BioEngineering 221/Radiology 221

Production of Radionuclides & Interaction of Radiation with Matter

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Aspects of the Radiotracer

biomolecule +

radioactive element =

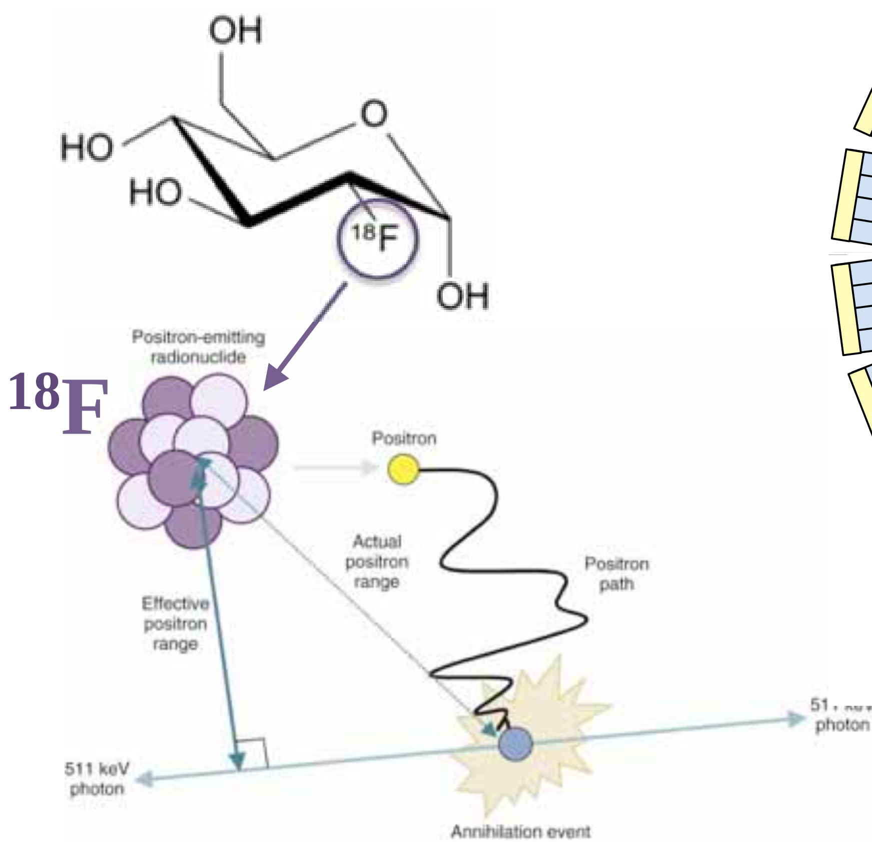
radiotracer

- What modes of radioactive decay are used?
- How do radionuclides decay to produce emissions for imaging?
- How are relevant radionuclides produced?
- How do radionuclide emissions interact in tissue and detectors?

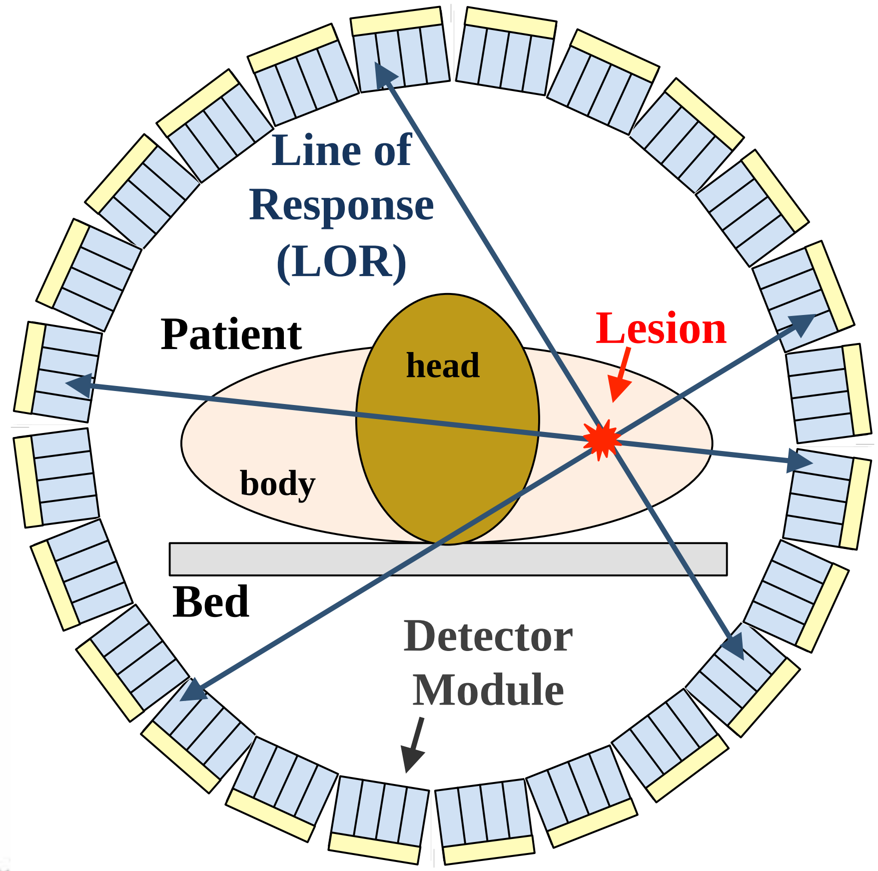
Illustration of Course thus Far and Future

Visualize molecular analog chemically labeled with positron-emitting radionuclide:

^{18}F-Fluorodeoxyglucose



PET Detector Ring

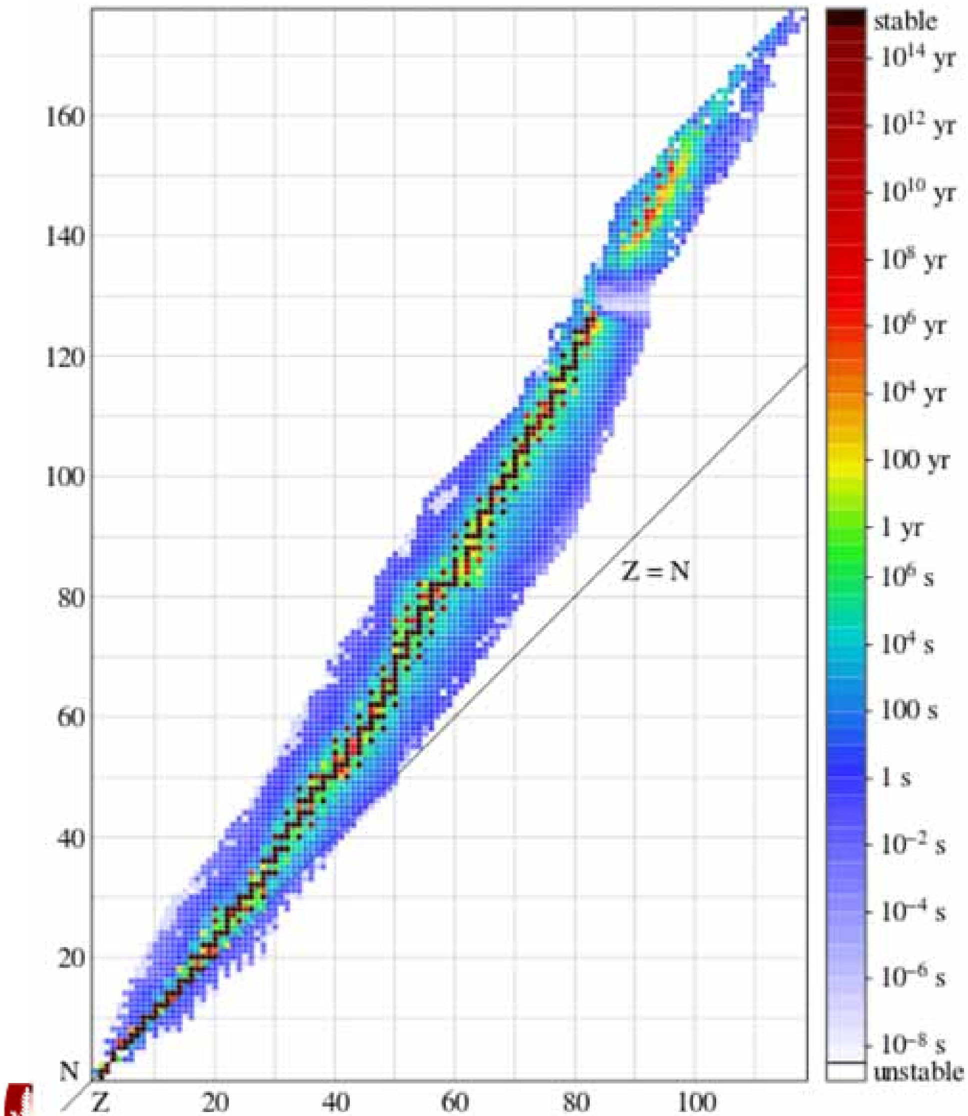


Production of Radionuclides

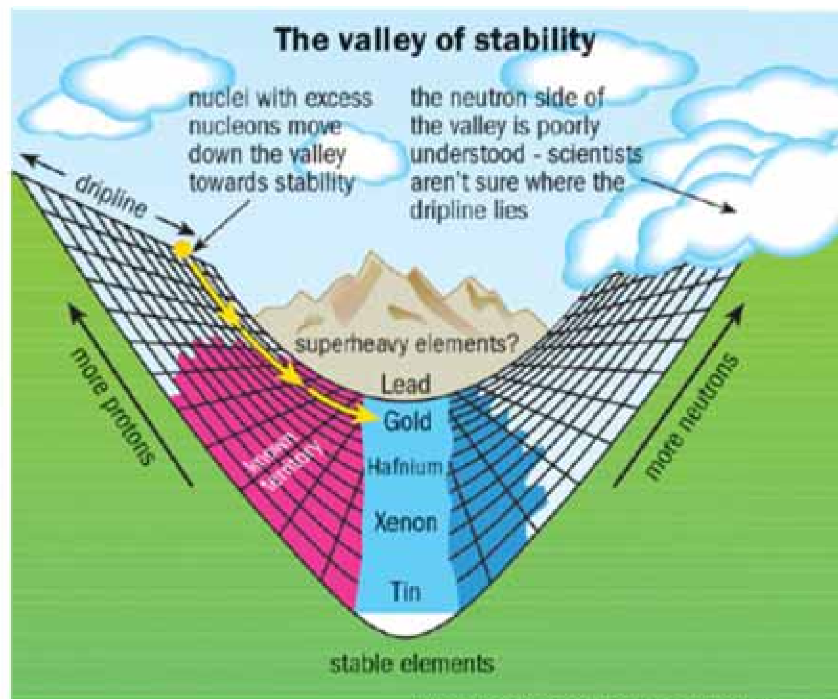
Nuclear transitions & Radioactive Decay

Stimulated transitions	Spontaneous transitions
Nuclear reactions ↓ Radionuclide production	• α decay • β decay • γ de-excitation
Increase Energy	Decrease Energy

Nuclear Transitions



- Adding energy to the nuclei, pushes nuclei to the edge of the valley of stability
- Energy needed for this process



Producing Radioactive Nuclei

- Naturally occurring radioactive isotopes :
  - Typically have long half-life
  - Very heavy elements that are not endogenous to human biology

↓

Use methods to produce radioactive isotopes

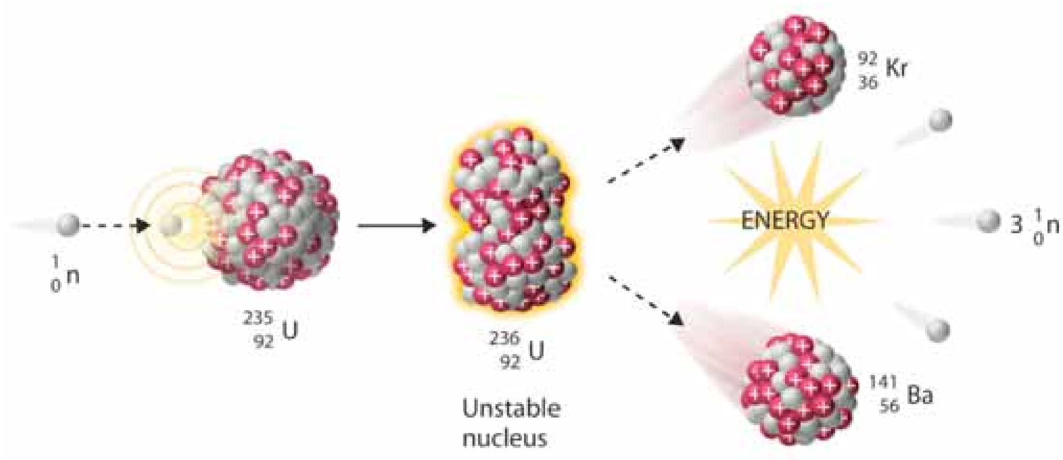
↳ Produced through **Nuclear Reactions**

Overview

1. **Reactor-Produced** Radionuclides: Neutron activation and fission products
2. **Accelerator-Produced** Radionuclides: Proton activation and cyclotron
3. Radionuclide **Generators** (^{99m}Tc)

A common neutron source

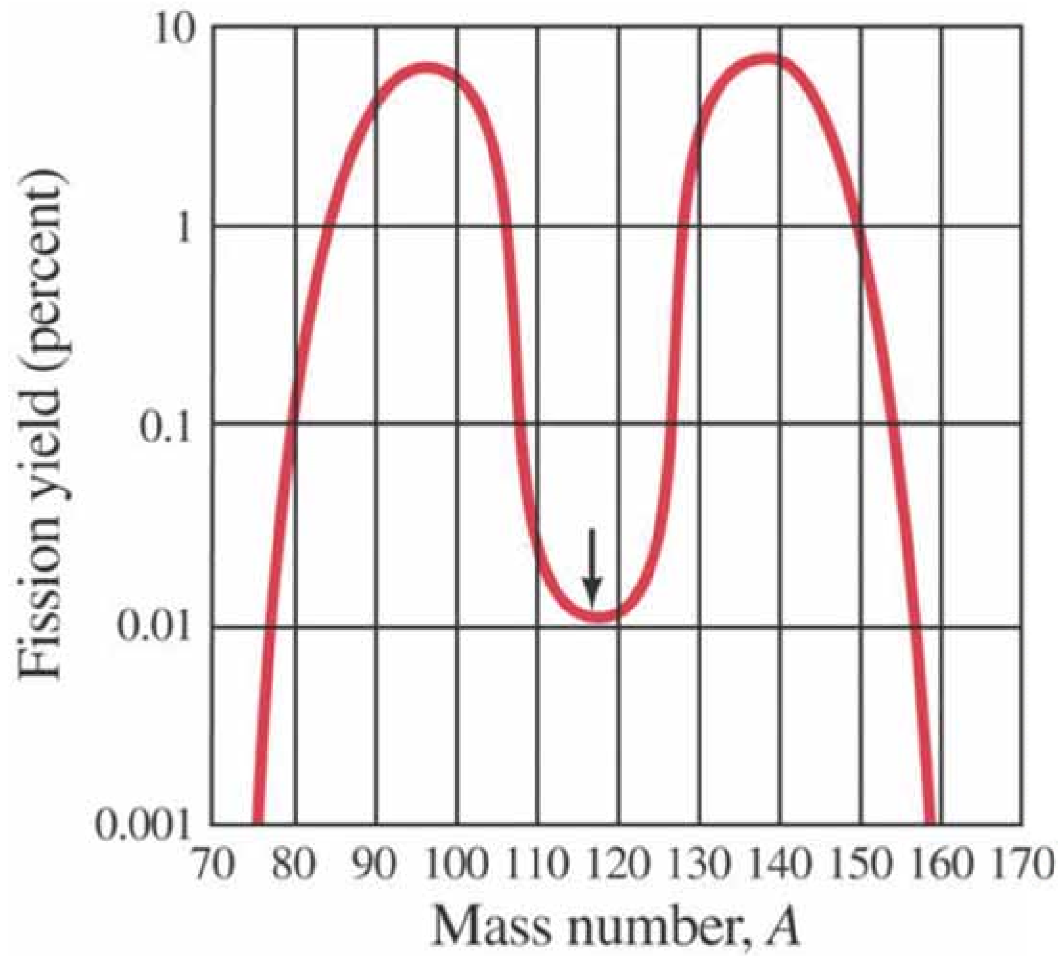
$$^{235}_{92}U + n \rightarrow {}^{236}_{92}U^* \rightarrow {}^{144}_{56}Ba + {}^{89}_{36}Kr + \#n + \#\gamma + \#\nu + E$$



- Stimulated fission is the **source of energy** in a nuclear power plant
- Production of a statistical # of neutrons enables a **chain reaction**
- Excited ^{236}U has more than 100 nuclides among its fission products

Fission Yield of U-235

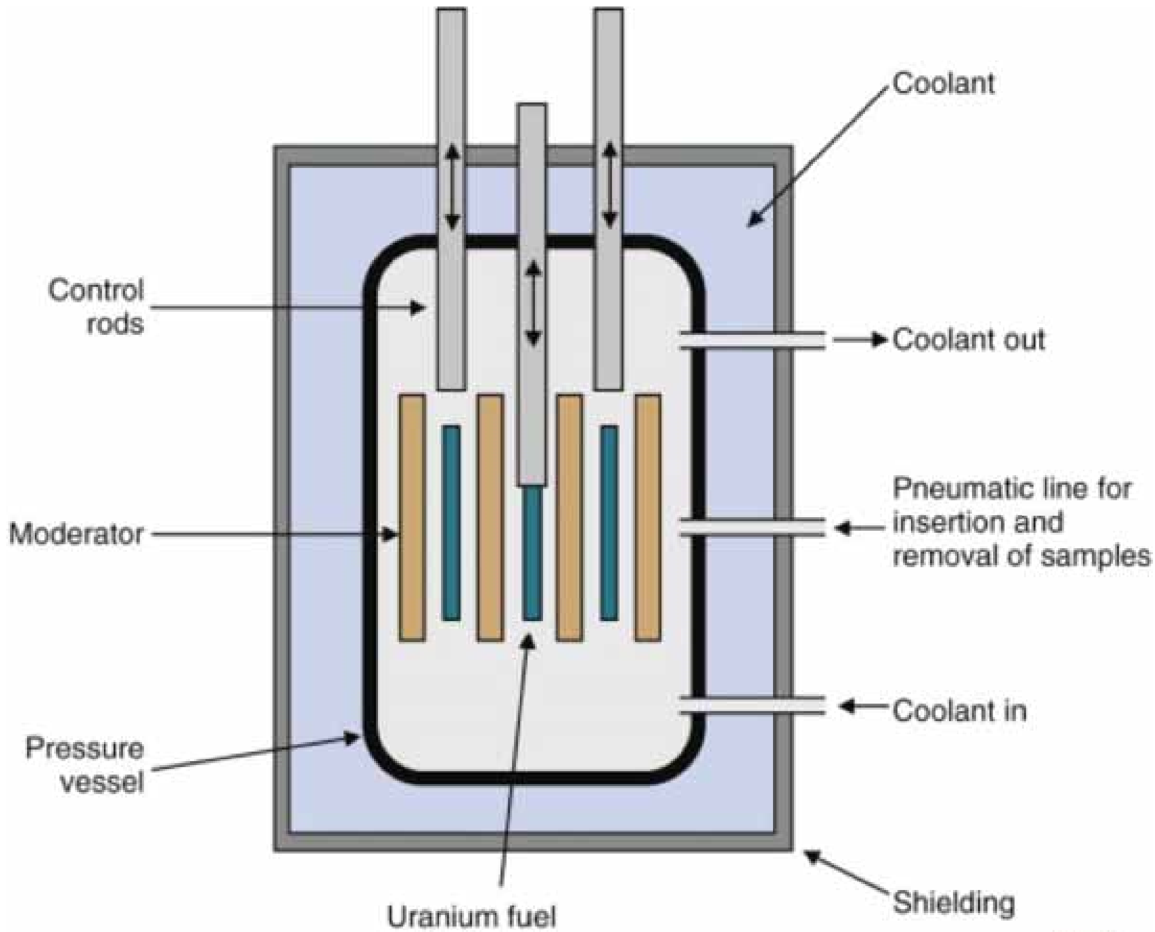
- In general one fragment with A between 130 and 150; and another between 85 and 105
- Fission products with equal masses are least likely



A Nuclear Reactor

- Nuclear reactors have provided large quantities of radioactive isotopes for nuclear medicine

- Fuel cells contain fissionable material (~4-5% of U-235 by weight)
- Moderator to slow down the neutrons (water or 'heavy' water D_2O)
- Control rods contain strong neutron absorbers to moderate the reaction
- Each fission events creates about ~200 MeV of energy, mainly released as heat to moderator
- Radionuclides are produced in samples surrounding the reactor core

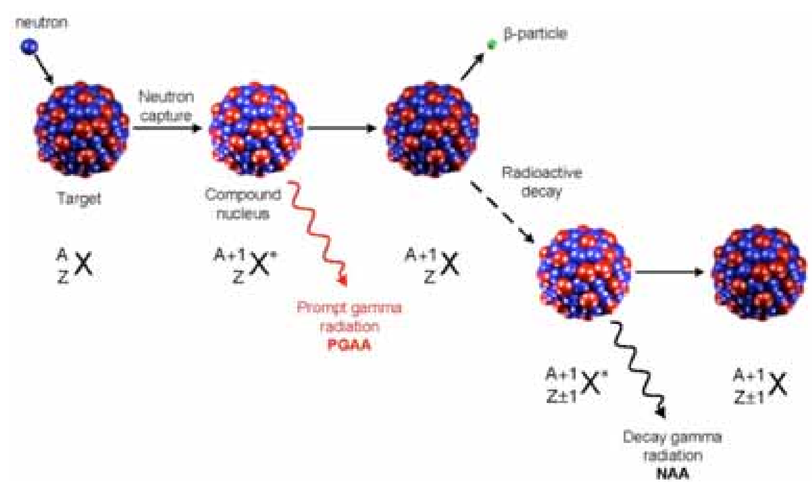


Reactor produced Radionuclides

- Fission products have excess neutrons and thus decay by β^- decay
- If a radioactive intermediate has sufficiently long half-life it can be extracted and used as a medical radionuclide

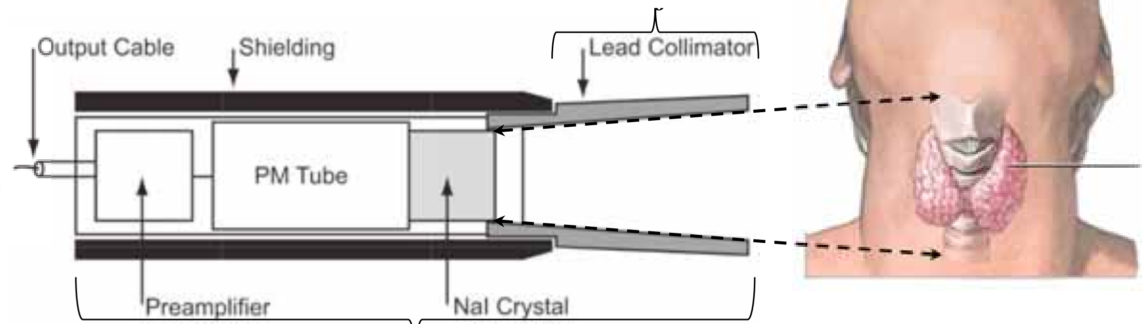
$$^{99}_{39}Y \xrightarrow{\beta^-,1.5s} {}^{99}_{40}Zr \xrightarrow{\beta^-,21s} {}^{99}_{41}Nb \xrightarrow{\beta^-,15s} {}^{99}_{42}Mo(T_{1/2} = 65.9hr)$$

- ^{99}Mo is used to generate ^{99m}Tc (**More on this in just a bit**)
- Also ^{131}I and ^{133}Xe produced by **neutron activation**, these are important for nuclear medicine as well

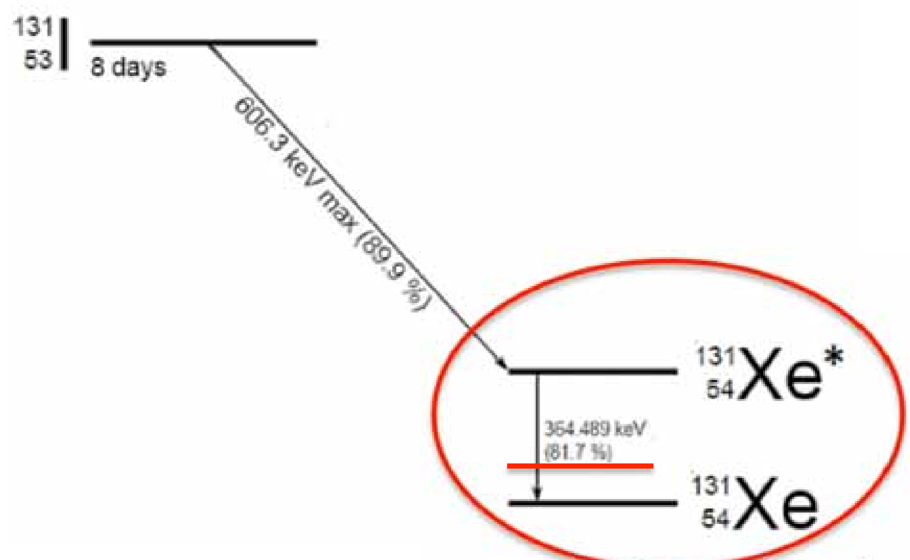


Reactor produced Radionuclides

Detector Head

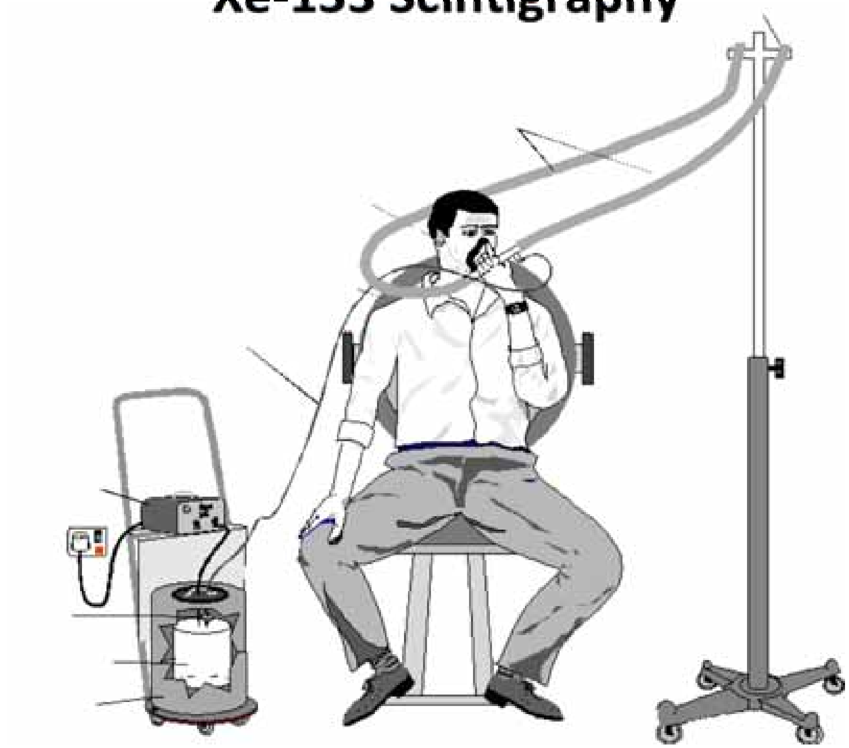


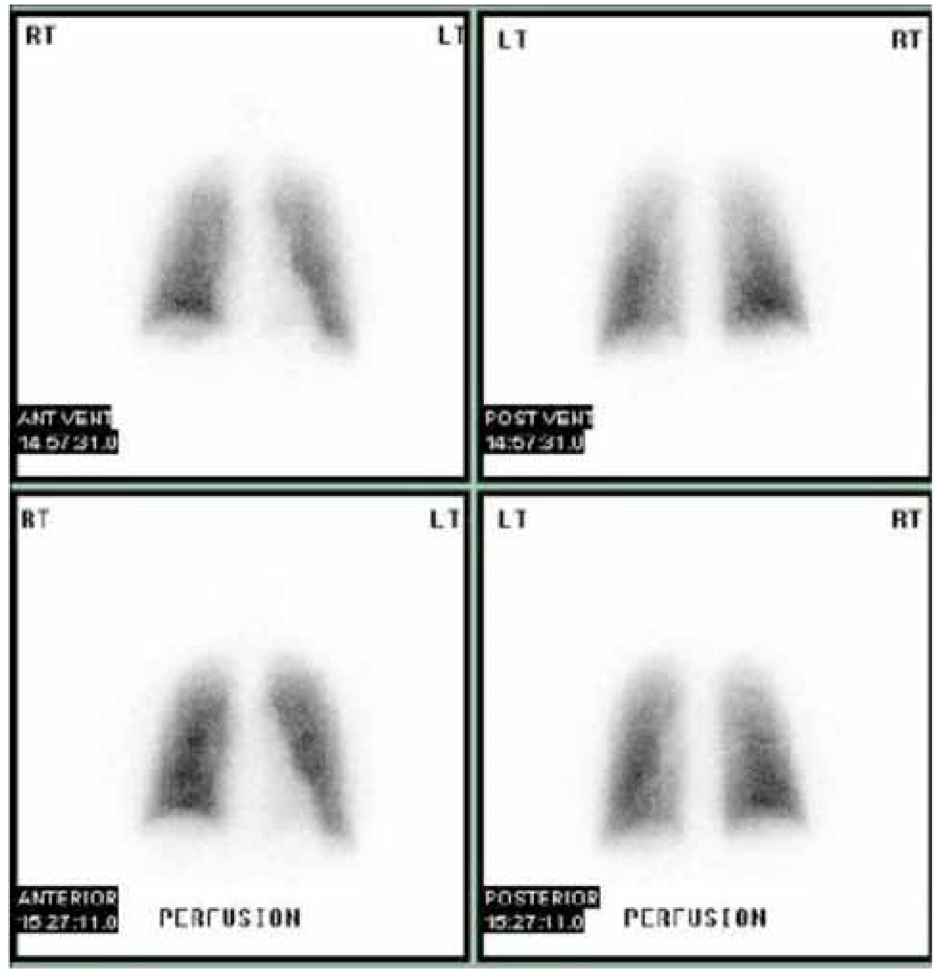
Thyroid uptake of radioactive Iodine (I^{131})



Reactor produced Radionuclides

Xe-133 Scintigraphy

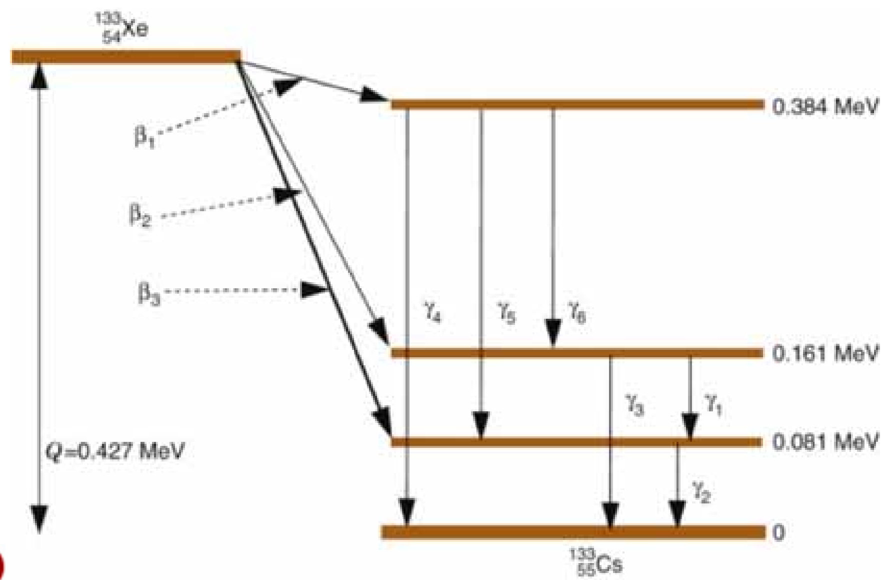




Radionuclides by fission

General properties:

- Excess of neutrons, hence β^- decay
- Products may be carrier free, thus radionuclides have high specific activity by chemical separation
- Lack of specificity in fission products is a drawback



Overview

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3. Radionuclide **Generators** (^{99m}Tc)

Nuclear reactions: proton activation

Proton needs to be energetic to make it to the atomic nucleus, typically 10-20 MeV

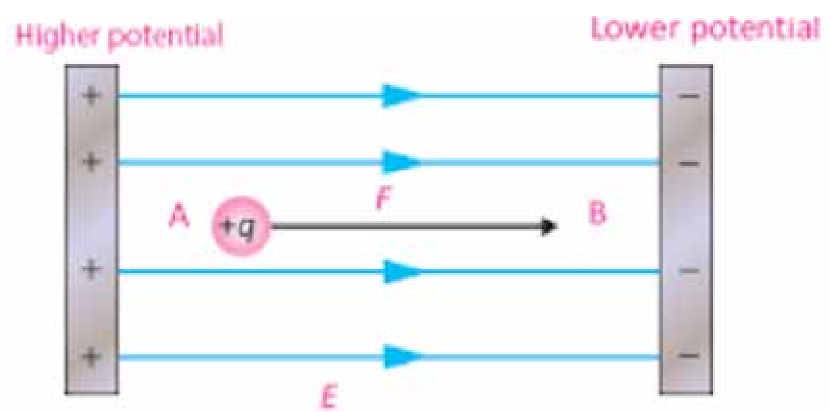
➔ Need particle accelerators

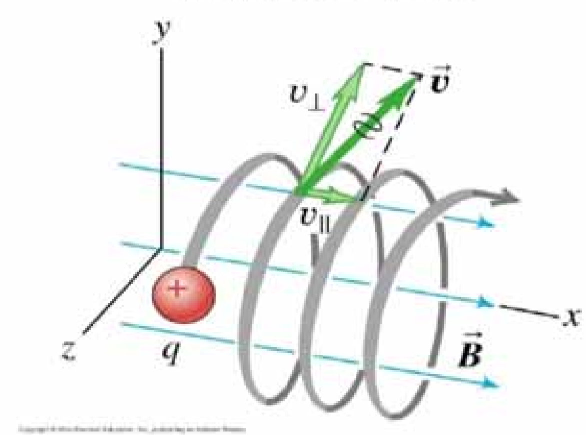
- Different kind of particle accelerators
- Most common: **cyclotron**

Proton acceleration: Cyclotron

- Charged particle in **electric** field: **acceleration**
- Charged particle in **magnetic** field: **change of direction**

➔These principles are combined in a cyclotron.



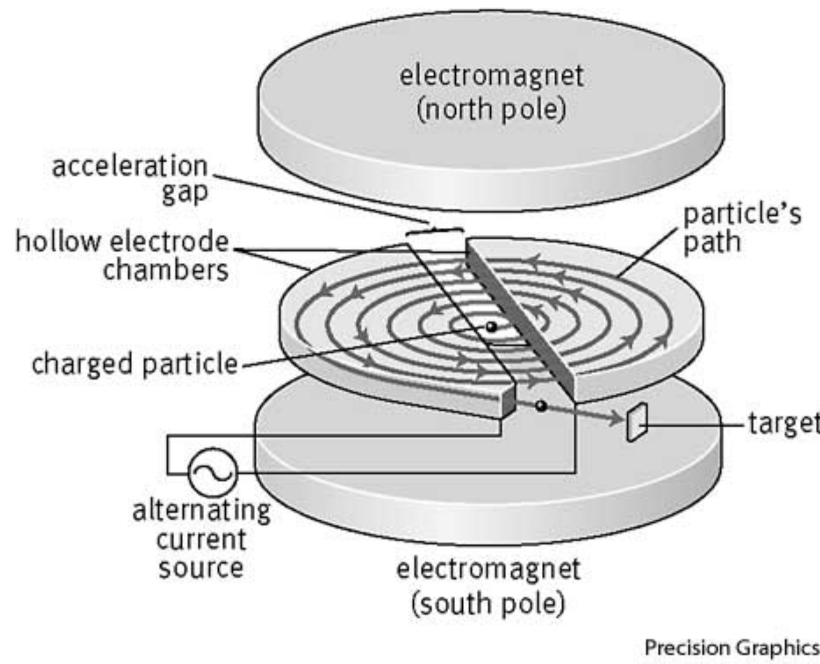


Proton acceleration: Cyclotron

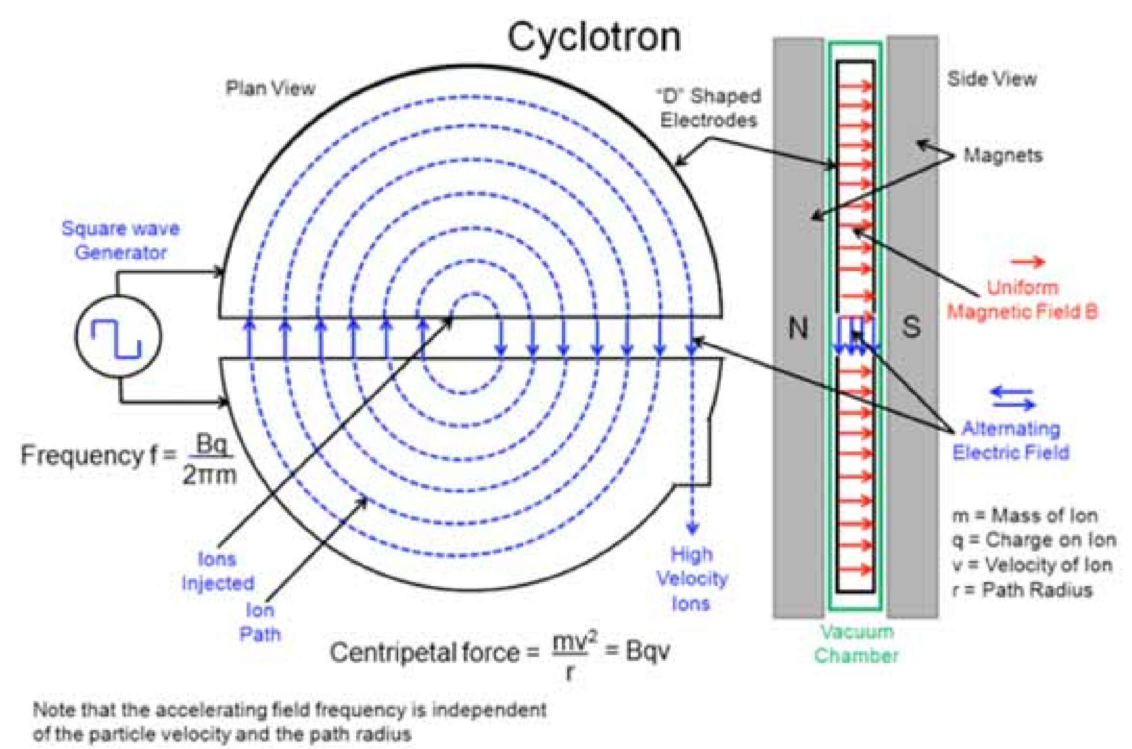
- Charged particle in **electric** field: **acceleration**
- Charged particle in **magnetic** field: **change of direction**

➔These principles are combined in a cyclotron.

- Pair of hollow 'dees', positioned between poles of magnet
- Ion source at the center
- Electric field between dees



Proton acceleration: Cyclotron



- Particle gains energy in gap between dees
- Upon increased energy, the ion will have a larger radius in the dee
- Electric field is reversed after every transition

Proton acceleration: cyclotron

- When maximum orbital radius is reached, particles are extracted, using targets or a stripping foil
- Cyclotron produce in general smaller quantities of radioactivity than nuclear reactors due to
  - Lower beam intensities
  - Lower cross section
- Special interest are short-lived positron emitters: ^{11}C (20 min), ^{13}N (10 min), ^{15}O (2 min), these require a local cyclotron
- Also ^{18}F (110 min) important, but a regional distribution center is sufficient

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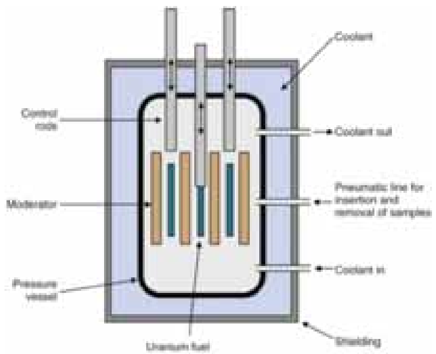
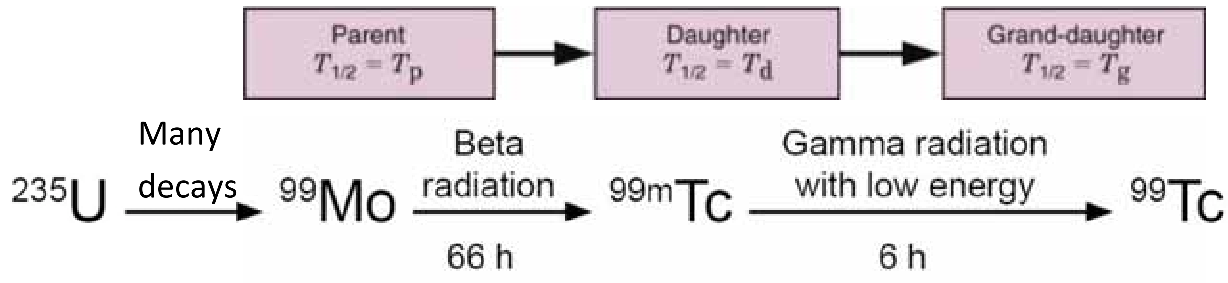
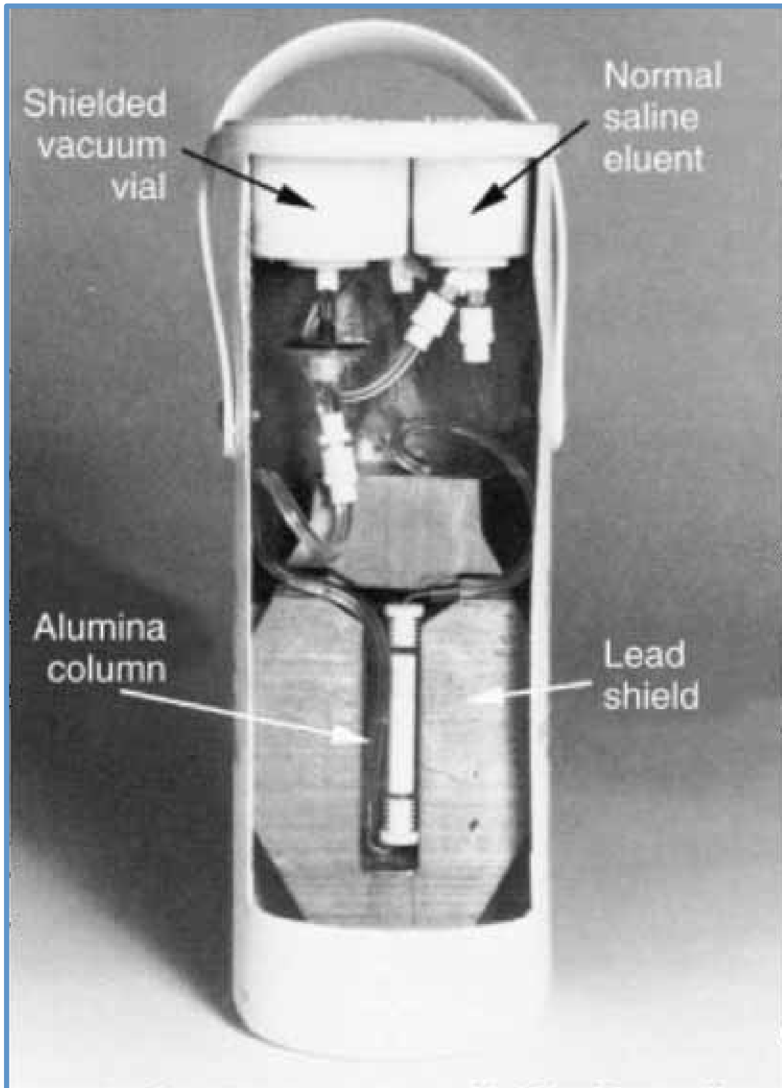
Radionuclide Generators





- Parent-daughter radionuclide pair contained in apparatus that permits separation
- Most important generator: ^{99}Mo – ^{99m}Tc
- Very common because of wide spread Tc use (more than 1850 TBq of ^{99}Mo required *per week*)
- Also ^{68}Ga, ^{82}Rb, ^{62}Cu are generator produced

Radionuclide Generators



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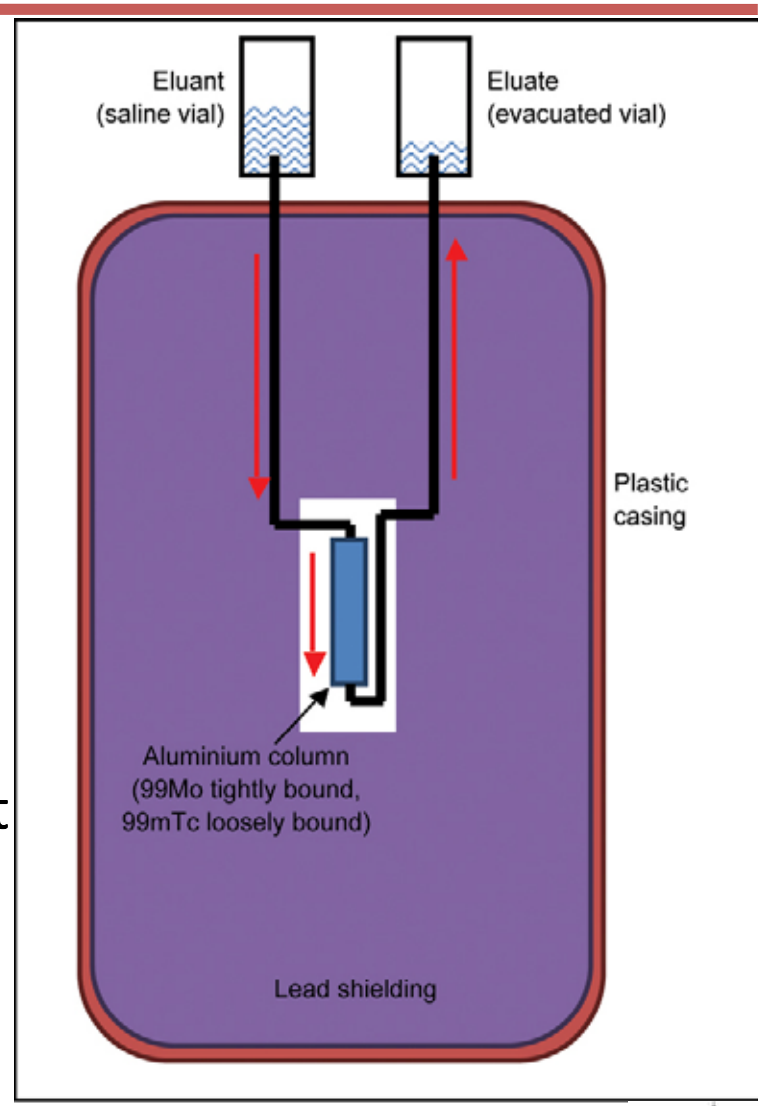
  parent, maximum 0.15 Bq allowed



Radiotracers

- Many candidate radionuclides, yet relatively small number of practical radionuclides because of following considerations:
  - **Type** and **energy** of emissions and the branching ratio: ideally no other processes than γ-emission at energies 50-600 keV
  - Physical **half-life of radionuclide**:
    - If too short: no time for preparation
    - If too long: high radiation contamination for disposal and most of the activity emitted outside of examination time
  - **Specific activity**: need as many as possible radioactive molecules in a sample; must not be biologically perterbing
  - **Radionuclidic purity:** fraction of the radioactivity in the desired form, i.e. no contaminants
  - **Cost and complexity:** ease of production

Radiotracers

Radionuclide	Decay Mode	Principal Photon Emissions	Half-Life	Primary Use
^{11}C	β+	511 keV	20.4 min	Imaging
^{13}N	β+	511 keV	9.97 min	Imaging
^{15}O	β+	511 keV	2.03 min	Imaging
^{18}F	β+	511 keV	110 min	Imaging
^{32}P	β–	—	14.3 d	Therapy
^{67}Ga	EC	93, 185, 300 keV	3.26 d	Imaging
^{82}Rb	β+	511 keV	1.25 min	Imaging
^{89}Sr	β–	—	50.5 d	Therapy
^{99m}Tc	IT	140 keV	6.02 hr	Imaging
^{111}In	EC	172, 247 keV	2.83 d	Imaging
^{123}I	EC	159 keV	13.2 hr	Imaging
^{125}I	EC	27-30 keV x rays	60.1 d	In vitro assays
^{131}I	β–	364 keV	8.04 d	Therapy/imaging
^{153}Sm	β–	41, 103 keV	46.7 hr	Therapy
^{186}Re	β–	137 keV	3.8 d	Therapy
^{201}Tl	EC	68-80 keV x rays	3.04 d	Imaging

Production of Radionuclides: Major Takeaways

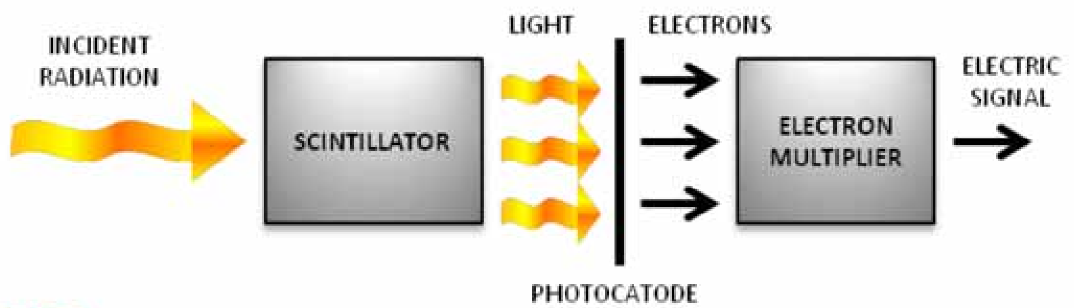
1. Naturally abundant radionuclides are long-lived, not generally useful for nuclear medicine studies
2. Produce short-lived radionuclides via stimulated transitions: ex. neutron activation or fission in reactor, proton activation in cyclotron
3. Work horse isotope Tc-99m eluted from Mo-99 product in radionuclide generator
4. Radionuclide chemically labeled to biological analog, which predetermines application, specificity, and so much

Interaction of Radiation with Matter

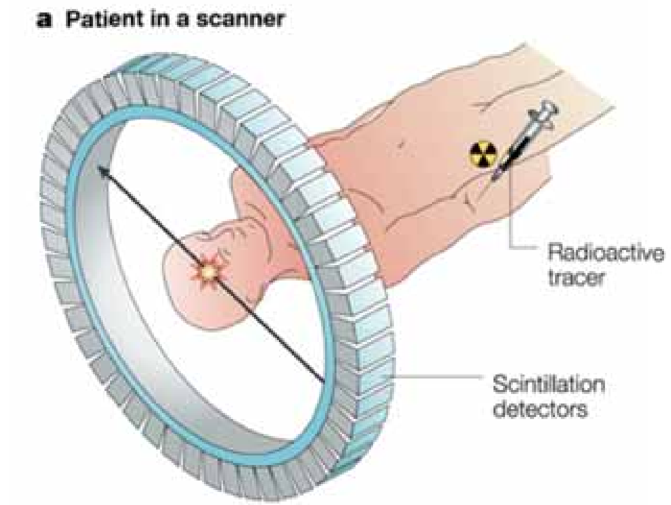
Interactions of rad. with matter: How it fits in

- Why is understanding interaction of radiation with matter important for imaging in nuclear medicine?
- Emissions from radioactive nuclei are too high in energy & too small to be seen with the naked eye
- We observe their existence only through the effects they produce in matter
- Effects caused by various forces and interactions the nuclear emissions experience as they traverse a material

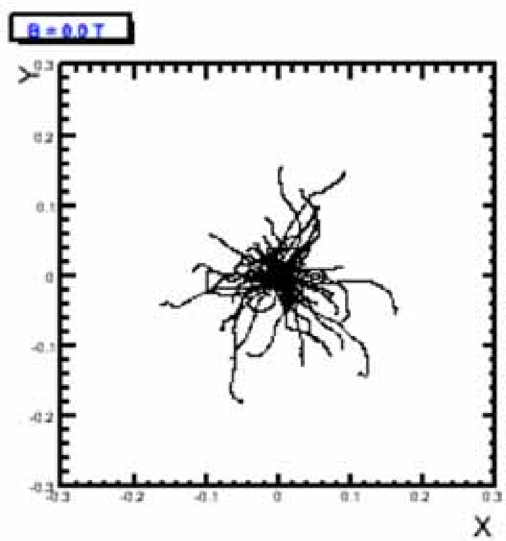
Example: Scintillation Detector

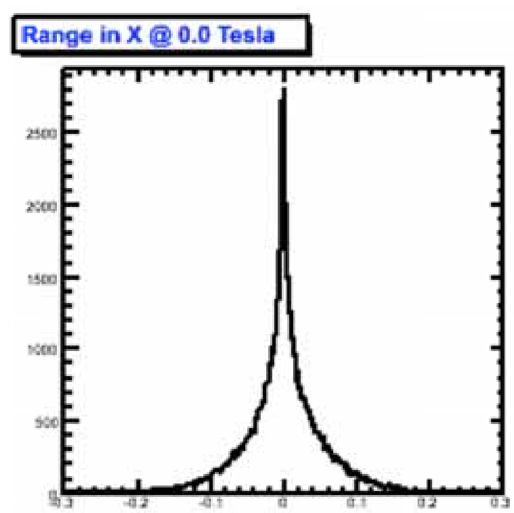


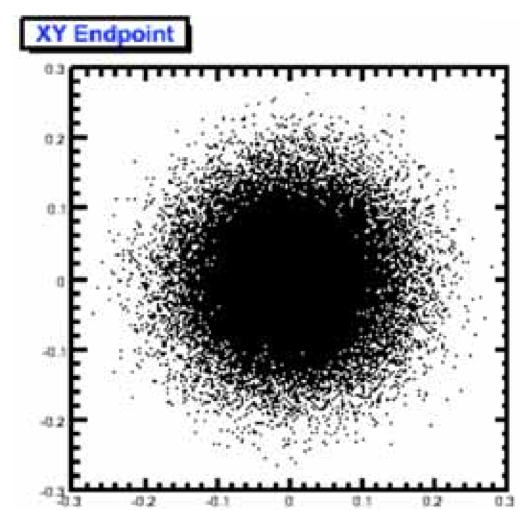
Range of ^{18}F positrons in water



- FWHM ~ 0.1 mm
  FWTM ~ 1 mm,
  average ~0.6 mm
- Average range
  ^{82}Rb ~ 4.3 mm

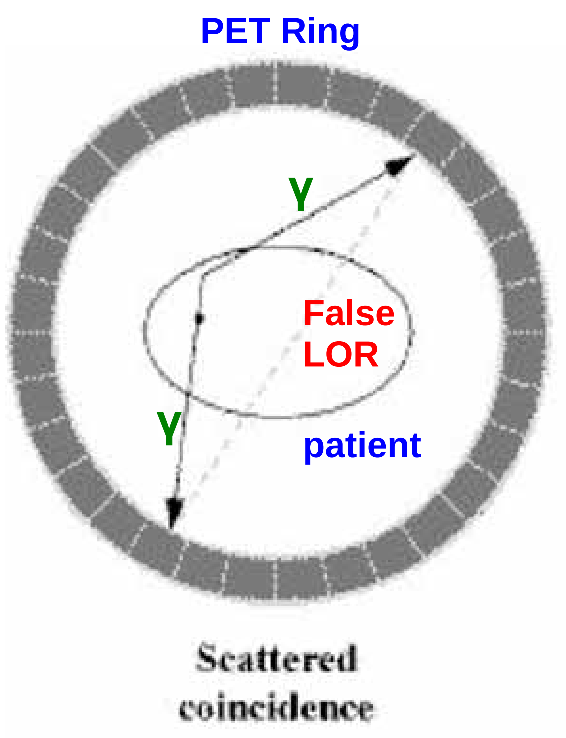






Interactions of rad. with matter: How it fits in

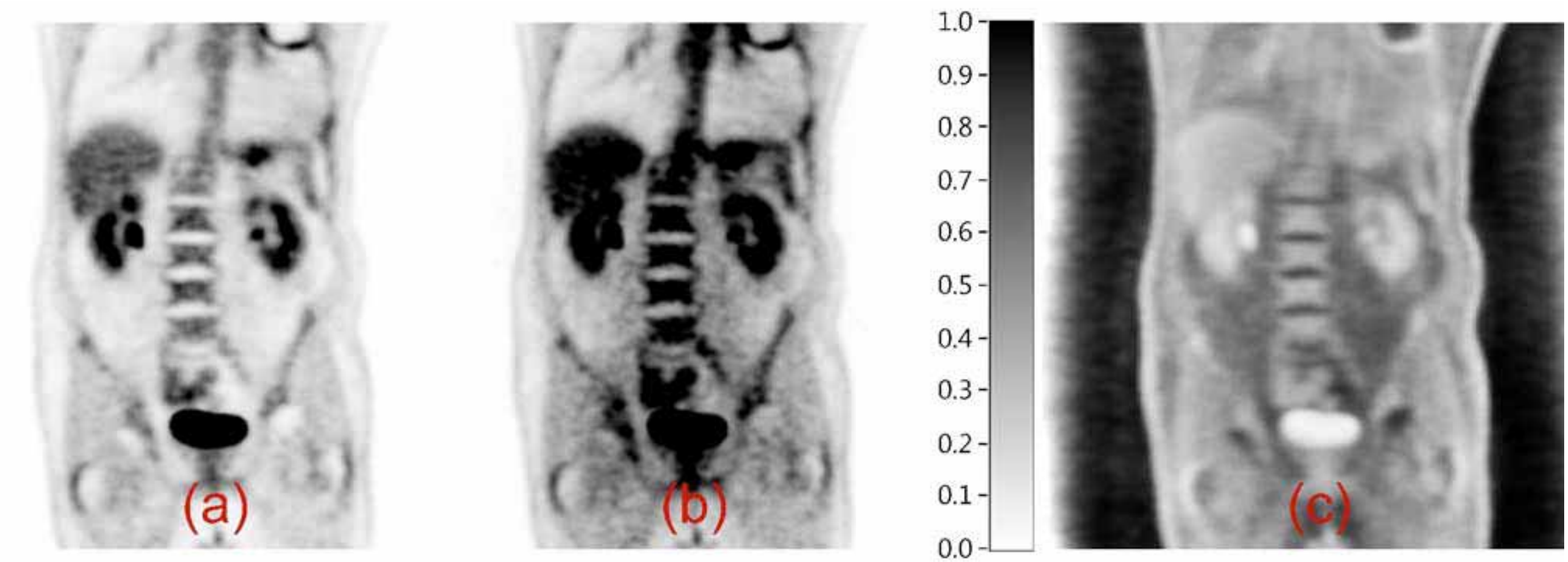
- The forces and interactions that nuclear emissions experience can also alter the state of the emissions
- This can directly impact imaging, ex. Compton scatter in PET:



Interactions of rad. with matter: How it fits in

- The forces and interactions that nuclear emissions experience can also alter the state of the emissions

(a) Scatter Correction | **(b) No Scatter Correction** | **Difference (b)-(a)/(b)**



Intro: interaction of radiation with matter

- Examples of highly penetrating radiation ?

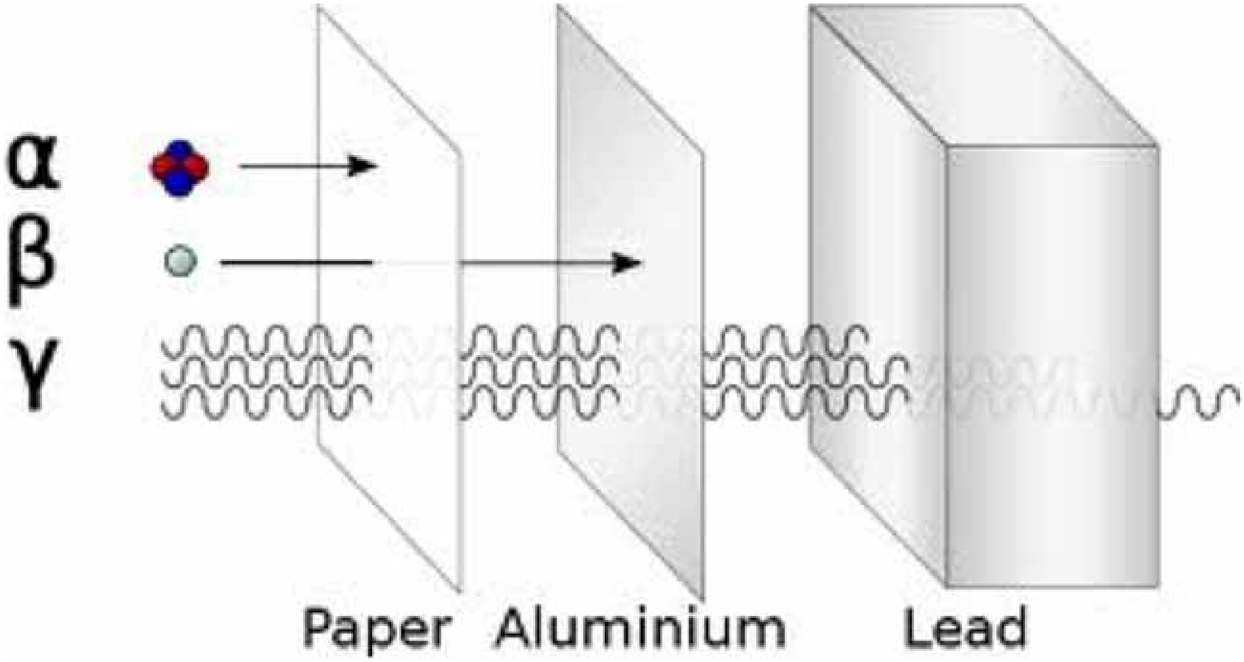
Rank in order of penetrating power:

a. Neutrino
b. Electron
c. Photon
d. Alpha
e. Neutron

1. Neutrino
2. Neutron
3. Photon
4. Electron
5. Alpha

any pattern ?

Intro: interaction of radiation with matter



- Incoming radiation interacts with the *electrons or the nucleus* of the material it encounters

Tissue penetration dependent on:

1. **Type of Radiation**
2. **Interaction Material (and thickness)**

Intro: interaction of radiation with matter

- Important for *detection* of radiation, assessing *radiation damage*, analyzing *radiation therapy*
- density ρ and atomic number Z of the interacting matter is important
- Interactions are statistical in nature:

$$P_{\text{int}} = 1 - e^{-\mu x}$$

  - μ = attenuation coefficient (1/cm)
  - x = distance travelled
  - 1/μ = ***mean* free path**
- Many particles per unit length so low variations in average numbers

Interaction of radiation with matter

Distinction between three types:

1. **Heavy charged particles:**
   - Short, well defined range
   - Collisional losses (at Nuc Med energies)
2. **Light charged particles:**
   - Longer, largely varying paths
   - Collisional and some radiative losses
3. Photons
   - Rayleigh Scatter (non-ionizing)
   - Photo-electric Effect
   - Compton Scatter
   - Pair Production

Interaction of Ionizing radiations will ultimately result in a cascade of lower energy electrons

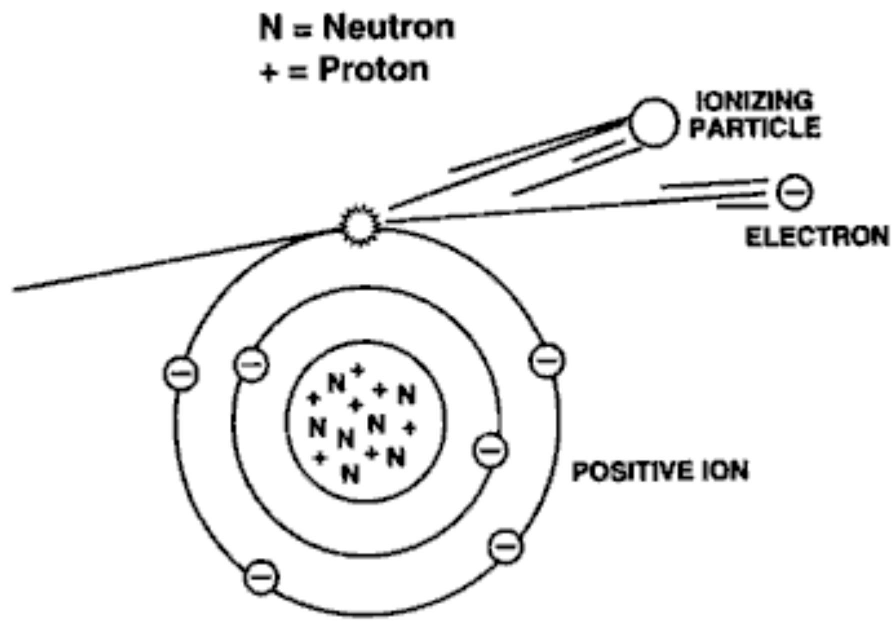
Intro: interaction of radiation with matter

- Charged particles undergo two primary energy transfer mechanisms:
  - Collisional Energy Transfers
  - Radiative Energy Transfers

I: Collisional losses

Collisional losses

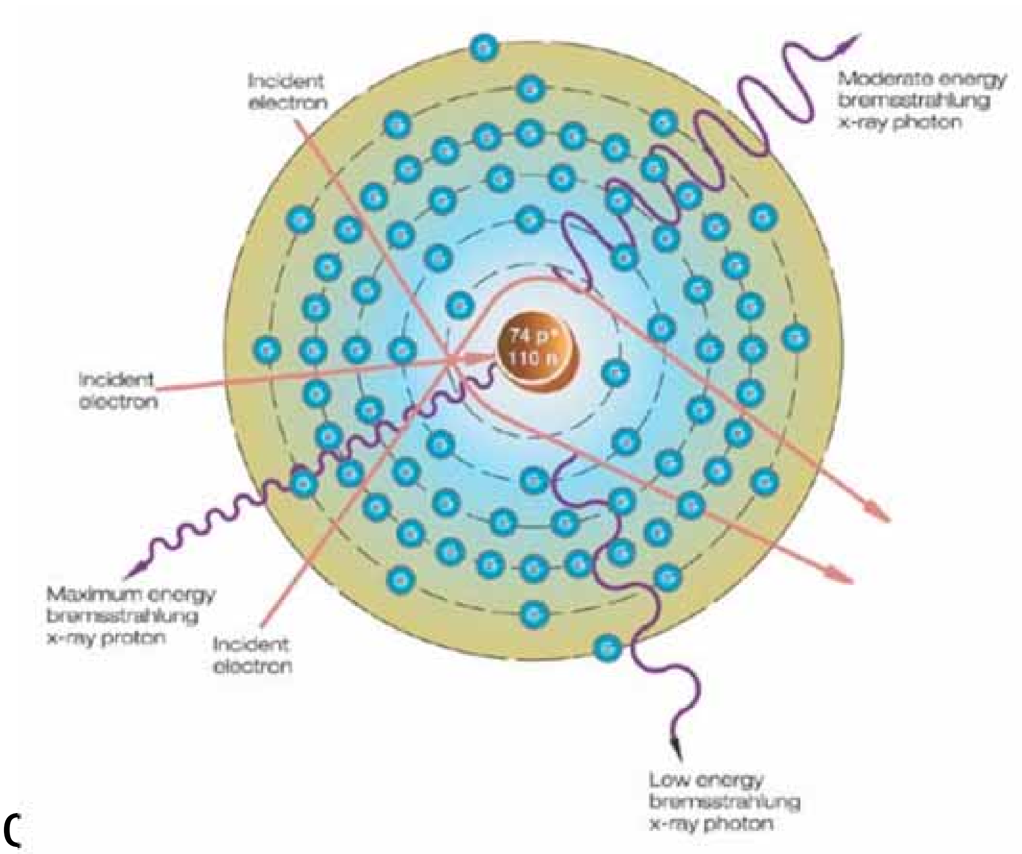
(ionization)



- When incoming radiation has a lot of kinetic energy, it may ionize the material; i.e. we have **ionizing radiation**
- Alternative: excitation of the atom (elastic)

II: Radiative losses

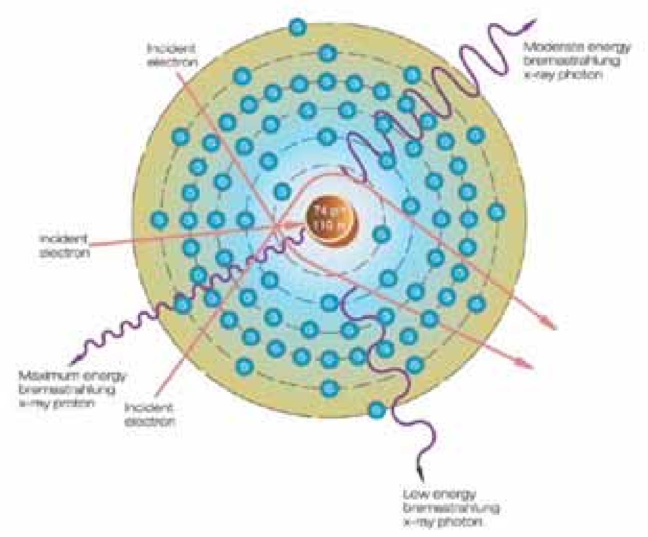
Competing process: **Radiative loss**

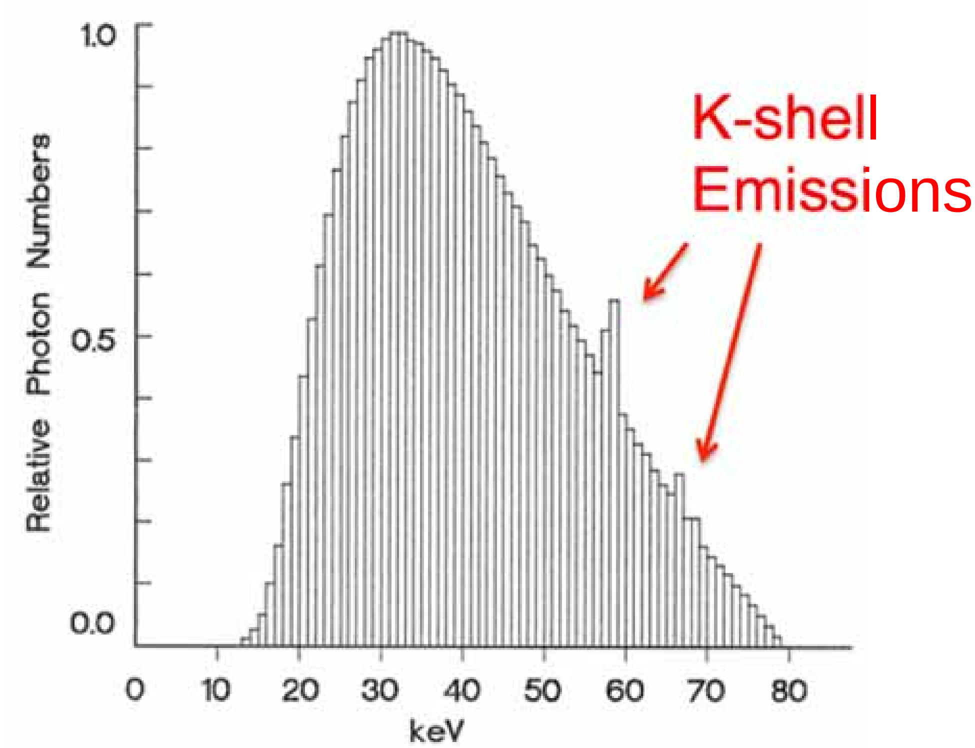


Charged partic the nucleus,
loses energy, emits a *Bremsstrahlung* photon

II: Bremsstrahlung

Results in a continuum of energies produced:

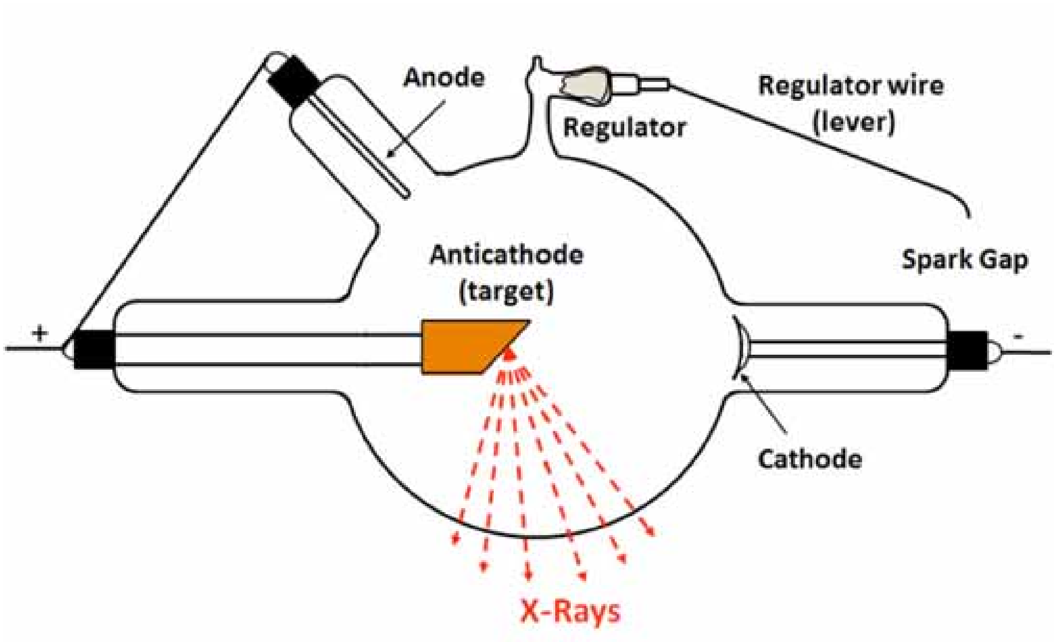




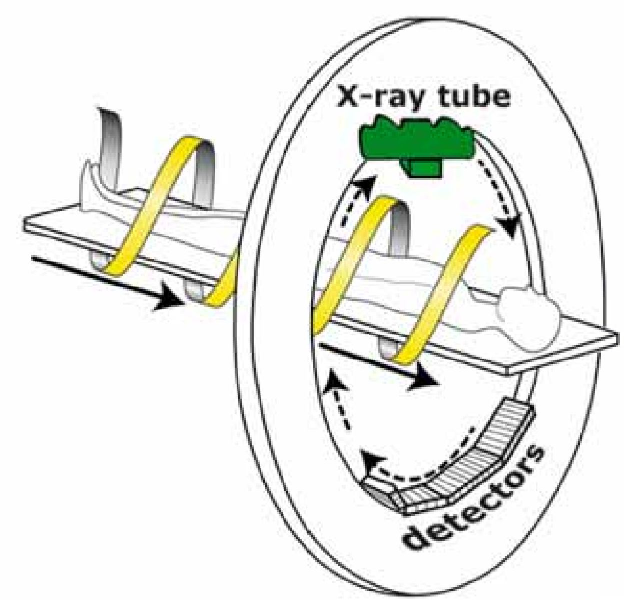
II: Bremsstrahlung

Xray-CT Imaging exploits bremsstrahlung to visualize anatomy

X-ray tube



X-ray CT Scan



I: Heavy Charged Particles

- Interact mainly through Coulomb interaction with atomic electrons
- Range is short: 10 MeV proton loses all its energy in only 0.25 mm copper
- *Inelastic* scattering: # particles in ≠ # particles out:
  $\alpha + Z \rightarrow \alpha + Z^{+} + e^{-}$
- Energy transferred to the atom
- Ionizing radiation: target becomes ionized, may yield biological damage
- Other interaction may be elastic scattering from nucleus, or nuclear reactions

II: Light Charged Particles: Electrons/Positrons

- Electrons behave similarly as heavy charged particles
- Lose energy through interactions with atomic electrons, *however* :
  - More energy is transferred in a collision
  - Secondary electrons may become ionizing: ***delta-rays***
  - Path subject to large variations
- Q: What about positrons ?

  A: exactly the same, except for *annihilation* after thermalization

Bremsstrahlung vs Collisional Losses

- Okay – so there are two competing processes: Collisional and radiative energy transfers
- Which is dominant?
- Relatively more Bremsstrahlung at higher or lower energies ?
- Relatively more Bremsstrahlung at high Z or low Z ?

II: Radiative vs. collisional losses

$$\frac{\text{Loss}_{\text{Bremsstrahlung}}}{\text{Loss}_{\text{collision}}} \approx \frac{\text{Z}E_{\beta}^{\max}}{3000}$$

- Radiative losses more prominent for increasing particle energy and increasing absorber Z
- Radiative losses more prominent for increasing particle energy

Are radiative (bremsstrahlung) or collisional losses more dominant for charged particles at energies relevant to nuclear medicine imaging studies?

$$\frac{\text{Loss}_{\text{Bremsstrahlung}}}{\text{Loss}_{\text{collision}}} \approx \frac{ZE_{\beta}^{\text{max}}}{3000}$$

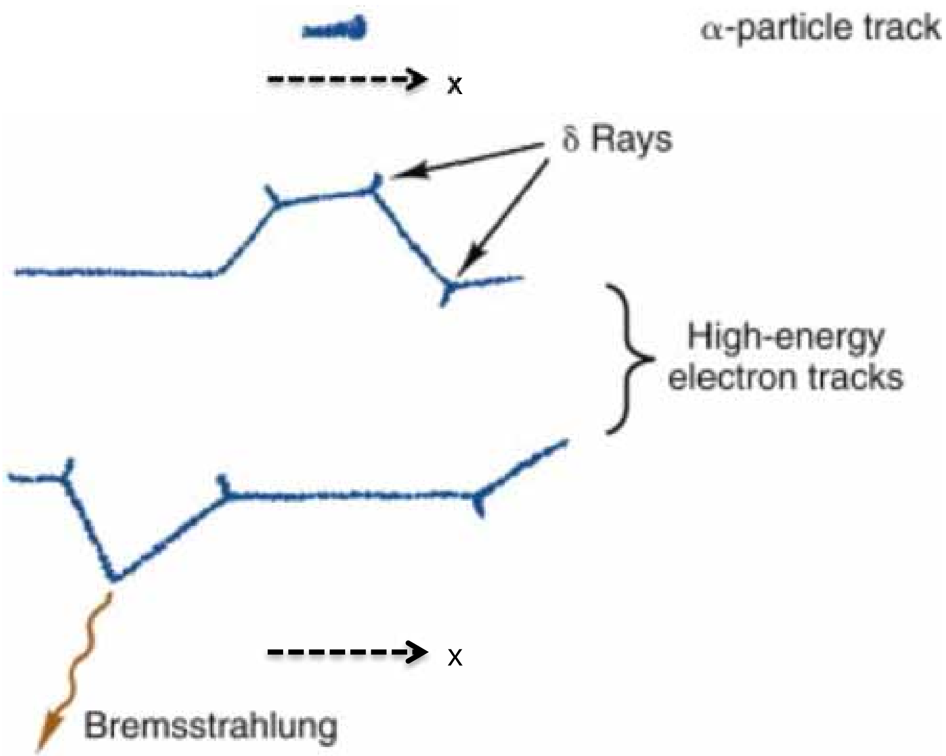
Are radiative (bremsstrahlung) or collisional losses more dominant for charged particles at energies relevant to nuclear medicine imaging studies?

$$\frac{\text{Loss}_{\text{Bremsstrahlung}}}{\text{Loss}_{\text{collision}}} \approx \frac{ZE_{\beta}^{\max}}{3000}$$

- Z for tissue is low H20 ~7.4
- Energy range for nuclear medicine studies ~0.1-0.5 MeV

Very small fraction of energy transferred from interaction of charge particles in tissue result in radiative yields, and dose is predominantly locally deposited.

II: Compare particle tracks

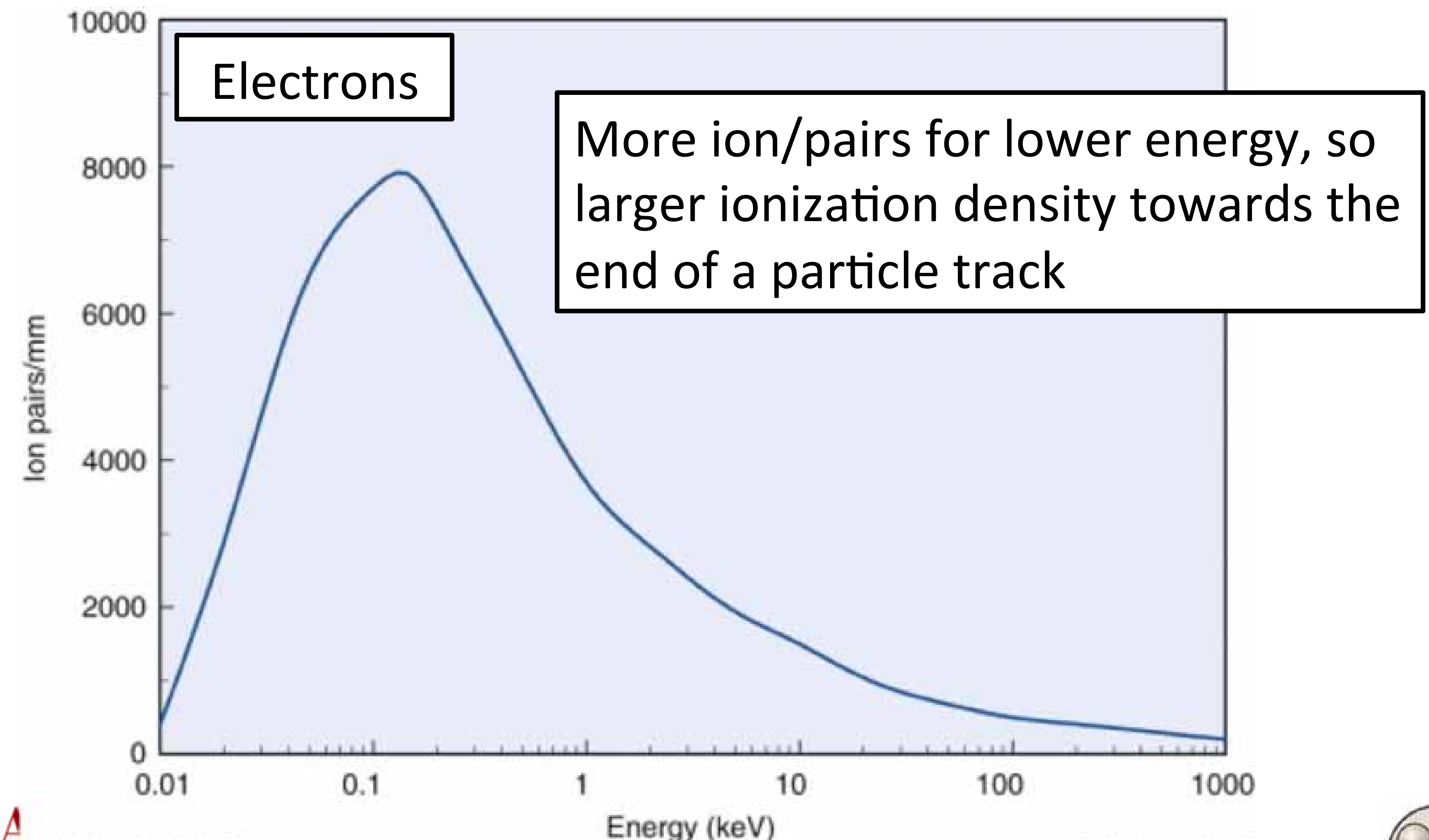


1. e- mass much lower
2. e- charge lower
3. e- experience large angle deflections (bremsstrahlung)

- Heavy charged particles travel in “straight lines, energy deposited locally
- Electrons undergo large angle deflections

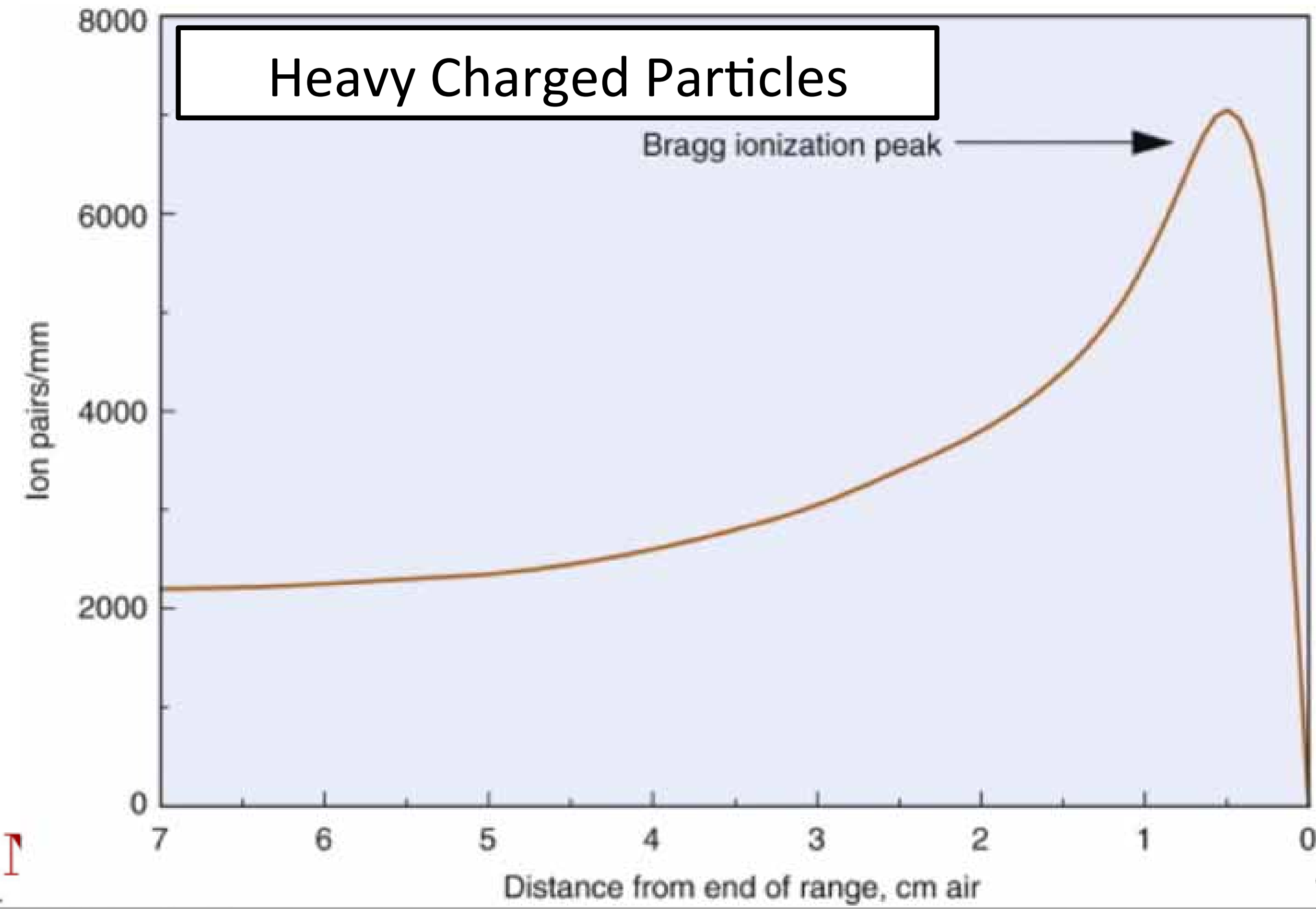
Specific ionization

- Specific ionization: number of ion pairs per distance
- The value is energy dependent

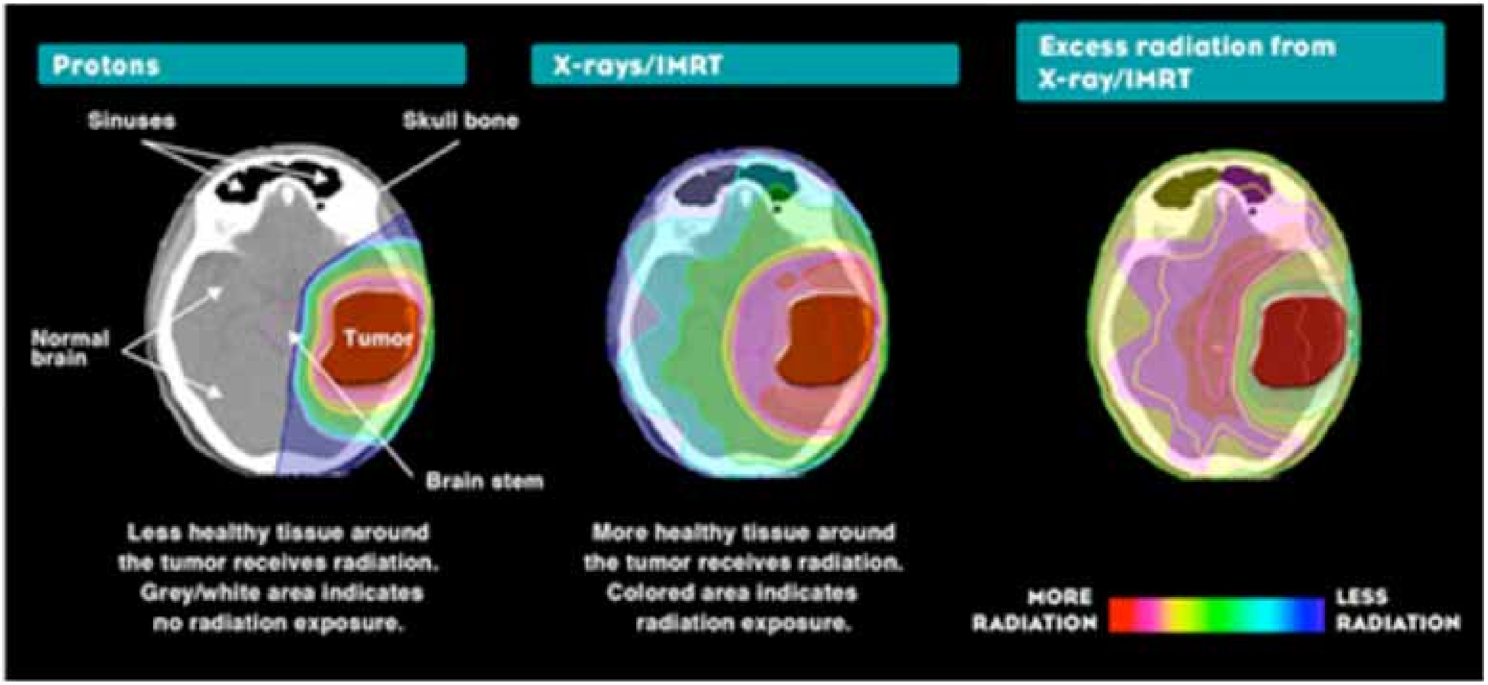


Specific ionization

- More energy deposited towards the end of track
- **Bragg Peak**, in particular for alpha particles

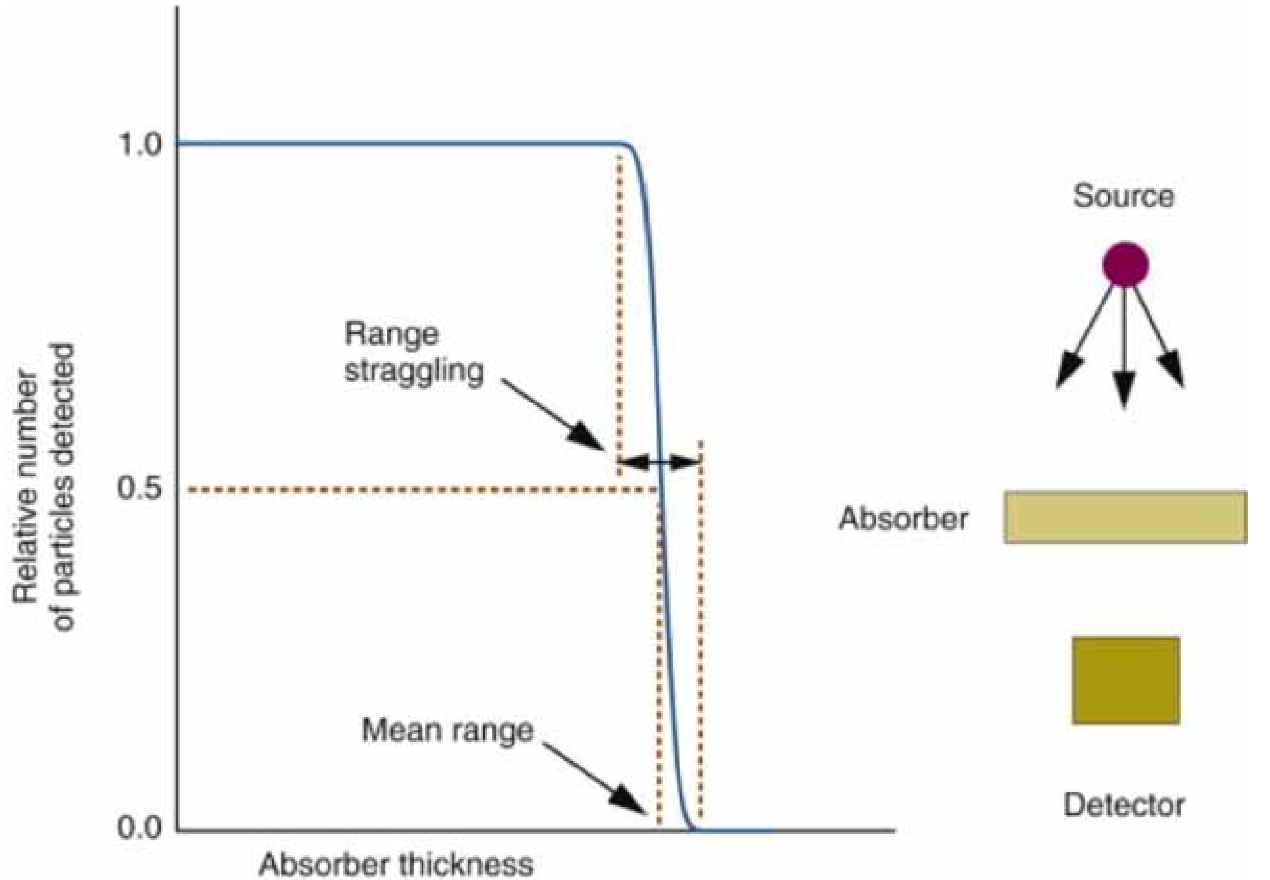


Proton Therapy



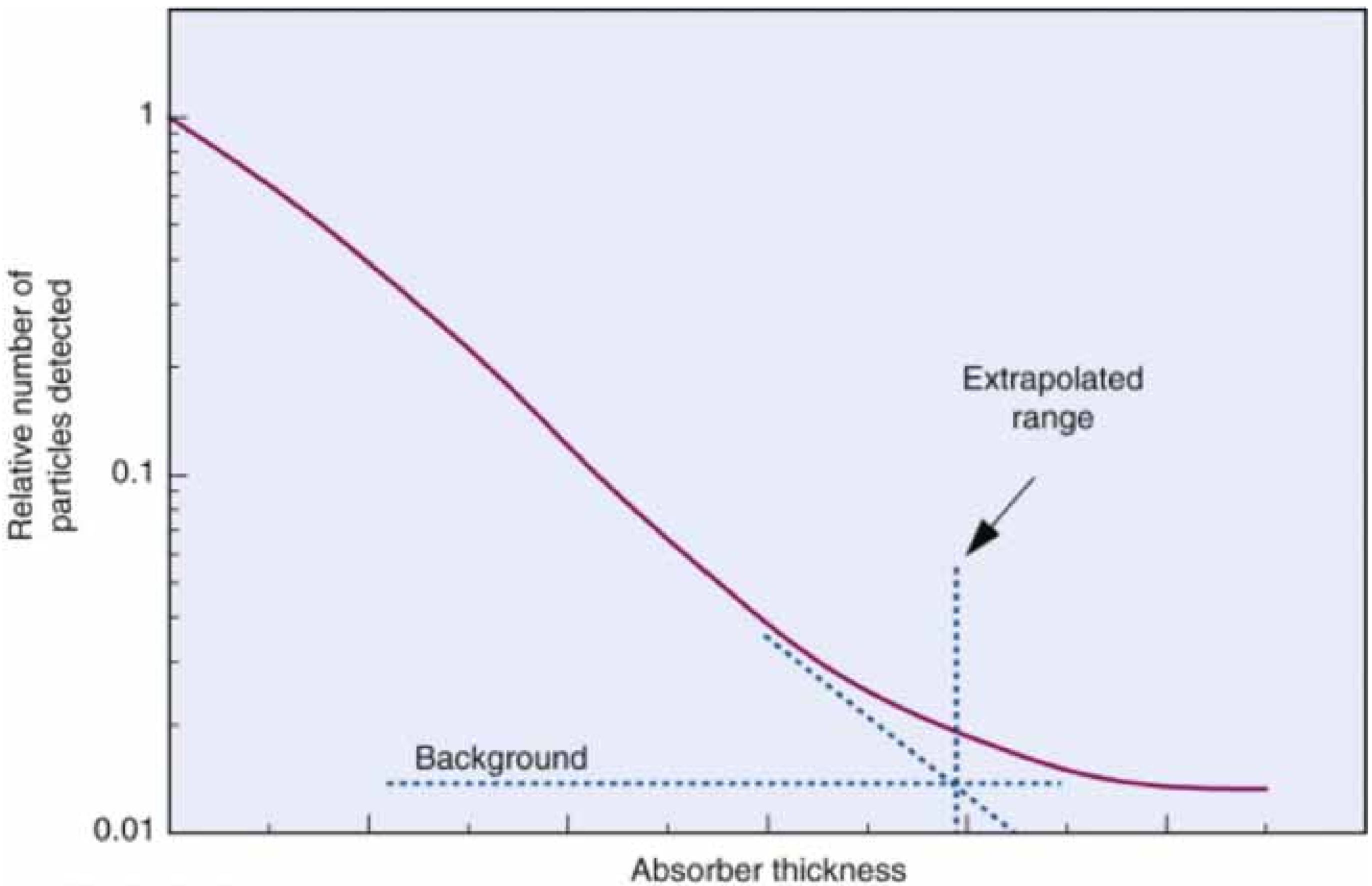
Particle Range

- Range of heavy particles (ex. Alpha particles & protons)



Particle Range

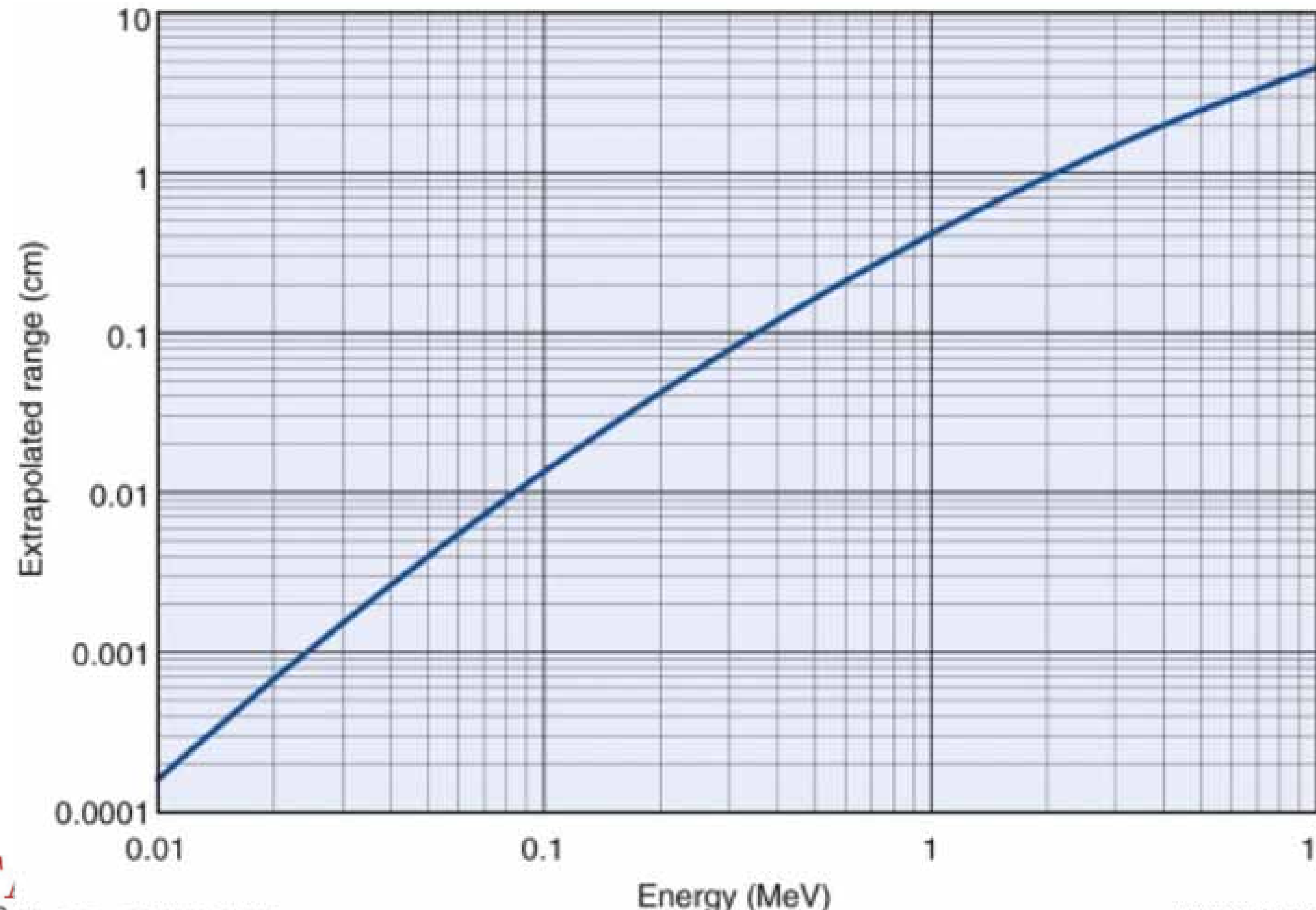
- Range of electrons/positrons
- More spread than heavy particles



Particle Range

- Range of electrons/positrons
- Strongly energy dependent

Electrons in water



Stopping power and Range

	Material	Density	Stopping Power		Range		
		(g/cm^3)	MeV cm/g	(MeV/cm)	(g/cm^2)	(cm)	(um)
1 MeV proton	Air	0.00120	222	0.266	0.00287	2.39	23900
1 MeV electron			1.66	0.00199	0.0490	408	408x10^6
1 MeV proton	Water	1.00	260	260	0.00246	0.00246	24.6
1 MeV electron			1.85	1.85	0.437	0.437	4370
1 MeV proton	Tungsten	19.3	63.5	1220	0.0122	0.00063	6.34
1 MeV electron			1.02	19.6	0.768	0.0399	399

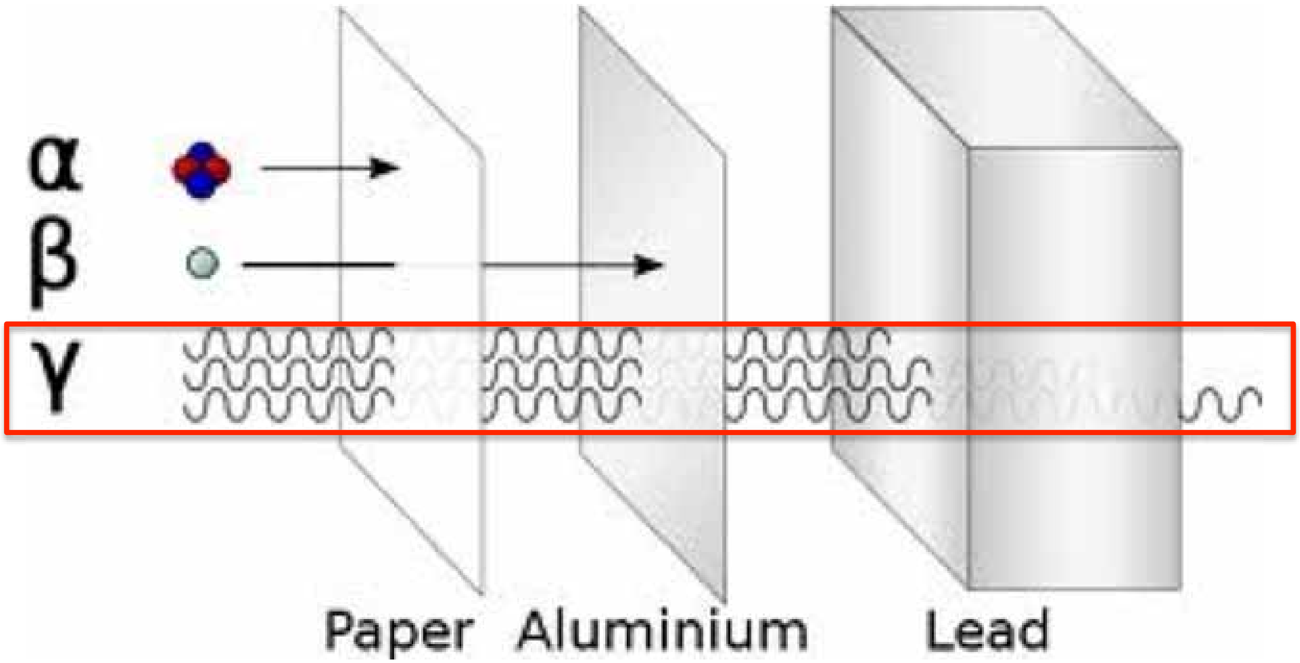
- Density is crucial
- Stopping power decreases as Z/A
- Electrons about 2 orders of magnitude **larger range**
- Source NIST pstar and estar:

http://physics.nist.gov/PhysRefData/Star/Text/ESTAR.html

Heavy and Light Charged Particles: Takeaways

- Interaction of Radiation in Matter in two categories:
  - Charged Particles
    - Heavy Charged Particles
    - Electrons/Positions
- Also two primary energy transfer mechanisms for charged particles:
  - Collisional Energy Transfers
    - Inelastic Coulomb scattering
    - Elastic nuclear interactions
  - Radiative Energy Transfers
    - Bremsstrahlung

Photon Interactions



Photons are highly penetrating electromagnetic radiation

Interaction of radiation with matter

Distinction between three types:

1. Heavy charged particles:
   - Short, well defined range
   - Collisional losses (at Nuc Med energies)
2. Light, charged particles:
   - Longer, largely varying paths
   - Collisional and some radiative losses
3. **Photons**
   - **Rayleigh Scatter (non-ionizing)**
   - **Photo-electric Effect**
   - **Compton Scatter**
   - **Pair Production**

Photon Interactions

- For a photon to deposit energy, energy needs to be transferred to an electron first

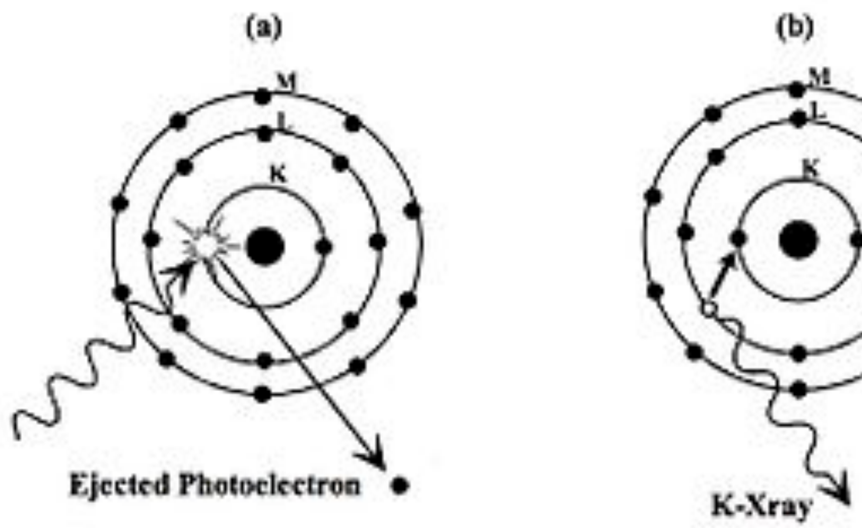
Two processes most relevant at Nuclear Medicine Energies:

1. Photoelectric absorption
2. Compton Scatter

Important: the electron that receives energy from the photon will deposit energy in the material (i.e. ionize the material)

Photons: Photo-Electric Absorption

1. **Photon absorbed by atom**
2. Atom emits *photoelectron,* with energy:
   $E_{pe} = E_{\gamma} - BE$ (BindingEnergy)
3. Photo-Electron now is ionizing
4. An higher shell electron fills the vacancy and emits an X-Ray photon

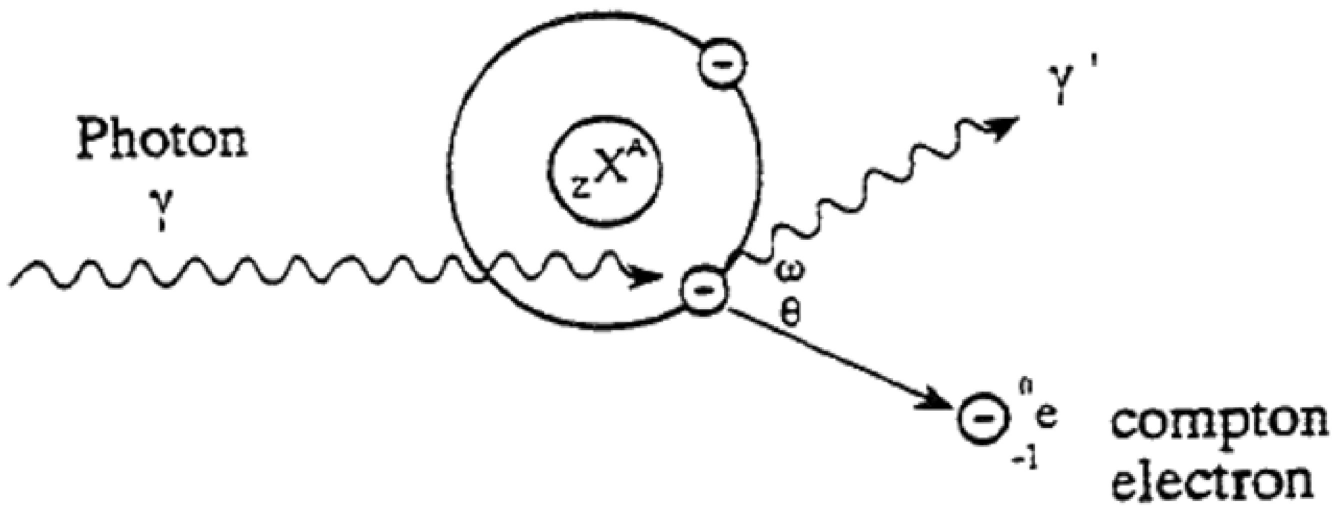


III: Photons: Compton Scatter

1. **Photon *scattered* by electron**
2. Electron overcomes the binding energy and gets ejected :

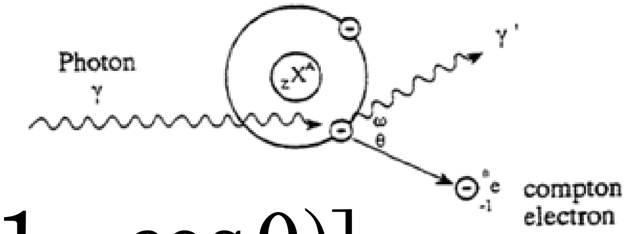
$$E_e = E_\gamma - E_\gamma^{'} - E_{binding}$$

3. Scattered -*unbound*- electron deposits energy



III: Photons: Compton Scatter

1. Photon *scattered* by electron



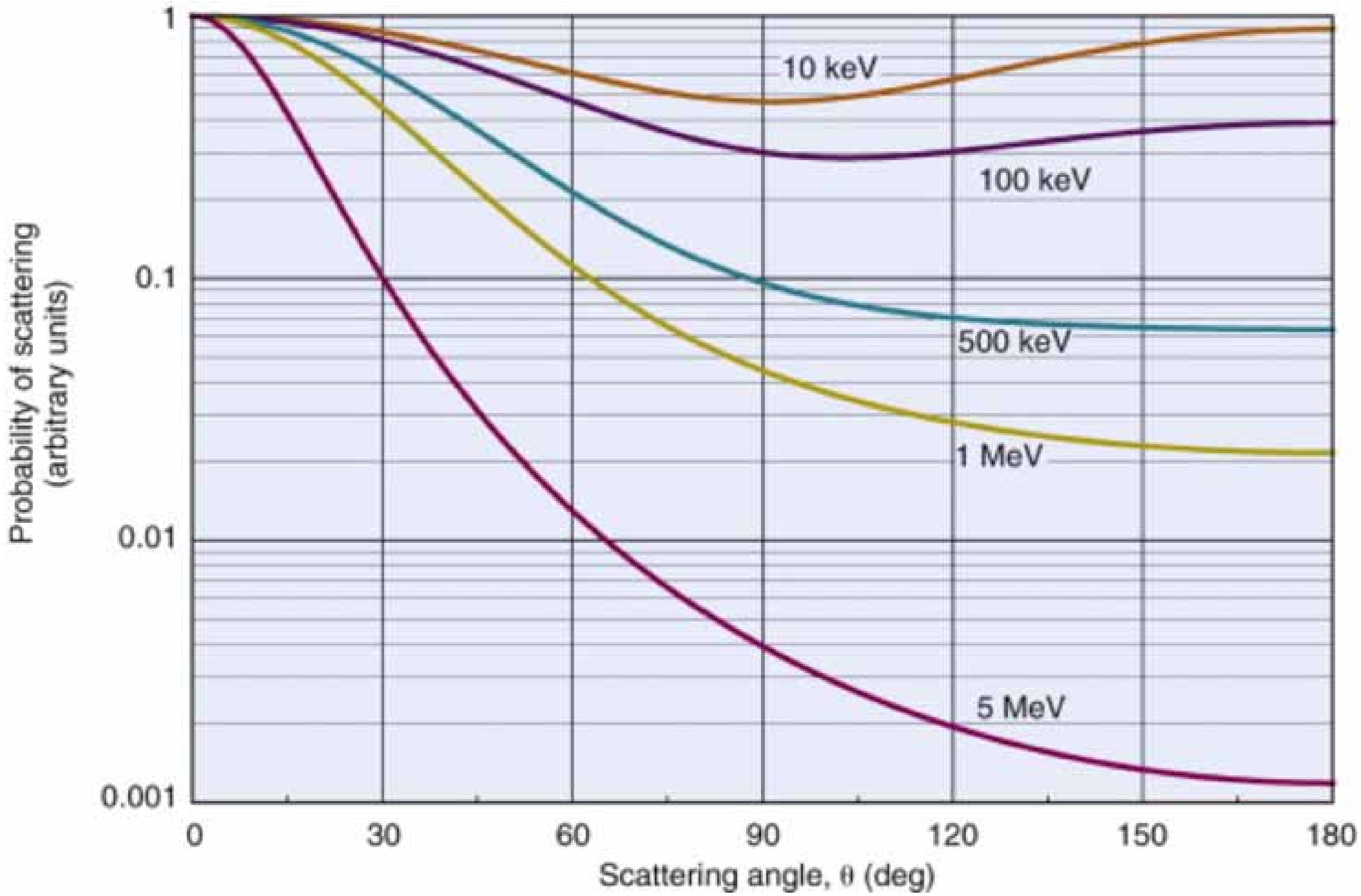
$$E_{sc} = E_0/[1 + (E_0/0.511)\,(1 - \cos\theta)]$$

TABLE 6-2

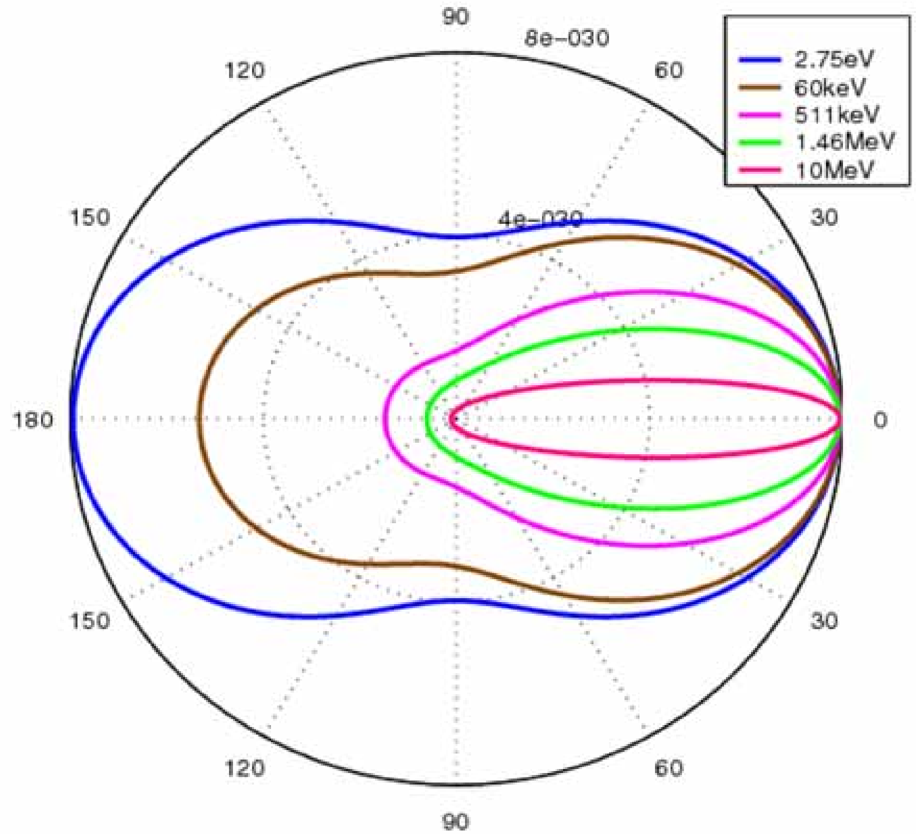
SCATTERED PHOTON AND RECOIL ELECTRON ENERGIES FOR 180-DEGREE COMPTON SCATTERING INTERACTIONS

Radionuclide	Photon Energy (keV)	E_{sc}^{min} (keV)	E_{re}^{max} (keV)
^{125}I	27.5	24.8	2.7
^{133}Xe	81	62	19
^{99m}Tc	140	91	49
^{131}I	364	150	214
β^+ (annihilation)	511	170	341
^{60}Co	1330	214	1116
—	∞	255.5	—

III: Photons: Compton Scatter



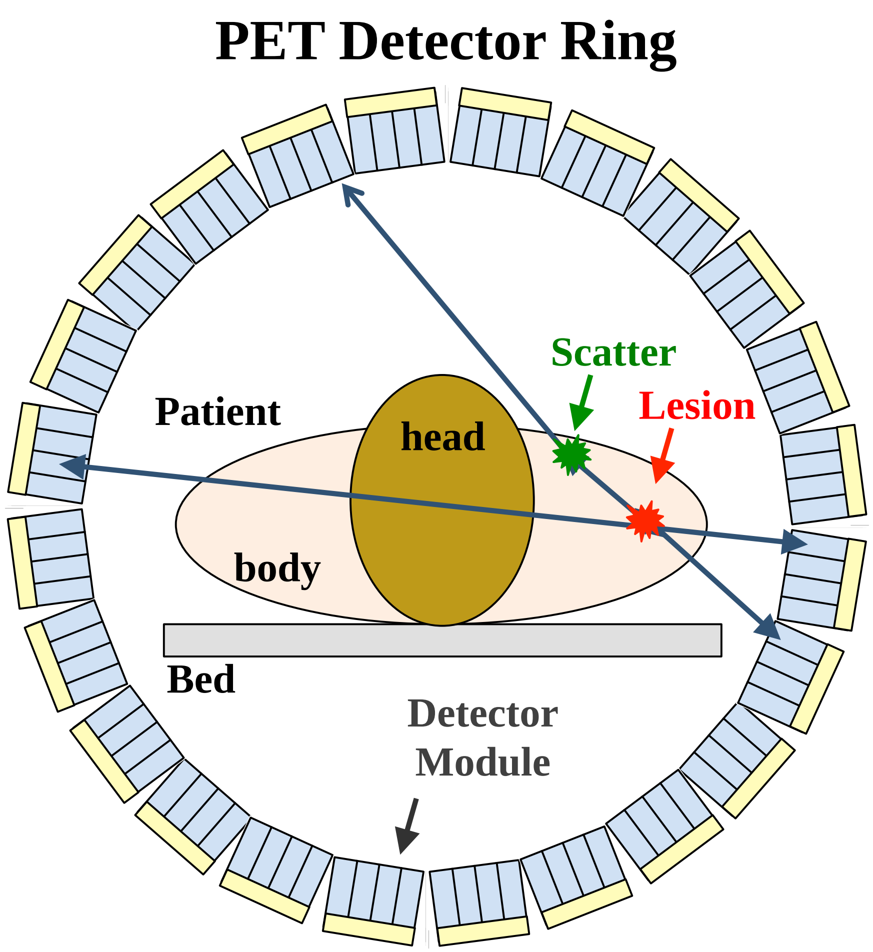
III: Photons: Compton Scatter

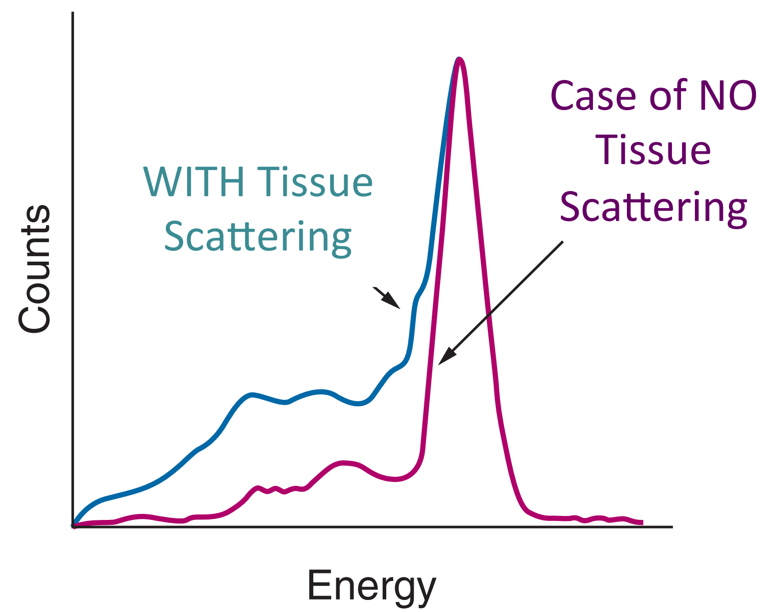


- Scatter more forward for higher energies
- Electron obtains most energy when photon backscatters (most energy transfer

How Angular Dependency Matters in PET

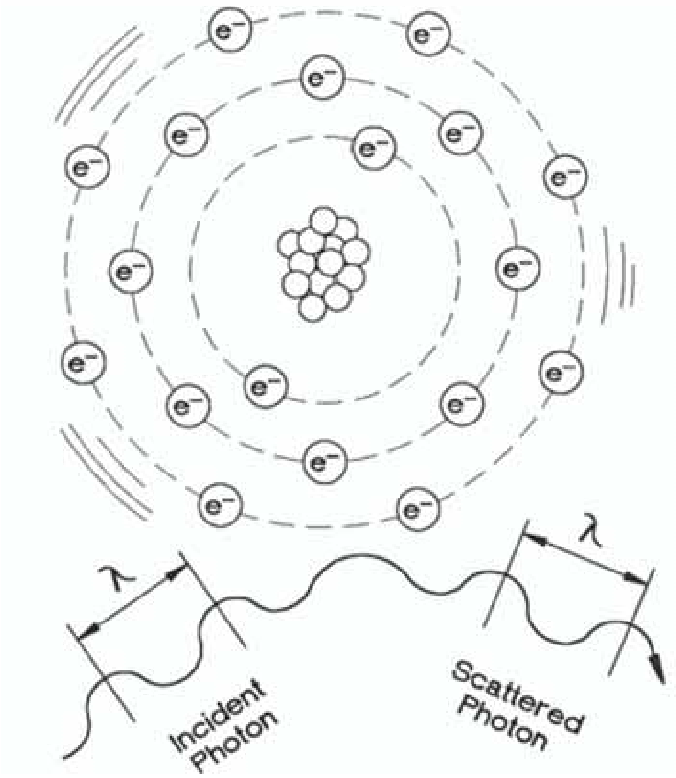
(One Example)





Photons: Rayleigh Scatter

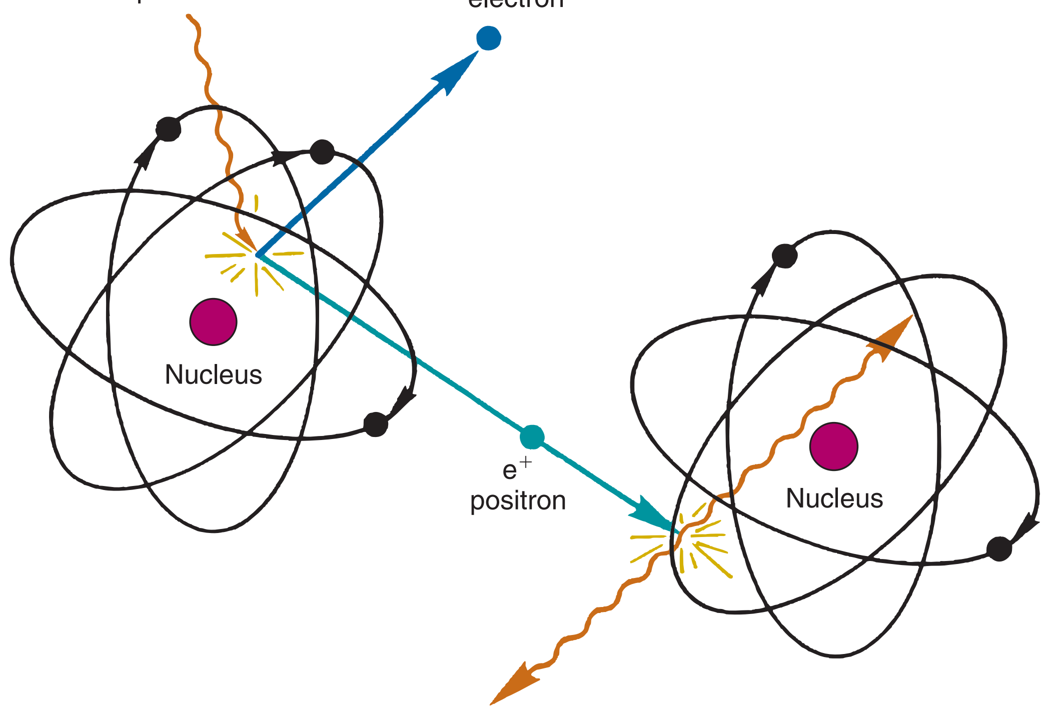
1. Elastic scatter of a photon off the entire atom



- 10 % of interactions at 30 keV (in soft tissue) - mammography
- 5 % of interactions at 70 keV (in soft tissue) - X-ray imaging
- Interaction probability goes up with $\sim Z^3$
- **Non-ionizing!**

III: Photons: Other processes

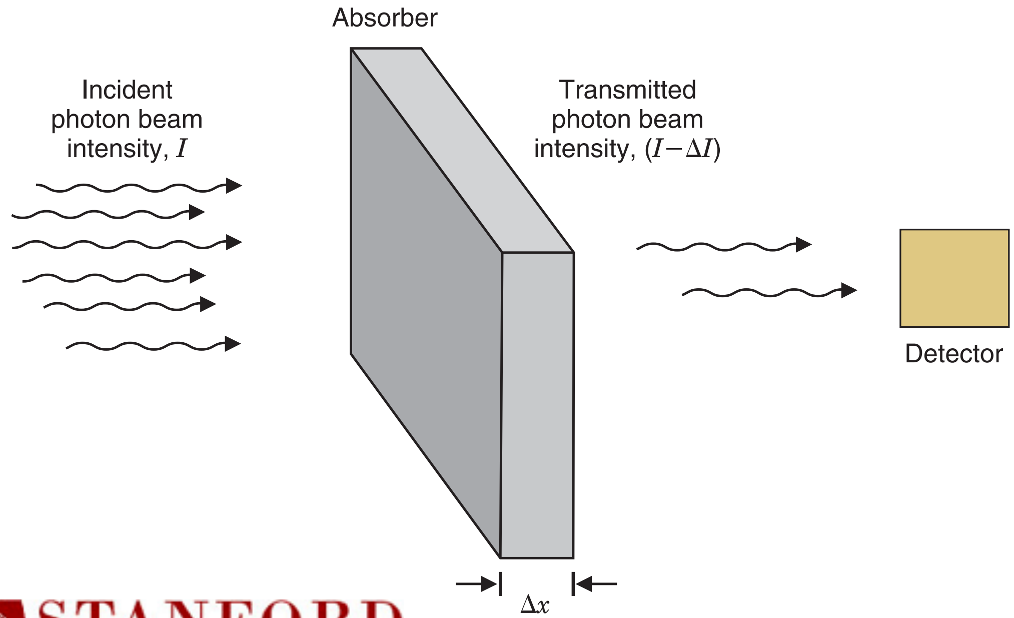
- **Pair production:** higher energy photons are able to create electron-positron pairs (E>1.022 MeV), this process quickly becomes dominant (~ Z log(E))

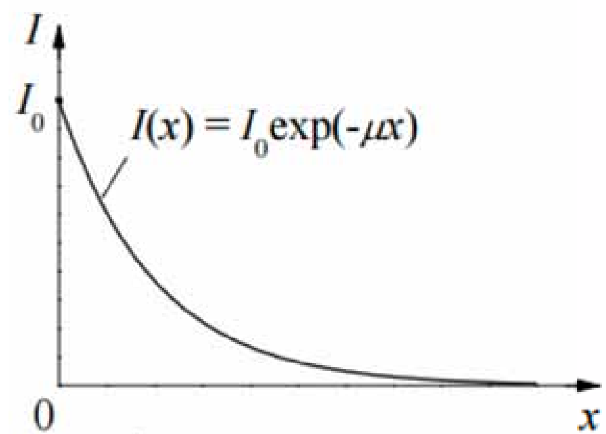


Photon interactions

- Interactions alter emissions from the radionuclide carefully selected for a molecular probe for imaging
- It is important to know how likely these interactions will affect emissions

Simple Experiment to Extract this Parameter

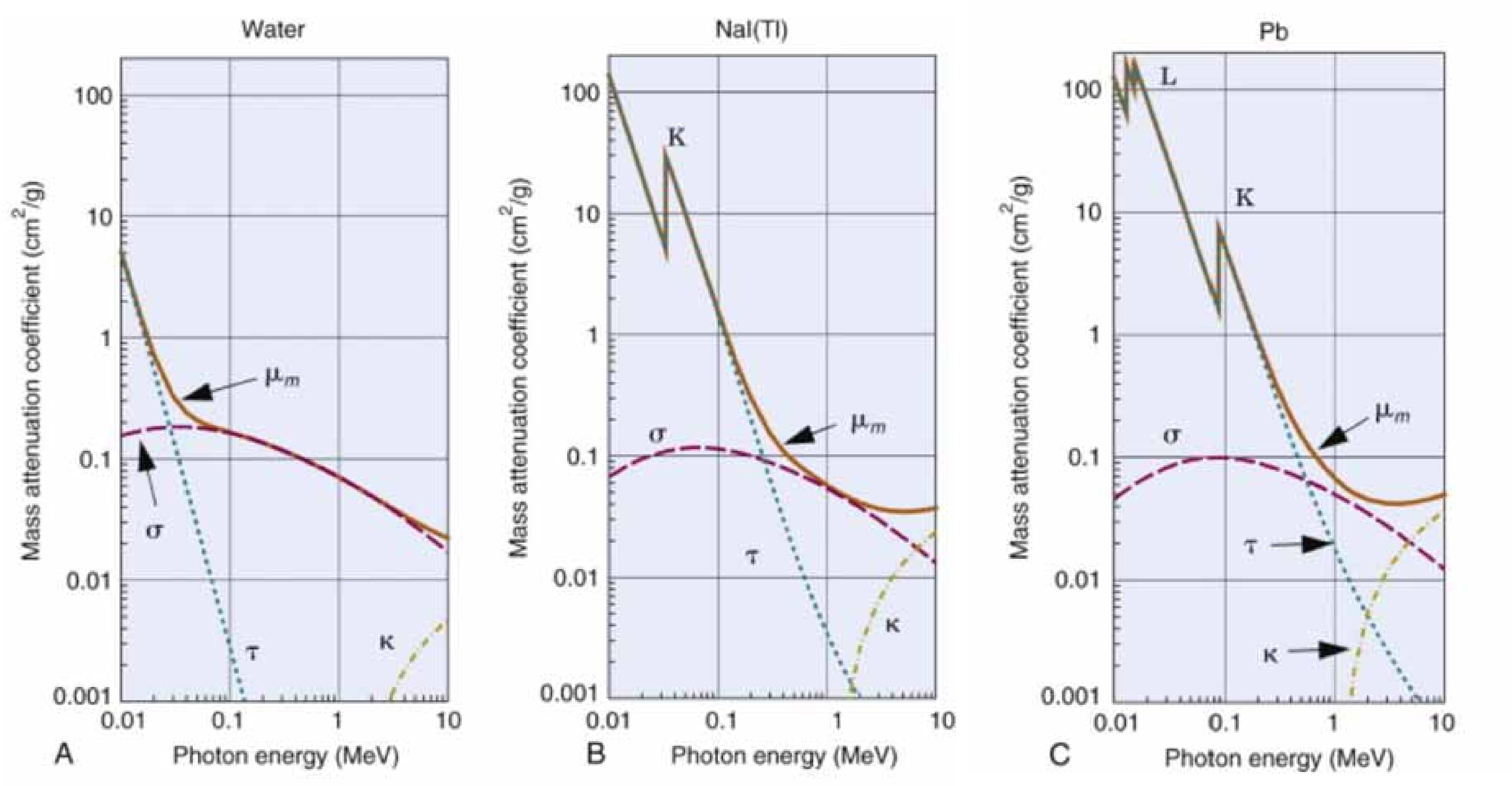




$$\frac{I}{I_0} = \exp(-\mu x)$$

μ is the probability of interaction per unit path length (1/cm)

Photon Probability of Interaction

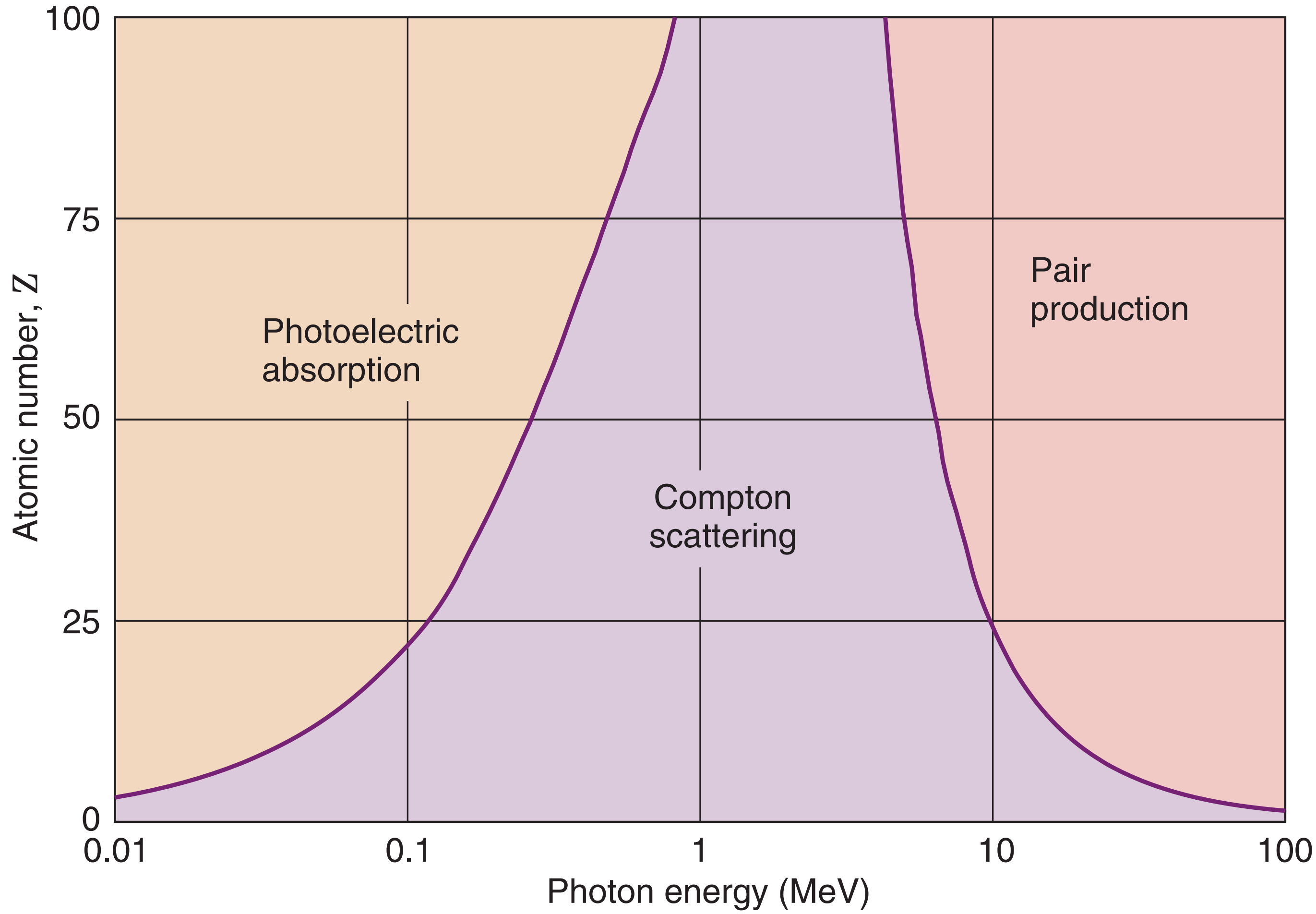


τ = photoelectric absorption

σ = Compton Scatter

K = Pair production

Dominant Photon Interactions Z vs. E

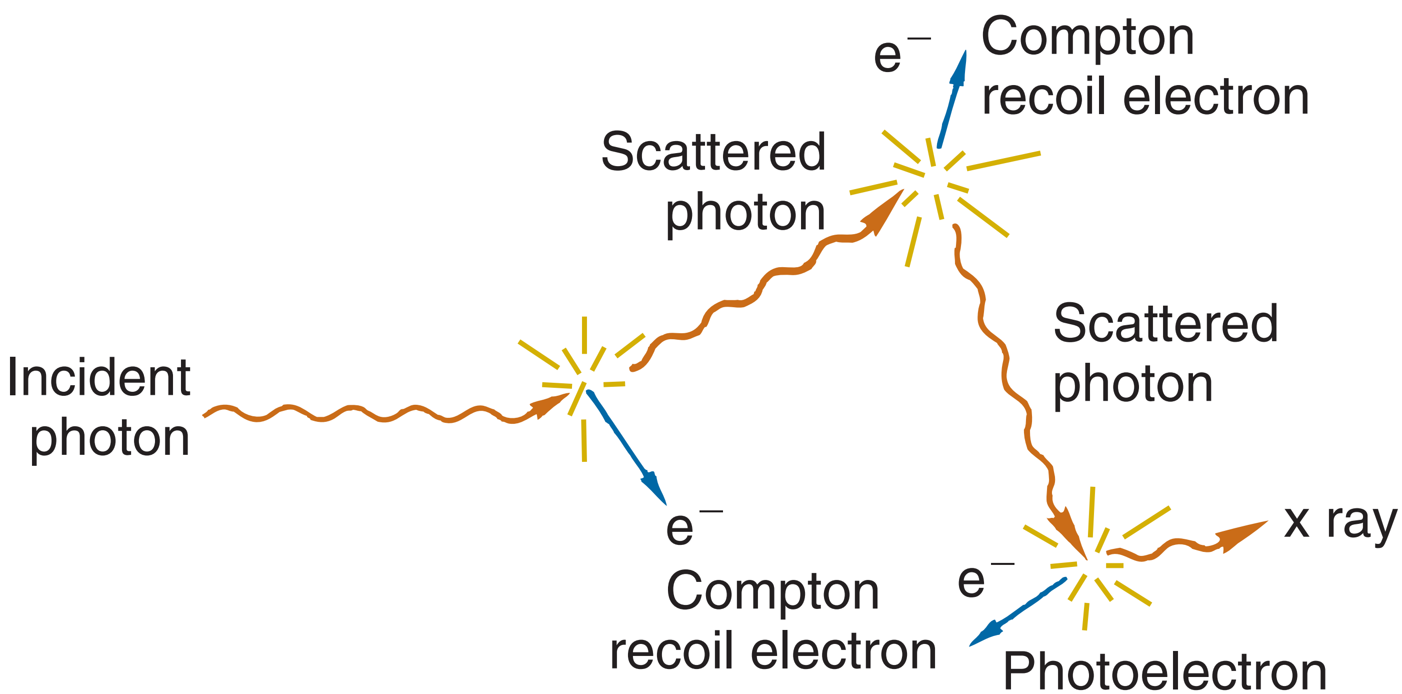


Different processes dominant at different energies

Photon interactions

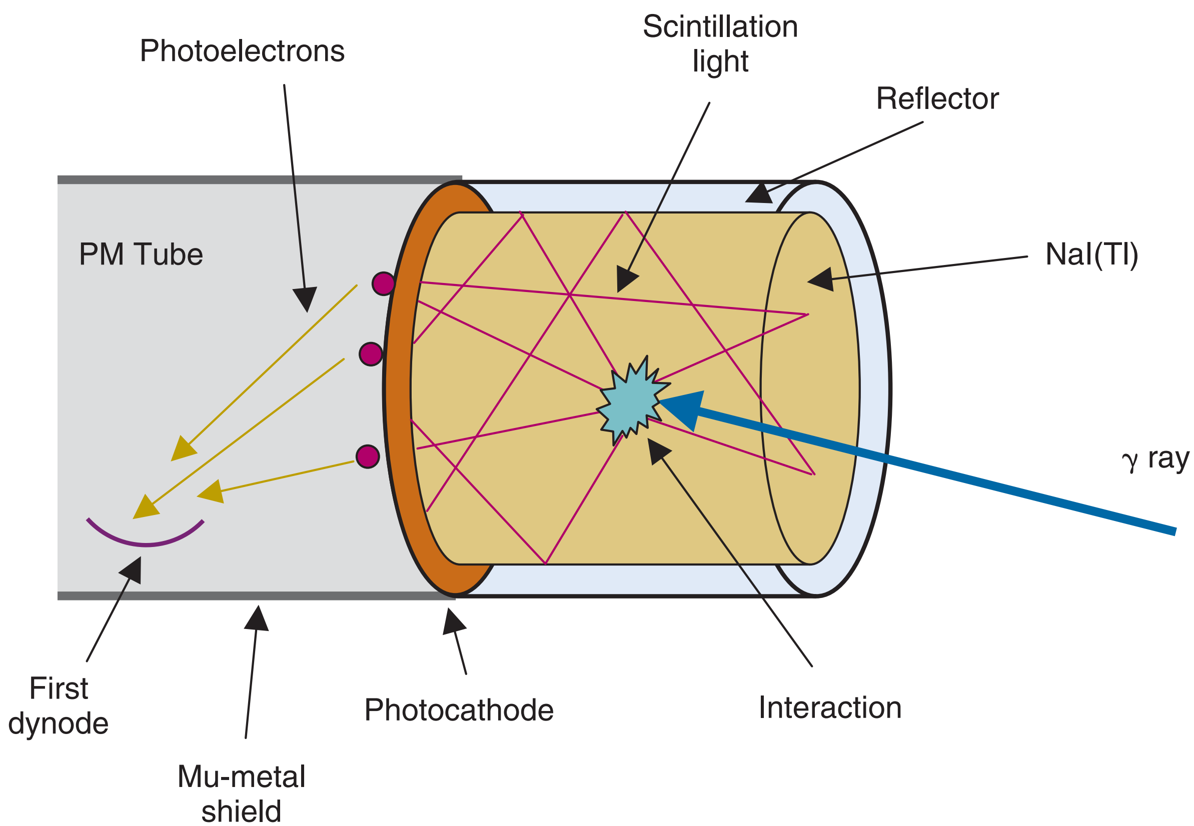
- **Rayleigh Scatter:** coherent scatter whereby the photon changes direction, can be significant at low energies
- **Photoelectric**: γ -> photoelectron (-BE). Probability ~ Z^4/E^3
- **Compton Scatter**: γ -> γ' + e'. Probability ~ Z/E
- **Pair production:** higher energy photons are able to create electron-positron pairs (E>1.022 MeV), this process quickly becomes dominant (~ Z log(E))

How Photons Deposit Energy in Matter



- Interactions of photons and charged particles with matter are coupled
- Secondary electrons ionize and deposit dose

A look forward: The Scintillation process



1. **Gamma** interaction

- Photoelectric Absorption
- Compton Scattering

2. Photo- or Compton **electron** deposits energy in scintillator

- Ionization
- Excitation of Medium

3. Scintillator atoms get excited

- Thermalization of charge carriers

4. Scintillator atoms de-excite by emitting optical photons

one gamma photon yields **one** electron, but **many** optical photons

Photon interactions

Energy (keV)		Air (ρ = 1.2 10^{-3} g/cm^3) Attenuation (10^{-3} cm^2/g)	Mean free path (10^6 cm)	Total mean free path (cm)	H_2O (ρ = 1 g/cm^3) Attenuation (10^{-3} cm^2/g)	Mean free path (10^3 cm)	Total mean free path (cm)	Tungsten (ρ = 19 g/cm^3) Attenuation (10^{-3} cm^2/g)	Mean free path (cm)	Total mean free path (cm)
140	R	2.57	0.324	6030	2.79	0.358	6.51	100	0.519	0.0277
	C	135	0.006		150	0.007		98.5	0.528	
	PE	0.67	1.24		0.915	1.09		2000	0.031	
511	R	0.20	4.23	9640	0.22	4.65	10.4	9.14	5.68	0.388
	C	86.2	0.010		95.8	0.010		68.1	0.763	
	PE	0.01	64.4		0.02	56.2		56.6	0.918	
1000	R	0.05	16.2	13100	0.06	17.8	14.1	2.48	21.0	0.785
	C	63.6	0.013		70.7	0.0141		50.9	1.02	
	PE	0.003	311		0.004	2.72		12.8	4.06	

- Higher energy results in higher mean free path
- Mean free path = average distance between interactions
- Air almost no attenuation
- In water Compton dominant at E > 140 keV
- In tungsten Compton dominant at E > 500 keV

Z_{eff} air = 7.6 ; Z_{eff} H_2O = 7.4