Basics of PET Imaging

Physics, Chemistry, and Regulations

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With 64 Illustrations

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To my
teachers, mentors, and friends

Preface

From the early 1970s to mid-1990s, positron emission tomography (PET) as a diagnostic imaging modality had been for the most part used in experimental research. Clinical PET started only a decade ago. ^{82}Rb-RbCl and ^{18}F-Fluorodeoxyglucose were approved by the U.S. Food and Drug administration in 1989 and 1994, respectively, for clinical PET imaging. Reimbursement by Medicare was approved in 1995 for ^{82}Rb-PET myocardial perfusion imaging and for ^{18}F-FDG PET for various oncologic indications in 1999. Currently several more PET procedures are covered for reimbursement.

Based on the incentive from reimbursement for PET procedures and accurate and effective diagnosis of various diseases, PET centers are growing in the United States and worldwide. The importance of PET imaging has flourished to such a large extent that the Nuclear Medicine Technology Certification Board (NMTCB) is planning to introduce a PET specialty examination in 2004 for nuclear medicine technologists, as well as an augmented version of the PET specialty examination in 2005 for registered radiographers and radiation therapy technologists. Courses are being offered all over the country to train physicians and technologists in PET technology. Many books on clinical PET have appeared in the market, but no book on the basics of PET imaging is presently available. Obviously, such a book is needed to fulfill the requirements of these courses and certifications.

This book focuses on the fundamentals of PET imaging, namely, physics, instrumentation, production of PET radionuclides and radiopharmaceuticals, and regulations concerning PET. The chapters are concise but comprehensive enough to make the topic easily understandable. Balanced reviews of pertinent basic science information and a list of suggested reading at the end of each chapter make the book an ideal text on PET imaging technology. Appropriate tables and appendixes include data and complement the book as a valuable reference for nuclear medicine professionals such as physicians, residents, and technologists. Technologists and residents taking board examinations would

benefit most from this book because of its brevity and clarity of content.

The book contains 11 chapters. The subject of each chapter is covered on a very basic level and in keeping with the objective of the book. It is assumed that the readers have some basic understanding of physics and chemistry available in standard nuclear medicine literature. At the end of each chapter, a set of questions is included to provoke the reader to assess the sufficiency of knowledge gained.

Chapter 1 briefly reviews the structure and nomenclature of the atoms, radioactive decay and related equations, and interaction of radiation with matter. This is the gist of materials available in many standard nuclear medicine physics book. Chapter 2 describes the properties of various detectors used in PET scanners. Descriptions of PET scanners, hybrid scintillation cameras, PET/CT scanners, small animal PET scanners, and mobile PET scanners from different manufacturers as well as their features are given. Chapter 3 details how two-dimensional and three-dimensional data are acquired in PET and PET/CT imaging. Also included are the different factors that affect the acquired data and their correction method. Chapter 4 describes the image reconstruction technique and storage and display of the reconstructed images. A brief reference is made to DICOM, PACS, and teleradiology. The performance characteristics of different PET scanners such as spatial resolution, sensitivity, scatter fraction, and so on, are given in Chapter 5. Quality control tests and acceptance tests of PET scanners are also included. Chapter 6 contains the general description of the principles of cyclotron operation and the production of common PET radionuclides. The synthesis and quality control of some common PET radiopharmaceuticals are described in Chapter 7. Chapter 8 covers pertinent regulations concerning PET imaging. FDA, NRC, DOT, and state regulations are discussed. In Chapter 9, a historical background on reimbursement for PET procedures, and different current codes for billing and the billing process are provided. Chapter 10 outlines a variety of factors that are needed in the design of a new PET center. A cost estimate for setting up a PET facility is presented. Chapter 11 provides protocols for four common PET and PET/CT procedures.

I do not pretend to be infallible in writing a book with such significant scientific information. Errors of both commission and omission may have occurred, and I would appreciate having them brought to my attention by the readers.

I would like to thank the staff in our Department of Molecular and Functional Imaging for their assistance in many forms. I am grateful to Ms. Lisa M. Saake, Director of Healthcare Economics, Tyco Healthcare/Mallinckrodt Medical, for her contribution to Chapter 9 in clarifying several issues regarding reimbursement and reshaping the front part of the chapter.

It is beyond the scope of words to express my gratitude to Mrs. Rita Konyves, who undertook the challenge of typing and retyping the manu-

script as much as I did in writing it. Her commitment and meticulous effort in the timely completion of the manuscript deserves nothing but my sincere gratitude and thanks.

I am grateful and thankful to Robert Albano, Senior Clinical Medical Editor, for his suggestion and encouragement to write this book, and others at Springer for their support in publishing it.

Cleveland, OH *Gopal B. Saha, PhD*

Contents

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Radioactive Decay and Interaction of Radiation with Matter

Atomic Structure

Matter is composed of atoms. An atom consists of a nucleus containing protons (Z) and neutrons (N), collectively called nucleons, and electrons rotating around the nucleus. The sum of neutrons and protons (total number of nucleons) is the mass number denoted by A. The properties of neutrons, protons, and electrons are listed in Table 1.1. The number of electrons in an atom is equal to the number of protons (atomic number Z) in the nucleus. The electrons rotate along different energy shells designated as K-shell, L-shell, M-shell, etc. (Figure 1-1). Each shell further consists of subshells or orbitals, e.g., the K-shell has s orbital; the L-shell has s and p orbitals; the M-shell has s, p, and d orbitals, and the N-shell has s, p, d, and f orbitals. Each orbital can accommodate only a limited number of electrons. For example, the s orbital contains up to 2 electrons; the p orbital, 6 electrons; the d orbital, 10 electrons; and the f orbital, 14 electrons. The capacity number of electrons in each orbital adds up to give the maximum number of electrons that each energy shell can hold. Thus, the K-shell contains 2 electrons; the L-shell 8 electrons, the M-shell 18 electrons, and so forth.

A unique combination of a given number of protons and neutrons in a nucleus leads to an atom called the nuclide. A nuclide X is represented by ${}^{A}_{Z}X_{N}$. Some nuclides (270 or so) are stable, while others (more than 2700) are unstable. The unstable nuclides are termed the radionuclides, most of which are artificially produced in the cyclotron or reactor, with a few naturally occurring. The nuclides having the same number of protons are called the isotopes, e.g., ${}^{12}_{6}C$ and ${}^{14}_{6}C$; the nuclides having the same number of neutrons are called the isotones, e.g., ${}^{16}_{8}O_{8}$ and ${}^{15}_{7}N_{8}$; the nuclides having the same mass number are called the isobars, e.g., ${}^{131}I$ and ${}^{131}Xe$; and the nuclides with the same mass number but differing in energy are called the isomers, e.g., ${}^{99m}Tc$ and ${}^{99}Tc$.

This chapter is a brief overview of the materials covered and is written on the assumption that the readers are familiar with the basic concept of these materials.

TABLE 1.1. Characteristics of electrons and nucleons.

Particle	Charge	Mass (amu)[a]	Mass (kg)	Mass (MeV)[b]
Electron	–1	0.000549	0.9108×10^{-30}	0.511
Proton	+1	1.00728	1.6721×10^{-27}	938.78
Neutron	0	1.00867	1.6744×10^{-27}	939.07

[a] amu = 1 atomic mass unit = 1.66×10^{-27} kg = 1/12 of the mass of ^{12}C.
[b] 1 atomic mass unit = 931 MeV.

Radioactive Decay

Radionuclides are unstable due to the unsuitable composition of neutrons and protons, or excess energy, and therefore, decay by emission of radiations such as α particles, β^- particles, β^+ particles, electron capture, and isomeric transition.

α decay: This decay occurs in heavy nuclei such as ^{235}U, ^{239}Pu, etc. For example,

$$^{235}_{92}\mathrm{U} \rightarrow {}^{231}_{90}\mathrm{Th} + \alpha \tag{1.1}$$

Alpha particles are a nucleus of helium atom having 2 protons and 2 neutrons in the nucleus with two orbital electrons stripped off from the *K*-shell. The α particles are emitted with discrete energy and have a very short range in matter, e.g., about 0.03 mm in human tissues.

β⁻ decay: β^- decay occurs in radionuclides that are neutron rich. In the process, a neutron in the nucleus is converted to a proton along with the emission of a β^- particle and an anti-neutrino, $\bar{\nu}$.

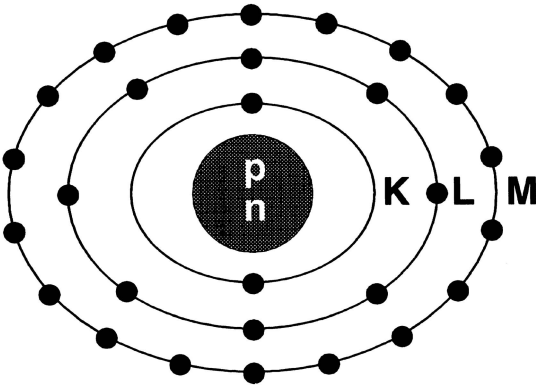

FIGURE 1-1. Schematic structure of a ^{28}Ni atom. The nucleus containing protons and neutrons is at the center. The *K*-shell has 2 electrons, the *L*-shell 8 electrons, and the *M*-shell 18 electrons.

$$n \rightarrow p + \beta^- + \bar{\nu} \tag{1.2}$$

For example,

$$^{131}_{53}I_{78} \rightarrow ^{131}_{54}Xe_{77} + \beta^- + \bar{\nu}$$

The energy difference between the two nuclides (i.e., between ^{131}I and ^{131}Xe in the above example) is called the decay energy or transition energy, which is shared between the β^- particle and the antineutrino $\bar{\nu}$. Therefore, β^- particles are emitted with a spectrum of energy with the transition energy as the maximum energy, and with an average energy equal to one-third of the maximum energy.

Positron (β^+) decay: When a radionuclide is proton rich, it decays by the emission of a positron (β^+) along with a neutrino ν. In essence, a proton in the nucleus is converted to a neutron in the process.

$$p \rightarrow n + \beta^+ + \nu \tag{1.3}$$

Since a neutron is one electron mass heavier than a proton, the right-hand side of Eq. (1.3) is two electron mass more than the left-hand side, i.e., $2 \times 0.511\,\text{MeV} = 1.022\,\text{MeV}$ more on the right side. For conservation of energy, therefore, the radionuclide must have a transition energy of at least 1.022 MeV to decay by β^+ emission. The energy beyond 1.022 MeV is shared as kinetic energy by the β^+ particle and the neutrino.

Some examples of positron-emitting nuclides are:

$$^{18}_{9}F_{9} \rightarrow ^{18}_{8}O_{10} + \beta^+ + \nu$$
$$^{82}_{37}Rb_{45} \rightarrow ^{82}_{36}Kr_{46} + \beta^+ + \nu$$

Positron emission tomography (PET) is based on the principle of coincidence detection of the two 511 keV photons arising from positron emitters, which will be discussed in detail later.

Electron capture: When a radionuclide is proton rich, but has energy less than 1.022 MeV, then it decays by electron capture. In the process, an electron from the nearest shell, i.e., *K*-shell, is captured by a proton in the nucleus to produce a neutron.

$$p + e^- \rightarrow n + \nu \tag{1.4}$$

Note that when the transition energy is less than 1.022 MeV, the radionuclide definitely decays by electron capture. However, when the transition energy is more than 1.022 MeV, the radionuclide can decay by positron emission and/or electron capture. The greater the transition energy above 1.022 MeV, the more likely the radionuclide will decay by positron emission. Some examples of radionuclides decaying by electron capture are:

$$^{111}_{49}\mathrm{In} + \mathrm{e}^- \rightarrow {}^{111}_{48}\mathrm{Cd} + \nu$$

$$^{67}_{31}\mathrm{Ga} + \mathrm{e}^- \rightarrow {}^{67}_{30}\mathrm{Zn} + \nu$$

Isomeric transition: When a nucleus has excess energy above the ground state, it can exist in excited (energy) states, which are called the isomeric states. The lifetimes of these states normally are very short (~10^{-15} to 10^{-12} sec); however, in some cases, the lifetime can be longer in minutes to years. When an isomeric state has a longer lifetime, it is called a metastable state and is represented by "m." Thus, having an energy state of 140 keV above ^{99}Tc and decaying with a half-life of 6 hr, ^{99m}Tc is an isomer of ^{99}Tc.

$$^{99\mathrm{m}}\mathrm{Tc} \rightarrow {}^{99}\mathrm{Tc} + \gamma$$

$$^{113\mathrm{m}}\mathrm{In} \rightarrow {}^{113}\mathrm{In} + \gamma$$

A radionuclide may decay by α, β^-, β^+ emissions, or electron capture to different isomeric states of the product nucleus, if allowed by the rules of quantum physics. Naturally, these isomeric states decay to lower isomeric states and finally to the ground states of the product nucleus, and the energy differences appear as γ-ray photons.

As an alternative to γ-ray emission, the excitation energy may be transferred to an electron, preferably in the K-shell, which is then ejected with energy $E_\gamma - E_B$, where E_γ and E_B are the γ-ray energy and binding energy of the electron, respectively. (Figure 1-2) This process is called the internal conversion, and the ejected electron is called the conversion electron. The

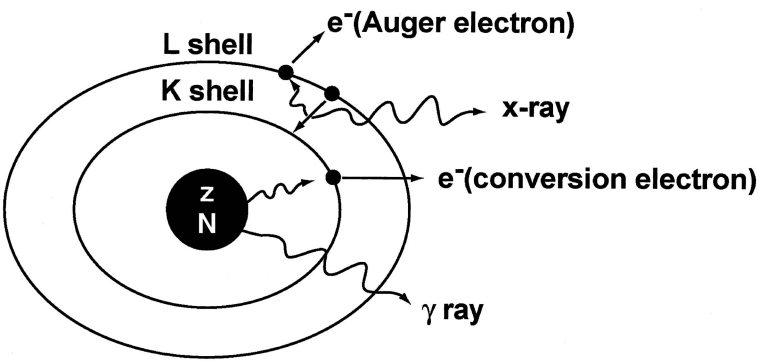

FIGURE 1-2. γ-ray emission and internal conversion process. In internal conversion process, the excitation energy of the nucleus is transferred to a K-shell electron, which is then ejected, and the K-shell vacancy is filled by an electron from the L-shell. The energy difference between the L-shell and K-shell appears as the characteristic K x-ray. The characteristic K x-ray energy may be transferred to an L-shell electron, which is then ejected in the Auger process.

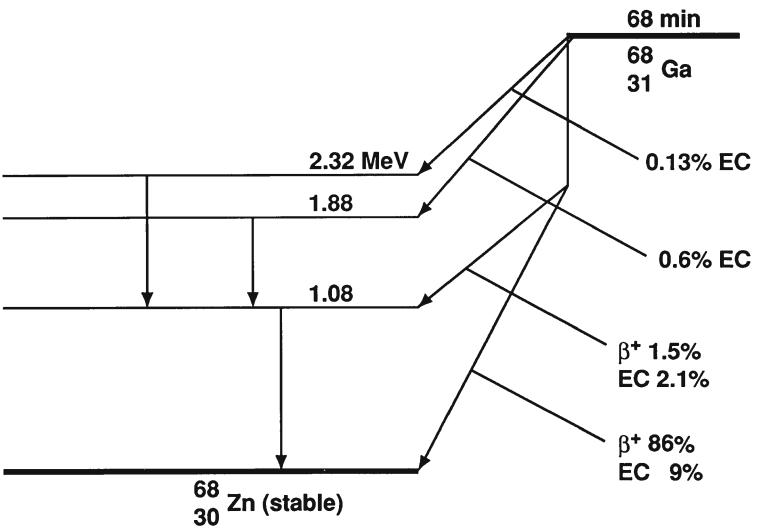

FIGURE 1-3. The decay scheme of ^{68}Ga. The 87.5% of positrons are annihilated to give rise to 175% of 511keV photons.

vacancy created in the *K*-shell is filled by the transition of an electron from an upper shell. The energy difference between the two shells appears as a characteristic *K* x-ray. Similarly, characteristic *L* x-ray, *M* x-ray, etc. can be emitted if the vacancy in the *L* or *M* shell is filled by electron transition from upper shells. Like γrays, the characteristic x-ray energy can be emitted as photons or be transferred to an electron in a shell which is then ejected, if energetically possible. The latter is called the Auger process, and the ejected electron is called the Auger electron.

The decay of radionuclides is represented by a decay scheme, an example of which is given in Figure 1-3.

Radioactive Decay Equations

General Decay Equations

The atoms of a radioactive sample will decay randomly, and one cannot tell which atom will decay when. One can only talk about an average decay of the atoms in the sample. This decay rate is proportional to the number of radioactive atoms present. Mathematically,

$$-\frac{dN}{dt} = \lambda N \tag{1.5}$$

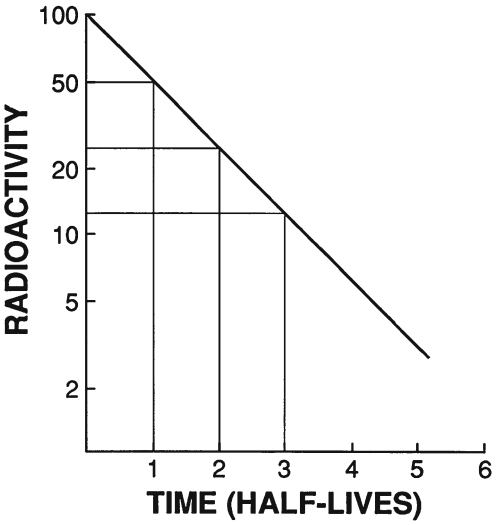

FIGURE 1-4. Plot of activity A_t against time on a semi-logarithmic graph indicating a straight line. The slope of the line is the decay constant λ of the radionuclide. The half-life $t_{1/2}$ is calculated from λ using Eq. (1. 8). Alternatively, the half-life is determined by reading an initial activity and half its value and their corresponding times. The difference in time between the two readings is the half-life.

where $-\frac{dN}{dt}$ is the rate of decay denoted by the term activity A, λ is the decay constant, and N is the number of atoms of the radionuclide present. Thus,

$$A = \lambda N \tag{1.6}$$

Integrating Eq. (1.5) gives the activity A_t at time t as

$$A_t = A_o e^{-\lambda t} \tag{1.7}$$

where A_o is the activity at time $t = 0$. The plot of A_t versus t on a semi-log scale is shown in Figure 1-4. If one knows activity A_o at a given time, the activity A_t at time t before or later can be calculated by Eq. (1.7).

Half-life ($t_{1/2}$): The half-life of a radionuclide is defined as the time required to reduce the initial activity to one-half. It is unique for every radionuclide and is related to the decay constant as follows:

$$\lambda = \frac{0.693}{t_{1/2}} \tag{1.8}$$

The half-life of a radionuclide is determined by measuring the radioactivity at different time intervals and plotting them on semi-logarithmic

paper, as shown in Figure 1.4. An initial activity and half its value are read from the straight line, and the corresponding times are noted. The difference in time between the two readings gives the half-life of the radionuclide.

The mean life τ of a radionuclide is defined by

$$\tau = \frac{1}{\lambda} = \frac{t_{1/2}}{0.693} = 1.44 t_{1/2} \tag{1.9}$$

A radionuclide decays by 63% in one mean life.

Effective half-life: Each radionuclide decays with a definite half-life, called the physical half-life, which is denoted by T_P or $t_{1/2}$. When radiopharmaceuticals are administered to patients, analogous to physical decay, they are eliminated from the body by biological processes such as fecal excretion, urinary excretion, perspiration, etc. This elimination is characterized by a biological half-life (T_b) which is defined as the time taken to eliminate a half of the administered activity from the biological system. It is related to the decay constant λ_b by

$$\lambda_b = \frac{0.693}{T_b}$$

Thus, in a biological system, the loss of a radiopharmaceutical is related to λ_p and λ_b. The net effective rate of loss (λ_e) is characterized by

$$\lambda_e = \lambda_p + \lambda_b \tag{1.10}$$

Since $\lambda = 0.693/t_{1/2}$,

$$\frac{1}{T_e} = \frac{1}{T_p} + \frac{1}{T_b} \tag{1.11}$$

$$T_e = \frac{T_p \times T_b}{T_p + T_b} \tag{1.12}$$

The effective half-life is always less than the shorter of T_p or T_b. For a very long T_p and a short T_b, T_e is almost equal to T_b. Similarly, for a very long T_b and a short T_p, T_e is almost equal to T_p.

Successive Decay Equations

In a successive decay, a parent radionuclide p decays to a daughter nuclide d, and d in turn decays to another nuclide c, and we are interested in the decay rate of d over time. Thus,

$$p \rightarrow d \rightarrow c$$

Mathematically,

$$-\frac{dN_d}{dt} = \lambda_p N_p - \lambda_d N_d \tag{1.13}$$

On integration,

$$A_d = \frac{\lambda_d (A_p)_o}{\lambda_d - \lambda_p}\left[e^{-\lambda_p t} - e^{-\lambda_d t}\right] \tag{1.14}$$

If the parent half-life is greater than the daughter half-life (say a factor of 10 to 100), and also if the time of decay (t) is very long, then $e^{-\lambda_d t}$ is almost zero compared to $e^{-\lambda_p t}$. Then

$$(A_d)_t = \frac{\lambda_d}{\lambda_d - \lambda_p}(A_p)_t \tag{1.15}$$

Equation (1.15) represents a *transient equilibrium* between the parent *p* and daughter *d* radionuclides, which is achieved after several half-lives of the daughter. The graphical representation of this equilibrium is shown in Figure 1-5. It can be seen that after equilibrium, the daughter activity is greater than the parent activity and the daughter appears to decay follow-

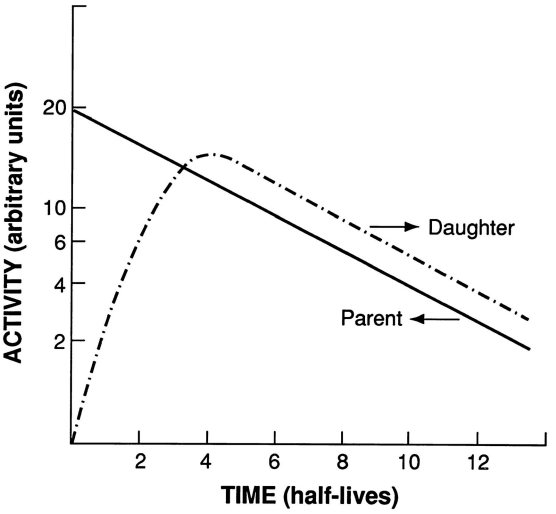

FIGURE 1-5. The transient equilibrium is illustrated in the plot of activity versus time on a semi-logarithmic graph. The daughter activity increases initially with time, reaches a maximum, then transient equilibrium, and finally appears to follow the half-life of the parent. Note that the daughter activity is higher than the parent activity in equilibrium.

ing the half-life of the parent. The principle of transient equilibrium is applied to many radionuclide generators such as the ^{99}Mo-^{99m}Tc generator.

If the parent half-life is much greater than the daughter half-life (by factors of hundreds or thousands), then λ_p is very negligible compared to λ_d. Then Eq. (1.15) becomes

$$(A_d)_t = (A_p)_t \tag{1.16}$$

This equation represents a *secular equilibrium* in which the daughter activity becomes equal to the parent activity, and the daughter decays with the half-life of the parent. The ^{82}Sr-^{82}Rb generator is an example of secular equilibrium.

Units of Radioactivity

$1\,\text{Ci} = 3.7 \times 10^{10}$ disintegration per sec (dps)
$1\,\text{mCi} = 3.7 \times 10^{7}\,\text{dps}$
$1\,\mu\text{Ci} = 3.7 \times 10^{4}\,\text{dps}$

Units of Radioactivity in System Internationale

1 Becquerel (Bq) = 1 dps
$1\,\text{kBq} = 10^{3}\,\text{dps} = 2.7 \times 10^{-8}\,\text{Ci}$
$1\,\text{MBq} = 10^{6}\,\text{dps} = 2.7 \times 10^{-5}\,\text{Ci}$
$1\,\text{GBq} = 10^{9}\,\text{dps} = 2.7 \times 10^{-2}\,\text{Ci}$

Calculations

Problem 1.1

A dosage of ^{18}F-FDG has 20 mCi at 10 a.m. Wednesday. Calculate the activity of the dosage at 7 a.m. and 2 p.m. that day. The half-life of ^{18}F is 110 minutes.

Answer:

$$\lambda \text{ for } ^{18}\text{F} = \frac{0.693}{110}\ \text{min}^{-1}$$

time from 7 a.m. to 10 a.m. = 3 hrs
= 180 min
time from 10 a.m. to 2 a.m. = 4 hrs
= 240 min

$$\text{Activity of } ^{18}\text{F-FDG at 7 a.m.} = 20 \times e^{+\frac{0.693}{110} \times 180}$$
$$= 20 \times e^{+1.134}$$
$$= 62\,\text{mCi}\ (2.29\,\text{GBq})$$

$$\text{Activity of } {}^{18}\text{F-FDG at 2 p.m.} = 20 \times e^{-\frac{0.693\times240}{110}}$$
$$= 20 \times e^{-1.512}$$
$$= 20 \times 0.22$$
$$= 4.4 \text{ mCi (163.1 MBq)}$$

Problem 1.2

A radioactive sample decays 40% per hour. What is the half-life of the radionuclide?

Answer:

$$\lambda = 0.4\text{hr}^{-1} = \frac{0.693}{t_{1/2}}$$
$$t_{1/2} = \frac{0.693}{0.4}$$
$$= 1.73\text{hr}$$

Interaction of Radiation with Matter

Radiations are either particulate type, such as α particle, β particle, etc. or nonparticulate type, such as electromagnetic radiation (e.g γ rays, infrared rays, x-rays, etc.), and both kinds are ionizing radiations. The mode of interaction of these two types of radiations with matter is different.

Interaction of Charged Particles with Matter

The energetic charged particles such as α particles and β particles, while passing through matter, lose their energy by interacting with the orbital electrons of the atoms in the matter. In these processes, the atoms are ionized in which the electron in the encounter is ejected, or are excited in which the electron is raised to a higher energy state. In both excitation and ionization processes, chemical bonds in the molecules of the matter may be ruptured, forming a variety of chemical entities.

The lighter charged particles (e.g., β particles) move in a zigzag path in the matter, whereas the heavier particles (e.g., α particles) move in a straight path, because of the heavy mass and charge. The straight line path traversed by the charged particles is called the range R. The range of a charged particle depends on the energy, charge and mass of the particle as well as the density of the matter it passes through. It increases with increasing charge and energy, while it decreases with increasing mass of the particle and increasing density of the matter. The range of positrons and other properties of common positron-emitters are given in Table 1.2.