

Radioisotope Imaging

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1 Radioisotope Imaging in Clinical Practice

- Radionuclide imaging is involved in the production of images showing the distribution of **radio-labelled** agents within biological tissue.
- The uptake of **radio-pharmaceuticals** reflects **dynamic physiological function** and in general does not imply a structural parameter.
- The majority of radio-pharmaceuticals are not disease specific but instead are capable of illustrating differences in **dynamic** function between normal and abnormal tissue.

2 Examples of Radioisotope Imaging in Clinical Practice

- **Blood Flow**
 - rCBF (regional cerebral blood flow)
 - ventriculography (left ventricular ejection fraction (LVEF))
 - renal filtration (GFR and ERPF)
 - respiratory ventilation-perfusion (V-Q) studies
- **Metabolic**
 - cerebral glucose metabolism (2-deoxyglucose)
 - neurotransmitter amino-acid metabolism and receptor binding
 - turnover of metabolically active skeletal bone mineral (hydroxyapatite)
- **Organ Function**
 - Liver - phagocytic (Kupfer) cell function and hepatobiliary function
 - Thyroid - radio-iodine uptake
- **Disease Specific**
 - uptake of radiolabelled antibodies

3 Overview of the Common Radioisotope Imaging Modalities

The most common radio-isotope imaging modality in clinical use is that of the **planar scintigram**, being used particularly in the evaluation of heart, lung, kidney and thyroid function.

- Static Planar Scintigraphy

- Dual Isotope Imaging
- Dynamic Planar Scintigraphy
 - Dynamic Cardiac Imaging
 - Dynamic Renal Imaging
- Emission Computed Tomography
 - Single Photon Emission Computed Tomography (SPECT)
 - Positron Emission Tomography (PET)

4 Static Planar Scintigraphy

Static planar scintigraphy consists of the following major components

- an electromechanical gantry to position camera
- collimation to reduce image scatter
- gamma camera to record “disintegrations”
- analog/digital image production/storage/analysis

The following are factors important in image quantification

- the resultant image is a 2-D superposition of 3-D information.
- spatial resolution degrades with increasing distance from the collimator due to source dependent scattering.
- attenuation increases with depth. In general depth correction attenuation will only be possible when relative organ measurements are available and in general will only be useful if the relative dimensions of the imaged organ are small.
- for larger organ structures, e.g liver, anterior and posterior images can be collected via a rotating gantry to reduce the effects of depth dependent photon attenuation. **Iso-sensitive** or **quantitative** scanning can reduce this effect by taking an arithmetic or geometric mean of the anterior and posterior images.

4.1 Limited Attenuation Correction

Let the activity (e.g disintegrations per second), A , at x give rise to a response at the anterior gamma camera, C_A , i.e

$$C_A = kA \exp[-\mu x]$$

where μ is the linear attenuation coefficient for the particular corpuscular or EM radiation. Similarly for the posterior gamma camera

$$C_P = kA \exp[-\mu(T - x)]$$

These opposing images can be combined to ameliorate the effects of photon attenuation with increasing distance by forming the **geometric** or **arithmetic** means of C_A and C_P assuming homogeneous μ . Thus

arithmetic mean:

$$\begin{aligned} C_{AM}(x) &= C_{AM}(T - x) = (C_A + C_P)/2 \\ &= \{\exp[-\mu x] + \exp[-\mu(T - x)]\}/2 \end{aligned}$$

geometric mean:

$$\begin{aligned} C_{GM} &= \sqrt{C_A C_P} \\ &= kA \exp[-\mu T/2] \end{aligned}$$

It should be noted that taking the geometric mean, *assuming* that μ is homogeneous, implies that the recorded “activity” is depth independent. As a consequence of this combination the spatial resolution can be made virtually independent of depth. Often such an approach is not successful due to inhomogeneities in the tissue linear attenuation coefficients.

5 Dual Isotope Imaging

Often it is possible to use more than one radio-pharmaceutical to better define the region of interest (ROI). This is because radio-pharmaceutical uptake is not specific and tissues or organs not of interest may take up radio-pharmaceutical in significant enough quantities to dramatically reduce spatial resolution. The technique of dual-isotope imaging allows images of the distribution of two radio-pharmaceuticals. The two images obtained can then be subtracted to better

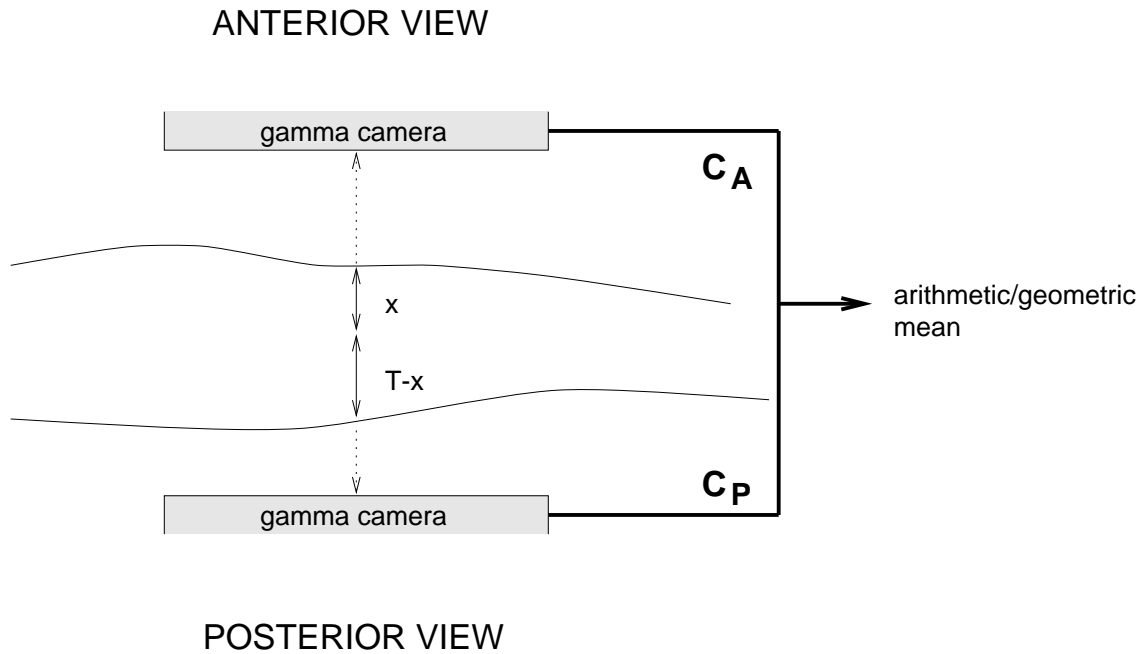


Figure 1: Geometry for combining anterior and posterior views in planar scintigraphy (adapted from Webb (1991))

define the ROI. Such a technique is of value in the diagnosis and detection of hepatoma. ^{67}Ga -citrate is metabolised by both normal and abnormal liver tissue whereas $^{99}\text{Tc}^m$ colloid is only taken up by normal liver tissue. Thus a subtraction of the two images (taken simultaneously using two or more image channels) is in principle capable of showing the location and dimensions of a liver tumour more clearly than if only one conjugated radio-isotope was used.

6 Dynamic Planar Scintigraphy

The basic technique involves the acquisition of image data in frame or list mode to illustrate temporal changes in radio-pharmaceutical distribution *in vivo*.

Two of the most common dynamic radioisotope imaging investigations are

- Dynamic Cardiac Imaging
- Dynamic Renal Imaging

6.1 Dynamic cardiac imaging (fast dynamic acquisition)

- *Multi-gated acquisition (MUGA)*: this requires ECG triggering (generally on the R wave), indicating the beginning of systole, is used to align the acquired data into a series of up to 32 images or frames during each heartbeat. Frames or images are **averaged** over successive heart beats. Acquisition

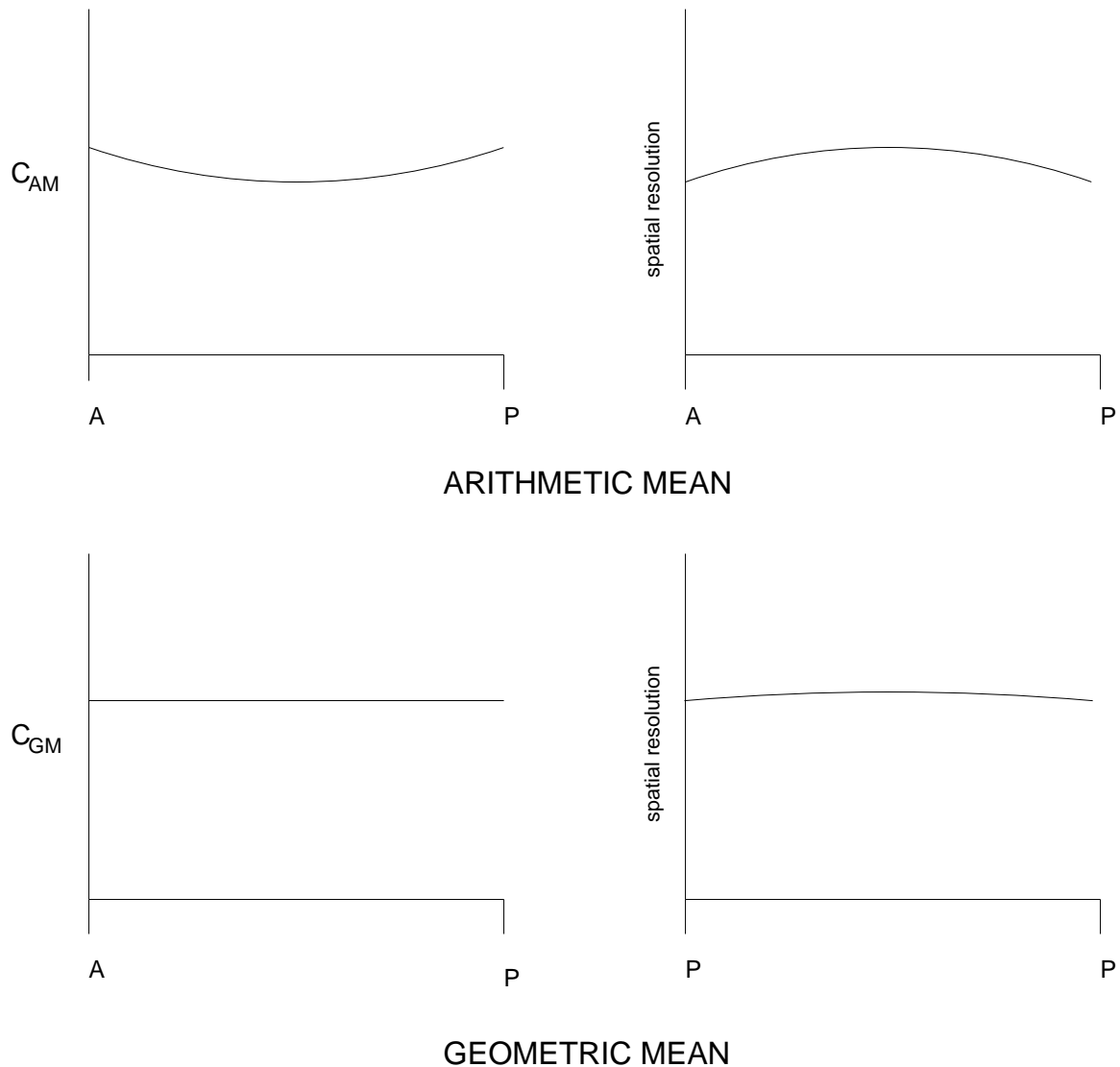


Figure 2: Comparisons between arithmetic and geometric mean combinations used in planar scintigraphy (adapted from Webb (1991))

continues until an acceptable count density is reached in each frame (≥ 100 beats). The most important measurement obtained from MUGA is **LVEF (left ventricular ejection fraction)**. Other measurements include parametric images of amplitude and phase of ejection from the left ventricle.

$$LVEF = \frac{V_{ED} - V_{ES}}{V_{ED}} \times 100\%$$

where V_{ED} is the **end-diastolic volume** and V_{ES} is the **end-systolic volume**.

- *First Pass studies:* the passage of injected activity is tracked through the left and right ventricles during the first few heart beats.

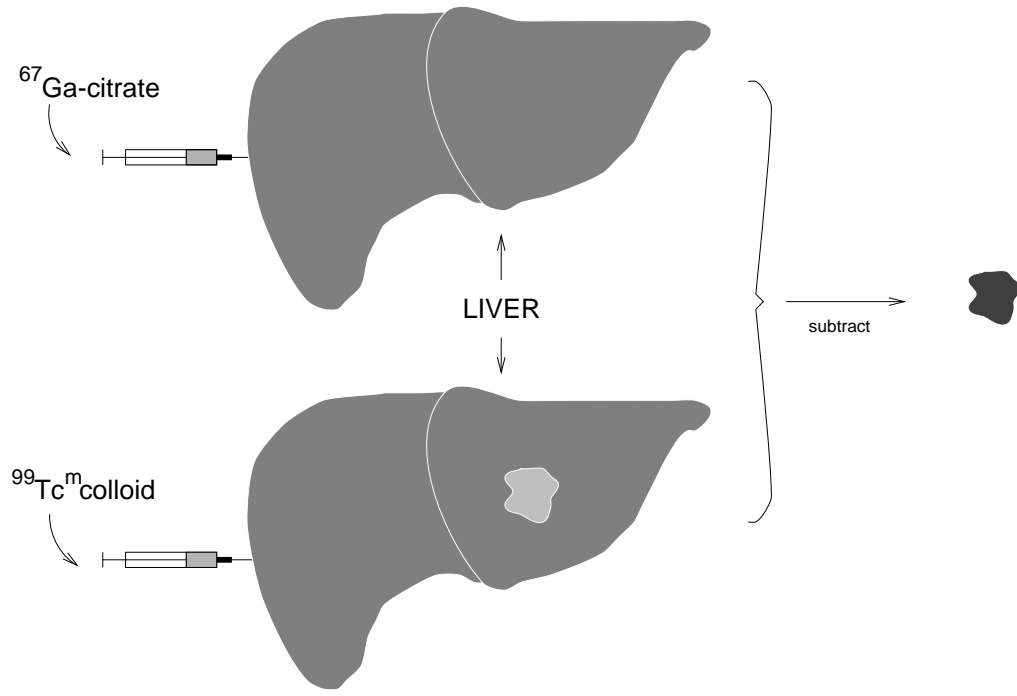


Figure 3: Simple diagrammatic illustration of dual isotope planar scintigraphy in the liver

6.2 Dynamic renal imaging (slow dynamic acquisition)

Dynamic renal imaging this involves the acquisition of multiple temporal images of the kidney obtained using an appropriate pharmaceutical (e.g $^{99}\text{Tc}^m$ -diethylene-triamine-penta-acetic acid (DPTA) or ^{123}I *o*-iodohippurate (OIH)) to produce **renograms**. Renograms are time-activity curves representing the various components of renal function. Renogram studies are able to provide the following information

- perfusion index, PI (the ratio of the rate of kidney perfusion to arterial activity).
- glomerular filtration rate (GFR) -absolute and relative.
- effective renal plasma flow (ERPF).
- excretion rates.

7 Emission Computed Tomography (ECT)

Two dimensional projection scintigraphy is seriously affected by the super-position of non-target activity. Emission Computed Tomography (ECT) allows multiple cross sectional images of radionuclide activity to be produced. Emission Computed Tomography is generally divided into two separate modalities;

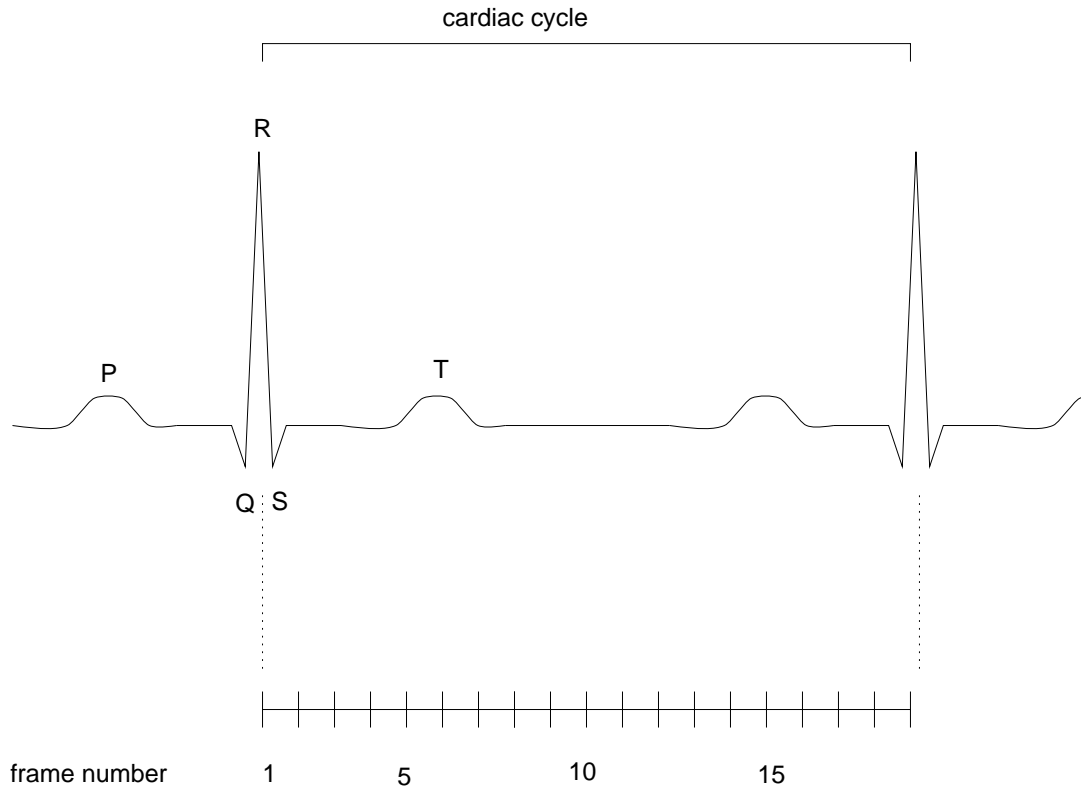
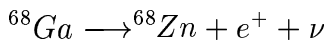


Figure 4: Illustration of MUGA studies that rely on timing information for acquisition of imaging data to define the duration of the cardiac cycle (adapted from Webb (1991))

- *Single Photon Emission Computed Tomography (SPECT)*: uses radio-isotopes (eg ^{99m}Tc) where a single γ -photon is emitted per nuclear disintegration.
- *Positron Emission Tomography (PET)*: Two γ -photons, traveling in approximate opposite directions, are emitted as a result of positron-electron annihilation. Typical positron emitters are ^{11}C , ^{18}F and ^{68}Ga . These unstable isotopes decay to produce a positron e.g



8 Radioactive Decay

Some nuclei have a combination of protons and neutrons which is not a stable configuration. Such nuclei are unstable and hence radioactive. A stable configuration is approached by the nuclei releasing certain particles. It has been observed that all radioactive processes follow an exponential law. Let N_0 be the initial number (i.e at $t = 0$) of unstable nuclei, then the number of unstable nuclei remaining after a time t is given by

$$N = N_0 \exp[-\lambda t]$$

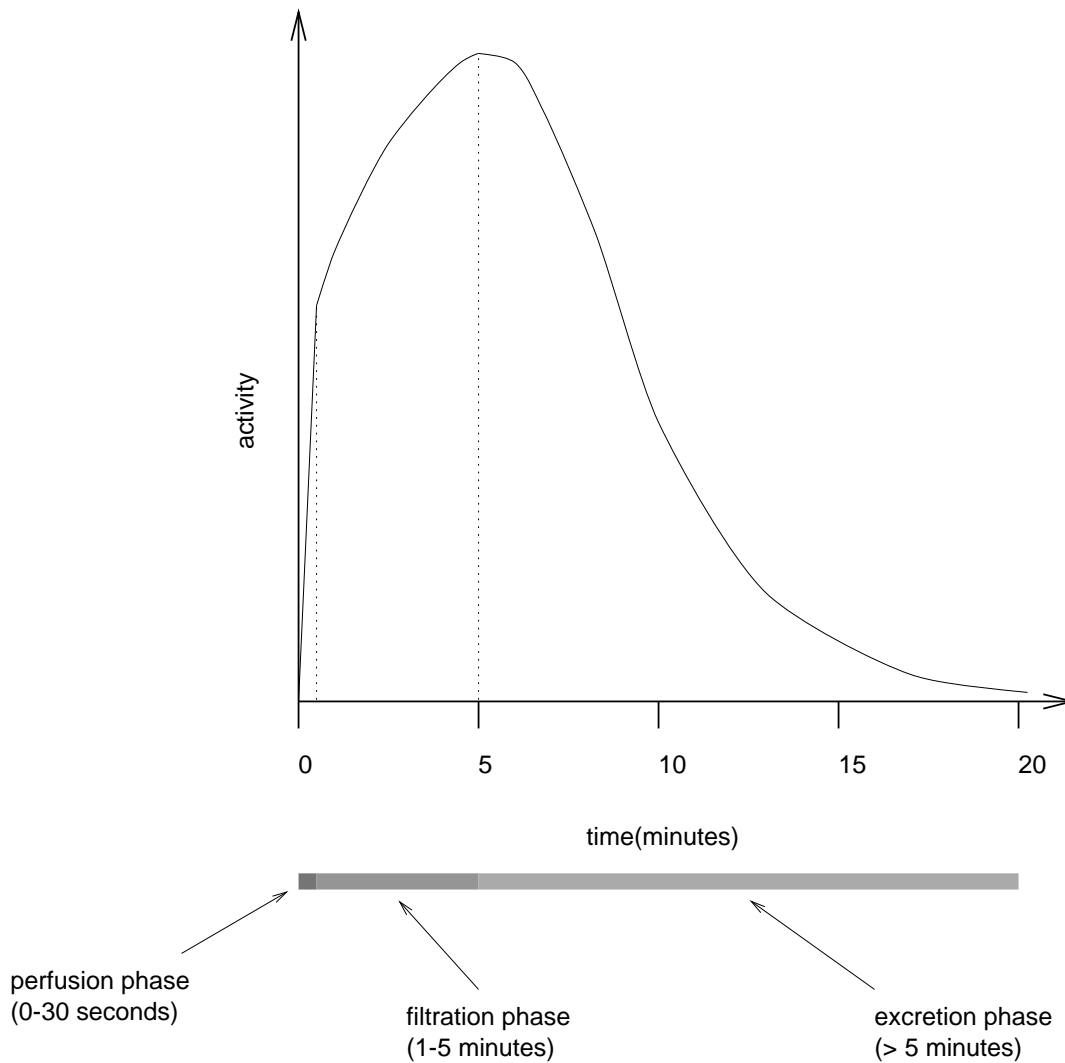


Figure 5: The three major phases of the renogram study (adapted from Webb (1991))

λ is a constant characteristic of each nuclide and is called the **disintegration** constant. The rate at which nuclei disintegrate follows from the above equation and is given by

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

The absolute value of the disintegration rate, $|\frac{dN}{dt}|$, is called the **activity** of the substance. Disintegration rates are often expressed in **curies**, abbreviated Ci. The Ci was originally defined as the activity of 1 g of Radium. However a more standard definition of the Ci is the activity of a substance in which 3.7×10^{10} nuclei disintegrate per second. In clinical practice it is more common to use the **Becquerel (Bq)** which is the number of disintegrations per second. Thus

$$1 \text{ Ci} = 37000 \text{ MBq}$$

The **half-life** ($T_{1/2}$) of a radionuclide is when $N/N_0 = 1/2$ i.e

$$T_{1/2} = \frac{\ln(2)}{\lambda}$$

8.1 Definitions

radionuclide: Atoms that disintegrate by the emission of corpuscular or EM radiation. Disintegration generally consists of either of the following

- *alpha particle:* this is equivalent to the nucleus of a *He* atom (i.e $2p2n$).
- *beta particles:* β^- (electron) or β^+ (positron).
- *gamma rays:* quanta of EM having $\nu > 10^{19} Hz$.

atomic number (Z): the number of protons within the atomic nucleus.

atomic weight (A): the relative weight of an atom on the basis that $^{12}C \equiv 12$. For a pure isotope the atomic weight, rounded off to the nearest integer gives the total number of *nucleons* ($n + p$) making up the nucleus.

isotope: two or more nuclides having the same atomic number (Z) but differing in atomic weight (A). i.e isotopes of a given element have the same number of nuclear protons but differing numbers of neutrons. Because of this imbalance many isotopes are unstable.

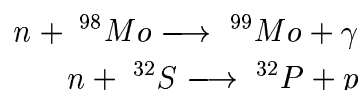
9 The Production of Radionuclides

Radionuclides are produced by four mechanisms

- neutron capture (neutron activation)
- nuclear fission
- charged particle bombardment
- radionuclide generators

9.1 Neutron Capture

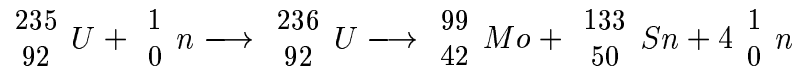
Examples are



- absorption of a thermal neutron ($E \approx 0.03 - 100 \text{ eV}$) by an atomic nucleus
- the ratio of radioactive (unstable) to stable atoms is relatively low. For this reason such radionuclides are principally used as tracers.

9.2 Nuclear Fission

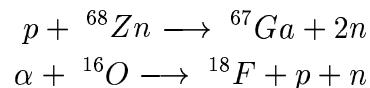
For example



- heavy nuclei (${}^{235}\text{U}$, ${}^{239}\text{Pu}$, ${}^{237}\text{U}$, ${}^{232}\text{Th}$) irradiated with *thermal neutrons* are rendered unstable and break up (hence *fission*) into two nuclei of similar atomic weight. Often more neutrons are produced which can be absorbed by other heavy nuclei. Thus the fissile process can continue until all the nuclear fuel is spent.
- fission has high specific activity.
- fission products, as indicated above, are usually rich in neutrons and principally decay via β^- emission. This latter property is generally undesirable and hence not useful for nuclear imaging but is important for radiotherapy.

9.3 Charged Particle Bombardment

Examples are



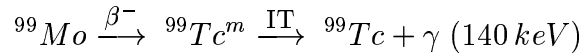
- radionuclide production is through charged particle (H^\pm , D^+ , ${}^3\text{He}^{2+}$, ${}^4\text{He}^{2+}$) bombardment of nuclei of stable atoms.
- the charged particles must have enough kinetic energy to overcome the repulsive effects of a positively charged nucleus ($1 - 100 \text{ MeV}$ per nucleon). Such energies are produced by accelerating particles using a linear accelerator or cyclotron.
- the desired isotope almost always has a different atomic number (Z) with respect to the target material.
- charged particle reactions yield radionuclides that are predominantly neutron deficient and therefore decay via β^+ emission or EC (electron capture).

9.4 Radionuclide Generators

Radioactive decay leading to the production of a radioactive daughter with a different atomic number (Z) allows for the possibility of simple chemical separation of the daughter-parent combination. It is desirable for the parent to be long-lived (i.e it has a long $T_{1/2}$) and the daughter radionuclide to have good characteristics for isotope imaging. The separation techniques used are

- chromatographic (this is the most widely used)
- distillation
- phase partitioning

The most widely used *generator produced* radionuclide in diagnostic radio-medicine is $^{99}\text{Tc}^m$ i.e



The following points should be noted

- ^{99}Mo is produced by neutron activation or nuclear fission.
- the half-life ($T_{1/2}$) of the parent radio-nuclide is approximately 66 *hr*.
- $^{99}\text{Tc}^m$ has a half life of approximately 6 *hr* and decays without the emission of any particulate radiation.

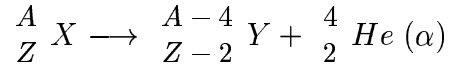
10 Types of Radioactive Decay

The principle modes of decay encountered in radio-isotope imaging and medicine are

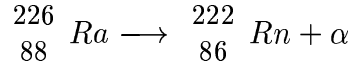
- alpha decay
- β^- emission
- β^+ emission
- electron capture (EC)
- isomeric transition (IT)

10.1 Alpha Decay

- Alpha decay is the spontaneous emission of an α particle from an unstable nucleus i.e



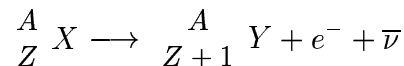
- Most α -emitters are heavy nuclei. This corresponds to nuclides at the end of the periodic table and is generally true for nuclides having $A > 200$ e.g



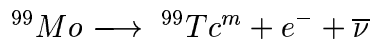
- the daughter nucleus resulting from α -emission may be in a **ground** state or in an excited **stationary state**. De-excitation of this state may occur via γ emission.
- the range of alpha particles depends on both energy and substance through which they move. In general their range in air at STP is only a few *cm* e.g ${}^{210}Po$ ($5.3 MeV$) = $3.8 cm$ and ${}^{214}Po$ ($7.7 MeV$) = $7.0 cm$. For this reason alpha-emitting nuclides are little used in imaging. They may be useful in targeted (local) therapy.

10.2 β^- Decay

- neutron rich radionuclides undergo β^- decay where an electron is emitted. In order to conserve charge a neutron is replaced by a proton and thus parent and daughter nuclei are **isobars** (i.e have the same atomic number) thus the general form of β^- decay is



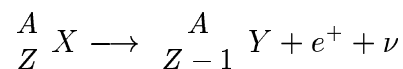
- An example of β^- decay is



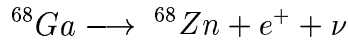
- as in alpha decay the daughter nucleus resulting from β^- decay may be left in a ground state or a stationary excited state. In the latter case the process is followed by γ emission.

10.3 β^+ Decay

- nuclei rich in protons or deficient in neutrons may decay via β^+ (positron) emission from the nucleus. The general form of β^+ decay is

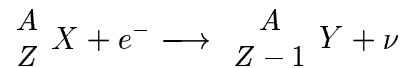


- the range of β^+ is about 1 *mm* in biological tissue. When β^+ comes to rest it is able to combine with an atomic electron from a nearby atom and is **annihilated**. Annihilation gives rise to two photons of energy 511 *keV* travelling approximately **anti-parallel** to each other.
- positron emission only takes place when the energy difference between parent and daughter nuclides is $> 1.02 \text{ MeV}$ e.g

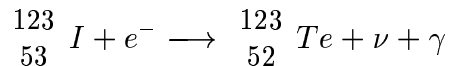


10.4 Electron Capture

- for proton rich nuclides an alternative to β^+ decay is **electron capture** (EC).
- EC involves the absorption within the nucleus of an atomic electron. In contrast to β^+ decay the energy difference between parent and daughter nuclides need only be small for such a process to occur. In general the probability of EC increases with Z , as the K-shell is closer to the atomic nucleus. The general form of the process can be written as



- In EC it is usually a K-shell electron that is captured. The vacancy created from EC is filled with electrons from outer orbits. The emitted energy due to this transition is seen as an X-ray characteristic of the daughter nuclide e.g

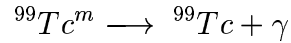


10.5 Isomeric Transition (IT)

- In addition to the ground-state of a nuclei, nuclei may also have several **excited** states. Unstable nuclei can be shown to have a collective angular momentum corresponding to a collective rotation in which all the component nucleons participate. The corresponding rotational energy is quantised.
- a nucleus may be carried to an excited energy level when it absorbs a photon or undergoes an in-elastic collision.
- the larger the difference in the collective angular momentum between an excited state and the ground state, the smaller the transition probability and the **longer** the lifetime of the excited state.
- nuclei which are in excited states ¹ and which have a *reasonably long* lifetime are called **isomers**. Transitions for which the change in angular momentum between the excited and ground states is > 3 are designated **isomeric transitions**.

¹called *isomeric* or *metastable* states if they are long lived

- An excited nucleus may give off its excess and undergo a transition to the ground level with the emission of an EM quantum i.e a γ ray e.g



11 Choosing a Radionuclide for Imaging

Broadly speaking the three factors influencing the choice of radio-nuclide (and its conjugate) are

- The effective rate of isotope “decay”, λ_E , is going to be equal to the sum of the rates of biological elimination/redistribution of the conjugate, λ_B , and the decay of the isotope λ_P i.e

$$\lambda_E = \lambda_B + \lambda_P$$

or

$$T_{1/2}^E = \frac{T_{1/2}^B T_{1/2}^P}{T_{1/2}^B + T_{1/2}^P}$$

It is desirable that $T_{1/2}^E$ and the duration of the radio-nuclide study, T_S , are closely matched thus the radio-nuclide chosen is based upon

$$T_{1/2}^P = \frac{T_S T_{1/2}^B}{T_{1/2}^B - T_S}$$

- the radio-nuclide decay via photon (EM) emission with the absence of any particulate (α or β) emission.
- the emitted photon energy
 - is high enough to penetrate tissue with minimal attenuation
 - is low enough to minimize collimator thickness
 - is low enough to minimize secondary particulate emission
- for the above reasons ${}^{99}\text{Tc}^m$ is used in approximately 90 % of all nuclear medicine studies.

12 Radiation Detectors and Configurations

The major mechanisms for detecting γ EM emission are

- Gas detectors

- traditional gas-filled ionization chamber
- Multiwire-proportional chamber (MWPC)
- Geiger counter
- Scintillation detectors
 - Gamma camera (NaI)
 - multi-crystal BGO/LSO systems
- Semiconductor detectors
- Semiconductor-scintillator combinations
- MWPC-scintillator combinations

12.1 Gas Detectors and Configurations

The traditional gas filled ionization chamber is relatively transparent to x - or γ -rays unless a high atomic number element is added to the detector. At high applied anode-cathode voltages the ionizing EM undergoes **gas amplification** ($\times 10^8$) and a large emf is produced that is proportional to the applied “grid” voltage. In general gas filled detectors have not found much utility in radionuclide imaging because of poor sensitivity and temporal resolution. However the **multiwire-proportional chamber (MWPC)** has been used widely in a research role and may find potential commercial utility in

- low cost PET
- low cost MWPC gamma camera
- quantitative autoradiography

Many different designs for MWPCs exist but all have the following in common

- lead foil cathodes to convert incident photons into **photo-electrons**. The introduction of lead foil cathodes increases the efficiency of such detectors from $\approx 1\%$ to $\approx 10\%$.
- an electric field (typically of the order of 10 kV cm^{-1}) towards a wire or metal plane where they are detected.

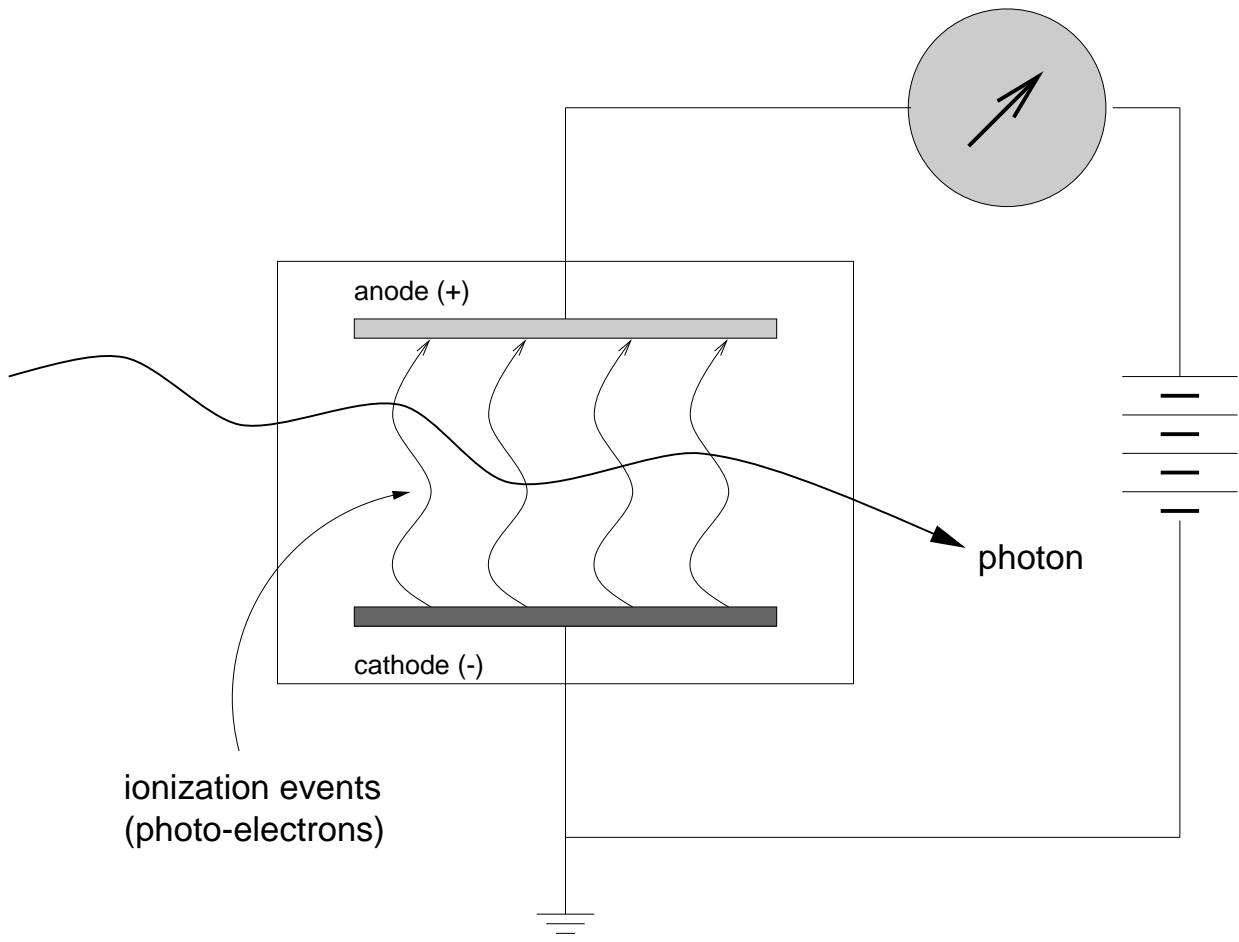


Figure 6: A simple gas ionization chamber

12.2 Scintillation Detectors and Configurations

The basis of the scintillation detector is the use of materials that emit visible or near visible light when energy is absorbed from EM radiation (x - or γ -rays). Such detectors are the most commonly used in both planar and tomographic radio-nuclide imaging.

The emitted light energy (and intensity) in such detectors will be proportional to the deposited energy (and intensity). The energy resolution of such detectors over the range $100 - 200 \text{ keV}$ is typically $10 - 15\%$. This allows discrimination between **scattered** and **un-scattered** γ radiation. The following requirements for a scintillator determines the scintillation material to be used

- it is transparent to its own light
- has a high atomic number, thus having good photon stopping power
- a close match between the emission characteristics of the scintillator and the **photo-multiplier tube** (PM).

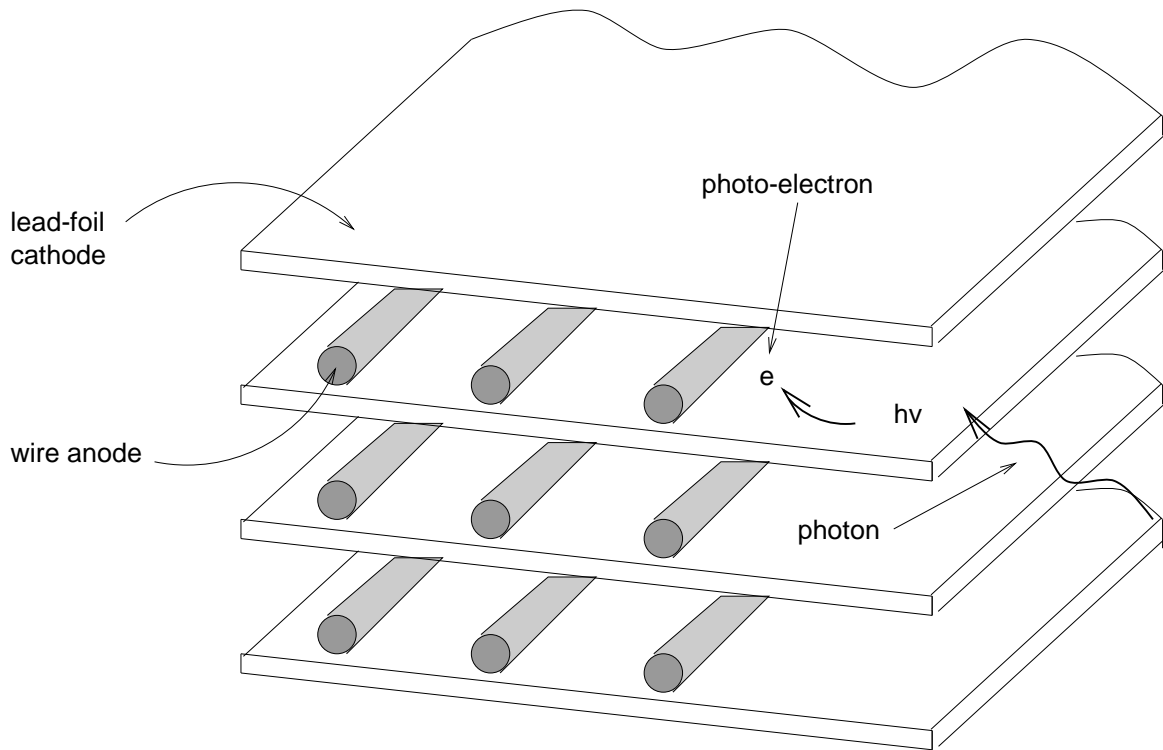


Figure 7: The multi-wire proportional chamber

material	ρ ($g\ cm^{-3}$)	effective Z	decay constant (ns)	wavelength of emission (nm)
Sodium iodide (NaI)	3.67	50	230	410 (blue-green)
Bismuth germanate (BGO)	7.13	74	300	480
Barium fluoride (BaF_2)	4.89	54	0.7	195-220

Table 1: Properties of commonly used inorganic scintillators

12.2.1 The Gamma Camera

The modern gamma camera consists of

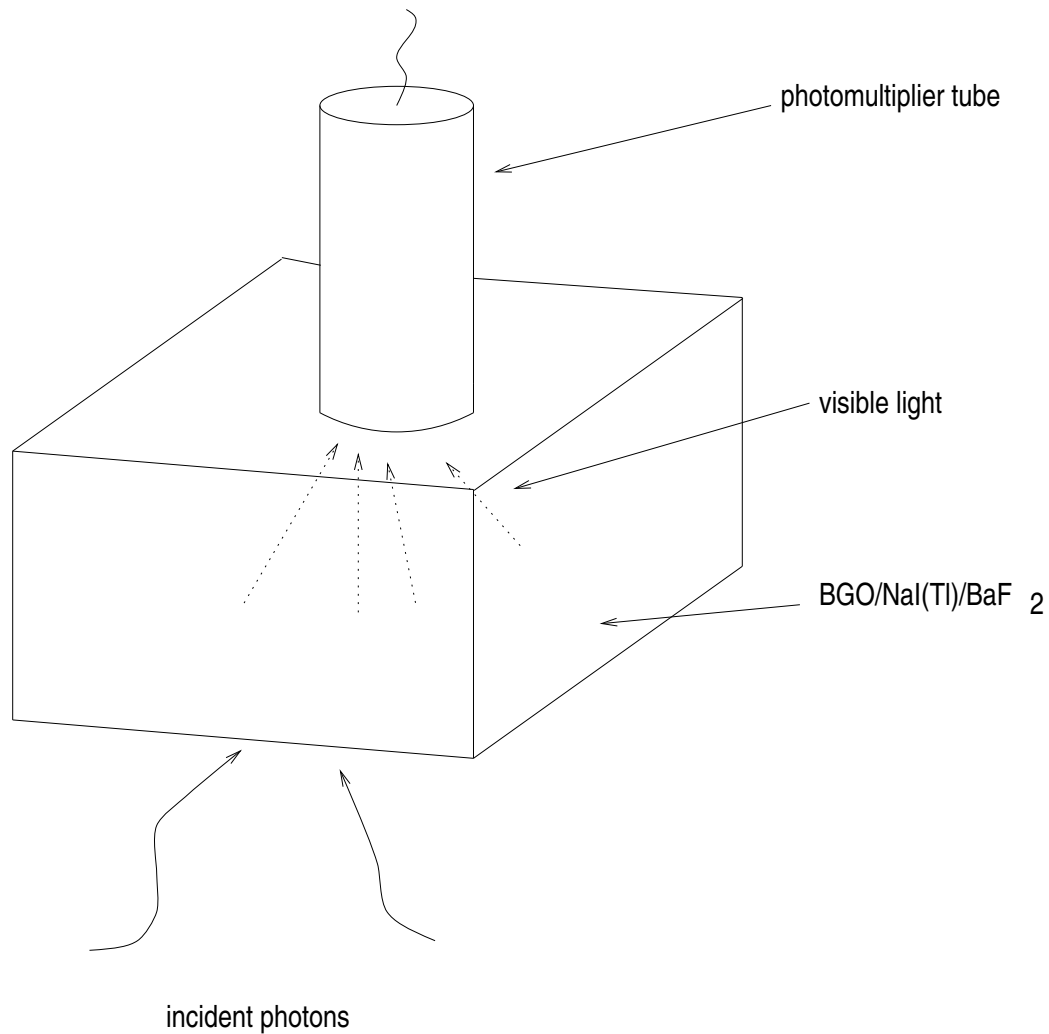


Figure 8: The basic configuration of the scintillation detector (adapted from Webb(1991))

- multihole collimator
- large area (e.g 10×10 cm) $NaI(Tl)$ (Sodium Iodide - Thallium activated) scintillation crystal
- light guide for optical coupling
- array (commonly hexagonal) of photo-multiplier tubes
- lead shield to minimize background radiation

A crucial component of the modern gamma camera is the **collimator**. The collimator selects the direction of incident photons. For instance a parallel hole collimator selects photons incident OS the normal. Other types of collimators include

- **pinhole** collimator often used in the imaging of small superficial organs and structures (e.g thyroid,skeletal joints) as it provides image **magnification**.

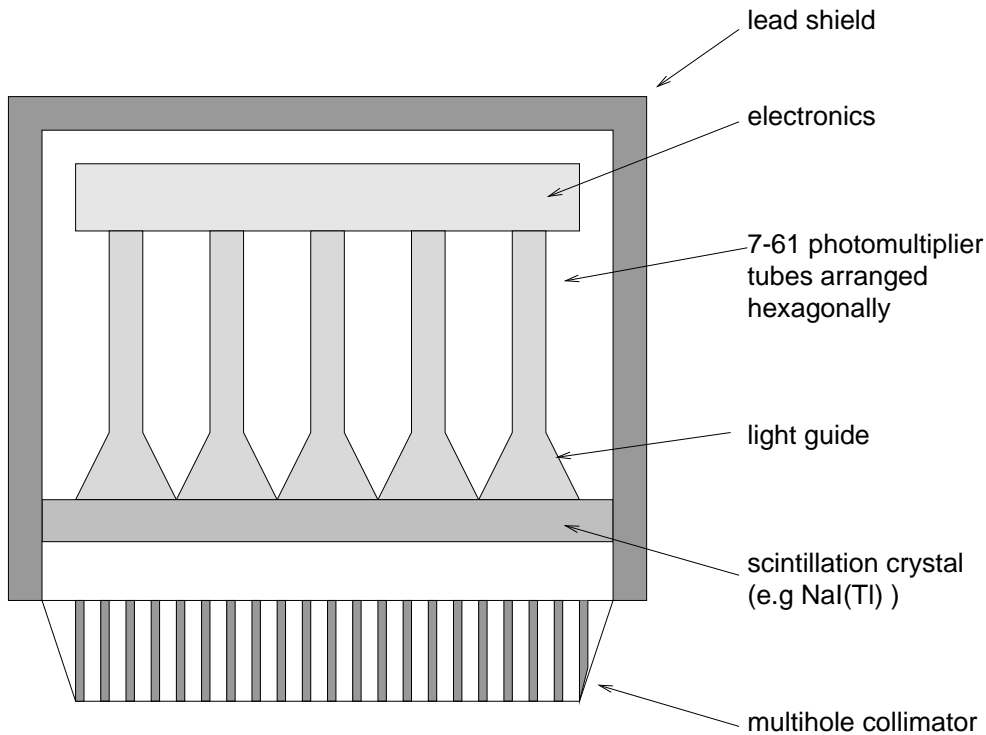


Figure 9: Construction of a simple gamma camera (adapted from Webb(1991))

- **fan beam** (diverging) and **cone beam** (converging) collimators are often used for whole body or medium sized organ imaging. Such collimators are useful because they increase the detection efficiency because of the increased solid angle of photon acceptance.

The collimator also determines the **geometrical field of view** and **spatial resolution**. This will be illustrated for the parallel hole collimator (see Figure 12)

From the above figure R will be a measure of spatial resolution with

$$R = (L + z) \tan(\theta) = d + \frac{zd}{L}$$

The following are the typical features of the scintillation crystal used in modern gamma cameras

- most gamma cameras use thallium-activated NaI ($NaI(Tl)$)
- $NaI(Tl)$ emits blue-green light at about $415nm$
- the spectral output of such a scintillation crystal matches well the response of standard **bi-alkali** photomultipliers (e.g SbK_2Cs)
- the linear attenuation coefficient of $NaI(Tl)$ at $150 keV$ is about $2.2 cm^{-1}$. Therefore about 90% of all photons are absorbed within about $10 mm$

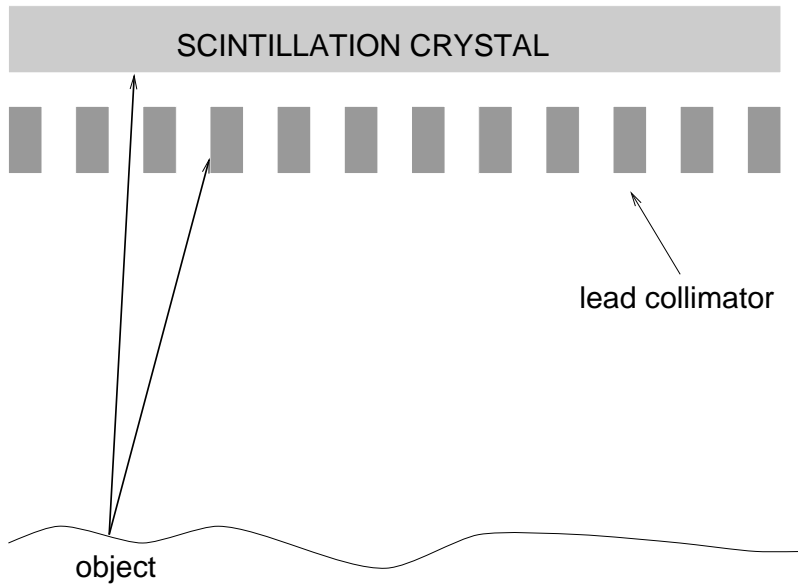


Figure 10: The action of a parallel hole collimator

- $NaI(Tl)$ is hygroscopic and therefore requires hermetic encapsulation
- $NaI(Tl)$ has a high refractive index (≈ 1.85) and thus a **light guide** is used to couple the scintillation crystal to the photomultiplier tube
- the scintillation crystal and associated electronics are surrounded by a lead shield to minimize the detection of unwanted radiation
- digital and/or analog methods are used for image capture

13 References

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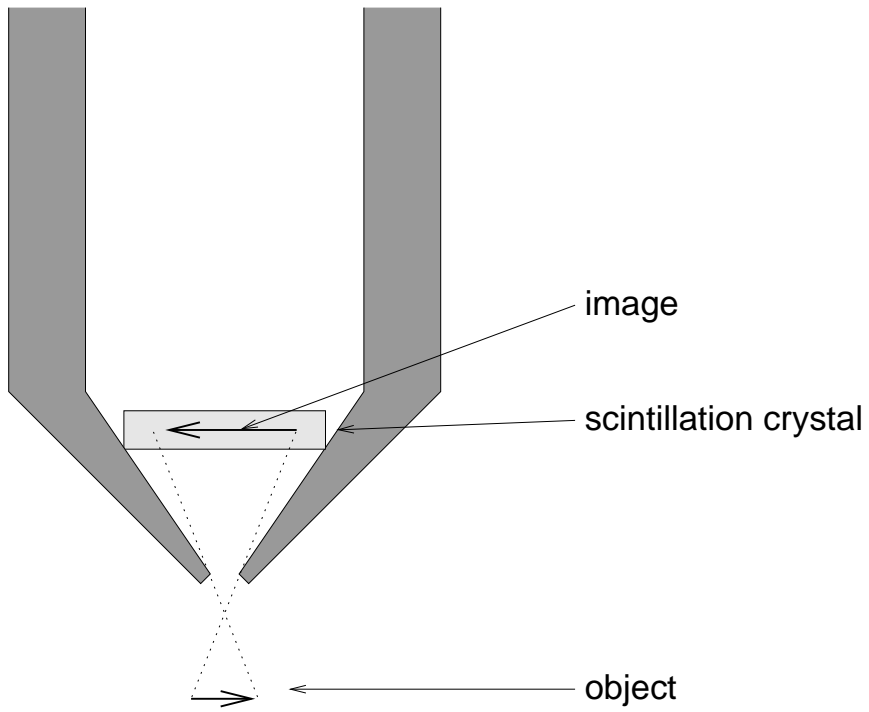


Figure 11: The pin-hole collimator

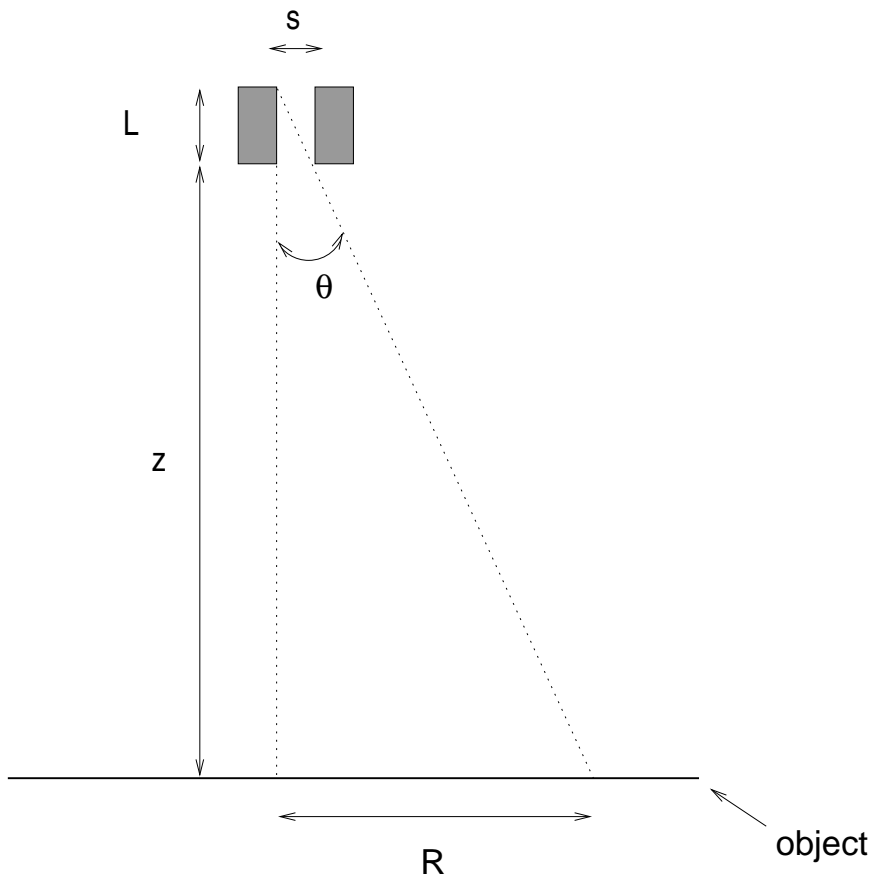


Figure 12: Spatial resolution for a parallel hole collimator