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Medical Applications of Accelerators

Sarajevo School of High Energy Physics, October 15, 2022

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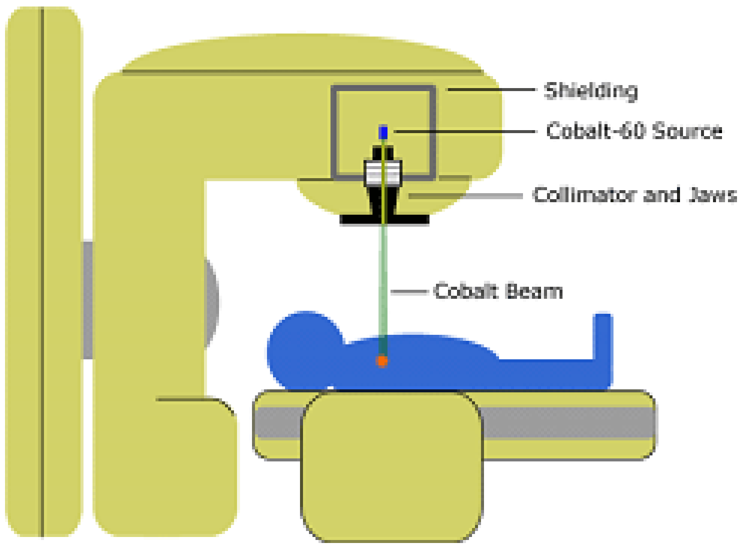
Outlook

1. A few words about accelerators in general
2. Medical imaging – the first application
3. Therapy with photon (X-ray) beam
4. Proton therapy and three main types of machines
5. Ion therapy – big machines
6. Transporting the beam to the patient - gantry
7. FLASH with electrons
8. Radioisotope production
9. Boron Neutron Capture Therapy
10. Summary

Accelerators in general

1. Accelerators are machines to produce a beam of charged particles
   – beams of neutral particles (e.g. neutrons, X-rays) are produced in interaction of primary beams (e.g. protons, electrons) with a target
   – sometimes we do not need an accelerator to produce a beam:



$^{60}Co \rightarrow {}^{60}Ni + (..) + \gamma$

γ energy = 1.2 and 1.3 MeV

^{60}Co is produced in nuclear reactors

Half-lifetime 5.3 years

Has been (and still is) widely used for radiotherapy!!!

2. To do this they use variable electromagnetic field (RF, from radiofrequency)

RF accelerators – why RadioFrequency?

fundamental forces

gravity

too weak at human scale - proton Energy after 57 m free fall: 6 μeV

electromagnetism

nuclear: strong and weak

too small range (nucleus size)

electric field

$$\vec{F} = \underbrace{q\vec{E}}_{\text{Electric force}} + \underbrace{q\vec{v} \times \vec{B}}_{\text{Magnetic force}}$$

magnetic field

acts perpendicular to the direction of motion – no energy gain (good to steer the particles)

oscillating

synchronize particle movement with electric field oscillation - much higher final enegies!

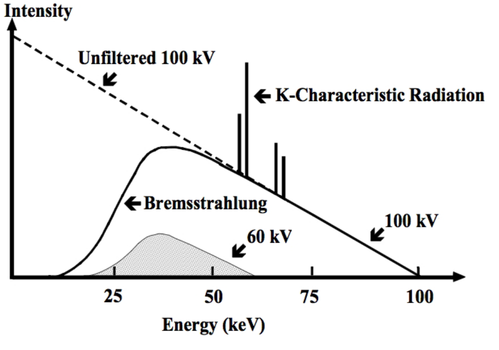
static

acceleration limited by maximum electrostatic potential (~1 MV)

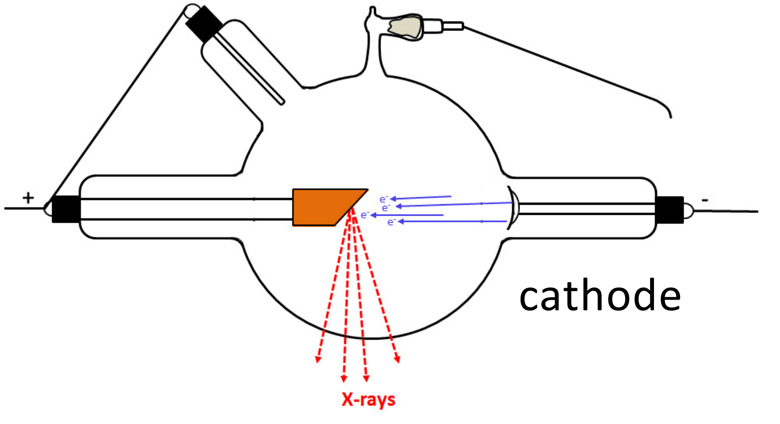
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Accelerators for (medical) imaging: X-ray tube

1. The discharge tubes with partial vacuum (called Crookes tubes) were first accelerators used in 1860s
2. In 1895 W. Roentgen discovered X-rays using Crookes tube
3. It is electrostatic (not RF) accelerator. How it works:
   - Metal cathode emmits electrons
   - Electrons are accelerated in vacuum using potentials of the order of 100 kV
   - When electrons collide with anode they produce X-rays (brehmstrallung)
4. X-ray tubes started era of modern medical diagnostic



Brehmsstrahlung spectrum



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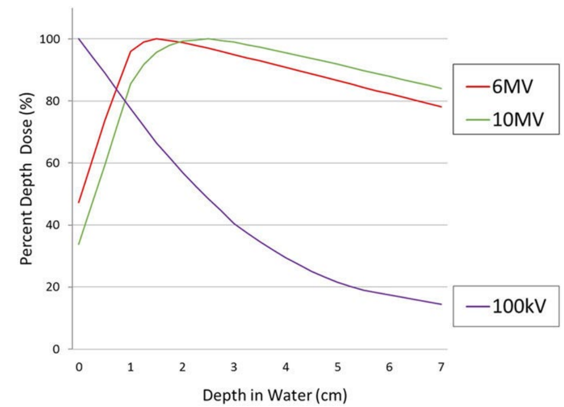
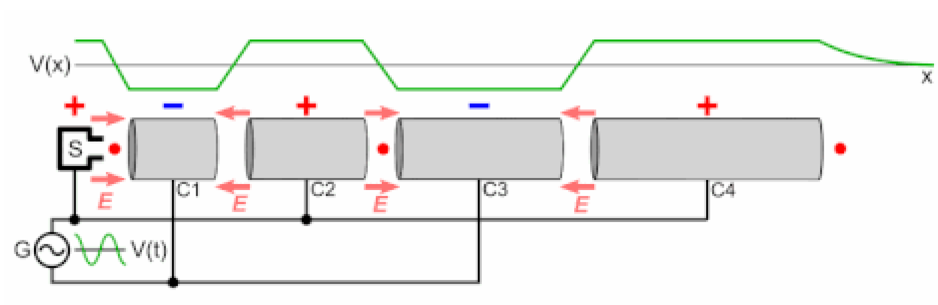
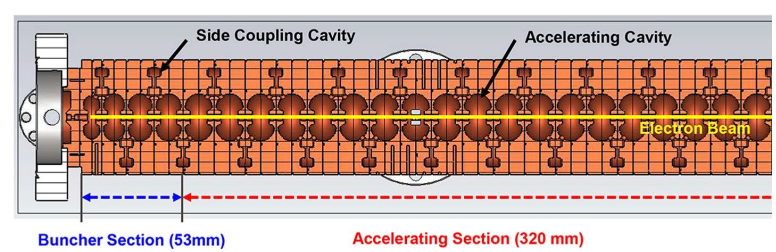
Photon radiotherapy

1. The radiation dose = Energy deposited in the body by radiation: Gy=J/kg
2. X-ray chest radiography – dose 0.0001 Gy (BTW environmental dose is 0.002 Gy/year)
3. Lethal dose is several Gy, if this dose goes to the tumor it can kill it –
   external beam radiotherapy
4. First cancer treatment – in 1896!
5. Using photons we must boost the energy with respect to X-ray machines from 100 kV to tens of MV
6. This cannot be done by electrostatic voltage, RF accelerator must be used.





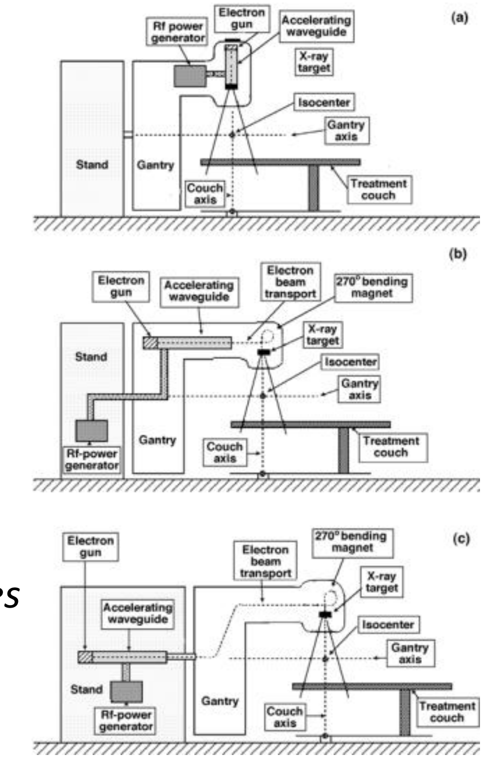
Linear accelerator for non-relativistic particles



relativistic particles

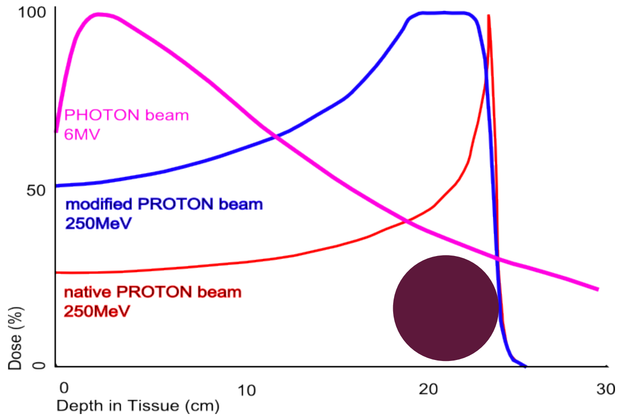
RF linac for photon radiotherapy

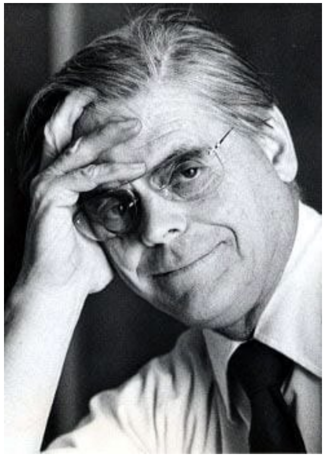
1. The accelerating RF structure is called waveguide
2. Typically uses 3 GHz frequency (S-band)
3. Recently moving to X-band (12 GHz) to reduce the size
4. Radiation does not only kill cancer cells but it can cause cancer, so…
5. … progres in precision, since the first machines, for example:
   – *Conformal radiation therapy (CRT) – using tomographic images*
   – *Intensity-modulated radiation therapy (IMRT) – shooting from many directions with different intensities*



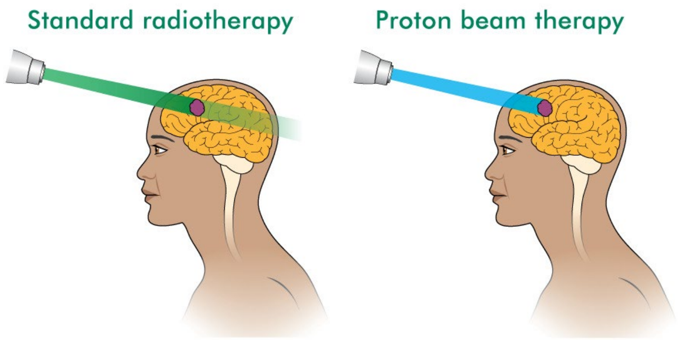
Proton radiotherapy

1. Photons never stop, some of them are absorbed but large fraction damage the tissue behind the tumor
2. Protons are completely stopped in the tissue
3. They deposit maximum energy at the end of the track (Bragg peak)
4. This observation lead to development of proton therapy
5. The idea was first suggested in 1946 by Robert R. Wilson
6. Clinical tests from 1954 to 1988 (Berkley, Uppsala, Massachusetts General Hospital at Harvard)
7. 1991 – first hospital-based center (Loma Linda)



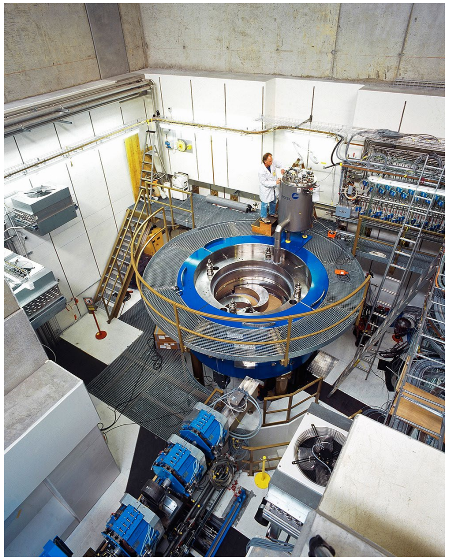


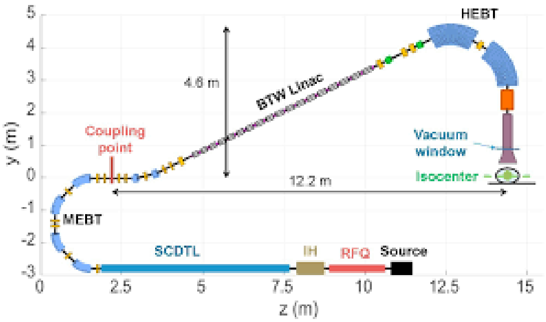
R. Wilson, Fermilab's first director and promoter of proton therapy; Loma Linda synchrotron was designed by Fermilab experts.



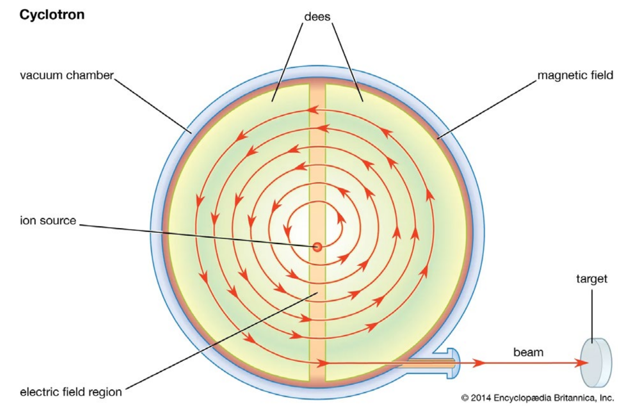
Machines for proton therapy

1. Protons are almost 2000 heavier than electrons and need to be accelerated to much higher energies (electron LINACs: tenths of MeV, protons: 230 MeV)
2. In 1950's cyclotrons were machines to reach needed energy and intensity
3. And still they are the most popular proton therapy devices
4. Synchrotons are also used (e.g. Loma Linda, Hitachi, ProTom)
5. A week ago a first proton LINAC for therapy (LIGHT system from AVO-ADAM) reached nominal energy !
6. Main technologies: cyclotron, synchrotron and linac
7. Others, not discussed because not used yet, eg: Fixed Field Alternating Gradient, laser accelerators, plasma, dielectric





Cyclotron



Constant B-field
and RF frequency

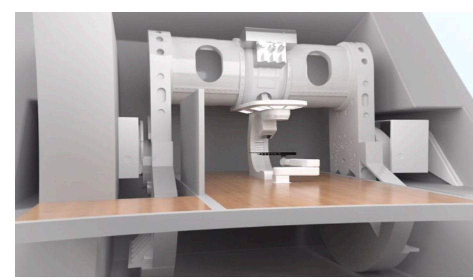
- Developed in 1930s by Lawrence and Livingstone

Advantages:

- Continous beam (but MHz bunches)
- Relatively simple construction and operation
- Small size (Mevion, diameter 1.5 m)
- Energy efficient (especially with superconducting magnet)

Disadvantages:

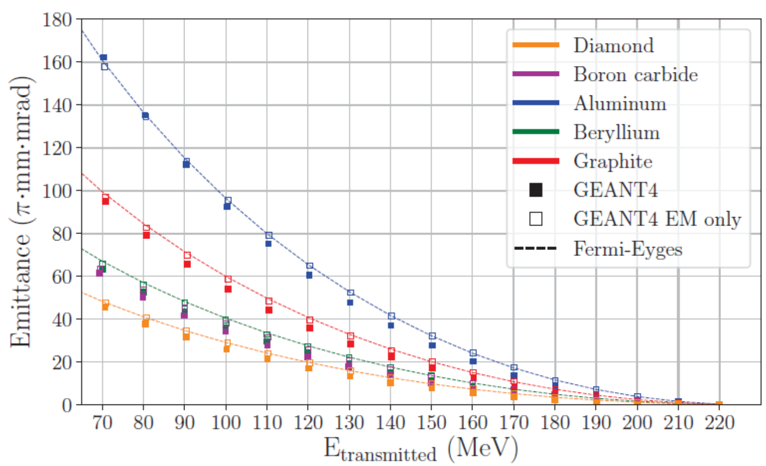
- Fixed energy – need degrader to reach lower energies, this generates lots of radiation (massive shielding)
- Low energy beam intensity < 1% of exit intensity
- Practically impossible to change ion type (eg. protons to 4He)

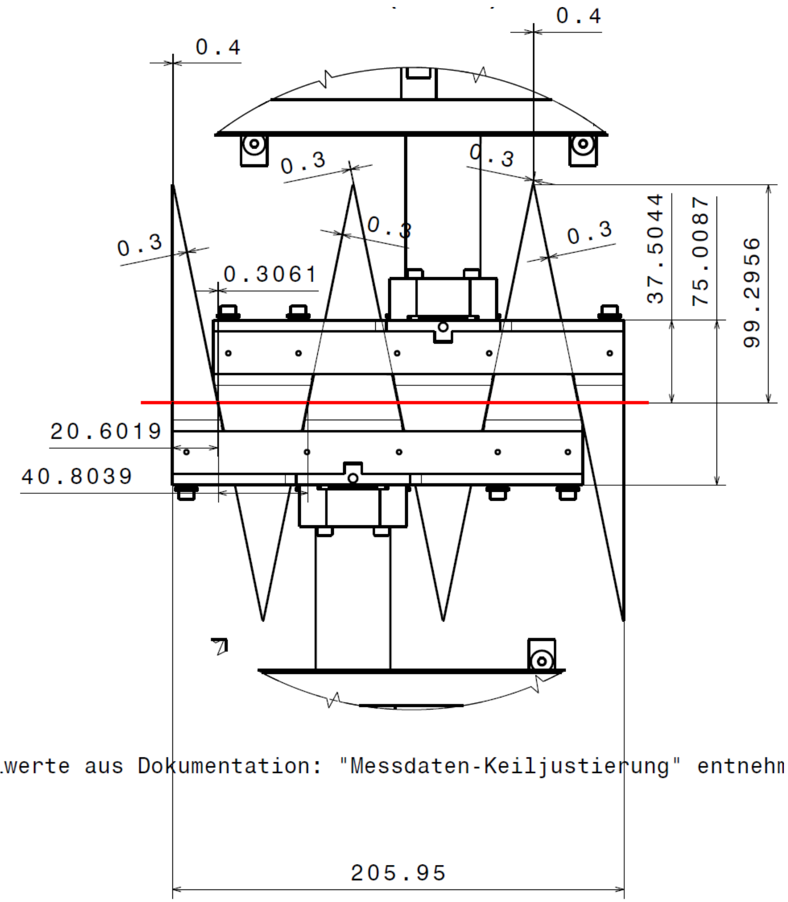


Established commercial systems:
IBA (e.g. CCB), Varian, Mevion, Hitachi.

Cyclotron - degrader

- This weekend we are changing degrader of COMET synchrotron, 100 m from where I am.
- Graphite degrader is exchanged to B4C (boron carbide)
- Boron is lighter than Carbon (Z=5 compared to Z=6), what leads to smaller transverse scattering and better beam transmission
- In addition B4C is mechanically very robust material





Reaction time <0.1 s

Synchrotron

- First machine E. McMillan, 1945

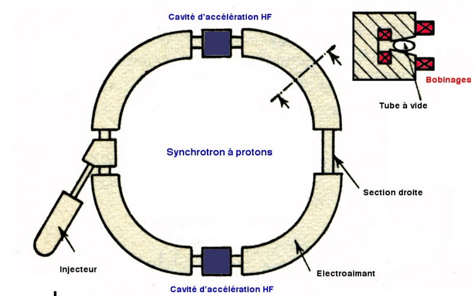
Advantages:

- Variable output Energy
- Relatively low radiation (no degrader)
- Can be tuned for various ion types

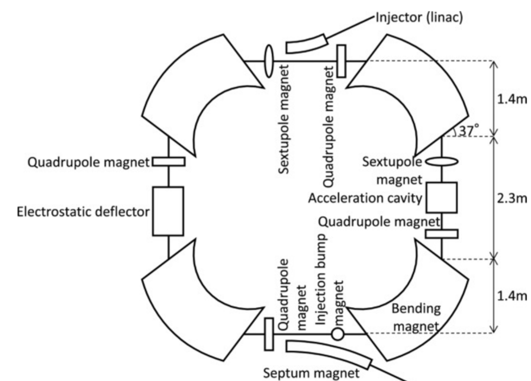
Disadvantages:

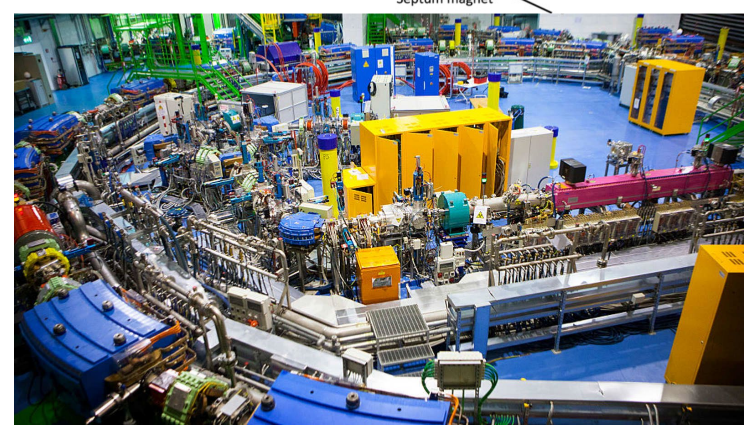
- Pulsed beam (0.2-10 s)
- Larger size (>5 m diameter for protons and 22 m for **Carbon**)
- Complexity (injector linac, synchronization of RF and magnets)

Commercial systems, less common than cyclotrons:
Hitachi, Protom – protons
Hitachi - carbon
CNAO/MedAustron - semicommercial



zmienne pole
magnetyczne i częstotliwość mikrofal





Linac

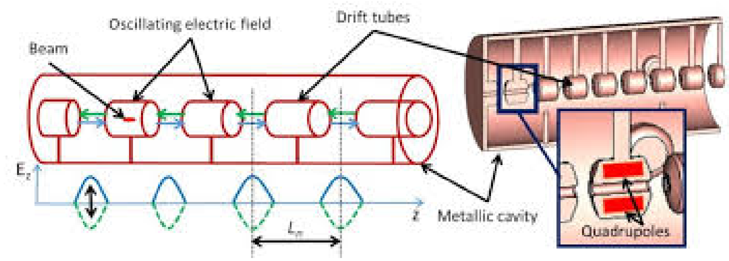
- Idea: Rolf Wideroe, 1928!
- Currently single proton therapy system is being commissioned (Daresbury lab)!

Advantages:

- 200 pulses/s, each pulse can have different energy
- Very small beam size (1mm)

Disadvantages:

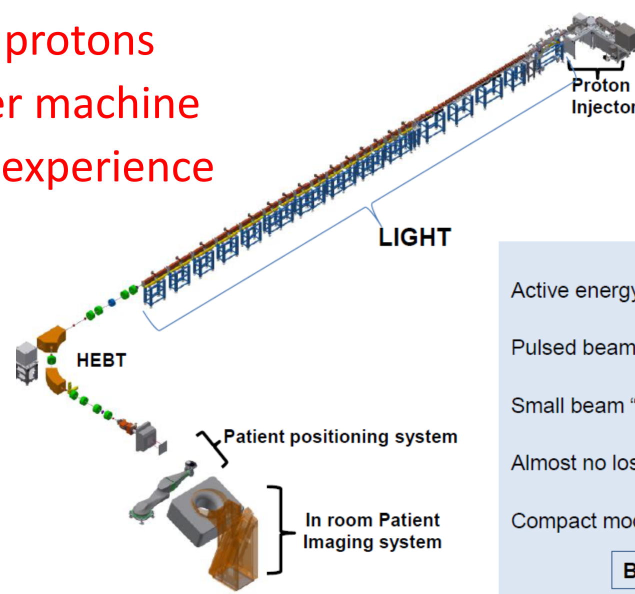
- Long (but narrow) – 25 m for protons
- Can do light ions but 2x longer machine
- Young technology, no clinical experience



Fixed B-field and RF-frequency

One commercial system:
AVO-ADAM (LIGHT system)

Systems for He-4 and C-12
in conceptual phase (CERN)

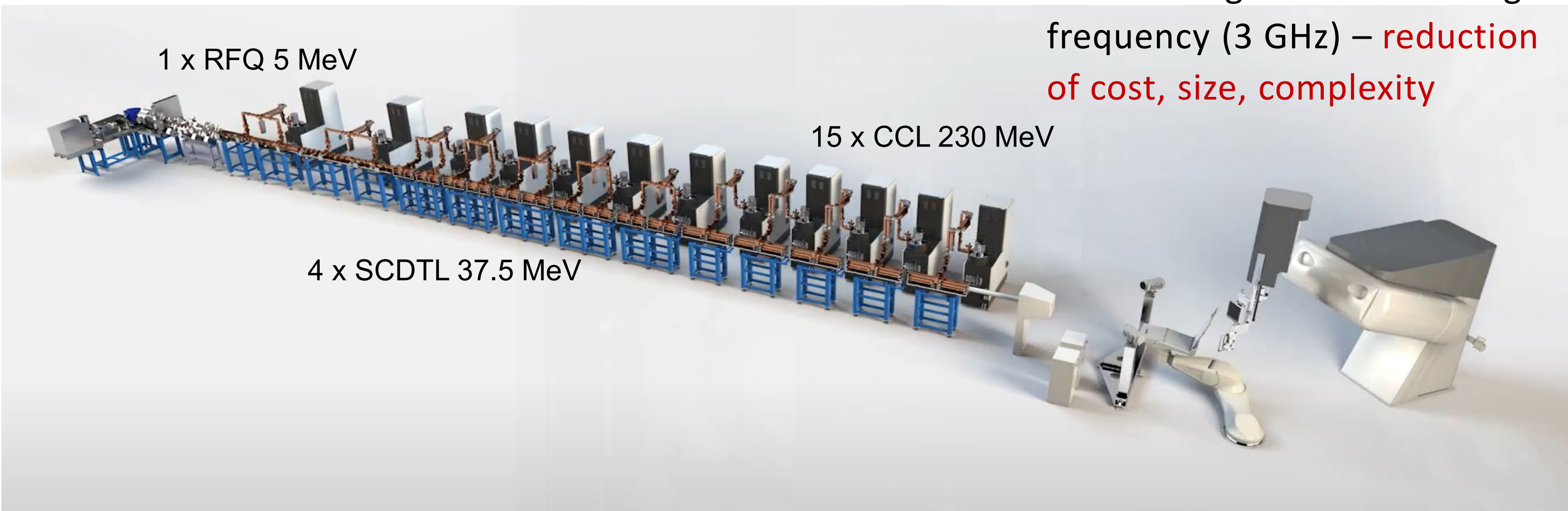


Active energy modulation	→ no absorber and degrader
Pulsed beam up to 200 Hz	→ fast intensity and energy change
Small beam "emittance"	→ small magnets aperture
Almost no losses!	→ reduced shielding
Compact modular design	→ easier installation

Beam suited for 3D spot scanning

Linac – LIGHT system

Why possible now?
Use energy adopted accelerating structures at high frequency (3 GHz) – reduction of cost, size, complexity

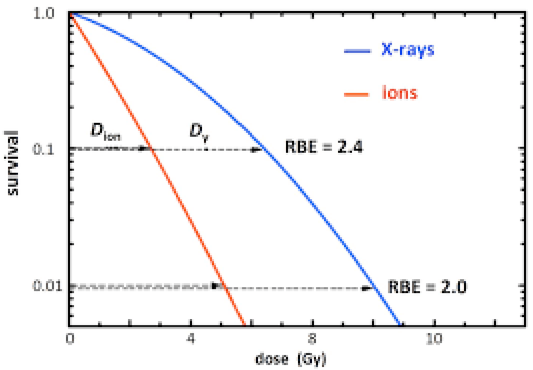


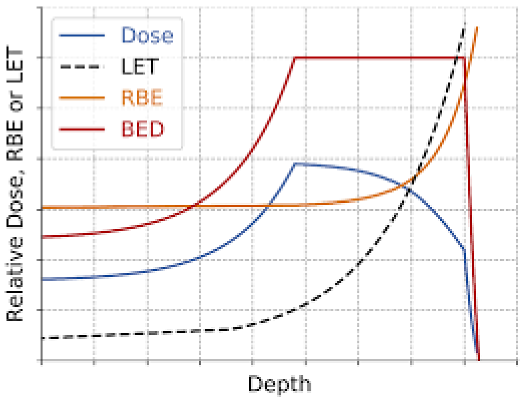
Challenge:

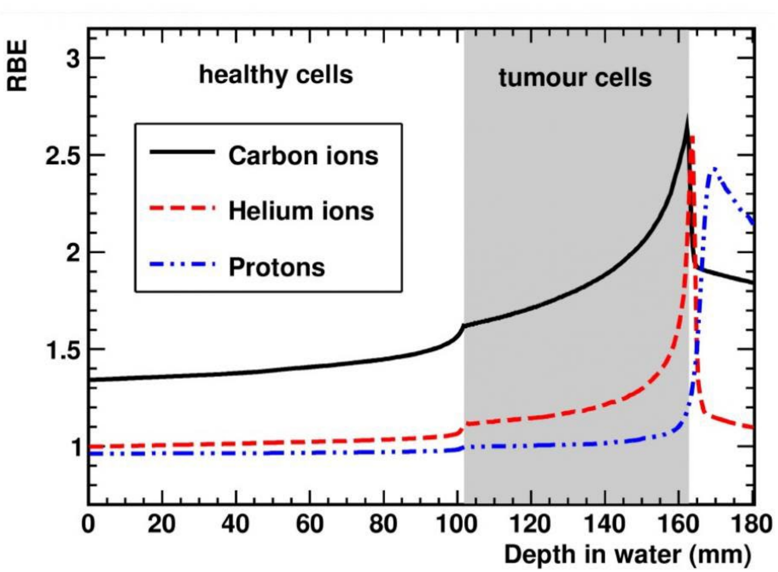
Install and Operate a high energy Proton Therapy Center here

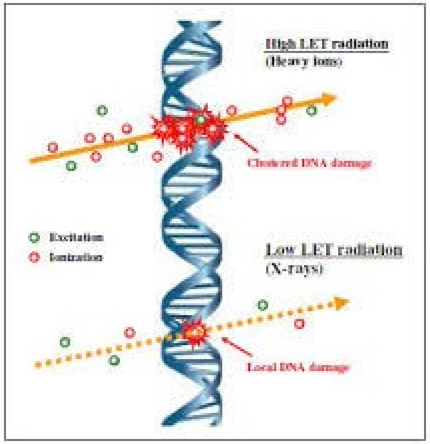
Ion therapy - motivation

- RBE = Relative Biological Efficiency
  = D (gamma, 250 keV)/D (other radiation)
- Biologically Effective Dose = D*RBE
- RBE depends on Energy (changes along path) and tissue type
- Proton RBE = 1.1, Carbon RBE = 2-5
- Ions can treat radioresistant tumors!
- DNA damage mechanism is different than gamma/p



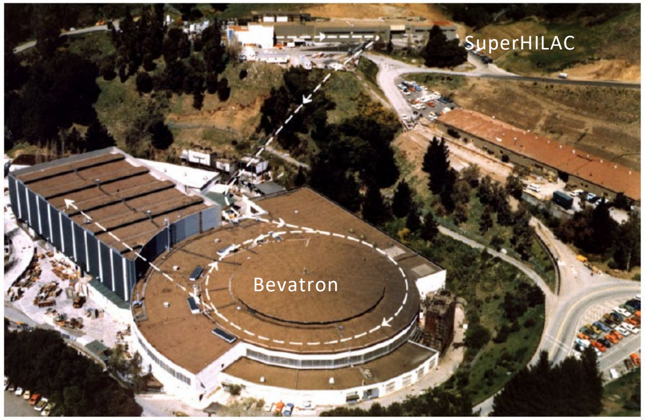


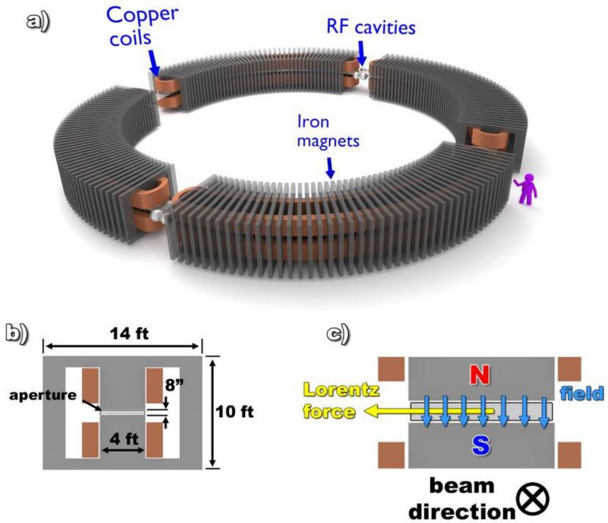




Ion therapy - accelerator

- Berkley 1975-1993 – BEVALAC accelerator complex – study of ion therapy (He-4, C-12, Ne-20, Si and Ar and even radioactive Ne-19 – treatment and PET diagnostics)
- Bevatron was a weak-focusing synchrotron (without quadrupoles),build in 1954, it had 122 m circumference
- Results were promising
- After 1993 US had only proton therapy, and ion therapy moved to Japan and Europe
- First machine was HIMAC (Heavy Ion Medial Accelerator in Chiba), actually made of 2 synchrotrons and multiple experimental rooms, commissioning in 1993
- GSI (200 m heavy ion synchrotron) experiments started in 1997
- All medical ion machines are synchrotrons

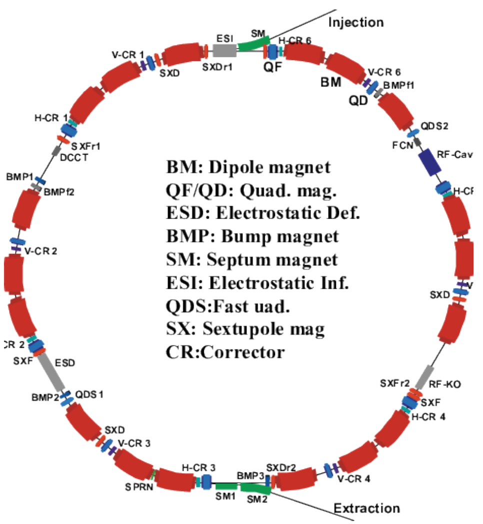




Standard Ion therapy synchrotron

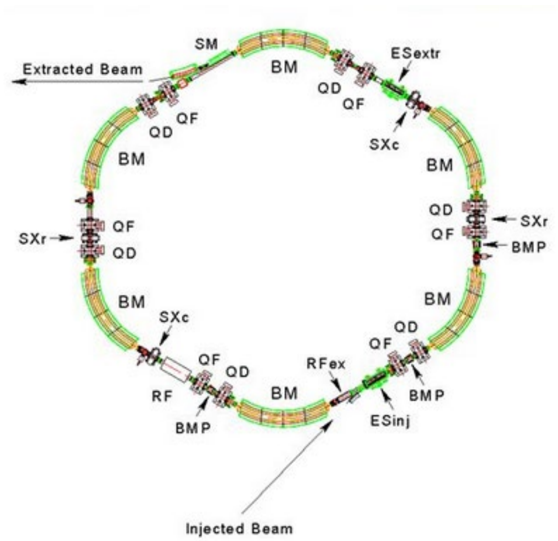
- Japaneese program resulted in ever-improving synchrotron design
- GSI program resulted in HIT (Heidelberg Ion Therapy center) compact synchrotron design, later modified by Siemens
- CERN made another design called PIMMS (Proton Ion Medical Machine Study)

Gunma/HITACHI(?)



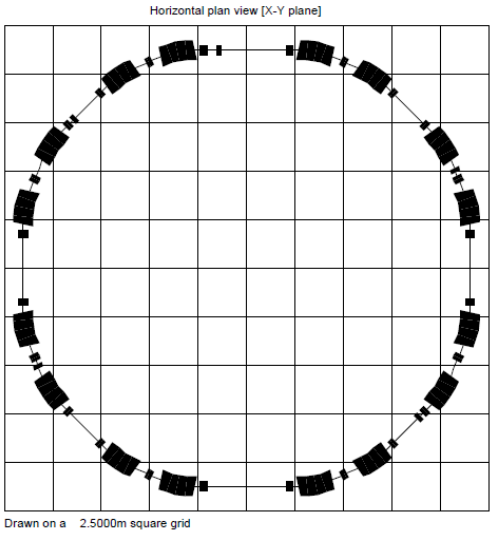
18 dipoles
62 m/ 400 MeV/u

HIT



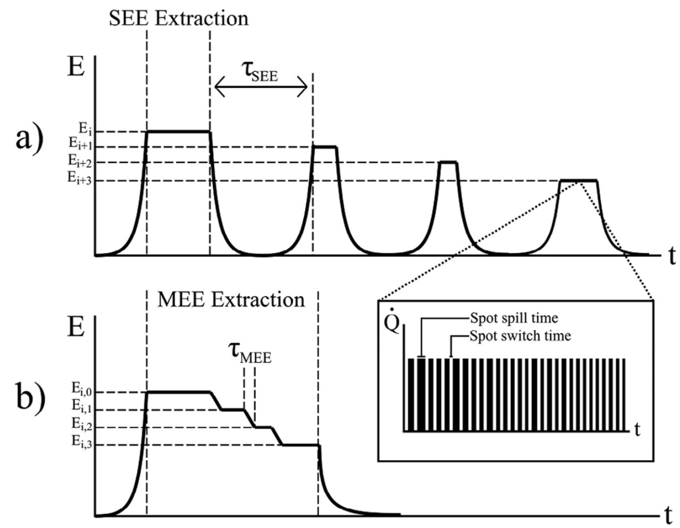
6(12) dipoles
65 m/ 430 MeV/u

PIMMS



16 dipoles
75 m / 400 MeV/u

Ion therapy synchrotron – intensity issue



- Synchrotrons are similar, but devil in details
- Crucial differences are in Operation
- Advanced feature – Multi-Energy Extraction (MEE):
  - reduces irradiation time by 2-4 x
  - requires high intensity and co called RF-KO extraction
  - Standard use in Japan, successfully tested in HIT
  - PIMMS (CNAO and MedAustron) need to change they extraction method first
  - Lesson: operational changes on working medical machines take lots of time and paperwork
- A lot of technical and legal issues must be solved to use synchrotrons for FLASH (*) therapy

* Standard irradiation rate: 2 Gy/min, FLASH: 40 Gy/s

Current situation

1. 95 proton therapy centers (data from 2020):
   - USA: 41
   - Europe: 31
   - Asia: 23
2. 13 Carbon therapy centers:
   - Japan: 7
   - Europe: 4 (HIT, MIT, CNAO, MedAustron)
   - China: 2
   - In construction: Mayo clinic (USA), South Korea (x2), Xuzhou (China), Taiwan
   - Concept phase: SEEIIST (South East Europe International Institute for Sustainable Technologies)
   - IBA works on project ARCHADE in Caen France – superconducting Carbon cyclotron - theoretically ready in 2023

SEEIIST/NIMMS

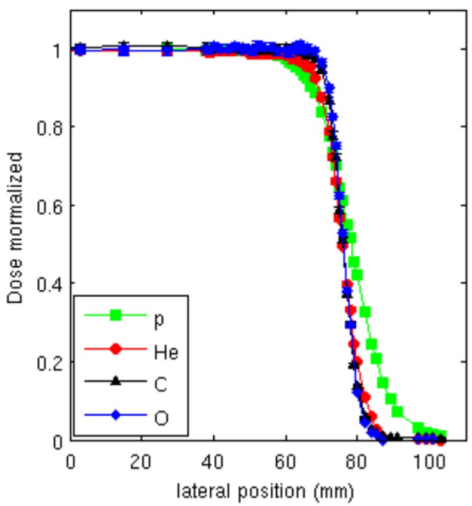
Well-tested concepts: synchrotron PIMMS version CNAO 2.0.

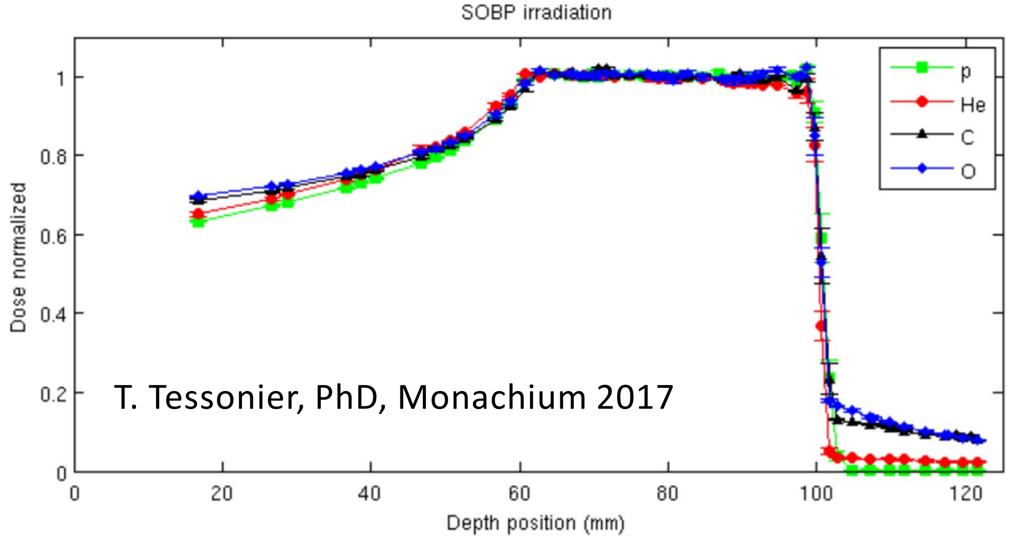
Advanced machine: beam intensity increase by 10-20 Times, MEE, FLASH

Superconducting gantry.

Trend – He-4 therapy

- He-3 i He-4 are more precise than protons (less scattering) and Carbon ions (smaller fragmentation tail)



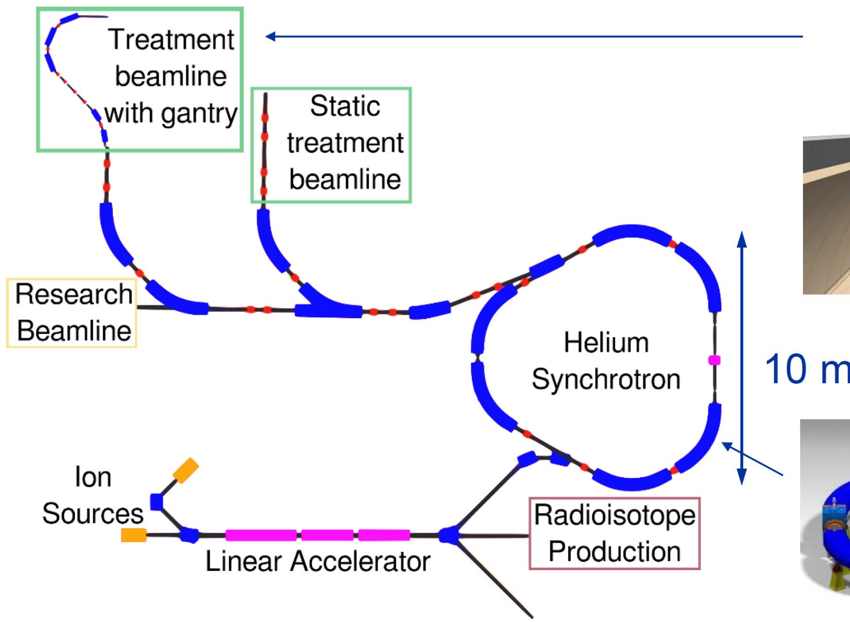


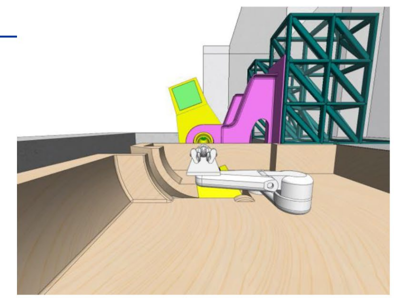
- They should work for FLASH therapy as protons
- HIT/MedAustron/CNAO want to replace protons with He-4 in their machines
- Heidelberg is most advance, first patient treated in 2021 roku
- (nb. BTW several hundred of patiens were treated with He-4 in Berkley)

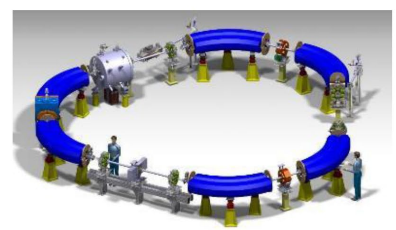
C.A. Tobias, H.O. Anger and J.H. Lawrence, "Radiological use of high energy deuterons and alpha particles," Am. J. Roentgenol. Radiat. Ther. Nucl. Med. 67: 1-27 (1952).

Dedicated helium therapy machine

- CERN currently designs He-4 system
- It can also accelerate protons but not Carbon
- It is 30% smaller and cheaper than Carbon machine







- Baltic countries are interested in this project

CERN Baltic Group

Draft concept paper
Advanced Particle Therapy Center for the Baltic States

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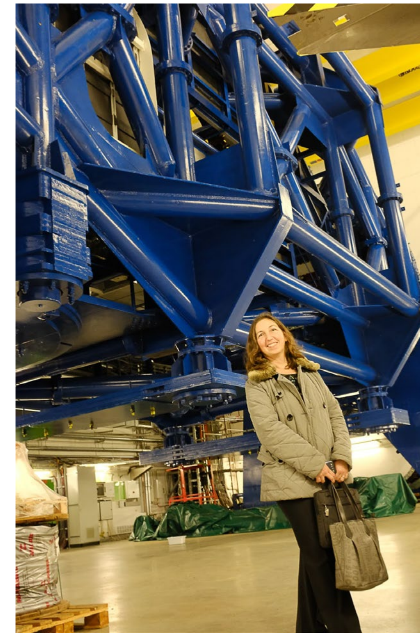
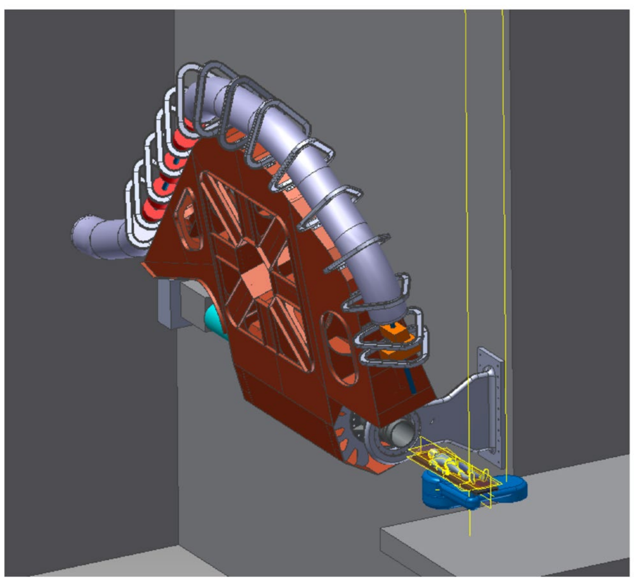
Superconducting Carbon gantry

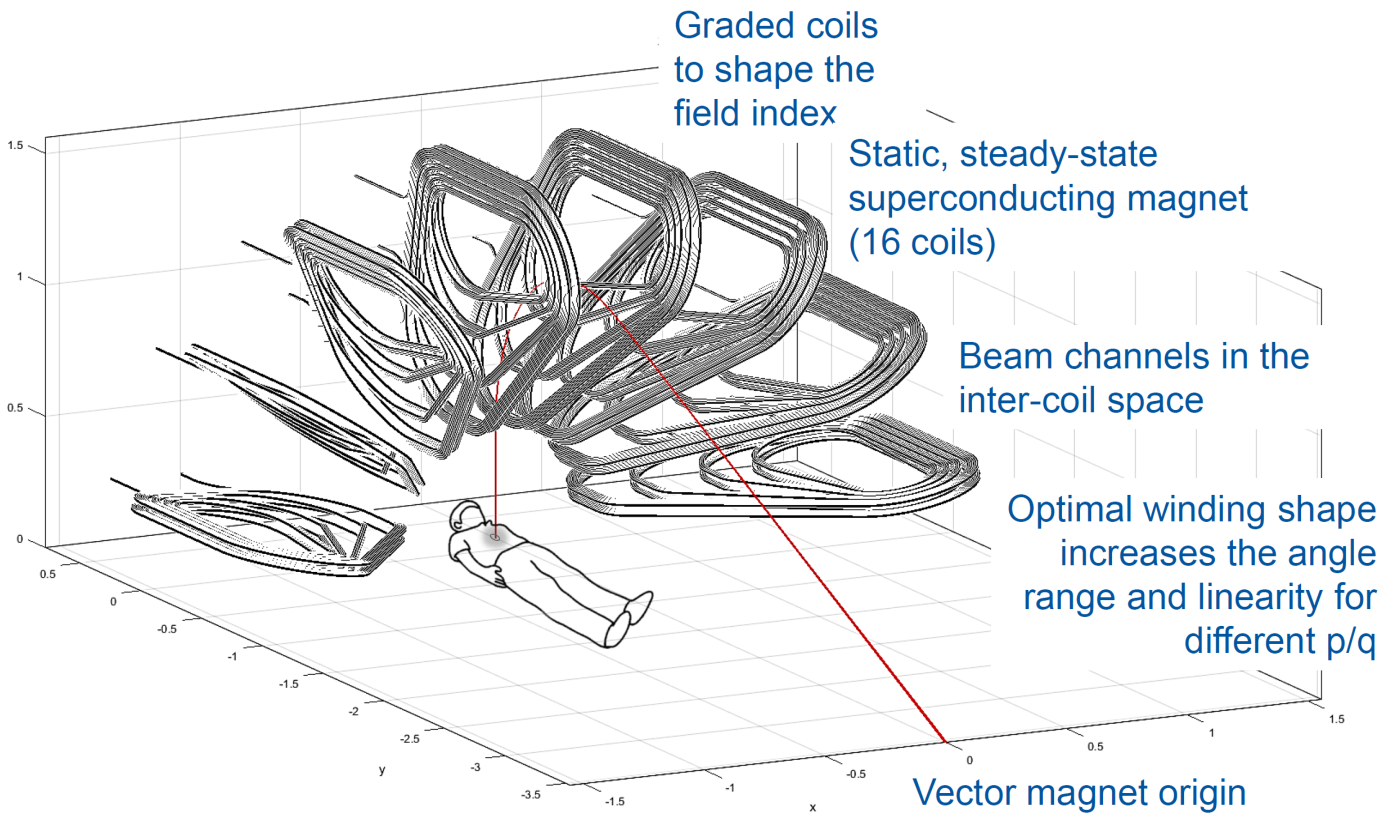


1. Gantry rotates around the patient providing beam from various angles
2. Currently in Europe there is one carbon gantry – it is normal conducting and weights 600 ton!
3. Japonia build 2 superconducting gantries, significantly lighter (1st generation: 300 ton)
4. CERN, INFN, MedAustron and CNAO work on European superconducting gantry



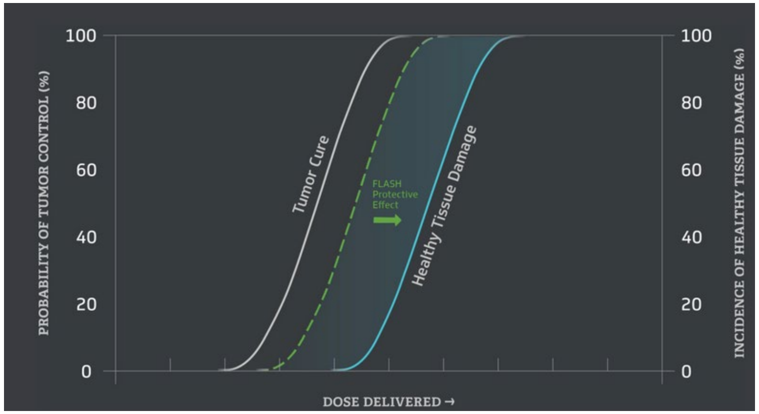
GaToroid

1. Gantry is a mechanical device, it takes long time to rotate it
2. What if we use toroid field (as for instance in ATLAS detector)
3. Elegant, no moving parts
4. GaToroid is CERN project, in design phase
5. It is 2x smaller, 10x lighter and much faster than standard gantry



FLASH

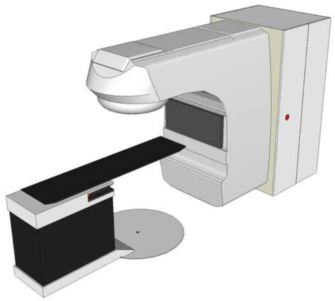
1. FLASH effect is sparing healthy tissue at very high dose rates
2. It does not affect tumor, only healthy tissue
3. It was observed in 1970s, but remain forgotten and unexplored until a few years ago
4. The dose rate must be at least 40 Gy/s
5. Current rates with pencil beam scanning, are of the order of 2 Gy/min
6. Passive dose delivery must be used
7. FLASH does not depend on type of radiation
8. First patient was successfully treated in Lausanne (CHUV)
9. It was a skin cancer and a modified standard therapy linac was used
10. FLASH dream: a single sub-second irradiation without side effects curing leathel tumors!

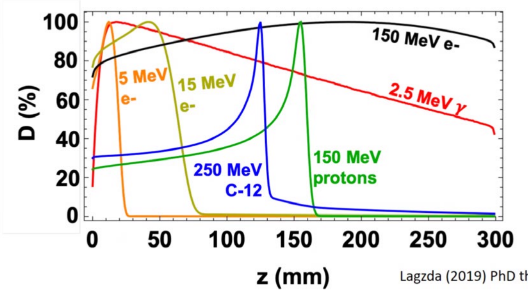


1a : Day 0
1b : 3 weeks
1c : 5 months

FLASH – what accelerator

1. Because FLASH does not depend on radiation type, it is tempting to use the simplest (and cheapest) electron linac
2. However e->X-ray conversion efficiency is very low and no cathode can survive current needed to produce FLASH effect
3. Solution: remove cathode and use directly electrons!
4. Unfortunately penetration depth of 5 MeV electrons is shallow
5. Therefore only skin cancers can be treated with modified standard linacs
6. For deep-seated tumors we need protons, ions, or Very High Energy Electrons (VHEE) – 100-250 MeV
7. (BTW ions heavier than Helium are probably not useful because of high RBE)

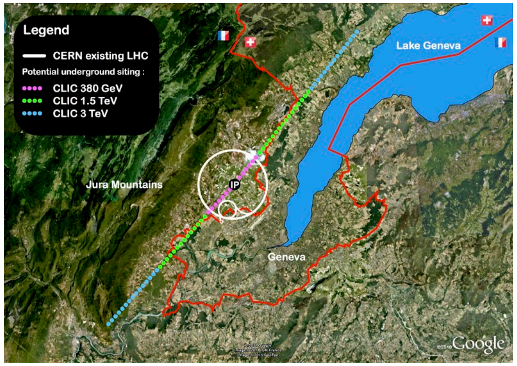


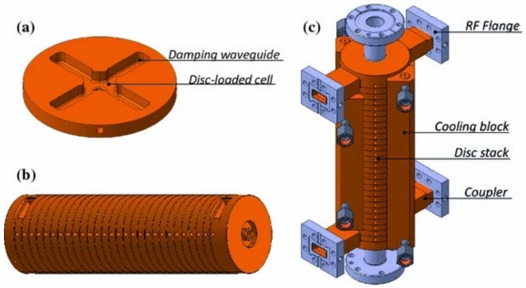


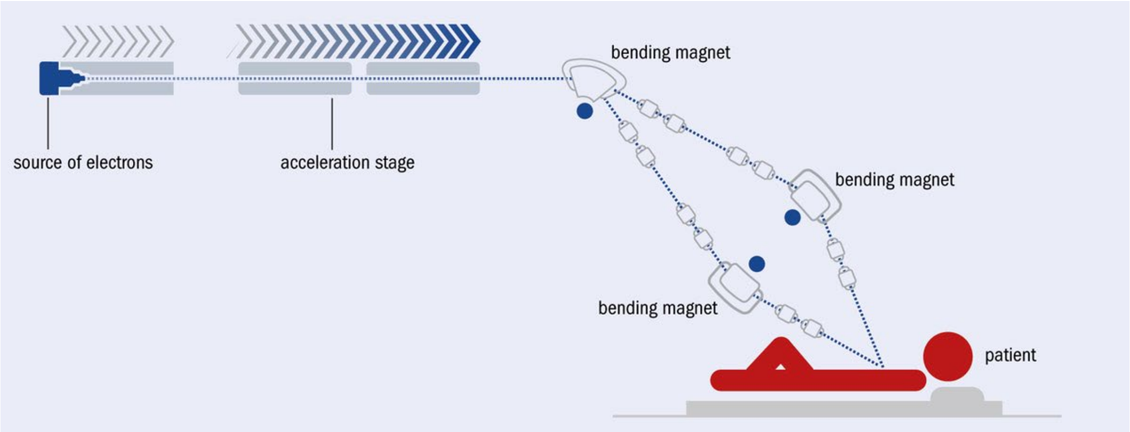
Lagzda (2019) PhD thesis

FLASH – VHEE machine

1. CLIC project: 50 km long electron-positron collider
2. Novel X-band (12 GHz) high-gradient (100 MV/m) accelerating structures
3. Ideal to be applied in VHEE machine for FLASH
4. Deep Electron FLASH Therapy (DEFT) project CERN-CHUV







5. Very vivid area, other projects: PHASER, demonstrations with protons (IBA), experiments with Carbon (GSI), etc, etc…

Radioisotope production

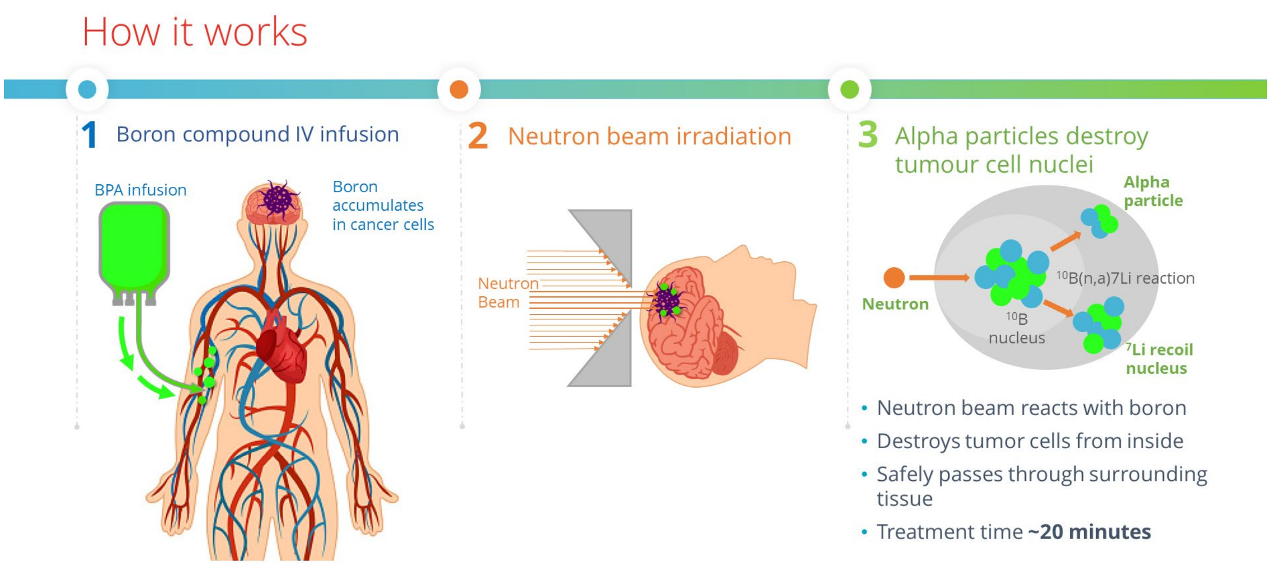
1. Radioisotopes are used in medicine for diagnostics and treatment
2. Diagnostics example: Tc-99m used for PET scans, Tc-99m is produced mainly in reactors, but also in accelerators.
3. Treatment example – Targeted Alpha Therapy (TAT): Astatin-211 using He beams

   209Bi(4He,2n)211At
4. Other radioisotopes: I-123, I-124, Zr-89, Cu-64, Ga-67, Ga-68, In-111, Y-86 and Sc-44
5. Typically low-Energy high-intensity cyclotrons are used, with H- beam and stripping extraction:

Manufacturer	Model	Particles	Energy (MeV)	Max. Beam Current (μA)	Source	Extracted Beams
ACSI	TR19	H^- (D^-)	14-19 (9)	>300 (100)	Ext. Cusp	2
ACSI	TR24	H^-	15-24	>300	Ext. Cusp	2
Best	15p	H^-	15	400	Ext. Cusp	2
Best	25p	H^-	25	400	Ext. Cusp	2
GE	PETtrace	H^- / D^-	16.5 / 8.4	>80 / 60	Int. PIG	6
IBA	Cyclone 18/9	H^- (D^-)	18 (9)	>100 (65)	Int. PIG	8
IBA	KIUBE	H^-	18	200	Int. PIG adjustable	8
Sumitomo	HM-18	H^- / D^-	18 (10)	>90 / 50	Int. PIG	2

Boron Neutron Capture Therapy

1. What if we could produce alpha-emitting isotope inside the patient?



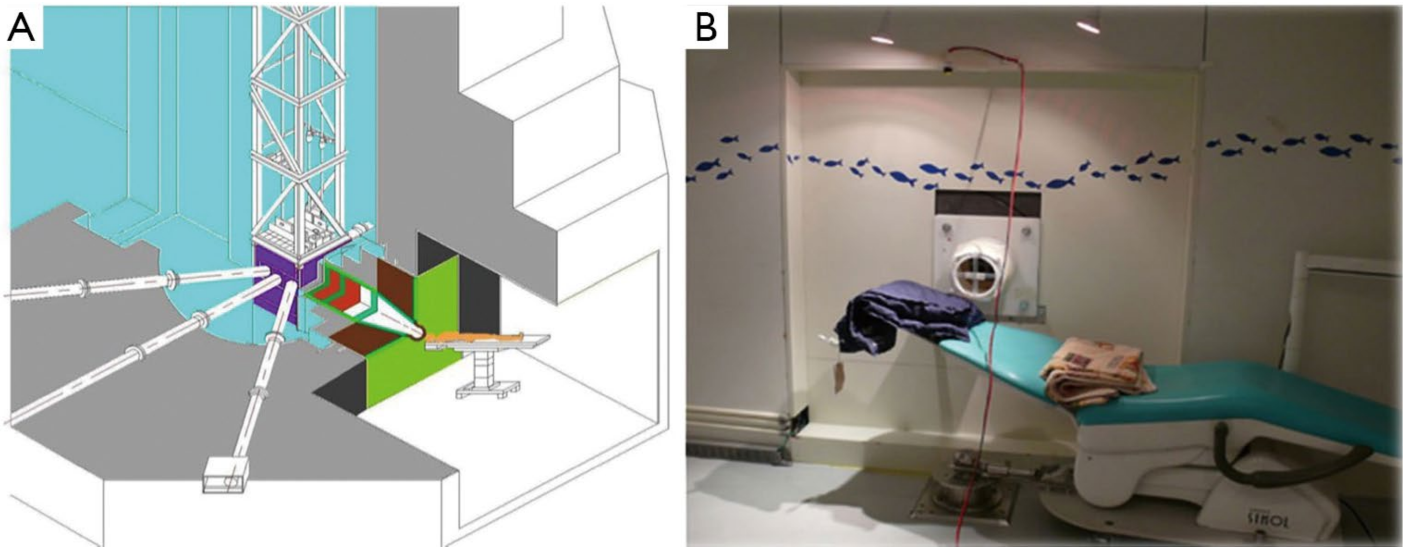
2. Base of BNCT:

$$^{10}B + n_{th} \rightarrow [^{11}B]^* \rightarrow \alpha + {}^{7}Li + 2.31\ \underline{MeV}$$

3. Low-Energy alpha particles have RBE = 6-20 – significantly more than Carbon!
4. Neutron have low Energy (thermal)

Boron Neutron Capture Therapy - reactors

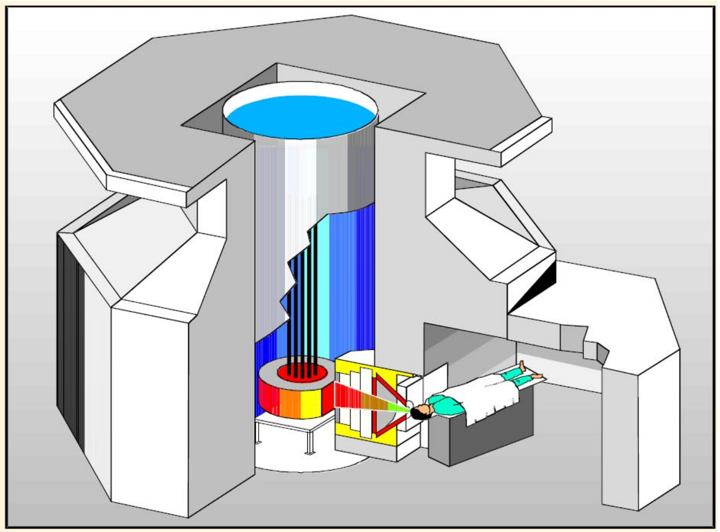
Until 2014 patients were irradiated in the nuclear reactors



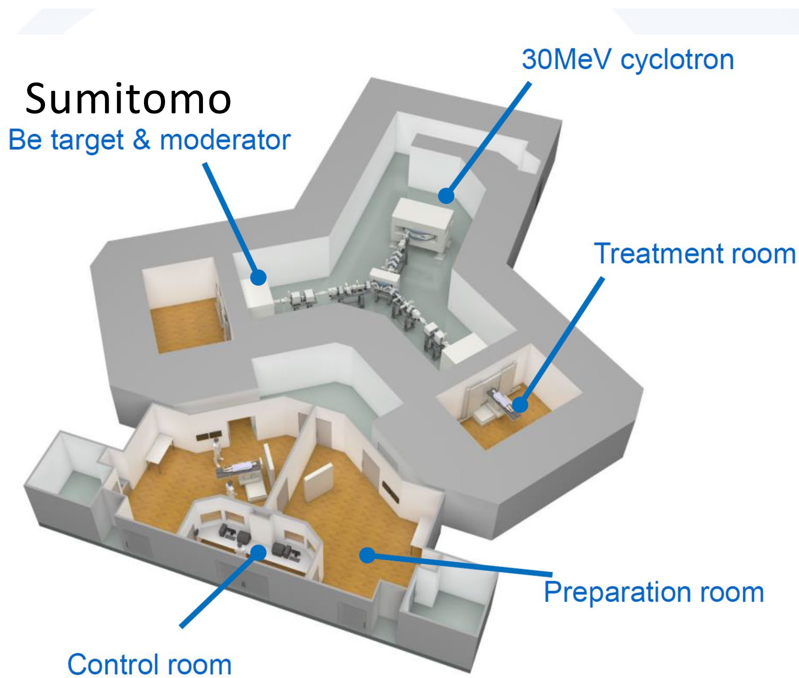
Reactor in Finland

Boron Neutron Capture Therapy - accelerators

Where to shop for neutrons? In nuclear reactors! But who wants to spend time near reactor core?



Sumitomo



Commercial systems:

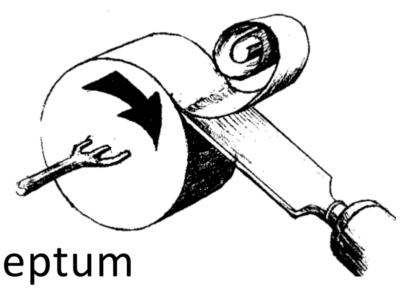
TAE Life Sciences, NeuBoron, Neutron Therapeutics

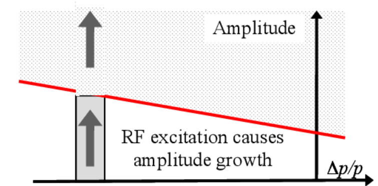
- **Accelerators are used in medicine for more than 100 years**
- **For diagnosis and treatment, either directly or via radioisotopes**
- **Standard radiation therapy with photons is mature, very precise technique**
- **Particle radiation therapy is still developing new, advanced techniques**
- **Exciting new techniques like FLASH, BNCT, He-4, promise huge improvements**
- **Need still lot of R&D to understand optimal radiotherapy**
- **Challenges are also economical and social: how to provide treatment to as many people as possible**
  (prices, medical protocols etc)

Spare slides

Projekty Europejskie – zaawansowany „ciepły” synchrotron węglowy

1. Cel: skrócenie czasu naświetlania pacjenta oraz terapia FLASH
2. Metody: usprawnienie procesów wypełniania (injection) i opróżniania (extraction) synchrotronu
3. Ekstrakcja przypomina „obieranie” wiązki z kolejnych warstw:
4. „Nóż” to specjalny magnes nazywany „septum”
5. Wiązkę wprowadza się w rezonans, aby ułatwić cząstkom przeskakiwanie na drugą stronę septum





P. Bryant

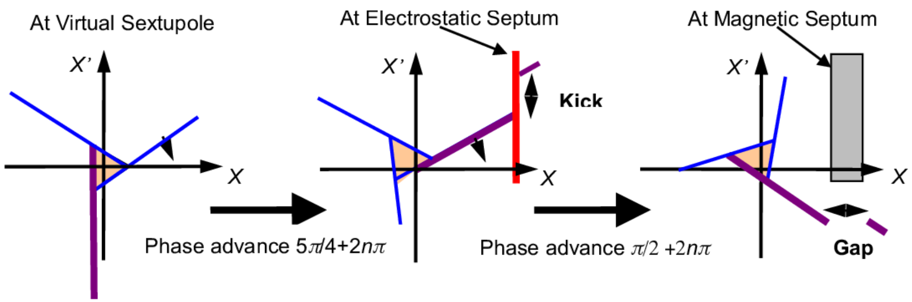
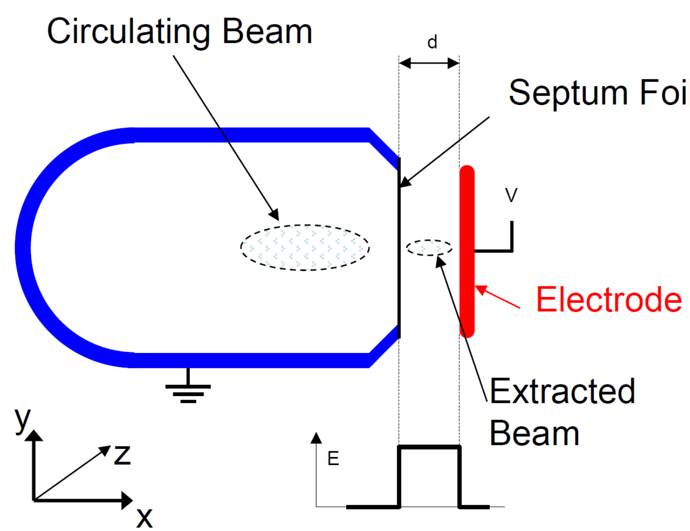
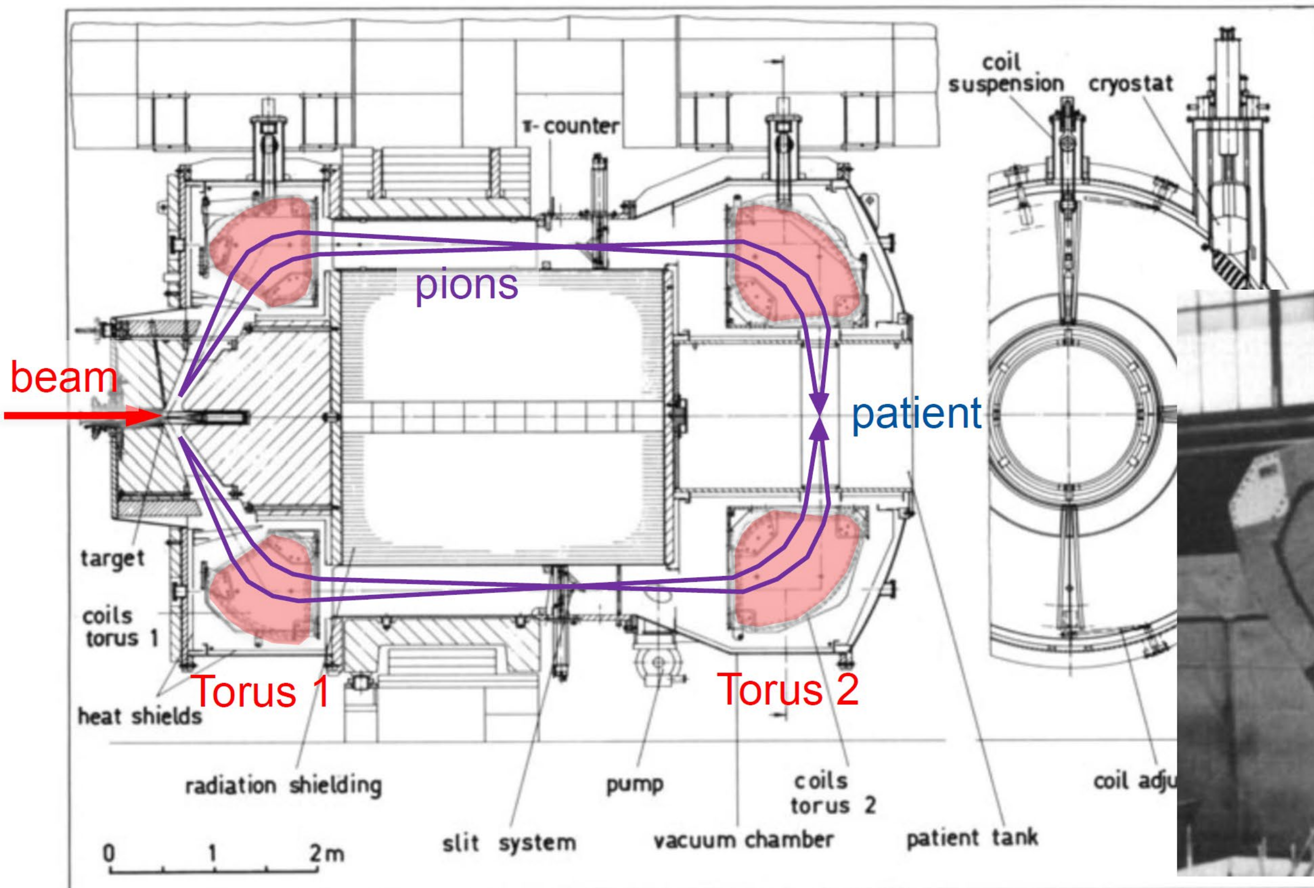


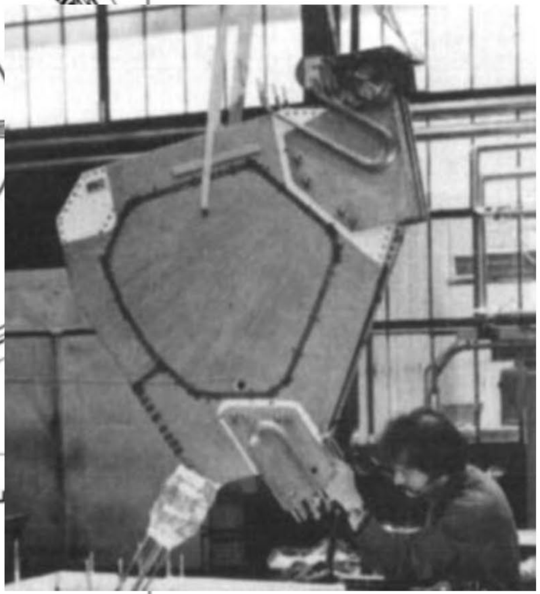
Fig. 9: Configuring the ES and MS for a slow extraction scheme



Previous art: the PIOTRON at PSI



J. Zellweger, Adv. Cryo. Eng.ng, 35A, 232-238, 1980

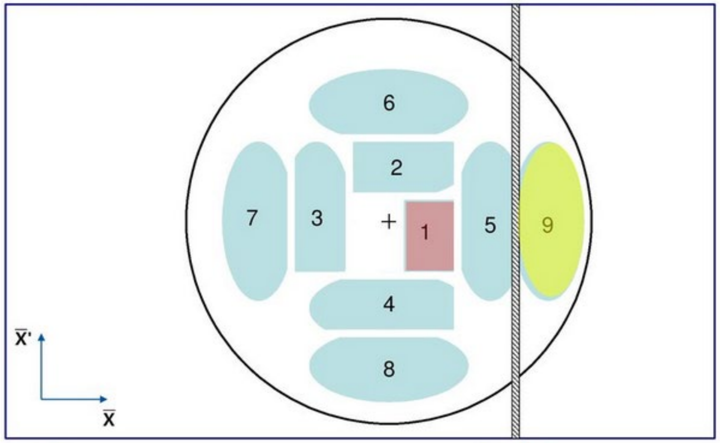


Prototype torus 1 coil
H. Benz, Cryogenics, 19, 435, 1979

Projekty Europejskie – zaawansowany „ciepły” synchrotron węglowy - intensywność

1. Aby MEE i FLASH miały sens, intensywność wiązki w składowanej maszynie przed ekstrakcją musi być 10-20 x większa niż obecnie
2. To zależy od intensywności źródła, apertury i obwodu synchrotronu oraz detali procesu wstrzykiwania wiązki

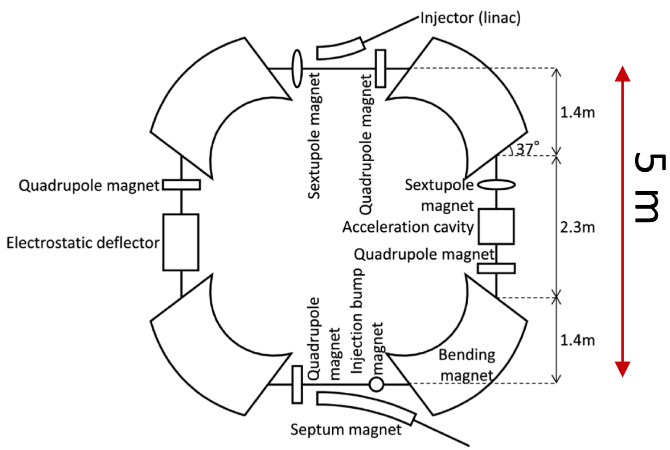
Źródło jonów ECR: intensywności OK dla protonów i He, R&D dla węgla

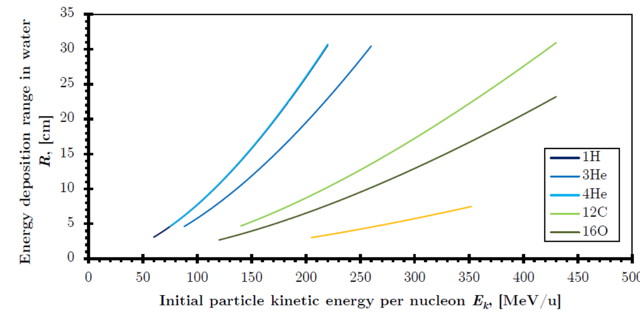


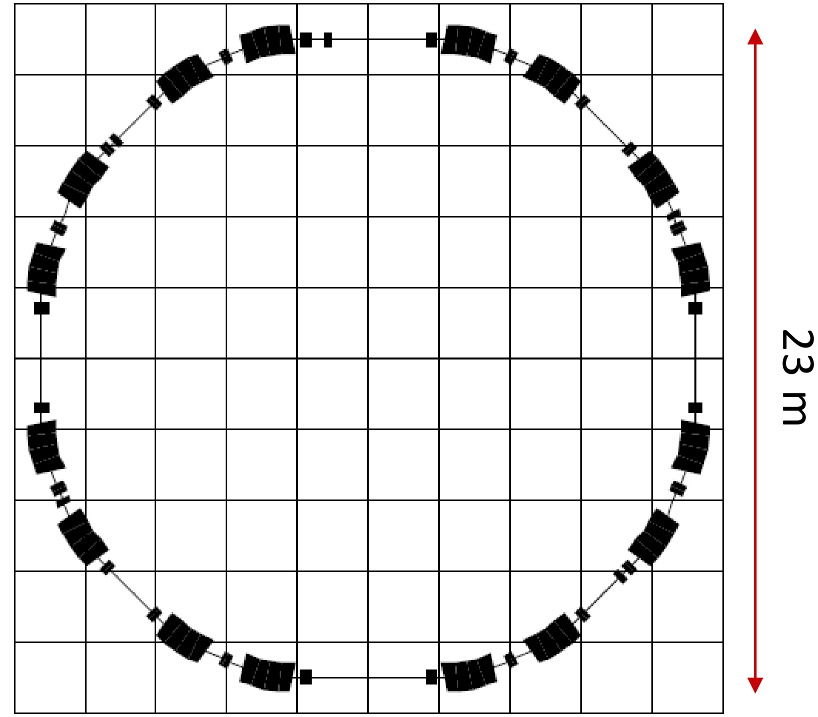
Wiązki w Euopejskich maszynach są „okrągłe”, natomiast Japończycy używają elipsoidalnych, spłaszczonych wiązek, do których można „upakować” dużo więcej jonów…

Trendy – Terapia helem

- Ponadto do terapii helem potrzebne są mniejsze energie a więc mniejsze akceleratory niż do terapii węglem:
- Synchrotron protonowy (HITACHI):







- Synchrotron He-4 musi być 2x większy niż protonowy ale maszyna węglowa
  musi być 3.5x większa
- Synchrotron He-4 może również produkować protony do energii ok. 500 MeV (radiografia)