PRT/BD/151544/2021

7th IDPASC/LIP Students Workshop
6-7 July 2022

New Radiobiological and Nanodosimetric insights into Proton Therapy

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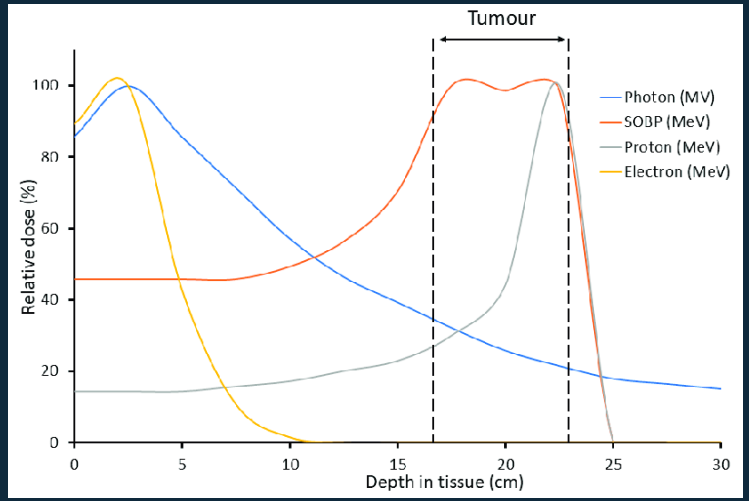
Proton Therapy (PT)

- Form of radiation therapy that uses protons as the primary particle;
- First proposed in the 1940s due to the advantages protons presented in comparison to photons or electrons:
  - Relatively low entrance dose
  - Bragg Peak at depth
  - Rapid distal-falloff of dose
  - Energy/Range modulation
- FDA approves PT in 1988 and the first proton treatment center opens in 1990 (Loma Linda, USA)



Hughes, Jonathan & Parsons, Jason. (2020). FLASH Radiotherapy: Current Knowledge and Future Insights Using Proton-Beam Therapy. International journal of molecular sciences. 21. 10.3390/ijms21186492

Proton Therapy (PT)

- It is particularly beneficial for patients whose tumors are near critical organs or structures:
  - Brain tumors
  - Lung Cancer
  - Prostate Cancer
  - (…)
- The enhanced biological effectiveness is represented by the quantity Relative Biological Effectiveness (RBE).

Relative Biological Effectiveness (RBE)

The RBE is defined as a ratio, between two absorbed doses delivered with two radiation qualities, one of which is a 'reference radiation', that result in the same effect in a given biological system, under identical conditions

$$RBE_X = \frac{D_{ref}}{D_X}\bigg|_{SF}$$

Proton Therapy (PT)

- Proton doses are often prescribed based on the required photon dose it would be necessary, denoted as Gy[RBE].
  - This shows how important it is to know with low uncertainty the value of RBE for protons.

- To this day, the clinical convention is to use a “generic” RBE equal to 1.10 for PT.
  - This value disregards new evidence that RBE is a function of Linear Energy Transfer (LET), biological endpoint, cell type, dose per fraction, and others.
  - The use of a SOBP worsens the RBE problem even further.
  - In 2014, Paganetti reported different values of RBE across the SOBP: 1.1 in the entrance region, 1.15 in the centre, 1.35 at the distal edge and 1.7 in the distal fall-off

Harald Paganetti 2014 Phys. Med. Biol. 59 R419

Biological Target

- The cell survival following the exposure to protons is usually parameterised with dose or LET, however this concepts fail to provide a complete view of the energy deposition at the relevant scale.

- **DNA** is considered to be the main biological target of ionizing radiation.

Nanoscale

Two new concepts

Nanodosimetry

Ionization Detail (ID)

Nanodosimetry

- Aims to establish a new concept of radiation quality.
- Describe the radiation by physical quantities that are related to the particle **track structure** at the nanometer level.
- Characterization of particle track structure is based on the formation of ionization clusters.
  - ionization is considered the most consequential form of energy deposition in radiobiology.
  - the ionization is considered to be representative of the entire track.

Ionization Detail (ID)

- Class of nanodosimetric quantities that accurately model the effect of the physical stage of energy deposition.

Notation	Description
ν	The ionization cluster size defined as the number of ionizations produced in the target volume by a single primary particle track, including those produced in interactions of secondary electrons.
$P_\nu(Q,V)$	The probability distribution of ν, which depends on the radiation quality, Q, (particle type and velocity) and on the shape, size and material of the target volume, V.
$M_k(Q,V)$	$= \sum_{\nu=0}^{\infty} \nu^k P_\nu(Q, V)$ The kth statistical moments of the distribution, $P_\nu(Q,V)$. The first moment, $M_1(Q,V)$, is also called mean ionization yield.
$F_k(Q,V)$	$= \sum_{\nu=k}^{\infty} P_\nu(Q, V)$ The complementary cumulative probability distribution of ν, representing the probability of measuring k or more ionizations in the target, V.

Conte, V., Selva, A., Colautti, P., Hilgers, G., Rabus, H., Bantsar, A., Pietrzak, M., & Pszona, S. (2018). NANODOSIMETRY: TOWARDS A NEW CONCEPT OF RADIATION QUALITY. Radiation protection dosimetry, 180(1-4), 150–156. https://doi.org/10.1093/rpd/ncx175

Hypothesis

Relevant ID quantities are better predictors for cellular biological effects than LET or RBE

Correlate ID with early and late cellular effects after irradiation

Experimentally test the biological effect prediction based on ID parameters

Methodology

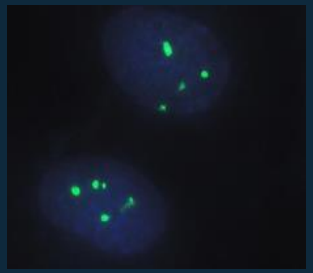


Fig.1 Foci Assay: Cell nucleus (blue) and DSB-foci (green) seen with fluorescence microscopy

1. MCTS [1] Simulations

Characterize the radiation track structure at the nanoscale of different types of IR and calculate ID quantities.

[1] Monte Carlo Track Structure Simulations

2. Radiobiological Studies (1)

Perform radibiological experiments and quantify early (foci) and late (cell survival) cellular effects induced by helium ion and proton microbeams, as well as clinical proton beams.

Methodology

3. Mathematical Modelling

Identify ID predictors that show potential for a treatment planning of a uniform biological effect, using machine learning techniques

4. Radiobiological Studies (2)

4.1. Measure early and late cellular effects after irradiation with protons and helium ions of different energies but with the similar ID.

4.2. Plan and deliver a PT treatment plan with uniform ID in a head phantom.

Hypothesis

Relevant ID quantities are better predictors for cellular biological effects than LET or RBE

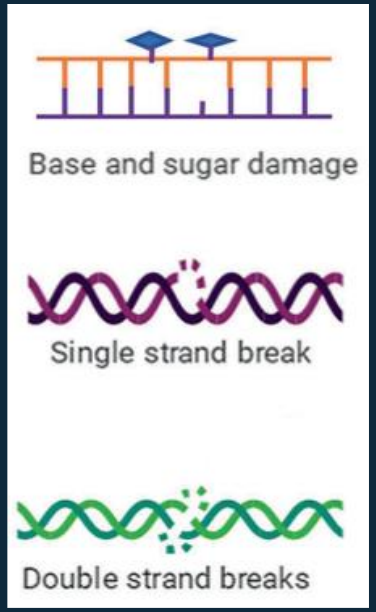
Expectations

1. If two different radiation qualities Q_1 and Q_2 have similar ID characteristics, then experiments with exposed cells will have the same biological outcome (within statistical uncertainty), but different values of LET and RBE.

2. An irradiation of a volume in an anthropomorphic head phantom with a treatment plan that produces a uniform spatial distribution of the ID will generate a uniform geometric distribution of biological endpoints and a non-uniform distribution of LET and RBE across the volume.

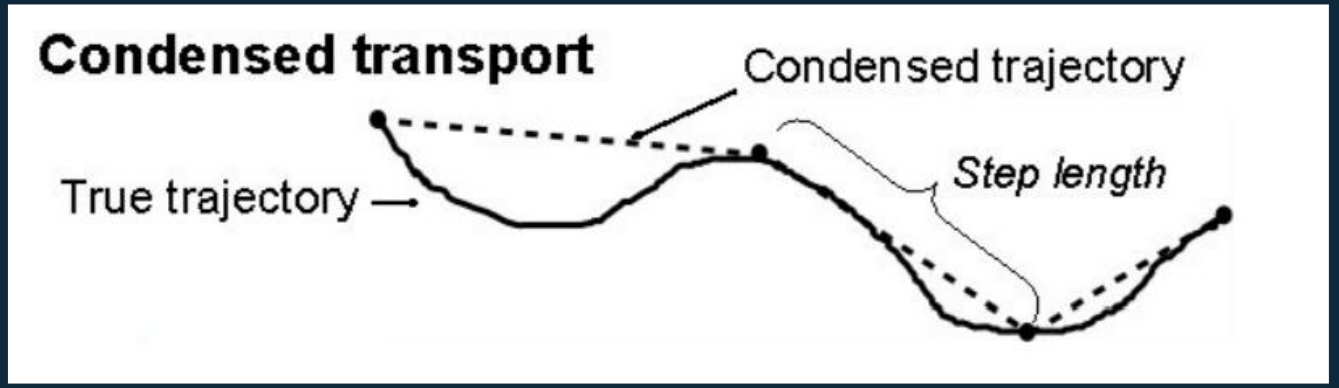
Backup

Biological Damage



MC CH vs TS

- MC CH: For each step, the stopping power is used to account the energy loss and Multiple Scattering theories are used to determine the particle's new position and momentum.
- MC TS: Every single interaction of a particle is explicitly simulated. The particle's next position is calculated using the total mean free path.



Clonogenic Assay