while avoiding the brainstem. The lower figure shows the combined thru/patch field combination. All doses are given in percent. (Bussiere and Adams, 2003)

Paganetti & Bortfeld in ‘New technologies in Radiation Oncology’ (Eds. Schlegel, Bortfeld, Grosu)
Biophysical aspects of current proton treatment planning approaches

Zeng et al. Medical Physics (2013)
Biophysical aspects of current proton treatment planning approaches

Thus, in IMPT, optimizing to OAR dosimetric constraints is achieved by using the distal edge to conform the beam, yielding higher LET values, a fact currently not considered in treatment planning. The question becomes whether a decrease in (mean) dose to an OAR may be negated by an increase in (mean) LET and the associated expected increase in biological effect. To answer this question, we analyzed the RBE-weighted dose in correlation with the LET and physical dose for each structure.
Navigating the dose-optimized Pareto space, a tradeoff between low doses and low LET values for the OARs was observed, indicating the need for a method to gauge the relative importance of dose and LET to the clinical outcome of the patient. Substantial RBE variations among BPs for all patients considered in this study were associated with substantial variations in $\text{LET}_{\text{mean}}$ values, along with variations in dose. Higher
Biophysical aspects of current proton treatment planning approaches

**Fig. 4.** (a) Plot showing how differences in mean RBE-weighted doses ($\Delta DRBE,_{\text{mean}}$) correlate with differences in mean LET ($\Delta LET,_{\text{mean}}$) and mean dose ($\Delta D,_{\text{mean}}$) values for both beam spot sizes (large: 12 mm on average; small: 3 mm on average). The $R^2$ values on the legend represent the coefficient of determination for each set of data. (b) Schematic diagram of Equation 3 accounting for the inverse correlation between $\Delta D,_{\text{mean}}$ and $\Delta LET,_{\text{mean}}$. LET = linear energy transfer; RBE = relative biological effectiveness.
Can we exchange dose for LET while maintaining the same biological effect in the target volume?

If we can, that would mean:

1- we could decrease the required prescribed dose (or even the number of fractions) of the treatment without loosing its biological effectiveness.

2- reduce the dose (by default from 1) in the normal tissue

3- reduce the LET in the normal tissue

Work done by: Marcus Fager – University of Pennsylvania
Disease control will depend on dose and LET.

Normal tissue shielded from the region of the beam with enhanced biological effectiveness.
Split Target – 2 Fields – CTV – PBSTV
Split Target – 2 Field - LET\textsubscript{d} distributions

Dose averaged contribution

RT - Lateral

LT – Lateral
Split Target – 4 Field – CTV
Split Target – 4 Field - $\text{LET}_d$ distributions

$\text{LET}_d$ [keV/\(\mu\text{m}\)]

0

5

10
Split Target – 7 Field - LET_d distributions

LET_d [keV/µm]

0

5

10
Dose – $\text{LET}_d$ Comparison

Standard Full Target

2 Field Split Target

4 Field Split Target

7 Field Split Target
Biophysical aspects of current proton treatment planning approaches

\[ D_{\text{RBE}} \text{ [Gy (RBE)]} \]

Fractional Volume vs. LET\(_d\) [keV/\(\mu\)m] for CTV, Rectum, and Bladder.

Fractional Volume vs. \(D_{\text{RBE}}\) [Gy (RBE)] for CTV, Rectum, and Bladder.

LETRAQUANTEC
Biophysical aspects of current proton treatment planning approaches

**Purpose:** To propose a proton treatment planning method that trades fractional physical dose (d) for dose-averaged Linear Energy Transfer (LET$_d$) while keeping the radiobiological weighted dose $D_{RBE}$ to the target the same.

**Methods:** The target is painted with LET$_d$ by using 2, 4 and 7 fields aimed at the proximal segment of the target (split target planning, STP). As the LET$_d$ within the target increases with the increasing number of fields, the physical dose per fraction decreases to maintain the $D_{RBE}$ the same as the conventional treatment planning method using beams treating the full target (full target planning, FTP).

**Results:** The LET$_d$ increased inside the target by 61% for 2STP, 72% for 4STP and 82% for 7STP, compared to FTP. This increase in LET$_d$ led to a decrease of d with $0.16\pm0.01$Gy for 2STP, $0.2\pm0.03$Gy for 4STP and $0.21\pm0.01$Gy for 7STP keeping the $D_{RBE}$ constant to FTP.

**Conclusions:** LET$_d$ painting offers a method to reduce prescribed dose at no cost for the biological effectiveness of the treatment.

Fager et al., 2014 (submitted)
What dose decrease percentage can we get if we go from discrete beams to…
... continuous beam delivery

PROTON MODULATED ARC THERAPY (PMAT)
PMAT feasibility in PBS

- Multiple energy layers per angle
- Gantry cannot rotate continuously
- PMAT is not feasible in PBS mode
But, what if… shut a mono-energetic beam
PMAT feasibility in PBS

… and let the gantry rotation take care of the target dose painting
PMAT feasibility in PBS

... and let the gantry rotation take care of the target dose painting
PMAT feasibility in PBS

... and let the gantry rotation take care of the target dose painting
PMAT feasibility in PBS

... and let the gantry rotation take care of the target dose painting
PMAT feasibility in PBS

But one single energy will not be able to cover targets within irregular/inhomogeneous body shapes.
PMAT feasibility in PBS
PMAT vs PBS treatment of Brain tumor

- 7920cGy / 44 fraction
- Cochlea
- Optic Chiasm
- Brainstem
PMAT in Brain tumor

ARC 1

\(E_1 = 113.2 \text{MeV}\)
PMAT in Brain tumor

ARC 2
\((E_1=110.2\text{MeV})\)
PMAT vs PBS: DVH
PMAT vs PBS: LET-VH

LET (keV/um) x 100

- BRAINSTEM
- Brain
- COCHLEA_L
- COCHLEA_R
- OPTIC CHIASM
- CTV 59.4 rev

Perelman School of Medicine
University of Pennsylvania
Inverse TPS prototype based on MLC

Work done by: Daniel Sanchez-Parcerisa – University of Pennsylvania

Example: DS-PAT in a cylindrical phantom

TARGET

OAR

PHANTOM example
13 fields, every 15 deg

Poster: SU-E-T-214

Sanchez-Parcerisa et al. (2014)
Elements of Radiobiological Optimization

- Microdosimetry
- Biophysical Modeling
- Innovative Treatment Planning
- Experimental Radiobiology
Correct calculations of LET

Work done by: M. A. Cortés-Giraldo – University of Seville (Spain)

- To analyze the difference in the $LET_d$ values predicted by the different definitions presented in the literature used for these calculations.

- To prove the correct definition based on the $LET_d$ obtained as the limiting value of a microdosimetric experiment.
Consider a certain voxel irradiated by $N$ events (primary particles):

- $T_n$ tracks transported along the voxel at event $n$.
- Each track $t$ makes $S_{tn}$ steps within the voxel.

Monte Carlo calculation of $LET_d$:

$$\bar{L}_d(x) = \frac{1}{\rho} \frac{\sum_{\text{evt}} \left( \frac{dE}{dx} \right) dE}{\sum_{\text{evt}} dE}$$

- $n = \text{event index}$
- $t = \text{track index}$
- $s = \text{step index}$
Difference between calculation methods

- $\omega$ = track weight
- $\varepsilon$ = energy deposited per step (\*)
- $l$ = step length

$dE/dL$ computed along the voxel

$dE/dL$ computed step by step

\( \bar{L}_d(x) = \frac{1}{\rho} \sum_{\text{evt}} \left( \frac{dE}{dx} \right) dE \)

Method A

Method B

Method C

$\bar{L}_d$ obtained from ICRU 49 stopping power tables for particle

Residual range

\( L_{sn} \) obtained from ICRU 49 stopping power tables for particle

\( \varepsilon_{sn} \) obtained from ICRU 49 stopping power tables for particle

\( (*) \) Kinetic energy of secondary electrons included in $\varepsilon$ (unrestricted LET)
Macro-dosimetric calculations (LET)

Dose and $LET_d$ simulation with Geant4 (v9.6.2)

Geometry

Proton Beam

- Water tank – cylindrical symmetry
- $\Delta z$ value from 0.2 – 2.0 mm
- $\Delta r = 2.0$ mm
- Dedicated scorers for $LET_d$

Physics

- StandardEM_option3
- QGSP_BIC_HP
- Prod. cut = 0.05 mm

Proton Beam

- 160 MeV beamlet
- Broad beam for SOBP
Macro- vs Micro-dosimetric comparison

According to Kellerer (1985)

\[ \overline{L_d} = \frac{8}{9} \left( \overline{y_D} - \frac{3\delta_2}{2d} \right) \]

Where:
- \( \delta_2 \) represents the weighted average of the energy loss per collision, \( \varepsilon_c \), of the traversing charged particle.
- \( d \) represents the site diameter
Results – \( \text{LET}_d \) calculations

protons @ 160 MeV

Method A (step-by-step)
Method B (along voxel)
Method C: \( dE/dx \) tables

Poster: SU-E-T-78

Integrated over 5mm around central axis
Results – LET<sub>d</sub> calculations

Differences – entrance region

\[ \Delta z = 0.5 \text{ mm} \]

\[ \delta \text{-ray steps} \]

\[ \text{Method A} \]

\[ \Delta z = 0.5 \text{ mm} \]

\[ L \approx \frac{0.900 + 0.100}{1.0} \frac{\text{MeV}}{\text{mm}} = 1 \frac{\text{MeV}}{\text{mm}} \]

\[ \delta \text{ with } \varepsilon = 100 \text{ keV} (>0.06 \text{ MeV}) \]

\[ \varepsilon = 124 \text{ MeV} \]

\[ \varepsilon = 125 \text{ MeV} \]

\[ \Delta \varepsilon_{\text{cont}} = 900 \text{ keV} \]

\[ s_1 \quad 1.0 \text{ mm} \]

\[ s_2 \]

\[ \varepsilon = 125 \text{ MeV} \]
Results – LET$_d$ calculations

Differences – entrance region

\[ \Delta \varepsilon_{\text{cont}} = 300\text{keV} \]

\[ \varepsilon = 125\text{MeV} \quad \Delta \varepsilon_{\text{cont}} = 300\text{keV} \quad \Delta \varepsilon_{\text{cont}} = 300\text{keV} \quad \varepsilon = 124\text{MeV} \]

\[ s_1 \quad 0.33\text{mm} \quad s_2 \]

\[ L \approx \frac{0.300 + 0.100}{0.33} \text{MeV/mm} = 1.21 \text{MeV/mm} \]

\[ \delta \quad \text{with} \quad \varepsilon = 100\text{keV} (>0.06\text{MeV}) \quad (0.06\text{MeV} = 0.05\text{mm e- range}) \]
Conclusions on LET calculations

- Different monte carlo implementation of $LET_d$ lead to significant deviations in the calculated values, especially at the Bragg Peak region.

- Systematic variations of the calculated $LET_d$ dependant on the voxel size along the beam direction. Its cause is different between entrance and Bragg Peak regions.

- These differences resulted in significant deviations when calculating $LET_d$ distributions for an arbitrary SOBP. (poster)

- Method C recommended for $LET_d$ calculations, as it is independent of voxel size.

- Regardless the method used, calculations need to be contrasted with actual measurements.
Microdosimetric Measurements: 3D microdetectors

Work done by: Consuelo Guardiola – University of Pennsylvania & Microelectronic National Center – CSIC (Barcelona)

Soon to be carried out:

![Diagram of 3D electrode and HeLa cell](image)

- HeLa cell (700 µm³)
- Unit cell (minimum sensitive volume) of sensor

Poster: SU-E-T-380
Microdosimetric Measurements: 3D microdetectors

- Use IMB-CNM’s 3D sensor technology to create cylindrical structures that completely confine the active volume – “cell-like”
  - P+ implanted electrode surrounded by N+ cylindrical 3D electrode (trench)
  - SOI wafer with backside removed to avoid backscattered particles
- Array of independent active volumes with individual (pixel) or serial (strip) readout – spatial resolution
- Patent design approved (2014)
- Fabrication ongoing at IMB-CNM’s clean room on 3, 6, 10 and 20 µm SOI wafers.
Microdosimetric Measurements: 3D microdetectors
Bragg curve of the 62 MeV proton beam acquired with a solid water phantom with an ultra-thin 3D silicon detector of 10 µm thickness at the Louvain cyclotron.

The ultra-thin 3D silicon sensors are reliable for microdosimetry measurements.

Pulse height spectra in the water phantom along the Bragg peak

- 10 µm backthinned sensor, 7x7 mm² area
- Proton energy 62 MeV, range 32 mm.
- Proton flux $10^4$ p/cm²s
- 180 s acquisition
- LLD = 90 keV
Microdosimetric Measurements: 3D microdetectors

\[ l = \frac{2abh}{bh + ab + ah} \Rightarrow \bar{l} = 4 \frac{V}{S} \Rightarrow y = \frac{\varepsilon}{l} \Rightarrow d(y) = \frac{y f(y)}{y_F} \]

LET ~ average area under the curve

[Graph showing energy vs. detected counts for different solid water depths, with a legend indicating various depths from 0 mm to 32 mm. The LET graph is also shown with a note indicating the average area under the curve.]
Overall Conclusions

- Radiobiological optimization in particle radiotherapy requires input from many different ‘corners’ to significantly reduce uncertainties.
- Full RBE based optimization in proton radiotherapy might still be a premature step, but LET guided treatment planning is doable.
- When performing LET based treatment plans, especial considerations must be given to the methodology used to calculate LET.
- Calculations of LET must be contrasted with measurements, i.e. TPS must be commissioned not only for dose but also for LET. If microdosimetric models are used, TPS cannot rely only on MC calculations but microdosimetric measurements are advisable.
- Consideration of LET in proton treatment planning may lead to alternative method of planning still to be fully explored.
Overall Conclusions

- PMAT is an interesting option that might allow simultaneous dose and LET painting of a target while delivering the dose in an efficient manner

http://youtu.be/L2zdXh3XCdI
Acknowledgements

- Dr Daniel Sanchez-Parcerisa
- Dr Consuelo Guardiola-Salmeron
- Dr Miguel Cortes-Giraldo
- Dr Steve Tuttle
- Mr Marcus Fager
- Mrs Maura Kirk
- Mrs Malorie Stowe
- Mr Brendan Burgdorff
- Mr Mark Kondrla
- Mr Ryan Rue
- Mr Nicole DiGiovanni
- Mr Dan Douglas
- Mrs Alex Shaindlin
- Mrs Oksana Vovchuk

- Prof Tim Solberg
- CNM (Barcelona)