Radiobiological characterization of clinical proton and carbon-ion beams:

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Improvement of radiotherapy

- **Ballistic selectivity**
  
  Increasing the dose to the tumor while reducing the dose to the surrounding normal tissues

- **Differential effect**
  
  Compared to conventional radiations, the effect is relatively more marked on the tumor than on the normal tissues (RBE)
There are several arguments pointing at the DNA as the main target of ionising radiation.
Ionisations along an electron track (secondary electron after low LET irradiation)
Sequence of events

- Energy deposits (primary and secondary electrons)
- DNA damage.
- DNA re-arrangement.
- Repair induction (enzyme synthesis).
- Cell cycle arrest.
- Repair vs. apoptosis.
- Cell death
- Tissue failure
DNA is the primary target

Double strand break

Ionisation and section of a DNA strand (single strand break)
Various types of DNA damage
Possible consequence of DNA damage

DNA damage

- Repair
- Misrepair
  - Cell death
  - Mutation

- Apoptosis

Cell

Ionisation
Cell death after misrepair (lethal mutation)

Apoptosis
Base pairs can be substituted, or deleted, or added, all resulting in an alteration of information.

A gene can be inactivated or mutated.

A mutation can amplify or decrease the gene expression.
A dose increment kills a fixed proportion of cells

Exponential survival curve of prokaryotes and bacteria

Poisson’s law

\[ S = e^{-\alpha D} \]
Cell survival curve

Clones can be seen

- 6 Gy
- 2 Gy
- 4 Gy

Survival curve

Dose

Experimental points

Unsaturated repair

Saturated repair
Survival without repair
Initial part of the survival curve

A steep initial part exists on survival curves, particularly in resistant cells. It is interpreted as a sign of repair induction when and if the damage concentration is sufficient to « trigger » repair enzyme synthesis.
The linear quadratic model

\[-\log S = \alpha d + \beta d^2\]

Survival curve

DNA

Double-strand break

Single-strand break

the model of radiation action
Ionisation along a particle track

Low density of ionisation

High density of ionisation

Low LET tracks

High-LET track

~25 nm
Direct and indirect effects

G Montarou, radiobiology in medicine, 17-12-2013
Protons

Protons are sparsely ionising, majority of indirect effects
Carbon ions

Carbon ions are densely ionising, majority of direct effects
Scattered energy deposits, repair inefficient

Dense energy deposits, repair inefficient

Densely ionizing: e.g.; α particle, proton

Sparsely ionizing: e.g.; γ-ray or X-ray

Dose (Gy)

S.F.

Densely ionizing

Sparsely ionizing

H₂O

OH⁻
Induction of repair enzymes with X-rays and carbon ions, same absorbed dose
Track structure depends on energy and Z
Size of radiosensitive structures

“waste” of energy

RBE

Ionization density (LET)

Maximum 50 - 150 keV/µm
Maximum
50 - 150 keV/µm

“Size » of radiosensitive structures

Ionization density (LET)
Ionization density (LET)

- Maximum 50 - 150 keV/µm

"Size » of radiosensitive structures"
Microdosimetry

Tissue-equivalent proportional counter:

- The sphere is the cathode, in tissue equivalent material.
- The anode is central.
- The gas filling the sphere is tissue equivalent (C, N, O, H).
- Its pressure can be adjusted to simulate small volumes of tissue.
- Irradiation is delivered at extreme low dose rate.
- Electric charges are collected, proportional to the individual energy deposits.

TEPC of Rossi, Columbia University
Microdosimetric spectra: a tool for tracking the RBE variations

Energy deposition along the diameter of a sphere of the same size as the **vital radiosensitive structures**
The diagram illustrates the dose distribution ($y.d(y)$) as a function of lineal energy ($y$) in keV/µm for different types of radiation:

- **Neutrons**
- **Protons**

The RBE (Relative Biological Effectiveness) values are shown for each type of radiation:

- **Co $\gamma$-rays**: RBE = 1
- **Co $\gamma$-rays, RBE = 1.8**
- **Protons, RBE = ?**

The graph compares the dose distribution for neutrons and protons, highlighting the differences in their effectiveness based on their RBE values.
Energy of the incident particles...
Indentical nominal energy and identical nuclear reaction ...
Depth ...

- Gamma
  - Surface = 2
  - Depth = 1

- p(34)+Be neutrons

- Absorbed dose / Gy
  - 5.5
  - 6.0
  - 11.0

- Percentage of survival at 5.5 days
  - Surface: 7 cm

- Lineal Energy: \( y / \text{keV} \mu \text{m}^{-1} \)

- October 2-5, 2003 - Lyon (France)
  - 9th Workshop on heavy Charged Particles in Biology and Medicine 2003 (HCPBM 2003)
  - General Meeting on the European Network for Light Ion Hadrontherapy (ENLIGHT 2003)
Summary of pertinent conclusions (1)

- Conceptually, RBE is a measure of the biological effectiveness differences related to *radiation quality only*.

- RBE is essentially *variable* and depends on numerous factors related 1) to *biology* or, 2) to the *beam delivery technique*.

- **Biology**: the main sources of RBE variation are: • the biological system (tissue, endpoint, etc.) and • dose, dose rate and fractionation.

- **Beam**: the main sources of RBE variation are: • Depth (for heavy ions), • filtration (for fast neutrons), • collimation, etc.

- RBE is correlated with ionization density. *Roughly speaking*, it increases with LET.
Summary of pertinent conclusions (2)

- When determining RBEs, **all conditions** - but the radiation quality - have to be the same for the intercompared beams.

- Inherent performance of the beam generators as well as practical reasons (e.g., distance) prevent from adopting **ideal** experimental procedure.

- Recourse to **indirect method** for RBE determination is often required (RBE ratios).

- Recourse to **fractionated** irradiations is most of the time required to determine **RBEs for small doses**.

- **Microdosimetry** is a powerful tool for **tracking** the potential RBE variations.
Bragg peak
Plateau region
Fall-off region
Fragmentation region
PROTONS
HEAVY IONS
Depth in tissue
Relative dose
Most events are in the 1 keV/mm range, with a significant component around 100.

Plateau (entry beam)
Most events are in the range 10-30 keV/mm range, with a significant component around 10.

End of Bragg peak
Most events are in the range 10-30 keV/mm range, with a significant component around 100.

Spectrum: sum of individual energy deposits
Proton beam (Nice)

Let increases as the beam progresses in depth (SOBP)
Density of energy deposits in the Bragg peak of carbon ions
Linear energy transfer (LET)

- LET is the physical quantity of ionisation density; its unit is the keV/µm.
- The higher the LET, the broader the DNA damage and, hence, the larger the biological effect.
The relative biological effectiveness is a ratio of dose:

$$\frac{D_{\text{low LET}}}{D_{\text{high LET}}}$$

for any given level of effect.
All the irradiations performed under the same conditions, e.g.:

- Irradiation in a single fraction
- Acute dose rate
- Same day (and moment in the day)
- Animals from the same population
- Randomized (dose / radiation quality)
- Same experimenters
- Reliable dosimetry
- Etc.

RBE accounts for the *biological effectiveness difference* related only to the *radiation quality difference*.
Different radiation quality have different RBE's

Intestinal crypt regeneration in mice (single dose)

Best estimates of LET or $y$ (keV$\mu$m)

Gamma & X-rays

Protons

Neutrons

Carbon ions

RBE (ref. cobalt-60 $\gamma$-rays)
Oxygen effect

Indirect Action
Dominant for X-Rays

Direct Action

Indirect Action

Direct Action
Dominant for High LET Radiation
Reduced effect of oxygen

100% n
OER = 1.66

4MeV d-Be

OER = 1.7

100% X
OER = 3.13

As LET increases, OER decreases.
**Reduction of radiosensitivity differences**:

**Potential therapeutic advantage**

when the tumor is radioresistant in comparison with healthy tissues

---

**unfavourable**!

![Graph showing dose vs. surviving fractions for healthy tissues and tumor, comparing gamma and neutrons.](image)

**less unfavourable**!

---

Potential therapeutic benefit due to the **reduction of** an **unfavourable** differential effect
Reduction of radiosensitivity differences:

contra-indication

when the healthy tissues are radioresistant

In comparison with the tumor

Contra-indication due to the reduction of

a favorable differentiel effect
<table>
<thead>
<tr>
<th>Hadron RBE is different than that of photons</th>
<th>Build-up of radiobiological experience and disclosure of potential benefits</th>
<th>« Pretherapeutic » experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBE varies with « radiation quality »</td>
<td>Safe and optimum clinical application</td>
<td>« Preclinical » experiments</td>
</tr>
<tr>
<td>All the beams are different</td>
<td>Transfer of radiobiological / clinical information and coherency of treatments</td>
<td>Radiobiological Calibration / Intercomparison</td>
</tr>
</tbody>
</table>
Summary of in vivo data on jejunal crypt cells
RBE variations related to biological system

RBE variation related to radiation quality (energy)

Rationale for clinical application of high-LET radiations

Emergence of problems related to:
- Transferring clinical and radiobiological information
- Pooling clinical data
- Optimizing clinical applications
- Comparing with conventional radiations
Differential Effect (neutrons, ions)

Proton RBEs
Reviewed by Robertson et al.
(Cancer 35, 1664-1677, 1975)

Differential Effect (neutrons, ions)

NO differential effect (protons)

Proton RBE relative to gamma

Proton energy / MeV

Miscellaneous systems

Cataract formation

Low dose rate

NO differential effect (protons)
Potential advantage of protons is essentially **ballistic**

Proton RBEs are **too small** to result in a *workable* differential effect

Proton RBEs are **big** in comparison with dose accuracy requirements ...

*and raise essentially* **Bio-dosimetry questions**
Gamma Equivalent Dose = physical dose $\times$ RBE

Uncertainties in RBE values lead to equal uncertainties in the derived Gamma Equivalent Doses

The dose accuracy required in radiotherapy is 3.5 %
**In vitro systems**  
*(Proton RBE = 0.94 - 1.63)*

*Substantial spread between cell lines and conflicting conclusions about:*

- RBE value in reference conditions (energy, depth)
- Possible RBE increase with depth
- Possible RBE increase with SF (or fractionation)
Possible causes of the spread of the data:

- Dosimetry?
- Underlying theory (model to fit the data)
- Randomization?
- Platting efficiency?

Uncertainties above 20%
In vivo systems
Proton RBE 1.08 - 1.17

Limited amount of data. Present-day questions are:

- RBE increase with fractionation?
- RBE difference for early and late tissue tolerance?
- RBE increase with depth?
Which system to use for calibrating and intercomparing clinical proton beams?
Systems and endpoints which result in widely different values for the RBE of neutron relative to X-rays ...

\[ \text{EBR} = \frac{n_1}{\gamma} \]

... give similar values for the \textit{RBE differences} between two closely related neutron energies

\[ \text{EBR} = \frac{n_2}{n_1} \]

\[ \text{EBR} = \frac{\gamma}{\gamma} \]
Consequently, the choice of a biological system for intercomparisons should be governed largely by its

- portability,
- repeatability
- and convenience.

J. Hall, 1979
Intestinal crypts regeneration in mice

*In-vivo* system, based on Cell lethality
**Irradiation**

10 - 17 Gy

**Faure (South Africa)**

RBE = 1.55 - 1.59

**p(66)+Be**

**Cobalt-60**

<table>
<thead>
<tr>
<th>Dose / Gy</th>
<th>Number of regenerated crypts per circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>10^6</td>
</tr>
<tr>
<td>8</td>
<td>10^6</td>
</tr>
<tr>
<td>12</td>
<td>10^5</td>
</tr>
<tr>
<td>16</td>
<td>10^4</td>
</tr>
<tr>
<td>20</td>
<td>10^3</td>
</tr>
</tbody>
</table>

**Irradiation to the whole body**

**84 h**

**Irradiation**

**Sacrifice**

**Fixation**

**Microtome**

**Histology**

**Counting regenerated crypts (microscope)**

**Tested beam**

- Clinical dose rate
- Position depending on the type of beam

**Reference beam**

- Cobalt-60 or 7 MV
- 1 Gy / min
- Depth of the peak dose

**Irradiation**

- Single fraction

**Irradiation to the whole body**
Reproducibility...

**Neutrons**

- Neutrons p(65)+B (1992)
  - EBR = 1.53 ± 0.04
  - Dosage: 9.9 Gy, 15.1 Gy

- Neutrons p(65)+Be (1995)
  - EBR = 1.52 ± 0.04
  - Dosage: 9.5 Gy, 14.4 Gy

**Protons**

- Protons (1995)
  - Dosage: 8, 10, 12, 14, 16, 18, 20 Gy

- Protons (1992)
  - Dosage: 8, 10, 12, 14, 16, 18, 20 Gy

- PSI 1997
  - RBE = 1.16
  - Dosage: 9.9 Gy, 15.1 Gy

- PSI 1998
  - RBE = 1.18
  - Dosage: 9.9 Gy, 15.1 Gy

- NAC 1994
  - RBE = 1.16
  - Dosage: 9.9 Gy, 15.1 Gy

- NAC 1996
  - RBE = 1.14
  - Dosage: 9.9 Gy, 15.1 Gy

- NAC 1998
  - RBE = 1.15
  - Dosage: 9.9 Gy, 15.1 Gy
Radiobiological characterization (protons)
Influence of depth
Biological weighting function

Co$_{60}$ $\gamma$-rays
200 MeV protons
NAC (Faure, South Africa)

Cobalt-60 gamma-rays

\[14.38 \text{ Gy}\]

Reference

RBE = 1.16 ± 0.05

Protons Initial plateau (unmod. beam)

\[12.38 \text{ Gy}\]

Initial plateau

RBE = 1.10 ± 0.04

Protons Beginning 7 cm SOBP

\[13.03 \text{ Gy}\]

Protons Initial plateau (modulated beam)

RBE = 1.18 ± 0.04

Protons Middle 7 cm SOBP

\[12.19 \text{ Gy}\]

Protons End 7 cm SOBP

RBE = 1.23 ± 0.03

\[11.68 \text{ Gy}\]

Absorbed dose / Gy

Number of regenerated crypts per circumference

250

200 MeV protons
NAC (Faure) South Africa

Relative dose (%)

0

100

200

300

400

500

600

700

800

900

1000

Depth in Perspex / mm

Crypts regeneration in mice after a single fraction

< 5 %
Protons: initial plateau
RBE = 1.11

Protons: middle SOBP
RBE = 1.16

Protons: end SOBP
RBE = 1.21

Cobalt-60
RBE = 1.11

Spot scanning

\[ \text{PSI} \]

\[ \text{RBE} = 1.11 \quad 1.16 \quad 1.21 \]

\( \sim 4\% \)
RBE difference of 7%
**Intestine (10 fractions)**

RBE (end) / RBE (middle) ≈ 1.08
Selective thoracic irradiation in mice

Irradiation in 10 fractions (i = 12 h)

(middle vs end of the SOBP)

Proportion of surviving animals

Absorbed dose /

< 6 %
RBE increases suddenly by $6 - 10\degree\%$ from the middle to the end of the SOBP.
More precise irradiation is possible

200 MeV protons

1.5 cm
iThemba LABS (2006)
200 MeV protons, 7-cm SOBP

Number of regenerated crypts per circumference vs Dose / Gy

RBE (end) / RBE (middle) = 1.10
As an increase in RBE is observed at the end of the SOBP in all biological systems, it is advisable to allow for it.

**TPS** should include biological weighting functions.
Influence of fractionation (or dose)
Crypt regeneration in mice

Cobalt-60 gamma-rays and 200 MeV protons

- Cobalt-60 irradiations at the depth of the peak dose
- Proton irradiations at the middle of a 7 cm SOBP (irradiation in 10 fractions were also performed at the end of the 7 cm SOBP)

- 7 dose / effect relationships
- 9 increasing doses
- 8 mice per point
Number of regenerated crypts per circumference

Total dose / Gy

Protons

Cobalt

1 fract.

0,1

10

100

1000

0

4

8

12

16

20

24

28

32

36

Bloomington, IN (USA)  Midwest Proton Radiation-therapy Institute, Friday, July 9, 2004
Number of regenerated crypts per circumference

Total dose / Gy

Bloomington, IN (USA) Midwest Proton Radiation-therapy Institute, Friday, July 9, 2004
Irradiation at the middle of a 7 cm SOBP in the 200-MeV proton beam produced at the National Accelerator Centre (NAC) of Faure (South Africa).
Late tolerance

(Survival after selective irradiation of the thorax in mice)
For both systems (10 fraction irradiations)
RBE at the end of the SOBP ~ 6 % greater that at the middle
Proton RBE (at the middle of the SOBP) does not vary with dose (or fractionation) for in vivo systems.

A generic RBE value of 1.10 at the middle of the SOBP (i.e. point of dose specification) seems to be appropriate.
Proton RBE **In-vitro**, as a function of dose, for all “clinical” energies

**Proton RBE In-vivo**, as a function of dose, for all “clinical” energies

---

From Paganetti et al. (2002)
HEAVY IONS
He
C
P
Megavoltage X rays

Ar
Si
Ne
Pions

250 kV X-rays

60Co
Neutrons

Megavoltage X rays

LET

RBE

Quality of dose distribution
Salivary gland tumour treated with fast neutrons
Study results (± 1985)

17% ± 11 vs. 67% ± 14
25% ± 14 vs. 62% ± 14
Randomized clinical trial of photons vs mixed beam neutrons plus photons for prostate Ca

RTOG 77-04
Prostate carcinomas are slow growing and hence should be well suited for neutron therapy. The neutrons are usually used for the small “boost” volume in order to minimize late normal tissue damage.
Neutron Prostate Study
Major Complications

% Major Complications

Months from Randomization

- Neutrons
- Photons

p < 0.01

Laramore, 1993
CARBON COUNT

Around 12,000 patients worldwide have been treated at dedicated carbon-ion facilities in Europe, China and Japan. The construction of two new facilities, encouraging clinical-trial results and advances in the technology mean those numbers are likely to grow.

- **Heidelberg, Germany**: Opened 2009, People treated: 1,368
- **Lanzhou, China**: Opened 2006, People treated: 213
- **Pavia, Italy**: Opened 2012, People treated: 105
- **Shanghai, China**: Slated to open in 2014
- **Gunma, Japan**: Opened 2010, People treated: 968
- **Hyogo, Japan**: Opened 2002, People treated: 1,523
- **Chiba, Japan**: Opened 1994, People treated: 8,158

**Japan** began treating patients with carbon ions in 1994.
Which RBE to apply?

- Late tolerance of healthy surrounding tissues
- Dose per fraction of 2 Gy photon equivalent

Not a single value

- due to the diversity of the clinical situations
- due to variation of RBE with depth/dose
Density of energy deposits in the Bragg peak of carbon ions
Carbon ions

higher LET and variation in LET

RBE uncertainty Gy (RBE), because dose distribution is optimized in terms of biol. effective doses

Suit et al. 2010

range of true RBE 2.5 - 3

From Peter Peschke, Heidelberg
### Results

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<td>1.43±0.08</td>
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<td>34.2±0.7</td>
<td>24.9±0.7</td>
<td>1.37±0.05</td>
</tr>
<tr>
<td>6 Fx</td>
<td>57.0±4.0</td>
<td>42.8±1.5</td>
<td>1.33±0.10</td>
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<tr>
<td>18 Fx</td>
<td>88.6±2.0</td>
<td>62.2±3.5</td>
<td>1.42±0.09</td>
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Clear fractionation effect in the **plateau**, which allows sparing of normal tissues. **RBE constant**, when number of fractions increase.
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<td>Peak (91 keV/μm)</td>
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<tr>
<td>1 Fx</td>
<td>24.5±0.8</td>
<td>13.9±0.8</td>
<td>1.76±0.12</td>
</tr>
<tr>
<td>2 Fx</td>
<td>34.2±0.7</td>
<td>15.8±0.7</td>
<td>2.16±0.11</td>
</tr>
<tr>
<td>6 Fx</td>
<td>57.0±4.0</td>
<td>19.2±0.2</td>
<td>2.97±0.21</td>
</tr>
<tr>
<td>18 Fx</td>
<td>88.6±2.0</td>
<td>17.7±1.3</td>
<td>5.01±0.37</td>
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Effective response in the Bragg-Peak, with little change in isoeffective total dose with fractionation. 
RBE raises rapidly with decreasing dose per fraction.
HIMAC (Japan): Carbon-12 (290 MeV/uma)

- EBR = 1.3
- EBR = 1.6
- EBR = 1.7
- EBR = 1.9

Depth in water / mm

6-cm SOBP
Compensate the RBE increase by decreasing the physical dose by factors corresponding to the (local) RBE.

Method used in static beam delivery systems (Chiba, Japan)
A given dose of carbon is biologically equivalent to the same dose of gamma multiplied by the carbon RBE.

Iso-doses (in Gy) in a given tissue do no longer correspond to iso-biologically effective doses!!!
CARBON ION BEAM
290 MeV / amu

Depth in water / mm

Normalized absorbed dose

Normalized isoeffective dose

X 2.7
X 3.0
X 3.4

X 2.1
LEM

“Local effect Model” (Scholz et Kraft, 1994)

Derivation of parameters determining the biological response to a Carbon ion exposure from the response parameters to a photon irradiation
The biological effect in a cell nucleus sub-volume is **exclusively** determined by the energy deposit in this sub-volume.

The biological effect is **independent** from the radiation quality of the beam.

A local dose deposit with Carbon ions produces the **same biological effect** than the same dose deposit with photons.

Therefore, the different biological effects of Carbon ion and photons result from **differences in spatial dose deposition**.
Local Effect Model (LEM)  
(Scholz and Kraft)

Parameters **exclusively** determined on the basis of:

- Dose-effect relationship **for photons** (low LET)
- Probability of a lethal event
- Physical data on **track structures**
- Determination of local dose deposits
- **Experimental** measurement of cell nucleus size
- Determination of radiosensitive area size (nucleus diameter)
Advantages:

- Conformational possibilities
- Possibility to treat sub-volumes
- Possibility of dose « modulation » within each volume of interest
- All RBE variation taken into account

Inconveniences:

- Uncertainties on RBE calculation algorithm (LEM, other…)
- Lack of transparency and total confidence in calculation model
- Impossibility (for the physician nor for the physicist) to judge directly the appropriateness of treatments plans. Dose distributions have to be re-calculated with the model.
RBE
NIRS neutrons

80 keV/µm

8 mm apart from the distal edge
Neutron clinical RBE = 3

Carbon clinical RBE at the center of the SOBP = 2.38
Raster scan system at GSI, Germany

from: D. Schulz-Ertner, O. Jäkel, W. Schlegel
i.e. a system where:

“several thousands of narrow ion pencil beams with individual lateral positions, ion energies and particle fluences are combined to form an intensity-modulated field of high granularity”

(M. Krämer, 2001)

Consideration of RBE variations is only possible in an integrated calculation code allowing iterative interaction between both physical and biological input parameters
An **RBE weighting factor** should be applied at each point of the irradiated volume, taking RBE variation with **energy**, **dose**, **biological system**, etc, into account.

**Particules of variable energy** are also delivered at **variable dose rates** or in multi-**micro** fractions.

**Integrated algorithm** allowing for the **iterative interaction** between **physical** (e.g. energy/LET) and **biological parameters** (e.g. intrinsic radiosensitivity, oxygenation, dose rates, micro-fractionation, etc.)
The “Inter–play” effect (Protons, PSI)

Under dosage

Over dosage

Dose heterogeneity
~ 15% / mm

Standard deviation

Number of regenerated crypts per circumference

PBS
diffusion
Pitfalls...
Surviving fraction

Absorbed dose (Gy)

85 MeV protons: 1 cm spread plc

60-Cobalt
~ 1 % of the surface
~ 1 % of the surface
Finally, which recommendation for irradiation schedule?

*Short hypofractionated schedules*

- Less tumour repopulation.
- More damage to quiescent cells.
- More microvascular damage.
- Differential release of cytokines and special immunologic effects?
- Too much assumptions in radiobiological models??