Istituto Nazionale di Fisica Nucleare

Politecnico di Bari

Data Science Applications in Physics, Balkan School in Tirana 2024

Radiotherapy with Hadrons

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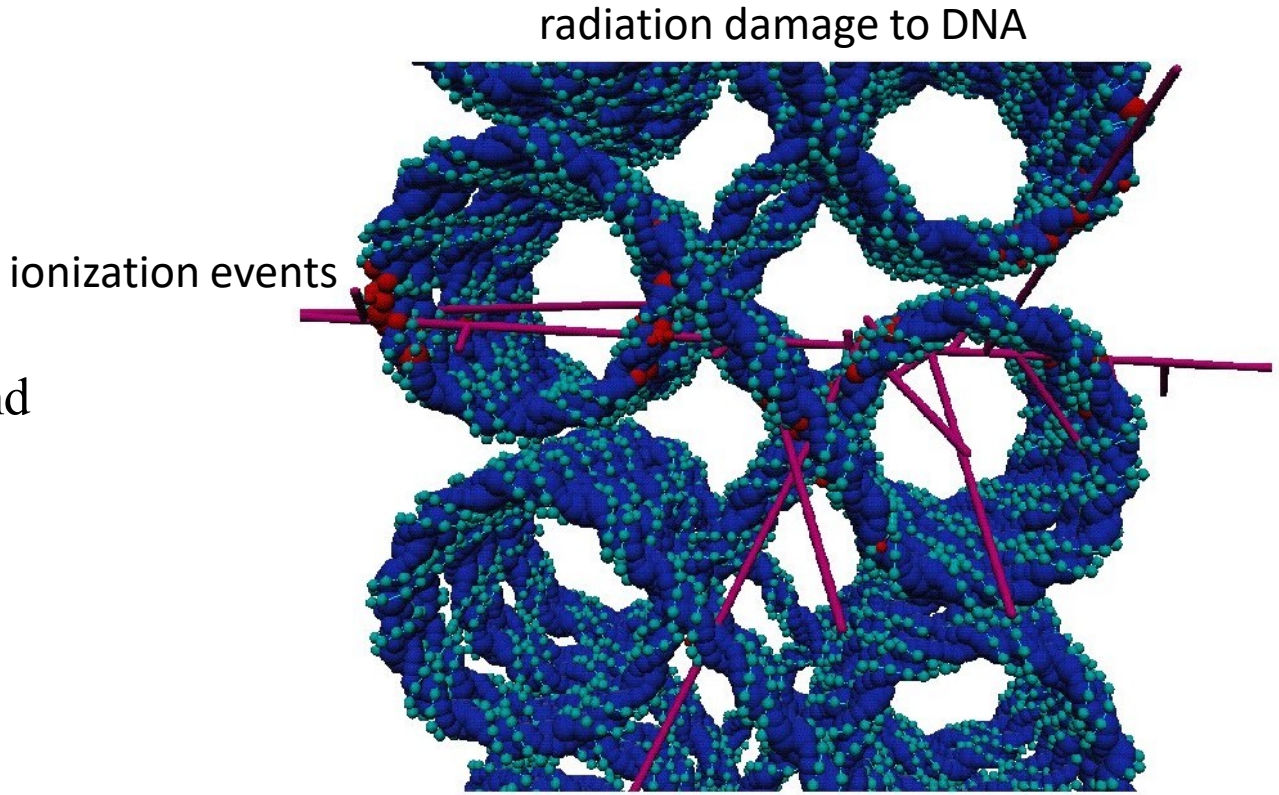
Outline

- Basics of Hadron Therapy
  - Ion sources: particle accelerators in Medical Physics
  - Spread-Out Bragg Peak and beam modulation
  - Relative Biological Effectiveness
  - Flash Therapy concept
- Boron Neutron Capture Therapy (BNCT)
  - BNCT principles
  - Neutron Sources
  - Dosimetry in BNCT

Radiotherapy basic principle

Induce the cancer cell death by radiation damage to DNA:

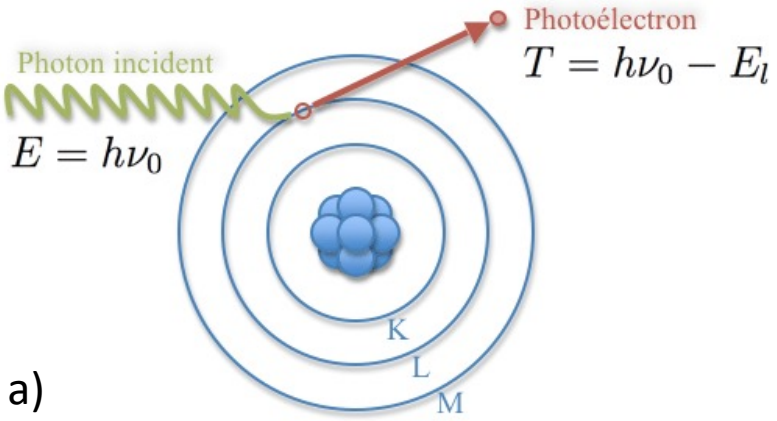
Ionization events produced by radiation flux break direct single/double strand generating free radicals and damaging the DNA to finally induce the cell death



Interaction of radiation with matter

Photons

- Interactions are all processes that change the energy and/or the direction of the photon and will have direct influence on the shape of photon spectra
- The main processes of interaction of photons with matter are the following:
  a) Photoelectric absorption,
  b) Compton scattering,
  c) Pair production.



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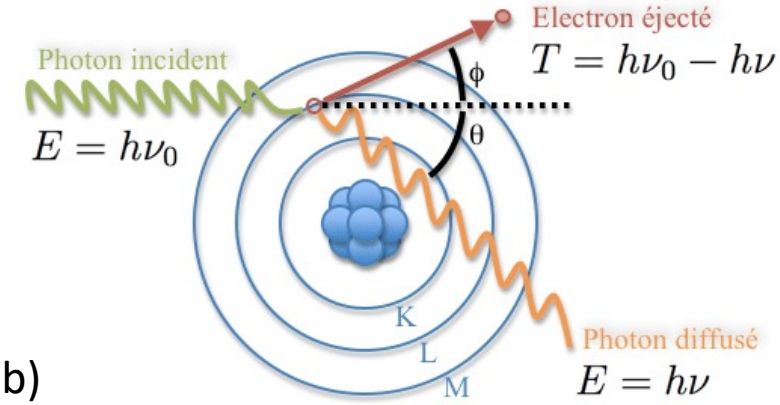

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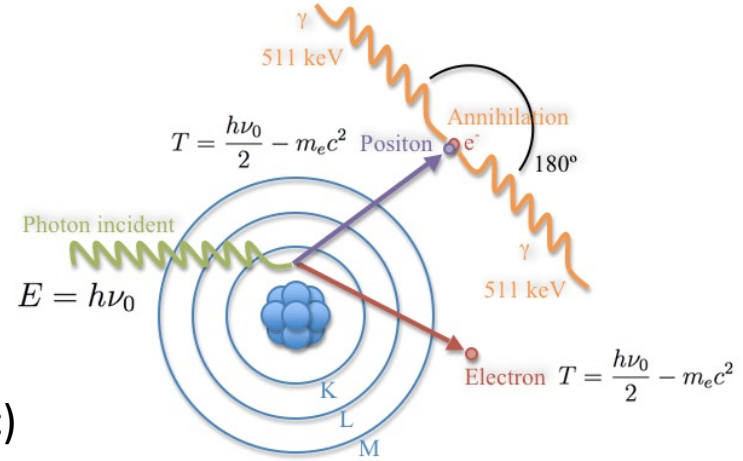

c)

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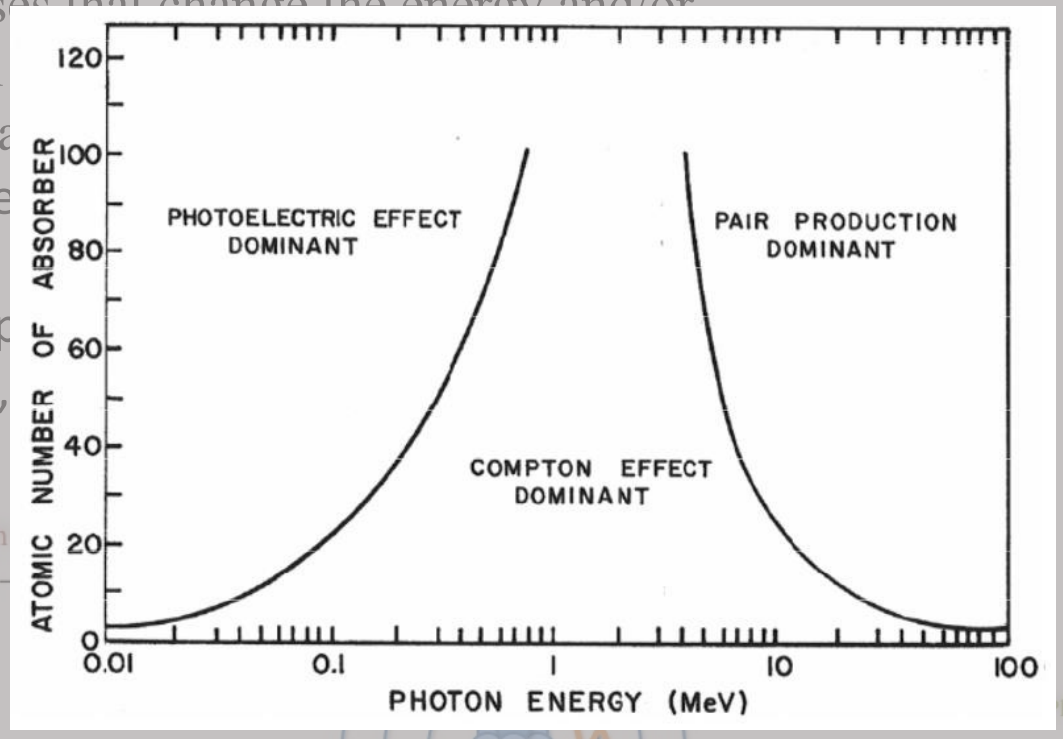
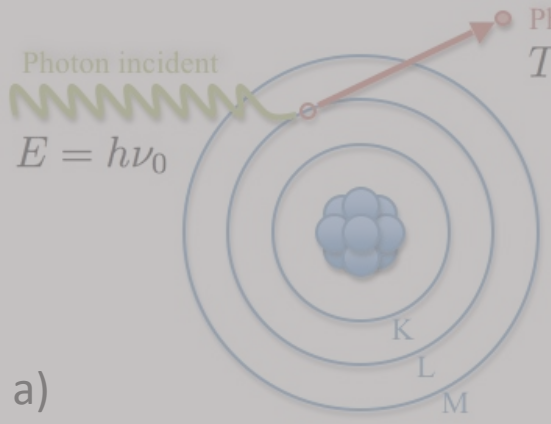


Relative importance of the processes of interaction of photons with matter as a function of their energy and the medium composition



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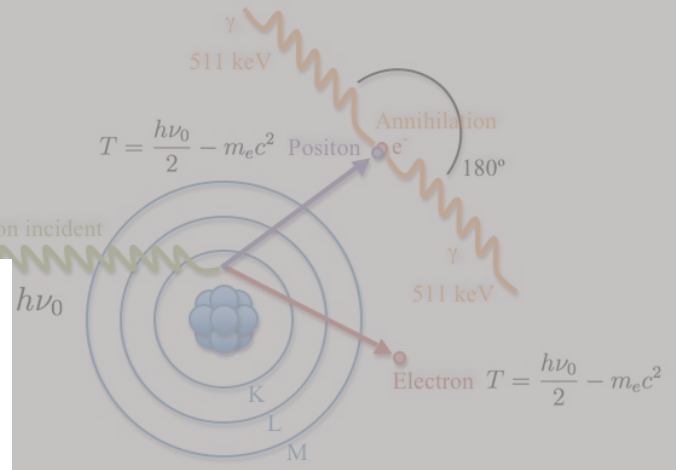
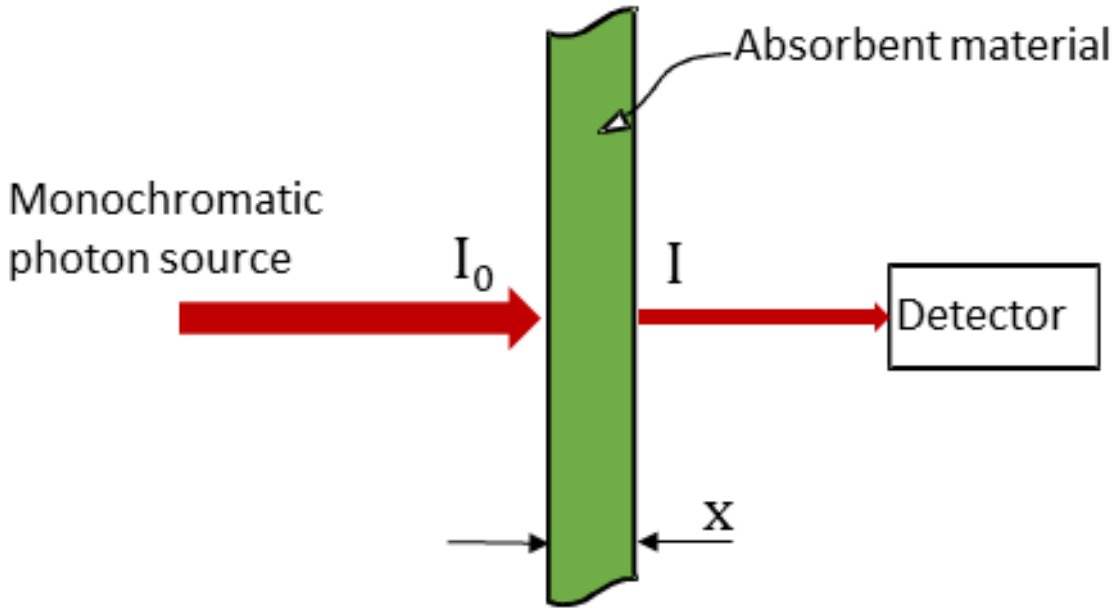


Interaction of radiation with matter

Photons

- The **attenuation** of a collimated photon beam arriving under normal incidence on a material of thickness x follows an exponential law:
  - $I = I_0 e^{-\mu x}$



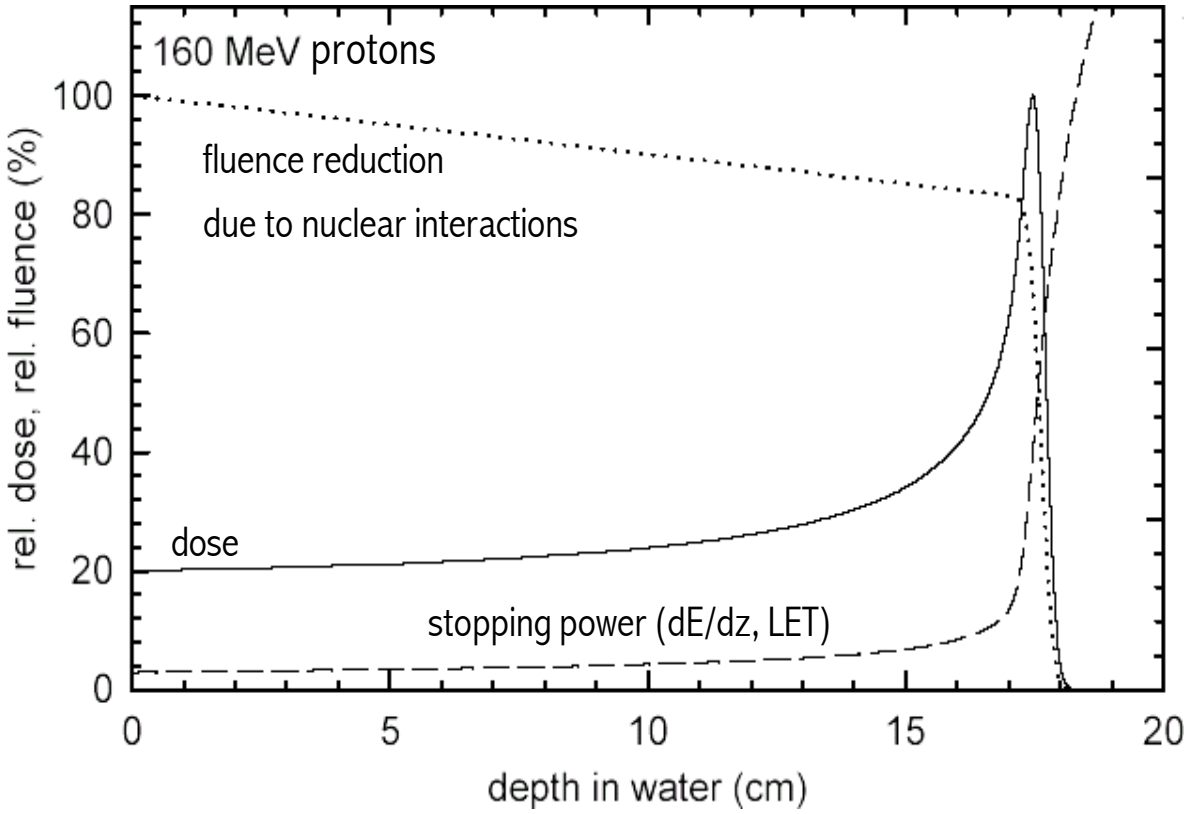
Interaction of radiation with matter

Heavy charged particles: protons

- Energy losses mainly due to **ionization processes → Bragg peak**

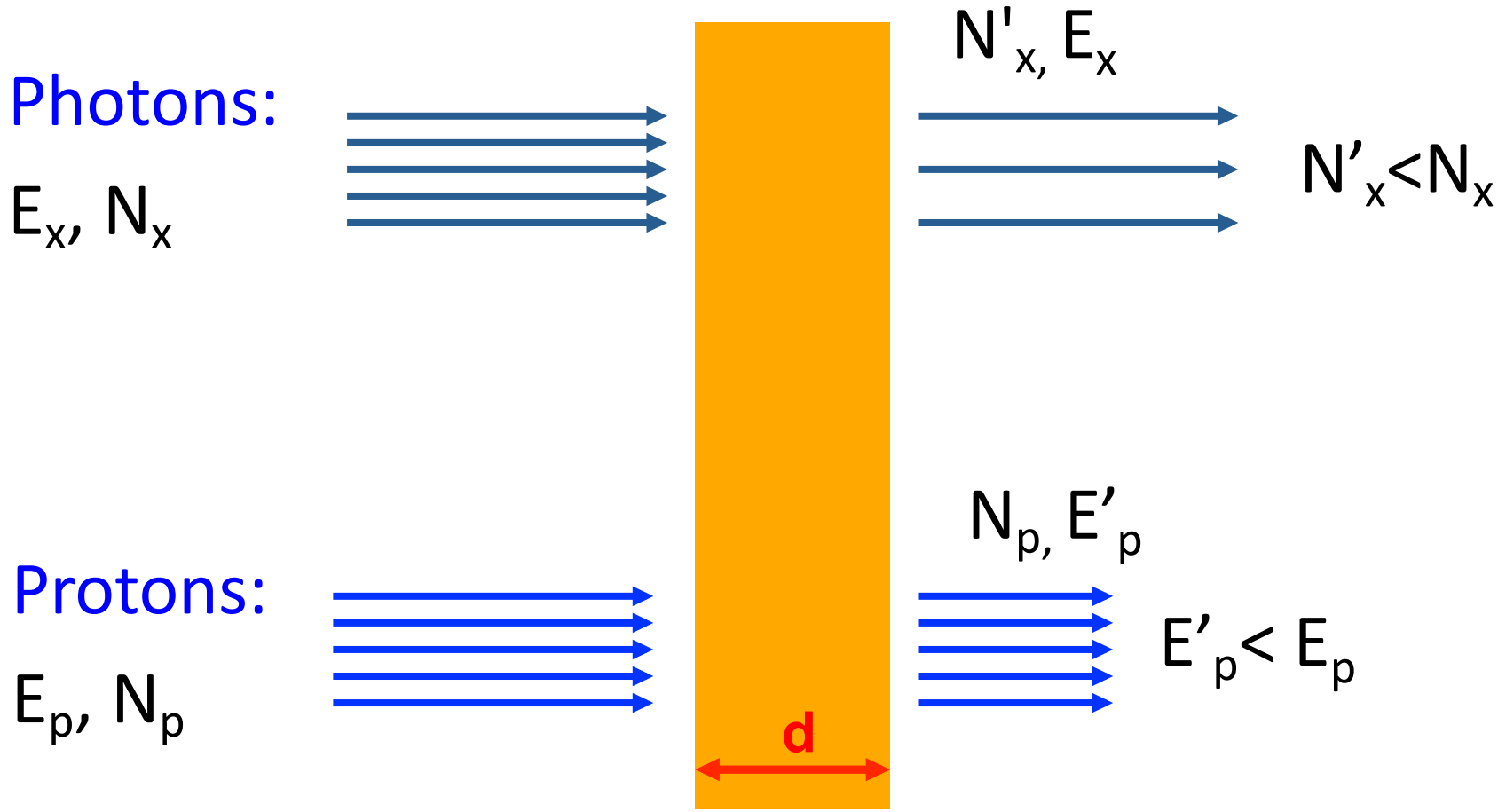
$$\frac{dE}{dz} = -4\pi n \frac{Z_{eff}^2 e^4}{m_e v^2} \left\{ \ln \frac{2 m_e v^2}{I(1-(v/c)^2)} - (v/c)^2 \right\}$$

peak position depends on particle energy ⇒ properly selecting the energy, one can reach the "right" depth into the target material

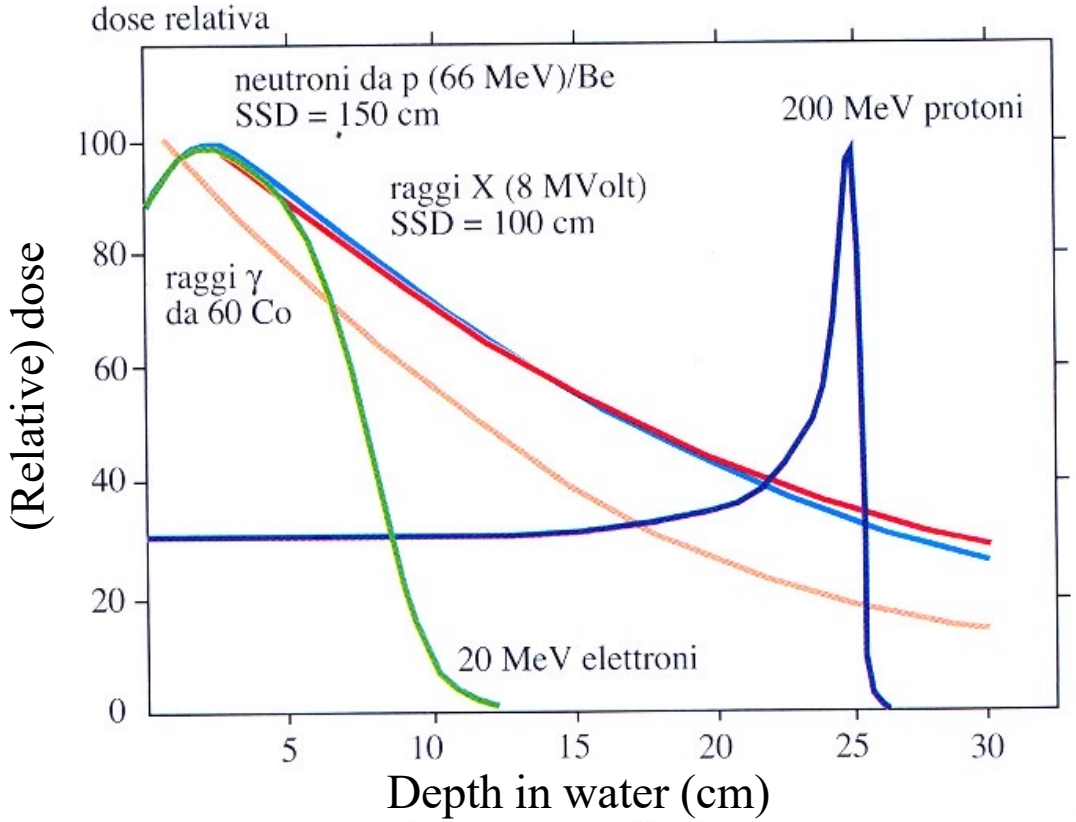


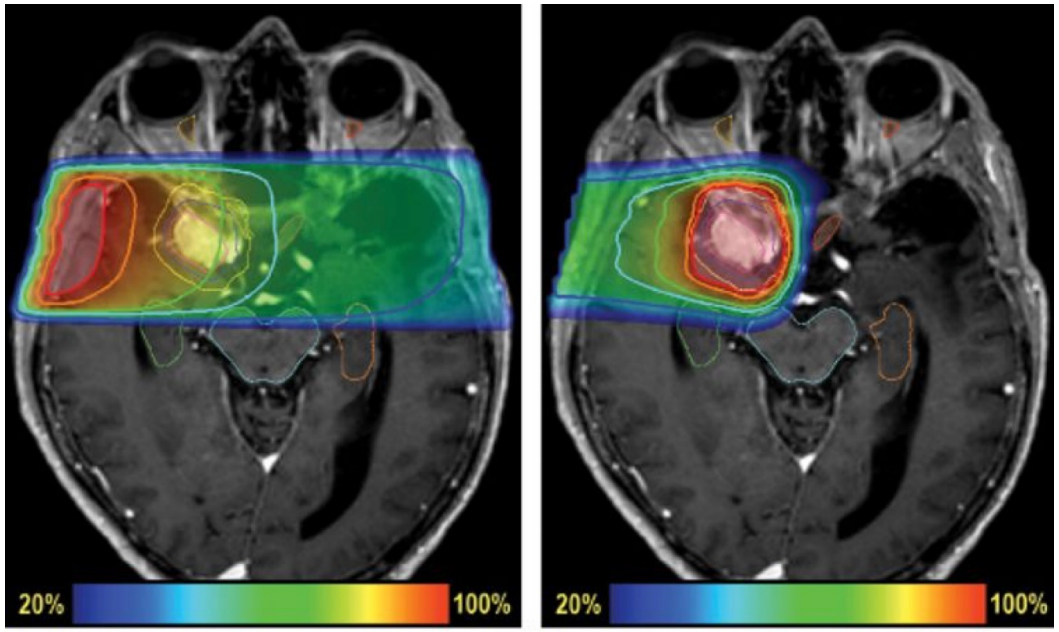
Photons vs Protons

Main difference related to energy delivery



Photons vs protons



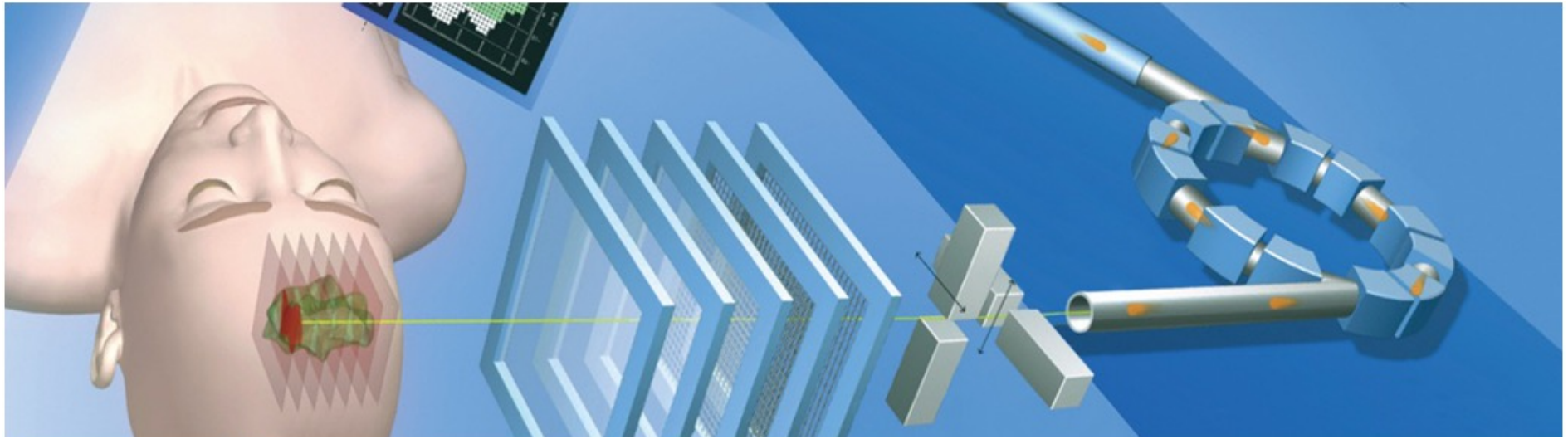


X-ray (traditional) radiation beam

Proton radiation beam

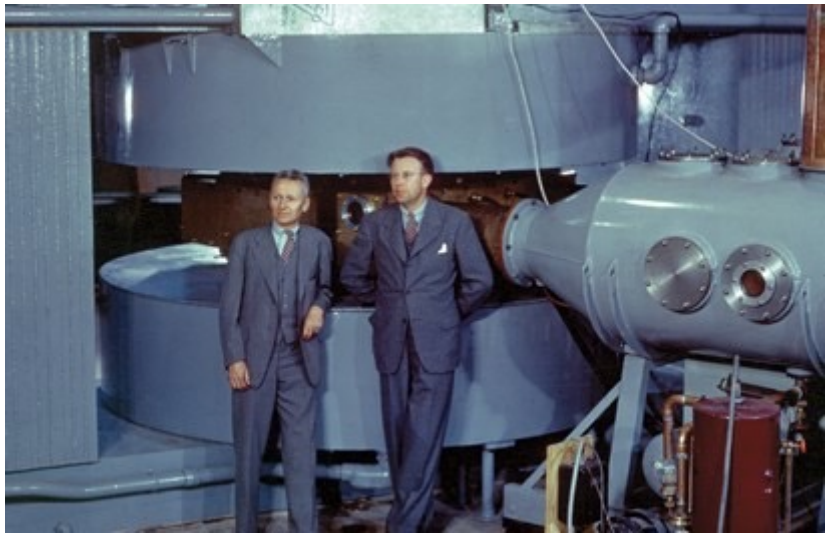
Hadron therapy

- **Cancer therapy based-on irradiation with “hadrons”**
- now: protons or Carbon ions
- future: He ions (and possibly other ion types) will be soon used at HIT (Heavy Ion-beam Therapy centre) in Heidelberg, Germany and then at CNAO in Pavia



Hadron Therapy: brief history

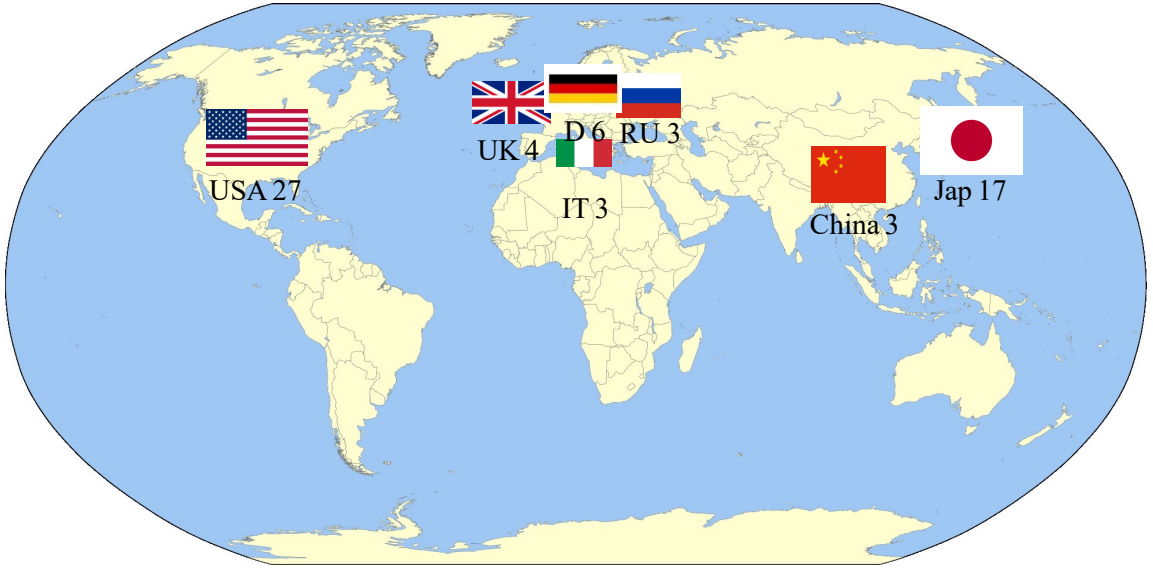
1954: first patient with protons in Berkeley, CA, USA
1957: first patient with He-ions in Berkeley *(2,800 patients)*
1961: starting of the Harvard cyclotron, where > 9,000 patients were treated with protons
1975: heavy ions like Ar, Si and Ne in Berkeley ⇒ non tolerable side effects
'90s: the first clinical centres for protons *(Clatterbridge, UK; Loma Linda, CA)*
1994: C-ion therapy starts in Chiba, Japan
1997-2008: the C-ion pilot project at GSI *(Darmstadt, Germany)*
2009: C-ion therapy starts in Europe (Heidelberg)
2012: C-ion therapy starts in Italy (CNAO, Pavia)



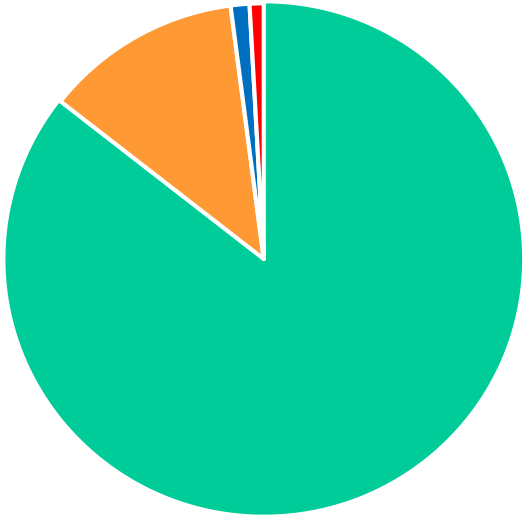
Hadron therapy in the world

104 centres in dec 2019, of which 13 with C-ions *(6 Jap, 3 Chi, 2 Ger, 1 Ita, 1 Aus)*

38 facilities under construction *(dec 2019)* + 27 planned



https://www.ptcog.ch



protons: ~250,000
C: ~40,000
He: ~2000
other ions: ~1500

patients treated worldwide until 2020: >290k
(https://www.ptcog.ch)

Ion production and acceleration

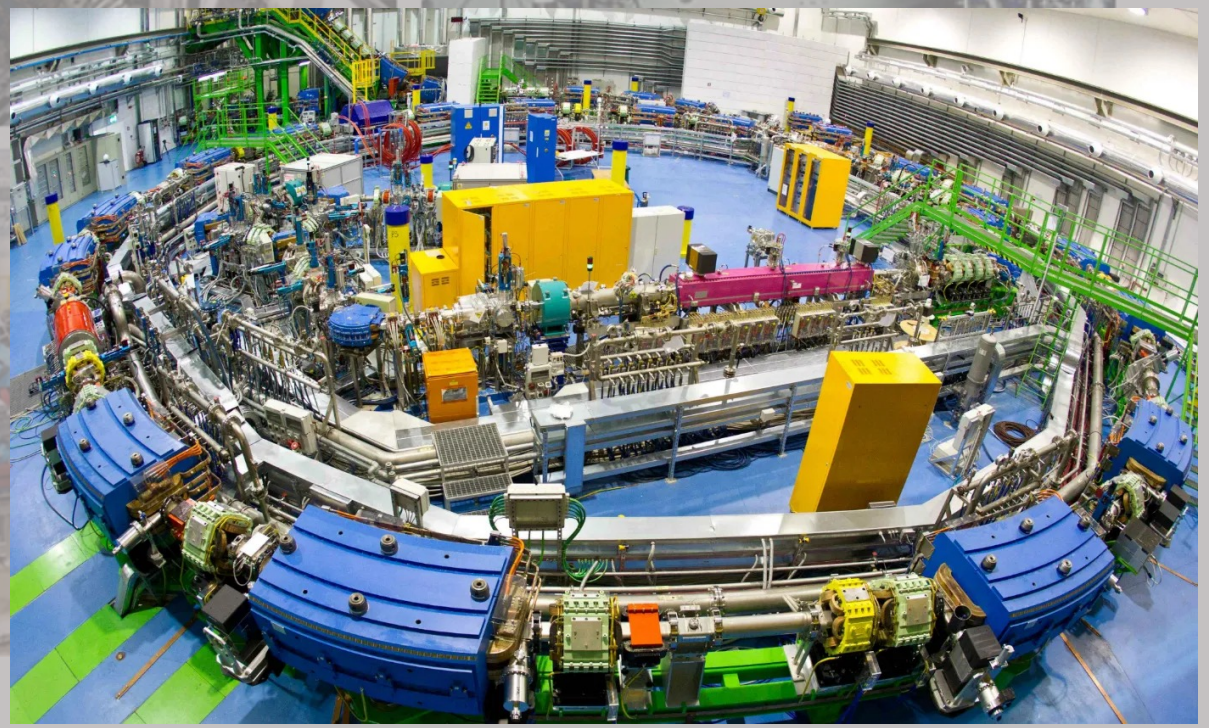
LINAC less compact (worse for clinical centres)
Cyclotrons for proton
Synchrotrons for protons and other ions

U. Amaldi 2010

Ion … n

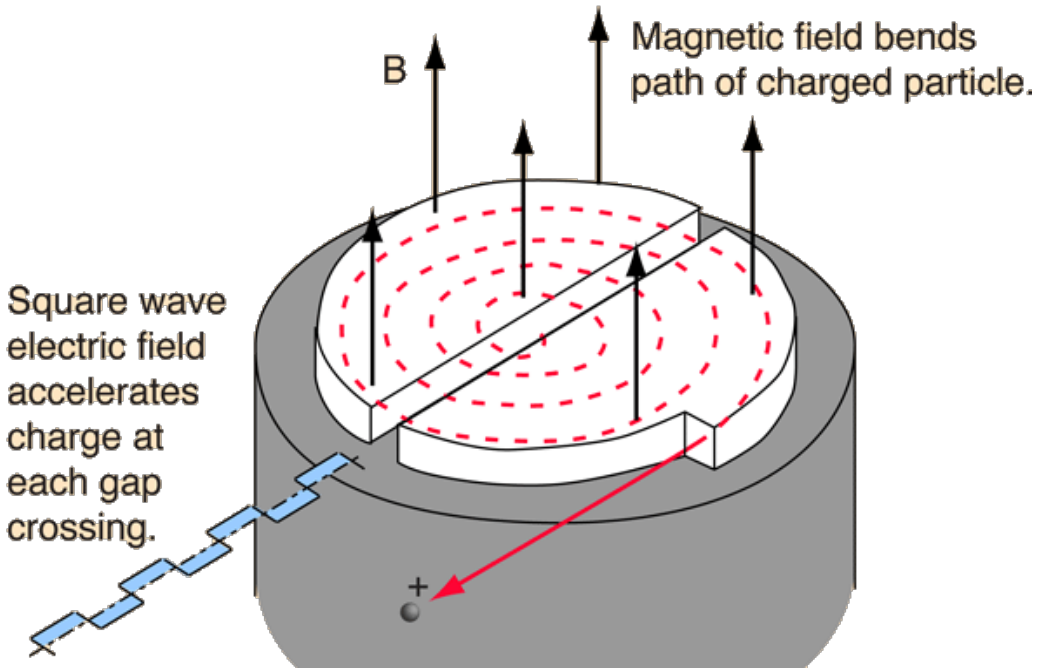
	LHC	CNAO
Circunference	27 km	80 m
Magnets	>9k	<200
Particle per bunch	10^{11}	10^{9}
Enegy	7 TeV	60-200 MeV

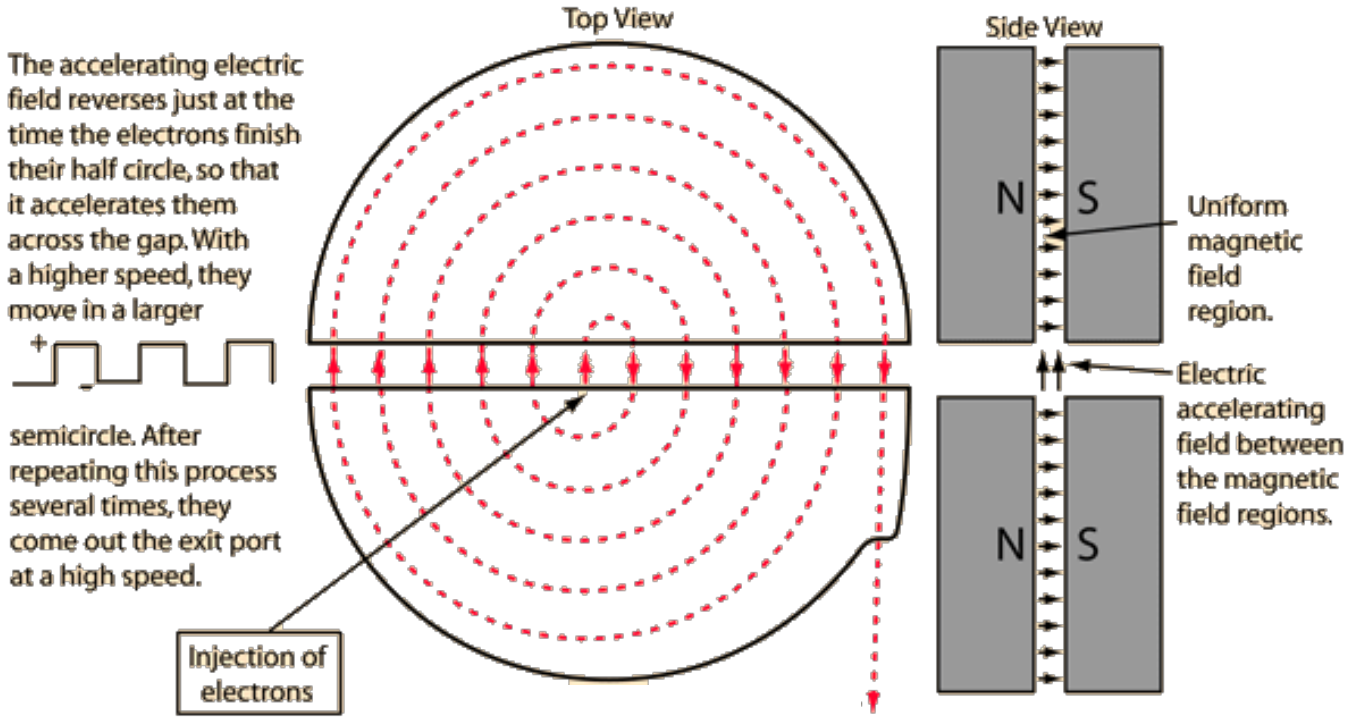
LINAC less compact (wo…
clinical centres)
C…
S…
o…



Cyclotron

the particles are held to a ***spiral*** trajectory by a ***static*** magnetic field, and are accelerated by a rapidly varying (radiofrequency) electric field.





Cyclotron

H. Lorentz, Nobel in 1902

$\mathbf{F} = q\,\mathbf{v} \times \mathbf{B}$, $\mathbf{v}$ perp. $\mathbf{B} \Rightarrow F = qvB$

$$ma = mv^2/R = qvB \Rightarrow$$

$$R = mv/qB$$

increasing v $\Rightarrow$ R increases $\Rightarrow$ spiral trajectory

- advantage: the particles are accelerated many times, so the output energy can be many times the accelerating voltage
- disadvantage: the final value of v is limited by B and by the radius R, because *high v needs large R*

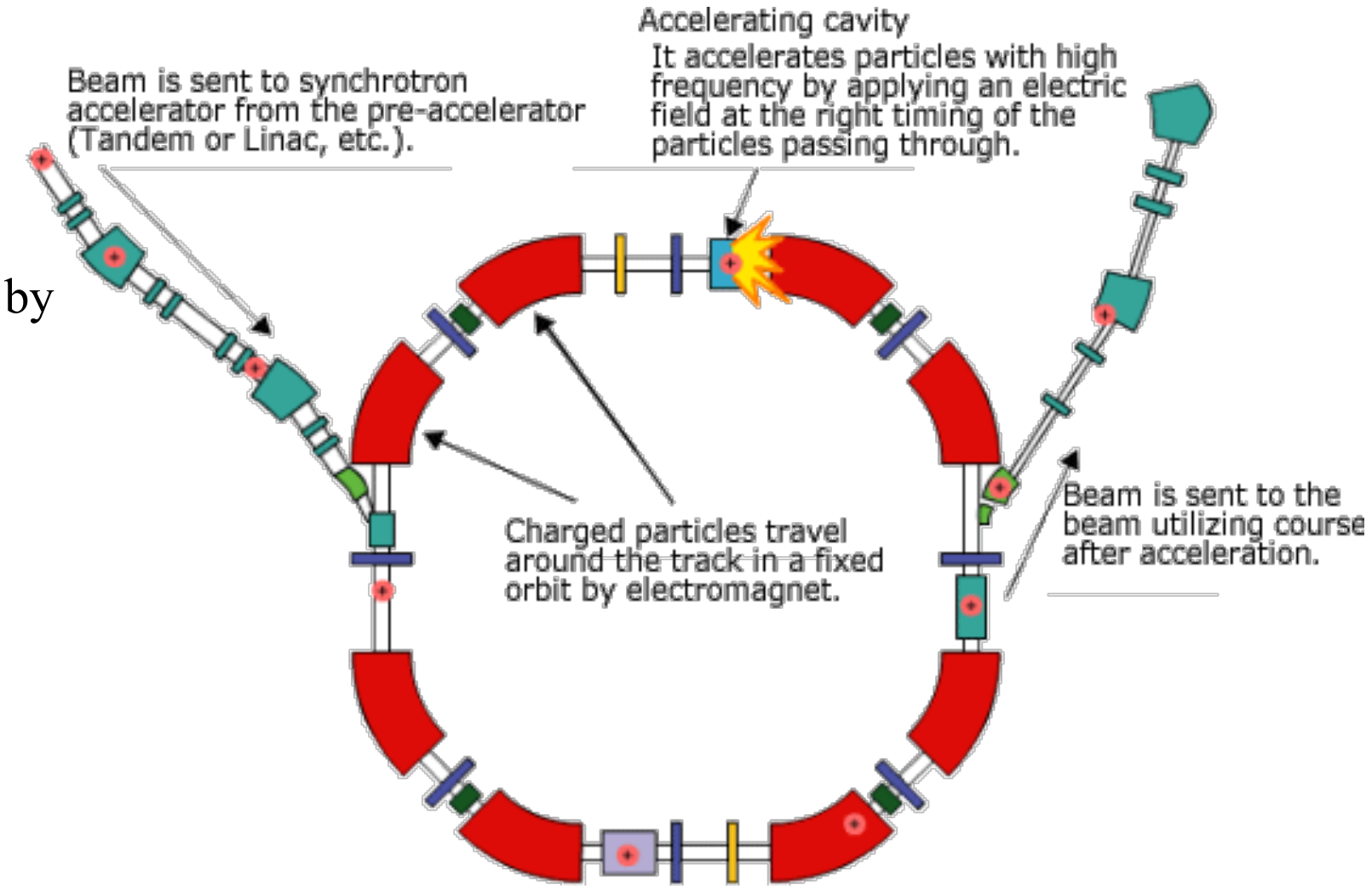
Syncroton

Increase velocity at fixed orbit by increasing the magnetic field

$$B = mv/qR$$

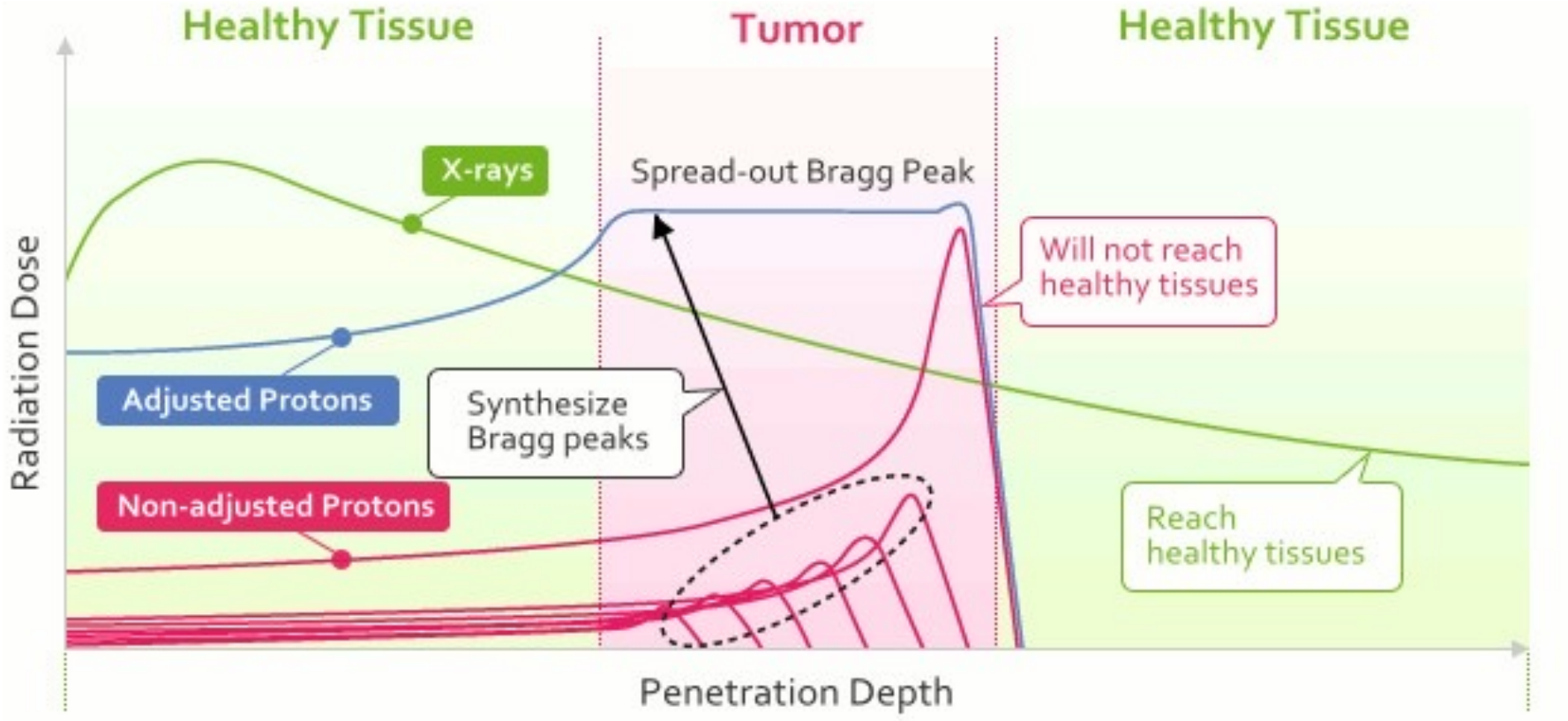
Can reach high energies

High cost on market



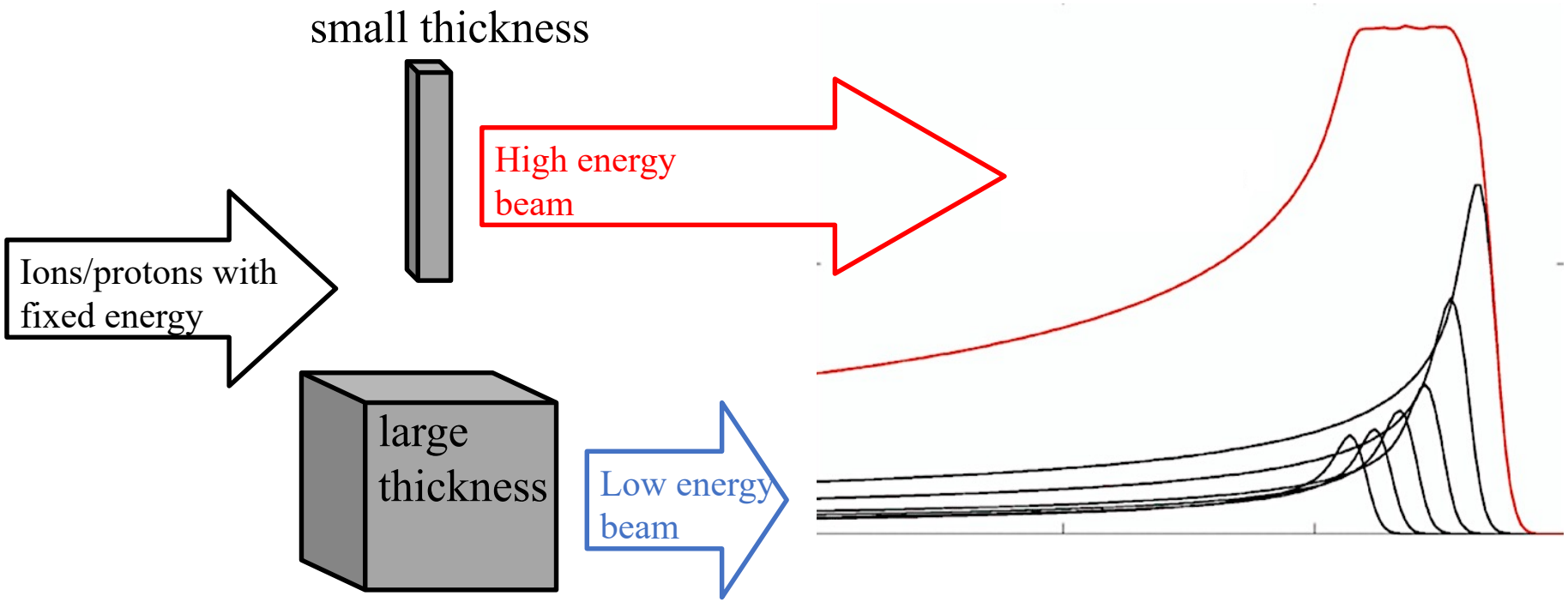
The Spread-Out Bragg Peak (SOBP)

a tumour is larger than a single Bragg peak → many different peaks are summed up *(beam "modulation")*, producing the "Spread-Out Bragg Peak (SOBP)"



Beam modulation

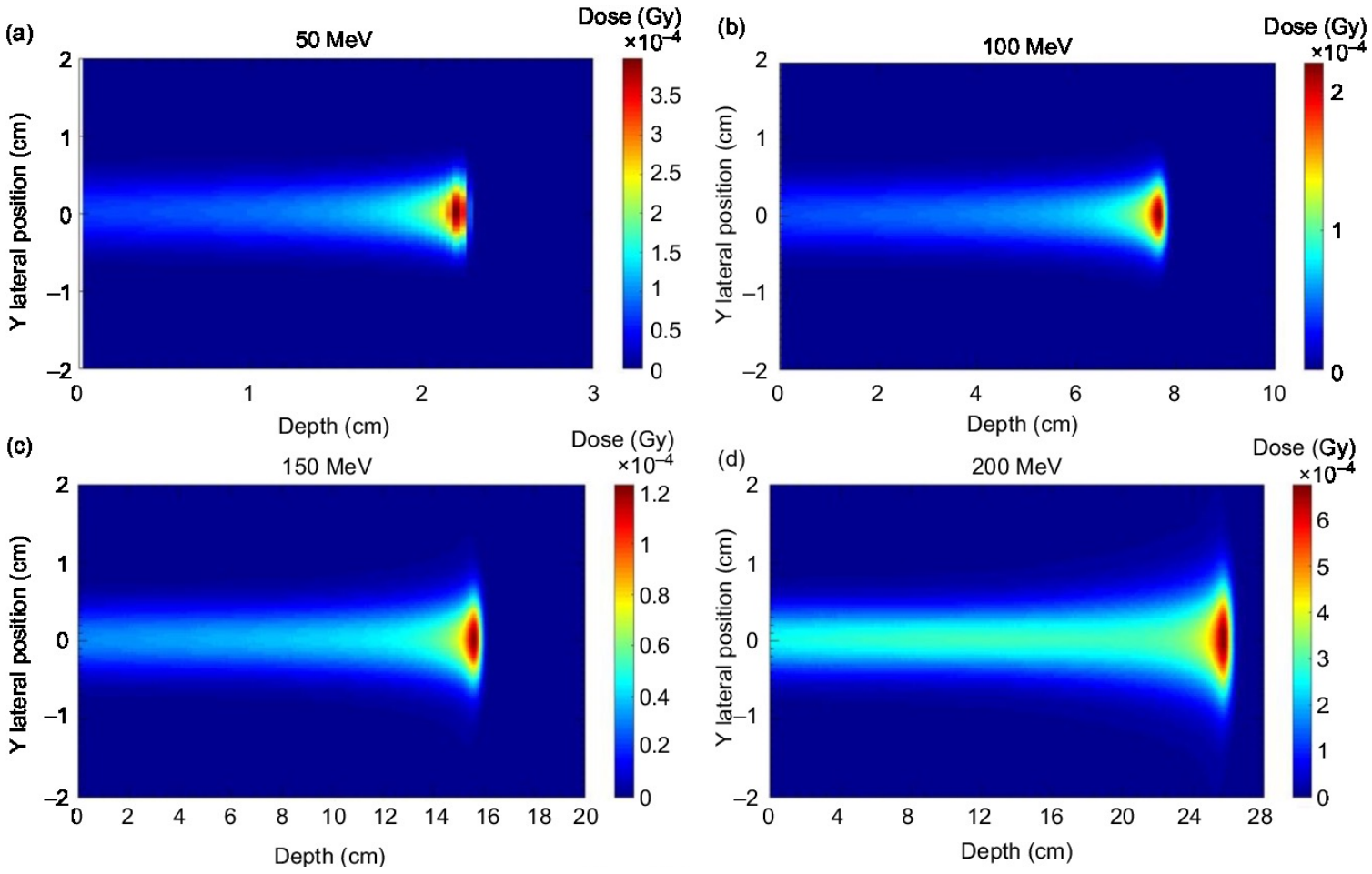
Passive energy modulation: the beam energy is changed by attenuation through pieces of different thicknesses



Active energy modulation: the beam energy is variable and dynamically adjusted to the dose required in each scan slide

Beam modulation

Bragg peak of proton beam within therapeuthic energy range.



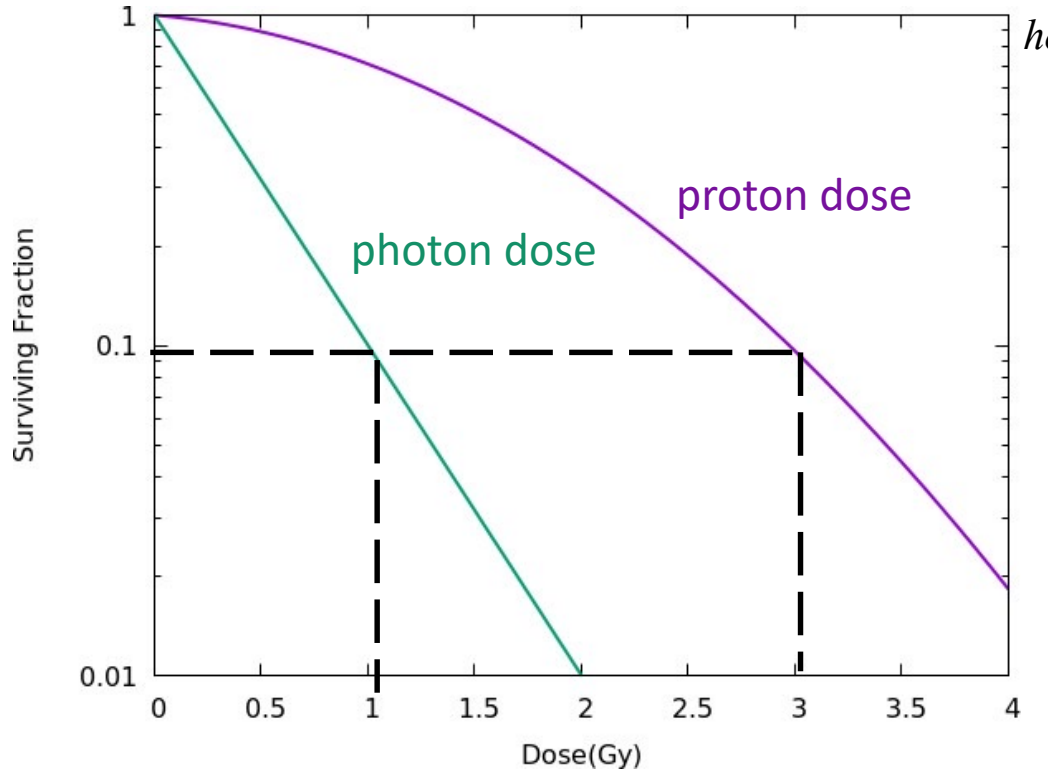
https://doi.org/10.1017/S1460396919000554

Heavy ions advantage

Heavy ions have higher "relative biological effectiveness" (RBE) than photons and protons

RBE ≡ photon dose / ion dose

to obtain the same biological effect



here, RBE = 3/1 = 3

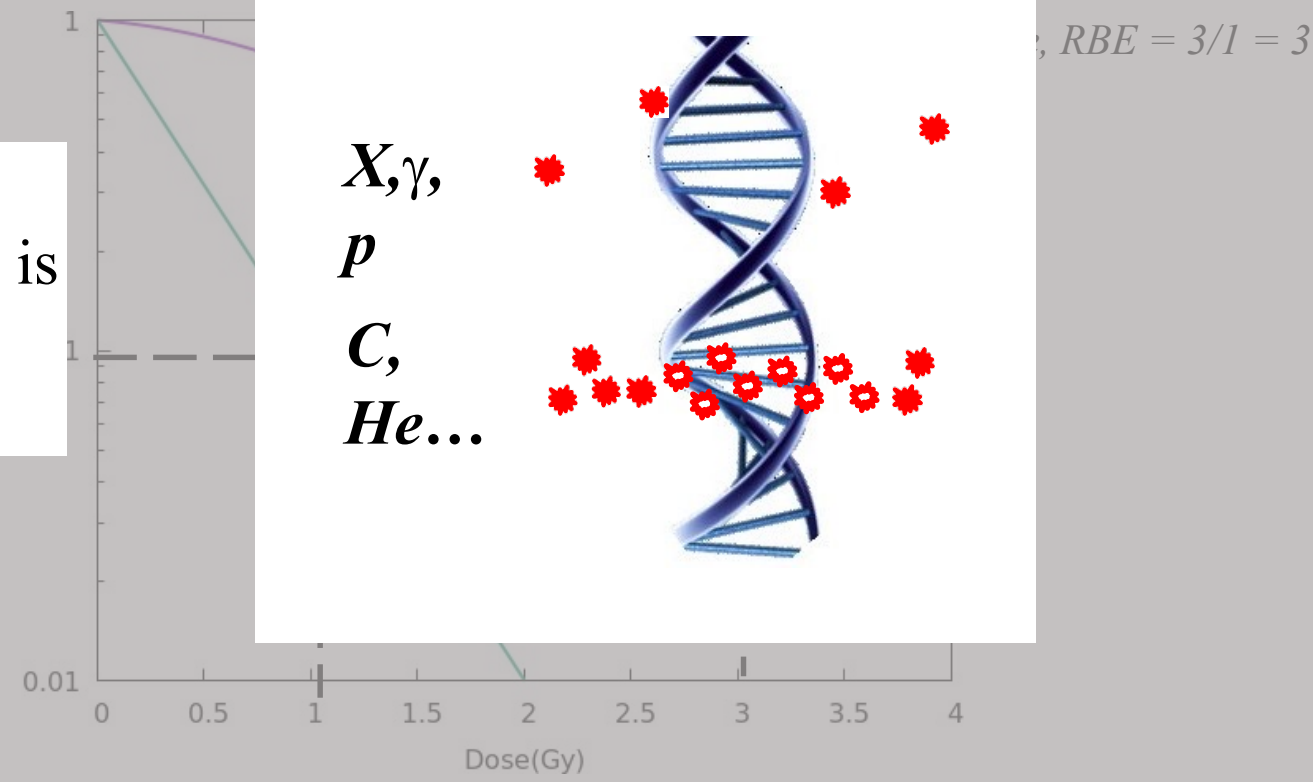
Heavy ions advantage

Heavy ions have higher "relative biological effectiveness" (RBE) than photons and protons

RBE ≡ photon dose / ion dose

to obtain the same biological effect

Heavy ions produce more "complex" damage to the DNA and the cell death is more likely → heavy ions high LET (Linear Energy Trasfer)



, RBE = 3/1 = 3

Heavy ions advantage

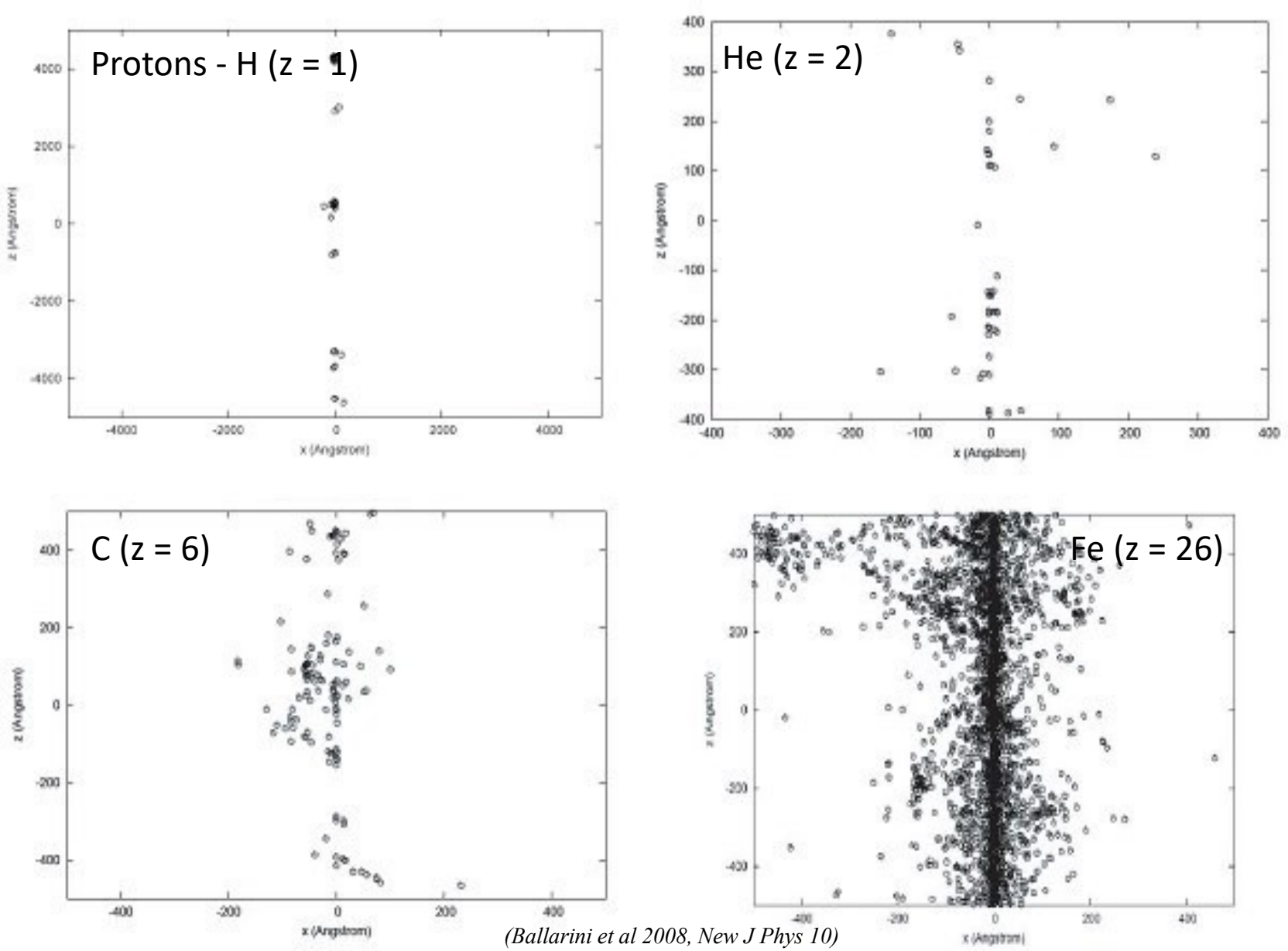
...and why heavy ions produce more complex DNA damage?

$dE/dx \propto z^2$ → Heavy ions have higher z thus the stopping power is higher

Heavy ions advantage

...and why he

$dE/dx \propto$



(Ballarini et al 2008, New J Phys 10)

Heavy ions advantage

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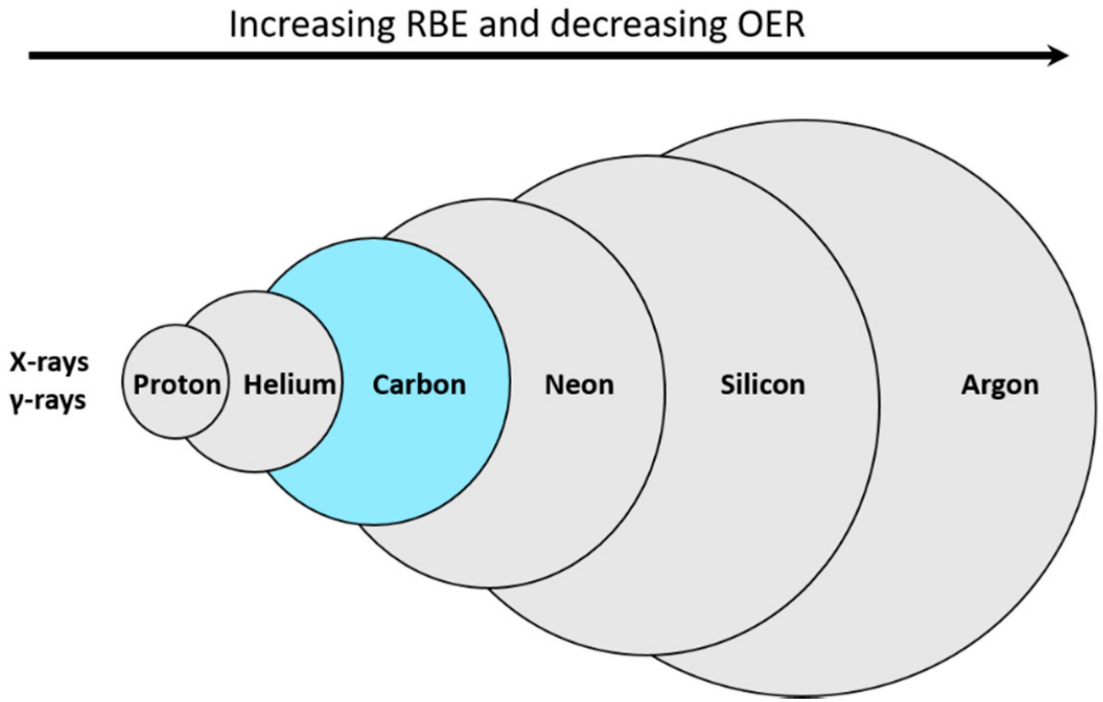
Why just C-ions ?



Where,

OER (oxygen enhancement ratio)
= Dose without Oxygen / Dose with Oxygen
= Dose in hypoxia / Dose in air

Takeaway More O → Less Repair → More Damage

Also, higher dose due to bigger fragmentation tail effect

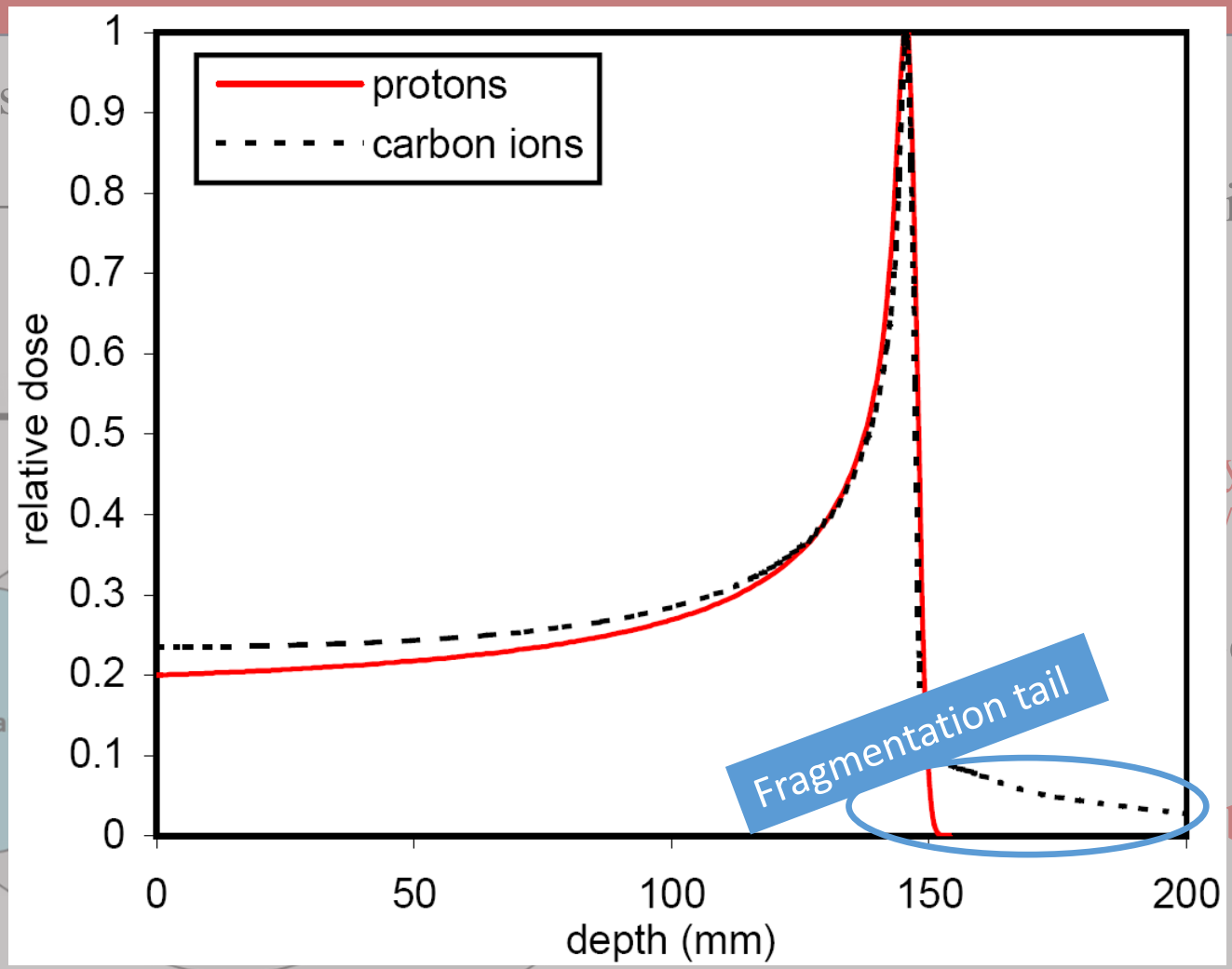
Heavy ions advantage

...and why heavy ions

$dE/dx \propto z^2$

Why just C-ions ?

Increasing



igher

ygen / Dose with Oxygen
/ Dose in air

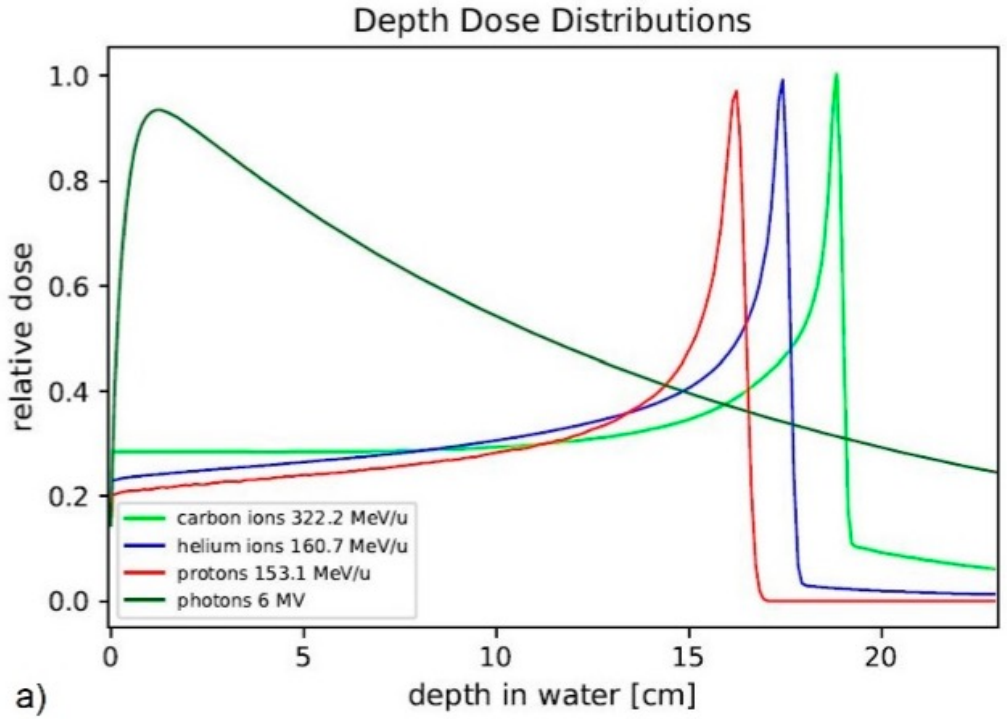
ess Repair →

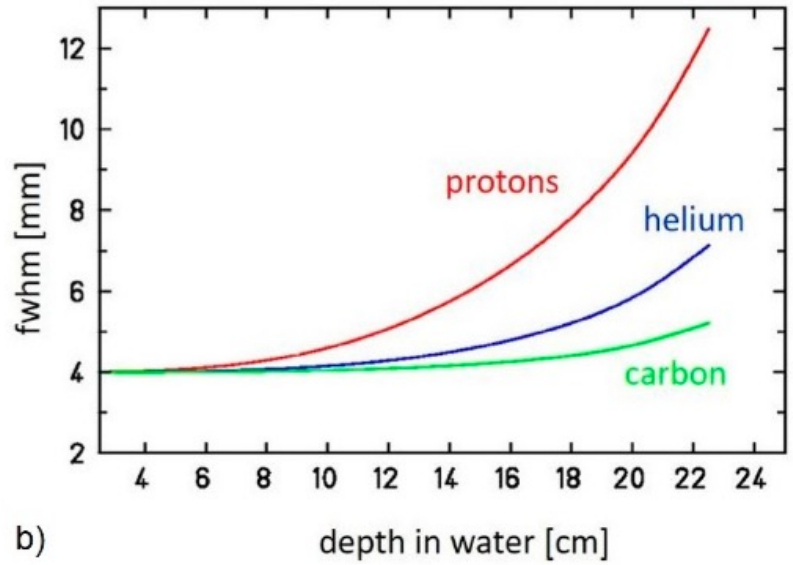
bigger fragmentation tail

X-rays
γ-rays
Proton
Helium

He-ion therapy

- Lower dose in the fragmentation tail region with respect to C-ion beams → less dose in healthy tissue
- Higher LET, and RBE with respect to proton beams
- Lower lateral spread (fwhm) → more focused beams and localized therapy





FLASH therapy

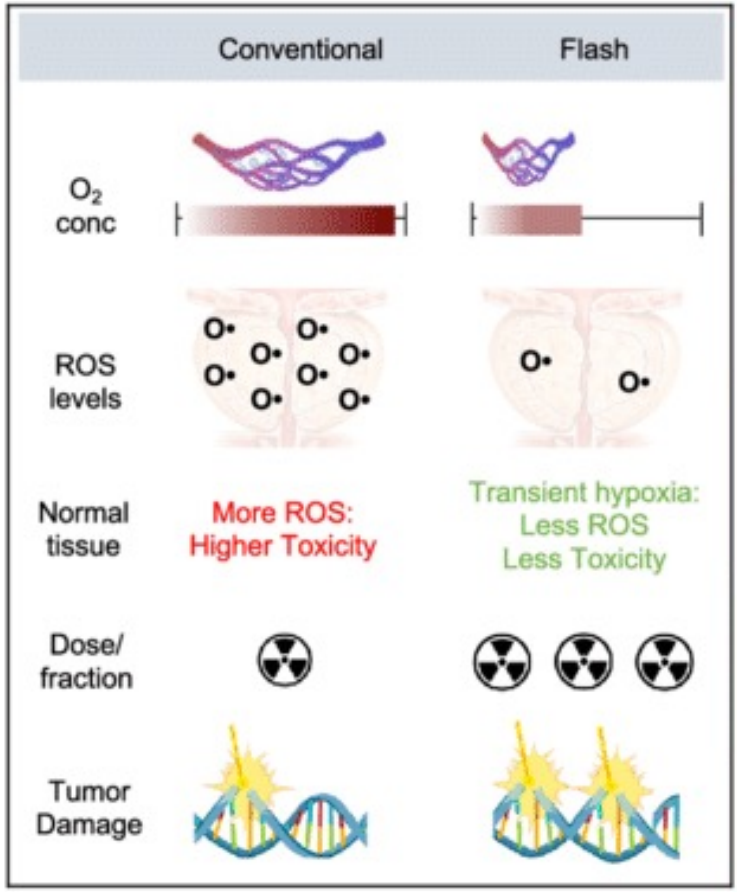
FLASH radiotherapy is a technique involving the delivery of ultra-high dose rate radiation to the target. FLASH has been shown to reduce radiation-induced toxicity in healthy tissues without compromising the anti-cancer effects of treatment compared to conventional radiation therapy.

High dose rate: > 40 Gray/sec (possible); > 100-150 Gray/sec (likely)

Reproducible effect

- Dose / pulse (> 1.5 Gy & few pulses)
- Dose rate in the pulse (>= 106 Gy/s)
- Overall time (< 100 ms)

Dose/fraction No dose limiting effect observed in animal models between 25-41 Gray



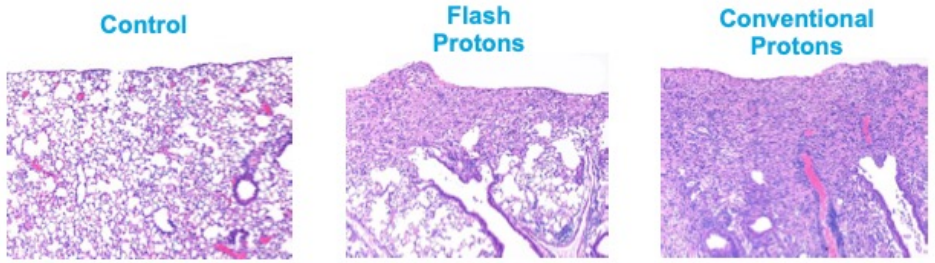
* ROS: Reactive oxygen species

FLASH therapy

Flash resulted in a reduction in radiation induced dermatitis and fibrosis

Normal tissue toxicity studies

25% reduction in fibrosis* with FLASH vs. Conventional (17.5 Gy)



35% reduction in dermatitis* with FLASH vs. Conventional (17.5 Gy)

*Average dermatitis scores

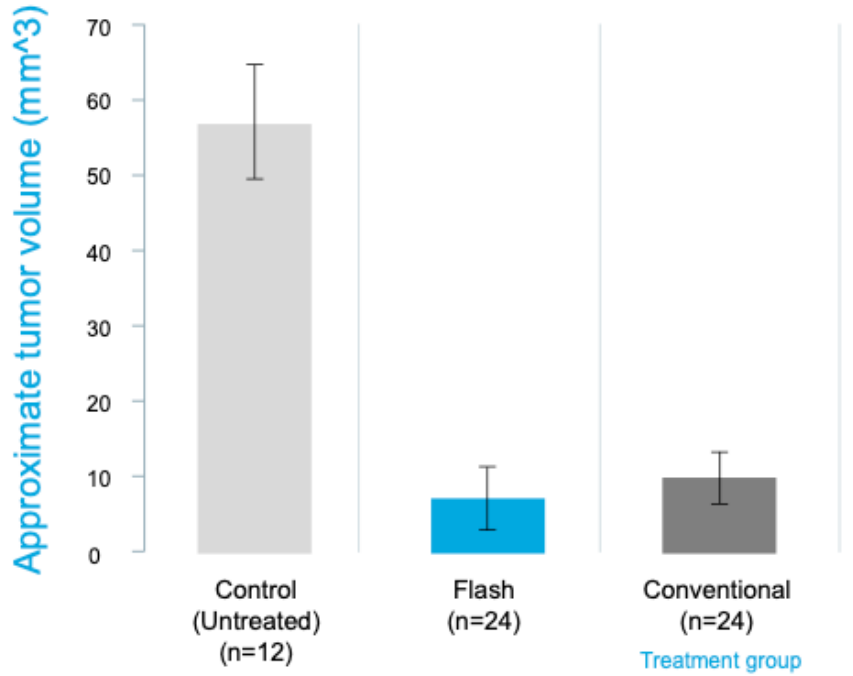
LUNG FIBROSIS
(Graded by independent pathologist, blinded on treatment groups)

DERMATITIS

*Average fibrosis scores

Tumor control preliminary results:

Proton FLASH vs Proton Conventional vs No RT

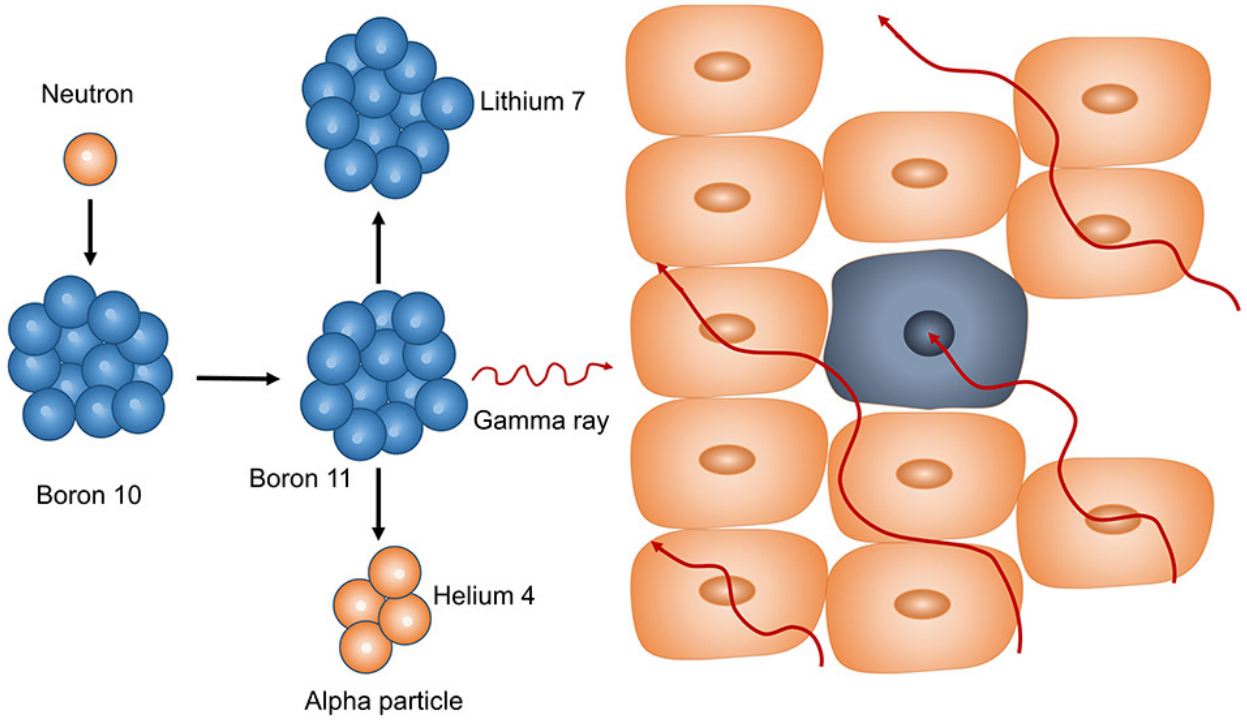


Summary

- Hadron Therapy: particle therapy based-on irradiation with hadrons
- Localized delivery dose → tumor scanning by changing the beam energy (SOBP)
- High RBE and LET ($dE/dx \propto z^2$)
- Lower lateral spread (fwhm) when using heavy ions → more focused beams and localized therapy

Boron Neutron Capture Therapy (BNCT)

is a **high-linear energy transfer (LET) radiotherapy** exploitable for cancer treatment, based on the **nuclear capture and fission reactions** that occur when ^{10}B is irradiated with **thermal and epithermal neutrons.**

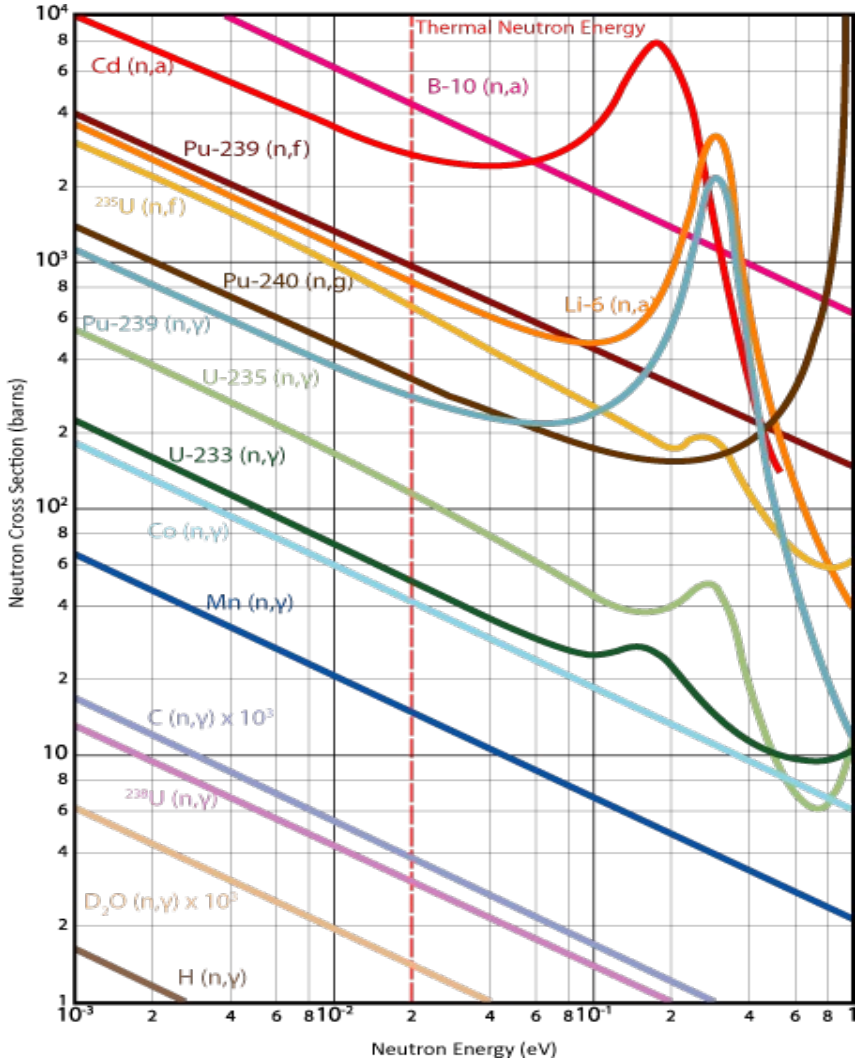


Boron Neutron Capture Therapy (BNCT)

Why B-10 for the therapy?

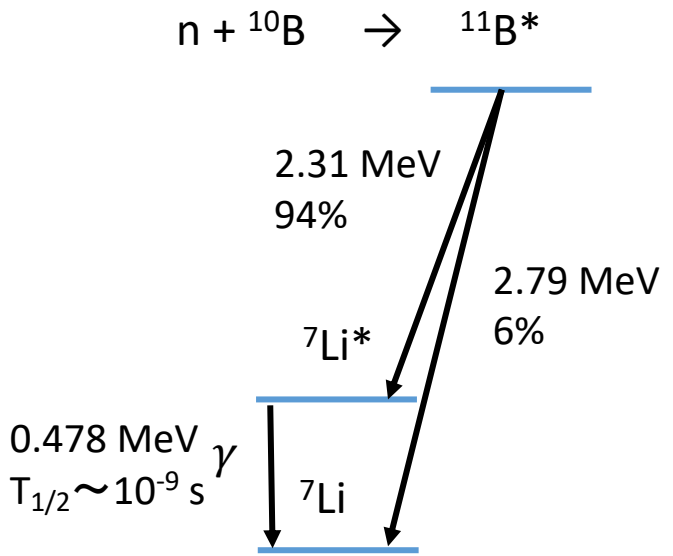
$^{10}B(n,\alpha)$ has a **high capture reaction cross section** at thermal/ephitermal energies → increase dose delivery efficiency.

σ ≈ 3800 b around thermal neutron energy



Boron Neutron Capture Therapy (BNCT)

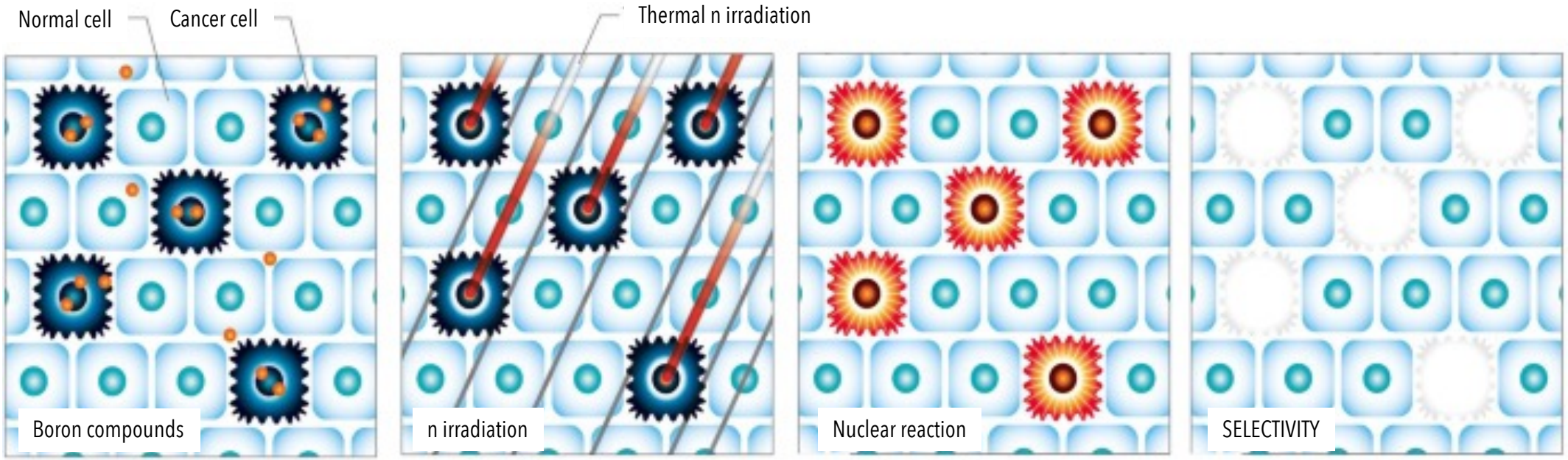
- The reaction channel is 94% through 7Li* + **α**, and **γ**(478 keV) is emitted which can be used to monitoring the treatment dose.
- **α** range between up to 11 μm damaging the full cell with high LET **→ Hadron Therapy at level of single cell.**



	Energy (MeV)	Range (μm)
α	1.47-178	9-11
^{7}Li	0.84-101	4-5
γ	0.48	

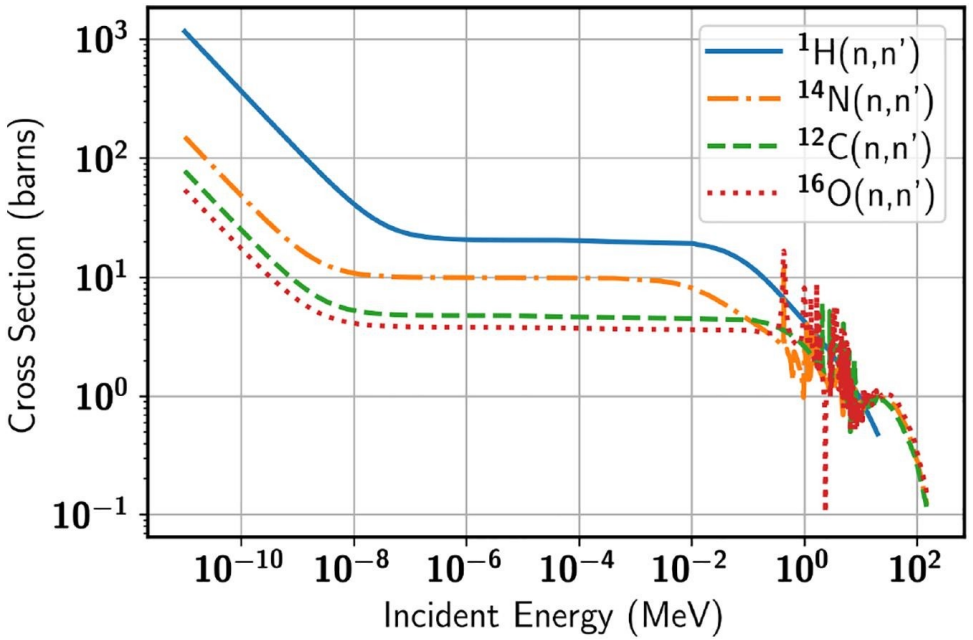
Boron Neutron Capture Therapy (BNCT)

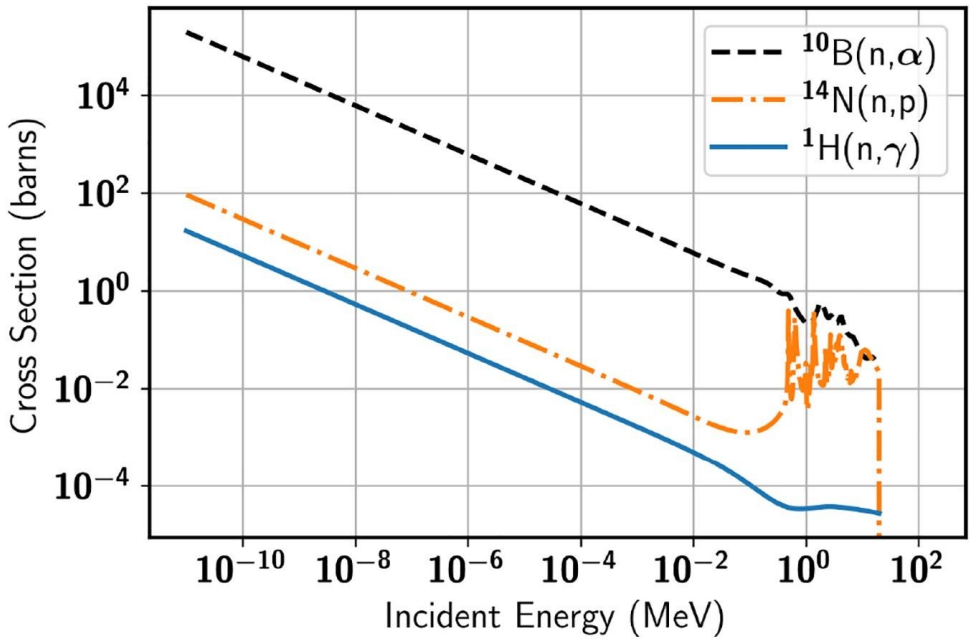
- The **SELECTIVITY** at cell level depends on microscopic distribution of ^{10}B
- Selectivity: lethal dose only in the tumour; sparing effect of healthy tissue.
- Dose in healthy tissues $D_S \propto C_S \cdot \Psi_n$ and in tumour tissues $D_T \propto C_T \cdot \Psi_n$ then: **Therapeutic ratio is $T = C_T / C_S$** $(T > 1.0)$
- T is the boron concentration ratio between tumuor and healthy tissues and clinical studies give as good compromise **T ~ 3.0 or more.**



Boron Neutron Capture Therapy (BNCT)

- Another reactions occurs with the main elements that compound the tissue: **hydrogen**, **carbon**, **nitrogen** and **oxygen**.
- **^{1}H(n,n') p** emission at various E, **^{1}H(n, γ)** low LET.
- **^{14}N(n,p)^{14}C** high LET.





Boron Neutron Capture Therapy (BNCT)

Not only ^{10}B…

generally, **(n,γ) reactions**

loss the cell-level selectivity;

few radionuclides and/or toxic elements (such as **Cd, Gd, Hg, U, Pu, Am, ^{3}H**…);

few nuclides are noble gases (**He, Xe**)

few nuclides are key elements in weapons (**U**)

Nuclide	Interaction	Cross section σ_{th} (b)	Recoil nucleus	Q-val (MeV)
^{3}He	(n,p)	5,333	^{3}H	0,764
^{6}Li	(n,α)	940	^{3}H	4,78
^{10}B	(n,α)	3,835	^{7}Li	2,79
^{113}Cd	(n,γ)	20,600	same of entrance ch	
$^{135}Xe^{a}$	(n,γ)	2,720,000	"	
^{149}Sm	(n,γ)	42,080	"	
^{151}Eu	(n,γ)	9,200	"	
^{155}Gd	(n,γ)	61,100	"	
^{157}Gd	(n,γ)	259,000	"	7,94
^{147}Hf	(n,γ)	561	"	
^{199}Hg	(n,γ)	2,150	"	
$^{235}U^{a}$	(n,f)	681	fission fragments	< 200
$^{241}Pu^{a}$	(n,f)	1,380	"	
$^{242}Am^{a}$	(n,f)	8,000	"	

[a]Radioactive

Neutron Capture Therapy timeline

- **1932:** neutron discovery by Chadwick (Nobel prize 1935)
- **1935:** description of $^{10}B(n,\alpha)^{7}Li$ reaction by Taylor&Goldhaber
- **1936:** Locher proposes the use of neutron capture reactions in cancer treatment
- **1940:** Kruger published the first experiment on BNCT (in vitro tumour fragments treated with boric acid + n-irr => in living animals); Zahl et al. Perform the first in vivo BNCT on mouse sarcoma
- **1950's:** first CLINICAL trials (brain tumours)

Neutron sources for BNCT

Thermal neutron flux as function of depth inside a tissue equivalent phantom due to primary beams of thermal (< 0.5 - 1 eV) VS epithermal (0.5 eV - 10 keV) neutrons

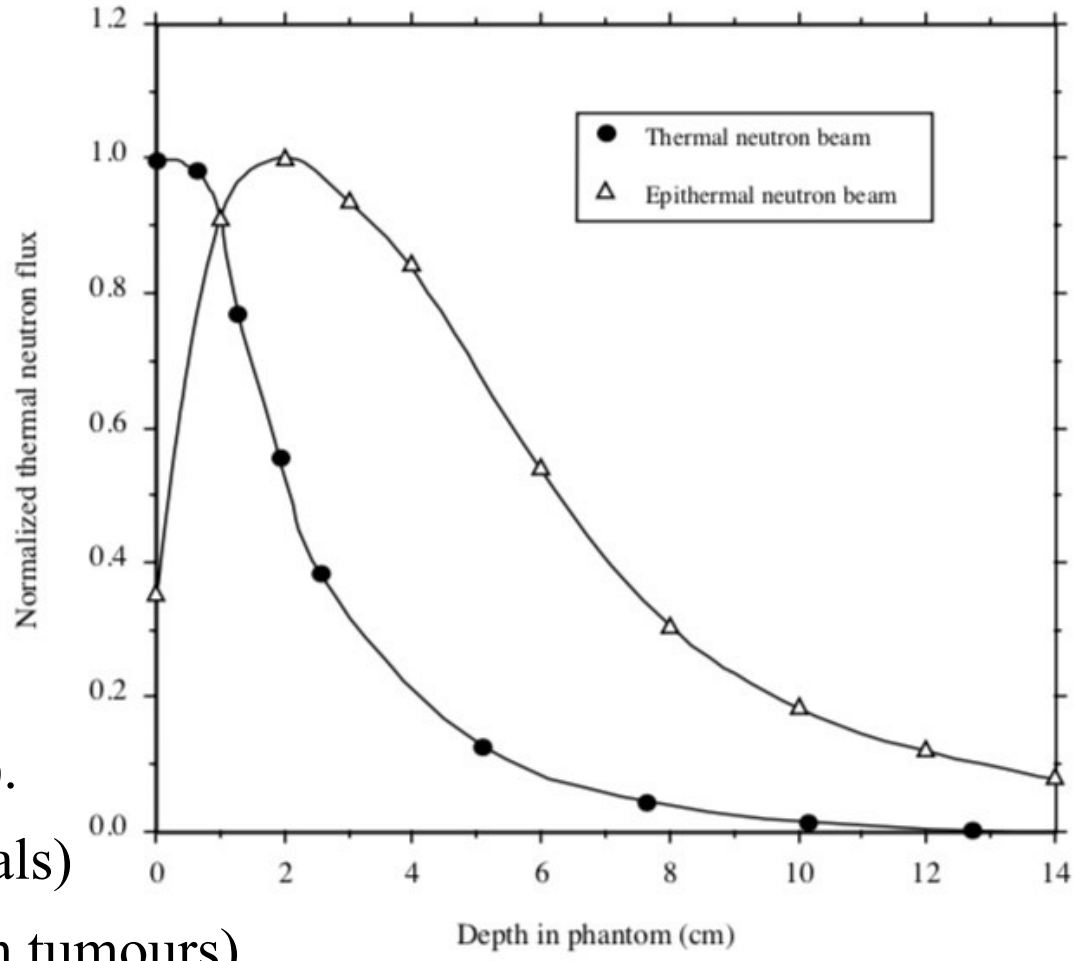
- High flux/fluence of thermal **n** at ^{10}B loaded V-Target depth
- epithermal **n**: skin-sparing effect → increased beam penetration by $\langle E_0 \rangle$ and forward direction (collimation)

Always epithermal n? Which E?

thermal **n** for shallow tumours (skin melanoma).

and preclinical investigation (cells, small animals)

VS epithermal **n** for deep seated tumours (brain tumours)



Neutron sources for BNCT

Beam design objectives (for clinical BNCT): to produce an epithermal fluence at beam port within a reasonable treatment time (about 1h) sufficient to have a high enough thermal **n** fluence at tumour depth with the less possible contamination by other radiation (non-thermal n, photons…)

INTENSITY

- Low irradiation time (T_{irr})
- No interaction at beam port
- Strongly dependent on ^{10}B ppm in tumours

QUALITY

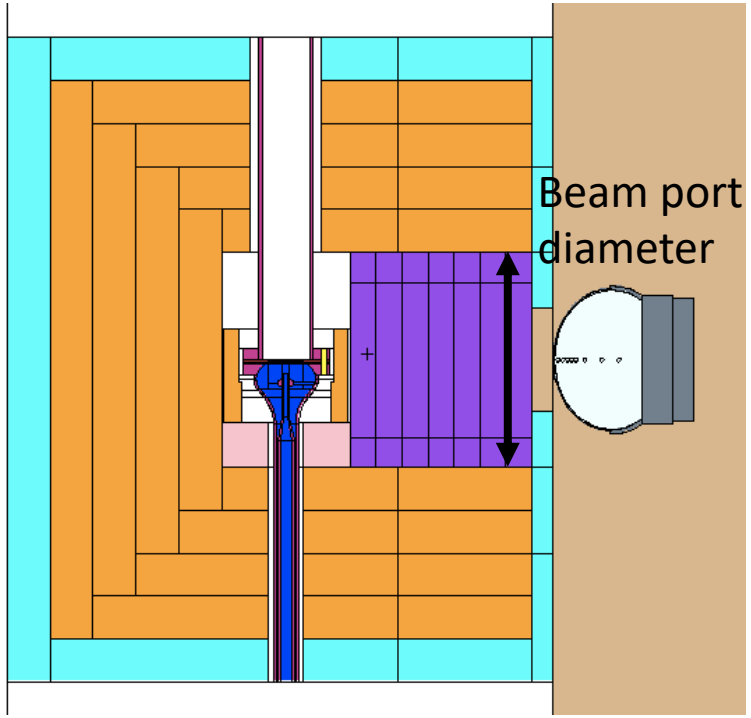
Free beam parameters:

- Fast neutron contamination
- Photon contamination
- Geometrical and energy neutron ratios

Neutron sources for BNCT

Other important features of the beam:

- variable dimension (typically circular shape)
- protruding collimator → to improve patient positioning
- Beam always fix → the patient must place and adapt



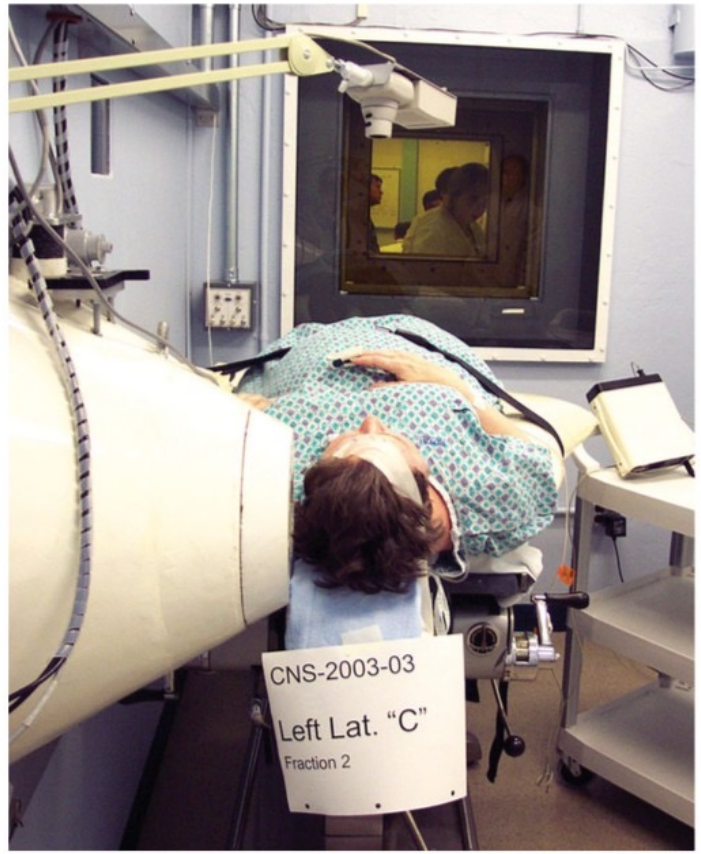


Fig. 2.1 A lateral field irradiation setup using the long protruding collimator in the MIT FCB and an air gap of 3 cm

Neutron sources for BNCT

Some lucky numbers:

IAEA TecDoc-2001	
Φepi (n/cm^{2}s)	> 10^9
R th/epith	< 0.05 (5%)
Df/Φepi (Gycm^2/n)	< 2x10^{-13}
Dγ/Φepi (Gycm^2/n)	< 2x10^{-13}
J/Φepi	> 0.7

AD = Advantage Depth = depth at which the tumour total dose equals the maximum dose to healthy tissue

Table 2.1 Suggested performance characteristics of epithermal neutron irradiation facilities for BNCT of brain tumors (or comparable soft tissue) using the tumor-targeting agent BPA and associated weighting factors [14]

Characteristics	Desired facility performance for BPA
Neutron and photon beam contamination	$<2\times10^{-12}$ Gy cm^{2a}
Advantage depth (useful penetration)	>8 cm
Energy	~0.4 eV < E < ~10–20 keV
Collimation (calculated current to flux ratio)	$J/\varphi>0.75$
Beam aperture	Adjustable size and shape, 0–16 cm diam. for brain
Intensity, epithermal neutron flux	$\geq2\times10^9$ n cm^{-2} s^{-1b}
Treatment time	~10 min
Patient positioning	Beam placement on any part of the body facilitated by a long protruding collimator, large irradiation room, visual field alignment tools
Beam control	Fluence delivery to ± 1 % of prescription
	Safety interlocks to protect staff and patient
Patient support	Visual and audio communication for monitoring patient, rapid egress during emergencies

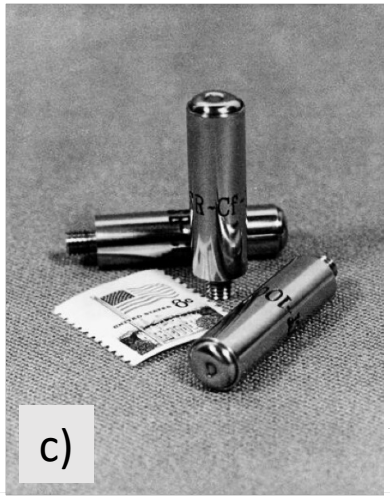
[a]Equivalent to 2.8×10–12 Gy cm^2 when applying weighting factors of 3.2 and 1.0 for photons and neutrons respectively

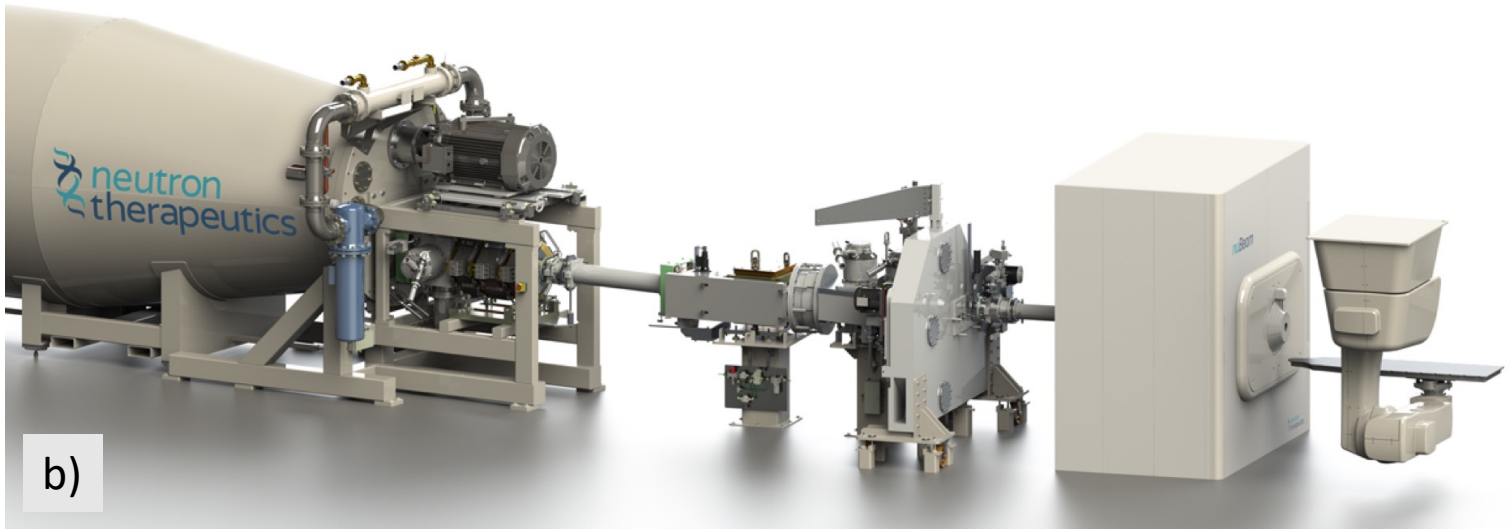
[b]Higher intensities are desirable for tumors with deeper target volumes or when using more advanced compounds with lower uptake in tissue (but with improved selectivity) to keep irradiation times as short as possible

Neutron sources for BNCT

a) Nuclear reactors
b) Accelerator based sources
c) ^{252}Cf source
d) Compact neutron generators

Radiation source and compact generators are not suggested due to **low neutron flux**
Nuclear reactor and AB most used neutron sources for BNCT

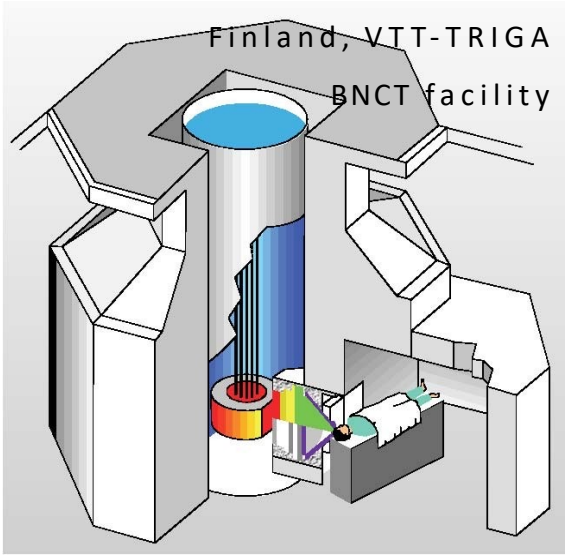


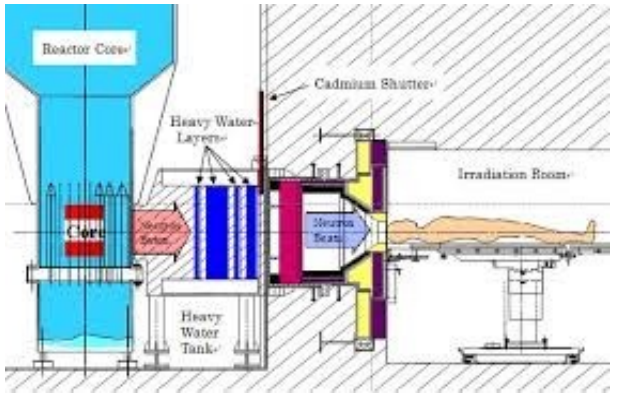


Neutron sources for BNCT

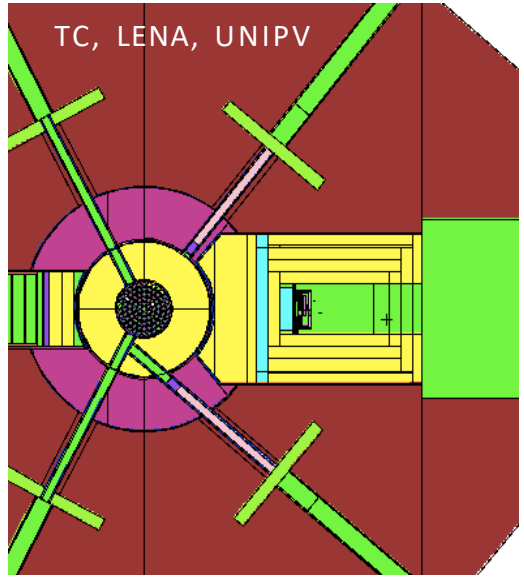
a) Nuclear reactors

- Complex to install, maintain and dismantle, high costs and bad public opinion.
- Not so common and diffuse technology (in particular in Italy).
- Generally ("NCT history") used for other goals such as radiopharmaceutical production → conflicts or limitations in the availability of the beam for medical use.
- Usually are located far from hospitals → long road transfer of the patient during the BNCT procedure.





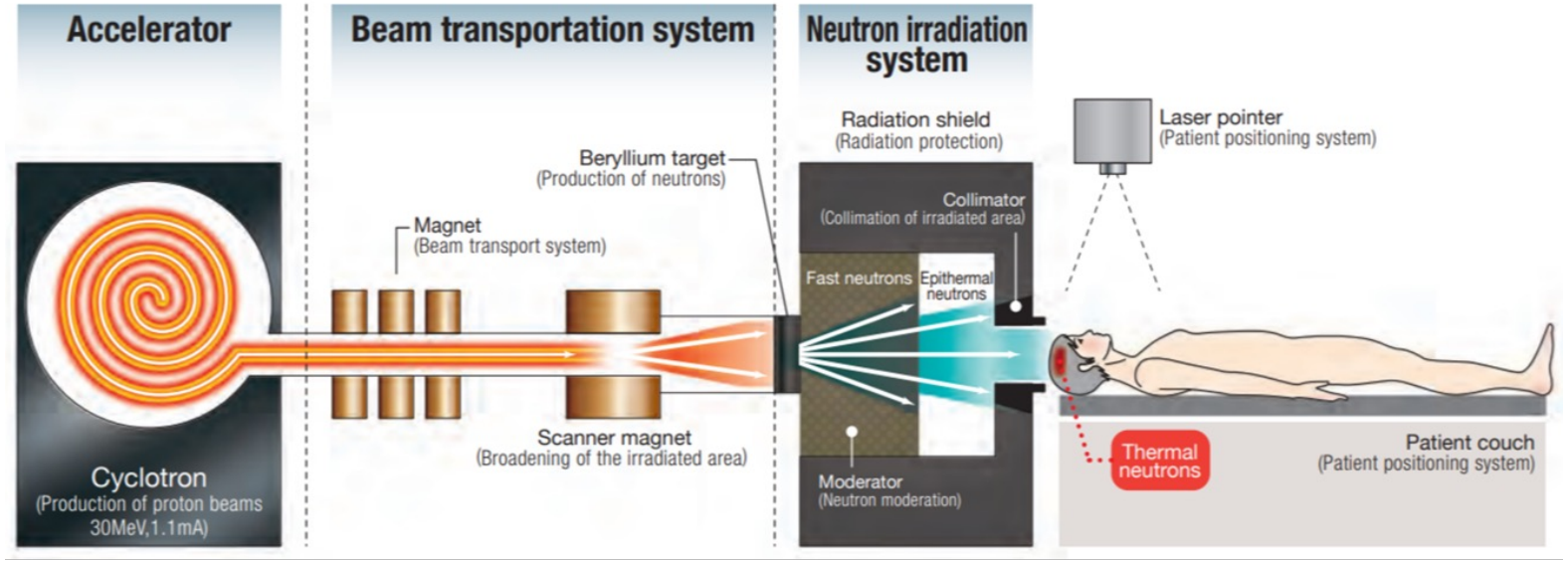
Japan, KURRI BNCT facility



Neutron sources for BNCT

b) Accelerator based sources

Neutron production by nuclear reaction of charged particles accelerated at low energy with determinate target



Advantages compared to nuclear reactors:

- Nice public opinion
- Located directly inside hospitals
- Easier to install, operate and remove
- Costs comparable to those of conventional RT accelerators
- Neutron energy spectrum at beam port (without moderation or filters) is already less contaminated than that coming from a nuclear reactor (soft spectrum → no or less "non-thermal" neutron contamination)

Neutron sources for BNCT

b) Accelerator based sources

Most useful nuclear reactions for neutron production:
^{7}Li(p,n)^{7}Be and **^{9}Be(p,n)^{9}B** → hight neutron yields, low **E_{th}**, no neutron contamination with **E_n** > 1 MeV

Table 3.1 For different neutron-producing reactions, the table lists the threshold and bombarding energy, the total thick target neutron production for different bombarding energies, the percentage for which the maximum neutron energy is less than 1 MeV, and the maximum and minimum neutron energies [17, 22, 39, 40]

Reaction	E_{th} (MeV)	E_{in} (MeV)	Total production (n/mA s)	Fraction E_n<1 MeV (%)	$E_{n,max}$ (keV)	$E_{n,min}$ (keV)
^{7}Li(p,n)^{7}Be	1.880	1.880	0	100	30	30
		1.890	6.3×10^{9}	100	67	0.2
		2.500	9.3×10^{11}[a]	100	787	60
		2.800	1.4×10^{12}[b]	92	1,100	395
^{9}Be(p,n)^{9}B	2.057	2.057	0	100	20	20
		2.500	3.9×10^{10}	100	574	193
^{9}Be(d,n)^{10}B	0	0	0	50	3,962	3,962
		1.500	3.3×10^{11}	50	4,279	3,874
^{13}C(d,n)^{14}N	0	0	0	75	4,974	4,964
		1.500	1.9×10^{11}	70	6,772	5,616
^{12}C(d,n)^{13}N	0.327	0.327	0	100	4	3
		1.500	6.0×10^{10}	80	1,188	707
d(d,n)^{3}He	0	0	0	0	2,451	2,451
		0.120	3.3×10^{8}[c]	0	2,898	2,123
		0.200	1.1×10^{9}	0	3,054	2,047
t(d,n)^{4}He	0	0	0	0	14,050	14,050
		0.150	4.5×10^{10}	0	14,961	13,305

[a] Average between the values reported in Colonna et al. [17] and Lee and Zhou [39, 40]
[b] Allen and Beynon [2]
[c] Ganda et al. [22]

Neutron sources for BNCT

b) Accelerator based sources

^{7}Li(p,n)^{7}Be

- Q-val = -1.644 MeV
- Eth(p) = 1.88 MeV (forwarded n in m.c.s. with E about 30 keV in the l.s.) → at higher E, forwarded neutron emission is more likely
- Resonance of the cross section (at 580 mb) at E = 2.25 MeV → if I work a tiny harder, @ 2.3 MeV:
  - Emax(n) = 573 keV
  - Emin(n, at 180°) = 35 keV
  - Emean(n) = 233 keV
  - thick target (p-beam stopper)

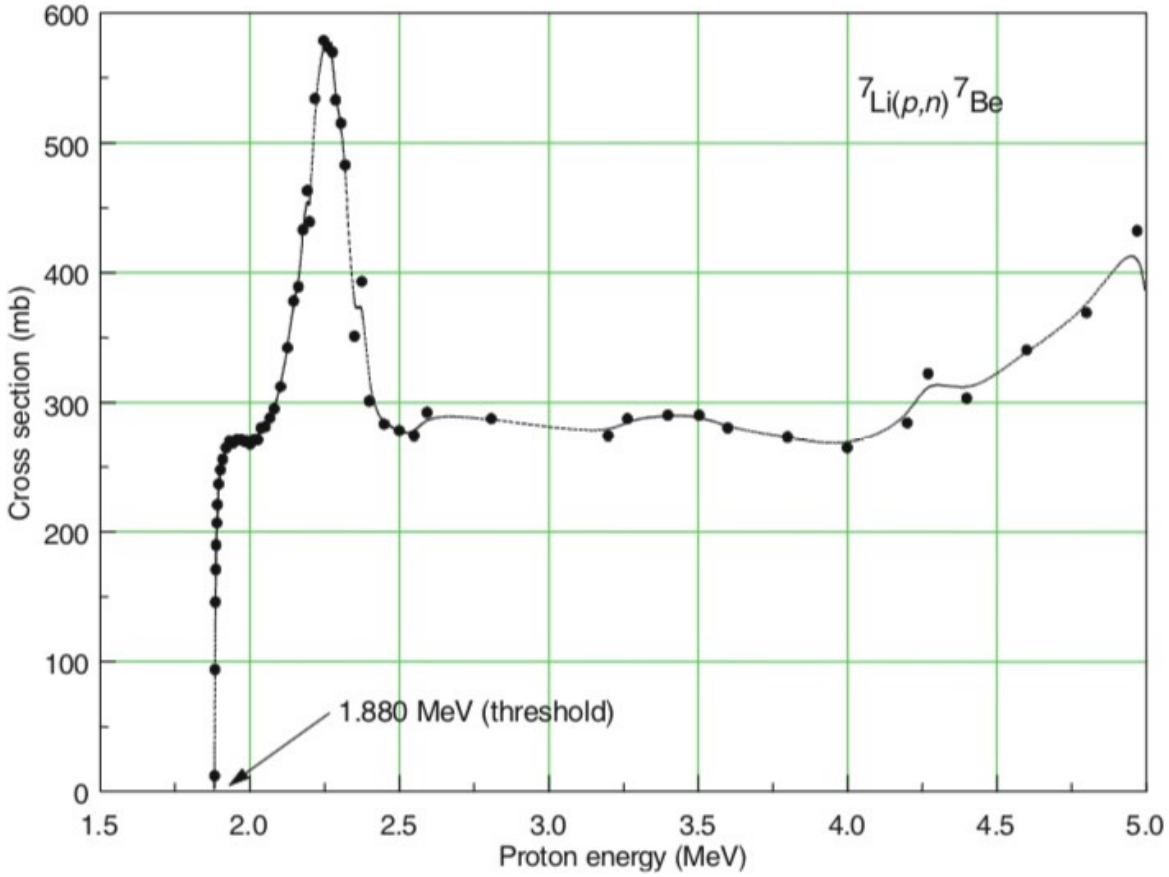


Fig. 3.1 Reaction cross section for ^{7}Li(p,n) for different proton bombarding energies. The pronounced resonance is at 2.25 MeV [42]

Neutron sources for BNCT

b) Accelerator based sources

^{7}Li(p,n)^{7}Be

- High I (tens of mA) to produce n-epithermal fluxes required in BNCT → 1 kW/cm^2 vs 180.5 °K melting point and 85 W/mK thermal conductivity → LIQUID target?!
- after irradiation Li is activated (477 keV γ from Be-7)
- Li is highly reactive with O (sealed system)

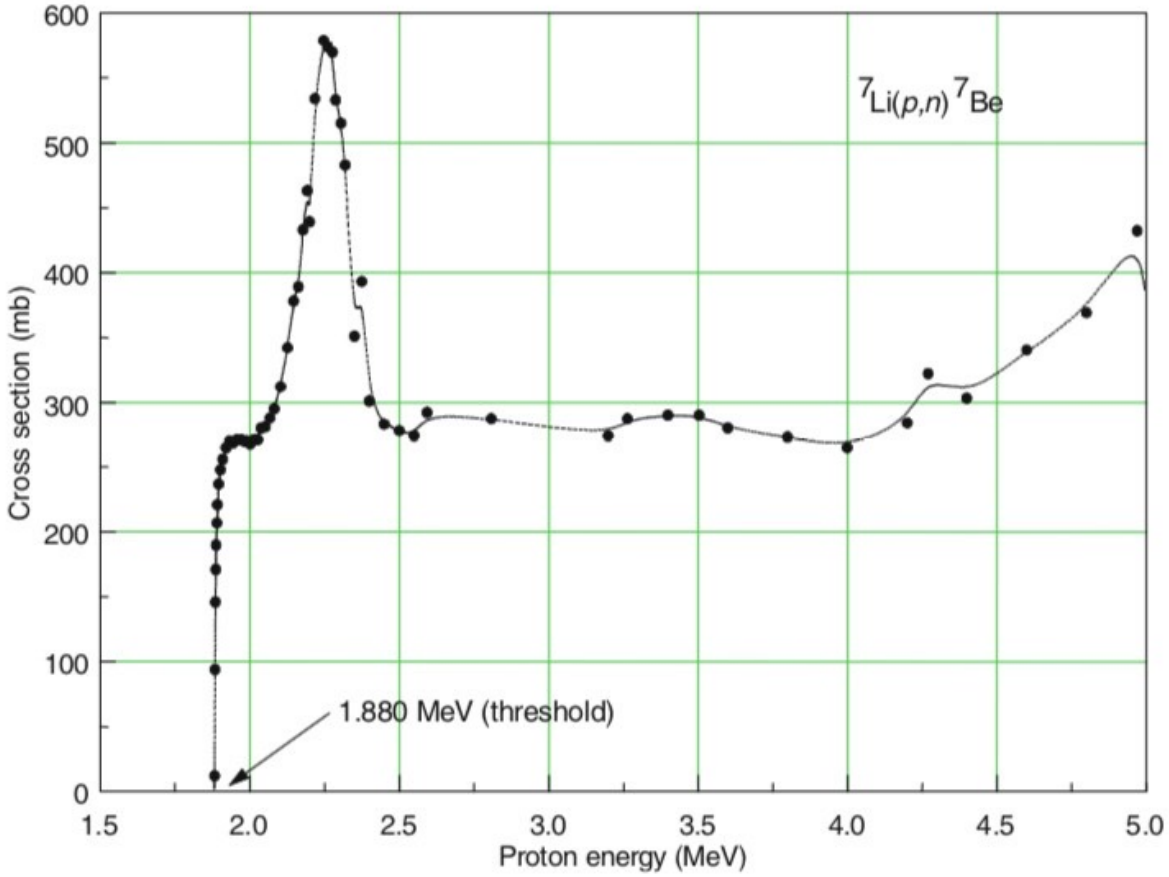


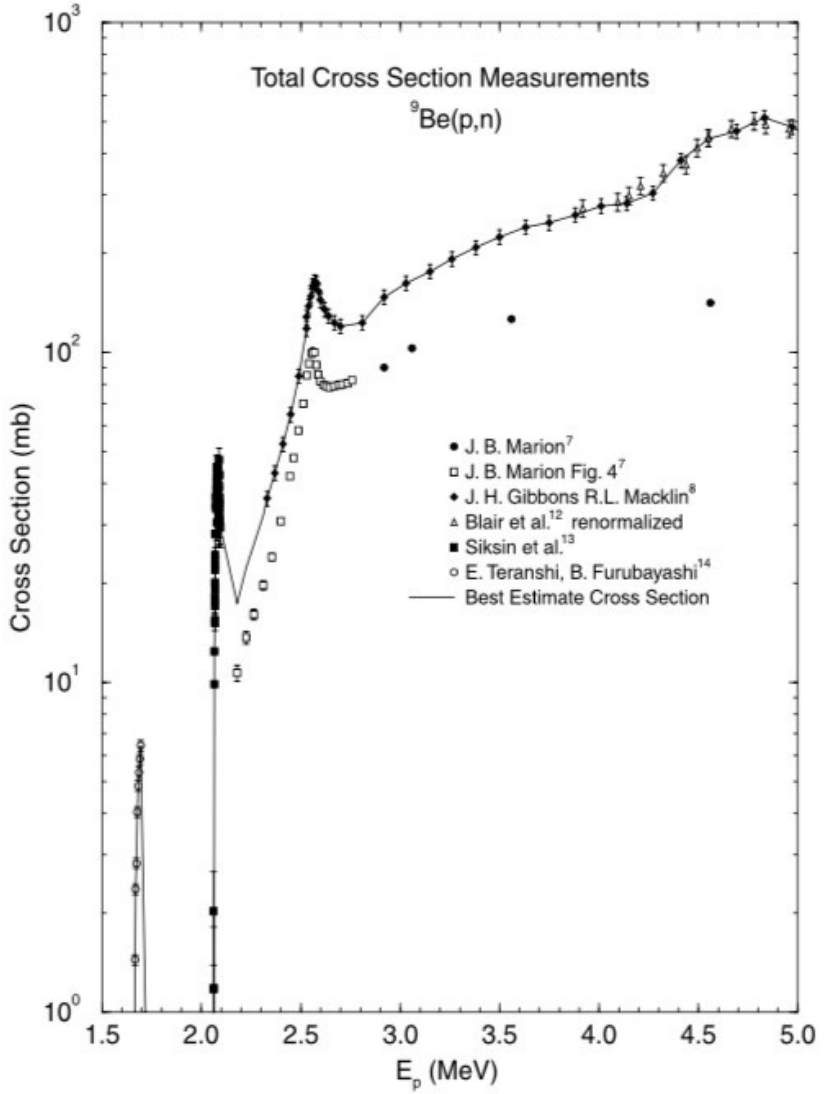
Fig. 3.1 Reaction cross section for ^{7}Li(p,n) for different proton bombarding energies. The pronounced resonance is at 2.25 MeV [42]

Neutron sources for BNCT

b) Accelerator based sources

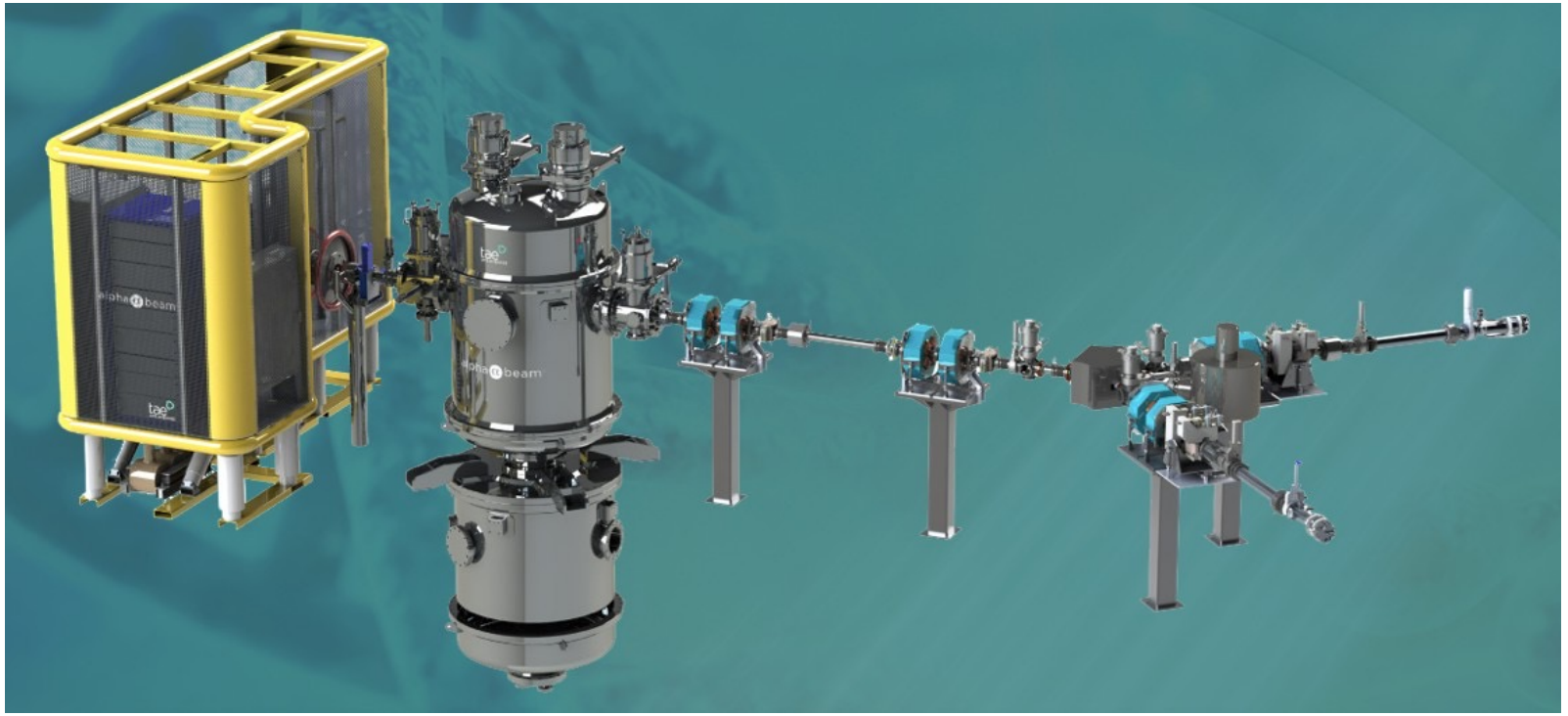
^{9}Be(p,n)^{9}B

- To have high BNCT neutron fluxes, E(p) at least 2 times the Eth → Eth(n)_Be > Eth(n)_Li, energy spectrum is harder than in Li-target
- Low permeability of H: thick targets (p-beam stoppers) load H thus leading to blistering (target damage)
- Main advantage over Li target: no activation and better thermal properties



Accelerator based sources for BNCT: examples

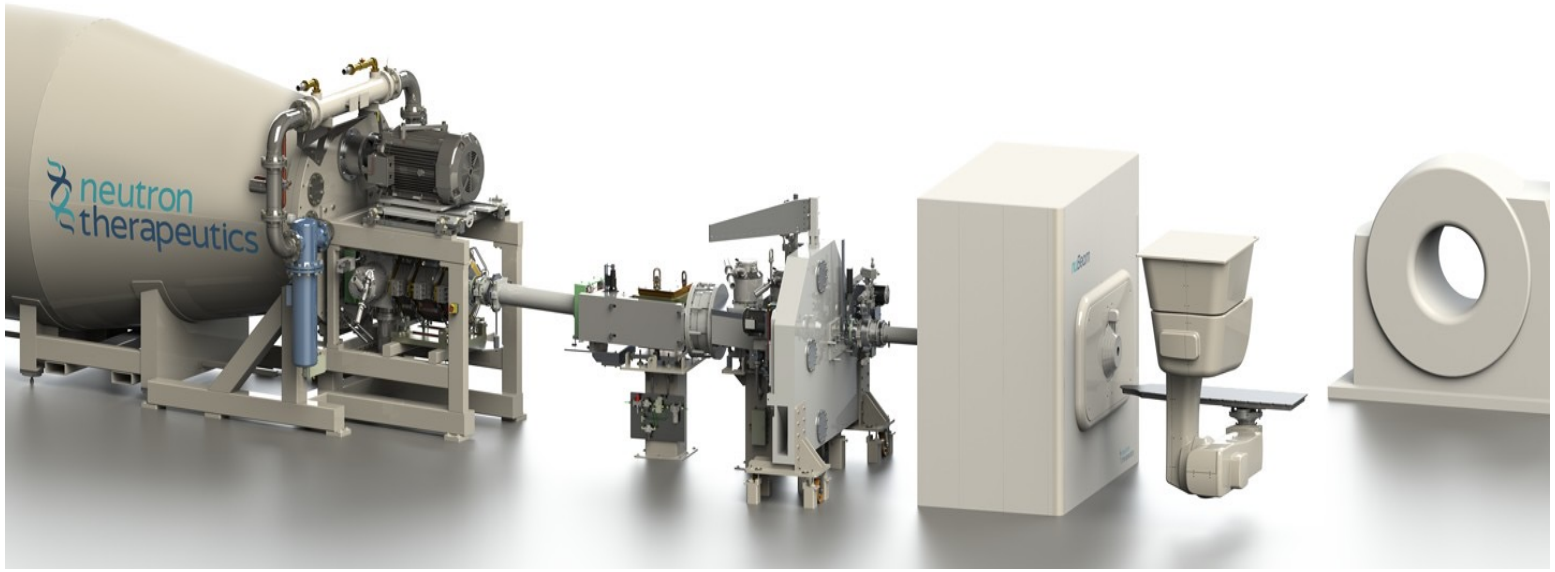
TAE-Lifescience (USA) → CNAO, PV and BNCT clinical center, China



- low En spectrum: 2.5 MeV protons, 10 mA
- solid Li target (proprietary technology)
- electrostatic tandem accelerator
- TLS's AlphabeamTM system → https://taelifesciences.com/alphabeam-neutron-system/

Accelerator based sources for BNCT: examples

Neutron Therapeutics (USA) → Helsinki, FI & Birmingham, UK (but not for clinical BNCT)

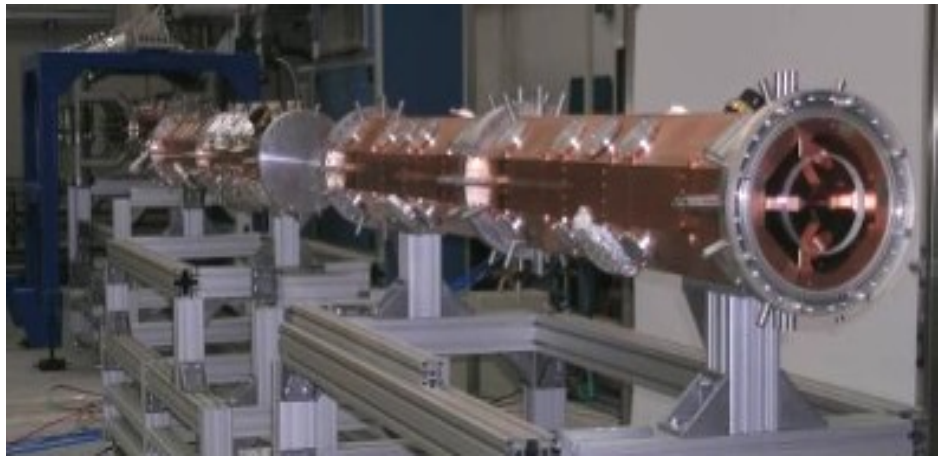


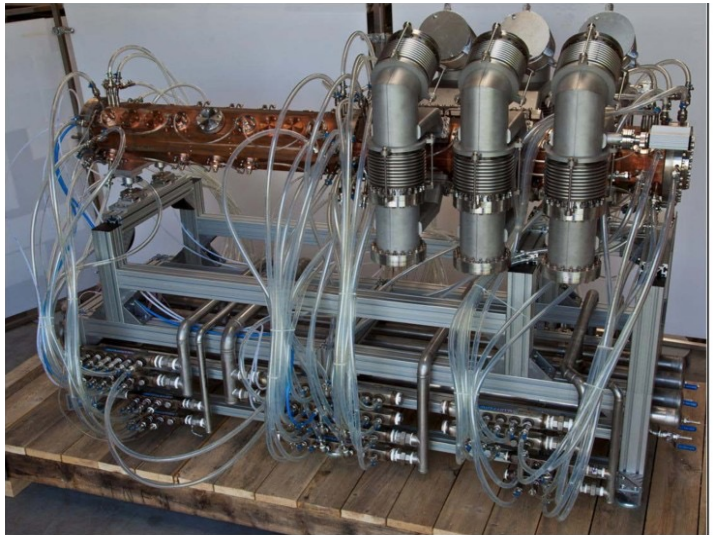
- 2.6 MeV electrostatic proton accelerator
- Operation at 30 mA
- rotating, solid Li target (proprietary technology)
- in-treatment room CT for positioning validation
- nuBeam suite → https://www.neutrontherapeutics.com/technology/

Accelerator based sources for BNCT: examples

INFN-RFQ: MUNES project (MUltidisciplinary NEutron Source)

Accelerator type	LINAC
Particle	Proton
p input energy	0.08 MeV
p output energy	5 MeV
Frequency	252.2 MHz
Proton current	Up to 50 mA
Beam power	Up to 250 kW
RF power consumption	< 800 kW
Operative power density on Be target	700 W/cm2
Time structure	Continuous wave (CW)
Neutron converter	Be
Neutron source intensity	1014 s-1
Total accelerator length	7.2 m

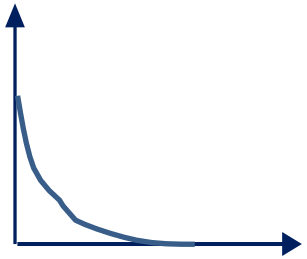




Dosimetry in BNCT

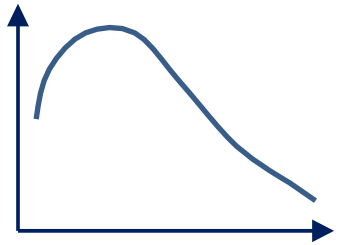
Components of the total dose

In BNCT we must correctly account for four separate radiation components, which have different biological characteristics and spatial distributions



- Incident neutrons (D_n)
  Leading to dose deposition via (n,p) and capture reactions

- Photons (D_γ)
  Incident with the beam and internally generated – mainly 2.2 MeV from ^{1}H (n, γ)



- Thermal neutrons (Dp or D_{TH})
  Mainly from $^{14}N(n,p)^{14}C$ reactions

- **Boron dose (D_B)**
  from $^{10}B(n, \alpha)^{7}Li$ reactions

Dosimetry in BNCT

Present Method of Biological Dose Transformation:
Weighted dose D_W:

$$D_W = W_n D_n + W_\gamma D_\gamma + W_{TH} D_{TH} + W_B D_B$$

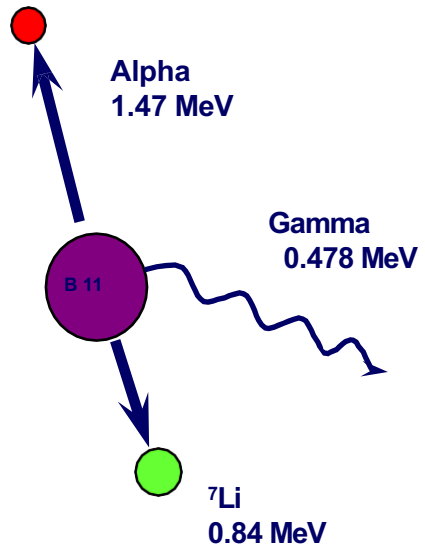
Where the D values are absorbed doses for each dose component, and the W values are weighting factors

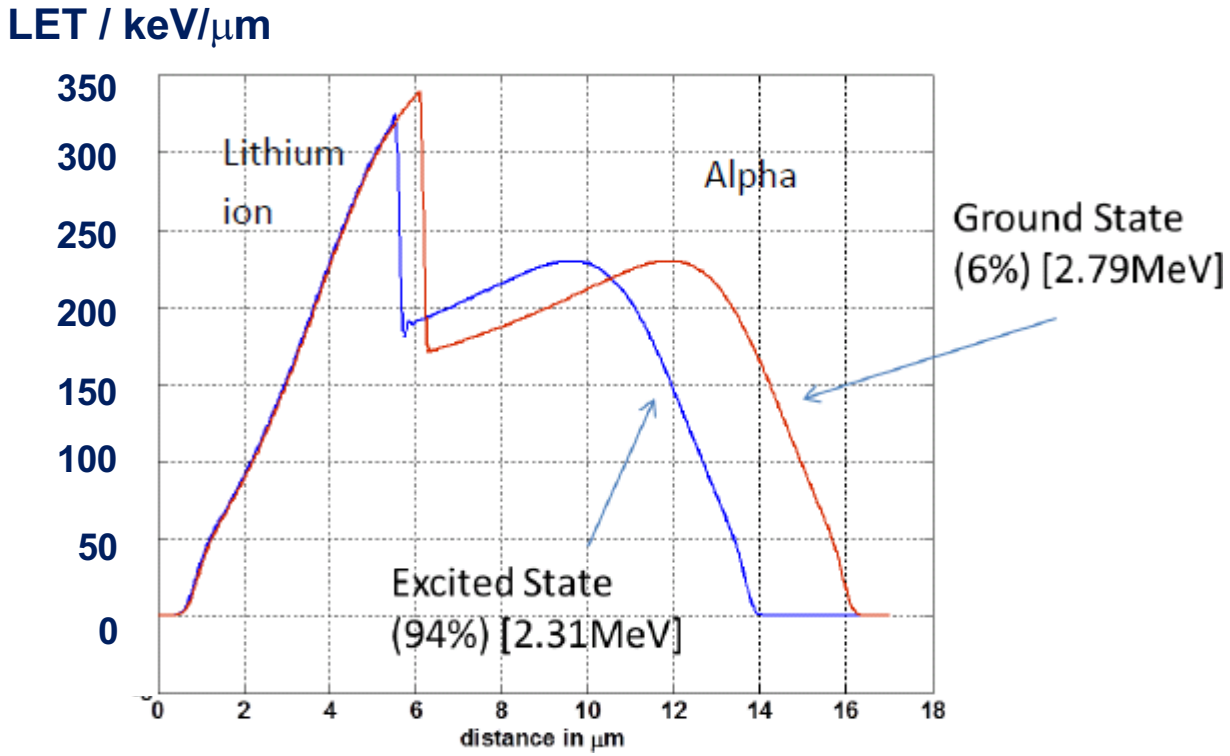
This method relies on weighting factors that are fixed - whereas in reality they will change for different dose levels applied

Dosimetry in BNCT

BNCT reactions deliver dose in high density events

The density of the ionisation delivered is described via the quantity Linear Energy Transfer (LET)





Dosimetry in BNCT

Values derived for Weighting factors

	W_n	W_γ	W_{TH}	W_B (for BPA)
Tumour	3.2	1.0	3.2	3.8
Skin	3.2	1.0	3.2	2.5
Other Tissue	3.2	1.0	3.2	1.3

Typical (assumed) ^{10}B concentrations
15 μg/g in Blood and Brain,
52.5 μg/g in Tumour

Dosimetry in BNCT

Values derived for Weighting factors

	Wn	Wɣ	W_{TH}	W_B (for BPA)
Tumour	3.2	1.0	3.2	3.8
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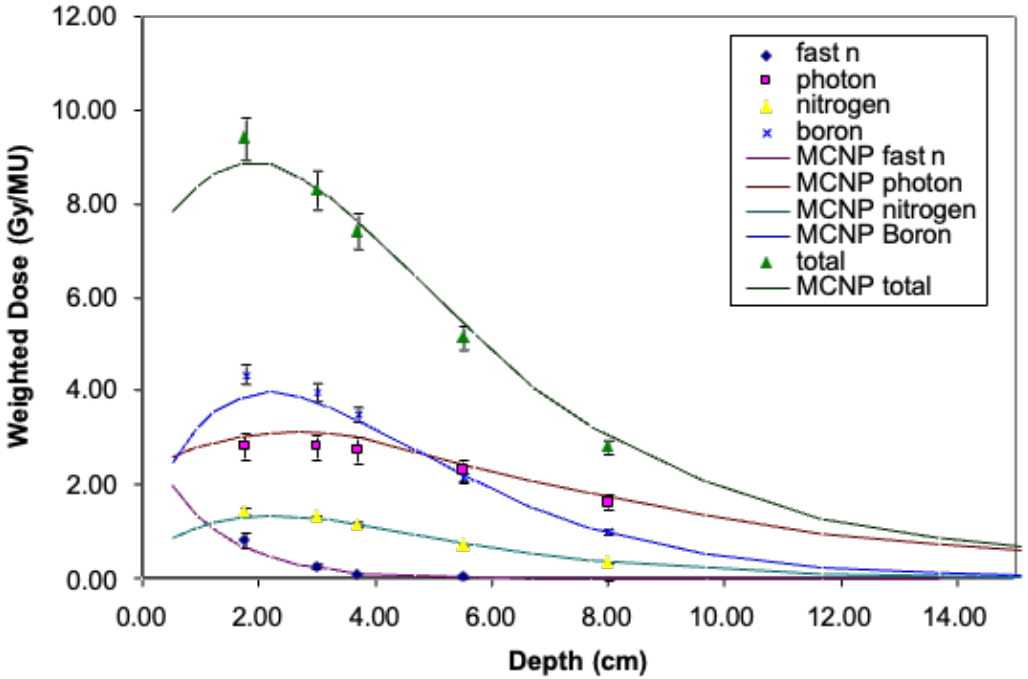
Other Tissue	3.2	1.0	3.2	1.3

Typical (assumed) ^{10}B concentrations
15 μg/g in Blood and Brain,
52.5 μg/g in Tumour

Measurements and MCNP, Weighted Doses (for healthy brain tissue)



Assuming ^{10}B at 15 μg/g, N at 2.2% and "usual" RBE/CBE factors

Recommendations for the Dosimetry of Boron Neutron Capture Therapy

NRG 21425/03.5539

Published in 2003: Emphasis on *recommendations* and production of a document reflecting a distillation of knowledge on practical measurement techniques in BNCT

Dosimetry in BNCT

2003 Recommendations – Summary of scope

In-air beam characterisation

- Neutron spectrum
- Neutron beam profile in air
- Photon beam profile in air

In-phantom beam calibration

- Define reference phantom (geometry and material)
- Define reference depth
- Recommend methods for determination of dose components
- Show translations from dose to water to dose to ICRU reference brain (can be applied to any other tissue as required)

Beam Monitoring Systems and MU calibration

In-air measurements are intended for validation of beam design calculations, to validate codes used to determine dose-conversion factors in-phantom

Dosimetry in BNCT

Birmingham accelerator moderator system

Proton beam-tube

Heavy water reservoir

FLUENTAL™ moderator

Li-polythene delimiter / shield

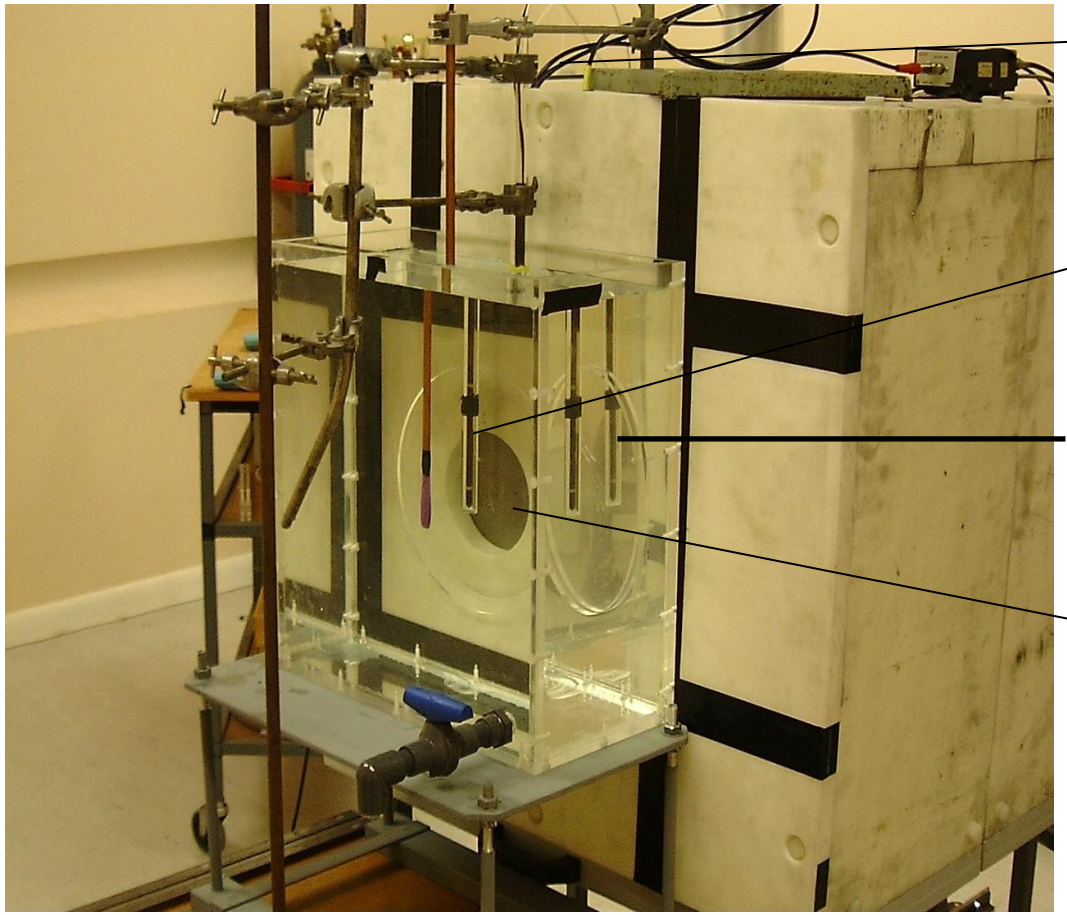
Heavy water inlet

To pumps / chiller

Neutron source is $> 1 \times 10^{12}$ s^{-1}

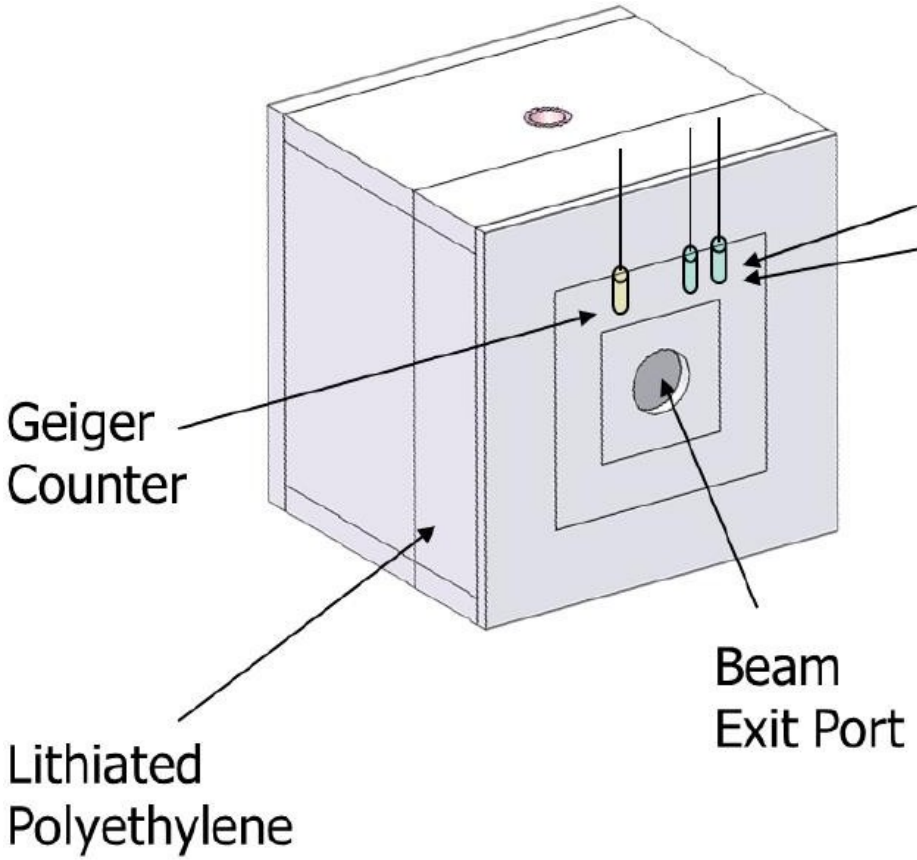
Dosimetry in BNCT

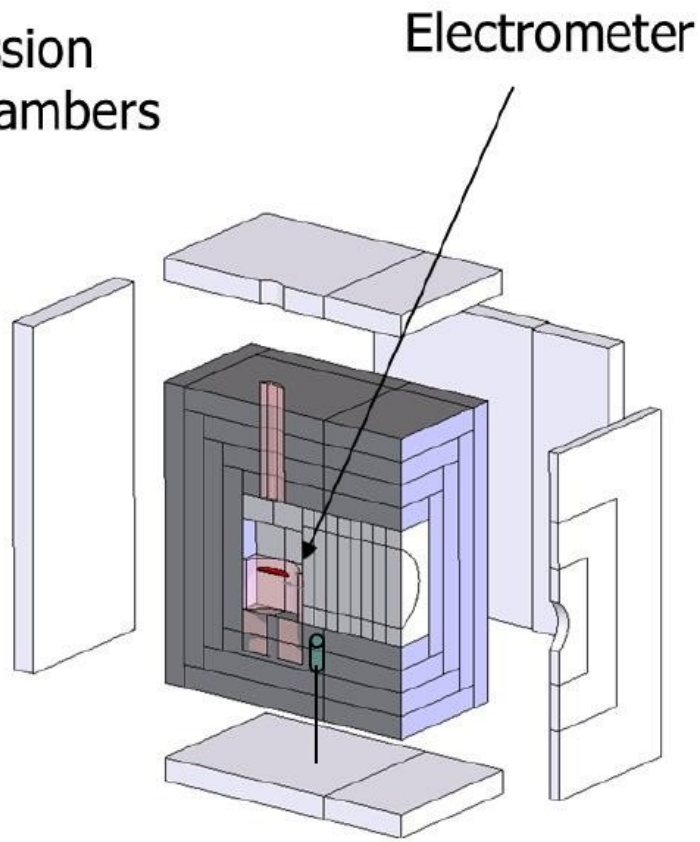
In-phantom dosimetry



Dosimetry in BNCT

Calibration – Beam monitoring





Dosimetry in BNCT

Alternative Methods for validation

The use of alternative or back-up dosimetry methods was a consistent theme in dosimetry protocols in the past..

ICRU 1969 - Made recommendations which were very similar to those contained in HPA 1969. They reviewed the accuracy attainable with 4 methods of determining absorbed dose at a point

- Absolute ion chamber method relying on the Bragg-Gray principle as per HPA 1969 - ie a dosemeter with a traceable calibration
- Fricke ferrous sulphate dosimetry
- Calorimetry

AAPM 1971. Recommended the use of alternative methods such as Fricke dosimetry and the absolute Bragg-Gray cavity chamber to cross-check the traceable ion chamber method.

Dosimetry in BNCT

Summary of Recommended in-phantom measurement techniques

Gamma ray and epithermal neutron dose measurements

- **Reference method**

  Paired ionisation chamber technique. Measurements are performed with Mg(Ar) and TE(TE) chambers.

- **Supplementary method**

  No definite recommendation; however tissue equivalent proportional counter micro-dosimetry and the thermo luminescence detector technique are considered

Boron and Nitrogen Dose

- **Reference method**

  A set of activation foils consisting of a gold (diluted in aluminium), and manganese is recommended.

- **Supplementary methods**

  Gold foils with and without cadmium cover.

Properties of a good BNCT agent

The BNCT agent refers to the to the drug in charge to deliver the ^{10}B into the cancer cell granting the selectivity of the treatment. The requirement for these agent are:

- Low systemic toxicity;
- Tumor concentration 20-35 μg of ^{10}B/g of tumor (~10^9 atoms of ^{10}B for tumor cell);
- Tumor tissue/normal tissue concentration ratio between 3÷5:1;
- Tumor tissue/blood concentration ratio of 5:1;
- Easily monitored.

Chemical properties of ^{10}B

- Not radioactive, 20% of natural boron
- Many boron compounds can be synthesized having hydrolytically stable linkages between
- Boron and other elements such as C, O, and N
- Its small atomic size permits its replacement of carbon in many organic structures,
- Isosteres that offer the potential for simulating biologically those compounds from which they are derived.
- Boron clusters that possess remarkable hydrolytic and metabolic stability (e. g. carboranes).

Boron BNCT agents

First generation

- borace, boric acid, sodium pentaborate
- Advandages: commercialy availables, tumor concentrations, not toxics
- Bad results in brain tumour due to thermal neutron flux delivered inadequate and its differentials transient reached unity within a relatively short period
- Low selectivity

Second generation

- Sulfur derivatives supplied by DuPont (chemical industry): **BSH**
  - High boron content and non-toxic. BSH also contains some dimer which increases the concentration of boron but is toxic
  - Acceptable tumor/blood concentration ratio
  - Positive clinical trials. BSH approved by Japanese authorities in 2020
- **BPA**: derivative of amino acids, for this reason it is considered interesting for BNCT because it is aromatic and lipophilic and can therefore guarantee good concentrations in tumor tissue.
  - Positive clinical trials, even superior to BSH.
- Problem: Poor selectivity for both BSH and BPA

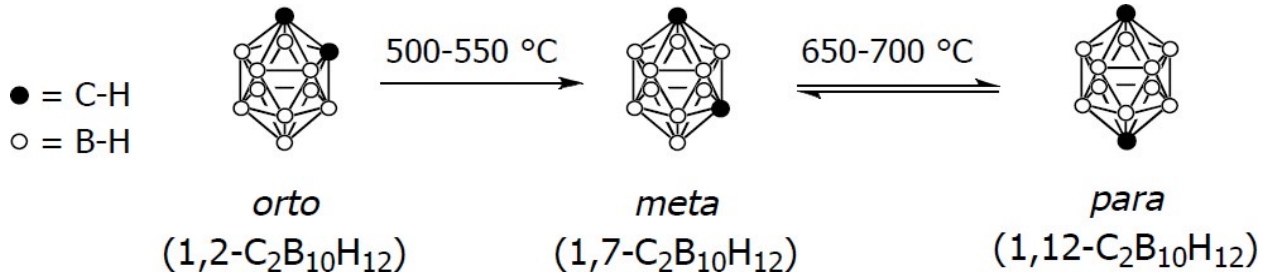
Boron BNCT agents

Third generation

Strategies:

- modulation of properties through small structural variations
- use of multiple agents to exploit a synergistic effect

Example: **carboranes**



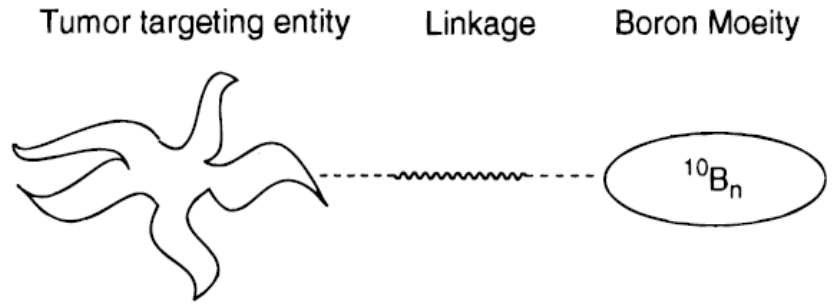


Figure 8. NCT compound design.

- Three isomeric forms.
- High chemical and metabolic stability: possibility of preparing many derivatives by modulating their properties and use in vivo.
- Greater possibility of interaction with the active site.

Recent studies have used **nanobiosensores boron dopped**

Summary

- BNCT high-linear energy transfer radiotherapy based on the nuclear capture and fission reactions $^{10}B(n,\alpha)^{7}Li$
- BNCT can be considered as hadrontherapy inside cell (products: α and ^{7}Li)
- The selectivity at cell level depends on microscopic distribution of ^{10}B (T ~ 3.0 or more)
- Accelerator based (AB) and nuclear reactors are the main neutron sources for BNCT. More advantages from the clinical point of view for AB-BNCT
- Several components of the total dose during the treatment. Main contribution from boron dose