Development of silicon micordosimeters for RBE determination in ^{12}C heavy ion and proton therapy

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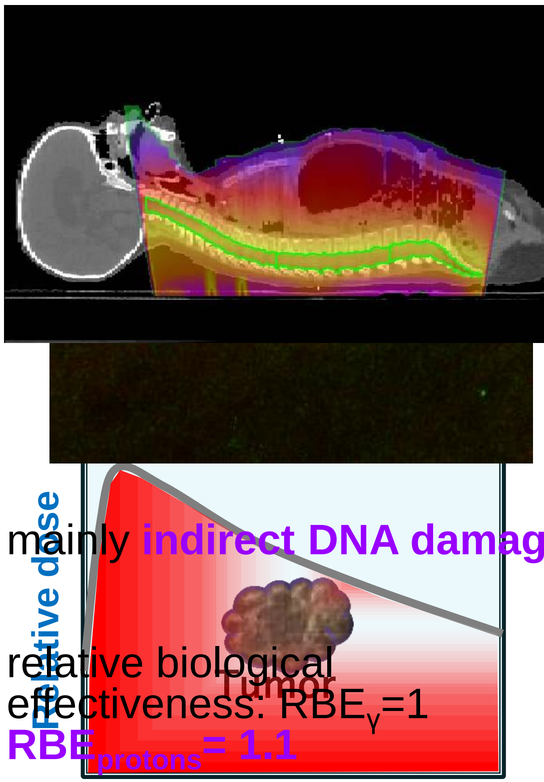
Heavy Ion Therapy

X rays

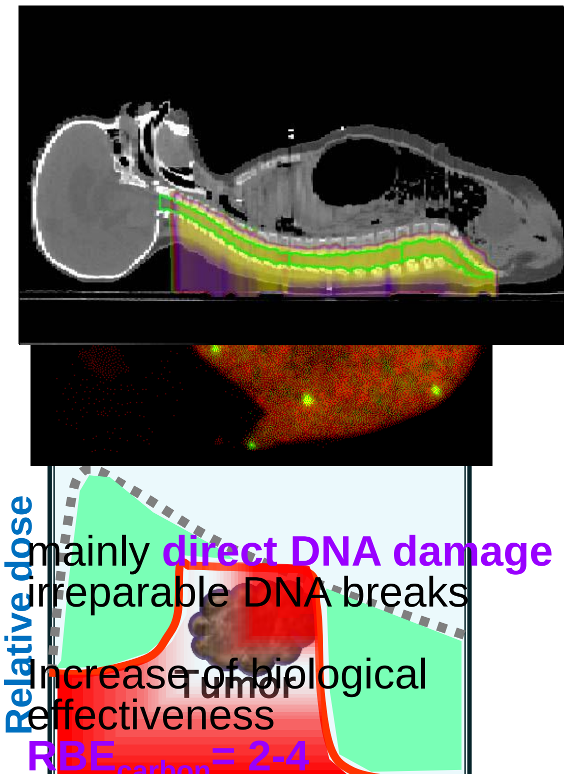


mainly **indirect DNA damage**

relative biological effectiveness: $RBE_{\gamma}=1$

$RBE_{protons} = 1.1$

Carbon Ion beams



mainly **direct DNA damage**

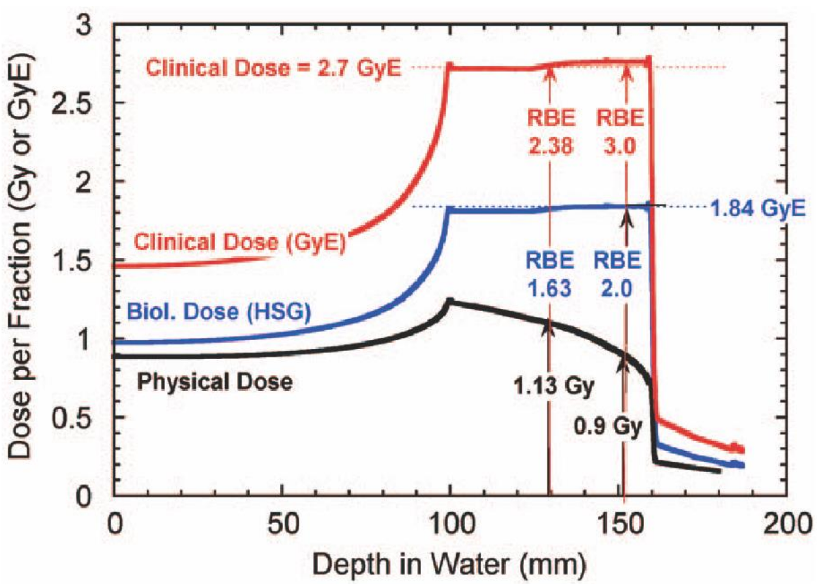
irreparable DNA breaks

Increase of biological effectiveness

$RBE_{carbon} = 2\text{-}4$

→ Radioresistant tumours!

Relative Biological Effectiveness (RBE)



[1] O. Jäkel et al Technology in Cancer Research & Treatment, ISSN 1533-0346 ,Volume 2, Number 5, October (2003)

[2] O. Steinsträter et al "Mapping of RBE-weighted doses between HIMAC- and LEM-based treatment planning systems"

[3] N. Matsufuji et al Specification of Carbon ion dose at NIRS, JRS 2007.

HIMAC (Japan)

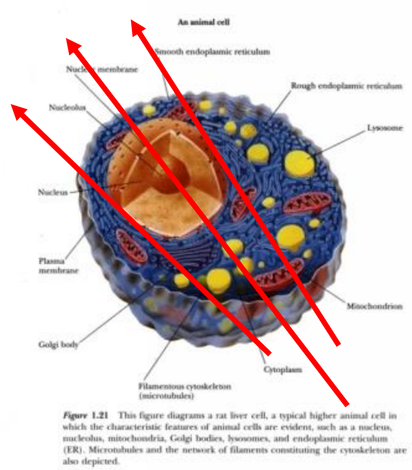
- Passive beam
- RBE values are derived from in vitro experimental data in conjunction with clinical neutron experience and Microdosimetric Kinetic Model - MKM).
- RBE estimation at HIMAC is independent of the tumor type

GSI (Germany)

- Scanning beam
- RBE values for planning were estimated using Local Effect Model – LEM)
- RBE estimation are based on photon dose response curves under the cell lines

Microdosimetry and Dose Equivalent

- **Microdosimetry**
  - Lineal energy: $y = \frac{E}{<l>}$ where
    - E is the energy deposited in the cell and ,
    - $<l>$= average chord distribution
  - Microdosimetric spectra of a radiation field, (i.e. $y^2 f(y)$ vs $\log(y)$)
  - **Dose Equivalent** : $H = D \int Q(y) y^2 f(y) d(\log(y))$



Biological Cell (um)

Image from Garret and Grisham, "Biochemistry"
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Experimental microdosimetry

Tissue Equivalent Proportional Counter

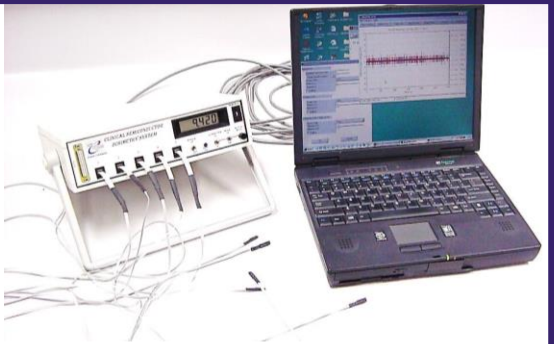
5-10cm

✓ Spherical SV in shape
✓ Tissue equivalency

- Large size of assembly which reduces spatial resolution and introduces wall effects
- Can not measure an array of cells.
- High voltage applied

Centre For Medical Radiation Physics (CMRP)

- Research strength of the University of Wollongong
- Research to **improve radiotherapy treatment**
  - New radiotherapy methodologies (e.g. use of nanoparticles)
  - New QA instrumentation for X-ray radiotherapy, brachytherapy, charged particle therapy
- Development of detectors for **radiation protection** in nuclear facilities, aviation and space missions



MO*Skin, real time dosimetry*

Magic Plate
in-vivo and *realtime* Fluence verification in RapidArc and IMRT

Technology SOLUTIONS

Excellence in EDUCATION AND RESEACH

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TIMOR SEA
Melville I.
Darwin
Cape York
PAPUA NEW GUINEA
INDIAN OCEAN
Arnhem Land
Katherine
Gulf of Carpentaria
Wyndham
Kimberley
CORAL SEA
NORTHERN TERRITORY
Great Barrier Reef
Cairns
Broome
Halls Creek
Tennant Creek
Port Hedland
Great Sandy Desert
Mount Isa
Townsville
Mackay
North West Cape
AUSTRALIA
QUEENSLAND
Great Dividing Range
Alice Springs
Tropic of Capricorn
Rockhampton
Gibson Desert
Longreach
Gascoyne
Uluru (Ayers Rock)
Simpson Desert
Diamantina
Fraser I.
Carnarvon
WESTERN AUSTRALIA
Great Victoria Desert
Charleville
Sunshine Coast
Coober Pedy
Lake Eyre
Cooper Ck
Brisbane
Geraldton
Gold Coast
Nullarbor Plain
SOUTH AUSTRALIA
Darling
Bourke
Kalgoorlie
Port Macquarie
Port Augusta
Broken Hill
NEW SOUTH WALES
Perth
Fremantle
Esperance
Great Australian Bight
Port Lincoln
Barossa Valley
Blue Mtns
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CANBERRA

Meet the CMRP team

Prof Anatoly Rozenfeld
Founder and Director

A/Prof Michael Lerch

Dr George Takacs

Dr Iwan Cornelius

Prof Peter Metcalfe

Dr Dean Cutajar

Dr Marco Petasecca

Karen Ford
Admin Officer and PA

Dr Susanna Guatelli

Dr Mitra Safavi-Naieni

Dr Yujin Qi

Dr Elise Pogson

Dr Michael Weaver

Dr Engbang Li

Dr Alessandra Malaroda

Dr Linh Tran

Dr Moeava Tehei

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CMRP Proton and Heavy Ion Therapy Team

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Microdosimetry in Radiation Protection

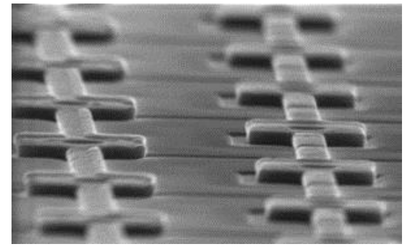
Tissue Equivalent Proportional Counter

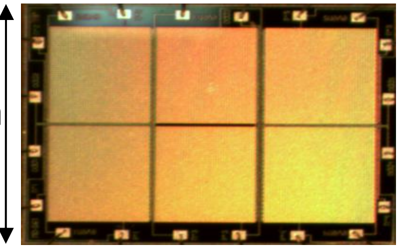
5-10cm

- ✓ Spherical SV in shape
- ✓ Tissue equivalency

- Large size of assembly which reduces spatial resolution and introduces wall effects
- Can not measure an array of cells.
- High voltage applied

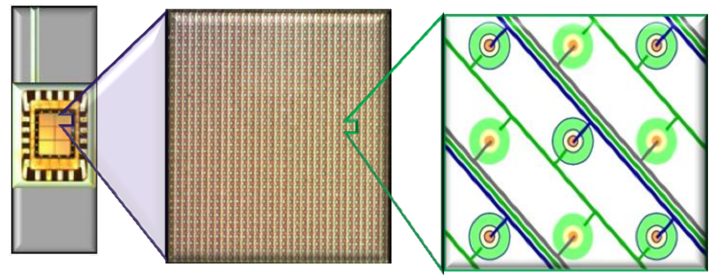
Silicon Microdosimeter

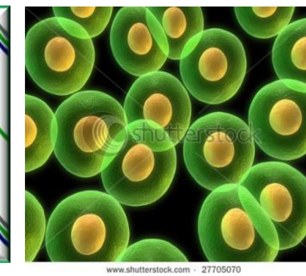




3mm

4mm





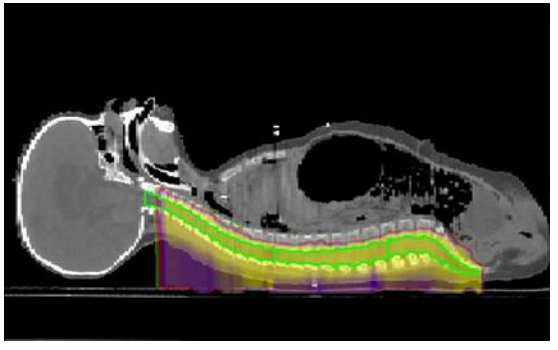
- ✓ Can measure an array of cells
- ✓ Micron sized SV
- ✓ Provide true microscopic SV
- ✓ Compact size and low voltage for operation
- ✓ High spatial resolution.

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

Silicon microdosimetry applications

Radiotherapy

Radiotherapy	Radiation protection



Proton and Carbon Ion therapy
Fast Neutron Therapy
BNCT

Microdosimetry for BNCT

- Separate varying LET components

  Measure dose due to ^{10}B neutron capture and total dose

Performance of silicon microdosimetry detectors in boron neutron capture therapy

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Radiation Physics Group, University of Wollongong, Northfields Ave., Wollongong, NSW, 2522, Australia.

Barry Allen.
St George Hospital, Cancer Care Centre, Gray St, Kogarah, NSW, 2217, Australia

Jeffrey Coderre, Jacek Capala.
Medical Department, Brookhaven National Laboratory, Upton, New York, 11973.

NOTE: Footnotes and Figures are at the end of the file (similar to journal submission form)Figures have been bookmarked use the PDF reader bookmark facility

Abstract

Bradley, P.D., Rosenfeld, A.B , Allen, B, Coderre, J., and Capala, J, Performance of silicon microdosimetry detectors in boron neutron capture therapy

Reverse-biased silicon p-n junction arrays using Silicon-On-Insulator technology have been proposed as microdosimeters. The performance of such detectors in boron neutron capture therapy (BNCT) is discussed. This work provides the first reported measurements using boron coated silicon diode arrays as microdosimeters in BNCT. Results are in good agreement with proportional gas counter measurements. Various boron-coating options are investigated along with device orientation effects. Finally, a U-235 coating is tested to simulate device behavior in a heavy ion therapy beam.

I. INTRODUCTION

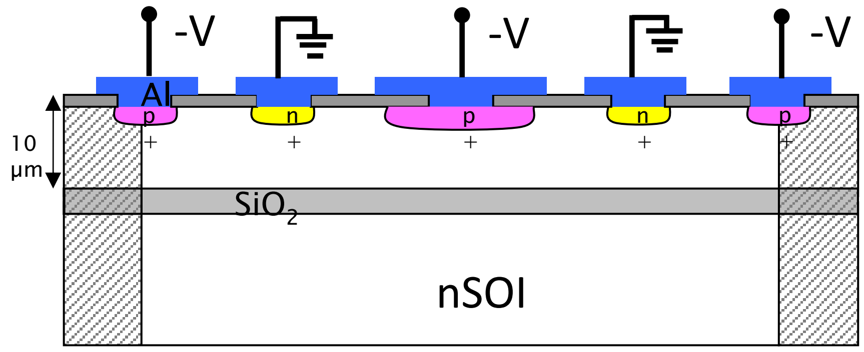
Boron neutron capture therapy involves the thermal neutron irradiation of a tumor site that has been selectively sensitized to thermal neutrons via the concentration of boron-10 (B-10) within or near cancer cells (*1*). The capture of thermal neutrons by B-10 results in the following nuclear fission process:

$$^{10}_{5}B+^{1}_{0}n \xrightarrow{6.3\%} {}^{7}_{3}Li+^{4}_{2}He \qquad Q=2790keV$$
$$\xrightarrow{93.7\%} {}^{7}_{3}Li+^{4}_{2}He+\gamma \qquad Q=2310keV$$

The alpha and lithium reaction products are high LET particles that deposit their energy in ranges of 4.1 and 7.7μm respectively, comparable to typical mammalian cell dimensions. The energy deposition is highly localized in nature and depends strongly on the subcellular spatial deposition of the B-10 nuclei and the subcellular morphology. In addition to the dose due to B-10 neutron capture, many other dose components are present. Protons are present as recoil products from the interaction of fast and epithermal neutrons with H-1 nuclei and as a product of N-14 neutron capture. Gamma rays arise from H-1 neutron capture and from the neutron source and surrounding materials. Studying complex radiation environments with such localized energy deposition is accomplished using the tools of experimental and theoretical microdosimetry. In particular, experimental microdosimetry provides techniques for separating varying LET components

Radiation Research: March 1999, Vol. 151, No. 3, pp. 235–243.

CMRP MICRODOSIMETERS: THIRD GENERATION



- SOI devices – large area 4x5 mm^2 segmented microdosimeters with separated cylindrical 2D planar SVs (10 µm in diameter),
- Fabricated on 10 µm thick n-SOI and demonstrated a 100% yield of working SVs

- Charge sharing between SVs which is leading to excessive deposition of low energy events. *[J. Livingstone et al 2012]*

3D Mesa "Bridge" Microdosimeter: Design and packaging

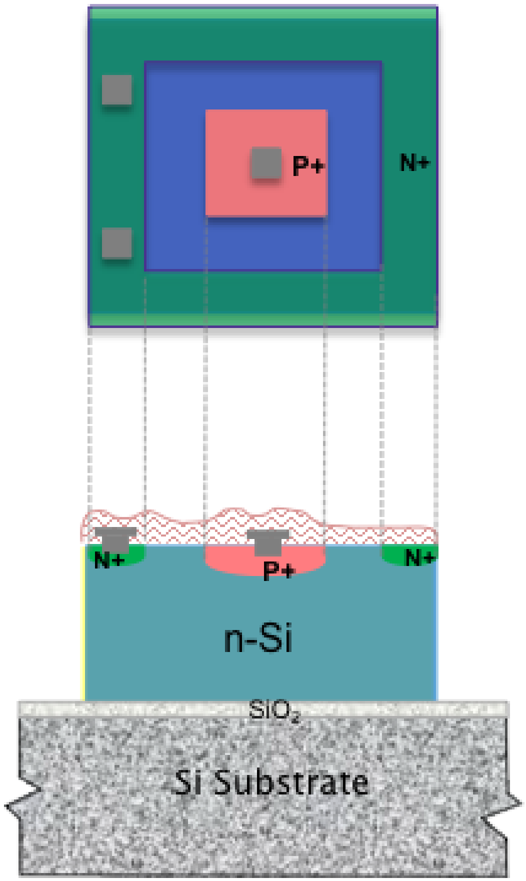
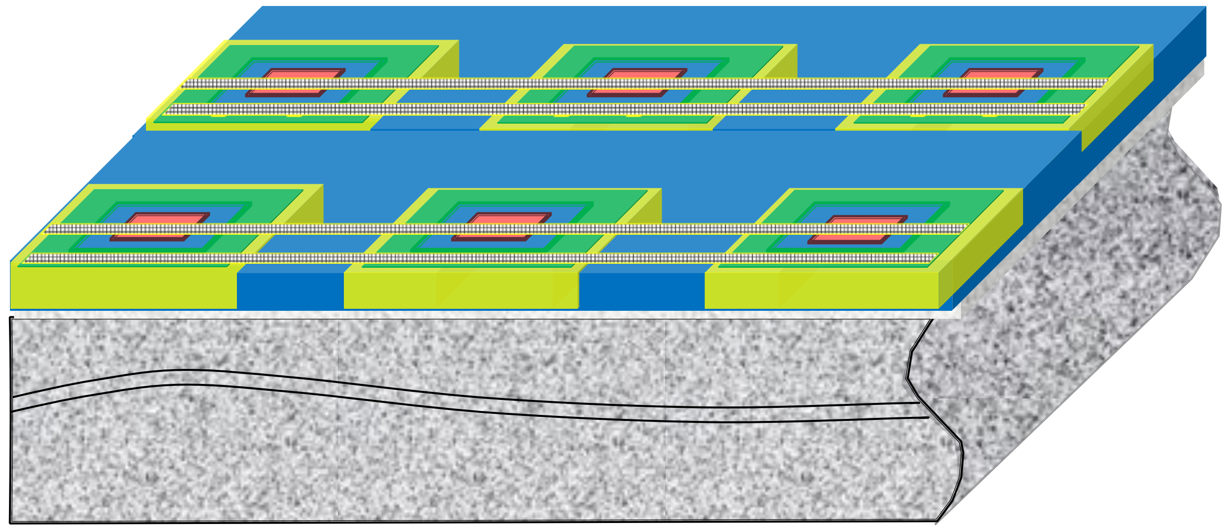
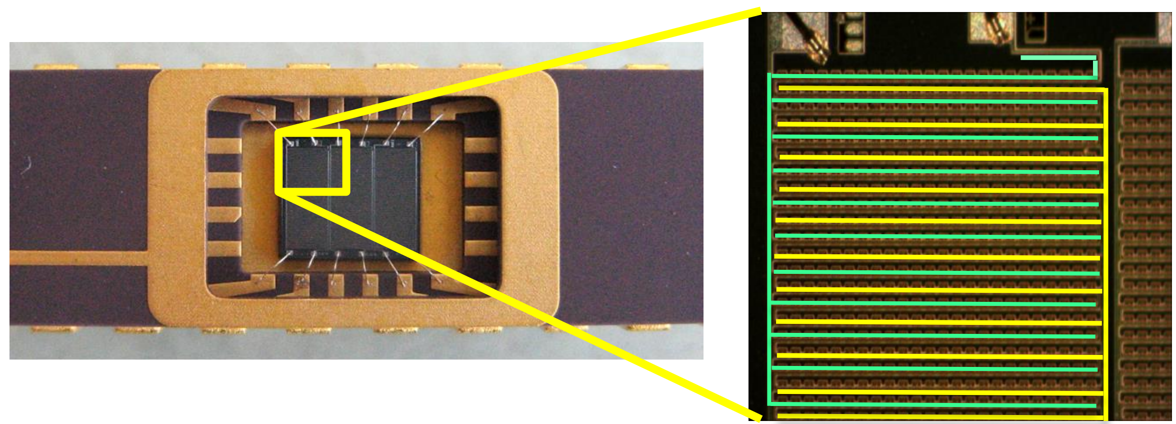


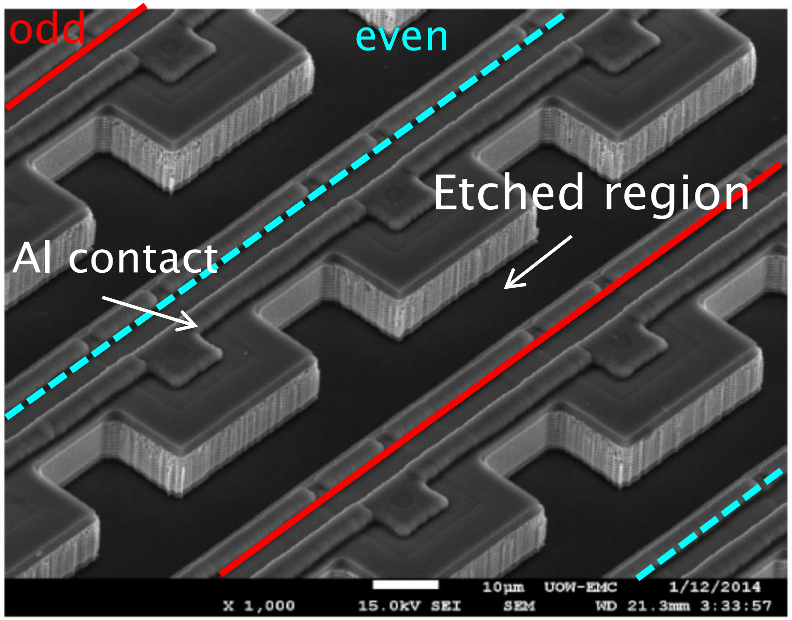
Figure 1. Top and side-on schematic of a sensitive volume



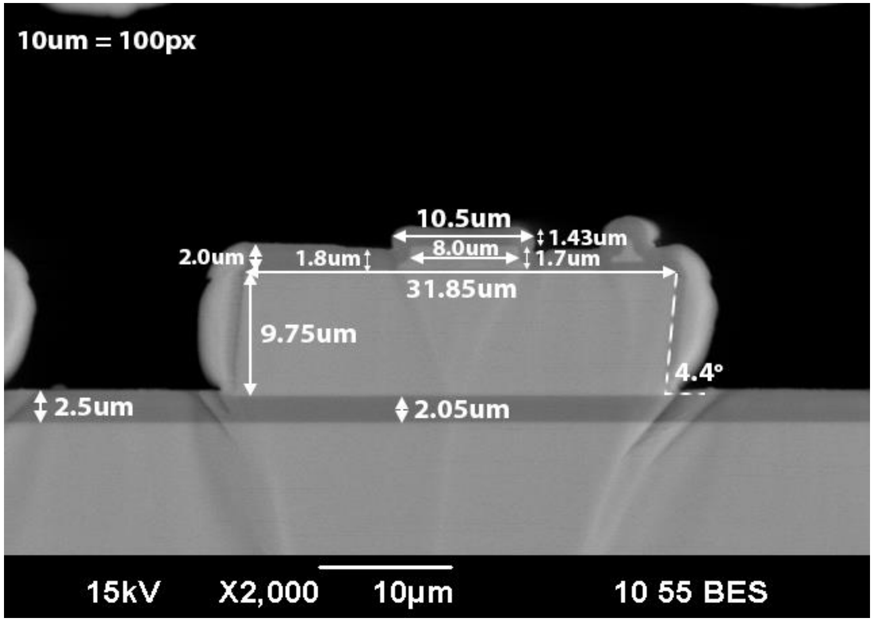


Area of whole chip : 3.6 x 4.1mm^2; 4320 cells

3D Mesa “Bridge” Microdosimeter: SEM Images



a) Array of sensitive volumes



b) Cross-section image of SV

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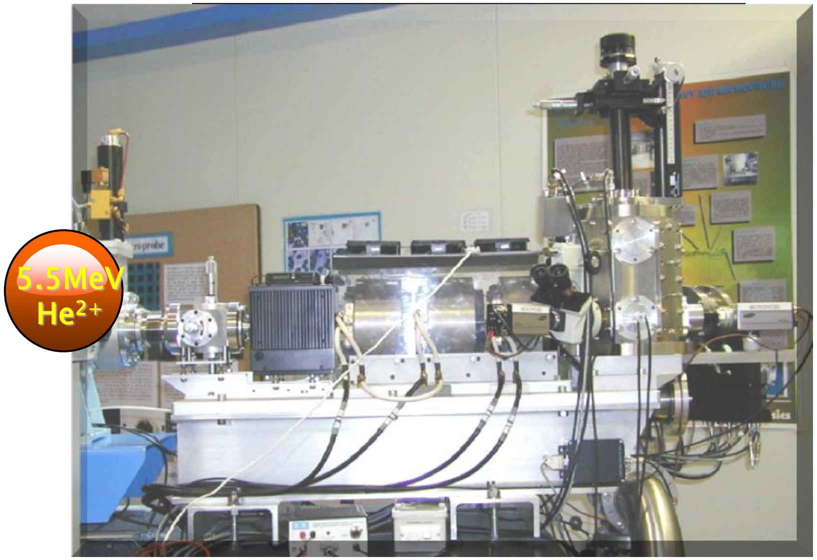
Ion Beam Induced Charge Collection (IBICC)



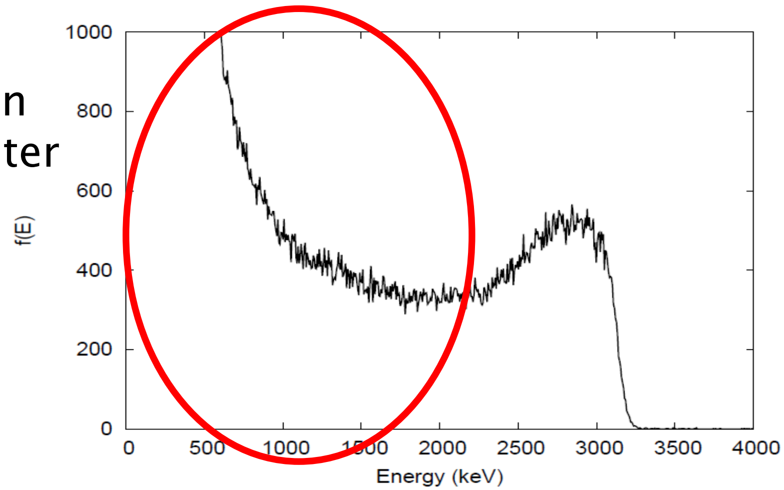
- Purpose: Study the charge collection properties of the SVs in 3D mesa bridge microdosimeter.
- Beam focal diameter: 1μm

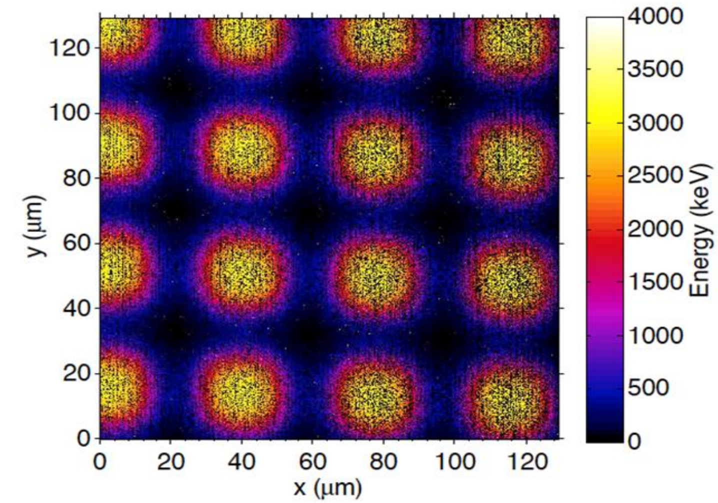
Ion	Energy (MeV)	Entrance LET in Si (keV/µm)	Range in Si (µm)
^{1}H	2.0	26.09	47.69
^{4}He	5.5	133.4	28.02

[] R. Siegele, D. Cohem, and N. Dytlewski, —The ANSTO high energy heavy ion microprobe, Nucl. Instrum. Methods Phys. Res. B, vol. 158, pp. 31-38, 1999.

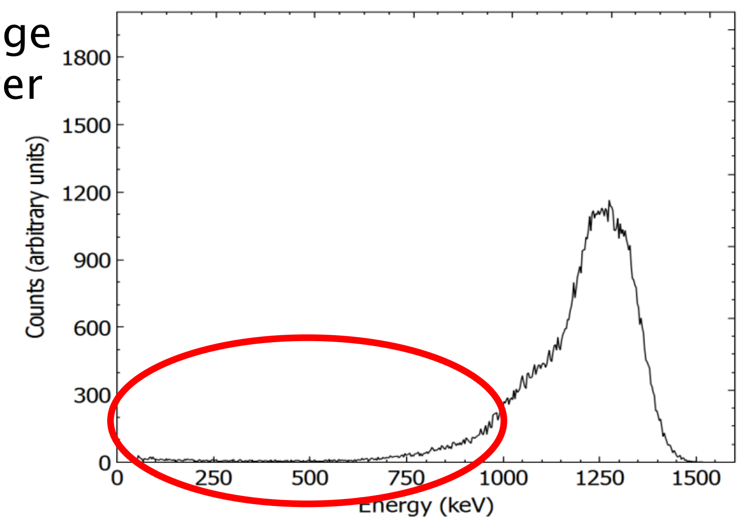
IBICC Results: 5.5 MeV He^{2+}

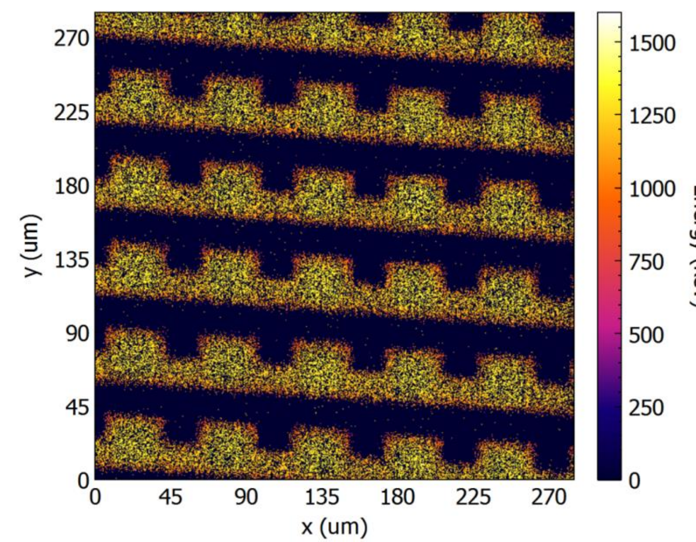
3[rd] generation microdosimeter





3D Mesa-Bridge microdosimeter





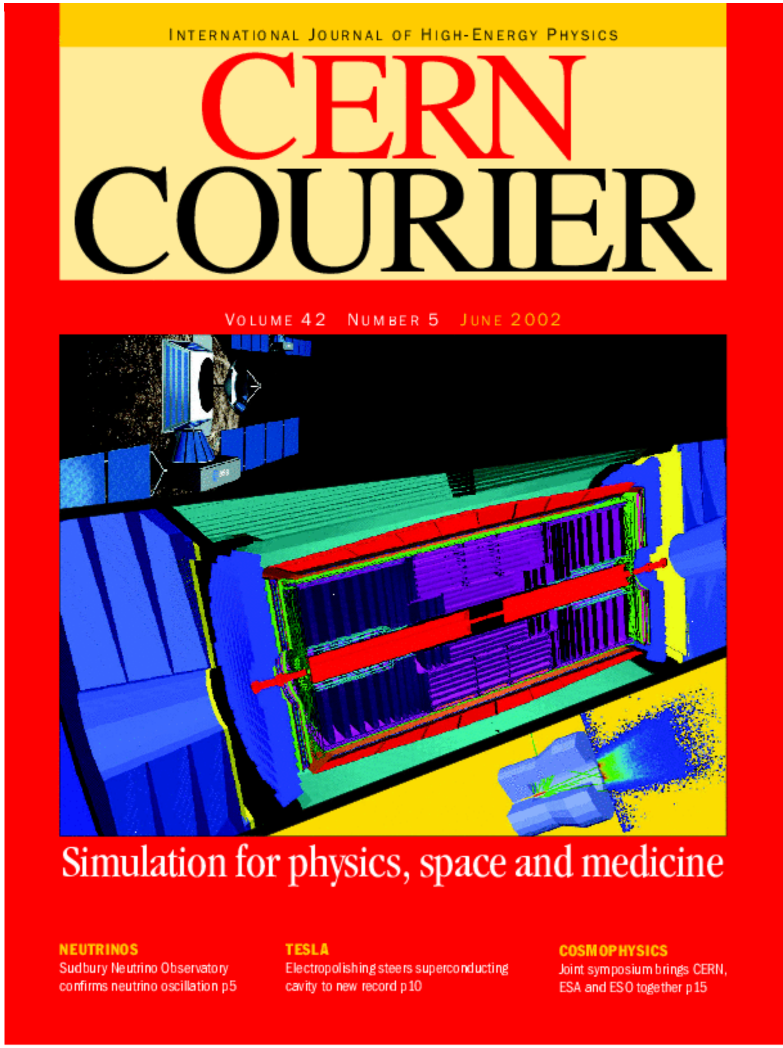
Energy spectrum and median energy map showing the spatial distribution of energy deposited by 5.5 MeV He^{+} ions in the SVs of the odd and even arrays. The detector was at −10 V

How to convert measurements in silicon to tissue

- By Geant4 simulations

Geant4 Toolkit
www.cern.ch/geant4

- Geant4 handles:
  - Complex geometries and materials
  - Particle tracking
  - Physics processes
  - Detector response
  - User interface
  - Visualisation of the experimental set-up
  - Variance reduction techniques
  - Analysis tools



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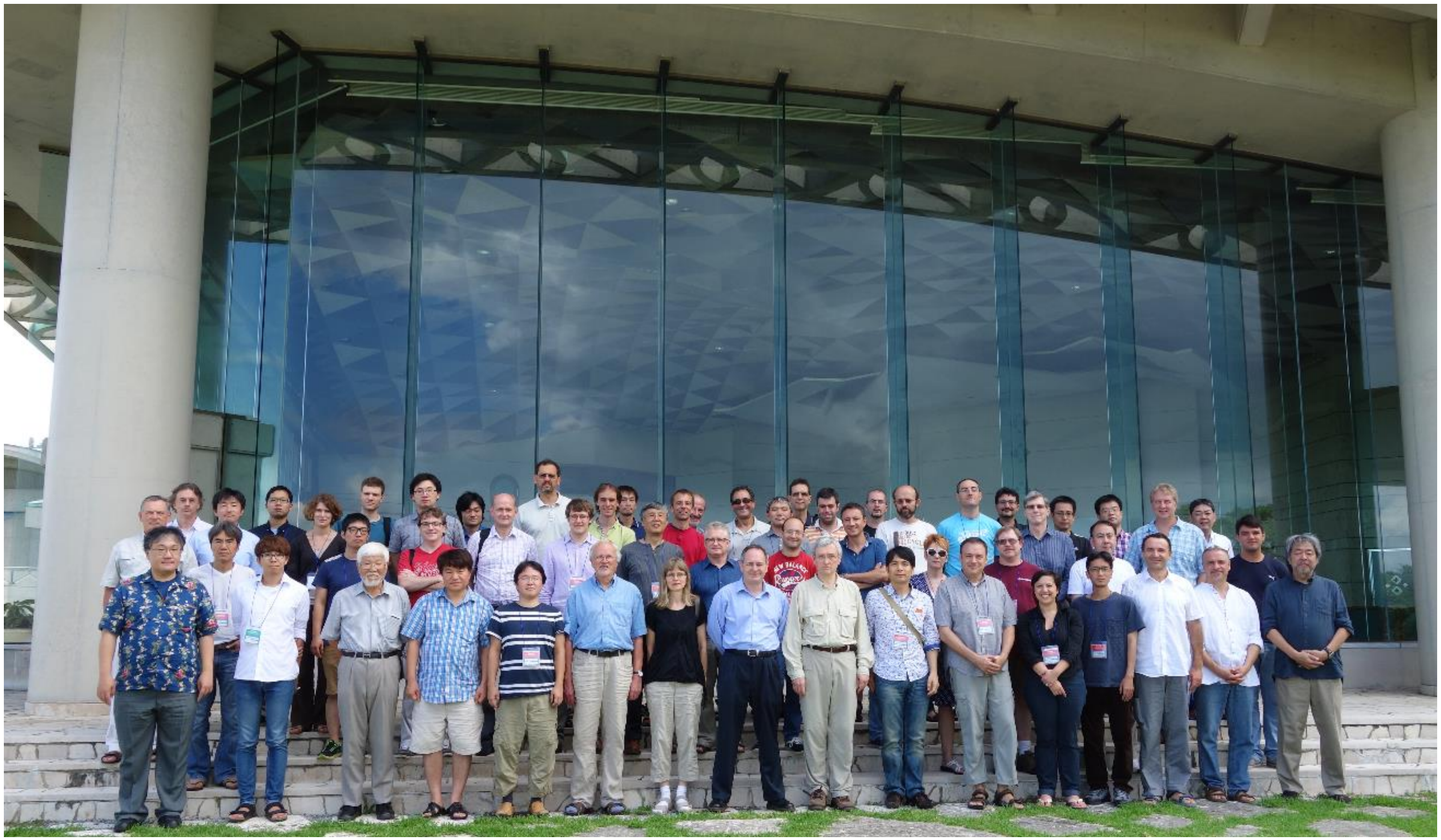
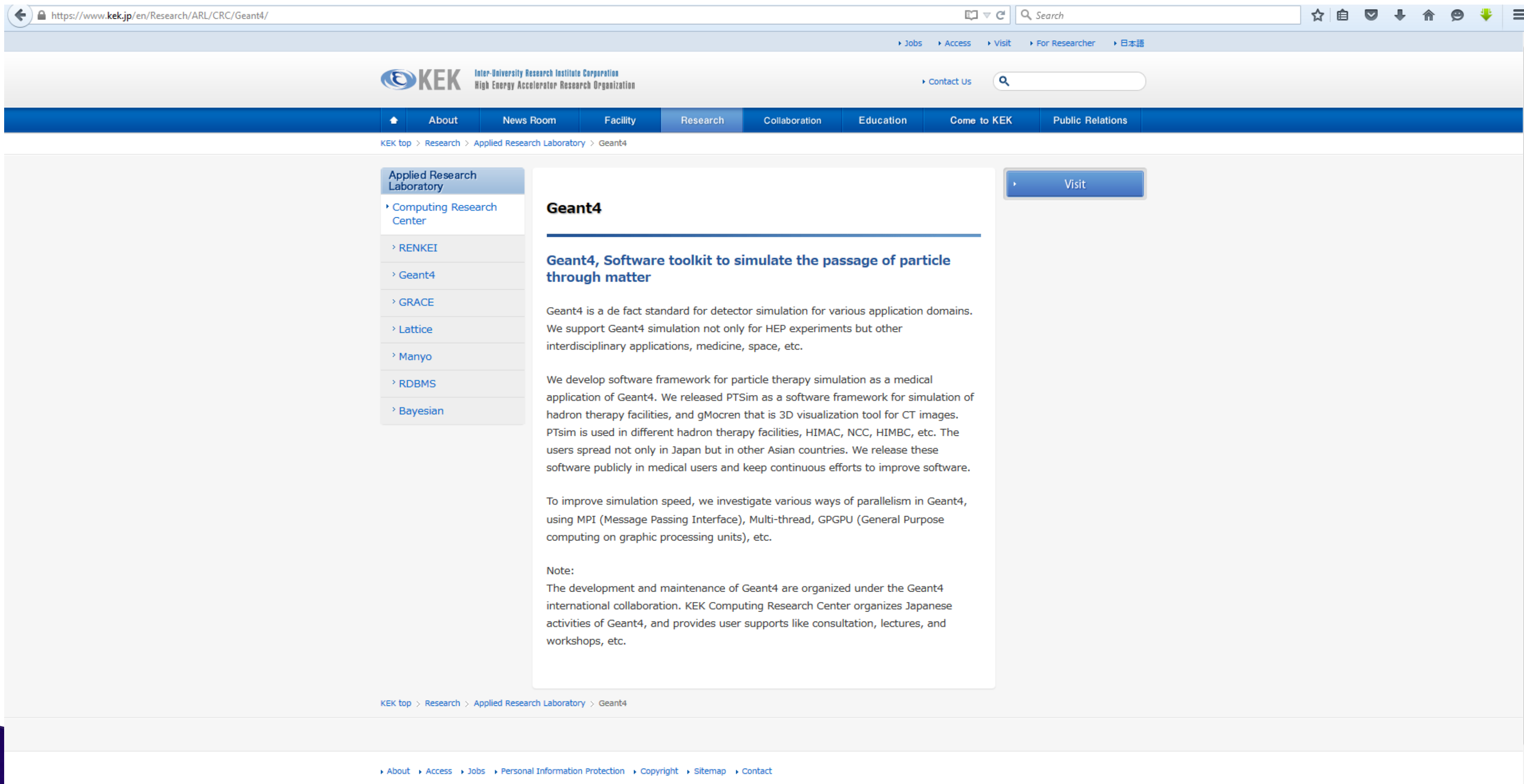
Geant4 Collaboration
>100 scientists worldwide



Geant4 20th Anniversary Symposium & 19th Collaboration Meeting, September 29th – October 4th, 2014 Okinawa, Japan

KEK Geant4 Collaborators

- Katsuya Amako, Koichi Murakami, Takashi Sasaki



My story in the G4Collaboration

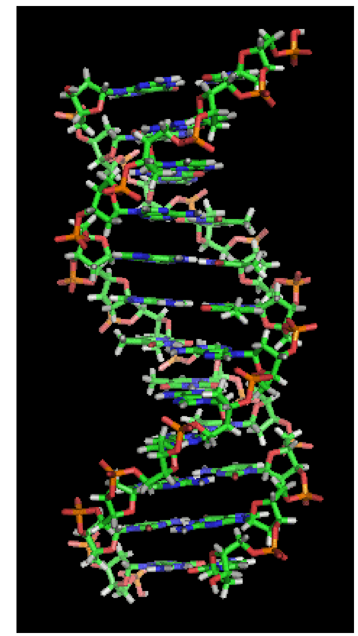
- CMRP is a Member of the Geant4 Collaboration since 2002
- Validation of physics models
- Development of Geant4 advanced examples
  - Brachytherapy
  - Radioprotection
  - Human phantom
- Member of the Geant4 Low Energy Group, Geant4-DNA and Geant4 Advanced examples group
- Geant4 user support
- Organiser of Geant4 schools

2nd Geant4 School and Monte Carlo Workshop, CMRP, UOW, April 2013

Geant4: One tool for multiple approaches

Dosimetry (macroscopic scale)
Absorbed dose
Linear energy transfer (LET)/Stopping power

Microdosimetry (cellular scale)
Specific energy distributions
Lineal energy distributions



Nanodosimetry (DNA scale)

Spatial distribution of interactions on a nanometre scale to estimate biological effectiveness

» Physics capability

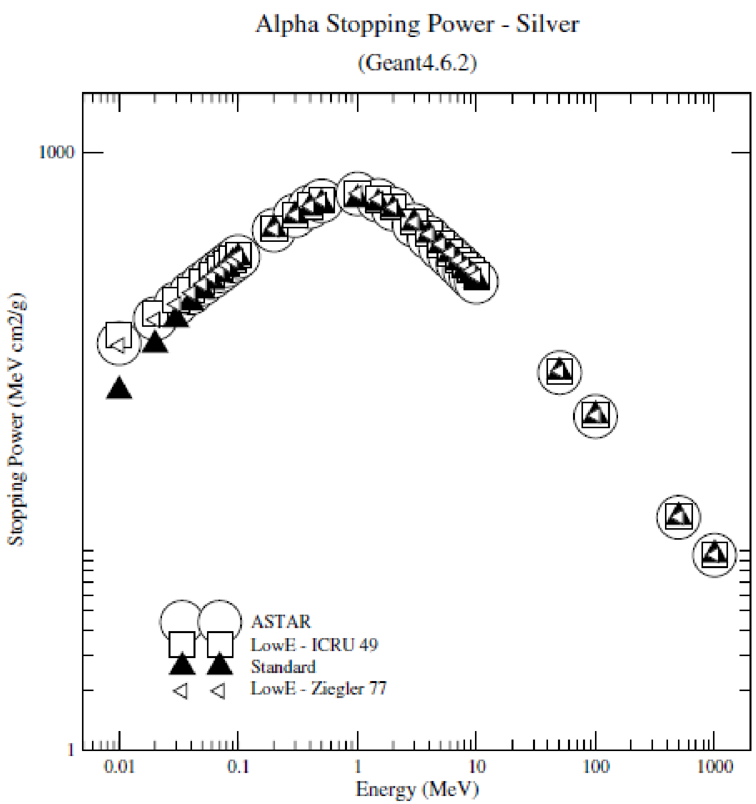
Slides adapted from
Marc Marc Verderi, LLR – Ecole Polytechnique, France
Sebastien Incerti, CENBG, Bordeaux, France

Physics processes provided by Geant4: an overview

- **EM physics**
  - "standard" processes valid from ~ 1 keV to ~PeV
  - "low energy" valid from 250 eV to ~PeV
  - Down to eV for Geant4-DNA in liquid water
  - optical photons
- **Weak interaction physics**
  - decay of subatomic particles
  - radioactive decay of nuclei
- **Hadronic physics**
  - pure strong interaction physics valid from 0 to ~TeV
  - electro- and gamma-nuclear valid from 10 MeV to ~TeV
- **Parameterized or "fast simulation" physics**

Electromagnetic Processes

- **Standard** : Complete set of processes covering charged particles and gammas.
  - Energy range 1 keV – ~PeV
- **Low Energy** : More precise description at low energy for e^+, e^-, γ, charged hadrons incident particle.
  - More atomic shell structure detail
  - Some processes valid down to hundreds of eV
  - Down to eV scale for Geant4-DNA
  - Two alternative flavours:
    - Based on Livermore Evaluated data Libraries
    - Penenope MC code models
- Atomic de-excitation
  - Fluorescence and Auger electrons



α stopping power in silver as a function of the α incident energy.

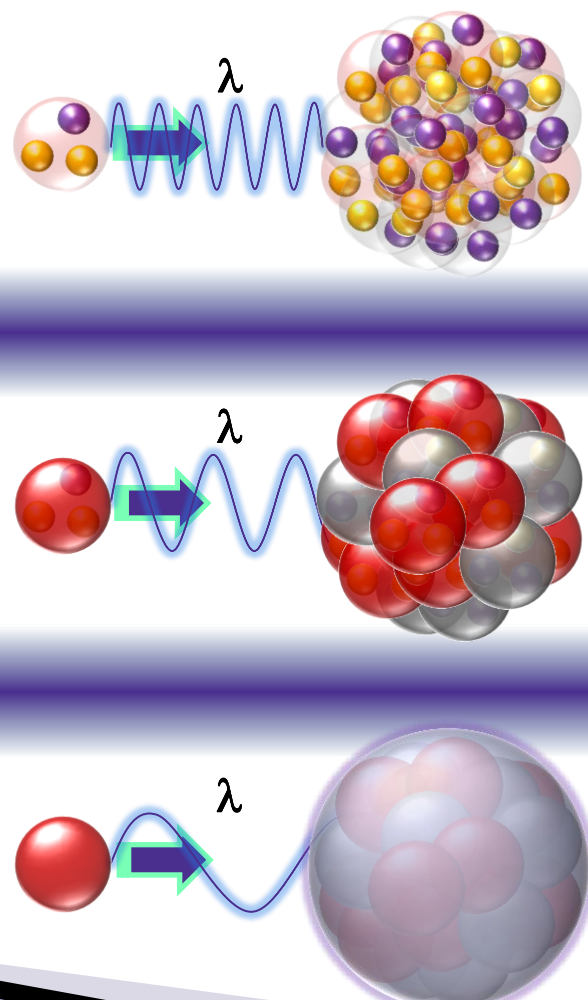
K. Amako, S. Guatelli, et al, "Validation of Geant4 electromagnetic physics versus the NIST databases", IEEE Trans. on Nucl. Sci., vol. 52 (4), 2005, pp. 910-918.

Variety of Hadronic Physics Models

High Energy
Quark/gluon dominating behavior

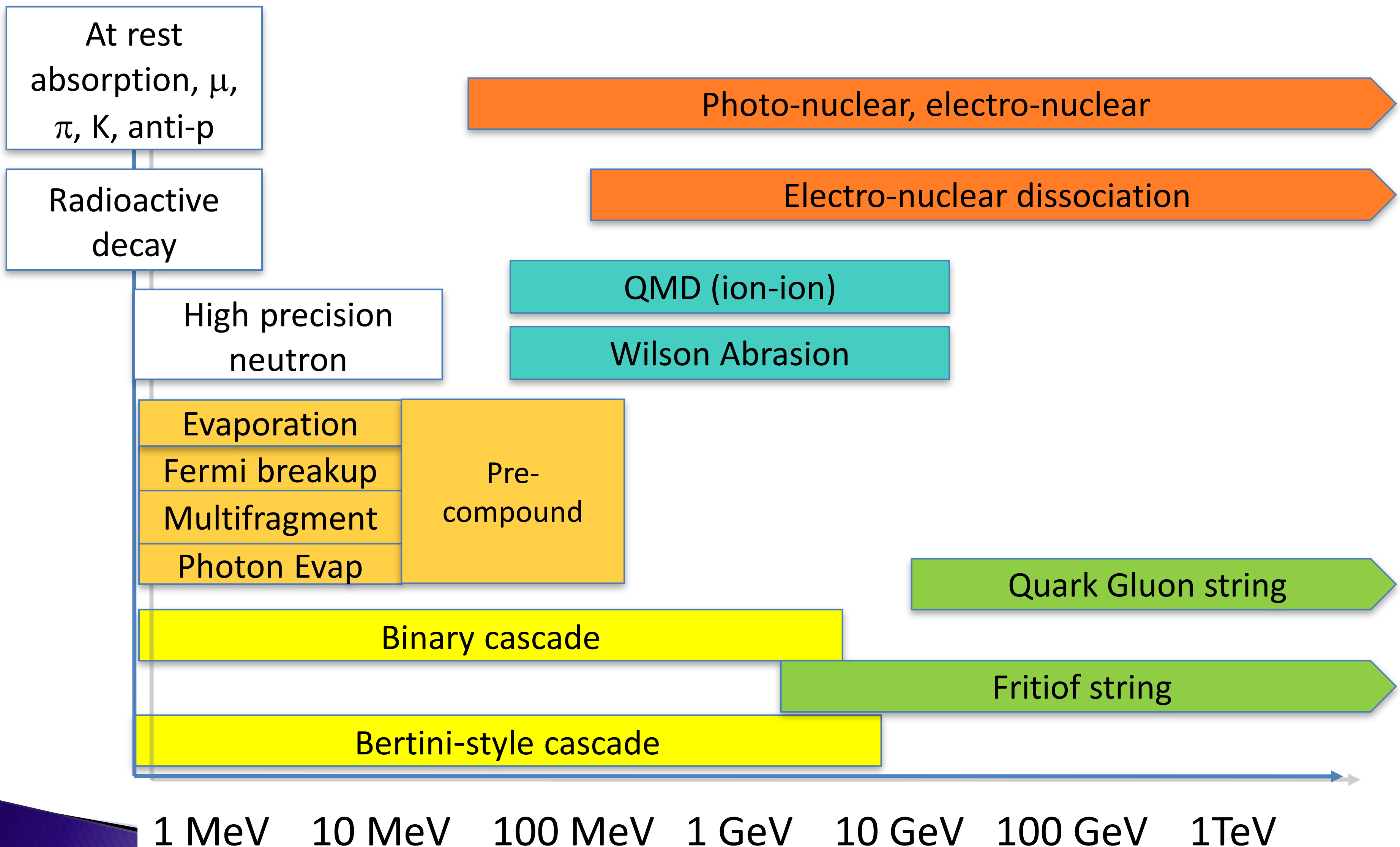
Intermediate Energy
Nucleon dominating behavior

Low Energy
Nucleus dominating behavior



Main Models	Energy
String Models: Quark Gluon String, Fritiof	E > 20 GeV
Intra-Nuclear Cascade Models: Binary, Bertini	170 MeV – 20 GeV
Precompound Fission / evaporation Capture at rest Radioactive decay	E < 170 MeV

Partial Hadronic Model Inventory

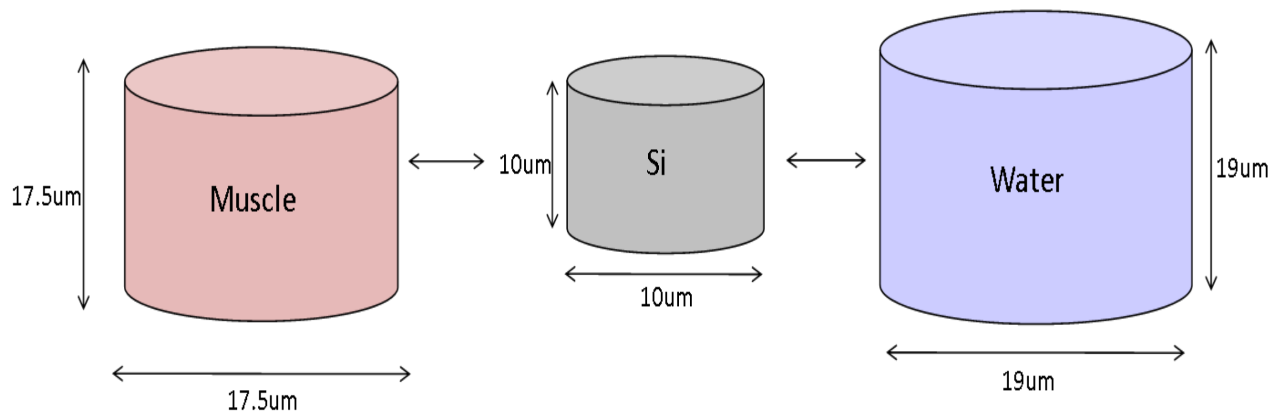


Geant4 Simulation study

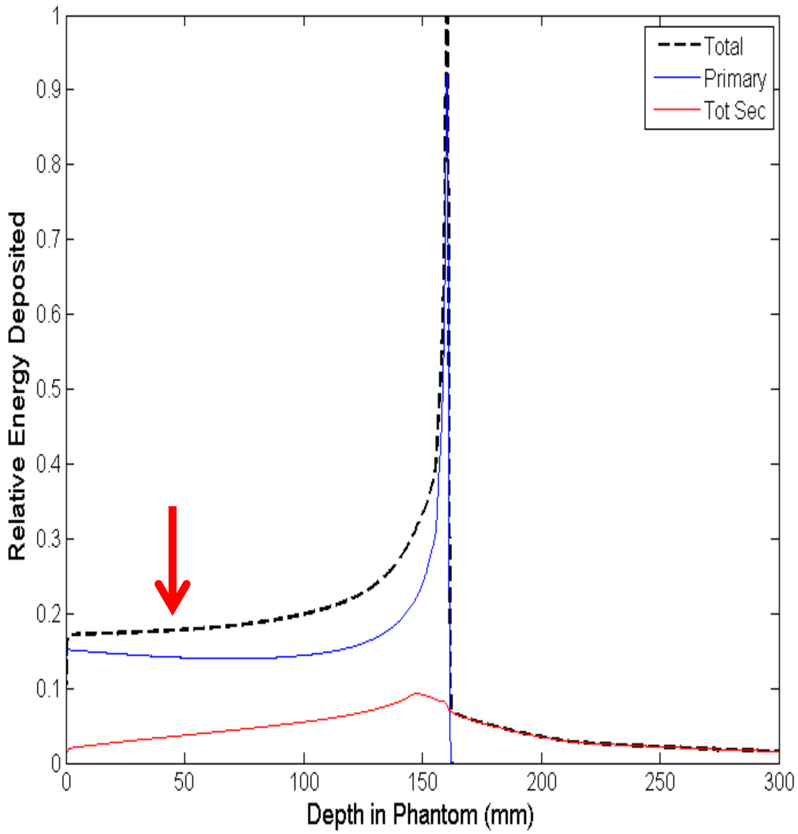
- Measure energy deposition in Si cylinder modelling microdosimeter in 290 MeV/u ^{12}C radiation field

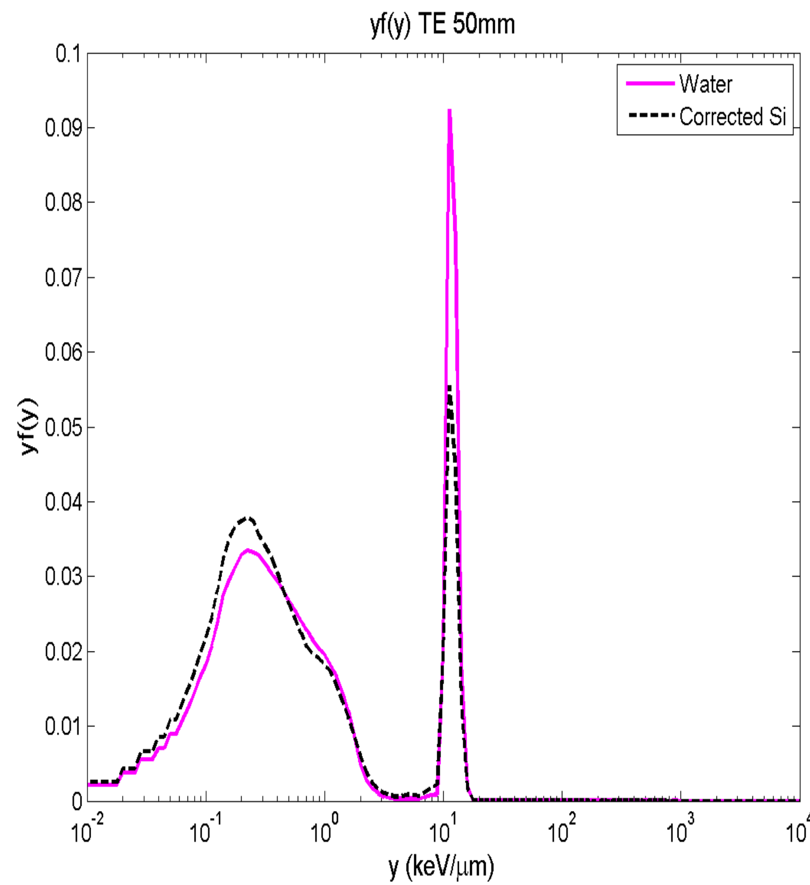
- Find size of water cylinder that matches the energy deposition in Si
  - Described in (S. Guatelli et al *IEEE Trans on Nuc. Sci*, **55**, 3407-3413 (2008); P.Bradley *at al* Med.Phys.)

  - **Correction factor =0.53**

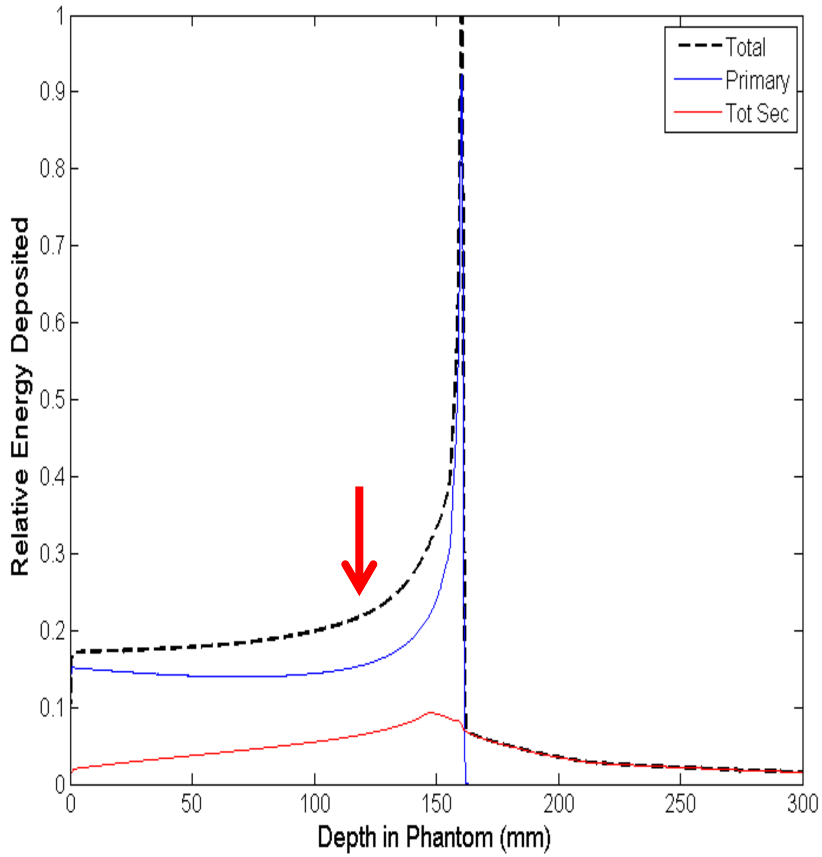


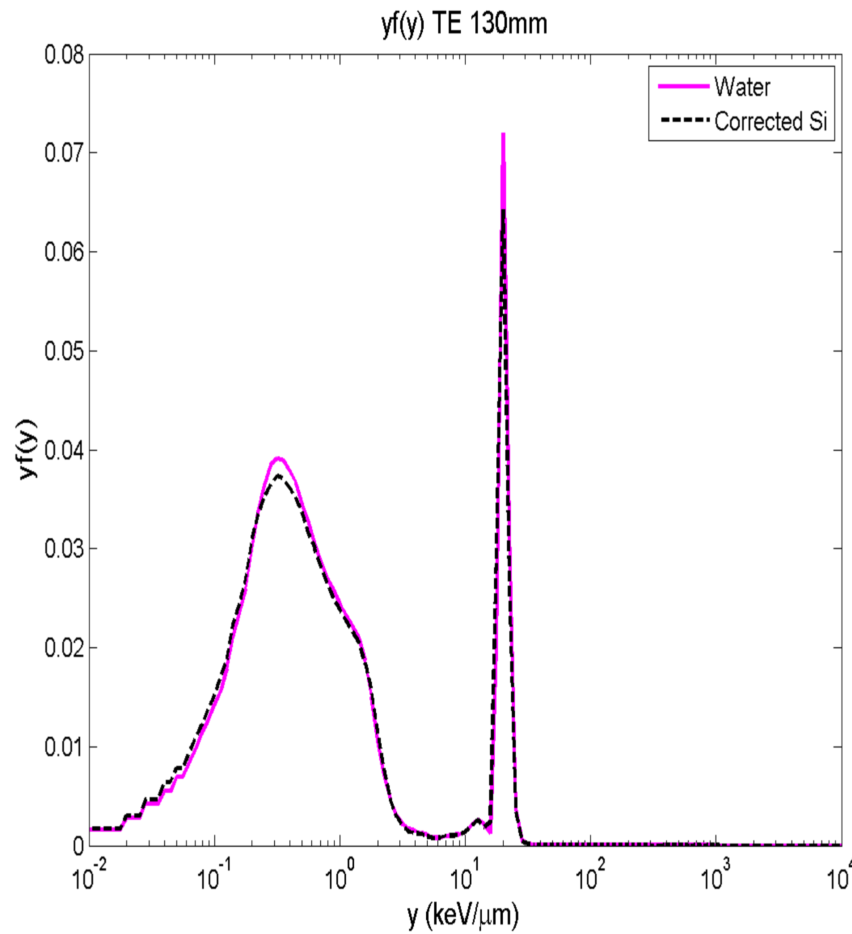
Silicon-tissue equivalence





Silicon–tissue equivalence





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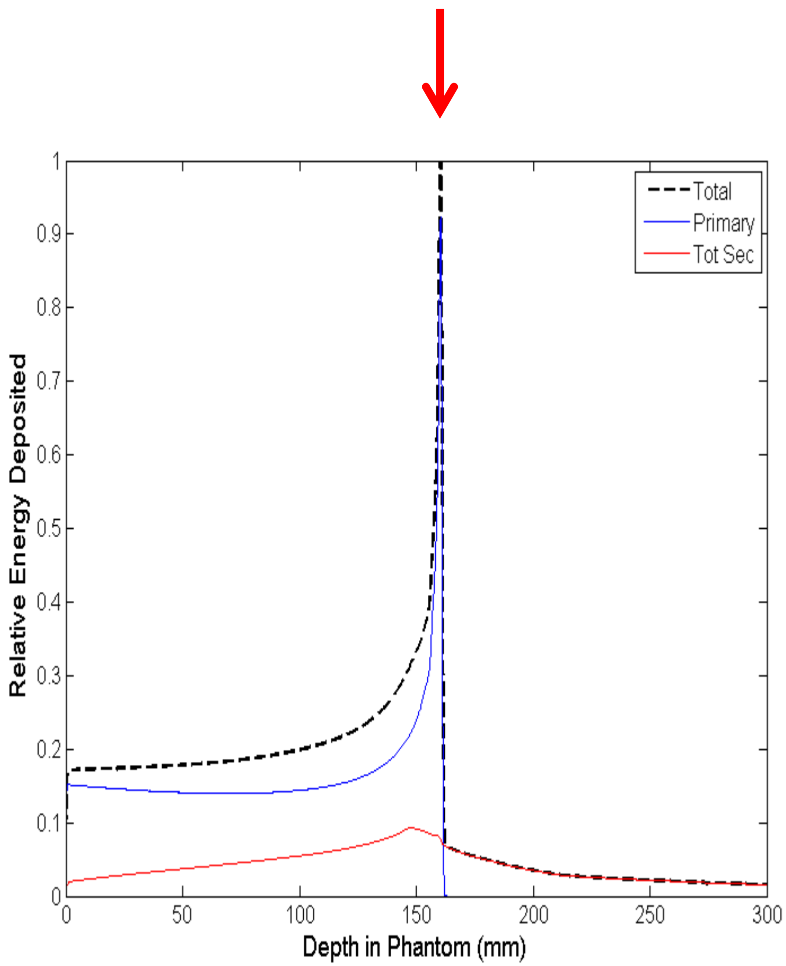
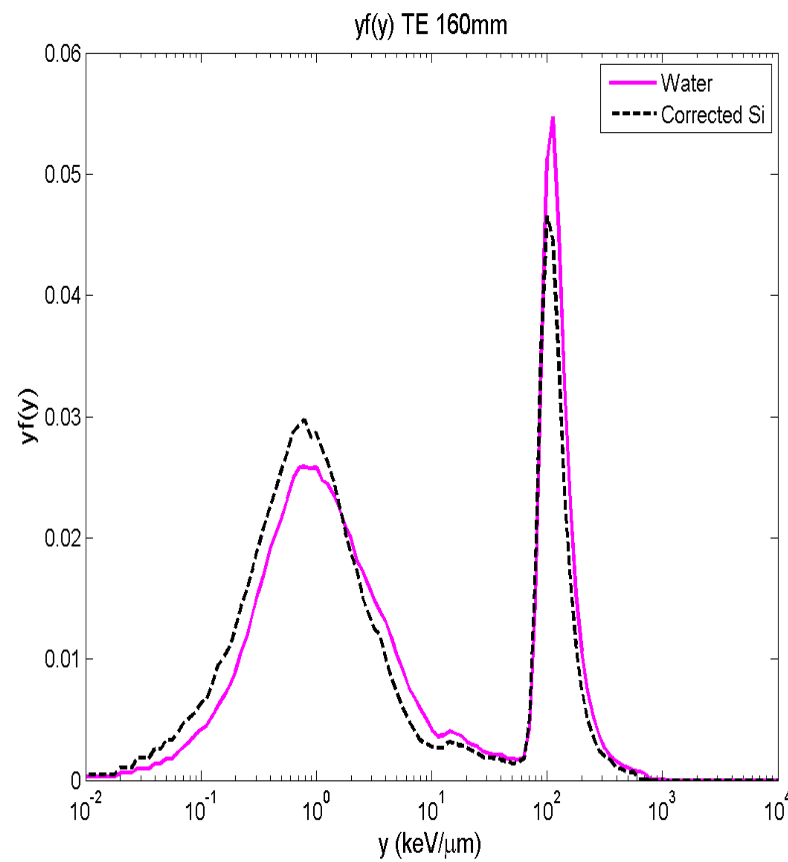
Silicon-tissue equivalence





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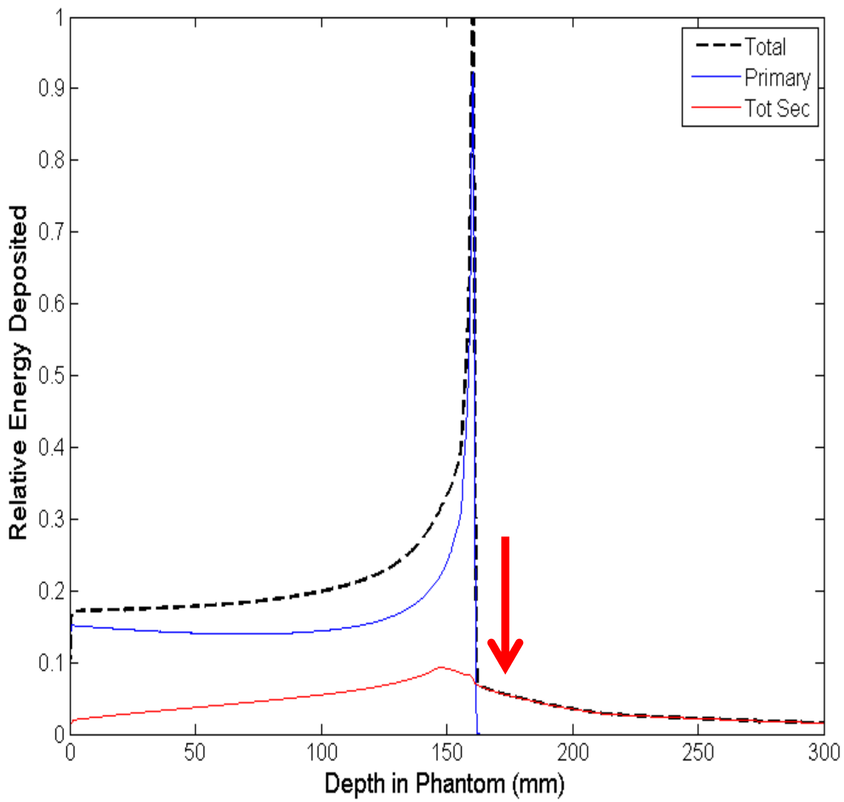

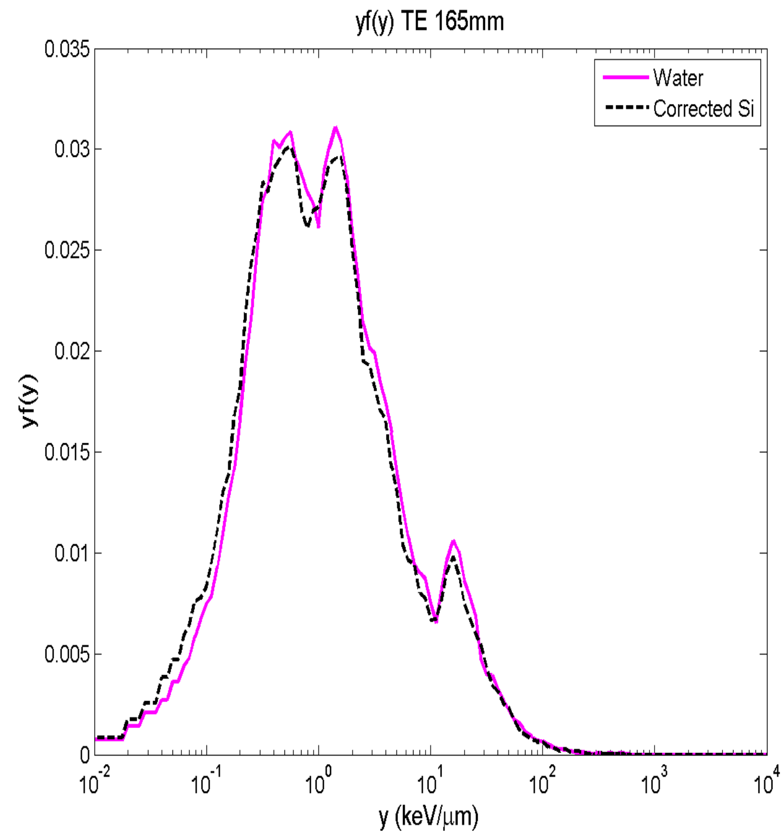

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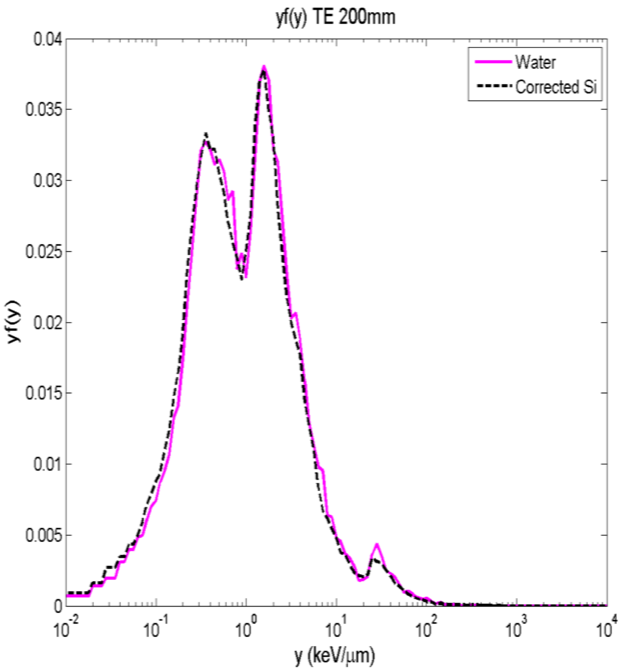
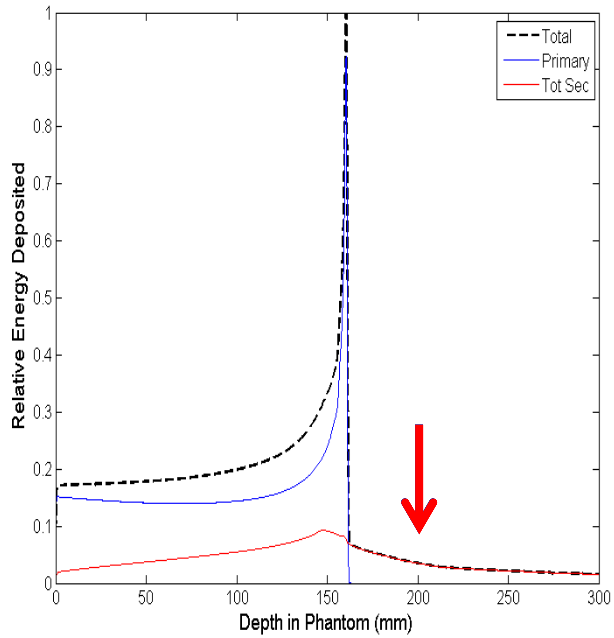
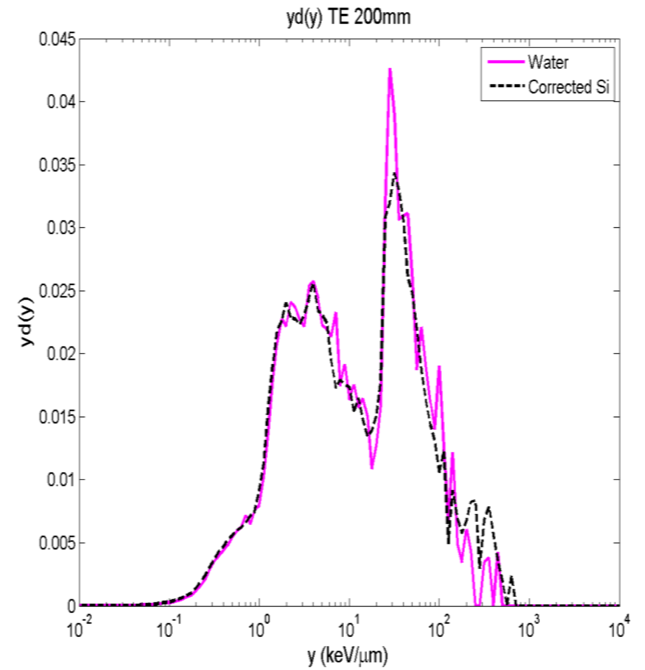
Silicon–tissue equivalence

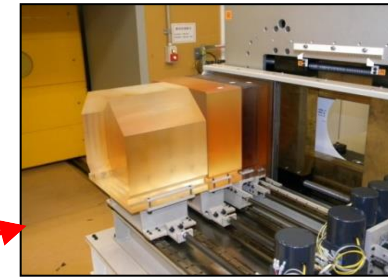


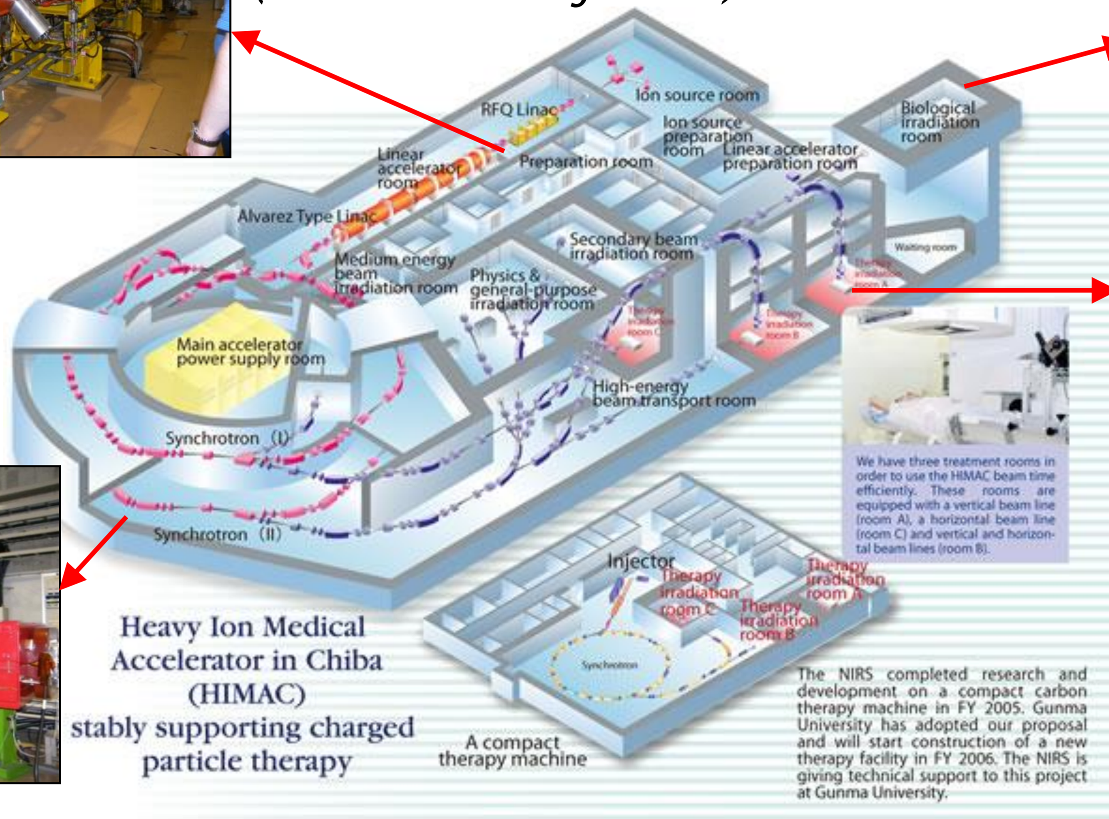




HIMAC Heavy Ion Therapy facility

CMRP collaboration with NIRS, Japan (Prof. Matsufuji et al)





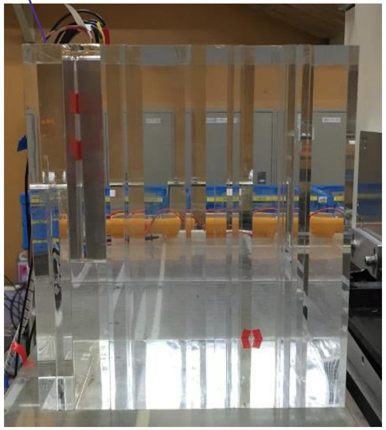
http://www.nirs.go.jp/ENG/research/charged_particle/index.shtml

290MeV/u ^{12}C SOBP Irradiation
Experiment in PMMA phantom

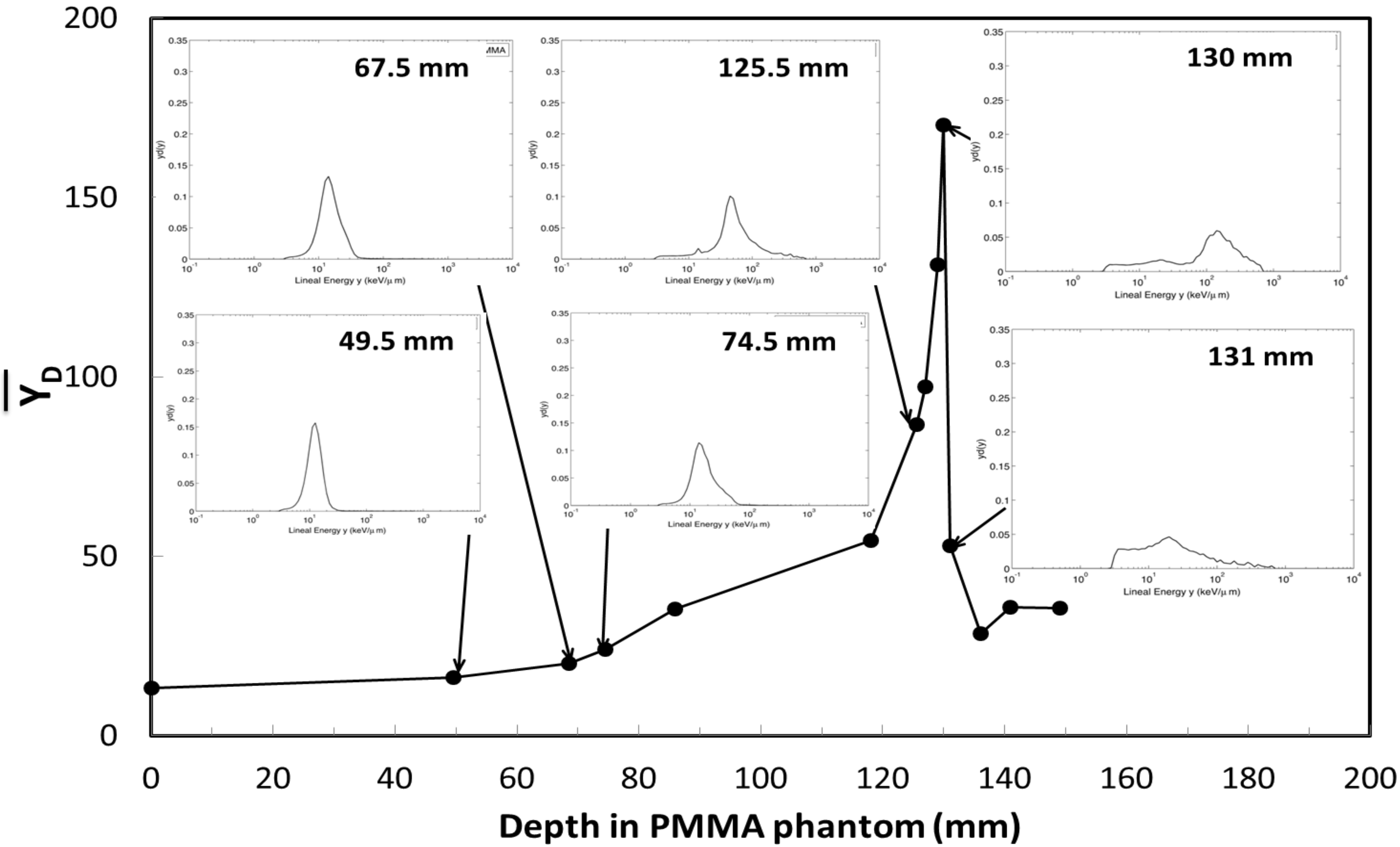
3D Mesa bridge MD connected to preamplifier and electronics

- Purpose: observe detector response with therapeutic ^{12}C beam, determine RBE in PMMA, and measure biological dose distribution.

- Passive beam delivery: lead scatterer, ridge filter and collimators produce a 10x10 cm^2 field, 6cm SOBP, 290MeV/u



HIMAC: Microdosimetric spectra



Dose-mean lineal energy deposition and microdosimetric spectra obtained along the SOBP

RBE_{10}: 3D mesa bridge microdosimeter vs TEPC

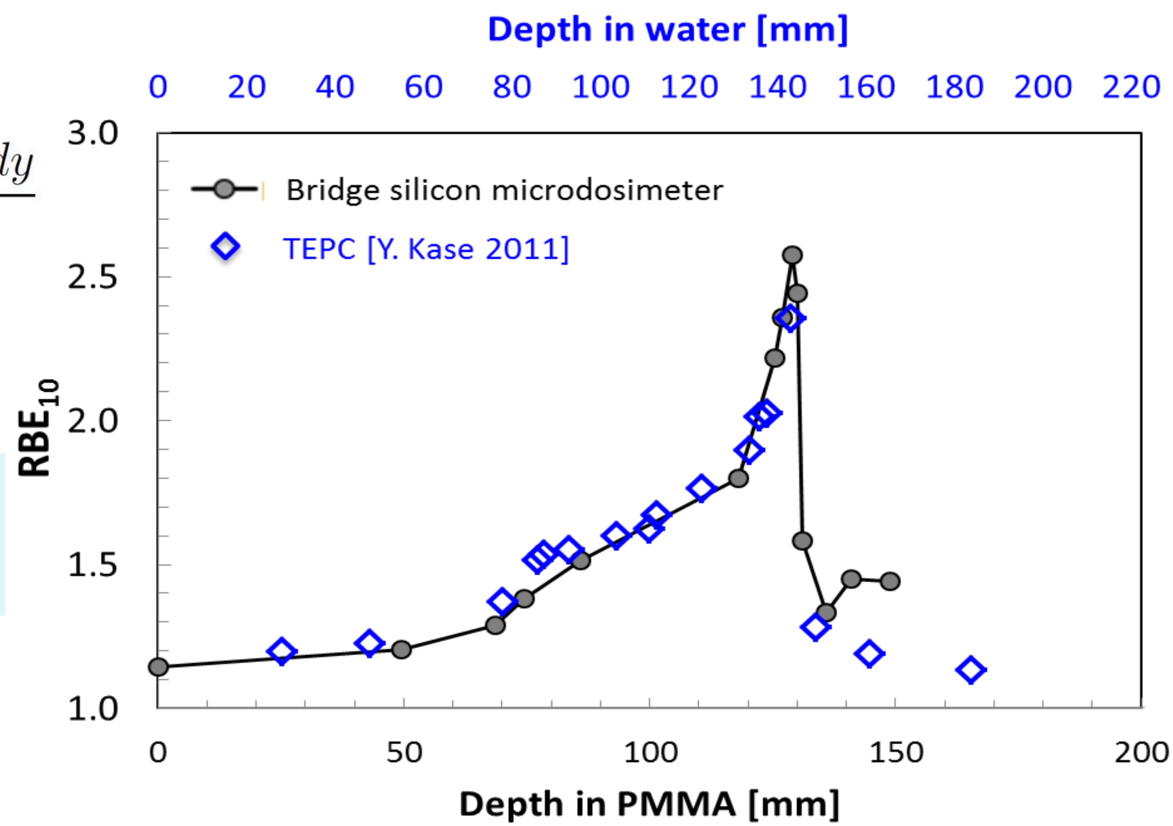
y_0=150keV/um

$$y^* = y_0^2 \frac{\int (1 - \exp(-y^2/y_0^2)) f(y) dy}{\int y f(y) dy}$$

$$\alpha = \alpha_0 + \frac{\beta}{\rho \pi r_d^2} y^*$$

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

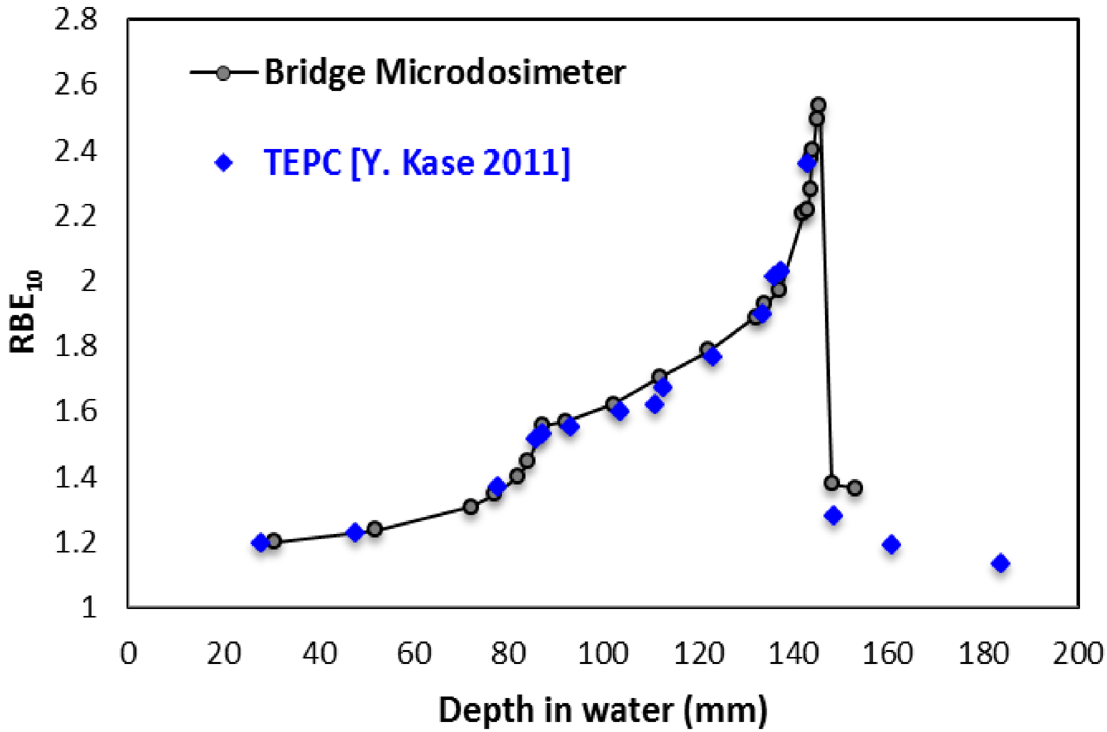
- α_o= 0.13 Gy^{-1}; β= 0.05 Gy^{-2} ; r_d = 0.42 µm is radius of sub cellular domain in MK model
- Where $D_{10,R}$ = 5Gy is 10% survival of 200 kVp X rays for HSG cells

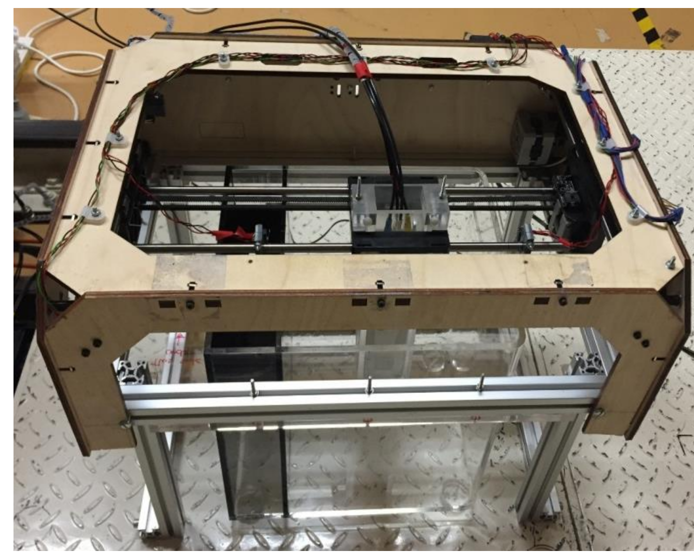


290MeV/u ^{12}C SOBP Irradiation
Experiment in Movable Water phantom

Low noise electronics probe "MIcro*Plus*" and microdosimeter in water-proof sheath

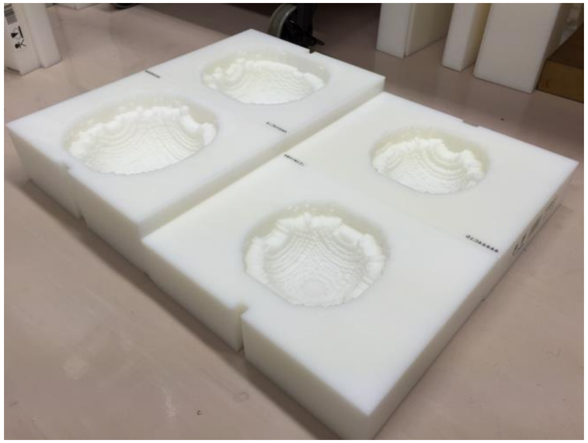
- A new system was developed whereby a microdosimeter can be moved sub-mm increment depths and undergo motion similar to that of organs.





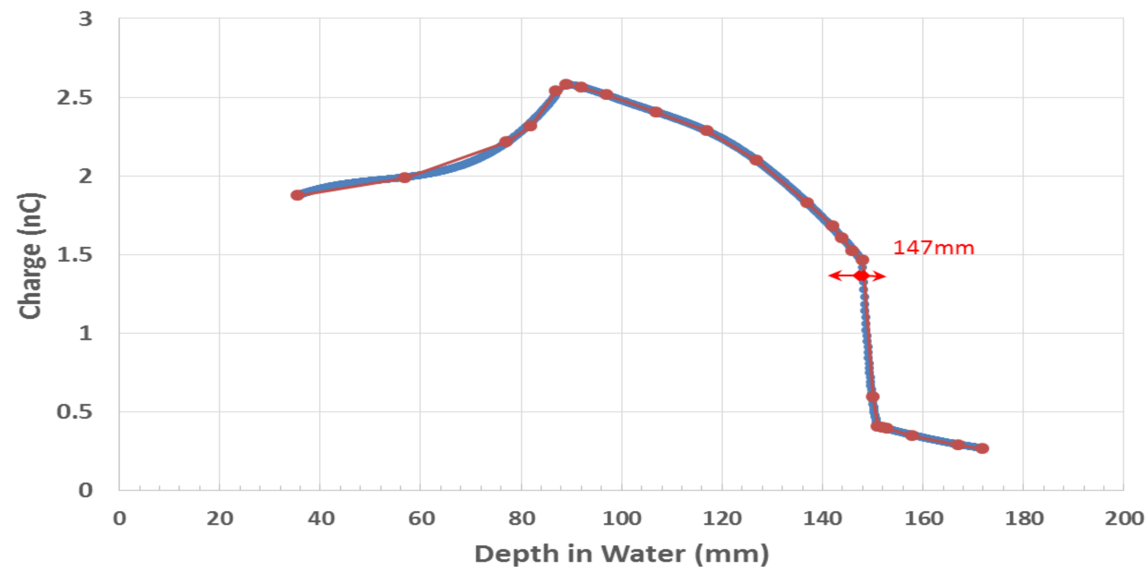
XY-stage with water tank and Micro*Plus* probe

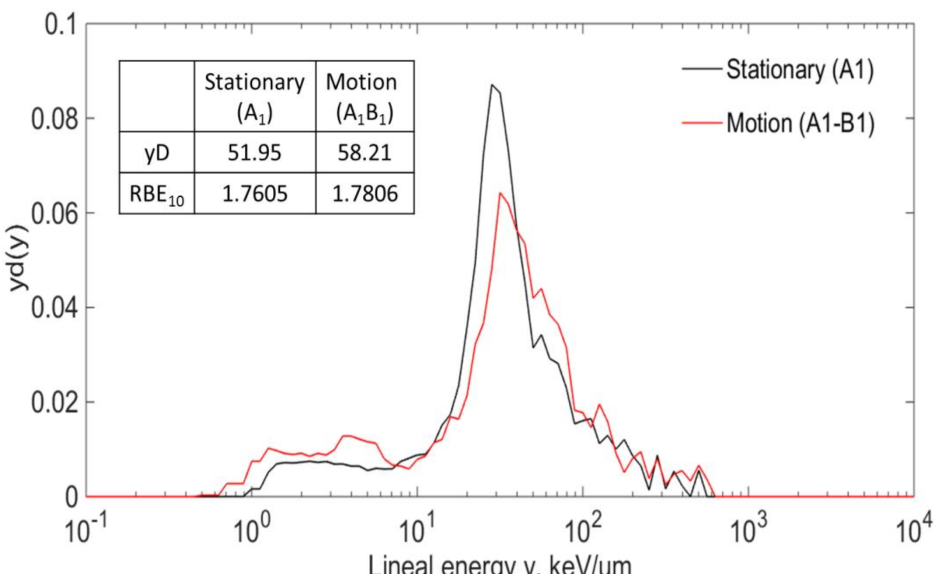
Experiment with bolus in HIMAC



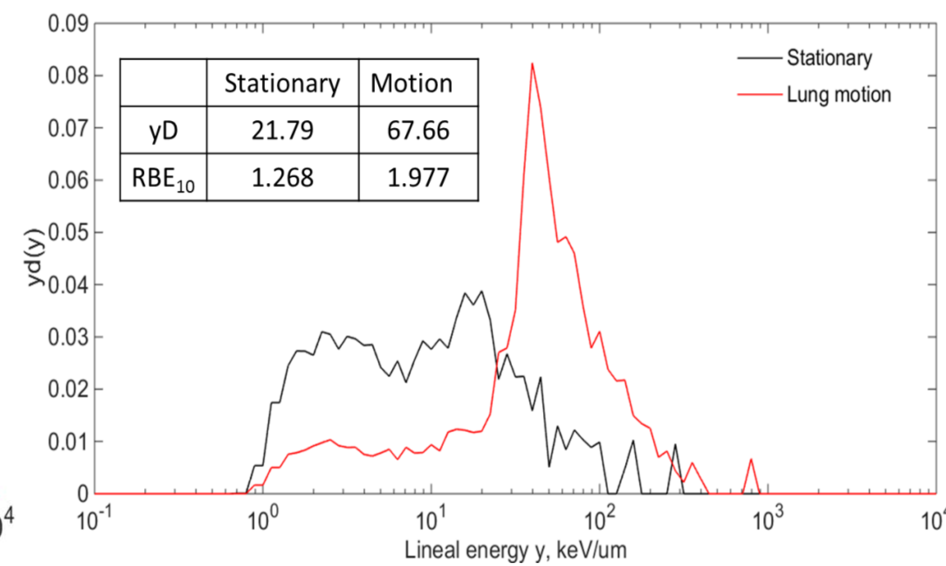
Spherical bolus made from PE

^{12}C →





	Stationary (A_1)	Motion (A_1B_1)
yD	51.95	58.21
RBE_{10}	1.7605	1.7806



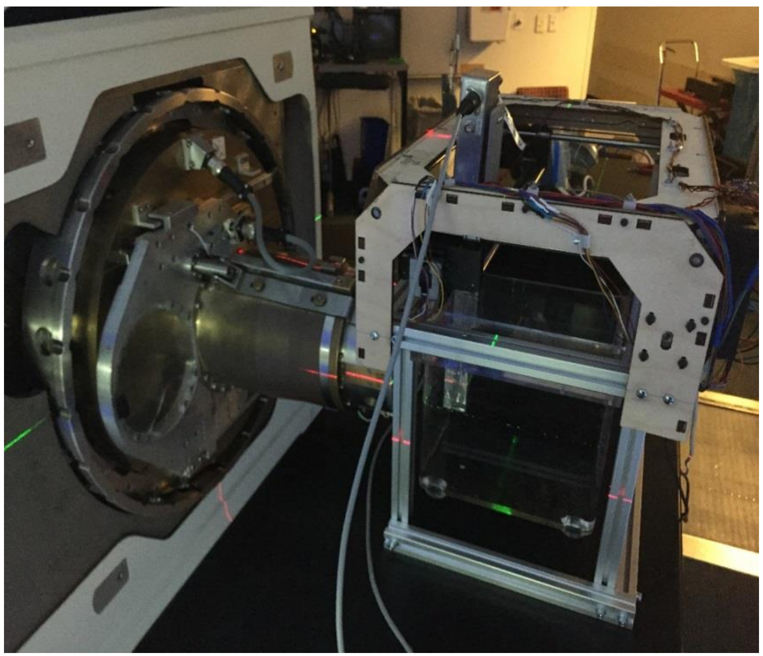
	Stationary	Motion
yD	21.79	67.66
RBE_{10}	1.268	1.977

CENTRE FOR MEDICAL RADIATION PHYSICS

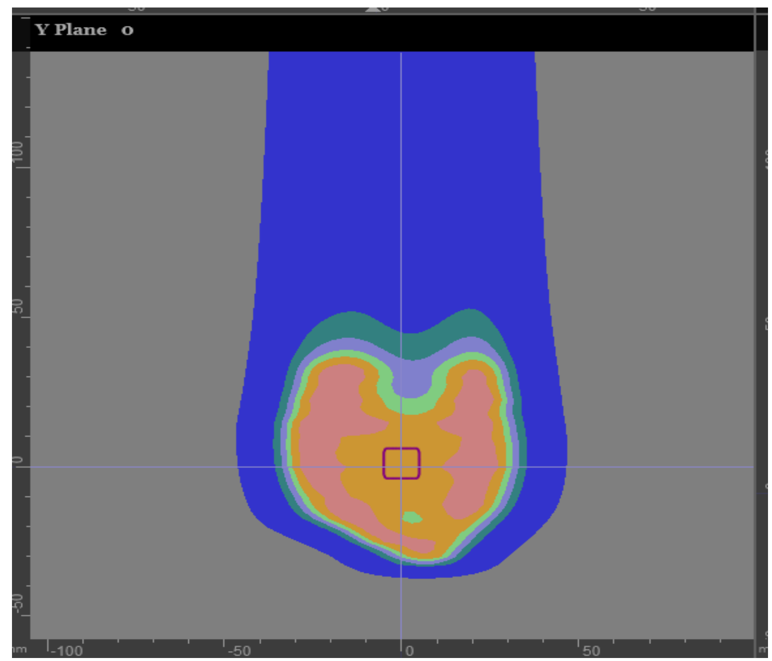
UNIVERSITY OF WOLLONGONG

Scanning Beam Proton Irradiation, Massachusetts General Hospital (MGH), Boston, USA *(July 2015)*

- Aim: Observe response to a clinical scanning proton beam, to measure $\overline{y_D}$ depth distribution, investigate effect of motion on microdosimetric spectra
- Fields: 130MeV pencil beam ($\sigma = 11$mm) and clinical patient plan (spinal)



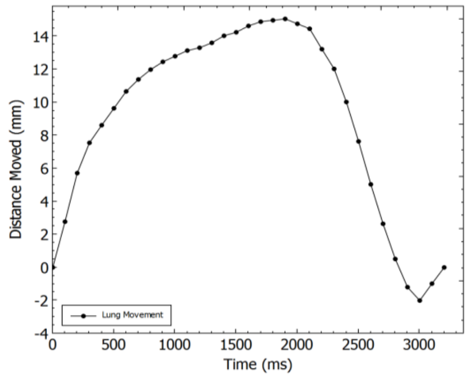
Left: Moveable water phantom with Bridge Microdosimeter in front of PBS nozzle.

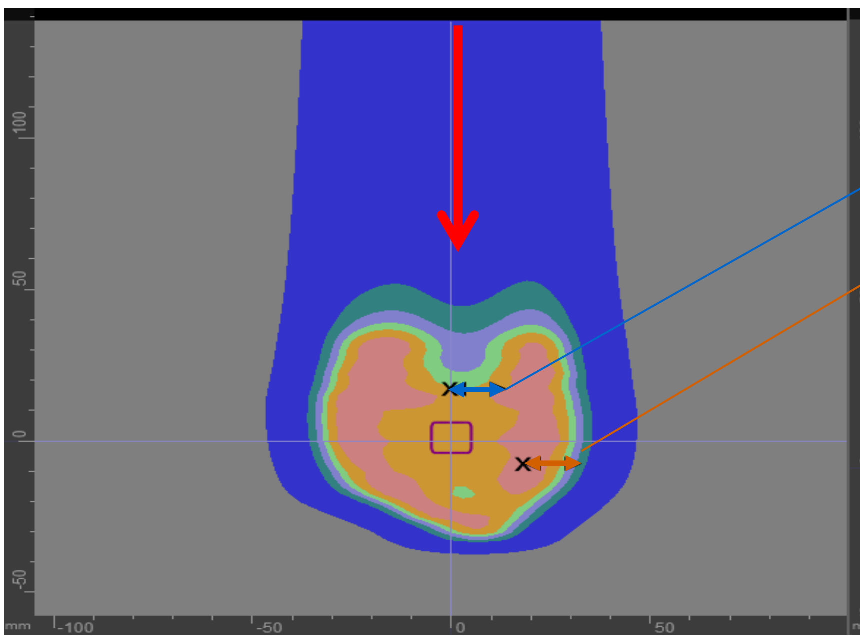


Right: Patient plan shown in Asteroid TPS

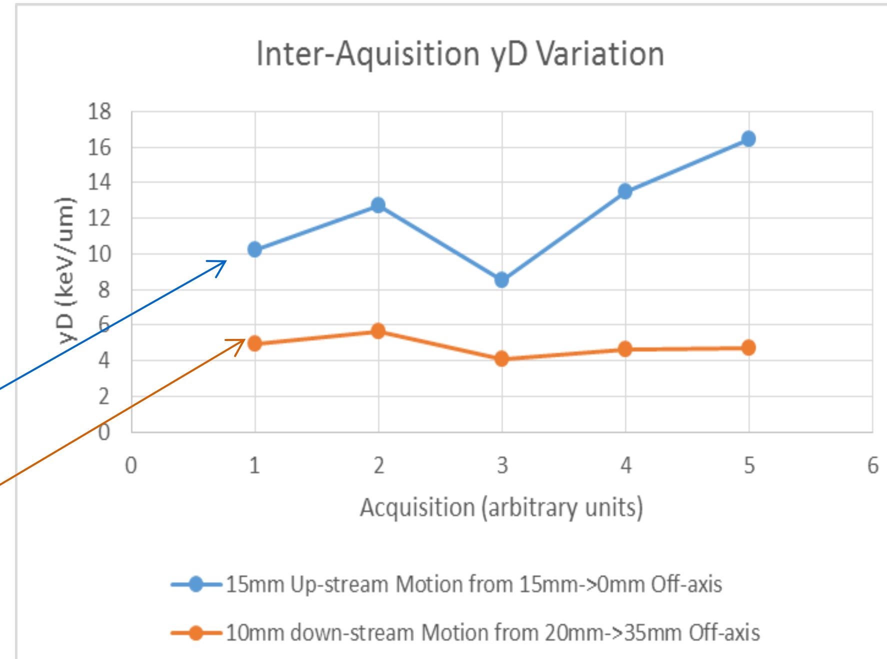
Patient Plan with Motion – Preliminary Results

Temporal lung motion pattern used to move detector during irradiation





Treatment plan showing movement (arrow) and stationary (x) locations



y_D when moving and stationary, 10mm Down Stream and 15mm Up Stream from isocentre

Conclusions (1)

- This work presented the first high spatial resolution RBE_{10} derivation in ^{12}C ion therapeutic beam line
  - SOI microdosimeter
  - The RBE_{10} values are in good agreement with values obtained using a TEPC, with an exception at the distal part of the SOBP. This is due to TEPC measurements being carried out in water which lacks the C atoms that comprise PMMA.

- Significant difference observed between the stationary microdosimetric spectra at distal part of the SOBP and the case where the detector mimicked lung motion.
  - Microdosimetric spectra and dose mean lineal energy obtained out-of-field in proton beam scanning allow the determination of neutron dose equivalent and the comparison with passive treatment delivery.

Conclusions (2)

- The Centre for Medical Radiation Physics has developed a new microdosimeter probe, with measurement threshold as low as ~ 0.3 keV/μm.
- The motion can lead to changes in the microdosimetric spectrum and consequently the RBE.
- The microdosimeter has the ability of measuring neutrons dose outside of the treatment field.
- Silicon microdosimeters can be used for BNCT

Our collaborators

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- **Mayo Clinic, USA**

Dr. Chris Beltran

Australian Government

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