RADIOBIOLOGICAL RESEARCH WITH CHARGED PARTICLES BEAMS IN ITEP

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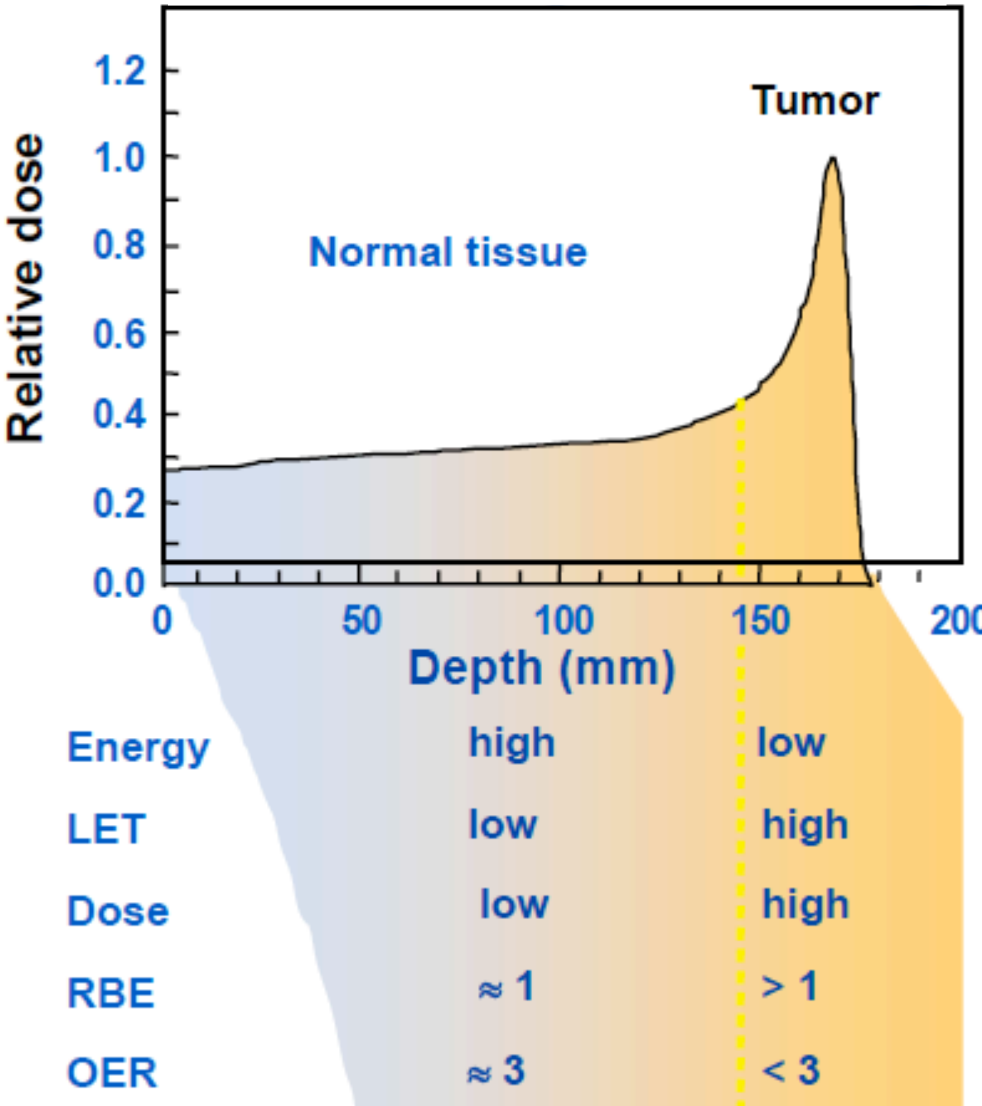
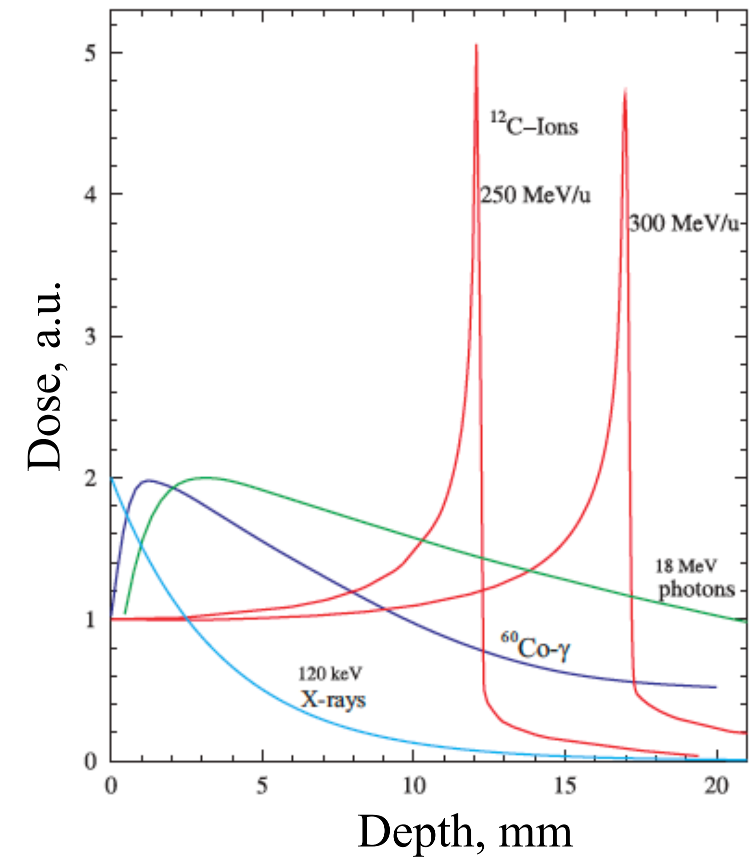
Motivation: Heavy Ion Therapy

Biological Advantages of high LET RT





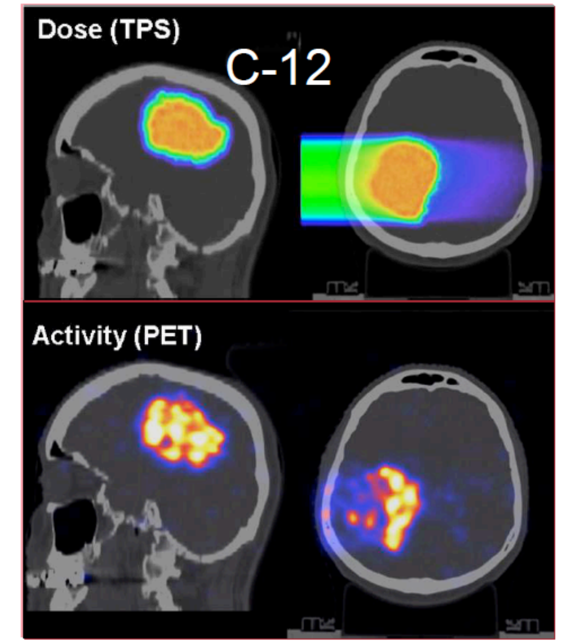
Tumor dose >> normal tissue

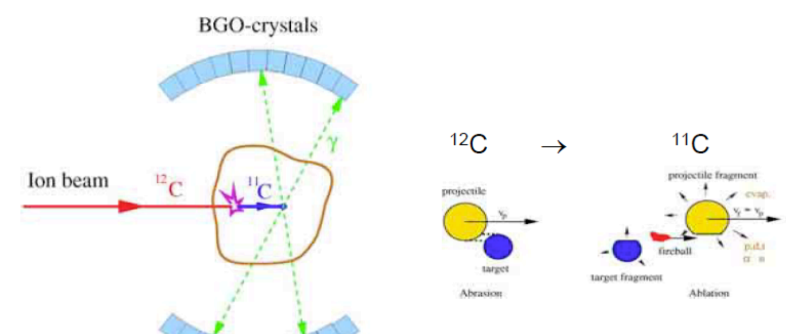
Effective for radioresistant tumors

Effective in hypoxic tumor cells

Durante & Loeffler, Nature Rev Clin Oncol 2010

In vivo PET Monitoring





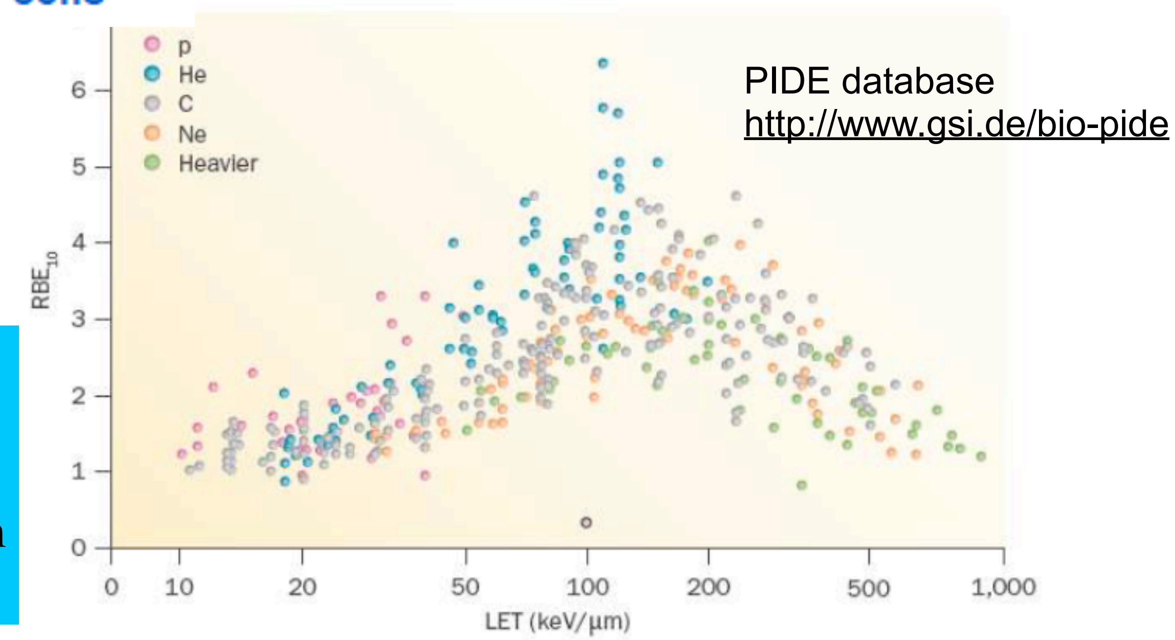
K. Gunzert-Marx

Key research areas in hadrontherapy

1. Moving targets
2. TPS: RBE modeling, reducing uncertainly
3. Secondary cancer risk
4. Individual radiosensityvity
5. Genetic background
6. Cancer stem cells
7. Hypofractionation

Availability of Heavy Ion Therapy is increasing worldwide - 8 centers in operation, 3 under construction. Approx. 11000 patients were treated with C-ions since 1994 (http://www.ptcog.ch)

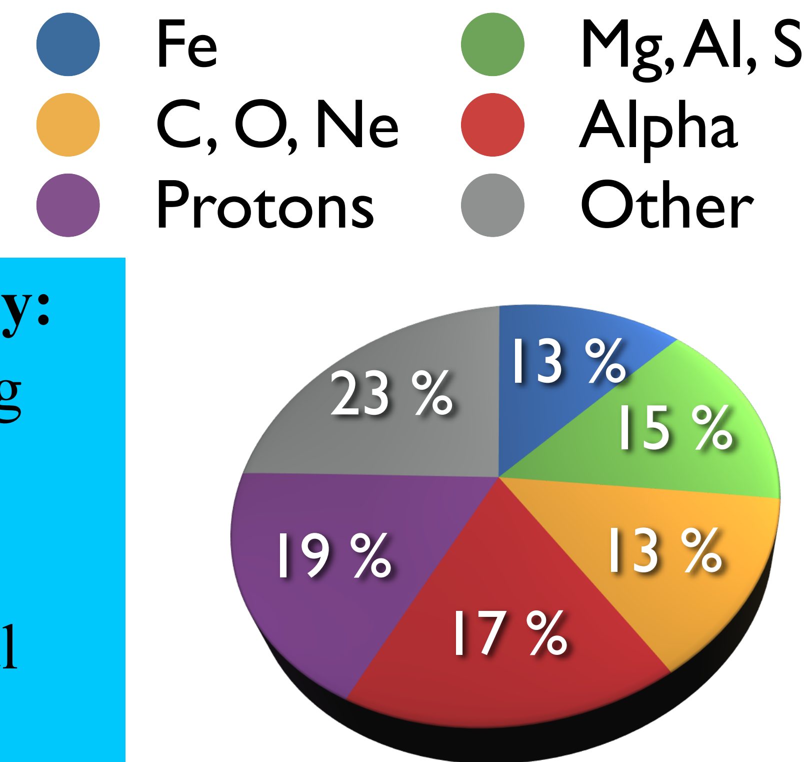
Dependence of RBE on LET



Motivation: Radiobiology for Space Research

1. Galactic Cosmic Rays (GCR) - high energy protons; highly charged, energetic atomic nuclei (HZE particles)
2. Solar Particles Events (SPE) - medium and high energy protons
3. Trapped Radiation - medium energy protons and electrons

Relative Contribution of Different Components of GCR to Dose Equivalent

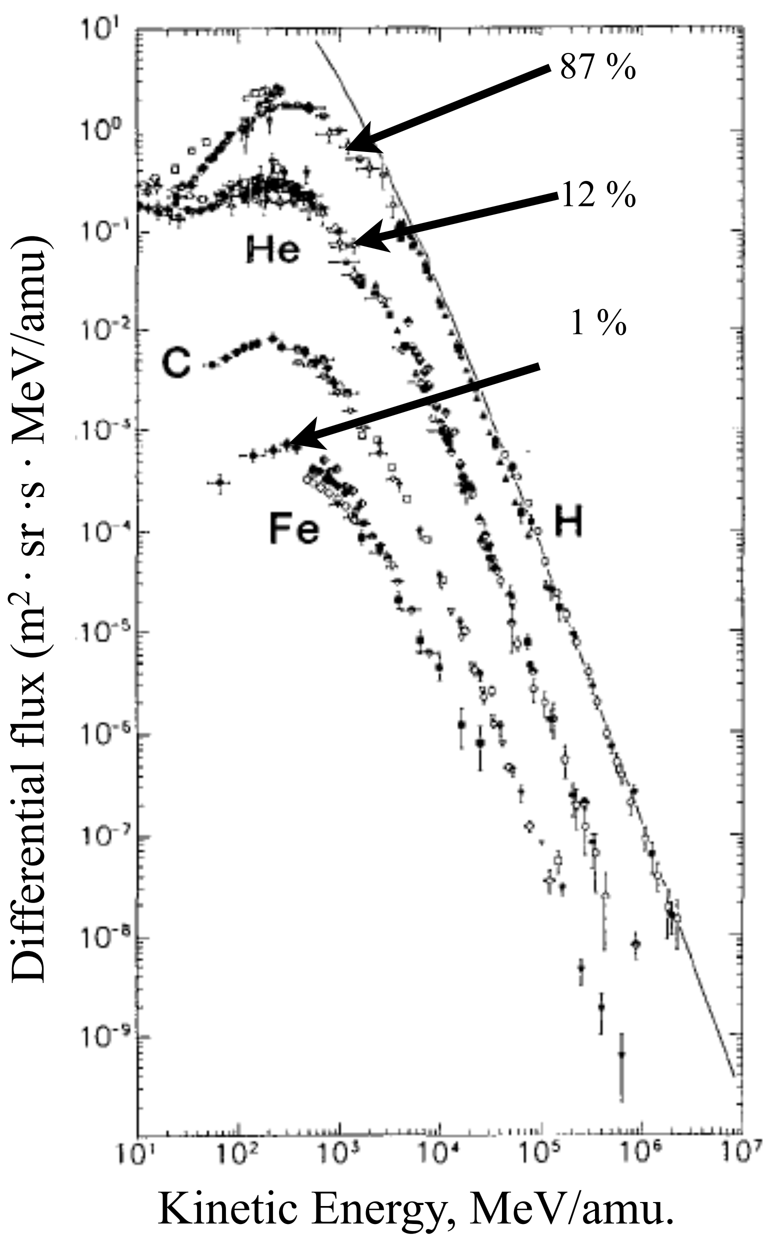


* behind aluminum of 5g/cm^2

Main objectives of space radiobiology:

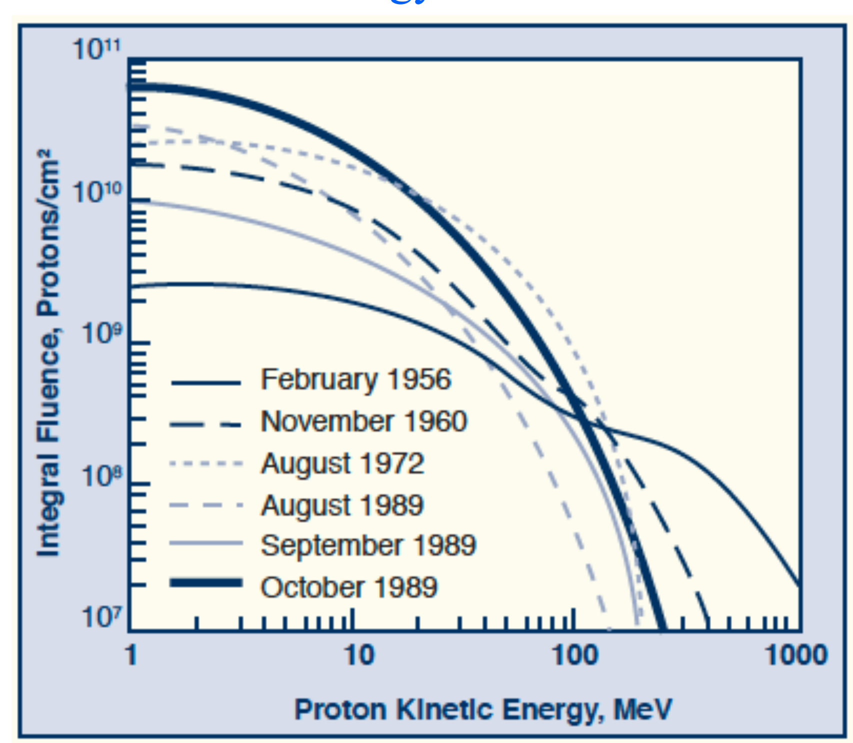
- Development of an effective shielding against space radiation;
- Reduction of biological uncertainty;
- Estimation of the risks of the harmful radiation effects (neurodegeneration, cancer induction);

Energy Spectra of GCR



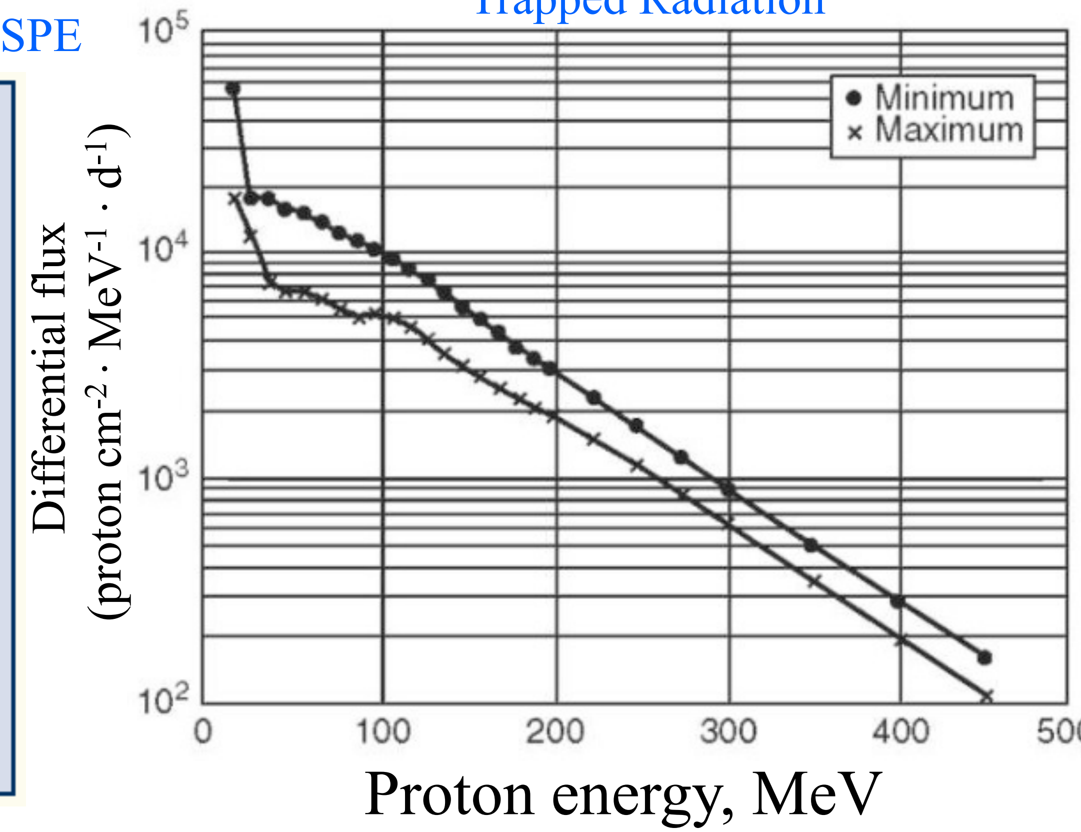
J.A. Simpson

Distribution in Energy of Proton Fluxes in SPE



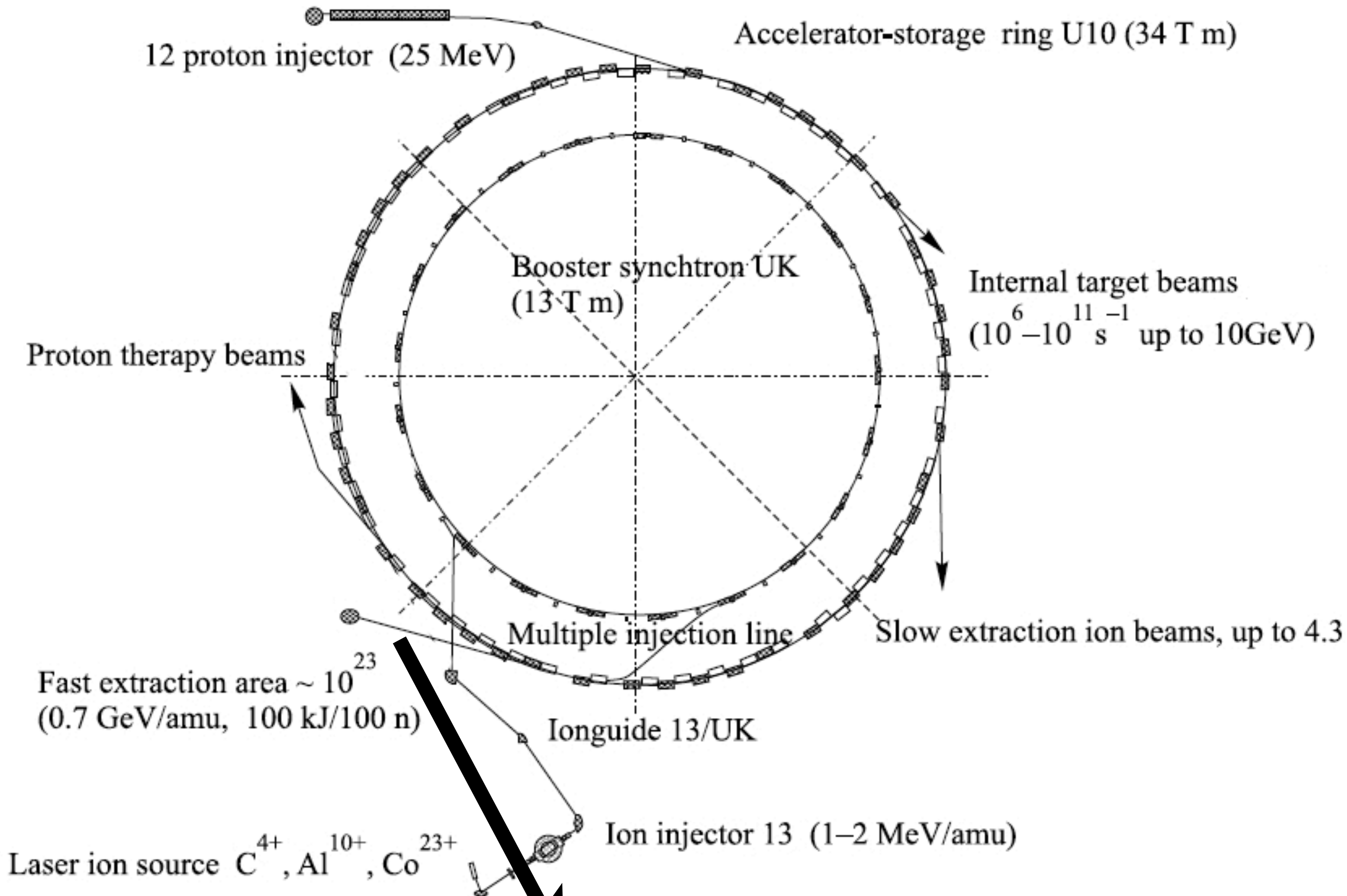
NASA Strategic Plan

Trapped Radiation



Heavy ions for radiobiology in ITEP

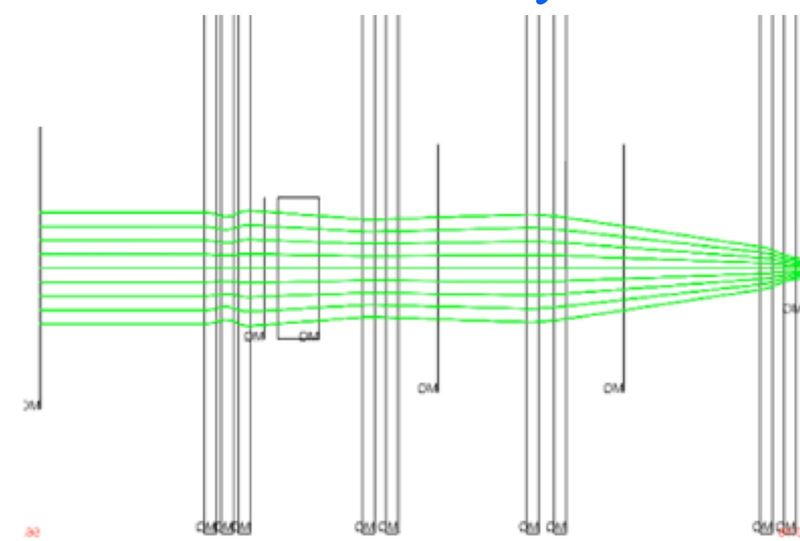
ITEP-TWAC accelerator facility

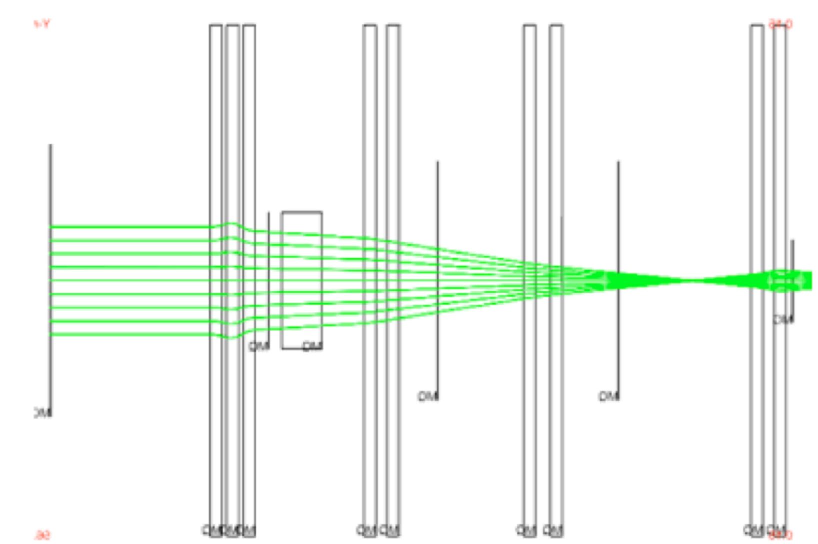


Beam parameters

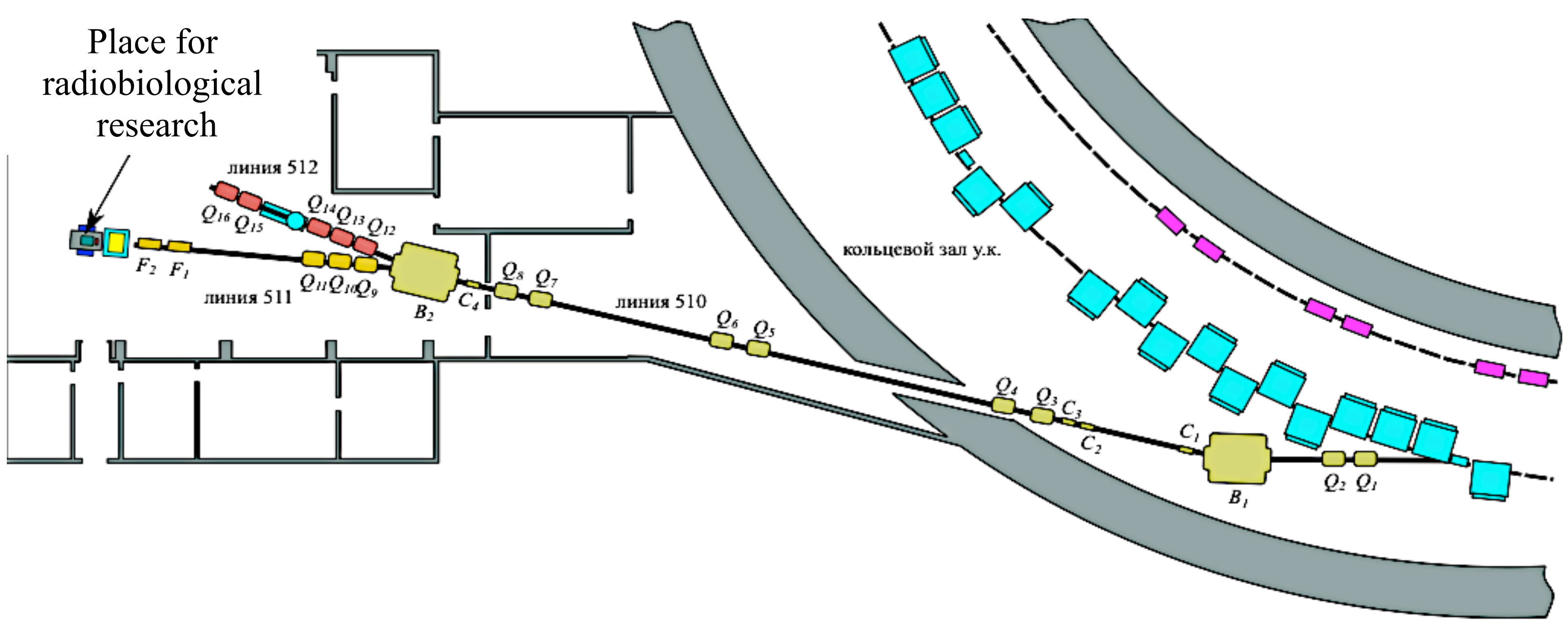
Ion	$^{12}C^{6+}$	$^{56}Fe^{26+}$
Energy	215 MeV/amu	230 MeV/amu
Particles per pulse	10^6 - 10^9	10^6 - 10^8
Pulse width	800 ns	800 ns

Results of beam dynamic calculation with COSY Infinity

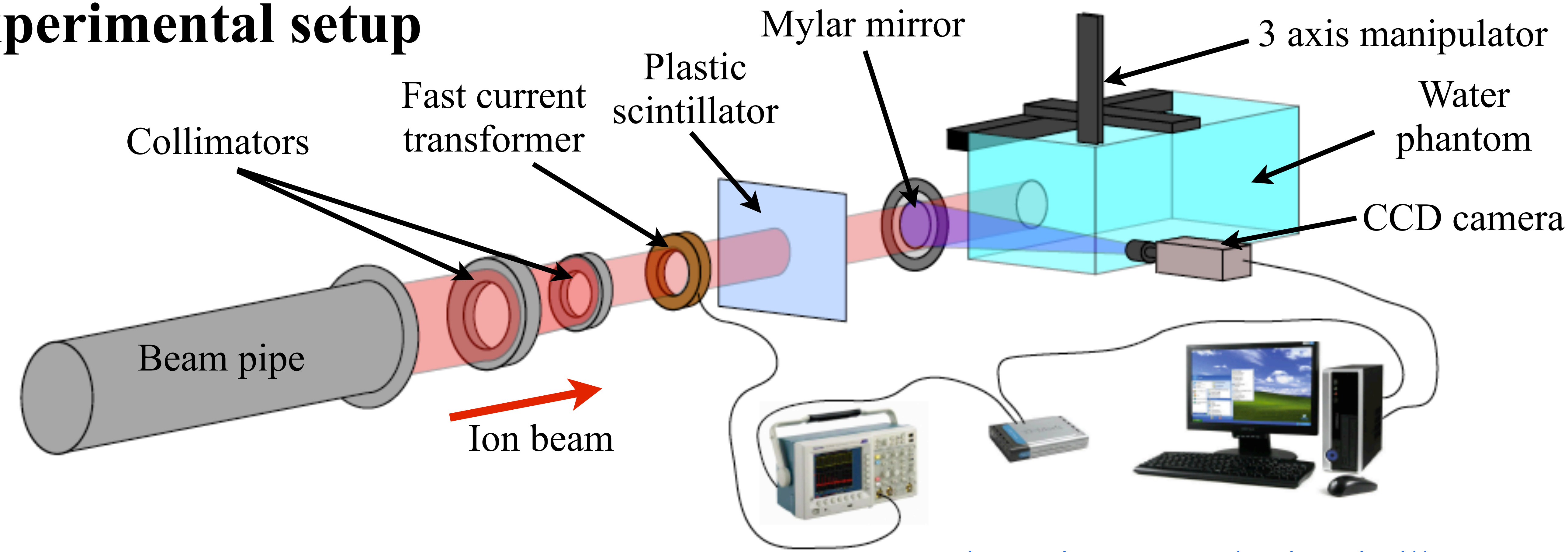




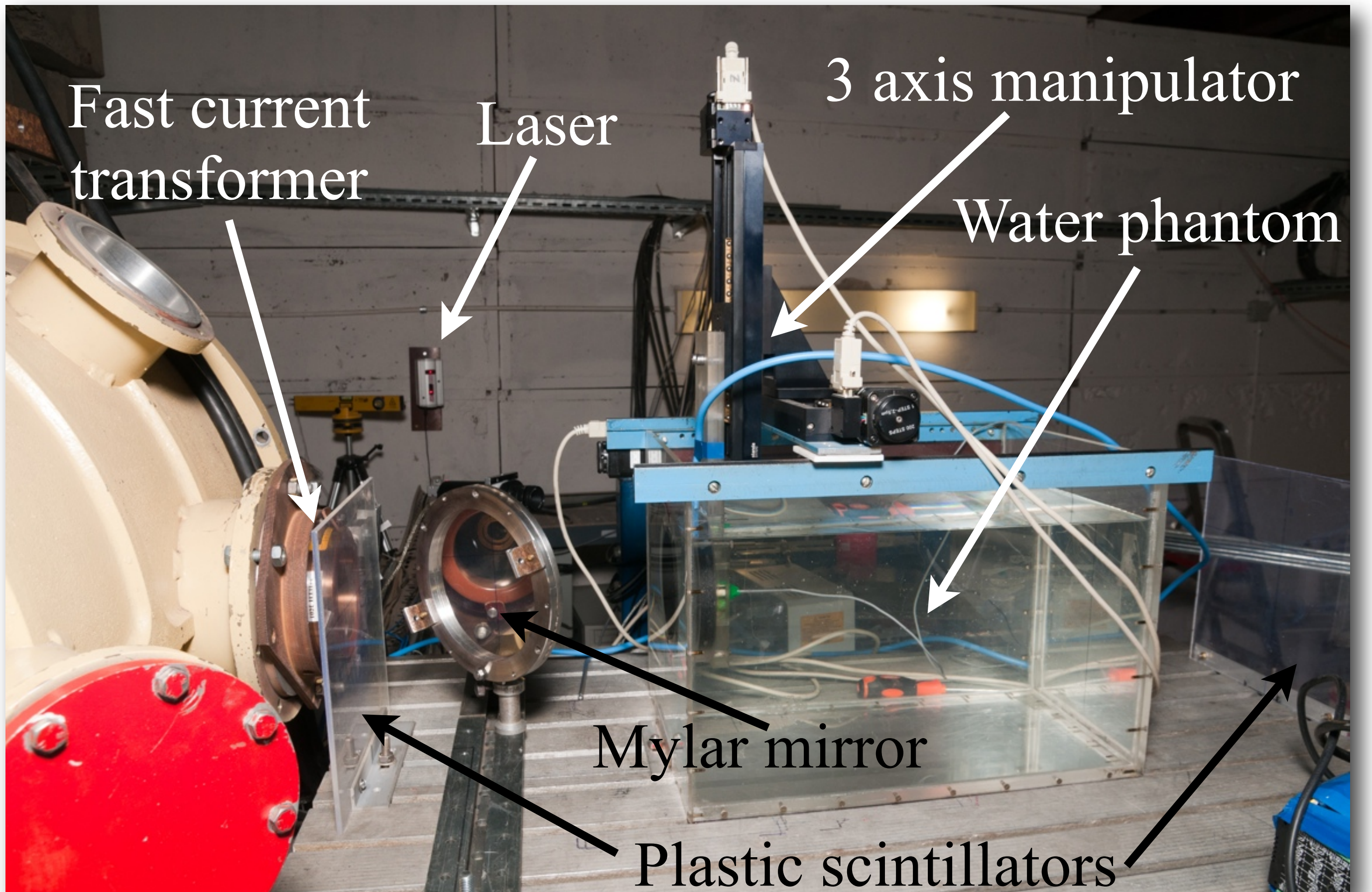
Fast extraction beam line



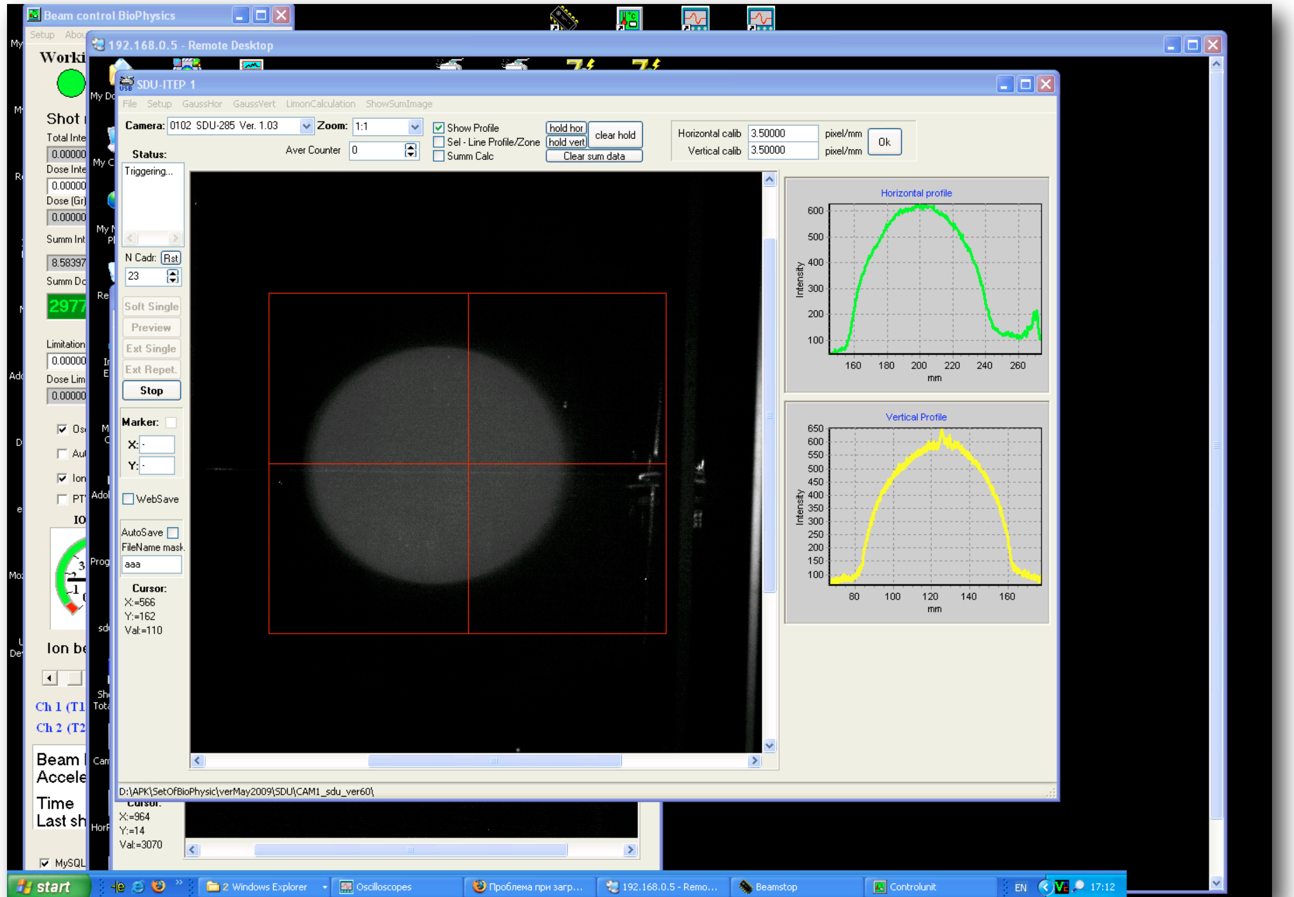
Experimental setup



Experimental setup



Ion beam image on plastic scintillator

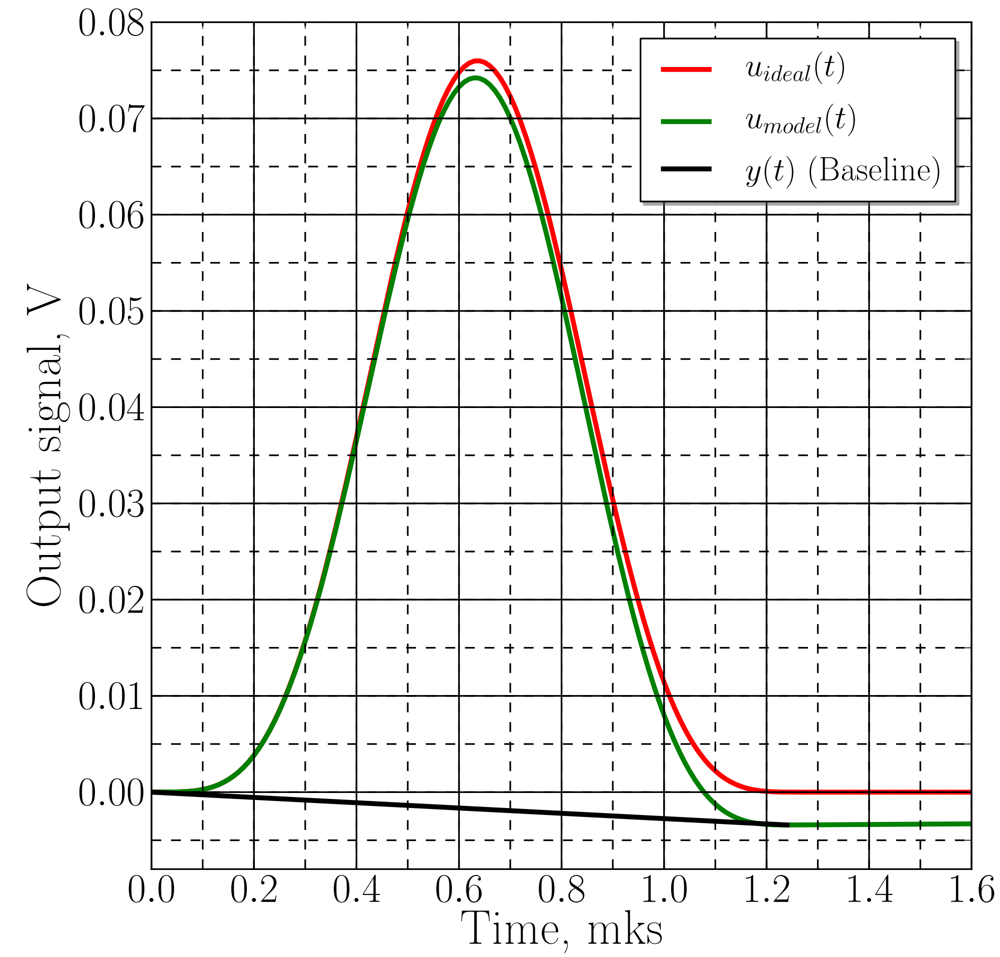


Particles measurements

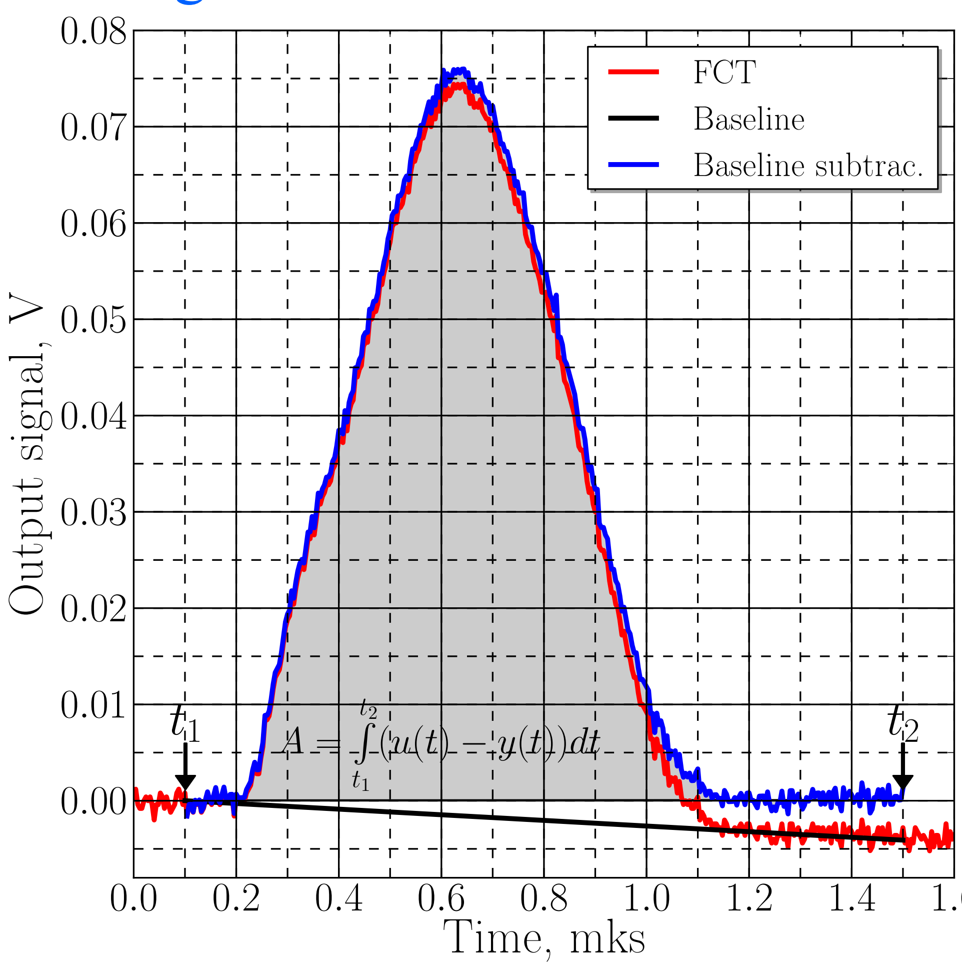
Fast current transformer FCT-082 (Bergoz)

Sensitivity	5 V/A
Rise time	500 ps
Droop	< 20 %/mks
Upper cutoff frequency -3dB	700 MHz
Lower cutoff frequency -3dB	< 32 kHz
L/R time constant (min.)	5 mks

Numerical calculation of FCT signal



Signal from current transformer



1. Beam pulse function

$$i_b(t) = \begin{cases} a(\cos(bt)^2 - 1)^2 & t \in [0, \frac{\pi}{b}] \\ 0 & t \notin [0, \frac{\pi}{b}] \end{cases}$$

2. FCT transfer function

$$G(p) = S\frac{p}{p + \frac{1}{\tau_d}} = S\left(1 - \frac{1}{\tau_d\left(p + \frac{1}{\tau_d}\right)}\right) \Rightarrow$$

$$\Rightarrow g(t) = \mathcal{L}^{-1}\{G(p)\} = S\left(\delta(t) - \frac{1}{\tau_d}e^{-\frac{t}{\tau_d}}\right)$$

3. FCT output signal

$$u_{model}(t) = i_b(t) * g(t) = \int_0^t i_b(t - t')g(t')dt'$$

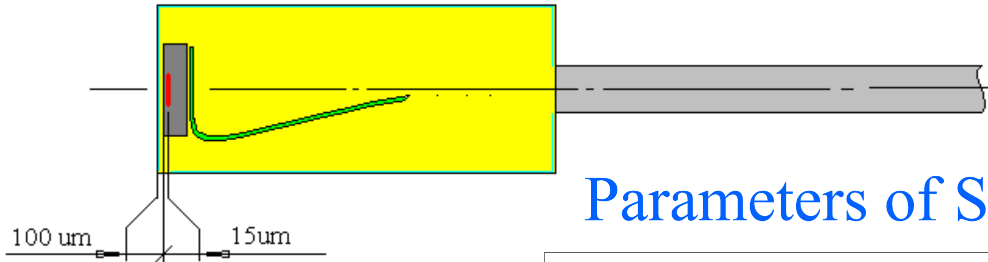
4. Relative error

$$\sigma_{Bl} = \left(\frac{\int(u_{model}(t) - y(t))dt}{\int u_{ideal}(t)} - 1\right) \cdot 100\% \longrightarrow$$

Total relative error in number of particles per pulse: $\sigma_N \leq 3.5\%$

Depth-dose curve measurements

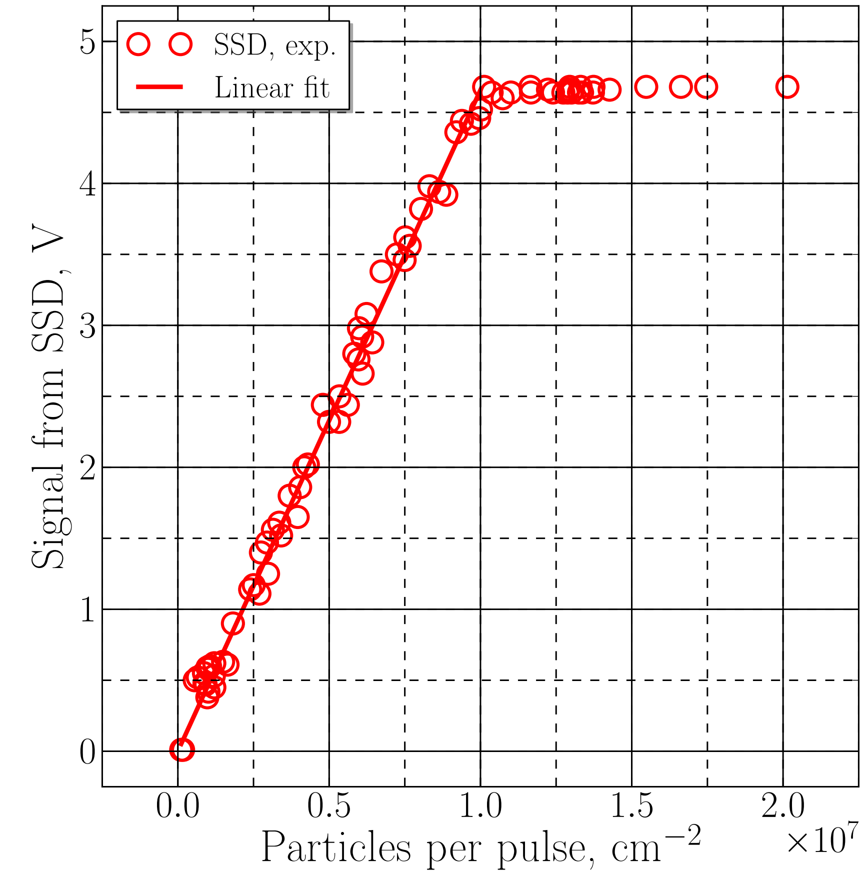
Silicon Semiconductor Detector (SSD)



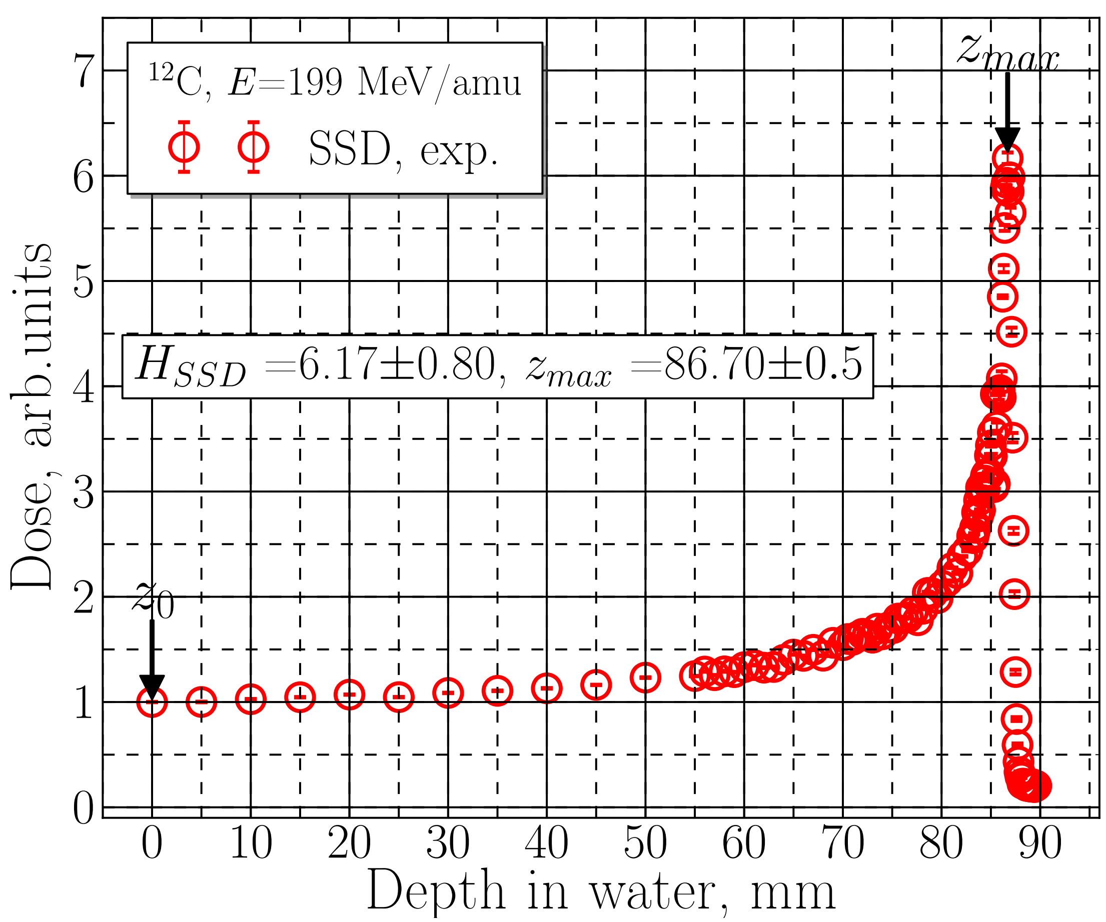
Parameters of SSD used in exp.

Detector type	Hi-p-type
Thickness of Si plate	0.2 mm
Thickness of sensitive layer	15 mkm
Sensitive area	1x1 mm^2

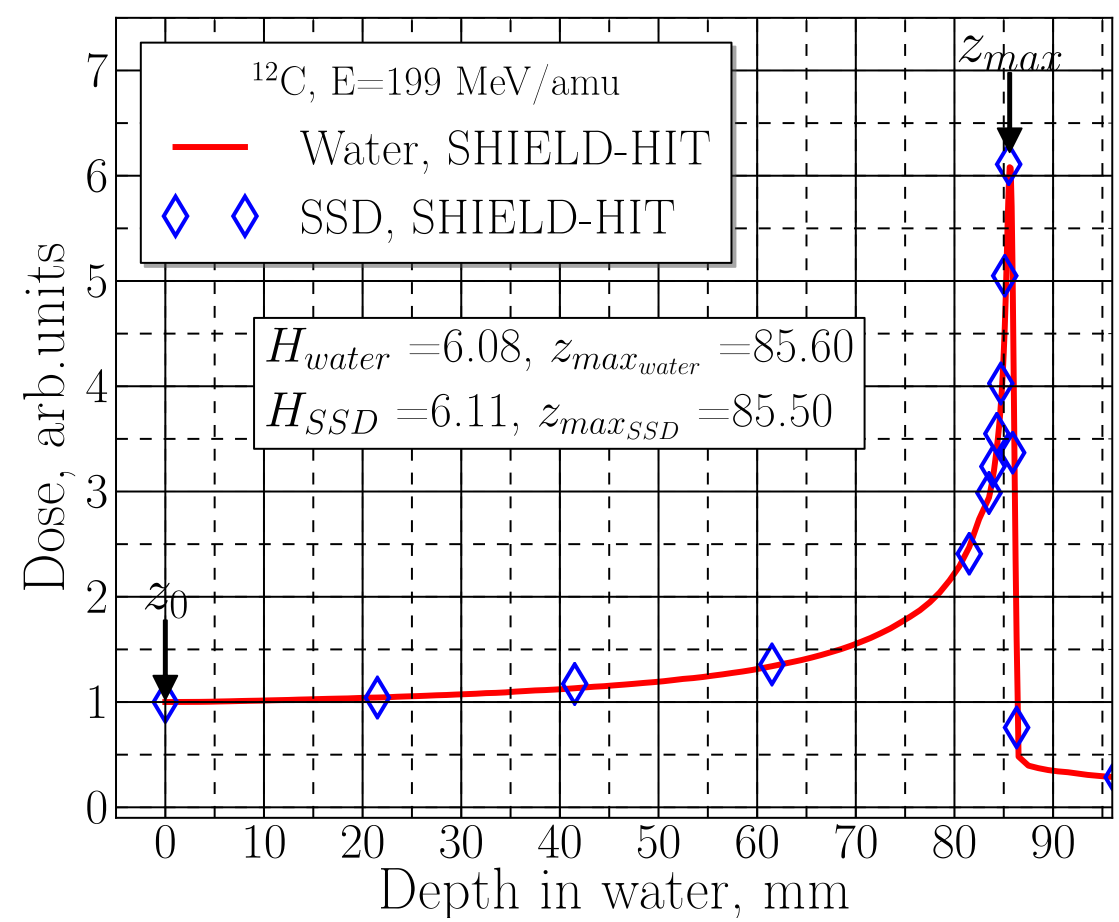
SSD dose rate linearity in entrance region



Depth-dose curve measured with SSD



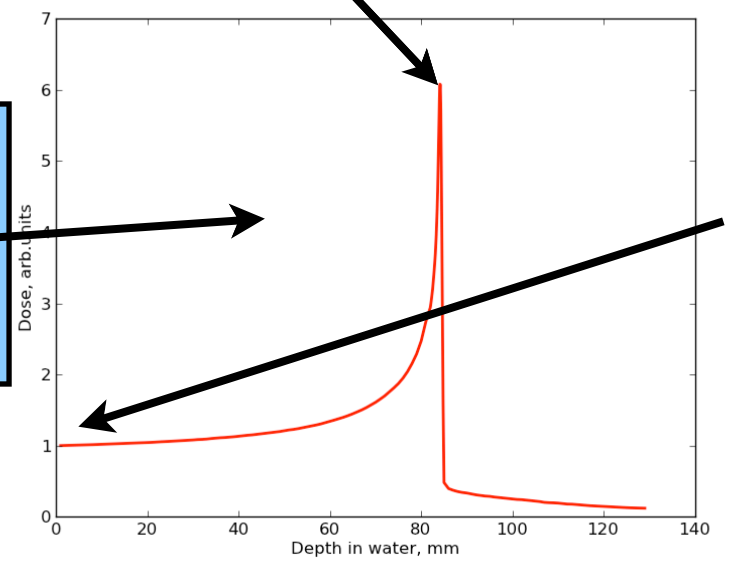
Results of SHIELD - HIT calculation



Absorbed dose determination

2. Position of the Bragg peak

1. Measurements of the depth-dose curve



3. Calculation of the ion beam energy E at the point z_0 (with TRIM code)

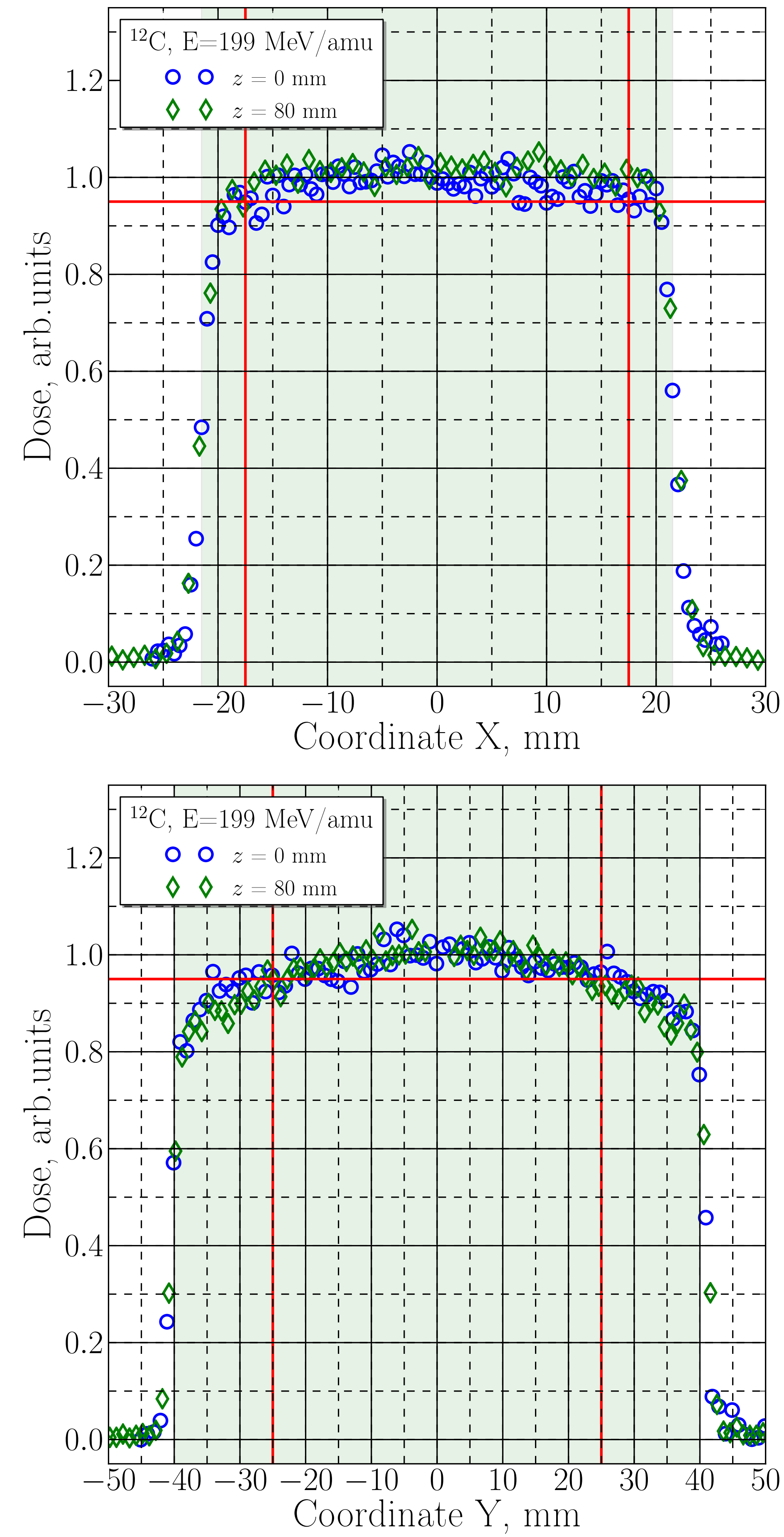
4. Absorbed dose for a thin layer at the point z_0

$$D = 1.602 \cdot 10^{-9} \left(\frac{dE}{dx}\right)_E \times \frac{N}{S} \times \frac{1}{\rho}$$

Uncertainty in absorbed dose

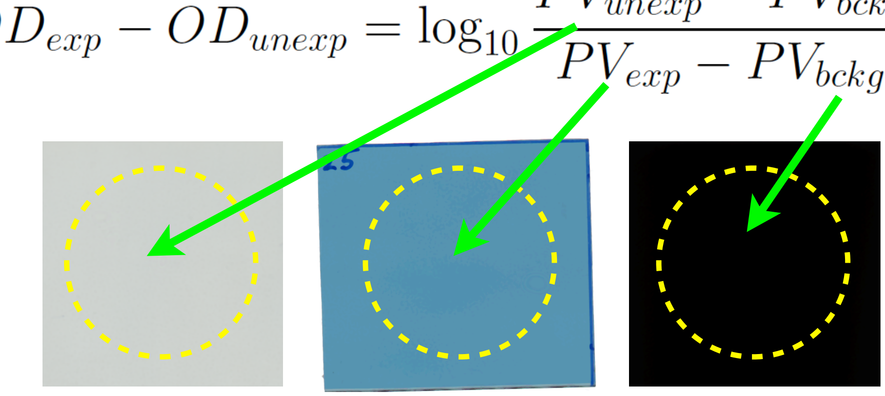
	Relative uncertainty, %
Number of particles	≤ 3.5
Field size	1
Ion energy	1
Stopping power	2 - 3
Total	< 5

Transversal distributions

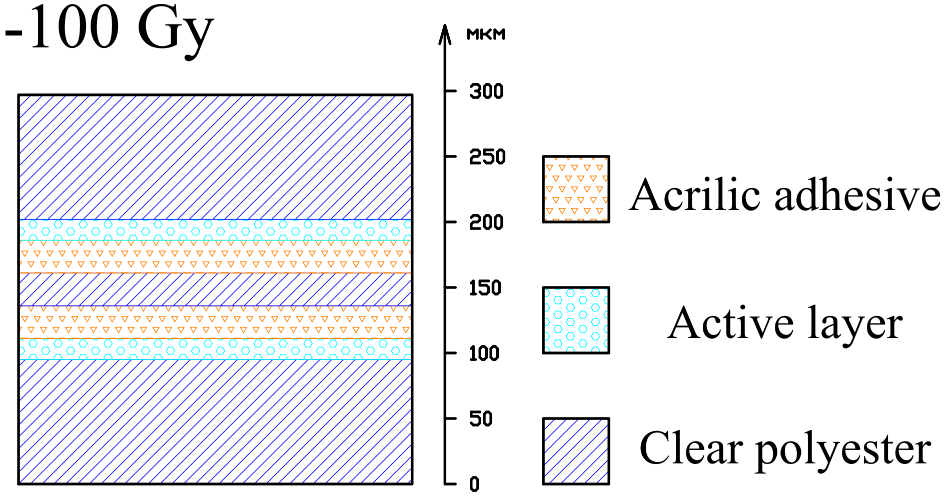


Radiochromic Film Dosimetry

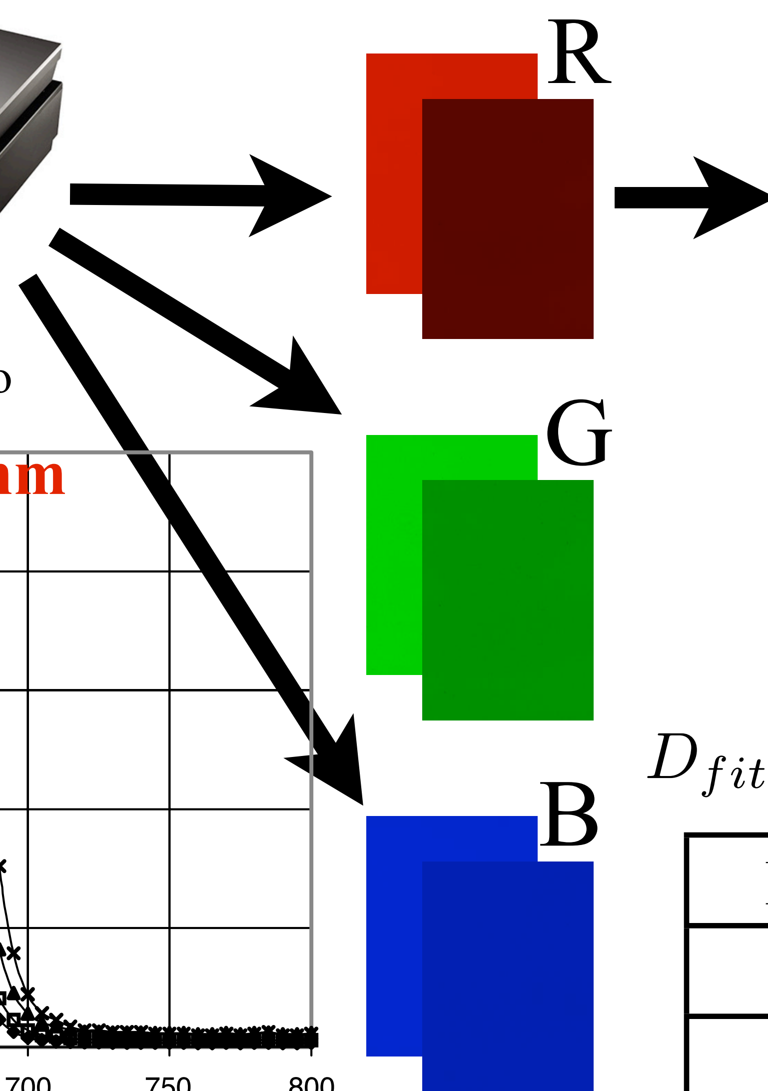
$$netOD = OD_{exp} - OD_{unexp} = \log_{10}\frac{PV_{unexp} - PV_{bckg}}{PV_{exp} - PV_{bckg}}$$

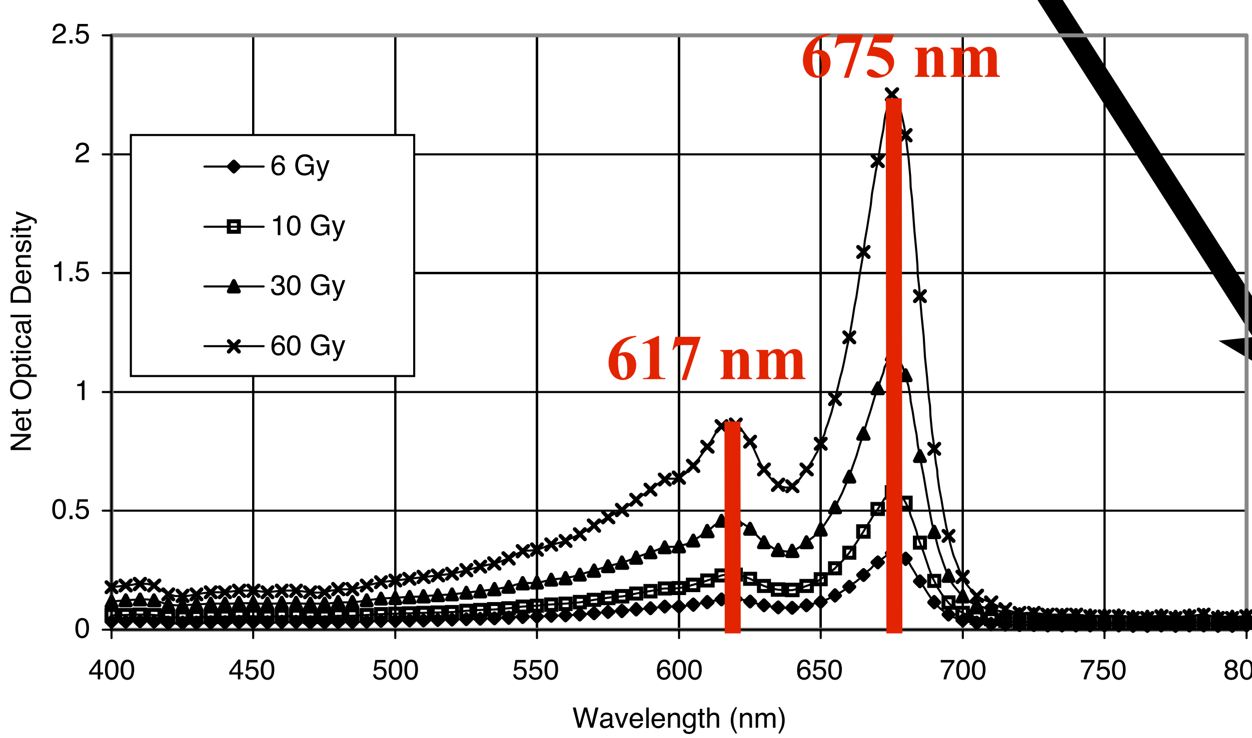


MD-V2-55: 1-100 Gy



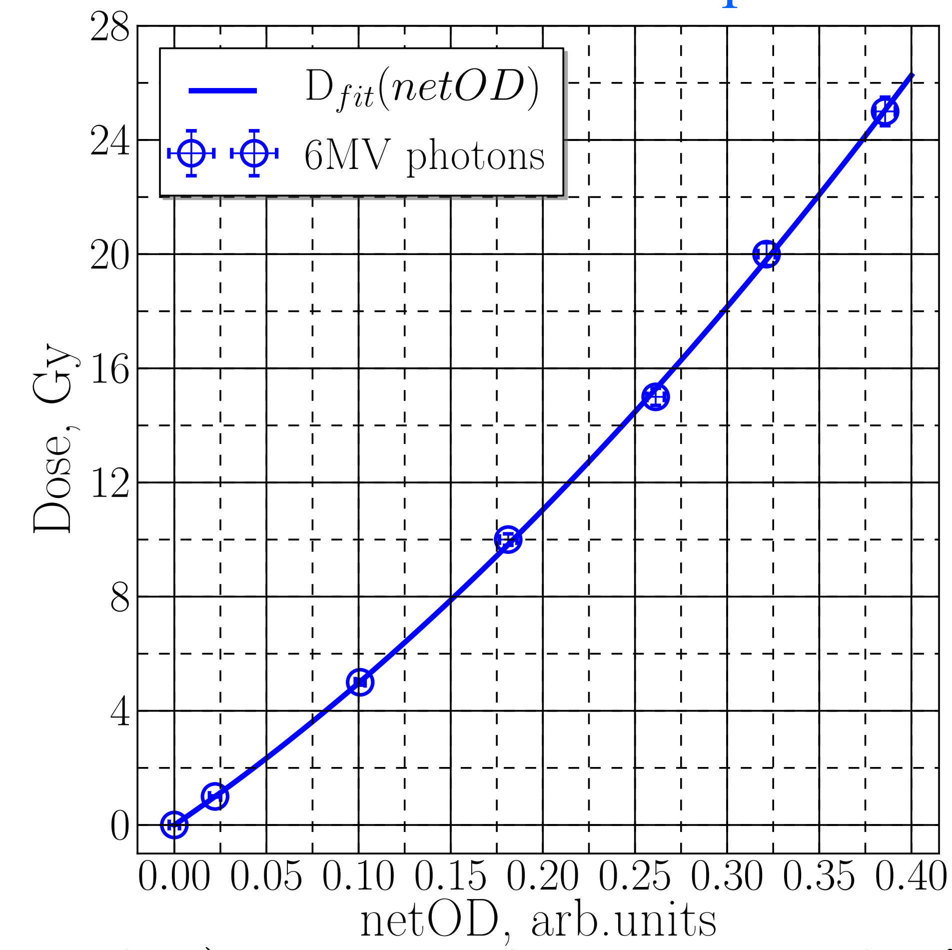
Films processing algorithm





Butson J., Materials Science and Engineering R41 (2003) 61- 120

Calibration with 6 MV photons

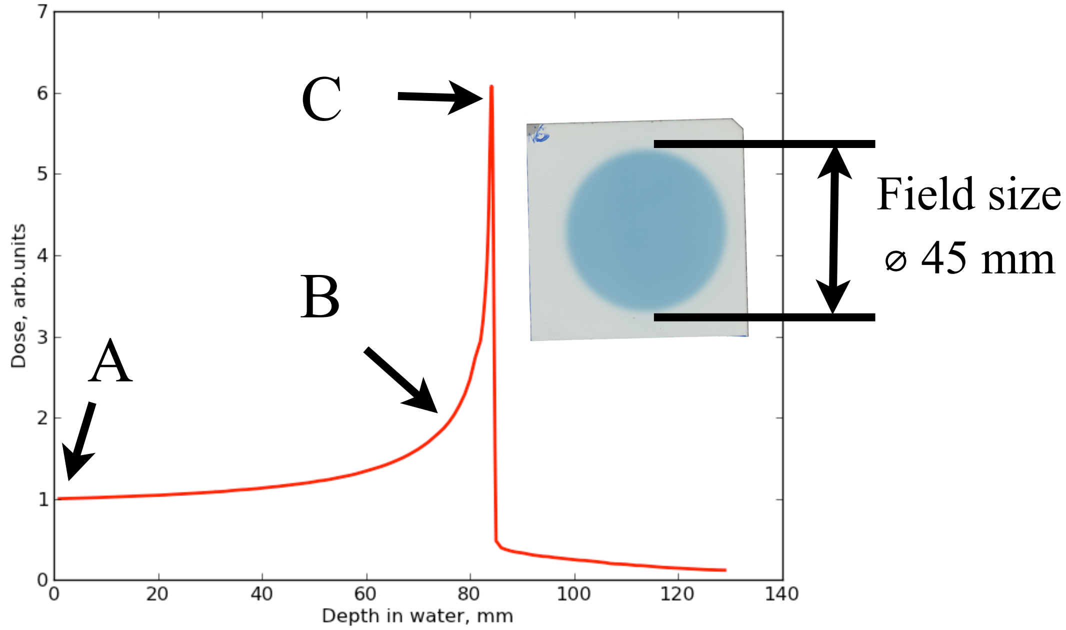


$$D_{fit}(netOD) = b \cdot netOD + c \cdot netOD^n$$

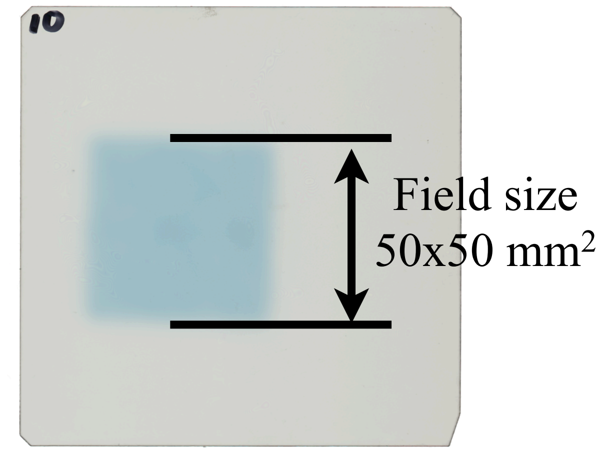
Param.	Value	SD
b	43.57	1.62
c	51.34	3.38
n	1.92	0.13

Radiochromic Film calibration with 12C ions beams

1. Calibration with 215 MeV/amu ions in ITEP

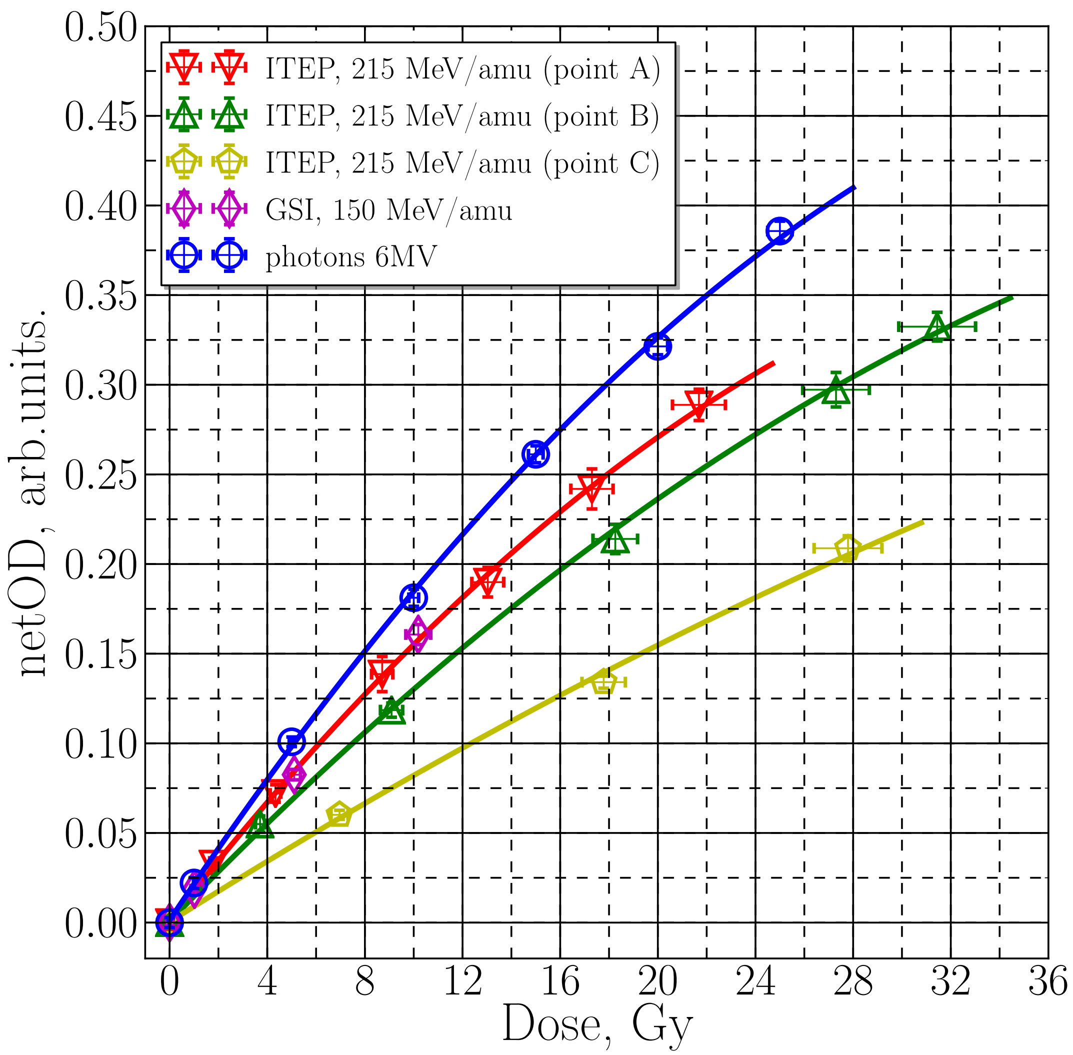


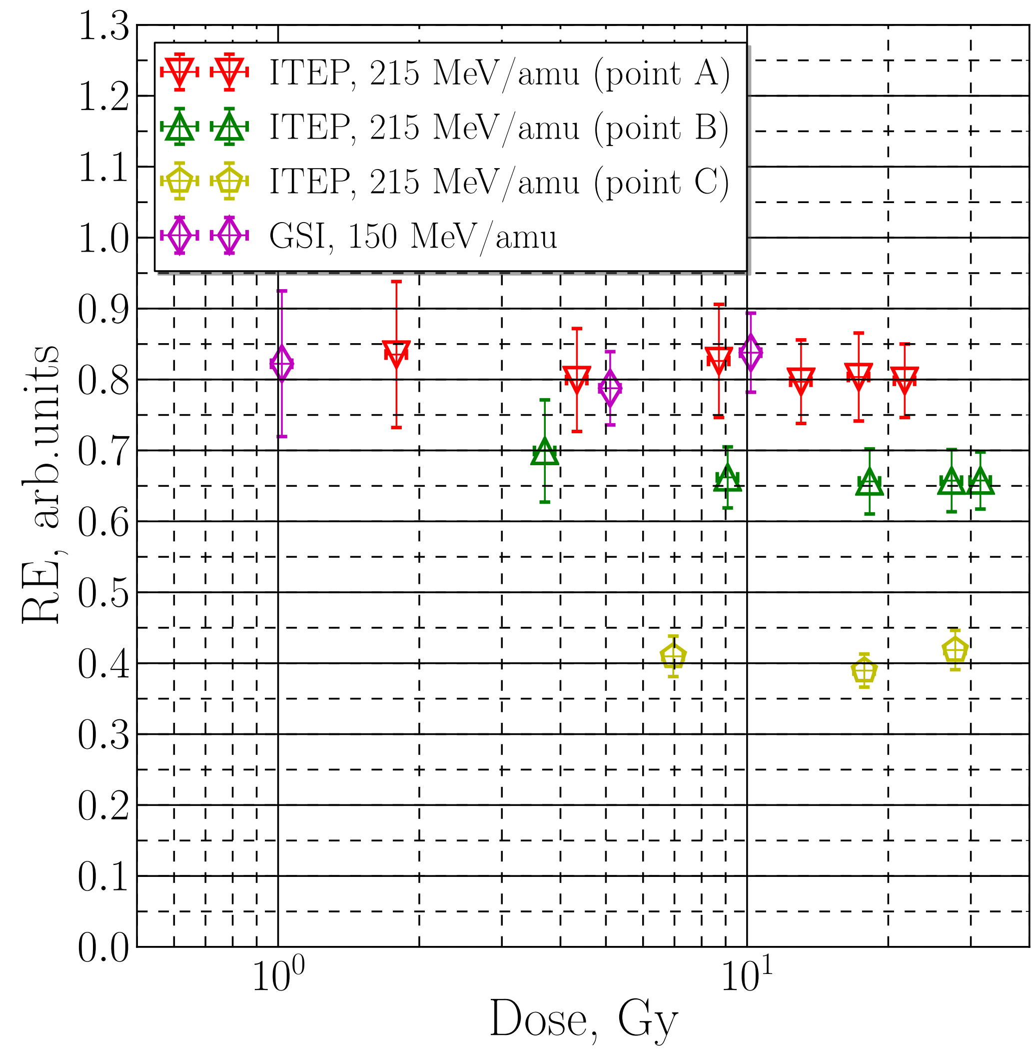
2. Calibration with 150 MeV/amu ions in GSI



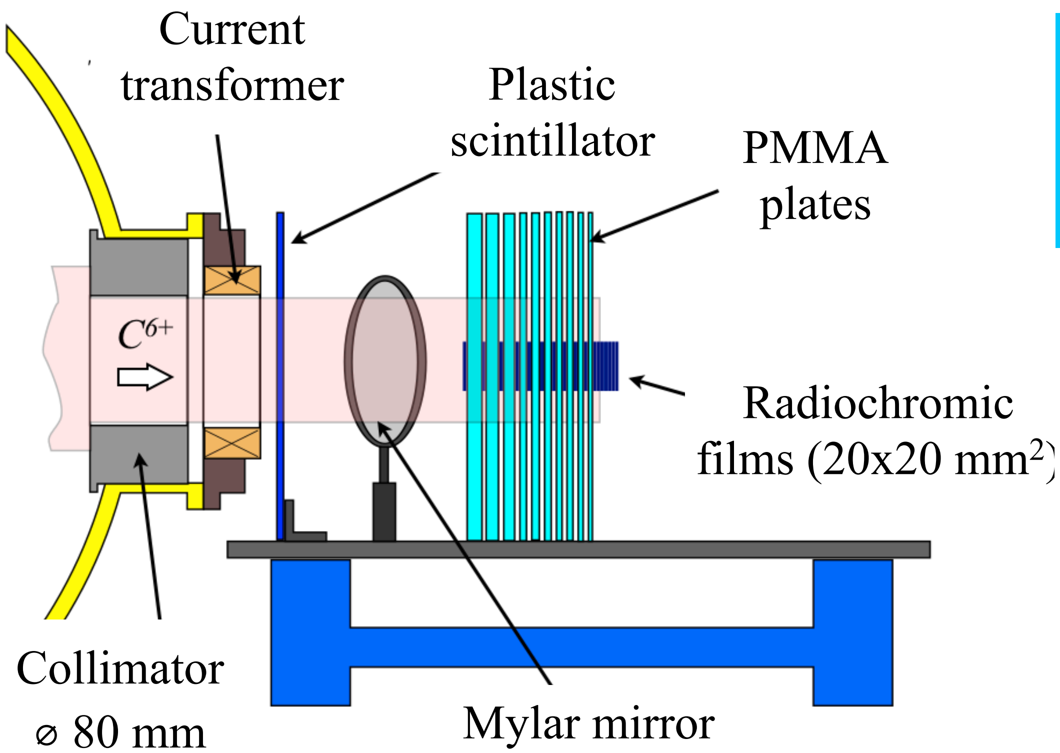
For uniform irradiation a raster scanning system with a "pencil" beam was used.
"Pencil" beam - Gaussian shape, with FWHM 2 mm

Relative effectiveness: $$RE = \left.\frac{D_{photons}}{D_{ions}}\right|_{netOD}$$

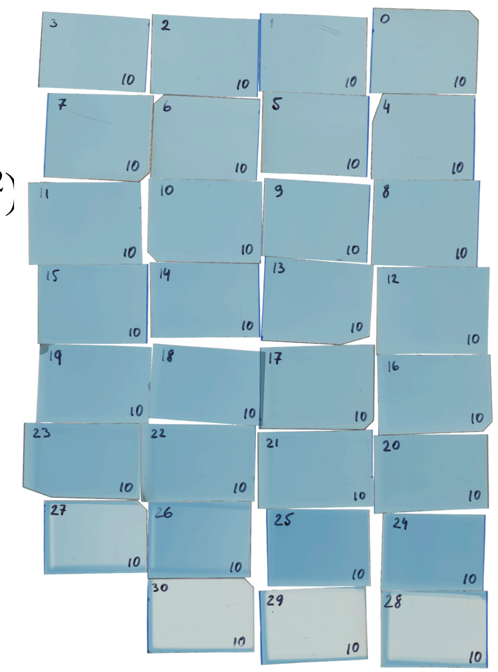


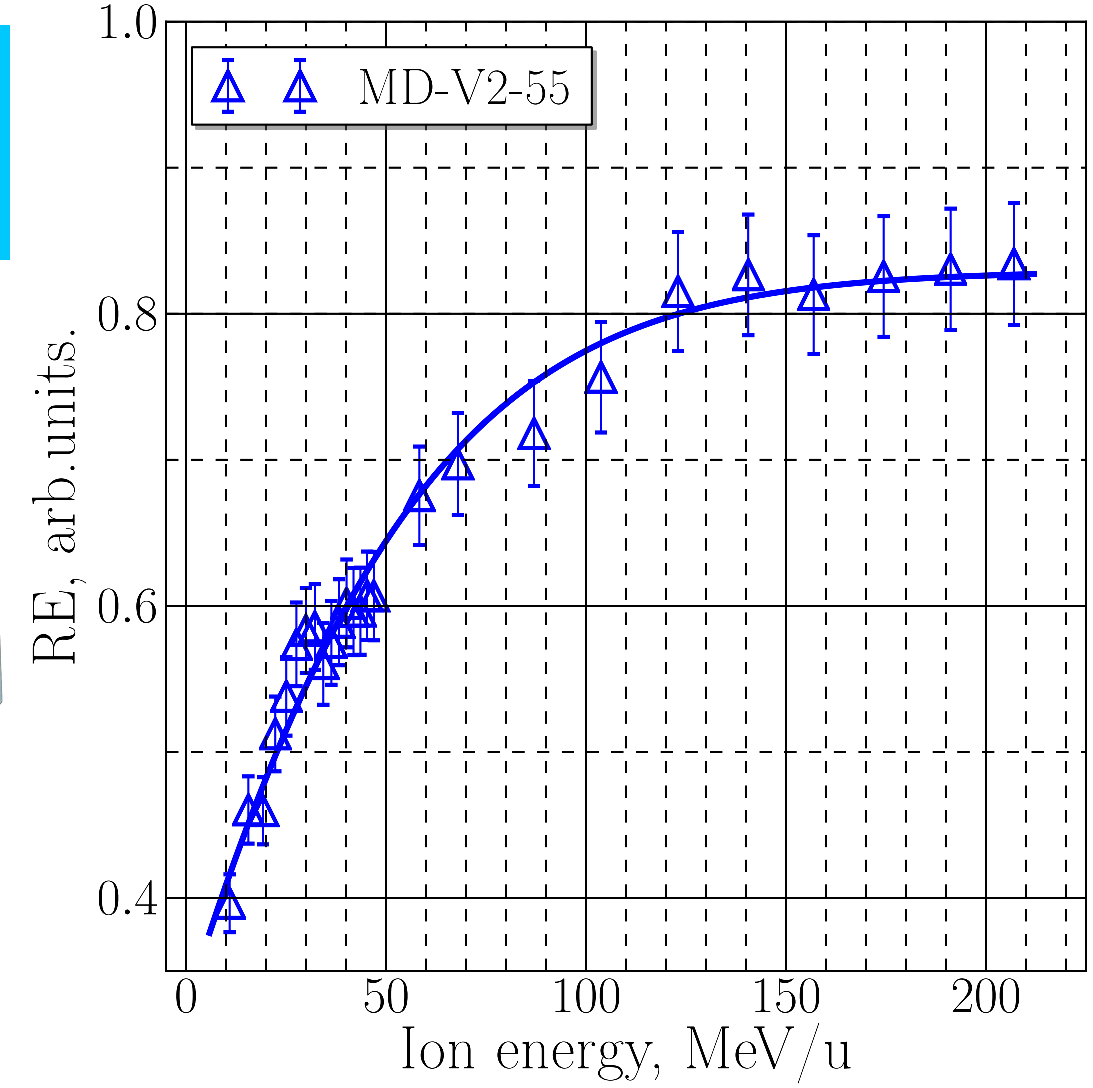


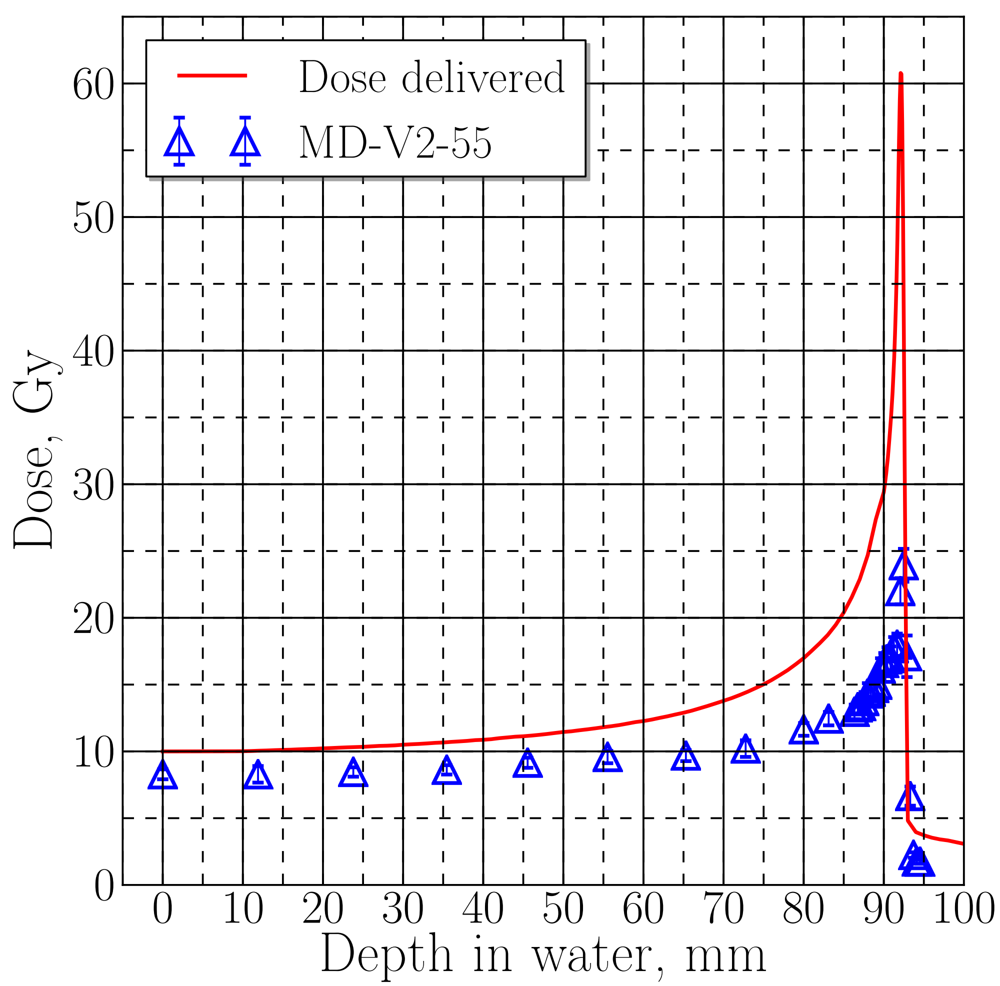
Depth-dose curve measurements with radiochromic films



Water Equivalent Path Length of PMMA 1.16







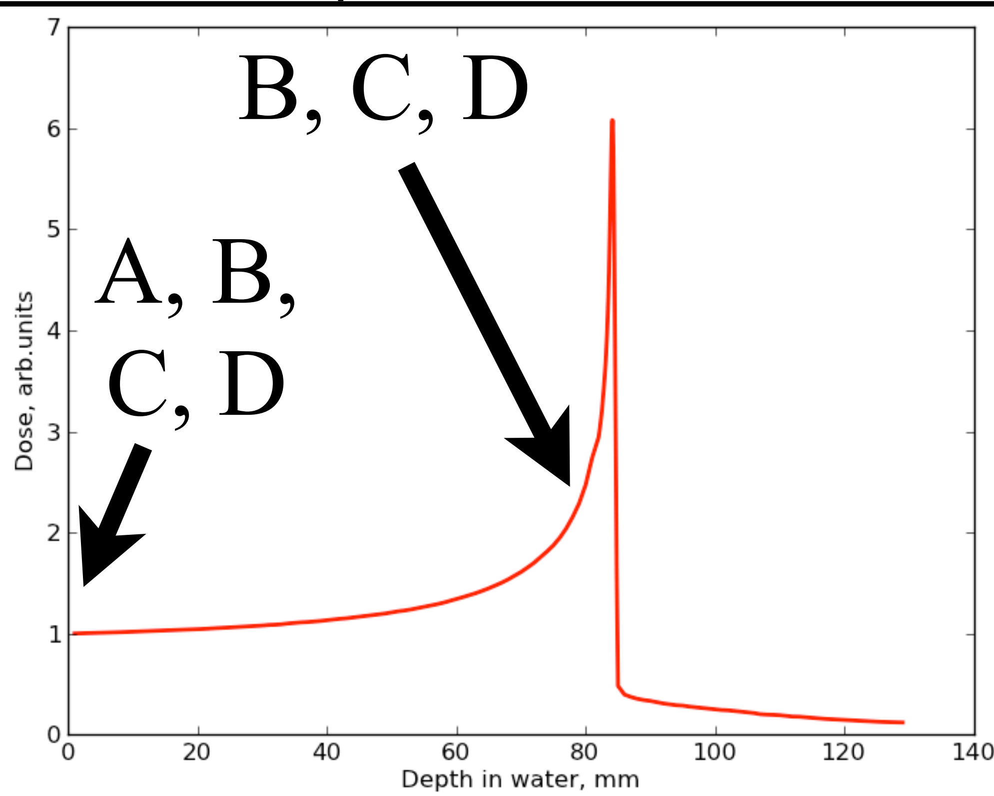
	Bragg peak position	$D_{peak}/D_{entrance}$
MD-V2-55	92.48 ± 0.65	2.77 ± 0.12
SSD	92.5 ± 0.5	6.19 ± 0.41

$$RE_{fit}(E) = A_0 + \frac{A_1 E}{1 - e^{A_2 E}}$$

Particles/cm2	A_0	A_1	A_2
4×10^7	0.83 ± 0.01	0.018 ± 0.002	0.035 ± 0.003
1.2×10^8	0.82 ± 0.02	0.024 ± 0.003	0.041 ± 0.005
1.9×10^8	0.83 ± 0.01	0.020 ± 0.002	0.037 ± 0.003

Radiobiological experiments “in vitro” with 12C ions

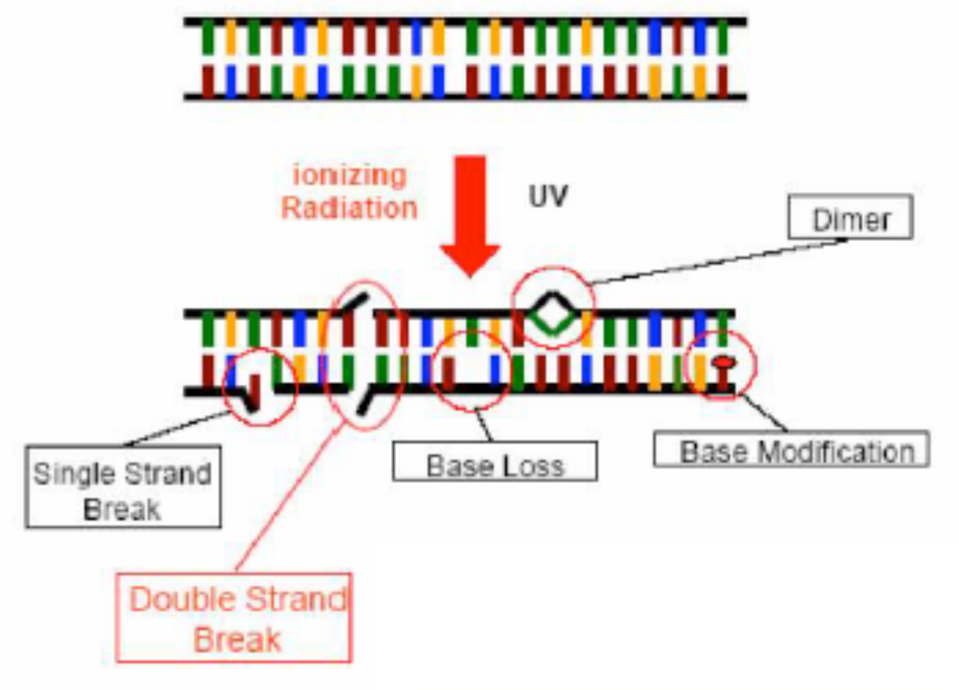
A	Human peripheral blood lymphocytes. For irradiation cells were placed in tubes (eppendorf 5 ml). Chromosome aberrations were analyzed in metaphases 48h after radiation exposure.
B	Breast cancer cell line Cal51 with normal karyotype. For irradiation cells were grown as monolayer and placed in 12.5 cm^2 culture flasks. After irradiation chromosome aberration were analyzed
C	Chinese hamster ovary cells CHO-K1. For irradiation cells were grown as monolayer and placed in 12.5 and 25 cm^2 culture flasks. After irradiation cell survival was measured with a colony assay.
D	Melanoma B16F10 cells. For irradiation cells were grown as monolayer and placed in 25 cm^2 culture flasks. After irradiation cell survival was measured with a colony assay.



1. Eppendorf

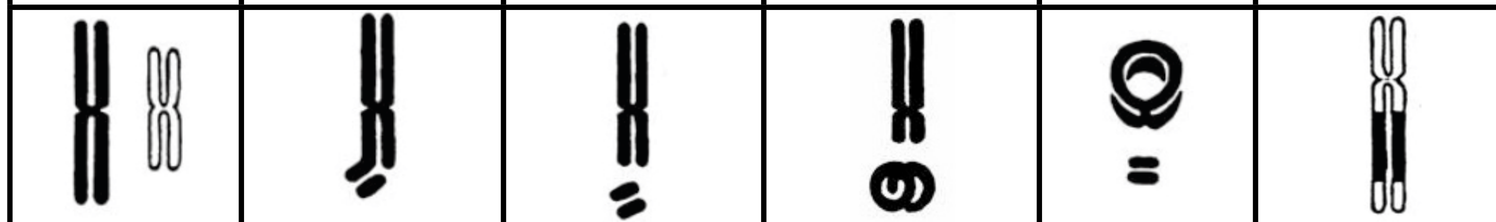
2. Culture flasks

Methods of analysis

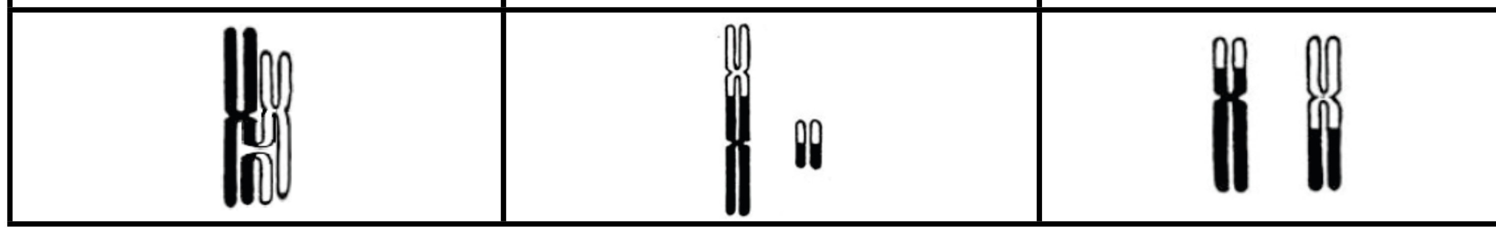


1. Analysis of chromosome aberration

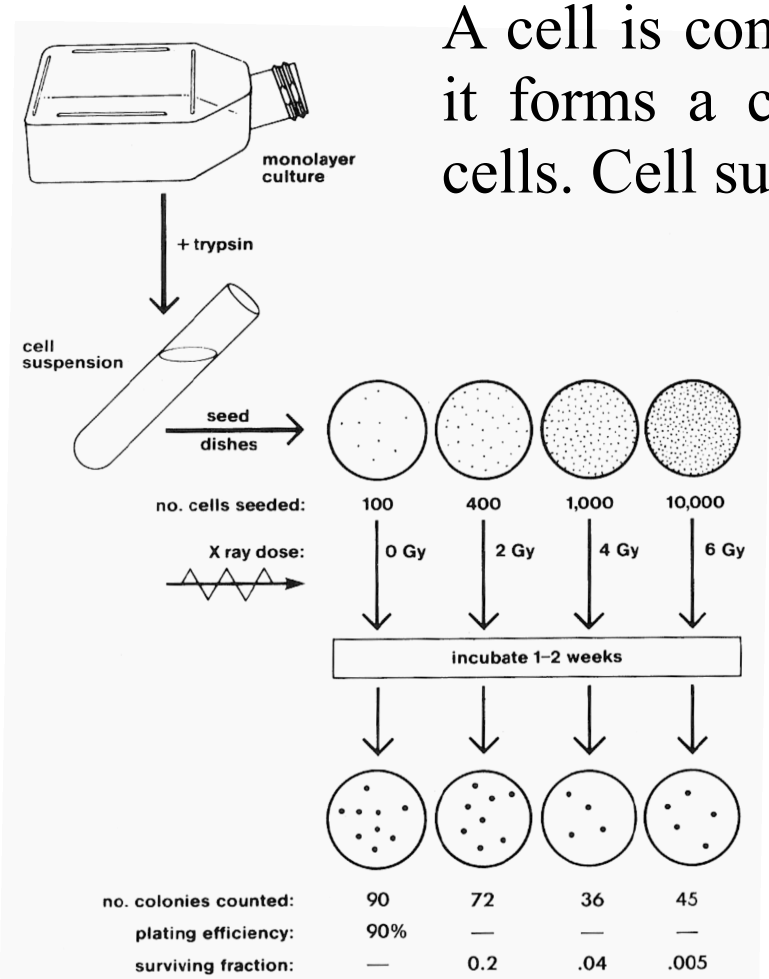
Normal	Chromatid break	Chromosome fragment	Acentric ring	Centric ring with fragment	Translocation



Chromatid exchange	Dicentric with fragment	Reciprocal exchange



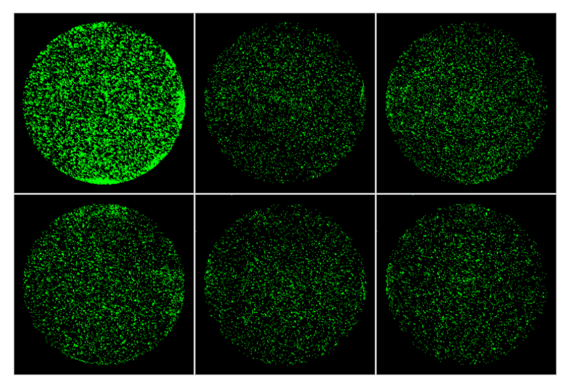
2. Cell survival based on a colony assay



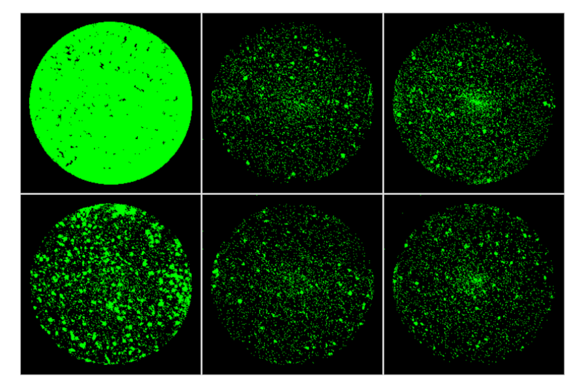
A cell is considered surviving after exposure, if it forms a colony consisting of more than 50 cells. Cell survival was determined as follows:

$$S = \frac{N_{col}}{(N_{cells} \times (PE/100))}$$

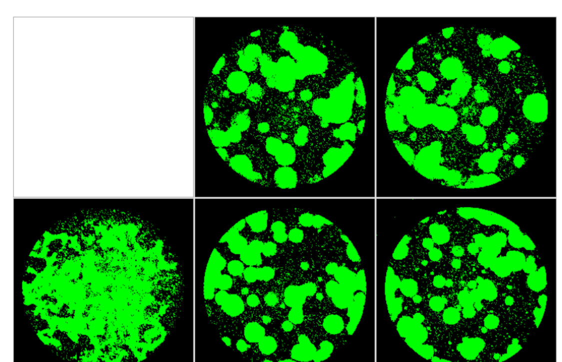
1-day



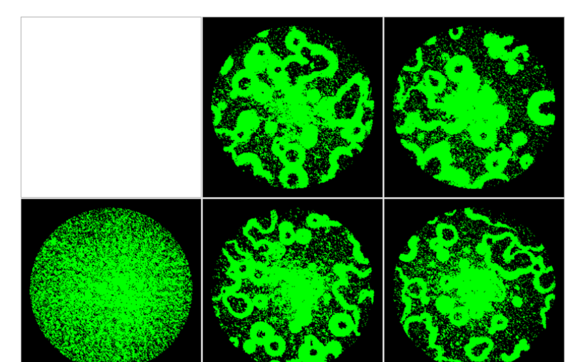
3-days



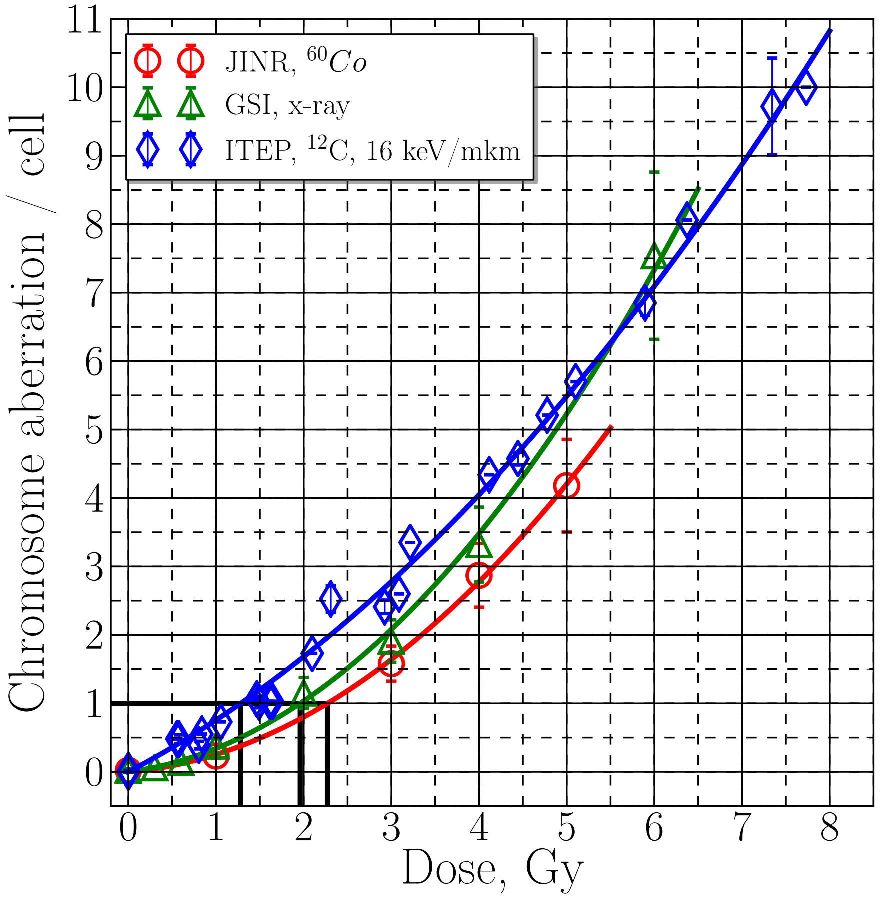
5-days

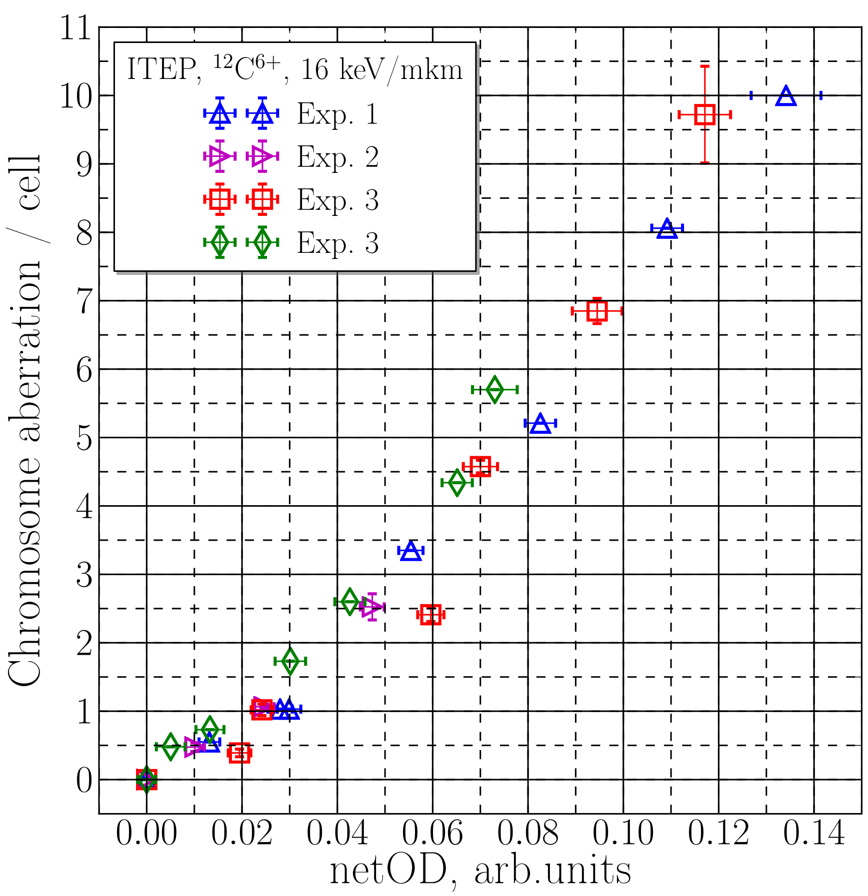


7-days

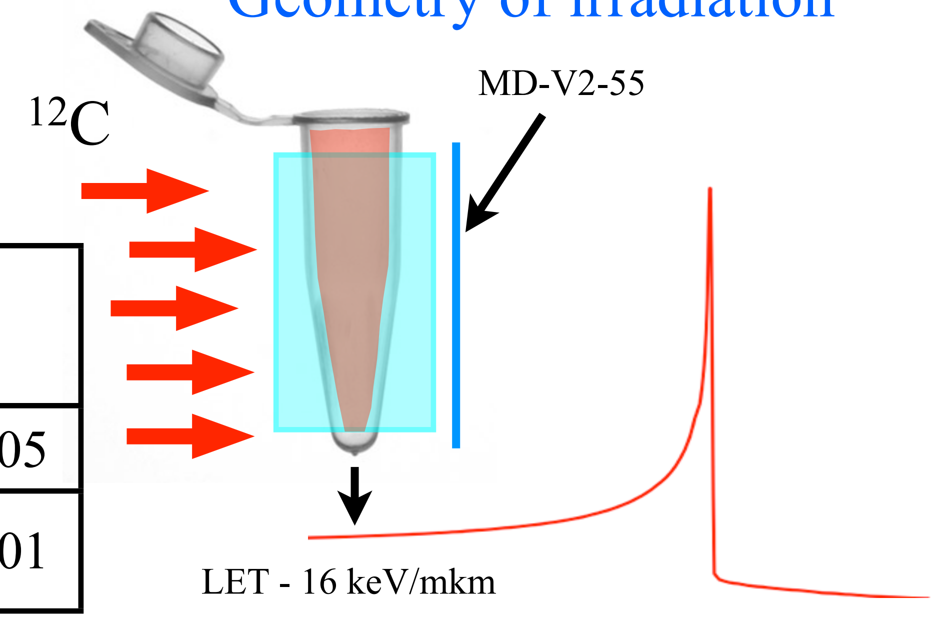


Results of lymphocyte irradiation



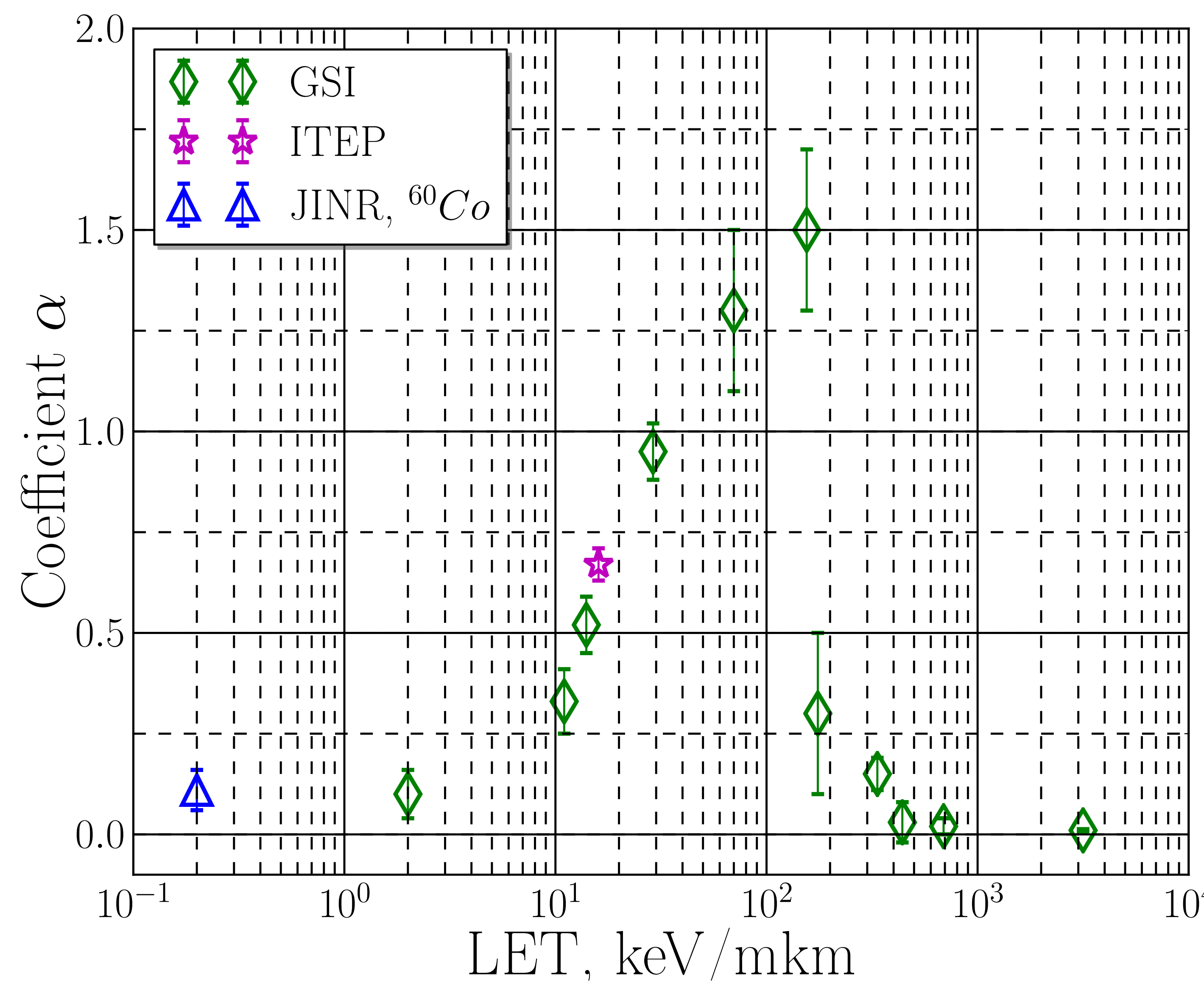


Geometry of irradiation



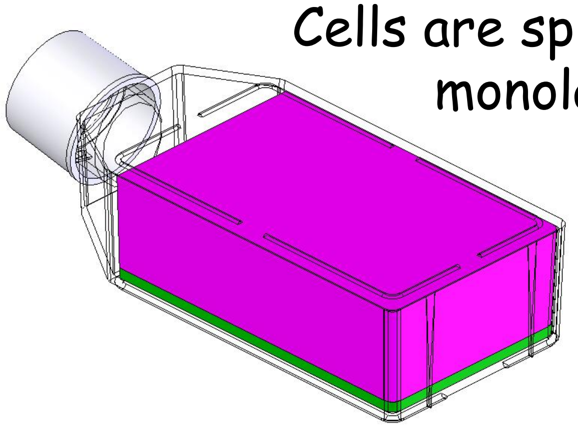
$$Y = \alpha \cdot D + \beta \cdot D^2$$

Param.	^{12}C, 16 keV/ mkm	^{60}Co
α	0.67 ± 0.04	0.11 ± 0.05
β	0.09 ± 0.01	0.15 ± 0.01

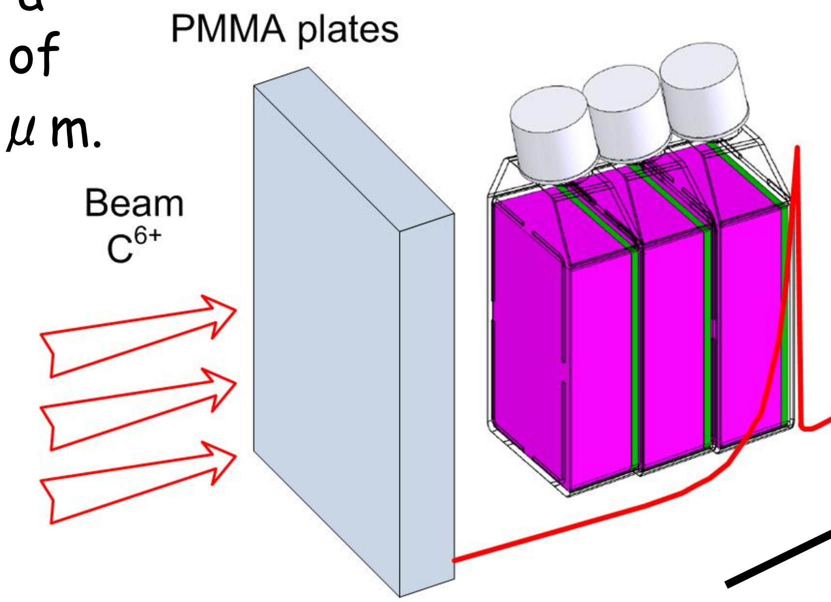


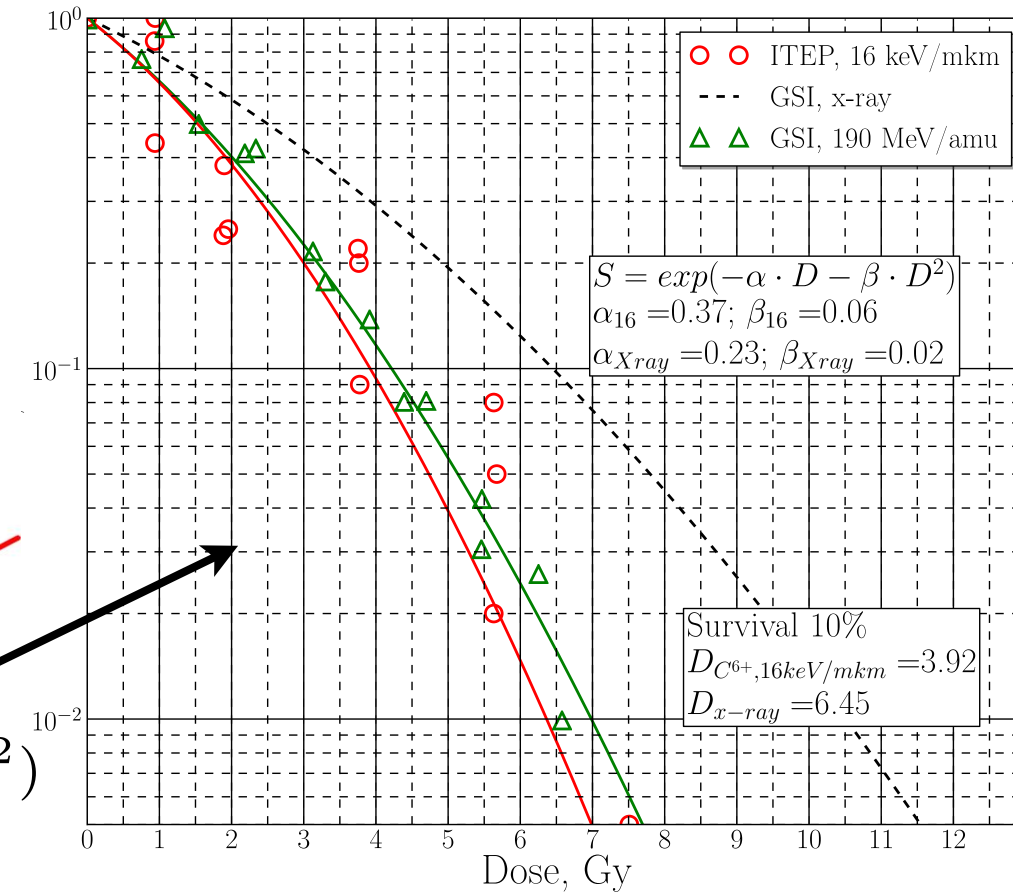
Ryonfa Lee, Elena Nasonova, et al, Radiat. Environ. Biophys (2011) 50(3) 371-81

Results of CHO-K1 and Cal51 cells irradiation

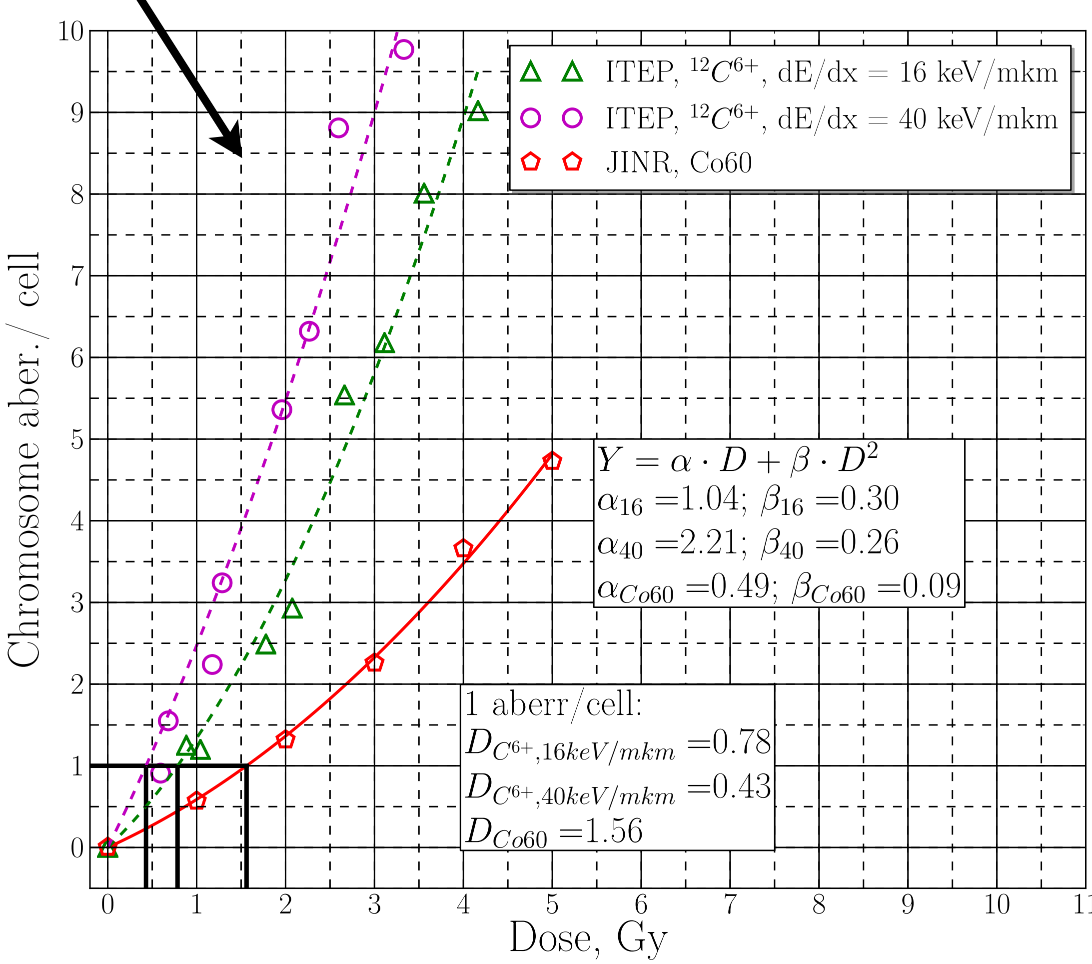


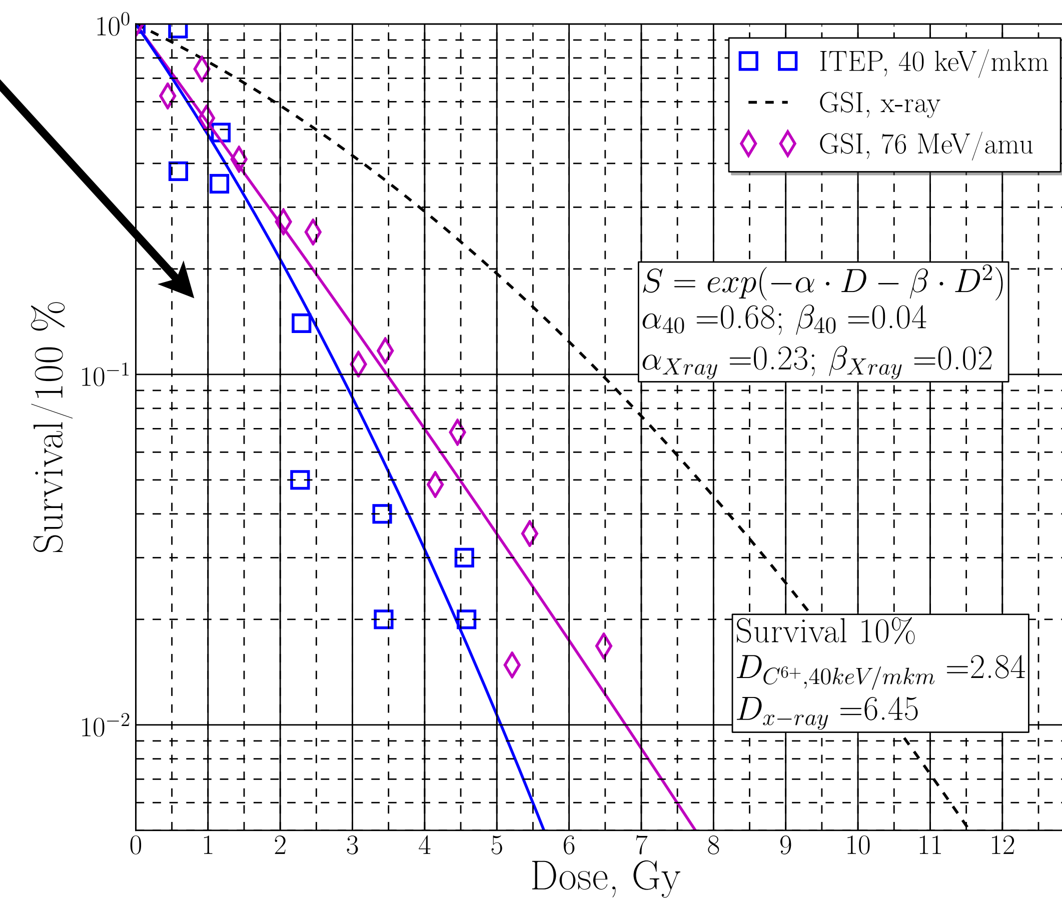
Cells are spread over a monolayer with a thickness of ~ 50 μm.





Cal51: $Y = \alpha \cdot D + \beta \cdot D^2$ **CHO-K1:** $S = e^{-(\alpha D + \beta D^2)}$



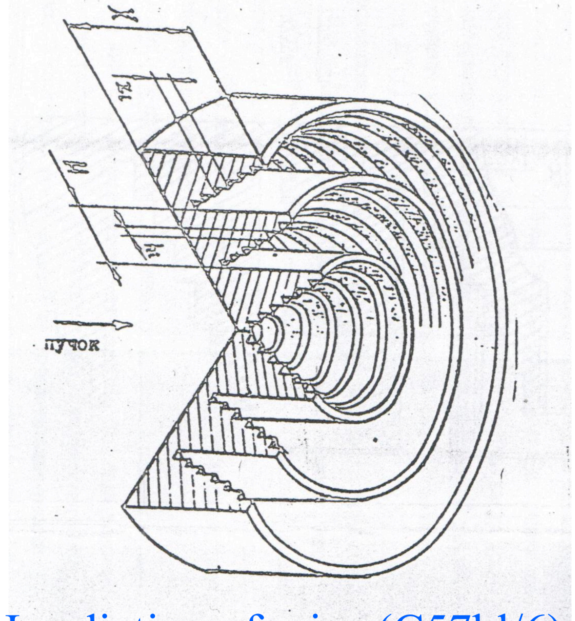


Summary of radiobiological experiments “in vitro”

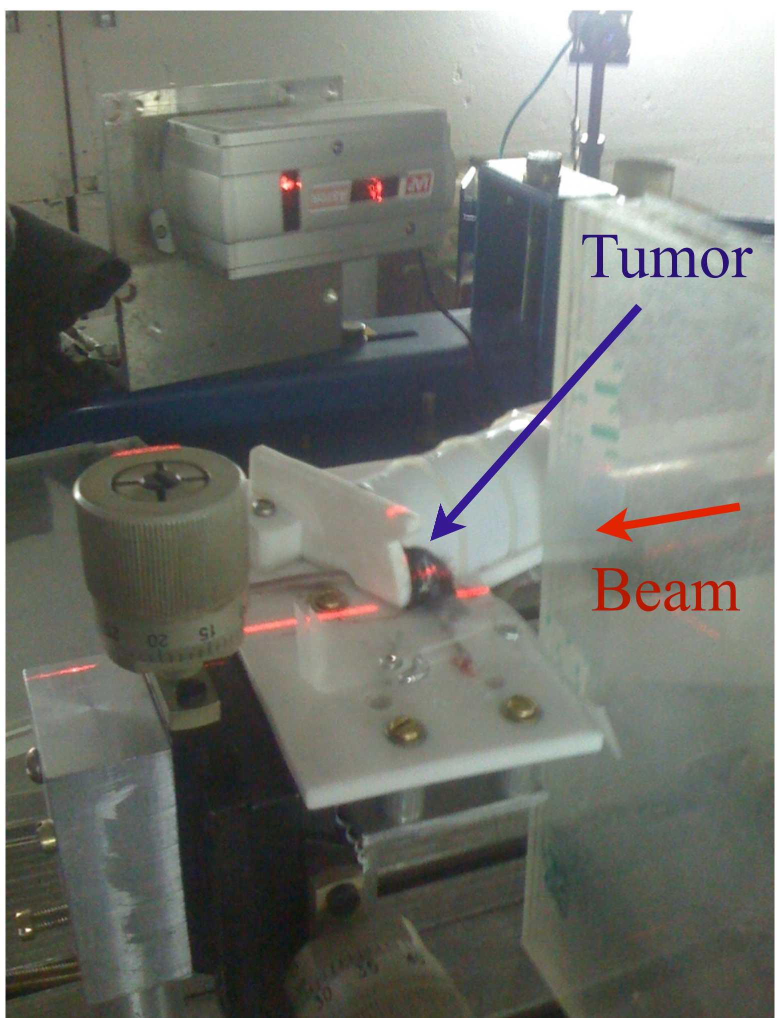
	Cell type	Depth in water eq., mm	LET, kev/mkm	Dose range, Gy	RBE (x-ray)	RBE (60Co)
1	Lymphocyte	0	16	0 - 8	1.53 $\pm$ 0.11	1.77 $\pm$ 0.13
2	Cal51	0	16	0 - 4	-	2.02 $\pm$ 0.11
		82	40	0 - 4	-	3.63 $\pm$ 0.16
3	B16F10	23	20	0 - 10	-	1.45 $\pm$ 0.12
		85	44	0 - 8	-	2.46 $\pm$ 0.15
4	CHO-K1	0	16	0 - 8	1.65 $\pm$ 0.11	-
		82	40	0 - 5	2.27 $\pm$ 0.13	-

Radiobiological experiments “in vivo”

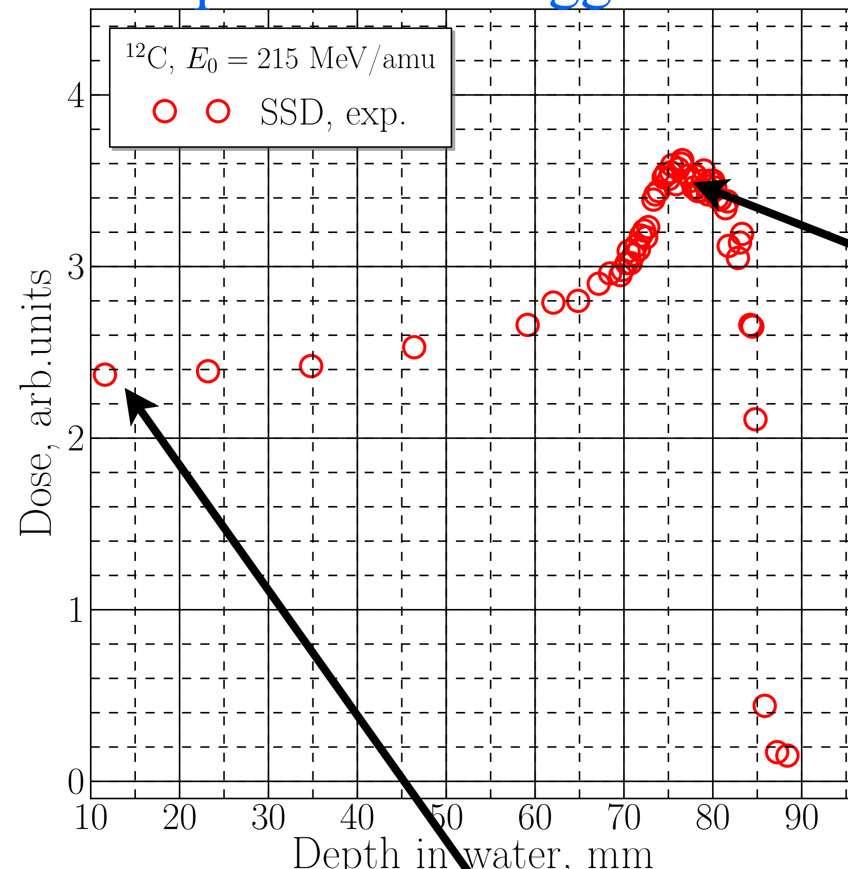
Structure of the ridge filter



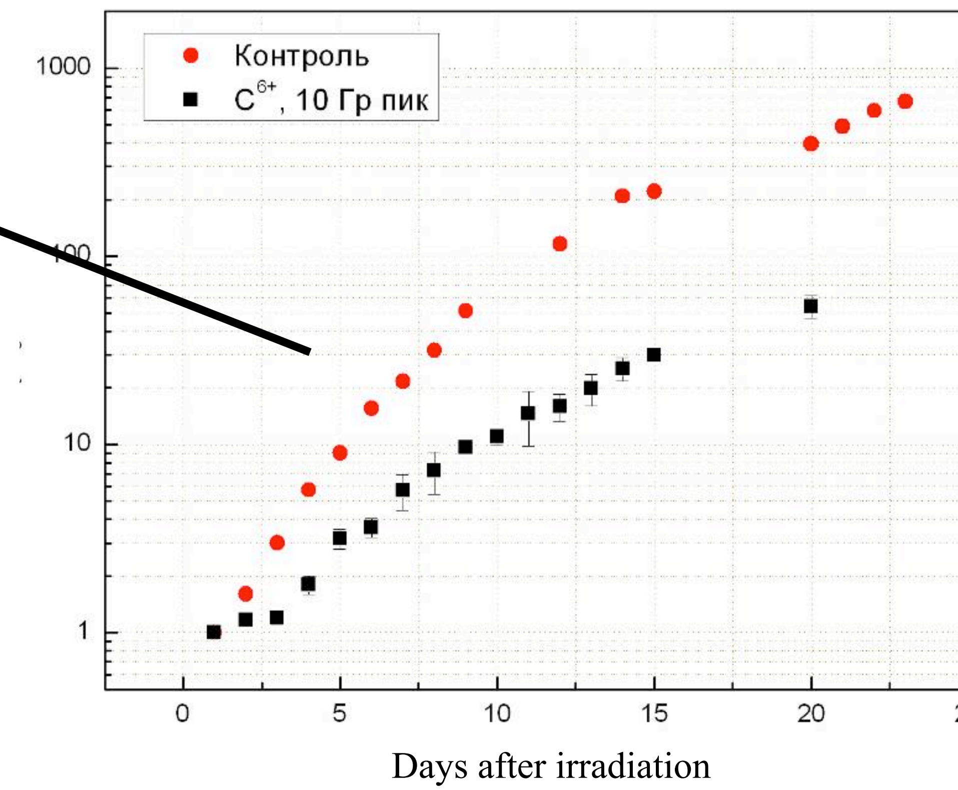
Irradiation of mice (C57bl/6)with inoculated B16F10 cells

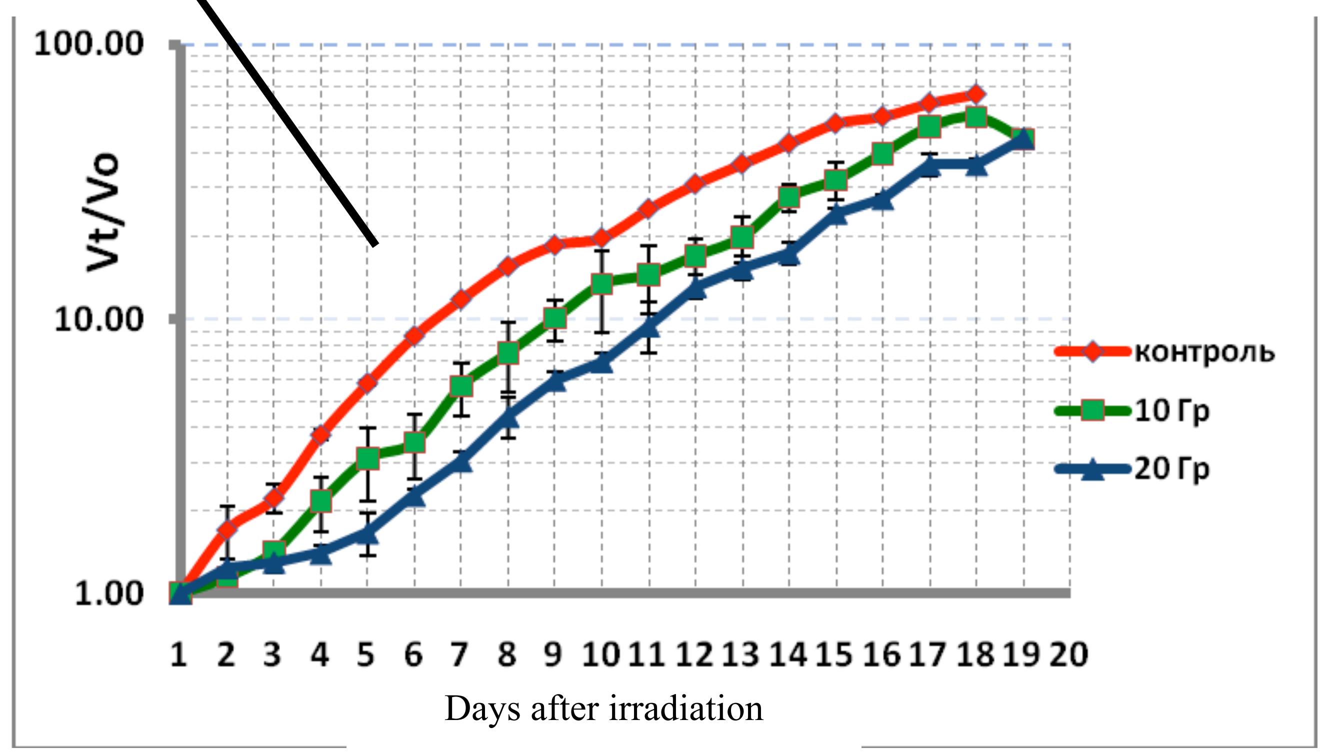


Spread-out Bragg Peak



Results of mouse irradiation

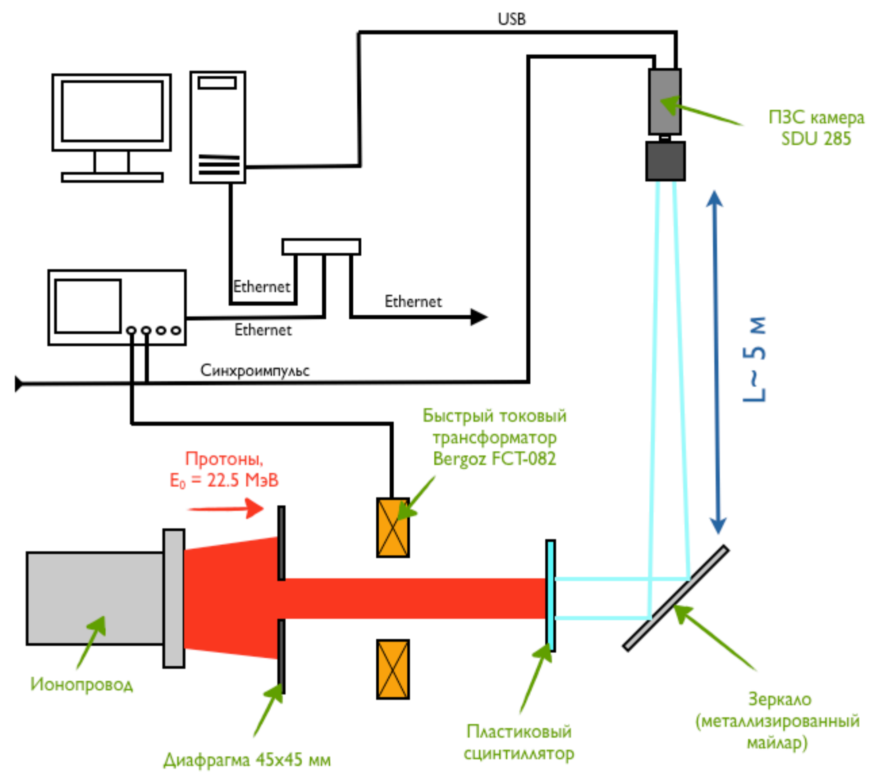




Further radiobiological research in ITEP

Proton linear accelerator I-2

Max. Energy, MeV	22.5
Pulse width, mks	2 - 30
Max. field size, mm	85
Particles per pulse, protons/cm^2	10^7 - 10^{11}
Range in water, mm	~ 5
Min. LET, keV/mkm	2.4



1. RBE of low energy protons
2. Bystander effect
3. Micro-beams (single cell - single particle)