OPENMED – BioLEIR
Topics, Issues and Wishes (Physics)

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OPENMED Physics Task Force , Geneva, February 18-20, 2016

The New CERN Initiatives

((Ghislan Roy, et al. Presentation of 2015-03-27))

1. Medical Accelerator Design

   Coordinate an international collaboration to design a new compact, cost-effective accelerator facility, using the most advanced technologies

2. Biomedical Facility

   Creation of a facility at CERN that provides particle beams of different types and energies to external users for radiobiology and detector development

   Iterative experimental verification of simulation results

3. Detectors for beam control and medical imaging
4. Diagnostics and Dosimetry for control of radiation
5. Radio-Isotopes (imaging and possibly treatment)
6. Large Scale Computing (simulations, treatment planning telemedicine etc)
7. Applications other than cancer therapy

Motivation

((Ghislan Roy, et al. Presentation of 2015-03-27))

Need for radiobiological research with ion beams:

- Protons and Carbon ions in clinical use
  - Improved dose distribution, but limited understanding of all effects
  - Other ions than p and C could be better suited (for certain cases)
- Incoherent sets of data (radiobiological and clinical) observed under different conditions
- New dosimetry and imaging modalities to be developed for full potential of ion beam therapy
- Radiobiology: cell survival for different ions/LET/doses, bystander effects, RBE …
- Detector Development: in-beam prompt gamma/PET imaging, radiography, …
- Physics: fragmentation, …

Lack of Beam-Time for ions with an energy of more than 50 MeV/n:

- Nuclear physics laboratories (e.g. GANIL, GSI, INFN LNS, ITEP, JINR …)
  - Limited beam time available
- Ion Beam Therapy Centers (HIT, CNAO, MedAustron)
  - Limited range of ions
  - Priority given to clinical use (treatments, dosimetry, quality assurance …)

Requirements - Ion Species

- There is no need for a complete range of ions of all possible z numbers, because the range of energies that cover the tissue depths required for human radio therapy, and their event size, are given by the lighter ions.

- The lighter ions most suitable for radiobiology and radiotherapy are: **H, He, Li, Be, B, C, N and O.**

- Heavier ions useful for research in biophysics (such as fragmentation), dosimetry, medical detector development, radiation protection and some aspects of fundamental radiobiology, including cosmic radiation, include **Ne, Ar, Fe, Ar, Kr, Xe, Pb and U**.

- Ion species to be **changeable within an hour or two** for most experiments, but mixed ion irradiation may be suggested as a future development, where changes **within a few minutes** might be required.

Requirements - Ion Energies, Rates & Size (horizontal & upward vertical beams)

Energies (± 0.15%?)**:**

- **Lower:** < **70 MeV/u** for radiobiology (around RBE maximum)
- **Medium**: **50-500 MeV/u**, for medical applications (RT, dosimetry)
- **High: >1 GeV/u**, for fundamental biophysics and dosimetry.

Energy variability:

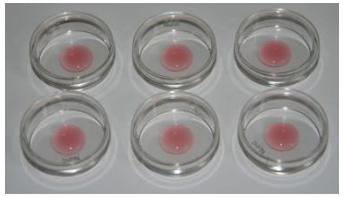
- **fast (10-15ms**), spill by spill or fill by fill, directly in synchrotron mode,
- **stable**, with range shifters (to compare with cyclotron-based RT).

Beam size:

- **Broad beam**: minimum **5 x 5 cm^2** , maximum **40 x 40 cm^2 at SSD 100 cm**,
- **Pencil beams**: **5-10 mm FWHM** (or better?), **with RT scanning heads**.

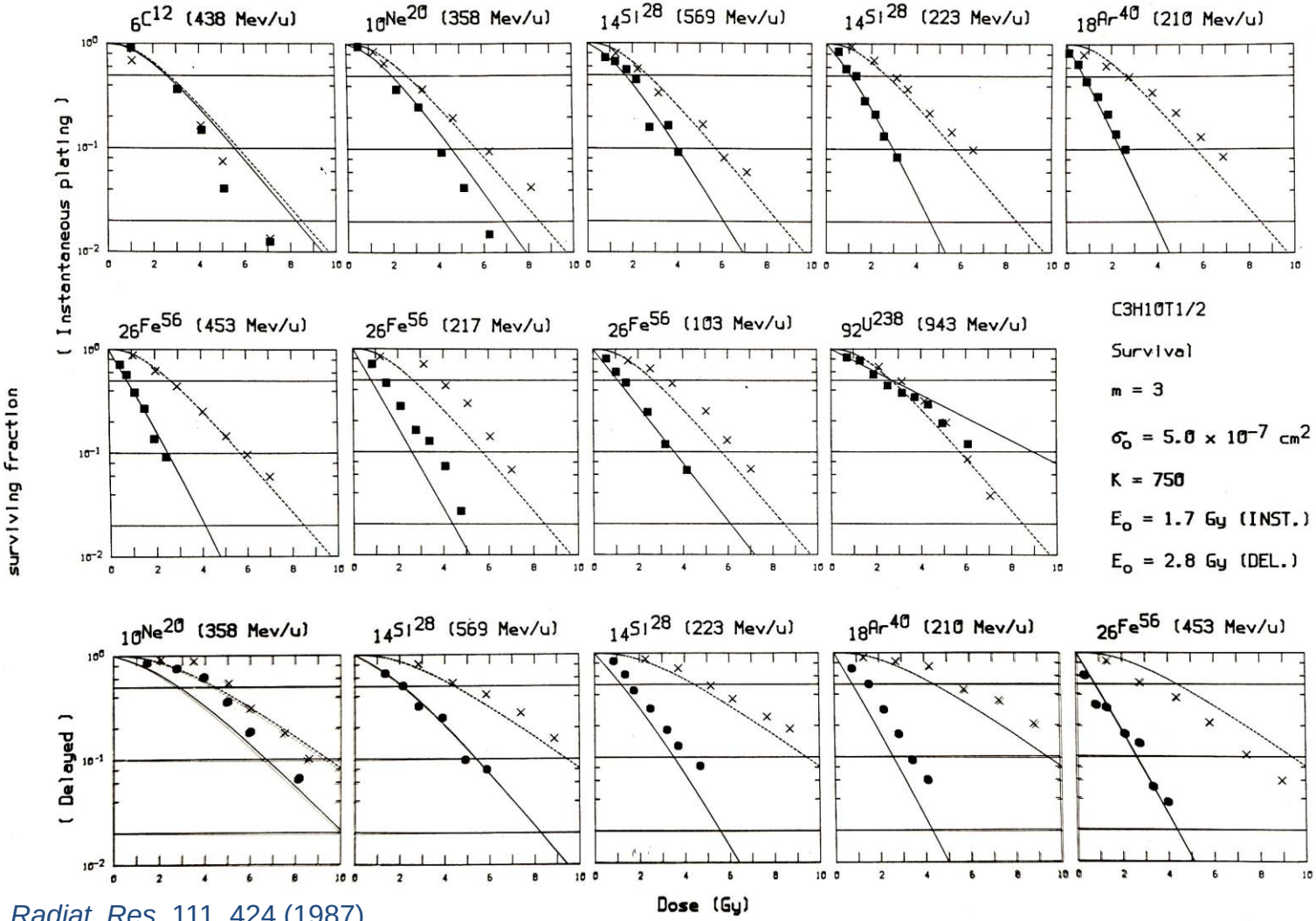
Beam intensity & stability:

- variable from ~ **10^9 /s downwards**, stable (2%?), or pulsed (?%), for flat & pencil beams,
- **gated?** (by organ motion).



Radiobiology – *in vitro* (modelling)

Survival in C3H10T1/2 Cells



Waligórski et al. *Radiat. Res*. 111, 424 (1987)

Data: Yang et. al. *Radiat. Res.* 104 S-188 (1985)

Radiobiology – *in vitro* (modelling)

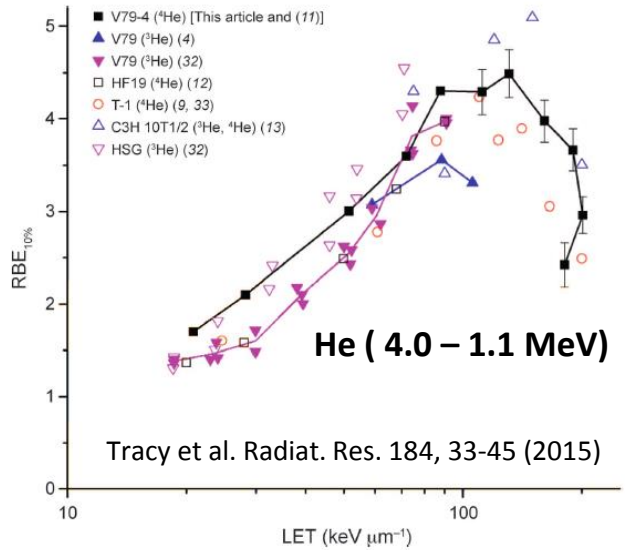


FIG. 8. Variation in RBE for 10% survival as a function of LET of helium ions (^{3}He and ^{4}He) for a range of experimental data on V79 cells (closed symbols) and other cell lines (open symbols).

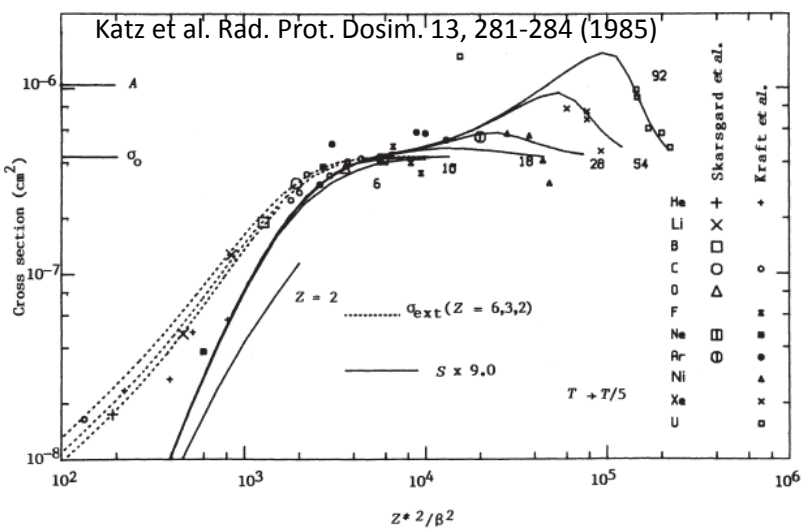


Figure 3. Using the dose distribution based on maximal radial penetration of delta rays of T/5, we have recalculated the ion-kill cross sections. The agreement with data is substantially improved over that of Figure 1. Symbols etc. as for Figure 1.

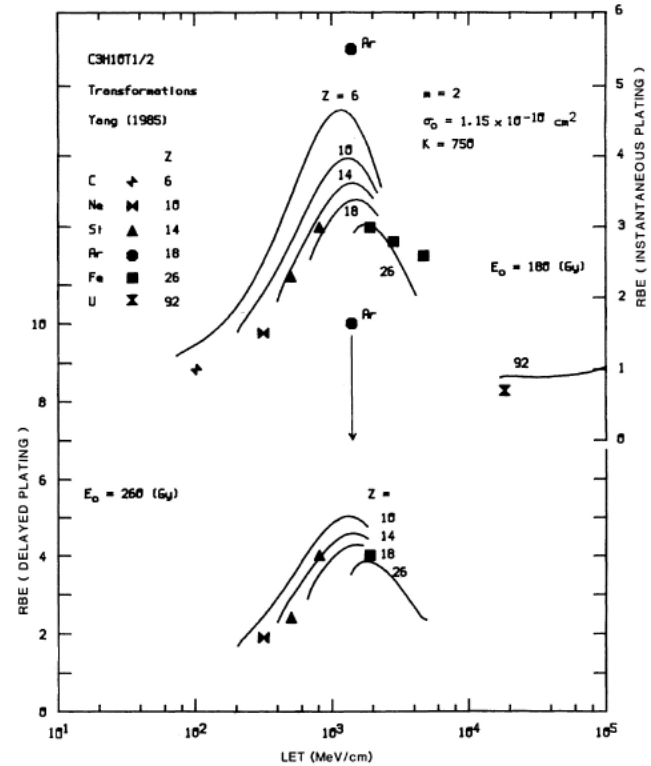


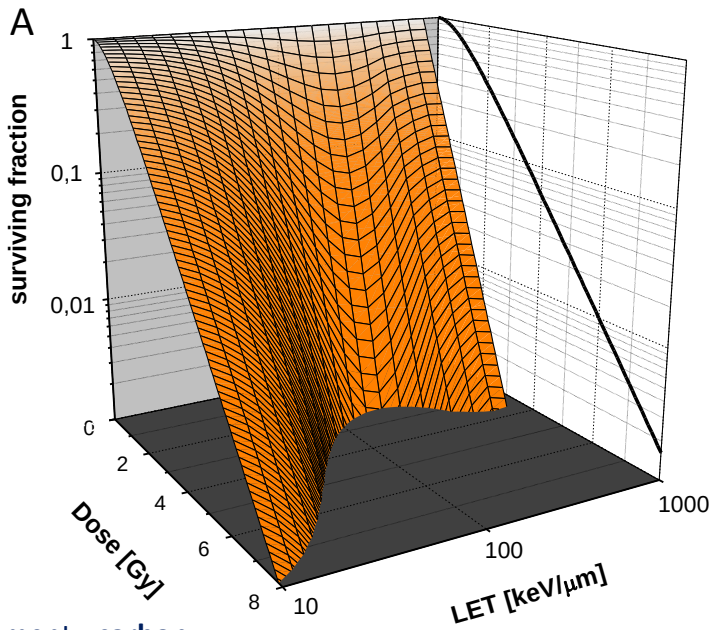
Figure 5. Measured (□) and calculated RBE for transformations in C3H10T1/2 cells at levels corresponding to 50% survival, indicated in Figure 4, for instantaneous (upper panel, upper right-hand ordinate) and delayed (lower panel, lower left-hand ordinate) plating. $m = 2$ target parameters were used.

Ions: p, He, Li, B, F, C, Ne, Si, Ar, Fe, U

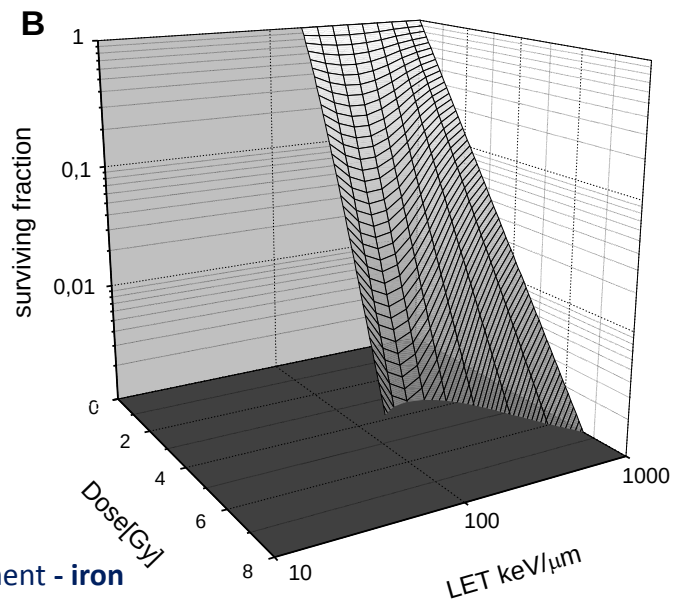
Energy: 425 – 960 MeV/amu,

Range in water: 0.7 – 32 cm

Radiobiology – *in vitro* (modelling)



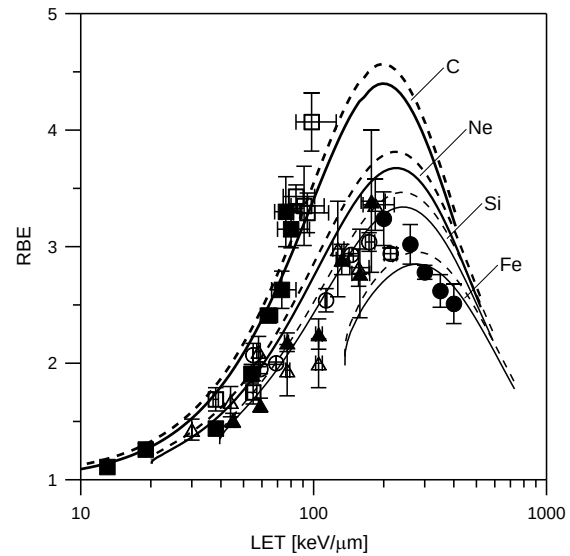
Track segment - **carbon**



Track segment **- iron**

TST-predicted *in vitro* survival of **normal human skin fibroblasts** irradiated by: A – carbon ions, and B – iron ions, over the available ranges of LET values of these ions.

Korcyl & Waligórski, Int.J.Rad.Biol. **85:**12,1101-1113 (2009)



RBE vs. LET for cell killing, at 10% survival

The required range of ion species and their energies will depend on the radiosensitivity characterstics of the biological objects studied.

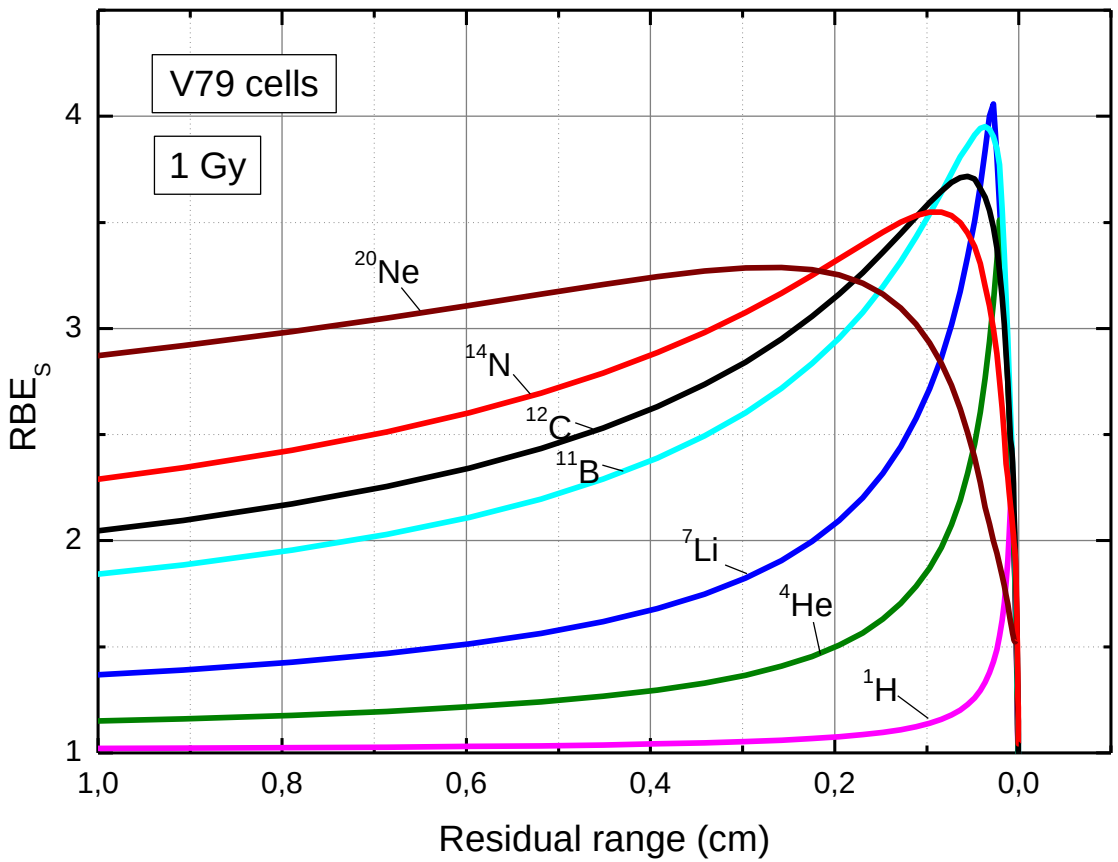
Radiotherapy - Beam requirements

The CSDA range of all ion beams is R = 26.0 cm, in water

Ion	Z	A	E_{in} MeV/A	β_{in}	LET(Z, β_{in}) keV/μ	Fluence/1Gy 10^7 ions cm^{-2}	σ_Z mm
p	1	1	199.2	0.5669	0.4469	139.87	2.78
He	2	4	199.2	0.5669	1.7874	34.97	1.38
Li	3	7	230.9	0.5982	3.666	17.05	1.05
B	5	11	324.8	0.6710	8.3644	7.472	0.82
C	6	12	385.2	0.7067	11.027	5.668	0.78
N	7	14	424.0	0.7265	14.328	4.362	0.72
O	8	16	461.3	0.7434	18.006	3.471	0.67
Ne	10	20	532.2	0.7713	24.476	2.307	0.59

All data are beam entrance values, σ_z is range scatter (mm)

Radiotherapy - Beam & RBE modelling

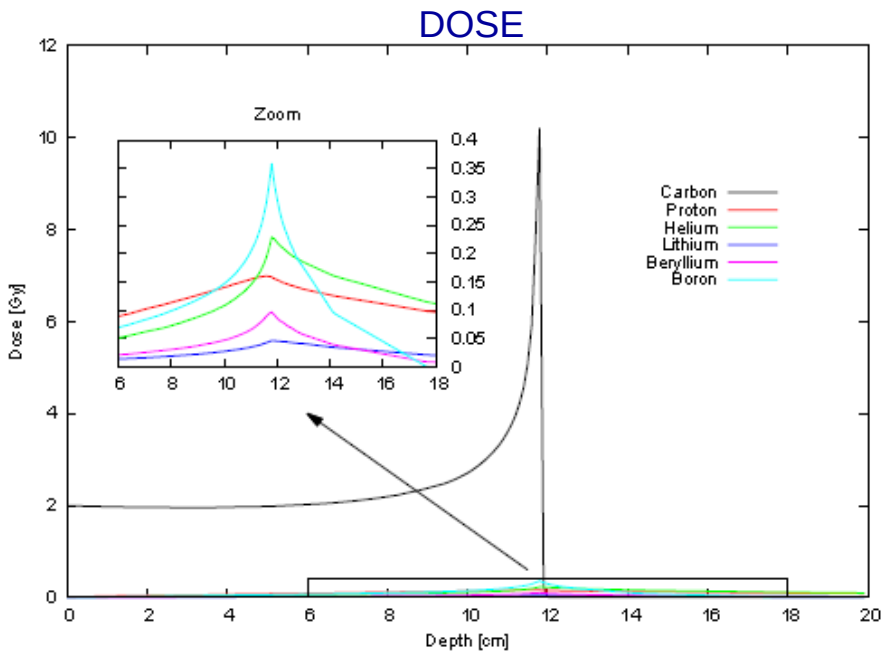


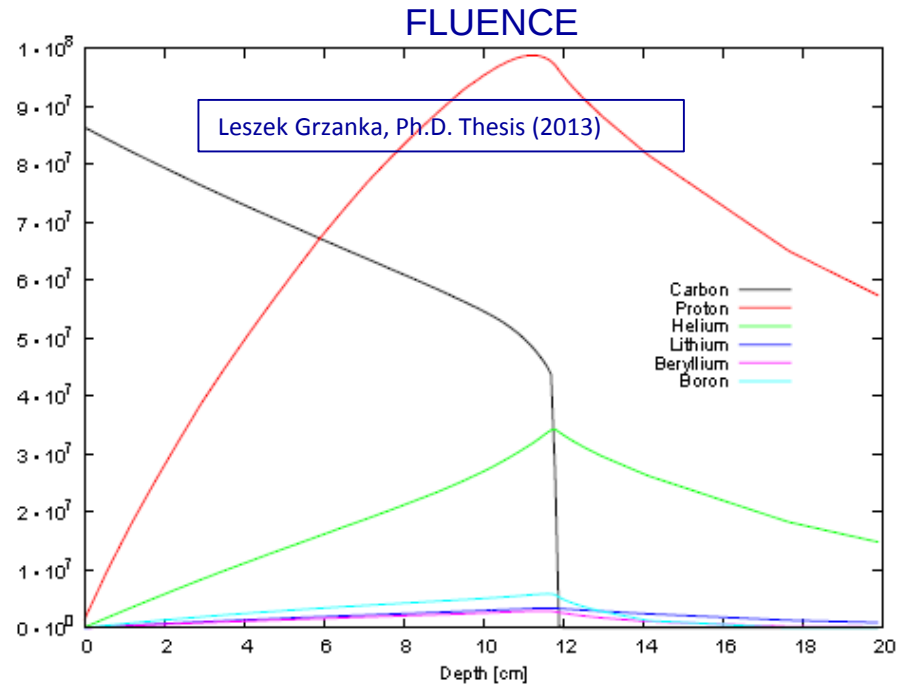
RBE$_S$-depth dependences of V79 cells over the last 1 cm of CSDA residual ion ranges, for light ion beams of range 26 cm, delivering an entrance dose of 1 Gy. Calculation is for aerobic V79 cells, based on data of Furusawa *et al.* (2000). RBE$_s$ at depth d is the RBE at the level of survival at that depth, S(d), RBE$_s$(d) is calculated as the ratio of the Co-60 dose required to obtain S(d) and the "ion track segment dose", which is D_i = Fx LET$_i$(β) at that depth.

Radiotherapy - Beam modelling

The physical beam transport component - a set of Monte Carlo-calculated carbon beams of energies 50-500 MeV/u in liquid water;

The radiobiological component - Katz model-calculated cellular survival

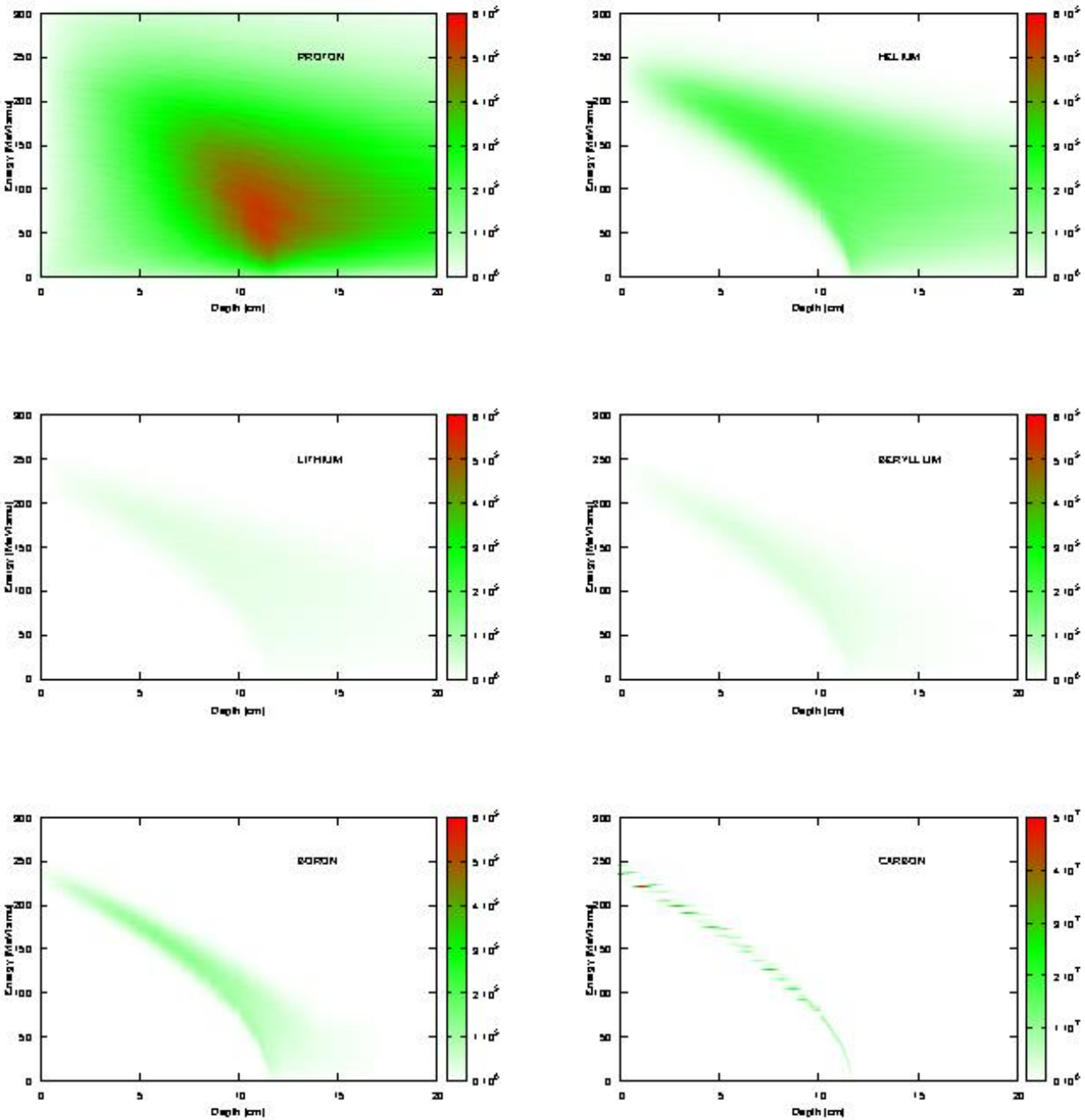




Depth distributions in a 270 MeV/u carbon beam in water (beam entrance dose – 2 Gy)

To calculate cell survival vs. depth, knowledge of dose vs. depth of the carbon beam is not sufficient. Energy-fuence spectra of all primary and secondary ions are required at all depths by the Katz model. The summary effect (survival) then results from non-linear addition of all ion action cross-sections via a fluence-based calculation.

Calculated Energy-Fluence Spectra in a 270 MeV/u Carbon beam (in water)



Entrance dose 2Gy
SHIELD-HIT10A MC

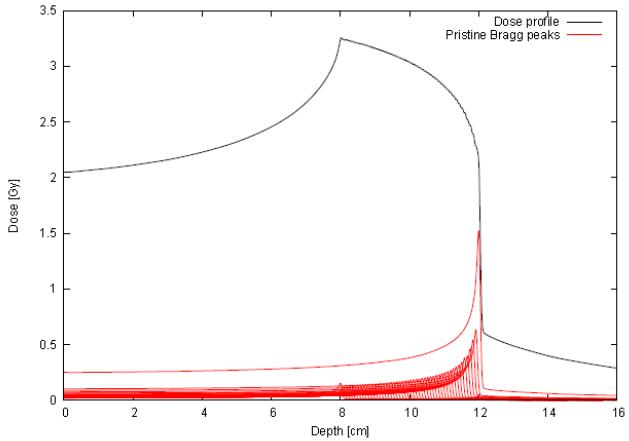
To obtain energy-fluence spectra at the desired depths for each ion, **interpolation** is performed:

- over the initial beam energy,
- over penetration depth,
- over energy in the energy-fluence spectrum

Survival at the desired depth can then be calculated directly by the Katz TST model.

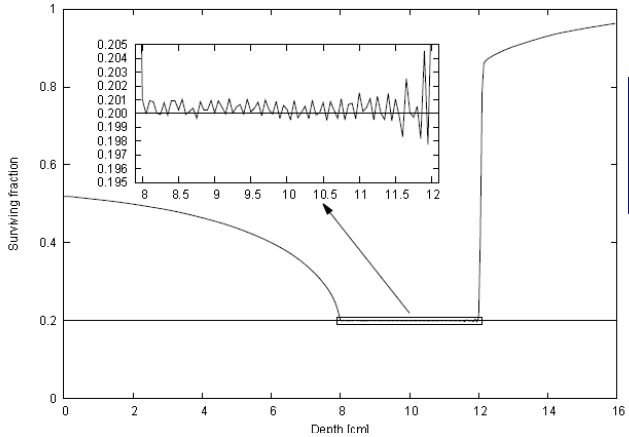
Leszek Grzanka, Ph.D. Thesis (2013)

Optimization of a constant depth-survival distribution

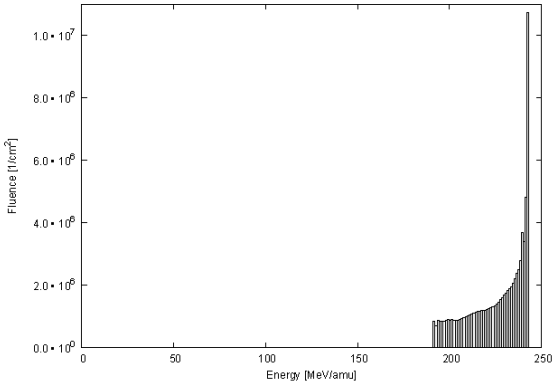


CHO cells - Katz model parameters:
$m=2.31$; $D_0=1.69$ Gy; $\sigma_0=5.96\cdot10^{-11}$ m^2; $\kappa= 1693$
desired survival S = 20% at 8-12 cm depth
Optimisation by L-BFGS-B algorithm.

Resulting dose profiles (49 pristine beams, and total dose)



Optimised survival level of 20% between 8-12 cm depth; CHO cells; 49 carbon beams in water,



Resulting initial energies and fluences of the 49 pristine carbon beams

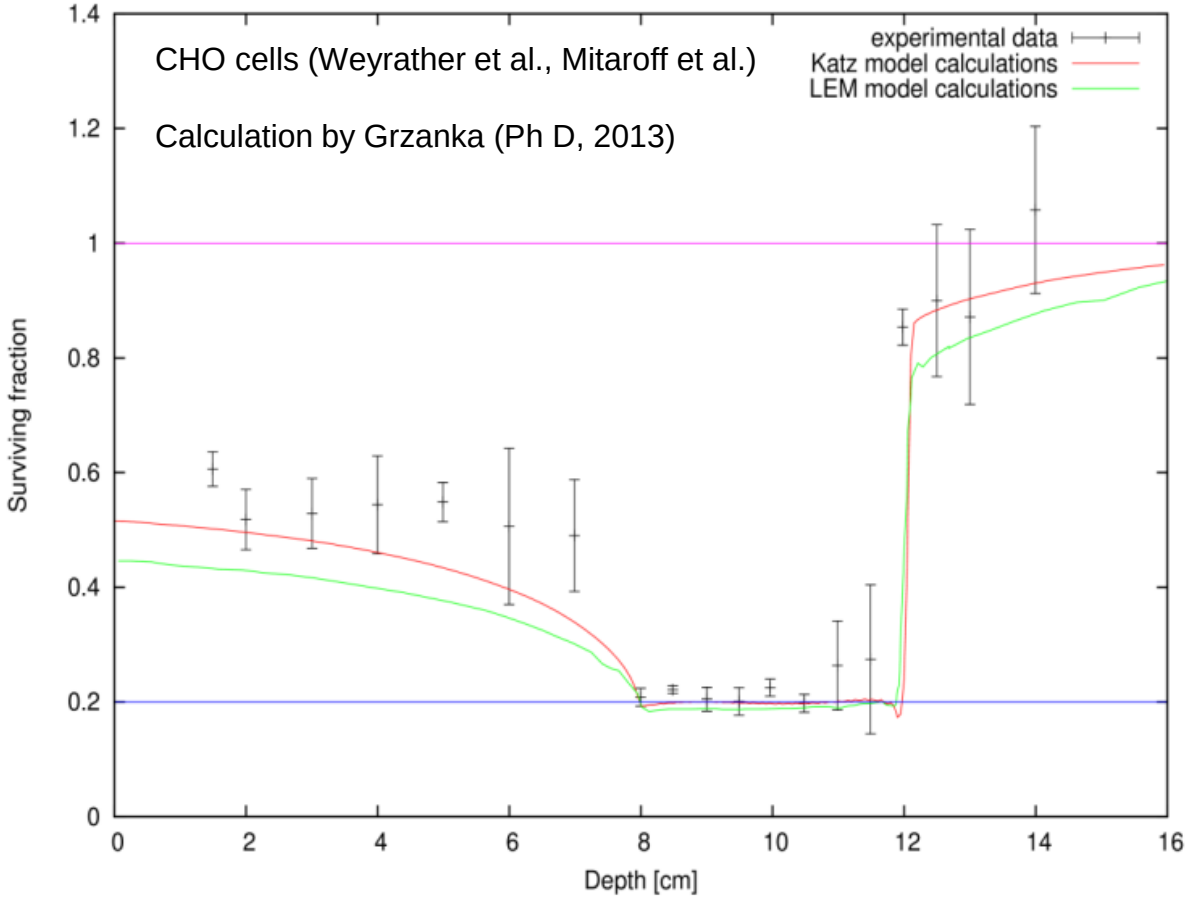
Leszek Grzanka, Ph.D. Thesis (2013)

Katz model calculation of survival uses the energy-fluence spectra at the desired depths for each ion, and superposes the „ion kill" and „gamma kill" components:

- over the energies of each ion species
- over the fluences of each ion species,
- over all ion species at a given depth

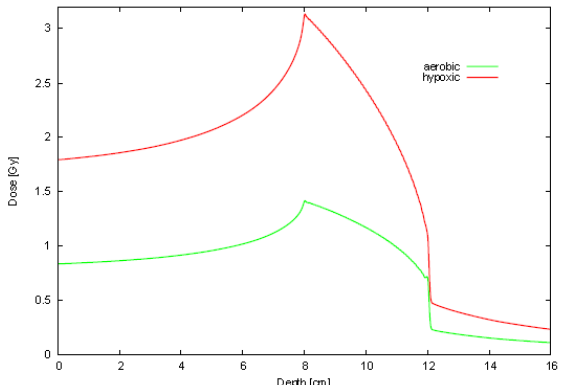
The optimisation routine then repeats this calculation until the desired depth-survival profile is achieved.

Comparison with LEM-calculated depth-survival distribution and with experimental data



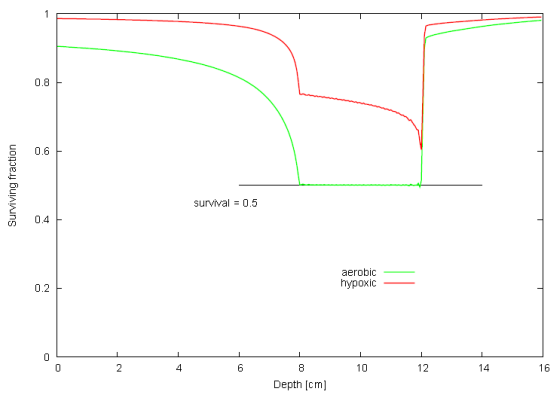
In carbon ion radiotherapy, secondary ion production must be accounted for, as well as the RBE of the carbon ions and secondaries, to evaluate the biological effect in the Spread Out Bragg Peak (SOBP) region and beyond.

Comparison of optimised depth-survival distributions for aerobic and anoxic V79 cells

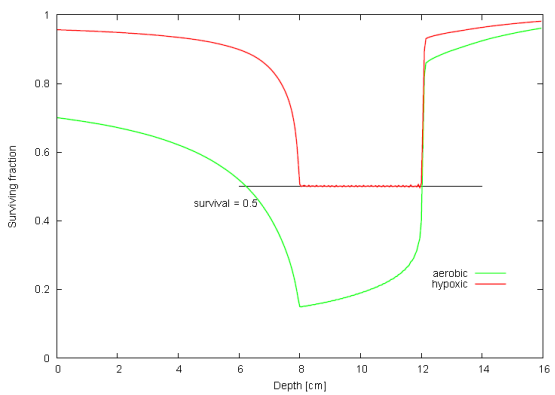


Resulting total depth-dose profiles, for 49 pristine carbon beams

V79 cells - aerobic
(m=2.91; D_0=2.05 Gy; σ_0=5.06·10^{-11} m^2; κ= 689)
V79 cells - hypoxic
(m=3.22; D_0=5.26 Gy; σ_0=5.53·10^{-11} m^2; κ= 1002)
desired survival S = 50% at depths 8-12 cm



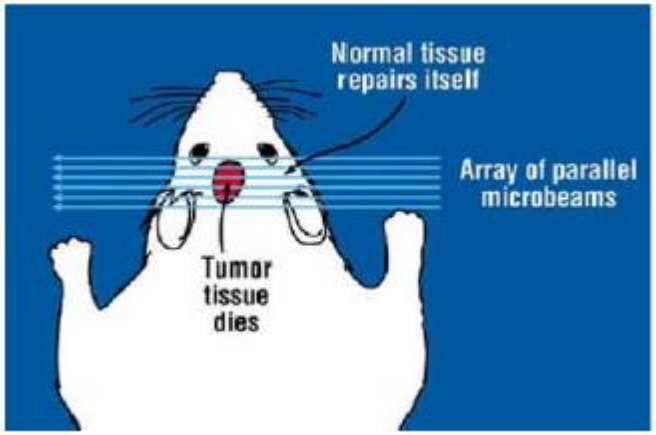
Optimised depth-survival of aerobic or hypoxic CHO cells at 50% survival between 8-12 cm depths.
49 pristine carbon beams in water were used in this calculation.



Leszek Grzanka, Ph.D. Thesis (2013)

Different depth-dose profiles have to be used to obtain 50% survival over 8-12 cm depths, for aerobic or hypoxic V79 cells, representing normal tissue and cancer cells, respectively.
This example illustrates the capability of the developed TPS kernel calculation to predict the required carbon beam characteristics in various radiotherapy situations.

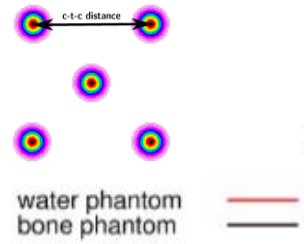
Novel radiotherapy beams (modelling)

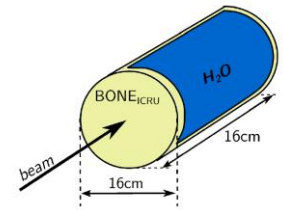


Proton microbeams

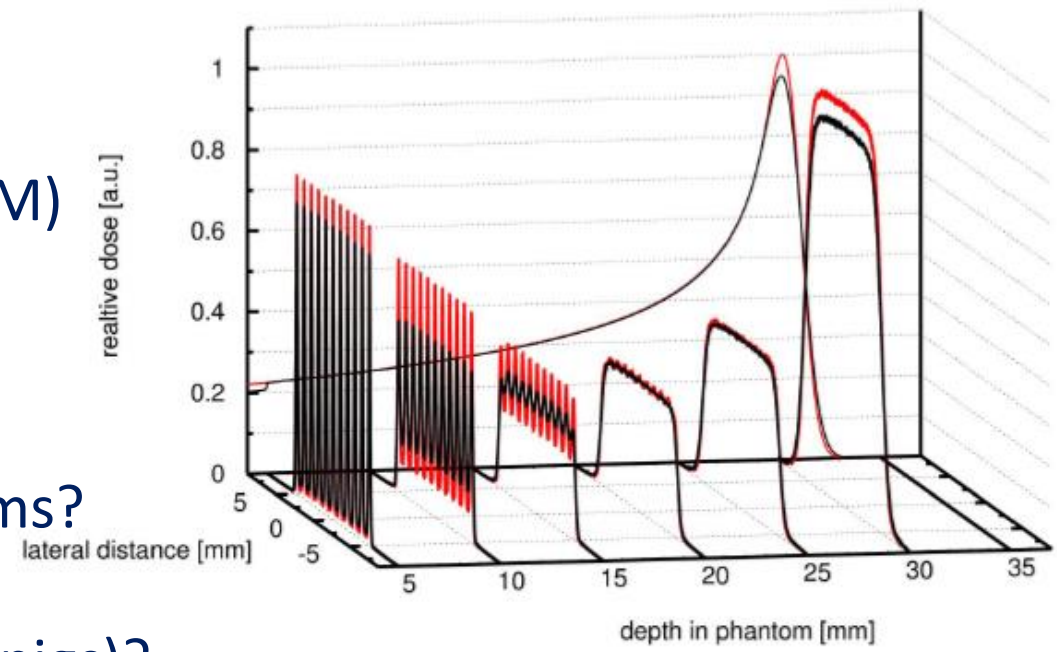
(Dilmanian et al. Int. J. Rad. Oncol., 2014)
(Kłodowska et al. Physica Medica, 2015)

(FLUKA MC)

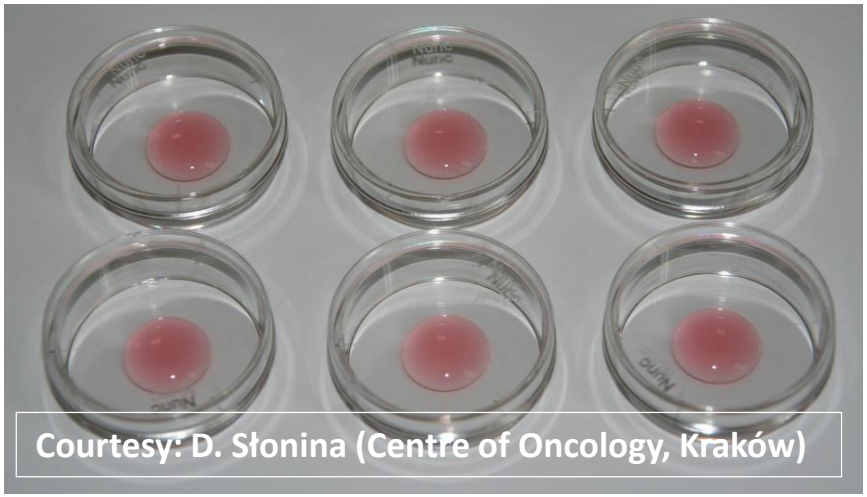




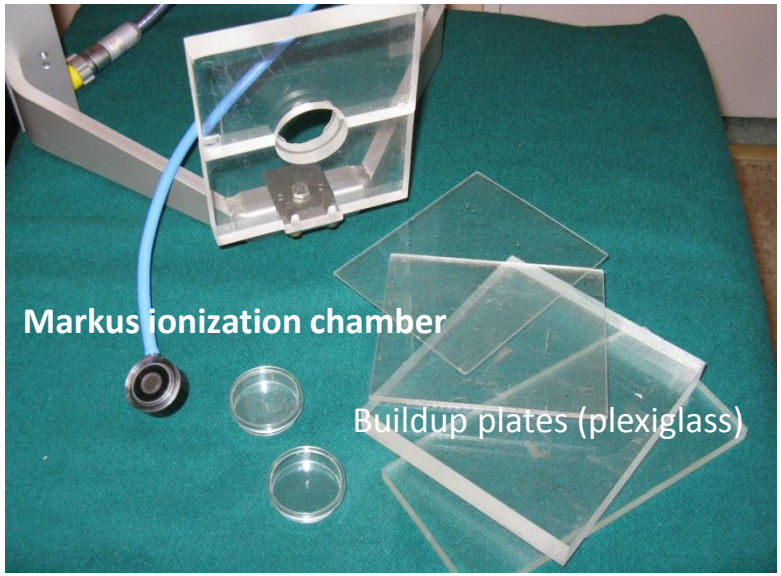
Ions: p, (He - C ??)
Energy: 60-120 MeV
Microbeam: ø = 100 µm (FWHM)
Separation : 1-6 mm
Horizontal/vertical beams?
Dosimetry: to be developed
SOBP: Passive & Scanning beams?
Skin culture?
Animals: small or larger (mice/pigs)?

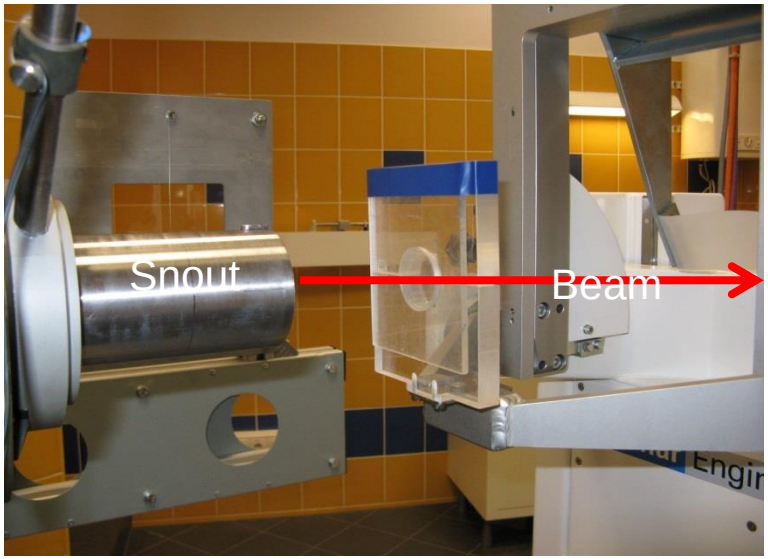


Experimental- Dosimetry, Radiobiology & RT



Cells ($1x10^5$) in 400 µl of medium, plated as a drop in the centre of a 35 mm Petri dish and left overnight to adhere (cells occupied an area ~ $1cm^2$)





Proton ocular radiotherapy facility
At IFJ PAN (AIC-144 cyclotron)

Energy: 60 MeV

Range in water: 35 mm

Beam c/s: ϕ5 cm (flat dose distr.)

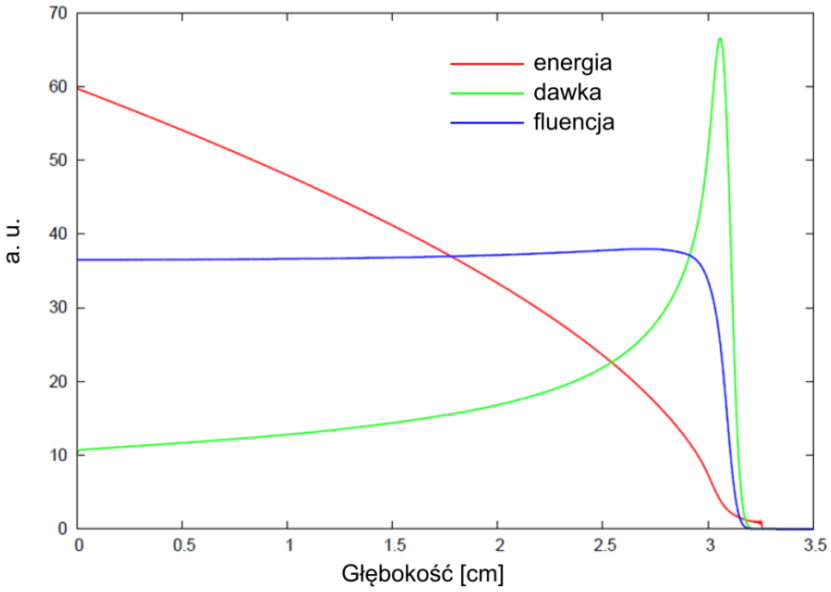
Dose rate at reference pt.~ 10 Gy/min.

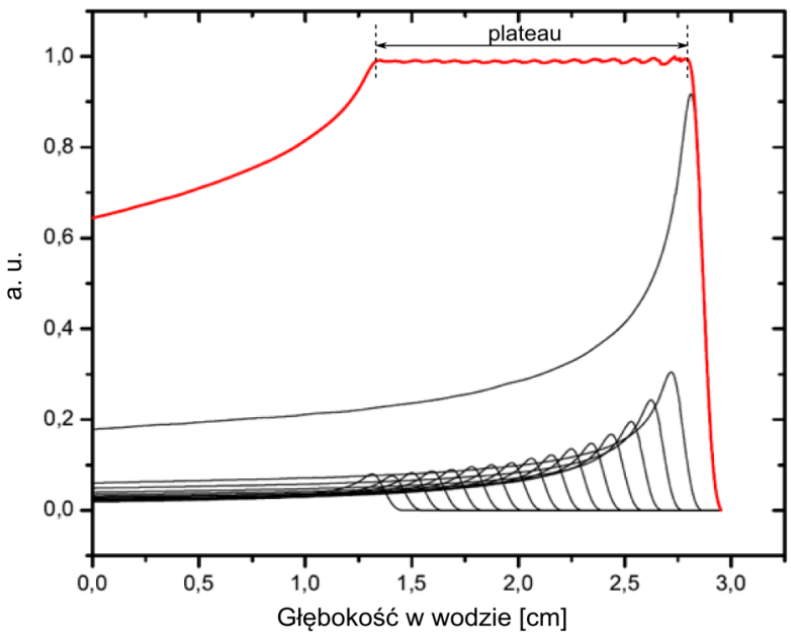
Horizontal beam

Dosimetry protocol: TRS 398

The 60 MeV proton cyclotron beam (AIC-144 @ IFJ PAN)

A 60 MeV proton beam is accelerated by AIC-144 cyclotron and applied in treating ocular melanoma patients. Passive SOBP is achieved by rotating step PMMA wedges



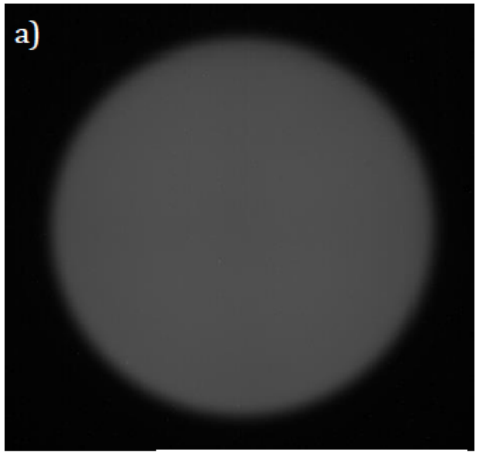


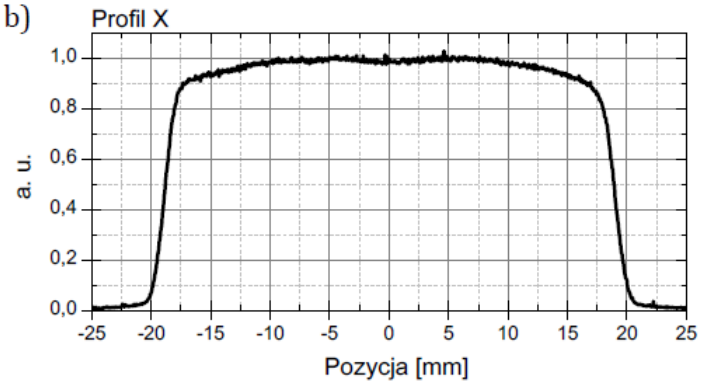
Fluca MC - calulated energy, dose & fluence vs depth in pristine and SOBP beams

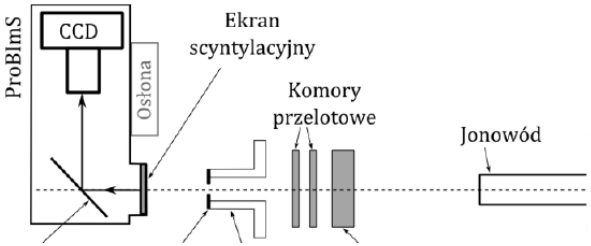
All calculations by Leszek Grzanka (2013)

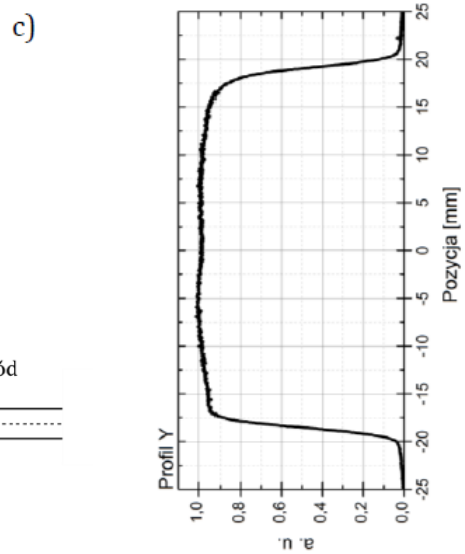
Experimental – 60 MeV proton cyclotron beam (IFJ PAN)

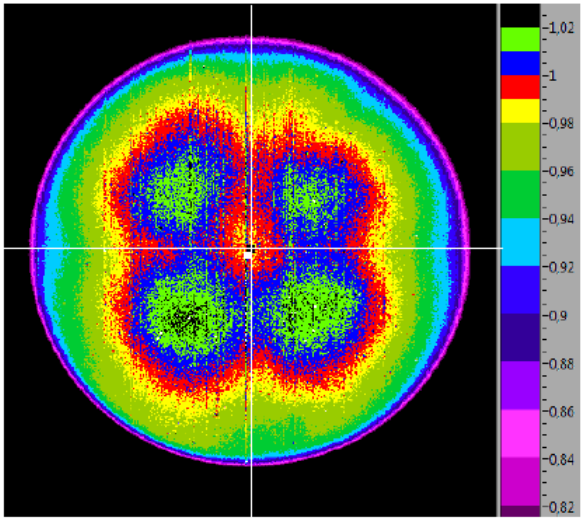
Beam specification by scintillator screen and CCD camera





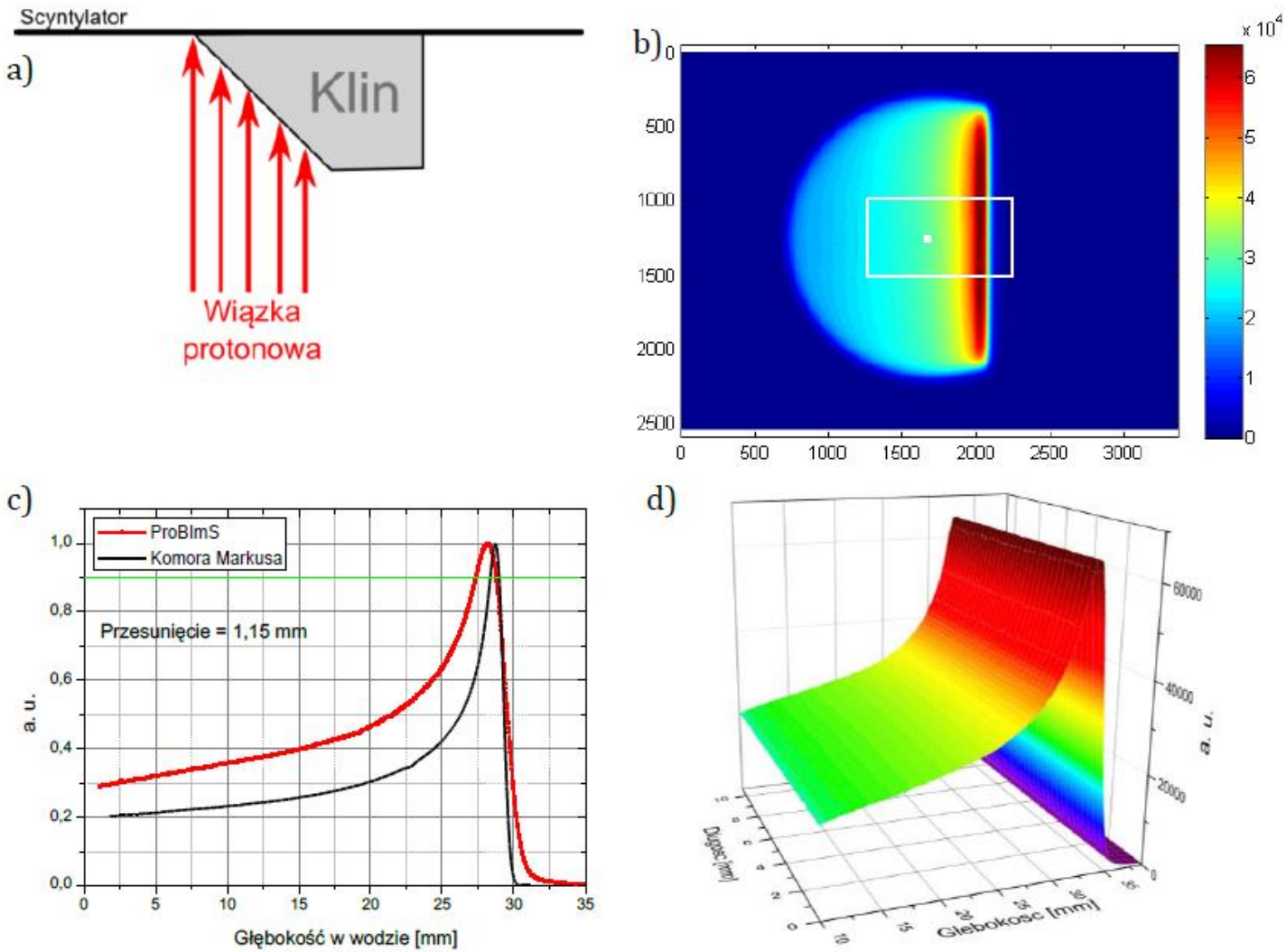






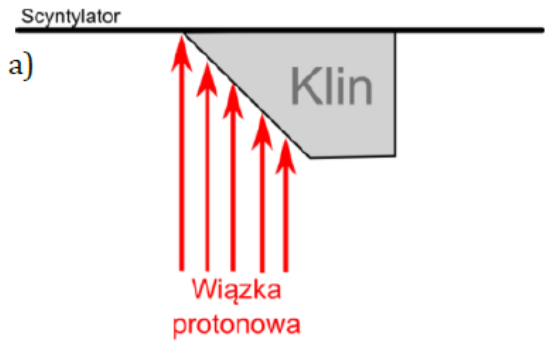
Experimental – 60 MeV proton cyclotron beam (IFJ PAN)

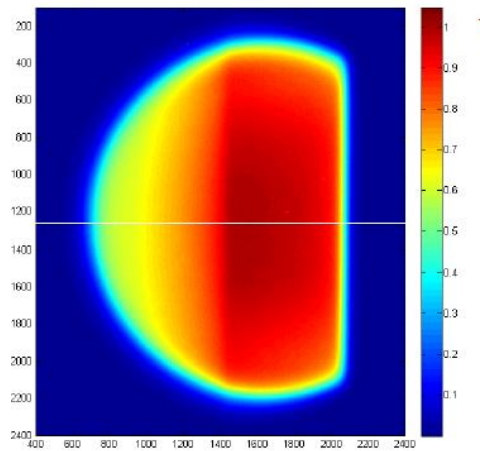
Beam specification by scintillator screen and CCD camera with PMMA wedge – pristine BP

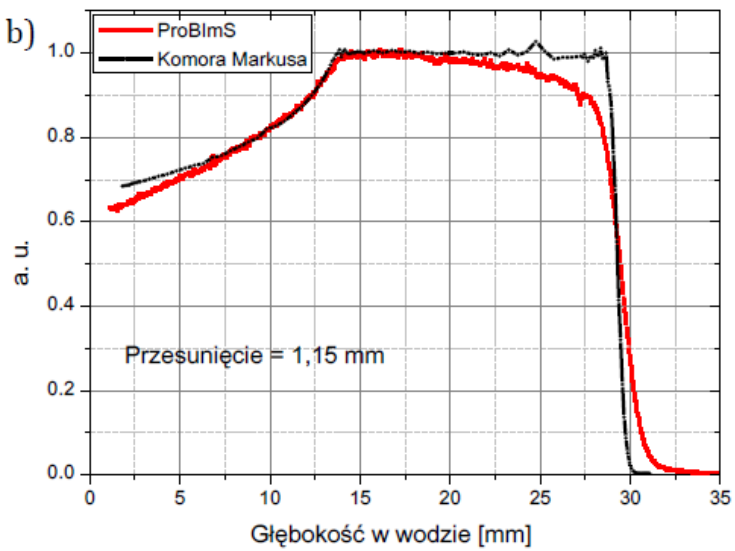


Experimental – 60 MeV proton cyclotron beam (IFJ PAN)

Beam specification by scintillator screen and CCD camera with PMMA wedge - SOBP



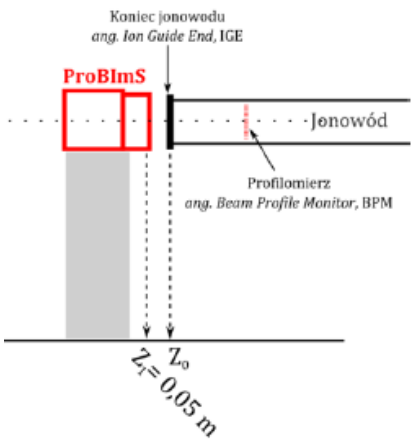




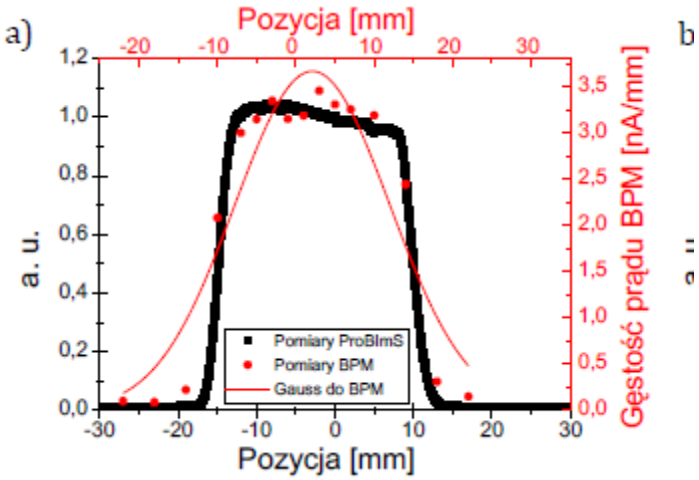
Marzena Rydygier, Ph. D. Thesis (2016)

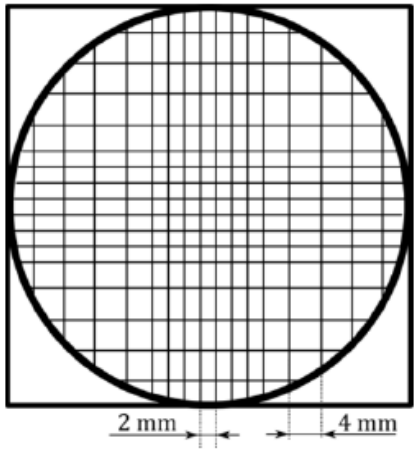
Experimental – 70 MeV proton cyclotron beam (IFJ PAN)

Beam specification by scintillator screen and CCD camera – comparison with BPM

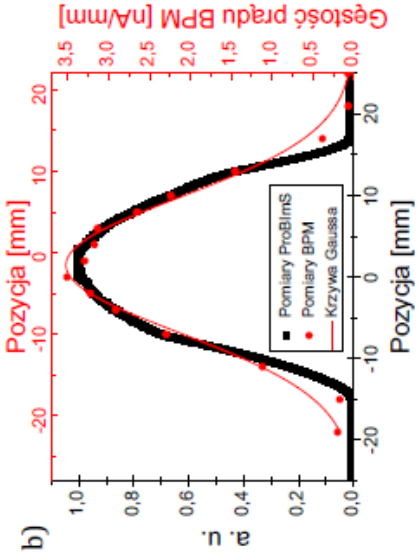


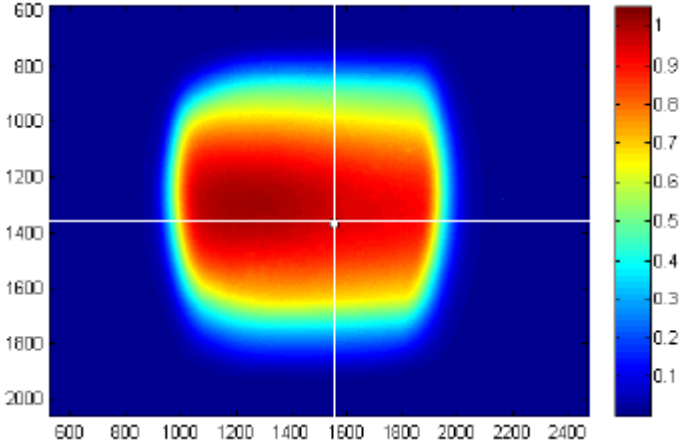
IBA Proteus C 235 Cyclotron





Wires in the Beam Profile Meter





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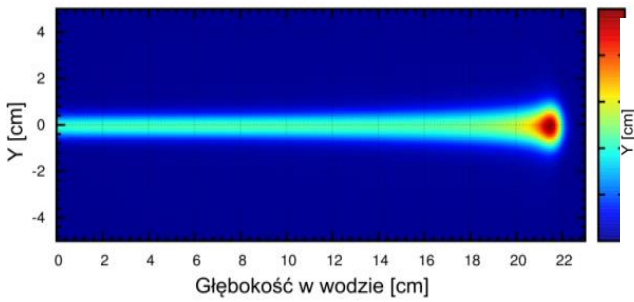
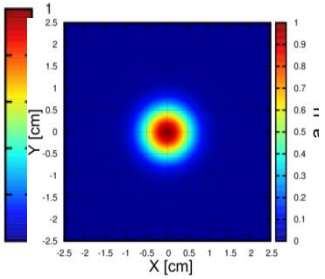
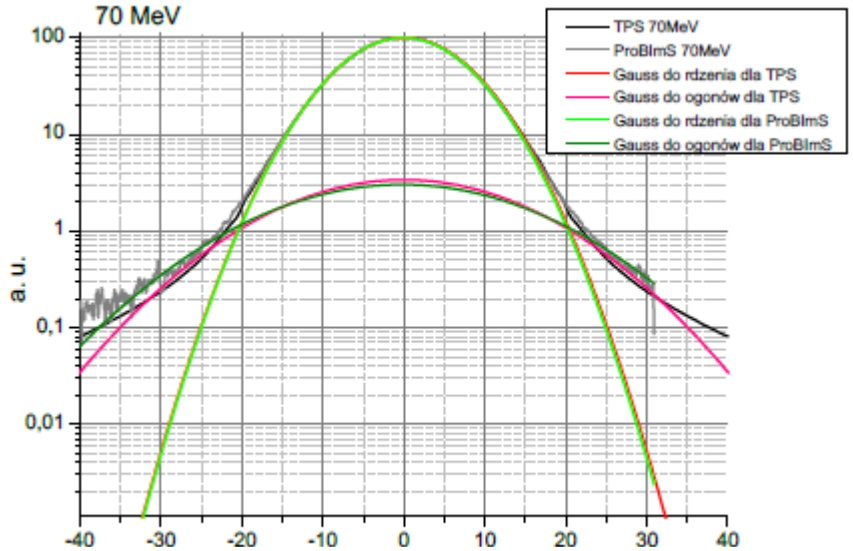
Proton cyclotron pencil beams (Proteus C 235, IFJ PAN)



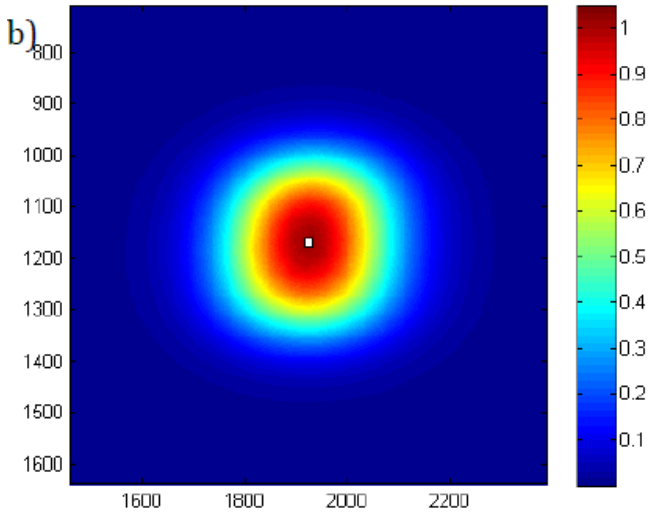
Fluka calculation of 180 MeV proton pencil beam in water

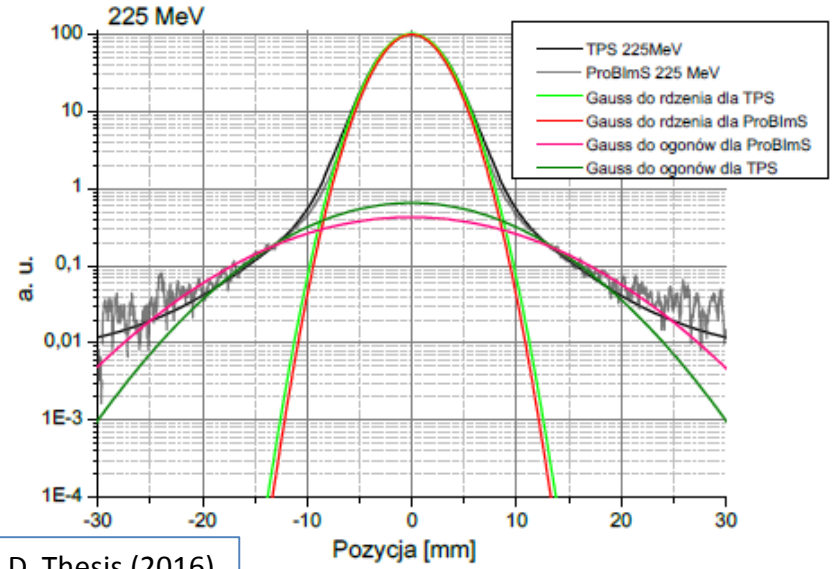


c/s at 20 cm depth



Pencil beam specification by scintillator screen and CCD camera (70 MeV & 225 MeV)





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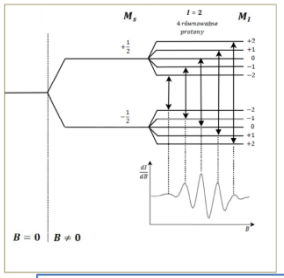
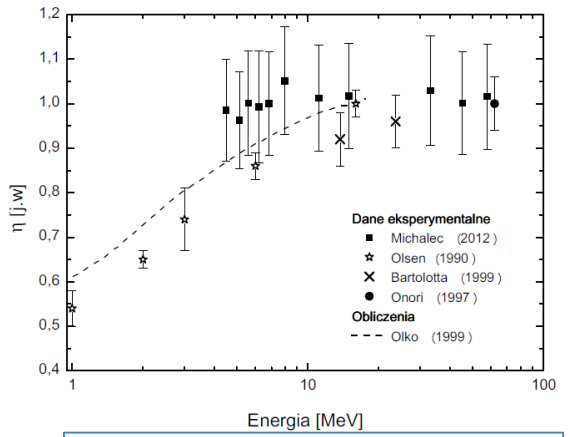
Experimental – 60 MeV proton cyclotron beam (IFJ PAN)

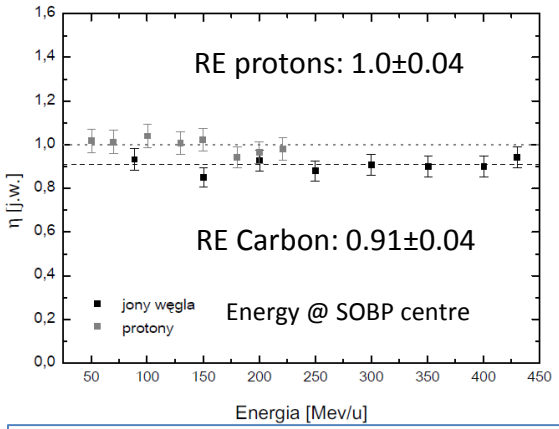
Alanine ESR Free Radical dosimetry



ESR spectrum

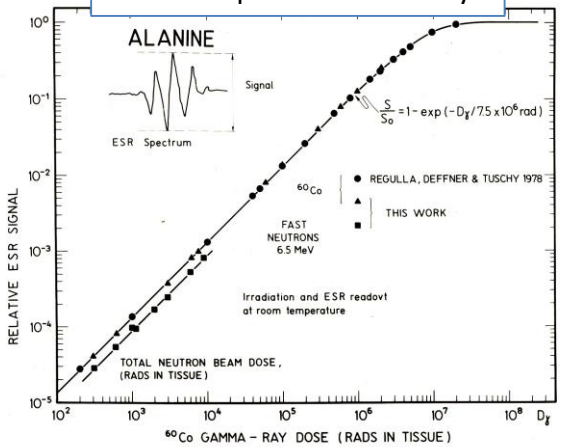


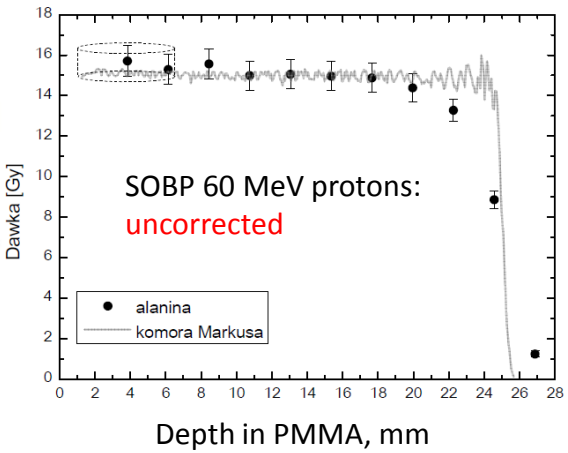
Relative Effectiveness ~ 1 above 10 MeV p

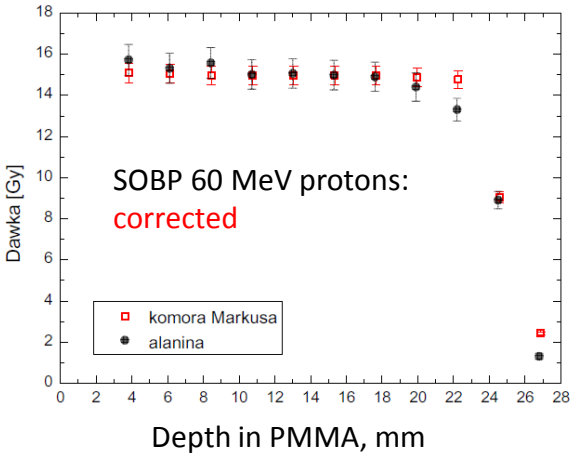


Relative Effectiveness in SOBP @ 60-400 MeV p,C

Linear response: 1- 1000 Gy







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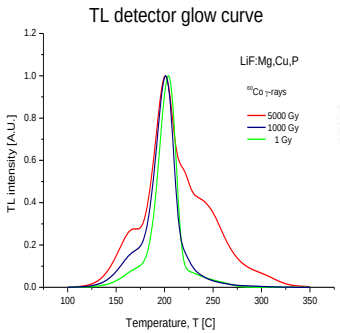
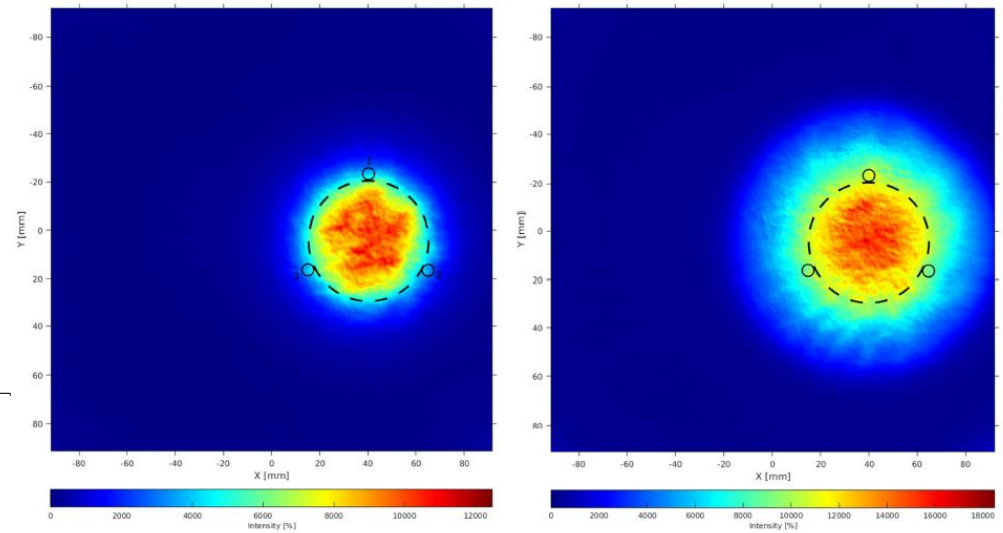
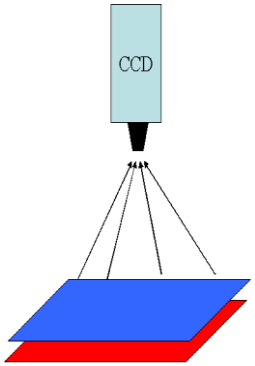
Experimental – 60 MeV proton cyclotron beam (IFJ PAN)

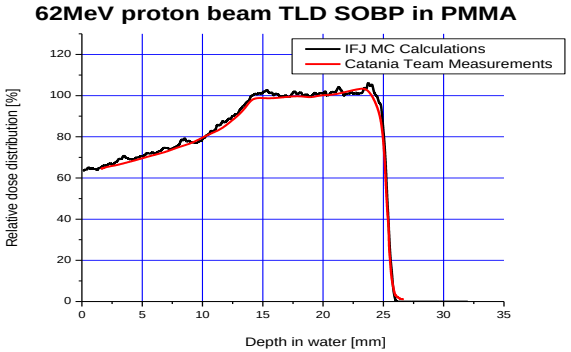
Thermoluminescent dosimetry- foils





60 MeV proton AIC-144 beam measured by TLD foils:
Positions of Φ 5 cm collimator and of alanine detectors marked





A Wish List - Accelerator requirements (1/2)

(compiled with the help of Mike Holzscheiter, Niels Bassler, and Alberto Del Guerra)

Ion species: Lighter (H, He, Li, Be, B, C, N, O), heavier (Ne, Ar, Fe, Ar , Kr?,Xe?, Pb? U?) No need for a complete range. The lighter ions are for radiobiology and radiotherapy, the heavier for physics, dosimetry , detector studies, radiation protection and some radiobiology;

Ion energy: **Lower (< 70 MeV/u) , higher (50 -500 MeV/u) and highest (>1 GeV/u)** Lower energies for radiobiology, higher for medical applications (radiotherapy , dosimetry) , highest for physics and dosimetry. Physical data (for MC and therapy planning) to be gathered at all energies for all ion species;

Beam Lines: Vertical (50 or 70 MeV/u) for radiobiology and radiotherapy (animals); **Horizontal** (all energies);

Extraction: Fast uncomplicated energy switching (spill by spill), either directly in synchrotron mode, or by a range shifter;

A Wish List - Accelerator requirements (2/2)

Irradiation field : Uniform over at least some 5 x 5 cm^2 (1-2% homogeneity over entire field) for radiobiology, for both **vertical and horizontal beams**. **SOBP: passive** (wobbler, or wedge filters) **and active** (commercial scanning head?), **preferably for vertical and horizontal beams**. Ripple filter (3 or 5 mm) for building flat SOBPs; passive SOBP using ridge filters, should be provided for most common ions; **Pencil beams** should be available upon request, with good knowledge of FWHM, divergence and focus point (multi-spot rather than a single pencil beam);

.

Dosimetry and fluence monitoring: with precision at isocenter to within 2% or better, basic dosimetry support required (ionization chambers, etc.);

Beam Intensity: continuously variable (from over some 10^9 ions/sec downwards). The higher intensities are for radiotherapy and detector tests, the lower for radiobiology. During a therapy spill the intensity should be no lower than 10^9 ions/sec and must be tailored in a continuous way for physics or for specific experiments.

A Wish List – Equipment & Support

At target area (isocenter): XYZ translator, with sub mm precision; water phantom (PTW MP3 or similar); laser guides; video surveillance, data transfer systems & power supplies;

Access to machine shop facilities: tasks include building custom sample holders, custom phantoms, etc.;

Access to reference sources: Co-60 reference unit (c. 2 Gy/min.), X-ray reference unit (e.g. 250 kVp, variable dose rate, 0.5 Gy/min – c.. 5 Gy/min);

On-site tissue culture laboratory, equipped (see next slide)**;**

Dedicated office space for visiting groups (how large?) ;

Managing officer (to instruct on use of equipment, collaborate with users, liaise with accelerator staff, workshop, to design and maintain dosimetry and control equipment, power supplies, communication networks, data tranfer, etc.) Also to perform his own research on site.

Flexible design of research area: to incorporate future themes, research issues and technology development;

Stable financing: European/world collaboration programmes (Horizon 2020?)

A Wish List – The Clean Room

The dedicated clean room for biology & radiobiology experiments should contain:

- 4 incubators, or more (bottleneck)
- 3 flowbenches for handling of sterilesamples
- 1 fumehood
- refrigerators for and grow media
- freezer -20 for cell cultures
- freezer -80 for cell cultures
- 2 centrifugues
- cell counter
- autoclave
- special glassware dishwasher
- 2 standard microscopes
- 1 UV microscope (nice to have)
- Biohazard disposal?
- Gas supply (CO_2 for incubators)
- Water-sterilizer
- ~ 10 meters of bench space
- consumables (gloves, pipettes, etc.?) to be provided by visiting groups

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