Production of radioisotopes and separation methods

Antonia Denkova

a.g.denkova@tudelft.nl

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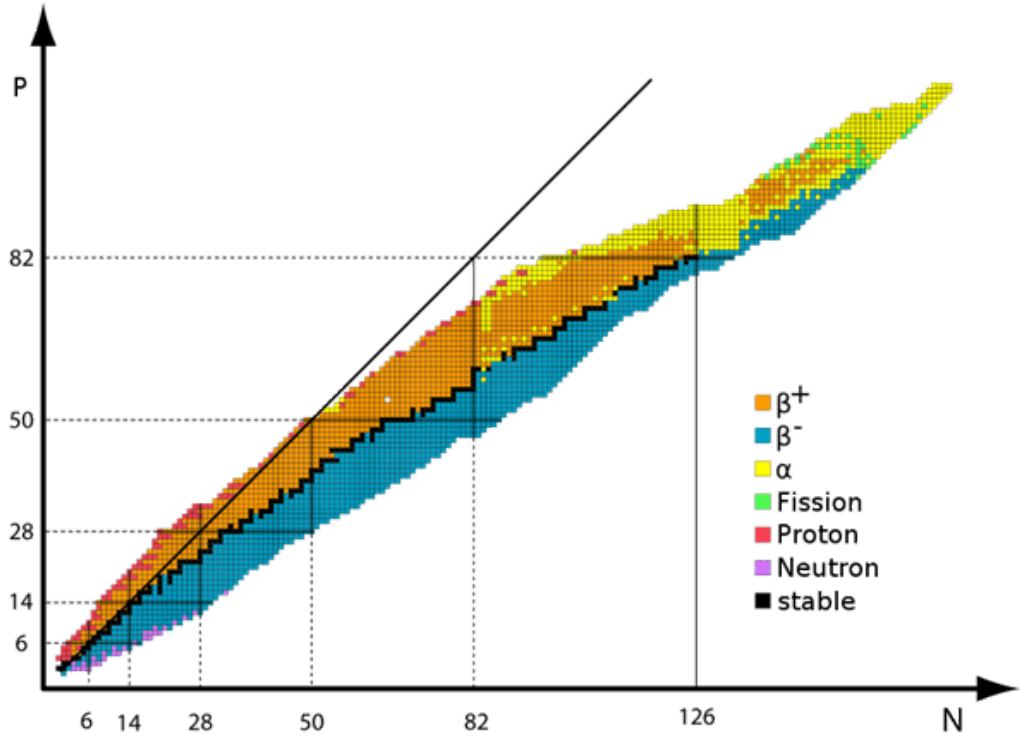
Learning Objectives

- Choose the most suitable production facility by weighing their respective advantages and disadvantages
- Calculate production levels
- Evaluate which chemical separation methods are applicable in different situations

Radioisotopes in Nuclear Medicine



- There are more than 100 radioisotopes used in nuclear medicine (almost all man made)
- More than 40 million nuclear medicine procedures and demand for radioisotopes is increasing at up to 5% annually
- More than 10 000 hospitals worldwide use radioisotopes, 90 % of the procedures is diagnostic
- The global radioisotope market was valued at $12 billion in 2024 and is expected to increase to $35 in 2034

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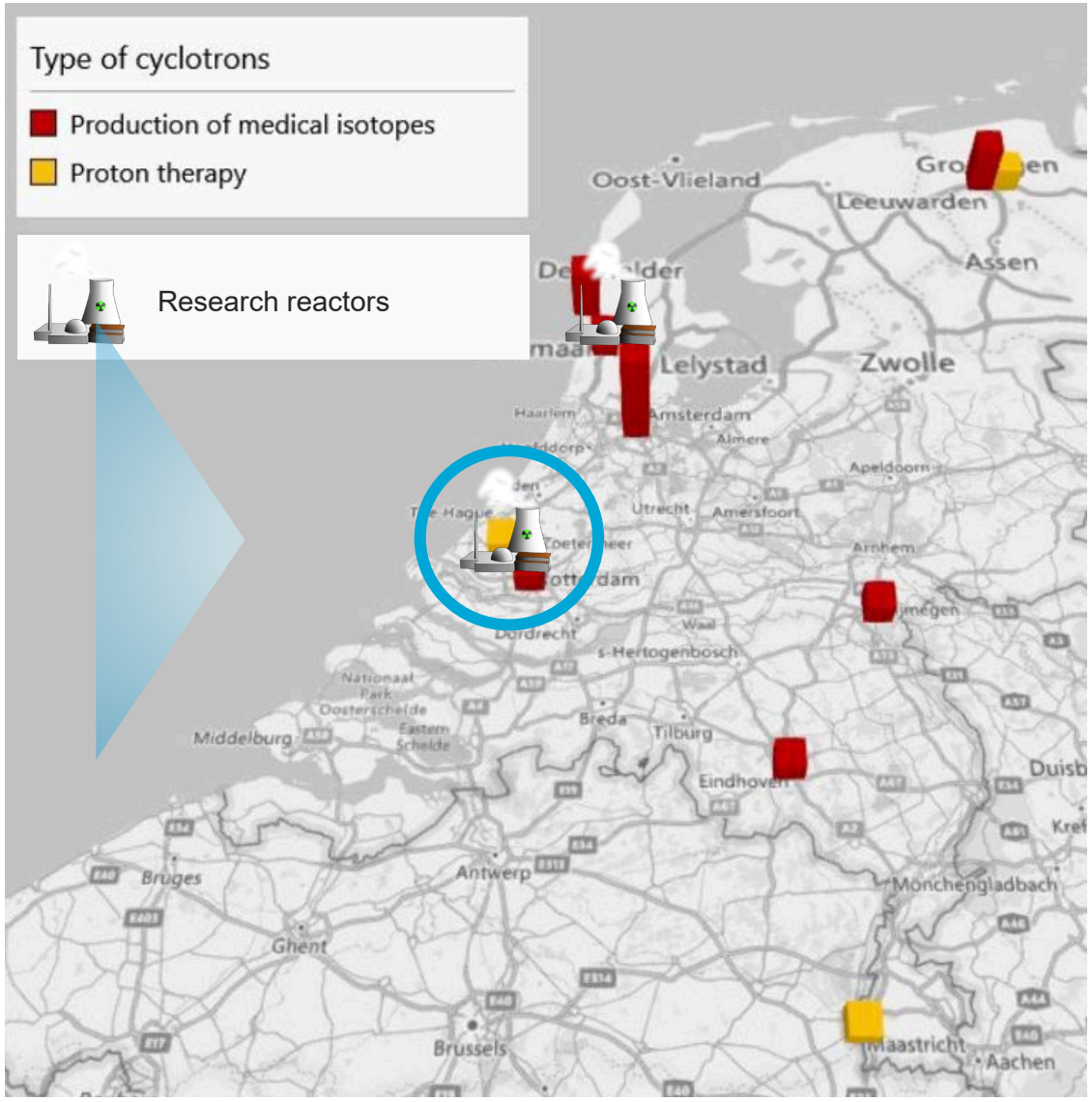
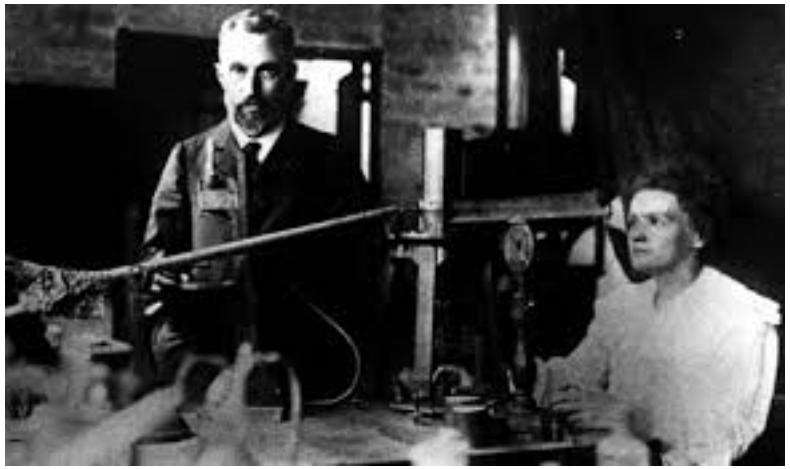
Radonuclide production in the Netherlands





Adapted from: Medical isotope production using local cyclotrons, technopolis, 2022

Discovery of artificial radioisotopes



Marie Curie and Pierre Curie discover radioactivity (isolate ^{226}Ra, an alpha emitter)



Irene and Frederic Joliot Curie produce the first artificial radioisotope using the alpha particles of the source isolated from the parents of Irene

$^{27}Al + \alpha \Rightarrow {}^{30}P + n$ or like this $^{27}_{13}Al + {}^{4}_{2}He \Rightarrow {}^{30}_{15}P + {}^{1}_{0}n$

Decay of P-30 is: $^{30}_{15}P \Rightarrow {}^{30}_{14}Si + \text{positron}$ Energy 3.24 MeV

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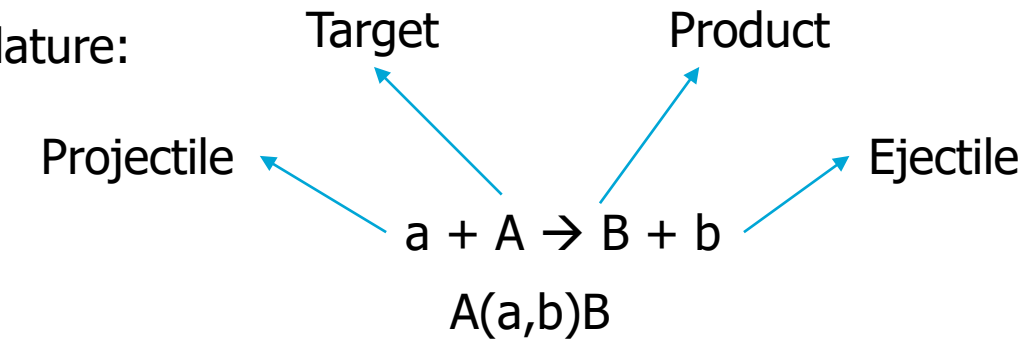
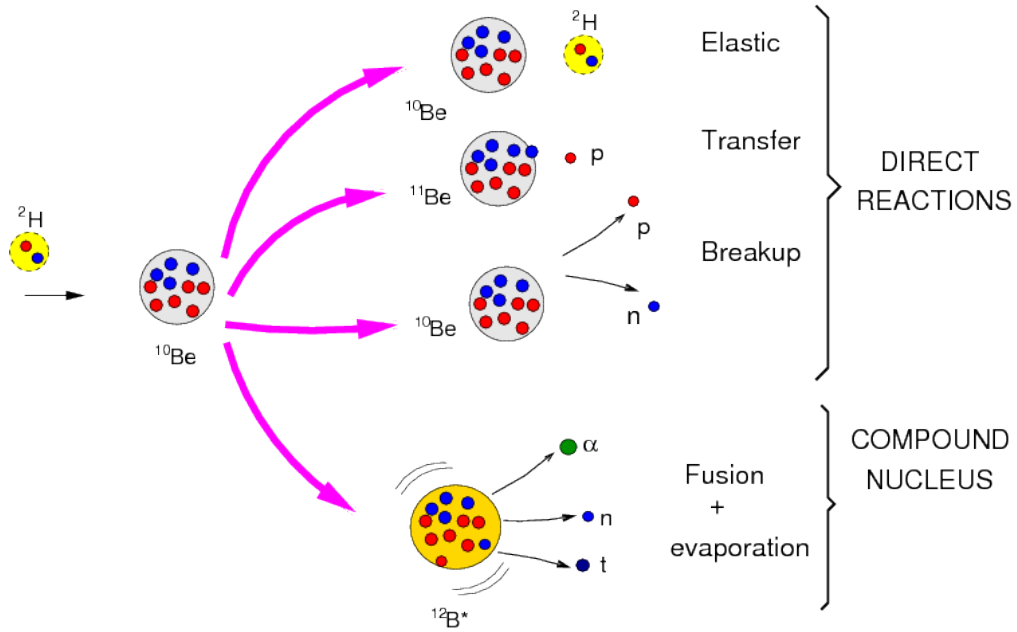
Nuclear reactions to produce radionuclides

Nomenclature:





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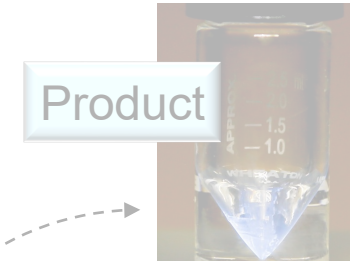
Radionuclide production

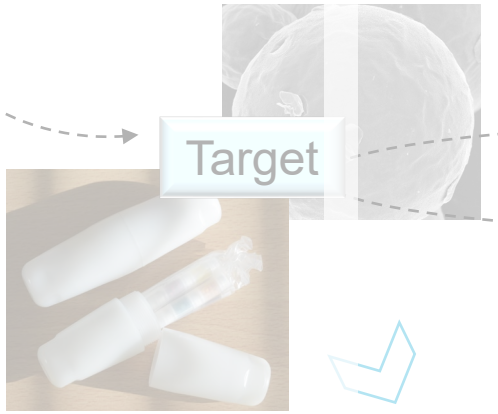
$$\left(\frac{dN_B}{dt}\right)_{Total} = \varphi\sigma N_A - \lambda N_B$$

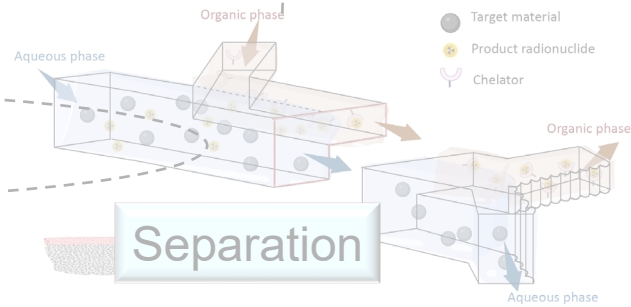
Calculations

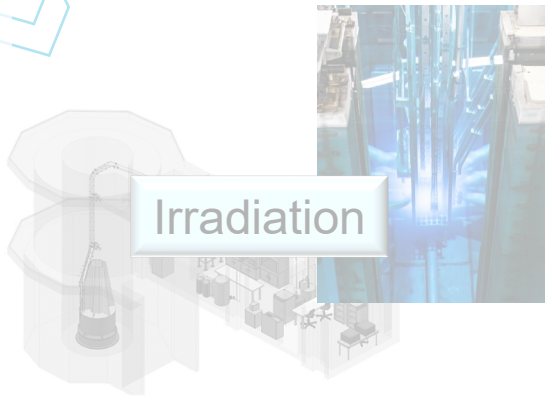
$$A_B = \varphi\sigma N_A\left(1 - e^{-\lambda t_{irr}}\right)$$











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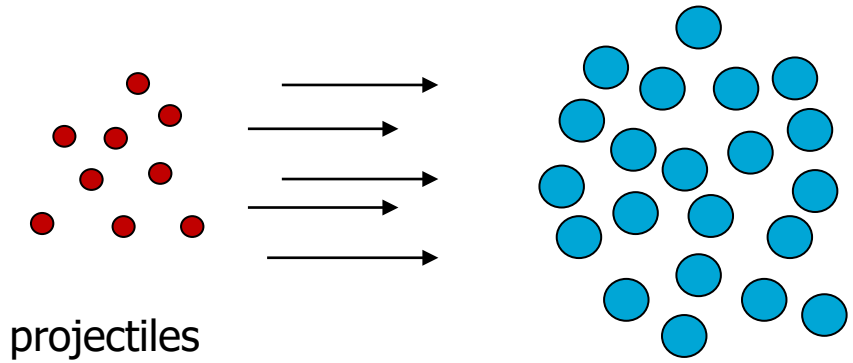
How much can be produced (yield)?

- The produced activity (A_B) after irradiation depends on:
  - Number of particles used for irradiation
    - Flux (φ)
  - Number of target atoms (N_A)
  - Reaction probability (σ)
    - Cross section



$$A_B \sim \varphi N_A \sigma$$

- **Always** given as **Activity** [Bq = decays per second] not as mass

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Particle flux (Φ)

- **For reactors: [neutrons·cm^{-2}·s^{-1}]**
  - Thermal neutron flux:
    - research reactor: 10^{10} to 10^{13} n·cm^{-2}·s^{-1}
    - production reactor: 10^{14} to 10^{15} n·cm^{-2}·s^{-1}

- **For accelerators: [μA]**
  - $A(Ampere) = \frac{C\,(Coulomb)}{s\,(second)}$; $1.6 \cdot 10^{-19} C/proton$

  - Proton flux in a medical cyclotron 20 μA – 300 μA

    - 20 μA = 1.25·10^{14} protons/s
- Important!
  - Particle flux and energy will change due to absorption and scattering depending on the thickness of target.

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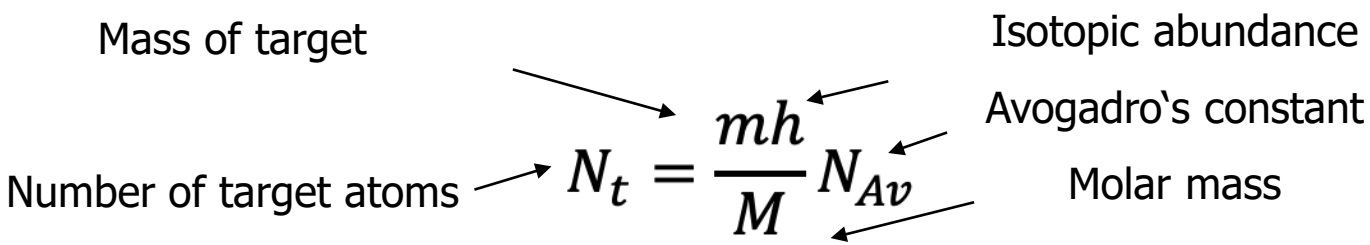
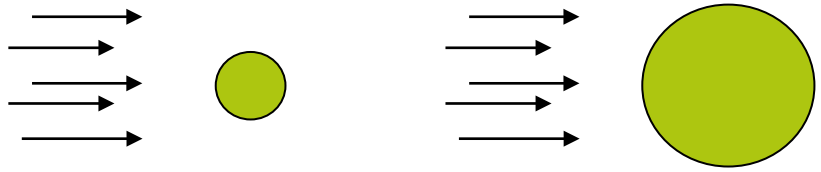
Number of target atoms (N_t)

How many atoms are irradiated?

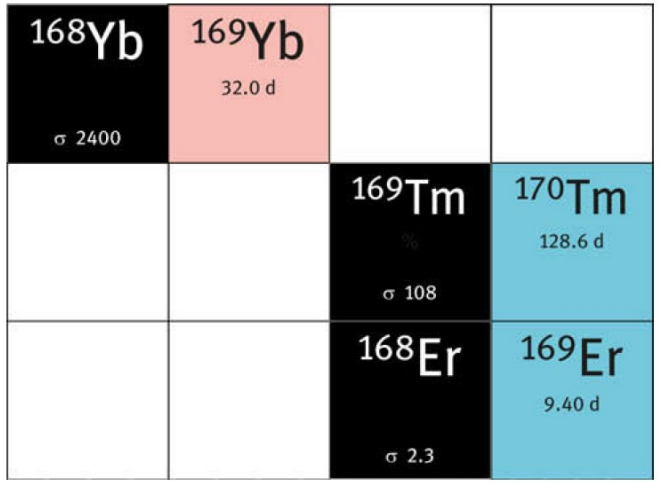


Cross section (σ)

- What is a cross-section?



- Reaction probability (σ)
- Unit: 1 barn = 100 fm^2 = 10^{-28} m^2 = 10^{-24} cm^2



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Yields of nuclear reactions

Decay of product has to be taken into account:

$$\left(\frac{dN_B}{dt}\right)_{Production} = \varphi\sigma N_A \qquad \left(\frac{dN_B}{dt}\right)_{Decay} = -\lambda N_B$$

$$\left(\frac{dN_B}{dt}\right)_{Total} = \varphi\sigma N_A - \lambda N_B \quad \Rightarrow \quad N_B = \frac{\varphi\sigma N_A}{\lambda}\left(1 - e^{-\lambda t_{irr}}\right)$$

Activity at the end of the irradiation:

$$A_B = \lambda N_B = \varphi\sigma N_A\left(1 - e^{-\lambda t_{irr}}\right)$$

Waiting time after irradiation end shad to be taken into account by multiplying A with $e^{-\lambda t_{waiting}}$

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Irradiation time and saturation factor

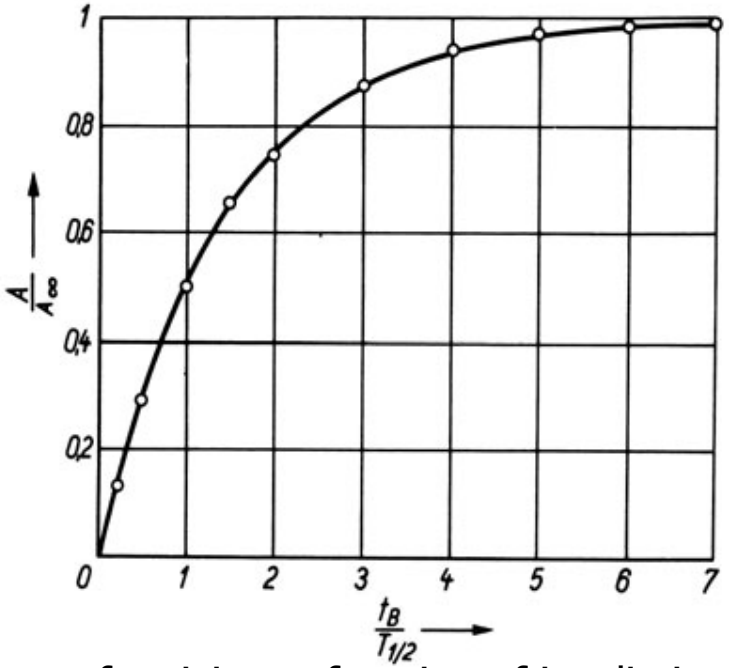
Saturation activity is reached

- When the number of nuclides produced equals the number of nuclides decaying
- When irradiation time greater is than the half-life of the product isotope

Saturation factor:

$$\lim_{t_{irr}\to\infty}\left(1-e^{-\lambda t_{irr}}\right)=1$$

$$A_{sat}=\varphi\sigma N_A$$



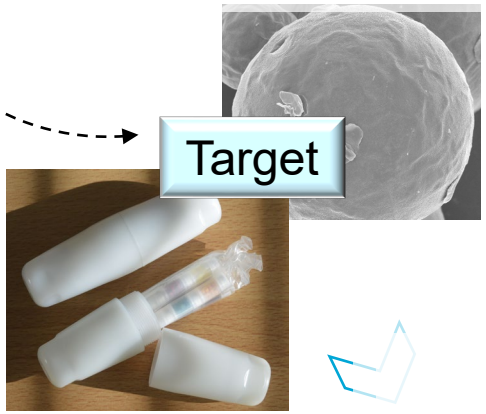
Increase of activity as function of irradiation time

Radionuclide production

$$\left(\frac{dN_B}{dt}\right)_{Total} = \varphi\sigma N_A - \lambda N_B$$

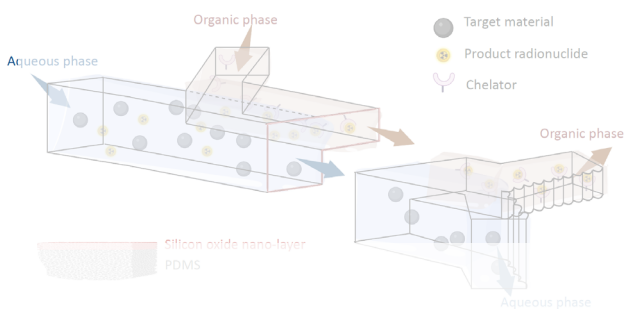
Calculations

$$A_B = \varphi\sigma N_A\left(1 - e^{-\lambda t_{irr}}\right)$$











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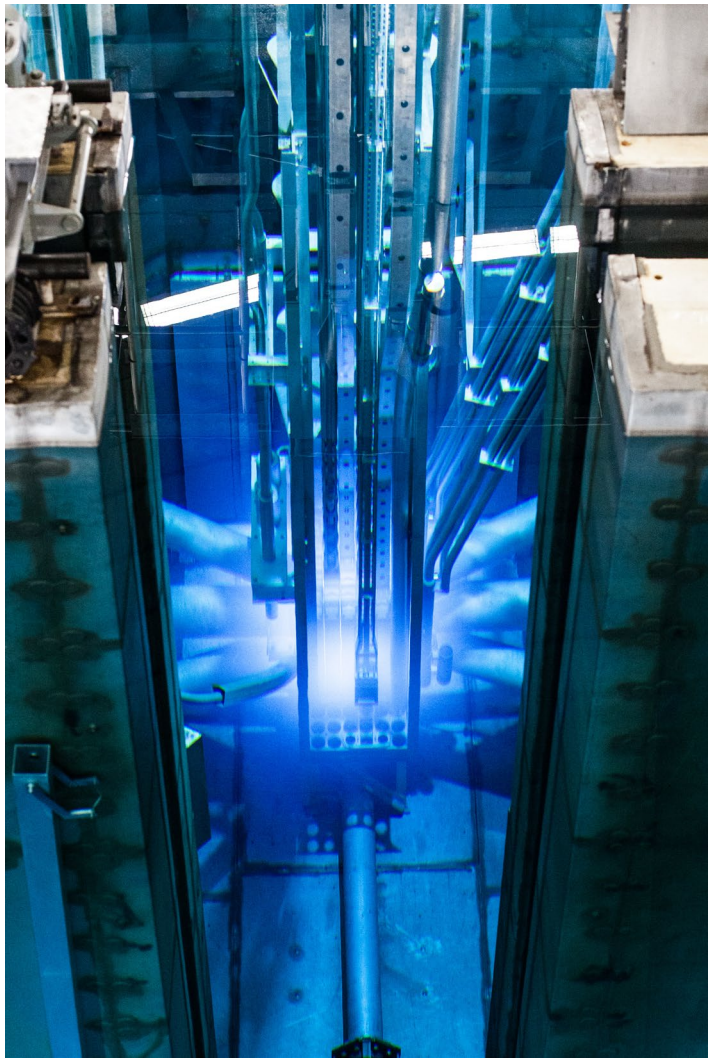
Target Considerations

- Elemental and isotopic content of target
  - What other isotopes are made during irradiation?
- Stability of target
  - Thermal or chemical (radiolysis) decomposition of chemical compounds – formation of gases
  - Behaviour of liquids under heating
  - Chemical reactions with containment



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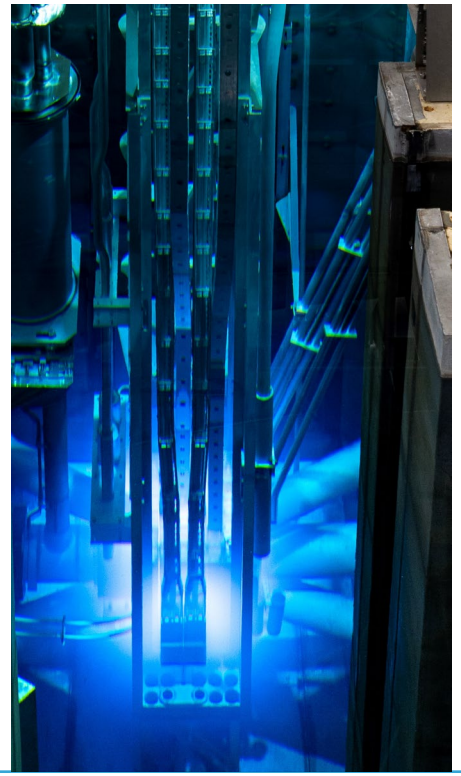
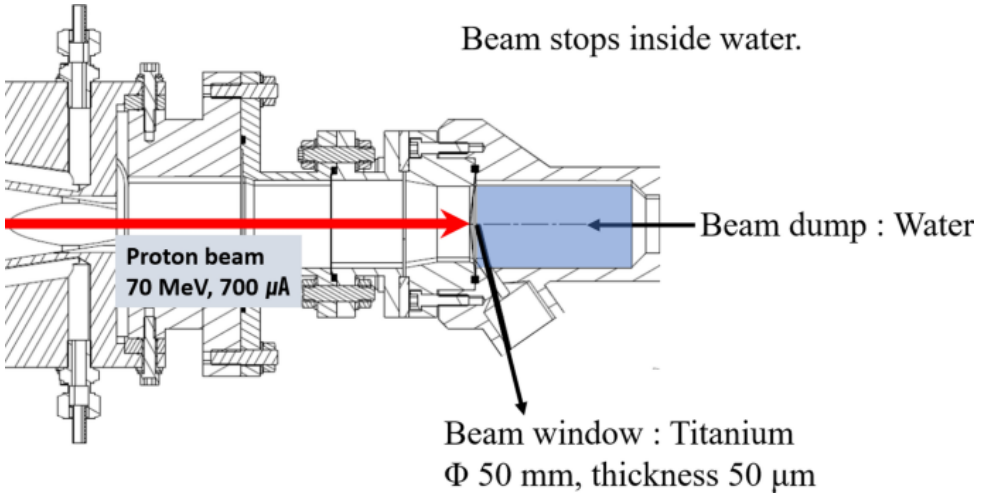
Target Considerations

Difference between reactors and accelerators:

Reactor	Accelerator
• Immersion of small target in sea of neutrons • N_t = total number of atoms in target	• Beam is generally smaller than target • $N_t = \frac{N_v}{A}$ (atoms/area; i.e. [atoms/cm^2])





https://link.springer.com/article/10.1007/s40042-023-00803-z

Target - Reactor

- Encapsulation of Target
  - Targets are almost always sealed
  - Polyethylene capsules for short irradiations
  - Quartz for longer irradiations
  - No glass – why?

- Transport systems
  - Pneumatically (rabbits)
  - Mechanically (cables)





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Target - Reactor

- Effect of radiation on polyethylene capsules



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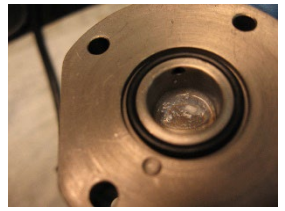
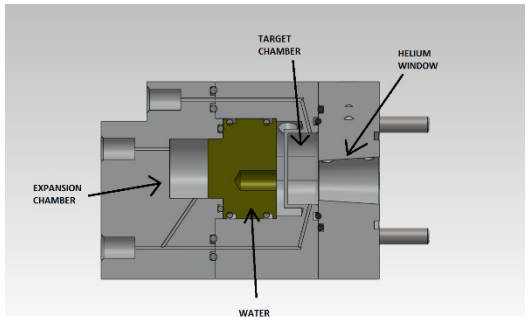
Targetry - Accelerator

- Confusing: The containment of the target material is called „target“
- Stability against price of target (containment) material
  - Aluminium (cheapest option, easiest to manufacture)
  - Niobium, Tantalum etc.
- Transport systems
  - Fluids and gases are transported through tubing/valves
  - Solid target materials are handled pneumatically or mechanically

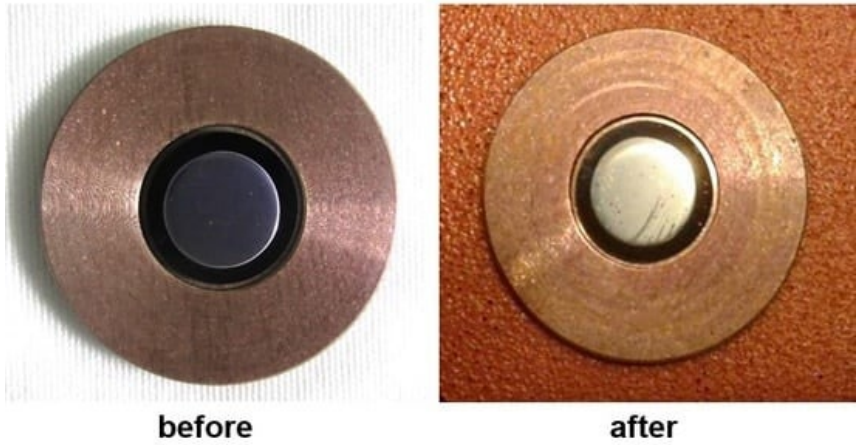






Cyclotron target irradiation

15.6MeV p^+ 60µA (~1kW/cm^2) for 30 min



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Radionuclide production

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Calculations

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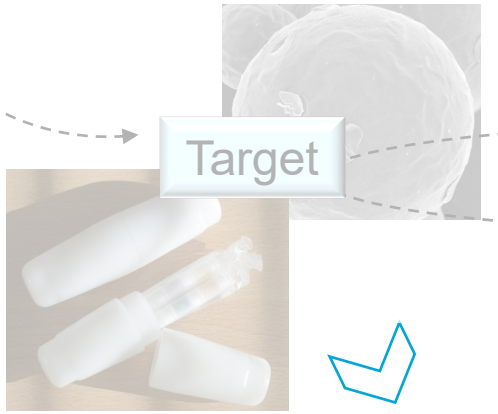
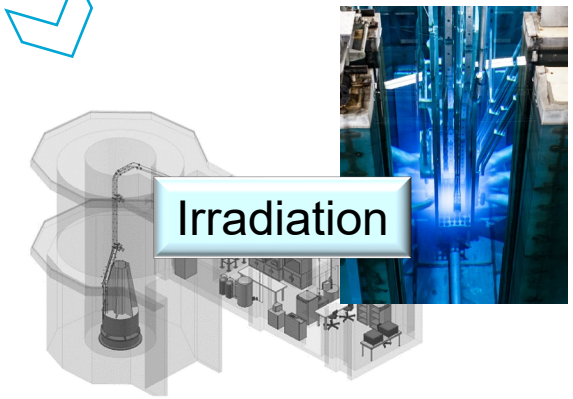


Target

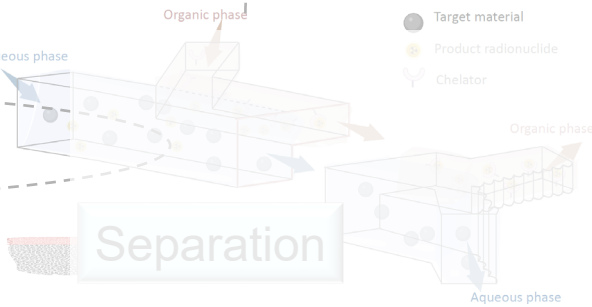


Irradiation

Recycling



Product



Separation

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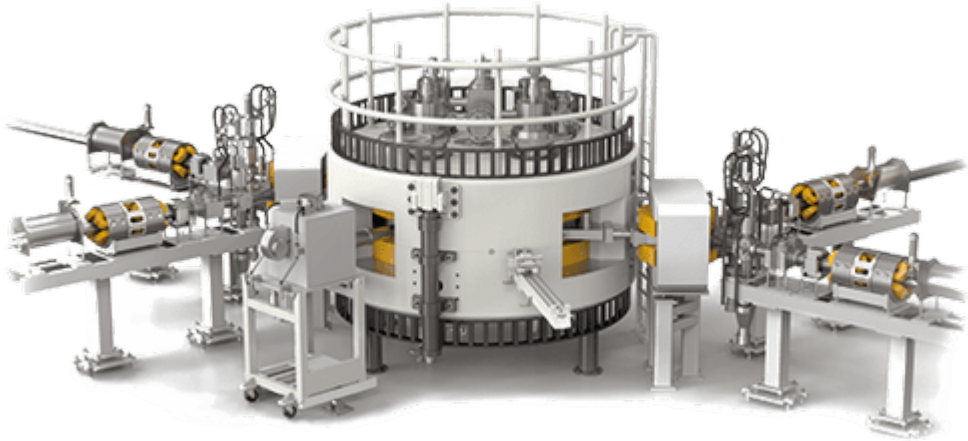
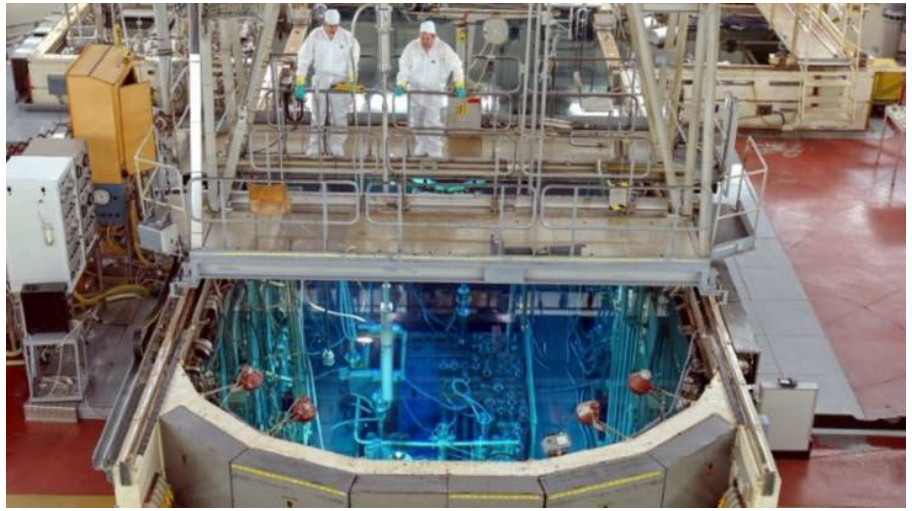
Irradiation facilities

- Nuclear reactors



- Accelerators
  - Cyclotrons
  - Linear Accelerators





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Nuclear reactor

- Production in **research reactors**
  - maximal neutron flux
  - minimal thermal power
- Neutron classification
  - Thermal neutrons
    $E_n < 0.5$ eV

in temperature equilibrium with surroundings

  - Epithermal neutrons
    $0.5 \text{ eV} < E_n < 0.5 \text{ MeV}$
  - Fast neutrons
    $0.5 \text{ MeV} < E_n < 20 \text{ MeV}$
  - Very fast neutrons $E_n > 20$ MeV



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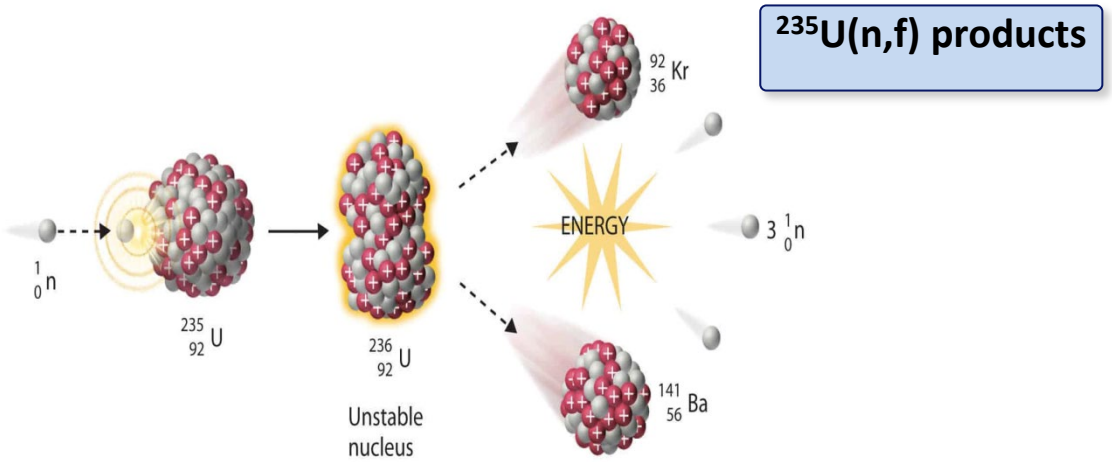
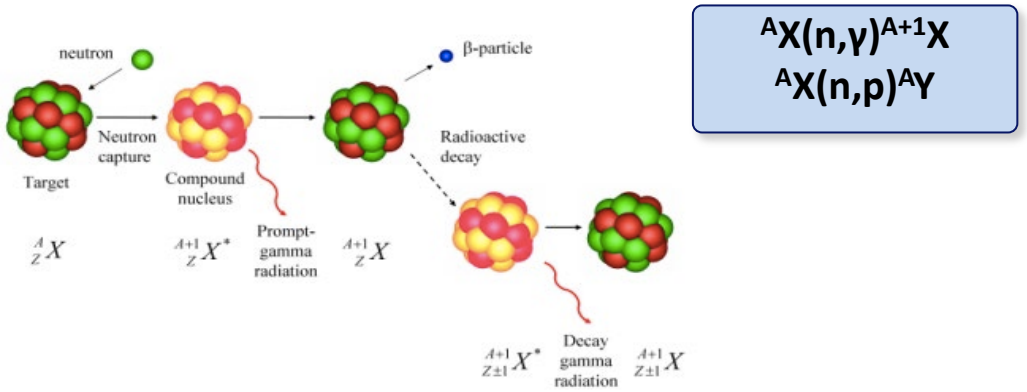
Nuclear reactors

- Two possible reactions:
  - Fission of uranium
  - Neutron capture

- Usually neutron rich radionuclides produced (therapy or SPECT)
  - Specific activity is high in radionuclides of ^{235}U fission
  - Specific activity is usually low by neutron capture





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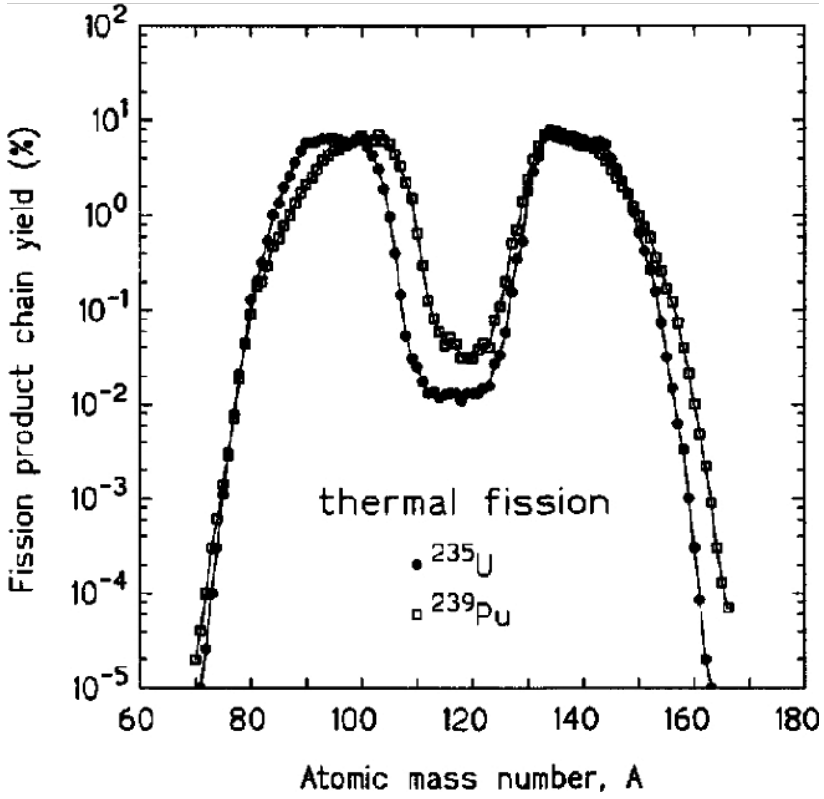
Fission of uranium

- Complex mixture of radioactive nuclides

- Isolation of nuclides from
  - Spent fuel
  - **Separately irradiated uranium targets**



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Fission of uranium

- One irradiation gives around 7 PBq in total of radionuclides
- Contains approximately 150 TBq ^{99}Mo and 50 TBq ^{131}I



U-Al alloy targets

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Fission of uranium

- The useful radionuclides are extracted from the targets

- Extraction process requires many steps and is carried out in hot cells



Hot cells



^{99}Mo solution

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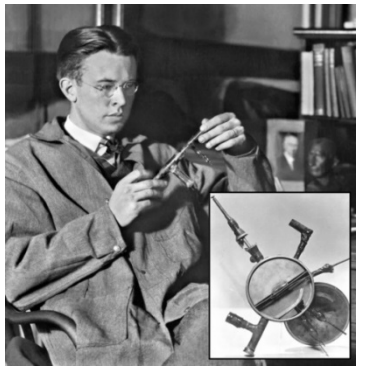
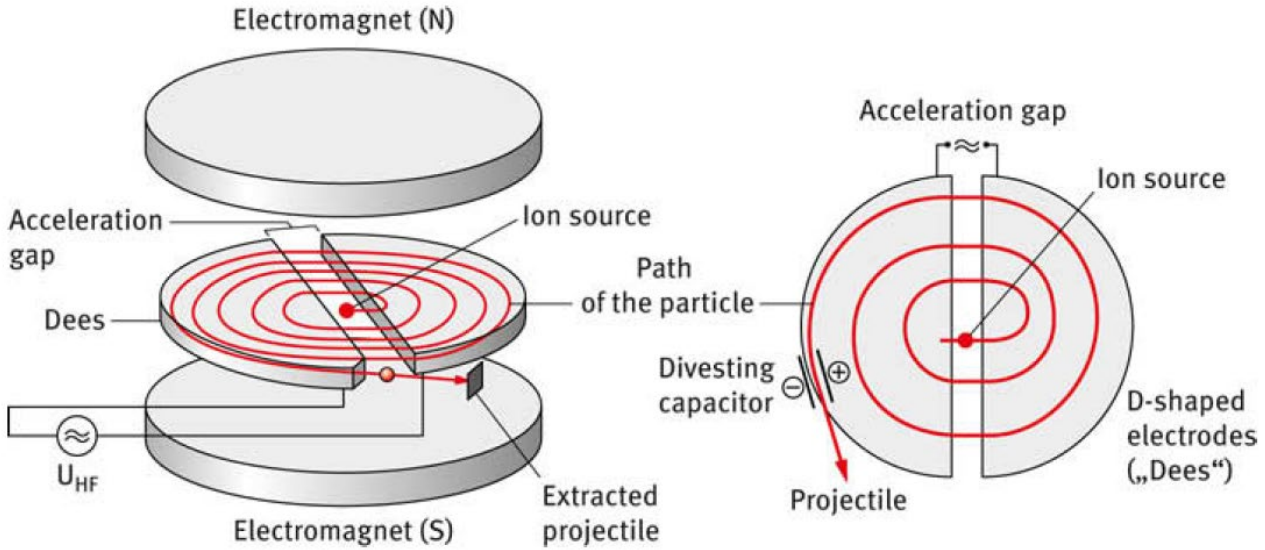
Cyclotron

- Ions are released from the ion source at the center of the magnetic field
- Accelerating ions are forced to move along a spiral trajectory by a static magnetic field B provided by two electromagnets
- The ions are extracted at a desired energy



1930 E.O. Lawrence & M.S. Livingston – 80 keV cyclotron



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Cyclotron products

Diagnostic isotopes

Radionuclide	Half-life	Reaction	Energy (MeV)
Tc-99m	6.0 h	^{100}Mo(p, 2n)	30
I-123	13.1 h	^{124}Xe(p, 2n)^{123}Cs	27
		^{124}Xe(p, pn)^{123}Xe	
		^{124}Xe(p, 2pn)^{123}I	
		^{123}Te(p, n)^{123}I	15
		^{124}Te(p, 2n)^{123}I	25
Tl-201	73.1 h	^{203}Tl(p, 3n)^{201}Pb $\rightarrow$ ^{201}Tl	29
C-11	20.3 min	^{14}N(p, α)	11–19
		^{11}B(p, n)	10
F-18	110 min	^{18}O(p, n)	15
		^{20}Ne(d, α)	14
		^{nat}Ne(p, X)	40
Cu-64	12.7 h	^{64}Ni(p, n)	15
		^{68}Zn(p, αn)	30
		^{nat}Zn(d, αxn)	19
		^{nat}Zn(d, 2pxn)	19
I-124	4.14 d	^{124}Te(p, n)	13
		^{125}Te(p, 2n)	25

Therapeutic isotopes

Radionuclide	Half-life	Decay mode	Reaction	Energy (MeV)
Br-77	2.4 d	Auger electrons	^{75}As(α, 2n)	27
			^{77}Se(p, n)	13
			^{78}Se(p, 2n)	24
			^{79,81}Br(p, xn)^{77}Kr	45
			^{nat}Mo(p, spall.)	>200
Pd-103	17.5 d	Auger electrons	^{103}Rh(p, n)	19
			^{nat}Ag(p, xn)	>70
Re-186	90.6 h	β^-	^{186}W(p, n)	18
			^{186}W(d, 2n)	20
			^{197}Au(p, spall.)	>200
			^{nat}Au(p, spall.)	>200
			^{nat}Ir(p, spall.)	>200
At-211	7.2 h	α	^{209}Bi(α, 2n)	28
			^{209}Bi(^{7}Li, 5n)^{211}Rn	60
			^{232}Th(p, spall.)^{211}Rn	>200

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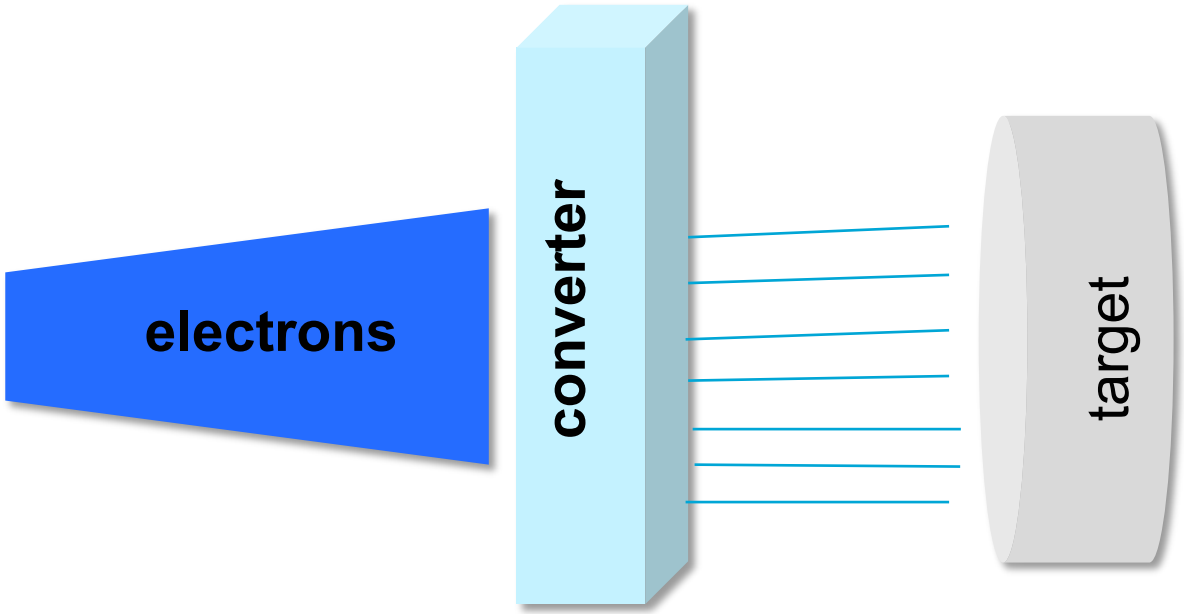
Production methods-Electron accelerators

- Usually proton rich
- Variety of reactions possible (γ, p); (γ, n) reactions
- Major problem is cooling target



W, Ta…

Most promising radionuclides

^{67}Cu, ^{47}Sc, ^{225}Ac

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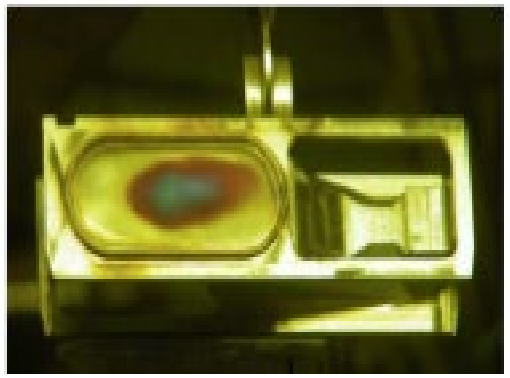
Reactor vs. accelerators - production

Rb target



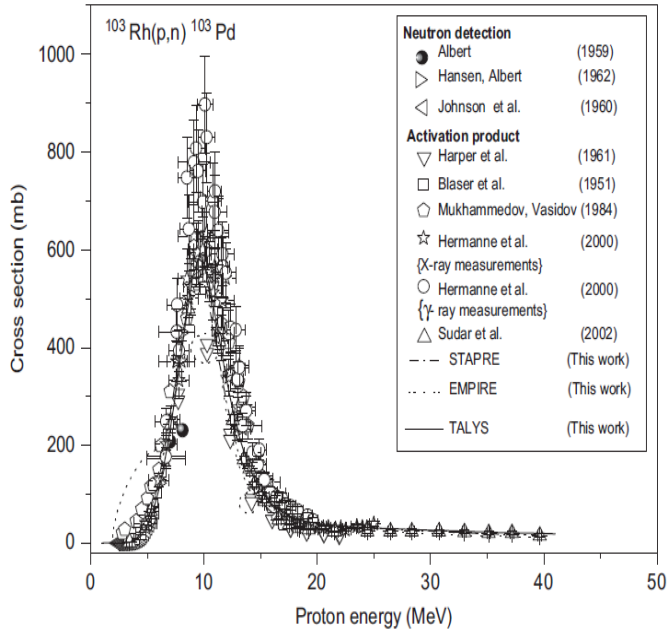
Los Alamos

Nuclear Reactors:

- Most nuclear data known
- Targets usually simple powders or solid metals
- Size targets more flexible
- A few large nuclear reactors available
- Separation product/target after irradiation not always necessary

Accelerators:

- Nuclear data not always known
- Targets can be complex. Liquid, gas, solids possible
- Size limited depending on cooling possibilities and yield
- Many accelerators available worldwide
- Separation always necessary



M. Hussain et al. Appl. Rad. Isot. 2009

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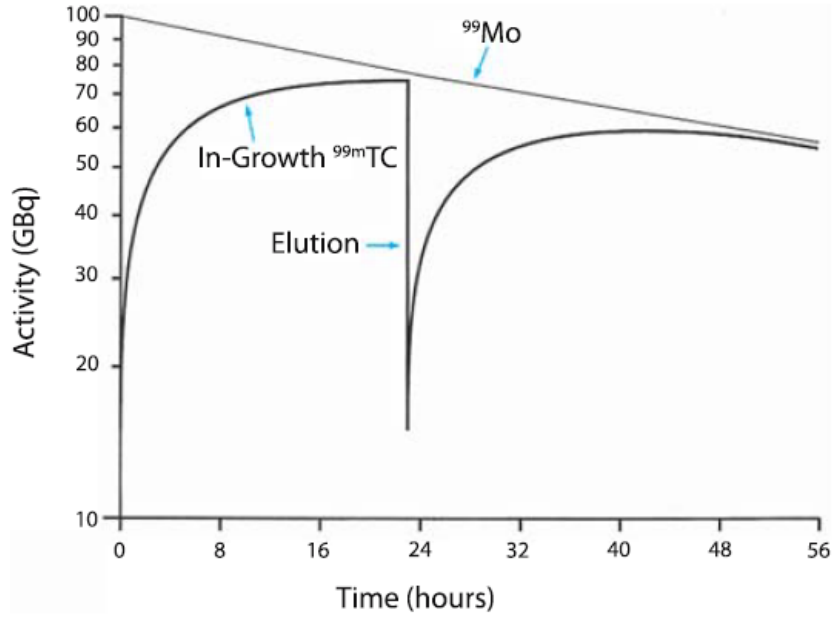
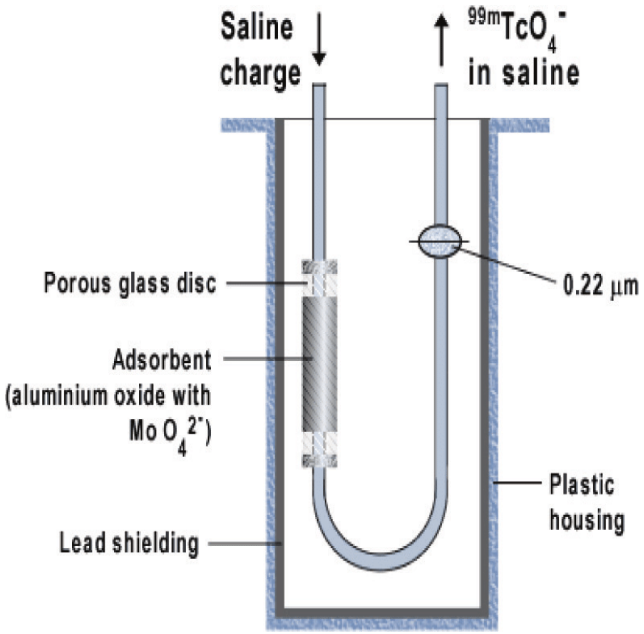
Generators

- Variety of generators exist
- Daughter radionuclide is eluted on demand
- $^{68}Ge/^{68}Ga$ (PET) – ^{68}Ge cyclotron produced
- $^{99}Mo/^{99m}Tc$ (SPECT) - ^{99}Mo reactor produced
- $^{188}W/^{188}Re$ (Therapy) – ^{188}W reactor produced
- $^{225}Ac/^{213}Bi$ (In vivo generator) - ^{225}Ac reactor produced
- Reduce supply issues





- ^{99m}Tc used in more than 30 million tests worldwide!

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Radionuclide production

$$\left(\frac{dN_B}{dt}\right)_{Total} = \varphi\sigma N_A - \lambda N_B$$

Calculations

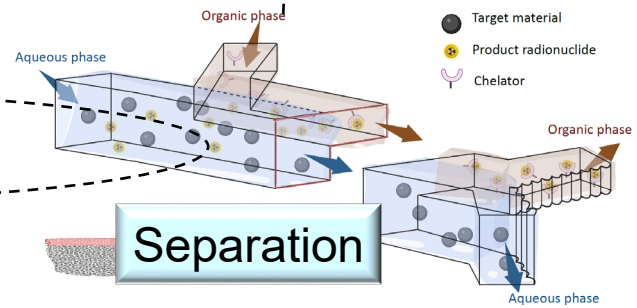
$$A_B = \varphi\sigma N_A\left(1 - e^{-\lambda t_{irr}}\right)$$

Recycling

Product



Target



Separation



Irradiation

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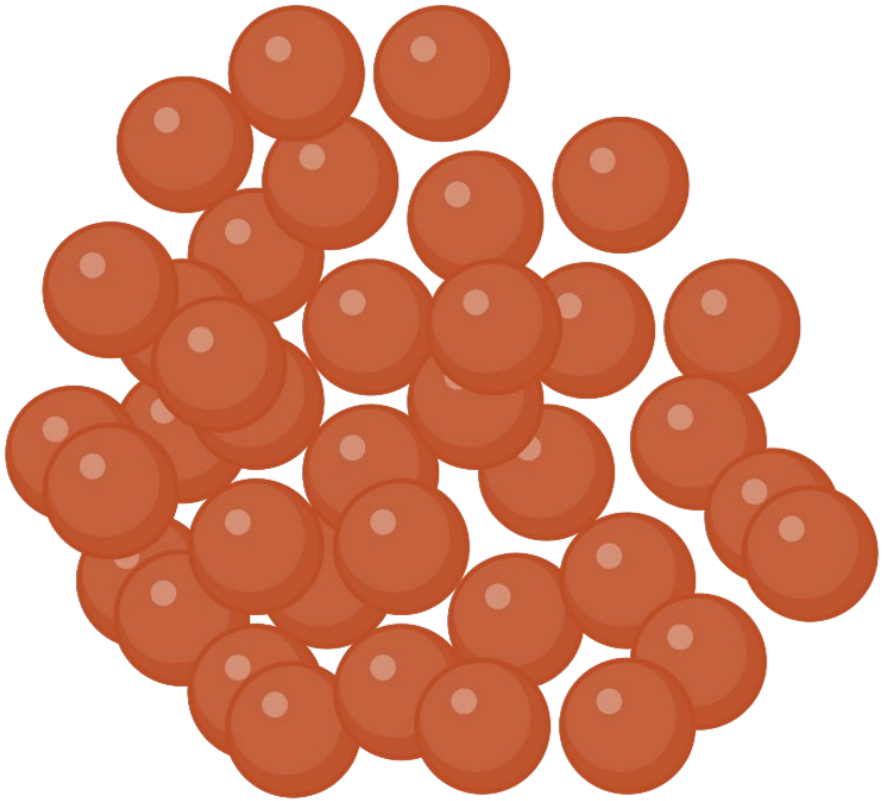
Production process of radionuclides

- Irradiation of target material



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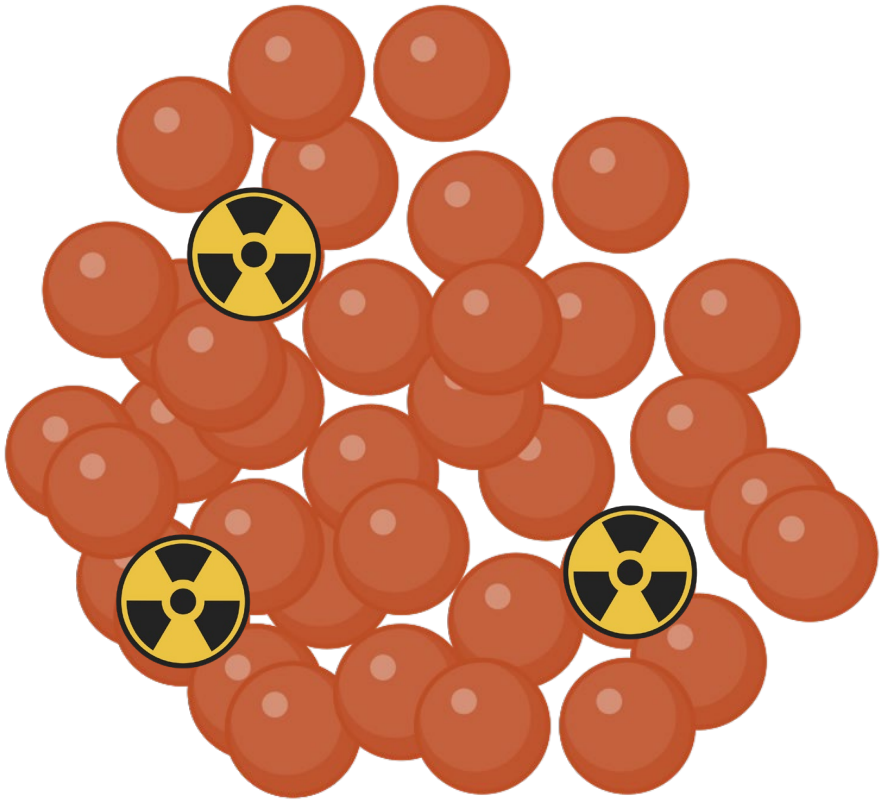
Production process of radionuclides

- Irradiation of target material



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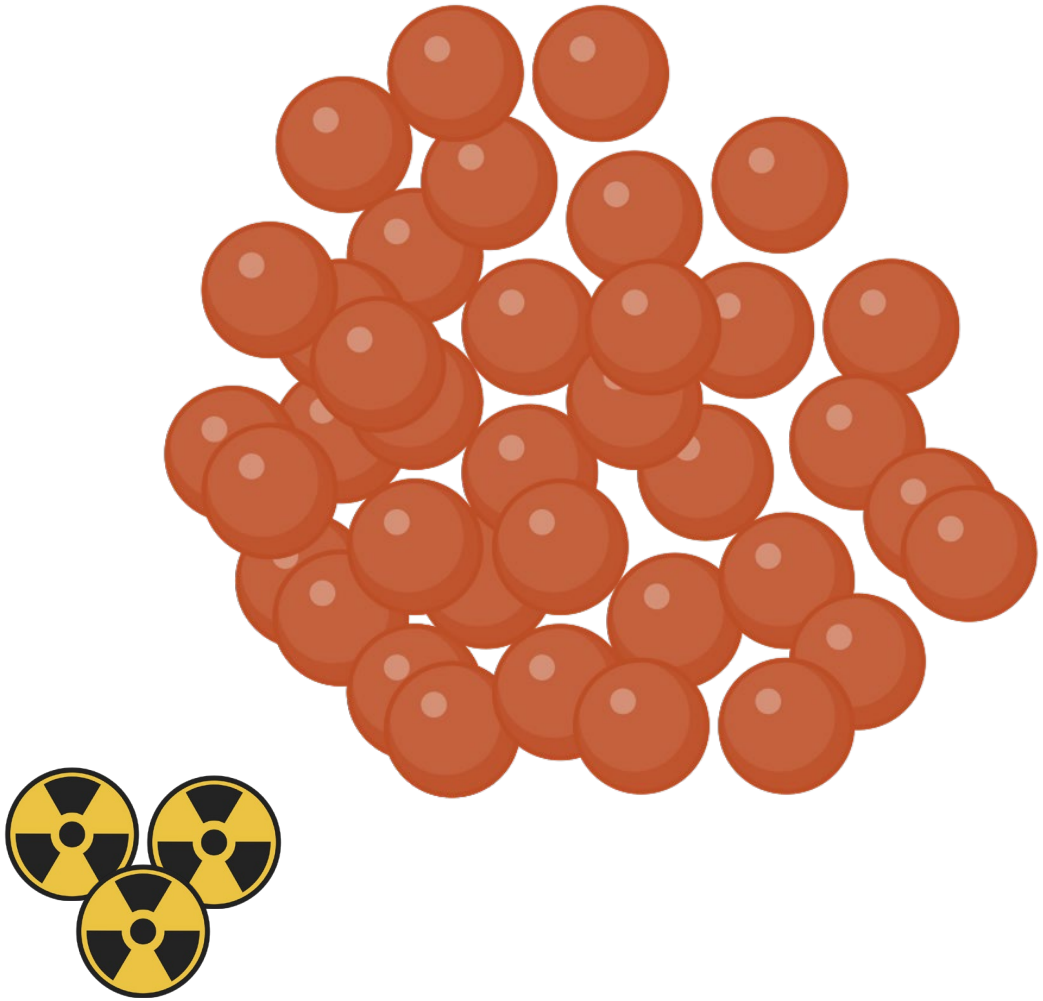
Production process of radionuclides

- Irradiation of target material



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Radiochemical separation techniques

- **Precipitation**
- **Chromatography**
- **Solvent extraction**
- Sublimation
- Electrochemical separation

Precipitation in radiochemistry

Marie Curie isolated radium using precipitation

Precipitation reactions often used to recover target material



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Precipitation in radiochemistry

Marie Curie isolated radium using precipitation

Precipitation reactions often used to recover target material

Radionuclide isolation tricky: low conc.

→ Co-precipitation



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Co-Precipitation

Suitable compounds:

- Isotopic carrier (e.g. Lu^{3+} for $^{177}Lu^{3+}$)

Effective, but decreases specific activity

- Non-isotopic carriers (chemically similar elements)

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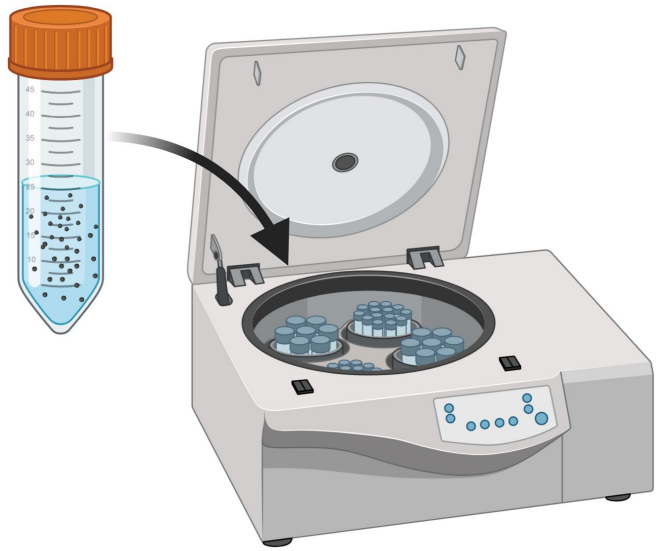
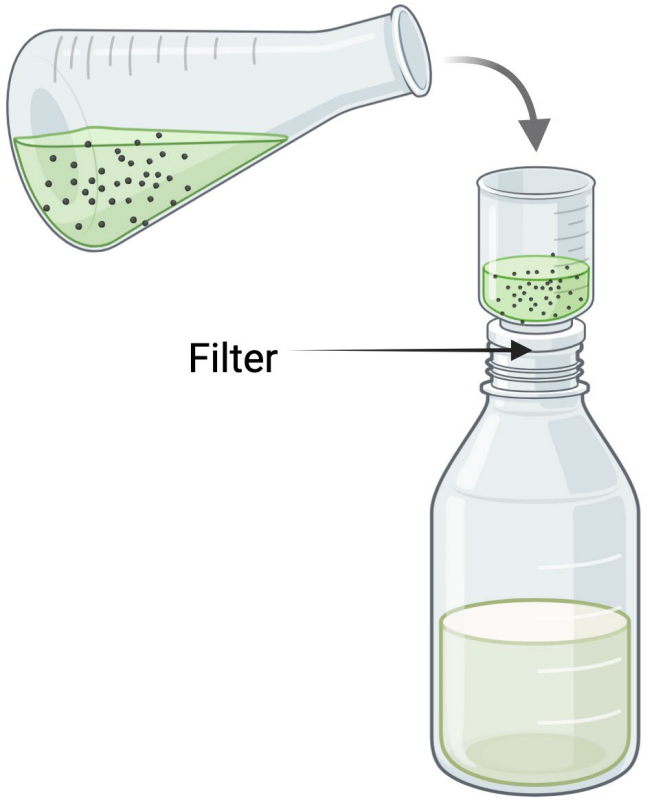
Separation: practical aspects



Centrifuge



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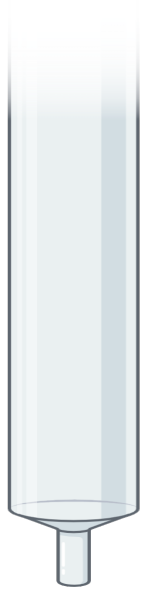
Chromatography

Separates components in the **mobile phase** based on affinity with the **stationary phase**

Column with stationary phase



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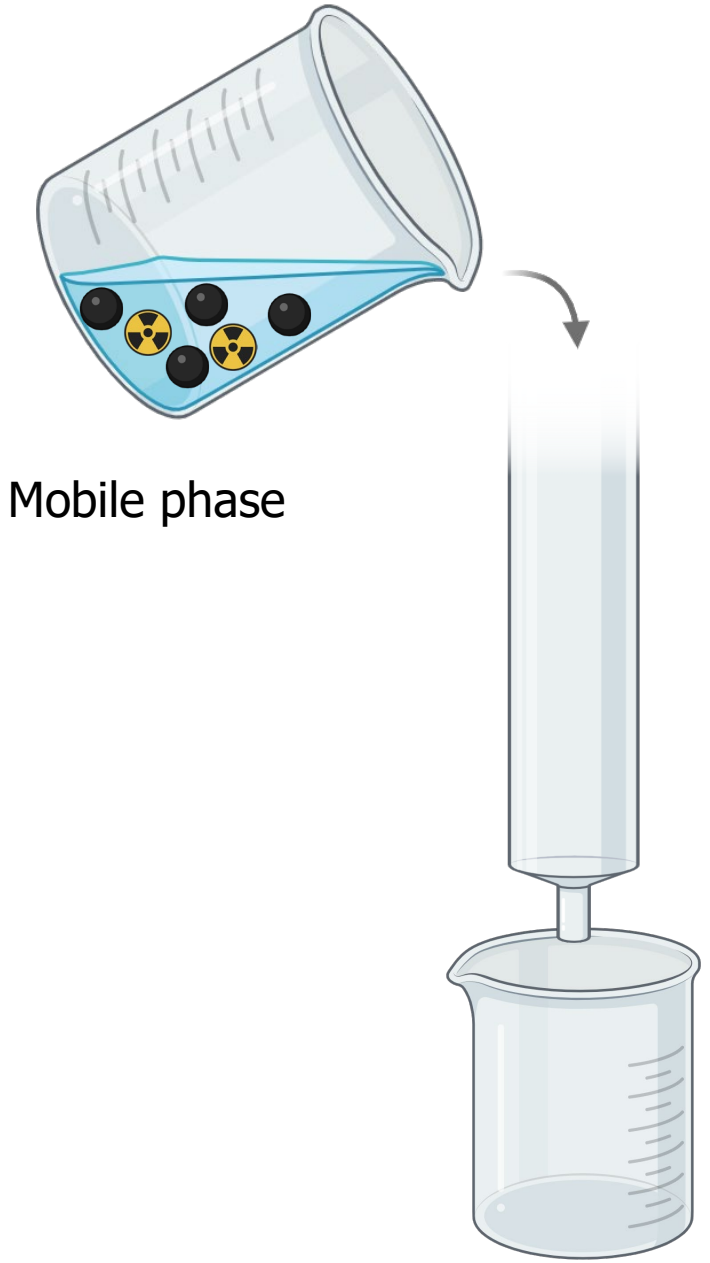
Chromatography

Separates components in the **mobile phase** based on affinity with the **stationary phase**



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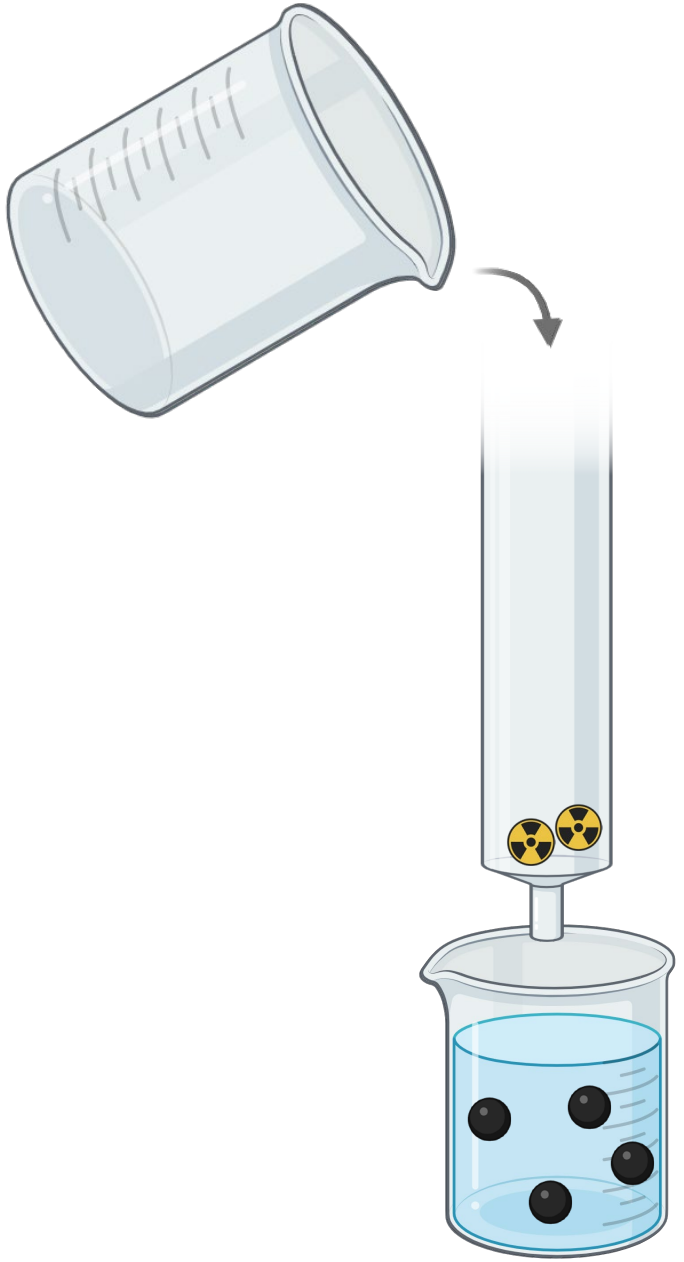
Chromatography

Separates components in the **mobile phase** based on affinity with the **stationary phase**



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Ion exchange resins

Consist of

- a **resin**, e.g. a cross-linked polystyrene matrix



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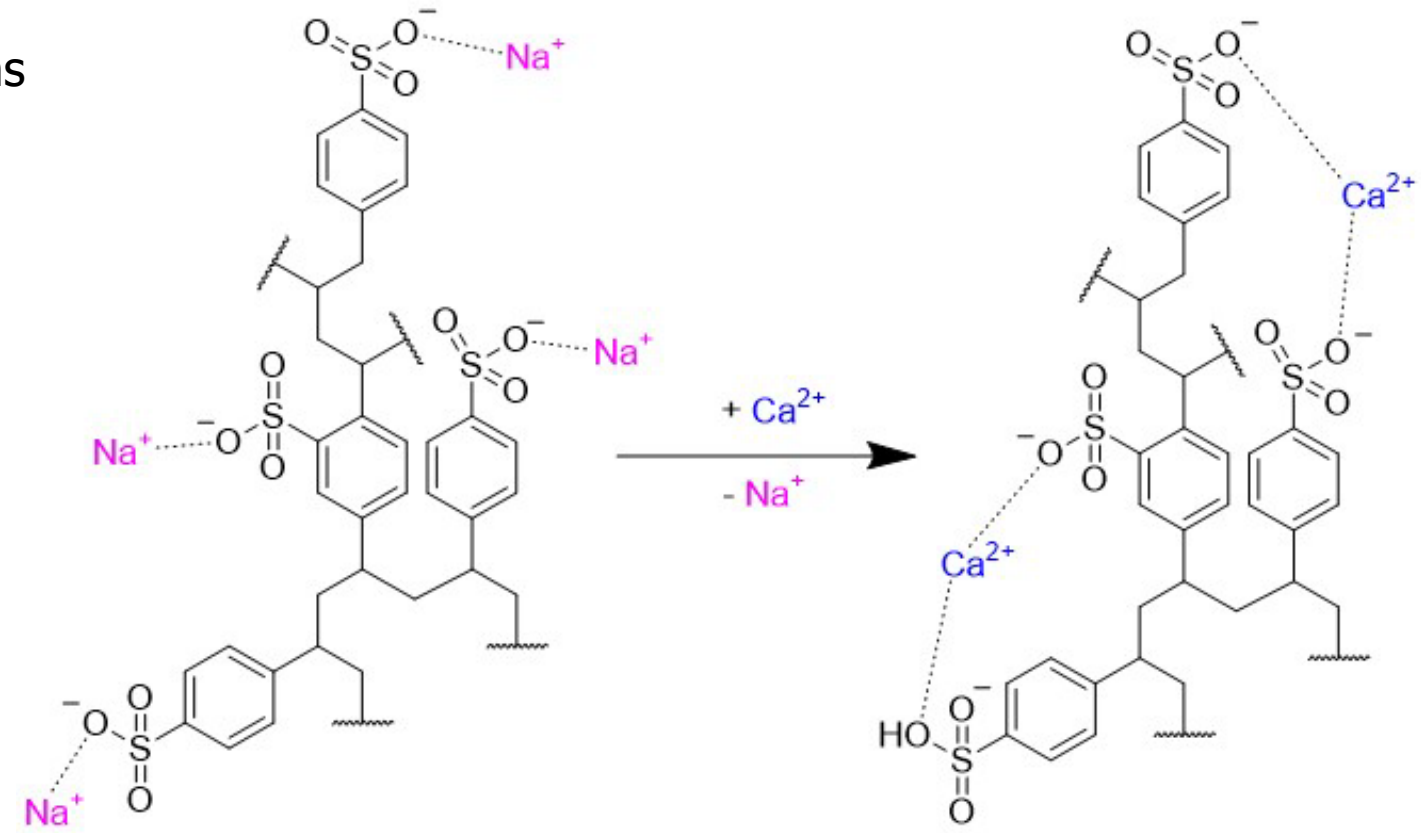
Ion exchange resins

Consist of

- a **resin**, e.g. a cross-linked polystyrene matrix
- **functional groups** that can exchange ions



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Solvent extraction

The process of transferring a substance from any matrix to an appropriate liquid phase.

Also called **liquid-liquid extraction**



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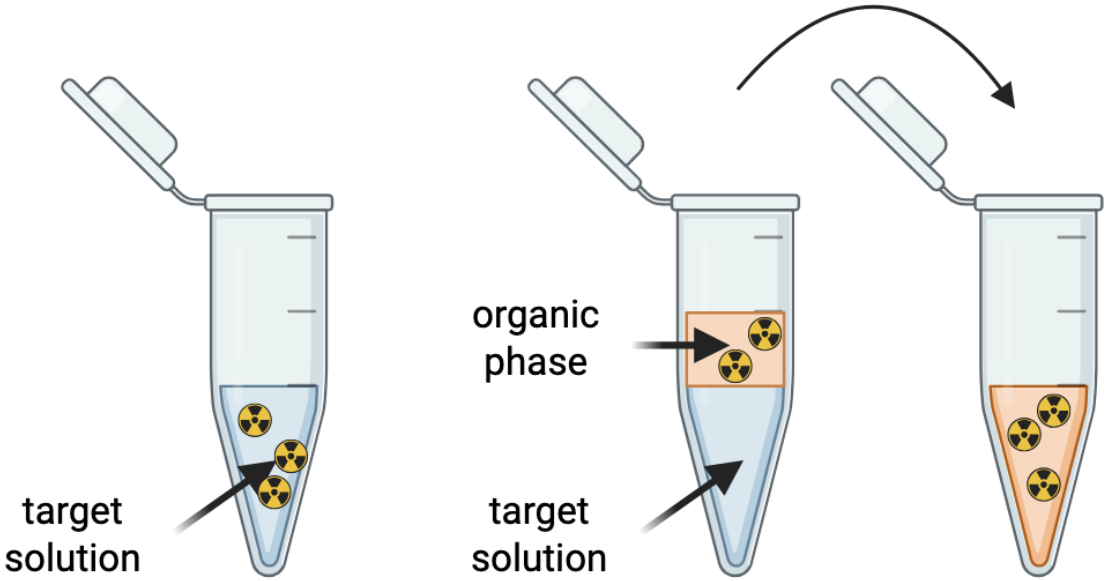
Solvent extraction



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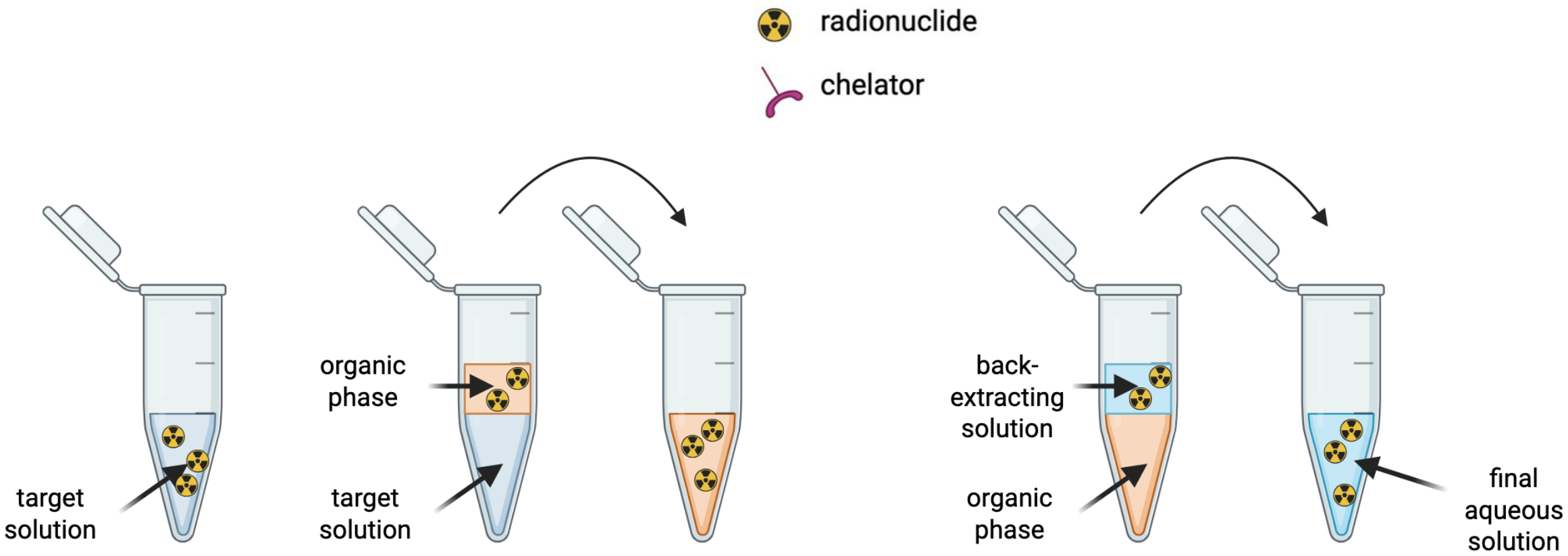
Solvent extraction and back-extraction



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Separation methods

- **Precipitation** suitable for large targets
- **Chromatography** suitable for small targets
- **Solvent extraction** suitable for large targets or liquid targets

Learning Objectives

- ✓ Choose the most suitable production facility by weighing their respective advantages and disadvantages
- ✓ Calculate production levels
- ✓ Evaluate which chemical separation methods are applicable in different situations

Questions?

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Exercise

What activity of ^{59}Fe can be achieved if 1g cobalt is irradiated with 5 MeV neutrons with a flux of $1x10^{9}$ n cm^{-2} s^{-1} and an irradiation time of 20 h?

$^{59}Co(n,p)^{59}Fe$

^{59}Co has an isotopic abundance of 100% and a neutron cross section of 70 mbarn.

^{59}Fe has a half-life of 45 d

Answer

$$A_B = \lambda N_B = \varphi \sigma N_A \left(1 - e^{-\lambda t_{irr}}\right)$$

A= 9.1 kBq

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Exercise

^{100}Mo (100% abundance) is irradiated on a 19 MeV cyclotron with a 300 μA proton beam for 6 h. The nuclear reactions occurring is ^{100}Mo(p,2n)^{99m}Tc (σ=2201 mb). The half-life of ^{99m}Tc is 6 h. The size of the target foil reached by the beam is 1.2 cm^3 with a Mo density of 10.2 g/cm^3. The surface area of the beam is 1 cm^2. The elemental charge is $1.609 \cdot 10^{-19}$ C.

How much ^{99m}Tc is produced at the end of irradiation?

$$A_{Tc} = 1.5x10^{14}\,Bq$$

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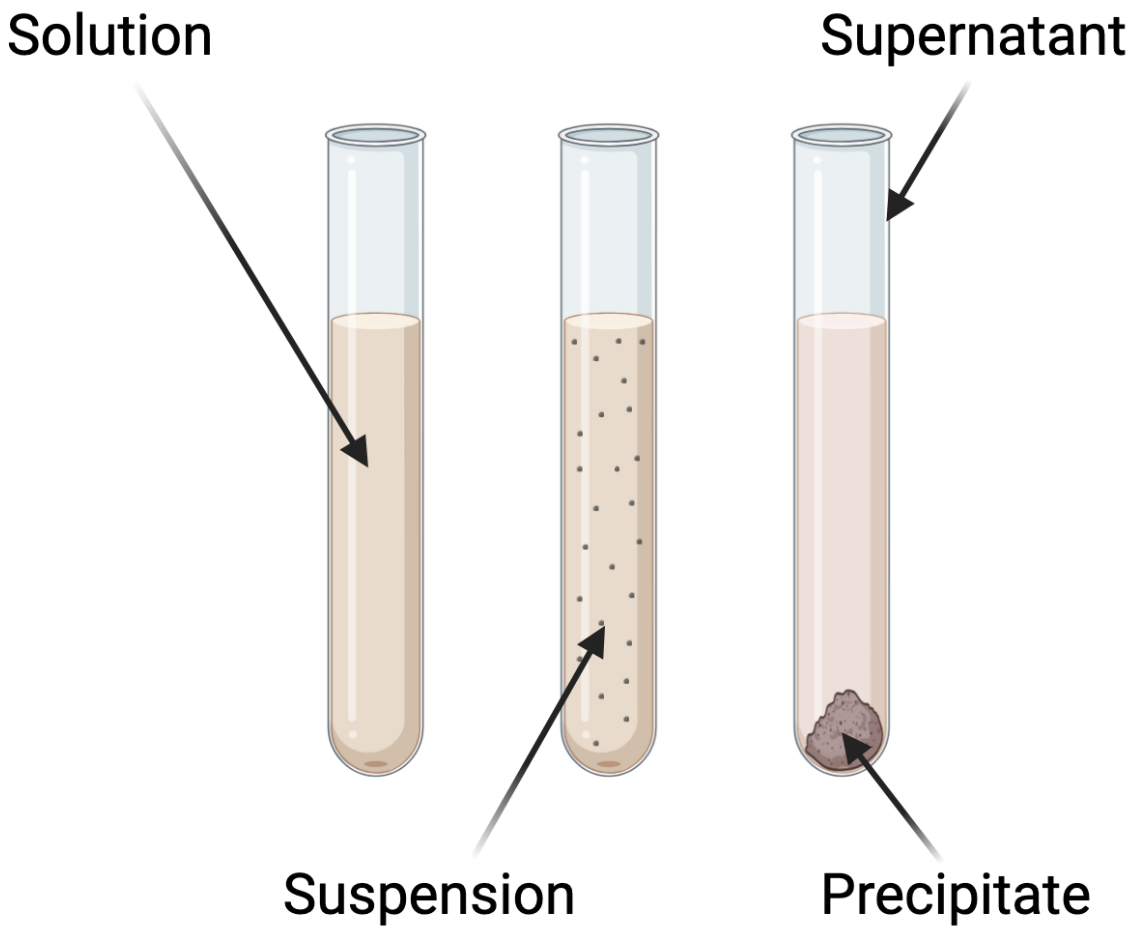
Nomenclature



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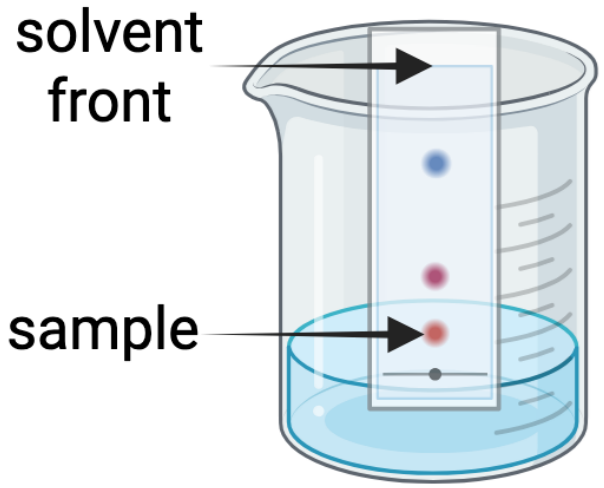
(Instant) thin layer chromatography (TLC)

Often used as easy, high-throughput method to determine radiochemical purity

Retention factor:

$$R_f = \frac{\text{distance traveled by sample}}{\text{distance traveled by solvent}}$$



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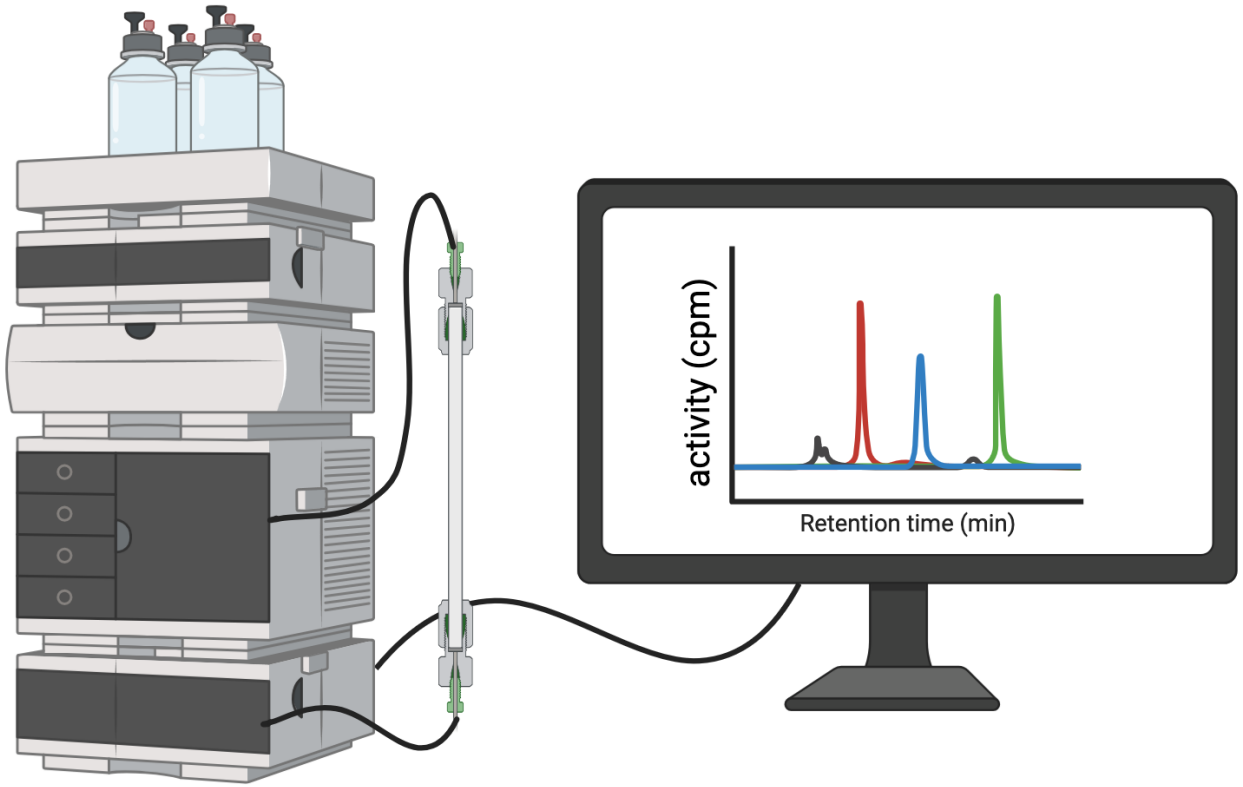
High-performance liquid chromatography (HPLC)

Uses high pressure pumps to pass mobile phase through stationary phase

Used for quality control:

- Radiochemical purity
- Specific activity
- Stability of radiopharmaceutical



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