Chapter 4: Radionuclide Production

Slide set of 101 slides based on the chapter authored by H. O. Lundqvist
of the IAEA publication (ISBN 978–92–0–143810–2):
Nuclear Medicine Physics:
A Handbook for Teachers and Students

Objective:

To familiarize the student with the fundamental concepts of radionuclide production.

IAEA
International Atomic Energy Agency

Slide set prepared in 2015 by R. Fraxedas (INEF, Havana, Cuba)

CHAPTER 4 TABLE OF CONTENTS

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1 THE ORIGIN OF DIFFERENT NUCLEI

The Origin of Matter

- All matter in the universe has its origin in an event called the “big bang”, a huge cosmic explosion.
- Since the planet Earth was formed, most of the atomic nuclei have undergone transformation to more stable (non-radioactive) combinations.
- However, some with very long half-lives remain: ^{40}K, ^{204}Pb, ^{232}Th and the naturally occurring isotopes of uranium.

4.1 THE ORIGIN OF DIFFERENT NUCLEI

Introduction

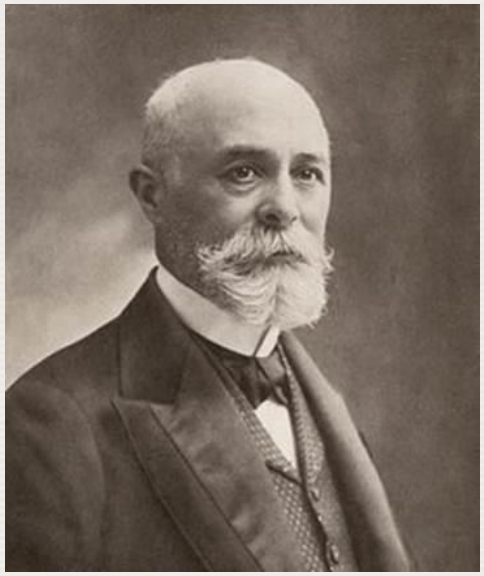
First steps in the history of radioactivity

- Discovery of spontaneous radioactivity.
- Separation of radioisotopes and elucidation of its properties.
- Demonstration of practical uses of the radioactive elements.

4.1 THE ORIGIN OF DIFFERENT NUCLEI

The Discovery of Natural or Spontaneous Radioactivity

- Henry Becquerel was born in Paris in 1852, into a family of scientists.
- This French physicist is considered one of pioneers in the history of radioactivity.
- He shared the Nobel prize of Physics in 1903 with Marie Skłodowska Curie and Pierre Curie, for the discovery of radioactivity.



Henri Becquerel (15 Dec 1852-25 Aug 1908)

4.1 THE ORIGIN OF DIFFERENT NUCLEI

The Isolation of Radioactive Isotopes

- Marie Sklodowska Curie (7 Nov 1867- 4 Jul 1934), born in Warsaw, Poland, conducted pioneering research on radioactivity, isolating the first radioisotopes.
- She was the discoverer of polonium and radium, and became the first woman to win a Nobel Prize, and the only person to win in multiple sciences (Physics and Chemistry).

Marie Sklodowska Curie (7 Nov 1867- 4 Jul 1934)

4.1 THE ORIGIN OF DIFFERENT NUCLEI

Radioactive tracers and metabolism

- Georg Hevesy was a Hungarian radiochemist, born in Budapest in 1885.
- He became a Nobel laureate, being recognized in 1943 for his key role in the development of radioactive tracers to study chemical processes such as in the metabolism of animals.
- He also co-discovered the element hafnium in 1922, with Dirk Coster.

Georg Karl von Hevesy (1 Aug 1885- 5 Jul 1966)

4.1 THE ORIGIN OF DIFFERENT NUCLEI

Uses of radioactivity in humans

- Hermann L. Blumgart and his coworker Otto C. Yens in 1925, with a modified cloud chamber detector, measured the arm-to-arm circulation time.
- Hermann Ludwig Blumgart (1895–1977) was the chair of the Department of Medicine at Beth Israel Hospital in Boston from 1928 to 1962.

Hermann L. Blumgart (1895-1977)

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.1 Induced radioactivity

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.1 Induced radioactivity

Discovery of artificial radioactivity

- Irène Joliot-Curie (12 September 1897 – 17 March 1956) was born in Paris, being the daughter of Maria and Pierre Curie.
- Jointly with her husband, Frederic Joliot, she was awarded the Nobel Prize for chemistry in 1935 for their discovery of artificial radioactivity.
- Irradiating stable isotopes with charged particles resulted into unstable isotopes, leading the way to the production of artificial radioactive materials.

Irene and Maria Curie

Irene Curie and Frédéric Joliot

Invention of the cyclotron

- Lawrence had built a cyclotron capable of accelerating deuterons up to about 3 MeV.
- He soon reported the production of ^{13}N with a half-life of 10 min.
- Thereafter, the cyclotron was used to produce several other biologically important radionuclides such as ^{11}C, ^{32}P and ^{22}Na.

Ernest Orlando Lawrence (8 Aug 1901- 27 Aug 1958)

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.1 Induced radioactivity

Nuclear chain reactions

- Fermi realized that the neutron was advantageous for radionuclide production and made a strong neutron source by sealing up ^{232}Ra gas with beryllium powder in a glass vial.
- The alpha particle emitted from ^{232}Ra caused a nuclear reaction in beryllium and a neutron was emitted $^{9}Be(\alpha, n)^{12}C$.
- In a few weeks he irradiated 60 elements and induced radioactivity in 40 of them.
- Years later Fermi also supervised the design and operation of the world's first artificial nuclear reactor (Chicago Pile-1)

Enrico Fermi (29 Sep 1901- 28 Nov 1954)

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.2 Nuclide chart and line of nuclear stability

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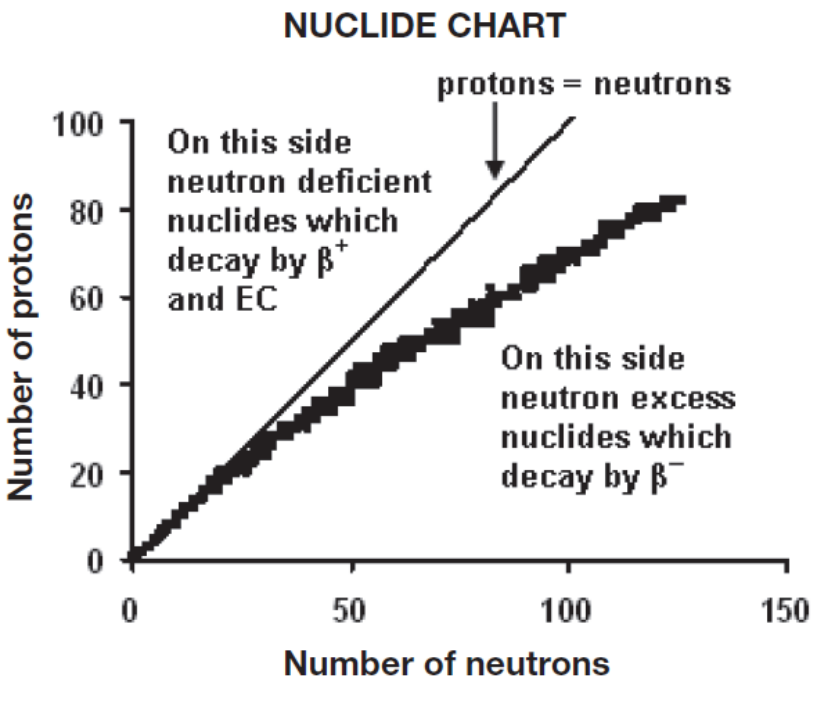
4.1.2 Nuclide chart and line of nuclear stability



- The nuclide chart consists of a plot with the number of neutrons in the nucleus on the x axis and the number of protons on the y axis.
- The line of stability divided the nuclides in neutron deficient and neutron excess nuclides, each decaying in a different way.

Classification of elements

- The periodic system was organized according to the number of protons (atom number) in the nucleus.
- In early 1900 the chemists had a good understanding of how to classify elements according to the periodic table.
- With the discovery of the radioactivity a conflict arose since elements with the same chemical behaviour could differ in physical properties.

Theory of isotopes

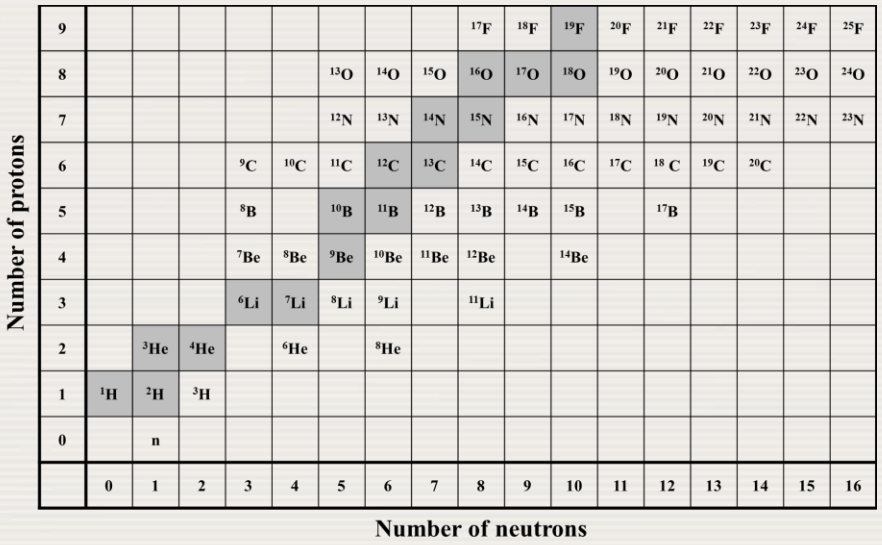
- To overcome the previous conflict, a new concept was developed.
- The concept of ‘isotopes’ or elements occupying the ‘same place’ in the periodic system was introduced by Soddy in 1913.
- A complete explanation had to await the discovery of the neutron by Chadwick in 1932.

Frederick Soddy (22 Sep 1877-22 Sep 1956)

James Chadwick (20 Oct 1891- 24 Jul 1974)

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.2 Nuclide chart and line of nuclear stability



Nuclide chart of light elements

Nuclide chart characteristics

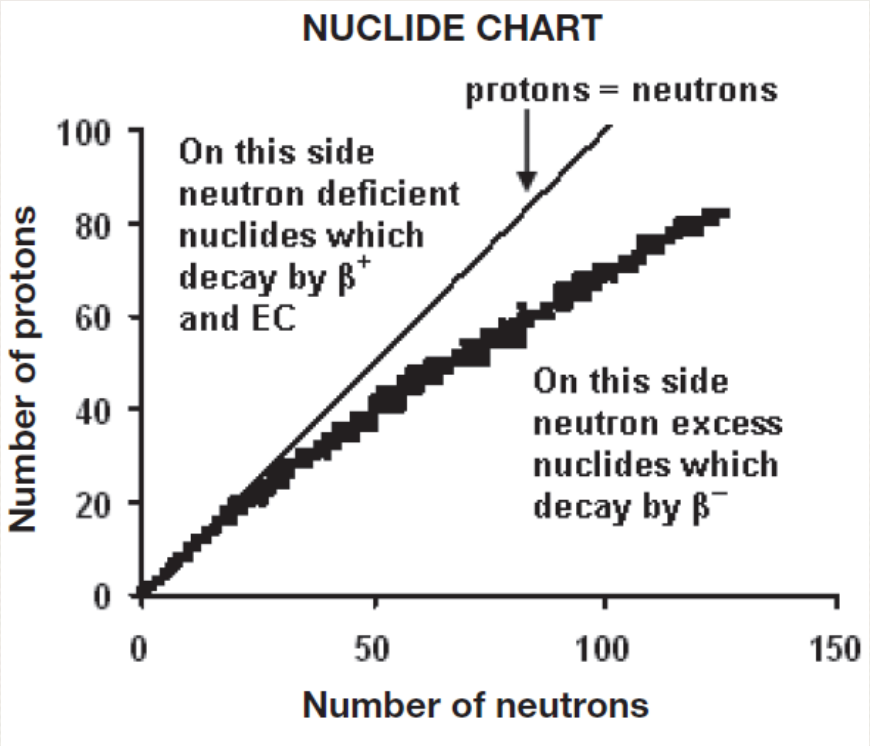
- The darkened fields of the nuclide chart represent stable elements.
- Nuclides to the left of the stable ones are deficient in neutrons and those to the right are rich in neutrons.

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.2 Nuclide chart and line of nuclear stability

Stability line

- Best stability is achieved when the number of protons and neutrons in the nucleus is about the same.
- For light elements, the stability line follows a straight line, for heavier elements there is a neutron excess.
- The neutron excess makes the Coulomb force decrease in heavy elements.



Nuclear stability

The stability of the nucleus is determined by competing forces. Two important ones are:

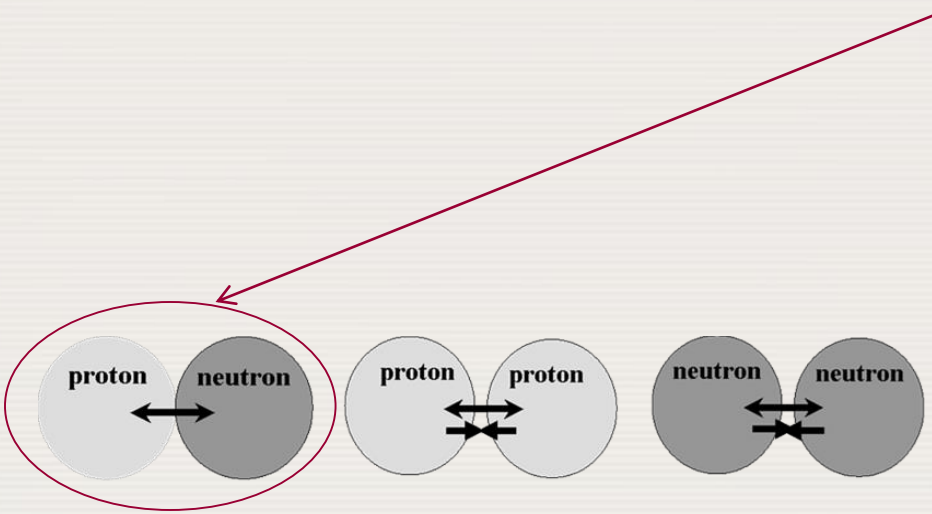
- the ‘strong force’ that binds the nucleons (protons and neutrons) together

  and

- the Coulomb force that repulses particles of like charge, e.g. protons

4.1 THE ORIGIN OF DIFFERENT NUCLEI

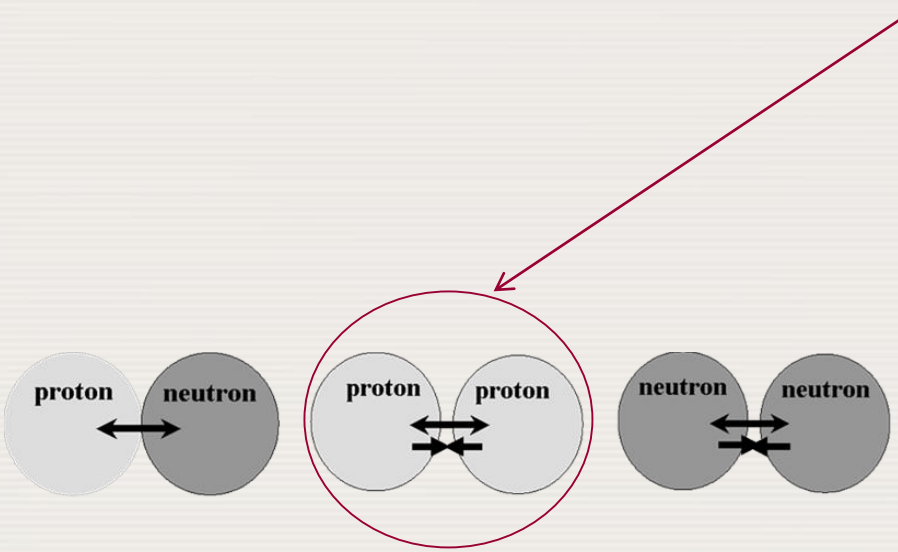
4.1.2 Nuclide chart and line of nuclear stability



Proton-neutron system

Between the proton and a neutron, there is a nuclear force that amounts to 2.225 MeV.

The nucleons form a stable combination called deuterium, an isotope of hydrogen.



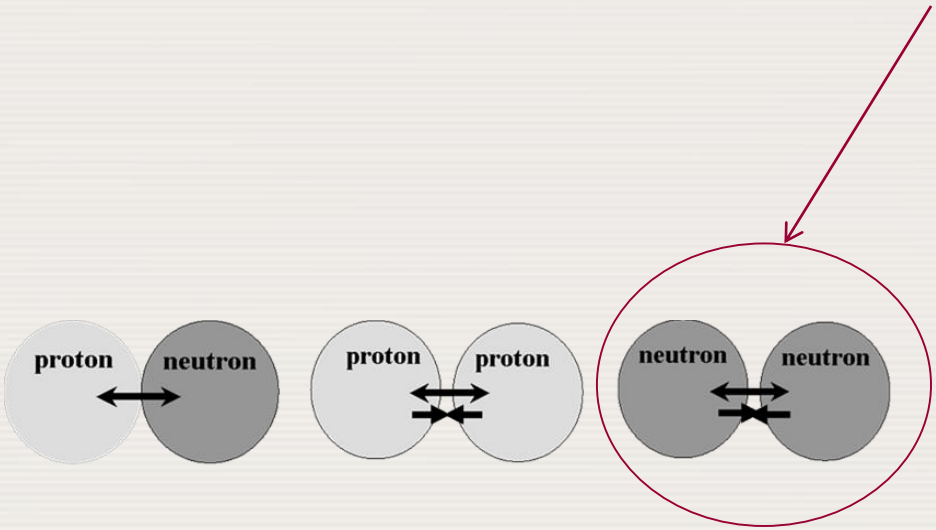
Proton-proton system

In a system of two protons, the nuclear force is equally strong to a neutron–proton, but the repulsive Coulomb forces are stronger.

Thus, this system cannot exist.

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.2 Nuclide chart and line of nuclear stability



Neutron-neutron system

The nuclear force between two neutrons is equally strong and there is no Coulomb force.

Nevertheless, this system cannot exist due to other repulsive forces, a consequence of the rules of pairing quarks.

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.3 Binding energy, Q-value, reaction threshold and nuclear reaction formalism

Nuclear reactions

- Q-value: energy gained or lost in a nuclear reaction.
- Q-value calculation: mass difference of particles before and after reaction.
- Radioactive elements have positive Q-values and decay spontaneously.
- Particle induced reactions have usually negative Q-values with the exception of thermal neutrons.
- Positively charged particles have to overcome the repulsive Coulomb force of the nucleus leading to higher threshold values than Q-values in number.

Nuclear reaction

$^{14}N(p,\alpha)^{11}C$

Q-value	-2.93 MeV
Threshold value	-3.14 MeV

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.4 Types of nuclear reaction, reaction channels and cross section

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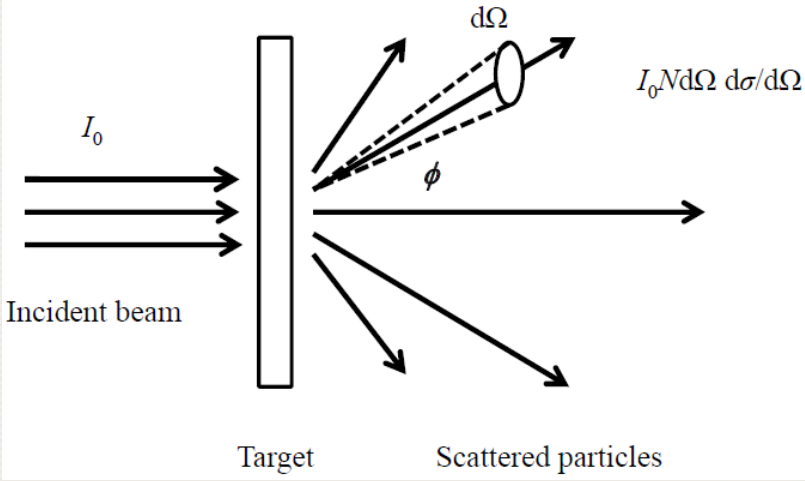
4.1.4 Types of nuclear reaction, reaction channels and cross section

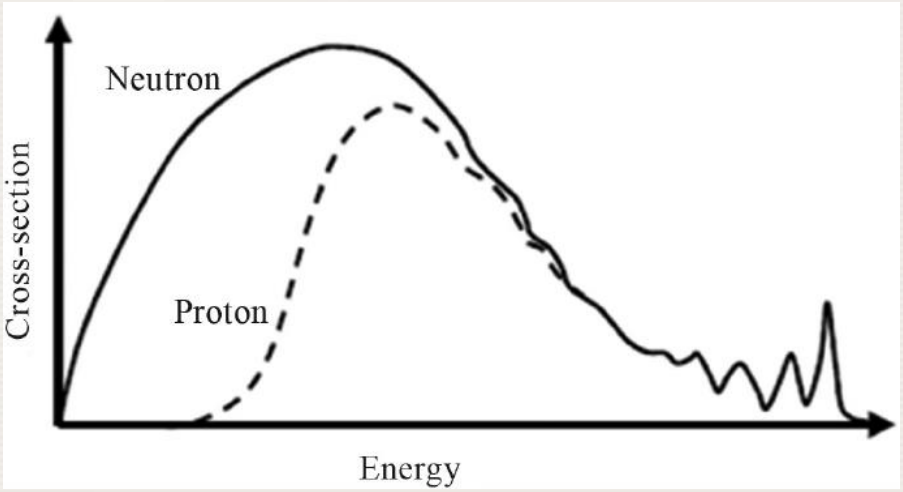


Scheme of target irradiation

- The incident beam irradiates the target, is scattered and absorbed.
- Energy can be transferred totally or partly to the target.
- Interaction can be with parts or the whole of the target nucleus.
- Target should be thick enough to ensure high activity of the product.

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.4 Types of nuclear reaction, reaction channels and cross section



Comparison of protons and neutrons reactions

- Protons have to overcome the Coulomb barrier, having a threshold energy for this reaction.
- Neutrons have no threshold energy, thus very low energy neutrons can penetrate into the nucleus to cause a nuclear reaction.

4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.4 Types of nuclear reaction, reaction channels and cross section

General equation for a nuclear reaction

a + A → b + B + Q

a: incoming particle.

A: target nucleus in ground state (entrance channel).

b: outgoing particle(s).

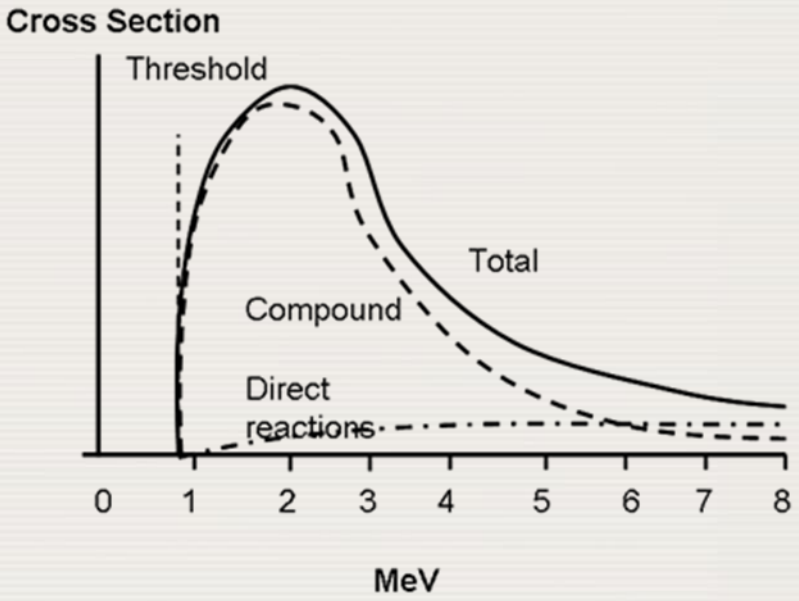
B: rest of the nucleus.

Q: reaction energy (positive or negative).

Depending on energy and particle involved, several nuclear reactions may happen , creating an outgoing channel, each with its own probability (cross-section).

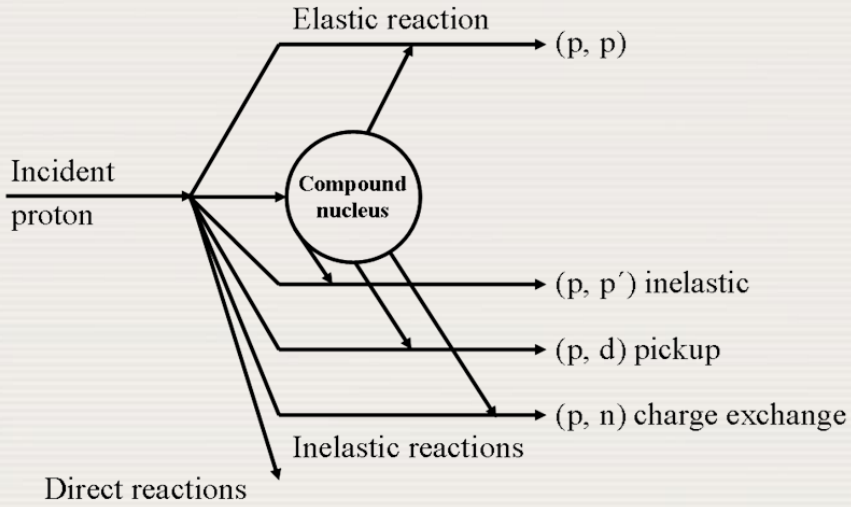
Characteristics of the reaction channel

- Energy threshold: an energy that makes the nuclear reaction possible.
- Probability (cross section) varying with the incoming particle energy.



4.1 THE ORIGIN OF DIFFERENT NUCLEI

4.1.4 Types of nuclear reaction, reaction channels and cross section



Reaction mechanisms

- Formation of a compound nucleus
- Direct reactions

Example:
Reaction channels for proton irradiation

Reaction mechanisms

Formation of a compound nucleus

- Large probability to be formed in a central hit.
- Preferable at low energies, close to the threshold energy.

Reaction mechanisms

Direct reactions

- Occur at the edge of the nucleus, at high energies.
- Associated with the geometry of nucleus.
- Small cross-section, fairly constant with energy.

4.2 REACTOR PRODUCTION

4.2 REACTOR PRODUCTION

Production of radionuclides

- There are two major ways to produce radionuclides: using reactors (neutrons) or particle accelerators (protons, deuterons, α particles or heavy ions).
- Since the target is a stable nuclide, either a neutron-rich radionuclide (reactor produced) or a neutron deficient radionuclide (accelerator produced) is generally obtained.

4.2 REACTOR PRODUCTION

Major ways of radionuclide production

Production device	Beam particles	Radionuclide produced
reactors	neutrons	neutron-rich
accelerators	protons deuterons α particles heavy ions	neutron-deficient

4.2 REACTOR PRODUCTION

4.2.1 Principle of operation and neutron spectrum

Reactor characteristics

- A nuclear reactor is a facility in which a fissile atomic nucleus (^{235}U, ^{239}Pu or ^{241}Pu) undergoes fission after irradiation with low energy neutrons.
- The reactor produces fast neutrons with energies up to about 10 MeV (fission neutron spectrum).

Reactor characteristics

Reactor regulation

- Neutrons are slowed down in a moderator (usually water) and the slowed down neutrons start new fissions.
- By regulating this nuclear chain reaction, there will be a steady state production of thermal neutron with a typical neutron flux in the order of 10^{14} neutrons • cm^{-2} • s^{1}.

Reactor characteristics

Target irradiation

- Targets are placed in different positions, exposed to neutrons of different energy.
- The neutron cloud irradiates the target isotropically.
- Irradiation positions have high temperature, may easily reach 200 ºC.

4.2 REACTOR PRODUCTION

4.2.1 Principle of operation and neutron spectrum

Characteristics of reactors

- Energy spectrum
- Flux (neutrons·cm^{2}·s^{1})
- Temperature (at irradiation position)

Important facts

- Most reactors in the world are used only for energy production.
- Usually, only research reactors are flexible enough for use in radioisotope production.

4.2 REACTOR PRODUCTION

4.2.2 Thermal and fast neutron reactions

Neutron reactions

- The most typical neutron reaction is the (n, γ) reaction

Example: $^{59}Co(n, \gamma)^{60}Co$

- The produced radionuclide is the same element as the target.
- Radionuclide production is not useful for labelling purposes due to low specific activity, and usually other reactions are used, both with thermal and fast neutrons.

Neutron reactions

TYPICAL NUCLEAR REACTIONS IN A REACTOR FOR RADIONUCLIDE PRODUCTION

Type of neutrons	Nuclear reaction	Half-life $T_{1/2}$	Cross-section σ (mb)
Thermal	$^{59}Co(n, \gamma)^{60}Co$	5.3 a	2000
	$^{14}N(n, p)^{14}C$	5730 a	1.75
	$^{33}S(n, p)^{33}P$	25 d	0.015
	$^{35}Cl(n, \alpha)^{32}P$	24 d	0.05
Fast	$^{24}Mg(n, p)^{24}Na$	15 h	1.2
	$^{35}Cl(n, \alpha)^{32}P$	14 d	6.1

General rules are not always applicable like in the production of the therapy nuclide ^{177}Lu

- The most common production route is still the (n, γ) reaction on ^{176}Lu, which opposes two conventional wisdoms in practical radionuclide production for biomolecular labelling:

  a) Not to use a production that yields the same product element as the target since it will negatively affect the labelling ability due to the low specific radioactivity.

  b) Not to use a target that is radioactive.

Production of ^{177}Lu

- ^{176}Lu is a natural radioactive isotope of lutetium with an abundance of 2.59%.
- ^{177}Lu needs to be separated from the dominant ^{175}Lu to decrease the mass of the final product.
- This method of production works because the high cross-section (2020 b) of ^{176}Lu results in a high fraction of the target atoms being converted to ^{177}Lu, yielding an acceptable specific radioactivity of the final product.

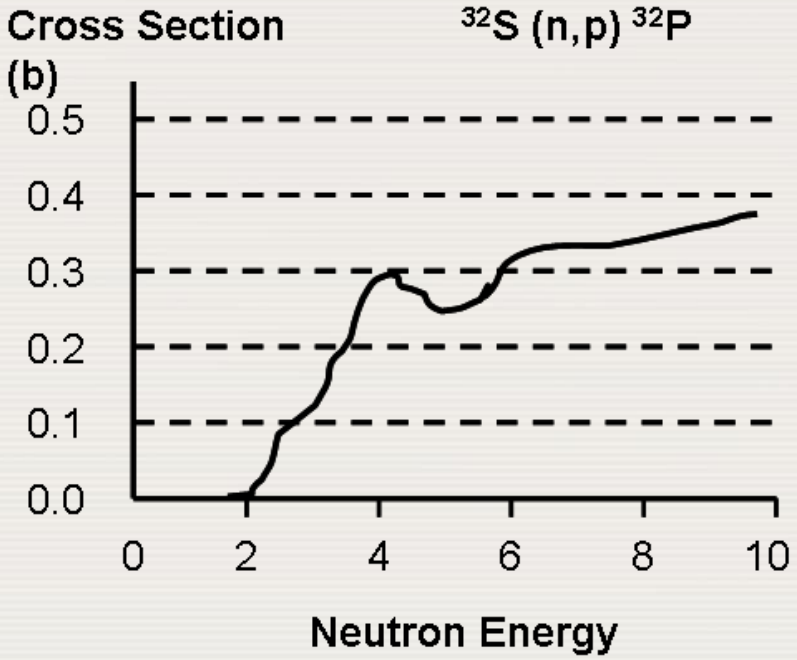
Production of ^{177}Lu from ^{176}Lu (left) and from ^{176}Yb (right).

	^{175}Lu	^{176}Lu	^{177}Lu	^{178}Lu
$T_{1/2}$	Stable	3.78 10^{10} a	6.734 d	28.4 min
Abundance (%)	97.41	2.59		
σ (mb)		2020		
	^{174}Yb	^{175}Yb	^{176}Yb	^{177}Yb
$T_{1/2}$	Stable	4.185 d	Stable	1.911 h
Abundance (%)	31.8		12.7	31.8
σ (mb)			2.85	

Production of ^{32}P

- Reactions involving fast neutrons usually have cross-sections that are of the order of millibarns, which, coupled with the much lower neutron flux at higher energy relative to thermal neutron fluxes, leads to lower yields.
- For ^{32}P, the reaction threshold is 0.51 MeV. There is no substantial yield until an energy of about 2 MeV.
- A practical cross-section can be calculated to about 60 mb.

Production of ^{32}P by the nuclear reaction $^{32}S(n, p)^{32}P$



	^{32}S	^{33}S	^{34}S
$T_{1/2}$	Stable	Stable	Stable
Abundance (%)	95.02	0.75	4.21
σ (mb)	varying	varying	varying
	^{31}P	^{32}P	^{33}P
$T_{1/2}$	Stable	14.26 d	25.4 d
Abundance (%)	100		
σ (mb)			

4.2 REACTOR PRODUCTION

4.2.3 Nuclear fission, fission products

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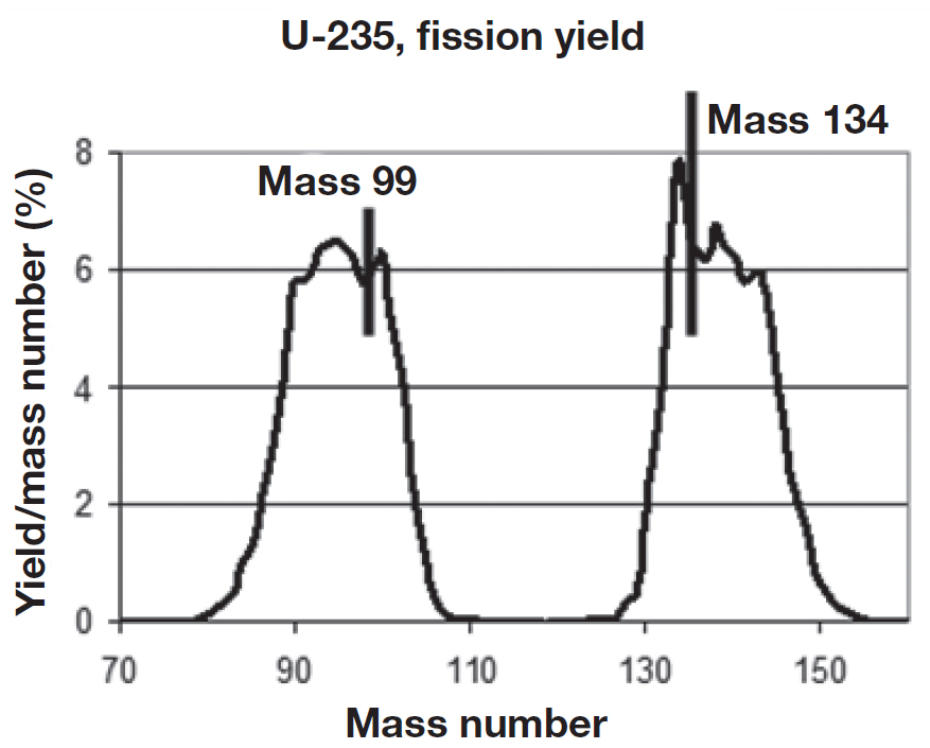


- Uranium-235 irradiated with thermal neutrons undergoes fission with a cross-section of 586 b.
- The fission process results in the production of two fragments of ^{235}U nucleus plus a number of free neutrons.
- The sum of the fragments' mass will be close to the mass of ^{235}U.

Medical radionuclides

- Some medically important radionuclides are produced by fission, such as ^{90}Y (therapy) and ^{99m}Tc (diagnostic).
- They are not produced directly but by a generator system.
- Another important product for diagnostics and therapy is ^{131}I.

^{90}Sr (28.5 a) → ^{90}Y (2.3 d)

^{99}Mo (2.7 d) → ^{99m}Tc (6 h)

4.3 ACCELERATOR PRODUCTION

4.3 ACCELERATOR PRODUCTION

Charged particles reactions

- Charged particles need to be accelerated to overcome the Coulomb barrier.
- They can easily be accelerated to higher energies than fast neutrons in a reactor, which makes it possible to open more reaction channels.

$$^{127}\mathrm{I(p,\,5n)}^{123}\mathrm{Xe} \rightarrow {}^{123}\mathrm{I}$$

$$^{124}\mathrm{Xe(p,\,np)}^{123}\mathrm{Xe} \rightarrow {}^{123}\mathrm{I}$$

$$^{123}\mathrm{Te(p,\,n)}^{123}\mathrm{I}$$

$$^{122}\mathrm{Te(d,\,n)}^{123}\mathrm{I}$$

$$^{124}\mathrm{Te(p,\,2n)}^{123}\mathrm{I}$$

$$^{121}\mathrm{Sb}(^{4}\mathrm{He},\,2\mathrm{n})^{123}\mathrm{I}$$

$$^{121}\mathrm{Sb}(^{3}\mathrm{He},\,\mathrm{n})^{123}\mathrm{I}$$

$$^{123}\mathrm{Sb}(^{3}\mathrm{He},\,3\mathrm{n})^{123}\mathrm{I}$$

Different reactions with charged particles that produce ^{123}I

4.3 ACCELERATOR PRODUCTION

Accelerators for radionuclide production

- They are smaller than the ones used for particle physics experiments.
- They need to accelerate particles to relatively low energies for radioisotope production.

4.3 ACCELERATOR PRODUCTION

CHARACTERISTICS OF ACCELERATORS FOR RADIONUCLIDE PRODUCTION

Proton energy (MeV)	Accelerated particles	Used for
<10	Mainly single particle, p or d	PET
10–20	Usually p and d	PET
30–40	p and d, ^{3}He and ^{4}He may be available	PET, commercial production
40–500	Usually p only	Often placed in national centres and have several users

4.3 ACCELERATOR PRODUCTION

Advantages of accelerator production

- Reactions where target and product elements are different are usually easy to find.
- Thus, high specific activity can be obtained (important for labelling biomolecules).

4.3 ACCELERATOR PRODUCTION

Drawbacks of accelerator production

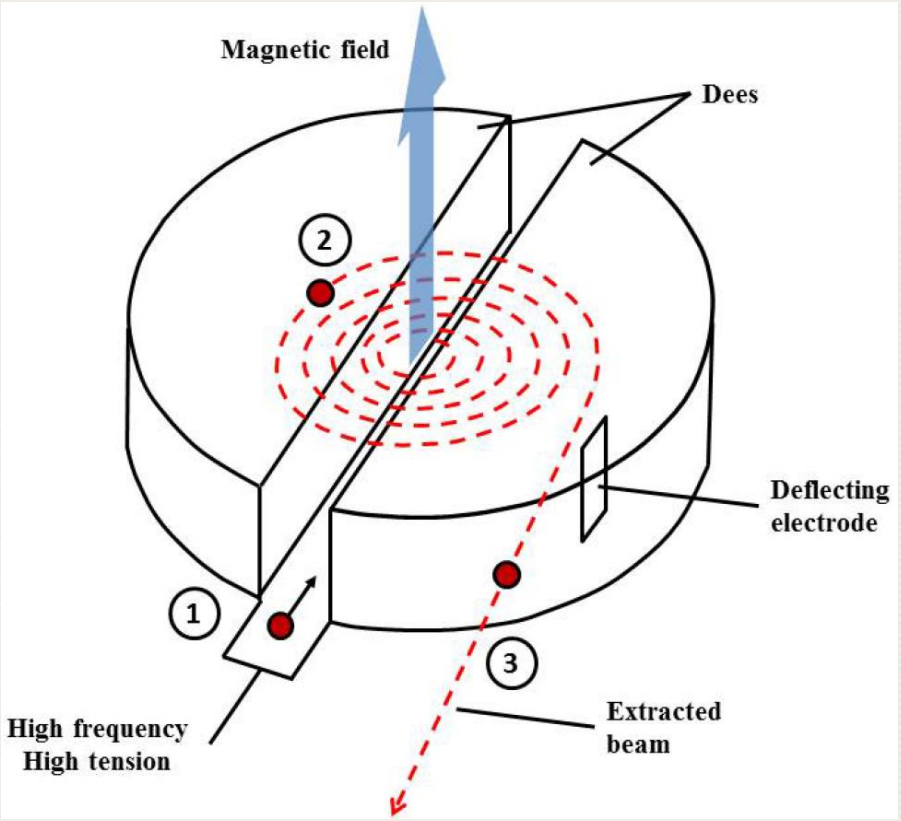
- Charged particles are stopped more efficiently than neutrons.
  - Targets will evaporate if not efficiently cooled.
- Acceleration occurs in vacuum while target irradiation is done at atmospheric pressure or higher (gas targets).
  - To separate vacuum from target, the beam penetrates foils that are also activated.

4.3 ACCELERATOR PRODUCTION

4.3.1 Cyclotron, principle of operation, negative and positive ions

4.3 ACCELERATOR PRODUCTION

4.3.1 Cyclotron, principle of operation, negative and positive ions

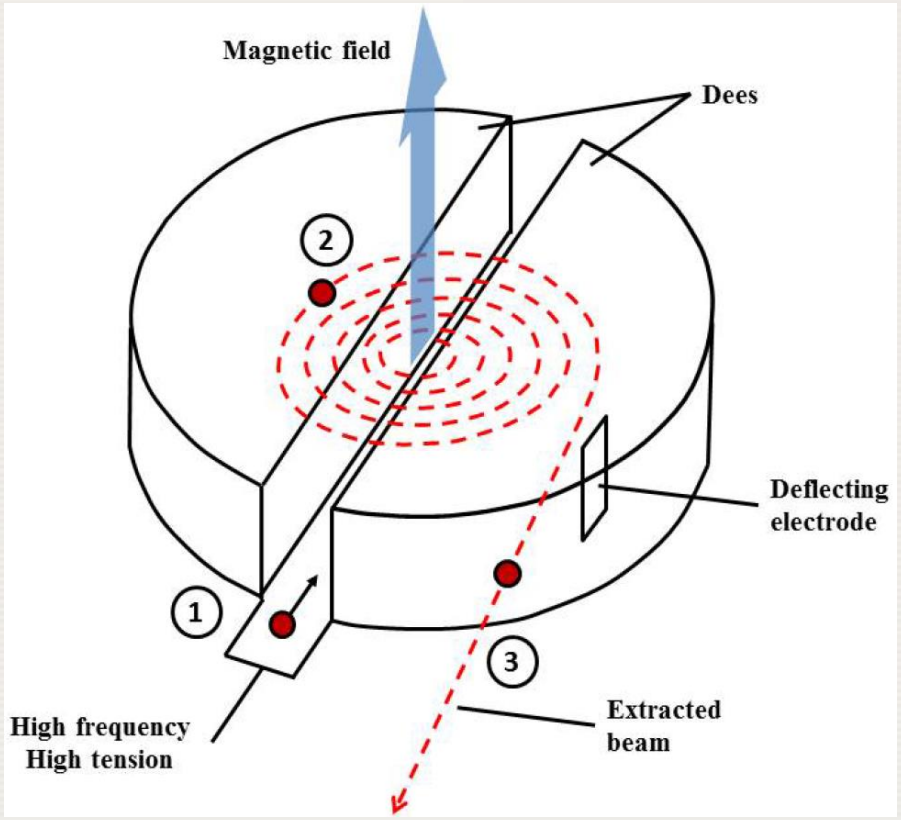


The cyclotron principle

- In a strong magnetic field caused by an electromagnet an ion is injected into the gap between ‘dee’ shaped electrodes (1).
- An alternating electric field is applied across the gap, which causes the ion to accelerate.

4.3 ACCELERATOR PRODUCTION

4.3.1 Cyclotron, principle of operation, negative and positive ions



The cyclotron principle

- The magnetic force on a moving charge forces it to bend into a circular orbit (2).
- The charged particle is accelerated each time it reaches the gap since the applied electric field is reversed in face. The higher energy forces the ion out in an increasing orbit radius until finally being ejected (3).

4.3 ACCELERATOR PRODUCTION

4.3.1 Cyclotron, principle of operation, negative and positive ions

Target location

- Internal targets
  - Used in commercial accelerators, with high beam currents
- External targets
  - Used in accelerators with beam currents < 100μA (e.g. hospital PET systems)

Beam extraction modes

- Not applicable
- Positive ions
  - Deflectors (static field)
- Negative ions
  - Carbon foil to strip electrons

Technical considerations

- The target is separated from the vacuum by metallic foils (must withstand pressure difference and heat from beam energy).
- Helium flow between foils is used as cooling agent.

4.3 ACCELERATOR PRODUCTION

4.3.2 Commercial production (low and high energy)

Technical considerations

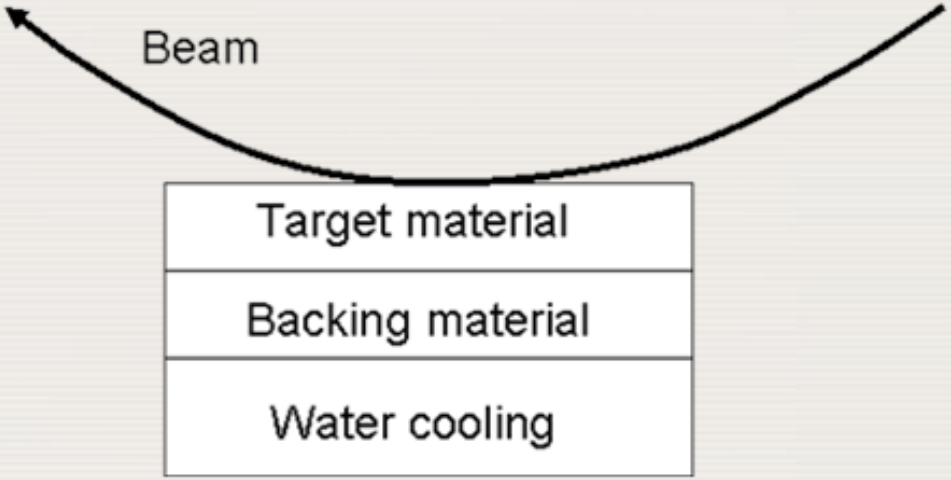
- For proton energy > 30 MeV the particles tend to be relativistic.
- Using a constant frequency accelerating field would cause ions to come out of phase.
- News methods were introduced to compensate these effects.

Compensation methods

- Increasing magnetic field as a function of cyclotron radius (isochronic cyclotrons).
- Decreasing the radiofrequency during acceleration (synchrocyclotrons).

Use of internal targets

- Most commercial accelerators, running beam currents of several mA, use internal targets.
- The target is water-cooled, facilitated by the large area spread of the beam.



Cyclotron produced radioisotopes

- SPECT radioisotopes
  - ^{67}Ga
  - ^{111}In
  - ^{123}I
  - ^{201}Tl
- PET radioisotopes
  - ^{18}F, ^{11}C, ^{15}O, ^{13}N
  - ^{124}I
  - ^{68}Ge (mainly for $^{68}Ge/^{68}Ga$ generators)
  - ^{52}Fe, ^{61}Cu (produced only in cyclotrons E>30 MeV)

4.3 ACCELERATOR PRODUCTION

4.3.3 In-house low energy production (PET)

4.3 ACCELERATOR PRODUCTION

4.3.3 In-house low energy production (PET)

Characteristics of commercial accelerators dedicated to PET radioisotopes

- Energy < 20MeV
- Beam current < 100μA
- Gases or water as target material (external targets pref.)
- Extraction is not a problem
- Choosing the right reaction and target material is crucial

DIFFERENT NUCLEAR REACTIONS FOR THE PRODUCTION OF ^{18}F

$^{20}Ne(d, \alpha)^{18}F$	The nascent ^{16}F will be highly reactive. In the noble gas Ne, it will diffuse and stick to the target walls; difficult to extract.
$^{21}Ne(p, \alpha)^{18}F$	Same as above; in addition, the abundance of ^{21}Ne is low (0.27%) and needs enrichment.
$^{19}F(p, d)^{18}F$	The product and target are the same element; poor specific radioactivity.
$^{16}O(\alpha, d)^{18}F$	Cheap target but accelerators that can accelerate α particles to 35 MeV are expensive and not common.
$^{16}O(d, \gamma)^{18}F$	Small cross-section and no practical yields can be obtained.
$^{18}O(p, n)^{18}F$	Expensive enriched target material but the proton energy is low (low cost accelerator), which makes this the nuclear reaction of choice.

Selection of reaction (cont.)

- Enriched ^{18}O water is a target of choice as ^{18}O is the dominant nucleus and hydrogen does not contribute to any unwanted radioactivity.
- There is usually no need for target separation as water containing ^{18}F can often be directly used in the labelling chemistry.
- The target water can also, after being diluted with saline, be injected directly into patients, e.g. ^{18}F-fluoride for PET bone scans.

Problems to take care of…

- Heat is a problem when the beam is stopped in a few ml of target water.
- Solutions for this problem are:
  - High pressure targets forcing water to remain liquid ($I_{beam} < 40\mu A$).
  - Gas and solid targets can withstand higher beam currents.

COMMONLY USED RADIONUCLIDES IN PET

Radionuclide	Nuclear reaction	Yield (GBq)
Oxygen-15	$^{14}N(d, n)^{15}O$ gas target	15
Nitrogen-13	$^{16}O(p, \alpha)^{13}N$ liquid target	5
Carbon-11	$^{14}N(p, \alpha)^{11}C$ gas target	40
Fluorine-18	$^{18}O(p, n)^{18}F$ liquid target	100

4.3 ACCELERATOR PRODUCTION

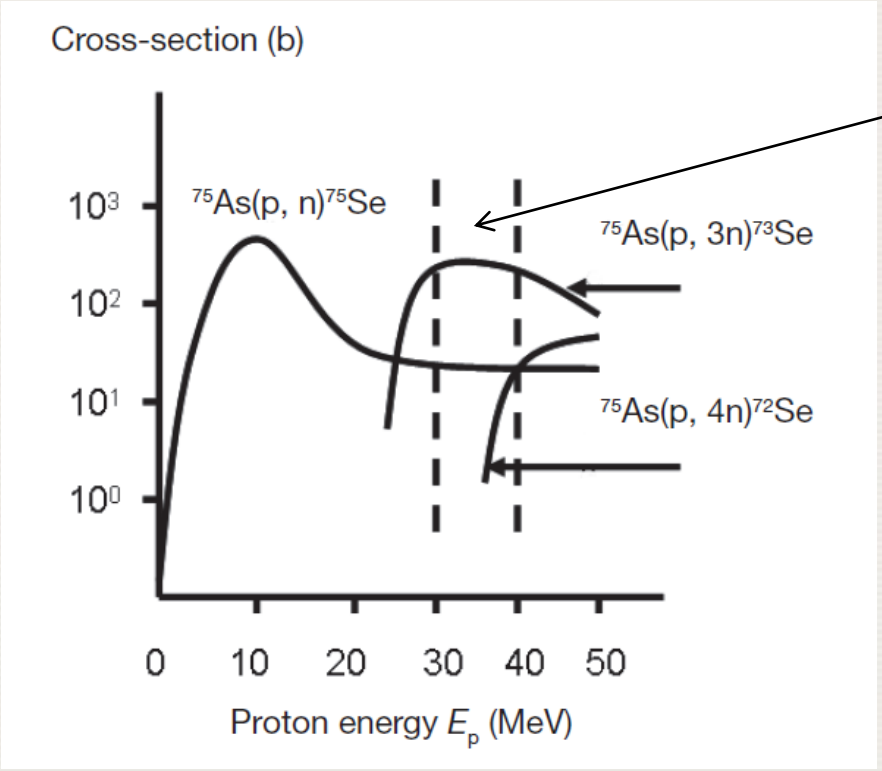
4.3.4 Targetry, optimizing the production regarding yield and impurities, yield calculations

Important parameters to control in radioisotope production

- Entrance particle energy.
- Target thickness.
- Reaction channel cross-sections for the particle energies in the target.

Rule of the thumb: 10 MeV energy per nucleon expelled

Example: Production of ^{73}Se by the $^{75}As(p, xn)^{72,73,75}Se$ reactions.



The optimal energy for the production of ^{73}Se is to use a proton energy of 40 MeV that is degraded to 30 MeV in the target.

Unwanted radionuclide impurities

- At low energy, there is a disturbing production of ^{75}Se and if excessively high proton energy is used, another unwanted radionuclide impurity is produced, namely ^{72}Se.
- The latter impurity can be avoided completely by restricting the proton energy to an energy lower than the threshold for the (p, 4n) reaction.

Minimizing impurity production

- The impurity that results from the (p, n) reaction cannot be avoided but can be minimized by using a target thickness that avoids the lower proton energies (having the highest (p, n) cross-sections).

4.4 RADIONUCLIDE GENERATORS

4.4 RADIONUCLIDE GENERATORS

Radionuclide generator definition

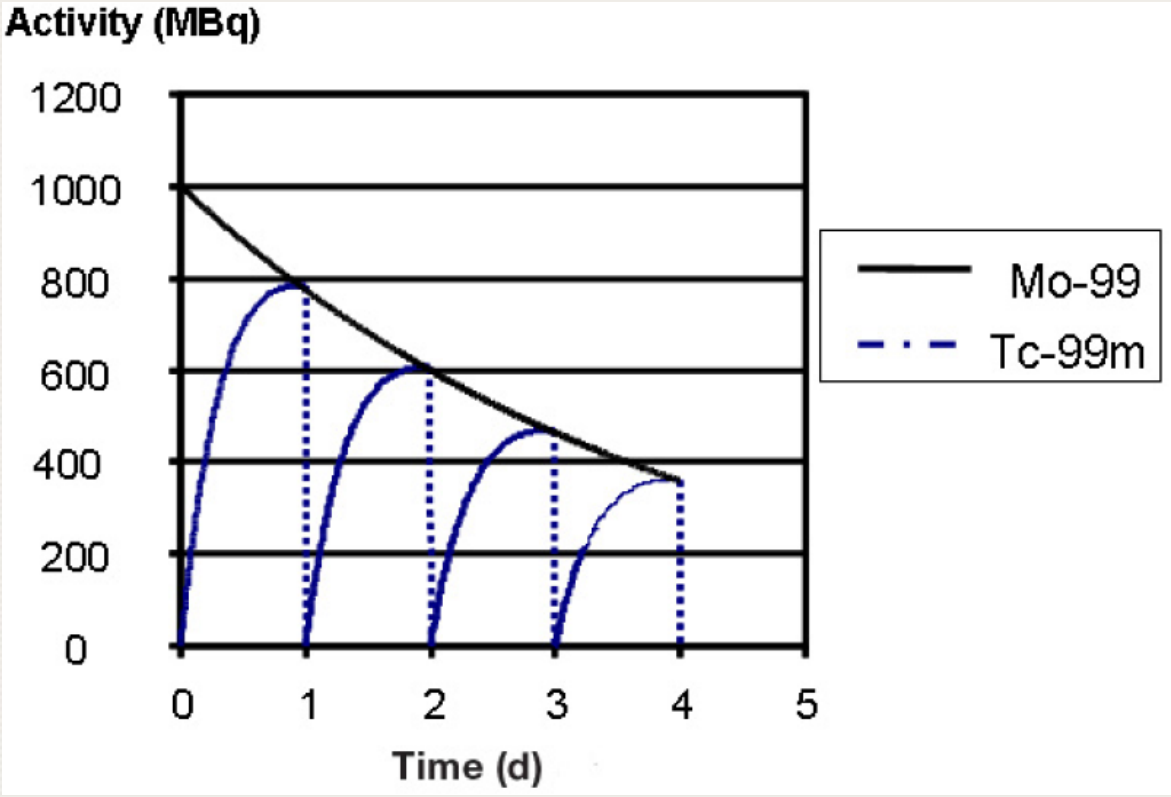
- Whenever a radionuclide (parent) decays to another radioactive nuclide (daughter), this is called a radionuclide generator.
- A special case is usually considered in which a long lived mother generates a short lived daughter, which after labelling is administrated to the patient.

4.4 RADIONUCLIDE GENERATORS

Generators used in nuclear medicine

- Several radionuclides used in nuclear medicine are produced by generator systems such as the ^{99}Mo production of ^{99m}Tc, which subsequently decays to ^{99}Tc.
- The half-life of the parent (2.7 d) is adequate for transport and delivery, and the daughter has a suitable half-life (6 h) for patient investigations.

4.4 RADIONUCLIDE GENERATORS



Elution of a $^{99}Mo/^{99m}Tc$ generator

^{99m}Tc, with an activity close to that of the ^{99}Mo-mother, is eluted daily. After elution the activity will be almost zero but with time the decay of ^{99}Mo produces new ^{99m}Tc and the activity will again be close to that of ^{99}Mo the next day.

4.4 RADIONUCLIDE GENERATORS

4.4.1 Principles of generators

Characteristics of generator systems

- Generator systems that can repeatedly produce a useful radionuclide for nuclear medical investigations require a mother radionuclide with a long half-life relative to the daughter nuclide.
- The mother nuclide is usually reactor or accelerator produced but the very first human investigation (slide 9) made is an example where a naturally occurring mother radionuclide was used.
- The daughter radionuclide of interest has to be easily separated from the mother nuclide
- Generator system where the mother nuclide is more short-lived than the daughter can be used, but not repeatedly.

Separation of the generator radionuclides

- Most generators in nuclear medicine use ion exchange columns due to its simplicity of handling.
- In the $^{99}Mo/^{99m}Tc$ generator, ^{99}Mo is adsorbed onto alumina.
- Eluting the immobilized ^{99}Mo on the column with physiological saline elutes the soluble ^{99m}Tc in a few millilitres of liquid.

Generators of interest in Nuclear Medicine

Generator	Usage
^{99}Mo-^{99m}Tc	General Nuclear Medicine
^{68}Ge-^{68}Ga	Peptide labelling
^{90}Sr-^{90}Y	β therapy
^{81}Rb-^{81m}Kr	Ventilation studies
^{82}Sr-^{82}Rb	Cardiac PET
^{225}Ac-^{213}Bi	α therapy

4.5 RADIOCHEMISTRY OF IRRADIATED TARGETS

4.5 RADIOCHEMISTRY OF IRRADIATED TARGETS

Target processing

- Fast, efficient and safe methods are required to separate the few picograms of radioactive product from the bulk target material which is present in gram quantities.
- Since many radionuclides are short-lived it is important that as few steps as possible are used to obtain the separation.
- Especially in gas and liquid targets one can achieve this by additives that, with help of hot-atom chemistry, lead to the desired chemical form that can be easily separated.
- An example is $^{14}N(p,\alpha)^{11}C$. If an ultra pure nitrogen gas is irradiated the chemical form of ^{11}C can vary unpredictably. If less than 0.5% oxygen gas is added the production will quantitatively yield $^{11}CO_2$ that is easily separated from the target.
- Solid targets are usually dissolved and chemically processed to obtain the wanted chemical form for separation.

4.5 RADIOCHEMISTRY OF IRRADIATED TARGETS

4.5.1 Carrier-free, carrier-added systems

Specific activity definition

- The specific activity *a* expressed as activity per number of radioactive atoms is then $A/N = \lambda = \ln(2)/T_{1/2}$.
- A more empirical way to define *a* is to divide the activity by the total mass of the element under consideration.

Processes and carriers

- If the radioactive atoms are produced and separated from the target without any stable isotopes, the product is said to be ‘carrier-free’.
- If stable isotopes are introduced as being a contaminant in the target or in the separation procedure, the product is said to be produced with ‘no carrier added’.
- Sometime it is necessary to have or to add stable isotopes in order to enable the production or the separation. The product is then said to be produced with "carrier added".

4.5 RADIOCHEMISTRY OF IRRADIATED TARGETS

4.5.2 Separation methods, solvent extraction, ion exchange, thermal diffusion

Separation methods

To separate the obtained radionuclide from the bulk of the target, two principles are used:

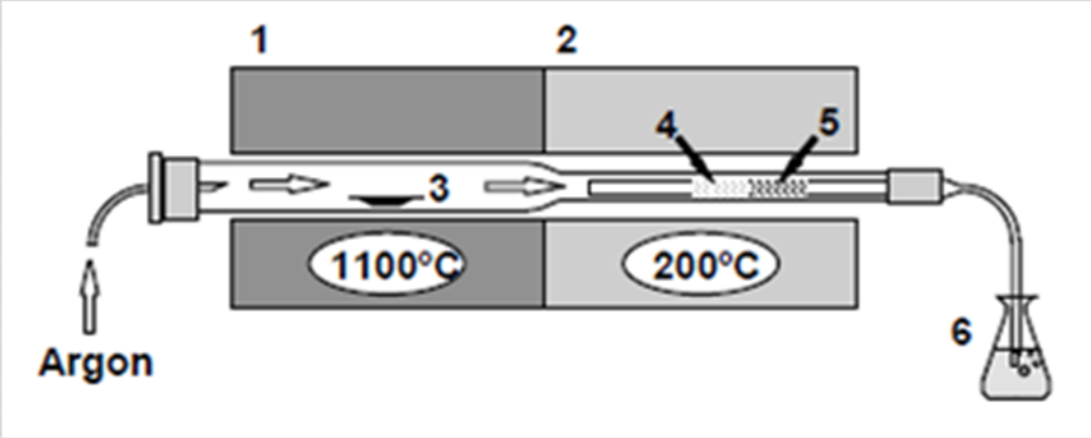
- Liquid extraction
  - Two non-mixing liquids are used, target and product must have different solubility in them.
- Ion exchange
  - An ion in liquid phase is transferred to a solid phase. A counter ion is released from solid phase to maintain charge balance.

Thermal separation methods

Occasionally, thermal separation techniques may be applied

- They do not destroy the target (important when expensive enriched targets are used).
- They lend themselves to automation.

Thermal separation methods



Schematic description of the ^{76}Br separation equipment:

(1) furnace
(2) auxiliary furnace
(3) irradiated target
(4) deposition area of selenium
(5) deposition area of ^{76}Br
(6) gas trap

4.5 RADIOCHEMISTRY OF IRRADIATED TARGETS

4.5.3 Radiation protection considerations and hot-box facilities

4.5 RADIOCHEMISTRY OF IRRADIATED TARGETS

4.5.3 Radiation protection considerations and hot-box facilities

Radiation protection has to consider:

- Use of an adequate production process, to avoid the presence of highly energetic and long-lived contaminants.
- A place for “cooling period”, to allow short lived radionuclides to decay before processing.
- The type of emitter involved (alpha, beta or gamma).
- Handling reactor or accelerator products of several hundreds gigabecquerels requires adequate radiation protection, usually in the form of lead shields.

DOSE RATES AND LEAD SHIELDING REQUIRED FOR DIFFERENT RADIONUCLIDES, DETERMINED BY THE GAMMA RADIATION ABUNDANCE AND ENERGY[a]

	Dose rate (mSv/h) at 1 m per TBq			
	^{99m}Tc	^{111}In	^{18}F	^{124}I
	18	81	135	117

	Thickness of lead shield (cm) giving 1 μSv/h			
TBq	^{99m}Tc	^{111}In	^{18}F	^{124}I
0.1	0.28	1.0	5.8	20
1.0	0.36	1.3	7.1	22
10.0	0.43	1.6	8.5	27

[a] Calculations made with RadProCalculator (http://www.radprocalculator.com/).

Radiation protection considerations

- Radiopharmaceuticals are handled in hot-boxes that protect the operator from the radiation and the pharmaceutical from the environment.
- Classical hot-boxes have manipulators to manually process the radioactivity remotely.
- They are being replaced by lead shielded automatic chemistry systems or chemical robots.

4.5 RADIOCHEMISTRY OF IRRADIATED TARGETS

4.5.3 Radiation protection considerations and hot-box facilities

Examples of modern hot-box designs