Lecture

Accelerators for Ion-Beam Therapy

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MIT: A synchrotron-based ¹²C⁶⁺ / p therapy centre



High Speed Ion



Accelerators for ion-beam therapy

MIT: A synchrotron-based ¹²C⁶⁺ / p therapy centre



Heavy-ion beam

varian.com

High-energy X-rays



Radiation leads to ionisation damage of the DNA molecule in the cellular nucleus.



- \rightarrow 3 fundamentally different outcomes possible:
- (1) Repair mechanisms reconstitute the DNA in its original state \rightarrow Cell survives.
- (2) DNA damage cannot be repaired (in time) \rightarrow Cell dies ("apoptosis").
- (3) DNA repair leads to a non-original state \rightarrow
- Cell survives, potentially leading to mutations.



Radiation leads to ionisation damage of the DNA molecule in the cellular nucleus.



Radiation leads to ionisation damage of the DNA molecule in the cellular nucleus.



Radiation therapy tries to induce apoptosis **preferentially in the tumour cells**, while allowing healthy tissues to survive.

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- Cell survives, potentially leading to mutations.

Physical differences in particle-matter interaction



- <u>Ion beams</u>: **Well-defined range** in human tissue, with energy deposition peaking near the end-of-travel ("*Bragg peak*").
- <u>X-rays</u>: Energy deposition characterised by **exponential attenuation** of the photon beam.



Particle-matter interaction: Photons



Particle-matter interaction: Photons



 \rightarrow Actual *depth-dose profile* is blurred with respect to 1/e-law.



Particle-matter interaction: Ions



Particle-matter interaction: Ions

dE/ds rises as the particle velocity decreases:





Radiation therapy with ions uses this as an advantage:

- 1) Particle stops at a range *defined* by its initial energy.
 - \rightarrow Avoids irradiation of (healty) tissue **behind the target volume**.
- 2) d*E*/ds is largest near the end-of-travel ("*Bragg peak*").
 - \rightarrow Lower dose distribution in the (healty) tissue of the **entrance channel**.



Linear Energy Transfer

Higher d*E*/ds \rightarrow higher LET (effective energy deposition per length of track).

Mean distance between ionisation events depends on the nature of the projectile. Higher LET means higher likelyhood to "hit" a DNA molecule along the track.



Projectiles leading to higher ionisation density are more likely to cause irreversible damage ("*double strand breaking*") in DNA molecules.

 \rightarrow Higher "biological effectiveness".



Linear Energy Transfer



G. Montarou, Radiobiology in Medecine, 17-12-2013



Linear Energy Transfer



Physical differences in particle-matter interaction

Due to principle of interaction

- Diameter of photon beam is **largely independent** on irradiation depth.
- Ions scatter laterally, blurring the initially-defined beam edge. ("penumbra")





Scattering effect is strongest for light ions (protons).



Outline

lon-beam therapy

Accelerators for ion-beam therapy

MIT: A synchrotron-based ¹²C⁶⁺ / p therapy centre



- 1895 *Wilhelm Conrad Röntgen* (1845 1923) discovers X-rays at the University in Würzburg
- 1896 On 23rd January Röntgen announced his discovery and demonstrated the new kind of radiation by a photograph of the hand of his colleague *Albert von Kolliker*
- 1897 First treatments of tissue with X-rays by *Leopold Freund* at University in Vienna
- 1901 Physics Nobel prize for W. C. Röntgen









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- 1899 First X-ray treatment of carcinoma in Sweden by *Stenbeck* and *Sjögren*
- 1906 Vinzenz Czerny founded the "Institute for Experimental Cancer research" in Heidelberg – the first of its kind
- 1913/4 Invention of partly and fully rotatable radiation instrumentation
- 1920s Industrially manufactured X-ray apparatus' Right: Reiniger-Gebbert & Schall AG (later: Siemens), Erlangen; 1922) with a high-voltage of 150 kV – without shielding!
- 1930 RF linear accelerator principle invented by *Rolf Wideroe*
- 1949 *Newberry* developed first linear accelerator for therapy in England







1950s Development of compact linear accelerators by Siemens, Varian, Elekta, and other companies – reaching energies of 25 MeV (and above).



↑ ONCOR from Siemens

Layout of a modern electron ↑ "linac" for radiotherapy



- 1929 Invention of the cyclotron by *Ernest Lawrence*
- 1930s Experimental neutron therapy
- 1946 R. *R. Wilson* proposed proton & ion therapy
- 1950s Proton therapy, LBL Berkeley (184" cyclotron)
- 1945 *Edwin Mattison McMillan* at University of California and *Vladimir Iosifovich Veksler* (Soviet Union) invent the synchrotron principle.
- 1975 Begin of carbon therapy at the Bevalac synchrotron (Berkeley) (A total of >2000 patients were treated with He, C, Ne, Si, Ar until 1992)





since 1975

Radiotherapy with ion beams is a growing industry.





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Logitudinal distribution (along beam axis):

Generate a "Spread-Out Bragg-Peak" by

- 1) **stacking** of a sequence of beams of different energy, or
- 2) use of a single beam of "matching" broad **energy distribution**, or
- 3) a combination of the two.



Lateral distribution (transverse to beam):

Achieve the wanted *transverse dose profile* by

- 1) tumour-conformal **collimation** of a wide beam (e.g. scatterer + collimator),
- "painting" using a fine "pencil-beam" (scanning).



Integral dose + beam intensity:

$$D[Gy] \approx 0.1602 \times \varphi \left[\frac{10^9}{cm^2}\right] \times \frac{S}{\rho} \left[\frac{MeV}{g/cm^2}\right]$$

with

- D applied dose in Gy = J/kg
- ϕ particle fluence in billions per cm²

 S/ρ density-normalised stopping force d*E*/ds· ρ at Bragg peak in MeV cm² / g

Typical dose for therapy: ~ 1 Gy per fraction

Typical S/ρ (for protons): ~ 5 MeV cm²/g

 \rightarrow Need ~ 10⁹ protons per cm² of tumour cross-section (\leftarrow Simplified 2D picture!)

 \rightarrow An (average) proton rate of a few 10⁹ s⁻¹ (1 nA) looks like a reasonable beam intensity.



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Remarks

- (1) If the beam transport is lossy (e.g. due to energy degraders, collimators, ...) the intensity at the accelerator may need to be much higher.
- (2) Also much lower intensities should be available, e.g. for the fore-most pristine Bragg peak.



 \rightarrow An (average) proton rate of a few 10⁹ s⁻¹ (1 nA) looks like a reasonable beam intensity.





Traditional **"passive" scattering** and collimation technique requires only widening of the accelerator beam to a homogeneous, flat profile.

Tumour conformity of the dose distribution is ensured by the (patient-specific) collimating and filtering system.

\rightarrow No specific requirement on the time structure of the beam.



Ideal time structure of ion beam?

Since the 90ies:

"Active scanning" pencil beams (X/Y) +

"active" range stacking of beams of different energies (Z) and intensities from accelerator.

Advantages:

- (1) Better tumour conformity.
- (2) Less "wasted" beam in collimators and filters. (Secondary radiation!)

But:

Requires **quasi-DC beams**, whose position, spot-size, and intensity can be *monitored an controlled on-line*! **Typical pulses: 1...10 s**.





Key requirements for a therapy ion beam



Time structure (for raster scanning):

DC beam pulses of 1 ... 10 s duration

alternatively

Micro-bunches of high repetition rate and stable intensity (cw beam, "quasi-DC").



Use electric charge q of particles:

Electric potential difference \rightarrow Acceleration to kinetic energy E = qU





www.mpi-hd.mpg.de

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Later improved into **resonant** accelerator structures (*Alvarez* linac, IH linac)

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Encyclopedia Britannica (2007)

Radiofrequency Linacs

- Instead of one large proton electrostatic field, use an oscillating EM field,
- (2) synchronise particle motion with "accelerating" phase of EM wave
 - \rightarrow Net acceleration.

Alvarez structure of GSI's UNILAC

Original realisation: *Wideroe* drift tube linac (1928). Later improved into **resonant** accelerator structures (*Alvarez* linac, IH linac)







Cyclotrons

Idea: Re-use the same RF acceleration gap over-and-over again.



E. Lawrence's original concept of the cyclotron (1934 patent):

D-shaped RF electrodes ("*Dees*") placed in a disk-like vacuum chamber and embedded in a large (near-homogeneous) static magnetic field.

 \rightarrow Radius of particle trajectory increases at each passage through the gap.



Cyclotrons

Classical cyclotron:

From Lorentz force

$$F_{\perp} = m \omega^2 \rho = q \omega \rho B$$

 \rightarrow cyclotron frequency:

 $\omega_c = \frac{qB}{m}$

Kin. energy after *n* turns

 $E = 2 n q U_{RF}$

With $E = m \omega_c^2 \rho^2 / 2$, we obtain the cyclotron radius after *n* revolutions

$$\rho(n) = \frac{\sqrt{2 E m}}{q B} = \frac{\sqrt{4 n q U_{RF} m}}{q B}$$



Machine diameter ~ $E^{1/2}$

Lawrence's first machines (Berkeley) had



Cyclotrons: Transverse motion stability



Vertical direction:

In the classical cyclotron, the magnetic field *B* decreases (slowly) with *r*.



"Automatic" focussing in the axial direction.


Cyclotrons: Relativistic energies

For therapy, we need 220 MeV p (γ = 1.25) or 430 MeV/u ¹²C⁶⁺ (γ = 1.46)

→ Relativistic corrections are not negligible!

 $\omega_c = \frac{qB}{m} \rightarrow \omega_{c,rel} = \frac{\omega_c}{\gamma} = \frac{qB}{\gamma m} \rightarrow \text{Breaks synchronicity with RF. Solutions?}$



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(1) Synchrocyclotron

(2) Isochronous cyclotron

Keep **constant B**, **tune RF** frequency.



CERN Synchrocyclotron: 600 MeV p (1957)

/ikipedia.org

Drawback: Only a short train of particles is in sync with RF ramp.

→ pulsed operation, lower average current. Keep **RF** frequency **constant**, **increase** *B* with *r*.



Most modern cyclotrons are isochronous.

- \rightarrow cw operation
- → Most proton beam therapy facilities

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Cyclotrons: Relativistic energies

However, with positive gradient in *B*, there is no axial focussing "for free" anymore ...



Introduce "alternating gradients" (L. Thomas, 1938): Shape magnet faces to have "hills" and "valleys"

> Craddock, Rev. Accel. Sci. Technol. (2008)



 \rightarrow "Strong focussing" at sector edges.





Cyclotrons for ion-beam therapy

Isochronous cyclotron C230 by IBA

Designed for proton therapy.

Installed at 16 facilities.

Mass: 220 t

E = 230 MeV

I_{max} = 300 nA

 $B_{\text{max}} = 2.2 \text{ T} \rightarrow \rho \sim 2 \text{ m}$





Cyclotrons for ion-beam therapy



www.psi.ch

COMET superconducting cyclotron

Developed by ACCEL (now Varian Medical) for proton therapy

Mass: 80 t

E = 250 MeV

I = 1 ... 850 nA

$$B_{\text{max}}$$
 = 3.0 T $\rightarrow \rho$ < 1 m



Cyclotrons for ion-beam therapy: Energy selection



 \rightarrow *E*-reducion by degraders + momentum selection in analysing magnets

Cyclotrons for ion-beam therapy: ¹²C⁶⁺?

Cyclotron frequency:
$$\omega_c = \frac{q B}{\gamma m} \Leftrightarrow \frac{v}{\rho} \gamma m = q B \Leftrightarrow \frac{p}{q} = B \rho$$

Protons (230 MeV): $B\rho = 2.3 \text{ Tm}$
¹²C⁶⁺ (430 MeV/u): $B\rho = 6.6 \text{ Tm}$

"magnetic rigidity":

Relates particle momentum and charge to the product of field and bending radius.

I.e. to go from protons to carbon ion beams, one needs to increase either the **magnetic field** or the **size** of the machine by almost a factor 3.

Although they are very successful in proton therapy, there is no cyclotron for carbon-ion therapy yet.



Cyclotrons for ion-beam therapy: ¹²C⁶⁺?

There is a project ("ARCHADE") to install a carbon-treatment facility in Caen (France).

Should be based on a superconducting cyclotron ("C400") developed by IBA.



In 2014, it was decided to build a proton facility first (start 2018) and the C400 project seems to have been postponed ...



Synchrotrons



All carbon ion-beam therapy centres in operation use synchrotrons as main acceleration stages.



Synchrotrons



Advantage:

Synchrotrons



www.mpi-hd.mpg.de

Spule

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Synchrotrons: Transverse motion stability



Quadrupole magnet:

Focussing in $X \rightarrow$ Defocussing in Y (and vice-versa)

But: sequence ... -D-F-D-F- ... has a net focussing effect.

Mathematical description by harmonic oscillator formalism:

$$\frac{d^2}{ds^2}x + K(s)x = 0$$

with *K* periodic in *s* (Hill's equation)

Synchrotrons: Transverse motion stability

Synchrotrons: Ion injection

The ring defines a stable, closed orbit ...

... but how do we actually get particles onto that orbit in the first place?

Fundamental rule: Phase space density of injected beam cannot be enhanced by the ring optics (Liouville's theorem).

- (1) Kicker injection: Fast-switching deflection magnet.
- (2) **Stripping injection**: Strip H⁻ to p at ring entrance
 - → Bending magnet deflects stored and injected beam in opposite directions.
- (3) Multiturn injection: Accumulate beam by "winding up" injected pulse in transverse phase-space.
- (4) **RF stacking**: Use RF acceleration to distribute particles in momentum space.

Synchrotrons: Ion injection

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Synchrotrons: Ion extraction

After acceleration: How do we extract the fast particles into a directed beam?

(1) Kicker extraction:

Use a switching magnet that is fast compared to the revolution period.

 → That's too fast (~ µs)!!
 Therapy needs a ~DC beam of a few seconds ...

Slow extraction:

Use **resonance** between revolution period and betatron motion.

- → Transverse oscillations grow and ions enter an *extraction septum*.
- "Spill" of a few seconds.
 Used at all therapy synchrotrons.

Synchrotrons: Ion extraction

Add sextupole components to the magnetic fields.

- \rightarrow Betatron motion becomes **non-harmonic** at large amplitudes.
- \rightarrow "Separatrix" in (x,x') phasespace, where oscillation is n/3-resonant with revolution.
- \rightarrow For particles close to separatrix, amplitude grows beyond all limits.

Drive particles into resonance by

Albrecht, PhD, 1996

- (1) Slow shrinking of separatrix around particle phase-space.
- (2) **Transverse heating** of beam (stochastic noise kicker).

Cyclotron beam vs. Synchrotron beam

cw beam: continuous train of short pulses.

Energy variation by degraders in high energy beam transport. \rightarrow looses ions.

Fast current modulation at source.

No machine for carbon ions (yet)

SYNCHROTRONS

"almost DC" beam, interrupted by phases of beam preparation.

Energy variation in accelerator \rightarrow no beam loss.

Injector defines amount of ions in cycle. Some rings support fast spill modulation.

p and C available.

cern.ch

+ 4 dedicated carbon-ion treatment centres all over Japan.

Chiba, Japan:

HIMAC (Heavy-Ion Medical Accelerator in Chiba, NIRS, 1994)

Two 800 MeV/u synchrotrons, for ions up to ${}^{40}Ar^{18+}$, mostly ${}^{12}C^{6+}$.

> 10000 patients treated with ${}^{12}C^{6+}$ (2015)

Nature (2017) 548

Darmstadt, Germany

1997 - 2008

Experimental program on ¹²C⁶⁺ ion beam therapy using the **GSI accelerator complex**. Total 448 patients.

Established the **pencil-beam scanning** method.

First hospital-based p/C centre in Europe.

> 3000 patients (as of 2015)

First isocentric ¹²C⁶⁺ gantry.

Today, 3 more facilities in Europe, closely following the HIT design:

> CNAO (Pavia, Italy) MIT (Marburg, Germany) MedAustron (Wiener Neustadt, Austria)

Heidelberg, Germany

Heidelberg Ion-Beam Therapy Centre (HIT), from 2009, based on GSI experiments.

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Gantries

Idea: Allow patient to be irradiated from any side (similar to photon radiotherapy).

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Gantries

www.helmholtz.de

Up to $B\rho$ = 6.6 Tm

Diameter 13 m, length 25 m

Raster-scanning pencil beam

Overall weight 600 tons

Heidelberg ¹²C⁶⁺ Gantry (HIT)

www.uniklinikum-heidelberg.de

Gantries

Superconducting ¹²C⁶⁺ gantry at HIMAC (2016)

nirs.qst.go.jp

Raster-scanning pencil beam.

Lighter and smaller than normal-conducting gantry for heavy ions (\sim 300 t).

Iwata et al., NIM A 834 (2016)

Recent developments

Proton-beam therapy:

Many efforts to *shrink* accelerators and beam delivery systems.

- Easier and cheaper to fit into hospitals.
- Single-room solutions become possible.

S2C2 superconducting ↑ synchrocyclotron by IBA 2.5 m diameter

S250 system by Mevion

Gantry-mounted superconducting synchrocyclotron. Operating at 6 sites.

Recent developments

RF linear accelelarators

Partly superconducting to obtain shorter machines.

Can vary energy in accelerator by (de-)activating booster cells.

 RFQ
 S.C. DTL

 CCL
 0

 150 MeV
 230 MeV

 230 MeV
 230 MeV

↑ LIGHT

Proposed Linac-only proton accelerator for ion beam therapy.

Amaldi, Proc. of LINAC 2014

... also for carbon ions?

← TULIP project Partly gantry-mounted linac for proton beam therapy.

S. Benedetti et al., Phys. Rev. Accel. Beams (2017)

9 m

22 m

63

Recent developments

Zeil, Appl. Phys. B 110 (2013) 437

in-ear

tumou

IDOCIS

arrival of

laser pulse

BO

Dipole chicane

B.~ 10 T

Laser acceleration

Beam pulses of high intensity and broad energy distribution

- Energy selecting beam line
- No accelerator: compact
- High power (~ 100 TW) Laser required

Pulsed solenoid

lens

foil target

gold disks

E,<E,<E

target

laser

[Gy]

в⊗

Outline

lon-beam therapy

Accelerators for ion-beam therapy

MIT: A synchrotron-based ¹²C⁶⁺ / p therapy centre

MIT: The Marburg Ion-Beam Therapy Centre

MIT: The Accelerator

Rohdjeß et al., Proc. of PAC 2009 Lazarev et al., Proc. of IPAC 2011 Scheeler et al. Proc. of IPAC 2014 Designed by Siemens/Danfysik built 2008 – 2009

Commissioned by MIT + HIT in 2015

Similar to HIT accelerator and PIMMS-types (CNAO, MedAustron).

Prototype of **SPHIC** machine in Shanghai (start: 2014).

MIT: The Accelerator

Rohdjeß et al., Proc. of PAC 2009 Lazarev et al., Proc. of IPAC 2011 Scheeler et al. Proc. of IPAC 2014 Linear accelerator

Tragi, 1.0

RFQ (400 keV/u) + IH structure (7 MeV/u)

> then stripping to p and $C^{\rm 6+}$

2 ECR ion sources

Pantechnik Supernanogan

H₃⁺: 800 μA C⁴⁺: 180 μA

MIT: The Accelerator

Synchrotron (65 m circ.)

0.5 Tm - 6.6 TmRamping time ~1 s

Extraction 1 - 8 s (noise excitation)

Møller et al., Proc. of PAC 2007

High-energy beam transport

MIT: Synchrotron

MIT: Synchrotron extraction

Slow extraction via 2/3 resonance.

Active transverse beam heating by noise kicker ("KO-excitation").

→ Can control the extraction rate on ms-timescales!

High energy beams p: 48 ... 221 MeV ¹²C⁶⁺: 88 ... 430 MeV/u

MIT: Synchrotron extraction

Therapy Control System has direct control over ion extraction rate.

 \rightarrow Two orders of magnitude dynamic range!

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MIT: Synchrotron extraction



Therapy Control System has direct control over ion extraction rate.

 \rightarrow Two orders of magnitude dynamic range!



MIT: Therapy caves



Rohdjeß et al., Proc. of PAC 2009 Lazarev et al., Proc. of IPAC 2011 Scheeler et al. Proc. of IPAC 2014 \rightarrow 290 energies each

Protons: 4.10⁸ – 2.10¹⁰ ¹²C⁶⁺: **10**⁷ – **5**·**10**⁸ per spill

 \rightarrow 13 base intensities with "Dynamic Intensity Control"

5 beam widths



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Thank you for your attention.



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