

Radiofarmaceutici

Uvod i motivacija

- Nuklearna medicina zajedničko je ime za niz nuklearnih dijagnostičkih i terapijskih metoda koje se primjenjuju u medicini
- Ovdje možemo ubrojiti upotrebu radioaktivnih izotopa u terapiji raznih bolesti kancerogenog tipa, snimanja gama kamerom za praćenje toka radioaktivnih obilježivača, upotrebu nuklearne magnetske rezonancije u dijagnostičkom snimanju unutarnjih organa, različite vrste tomografija!
- Iz mnoštva metoda u ovom poglavlju odabrani su samo radiofarmaceutici.
- Ključni postupak promatranja metabolizma praćenjem kretanja radioaktivne tvari naziva se metodom radioaktivnih obilježivača

Proizvodnja radionuklida

Poznalo je da postoje umjetni i prirodni izotopi čije atomske jezgre nisu stabilne, nego se raspadaju. Produkti raspada, čestice i zračenja, oštećuju neposredno okolni materijal. Ako se broj jezgara, kandidata za raspad označi sa N , a vremenski interval u kojem su se raspadale sa Δt , tada je broj raspadnutih jezgara promatranog radioaktivnog uzorka nakon tog vremena:

$$-\Delta N = \lambda N \Delta t$$

gdje je λ konstanta raspada karakteristična za svaku radioaktivnu tvar. Taj se zakon može integriranjem prevesti u oblik:

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

Proizvodnja radionuklida

Umjetni radioizotopi stvaraju se bombardiranjem stabilnih jezgara projektilima: protonima, neutronima i alfa-česticama, što dovodi do njihove transformacije u nestabilne strukture.

Proces pretvorbe atomske jezgre A, koja apsorbira projektil a, pa zatim emitira produkt b, i pritom se pretvara u jezgru B bilježi se nuklearnom jednačinom:



Proizvodnja radionuklida

Glavni izvori radioaktivnih izotopa jesu procesi u nuklearnom reaktoru i ciklotronu. Povijesno, izotopi su se najprije stvarali u nuklearnim reakcijama u reaktorima, a danas se za to sve više upotrebljavaju reakcije u ciklotronima. U njima se lako stvaraju kratkoživi izotopi posebno emiteri pogodni za kompjutoriziranu tomografiju, tj. CT-analize.

Najčešće u blizini bolničkog centra radi mali (kompaktni) ciklotron, pa kratko vrijeme transporta do mjesta primjene omogućuje da se kratkoživi izotopi mogu iskoristiti.

Reaktorska produkcija radionuklida

Evo primjera reakcija za proizvodnju radionuklida u nuklearnom reaktoru:



Izotopi koji se koriste u nuklearnoj medicini

Izotop	Simbol	Z	T _{1/2}	Raspad	fotona	β
Imaging:						
<u>fluorine</u> -18	¹⁸ F	9	110 m	β ⁺	511 (193%)	0.664 (97%)
<u>gallium</u> -67	⁶⁷ Ga	31	3.26 d	ec	93 (39%), 185 (21%), 300 (17%)	-
<u>krypton</u> -81m	^{81m} Kr	36	13.1 s	IT	190 (68%)	-
<u>rubidium</u> -82	⁸² Rb	37	1.27 m	β ⁺	511 (191%)	3.379 (95%)
<u>technetium-99m</u>	^{99m} Tc	43	6.01 h	IT	140 (89%)	-
<u>indium</u> -111	¹¹¹ In	49	2.80 d	ec	171 (90%), 245 (94%)	-
<u>iodine</u> -123	¹²³ I	53	13.3 h	ec	159 (83%)	-
<u>xenon</u> -133	¹³³ Xe	54	5.24 d	β ⁻	81 (31%)	0.364 (99%)
<u>thalium</u> -201	²⁰¹ Tl	81	3.04 d	ec	69-83* (94%), 167 (10%)	-
Therapy:						
<u>yttrium</u> -90	⁹⁰ Y	39	2.67 d	β ⁻	-	2.280 (100%)
<u>iodine</u> -131	¹³¹ I	53	8.02 d	β ⁻	364 (81%)	0.807 (100%)

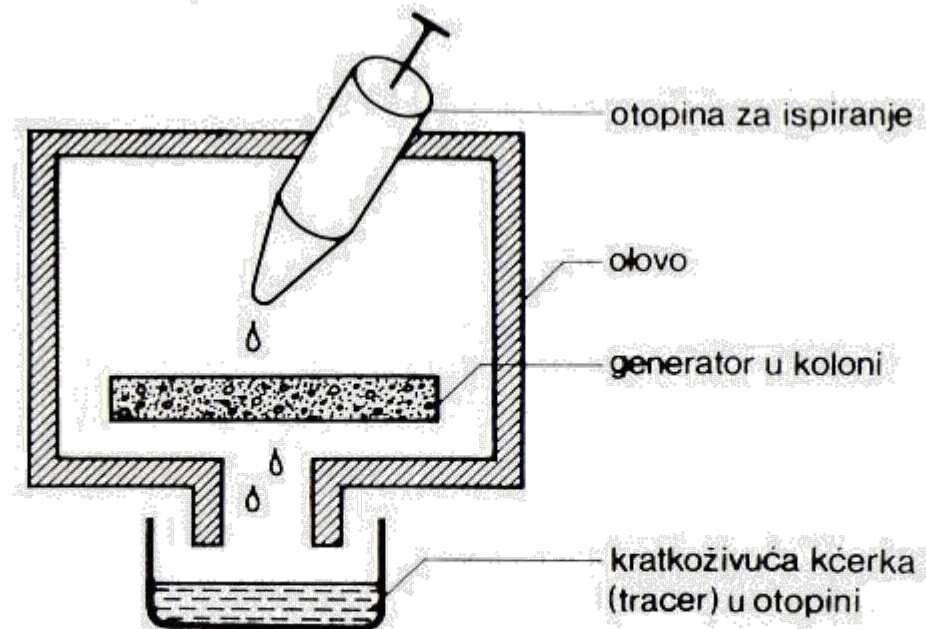
Ciklotronska produkcija radionuklida

- Bombardiranjem ^{23}Na neutronima i emisijom γ -zračenja stvoren je nuklid ^{24}Na . Kako se početni materijal izotop ^{23}Na i novostvoreni izotop natrija ^{24}Na kemijski ne razlikuju, nemoguće je jeftinim kemijskim postupkom odvojili interesantni izotop ^{24}Na od osnovnog nosača.
- Reakcija
$$^{27}\text{Al}(n,\alpha)^{24}\text{Na}$$
dobivamo isti izotop ^{24}Na , ali je razlika u kemijskim svojstvima elemenata ^{27}Al i natriju ^{24}Na dovoljna da omogući lako kemijsko odvajanje.
- Slično, povoljni su uvjeti i za odvajanje dobivenog izotopa fosfora u nuklearnoj reakciji izazvanoj bombardiranjem sumpora ^{32}S neutronima:
$$^{32}\text{S}(n,p)^{32}\text{P}.$$

Ciklotronska produkcija radionuklida

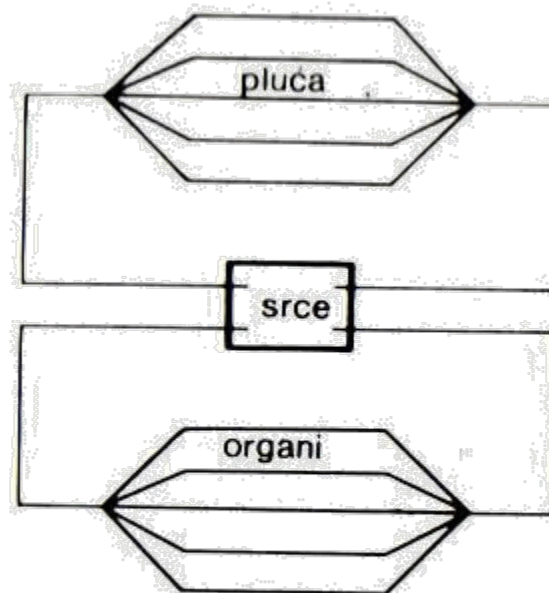
- za razliku od reaktora, gdje je riječ o neutronsom snopu, u ciklotronu bombardira se snopovima nabijenih čestica p, d, ^3He , ^4He . Najčešće slijedi emisija čestica α , p, β^+
- Za ciklotronske reakcije nastoji se utvrditi takva energija snopa čestica da bi udarni presjek za produkciju određenih radioizotopa bio maksimalan.
- Proizvodnja izotopa u ciklotronu skupa no mnogo efikasnija
- Posebno su zanimljivi pozitronski emiteri β^+
- Pri anihilaciji pozitrona s elektronom dobivaju se dvije (back-to-back) nasuprotne g zrake
- Na tom se načelu temelji pozitronska tomografija.

Skladištenje i transport radionuklida



Slika 12.1. Generator radionuklida: Radioaktivni preparat koji dugo živi unesen je u kolonu. Iz nje se kratkoživuća komponenta ispire. Cijeli uređaj je redovito u debelom olovnom štitu radi zaštite od radioaktivnog zračenja.

Radioobilježivačka (tracer) metoda

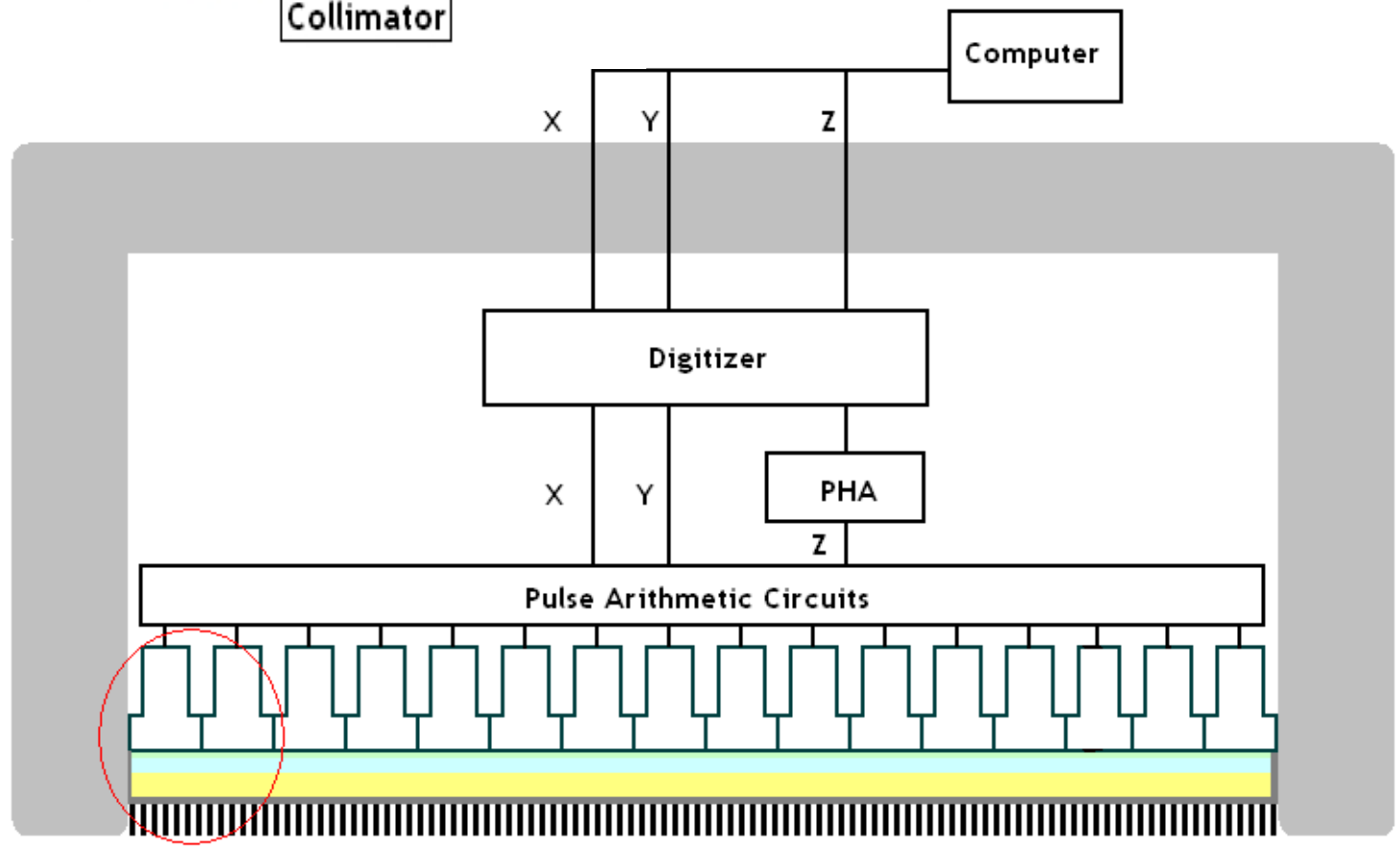
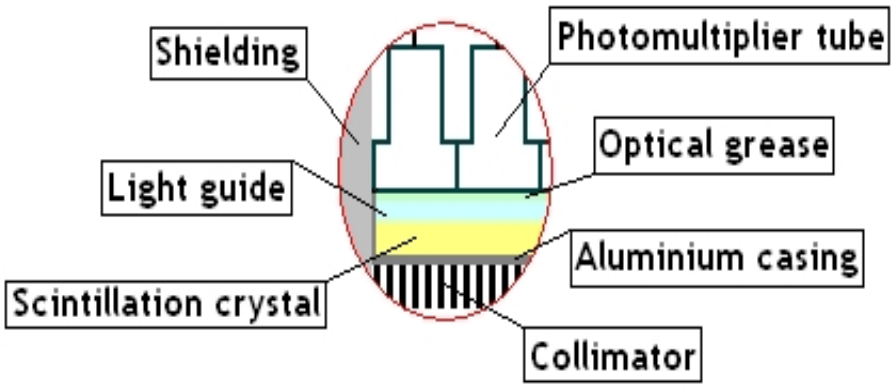


Slika 12.2. Modeliranje krvotoka. Shematskim prikazom srca (rezervoar), pluća i kapila povezanih žiljem možemo planirati mjerenja parametra za različite dijelove sistema.

Gama kamera – Slika pluća



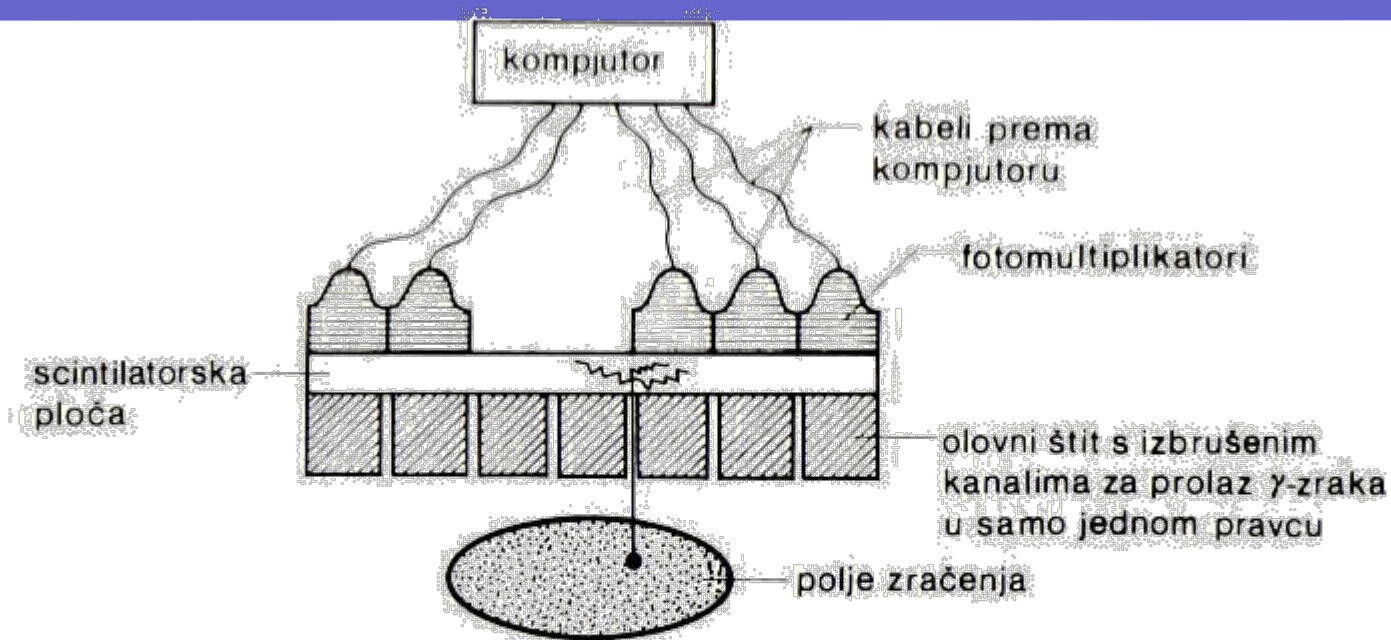
Gama kamera



Konstrukcija

- A gamma camera consists of one or more flat crystal planes or, detectors, optically coupled to an array of photomultiplier tubes, the assembly is known as a "head", mounted on a gantry. The gantry is connected to a computer system that both controls the operation of the camera as well as acquisition and storage of acquired images.
- The system accumulates events, or counts, of gamma photons that are absorbed by the crystal in the camera. Usually a large flat crystal of sodium iodide with thallium doping in a light-sealed housing is used. The highly efficient capture method of this combination for detecting gamma rays was discovered by noted physicist Robert Hofstadter in 1948 [1]).
- The crystal scintillates in response to incident gamma radiation. When a gamma photon leaves the patient (who has been injected with a radioactive pharmaceutical), it knocks an electron loose from an iodine atom in the crystal, and a faint flash of light is produced when the dislocated electron again finds a minimal energy state. The initial phenomenon of the excited electron is similar to the photoelectric effect and (particularly with gamma rays) the Compton effect. After the flash of light is produced, it is detected. Photomultiplier tubes (PMTs) behind the crystal detect the fluorescent flashes (events) and a computer sums the counts. The computer reconstructs and displays a two dimensional image of the relative spatial count density on a monitor. This reconstructed image reflects the distribution and relative concentration of radioactive tracer elements present in the organs and tissues imaged.

Gama kamera



Slika 12.3. Gama-kamera. Trodimenzionalno polje zračenja (ljudski organ) najprije se projicira u dvije dimenzije kanalima u olovu. Sistemom scintilator + fotomultiplikatori registrira se pozicija upada svake čestice radioaktivnog zračenja na detektor. Kompjutorom se obično rekonstruira slika polja zračenja.

Signal

- Sir Brian Barbour developed the first gamma camera in 1957. His original design, frequently called the Anger camera, is still widely used today. The Anger camera uses sets of vacuum tube photomultipliers. Generally each tube has an exposed face of about 3 inches in diameter and the tubes are arranged in hexagon configurations, behind the absorbing crystal. The electronic circuit connecting the photodetectors is wired so as to reflect the relative coincidence of light fluorescence as sensed by the members of the hexagon detector array. All the PMTs simultaneously detect the (presumed) same flash of light to varying degrees, depending on their position from the actual individual event. Thus the spatial location of each single flash of fluorescence is reflected as a pattern of voltages within the interconnecting circuit array.
- The location of the interaction between the gamma ray and the crystal can be determined by processing the voltage signals from the photomultipliers; in simple terms, the location can be found by weighting the position of each photomultiplier tube by the strength of its signal, and then calculating a mean position from the weighted positions. The total sum of the voltages from each photomultiplier is proportional to the energy of the gamma ray interaction, thus allowing discrimination between different isotopes or between scattered and direct photons.

Rezolucija

- In order to obtain spatial information about the gamma emissions from an imaging subject (e.g. a person's heart muscle cells which have absorbed an intravenous injected radioactive, usually thallium-201 or technetium-99m, medicinal imaging agent) a method of correlating the detected photons with their point of origin is required.
- The conventional method is to place a collimator over the detection crystal/PMT array. The collimator consists of a thick sheet of lead, typically 1-3 inches thick, with thousands of adjacent holes through it. The individual holes limit photons which can be detected by the crystal to a cone; the point of the cone is at the midline center of any given hole and extends from the collimator surface outward. However, the collimator is also one of the sources of blurring within the image; lead does not totally attenuate incident gamma photons, there can be some crosstalk between holes.
- Unlike a lens, as used in visible light cameras, the collimator attenuates most (>99%) of incident photons and thus greatly limits the sensitivity of the camera system. Large amounts of radiation must be present so as to provide enough exposure for the camera system to detect sufficient scintillation dots to form a picture.
- Other methods of image localization (pinhole, rotating slat collimator with CZT (Gagnon & Matthews) and others) have been proposed and tested; however, none have entered widespread routine clinical use.
- The best current camera system designs can differentiate two separate point sources of gamma photons located a minimum of 1.8 cm apart, at 5 cm away from the camera face. Spatial resolution decreases rapidly at increasing distances from the camera face. This limits the spatial accuracy of the computer image: it is a fuzzy image made up of many dots of detected but not precisely located scintillation. This is a major limitation for heart muscle imaging systems; the thickest normal heart muscle in the left ventricle is about 1.2 cm and most of the left ventricle muscle is about 0.8 cm, always moving and much of it beyond 5 cm from the collimator face. To help compensate, better imaging systems limit scintillation counting to a portion of the heart contraction cycle, called gating, however this further limits system sensitivity



KEOSYS - HEMA 19.10.2004 13:00:00
Patient: 0006
Date: 2005/01/01
Time: 13:00:00
Study: NM Siemens Scinti Pulmo # 0006
Protocol: Scintigraphie Pulmonaire
Technician: [Name]
Physician: [Name]
Patient ID: 0006
Study ID: 0006
Series: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
2350 x 3323

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UI icons: Folders, Import, Communicate, Display, Adjust, ROI/POI

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Zoom 1.0
Zoom controls: -, Q⁰, Q¹, Q², +, and navigation arrows

Advance layout
BONE
Vertical scroll bar and UI icons at the bottom

Scanning and use in PET

- SPECT (single photon emission computed tomography) imaging, as used in nuclear cardiac stress testing, is performed using gamma cameras, usually one, two or three detectors or heads, are slowly rotated around the patient's torso.
- Multi-headed gamma cameras can also be used for Positron emission tomography scanning, provided that their hardware and software can be configured to detect 'coincidences' (near simultaneous events on 2 different heads). Gamma camera PET is markedly inferior to PET imaging with a purpose designed PET scanner, as the scintillator crystal has poor sensitivity for the high-energy annihilation photons, and the detector area is significantly smaller. However, given the low cost of a gamma camera and its additional flexibility compared to a dedicated PET scanner, this technique is useful where the expense and resource implications of a PET scanner cannot be justified.

Mehanizmi za nakupljanje radioobilježivača

Proceski koji su odgovorni za nakupljanje radioobilježivača:

- Aktivni transport (jod u tiroidnoj žljezdi)
- Antigen-antitjelo reakcije
- Fagocitoza (jetra, slezena, koštana srž)
- Kapilarna blokada (prokrvljenost, pluća)

Spesifične upotrebe

- *Mozak:* Danas je u upotrebi kompjutorska tomografija, npr. mozga, osnovana na pozitronskim β^+ emiterima i anihilaciji β^+ čestica s elektronima. U prošlosti su s u krv ubrizgavali agensi koji ne postoje u mozgu. Ako bi postojali prodori krvnog sustava u mozak, agens bi ulazio i u to područje, što bi se na snimci vidjelo.
- *Pluća:* Moguće je uz perfuziju pluća mjeriti i njihovu ventilaciju ili protočnost zraka. Aktivnost je velika tamo gdje je protok velik, a u mirnim dijelovima, gdje protok slab, radioaktivnog obilježivača više nema jer se već sav raspao ili zbog slabog protoka do tih mjesta nije ni uspio doći. Veća ili manja izmjerena aktivnost tih dijelova komplementarne su radiografskim parametrima.
- *Jetra:* Pripremi se tvar u koloidnom slanju. U nju je ugrađen radioaktivni obilježivač. Tvar se ubrizgava u krvotok. Već opisanim mehanizmom nakupljanja koncentriraju se koloidne čestice u jetri. Jetru je zatim moguće dijagnostički pregledat snimujući gama kamerom.
- *Štitna žlijezda:* Mala količina radioaktivnog joda unosi se u organizam. Mehanizmom aktivnog transporta jod se koncentrira u štitnjači. Snimanjem aktivnosti radioaktivnog joda određuju se i dimenzije tog organa i njegova biološka aktivnost.
- *Traganje za tumorom:* Radioaktivno se obilježi antigen tumora. Nakon unošenja antigenog materijala u organizam pacijent se slavlja u detekcijski sistem koji snima cijelo tijelo (whole body counter). Ustanovljuje se mjesto gdje se koncentrira radioaktivna tvar, a ono odgovara lokaciji tumora.

Definicija aktivnosti

$$A(t = 0) = \frac{dN(t = 0)}{dt}$$

$$\frac{dN(t = 0)}{dt} = -\lambda N_A$$

Određivanje obujma krvi živa čovjeka

Pomoću jednadžbi (12.1) i (12.2) možemo izračunati na koju je vrijednost u vremenu τ pala ukupna aktivnost u krvi:

$$A(t = \tau) = \frac{dN(t = \tau)}{dt} = -\lambda e^{-\tau\lambda} N_0 \quad (12.5)$$

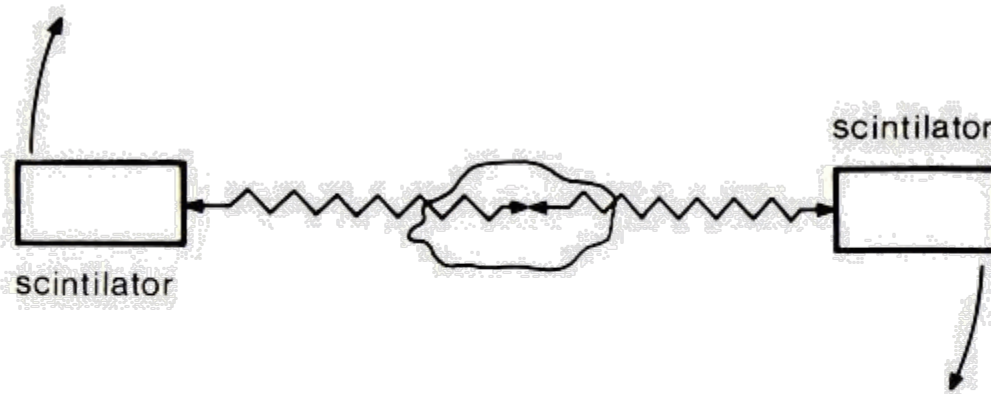
$$A(t = \tau) = e^{-\tau\lambda} A(t = 0) \quad (12.6)$$

Ta poznata ukupna aktivnost $A(t = \tau)$ i podaci o malom uzorku krvi, tj. a i v , jednostavno su povezani s ukupnim volumenom krvi V :

$$\frac{A(t = 0)e^{-\lambda\tau}}{V} = \frac{A(t = \tau)}{V} = \frac{a}{v}. \quad (12.7)$$

U prethodnom izrazu veličine $a, v, A(t = 0), \lambda$ i τ mjere se, pa se iz dobivenih podataka odredi ukupan obujam krvi V .

Pozitronska tomografija



Slika 12.4. Dvije čestice γ -zračenja koincidentno izlijeću pri svakoj β^+ anihilaciji. Nakon mjerenja broja raspada u jednoj konfiguraciji rotira se par scintilacijskih detektora u novi položaj dok se sukcesivnim rotacijama ne pokrije područje od 180° .

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