Advanced Silicon detectors for Micro-and Mini-dosimetry in particle therapy

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Space Science School, 4-8 September, 2018, University of Bergen, Norway.
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POWH: Dr Michael Jackson, MD
ANSTO: Dr Dale Prokopovich, Dr Mark Reinhard, Prof David Cohen,

SINTEF: Dr Angela Kok, Dr Marco Povoli and 3DMiMiC team
SPA BIT Ukraine, Dr V. Perevertaylo

HIT facilities in Japan: Prof N. Matsufuji, Prof T. Yamaya (NIRS), Prof T. Kanai, (GUMC)
Institute of Radiooncology, HZDR at OncoRay, Dresden: Dr A. L. Hoffman and team
MGH F Burr Proton Therapy Center and Harvard Medical School
Ben Clasie, PhD, Jay Flanz, PhD, Nicolas Depauw, PhD. Hanne Kooy, PhD, Harald Paganetti, PhD
Content

- Concept Microdosimetry and MKM
- Benefit of particle therapy
- 3D Microdosimetric detector: fabrication
- Silicon-Tissue conversion
- RBE in particle therapy: MicroPlus 3D probe results
- Other applications in hadron therapy
- Mini-dosimetry in particle therapy
- Conclusion and future work
Meet the CMRP team

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Human missions in space

Long journeys aboard the ISS occur more frequently.

Human missions to Mars are envisaged in the future.

The amount of radiation received by astronauts depends on several factors including orbital inclination, altitude, position in the solar cycle, and mission duration. The average altitude of space shuttle orbits is 170 Nautical Miles corresponding to 9 milliRad/day.
Integral proton fluences for several major SPEs over the last four solar cycles

This figure illustrates the rise and fall of fluxes of solar energetic particles during an SPE.
Mixed radiation field:  
*Aviation and Space environment*

- Long journeys aboard the ISS occur more frequently. Human missions to Mars are envisaged in the future.
- Protect astronauts from harmful effects of space radiation is crucial.
- Dosimetry for radiation protection in high energy mixed radiation fields is a challenging task.

Dosimeters for spacecraft crew

Doses are affected by…

- Altitude,
- Latitude and
- Solar activity
Bragg Peak (BP)

William Henry Bragg
William Lawrence Bragg

- 1895: the first recorded surgical use of the Roentgen ray in Australia
- 1905: ‘brought to light a fact, which we believe to have been hitherto unobserved. It is, that the a particle is a more efficient ionizer towards the extreme end of its course.’
- 1915: father and son won Nobel Prize

Bethe Formula

\[
-\frac{dE}{dx} = \frac{4\pi}{m_e c^2} \cdot \frac{n z^2}{\beta^2} \cdot \left( \frac{e^2}{4\pi \varepsilon_0} \right)^2 \cdot \left[ \ln \left( \frac{2m_e c^2 \beta^2}{I \cdot (1 - \beta^2)} \right) - \beta^2 \right]
\]
Proton therapy history

- In 1946 Harvard physicist Robert Wilson (1914-2000) suggested:
  - Protons can be used clinically
  - Accelerators are available
  - Maximum radiation dose can be placed into the tumor
  - Proton therapy provides sparing of normal tissues
  - Modulator wheels can spread narrow Bragg peak

First human patient treated in 1954 at the Lawrence Berkeley Laboratory (LBL) with proton therapy
First Human Treatment

• Cornelius Tobias was a pioneer for hadron beams and was part of first human patient treatment in 1954 at the Lawrence Berkeley Laboratory (LBL) with proton therapy

• Continued investigation for treatment using alpha and heavier ions in 1957 using Berkley’s newly constructed Heavy Ion Linear Accelerator (HILAC)

Cornelius Tobias
Tobias’ most famous work was his investigation of bright streaks, reported by the crew of Apollo-11. He irradiated himself (below) with alphas and neutrons and experienced the light himself
Advantages of Heavy Ion Therapy

- Secondary nuclear fragments
- Secondary neutrons

X rays:
- Cell damage due to indirect DNA damage

Carbon Ion beams:
- Cell damage due to direct DNA damage, irreparable DNA breaks

Courtesy of M. Scholz
Mechanistic understanding

- Chromosomal aberration will be fatal, especially if clustered.
- Energy deposition to the chromosomal size (~μm) is the keystone.
- Spatial energy deposition in \( \mu m \) scale is highly dependent on the incident radiation ... Microdosimetry
Definition

Microdosimetry quantifies:

- the spatial and temporal energy deposition by ionizing radiation in irradiated material at a scale where the energy deposition is stochastic in nature

- i.e. microdosimetry quantifies the spatial and temporal probability distribution of energy deposition by ionizing radiation in a irradiated volume
Stochastic nature of ionization events

At microscopic scale:
- Interactions between radiation and a medium occur in discrete events
- These events occur stochastically around a track

At macroscopic scale:
- The number of these events allows to treat the energy deposition in a volume as a deterministic quantity
Temporal considerations

Temporal evolution of concentration of radical species from a 4 keV electron track

Courtesy of Dr Marco Zaider
Track structure of ionizing radiation

Track structures in 100 nm water
Microdosimetry vs. (traditional) dosimetry

<table>
<thead>
<tr>
<th></th>
<th>Dosimetry</th>
<th>Microdosimetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>is a</td>
<td>deterministic quantity</td>
<td>stochastic quantity</td>
</tr>
<tr>
<td>measures</td>
<td>average energy deposition per unit mass</td>
<td>probability distribution of energy distribution</td>
</tr>
<tr>
<td>is expressed as</td>
<td>$D = \frac{\langle E \rangle}{m}$</td>
<td>$f(z)$</td>
</tr>
<tr>
<td>where</td>
<td>$\langle E \rangle$ is the average energy deposited in the mass $m$</td>
<td>$f(z)$ is the probability distribution of deposition of the specific energy $z$</td>
</tr>
</tbody>
</table>
Cell damage by Gamma and Heavy Ions radiation

**Sparsely ionising**

- mainly *indirect DNA damage*
- relative biological effectiveness: $R_{BE}$\(_\gamma\) = 1
- $R_{BE}$\(_\text{protons}\) = 1.1

**Densely ionising**

- mainly *direct DNA damage*
- irreparable DNA breaks
- Increase of biological effectiveness
  - $R_{BE}$\(_\text{carbon}\) = 2-4
  - → *Radioreistant tumours*


M Kraemer, GSI, Germany
Microdosimetry: Specific energy

- **Energy imparted** $\varepsilon$: is the energy imparted within a site
  \[\varepsilon = \sum \varepsilon_i\]
  Predictions on the energy imparted can be made based on a probability distributions of energy transfers.

- **Specific energy** $z$: is defined as the ratio of the imparted energy $\varepsilon$ and the site’s mass $m$:
  \[z = \frac{\varepsilon}{m}\]

- **Lineal energy** $y$: is defined as a ratio of the imparted energy and mean chord length
  \[y = \frac{\varepsilon}{l}\]

Energy per unit mass vs mass for **constant** dose $D$.

Reducing of the target is changing deterministic deposition of energy to stochastic. Each radiation type has own signature.

Each type of radiation has their own signature of a single event spectra.
Proportional Counters – TEPC

- TEPC - Measurable Quantities
  - Absorbed dose
  - Mean Quality factor
  - Dose equivalent
  - Microdosimetric averages

\[
\begin{align*}
\rho_g &= \left( \frac{\Delta X_t}{\Delta X_g} \right) \rho_t \\
\text{Density of Gas} & \quad \text{Density of Tissue Site (1000 kg.m}^{-3}\text{)}
\end{align*}
\]
Microdosimetric spectra

- Dose distributions $yd(y)$ as a function of energy (bottom) and site size (top)

**Average quality factor:**

$$\bar{Q} = \int_0^{\infty} Q(y)d(y)dy$$

$H = QD$

Dose Equivalent

---

Fig. VI.26 Different formulations of the quality factor, $Q(y)$, according to ICRU Report 40 (ICRU, 1986); $Q(L)$ according to ICRP publication 60 (ICRP, 1991); $Q(L)$ approximation according to Kellerer and Hahn (1988).
Local Effect Model (LEM): cell damage by ions

- LEM is based on corresponding biological effect for X rays
- The difference in biological effectiveness between photons and charged particles is due to track structure.

\[ S = \exp \left[ -\alpha D - \beta D^2 \right] \text{ Linear Quadratic Model} \]

\[
\frac{d\overline{N}(d(\vec{r}))}{\overline{V}_{\text{nucl}}} = -\ln S_X(d(\vec{r})) \frac{d^2}{\overline{V}_{\text{nucl}}}.
\]

\[
\overline{N}_c = -\frac{1}{\overline{V}_{\text{nucl}}} \int_{\overline{V}_{\text{nucl}}} \ln S_X(d_c(\vec{r})) \, d\vec{r}.
\]

\[
\overline{z}_c = \frac{1}{\overline{V}_{\text{nucl}}} \int_{\overline{V}_{\text{nucl}}} d_c(\vec{r}) \, d\vec{r}.
\]

\[
S_c = \exp(-\overline{N}_c).
\]

Courtesy Gustavo Russo, (INFN, Torino)
Single lesion in any domain leads to cell death

Microdosimetric Kinetic Model (MKM)

Hawkins et al. 1994, 2003

Radiobiological Effectiveness (RBE):

\[ RBE_{10} = \frac{D_{10,x}}{D_{10,\text{ions}}} \]

\[ = \text{Dose that gives 10% cell survival}_{\text{x-rays}} \]

\[ = \text{RBE} \times D \]

Biological dose = RBE × D
3D Mesa “Bridge” Microdosimeter: Design and packaging

Figure 1. Top and side-on schematic of a sensitive volume

Area of whole chip: 3.6 x 4.1mm$^2$; 4320 cells
3D Silicon Microdosimeters-Mushrooms (SEM images)

Full 3D (air-trenched)  Planar n+ 3D p+ (poly-trenched)
CMRP Silicon Microdosimeters

Bridge MD Version 2

Median energy map showing the charge collection distribution in the BridgeV2 microdosimeter, biased at -10V

SEM image of Mushrooms

Median energy map showing good sensitive volume yield in the Mushroom microdosimeter, biased at -10V

A. Rosenfeld “Novel detectors for silicon based microdosimetry, their concepts and applications”, NIM A, 809, 156-170, 2016
Heavy Ion Medical Accelerator in Chiba
HIMAC, Japan

HIMAC Bio-cave beam port with passive scattering delivery

$\mu^+$ microdosimeter probe in PMMA sheath

MicroPlus probe with 3D printer
XY-movement stage
Tissue Equivalence study: methodology

1. Calculate the lineal energy spectra along the Bragg peak
2. Substitute with a tissue equivalent (TE) material of variable size / Water and muscle
3. Compare the deposited energy distribution and microdosimetric spectra
4. Find size $l_{TE}$ giving the best match of detector response

Correction factor $C = \frac{l_{TE}}{l_{Si}}$

$$y_{tissue} = \left(\frac{\epsilon}{l}\right)_{Si} \cdot C$$
Tissue equivalence correction factors $C$

<table>
<thead>
<tr>
<th>Material</th>
<th>Water</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$</td>
<td>0.54</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Dose weighted distribution

Response in Si, corrected by $C$
Mean Chord Length (\( \bar{l} \))

- The theoretical mean chord length was formulated by Cauchy (1908) for an isotropic field.
- Hadron therapy is not an isotropic field.

**Calculation of chord length distribution**

\[
\bar{l} = \frac{4V}{S} \\
y = \frac{\epsilon}{\bar{l}} \\
y = \frac{\epsilon}{<l_{\text{Path}}>}
\]
Design optimisation of Mushroom Design

- A free standing SV
- First design with Height=Diameter
- Second approach: Height=$\bar{l}$
- Resulted in much more consistent $\bar{l}$
- SV design should adopt SV design with the thickness=Isotropic chord

D.Bolst *et al* “Correction factors to convert microdosimetry measurements in silicon to tissue in $^{12}$C ion therapy”, PMB, 2017
**RBE\textsubscript{10} and Biological Dose: 290MeV/u $^{12}$C**

Charge measured using a PTW ionisation chamber with fit and RBE\textsubscript{10} measured by the SOI MD.

Biological dose measured by Kase et al. using a TEPC with HSG cell measurements.

Biological dose depth distribution where $D_{\text{Bio}} = RBE_{10} \times D_{\text{Physical}}$

Dose mean lineal energy and RBE$_{10}$ distribution with microdosimetric spectra for each region along the Bragg Peak.

400 MeV/u $^{16}$O Ions

Entrance

Downstream

Dose mean lineal energy and RBE$_{10}$ distribution with microdosimetric spectra for each region along the Bragg Peak.
Characterization of Pencil Beam Scanning in Proton therapy

\[ RBE = \frac{D_X}{D_p} = \frac{\alpha_X^2 + 4\beta_X(\alpha_p D_p + \beta_p D_p^2)}{2\beta_X D_p} - \alpha_X \]

\[ \alpha_x = 0.13 \text{ Gy}^{-1} \]
\[ \beta = 0.05 \text{ Gy}^{-2} \]

\( y_D \) obtained using Bridge microdosimeter obtained with Bridge \( \mu^+ \) probe in water for spot PBS (MGH)

(a) Depth dose distribution and RBE for PBS spot for dose in BP 2Gy. (MGH)

a) $\gamma_D$ obtained using Bridge microdosimeter for 137.3 MeV SOBP in passive proton beam.

b) Depth dose distribution and RBE for 137.3 MeV SOBP in passive proton beam, dose in SOBP is 2Gy (MGH)
Radiobiology and New Technology

- Relative biological effectiveness values for the induction of DSB in DNA are plotted for pristine and modulated 160MeV proton beams (red line).
- Excellent agreement with RBE derived with MicroPlus.

Kevin Prise et al., IJROBP, 2017
290 MeV/u SOBP $^{12}$C Beam – Out-of-field

- Radiation protection approach determine Dose-equivalent:
  - Determine absorbed dose in microdosimeter: $D_{si} = \int_0^{\infty} f(E) dE \overline{\rho S_{si}} \rightarrow D_{ris} = D_{si} \overline{\zeta}_{12C}$
  - Determine average quality factor: $\overline{Q} = \int_0^{\infty} Q(y) d(y) dy$
  - Calculate dose-equivalent: $H = \overline{Q} D_{si}$

Dose-equivalent lateral to the field

Dose-equivalent downstream of SOBP
Motion Experiments

- Gemmel et al. (2011) undertook a study showing:
  - Dramatic effect on treatment plan due to motion
  - Compared cell survival and simulation with tracking adaptation

![](image1)

Microdosimeter undergoing lung motion using the moveable phantom

- Moveable water phantom enables microdosimeter to be moved sub-mm increments and undergo motion similar to that of organs

Figure 11. Treatment plans showing dose inhomogeneity due to motion

Lucite bolus, designed to shape dose to target volume
Motion Experiments: 290MeV/u $^{12}$C SOBP

Stationary and lung motion positions relative to the SOBP physical dose distribution

Schematic showing the effect of the bolus and positions of stationary acquisitions A and B each with 30mm lateral motion
Effect of target motion in $^{12}$C ion therapy: passive delivery

Spherical bolus made from PE

<table>
<thead>
<tr>
<th></th>
<th>Stationary</th>
<th>Motion</th>
</tr>
</thead>
<tbody>
<tr>
<td>$y_D$</td>
<td>51.95</td>
<td>58.21</td>
</tr>
<tr>
<td>$RBE_{10}$</td>
<td>1.7605</td>
<td>1.7806</td>
</tr>
</tbody>
</table>

![Graph showing charge distribution for different conditions](image)

290 MeV/u, SOBP

![Graph showing lineal energy distribution](image)

<table>
<thead>
<tr>
<th></th>
<th>Stationary</th>
<th>Motion</th>
</tr>
</thead>
<tbody>
<tr>
<td>$y_D$</td>
<td>21.79</td>
<td>67.66</td>
</tr>
<tr>
<td>$RBE_{10}$</td>
<td>1.268</td>
<td>1.977</td>
</tr>
</tbody>
</table>
Conclusions

- New SOI microdosimeter utilizing 3D detector technology was introduced for particle therapy QA.
- PT and HIT provide directional radiation that require using mean average path rather than average chord for TE conversion.
- Microdosimetric properties and RBE of passive $^{14}$N, $^{16}$O and pencil scanning beam of $^{12}$C, and effect of organ motion on RBE has been studied. RBE can be essentially different to planned.
- MicroPlus Probe with Bridge and Mushroom Microdosimeters have extremely high spatial resolution.
- Next version of Mushroom 2 microdosimeter will be with silicon etched out and filled with PMMA to increase tissue equivalence by avoiding secondaries production from silicon.
sDMG: Miniature multi-strip silicon detector designed by the Centre for Medical Radiation Physics (CMRP), University of Wollongong

- Two linear silicon diode arrays - 128 sensitive silicon strips in each.
- Pitch: 0.2mm
- Strip size: 2x0.02 mm²

sDMG housed in solid water phantom (GAMMEX, WI, USA)

- Small air volume surrounds the silicon to prevent damage of Si detector
Experimental Methodology – C-12

- The detection axis is aligned **parallel** to the direction of the C-12 beam.

- **C-12** ion beam, energy **290 MeV/u** and **10x10cm²** square field.
  - PBP (pristine Bragg peak)

- **Depth Dose Profiles:** PBP measurements conducted with increasing depth in PMMA (+/- 1mm).
Results: Energy Reconstruction for Heavy-Ions

Table III - Energy Reconstruction for C-12.

<table>
<thead>
<tr>
<th>Depth in PMMA (mm), (+/- 1 mm)</th>
<th>Measured Peak Location in Silicon (mm), (+/-0.4mm)</th>
<th>Reconstructed Energy, $E_r$ (MeV/u), (+/-3 MeV/u)</th>
<th>Simulated Energy (MeV/u), (+/-0.1%)</th>
<th>Reconstructed Residual Energy, $E_0$ (MeV/u), (+/-3 MeV/u)</th>
<th>Percentage Difference to Monte-Carlo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td>19.4</td>
<td>118</td>
<td>121</td>
<td>279</td>
<td>1.62</td>
</tr>
<tr>
<td>89</td>
<td>27.2</td>
<td>143</td>
<td>147</td>
<td>277</td>
<td>1.25</td>
</tr>
<tr>
<td>64</td>
<td>42.1</td>
<td>186</td>
<td>190</td>
<td>277</td>
<td>0.93</td>
</tr>
<tr>
<td>54</td>
<td>48.7</td>
<td>203</td>
<td>206</td>
<td>278</td>
<td>1.30</td>
</tr>
</tbody>
</table>

- $E_0$ determined by Monte-Carlo simulation to be **275 MeV/u +/- 0.01%**
- $E_0$ determined by detector reconstruction to be **(278 +/- 1) MeV/u**
### Proton Pencil Beam Range/Energy QA (MGH)

#### Table: Measured and Predicted Energies

<table>
<thead>
<tr>
<th>Depth (cm)</th>
<th>Absolute Depth in Phantom Material (mm)</th>
<th>Measured Bragg Peak Position in Silicon (mm)</th>
<th>Predicted Energy at Polystyrene Phantom face (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>50</td>
<td>29.4</td>
<td>128.7</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>24.4</td>
<td>129.2</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>18.8</td>
<td>129.1</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>13</td>
<td>128.9</td>
</tr>
<tr>
<td>9</td>
<td>90</td>
<td>7</td>
<td>128.6</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>4</td>
<td>131.8</td>
</tr>
</tbody>
</table>

Mean measured PBS energy = 129.4 MeV

TPS predicted 129.46 MeV

---

**Dual PBS peak: redundancy in range/energy fast verification with resolution 0.2mm**

GEANT 4 DMG response modelling

Proton beam energy: 70MeV, Beam diameter: 10mm

Pencil beam: Set Range = 12.64 g/cm²
Size of spot ($\sigma = 15$ mm @ 6.6cm water equivalent depth)
• Magic Plate 512 (MP512): Silicon detector consisting of 512 sensitive pixels: 2mm pitch
• Proton beam profiles acquired for beam diameters 13 mm, 25 mm, 36 mm
• Profiles acquired at changing depth in solid water (13 mm, 24 mm, 25 mm)
MP512: 2D Proton Beam Profile

13 mm beam diameter, 24mm solid water
In front of M512 (BP at 23 mm depth)

25 mm beam diameter, 24mm solid water
In front of M512 (BP at 23 mm)

Transmission cheap detector for 2D QA of proton beams
Profiles compared between DUO and MatrixX at each depth investigated.

A sample of the measurements taken is shown.
Conclusion

QA in particle therapy require sophisticated radiation dosimetry on micro and mini-scale for physical dose profile verification and RBE prediction with submillimetre spatial resolution.

Silicon microelectronics allows miracle in fabrication of suite of silicon radiation detectors for real time dosimetry: 3D micron size detector array measuring ionizing energy deposition on a cellular level- microdosimetry. RBE prediction of wide range of ions based on MKM in passive and high dose rate pencil scanning beam.

Accurate range/energy verification of protons and ions in materials of interest (Monte Carlo verification).

Pencil particle beam characterization.

Future development: Microdosimeters and Dosimeters for MiniBeam Particle Therapy for prediction of RBE and dose separately in Peak and Valley to reveal actual therapeutic ration of this modality.

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Hadron Therapy Collaboration

BNCT: Kyoto Reactor
HIT: Gunma Uni

HIT: NIRS

PT: MGH
PT: Mayo Clinic
FNT and PT: IThemba

Thanks to PhD students:

David Bolst
Lachlan Chartier
Emily Debrot
Aaron Merchant
CMRP International Collaborations
MMND & ITRO 2018
Mini-Micro-Nano Dosimetry and Innovative Technologies in Radiation Oncology

6TH-11TH FEBRUARY, 2018
MOOLOOLABA, QUEENSLAND

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- Medical sciences, including image reconstruction, image/data analysis, radiation therapy, and dosimetry.

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Abstract Submission Deadline: 9th May 2018

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- MIC Co-Chairs: Steve Meikle and Taiga Yamaya
- RTSD Co-Chairs: Ralph James and Michael Fiedler

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