Basic Science of PET Imaging

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أهدي هذ الكتاب إليأمي
غفر الله لها و تغمدها بر حمته
I dedicate this book to my Mother.
God Bless her at all times.

Preface

This book *Basic Science of PET Imaging* was designed to be a daughter element of the parent book *Basic Sciences of Nuclear Medicine* (Springer, Khalil MM (Ed), 2011) with special focus on positron emission tomography (PET) imaging with its rather extended scientific disciplines and clinical applications. The rapid growth and advances in medical imaging in general and in PET imaging in particular have motivated and required a dedicated volume recording this historical moment in the lifetime of nuclear medicine and molecular imaging. I think the release of the book is timely as it captures a snapshot of one of the most important and dynamically changing fields of medicine.

PET imaging technologies and their clinical and biomedical applications have become an integral part and indispensable tool in daily practice of modern medicine. It was a very exciting mission to collect most if not all of scientific bases and underlying fundamental concepts about PET imaging in a single volume. This has been made with careful attention to describe the basic scientific principles, highlighting new advances and shedding light on recent developments in most of the covered topics. The power of PET imaging is currently not residing only in diagnostic workup of oncology, cardiology, and neurology and other diseases but also stem from its ability to work with other modalities in an integrated fashion in the new era of personalized or precision medicine.

In the last few decades, there were several exciting developments in most aspects of PET imaging technology that have made it an attractive, invaluable, and clinically rich imaging modality. I believe that the future of PET is bright with promising findings that will help our patients, the core of the work, get diagnosed in their early disease development and supporting physicians in taking the most accurate decision in treatment and management. The multidisciplinary collaboration that is taking place among physics, chemistry, biology, mathematics, engineering, and biomedical as well as medical professions in shaping nuclear medicine and molecular imaging has changed the way how new educational courses of molecular imaging and therapeutics would be designed and presented. I wish this textbook would be a good source for those educational programs.

Here I am presenting all chapters individually highlighting the most notable points and angles that characterize each chapter.

Chapter 1 has initiated the marathon of PET imaging by explaining some fundamental concepts and principles in radiation physics starting from the electromagnetic radiation and atomic models going through production of radiopharmaceuticals, radioactivity and modes of decay, interactions of

radiation with matter, and positron-emitting radionuclides and finally describing some practically useful radiation detection and measurement devices.

Chapter 2 was written with special focus on radiation protection and safety parameters including shielding calculations and PET facility design, staff exposure, and optimization. X-ray computed tomography (CT) was the second important part of the chapter concentrating on technology developments, factors controlling dose in clinical examinations, as well as dose metrics such as CT dose index (CTDI) and its variants, dose length product, size-specific dose estimate, and effective dose. Other measures of CT dosimetry like diagnostic reference levels and optimization of CT image, attenuation correction, and whole body imaging were also described with some emphases placed on quality control of CT scanners.

Chapter 3 was dedicated to PET internal dosimetry with some details on radiation dose calculation scheme, biokinetic analysis and study design, animal data collection that includes tissue extraction and small animal imaging, small animal dosimetry, human imaging procedures, as well as dealing with kinetic analyses. Calculations of organ dose and standardized dose tables, patient-individualized dosimetry, and radiation dose concerns for pregnant/lactating mothers were also provided.

Chapter 4 covered labeling strategies used in the synthesis of PET radiopharmaceuticals. The authors discussed the commonly used positron-emitting radionuclides and electrophilic as well as nucleophilic substitution-based F18 labeling. Aliphatic and aromatic nucleophilic fluorination was also incorporated as well as F18 labeling of biomolecules. Labeling strategies of carbon-11 tracers were also mentioned with some details on methylation reactions, carbonylation reactions, and reactions with organometallic Grignard reagents. Other important labeling approaches for oxygen-15 and nitrogen-13 were mentioned. The emerging and the current G68-labeling methods were also outlined along with a discussion of the Ga3+ ions' physicochemical and labeling properties and associated chelation chemistry including conventional and new bifunctional chelators.

Chapter 5 was placed subsequent to Chap. 4 to describe the quality control procedures required for the release of PET radioactive drugs into the clinic. Most of the quality parameters including visual inspection, pH control, radiochemical and radionuclidic identity, half-life determination, radiochemical and radionuclidic purity, chemical purity, residual solvent determination, enantiomeric purity, sterility, and bacterial endotoxin test were explained. Analytical techniques of high-performance liquid chromatography (HPLC), thin layer chromatography (TLC), gas chromatography, and gamma spectrometry were described. Validation of analytical procedures and characteristics required, namely, specificity, precision, accuracy, linearity and range, detection limit, quantitation limit, and robustness, was discussed. Quality control of C11 tracers taking C11-methionine as an example as well as Ga68 radiopharmaceuticals taking ^{68}Ga-edotreotide as an example was also presented.

Chapters 6 and 7 were written to circumvent the regulatory aspects of PET tracer production in European countries and the United States, respectively. The former chapter has emphasized the development of pharmaceutical regulations and regulatory agencies as well as some attributes of a qualified person.

Regulatory framework and manufacturing authorization, clinical trials, magistral approach, and documentation were described. Drug development and approval steps were also explained along with data needed for submission and scientific writing. Good manufacturing practice (GMP) was presented with its required elements and components. Other topics such as new European clinical trial regulations, recognition of special status of radiopharmaceuticals, risk assessment approaches, and quality by design were also discussed.

Chapter 7 has made real focus on the framework of US regulations surrounding radiopharmaceutical production as well as the Food and Drug Administration (FDA) Modernization Act (the Modernization Act) of 1997. Discussion is extended to cover compounded and non-compounded PET drugs; current good manufacturing practice (cGMP); unique aspects of PET drug production; Part 210, 211, and 212 of 21 Code of Federal Regulations (CFR) and significant differences; quality assurance; quality control; personnel and resources; facilities and equipment; production and process controls; laboratory controls; finished drug product controls and acceptance criteria; packaging and labeling; distribution and complaint handling; and records. Other topics delineated were the *United States Pharmacopeia* (USP) < 823 > and revised USP < 823>, inspection of the PET drug production facility including types of FDA inspections, selection of inspection coverage, major issues identified in 2013/2014 PET drug inspections, and other related topics.

Chapter 8 provided details of PET instrumentation and physical principles underlying the detection theory of annihilation radiation, coincidence logic, and electronic collimation. Types of events, scintillation detectors, photosensors, detector design and geometry, data acquisition, and signal processing were described. System characteristics such as sensitivity, spatial resolution, energy resolution, coincidence timing resolution, count rate performance, multimodality PET/CT highlighting motivation, and review of fusion imaging of software and hardware approaches were also described. Attenuation correction, scatter correction, random correction, and issues related to PET/CT imaging protocols including low-dose and contrast injection were discussed. TOF technology was prominently outlined. Advances in PET imaging that include new photosensors, organ-specific imaging, and multimodality PET/MR were also briefly discussed.

Chapter 9 focused on PET/MR with some details of many technical and physical aspects of this relatively new hybrid imaging technology. Topics covered were system design of PET/MR scanners, technical challenges, as well as solutions implemented. PET imaging system and MR scanner hardware design and requirements were discussed. Different approaches devised for attenuation correction, data acquisition, imaging workflow, and motion correction were also explained, with the chapter closing with opportunities, challenges, and future directions of PET/MR imaging systems.

Chapter 10 has dealt with PET/CT scanner performance, acceptance testing, and quality control checks that should be performed for optimal operation. A comprehensive coverage of the topic and its various elements was made such as instrumental detection and data flow, detection and system calibration, acceptance testing considering NEMA performance parameters and other tests, and routine quality assurance that covers daily,

monthly/quarterly, and annual tests in addition to the use of PET scanners in clinical trials.

Chapter 11 was designed to discuss image reconstruction algorithms used in PET imaging classifying them into analytical versus iterative-based reconstruction methods. Advantage of iterative reconstruction was discussed along with requirements posed to yield significant improvements in image quality and quantitative accuracy. This has been discussed together with analysis of image properties and PET data corrections, such as normalization, attenuation, and scatter correction. Recent updates were also highlighted covering time-of-flight image reconstruction as well as parametric image reconstruction.

Chapter 12 has special focus on image processing tools and new measures introduced to support risk stratification, treatment response assessment, and prognosis. Morphological versus conventional image features of PET data were discussed together with static and dynamic data set. Extension to PET/CT and PET/MR was also made to utilize the unique features provided by combining morphological and molecular-based scanning procedures. Application of PET in radiotherapy treatment planning was also pointed out in the chapter with emphases on using PET in tumor delineation or biological target definition. PET image characteristics such as robustness and stability of extracted image features and improved PET-based outcome models as well as an outlook at improved PET-based outcome models were explained.

Chapter 13 discussed quantitative PET imaging highlighting the differences between static and dynamic data acquisition, describing the different types of information that can be extracted from each approach. Standardized uptake value (SUV) and its pros and cons, SUV variants, total disease burden, factors affecting quantitative results, response to treatment and evaluation criteria, and finally tumor texture analysis were covered.

Chapter 14 covered kinetic modeling and tracer kinetic analysis. The chapter outlined important definitions, assumptions, and solutions of 1-tissue compartment model (1TC), 2TC model, and 3TC model, general solution, as well as parameter estimation of PET data. Linearization of the kinetic model and use of graphical techniques such as Logan plot and Patlak plot were described, in addition to a discussion on spectral derivation and analysis. Physiological and biological basis of compartmental model was integrated within the chapter contents to provide more insight on underlying concepts behind derivation of quantitative parameters. Arterial input function and time activity curve, continuous infusion, and reference region model were also described and demonstrated.

Chapter 15 talked about partial volume effect and correction techniques with some details of historical background and varieties of methods/algorithms used in research and practice. Topics covered were point spread function, tissue fraction effect, deconvolution, motion, and partial volume. The correction techniques were also detailed including region-based, voxel-based, and combined methods. Practical consideration of partial volume correction was also described such as accuracy, resolution, co-registration, segmentation, and sampling. Alternative methods/approaches were outlined with clinical applications in cardiology, neurology, and oncology.

Chapter 16 covered motion artifact problems in PET/CT image acquisition. Illustrative description of artifacts caused by respiratory motion, mis-registration, and frequency of occurrence was explained. Average CT of less than 1 mSv to reduce mis-registration, benefits of average CT for radiation therapy, and 4D-PET as well as 4D-PET/CT data acquisition were demonstrated.

Chapter 17 stated the molecular basis and physiologic fundamentals of different PET tracers besides their utility in disease detection and patient diagnosis. F18-Fluorodeoxyglucose (F18-FDG) and tracers beyond were comprehensively described in many areas of cancer metabolism, angiogenesis, hypoxia, apoptosis, proliferation, growth factor receptors, somatostatin receptors, bone metabolism, chemokine receptor, as well as tracers used in multidrug resistance of cancer therapy.

Chapter 18 described the application of F18-FDG PET imaging in a number of oncologic disorders including lung, lymphoma, breast, malignant melanoma, head and neck, thyroid, esophageal, and colorectal cancers in addition to gynecological such as cervical and ovarian malignancies. Other topics of response monitoring, pitfalls, PET in clinical trials, and future outlook were also presented.

Chapter 19 dealt with cardiac PET imaging covering technical background and clinical applications. Major headings of the chapter were instrumentation, cardiac PET tracers, myocardial perfusion imaging, stress protocols, data interpretation, quantification of myocardial blood flow and flow reserve, ECG gating, and cardiac PET tracers. Moreover, the discussion is extended to highlight metabolic cardiac imaging including carbohydrate metabolism, fatty acid metabolism, oxidative metabolism, viability imaging, metabolic alteration studies, and quantification of metabolism, myocardial and vascular inflammation, and cell signaling. The latter has been classified into neurocrine, endocrine, paracrine, autocrine, juxtacrine, and matricrine pathways. The chapter is closed with discussions on cardiac PET in clinical trials and future directions.

Chapter 20 talked about PET in neurological and psychiatric disorders emphasizing technical advances and clinical applications. Many topics have been covered and included such as new aspects of long-standing diagnostic applications, role of F18-FDG in neurodegenerative disease, role of FDG in various conditions, contributions of FDG and other PET tracers to epilepsy characterization, important physiologic measures such as regional and global cerebral blood flow, oxygen extraction fraction, and tissue viability and amyloid imaging. The use of PET inclusion/progression parameter in clinical trials, drug development and dose finding by occupation/displacement, and biodistribution of new candidate compounds were also described. Additional points such as studying indirect neurochemical effects of acute pharmaceuticals and interventions onto radioligand targets, pressing diagnostic questions acceded by early investigatory tracers, pathophysiological studies of neurotransmission, targets of radioligands/radiosubstrates, ion channel-coupled receptors, enzymes, and enzyme transporters have been mentioned as well.

Chapter 21 was placed to discuss the role of PET/CT in pediatric malignancies. Technical and clinical considerations of PET imaging in pediatric population were discussed. Tumors of the sympathetic nervous system and

lymphoma including Hodgkin and non-Hodgkin with evaluation of response, relapse, or recurrence were demonstrated. Other pediatric disorders such as leukemia, tumors of the brain and central nervous system, osseous and soft tissue malignancy, nephroblastoma, hepatoblastoma, and thyroid malignancy were also described and outlined.

Chapter 22 focused on the role of PET/CT in radiotherapy treatment planning with an introduction that sheds light on the importance of integrating PET data into the planning strategy. Applications of PET in treatment planning for a number of critical malignancies were also discussed such as lung, head and neck, esophageal, breast, lymphoma, myeloma, brain, gynecological, colorectal, and prostate malignancies. The last section of the chapter discusses the important role of imaging hypoxia in radiotherapy and treatment outcome.

PET imaging technologies have become ever-fast-moving disciplines, and every effort was made to produce this volume covering basic principles along with recent advances in most aspects. It was aimed to be easy to read, illustrative, and scientifically rich without compromising other necessary requirements of different readers who are coming from various backgrounds. I would therefore appreciate comments, remarks, or any observation that the reader may find necessary for corrections or useful points for future update.

In this respect, I am so grateful to all the authors for their time and efforts to contribute and place their broad area of expertise in their writing. I am again thankful to all of them as without their participation this volume would not have been possible. I hope this book would be a valuable reference for practitioners and newcomers in the field as well for those involved in different educational programs. Researchers are also important targets since new developments and advances have been incorporated in many areas throughout the book chapters.

Thank you.

Magdy M. Khalil
Giza, Egypt
10th Feb, 2016

Acknowledgments

Thanks go to my God, for without him nothing can come into existence. I am so grateful and indebted to my parents who always are the driving and motivating force to my success and progress. I wish them all the best herein and thereafter. Special thanks go to my wife and my children who sacrificed a lot of their time for the sake of completion of this book. I am grateful to Springer Publishing and the editorial team for their efforts in bringing this volume out to the reader. I am thankful to all colleagues, friends, mentors, and professors who are too many to mention over the years for their time, collaborations, and advices. I would like also to take this opportunity to acknowledge and send my thanks and appreciation to all authors who were really professional and eminent at all stages of writing this textbook. I give thanks again for their time, efforts, and high expertise that have been shown very clearly in their respective chapters. Last but not least, I would like to express my deepest gratitude to my colleagues in the Department of Physics, Faculty of Science, Helwan University, Cairo, Egypt, for their support and encouragement.


رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ الَّتِي
أَنْعَمْتَ عَلَيَّ وَعَلَى وَالِدَيَّ وَأَنْ أَعْمَلَ
صَالِحًا تَرْضَاهُ وَأَدْخِلْنِي بِرَحْمَتِكَ فِي
عِبَادِكَ الصَّالِحِينَ
"My Lord!
Grant me the power and ability that I may be grateful for Your favors which You have bestowed on me and on my parents, and that I may do righteous good deeds that will please You, and admit me by Your mercy among Your righteous servants.

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Part I

Physics, Radiation Safety and Dosimetry of PET

Basic Radiation Physics

1

Taher Hosny, Eman Al-Anezi, and Magdy M. Khalil

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Abstract

This chapter provides a comprehensive overview of essential radiation physics required to understand many fundamental concepts of nuclear medicine in general and positron emission tomography (PET) imaging in particular. We aimed to introduce the most important elements of radiation physics as tightly related to daily practice and routine activities performed in clinical environment. Topics covered in this chapter have discussed definition of electromagnetic radiation, atomic models, atomic structure, radio-

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activity and radioactive modes of decay; production of radiopharmaceuticals including medical cyclotrons, saturation yield and reactor-produced radionuclides; and interaction of radiation with matter, linear and mass attenuation coefficients as well as mostly commonly used radiation detection and measurement devices. As this is the first chapter in the book, we made every effort to cover as many aspects that might come across the reader throughout or facilitate the understanding of other chapters.

1.1 Introduction

Radiation physics does broaden our understanding of many facts and theories that underlie clinical application of radioisotopes in medicine and other areas of biomedical research. More specifically, nuclear medicine practitioners are among those that must always keep an eye not only on fundamental radiation and nuclear physics but also on how this can be utilized and applied in practice. Many of the achievements in nuclear medicine were in large part related to those concepts with particular benefits to diagnostic imaging and radionuclide therapy. Therefore, it is an important course for those who attempt to learn the underlying bases such as the structure of the atom, electron as well as nuclear binding energy, radioactivity and its associated formulae, units and conversions in addition to production of radiopharmaceuticals, interaction of radiation with matter and other safety and radiation protection devices and measurements. Electromagnetic radiation and its associated wide spectrum, duality principle, structure of the atom, atomic models proposed over the years, mass defect and nuclear binding energy and other important issues are among the first topics that we will start with.

1.2 Electromagnetic Radiation

Electromagnetic radiation (EM) consists of self-sustaining oscillating electric and magnetic fields at right angles but in phase and perpendicular to each other and to the direction of propagation as shown in Fig. 1.1. It does not require a supporting medium and travels through empty space at the speed of light. EM radiation exhibits wave properties as well as particulate properties (duality principle). All different kinds of electromagnetic radiation (microwaves, radio waves, infrared, x-ray, gamma ray, etc.) differ in one important property which is its specific wavelength. When electromagnetic radiation is spread out according to its wavelength, the result is electromagnetic spectrum as explained in Fig. 1.2. The electromagnetic spectrum is divided into five major types of radiation. These include radio waves (including microwaves), light (including ultraviolet, visible and infrared), heat radiation and ionizing radiation such as x-rays and gamma rays.

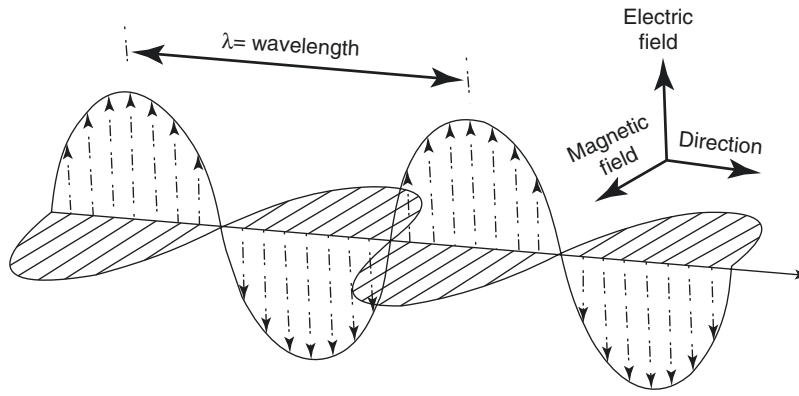

Fig. 1.1 Electric and magnetic field propagated as a transverse wave perpendicular to each other and perpendicular to the direction of propagation

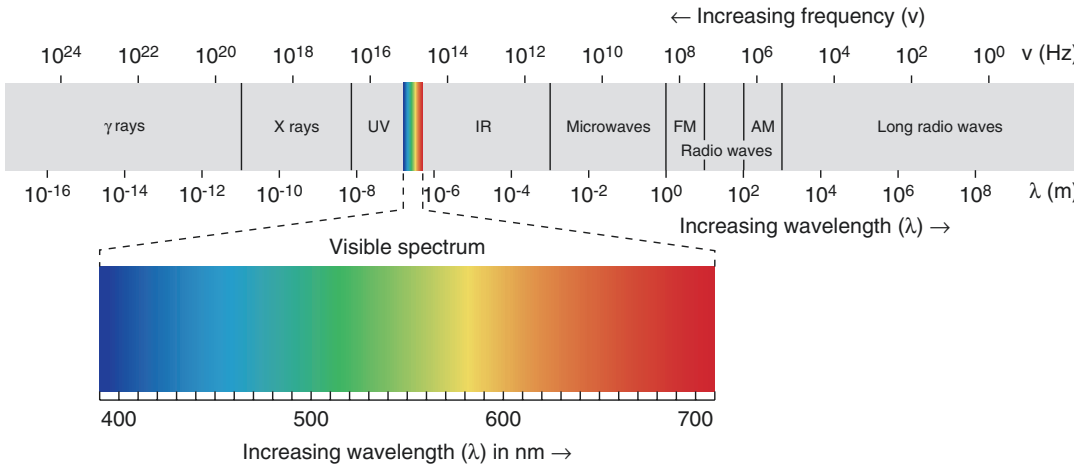

Fig. 1.2 Electromagnetic spectrum: Waves with shorter wavelength will have high frequency and vice versa. Ionizing radiation with high frequency is more energetic and can induce biological effects

1.2.1 Wave/Particulate Nature of Radiation

Although wave and particle having different physical characteristics, electromagnetic radiation can behave as both at once (wave-like and particle-like). Many experiments showed that radiation is sometimes behaves as wave and sometimes behaves as particle concluding that wave and particle cannot be separated, only together the phenomena can be explained. This has been proposed by a number of scientists leading to the theory of wave – particle duality.

1.2.2 Duality Principle

The duality principle describes the elementary particles and electromagnetic radiation in terms of wave and particle-like characteristics. It was not originated from a single scientist or revealed from only one experiment. Max Plank has stated that energy is transferred in a form of packets or quanta, while Albert Einstein thought of light as particle-like or localized in packets of discrete energy in contrast to its original definition as wave-like properties. Another contribution came from the phenomenon of photoelectric effect proposed also by Einstein. He stated that the emission of photoelectrons from metal plates does occur if and only if the incident photons on photoemissive plate have a threshold wavelength of energy that is able to liberate electrons from the metal. Then, Louis de Broglie proposed that electrons and other particles can behave as waves and has wavelength and frequencies. While this proposal was in 1927, the announcement of the understanding of the wave and particle aspects of matter was carried out in 1928. See Fig. 1.3.

Radiation can be described in terms of packet of energy, called photons. The energy of a photon is given by

$$E\left(\text{photon}\right) = h\nu = hc/\lambda \qquad (1.1)$$

where h is plank's constant ($h = 6.625\ 6 \times 10^{-34}$ J s); ν and λ are characteristics frequency and wavelength, respectively; and c is the speed of light in vacuum (Table 1.2).

Waves are characterized by frequency, wavelength and phase. Electromagnetic radiation is massless with no charge, while wavelength and frequency of oscillating fields are related to each other by the following equation:

$$c = \lambda\nu \qquad (1.2)$$

However, they are still affected by gravity.

It is of relevance to mention here that many diagnostic imaging modalities rely heavily on physical properties of different electromagnetic radiations. For example, in x-ray computed tomography (CT), a uniform x-ray beam interacts with

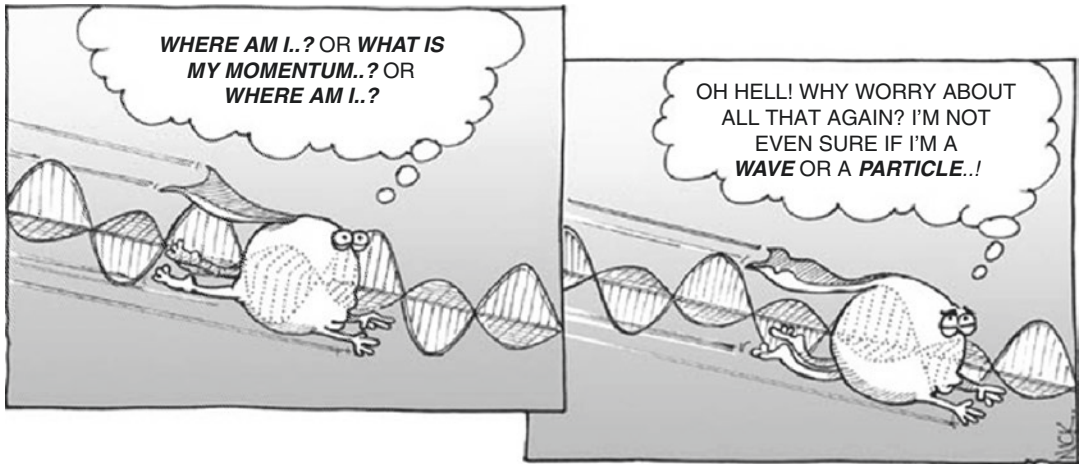

Fig. 1.3 Duality principle: Particles and electromagnetic radiation possess waves and particle characteristics (From http://www.lab-initio.com/quantum.html)

the human tissues, and the transmitted amount is measured by the CT detector to reveal an image that reflects the attenuation properties of the tissue covered in the scanning beam. Radiologic techniques such as fluoroscopy, angiography and x-ray radiography are also dependent on x-ray radiations in eliciting important diagnostic information for a wide range of human diseases and abnormalities.

Electromagnetic radiation is also associated with nuclear medicine in the sense that gamma emission is used in many diagnostic purposes utilizing the powerful penetrating capabilities of the radiation beam. This essentially takes place when patient is injected with pharmaceutical compound labelled to gamma-emitting radionuclide. After radiopharmaceutical administration, the body tissue will be the source of gamma ray emission that is used in the imaging process.

Another application of electromagnetic radiation in clinical practice is magnetic resonance (MR) imaging which is different from other imaging techniques such as CT and nuclear medicine, as it uses radio frequency (i.e. radio wave) as energy source rather than ionizing radiation. The procedure requires the usage of a strong magnetic field for spin alignment of hydrogen nuclei in the body. The spin synchronizes as the radio-frequency pulse matches the nuclear resonance frequency of the protons.

While radio wave energy is consistent with energy of nuclear spin in magnetic field, microwave matches rotational energy of the molecule. The infrared (IR) region in the spectrum lies beyond the region that the human eye perceives as red light. The absorption of infrared light causes increases in the frequencies at which the bonds between atoms stretch and bend. This is the idea behind infrared spectroscopy where there is a sort of matching between the IR radiation energy and the frequency of a specific molecular motion usually bond bending or stretching. However, the higher-frequency ultraviolet radiation that lies above the visible limit of the light spectrum is matching to different electronic transition states. In summary:

- Radio → nuclear spin in magnetic field
- Microwave → rotation
- Infrared → vibration
- Ultraviolet → electronic

1.3 Atomic Models

Atom is considered as the basic building unit of an element. An atom is the smallest unit of element that retains its physical and chemical properties. Each known element has atoms differ from the atoms of other elements; this gives each element a unique atomic structure. Many atomic models were proposed, and some have been adopted as ways to describe the atom. Neither of them is perfect, but they have relative contribu-

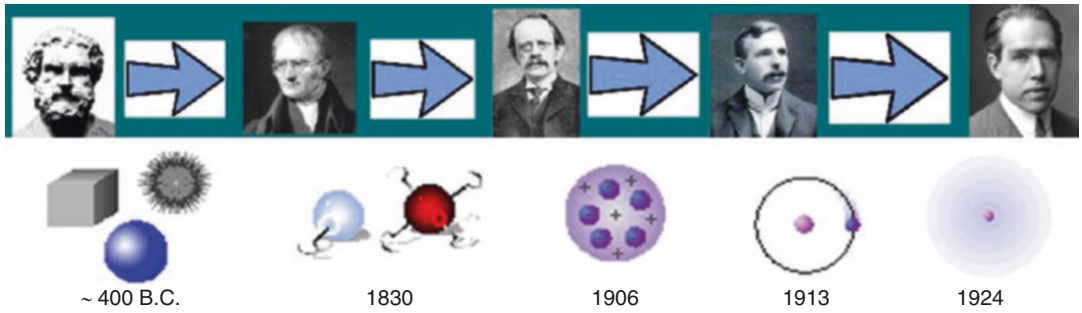

Fig. 1.4 Serial time line of atomic models proposed over the years and described by the following scientists (*left to right*): Democritus, Dalton, Thomson, Rutherford and Bohr. Taken from http://www.K12tlc.net/content/atomhist.htm

tions towards understanding these building blocks. See Figure 1.4 serial time line of atomic models.

1.3.1 History of Atomic Models

The first atomic model described in the literature is dated back to the Greek philosopher Democritus. He postulated the existence of invisible atoms, which are characterized only by quantitative properties such as size, shape and motion. His model described the atom as indivisible spheres representing the smallest piece of an element that still behave like the entire chunk of matter. There were no significant advances in definition and characterization of the atom until the English chemist John Dalton started to look at this in the 1800s. Dalton shared the same thoughts and impression as Democritus about atom in the sense that it is tiny and indivisible particles, but he introduced new assumptions about atom. The main assumptions of Dalton model were:

- All matter was composed of atoms, indivisible and indestructible. While all atoms of an element are identical and have the same properties, different elements have atoms of different size and mass.
- All compounds are composed of combinations of these atoms in defined ratios.
- Atoms can combine to form different compounds (e.g. carbon and oxygen combine to form carbon monoxide CO and carbon dioxide CO_2).
- Chemical reactions resulted in rearrangement of the reacting atoms.

In 1897, J.J. Thomson discovered the electron in series of experiments designed to study the nature of electric discharge in a high-vacuum cathode ray tube. In 1904, Thomson introduced a new atom model that differs from pervious atom models suggesting that the atom is uniform sphere of positively charged matter in which electrons are positioned by electrostatic forces.

A monumental breakthrough came in 1911 based on experimental results when Ernest Rutherford and his colleagues Hans Geiger and Ernest Marsden conducted the famous gold foil experiment intended to determine angles through which a beam of alpha particles (helium nuclei) would scatter after passing through a thin foil of gold. It was a new but exciting moment when they found few alpha particles recoiled almost directly backwards. It was Rutherford's interpretation that this happen when a positively charged and relatively heavy target particle, such as the proposed nucleus, could account for such strong repulsion. The negative electrons that balanced electrically the positive nuclear charge were regarded as travelling in circular orbits around the nucleus (Fig. 1.5) like planets that move around the stars, and therefore this model was called planetary model.

The planetary model was greatly inconsistent with Thomson's hypothesis in which the atom is a mixture of positive and negative particles that uniformly mixed throughout the atom. Based on the classical electromagnetic theory, however, the model failed to solve stability problem of the atom as the electrons lose energy and falling into the nucleus under the influence of attraction forces. The model proposed by Rutherford relied heavily on classical physics and was superseded in a few years by the Bohr atomic model, which

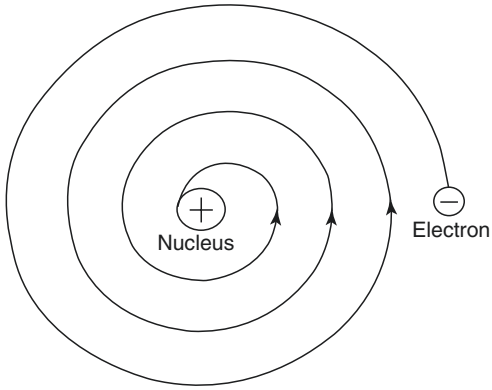

Fig. 1.5 Planetary model: In this model Rutherford proposed that electrons move in circular path around a central positive mass. This was contradicted by the fact that revolution makes electron lose energy while moving in spiral path and fall into the positively charged nucleus under influence of attraction force

incorporated some early quantum theory in combination with some classical concepts.

1.3.2 Bohr Model

In 1913, Bohr introduced a new model to explain atom stability. Bohr model of the atom was the first model that incorporated quantum theory and was the predecessor of wholly quantum-mechanical models. The model focused on electron description and based on spectroscopic observations. Bohr built up his model with the following postulates:

- The electron exists in certain energy levels (stationary states) with circular movement around the nucleus.
- Transition between these stationary states is accompanied with emission or absorption of electromagnetic radiation. The energy difference between these two energy levels is given by

$$\Delta E = \hbar v \tag{1.3}$$

where ħ (i.e. *h* bar) or sometimes reduced plank's constant is commonly associated with angular momentum and given by

$$\hbar = h / 2\pi \tag{1.4}$$

- Quantization of orbit. The only allowed orbits (stationary states) are those for which the angular momentum *L* is

$$L = n\hbar$$

where *n* is principal quantum number and takes values of 1,2,3,….., *n* and cannot be less than one.

Bohr's postulates were experimentally confirmed in experiments of Franck and Hertz (German scientists) in 1913 who studied the inelastic scattering of electrons of mercury atoms. This experiment showed that the energy levels of mercury atom were discrete. However, Bohr's model had no way of approaching non-periodic quantum-mechanical phenomena, like scattering. Furthermore, although Bohr' model served to predict energy levels, it was not able to explain transition rates between levels. Finally, the model was successful only for one-electron atoms like hydrogen and fails even for helium. To correct these drawbacks, one needs to apply a more completely quantum-mechanical treatment of atomic structure, and such an approach is used in Schrödinger theory.

1.3.3 Quantum Mechanics Model

The quantum mechanics model is derived from the quantum theory in which electron location and momentum are governed by the wave function. This hypothesis is denoted as uncertainty principle (Heisenberg principle) and states that the position and momentum of the electron can't be determined simultaneously with the same high precision. Stated another way, the more the precision in determining the electron location, the low the probability of determining the momentum and vice versa. The theory used the term orbitals to describe the location of the electrons, which are volumes in space used to define the probability distribution function. Four quantum numbers were introduced to define the electrons and their orbitals around the nucleus:

1. Principle quantum number (*n*): it is an integer number that indicates electron energy and orbital size, and it is the same number intro-

duced by Bohr. It takes values $n = 0,1,2,\ldots\ldots$, while the maximum number of electrons in certain energy level is equal to $2n^2$.
2. Angular quantum number (l) describes the orbital shape of a particular principal quantum number. It divides energy shells or levels into subshells (sublevels). These sublevels represented by letters like *s*, *p*, *d* and *f*. Angular quantum number takes values $l = 0,1,2\ldots,n-1$.
3. Magnetic quantum number, m_l ($m_l = -l,\ldots, 0,\ldots, +l$) specifies the orientation in space of an orbital of a given energy (n) and shape (l). This number divides the subshell into individual orbitals which hold the electrons; there are $2l+1$ orbitals in each subshell.
4. Spin quantum number, m_s ($m_s = +½$ or $-½$) defines the orientation of the spin axis of an electron. An electron can spin in only one of two directions.

1.4 Structure of the Atom

As mentioned earlier, an atom is the main building block of matter. The atomic mass is concentrated in the nucleus which considered the heaviest portion of the atom. The positively charged nucleus contains particles of nearly equal mass, protons and neutrons, electrically balanced with negatively charged electrons moving in certain orbitals around it. Any element can be represented as

$$\begin{matrix} A \\ Z \end{matrix} X$$

where A atomic mass number is the sum of protons number Z and neutrons number N. The atomic number Z equals also the number of electrons in stable nuclei. It is not applicable to have two different elements having the same atomic number. The periodic table is arranged by order of increasing atomic number, which is always an integer. On the other hand, different forms of the same element can have different masses (i.e. have same atomic number) which are called isotopes, while those that have the same number of neutrons are called isotones. Isobars are nuclide with different numbers of protons and neutrons but with the same mass number. Examples of the three different nomenclatures are described in Table 1.1.

1.4.1 Mass and Energy

Mass and energy were considered two different quantities. Early 1900s, Einstein proved by his equation that neither mass nor energy was conserved separately. Thus, the mass can be converted to energy and vice versa while total mass- energy was conserved. In the following section the conversion of mass and energy will be demonstrated.

1.4.2 Atomic Mass Unit

The first atomic weight was initially proposed by *John Dalton* in 1803 as the mass of the hydrogen atom, H-1. Then it was suggested by *Wilhelm Ostwald* that it can best expressed in terms in units of 1/16 of the weight of the oxygen atom. Atomic mass can be measured by approximating the weight of a proton or neutron which indicates the masses of atom nucleons. The atom mass is expressed by a unified unit called the atomic mass unit denoted by the symbol *u*. In 1961, the international union of pure and applied chemistry had adopted and defined the modern applications of atomic mass unit and related it to the mass of carbon-12.

The definition of the atomic masses has been based on the unified mass scale considering one mole of carbon-12 which by conversion equals 12 g as the best reference nuclide. Determination of ^{12}C atom mass in grams using Avogadro's number divided on the total number of the individual atom nucleons indicates the masses of these nucleons which used to convert one atomic mass unit (1 u) to grams. Therefore, the atomic mass unit is one-twelfth ^{12}C atom in its electronic and nuclear ground state:

Table 1.1 Some examples of isotopes, isobars and isotones

Isotopes	Same Z	$^{16}_{8}O$	$^{17}_{8}O$	$^{18}_{8}O$
		$Z = 8$		
Isobars	Same A	$^{18}_{9}F$		$^{18}_{8}O$
		$A = 18$		
Isotones	Same N	$^{19}_{9}O$		$^{18}_{8}O$
		$N = 10$		

$$1\ \text{u} = \frac{1}{12} m\left({}^{12}_{6}\text{C}\right)$$

$$\begin{aligned}\text{Thus, mass of one atom of } {}^{12}\text{C} &= \frac{12\,\text{g/mol}}{6.022\ 141\ 29\times10^{23}\,\text{atoms/mol}} \\ &= 1.992\ 646\ 705\times10^{-23}\,\text{g/atom}\end{aligned}$$

$$\begin{aligned}\text{The mass per nucleon} &= \frac{1.992\ 646\ 705\times10^{-23}\,\text{g/atom}}{12} \\ &= 1.660\ 538\ 921\times10^{-24}\,\text{g}\end{aligned}$$

Then, $1\ \text{u} = 1.660\ 538\ 921\times10^{-27}$ kg.

Now the mass of proton and neutron in terms of atomic mass unit can be determined by using its actual mass in grams:

$$\begin{aligned}\text{Proton mass}\left(m_{\text{p}}\right) &= \frac{1.672\ 621\ 777\times10^{-27}}{1.660\ 538\ 921\times10^{-27}} = 1.007\ 276\ 467\ \text{u} \\ \text{Neutron mass}\left(m_{\text{n}}\right) &= \frac{1.674\ 927\ 351\times10^{-27}}{1.660\ 538\ 921\times10^{-27}} = 1.008\ 664\ 916\ \text{u}\end{aligned}$$

Conversion of the energy unit from the SI scale to the unified atomic mass unit is being done by using Einstein's mass-energy relationship ($E = mc^2$ where c is the speed of light in vacuum) taking into account that $1\ \text{eV} = 1.602\ 176\ 565\times10^{-19}$ kg.m^2/s. Inserting this quantity of mass $1\ \text{u} = 1.660\ 538\ 921\times10^{-27}$ into Einstein's equation and applying conversion factors, the nucleons mass equivalent energy can be determined.

$$E = mc^2 \tag{1.4}$$

$$\begin{aligned}&= 1\ \text{u}\left(\frac{1.660\ 538\ 921\times10^{-27}\,\text{kg}}{\text{u}}\right)\times\left(299\ 792\ 458\ \text{m/s}\right)^2\left(\frac{1\ \text{N}}{1\ \text{kg}.\frac{\text{m}}{\text{s}^2}}\right)\left(\frac{1\ \text{J}}{N.m}\right) \\ &= 1.492\ 417\ 955\times10^{-10}\,\text{J}\left(\frac{1\ \text{MeV}}{1.602\ 176\ 565\times10^{-13}\,\text{J}}\right) \\ &= 931.494\ 060\ 9\ \text{MeV}\end{aligned}$$

Some of the constants and conversion factors used in the above derivations can be found in Table 1.2 which provides a number of useful physical quantities and constants used in converting mass into energy and vice versa.

1.4.3 Binding Energy and Mass Defect

For all nuclei, the mass of the nucleus that have been formed is always less than the total composed

Table 1.2 Summary of several physical quantities and constants in atomic and nuclear scale used in mass-energy conversion

Quantity	Symbol	Numerical value	Unit
Avogadro's number	N_A	6.022 141 29×10^{23}	mol^{-1}
Speed of light in vacuum	C	299 792 458	m/s
Electron volt	eV	1.602 176 565×10^{-19}	J
Atomic mass unit-kilogram relationship	1 u	1.660 538 921×10^{-27}	kg
Atomic mass unit-electron volt relationship	1 u (C^2)	931.494 061×10^{6}	eV
Atomic mass unit-joule relationship	1 u (C^2)	1.492 417 954×10^{-10}	J
electron Volt-atomic mass unit relationship	1 eV/C^2	1.073 544 150×10^{-9}	u
Electron mass Energy equivalent	m_e	9.109 382 91×10^{-31}	kg
	m_e	5.485 799 $094\ 6\times10^{-4}$	u
	$m_e\ C^2$	8.187 105 06×10^{-14}	J
	$m_e\ C^2$	0.510 998 928	MeV
Proton mass Energy equivalent	m_p	1.672 621 777×10^{-27}	kg
	m_p	1.007 276 466 812	u
	$m_p\ C^2$	1.503 277 484×10^{-10}	J
	$m_p\ C^2$	938.272 046	MeV
Neutron mass Energy equivalent	m_n	1.674 927 351×10^{-27}	kg
	m_n	1.008 664 916 00	u
	$m_n\ C^2$	1.505 349 631×10^{-10}	J
	$m_n\ C^2$	939.565 379	MeV

Source: NIST (2010 CODATA recommended values)

masses of the contributing nucleons. This is due to conversion of that mass difference to the required energy for holding these nucleons together (i.e. the conversion of mass to binding energy). This mass difference is known as the mass defect and represents the binding energy which is defined as the amount of energy that need to be supplied to a nucleus to completely separate its constituent nucleons. The mass defect can be calculated by adding up the masses of the constituent particles and then subtracting the known mass of that atom:

$$\Delta m = \left[Z\left(m_{\text{proton}} + m_{\text{electron}}\right) + \left(A - Z\right) m_{\text{neutron}} \right] - m_{\text{atom}} \tag{1.5}$$

where:

Δm = mass defect (u)

m_{proton} = mass of a proton

m_{electron} = mass of electron

m_{neutron} = mass of neutron

m_{atom} = mass of the nuclide

Z is the atomic number and A is the mass number.

Since 1 u is equivalent to 931.5 MeV of energy as calculated in Sect. 1.4.2, the binding energy can be calculated by

$$\text{B.E.} = \Delta m \left(\frac{931.5\ \text{MeV}}{1\ \text{u}} \right)$$

Example

Calculate the mass defect of ^{235}U provided that the mass of the atom is 235.043 9 u?

Solution:

The atomic number of the ^{235}U is 92. The mass defect can be calculated by using Eq. 1.5.

$$\Delta m = \left[Z\left(m_{\text{proton}} + m_{\text{electron}}\right) + \left(A - Z\right) m_{\text{neutron}} \right] - m_{\text{atom}}$$

$$\Delta m = \left[92\left(1.007\ 28 + 5.485\ 79\times10^{-4}\right) + \left(235 - 92\right)1.008\ 66 \right] - 235.043\ 9$$

$$= 1.914\ 71\,\text{u}$$

1.4.4 Nuclear Stability

Since Earth formation, there were about 275 stable nuclides found in nature, and more than 2000 nuclides are known to be unstable (i.e. radioactive). The constituents of the unstable nuclei are not arrayed in the lowest potential energy states; therefore, the nucleus undergoes spontaneous decay with time in such a way that this excess energy is emitted forming new nuclide. A study of the characteristics of the naturally stable nuclides provides clues of instability factors of the radioactive nuclides. An *N*/*Z* diagram of the 'line of stability' relates the naturally stable nuclides extending from $Z=1$ for hydrogen up to $Z=83$ for ^{209}Bi to those radioactive according to their neutron and proton numbers. Very long-lived nuclides are shown at the end of the line of stability although of their instability.

A major measure of nuclear stability is the neutron-proton ratio, as a result of the coulomb repulsion and exchange forces between them. Referring to Fig. 1.6 and closer look into light nuclei, the line of stability shows that neutron and proton numbers are equal ($N \approx Z$). For heavy nuclei, the coulomb repulsion between the protons is substantial, and extra neutrons are needed to supply additional binding energy to hold the nucleons together. Thus, the line of stability shows $N \approx 1.5\ Z$, that is heavy stable nuclides have nearly 50% more neutrons than protons. From $Z>83$ all heavier nuclides are unstable. Radioactive nuclides surround the line of stability; nuclides lying above the line are said to be

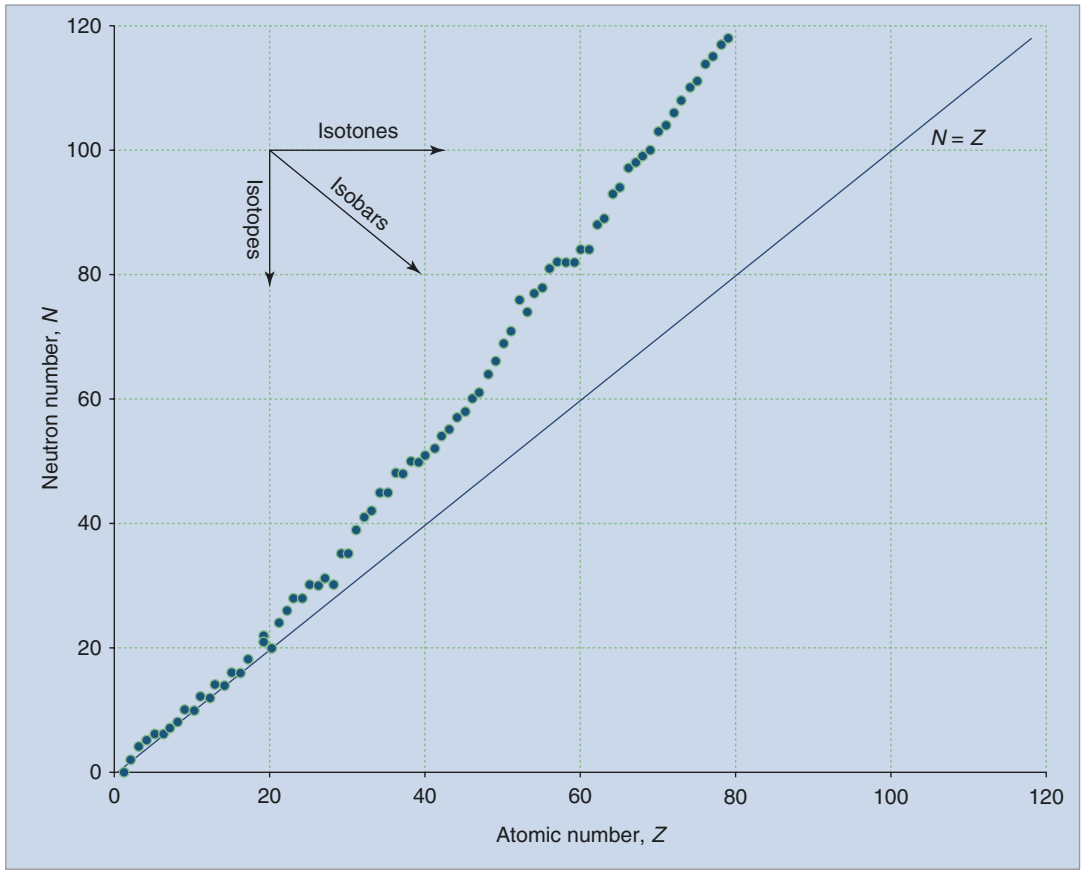

Fig. 1.6 Neutron number (*N*) versus atomic number (*Z*) for nuclides found in nature. The deviation of the stable nuclei from the line of identity (i.e. $Z=N$) is obvious and has been attributed to an increase in neutron number to moderate proton repulsion

'proton deficient', whereas nuclides lying below the line are 'neutron deficient'. Radioactive nuclei attempt to reach the stability by different modes of radioactive decay which is going to be discussed later. In the *N*/*Z* diagram (Fig. 1.6), the excess-neutron number is seen as the vertical distance between the stable nuclides and the diagonal $N=Z$ line. From the frequency distribution of stable isobars, isotopes and isotones, it has been concluded that even numbers of identical nucleons are more stable than odd numbers of the same nucleons (oddness of both *Z* and *N* tends to lower the nuclear binding energy).

1.5 Production of Radiopharmaceuticals

Nuclear medicine is a unique medical specialty that uses radiopharmaceuticals for diagnostic or therapeutic purposes. The diagnostic role is to interrogate valuable functional information about disease biochemistry not only on the cellular or subcellular level but also extend to extract molecular and genetic information. The other good facet of nuclear medicine is its ability to target but treat critical diseases using therapeutic radionuclides. Diagnostic radiopharmaceutical is a radioactive drug that is administered in a tracer quantity with no pharmacological effect on human body. Radiopharmaceuticals can be broadly classified into two different categories, single photon emitters that are commonly used in conventional gamma camera imaging examinations and positron emitter-based radiopharmaceuticals. The former class of compounds are commonly labelled with ^{99m}Tc solution eluted from molybdenum-99 generators. Radionuclides such as ^{201}Tl, ^{67}Ga, ^{111}In-, ^{123}I and ^{131}I belong also to the same class and have several diagnostic or therapeutic applications.

The other class of radiopharmaceuticals are based on labelling with positron emitters (such as ^{18}F, ^{11}C, ^{13}N, ^{15}O, etc.) and used in PET imaging applications such as oncology, cardiology and neurology. These kinds of radiotracers require medical cyclotrons and other essential infrastructures that include radiochemistry production facility, analytical and quality control equipments and other radiation detection and measurements devices. More details about medical cyclotron will be discussed later.

Since naturally occurring radioisotopes are relatively long half-lived and not handled well with human body, an artificially produced radioisotope which is cyclotron or reactor produced is being used. However, on-site radionuclide production is often required for positron emitter radionuclides with short half-lives such as ^{15}O (2.04 min), ^{13}N (10 min) and ^{11}C (20.38 min) which requires a local production to avoid loss of the material due to continuous decay. Since the radioisotopes need to be incorporated into some form of pharmaceutical, it should also be capable of being produced in a form which is amenable to chemical, pharmaceutical and sterile processing.

In March 2000, the fluorine-18-labelled glucose or F-18 fluoro-2-deoxyglucose (F-18 FDG) received Food and Drug Administration FDA approval for usage to evaluate and diagnose oncology patients although the first production was in 1978 for neurological applications. It is worth mentioning that first applications of FDG were focused on neurology and cardiac imaging, but its importance in oncology was realized on a later stage. F18-FDG limitations such as low specific targeting in PET imaging were an incentive for development of new PET tracers with special targeting capabilities. Newly developed PET traces are more specific and allow for imaging biological processes, such as angiogenesis, hypoxia, proliferation, apoptosis and many others. The expression of different receptors can be visualized like the somatization receptor 2, gene expression and dopamine and serotonin receptors in addition to large spectrum of potential cellular and molecular targets. Some of these approaches have found their way forward to the clinic, while others are still under extensive research and clinical evaluation.

1.5.1 Reactor Production Using Neutrons

Artificially produced radionuclide takes place in nuclear reactor by means of fission reaction or by using neutron flux to activate special target