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Cancer Center

Nuclear Imaging

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Summary of your feedback

- Generally happy and learning
- Activities very helpful
- Like the questions, the engagement etc
- Split on the pace and the novelty of information
- More equations
- More problem – solving and group projects

What is nuclear medicine?

- The use of radioactive materials to visualize and/or treat various diseases

Why is it called nuclear medicine?

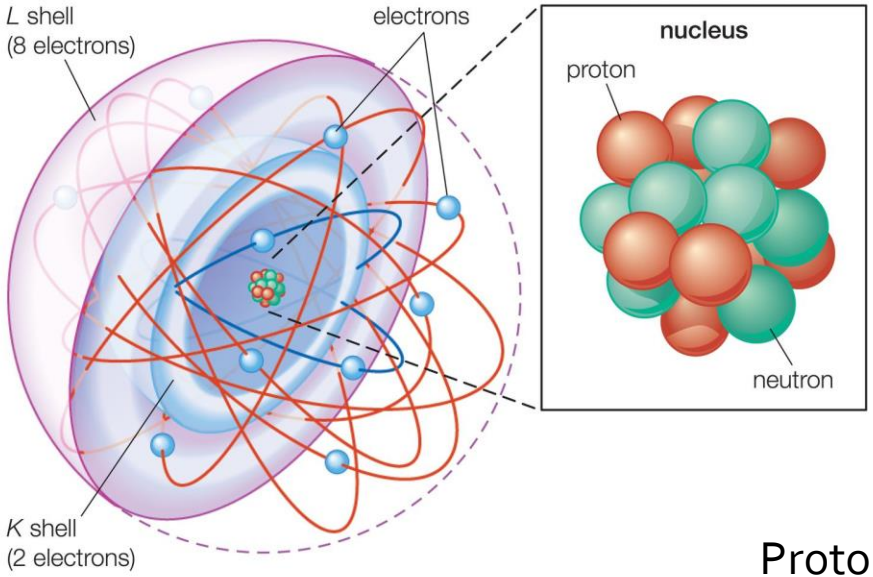
- The emitted particles, whatever they may be, originate in the nucleus.
- Or at least the mechanism for emitting particle starts in the nucleus

What does it mean for something to be a radioactive material?

- The material is unstable: it's composition is changing
- In particular, the nuclear composition is changing by release of energetic particles

We'll now look at the composition of atoms, dynamics of decay etc

Make up and representation of an atom



https://www.thoughtco.com/basic-model-of-the-atom-603799

$$^{12}_{6}C$$

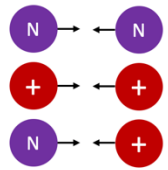
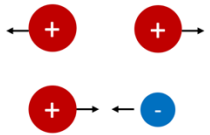
Protons and neutrons together are called *nucleons*

What determines the identity of the element: number of protons or number of neutrons?

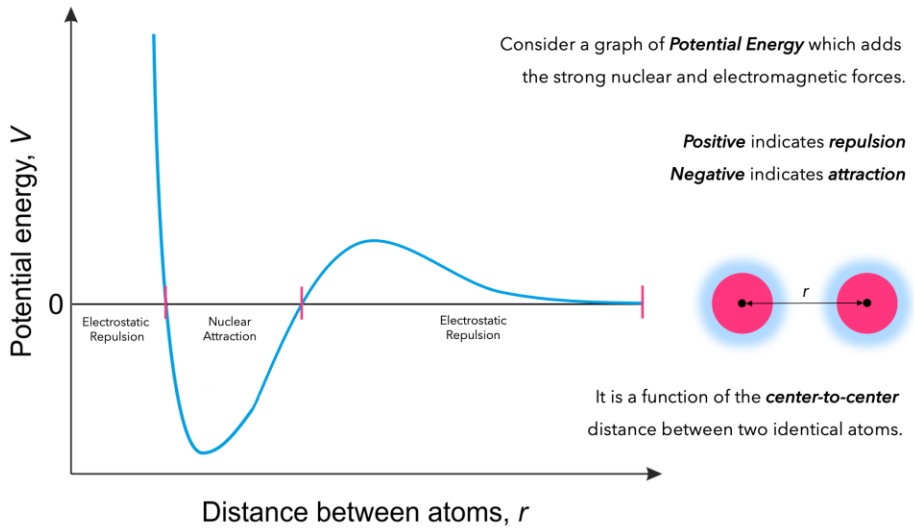
- # of protons gives the identity of the element. If that changes, the element is changes
- # of neutrons tells you what *isotope* of the element we are dealing with.
- Usually have a most abundant isotope, but also other natural ones and artificial ones

What holds protons together?

Nuclear strong force is one of the fundamental forces of nature. It is a super short-range interaction that binds protons (and neutrons) together

	Nucleon Interaction	Relative Strength	Range (m)
Strong Nuclear Force		137	10^{-15}
Electro-magnetic Force		1	∞

https://www.expii.com/t/strong-nuclear-force-vs-electrostatic-force-overview-8755



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How does the nuclear strong force become insufficient?

- When the nucleus gets too big, some nucleons are necessarily farther apart from "the group" and the nuclear strong force has less influence (the attraction drops off quickly)
- When a nucleus absorbs energy (from a collision or another source), if the nucleus is large enough it can become unstable and some particles can escape
- A strong collision can essentially split a nucleus causing particle to be emitted
- There is a phenomenon called quantum tunneling that allows particles to escape (with some small probability) the nuclear strong force even when they are within the range of influence.

- All in all, radioactivity is observed as a "random" process with statistically likelihood of a particle shedding event.
- Cannot determine which nucleus will be transformed, but can reliably predict on a population level how much of the sample will decay over time.

What are common unstable nuclei?

- Roughly either heavy elements (big nuclei) or elements (usually isotopes) where the balance of protons and neutrons is off.

- **Heavy elements:**

Plutonium: ^{239}Pu
Uranium: ^{238}U
Thorium: ^{232}Th
Radium: ^{226}Ra

- **Radioactive isotopes**

Carbon: ^{14}C
Potassium: ^{40}K
Rubidium: ^{87}Rb
All isotopes of uranium

- **Artificial isotopes**

Fluorine:	^{18}F	(PET applications)
Technetium:	^{99m}Tc	(SPECT applications)
Iodine:	^{131}I, ^{123}I	(thyroid treatment/imag)
Galium:	^{67}G	(tumors with SPECT)
Thallium:	^{201}Th	(cardiac imaging)
Yttrium:	^{90}Y	(cancer therapy)
Lutetium	^{177}Lu	(cancer therapy)

How do they decay?

As mentioned before, the radioactivity process is "random".

It is observed, however, that the rate of particle emission from a radioactive substance is proportional to the amount of radioactive substance that's there. This rate is called the **activity (A)**.

$$A = -\frac{dN(t)}{dt} \qquad A = \lambda\, N(t)$$

1. In groups, on the whiteboard, derive the equation for $N(t)$ as a function of N_0, t, λ

2. In terms of λ, how long does it take for half of the radioactive material to decay?

How do they decay?

As mentioned before, the radioactivity process is "random".

It is observed, however, that the rate of particle emission from a radioactive substance is proportional to the amount of radioactive substance that's there. This rate is called the **activity (A)**.

$$A = \lambda N(t)$$

$$A = -\frac{dN(t)}{dt}$$

$$\lambda N(t) = -\frac{dN(t)}{dt}$$

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

$$\tau = \frac{\ln(2)}{\lambda}$$ **Half-life**

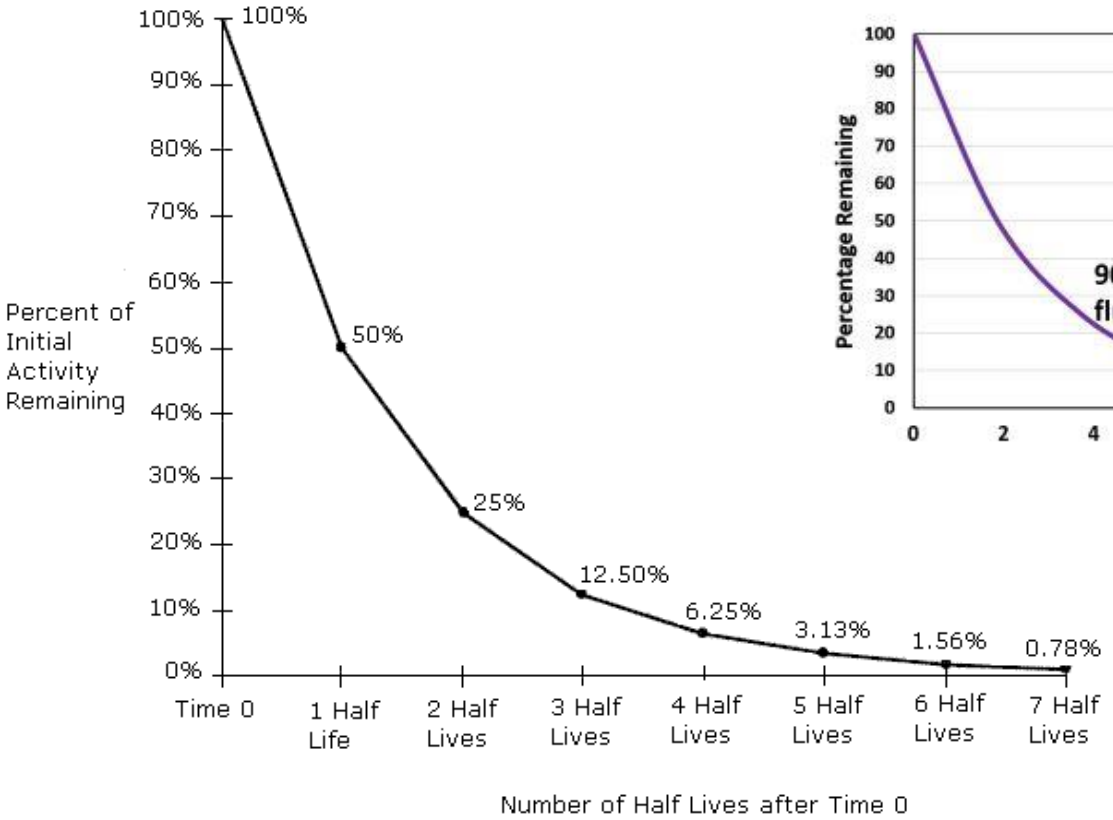
Activity is measured in Becquerels (Bq) = 1 decay/sec

More practical unit is Curie (Ci)

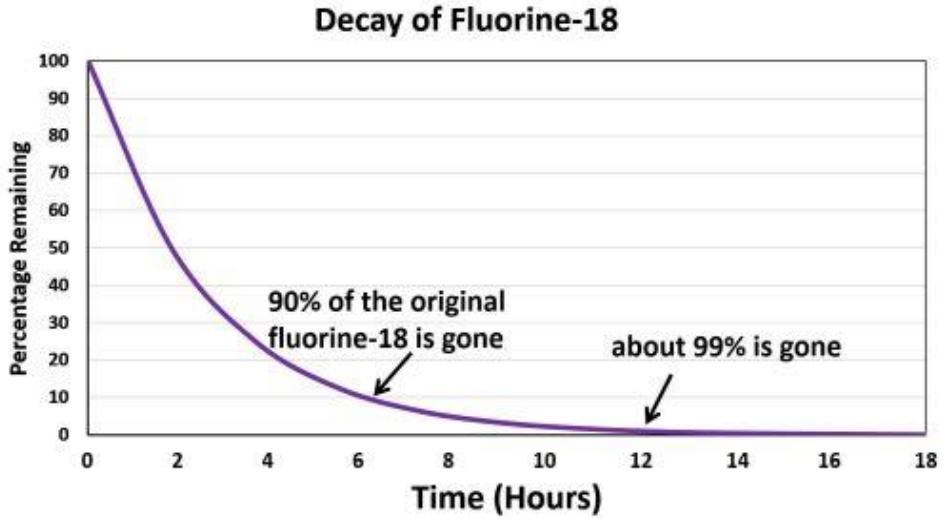
1 Ci = 3.7×10^{10} Bq

Half – life is measured in units of time (mins, hours, years)

How do they decay?



https://remm.hhs.gov/halflife.htm



- As time goes on, the number of emitted particles that are used for imaging or therapy decreases

Spot check our understanding

Is the activity of a given radioactive element a material property?

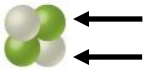
Is the activity then just about the number of radioactive nuclei I have in the sample? Just like the concentration?

Half-life of ^{18}F is 110min. How much radiation (activity, i.e. rate of particles released) is left after 440 minutes

(A) The same since activity doesn't change
(B) 50%
(C) 25%
(D) 6.25%

Most common decay mechanisms used in nuclear medicine

Type	Nuclear equation	Representation	Change in mass/atomic numbers



High energy alpha to destroy tumor

High energy beta to destroy tumor

SPECT

PET

SPECT

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How do we put it to medical use?

In applying this to medical imaging / therapy, the goal is two fold:

1. Get the radioactive element to the target of interest
   - Make sure the radiopharmaceutical makes it to the target
   - Ideally, it only gets to the target and nowhere else

2. Utilize the radiation particles
   - Capture them on a detector to visualize the target
   - Use the particles to destroy the tumor
   - Carry a therapeutic load and visualize

A bit of history in using radiation for medicine

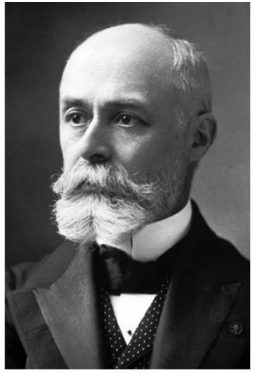
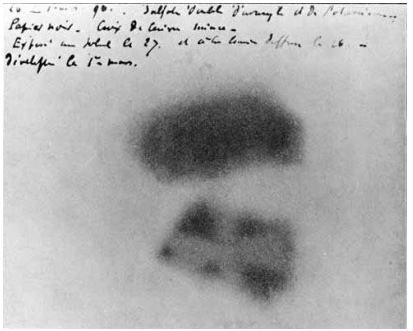


Photo from the Nobel Foundation archive.

Henri Becquerel. Nobel Prize in Physics 1903

French physicist who accidently discovered radioactivity by placing uranium salts on photographic plates. He saw marks on the plates although no light hit it and deduced that energy was coming off of the uranium salt.



Marie Curie. Nobel Prize in Physics 1903
Nobel Prize in Chemistry 1911

Following Becquerel's work, Marie and Pierre further developed spontaneous radiation. She then looked for other elements that exhibit radioactivity. She found and was able to isolate polonium and radium. Marie Curie coined the term "radioactivity"

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A bit of history in using radiation for medicine

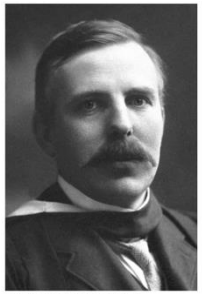


Photo from the Nobel Foundation archive.

Ernest Rutherford. Nobel Prize in Chemistry 1908

Discovered how radioactivity transforms particles and explained the phenomenon. Found alpha, beta and gamma radiation.

First crude attempts to use radiation in medicine started in early 1900's

Focused radiation and better precision in the 1920's

Invention and development of artificial radioisotopes expands opportunities in radiation therapy

First diagnoses with nuclear medicine (iodine) in the 1930's

Invention of PET in the 1970

Two kinds of nuclear medicine:

Two types of nuclear medicine:

1. **Diagnostic:** to visualize, localize, assess the tumor (in an oncological context)
2. **Therapeutic**: to destroy the tumor through high energy radiation

- **Design the radiotracer to emit a particle of interest**
  - With a half life appropriate for the goal (short enough to not overexpose, long enough to image if imaging)
  - With the right energy when appropriate to either kill cells or image
- **Couple the radioactive nucleus to something that will go to the target tissue**
  - The more selective the better
- **Capture the radiation to image the tumor**

Making radionucleotides: a few examples

Technetium-99m: ^{99m}Tc

1. Make the radioactive nucleus

- Start with stable Molybdenum (^{98}Mo) and convert to ^{99}Mo by neutron bombardment in a reactor. Can also break uranium 235 to get ^{99}Mo.
- Separate and purify ^{99}Mo
- ^{99}Mo is allowed to decay to ^{99m}Tc while ^{99}Mo is retained in the reactor.
- ^{99m}Tc is eluted to be used in a compound as a radiopharmaceutical
- ^{99m}Tc has a half-life of ~6 hours, which is great for imaging

2. Couple to a pharmaceutical

- Form a complex with a ligand of interest
- Can couple to monoclonal antibodies specific to a cancer to have it go to a tumor
- Other molecules for cardiac imaging, thyroid, bone etc.
- Purify to remove unbound radioactive nucleus

Making radionucleotides: a few examples

Technetium 99m: ^{99m}Tc

3. Inject into patient

- Introduce radiopharmaceutical via injection or ingestion
- Allow to circulate and accumulate in the body

4. Image the radiation

- What kind of decay does ^{99m}T undergo?
- Once the compound is accumulated, can start imaging
- Need to capture the time frame when already enough accumulation and still enough radiation / activity.

Making radionucleotides: a few examples

Fluorine-18: ^{18}F

1. Make the radioactive nucleus

- The most common route is by bombarding ^{18}O with protons in the cyclotron
- We start with water that is enriched with ^{18}O and that becomes the target
- Ionize hydrogen gas to separate protons
- Accelerate the proton in a cyclotron and direct towards the target (^{18}O water)
- The reaction is $^{18}O + p \rightarrow {}^{18}F + n$

Spot check:

If oxygen has 8 protons:

(1) How many neutrons does ^{18}O have?

(2) How many protons does fluorine have?

(3) How many neutrons does ^{18}F have?

- Impurities are then separates and ^{18}F eluted from the resulting reaction

Making radionucleotides: a few examples

Fluorine-18: ^{18}F

2. Couple to a pharmaceutical

- Many different chemistry tricks to couple it to a compound of interest
- Fluorodeoxyglucose (FDG) is one of the common tags. It's an analog of glucose and taken up in tissues with a high metabolic consumption.
  - Tumors
  - Alzheimers
  - Heart disease
- Dopa (part of dopamine synthesis)
  - Parkinson's and other neurological disorders
- Choline to track lipid metabolism, which is higher in tissues with quick turnover
  - Liver, prostate cancer
  - Metastases

Making radionucleotides: a few examples

Fluorine-18: ^{18}F

3. Inject into patient

- Allow to circulate and accumulate in the body
- Why inject as opposed to ingest?
  - Faster distribution (since digestion takes time). Particularly since $\tau_{1/2}$ ~ 110min
  - More reliable distribution for accumulation in targets (digestion more variable)
  - More reliable concentration delivery

4. Image the radiation

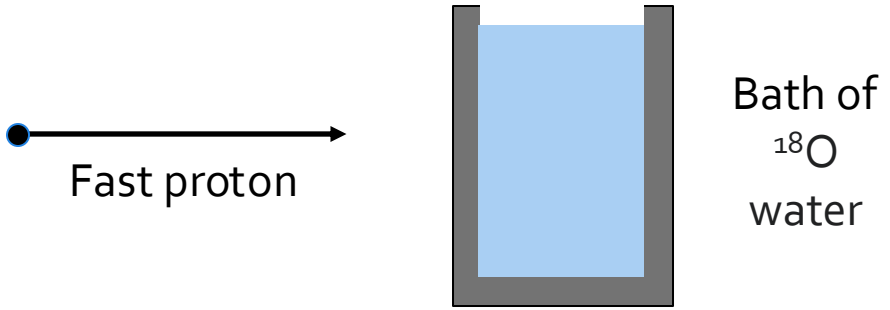
- ^{18}F undergoes positron emission
- Once the compound is accumulated, can start imaging in PET

Making radionucleotides: generators and cyclotron

^{99m}Tc generator as an example

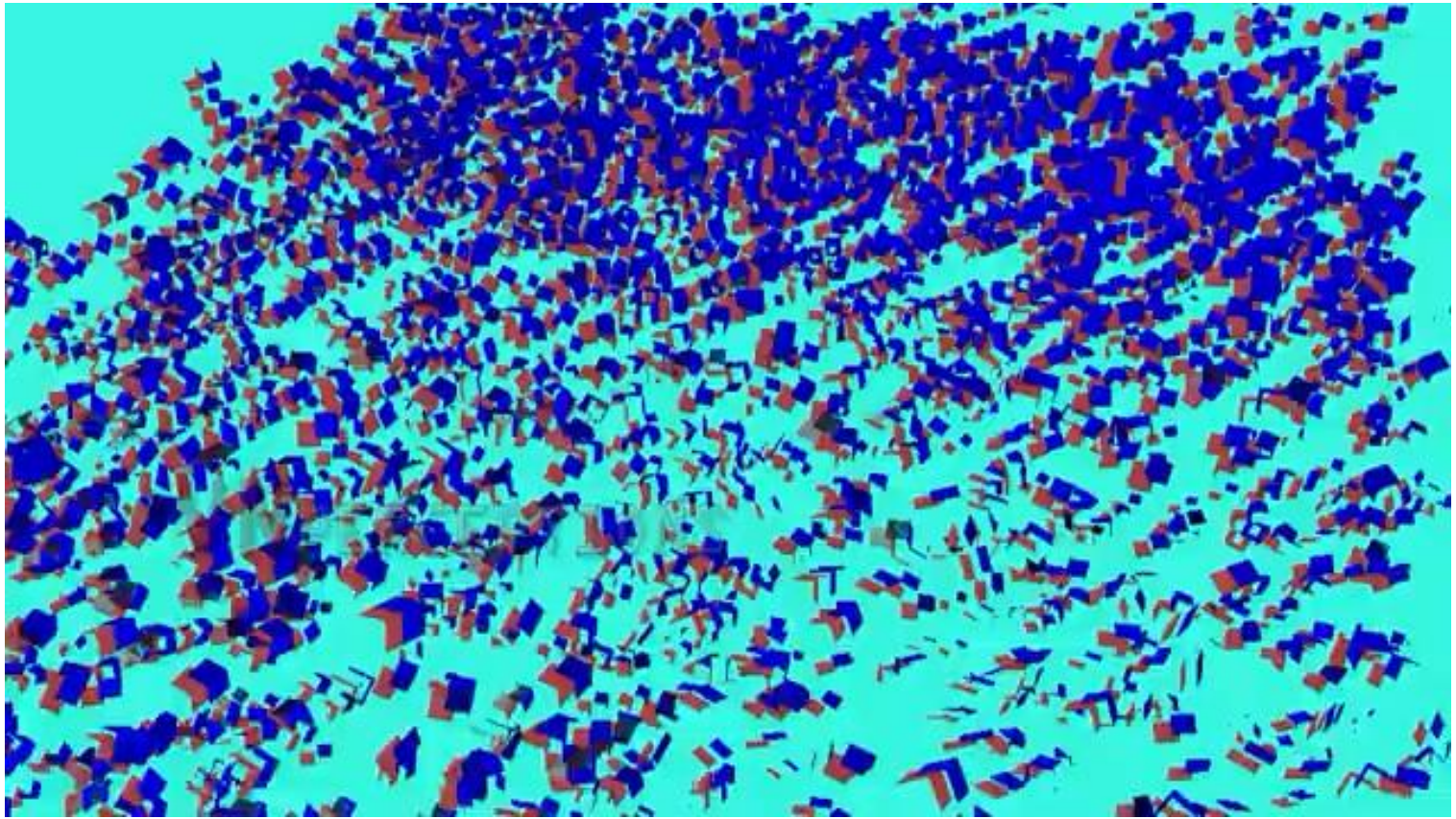
Making radionucleotides: generators and cyclotron
^{18}F and cyclotron example

$^{18}O + p \longrightarrow {}^{18}F + n$



1. Generate the fast proton
2. Get the ^{18}F out of the bath

Basics of a cyclotron: a particle accelerator



Having a cyclotron is a luxury

Cost of a cyclotron?

$1-$20 mil

Fig.1.1. Distribution of cyclotrons for production of PET tracers

(based on inputs from four major cyclotron manufacturers)

https://humanhealth.iaea.org/HHW/NuclearMedicine/IPET2011/Presentations/2011-11-10_Thursday/Afternoon/M3/PL3b_Schyler.pdf

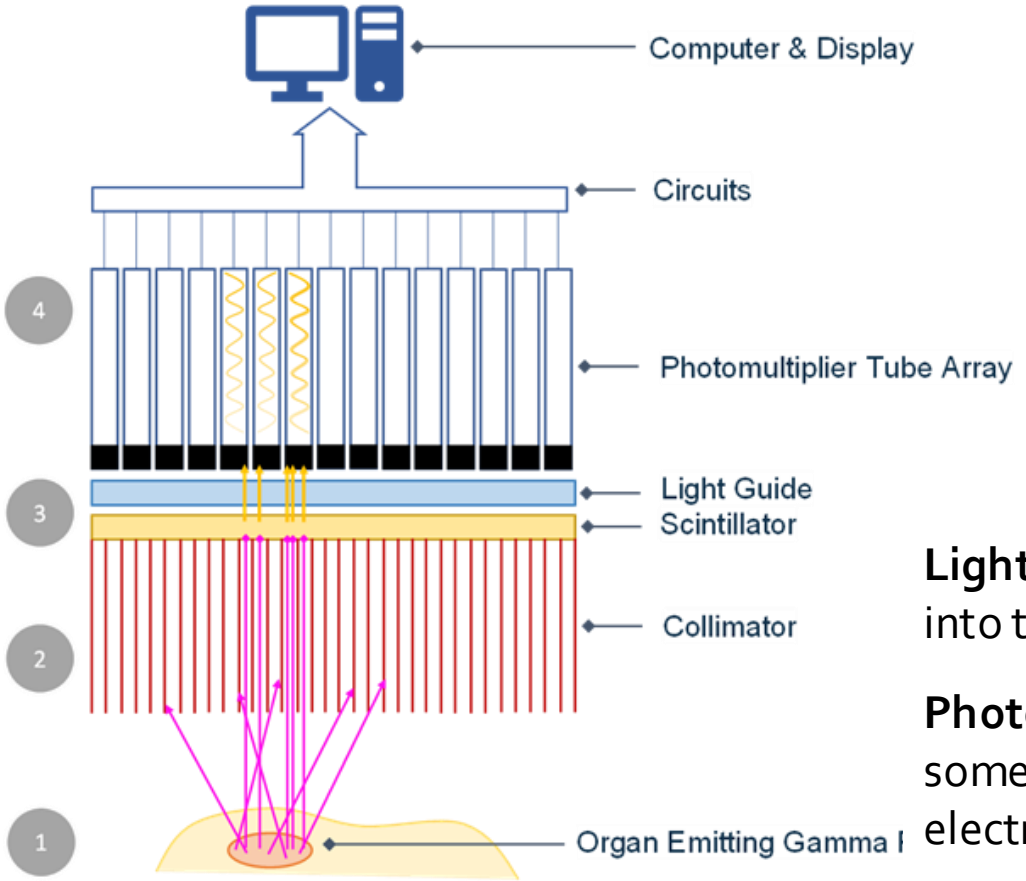
Detecting radiation: Gamma camera, SPECT, PET

Basically, two types of radiation are detected in nuclear medicine:

1. **Gamma decay (like ^{99m}T)**
   - Gamma photons fly out one by one
   - Energies are on the order of 200 keV (^{99m}T photons are 140 keV)

2. **Positron emission (like ^{18}F)**
   - β^+ or positron emission occurs during decay
   - The positron meets an electron almost immediately in tissue
   - The collision creates 2 gamma photons 511 keV each, flying in diametrically opposite directions

Detecting radiation: Gamma camera



Collimator: allows only certain directions of the gamma ray to enter (enhancing resolution)

Scintillator: A crystal (often thallium-activated sodium iodide (NaI(Tl))). Converts gamma photons into visible photons for further relay

Light guide: directs the created photons into the photomultiplier tube.

Photomultiplier tube: converts (and sometimes amplifies) photon counts into electric signal

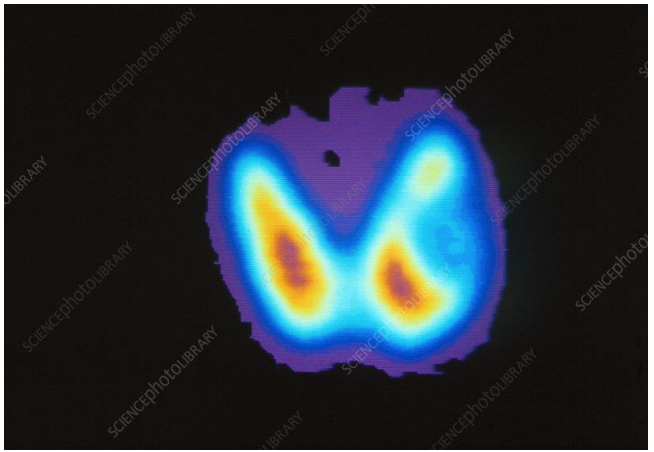
https://www.studysmarter.co.uk/explanations/physics/medical-physics/gamma-camera/

Gamma camera resolution

Gamma camera resolution largely depends on the collimator: the width of the opening and the length of the tube.

Why?

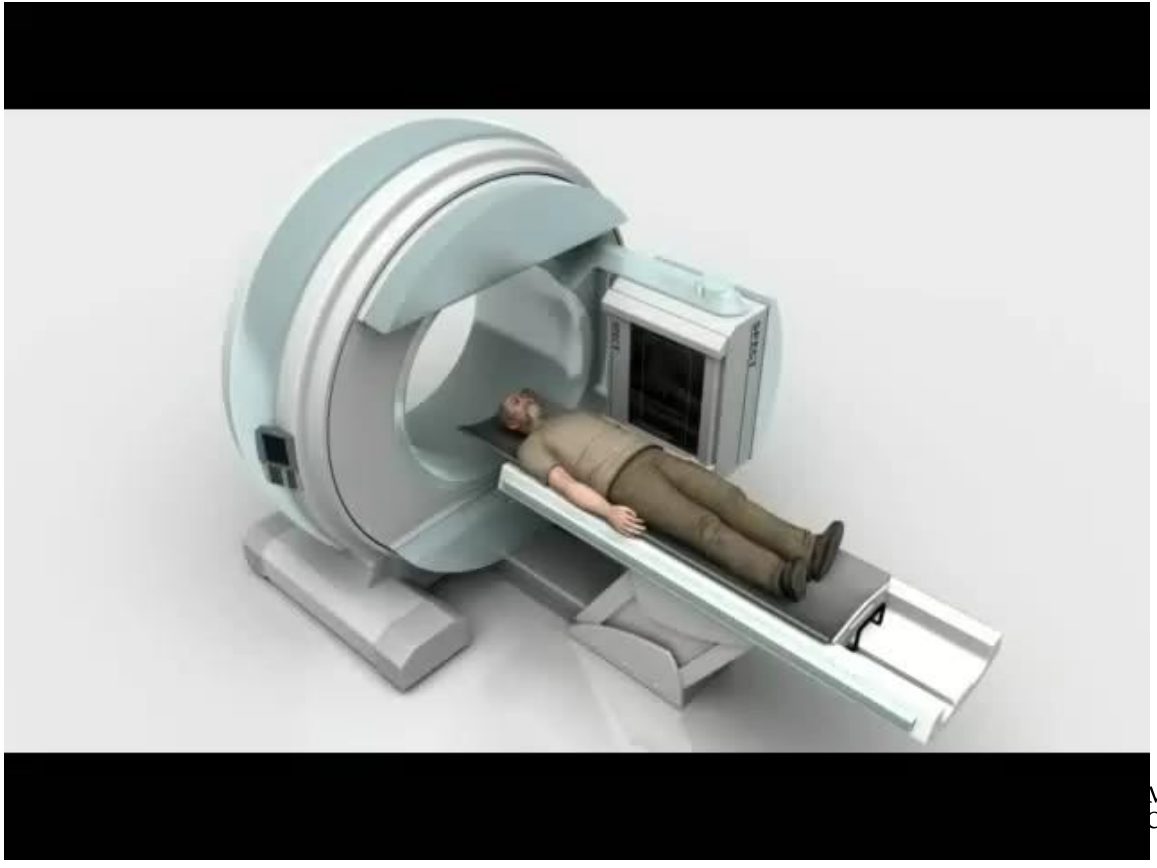
Why not make the opening super small and the tube super long?



What's missing from this approach?

Gamma camera 3D view: SPECT

SPECT: single-photon emission computed tomography



Example SPECT instrument from Siemens

https://www.siemens-healthineers.com/en-us/molecular-imaging/spect-ct-scanners/symbia-prospecta

Detecting radiation: Gamma camera, SPECT, PET

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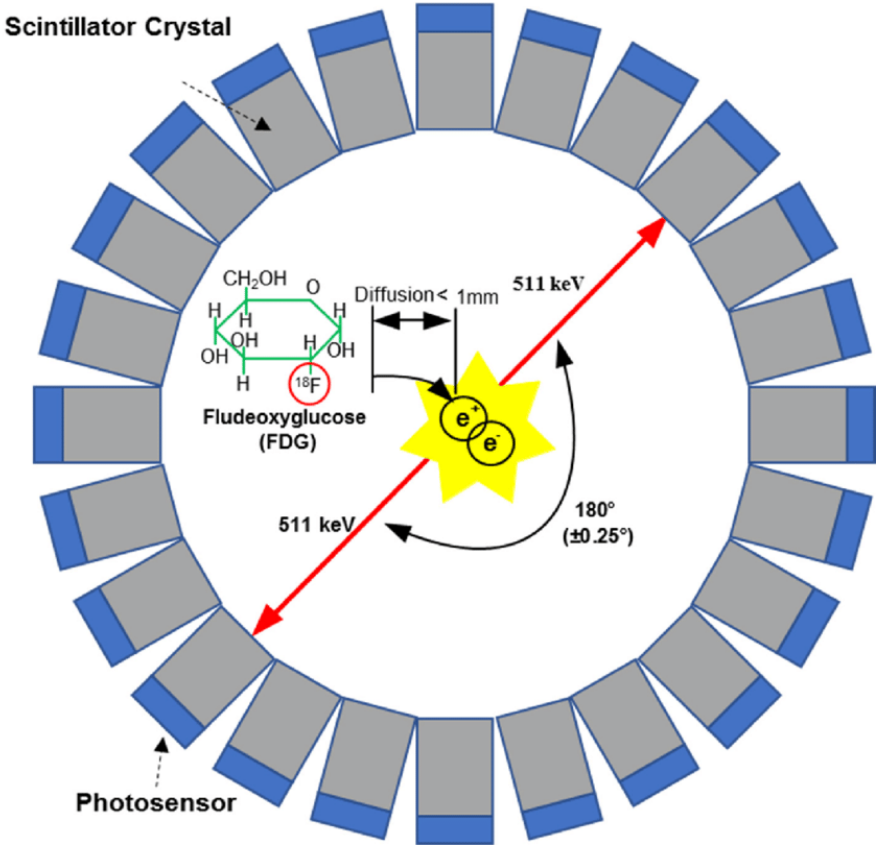
Detecting radiation with PET



Essentially **coincidental** events 180 degrees apart allow localization of the electron-positron collision.

The collision is usually very close to the positron emission location where the decay took place

Resolution depends on:

- Size of the scintillator crystal
- Positron range (how far positron travels before meeting electron
- Time of flight calculation
- Patient motion

Jiang, & Chalich, & Deen,. (2019). Sensors for Positron Emission Tomography Applications. Sensors. 19. 5019. 10.3390/s19225019

Detecting radiation with PET

Example PET scanner

https://toduaclinic.ge/en/technologies/pet-ge-discovery-iq

Specificity and contrast in nuclear medicine

Specificity: How well / how precisely did the radiotracer / radiopharmaceutical go to the target of interest? Did most of it go to the target? Did it go only to the target of interest?

- Passive accumulation
- Tagging with specific compounds to target tissues of interest

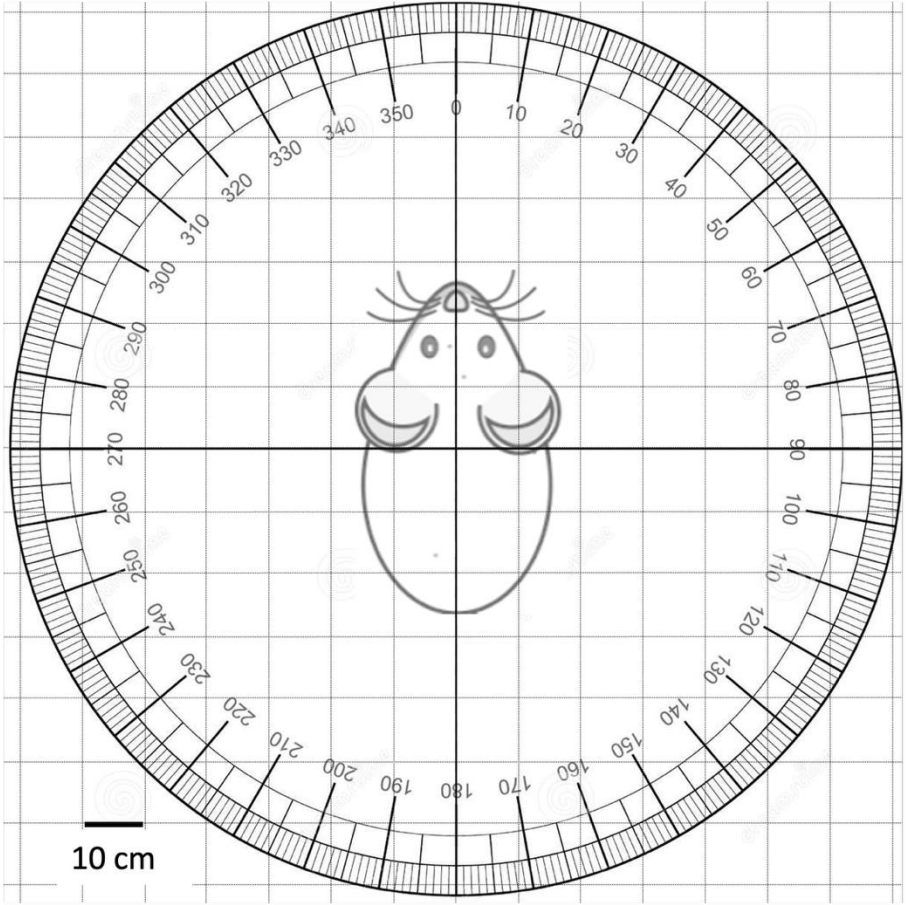
Contrast: How well does signal stand out from background

- Where is the radiopharmaceutical taken up? Is it cleared elsewhere?
- What dose of the radiopharm. was used?
- Higher acquisition time often better contrast.

Spot check:

- In most of nuclear imaging is contrast based on material property or biological function?
- Is the data we are getting quantitative or qualitative?

Exercise: a model for PET detection of a tumor



Emitted photons are traveling at 10^8 m/s

Position (deg)	Arrival time (ns)
130	10
132	201
139	1222
140	171
142	322
146	880
155	534
310	12.6
311	204.2
318	1225.4
320	173
322	324.8
326	883
334	536.6

When do you use PET and when do you use SPECT

- PET is generally higher resolution
- PET generally has higher sensitivity
- SPECT is more widely available and less costly
- SPECT radiotracers sometimes easier to make (in a generator)
- Different radiotracers with different decay mechanisms tailored to different diseases and different tumor types

Applications in cancer

- Diagnosing onset of cancer broadly
  - FDG accumulates in tissues with high metabolic activity
- Testing for cancer in a particular organ by specific targeting of radiotracers
  - NAF-18 (^{18}F labeled sodium fluoride) localized to bones and can be used to detect bone metastases.
- Identifying targets for therapy
  - With PET (and often another modality) check if a labeled tracer goes to the intended target. If so, couple therapeutic agents to it as well.
- Cancer staging
  - Measuring the extent of cancer spread (best with general tracer unless interested in specific tissue)
- Evaluation of treatment response or recurrence
  - Check what's left after radiation therapy or chemotherapy
  - Periodically check for recurrence
- Evaluating cancer aggression

Applications outside of cancer

- Alzheimers
  - FDG accumulates less in the brain with reduced metabolic activity
- Parkinsons
  - FDOPA (^{18}F-labeled DOPA) used for neuroendocrine diseases
- Stroke
  - Reduced blood flow using tracers
- Heart disease
  - Metabolically inactive regions are likely affected
- Inflammation
  - Inflammation also exhibits higher metabolic uptake
- Endocrine disorders
  - Hyperactive thyroid will be more metabolically active
- Bone and joint disease
  - Arthritis etc

How to distinguish between cancerous increased uptake and inflammation or other disorder

In general of course it's complicated and a huge part a continual effort to improve fidelity of diagnosis.

- Level of increased uptake can correlate with which disorder it is from empirical evidence. SUV: standard uptake value
- Shape of enhanced region (cancer sometimes more irregular): margins
- Can sometimes confirm with other, more specific tracers
- Of course, patient symptoms and history more wholistically
- Can sometimes image multiple time points even with one tracer.
- Progression over longer periods of time
- Multiple modalities for a confirmation
- If other methods fail, biopsy and histology

Combination of modalities

Most common two combinations are:

- PET-CT (or SPECT-CT)
- PET-MR (or SPECT-MR) :

PET-CT

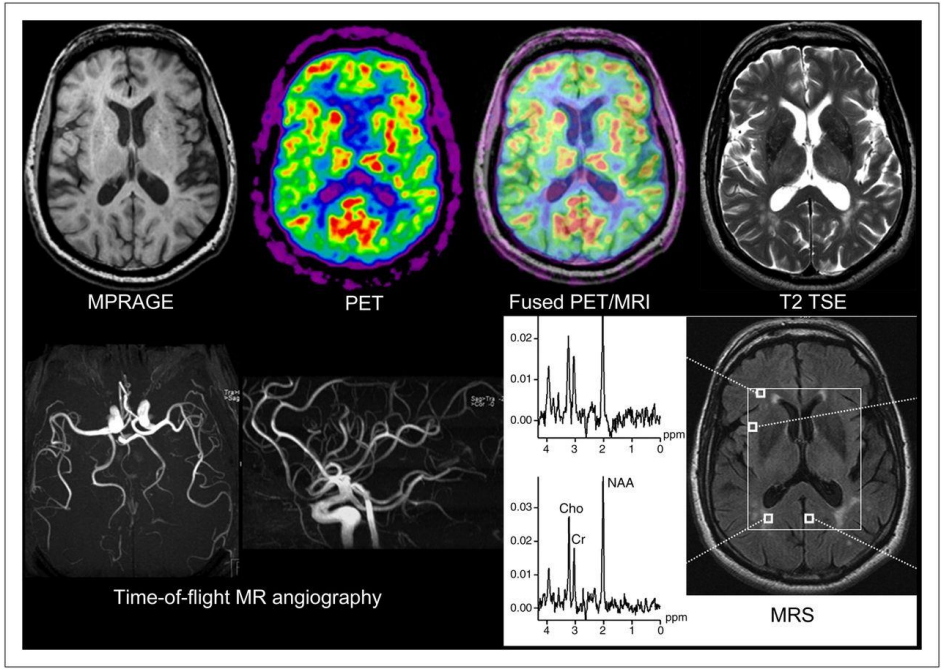
https://www.rgcirc.org/clinical-services/nuclear-medicine-services/basis-of-pet-ct-scan/

- X-rays for hard tissues (bones etc)
- Better localization

Combination of modalities

PET-MR

https://healthmatters.wphospital.org/news/white-plains-hospital-acquires-petmri-only-hospital-in-all-of-new-york-outside-of-nyc-to-offer-this-most-advanced-imaging-technology/



https://jnm.snmjournals.org/content/53/12/1916

- MRI for soft tissue contrast
- Better localization

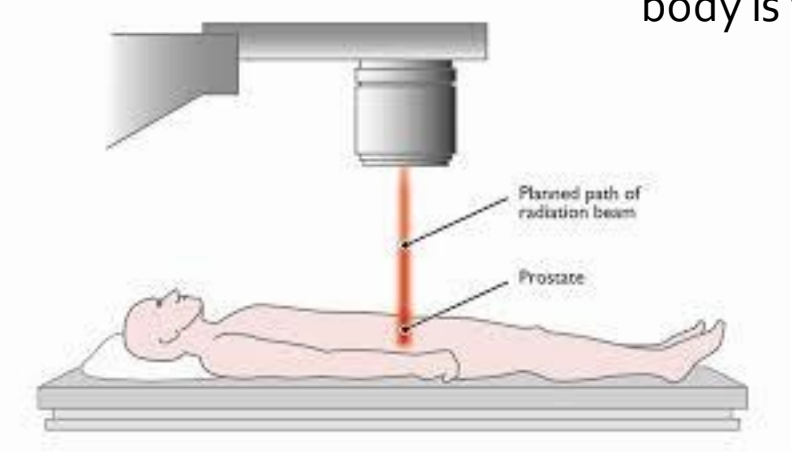
Theranostics in PET

- The basic idea is to use one radioisotope for imaging and another one for therapy
  - In PET for example, would have one positron emitting radiotracer and another high energy particle emitting radiotracer to destroy the tumor
  - Both radiotracers need to be coupled to an agent that will go to the target. Of course, the stakes are higher with nuclear medicine theranostics

Radiation Therapy

- The goal is to destroy tumor cells by radiation of some kind

External beam therapy: a beam of high energy particles originating outside of the body is focused on the malignant tissue.



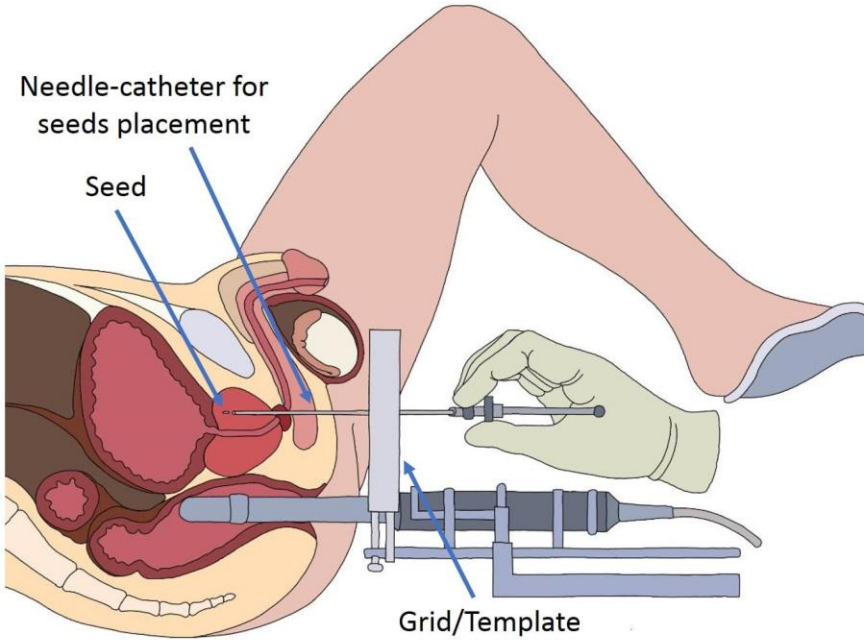
What kind of particles can you focus?

- High energy photons (like x-rays)
- Accelerated protons
- Accelerated electrons

Often accompanied by an anatomic image to help focus the beam in the right place: an MRI, a PET or an x-ray image.

Radiation Therapy

Internal radiation therapy/: Brachytherapy Place a radioactive source at the tumor site and let the resulting radiation destroy tumor from inside



https://www.prostatherapy.com/prostate-cancer-treatments/validated-treatments/brachytherapy/

Again this often takes place under imaging guidance from prior scans and maybe a continuous sonogram as well

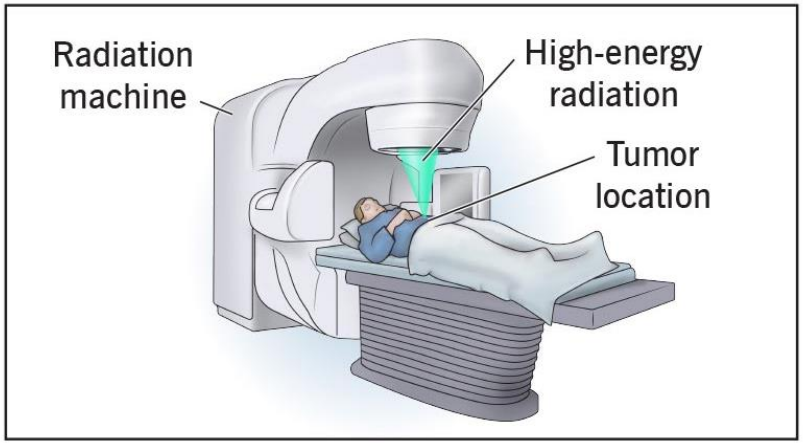
Radiation Therapy

Systemic radiation therapy:

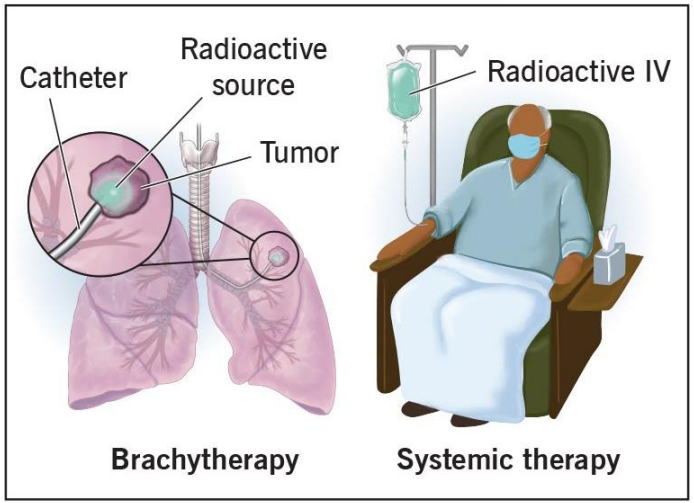
Internalize radioactive source (as with injection) and have it travel to the target through the bloodstream

Similarly to how we have been talking about for imaging but with a high energy particle to destroy the tumor as well. Sometimes with an imaging component as well.

External beam radiation therapy (EBRT)



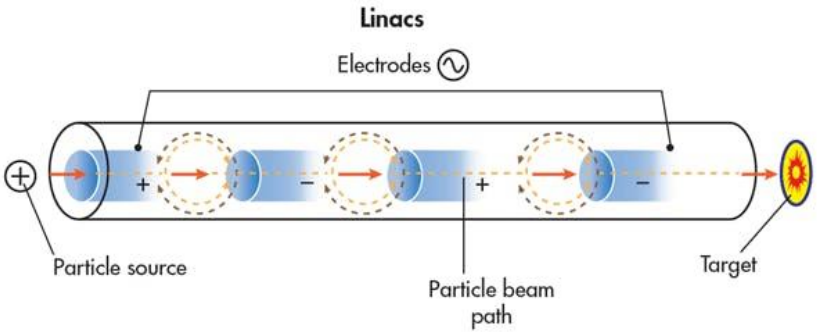
Internal radiation therapy

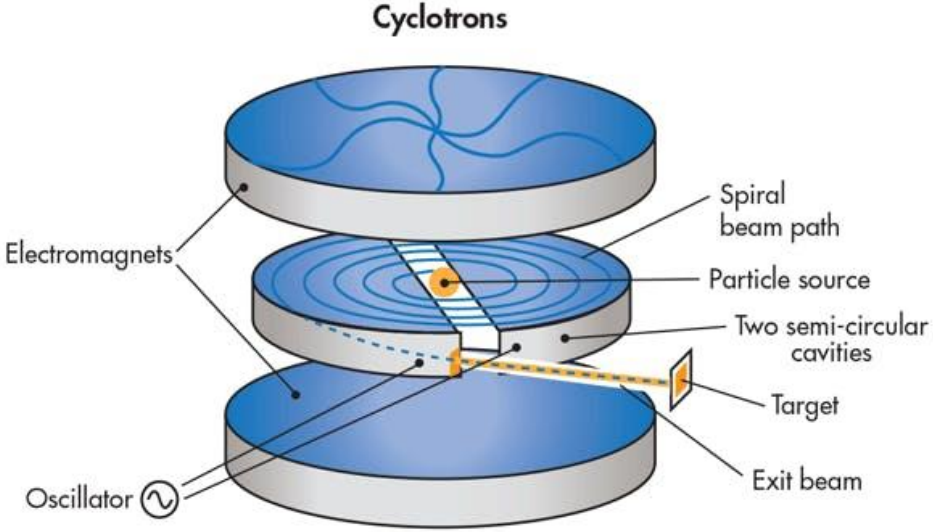


Sloan Kettering
enter

https://my.clevelandclinic.org/health/treatments/17637-radiation-therapy

Linear accelerator vs. cyclotron





https://www.machinedesign.com/learning-resources/whats-the-difference-between/article/21832184/what-are-the-differences-between-linear-accelerators-cyclotrons-and-synchrotrons

Linear accelerators are generally used more in external beam therapy for multiple reasons:

- Better aim
- More flexibility in how much to accelerate
- More flexibility in directing the beam

Radiation safety

- Safety becomes a much more serious concern in nuclear medicine
- Radiation can and sometime is intended to break DNA in cells
- Lots of concrete regulations and guidelines
- Monitor the dosage of radiation a clinician or research scientist is getting
- There is special PPE for radiation (lead aprons etc)
- Safe storage in lead containers
- Different safety regulations for spills etc
- Generally try to minimize exposure as much as possible

Group Project

Assignment: Designing a Theranostic Strategy

Work in small groups to design a theranostic approach for a specific disease target, integrating diagnostic imaging and targeted therapy concepts.

Each group will be assigned one disease target (e.g., prostate, thyroid, or colorectal cancer).

In your design, briefly address:

Target/Receptor: What molecule or pathway will you target, and why?

Imaging Agent: What isotope/modality will you use for detection?

Therapeutic Agent: What isotope or payload will deliver therapy?

Mechanism & Timing: How do binding and imaging/treatment timing work?

Challenges: Identify major translational or clinical hurdles (e.g., off-target effects, cost, availability).

Deliverable

Format: 15-minute summary with slides

You'll be assessed on scientific rationale, creativity, feasibility, and clarity. Feedback will focus on feasibility, innovation, and awareness of real-world constraints.