Medical Applications of Particle Accelerators

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Particle accelerators operational in the world

Three main applications:
1) Scientific research
2) Medical applications
3) Industrial uses

<table>
<thead>
<tr>
<th>CATEGORY OF ACCELERATORS</th>
<th>NUMBER IN USE (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-energy accelerators (E &gt;1 GeV)</td>
<td>~ 120</td>
</tr>
<tr>
<td>Synchrotron radiation sources</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Medical radioisotope production</td>
<td>~ 1,000</td>
</tr>
<tr>
<td>Accelerators for radiation therapy</td>
<td>&gt; 7,500</td>
</tr>
<tr>
<td>Research accelerators including biomedical research</td>
<td>~ 1,000</td>
</tr>
<tr>
<td>Industrial processing and research</td>
<td>~ 1,500</td>
</tr>
<tr>
<td>Ion implanters, surface modification</td>
<td>&gt; 7,000</td>
</tr>
<tr>
<td>TOTAL</td>
<td>&gt; 18,000</td>
</tr>
</tbody>
</table>

Adapted from “Maciszewski, W. and Scharf, W., Particle accelerators for radiotherapy, Present status and future, Physica Medica XX, 137-145 (2004)”
Particle accelerators for medical uses

• Production of radionuclides with (low-energy) cyclotrons
  - Imaging (PET and SPECT)
  - Therapy

• Electron linacs (6-25 MeV) for conventional radiation therapy, including advanced modalities

• Medium-energy cyclotrons and synchrotrons for hadron therapy with protons (250 MeV) or light ion beams (400 MeV/u $^{12}$C-ions)
  - Accelerators and beam delivery
  - New concepts
Radionuclide production
Radionuclide production

The use of radionuclides in the physical and biological sciences can be broken down into three general categories:

Radiotracers

Imaging (95% of medical uses)
- SPECT ($^{99m}$Tc, $^{201}$Tl, $^{123}$I)
- PET ($^{11}$C, $^{13}$N, $^{15}$O, $^{18}$F)

Therapy (5% of medical uses)
- Brachytherapy ($^{103}$Pd)
- Targeted therapy ($^{211}$At, $^{213}$Bi)

Relevant physical parameters (function of the application)
- Type of emission ($\alpha$, $\beta^+$, $\beta^-$, $\gamma$)
- Energy of emission
- Half-life
- Radiation dose (essentially determined by the parameters above)
Positron Emission Tomography

Cyclotron

Radiochemistry

PET camera

<table>
<thead>
<tr>
<th>ISOTOPES</th>
<th>Half-Life</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-C</td>
<td>20.4 min</td>
<td>“natural”</td>
</tr>
<tr>
<td>13-N</td>
<td>10.0 min</td>
<td>“natural”</td>
</tr>
<tr>
<td>15-O</td>
<td>2.0 min</td>
<td>“natural”</td>
</tr>
<tr>
<td>18-F</td>
<td>109.8 min</td>
<td>“pseudo-natural”</td>
</tr>
</tbody>
</table>

J. Long, “The Science Creative Quarterly”, scq.ubc.ca
Production methods

All radionuclides commonly administered to patients in nuclear medicine are *artificially* produced

Three production routes:
- $(n, \gamma)$ reactions (**nuclear reactor**): the resulting nuclide has the same chemical properties as those of the target nuclide
- Fission (**nuclear reactor**) followed by separation
- Charged particle induced reaction (**cyclotron**): the resulting nucleus is usually that of a different element
Reactor versus accelerator produced radionuclides

Reactor produced radionuclides
The fission process is a source of a number of widely used radioisotopes ($^{90}$Sr, $^{99}$Mo, $^{131}$I and $^{133}$Xe)

Major drawbacks:
• large quantities of radioactive waste material generated
• large amounts of radionuclides produced, including other radioisotopes of the desired species (no carrier free, low specific activity)

Accelerator produced radionuclides
Advantages
• more favorable decay characteristics (particle emission, half-life, gamma rays, etc.) in comparison with reactor produced radioisotopes.
• high specific activities can be obtained through charged particle induced reactions, e.g. ($p,xn$) and ($p,\alpha$), which result in the product being a different element than the target
• fewer radioisotopic impurities are produce by selecting the energy window for irradiation
• small amount of radioactive waste generated
• access to accelerators is much easier than to reactors

Major drawback: in some cases an enriched (and expensive) target material must be used
Tuning the beam energy, the example of $^{201}$Tl

The nuclear reaction used for production of $^{201}$Tl is the $^{203}$Tl(p,3n)$^{201}$Pb

$^{201}$Pb ($T_{1/2} = 9.33$ h) $\rightarrow$ $^{201}$Tl ($T_{1/2} = 76.03$ h)

*Cross-section versus energy plot for the $^{203}$Tl(p,2n)$^{202}$Pb, $^{203}$Tl(p,3n)$^{201}$Pb and $^{203}$Tl(p,4n)$^{200}$Pb reactions*

Below 20 MeV, production of $^{201}$Tl drops to very low level

Around threshold, production of $^{201}$Tl is comparable to that of $^{202}$Pb

Above 30 MeV, production of $^{200}$Pb becomes significant
Cyclotron-produced radionuclides for medical use

Most common radionuclides for medical use versus the proton energy required for their production

Four “reference” energy ranges

<table>
<thead>
<tr>
<th>Proton energy (MeV)</th>
<th>Radionuclide easily produced</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 10</td>
<td>$^{18}$F, $^{15}$O</td>
</tr>
<tr>
<td>11 – 16</td>
<td>$^{11}$C, $^{18}$F, $^{13}$N, $^{15}$O, $^{22}$Na, $^{48}$V</td>
</tr>
<tr>
<td>17 – 30</td>
<td>$^{124}$I, $^{123}$I, $^{67}$Ga, $^{111}$In, $^{11}$C, $^{18}$F, $^{13}$N, $^{15}$O, $^{22}$Na, $^{48}$V, $^{201}$Tl</td>
</tr>
<tr>
<td>$\geq$ 30</td>
<td>$^{124}$I, $^{123}$I, $^{67}$Ga, $^{111}$In, $^{11}$C, $^{18}$F, $^{13}$N, $^{15}$O, $^{82}$Sr, $^{68}$Ge, $^{22}$Na, $^{48}$V</td>
</tr>
</tbody>
</table>

Radionuclides for therapy

- High LET decay products (Auger electrons, beta particles or alpha particles)
- Radionuclide linked to a biologically active molecule that can be directed to a tumour site
- Beta emitting radionuclides are neutron rich → they are in general produced in reactors, but some interesting ones are better produced by accelerators

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Decay mode</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br-77</td>
<td>2.4 d</td>
<td>Auger electrons</td>
<td>$^{75}\text{As}(\alpha, 2n)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$^{77}\text{Se}(p, n)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$^{78}\text{Se}(p, 2n)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$^{79,81}\text{Br}(p, xn)^{77}\text{Kr}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nat $^{103}\text{Mo}(p, \text{spall.})$</td>
</tr>
<tr>
<td>Pd-103</td>
<td>17.5 d</td>
<td>Auger electrons</td>
<td>$^{103}\text{Rh}(p, n)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nat $^{107}\text{Ag}(p, xn)$</td>
</tr>
<tr>
<td>Re-186</td>
<td>90.6 h</td>
<td>$\beta^-$</td>
<td>$^{186}\text{W}(p, n)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$^{186}\text{W}(d, 2n)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$^{197}\text{Au}(p, \text{spall.})$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nat $^{197}\text{Ag}(p, \text{spall.})$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nat $^{197}\text{Ir}(p, \text{spall.})$</td>
</tr>
<tr>
<td>At-211</td>
<td>7.2 h</td>
<td>$\alpha$</td>
<td>$^{209}\text{Bi}(\alpha, 2n)$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$^{209}\text{Bi}(^7\text{Li}, 5n)^{211}\text{Rn}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$^{232}\text{Th}(p, \text{spall.})^{211}\text{Rn}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$&gt;200$</td>
</tr>
<tr>
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<td>$&gt;200$</td>
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<tr>
<td></td>
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<td>$&gt;200$</td>
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</tbody>
</table>
99Mo/99mTc radionuclide generator

Half-life $^{99}$Mo = 67 hours
Half-life $^{99m}$Tc = 6 hours

Transient equilibrium

- $^{99m}$Tc labels hundreds of different molecular probes: more than 30 million medical protocols/year = 80% of all diagnostics procedures
- World requirement of $^{99}$Mo: Europe represents approximately 22% of the total market, North America 52%, Asia / Pacific 20%, and other world regions 6%
- The worldwide supply chain of $^{99}$Mo is essentially based on the activity of five research reactors
Accelerator-production of $^{99}$Mo

Two alternative paths for the production of $^{99}$Mo by accelerators

- Electron accelerator $\rightarrow$ Photo-fission
- Proton accelerator $\rightarrow$ Adiabatic Resonance Crossing (ARC)
Nuclear processes for producing $^{99}$Mo

- **Neutron-fission of U-235** (present technique used in nuclear reactors)
  - $^{235}$U → Mo-99 + Sn-13x + ...

- **Neutron-capture process (ARC method)**
  - Mo-98 → Mo-99

- **Photo-neutron process**
  - Mo-100 → Mo-99 + ...

- **Photo-fission of U-238** (technique proposed by TRIUMF)
  - $^{238}$U → Mo-99 + Sn-13x + ...

From “Making Medical Isotopes, Report of the Task Force on Alternatives for Medical-Isotope Production, TRIUMF, Canada (2008)”
Linac conceptual design

- BNL-based design, 50 MeV, 100 mA = 5 MW beam power
- Superconducting RF accelerating structures operating at 704 MHz
- Single cryo-module housing five 5-cell cavities, each providing an energy gain of approximately 10 MeV
- Estimated cost 50 – 60 M Canadian $
- Construction timescale 3-4 years

From “Making Medical Isotopes, Report of the Task Force on Alternatives for Medical-Isotope Production, TRIUMF, Canada (2008)”

$I_0$ = 100 mA, 704 MHz
Adiabatic Resonance Crossing (ARC)

1. Lead has the **lowest capture cross-section** for non thermal neutrons “transparent” to high-energy neutrons being moderated into it
2. Because lead is a heavy element, high-energy neutrons loose energy in very **small steps**
3. At each collision neutrons loose a constant fraction of energy in small steps **neutrons progressively “scan”** the whole energy interval down to thermal energies, **“seeking”** the large values of the capture cross-section of the sample to be captured

Courtesy S. Buono, AAA
**Accelerator-driven neutron activator**

- Fast neutron flux generated in a **Be target** by protons
- Neutrons are down-scattered with low parasitic capture in a **lead/graphite** assembly surrounding the Be target (the C reflector ensuring a fast thermalisation)
- Material to be activated is located in **irradiation channels** where the neutron flux is optimized for the capture reaction of interest
- Activation yields measured for Au, Al, Mo, Ho and Re foils

**Test at the JRC Ispra**


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M. Silari – Medical Applications of Particle Accelerators
University of Freiburg, 25.04.2012
Industrial production of $^{99}$Mo by ARC

- A high-power proton accelerator (1 mA at 1 GeV = 1 MW beam power):
  - Linac (ESS in Lund)
  - Cyclotron (PSI)
  - FFAG (KEK)

  capable of providing a flux of neutrons equivalent to a research reactor but with the “quality” suited to enhance the ARC effect and therefore the production of $^{99}$Mo from Natural Enriched $^{98}$Mo

- One accelerator could cover 100% of the current world demand of $^{99}$Mo (not currently possible with reactors)
“Conventional” radiation therapy
Availability of radiation therapy worldwide

Number of radiation therapy machines per million people

Source: DIRAC/IAEA
Medical electron linacs

Varian Clinac 1800

- Energy: 6 - 25 MeV
- Dual $e^-/\gamma$ beams

$e^- + \text{target} \rightarrow \text{X-rays}$

Multi-leaf collimator
Intra-Operative Radiation Therapy (IORT)

- Small electron linac
- Energy 6 – 12 MeV
- Treatment with electrons only
- Single irradiation
- Three models of linac produced by three manufacturers
CyberKnife Robotic Surgery System

6 MV Linac mounted on a robotic arm

- No flattening filter
- Uses circular cones of diameter 0.5 to 6 cm
- Non-Isocentric
- Average dose delivered per session is 12.5 Gy
- 6 sessions/day
- Dose rate @ 80 cm = 400 cGy/min

http://www.accuray.com/Products/Cyberknife/index.aspx
Yet X-rays have a comparatively poor energy deposition as compared to protons and carbon ions.
Helical tomotherapy

• Integrated CT guidance
  • Integrated CT scanner allowing efficient 3D CT imaging for ensuring the accuracy of treatment
• A binary multi-leaf collimator (MLC) for beam shaping and modulation
• A ring gantry design enabling TomoHelical delivery
  • As the ring gantry rotates in simultaneous motion to the couch, helical fan-beam IMRT is continuously delivered from all angles around the patient
• Very large volumes can be treated in a single set-up
Hadron-therapy
Hadrontherapy: n, p and C-ion beams

- Carbon ion = 6 protons + 6 neutrons
- Hadrons are made of quarks
- Proton or neutron
- Quark “u” or “d”
Proton radiation therapy
Radiobiological effectiveness (RBE)

\[ \text{RBE} = \frac{D_{\text{x-ray}}}{D_{\text{particle}}} \]
A NEW TOOL FOR CONTROLLING CANCER

The Loma Linda University Medical Center Proton Treatment Center is the first in the world to offer proton therapy, designed to treat cancerous tumors without harming surrounding healthy tissue. The center cost $10 million, took four years to design and build, and contains the world’s smallest synchrotron built by Fermi National Accelerator Laboratory. It is as large as some hospitals, can serve up to 180 patients in a 10-hour day, and is a model for worldwide training and research.

THE GANTRY
Three gantries resembling giant fans wheels can rotate around the patient and direct the proton beam to a precise point. Each gantry weighs about 30 tons and stands three stories tall. The 35-foot diameter gantries support the bending and focusing magnets to direct the beam, and have counterweights for extra radiation shielding.

THE INJECTOR
Protons are stripped out of the nuclei of hydrogen atoms and sent to the acclerator.

SYNCHROTRON (ACCELERATOR)
The synchrotron is a ring of magnets, about 50 feet in diameter, through which protons circulate in a vacuum tube. As the magnetic field in the ring is increased, the energy of the protons is also increased. When the magnetic field reaches the value corresponding to a particular beam energy, the field is held constant while protons are slowly extracted from the ring. The synchrotron accelerates protons to a maximum energy (200 million electron volts) in one-quarter second and to maximum energy (250 million electron volts) in one-half second.

WHAT THE PATIENT SEES
The patient rests on a couch or sits in a chair, as appropriate for treatment. Alignment and verification of the patient to the beam, controlled from a room just outside the treatment room, will take most of the time. Actual beam time takes less than a minute. Most patients will be able to return to work or other activities immediately after the procedure.

THE STATIONARY BEAM
The stationary beam has two branches, one for sterilizing eye tumors and the other for central nervous system tumors.

HOW A PROTON BEAM WORKS
The beam strikes the body at a low absorption rate and increases in intensity at specific points, called the isodose peaks. A series of peaks are focused on the tumor, giving the highest concentration of radiation, killing the cells of the tumor. No only is the dose of radiation to normal tissue sharply reduced, compared to conventional radiation therapy, but the energy of the proton beam completely dissipates within the tumor, causing no damage to normal tissues beyond the tumor.
Loma Linda University Medical Center (LLUMC)

M. Silari – Medical Applications of Particle Accelerators University of Freiburg, 25.04.2012
Cyclotrons and synchrotrons for PT

IBA

Accel-Varian

Hitachi

Loma Linda (built by FNAL)
Proton versus carbon-ion synchrotrons

G. Coutrakon, Accelerators for Heavy-charged-particle Radiation Therapy, *Technology in Cancer Research & Treatment, Volume 6, Number 4 Supplement, August 2007*
A PT facility is not just the accelerator...

A gantry is a massive structure that allows directing the beam to the tumour from any direction. It carries:
- the final section of the beam line
- the beam spreading ‘nozzle’
- the proton ‘snout’ which carries the aperture and range compensator

What it looks like to the patient:
- gantry room at the Midwest Proton Radiotherapy Institute (MPRI)
- (modified IBA gantry)

Adapted from B. Gottschalk
A PT facility is not just the accelerator...

Passive (double scattering) versus active (scanning) beam delivery

A PT facility is not just the accelerator...

Passive (double scattering) versus active (scanning) beam delivery

Hadron-therapy in Europe

O in operation
◊ in construction
Δ planned

Yellow = p only
Orange = p and C

FIGURE 1. Map of Europe showing the present status of the ion beam therapy. The status of different projects is given by the symbols: in operation O; under construction ◊; planned Δ. The type of the facilities is indicated by the colors: yellow – proton only; orange – Carbon and protons.

Heavy Ion Therapy Unit at the University of Heidelberg clinics

The HIT heavy ion gantry, weight about 600 tons

Courtesy HIT
National Centre for Oncological Hadrontherapy (CNAO) in Pavia

Courtesy S. Rossi, CNAO
PROSCAN at PSI, Switzerland

ACCEL
SC cyclotron
250 MeV protons


M. Silari – Medical Applications of Particle Accelerators    University of Freiburg, 25.04.2012
Hadron-therapy in Japan

C: carbon ions, p: protons
- in operation
- under construction

Courtesy NIRS
K. Noda et al., Recent progress on HIMAC for carbon therapy, Proc. of PAC09

The gantry “only” weighs 350 t
New concepts
IBA 400 MeV/u C-ion cyclotron

“Archade” (at Ganil in Caen, France) is based on the new IBA 400 MeV/u superconducting cyclotron

- Maximum energy: 400 MeV/u, adjustable externally by ESS
- Superconducting magnet. Hill field 4.5 T
- Cooling by helium loop, with 4 external recondensers

Courtesy Y. Jongen, IBA
The energy is adjusted in 2 ms in the full range by changing the power pulses sent to the 16-22 accelerating modules. The charge in the next spot is adjusted every 2 ms with the computer controlled source. Courtesy U. Amaldi, TERA.
Mevion Medical Systems (formerly Still River)

Synchrocyclotron @ 10 Tesla
Proton energy: 250 MeV
Ion source tested up to 1,000 nA
Cooling is through cryo-compressors (NO liquid Helium)
Low maintenance requirements – quarterly only
Time structure: similar to linear accelerator with gating and scanning capabilities

Weight ≈ 20 tons

Courtesy L. Bouchet
Mevion Medical Systems (formerly Still River)

A novel concept in PT

Synchrocyclotron

Courtesy L. Bouchet
Multi-room versus single-room facilities

Advantages of single-room facility:
- Modularity
- Reliability / back-up
- PT treatment available at more hospitals
- (Hopefully) cost

Courtesy L. Bouchet, Still River Systems
FFAG accelerator for protons and light ions

**RACCAM** (Recherche en ACCélérateurs et Applications Médicales), Project leader F. Méot, CNRS

- **FFAG**: Fixed Field Alternating Gradient
  - ✓ a ring of magnets like a synchrotron
  - BUT
  - ✓ fixed-field like in a cyclotron
- Non-pulsed power supplies, simple RF system, multi-particle, multi-port extraction
- Fast cycling
  - ✓ High dose rate
  - ✓ Slice-to-slice energy variation (100 ms)
  - ✓ 3D conformal therapy

Layout of the RACCAM FFAG assembly

More advanced (exotic) concepts

- The dielectric wall uses a high-voltage-gradient insulator to handle high electric-field stresses, enabling a proton therapy accelerator to operate without short being short-circuited.
- The DWA would enable protons to be accelerated to energies ≈ 100 - 200 MeV per meter without using bending magnets.

G. Caporaso et al., Compact accelerator concept for proton therapy, NIM B 261 (2007) 777–781

- Very energetic beams of ions produced from laser-irradiated thin metallic foils
- Fast electrons, accelerated inward, induce a charge-separation electrostatic field at the critical surface interface. This field will in turn result in acceleration of ions swept from the target front surface (electric field up to 30 % of the laser field \( \Rightarrow TV/m \))

M. Borghesi et al., Fast ion generation by high-intensity laser irradiation of solid targets and applications, Fusion science and technology 49, 412-439 (2006)
Future accelerators for therapy: requirements

A Proton Therapy beam has **strict requirements** to ensure optimal deposition of the prescribed dose, allow accurate dosimetry and verification of dose delivery, minimize the dose to areas outside the desired treatment volume, and assure patient safety from accidental overdoses.

**Issues to be considered** for any future hadron-therapy system based on a new concept:

- Mature (cyclotrons and synchrotrons) versus emerging technology
- Beam energy (energy selection system)
- Energy variability and monochromaticity (\(\Delta E/E << 1\))
- Beam intensity
- Lateral field definition
- Dose conformation to the target volume
- Dose accuracy and dosimetry
- Isocentric delivery
- Radiation protection and patient protection
- Cost