Biological Optimization of Hadrontherapy

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Contents

- Introduction and General Framework
- Objective function and physical/biological input
- Dose Delivery and Biological Optimization
- Oxygen Effect
Depth dose curves

Bragg Peak: C12 (GSI) – Proton (HCL)

Relative Dose

Depth in Water (cm)

160 MeV p

260 MeV C12
Conformal Avoidance: Photons – Protons – C12

Photons

Protons

C12
Prostate Ca: Different Modalities

- Target V(D<90)
- Rectum D(av)
- Bladder D(av)

Legend:
- Photon-IMRT
- Proton-DET
- C12-DET
The framework of biological optimization

- Physical optimization hadron therapy
  - Dose constraints
  - DVH constraints
  - ....

- Biological Optimization
  - Biological effect: $E$

  Two main components
  - Macroscopic model for the dose dependence of $E$
  - Microscopic model describing the dependence of $E$ on intrinsic radiation quality only

  \[ E = \alpha D + \beta D^2 \]
Inverse Planning: Optimization Loop

- Treatment Parameters - DOF
- Physical Dose, LET
- RBE Data
  - RBE Model
  - Physical Photon Dose
    - Biological Effect
    - Objective Function
  - Optimization Alg.
    - Update of TP
    - Clinical Experience
Photons vs. DET protons

Reduction of integral dose and lower dose levels
Prostate Ca: DET Protonen vs. DET C12

DET Protons

DET C12

C12 : + Steeper Gradient at Target Edge
- Higher Integral Dose (Distal Tail)
Physical Optimization with different types of radiation

- Conformality
- Integral dose

- IMPT
- IMHIT
- 3D PT
- IMXT
- 3D XRT
Differential RBE
\[ = \frac{RBE_T}{RBE_{HT}} \]
RBE and LET

9 keV/\mu m
\Phi = 25/A

25 keV/\mu m
\Phi = 9/A
Spread-out Bragg Peak (SOBP)
RBE-measurement

![Graph showing relative dose vs. depth and distance from beam axis.](image)
RBE-results : LET dependency
RBE-results: dose dependency

![Graph showing RBE values vs. proton dose (Gy)]
Effect based objective function (LQ model):

$$F_E(\vec{w}) = \sum_{i \in T} (E_i(\vec{w}) - E_{\text{pres}})^2$$

Prescribed effect: $E_{\text{pres}} = \alpha_x D_{\text{pres}} + \beta_x D_{\text{pres}}^2$

Extend OF to OARs
Superposition of many beamspots in voxel $i$:

- **dose** $D_i = \sum_j w_j D_{ij}$

- **effect** $E_i(\tilde{w}) = \alpha_i(\tilde{w})D_i(\tilde{w}) + \beta_i(\tilde{w})D_i(\tilde{w})^2$

($\alpha_i$ and $\beta_i$ depend on radiation quality (energy (depth) of primary particles and tissue type)
Mixed radiation averaging

\[ \alpha_i = \sum_j w_j D_{ij} \frac{\alpha_{ij}}{D_i} \]

\( \alpha_{ij} \) derived from microscopic model or directly from experimental data

energy (depth) dependend radiation quality from bixel j at voxel i

Analogue for \( \sqrt{\beta_{ij}} \)
LET calculations

- dose-averaged LET
  - Monte Carlo simulations
  - analytical LET model


approximation:
laterally constant LET

\[ \text{LET}(d,r) \approx \text{LET}(d,0) \]
- What microscopic model for $\alpha_{ij}$?
- What clinical endpoints?

**University Clinic/GSI/DKFZ approach**

- Tumor (Chordoma, radioresistant)
  - $\alpha_x = 0.1 \, (1/\text{Gy}); \, (\alpha/\beta)_x = 2 \, \text{Gy}$
  - Healthy brain (late effects)
    - same parameters
    - Continuous biological dose at tumor boundaries

- Microscopic model for $\alpha, \beta$ TRiP98 (LEM) GSI
Dose and $\alpha$ as a function of depth

Input for optimization:

$D_{ij}$ and $\alpha_{ij}$

$\alpha$(depth, cell type)

from measurements or biological models, e.g., LEM/TRiP98*

* Krämer and Scholz (2000) PMB 45, 3319-3330
Alpha vs Distance to peak for different energies
chordoma cells: $\alpha=0.1$ Gy, $\beta=0.05$ (photons)

Alpha [1/Gy]

Distance to Peak [mm]

- 88.83 MeV
- 178.01 MeV
- 276.09 MeV
- 430.10 MeV
- SOBPS
- Multifield Optimization
- DET or 3D Scanning
Results: biologically optimized SOBP

carbon ions on chordoma cells
Biologically optimized SOBP

- Constant RBE: Carbon – Protons?
3D treatment planning for carbon ions

Single field plan
9314 spots

Optimization
time:
~10 min
- Multifield Optimization
Multifield optimization: two opposing fields

- single field optimization
- multifield optimization

carbon ions on chordoma cells

RBE x dose

both fields together

one field only
DET with „normal“ (dose) optimization

KonRad

patient with clivus chordoma

5 beams, DET

dose

RBE · dose

LET
DET with „biological“ optimization

dose

RBE · dose

LET
3D treatment planning for carbon ions

Single field plan
9314 spots

Five fields (IM)
DET* (3 layers)
11 329 spots

RBE x dose (100% = 3 GyE)  dose (100% = 1Gy)

* Deasy ICCR 1997
Differential RBE

- RBE increases with increasing LET
  - Enhanced RBE within the tumor

- RBE increases with decreasing dose
  - Enhanced RBE within normal tissue and OARs
Example: Protons vs. Carbons ions

Graph showing the difference in effective dose (GyE) and RBE between protons (p, RBE=1.1) and carbon ions (C12) as a function of depth (mm).
The Oxygen Effect:

TPS module for the optimization of Hypoxic Tumors
Aim

Create a TPS routine for carbon ions that optimizes the biological effect under consideration of the influence of the partial oxygen pressure \((pO_2)\) on radiosensitivity.

**Major Assumption:**
Volumetric images are available that represent tumor hypoxia and that large changes in hypoxia occur on a timescale shorter than the imaging to treatment end time.
Radiosensitivity changes with $pO_2$

$HRF(pO_2) = \frac{pO_2 + HRF_{max} \cdot K}{pO_2 + K}$

- Carlson et al. (2006)
- Koch et al. (1984)
- Whillans and Hunt (1982)
- Ling et al. (1980)

Carlson et al.
Change of $HRF_\alpha$ with $LET$, data from Furusawa et al. (2000)

$HRF_\alpha (LET) = r \cdot e^{-s \cdot LET} + 1$
- Dose and LET of a primary carbon ion spread out Bragg peak (SOBP).
Preparation

Repeat for each data point on the depth dose curves

Get
- LET
- aerobic LQ model parameters $\alpha_A$ and $\beta_A$

Calculate maximum HRF

Repeat for each averaged subvoxel pO$_2$ distribution

Calculate HRF in every histogram bin

Find LQ parameters $\alpha_h$ and $\beta_h$ for the total cell survival curve for this distribution and these $\alpha_A$ and $\beta_A$ values

Average subvoxel pO$_2$ distributions for different mean voxel pO$_2$ values (histogram)

TPS

Convert PET to pO$_2$ in each voxel

Select for each voxel and all this voxel irradiating pencil beams HRF corrected $\alpha_h$ and $\beta_h$ values

Optimize treatment plan for a homogenous biological effect

Table with $\alpha_h$ and $\beta_h$ as a function of depth and mean voxel pO$_2$ value
1. Analytic LET model

- Carbon ion beam splits up into fragments inside the patient
- Fragments have a different mass and charge than original carbon ions i.e. stopping power changes
- Contribution of fragments to dose and LET cannot be neglected
- Proposing a simple model based on the power law for the range of protons.

Depth dose and LET of a carbon ion beam

Results of analytic calculations compared to Monte Carlo results.
Maximum Hypoxia Reduction Factor (HRF) of carbon ions

\[ HRF_\alpha(LET) = r \cdot e^{-s \cdot LET} + 1 \]

- \( r = 6.689 \)
- \( s = 0.0188 \text{ \mu m/keV} \)
- \( R^2 = 0.838 \)
PET information on mm scale – pO$_2$ changes on µm scale:

a) Assume that PET information can be converted to the mean pO$_2$ of a voxel

b) Simulate subvoxel oxygen distributions on a 2D grid by randomly placing capillaries and solving the partial differential equation for the oxygen diffusion and consumption.

c) For each mean voxel pO$_2$ we obtain an average subvoxel distribution (histogram)

Petit et al. (2009)
Subvoxel oxygen distributions

Result of our own simulations displayed as in Petit et al. (2009)
Calculate the HRF for a given $pO_2$ and LET

$$HRF(p, LET) = 1 + \frac{K}{p + K} \cdot r \cdot \exp(-s \cdot LET)$$
Calculate LQ parameters $\alpha_H$ and $\beta_H$ for a given pO$_2$ distribution and LET

- Total cell survival in a given subvoxel oxygen distribution for dose $D$:

$$S(D) = \sum \left( x_i \cdot \exp(-\left( \frac{\alpha_A}{\text{HRF}_\alpha(p_i, LET)} D + \frac{\beta_A}{\text{HRF}_\beta(p_i, LET)^2} D^2 \right)) \right)$$

- Calculate total cell survival for doses from 0 Gy to 20 Gy
- Fit LQ model to the resulting cell survival curve
- Save fit parameters $\alpha_H$ and $\beta_H$ as a function of depth, initial carbon ion energy and pO$_2$
Table with $\alpha_H$ and $\beta_H$

HRF corrected $\alpha_H$ as a function of depth for a 276 MeV/u carbon ions beam.
Currently used:

Model by Chang *et al.* (2009) based on Fmiso PET localized Eppendorf electrode measurements in rats:

\[ p_i = -K_{50} + K_{50} \cdot \frac{x_{\text{max}}}{x_i} \]

To calculate the pO2 \( p_i \) in voxel \( i \). The PET value is \( x_i \) and the maximum PET value in the tumor is \( x_{\text{max}} \).

Example from Chang *et al.* (2009)
Summary

Fast optimization method for ion beams
based on the biological effect \( E = \alpha D + \beta D^2 \)

Multifield optimization
- improved sparing of normal tissues / OAR’s
- possible for IM techniques

Flexible biological input: \( \alpha, \beta \)
- measured or from any radiobiological model can be used
- consideration of oxygen effect might be possible
Challenges

- Robust biological optimization
  - Organ motion, Setup uncertainties
  - Uncertainties in biological input

- Locally variable RBE?
  - Volume effect for photons?
  - Do we need locally variable RBEs for protons?
Risk adapted treatment planning

- Worst case optimization

- Uncertainties
  - Range uncertainties
  - Setup uncertainties
  - Organ motion
  - Dose calculations
  - ...
Goal:

Find a treatment plan which is still acceptable and robust under the influence of the anticipated uncertainties of treatment variables.

Example: Range uncertainties

- Calc. dose only for minimal, maximal and nominal range.
- Instead of calculating every possible combination of ranges, use worst case dose distribution as lower bound.
Calculation of Worst Case Dose:

Target: Store the minimal dose as WC-dose for each voxel
OAR: Store maximal dose as WC-dose for each voxel
Worst Case Optimization:

To include the Worstcase dose distribution into the optimization, add another term to the objective function $F$:

$$F_{\text{new}} = F(\text{dose}) + wcp \times F(\text{wc\_dose})$$

$F =$ standard objective function  
$\text{Dose} =$nominal dose distribution  
$\text{wc\_dose} =$WorstCase dose distribution  
$wcp =$worst case penalty (tuneable parameter)
Example: 3 copl. IMPT beams

Range uncertainty: 5 mm
Range uncertainty: 5 mm

\[ pwc = 0 \]

\[ pwc = 1 \]
Setup uncertainties 2 mm

\[ \text{pwc} = 0 \]

\[ \text{pwc} = 1 \]
Range vs. Setup Uncertainties

Range: 5 mm

Setup: 0 mm
Range: 5 mm

Setup: 2 mm
Range vs. Setup Uncertainties

Range: 5 mm

Setup: 5 mm
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