Microdosimetry in hadron therapy as a bridge between physics and biology

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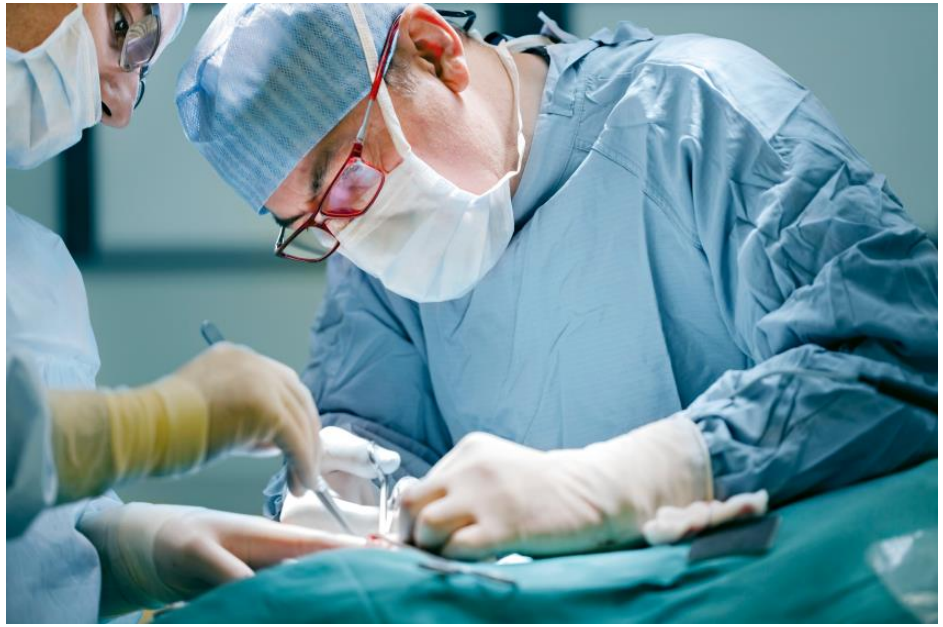
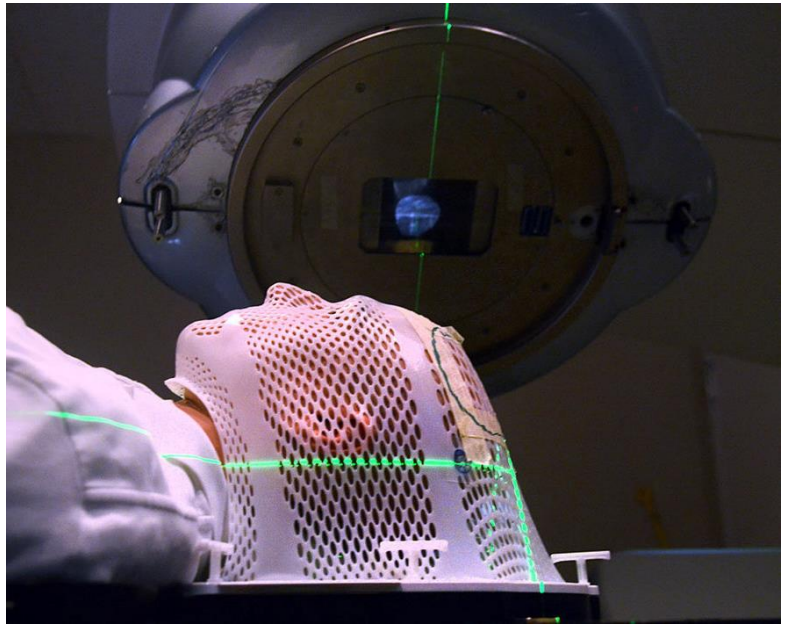
Cancer therapy



SURGERY

CHEMOTHERAPY



RADIOTHERAPY

The use of charged particle to treat cancer is increasing worldwide:
79 centers in operation, 45 in construction, 22 planned

Particle Therapy Co-Operative Group (PTCOG, https://www.ptcog.ch/)

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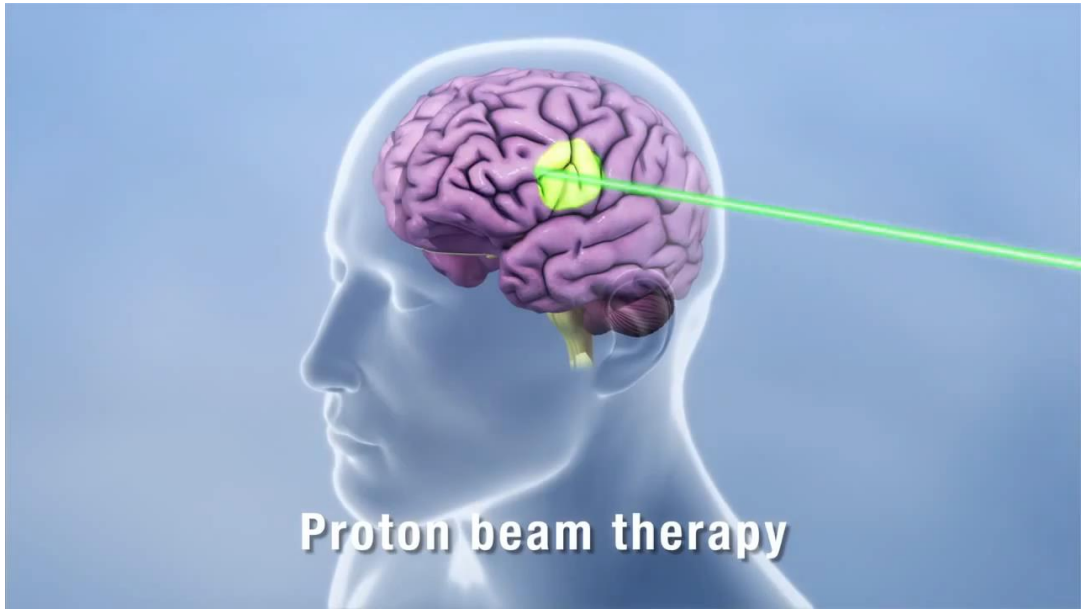
Hadron therapy has superior physical proprieties than conventional radiotherapy



- X-rays of conventional radiotherapy irradiate organs both in front of and behind the tumor
- on the other hand, charged particle energy deposition can be better controlled
- this allows a reduction of the doses to the surrounding organs → lower risk of secondary cancers

Mayo Clinic, United States of America (https://www.mayoclinic.org)

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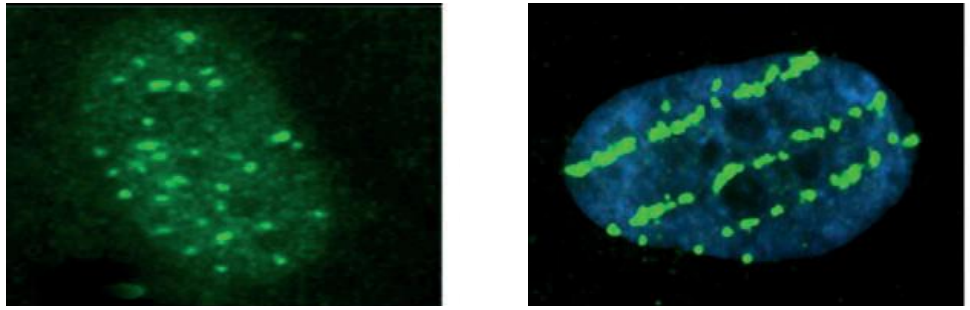
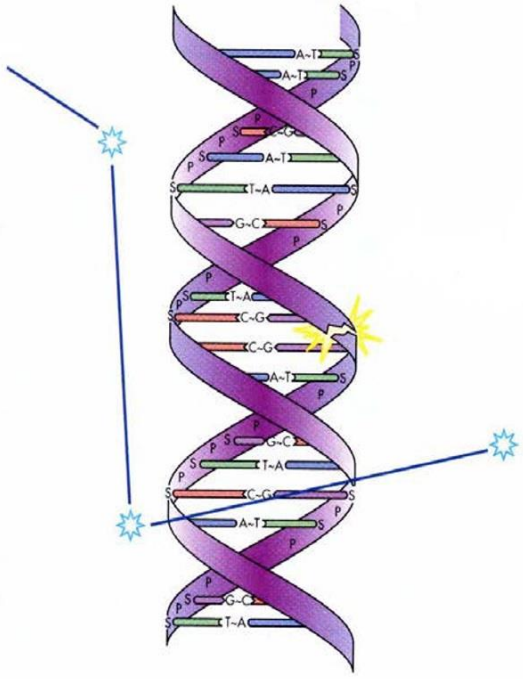
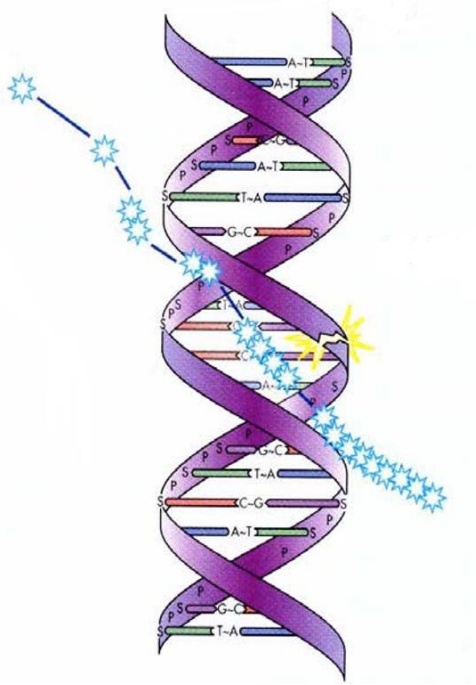
Charged particles are more effective in inducing lethal damages

cells exposed to photons (left) or charged particles (right)

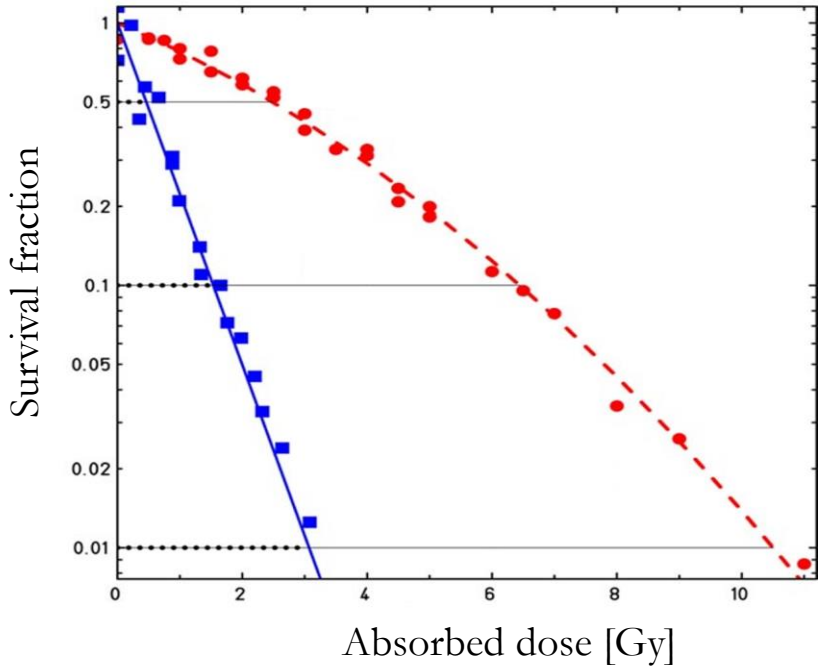






- the relative biological effectiveness (RBE) is a parameter indicating the effectiveness of a radiation in inducing a determined effect in comparison to a reference radiation

$$RBE = \frac{D_{reference\ radiation}}{D_{radiation\ under\ study}}$$



figures from Cucinotta and Durante, 2006, Weyrather and Kraft, 2004

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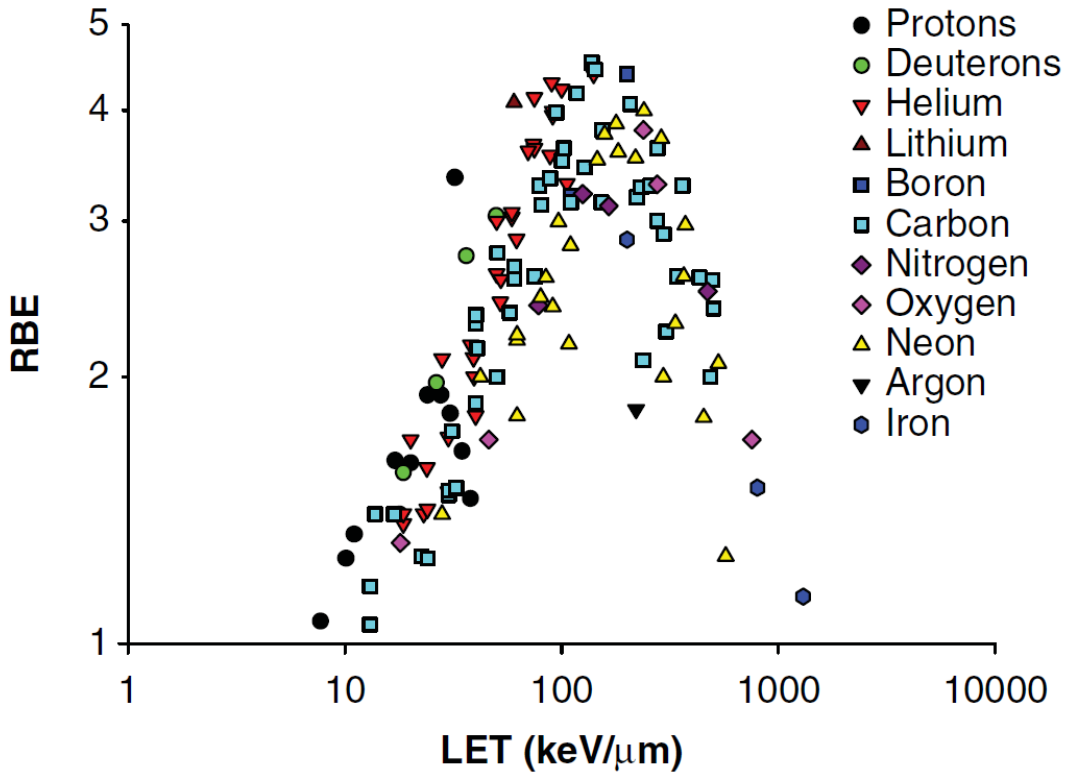
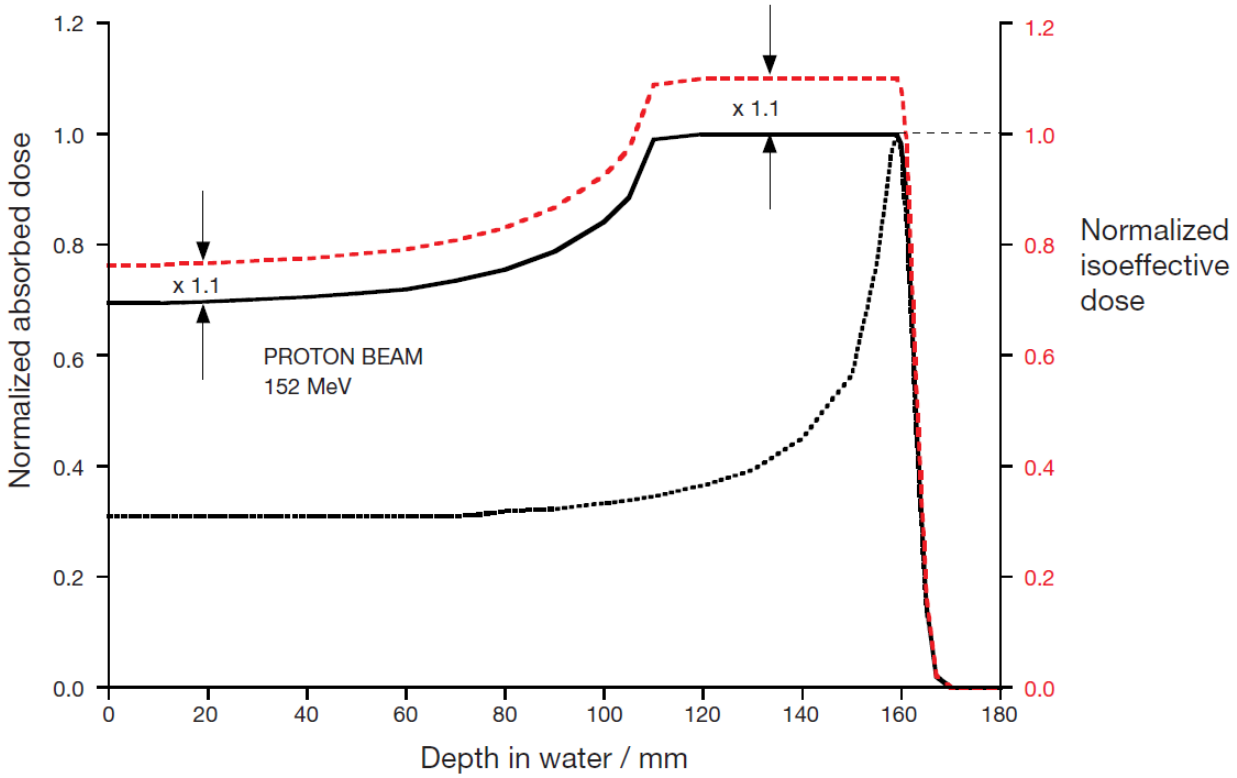
Charged particles are more effective in inducing lethal damages

- RBE is a complex function of particle type, its energy, cell line, biological endpoint…
- currently, in proton therapy a constant RBE value of 1.1 in respect to photons is used





figures from Sorensen et al., 2011 and IAEA, 2008

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Increased RBE at the distal part of treatment

- recent evidences have proven the inadequacy of using a constant factor, especially in the distal edge region
- this effect is due to the increased proton LET and the creation of high LET secondary fragments
- increased risks of secondary tumors

A novel method has been developed to assess **LET** and **RBE** in proton therapy beams using couples of **thermoluminescent detectors**

U87 → radioresistant human glioma
AG01522 → normal human skin fibroblasts

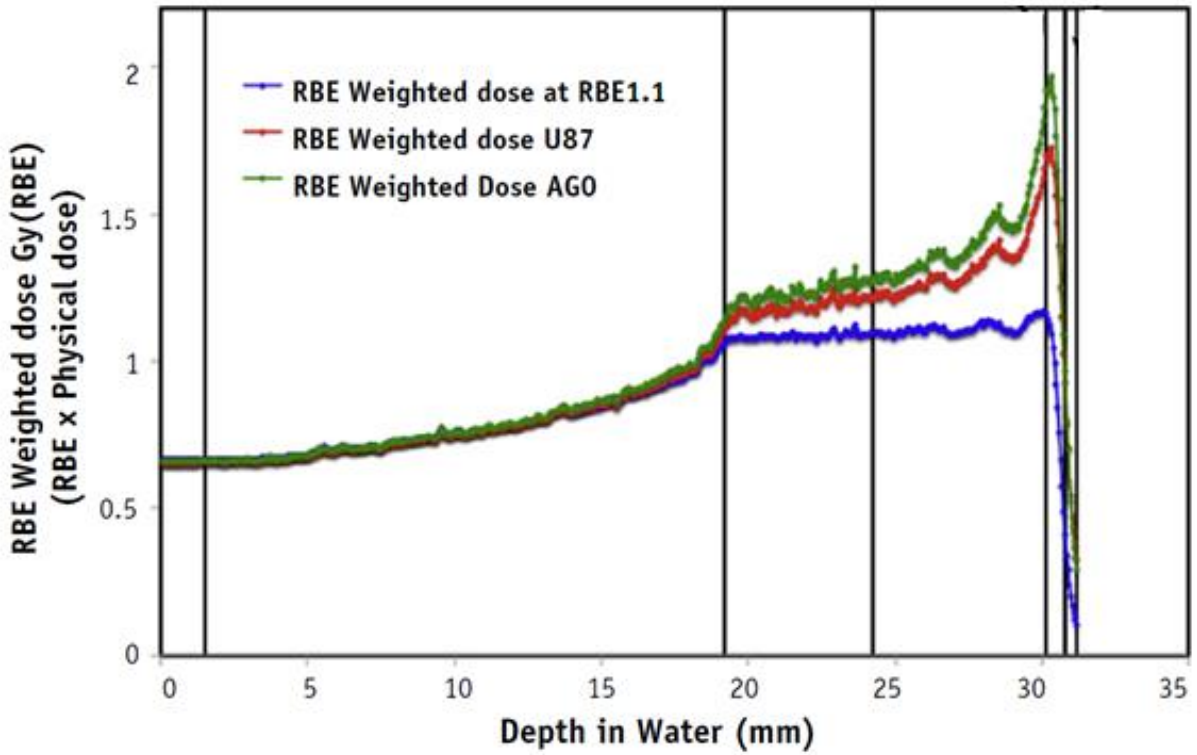

figure adapted from Chaudhary et al., 2014

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Methodology

- The response of two different types of detectors was predicted as function of the proton energy
  - LiF:Mg,Ti and LiF:Mg,Cu,P thermoluminescent detectors
  - Microdosimetric d(z) Model (Parisi, 2018) – key ideas and experimental validation

- The relative response of the two detectors was correlated with the proton RBE
  - Correlation between the expected response and the proton dose average LET_D
  - Database of experimentally determined RBE values as function of the LET_D (Paganetti, 2014)

- Validation of the methodology through a comparison with cell survival studies in a clinical SOBP
  - iThemba LABS (South Africa) proton therapy room
  - Chinese hamster ovary (CHO-K1)

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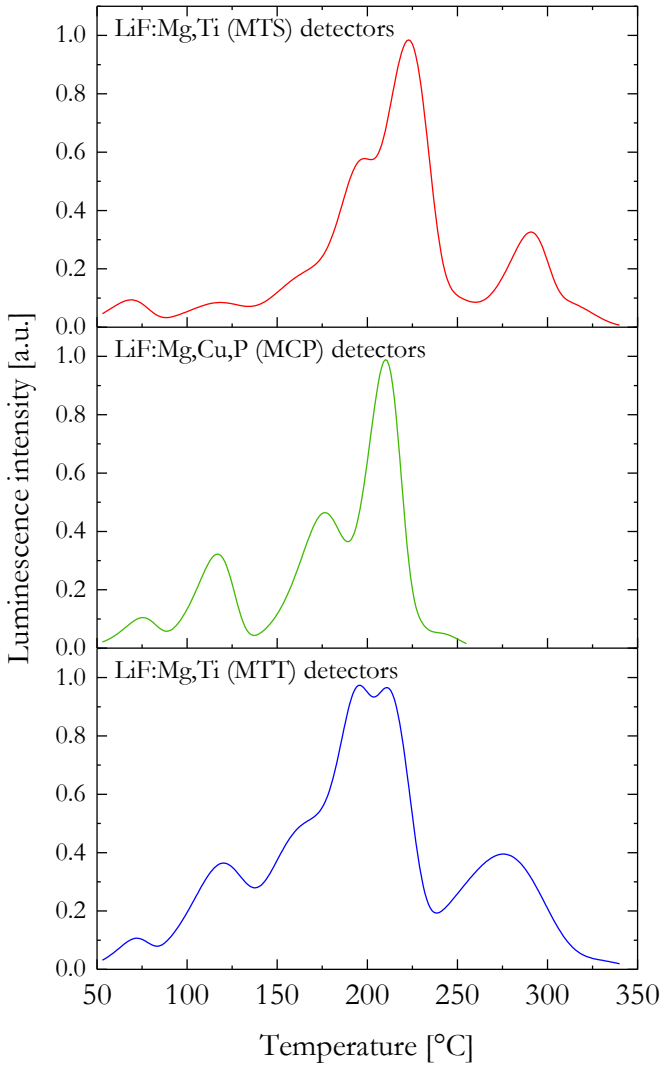
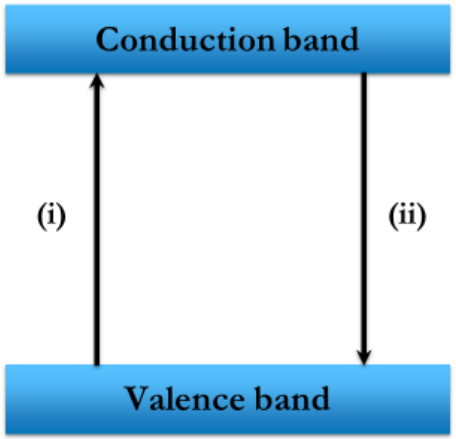
Luminescence phenomenon



- The luminescence phenomenon is explained as transition between a ground state (valence band) and a excited state (condition band)
- The radiation induced luminescent signal depends strongly on the microscopic structure of the detector
  - different materials → different trapping centers → different luminescent signal

a



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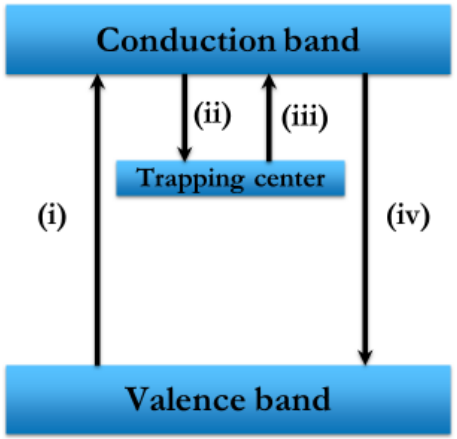

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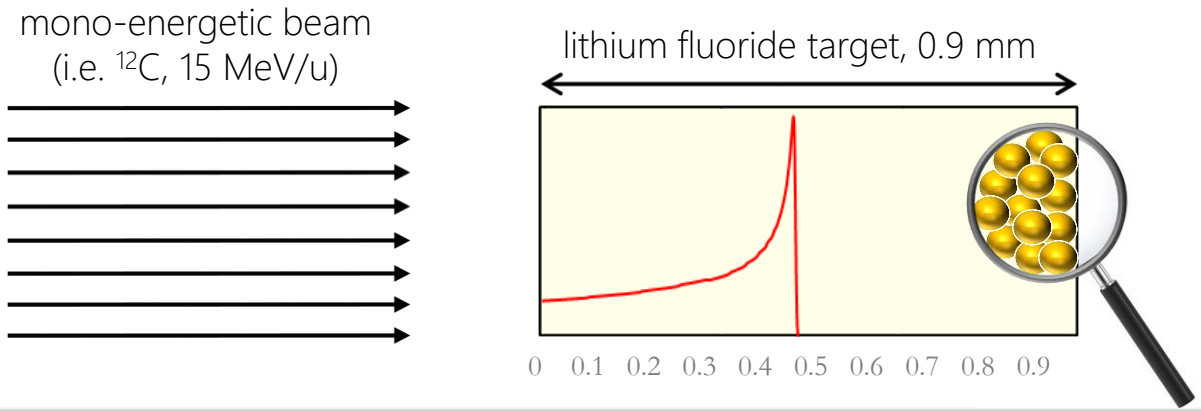
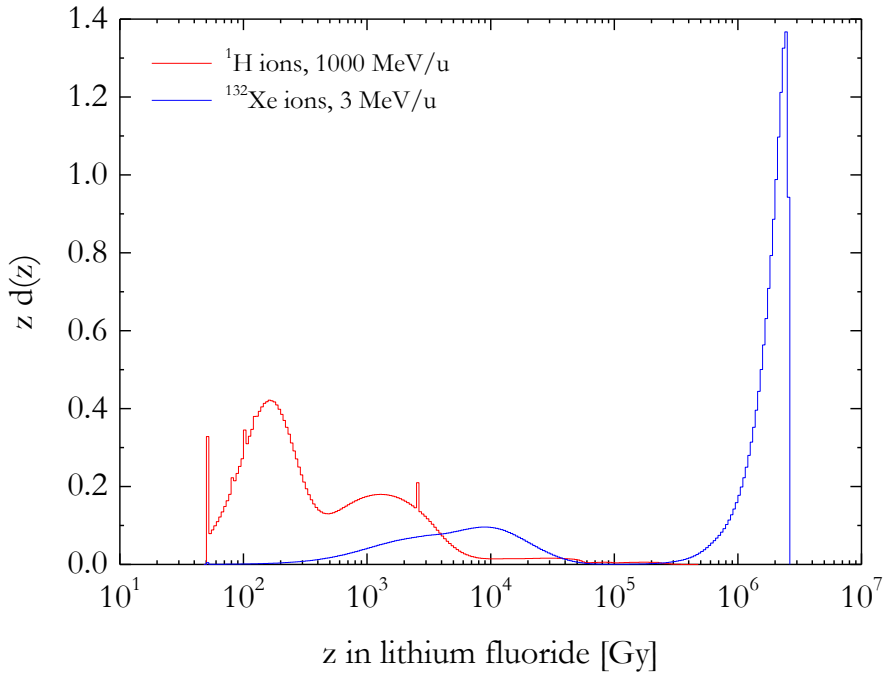
Microdosimetric d(z) Model – methodology

- Key ideas
  - the detector is supposed being composed by many independent structures called targets which act as sensitive volumes for measuring radiation
  - microdosimetric specific energy probability distributions are used to quantify changes in the pattern of energy deposition

$$\eta_{rel} = \frac{\left[\int_0^{+\infty} d(z)\, r(z)\, dz\right]_{radiation}}{\left[\int_0^{+\infty} d(z)\, r(z)\, dz\right]_{^{60}Co\ \gamma-rays}}$$

- Efficiency evaluated for a lot of particle-energy combinations
  - ions from ^{1}H to ^{132}Xe, photons, muons, antimatter
  - energy from keV to TeV





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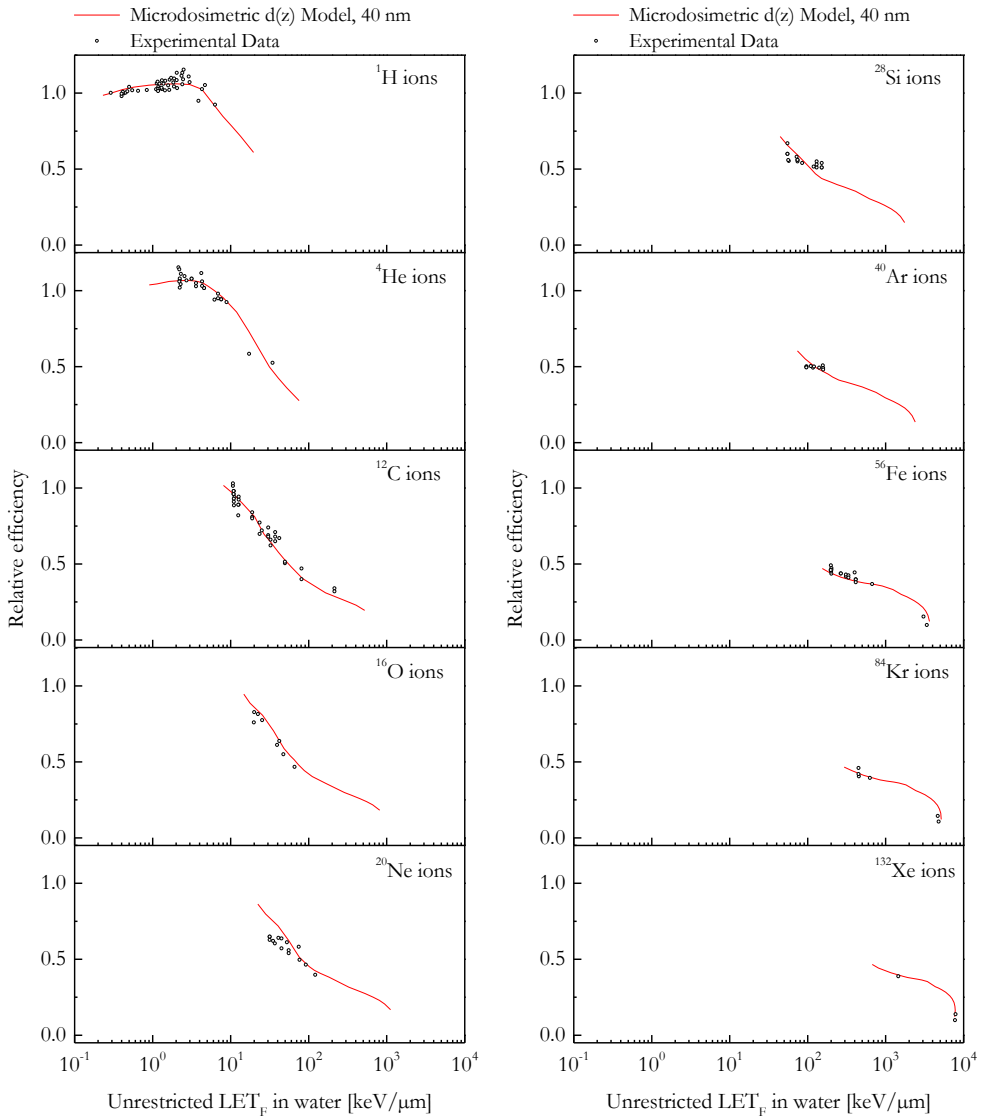
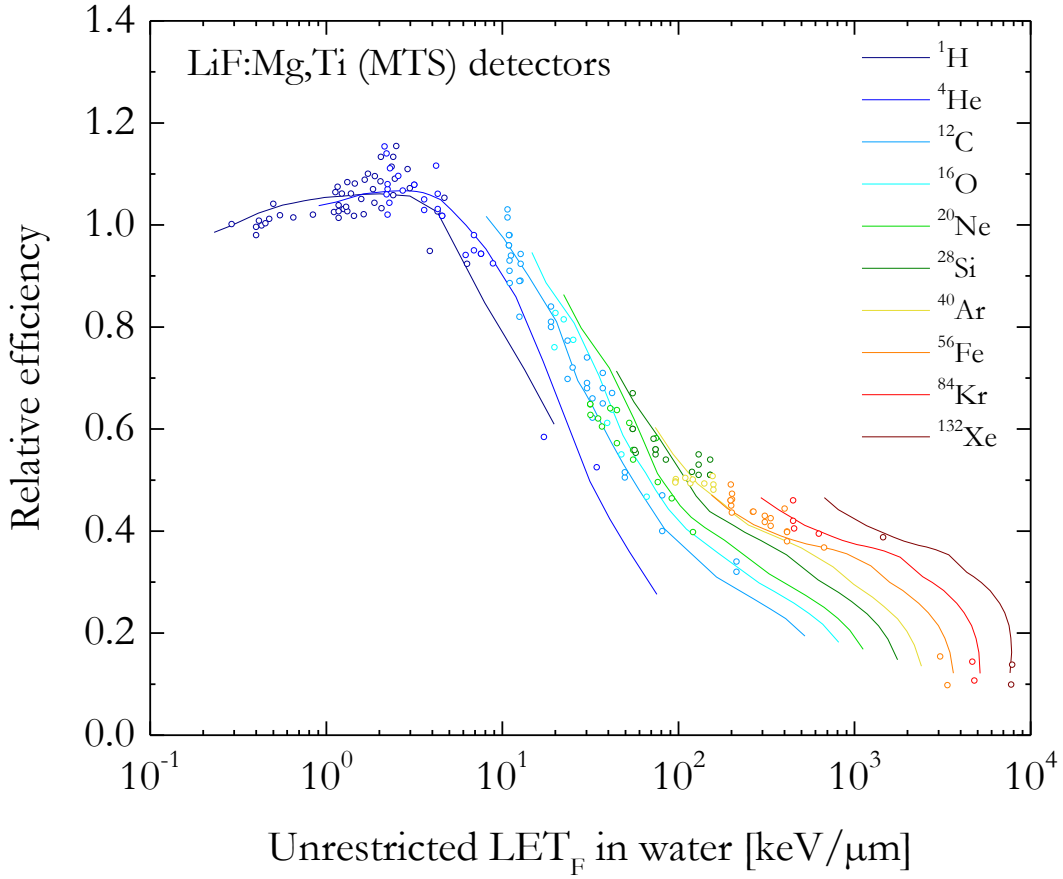
Microdosimetric d(z) Model – HCPs, results for LiF:Mg,Ti (MTS) detectors



- The results of the model are in **very good agreement** with experimental data for all particles and energies



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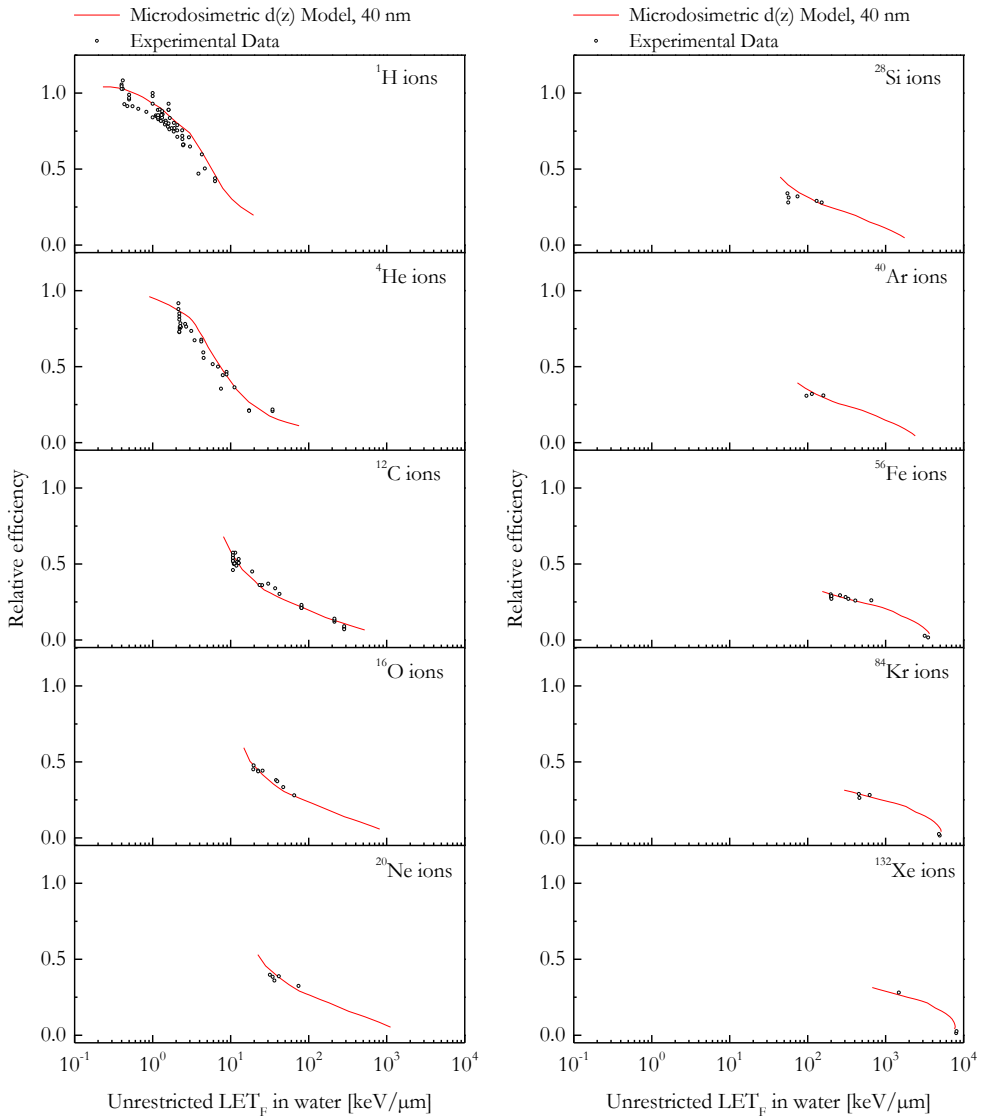
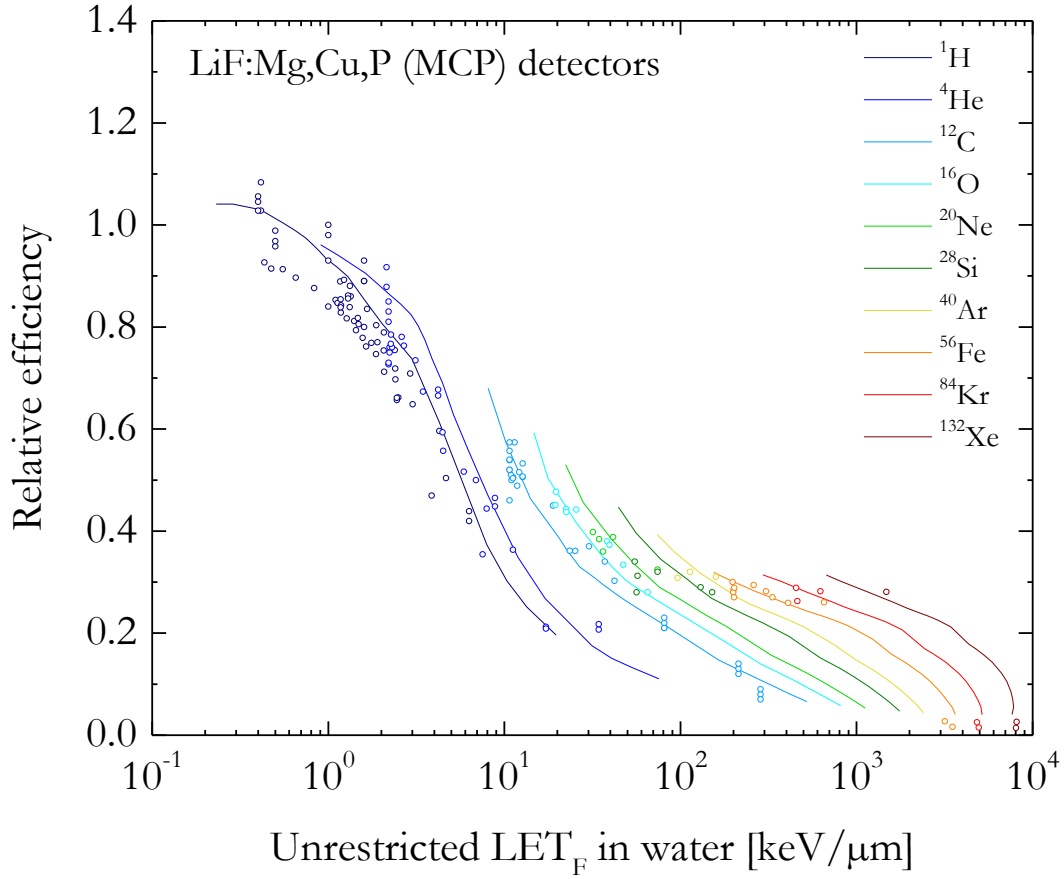
Microdosimetric d(z) Model – HCPs, results for LiF:Mg,Cu,P (MCP) detectors



- As for LiF:Mg,Ti (MTS) detectors, the results of the model are in **very good agreement** with experimental data



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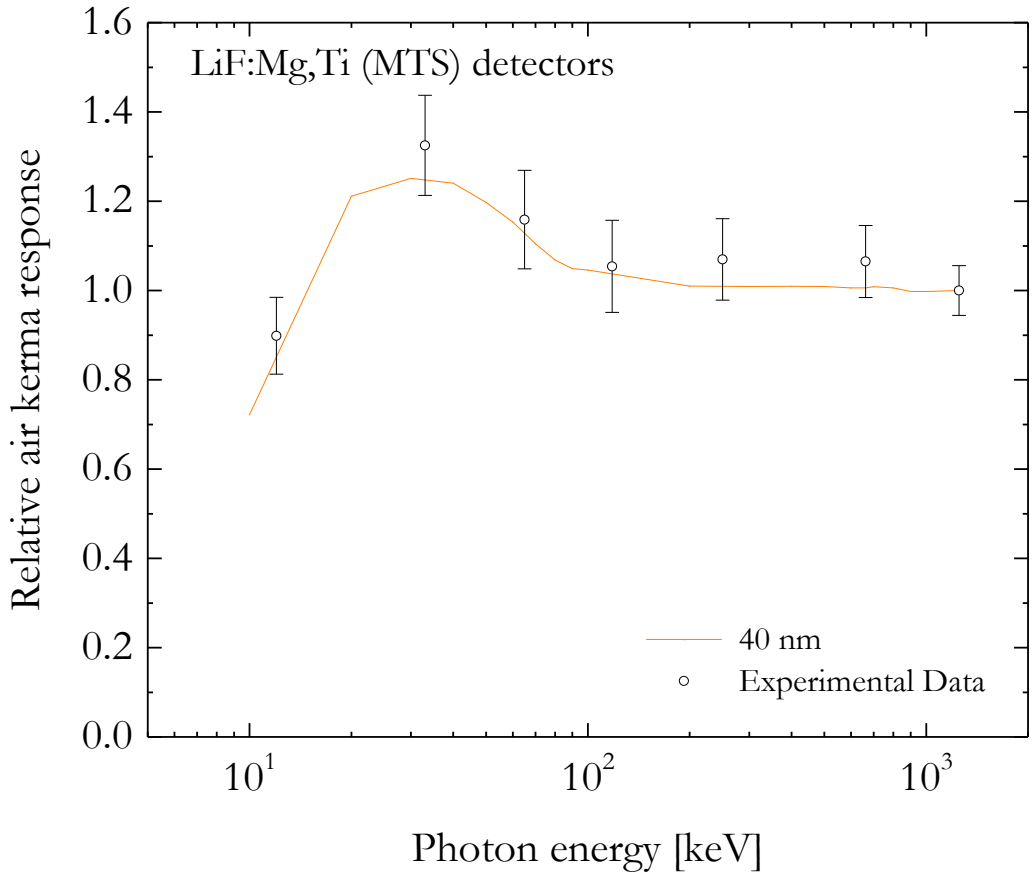
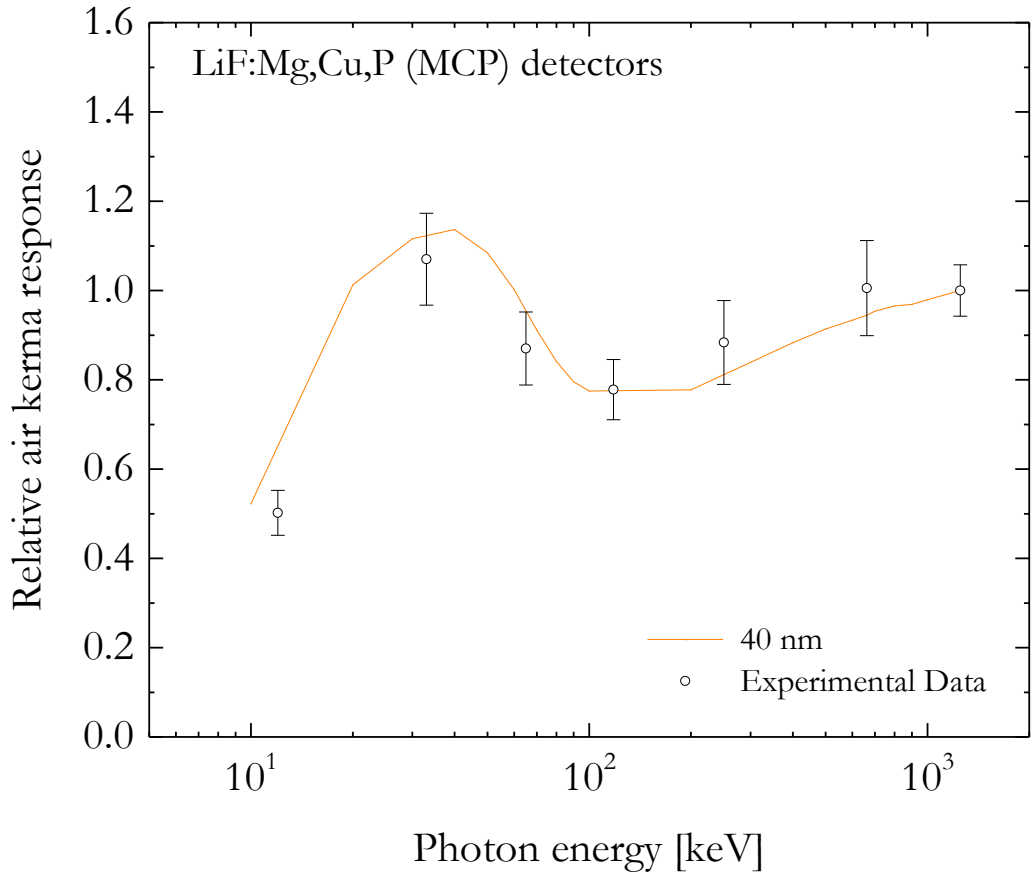
Microdosimetric d(z) Model – photons, relative air kerma response





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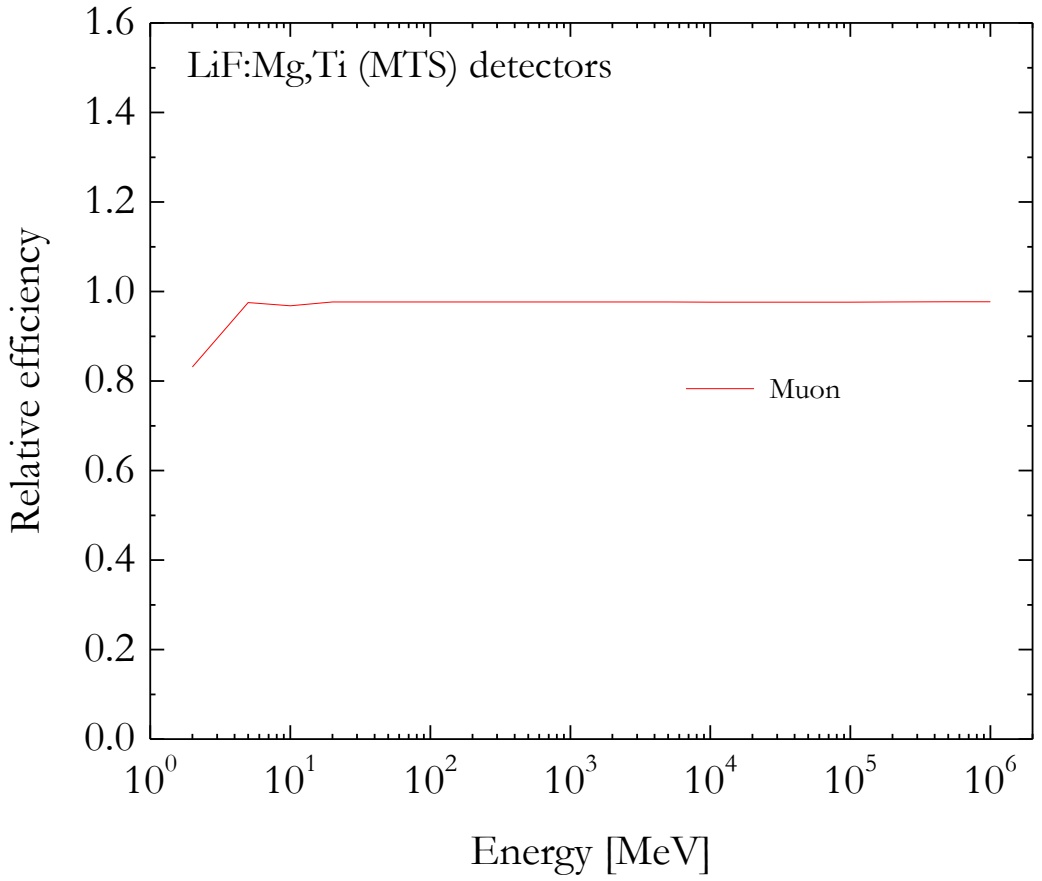
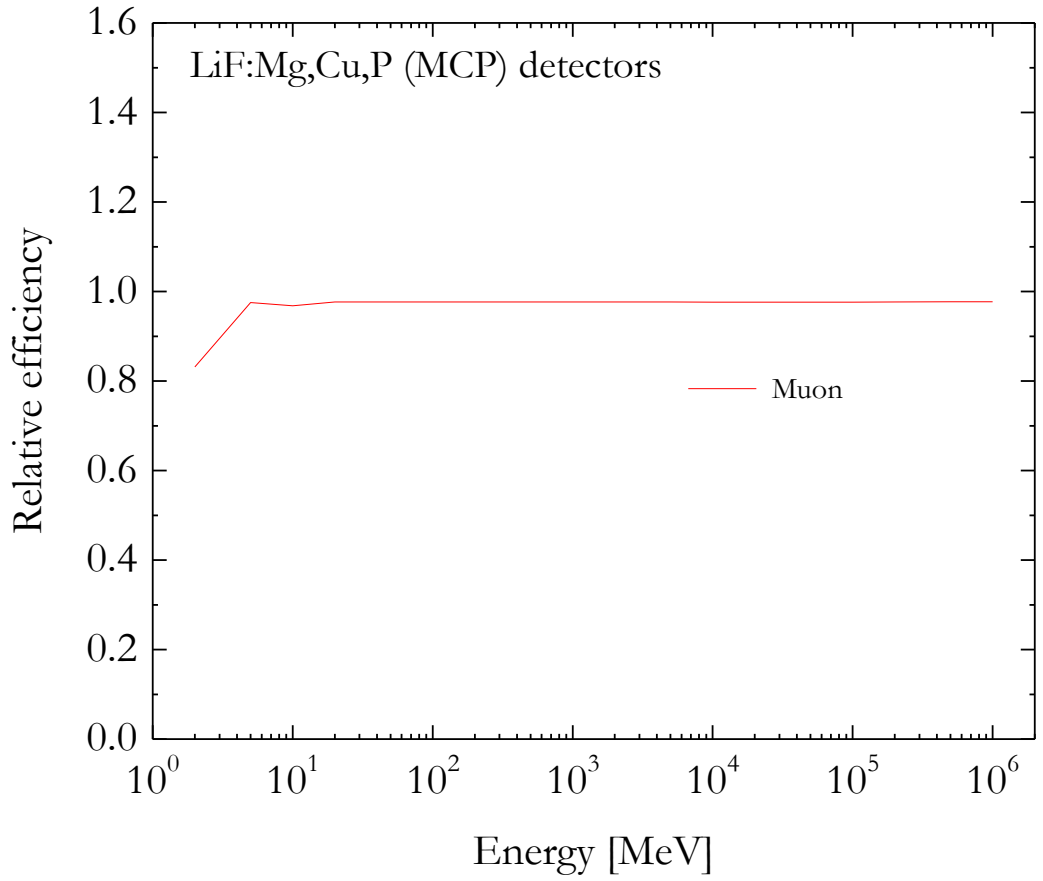
Microdosimetric d(z) Model – muons





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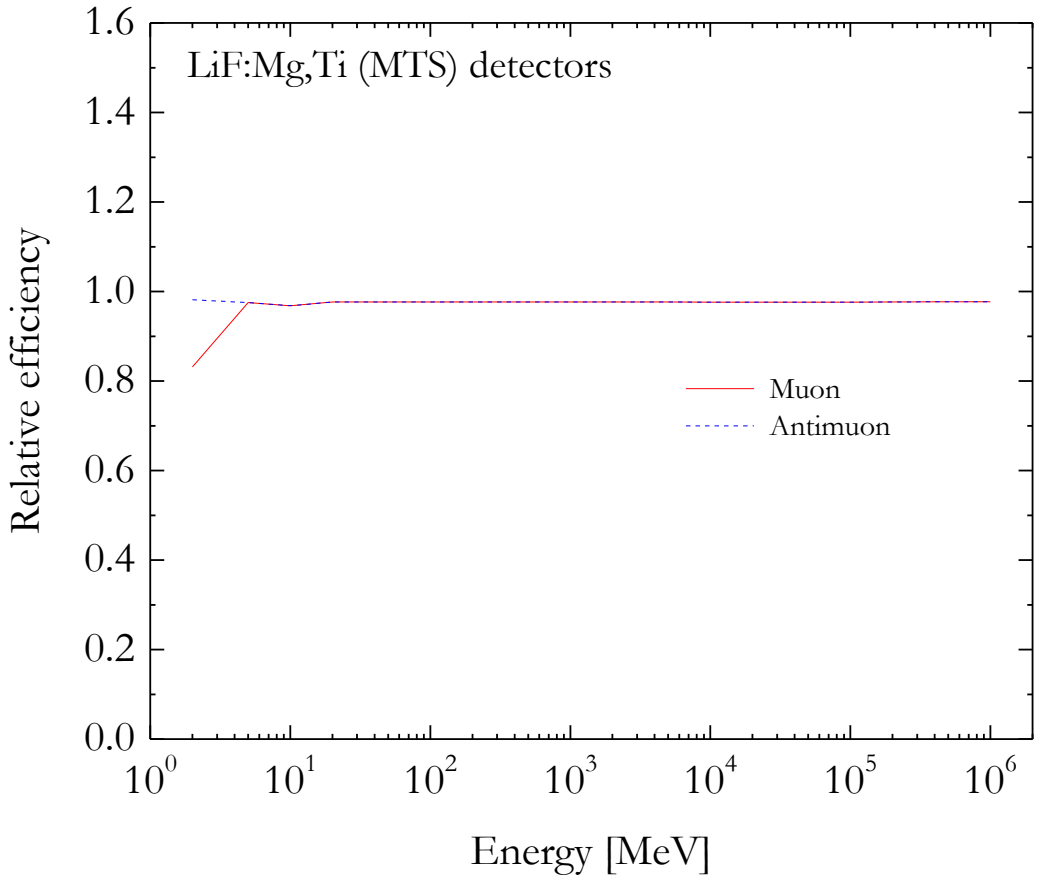
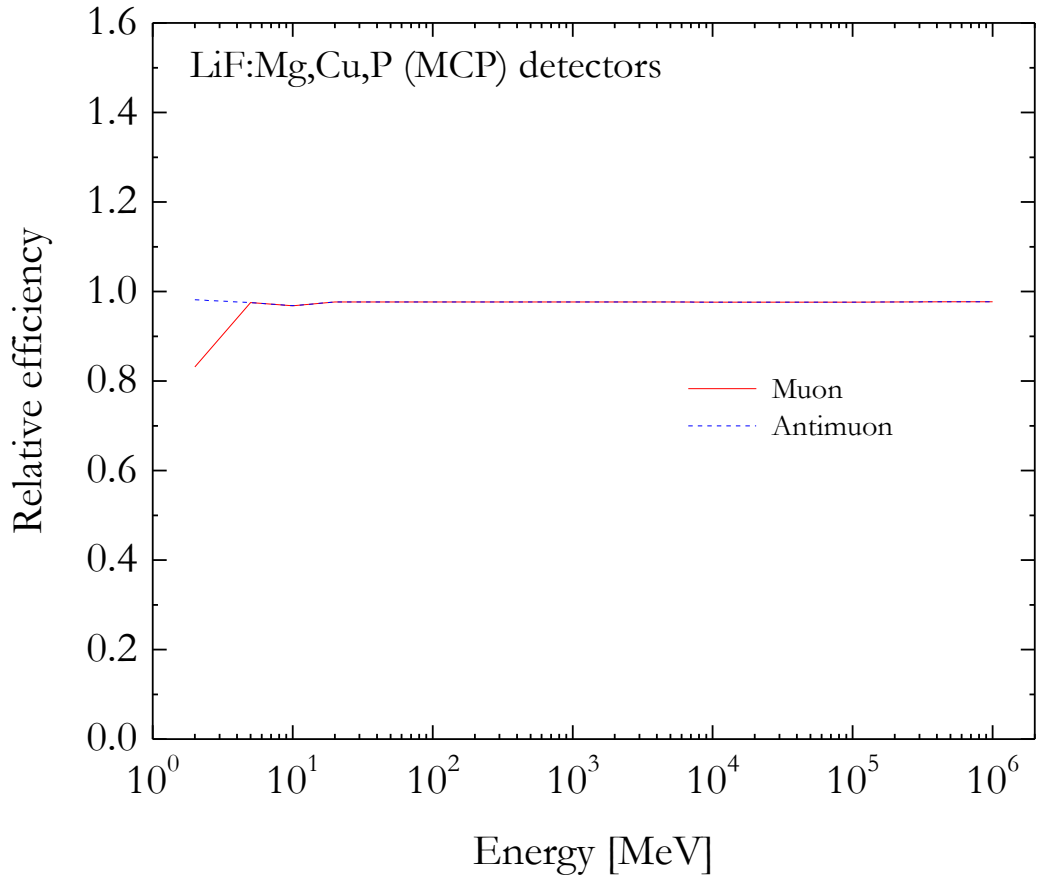
Microdosimetric d(z) Model – muons and antimuons





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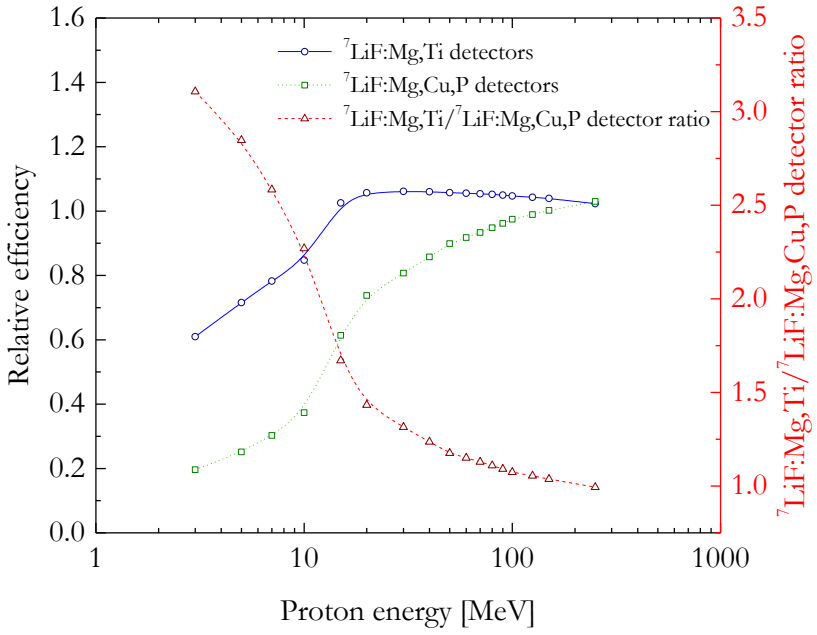
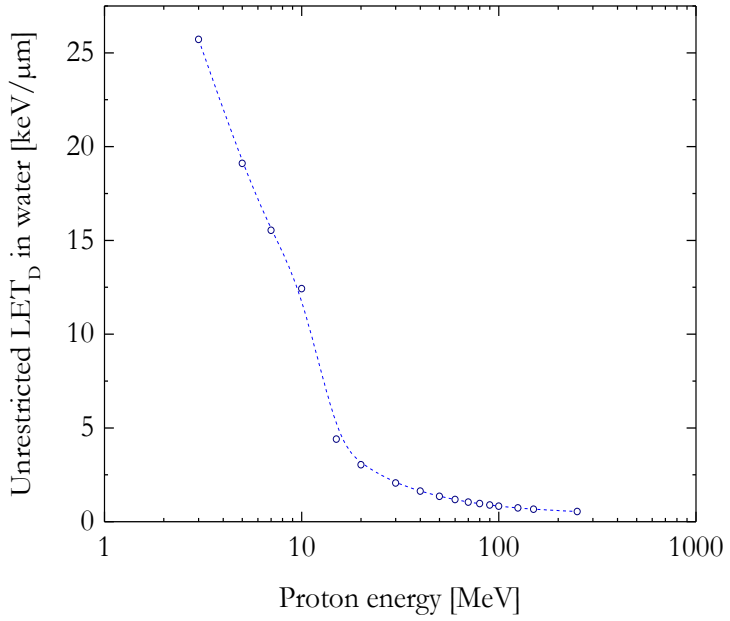
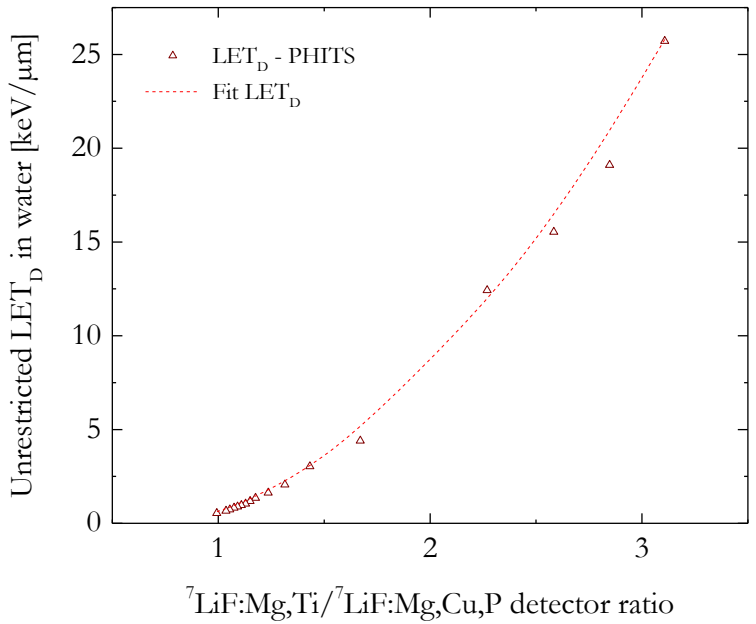
A novel method to assess LET and RBE in proton therapy using TLD couples







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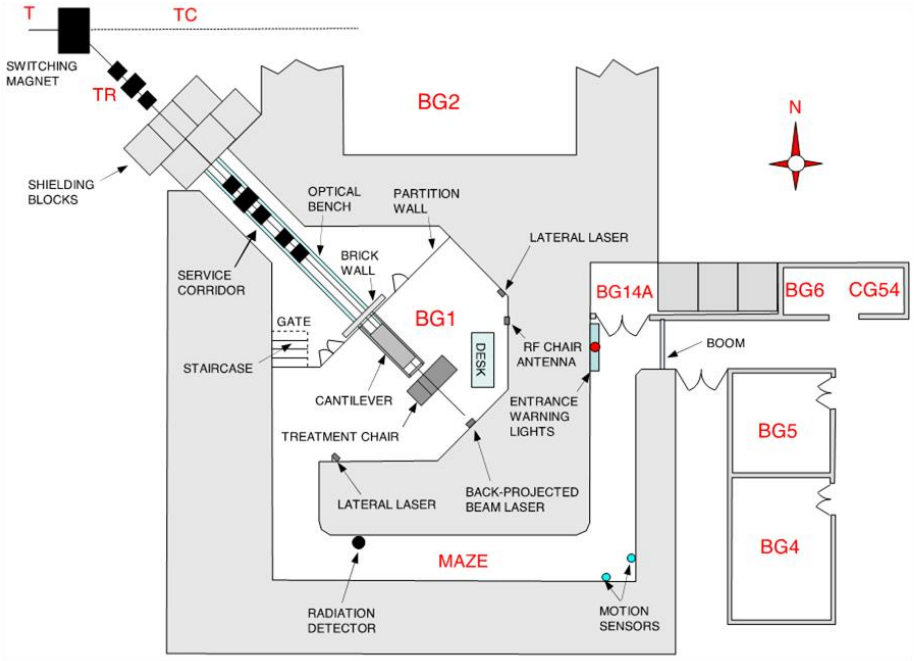
iThemba Labs measurement campaign

- Combined dosimetry-radiobiology experimental campaign
  - iThemba Labs (South Africa, April 2017)
  - Belgian Nuclear Research Centre SCK•CEN , Centre for Medical Radiation Physics – University of Wollongong
  - protons accelerated up to 200 MeV using a separated sector cyclotron



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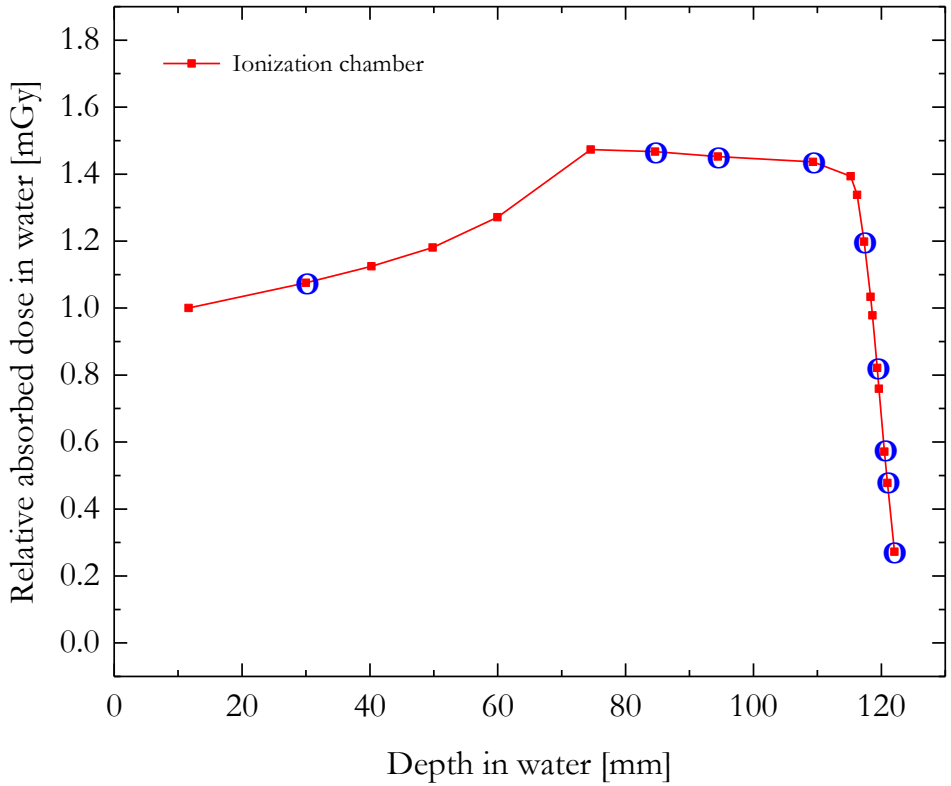
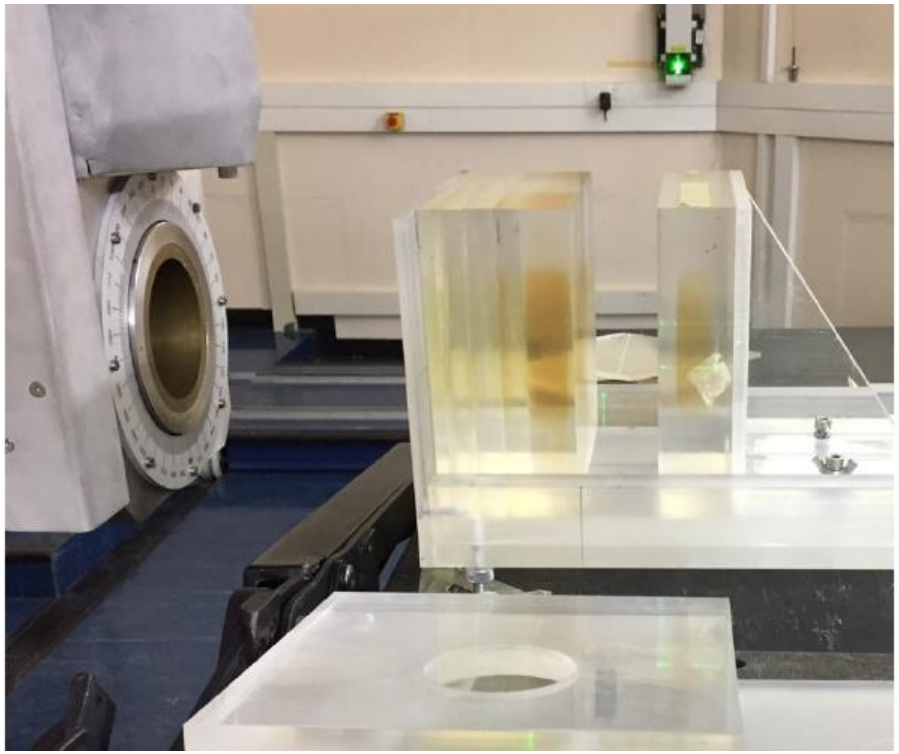
iThemba Labs measurement campaign

- Aim: study eventual RBE variations within a therapeutic SOBP with emphasis on the distal part of the treatment
  - SOBP: range = 120 mm, modulation = 50 mm, max proton energy = 198.5 MeV
  - thermoluminescent detectors exposed a different depths within the SOBP together with Chinese hamster ovary (CHO-K1) cells
  - PMMA phantom with positioning accuracy of 0.1 mm





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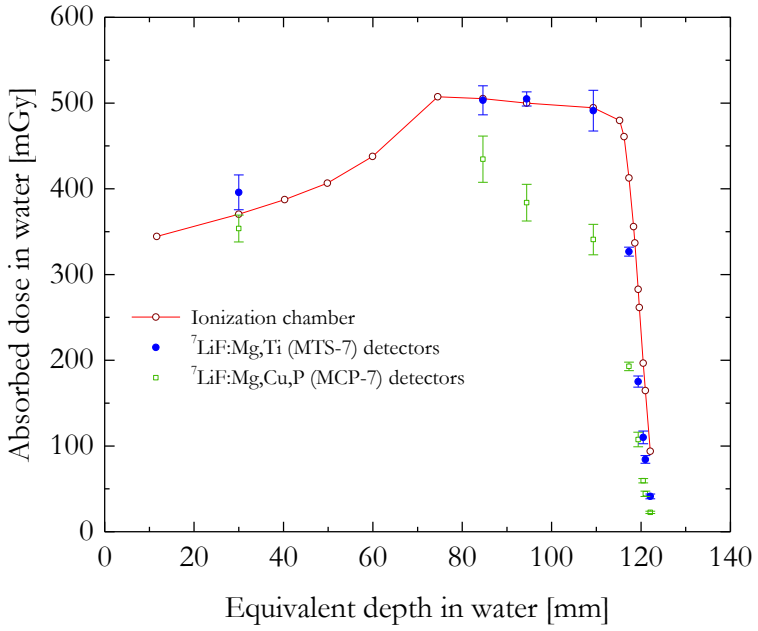
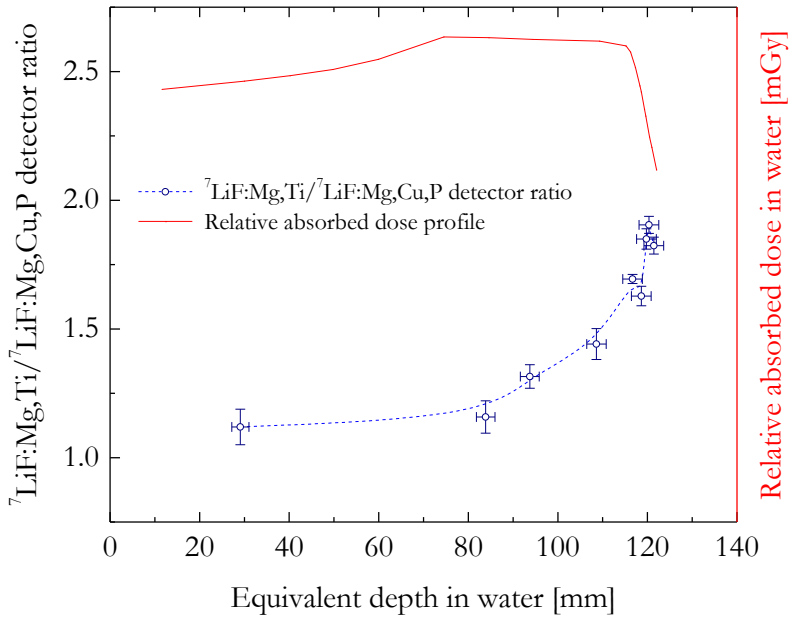
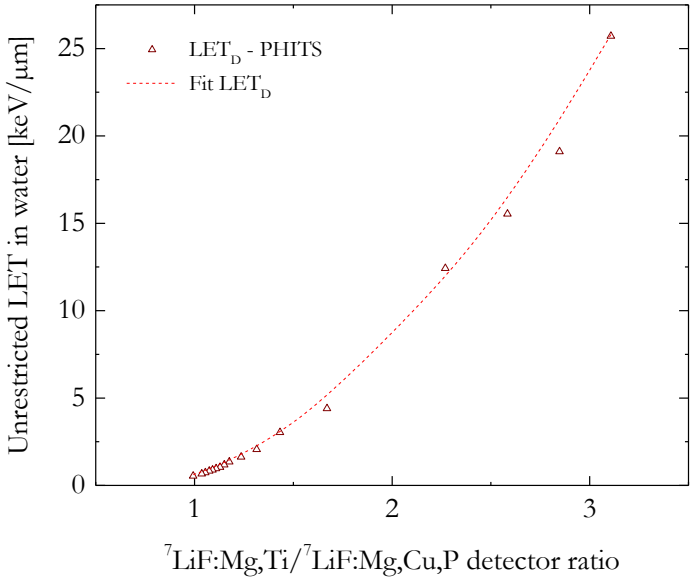
iThemba Labs measurement campaign







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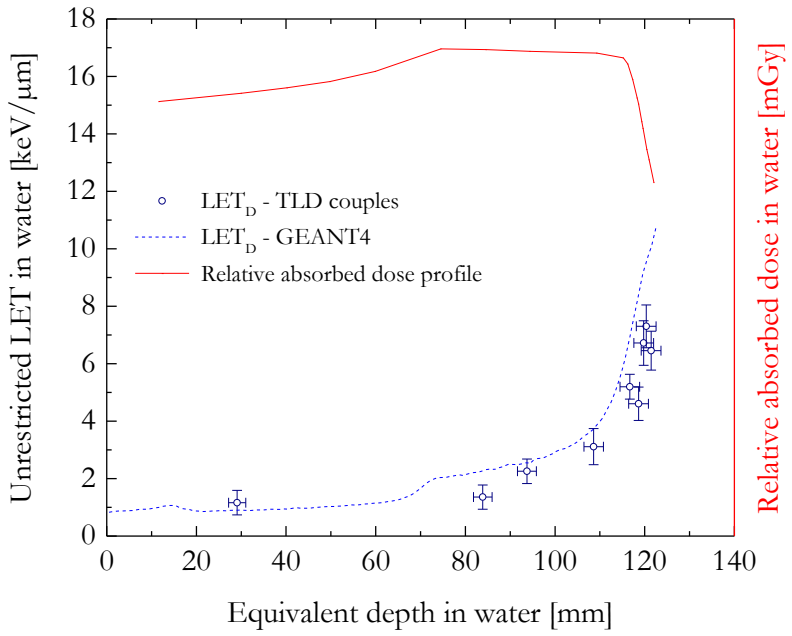
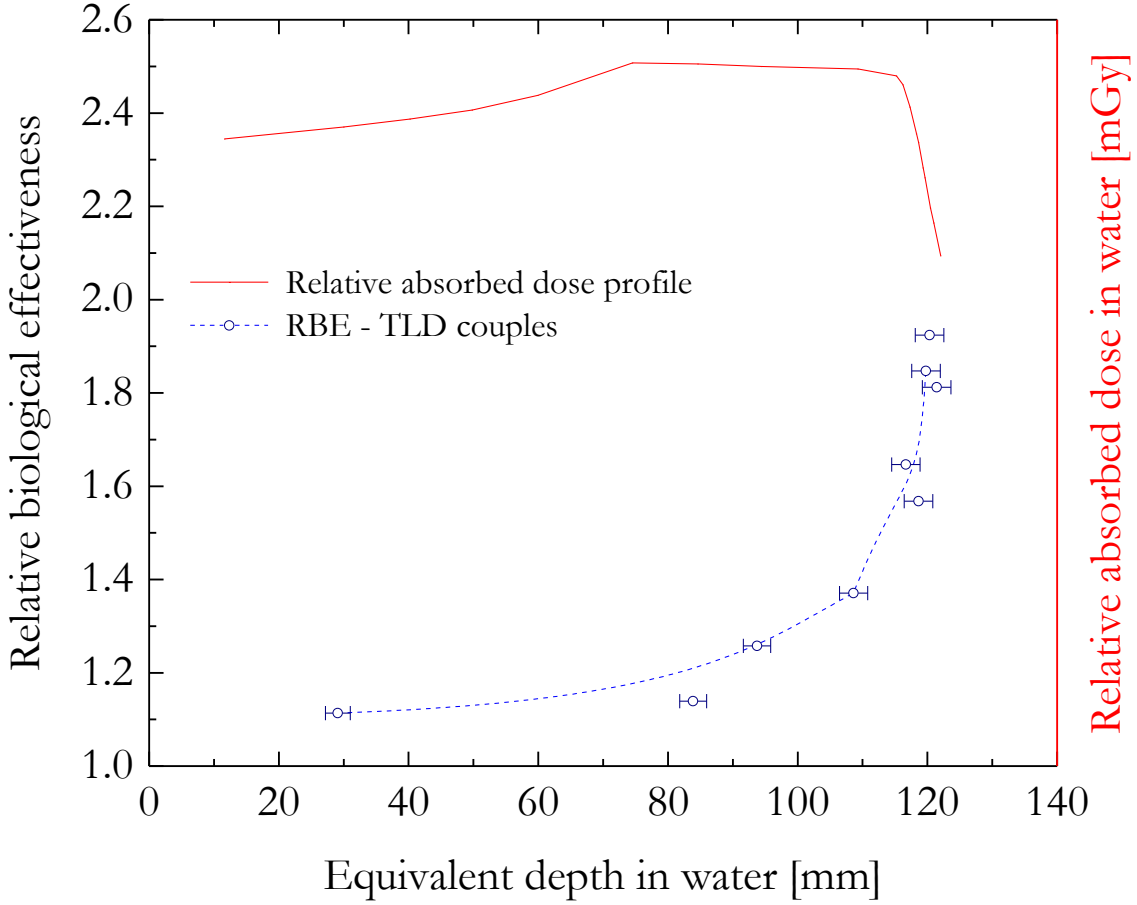
iThemba Labs measurement campaign – RBE assessment, TLDs



- CHO cell line → $(\alpha/\beta)_{ref}$ = 11.5 ± 1.5 Gy
- LET_D < 15 keV/µm and $(\alpha/\beta)_{ref}$ > 9 Gy (Paganetti, 2014)

$$RBE\ (2\ Gy)\ =\ 0.132\ LET_D\ +\ 0.96$$



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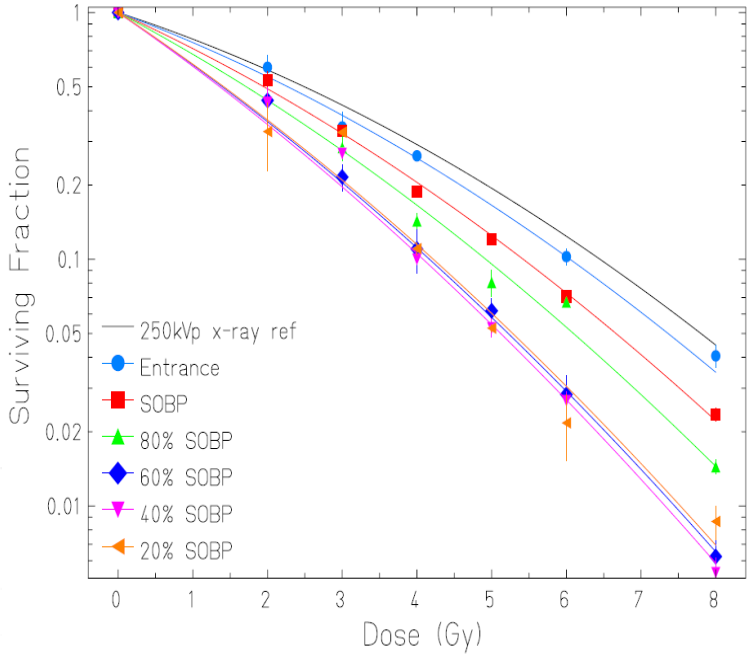
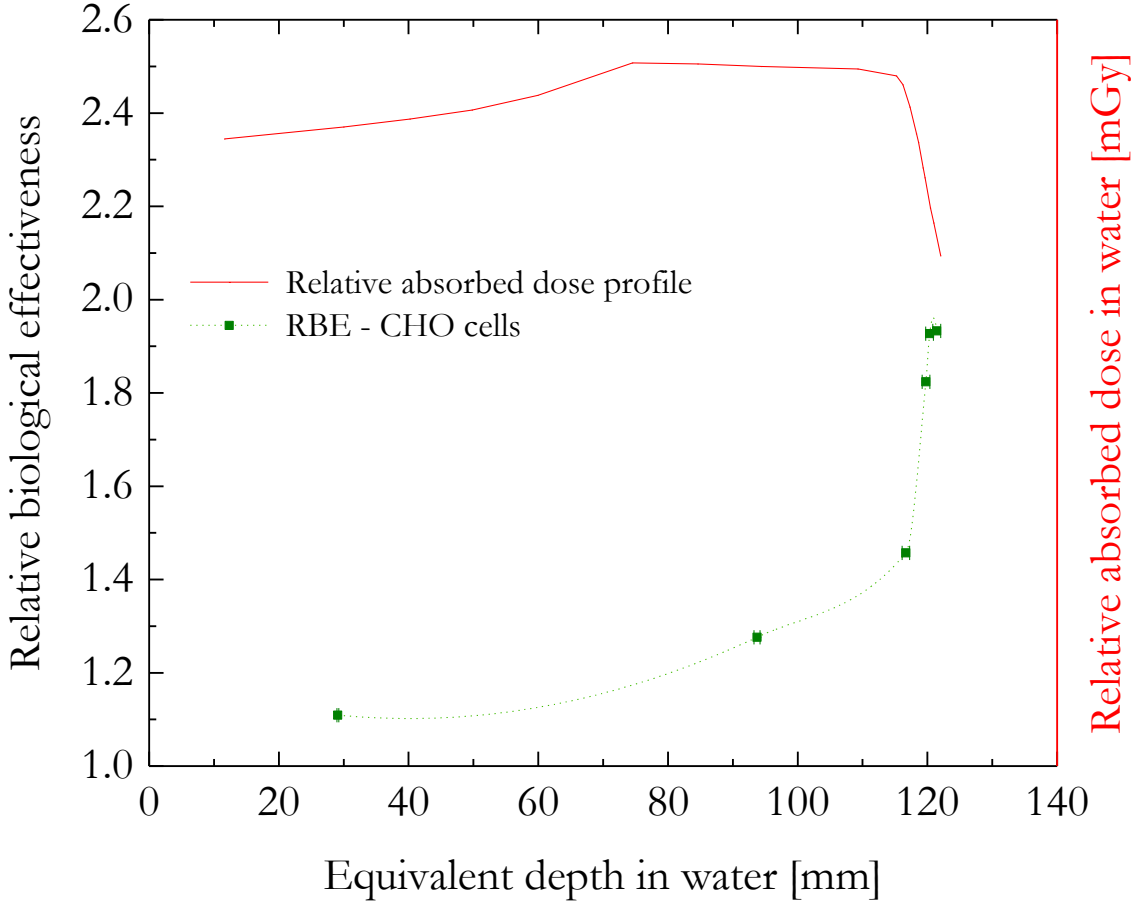
iThemba Labs measurement campaign – RBE assessment, CHO cells



- CHO cell line
- reference radiation: 250 keV X-rays,
- RBE relative to a clinical dose of 2 Gy



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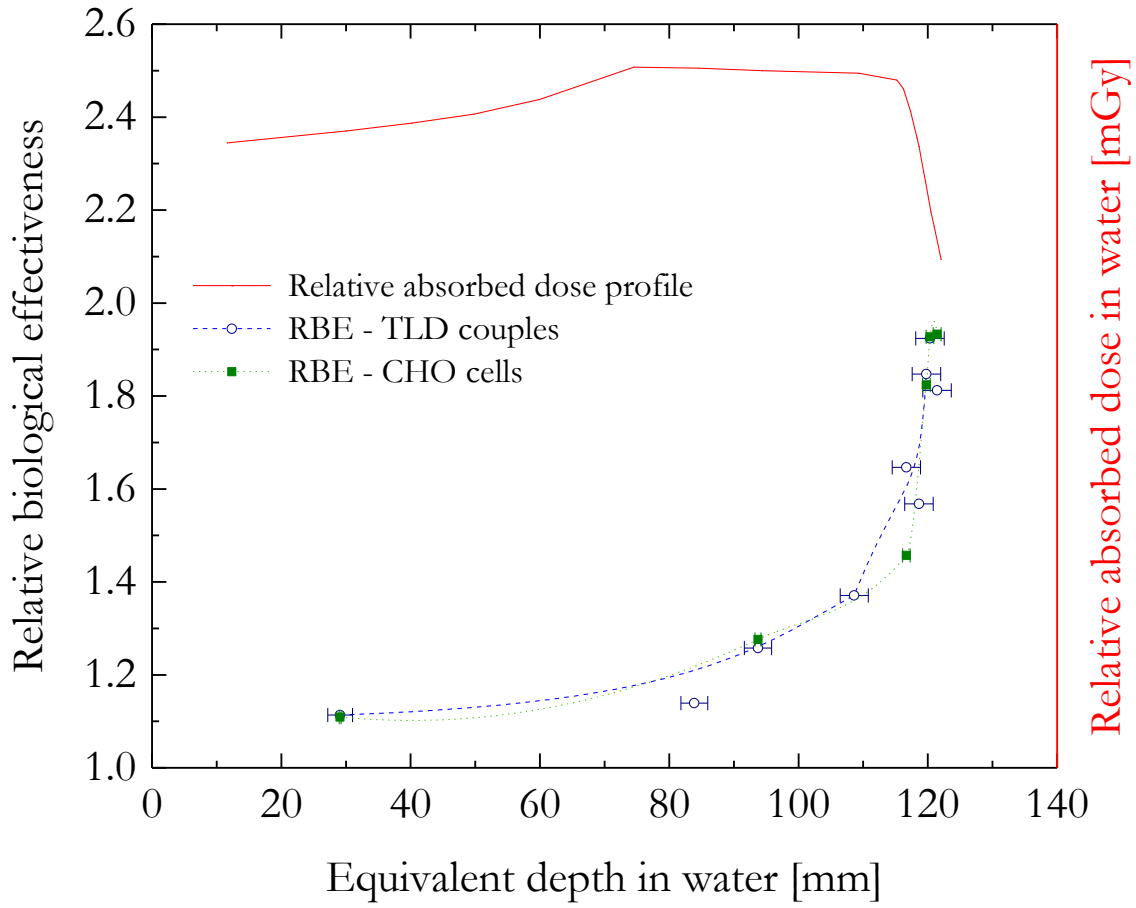
iThemba Labs measurement campaign – RBE assessment, comparison

- **Very good agreement** between the results of this new methodology and the *in vitro* cell survival study



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Conclusions

- The Microdosimetric d(z) Model is a very powerful tool
  - very good agreement with experimental data for charged particles and photons
  - possibility of predicting detector efficiency for other type of radiation (exotic particles, antimatter…) and mixed fields

- A new methodology has been proposed to correlate the relative light emission of two different crystals with the radiation induced cell death
  - based on the Microdosimetric d(z) Model
  - LET and RBE in proton therapy beams using pairs of differently doped thermoluminescent detectors
  - very good agreement with and in vitro cell survival studies

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