U O W

Recent development of solid state mini-and micro-dosimetry radiation detectors and its applications in particle therapy and space

Anatoly Rozenfeld

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UNSW, 1st November ,2022

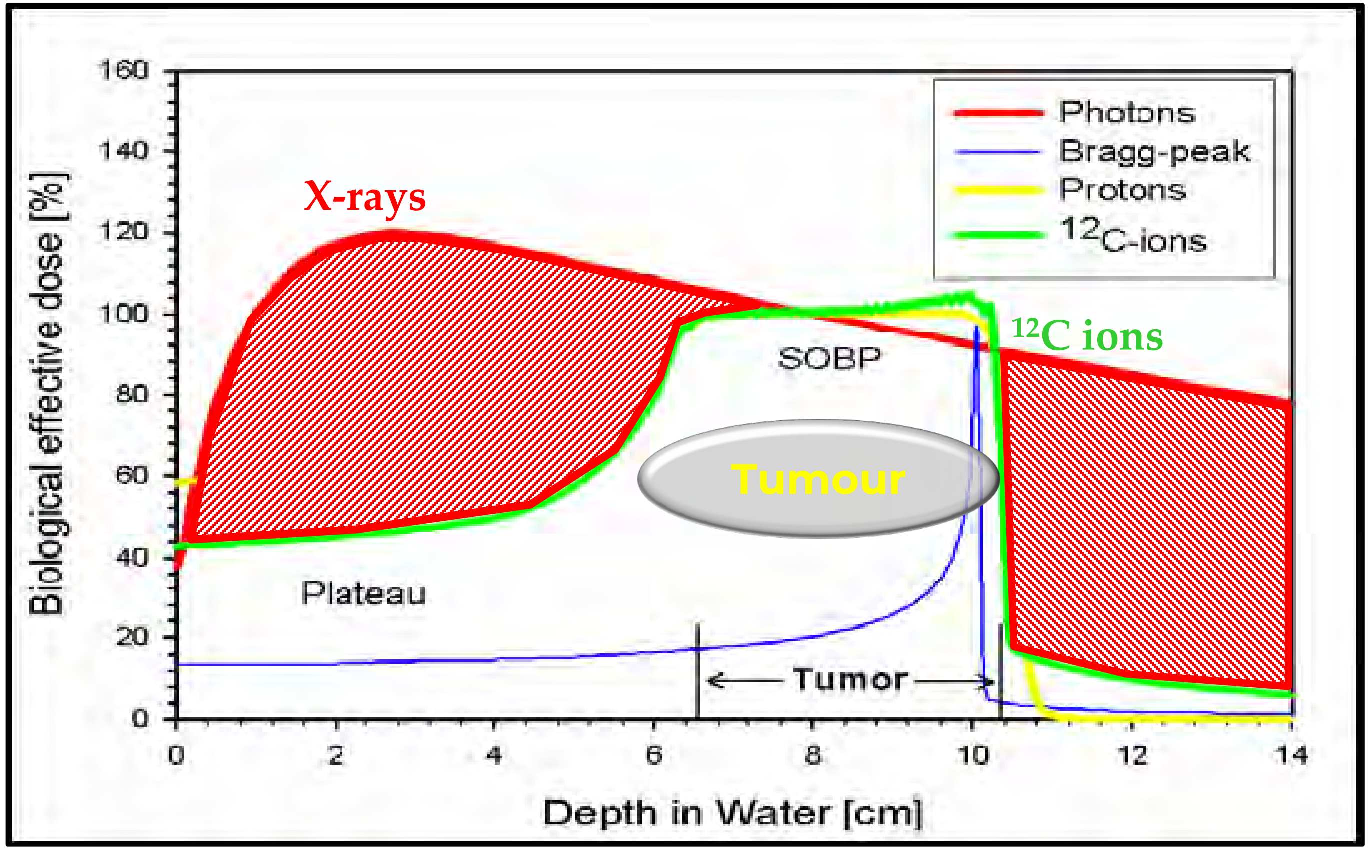
Proton and Heavy Ion Therapy

Protons & carbo[n]
Bethe Formula

$$-\frac{dE}{dx} = \frac{4\pi}{m_e c^2} \cdot \frac{nz^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0}\right)^2 \cdot \left[\ln\left(\frac{2m_e c^2 \beta^2}{I \cdot (1-\beta^2)}\right) - \beta^2\right]$$

Dose conformat

The cancerous tumors are removed most efficiently by the ion radiation as it had been previously (1946) recognized by R. Wilson.
[Radiological use of fast protons. Radiology 47:487-91, 1946].



Different: **biological effectiveness**

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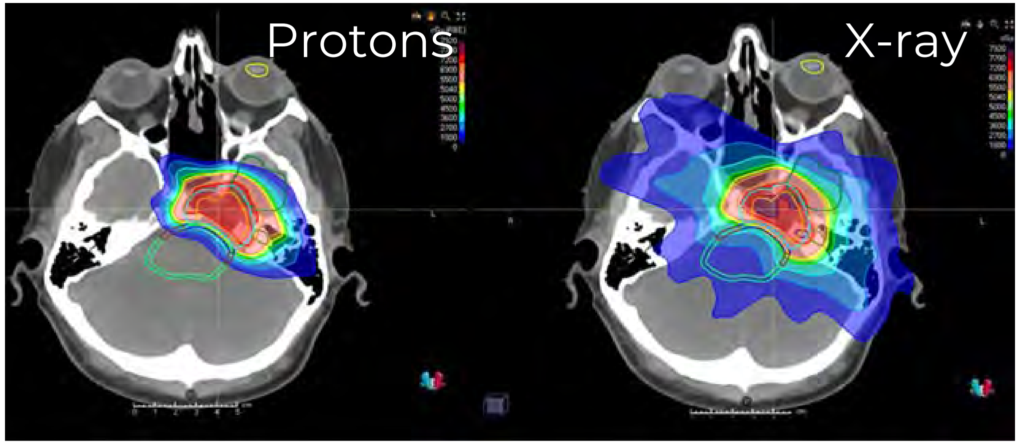
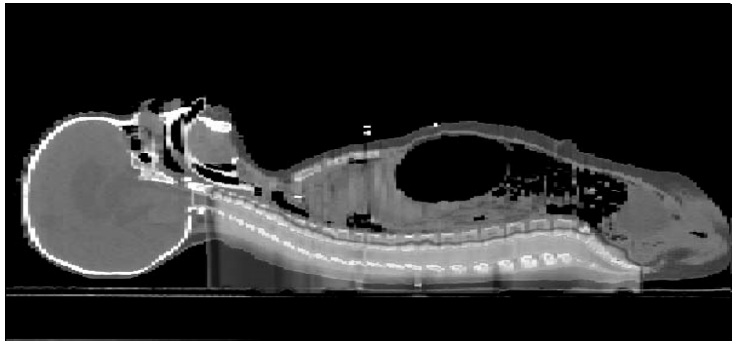
Application in proton and heavy ion therapy

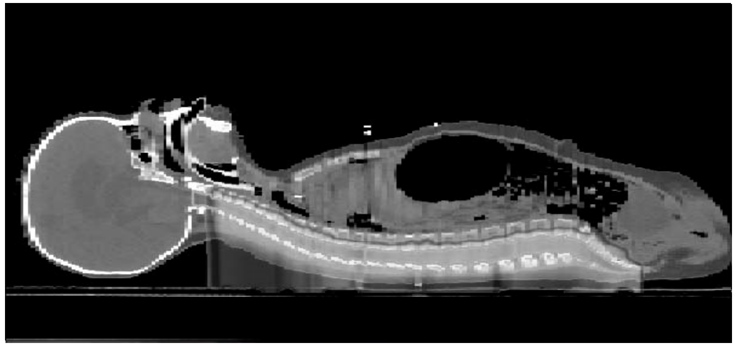


Patient brain scans show how proton therapy (left) specifically targets the tumour, with minimal radiation going to surrounding tissue and structures, whereas traditional photon (X-ray) radiation (right) can damage surrounding tissues and structures

Bragg Proton therapy Centre, Adelaide
to be finished by 2024



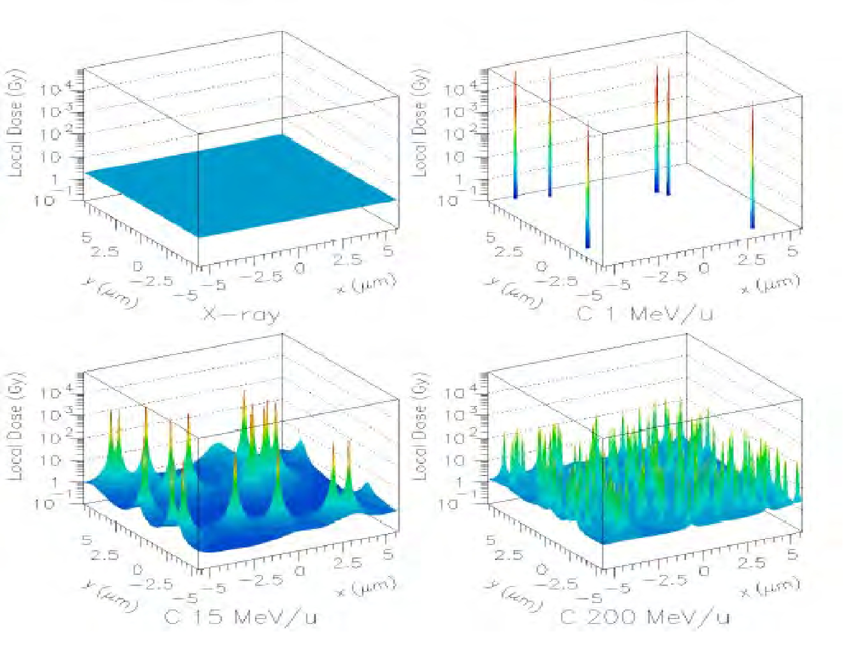
Photons

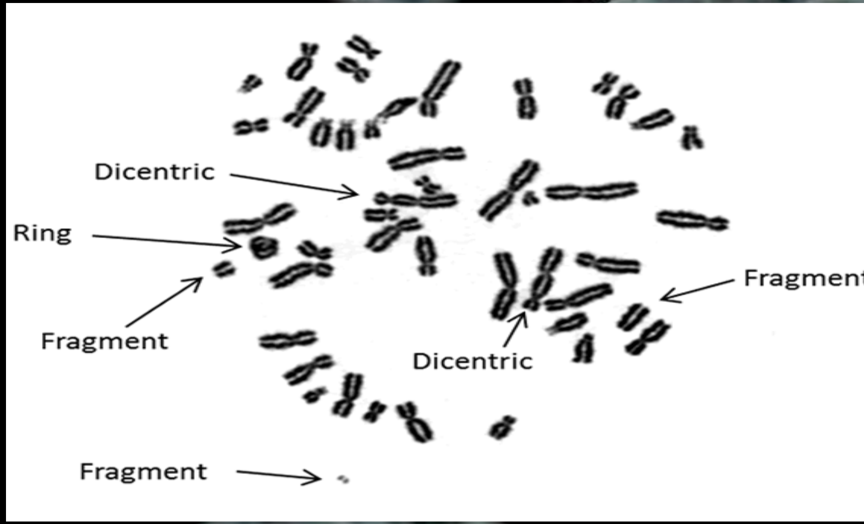


Protons

Mechanistic understanding

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





Courtesy Matsufuji (QST) and Scholz (GSI)

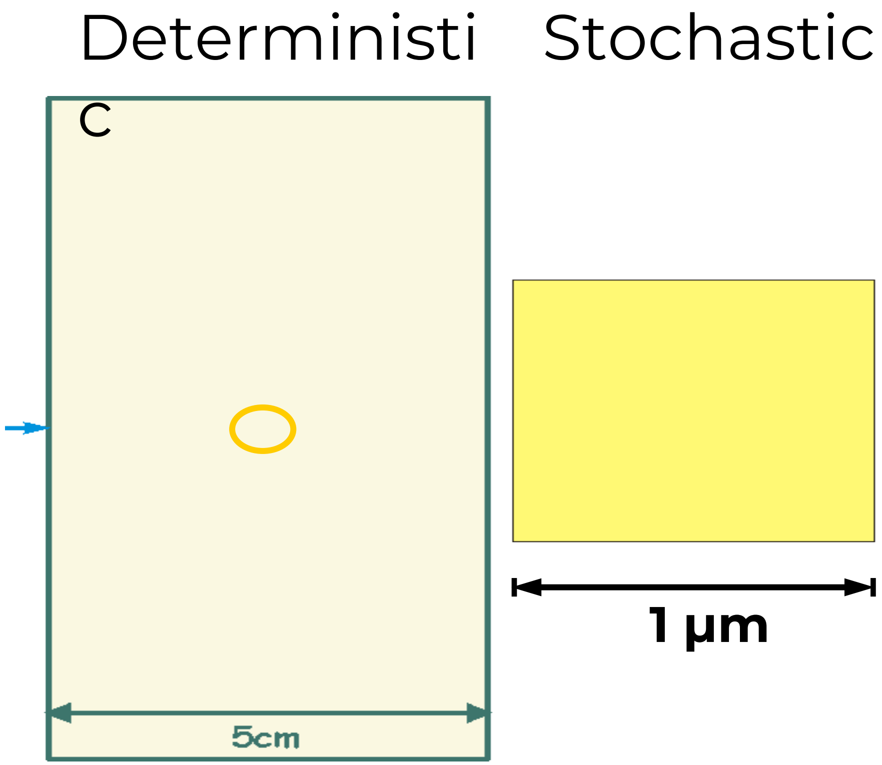
Definition

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

Microdosimetry vs. (traditional) dosimetry

	Dosimetry	**Microdosimetry**
is a	deterministic quantity	stochastic quantity
measures	average energy deposition per unit mass	probability distribution of energy distribution
is expressed as	$D = \frac{\langle E \rangle}{m}$	$f(z)$
where	*<E>* is the average energy deposited in the mass m	*f(z)* is the probability distribution of deposition of the specific energy z

Microdosimetry :Specific Energy

- *Energy imparted ε:* is the energy imparted within a site

$$\varepsilon = \sum_i \varepsilon_i$$

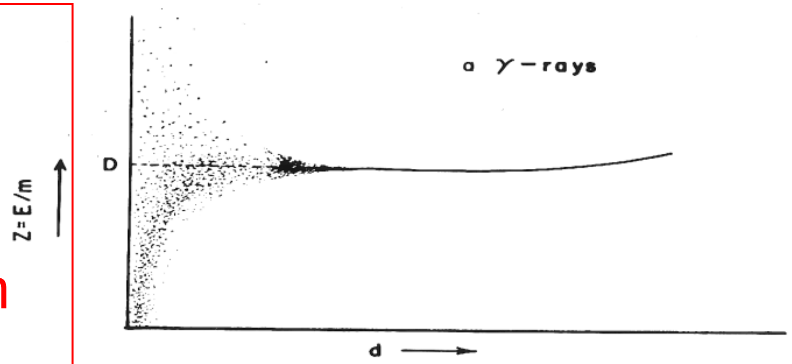
Predictions on the energy imparted can be made based on a probability distributions of energy transfers.

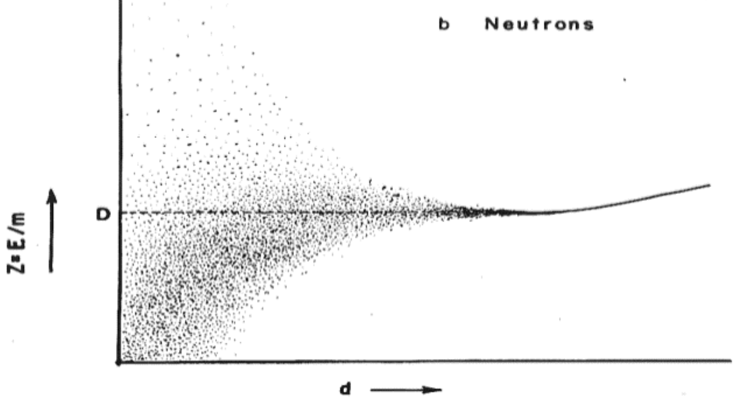
- *Specific energy z:* is defined as the ratio of the imparted energy ε and the site's mass m: $z = \frac{\varepsilon}{m}$
- *Lineal energy y:* is defined as a ratio of the imparted energy and mean chord length

$$y = \frac{\varepsilon}{l} \qquad \overline{y_F} = \int y f(y) dy \qquad \overline{y_D} = \frac{1}{\overline{y_F}} \int y^2 f(y) dy$$

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

Reducing of the target size is changing deterministic deposition of energy to stochastic.





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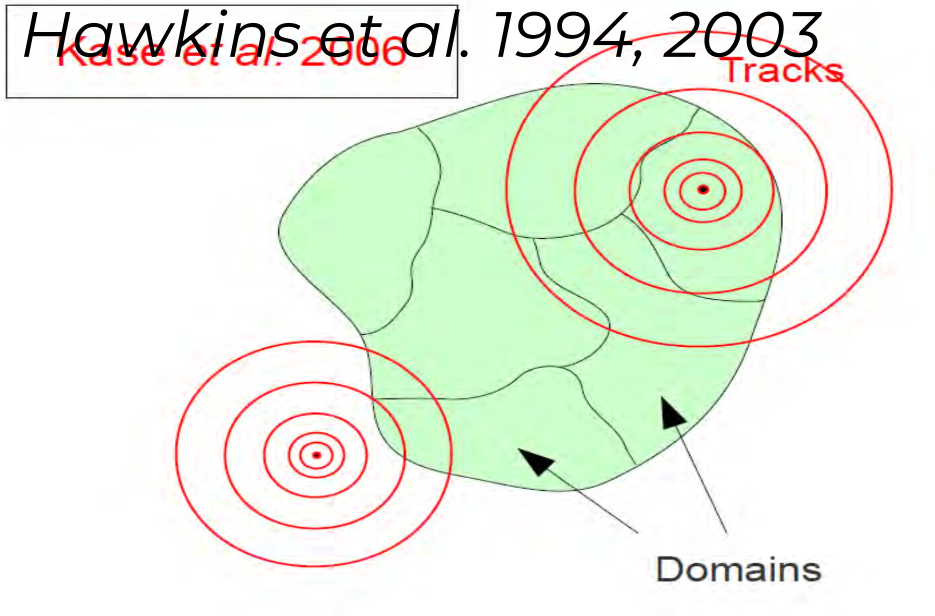
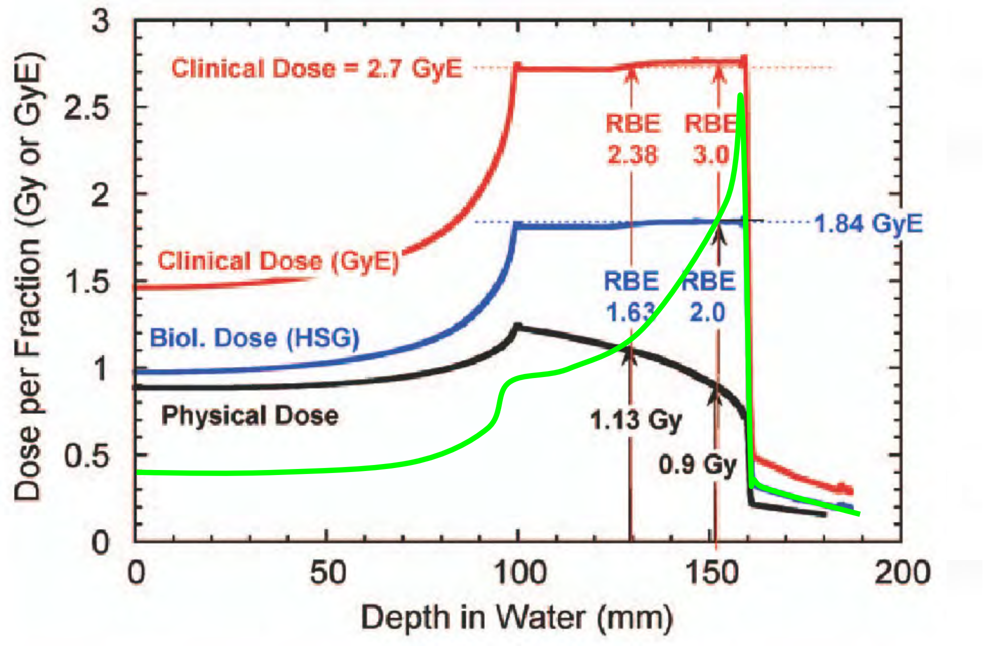
Each type of radiation has their own signature of a single event spectra

Microdosimetric Kinetic Model (MKM)

Hawkins et al. 1994, 2003





Radiobiological Effectiveness (RBE):

$$RBE_{10} = Dose\ that\ gives\ 10\%\ cell\ survival\Big|_{Radiation}^{X-rays} = \frac{D_{10,x}}{D_{10,ions}}$$

Biological dose = RBE × D

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Microdosimetric Kinetic Model (MKM)

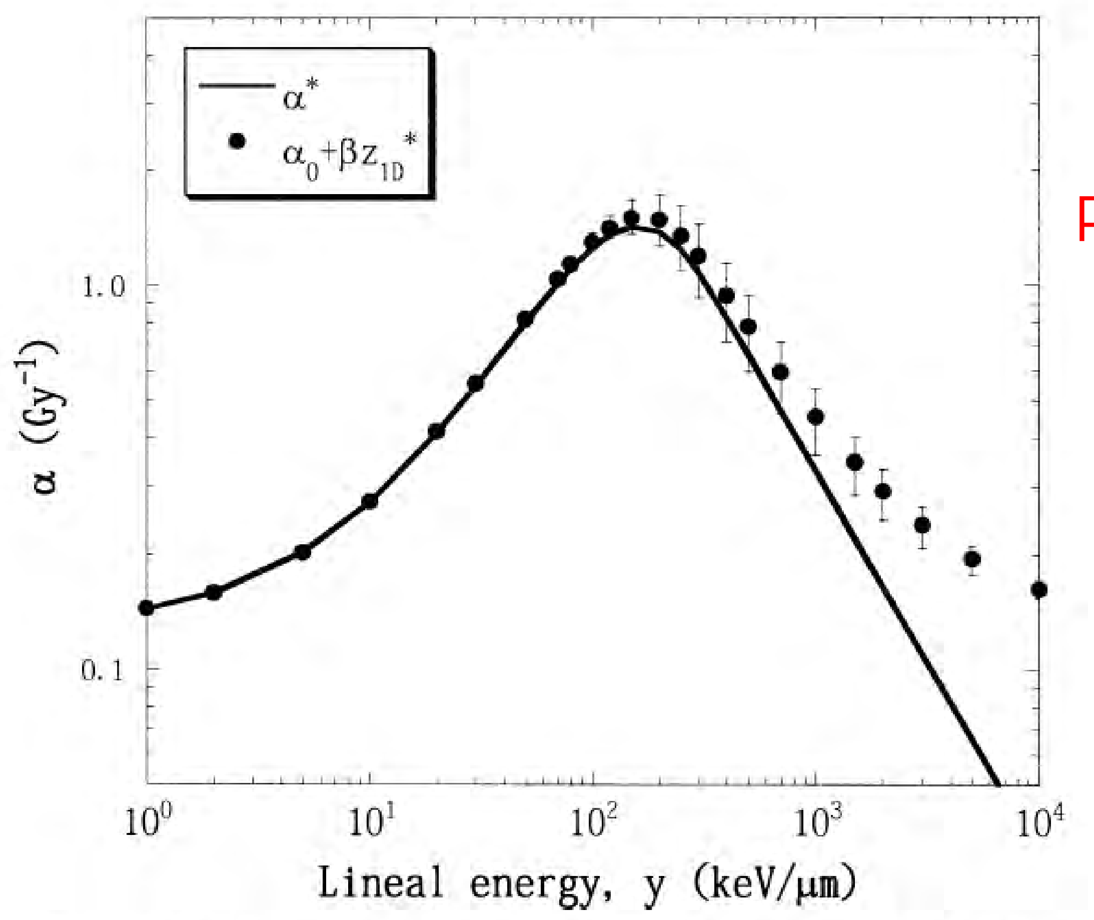

FIG. 4. The α^* value obtained with Eq. (5) and the value of $\alpha_0 + \beta z^*_{1D}$ in Eq. (7) as a function of lineal energy for a single event, with the biological parameters applicable for HSG cells. The error bars show a variation of 20 keV/μm for the saturation parameter, $y_0 = 150$ keV/μm.

Linear Quadratic Model

$S(D) = \exp[-\alpha D - \beta D^2]$

Physics/Biology

$$\alpha = \alpha_o + \frac{\beta}{\rho \pi r_d^2} y^*$$

$$y^* = \frac{y_o^2 \int_0^\infty \left(1 - exp(-y^2/y_o^2)\right) f(y) dy}{\int_0^\infty y f(y)\, dy}$$

$$RBE_{10} = \frac{2\beta D_{10,R}}{\sqrt{\alpha^2 - 4\beta ln(0.1)} - \alpha}$$

- α_o= 0.13 Gy^{-1}; β= 0.05 Gy^{-2} ; r_d = 0.42 μm is radius of sub cellular domain in MK model, y_o = 150 keV/μm
- Where $D_{10,R}$ = 5Gy is 10% survival of 200 kVp X rays for HSG cells

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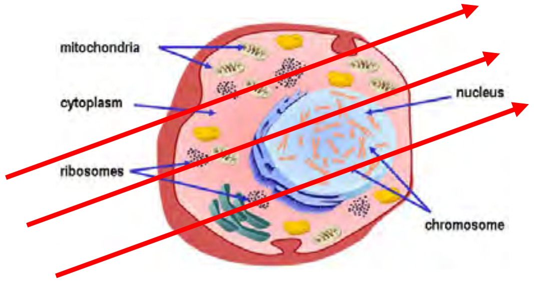
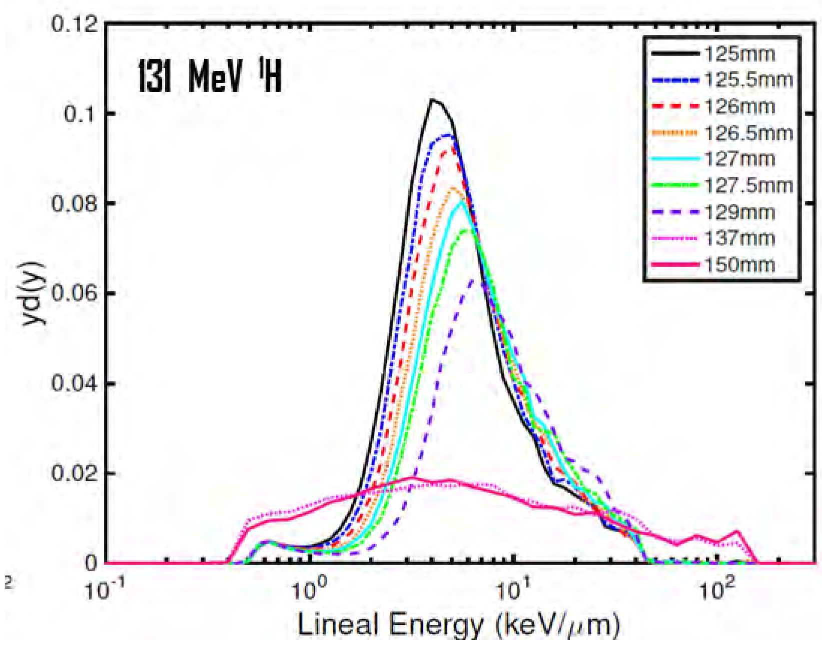
Microdosimetry devices for cell response (RBE) prediction in particle therapy



- Study of the distribution of deposited energy in well-defined microscopic volumes



Microdosimetric spectra measured with the SOI microdosimeter in proton beam

Tissue Equivalent Proportional Counter

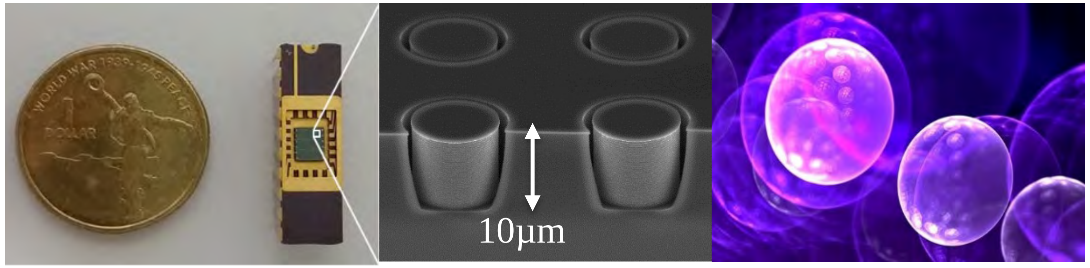
Intra-Vehicle TEPC, NASA

Weight: 8 kg

Bias: 700V

Courtesy of E. Semones

Silicon on insulator (SOI) Microdosimeter



- ✓ Can measure an array of cells
- ✓ Provides true microscopic SV
- ✓ Compact size (<100g)
- ✓ Low voltage
- ✓ High spatial resolution

- Tissue equivalence need to be considered & corrected when generating microdosimetric spectra

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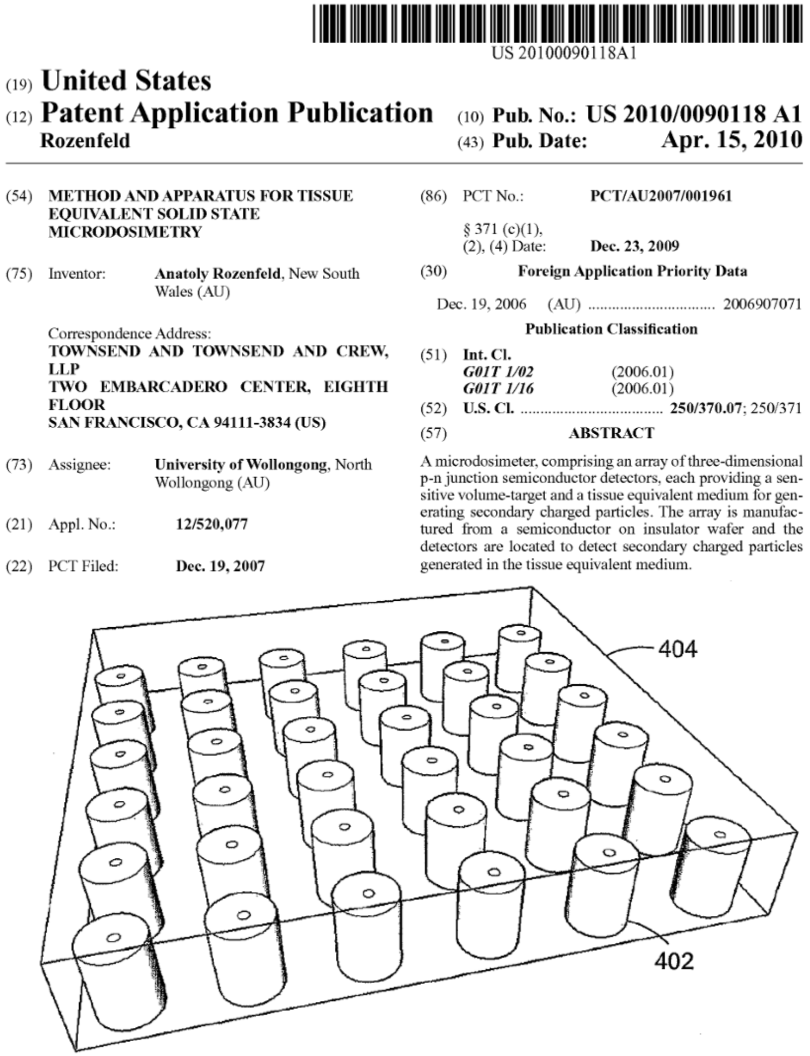
"Mushroom" microdosimeter: Patent to reality


US 20100090118A1

(19) **United States**
(12) **Patent Application Publication** (10) **Pub. No.: US 2010/0090118 A1**
Rozenfeld (43) **Pub. Date: Apr. 15, 2010**

(54) METHOD AND APPARATUS FOR TISSUE EQUIVALENT SOLID STATE MICRODOSIMETRY

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(21) Appl. No.: **12/520,077**

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(86) PCT No.: **PCT/AU2007/001961**

§ 371 (c)(1),
(2), (4) Date: **Dec. 23, 2009**

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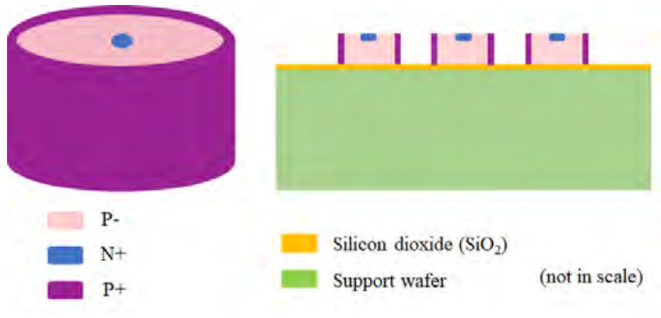
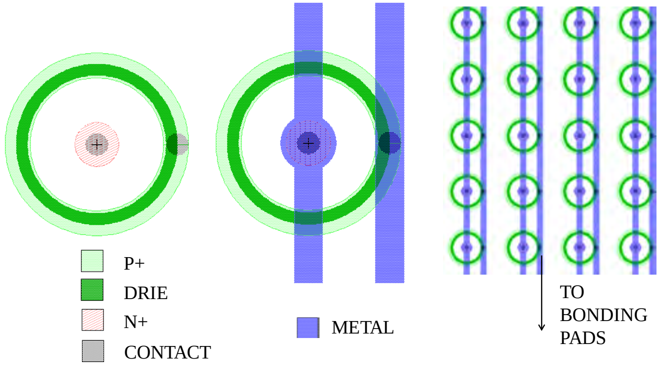
G01T 1/16 (2006.01)

(52) **U.S. Cl.** **250/370.07**; 250/371

(57) **ABSTRACT**

A microdosimeter, comprising an array of three-dimensional p-n junction semiconductor detectors, each providing a sensitive volume-target and a tissue equivalent medium for generating secondary charged particles. The array is manufactured from a semiconductor on insulator wafer and the detectors are located to detect secondary charged particles generated in the tissue equivalent medium.





SINTEF MINALAB

(Micro-and Nanotechnology Laboratory, Oslo)

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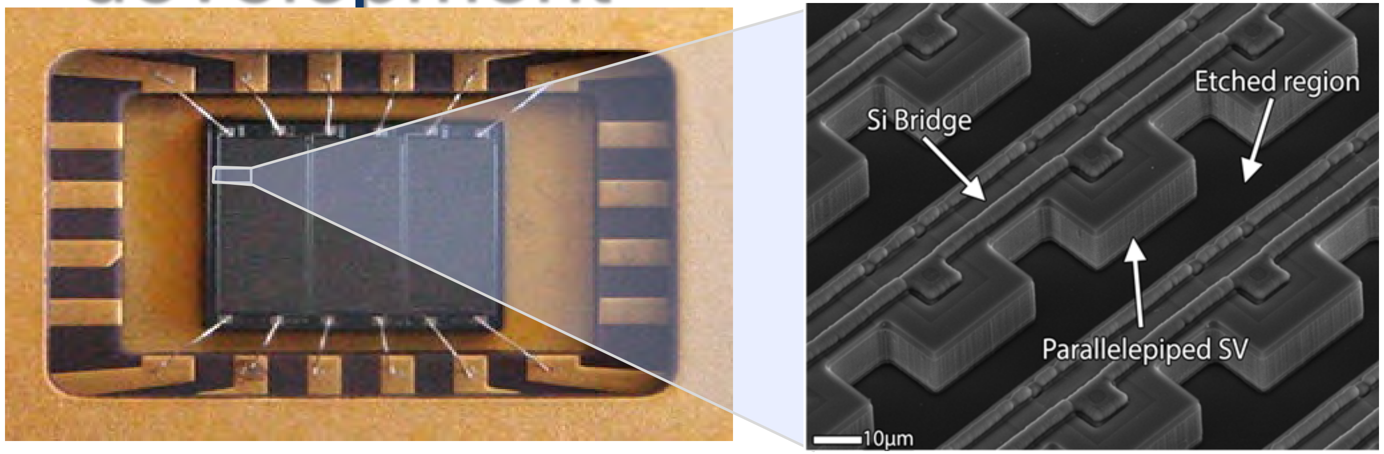
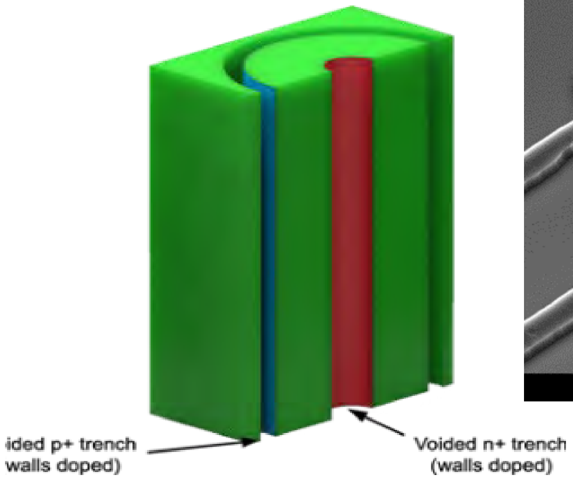
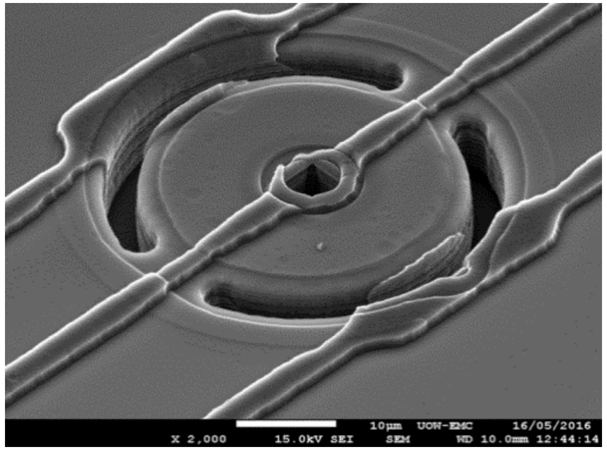
CMRP Silicon Microdosimeters:18 years of development

Bridge MD Version 2



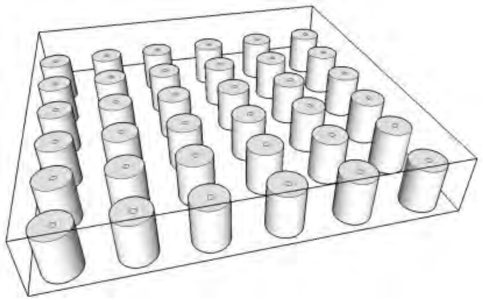




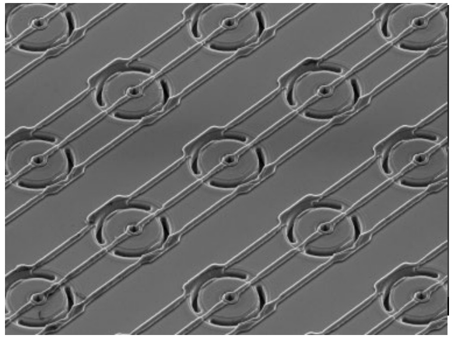
SEM image of Mushrooms

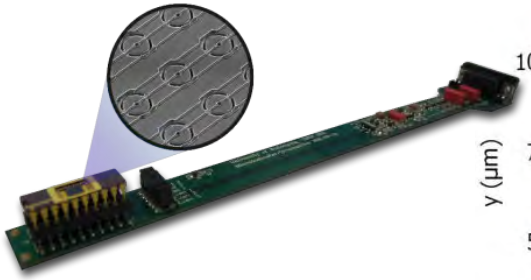
Patent **U.S.**

Patent No. 8421022
EP 2 102 685 B1

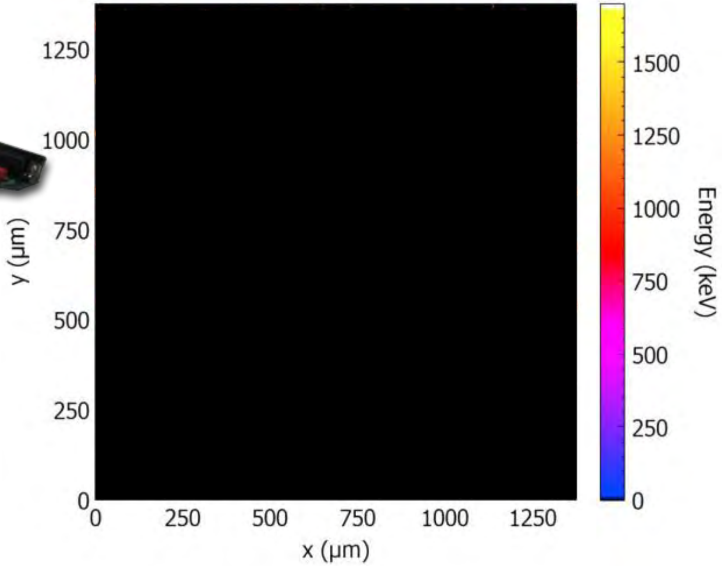


To reality





MicroPlus probe with SOI Mushroom Microdosimeter, and SEM image showing 3D sensitive volumes



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

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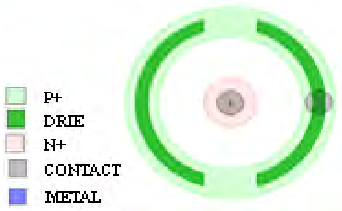
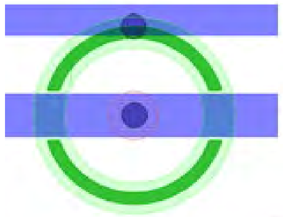
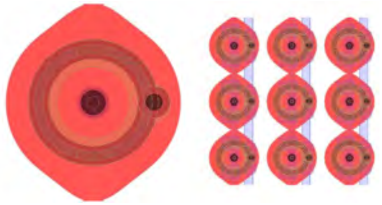
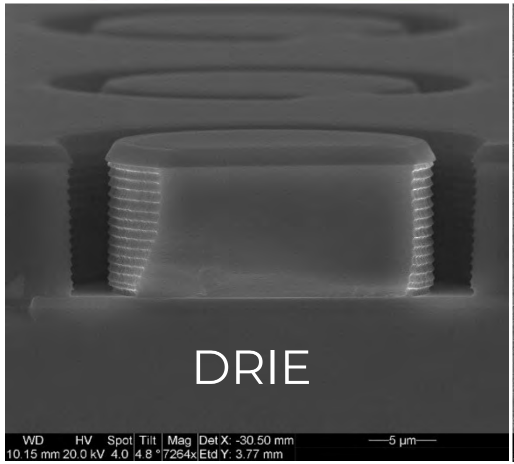
A.Rosenfeld "Novel detectors for silicon based microdosimetry, their concepts and applications", NIM A, 809, 156-170, 2016

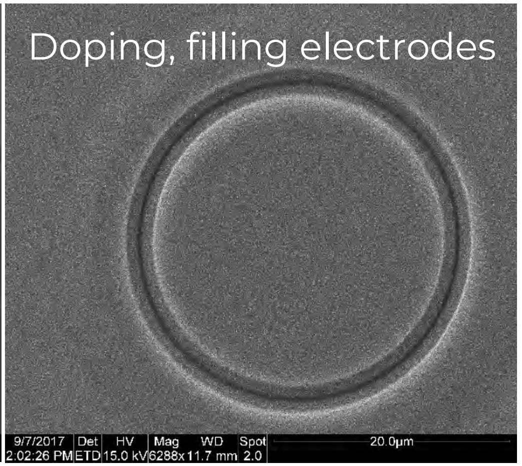
“Mushroom” microdosimeter: Fabrication process

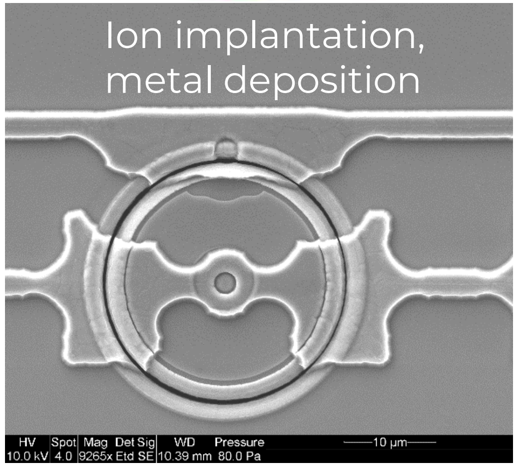


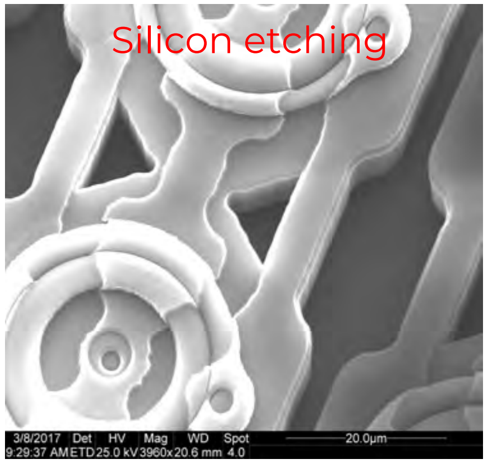








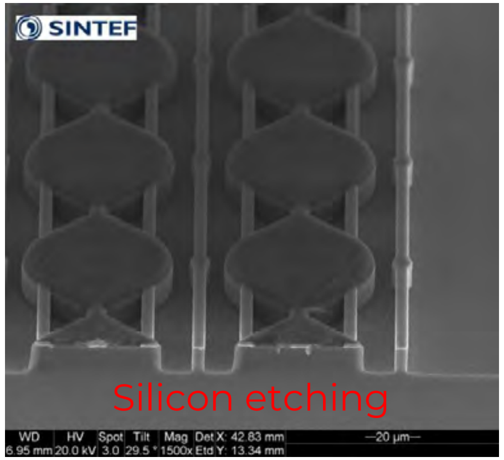


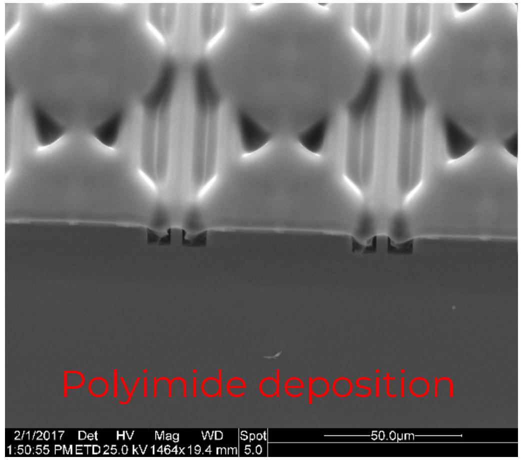


FABRICATION STEPS

Step	Description	Mask Layer/Electrode
#1	p-spray implantation	
#2	First oxidation	
#3	Photolithography	p-electrode
#4	Deep Reactive Ion Etching	p-electrode
#5	Doping	p-electrode
#6	Filling of electrodes (in some cases)	p-electrode
#7	Oxidation	p-electrode
#8	Photolithography	n-electrode
#9	Implantation	n-electrode
#10	Oxidation	n-electrode
#11	Photolithography	Contact
#12	Metal deposition	
#13	Photolithography	Metal
#14	Photolithography	Mushroom
#15	Silicon etching	Mushroom
#16	Polyimide deposition	

A summary of key fabrication steps for 3D silicon microdosimeters





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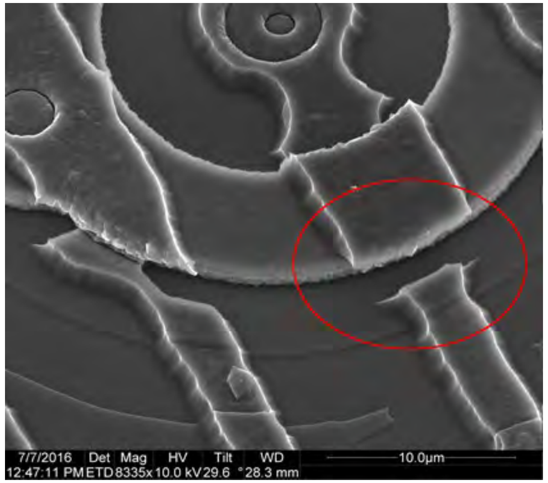
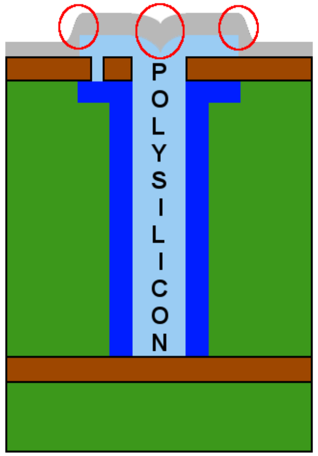
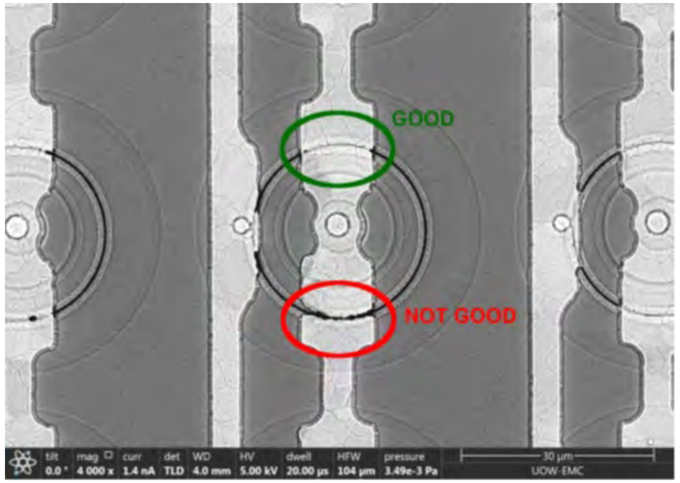
A.Kok et al.,“ Fabrication and First Characterisation of Silicon-based Full 3D Microdosimeters”, IEEE Trans. on Nucl. Sci. 63, N12 , 2490-2500, 2020

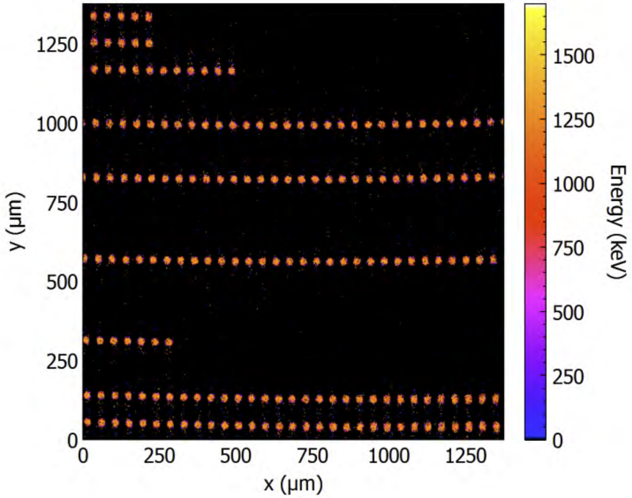
Improvement in fabrication process of Mushroom microdosimeter

Issues:

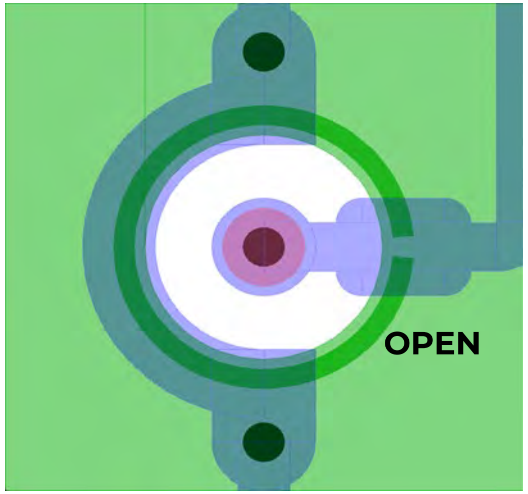


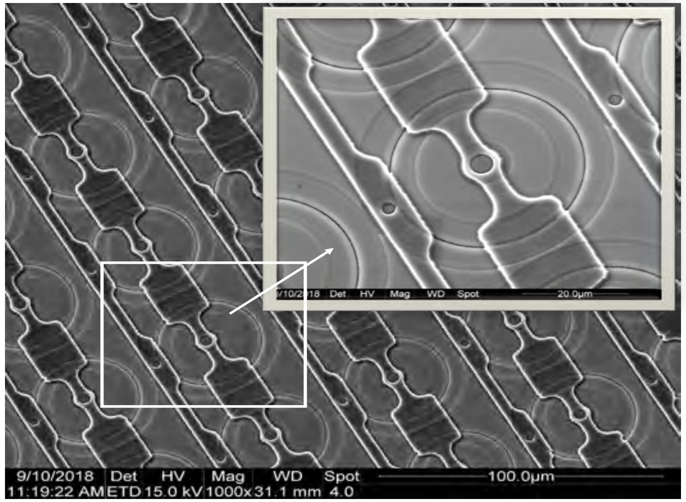


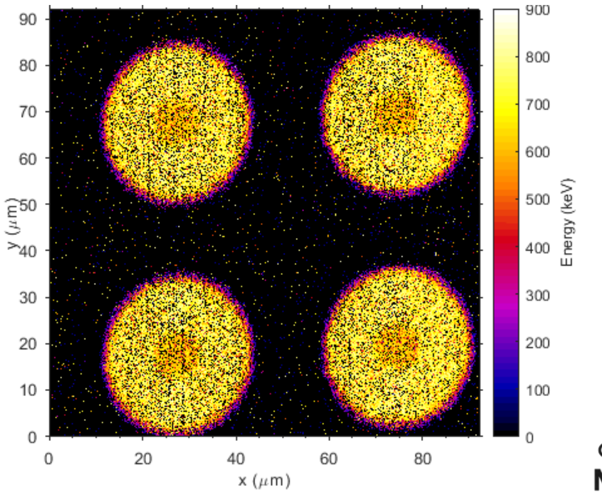


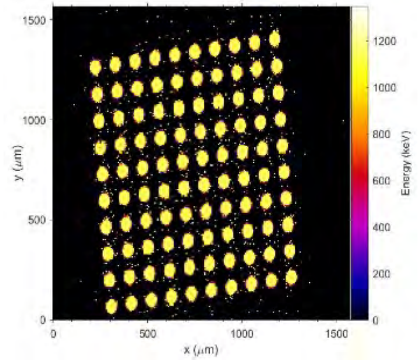


Solutions:









IBIC with 3 MeV He^{2+} ions, ANSTO

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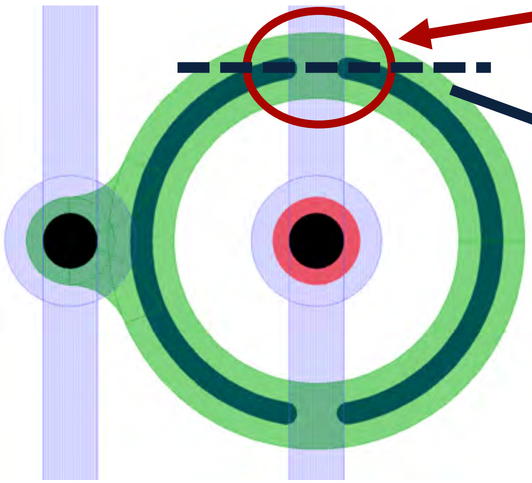
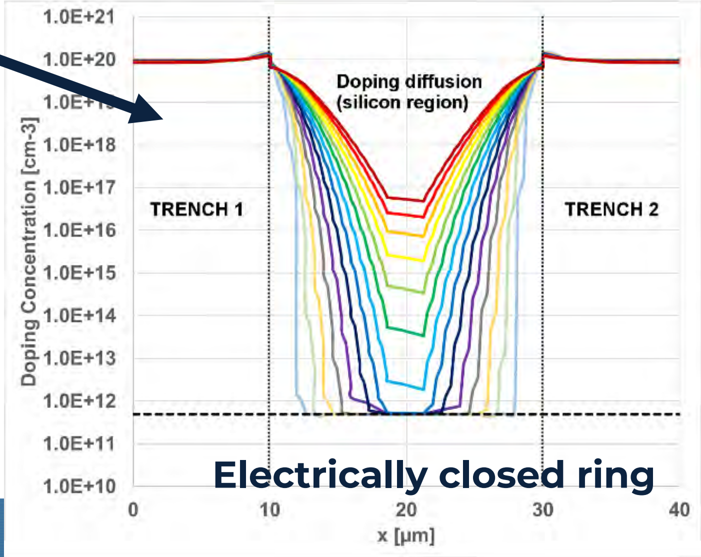
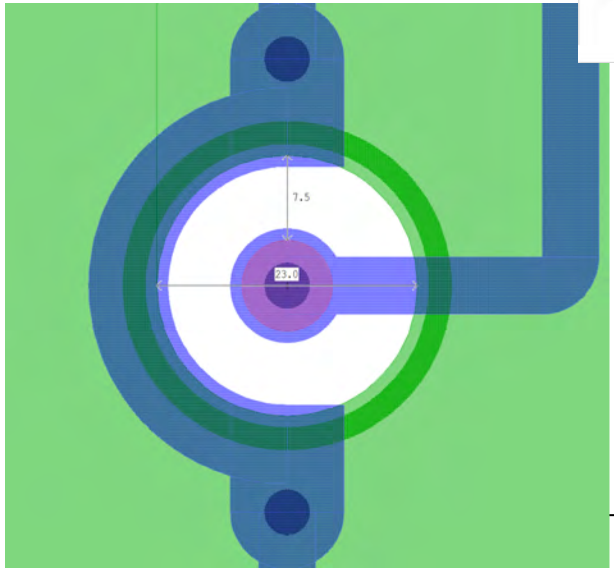
Improvement in fabrication process of Mushroom microdosimeter

Leaving a small physical gap for robust metal lines

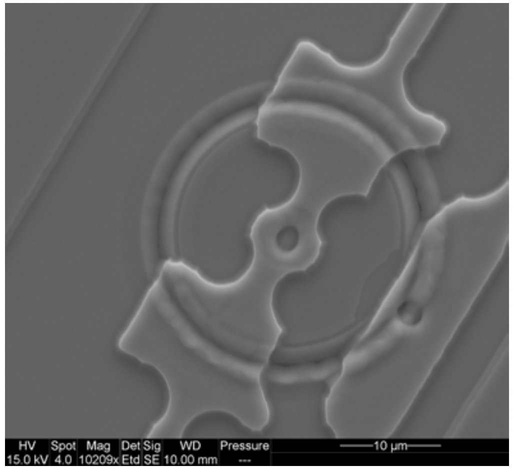


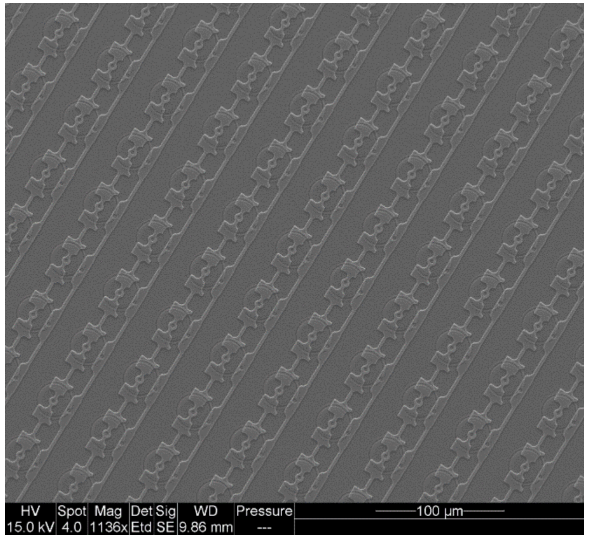


Electrically closed ring



N+ individually connected for more robust, losing only one SV at a time





Extra PECVD oxide to bridge the gap

Solving broken aluminium lines

- Process optimization by using PECVD oxide
- Design modification for more robust metal lines

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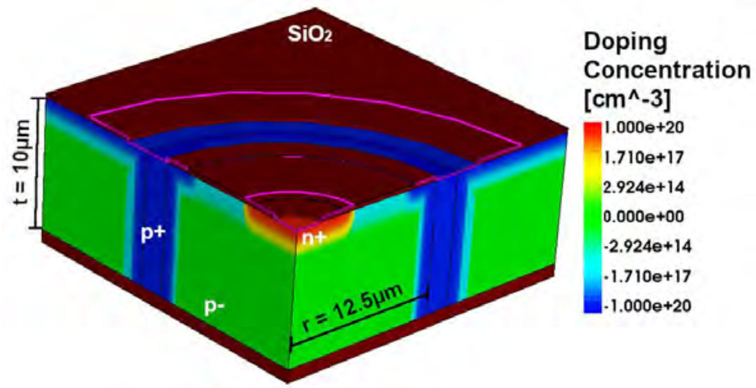
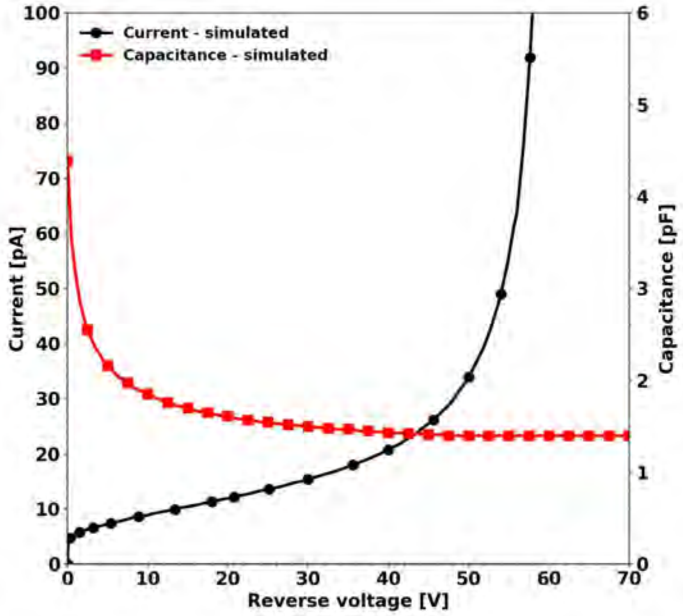
A.Kok et al.,“ Fabrication and First Characterisation of Silicon-based Full 3D Microdosimeters”, IEEE Trans. on Nucl. Sci. 63, N12 , 2490-2500, 2020

TCAD SIMULATION

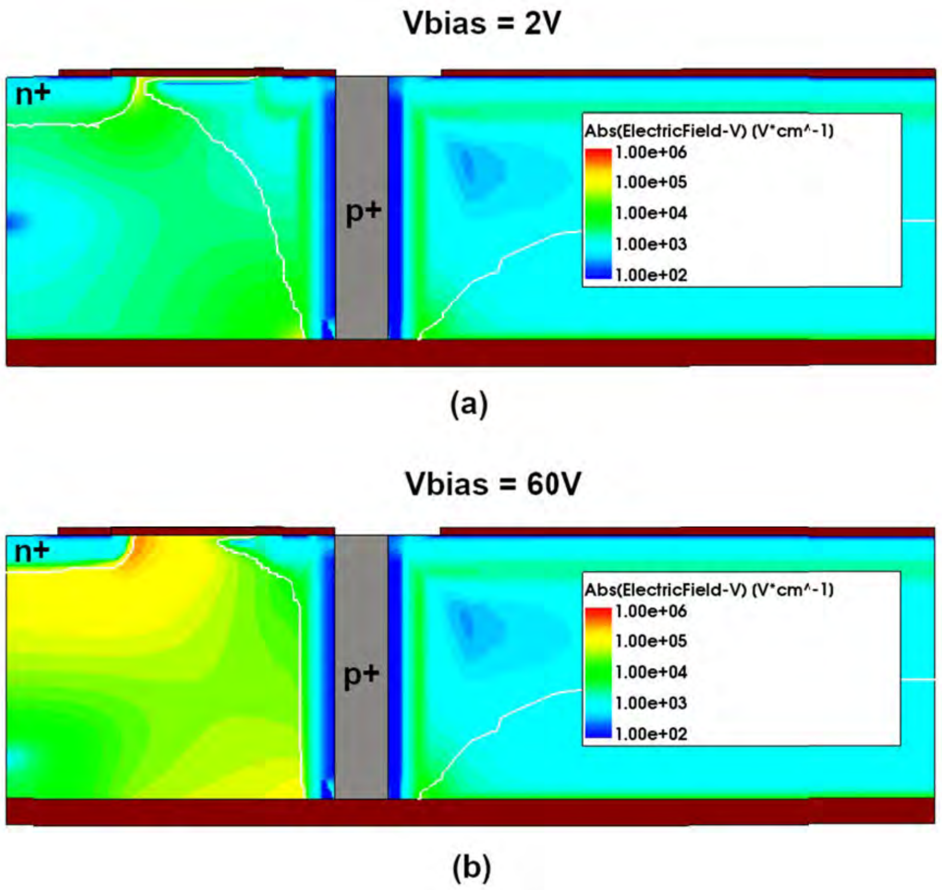
- SYNOPSYS TCAD tools



Simulated structure for a full 3-D microdosimeter (F3D). Given the symmetry of the real structures, only a quarter is simulated.

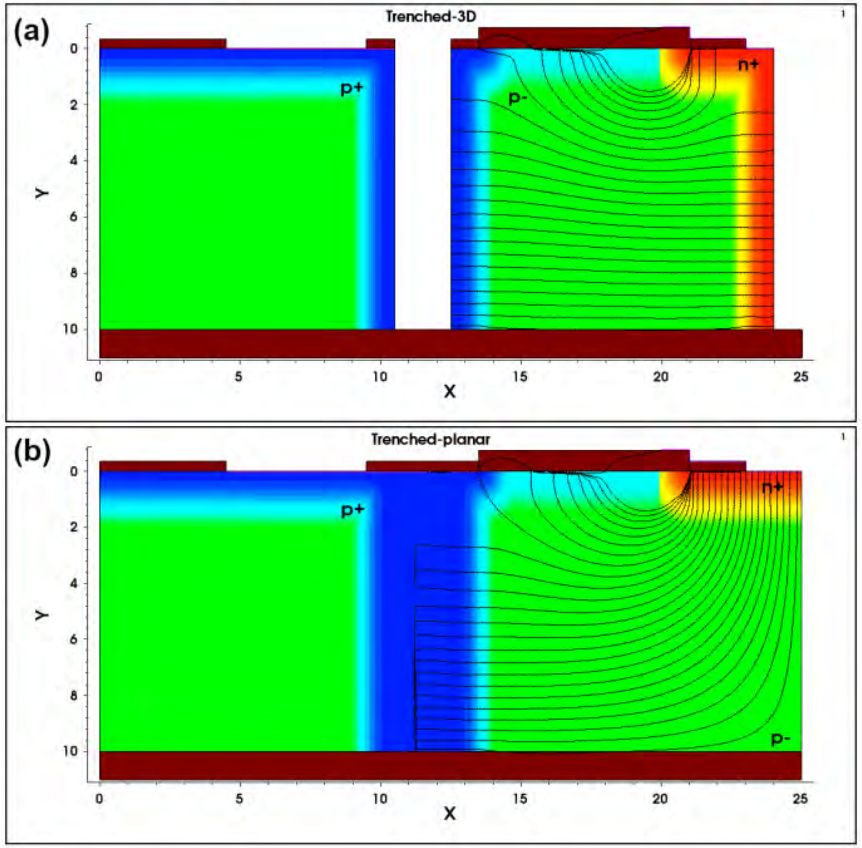


Numerical simulation results for reverse current (black dots) and reverse capacitance (red squares).

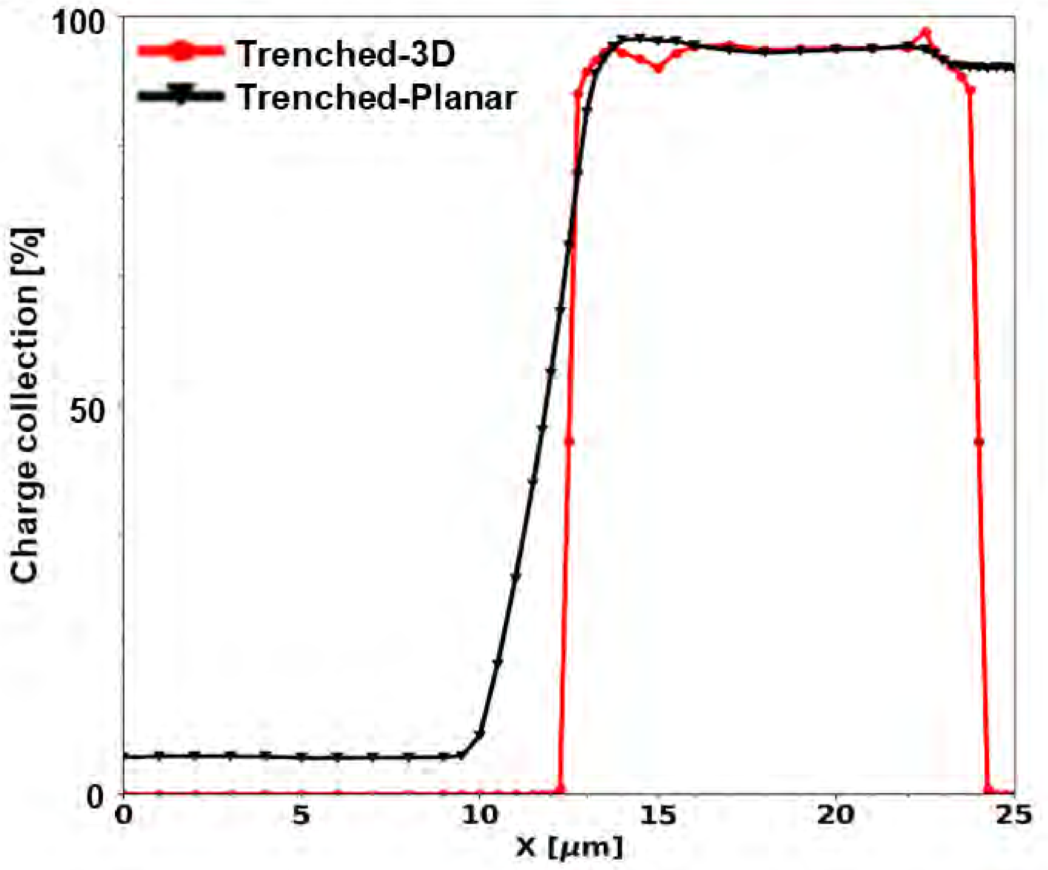


Electric field distribution inside the SV at a bias voltage (a) 2 V and (b) close to breakdown at −60 V.

TCAD SIMULATION



2D structures used for numerical simulations of (a) the Trenched-3D and (b) Trenched-planar sensors. The figures also show the drift lines based on the simulated electric field.



Comparison of the radial charge collection profiles for the Trenched-3D and Trenched-planar structures in response to a 5.5 MeV alpha particle for SOI thickness of 10 m.

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L.T.Tran et al "Silicon 3D microdosimeters for advanced quality assurance in particle therapy", Applied Sciences , **12**, 38 ,2022 (invited paper)

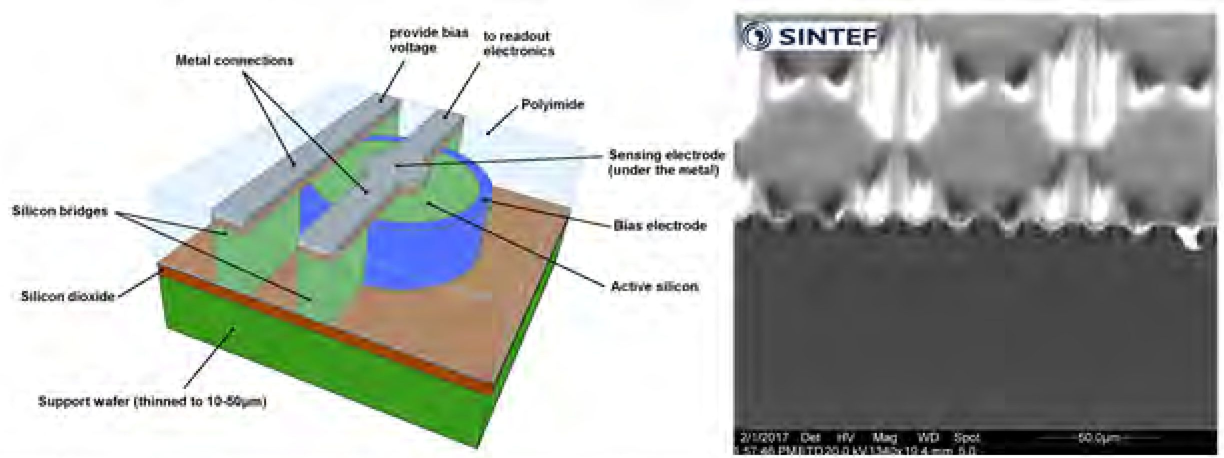

Figure 1. Sketch of a sensitive volume surrounded by a tissue-equivalent polymer (left) and a silicon 3D micro-dosimeter with integrated tissue-equivalent polymer.

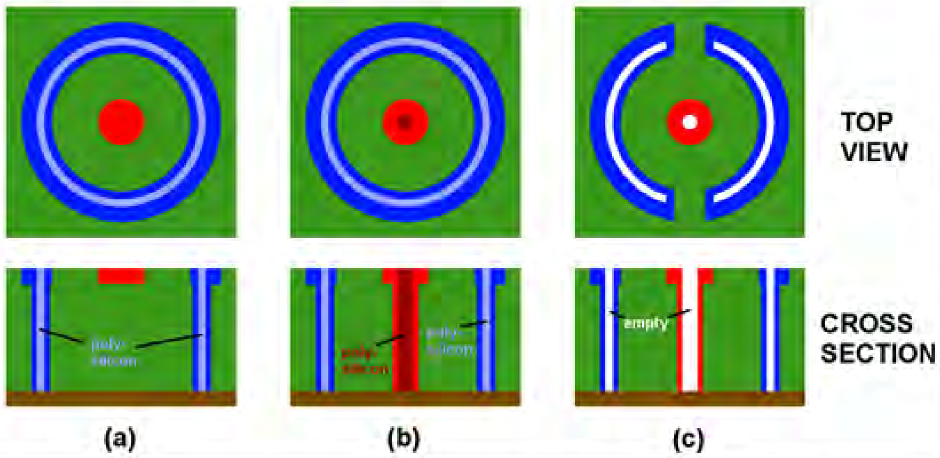

Figure 1. Top view and cross-section of the three most relevant sensitive volume implementation for a silicon 3D micro-dosimeter.

- Collaboration between CMRP and SINTEF
- Based on a CMRP patent (**US8421022B2**)
- Initial development in the Si-3DMiMic project (funded by the Norwegian Council for Research, NFR)
- Aims at delivering a reliable measurement of the Equivalent Dose and Radiobiological Effectiveness of a radiation field
- Integrated tissue-equivalent polymer to better mimic the interaction of radiation with tissue
- Design carried out with help of TCAD and GEANT4 simulations

The Research Council of Norway

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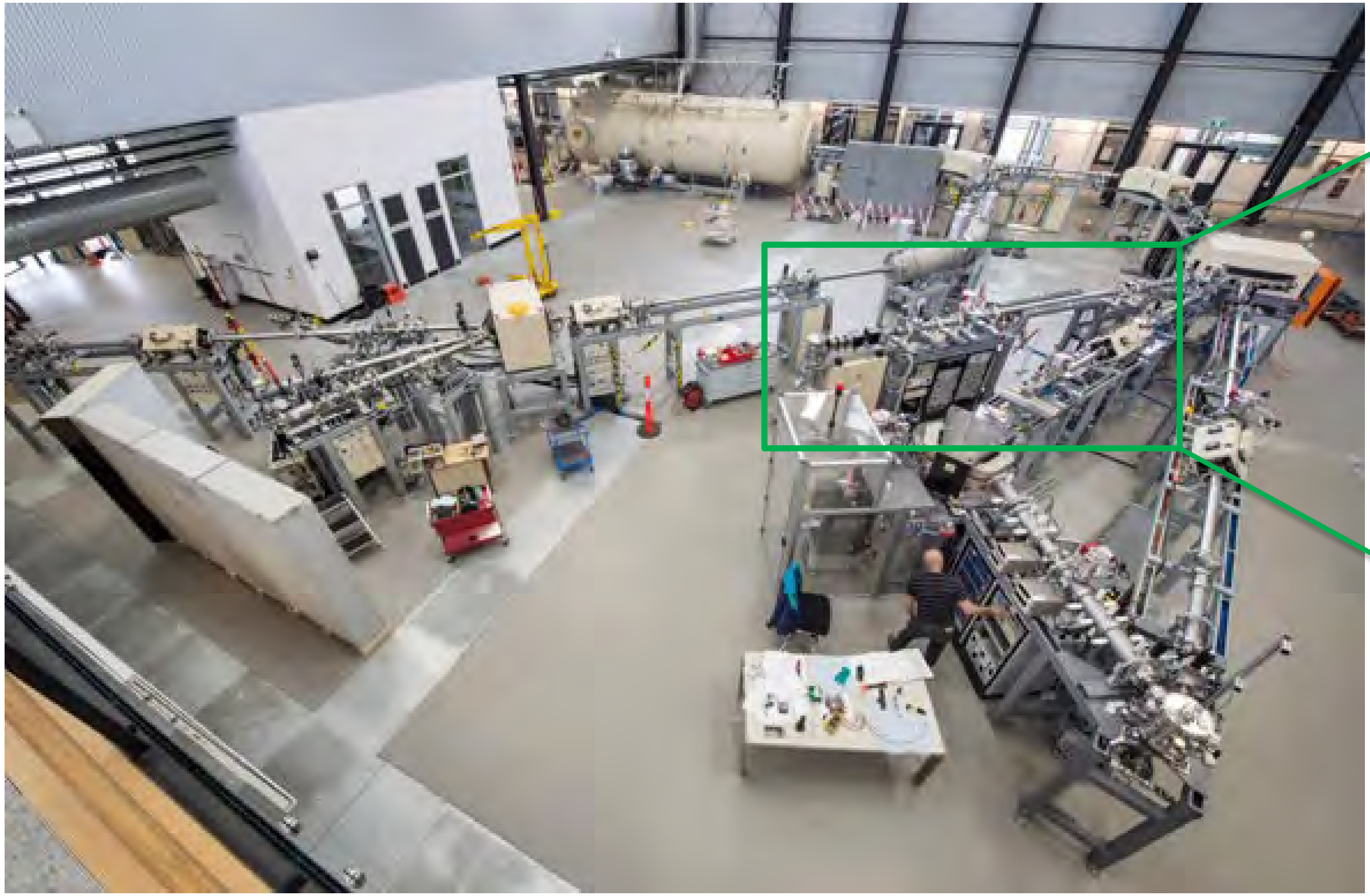
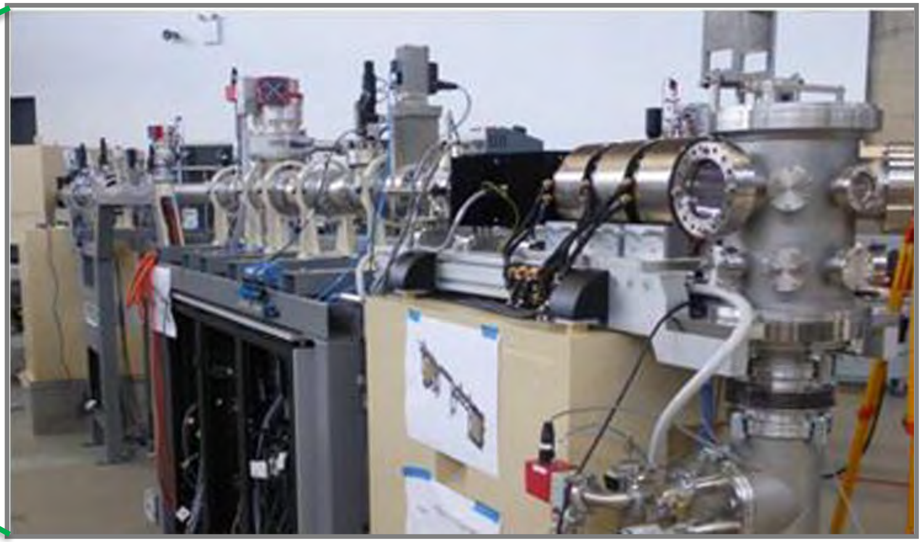
The 6MV SIRIUS Tandem Accelerator, ANSTO for Ion beam induced charge collection (IBIC) study



New nuclear microprobe–Confocal Heavy Ion Micro-Probe (CHIMP)



- **Microbeam spatial resolution:**
- 0.6 µm x 1.5 µm for 3 MeV H^{+}
- 1.5 µm x 1.5 µm for 6 MeV He^{2+}

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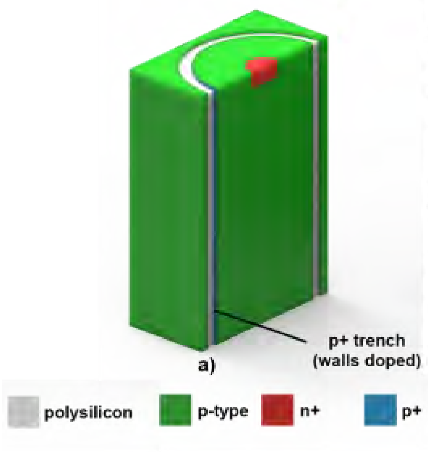
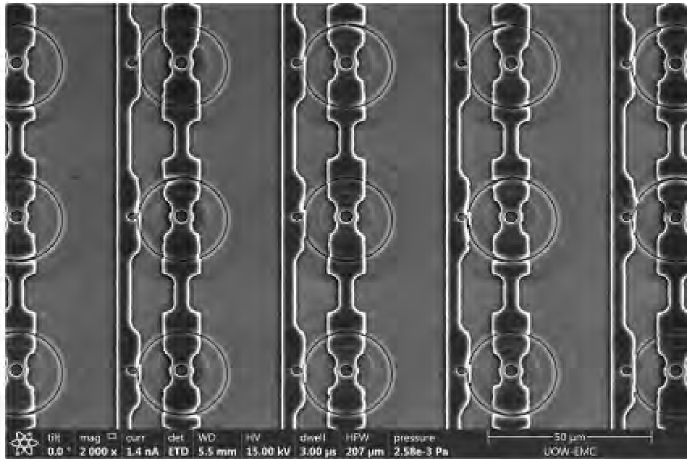
Mushroom microdosimeter (5- 10 μm thick)

IBIC 3 MeV He^{2+} ions

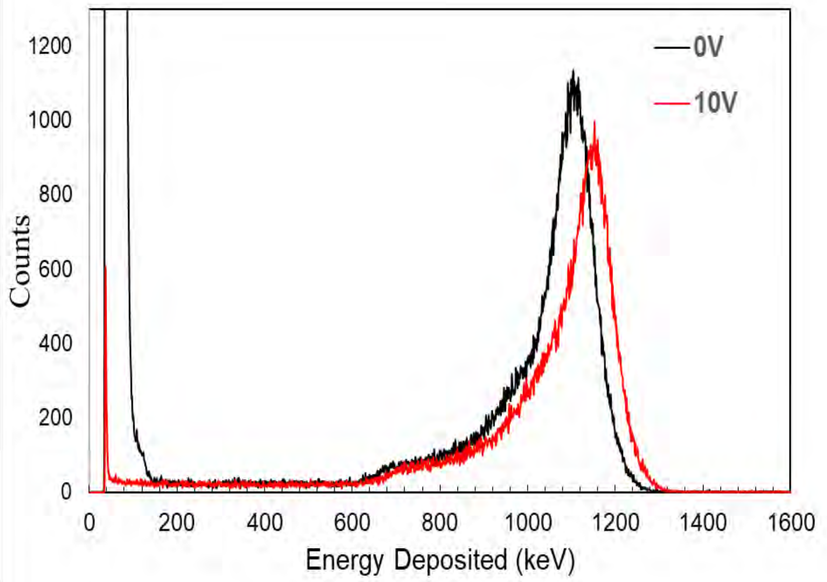
Poly-trenched

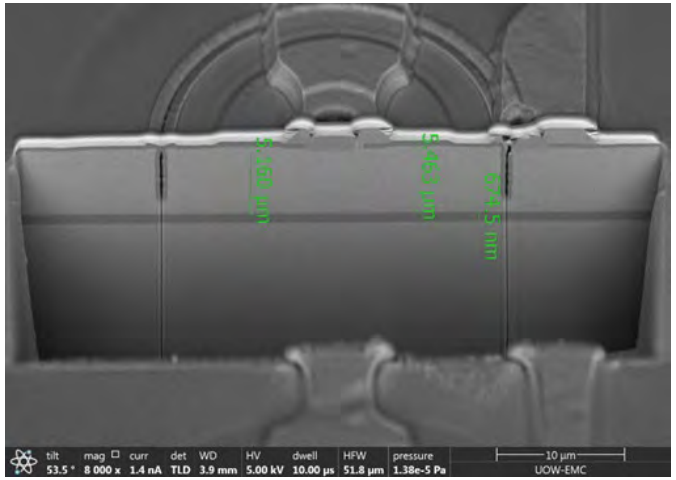


a)

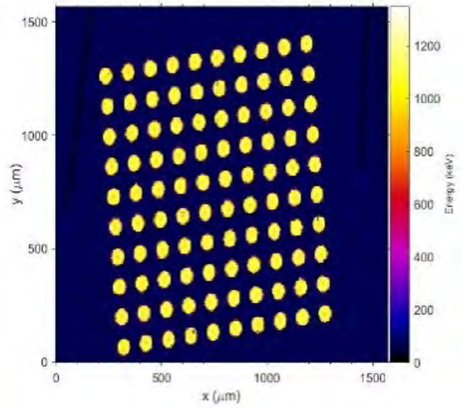


b)

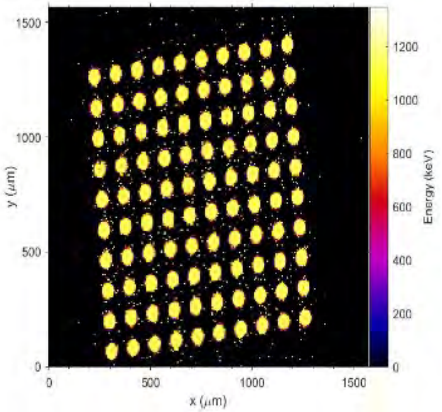




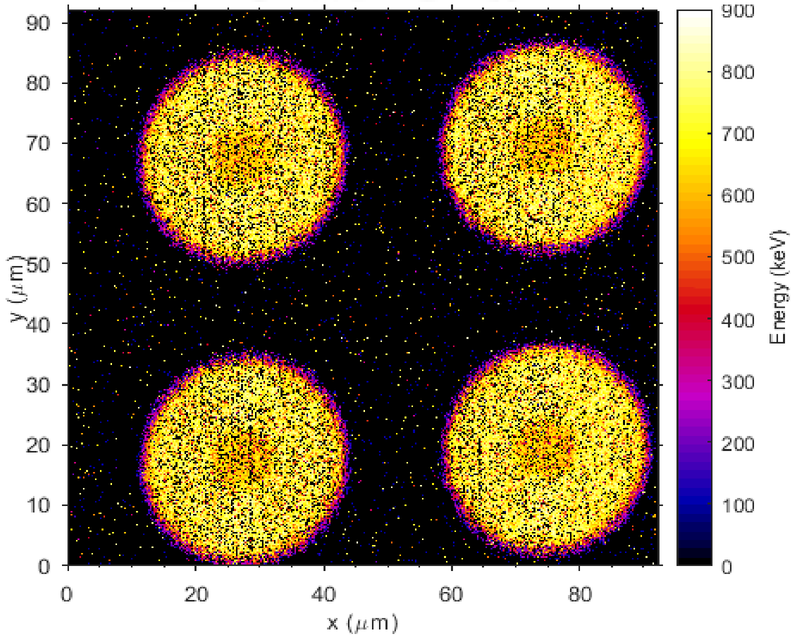
Cross-section image of the 5um thin mushroom microdosimeter.



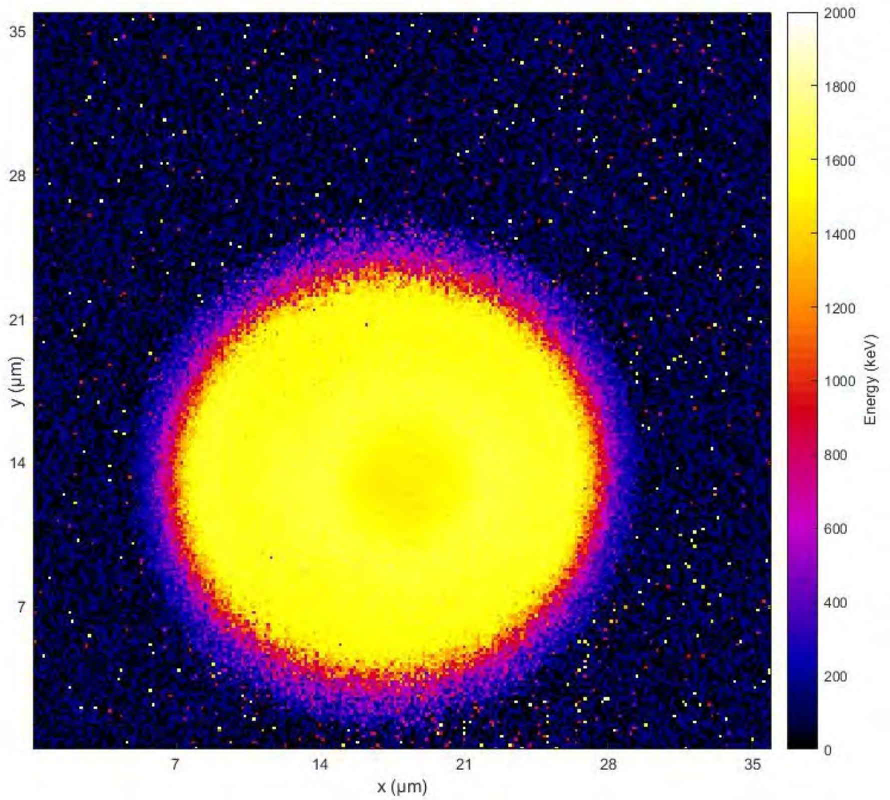
0V

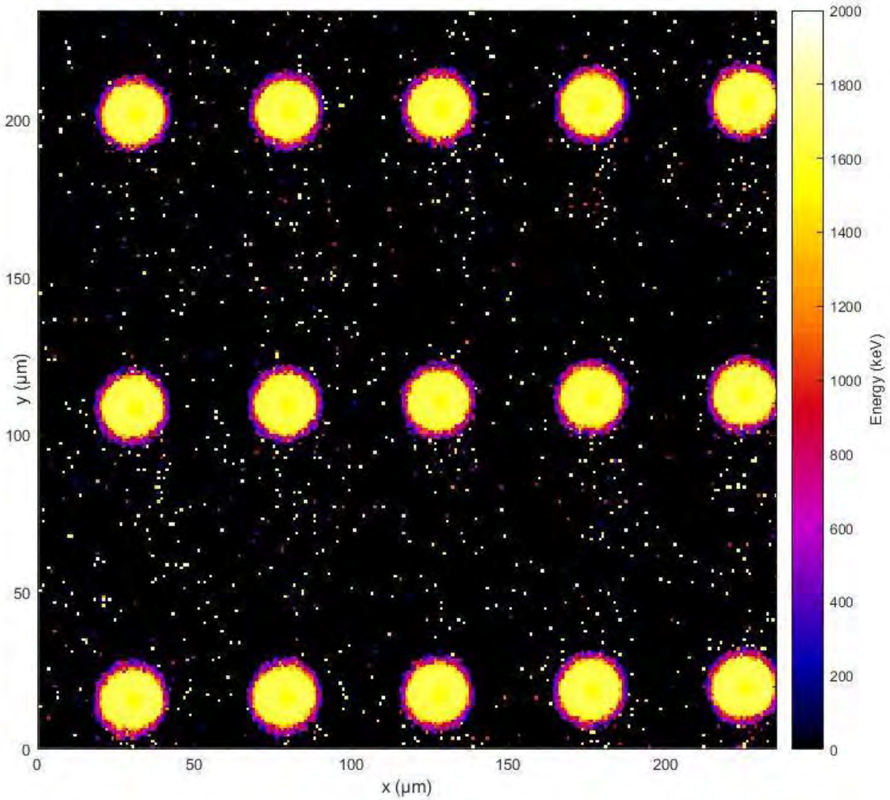


10V



Mushroom : Charge Collection study using 5.5 MeV He^{2+}





- Median energy maps generated using two different scan sizes, in both cases the detector is biased using 10V
- No cross-talk between adjacent sensitive volumes

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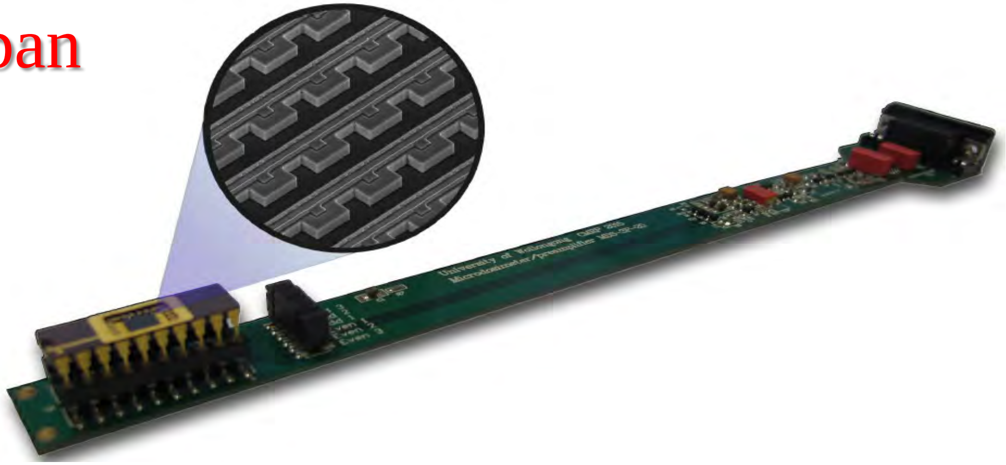
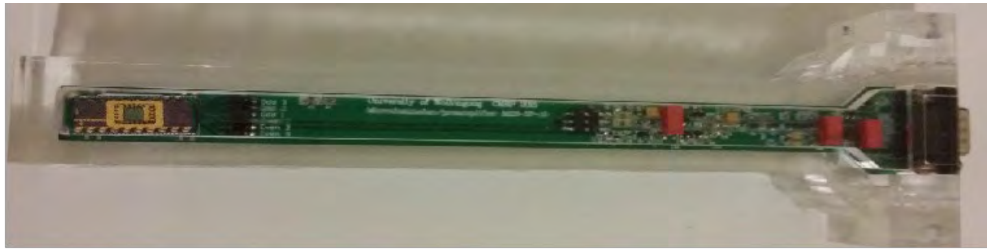
Application in proton and heavy ion therapy

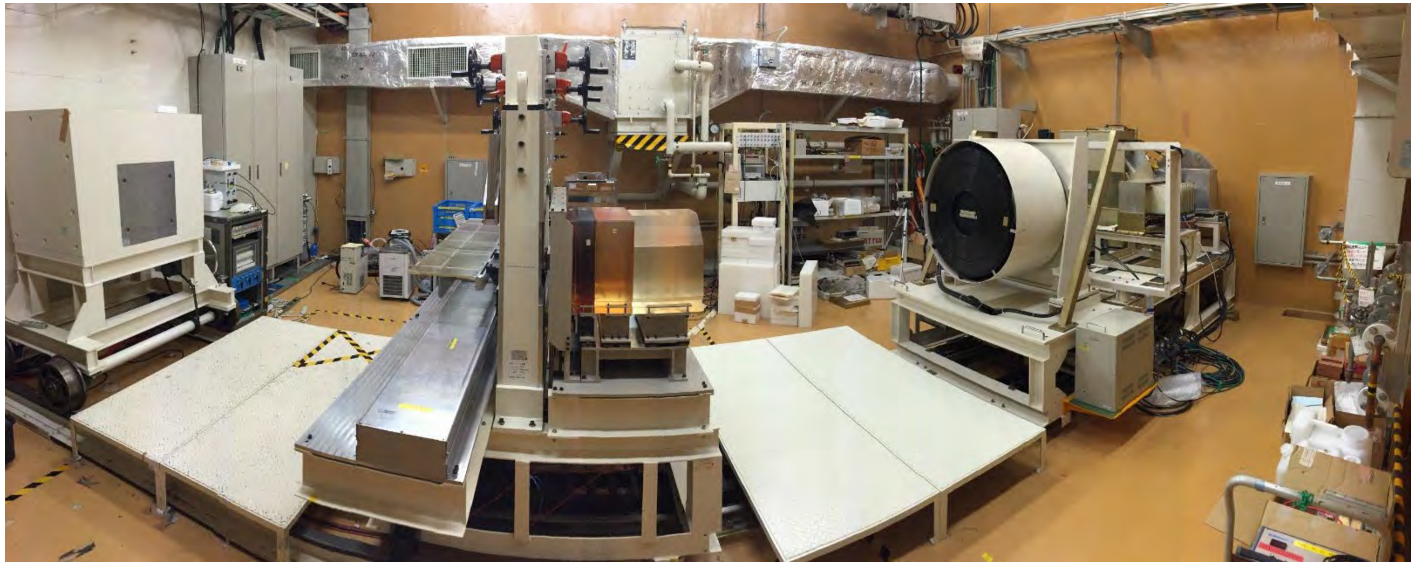
Heavy Ion Medical Accelerator in Chiba

HIMAC, Japan

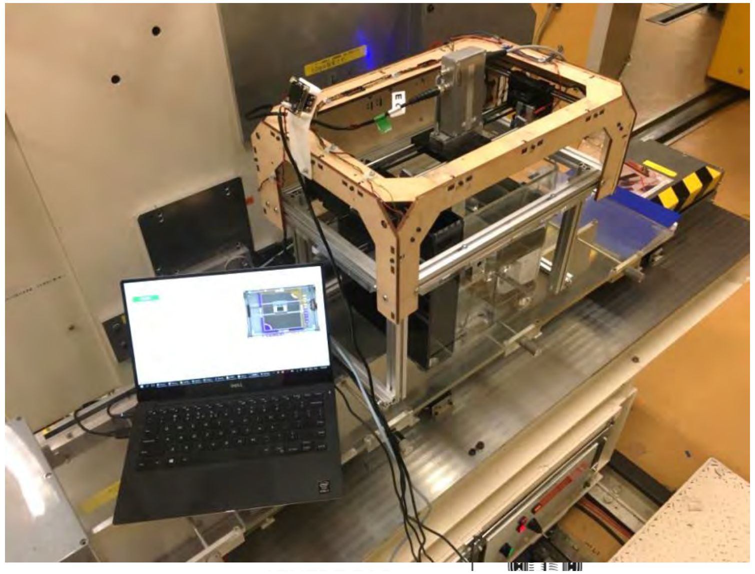




μ^+ microdosimeter probe in PMMA sheath



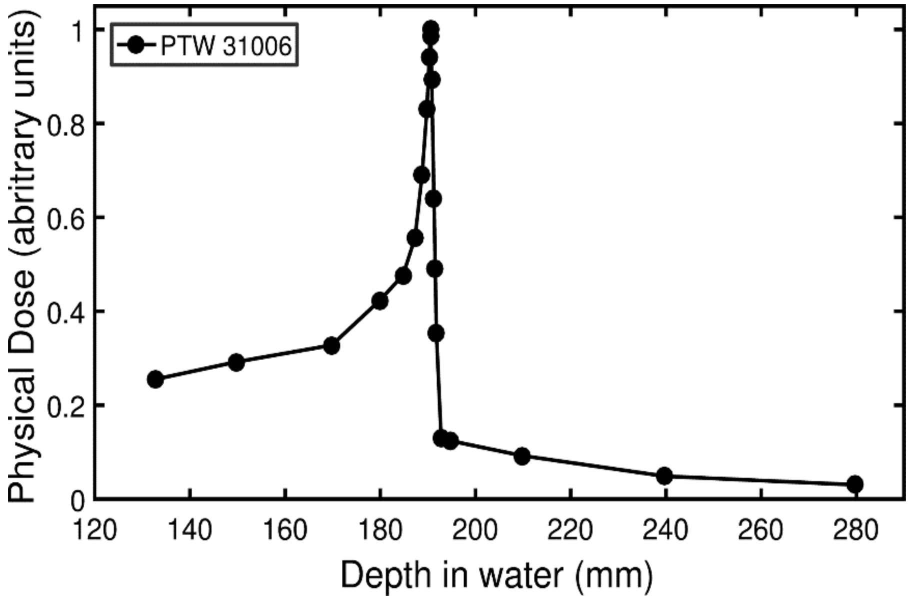
HIMAC Bio-cave beam port with passive scattering delivery



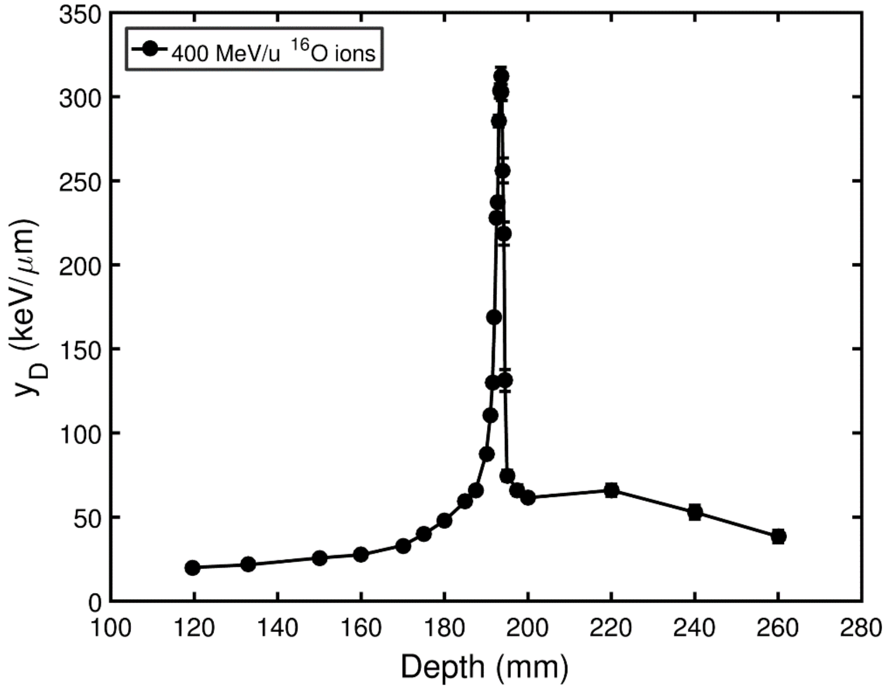
MicroPlus probe with 3D printer XY-movement stage

400MeV/u ^{16}O Ion Irradiation

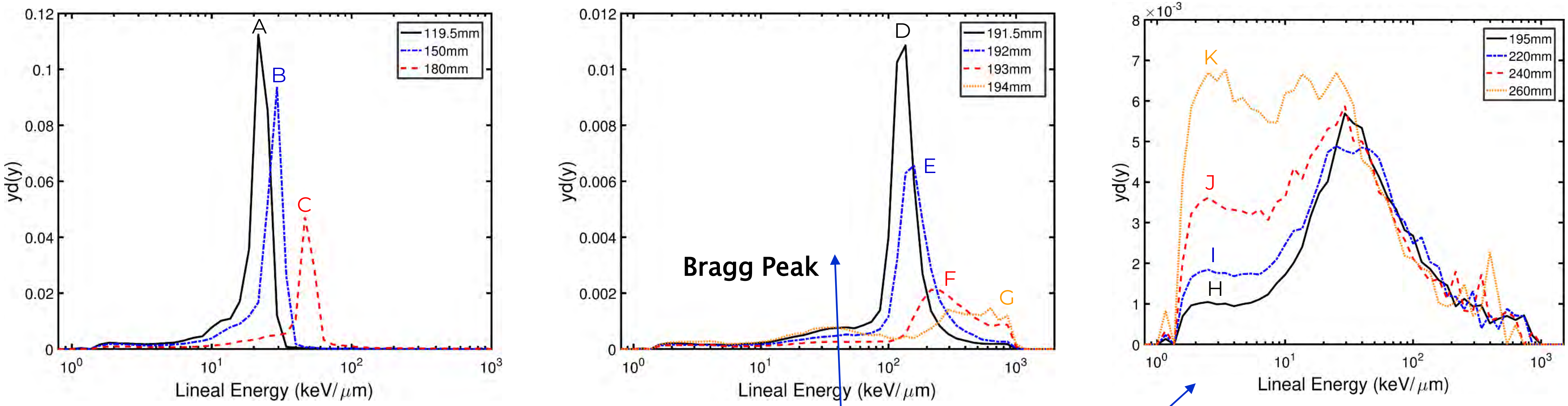
- Parameters measured:
  - Physical dose
  - Dose-mean lineal energy (y_D)
  - Relative Biological Effectiveness (RBE_{10})



Physical dose distribution of 400 MeV/u ^{16}O ions



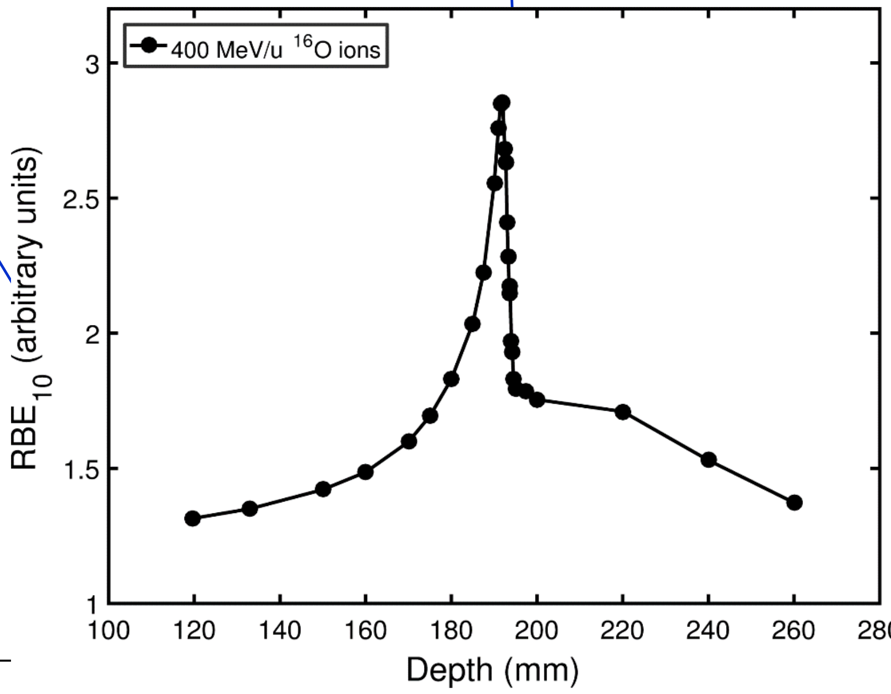
Dose-mean lineal energy measured for 400 MeV/u ^{16}O ions



Bragg Peak

Entrance

Downstream



400 MeV/u ^{16}O Ions

Dose mean lineal energy and RBE_{10} distribution with microdosimetric spectra for each region along the Bragg Peak

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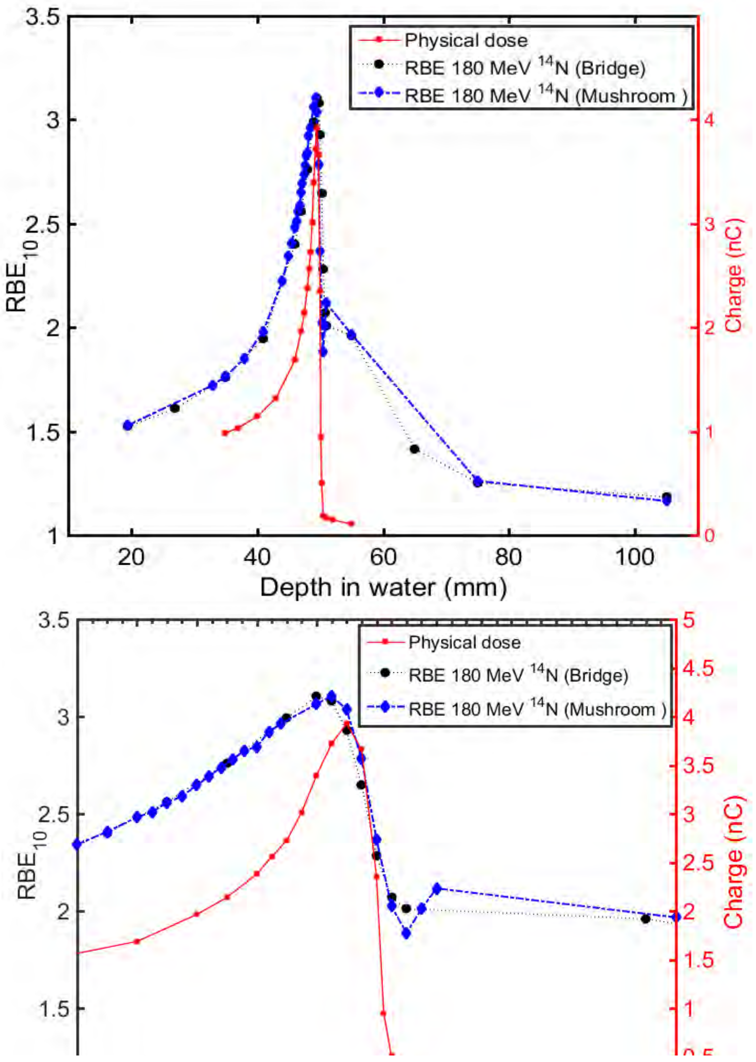
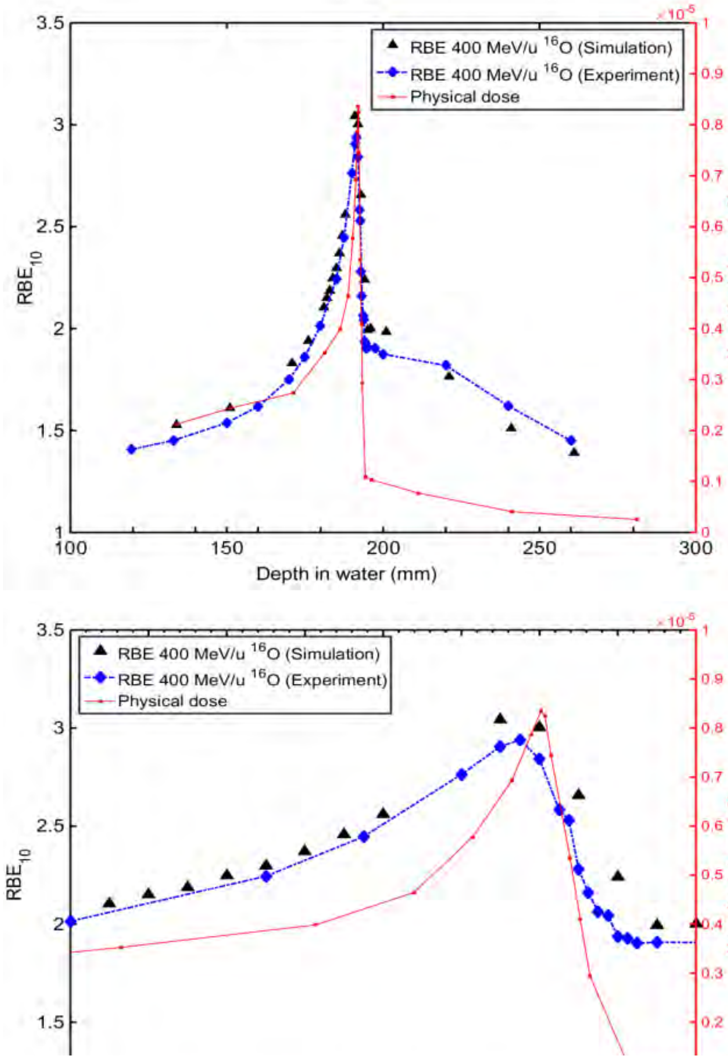
Ability for Multi-ion therapy: RBE$_{10}$ obtained with SOI microdosimeter in response to pristine BP of ^{14}N, ^{16}O and ^{12}C ion beam (HIMAC at NIRS, Japan

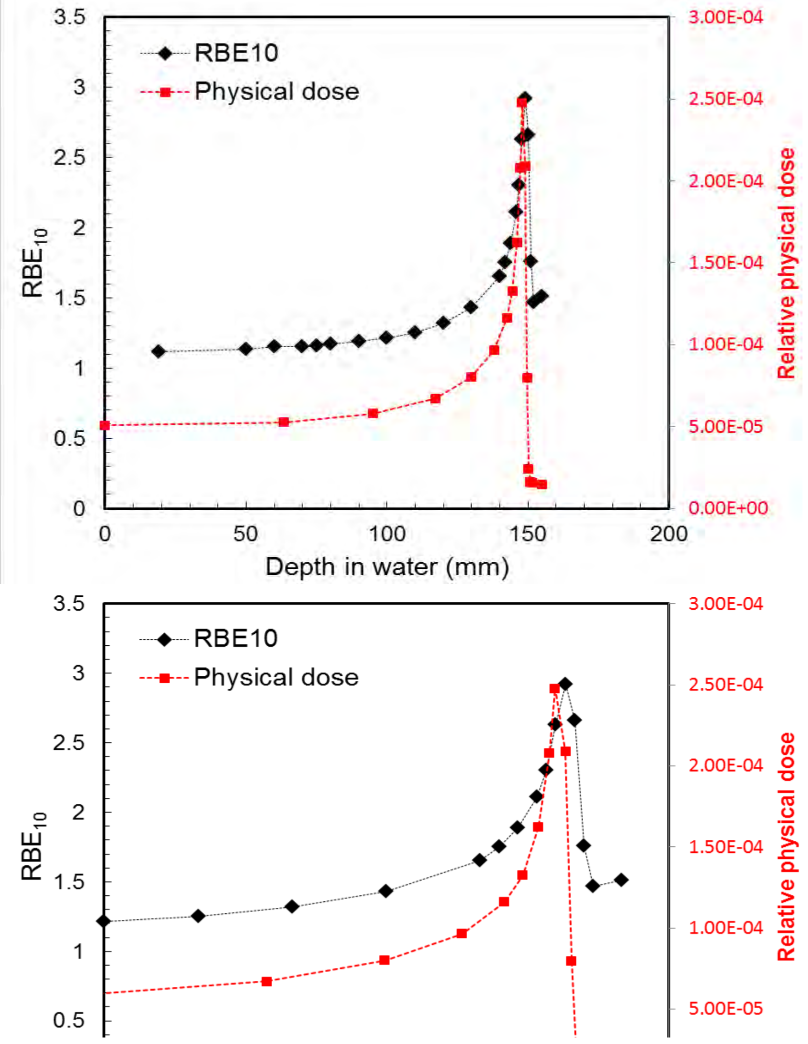
180 MeV/u ^{14}N



400 MeV/u ^{16}O



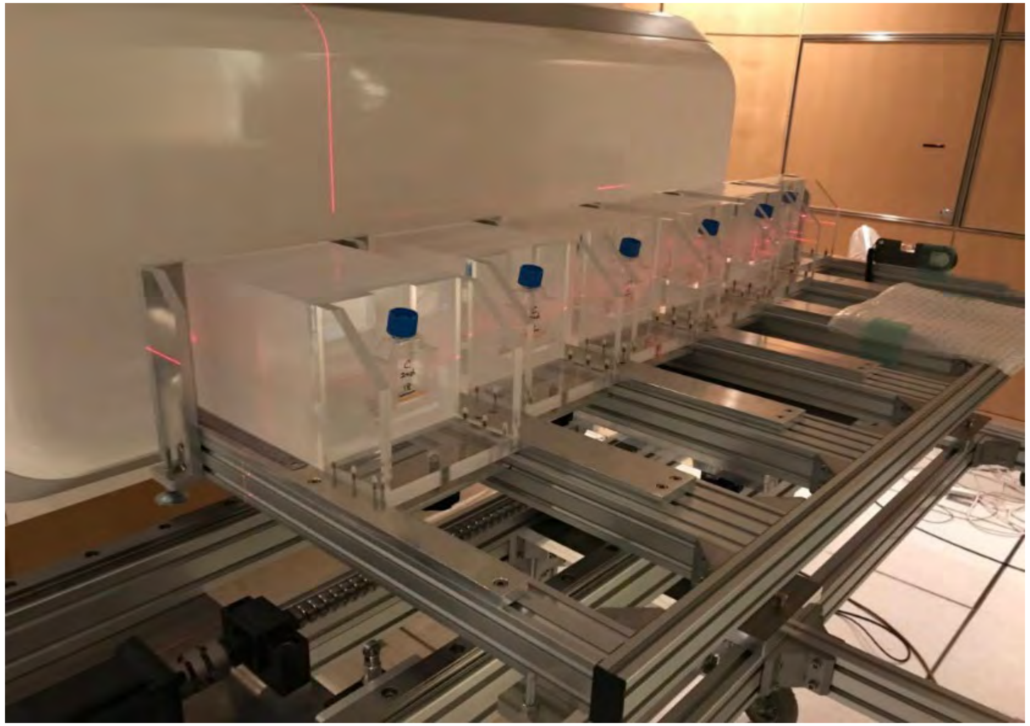
290 MeV/u ^{12}C



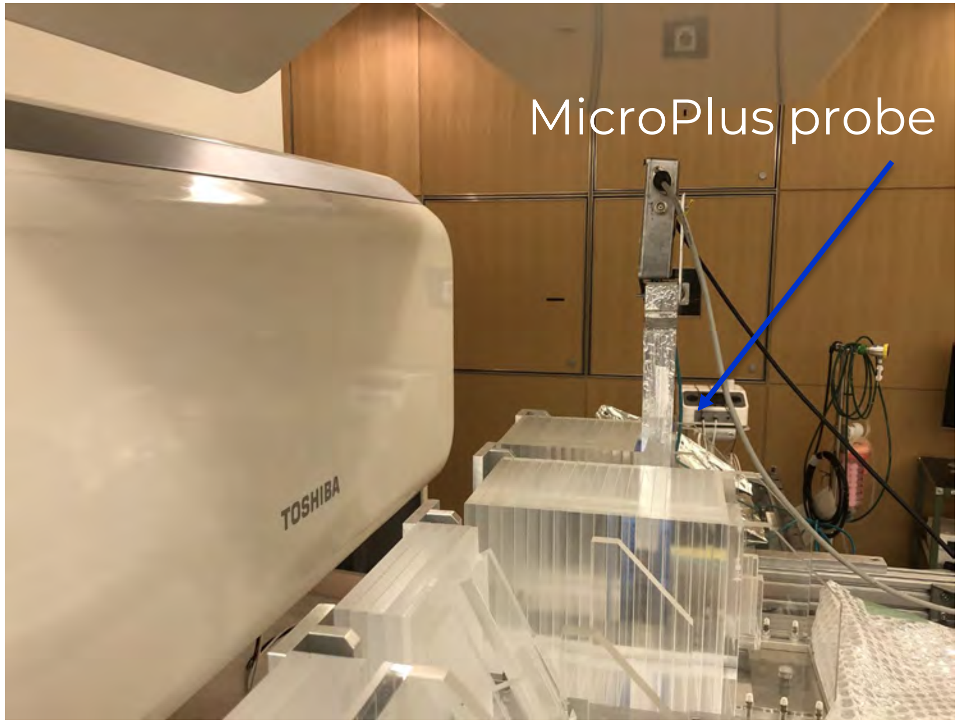
Linh T. Tran, *et. al*., ***"The relative biological effectiveness for carbon, nitrogen and oxygen ion beams using passive and scanning techniques evaluated with fully 3D silicon microdosimeters"*** Medical Physics, 2018 ,(AAPM Award: The best paper Med Phys. of 2018)

Validation of MK model in MIT

Microdosimetric spectra were measured with MicroPlus-mushroom probe at different depths along pristine BP for He, C, O, Ne ions to compare MKM predicted SF with measured from *in vitro* MiaPaca cells experiment in a wide range of LETs



Cell flasks were setup behind PMMA slabs of different thicknesses.



Measurements with MicroPlus probe at the same irradiation condition as cells

Pencil Beam Scanning dose delivery

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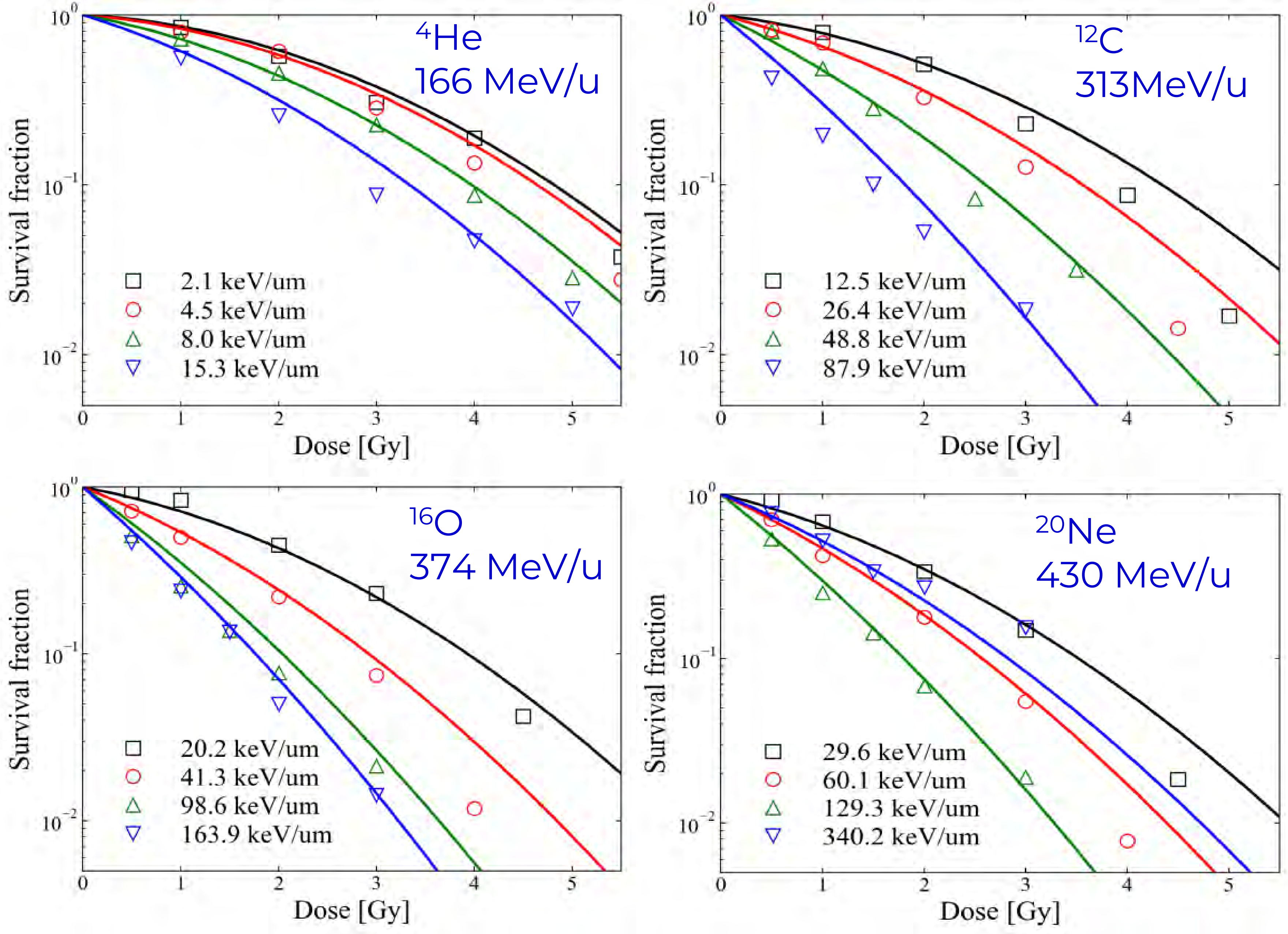
Survival Fraction of *in vitro* data compared to microdosimetric measurements



Survival fraction *(markers)* of in vitro data of the *MIA PaCa-2 cells* for each LET of He, C, O and Ne ion beams and the survival curves *(solid lines)* calculated from physical dose and ***lineal energy measured with SOI microdosimeter.***

MK model parameters of cells
α_0 = 0.001 Gy^{-1}, β = 0.085 Gy^{-2},
R_n = 6.8 μm,
r_0 = 0.57 μm and y_0 = 260 keV/μm.

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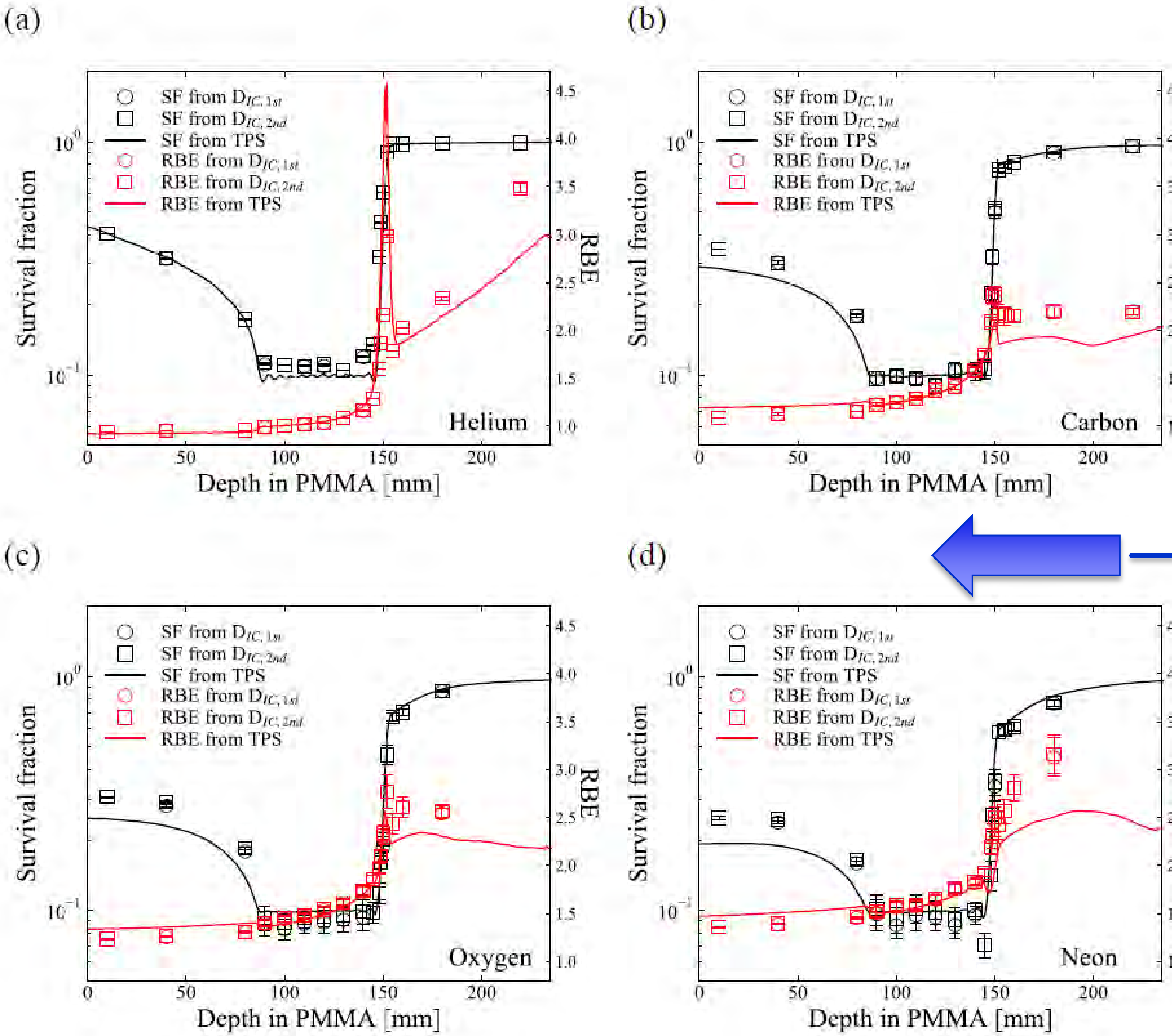
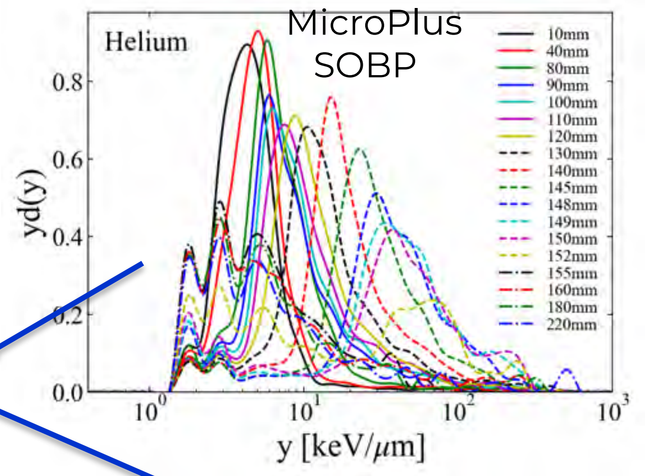
SF: MicroPlus predicted vs TPS in SOBP



TPS: RBE_{10}xD

10x10x6 cm^3

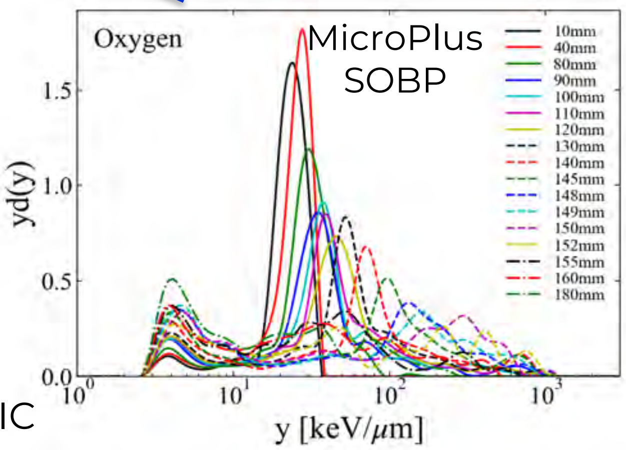


$$\alpha = \alpha_o + \frac{\beta}{\rho \pi r_d^2} y^*$$

Linear Quadratic Model

S(D) = exp [- αD - βD^2]

Dose in SOBP measured by Markus IC



Good prediction of SF

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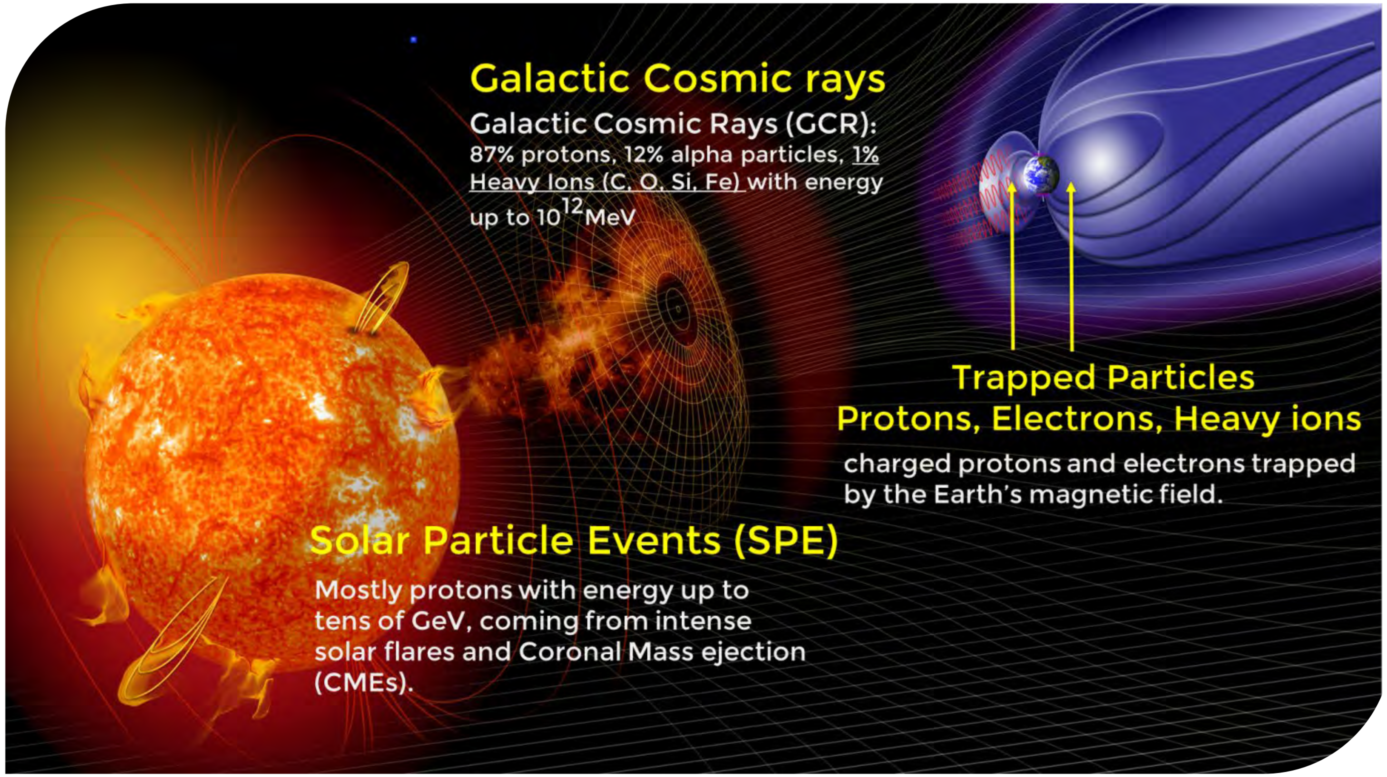
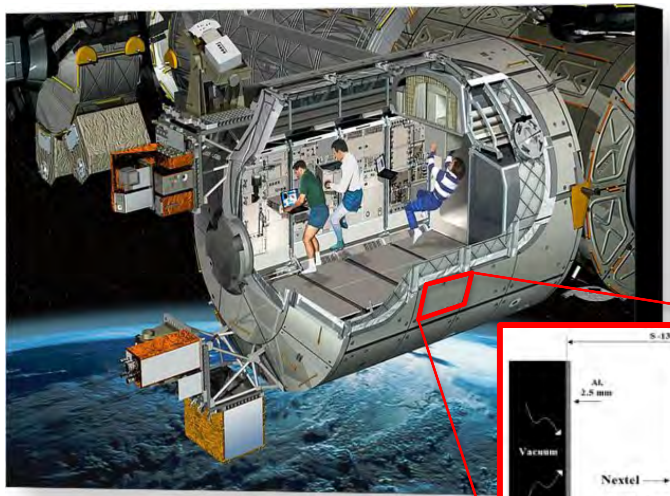
S.H.Lee et al "Estimating the biological effects of helium, carbon, oxygen, and neon ion beams using 3D silicon microdosimeters", PMB , **66**(4) 2021

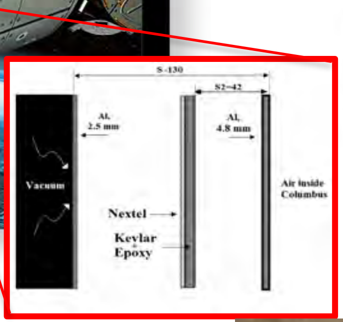
Application in space environment



- ✓ Measure dose equivalent for astronauts
- ✓ Predict Single Event Upsets (SEU)
- ✓ Radiation shielding optimization
- ✓ Real-time Space Radiation monitoring

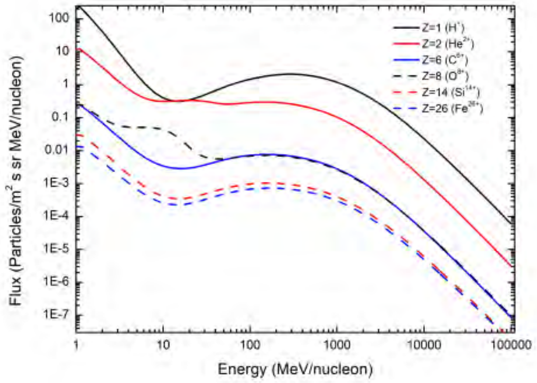
Columbus ISS space module: wall shielding properties optimization

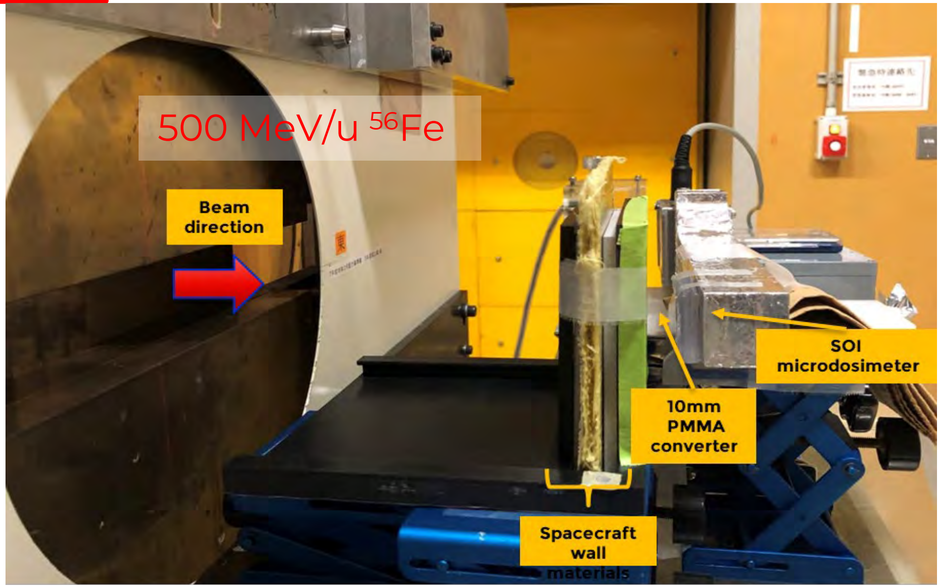


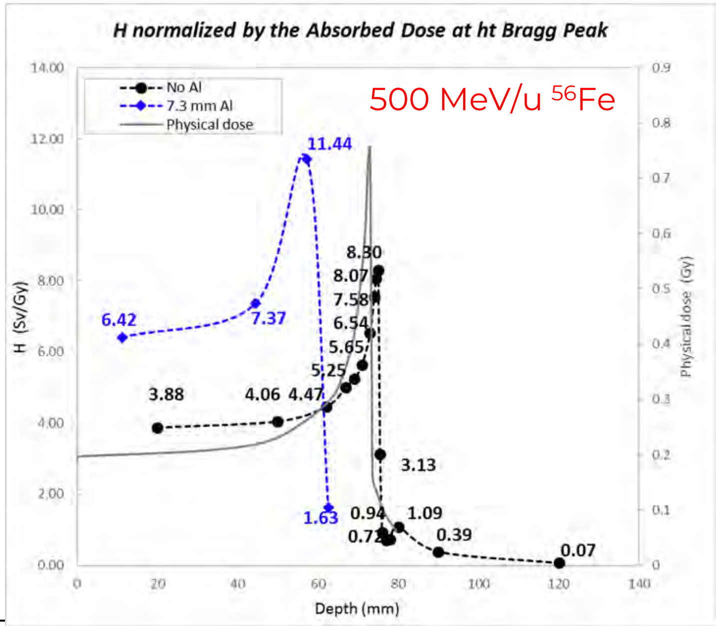


Layout of the Columbus debris shield configuration [R. Destefanis et. al.]

GCR: Heavy Charged Particles

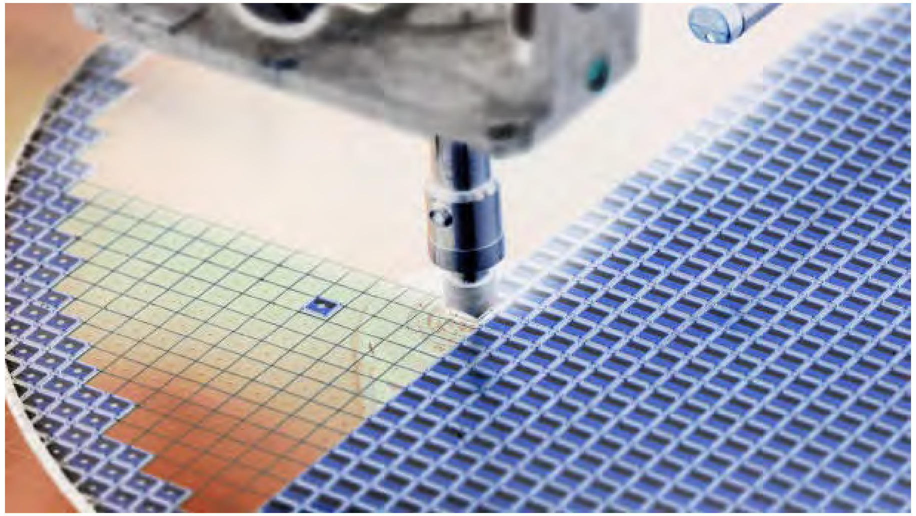


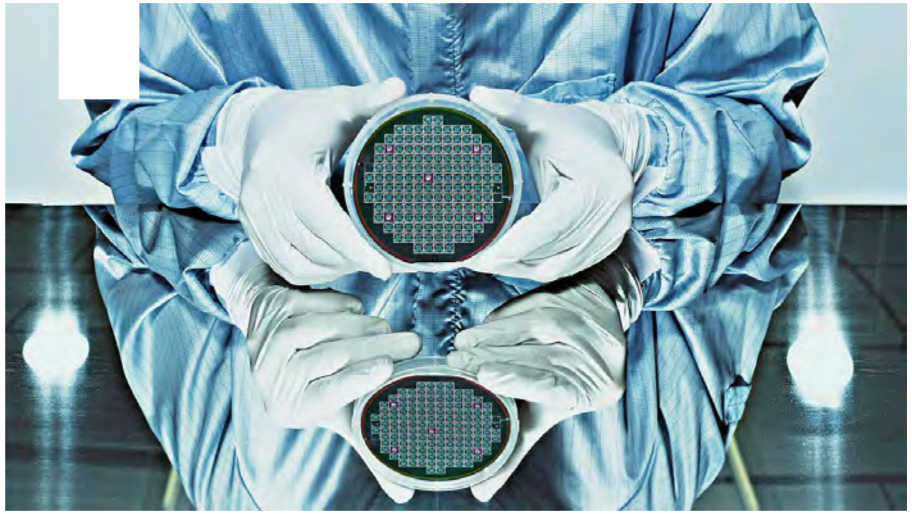


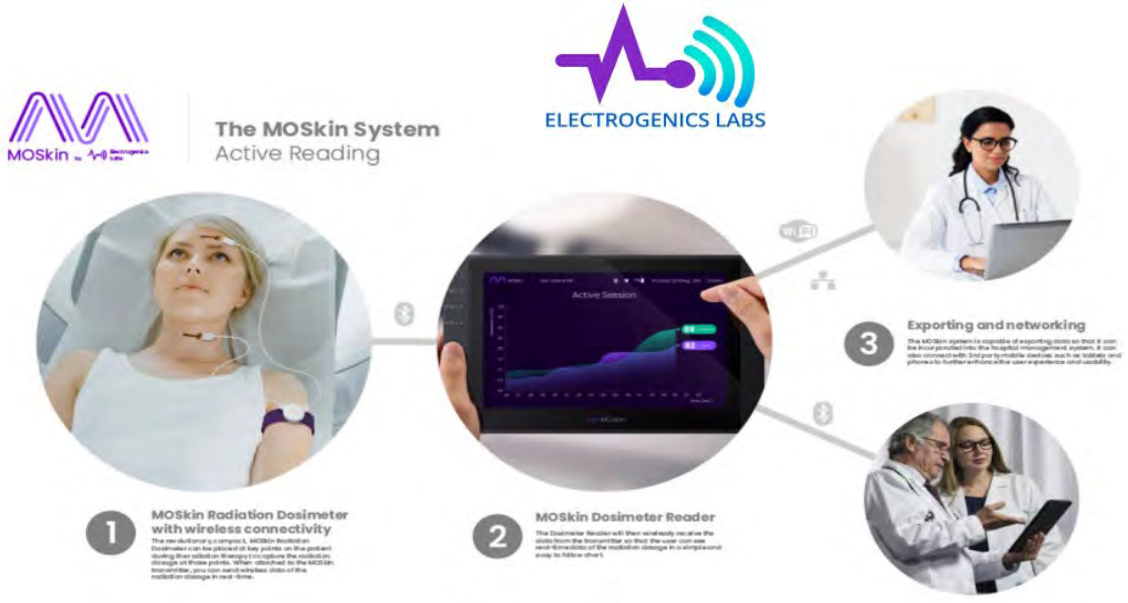


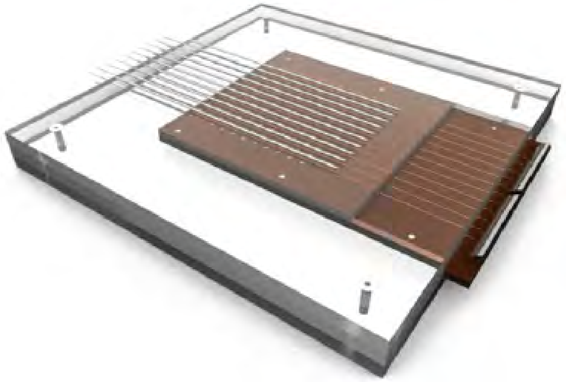
Experiment in HIMAC accelerator, Japan

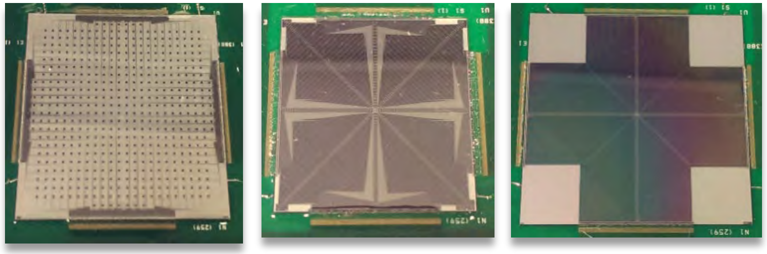
Development of radiation sensors at the Centre for Medical Radiation Physics, University of Wollongong











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Semiconductor sensors for radiation monitoring in Space radiation environment

SINTEF

esa

European Space Agency

Questacon travelling exhibition **Australia in Space**, 2021-2025

Meet the CMRP microdosimetry team

Dist. Prof Anatoly Rozenfeld
Founder and Director

Prof Michael Lerch

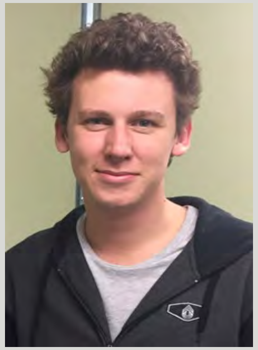
A/Prof Susanna Guatelli

Dr Linh Tran

Dr Dale Prokopovich

A/Prof Marco Petasecca

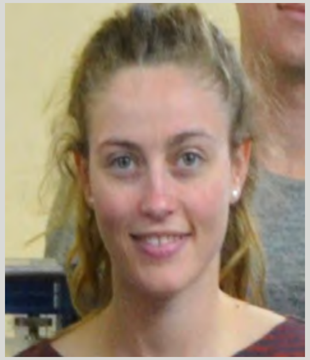
Dr David Bolst



Dr Lachlan Chartier

Ben James

Dr Stefania Peracchi



Dr Emily Debrot

Vladimir Pan

James Vohradsky

Master and Honours students:

- Dylan Hill
- Jesse Williams
- Daniel Bennett

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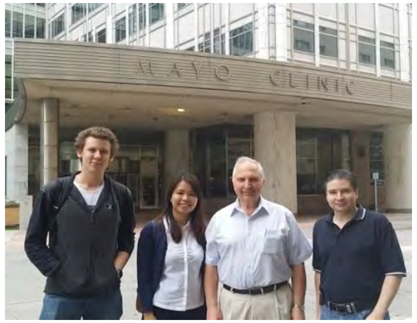
Acknowledgements

PT: MGH, USA



PT: Mayo Clinic, USA

Thank you
for your attention!

PT: University of Groningen, Netherlands

SINTEF

HIT: HIMAC, Japan

Australian Government ANSTO | SINTEF | umcg | NCRIS National Research Infrastructure for Australia An Australian Government Initiative | Australian Government Australian Research Council | QST

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Email: anatoly@uow.edu.au; tltran@uow.edu.au

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Space Qualification 2023

Noosa, 12-13 February

MMND & ITRO 2023

Mini-Micro-Nano Dosimetry and
Innovative Technologies in Radiation Oncology