Structure of the course

1) Introduction
2) Interaction of particles with matter } **principles / tools**
3) Therapy with proton and ion beams
4) Sources for nuclear medicine
5) X- ray sources
6) Image quality
7) X-ray imaging
8) Computed tomography
9) Planar scintigraphy
10) Emission tomography
11) Magnetic Resonance Imaging
12) Multimodal systems

Items 4–5: **sources**

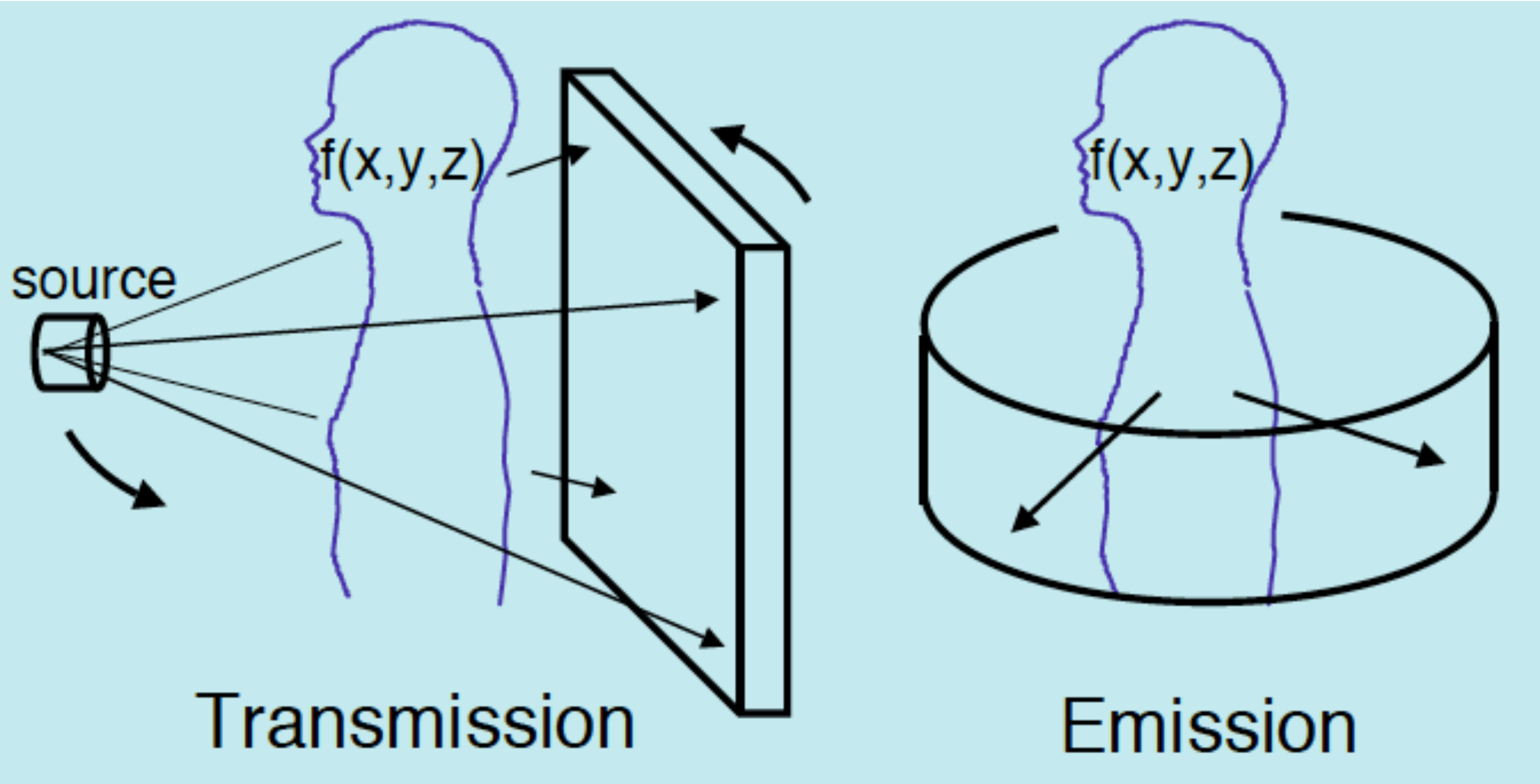
Item 6: **objective**

Items 7–12: **imaging modalities**

Items 4–12: **Medical imaging**

The course will not cover ultrasound and optical imaging

External versus internal radiation sources



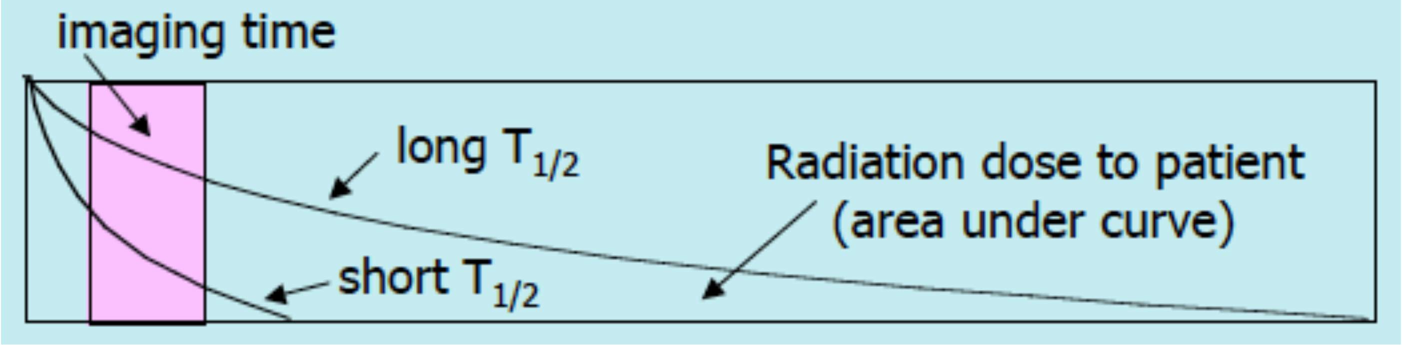
Internal radiation sources

- Inject the patient with a "source of radiation" ➔ define later

Problem:

Unlike an X-ray device, we cannot turn off the radiation after the image is taken.

Radiation decays exponentially (characterized by "half-time" $T_{½}$)



Solution: use short lived isotopes

Problem: short lived isotopes do not exist (obviously) in nature

Solution: we need to produce them ad hoc for the exam

Nuclear physics (recap)

Nuclide: unique combination of protons and neutrons in a nucleus

- mass number **A** = # nucleons
- atomic number **Z** = # protons = # electrons

- An element is denoted by $^{A}_{Z}X, \;\; i.e \;\; ^{12}_{6}C$

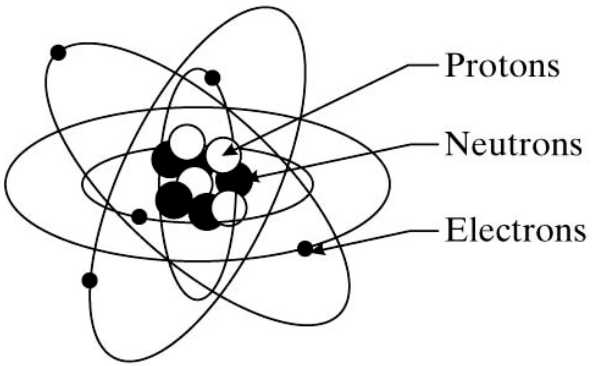
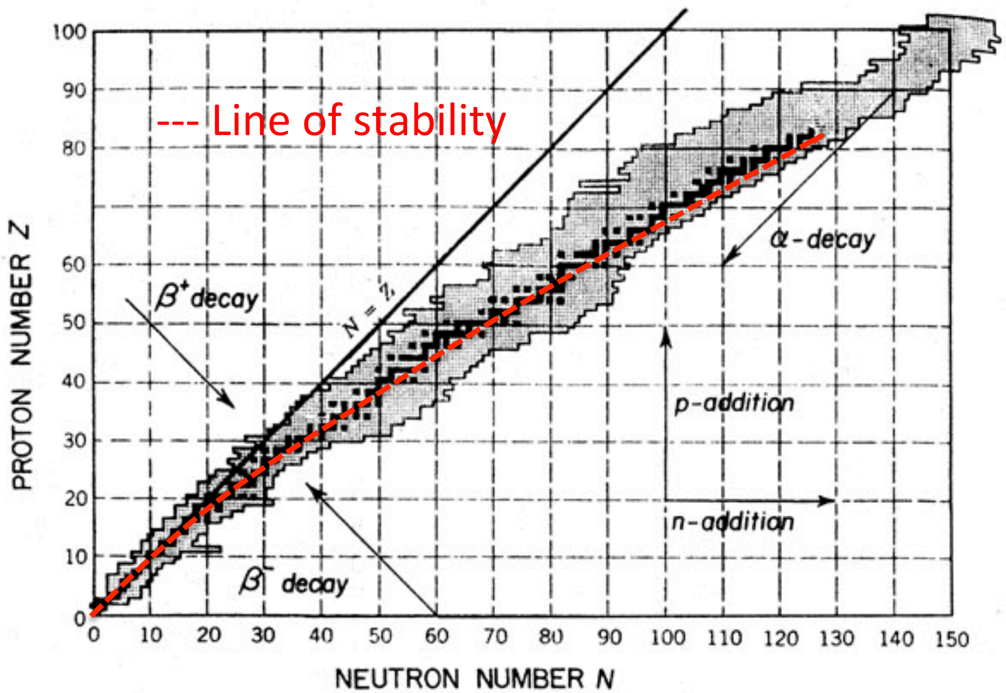


Figure 4.1



- Stable nuclides:
  - N ≈ Z (A ≈ 2Z) for small Z
  - N > Z for large Z
- Unstable nuclides (radionuclides, radioactive atoms)
  - Likely to undergo radioactive decay, which gives off energy and results in a more stable nucleus

Binding energy

Mass defect in an atom: $$\Delta M = \left(\sum_Z M_p + \sum_N M_n + \sum_Z M_e \right) - M_{atom}$$

ex. ${}_{6}^{12}C$: ΔM = *constituent sum* - M_{atom}=

= 6x1.007276 + 6x1.008665 + 6x0.000548 u - 12 = 0.098934 u

Binding energy:

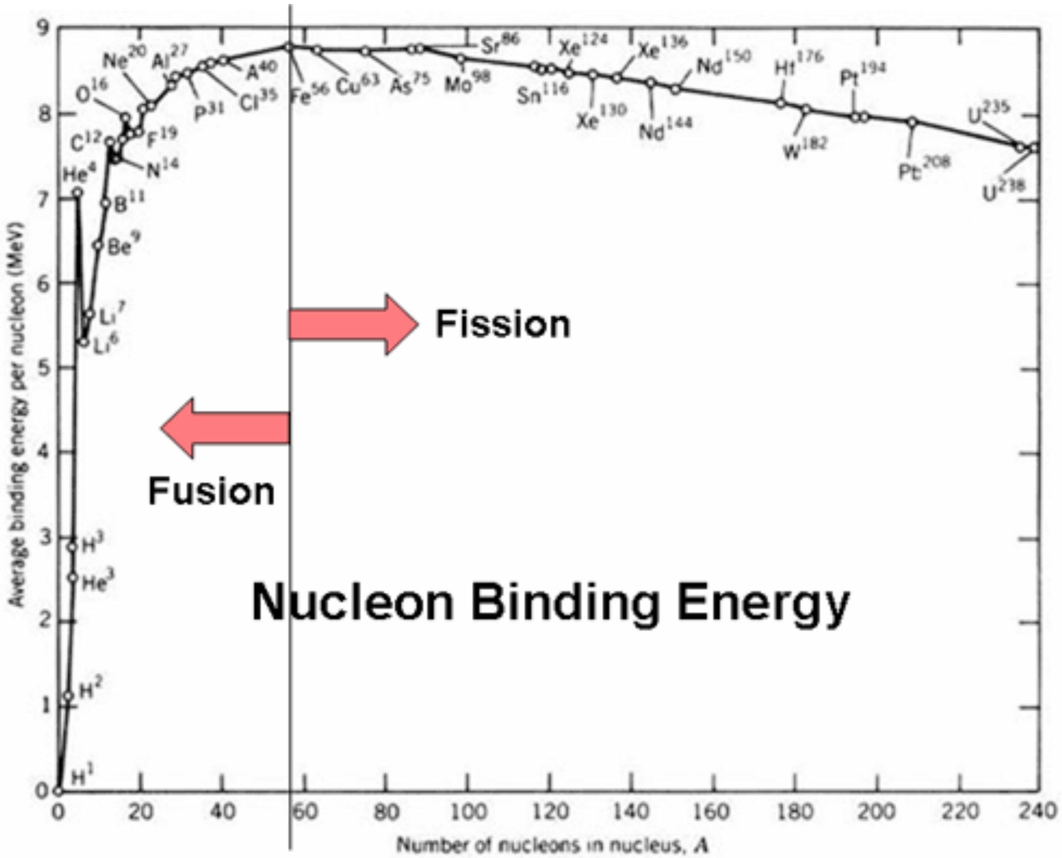
$E = \Delta M c^2$

More commonly quoted E/A

ex. ${}_{6}^{12}C$:

E/A = 0.098934 x 931 /12 MeV/A

= 7.67 MeV/nucleon



Radioactive decay

- The greater the binding energy/nucleon the more stable is the atom.
- Atoms in a state away from the line of stability can rearrange their nuclei to gain more stability.
- The daughter products of a radioactive decay have higher binding energy/nucleon = grater mass defect.
- In a radioactive decay energy is released from the atom.
- Four types of radioactive decays:
  - Alpha decay (2 protons, 2 neutrons)
  - Beta- decay (electron emission)
  - Beta+ decay (positron emission)
  - Gamma decay (emission of a gamma ray*)

Beta+ decay

Within a nucleus:

$$p \rightarrow n\ e^{+}\nu$$

$$^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y$$

Mass number A does not change,

proton number Z reduces by one unit

Application ➔ positron emission tomography (PET)

Gamma decay

- An unstable nucleus changes from a higher energy state to a lower energy state through the emission of electromagnetic radiation (called gamma rays).
- The daughter and parent atoms are isomers (same A, same Z).
- Gamma-rays and X-rays used in medical applications are both photons in the energy range 20-600 keV, but generated by different processes:
  - X-ray are produced by energetic electron interactions
  - Gamma-ray through isometric transition in nucleus

- Application → Single photon emission computed tomography (SPECT)

Radioactivity

Radioactivity: A = # of radioactive decays per second

1Bq = 1 dps

1 Ci = 3.7×10^{10} Bq

Radioactivity in nuclear medicine is in the range of 100 mCi or 100 MBq.

- Naturally occurring radioisotopes discovered 1896 by Becquerel
- First artificial radioisotopes produced by the Curie 1934

The intensity of radiation incident on a detector at range r from a radioactive source is:

$$I = \frac{AE}{4\pi r^2}$$

A: radioactivity of the material

E: energy of each photon

Ex. Intensity of 100mCi of Technetium-99m at 20 cm distance? (E_γ=140 keV)

$I = 0.37 \times 10^{10}$ Bq x 140 keV / $4\pi\,(0.2)m^2 = 0.1 \times 10^{10}$ keV/s/m^2 ~ 10^3 GeV/s/m^2

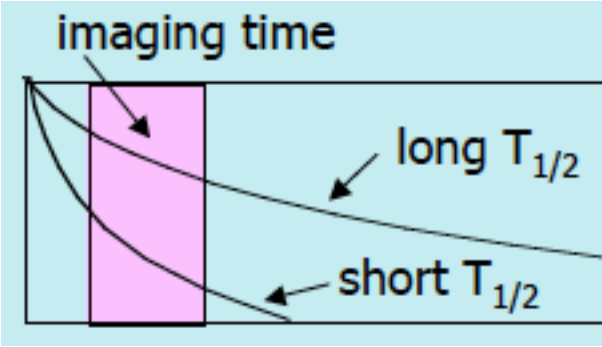
Radioactive Decay Law

N(t): the number of radioactive atoms at a given time

A(t): is proportional to N(t)

$$A = -\frac{dN}{dt} = \lambda N$$

λ : decay constant



Radioactivity always remains

Integrating one obtains:

$$N(t) = N_0 e^{-\lambda t}$$

$$A(t) = A_0 e^{-\lambda t} = \lambda N_0 e^{-\lambda t}$$

Half-life is the time it takes for the radioactivity to decrease by ½ .

$$\frac{A_{T_{1/2}}}{A_0} = \frac{1}{2} = e^{-\lambda T_{1/2}} \quad \rightarrow \quad T_{1/2} = \frac{0.693}{\lambda}$$

half-life

The number of photons generated (= # of disintegrations) during time T is:

$$\Delta N = \int_0^T A(t)\,dt = \int_0^T \lambda N_0 e^{-\lambda t}\,dt = N_0(1 - e^{-\lambda t})$$

Statistics of decay

- Radioactive decay is a random process so the exponential decay law only gives the average expected number of atoms (or the average expected radioactivity) at a certain time t.

The number of disintegrated atoms over a short time $\Delta t \ll T_{1/2}$ after time t=0 with N_0 atoms follows Poisson distribution:

$$\Pr\{\Delta N = k\} = \frac{a^k e^{-a}}{k!}; \quad a = \lambda N_0 \Delta t;$$ valid for a very short Δt

λN_0 is called the Poisson rate.

Example

A patient study needs to be completed in 10 min. and requires a statistics of 3.5 million photon counts to achieve the desired image quality.

Q: 6 K photons are detected in the first 1 sec. What is the half-life of the radionuclide for a successful study?

A: in 1 sec the number of detected photons (100% detection efficiency) is:

$$\Delta N = \int_0^1 \lambda N_0 e^{-\lambda t}\, dt = N_0(1 - e^{-\lambda}) = 6K$$

To get 3.5 millions counts in 10 min (600 sec)

$$\Delta N = \int_0^{600} \lambda N_0 e^{-\lambda t}\, dt = N_0(1 - e^{-600\lambda}) = 3500K$$

$$\frac{1 - e^{-600\lambda}}{1 - e^{-\lambda}} = \frac{3500}{6}$$

$$\rightarrow \lambda = 9.45 \times 10^{-5} s^{-1}$$

The minimal half-life needed is:

$$T_{1/2} = \frac{0.693}{\lambda} = 7333s \sim 2h$$

Radionuclides for medicine

- About 1500 known radionuclides, about 200 can be purchased
- About 12 suitable for nuclear medicine:
  - Clean γ emitters = no α or β emission / or β emitters
  - Energy high enough to have minimum attenuation in the body
  - Energy low enough to interact in the detector and be detected
    - ➔ typical accepted energy range $50 < E_\gamma < 511$ keV.
  - Acceptable half-life, order of minutes (long enough to prepare and perform the exam, short enough that exam can be short to minimize patient motion effects.
- Mono-energetic: Energy sensitive detectors can discriminate the primary photons from scattered ones.
- Generation of radiotracers: on-site generators, cyclotrons, radio pharmacy

Examples of decay processes

α decay

$$^{238}_{92}\mathrm{U} \rightarrow {}^{234}_{90}\mathrm{Th} + {}^{4}_{2}\mathrm{He}, \quad T_{1/2} \approx 4.5\times 10^{9}\,\mathrm{y}$$

β^{-} decay

$$^{234}_{90}\mathrm{Th} \rightarrow {}^{234}_{91}\mathrm{Pa} + e^{-} + \bar{\nu}_{e}, \quad T_{1/2} = 24.1\,\mathrm{d}$$

$$^{1}_{0}\mathrm{n} \rightarrow {}^{1}_{1}\mathrm{H} + e^{-} + \bar{\nu}_{e}, \quad T_{1/2} = 10.6\,\mathrm{m}$$

β^{+} decay

$$^{11}_{6}\mathrm{C} \rightarrow {}^{11}_{5}\mathrm{B} + e^{+} + \nu_{e}, \quad T_{1/2} = 20.38\,\mathrm{m}$$

$$^{10}_{6}\mathrm{C} \rightarrow {}^{10}_{5}\mathrm{B} + e^{+} + \nu_{e}, \quad T_{1/2} = 19.2\,\mathrm{s}$$

$$^{15}_{8}\mathrm{O} \rightarrow {}^{15}_{7}\mathrm{N} + e^{+} + \nu_{e}, \quad T_{1/2} = 122\,\mathrm{s}$$

Most of these naturally occurring processes are not useful for medical imaging applications, with too long half-time, too high energy.

They can be used as radio-therapeutic agents, if they can be targeted to tumors, to destroy diseased tissue and stop the cancer from proliferating.

How to produce (short-lived) isotopes

Via nuclear bombardment:

Hit nucleus of stable atoms with sub-nuclear particles: neutrons, protons, alpha particles etc.

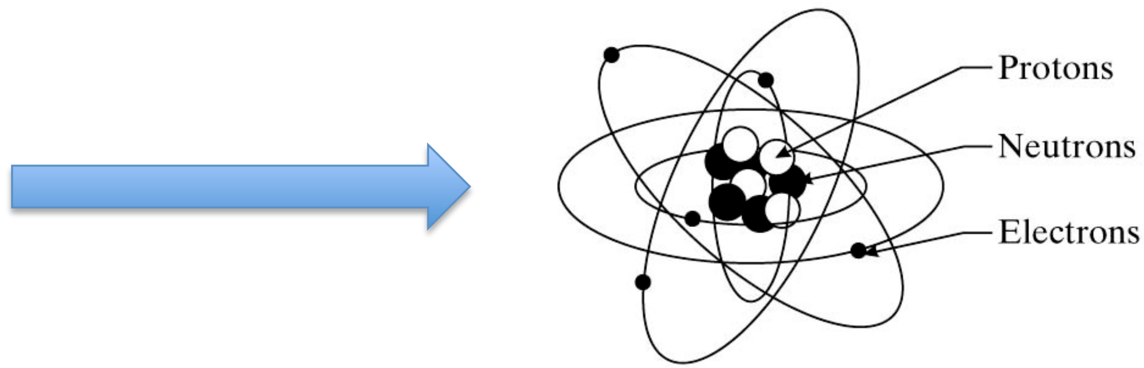


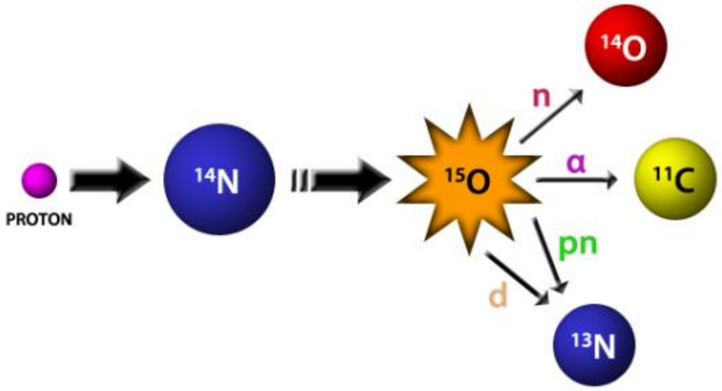
Figure 4.1

1. Inserting target in a nuclear reactor ➔ produce longer-lived isotopes extract and ship them ➔ Longer-lived isotopes decay to a short-lived ones (portable 'generator')

2. Using a charged-particle accelerator (cyclotron) – needed locally for short-lived isotopes ($T_{1/2}$ ~ 1 to 100 min).

Radionuclides from cyclotron

- Produced by bombarding the target nucleus with charged particles (e.g. protons) of defined energy.
- Remember: binding energy / nucleon in the nucleus is ~8 MeV.
- If $E_{projectile} > E_{binding}$ particles will be ejected from the target nucleus.
- By carefully selecting the target nucleus, the bombarding particle and its energy, it is possible to produce a specific radionuclide.



Types of accelerators routinely used for radioisotope production

Classification	Characteristics	Energy [MeV]	Major radionuclides produced
Level I	single particle* (d)	< 4	^{15}O
Level II	single particle (p)	≤ 11	^{11}C, ^{13}N, ^{15}O, ^{18}F
Level III	single or two particle (p, d)	≤ 20	^{11}C, ^{13}N, ^{15}O, ^{18}F (^{123}I, ^{67}Ga, ^{111}In)
Level IV	single or multiple particle ($p, d, {}^3He, {}^4He$)	≤ 40	^{38}K, ^{73}Se, $^{75-77}Br$, ^{123}I, ^{81}Rb (^{81}Kr), ^{67}Ga, ^{111}In, ^{201}Tl, ^{22}Na, ^{57}Co
Level V	single or multiple particle ($p, d, {}^3He, {}^4He$)	≤ 100	^{28}Mg, ^{72}Se (^{72}As), ^{82}Sr (^{82}Rb), ^{117m}Sn, ^{123}I
Level VI	single particle (p)	≥ 200	^{26}Al, ^{32}Si, ^{44}Ti, ^{67}Cu, ^{68}Ge (^{68}Ga), ^{82}Sr (^{82}Rb), ^{109}Cd, ^{95m}Tc, etc.

Cyclotron

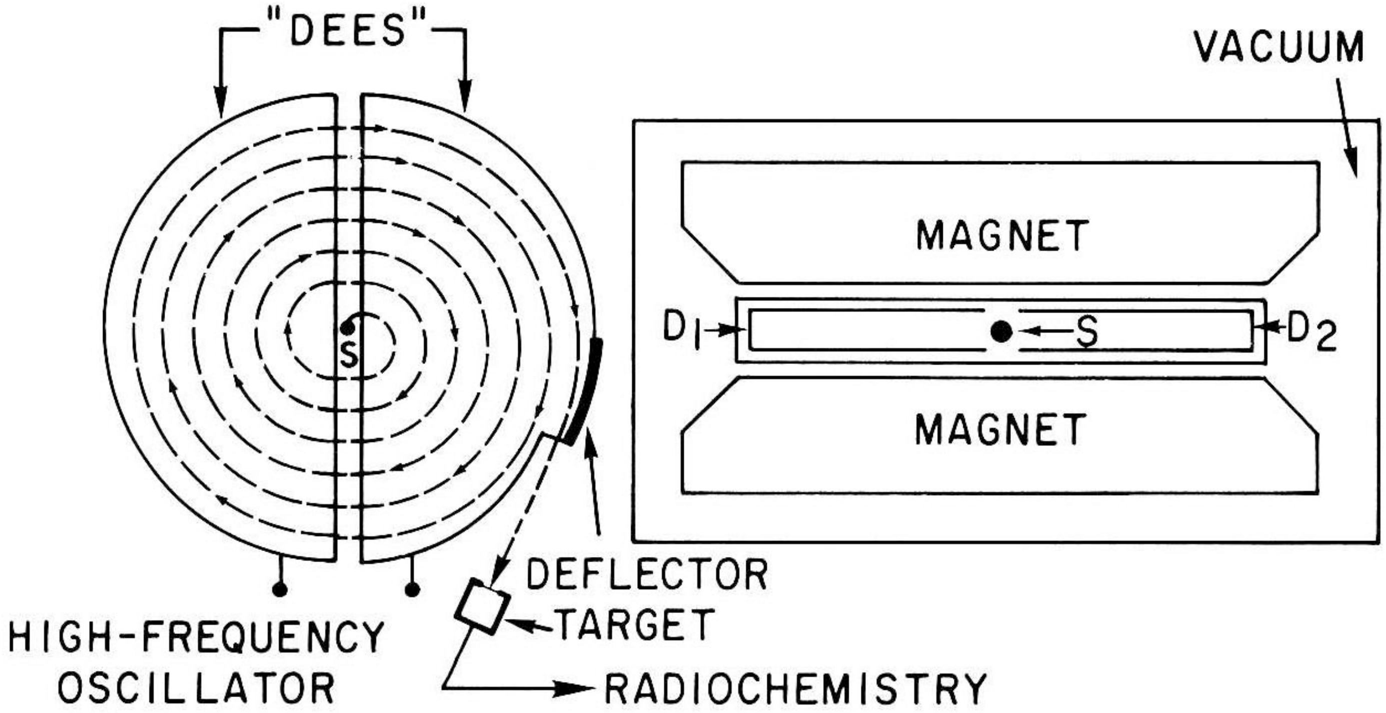
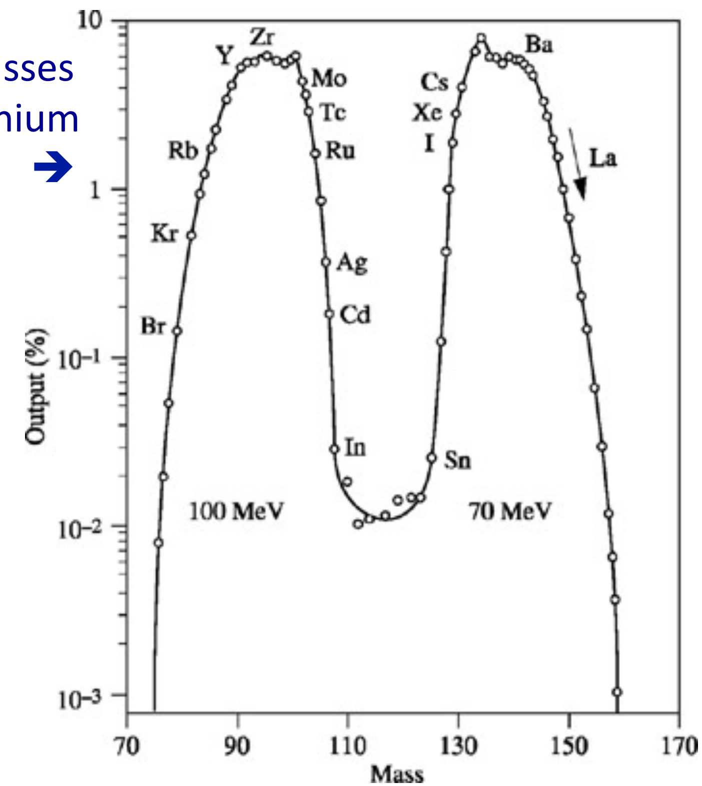


Fig. 7-2. Schematic representation of a cyclotron; top (left) and side (right) views. D_1 and D_2 are the "dees" to which the accelerating voltage is applied by a high-frequency oscillator. Target line may feed directly to a radiochemistry area.

Radionuclides from reactor

- The fission process is a source of a number of widely used radionuclides (e.g. ^{90}Sr, ^{99}Mo, ^{131}I and ^{133}Xe)
- They can be separated from uranium fuel cells or from targets of enriched ^{235}U placed in the reactor for radionuclide production directly.
- Highest efficiency for ^{99}Mo production ➔ most widely used in nucl. med.

Distribution of atomic masses of fission products of uranium ➔



Drawbacks:

- Nuclear waste
- Contamination with other isotopes
- Needs running reactors (!!)

Advantages:

- Passive mode production (if nuclear plants are running)

Radionuclide generators

A long-lived radionuclide ("parent") decays into a short-lived radionuclide ("daughter") of interest.

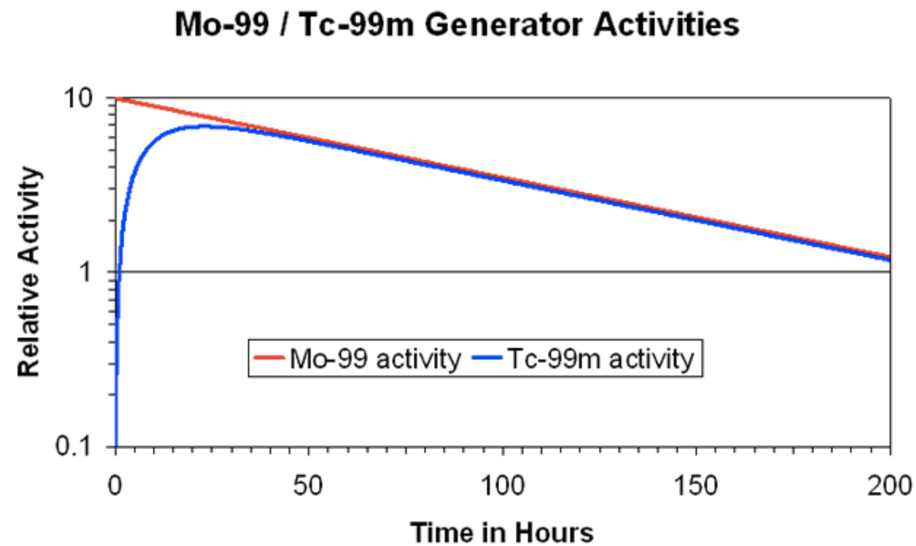
In "transient equilibrium generator" the parent radionuclide half-life is greater than the daughter's.

e.g. ^{99}Mo ($T_{½}$ = 66 h) → ^{99m}Tc ($T_{½}$ = 6 h)

the daughter will have different physical and chemical properties and can be eluted from the parent-daughter mixture.

Decay characteristics of ^{99m}Tc:

$$^{99m}Tc \xrightarrow{T_{1/2}=6\,\mathrm{h}} {}^{99}Tc + \gamma\,(140\,\mathrm{keV})$$



Over 80% of all nuclear medicine Procedures performed worldwide use ^{99m}Tc as the imaging radionuclide.

Specific tracers are produced to examine the brain, kidney, heart, bone, liver, lung, red blood cells, and thyroid (TcO_4)

Generator

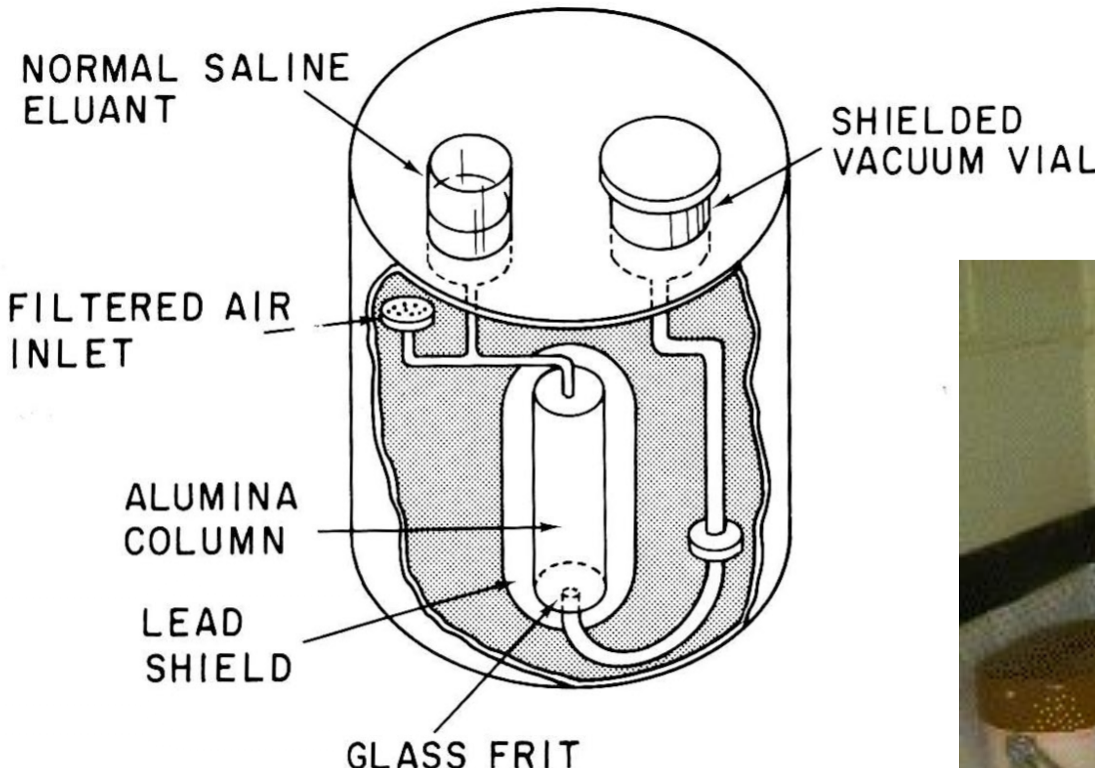


Fig. 7-5. Cross-sectional drawing of a ^{99}Mo-^{99m}Tc generator. Society of Nuclear Medicine and Thomas R. Gnau.)

Radiotracers

To be usable in medical imaging the radionuclides and the compounds to which they are attached must obey the three tracer principles:

- the tracer behaves or interacts with the system to be probed in a known, reproducible fashion,
- the tracer does not alter or perturb the system in any measurable fashion,
- the tracer concentration can be measured.

In order to be used for therapy the second principle must be broken (damage the unwanted tissues)

Radiotracers

- Radionuclide bound to pharmaceuticals specific to metabolic activities (cancer, myocardial perfusion, brain perfusion) are called radiotracers.

- The radiotracers that can be safely administered to humans are referred to as radiopharmaceuticals (radiochemical purity, sterile and free from micro-organisms that can cause fever)
- 95% of the radiopharmaceuticals are used for diagnostic purposes, the remainders are used in therapy.

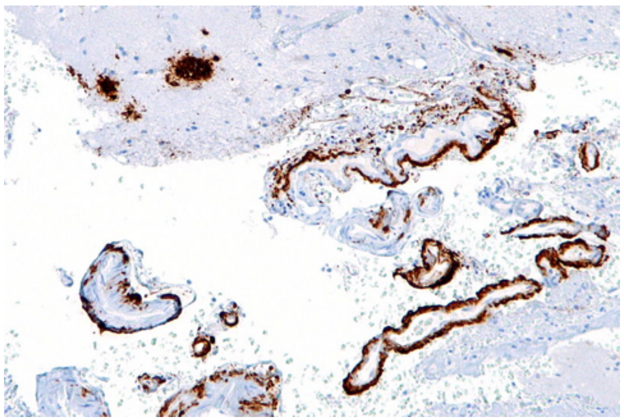
- A large number of radiotracers have been synthesized to probe metabolic turnover such as oxygen consumption, glucose utilization and amino acid synthesis ➔ biochemistry

Radiopharmaceuticals

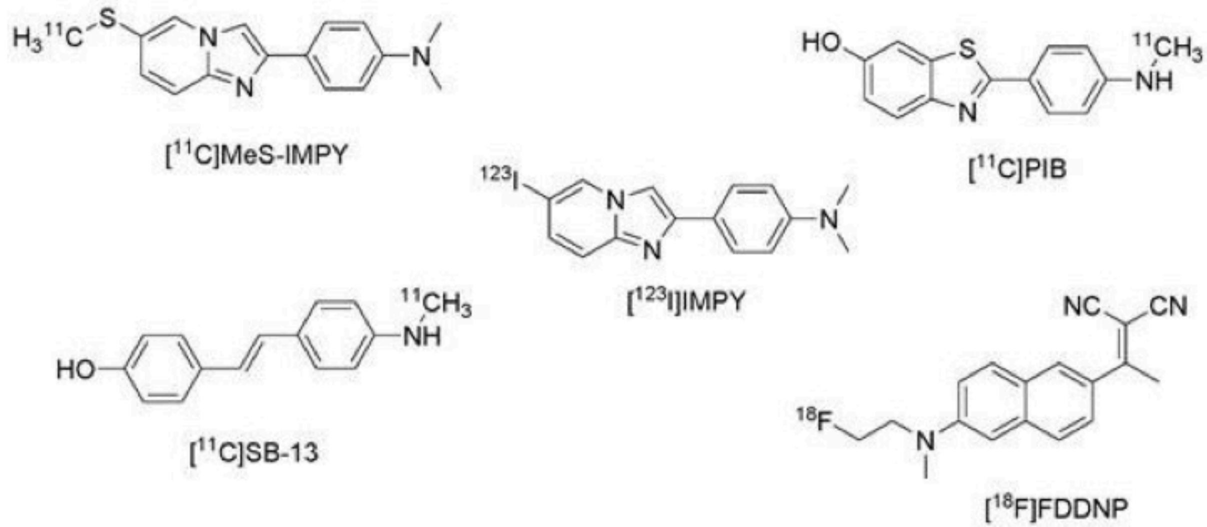
- Gamma emitter
  - ^{99m}Tc-Sestamibi (myocardial perfusion, cancer)
  - ^{99m}Tc-labeled hexamethyl-propyleneamine (brain perfusion)
- Positron emitters
  - ^{11}C, $T_{1/2} = 20$ min [^{12}C (p,pn) ^{11}C; ^{14}N (p,α) ^{11}C]:
    - many organic compounds (binding to nerve receptors, metabolic activity)
  - ^{13}N, $T_{1/2} = 10$ min [^{16}O (p,α) ^{13}N; ^{13}C (p,n) ^{13}N]:
    - NH_3 (blood flow, regional myocardial perf.)
  - ^{15}O, $T_{1/2} = 2.1$ min [^{15}N (p,n) ^{15}O; ^{14}N (d,n) ^{15}O]:
    - CO_2 (cerebral blood flow), O_2 (myoc. O_2 consumption), H_2O (myoc. O_2 consumption & blood perfusion)
  - ^{18}F, $T_{1/2} = 110$ min [^{18}O (p,n) ^{18}F; ^{20}Ne (d,α) ^{18}F]:
    - 2-deoxy-2-[^{18}F]-fluoroglucose (FDG, neurology, cardiology, oncology, metabolic activity)

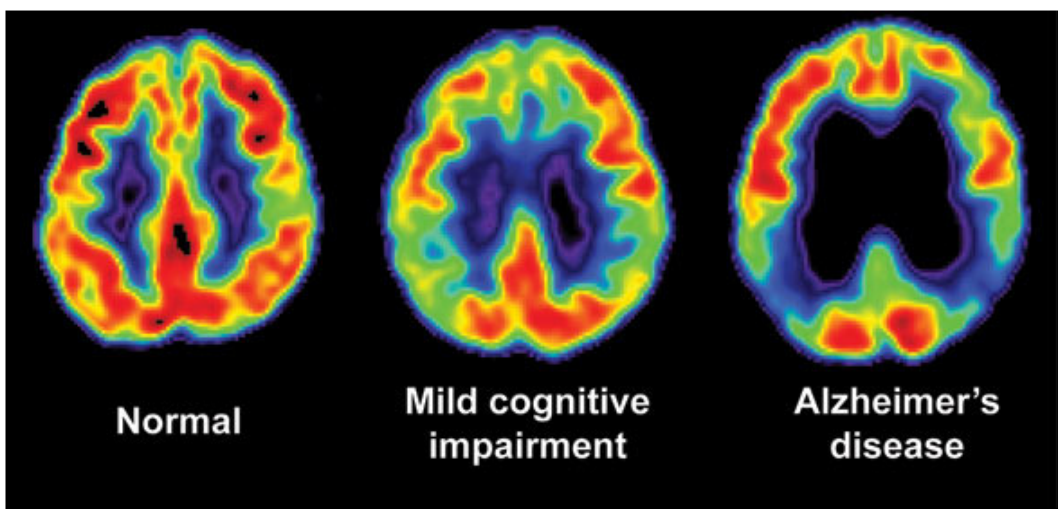
From H. Graber, Lecture Note, F05

PET radio-ligands for Imaging of ß-Amyloid in Human



amyloid beta peptide (brown) in senile plaques of the cerebral cortex (upper left of image)





Key points of this lecture

- Nuclear medicine relies on radiation (gamma rays) generated through radioactive decay

- Radioactive decay is the process when an unstable nuclide is changed to a more stable one

– Four modes of decay exist generating alpha particles, beta particles, positrons and gamma rays respectively

- Radioactivity follows an exponential decay law, characterized by the decay constant (λ) or the half-life ($T_{½}$)

- Desired properties for radio tracers
- Common radiotracers in nuclear medicine

Units for therapy

The gray measures the absorbed energy of radiation

$$1\ \mathrm{Gy} = 1\ \frac{\mathrm{J}}{\mathrm{kg}} = 1\ \frac{\mathrm{m}^2}{\mathrm{s}^2}$$

The biological effects vary by the type and energy of the radiation and the organism and tissues involved.

- A whole-body exposure to 5 or more gray of high-energy radiation at one time usually leads to death within 14 days.
- In radiation therapy, the amount of radiation varies depending on the type and stage of cancer being treated. For curative cases, the typical dose for a solid epithelial tumor ranges from 60 to 80 Gy, while lymphomas are treated with 20 to 40 Gy.
- The average radiation dose from an abdominal X-ray is 1.4 mGy, that from an abdominal CT scan is 8.0 mGy, that from a pelvic CT scan is 25 mGy, and that from a selective CT scan of the abdomen and the pelvis is 30 mGy.

Litterature

- Prince and Links, Medical Imaging Signals and Systems, Chap 7.

- "The uses of radiotracers in the life sciences" by Thomas J. Ruth (2008), online at stacks.iop.org/RoPP/72/016701

Table of nuclides:

- http://atom.kaeri.re.kr/ton/