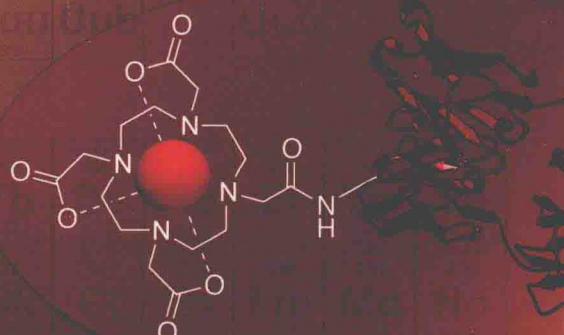
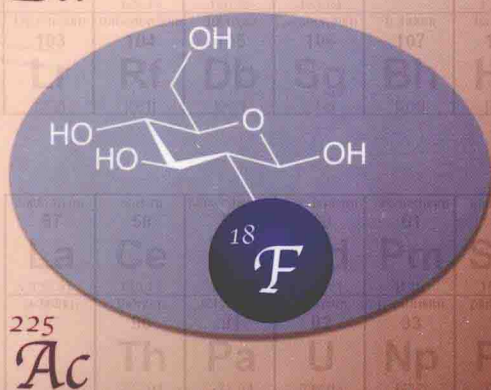
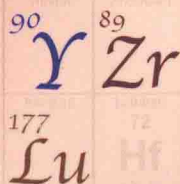
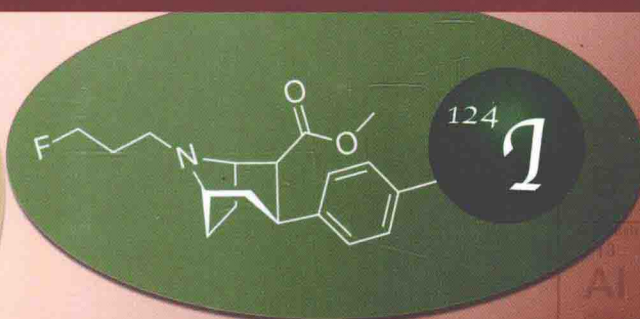
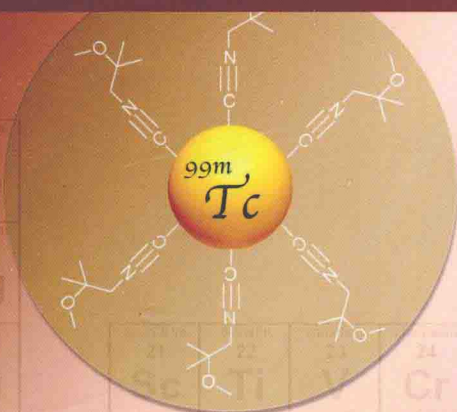
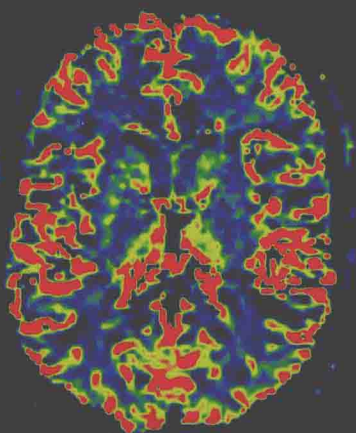


THE CHEMISTRY OF MOLECULAR IMAGING



Edited by
Nicholas Long • Wing-Tak Wong

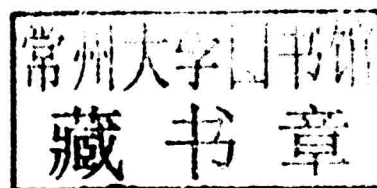


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THE CHEMISTRY OF MOLECULAR IMAGING

Edited by

NICHOLAS LONG
WING-TAK WONG



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THE CHEMISTRY OF MOLECULAR IMAGING

PREFACE

Since the emergence of molecular imaging over 30 years ago, it has arguably become one of the most rapidly growing fields of scientific research, spanning multiple disciplines such as medicine, pharmacology, chemistry, cell biology, and biomedical engineering. In contrast to conventional biomedical imaging by microscopy, where investigations are generally performed on excised tissues, molecular imaging includes *in vivo* techniques that provide visual and quantitative information on normal or pathological processes at the cellular or sub-cellular level. Most pertinently, these techniques have been designed to be noninvasive to the subject body. As a result, molecular imaging has revolutionised how one can monitor and characterise complex, dynamically changing molecular pathways within the living organisms, thus spurring its rapid development.

Nowadays, molecular imaging via Positron Emission Tomography (PET), Single-Photon Emission Computed Tomography (SPECT), Computed Tomography (CT) or Computed Axial Tomography (CAT), Magnetic Resonance Imaging (MRI), Optical Imaging, and Ultrasound (US) have already been regularly applied in the clinical environment as diagnostic tools. Each of these imaging modalities brings its own advantages and disadvantages, utilising a specific wavelength of electromagnetic or sound wave for excitation or detection. Due to their specific properties, imaging targets can range from cell surface markers or genes and their related products to a particular cellular or pathological process. Once the imaging target is identified, an appropriate imaging contrast agent is needed to be selected. This agent, mostly in the form of a small molecule, protein, or antibody, can bind to or enter the target environment upon injection into the subject body. Traditionally, imaging contrast agents are likely to be specific to one particular imaging mode, but in recent years, multimodality probes have been increasingly common as scientists strive for improvements in efficiency. For the first time in the area, we present a book dedicated to the *chemistry* of molecular imaging—other excellent texts and monographs describe the principles of biomedical imaging, focusing on the physics and mathematics behind the techniques.

Consisting of 16 chapters, this book is designed to provide (i) an in-depth discussion on the chemistry of various imaging contrast agents, probes, and biomarkers being applied in different imaging modalities and (ii) the methodology in which the agent becomes bound to its intended target and how it acts within *in vitro* and *in vivo* environments.

Following a general introduction to molecular imaging and the various imaging modes in Chapter 1, Chapter 2 lays out the principles with which imaging contrast agents achieve their labelling or bioconjugated status. In Chapters 3 to 7, radioactive isotopes employed in the nuclear medicine imaging techniques PET or SPECT are discussed, while agents for MRI are examined in Chapters 8 to 10. This is followed by the discussion of organic molecules, metal complexes, and nanoparticles being utilised in optical imaging, comprising Chapters 11 to 14. Chapter 15 details the applications of microbubbles in ultrasound, MRI, and more, and finally, the last two chapters of the book investigate the nature and properties of multimodality imaging contrast agents. Throughout this book, we hope to construct a comprehensive picture of imaging chemistry, with examples and illustrations, thus affording the readers a thorough understanding of the art of imaging contrast agent design.

We thank all the authors for the preparation of their individual contributions that really *make* this book, and their patience with the project. We hope that readers do enjoy the book and that it will prove useful and stimulating for their own research, helping to reinforce this burgeoning and exciting area of scientific discovery.

London and Hong Kong, June 2014

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CONTENTS

Preface	ix
List of Contributors	xi
1 An Introduction to Molecular Imaging <i>Ga-Lai Law and Wing-Tak Wong</i>	1
1.1 Introduction, 1	
1.2 What is Positron Emission Tomography (PET)?, 3	
1.3 What is Single Photon Emission Computed Tomography (SPECT)?, 6	
1.4 What is Computed Tomography (CT) or Computed Axial Tomography (CAT)?, 8	
1.5 What is Magnetic Resonance Imaging (MRI)?, 11	
1.6 What is Optical Imaging?, 15	
1.7 What is Ultrasound (US)?, 19	
1.8 Conclusions, 22	
References, 24	
2 Chemical Methodology for Labelling and Bioconjugation <i>Lina Cui and Jianghong Rao</i>	25
2.1 Introduction, 25	
2.2 Chemical Methods, 25	
2.3 Site-Specific Modification of Proteins or Peptides, 36	
2.4 Conclusions, 45	
References, 45	
3 Recent Developments in the Chemistry of [¹⁸F]Fluoride for PET <i>Dirk Roeda and Frédéric Dollé</i>	55
3.1 Introduction, 55	
3.2 Fluorine-18: The Starting Material, 56	
3.3 Reactive [¹⁸ F]Fluoride, 56	
3.4 The Radiofluorination, 58	
3.5 Labelling of Large Biological Molecules, 65	
3.6 Conclusions, 70	
References, 70	

4 Carbon-11, Nitrogen-13, and Oxygen-15 Chemistry: An Introduction to Chemistry with Short-Lived Radioisotopes	79
<i>Philip W. Miller, Koichi Kato and Bengt Långström</i>	
4.1 Introduction,	79
4.2 Carbon-11 Chemistry,	81
4.3 Nitrogen-13 Chemistry,	93
4.4 Oxygen-15 Chemistry,	98
4.5 Conclusions,	99
References,	99
5 The Chemistry of Inorganic Nuclides (⁸⁶Y, ⁶⁸Ga, ⁶⁴Cu, ⁸⁹Zr, ¹²⁴I)	105
<i>Eric W. Price and Chris Orvig</i>	
5.1 Introduction: Inorganic Nuclide-Based Radiopharmaceuticals,	105
5.2 Radiopharmaceutical Design,	107
5.3 Radiopharmaceutical Stability,	108
5.4 ⁸⁶ Yttrium Radiometal Ion Properties,	110
5.5 ⁶⁸ Gallium Radiometal Ion Properties,	116
5.6 ⁶⁴ Copper Radiometal Ion Properties,	120
5.7 ⁸⁹ Zirconium Radiometal Ion Properties,	123
5.8 ¹²⁴ Iodine Nuclide Properties,	125
5.9 Conclusions,	129
References,	129
6 The Radiopharmaceutical Chemistry of Technetium and Rhenium	137
<i>Jonathan R. Dilworth and Sofia I. Pascu</i>	
6.1 Introduction,	137
6.2 Technetium and Rhenium Radiopharmaceutical Chemistry,	139
6.3 Technetium and Rhenium(IV),	149
6.4 Technetium and Rhenium(III),	149
6.5 Technetium and Rhenium(I),	151
6.6 Imaging of Hypoxia with ^{99m} Tc,	155
6.7 Technetium and Rhenium Diphosphonate Complexes,	157
6.8 The Future for Technetium and Rhenium Radiopharmaceuticals,	157
References,	158
7 The Radiopharmaceutical Chemistry of Gallium(III) and Indium(III) for SPECT Imaging	165
<i>Jonathan R. Dilworth and Sofia I. Pascu</i>	
7.1 Introduction to Gallium and Indium Chemistry,	165
7.2 Gallium and Indium Complexes and Related Bioconjugates,	166
7.3 Auger Electron Therapy with ¹¹¹ Indium,	175
7.4 Prospects for ⁶⁷ Ga and ¹¹¹ In Radiochemistry,	176
References,	176
8 The Chemistry of Lanthanide MRI Contrast Agents	179
<i>Stephen Faulkner and Octavia A. Blackburn</i>	
8.1 Introduction,	179
8.2 Gadolinium Complexes as MRI Contrast Agents,	180
8.3 Minimising the Toxicity of Gadolinium Contrast Agents,	184
8.4 Rationalising the Behaviour of MRI Contrast Agents,	185
8.5 Strategies for Increasing Relaxivity,	188
8.6 Responsive MRI,	192
8.7 Conclusions and Prospects,	195
References,	195

9 Nanoparticulate MRI Contrast Agents	199
<i>Juan Gallo and Nicholas J. Long</i>	
9.1 Introduction,	199
9.2 T_2 Contrast Agents,	200
9.3 T_1 Contrast Agents,	203
9.4 T_1 - T_2 Dual MRI Contrast Agents,	208
9.5 Water Solubilisation,	209
9.6 Functionalisation and Surface Modification,	213
9.7 Applications,	216
9.8 Conclusions and Outlook,	220
References,	220
10 CEST and PARACEST Agents for Molecular Imaging	225
<i>Osasere M. Evbuomwan, Enzo Terreno, Silvio Aime and A. Dean Sherry</i>	
10.1 Introduction,	225
10.2 Diamagnetic CEST Agents,	226
10.3 Paramagnetic Chemical Exchange Saturation Transfer (PARACEST) Agents,	229
10.4 Responsive PARACEST Agents,	230
10.5 <i>In Vivo</i> Detection of PARACEST Agents,	233
10.6 Supramolecular CEST Agents,	235
10.7 LipoCEST Agents,	236
10.8 Conclusions,	241
References,	241
11 Organic Molecules for Optical Imaging	245
<i>Michael Hon-Wah Lam, Ga-Lai Law, Chi-Sing Lee and Ka-Leung Wong</i>	
11.1 Introduction,	245
11.2 Designing Molecular Probes for Bio-imaging,	246
11.3 Different Types of Organic-based Chromophores and Fluorophores for Bioimaging,	249
11.4 Mechanisms of Photophysical Processes and Their Applications in Molecular Imaging and Chemosensing,	258
11.5 Two/Multi-photon Induced Emission and <i>In Vitro</i> / <i>In Vivo</i> Imaging,	262
11.6 Time-Resolved Imaging,	266
11.7 Bioluminescence in Molecular Imaging,	267
11.8 Photoacoustic Imaging,	269
11.9 Conclusion and Future Perspectives,	270
References,	270
12 Application of <i>d</i>- and <i>f</i>-Block Fluorescent Cell Imaging Agents	275
<i>Michael P. Coogan and Simon J. A. Pope</i>	
Abbreviations,	275
12.1 Introduction,	275
12.2 <i>d</i> ⁶ Metal Complexes in Fluorescent Cell Imaging,	277
12.3 <i>f</i> -Block Imaging Agents,	285
12.4 Conclusions,	296
References,	296
13 Lanthanide-Based Upconversion Nanophosphors for Bioimaging	299
<i>Fuyou Li, Wei Feng, Jing Zhou and Yun Sun</i>	
13.1 Introduction,	299
13.2 Fabrication of Ln-UCNPs Suitable for Bioimaging,	299
13.3 Surface Modification of Ln-UCNPs,	304
13.4 <i>In Vivo</i> Imaging Applications,	306

13.5 Biodistribution and Toxicity of UCNPs, 316	
13.6 Future Directions, 317	
References, 317	
14 Microbubbles: Contrast Agents for Ultrasound and MRI	321
<i>April M. Chow and Ed X. Wu</i>	
14.1 Introduction, 321	
14.2 Classification of Microbubbles, 321	
14.3 Applications in Ultrasound Imaging, 324	
14.4 Applications in Magnetic Resonance Imaging, 327	
14.5 Applications beyond US Imaging and MRI, 330	
14.6 Conclusions: Limitations, Bioeffects, and Safety, 330	
References, 331	
15 Non-Nanoparticle-Based Dual-Modality Imaging Agents	335
<i>Reinier Hernandez, Tapas R. Nayak, Hao Hong and Weibo Cai</i>	
15.1 Introduction, 335	
15.2 PET/Optical Agents, 336	
15.3 SPECT/Optical Agents, 341	
15.4 MRI/Optical Agents, 345	
15.5 PET/MRI Agents, 348	
15.6 Conclusions, 348	
References, 350	
16 Chemical Strategies for the Development of Multimodal Imaging Probes Using Nanoparticles	355
<i>Amanda L. Eckermann, Daniel J. Mastarone and Thomas J. Meade</i>	
16.1 Introduction, 355	
16.2 Fluorescence-MRI, 357	
16.3 Near-Infrared Fluorescence/MRI, 359	
16.4 NIR-PET, 368	
16.5 Upconversion Luminescence, 372	
16.6 PET-SPECT-CT-MRI, 376	
16.7 Ultrasound, 382	
16.8 Magnetomotive Optical Coherence Tomography (MM-OCT), 383	
16.9 Photoacoustic Imaging, 384	
16.10 Conclusions, 384	
References, 385	
Index	389

AN INTRODUCTION TO MOLECULAR IMAGING

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1.1 INTRODUCTION

The aim of this book is to introduce the concepts of different imaging techniques that are employed for diagnostics and therapy and the role that chemistry has played in their evolution. The book provides a general introduction to the area of molecular imaging, giving an account of the role of molecular design and its importance in modern-day techniques, with an in-depth introduction of some of the probes and methodologies employed. This first chapter introduces the different types of imaging modalities currently at the forefront of imaging and illustrates some basic concepts underlying these techniques. It acts as a simplified background to set the scene for the following chapters, which will discuss the chemical properties of molecules and the role they play in different imaging modalities. For the interested readers, other textbooks are referenced that will provide more detailed information regarding the different techniques reviewed.

In life everything is incessantly changing. There is constant evolution in life sciences, evolution in the way problems arise, and evolution in the way they are solved. Diagnostics and therapy are both important, but as Einstein said, “intellectuals solve problems, geniuses prevent them.” The key challenge still remains to unravel the hidden knowledge within life sciences, which constantly challenges us with new diseases and mechanistic mutation of biological systems and pathways [1]. Again, as stated by Einstein, “once we accept our limits, we go beyond them.”

Molecular imaging aims to detect and monitor mechanistic processes in cells, tissues, or living organisms with the use of instruments and contrast mechanisms without perturbing their living system. Ultimately, it is a field that utilises molecular building blocks to bring solutions to problems by specialised imaging techniques that have matured into a large integrated field enveloped within various branches of science (Figure 1.1) [2]. In the area of modern-day imaging where technology is at its pinnacle, molecular design still holds a dominant role in the forefront of molecular imaging.

In the past, developments in contrast agents, probes, and dyes have brought about an era of creativity where new techniques, materials, and designs have flourished to form a concrete foundation resulting in today's achievements in diagnosis and therapy (Figure 1.2). The construction of better chemical molecules will continue to help us develop a more comprehensive picture of learning about life science. Figure 1.3 depicts a timeline in the development of the field [1–3].

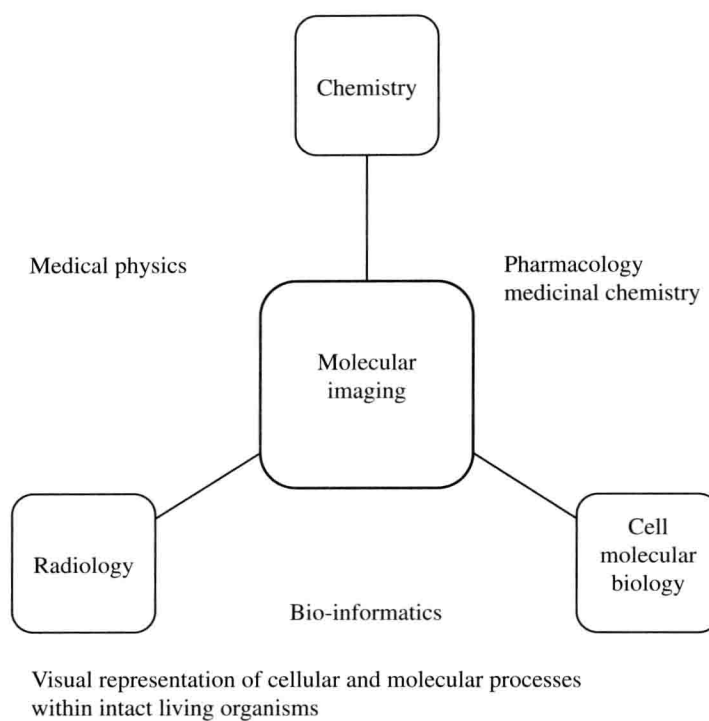


FIGURE 1.1 Types of multidisciplinary fields related to molecular imaging.

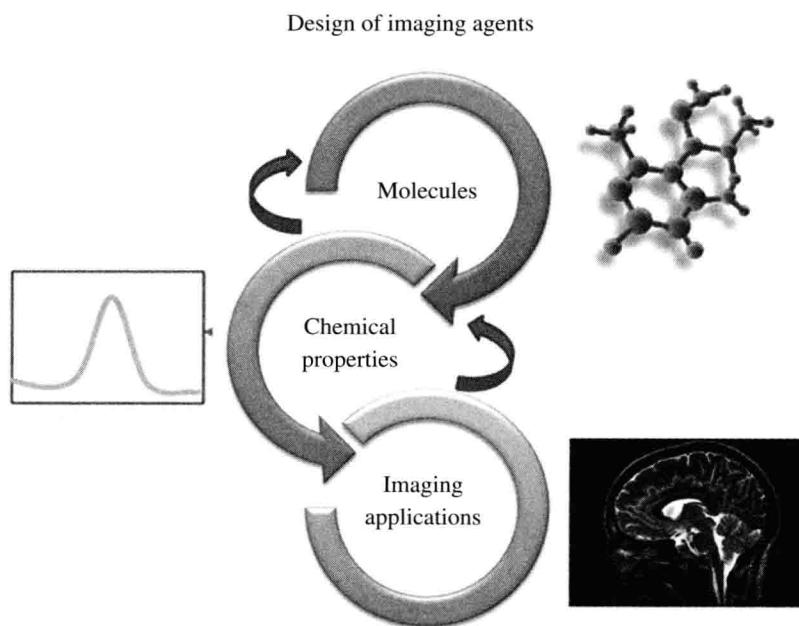


FIGURE 1.2 Diagram showing the links in the design rationale of imaging agents.

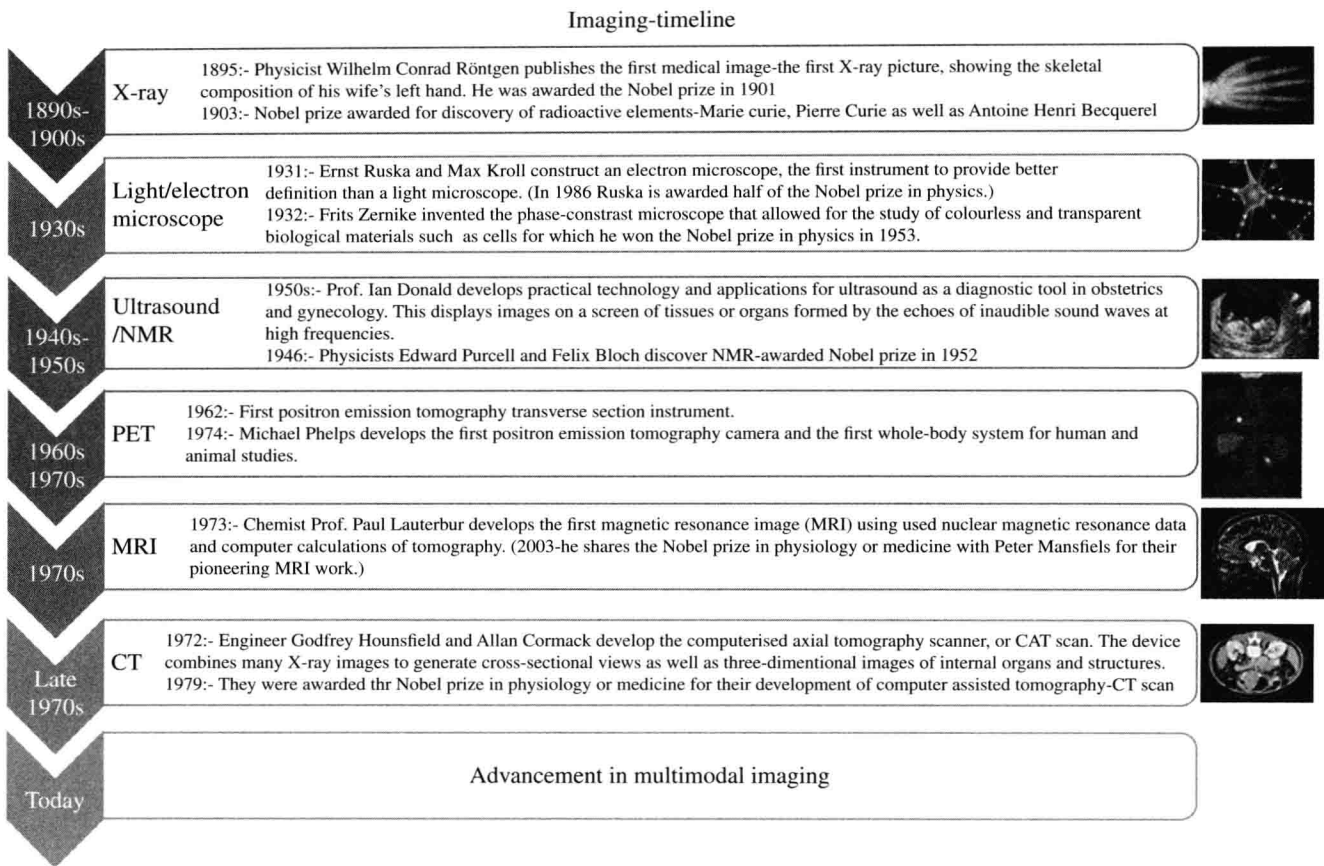


FIGURE 1.3 An approximate timeline showing the development of the different imaging modalities [1–3].

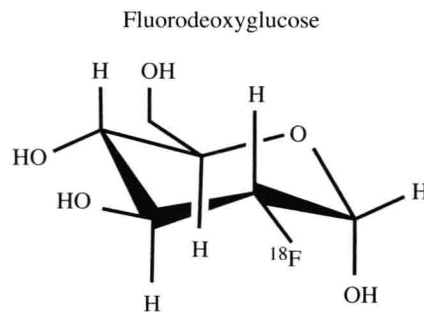


FIGURE 1.4 ^{18}F FDG, a typical contrast agent used in PET.

1.2 WHAT IS POSITRON EMISSION TOMOGRAPHY (PET)?

Positron Emission Tomography (PET) is a nuclear medicine tomographic modality and one of the most sensitive methods for quantitative measurement of physiologic processes *in vivo* [4]. This technique utilises positron-emitting radionuclides and requires the use of radiotracers that decay and produce two 511 keV γ -rays resulting from the annihilation of a positron and an electron. One of the most commonly used molecules is ^{18}F -labelled fluorodeoxyglucose (^{18}F FDG), which has radioactive fluorine and is readily taken up by tumours (Figure 1.4) [5].

1.2.1 Basic Principles

In PET, a neutron-deficient isotope causes positron annihilation to produce two 511 keV γ -rays, which are simultaneously emitted when a positron from a nuclear disintegration annihilates in tissue. PET imaging, unlike MRI, ultrasound, and optical imaging, does not require any external sources for probing or excitation; instead, the source is generated from radioisotopes and emitted from

but not transmitted through an object/patient, as in CT imaging [4–7]. Radionuclides are incorporated as part of a small metabolically active molecule to generate radiotracers such as ^{18}F FDG, which are then intravenously injected into patients at trace dosage for PET imaging. ^{18}F FDG is a favourable radiotracer because it is inhibited from metabolic degradation before it decays due to the fluorine at the 2' position in the molecule. Upon decay, the fluorine is converted into ^{18}O . There is generally a short period of time before accumulation of radiotracers into the targeted organs or tissues that are being examined, so it is important for radiotracers to have a suitable half-life—some commonly used radionuclides have very short half-lives. Some common radionuclides used in PET are ^{11}C (half-life ~20 min), ^{13}N (~10 min), ^{15}O (~2 min) and ^{18}F (~110 min). These are produced by a cyclotron, whereas ^{82}Rb (76 s), which is used in clinical cardiac PET, is produced by a generator [8–9].

When a radioisotope undergoes positron emission decay (positive β -decay), it emits a positron that travels through the tissue for a short distance ($\sim < 2\text{ mm}$) whilst decelerating by the loss of its kinetic energy until it collides with an electron. This results in back-to-back annihilation of γ -ray photons, which move in opposite directions and are emitted nearly 180 degrees apart before being detected by scintillators and a photomultiplier tube. This type of coincidence is a true coincidence event; to detect this, the detectors are designed like a ring that surrounds the patient during the scanning procedure. Several parallel rings form the complete detection panel of the PET system in a cylindrical geometry (Figure 1.5).

PET has relatively high sensitivity in detecting molecular species ($10^{-11} - 10^{-12}\text{ M}$), even though not all annihilation photons are used for image reconstruction because not all coincidences are true coincidences. A coincidence event is assigned to a line of response where the two relevant detectors are joined (detectors opposite to each other); this allows for positional information to be located from the detected radiation without any physical collimators. This is known as electronic collimation. There are four types of coincidence events in PET: true, scattered, random, and multiple (Figure 1.6). Only true coincidence, which is the simultaneous detection of two emissions from a single annihilation event, is useful. No other events are detected within this coincidence time-window.

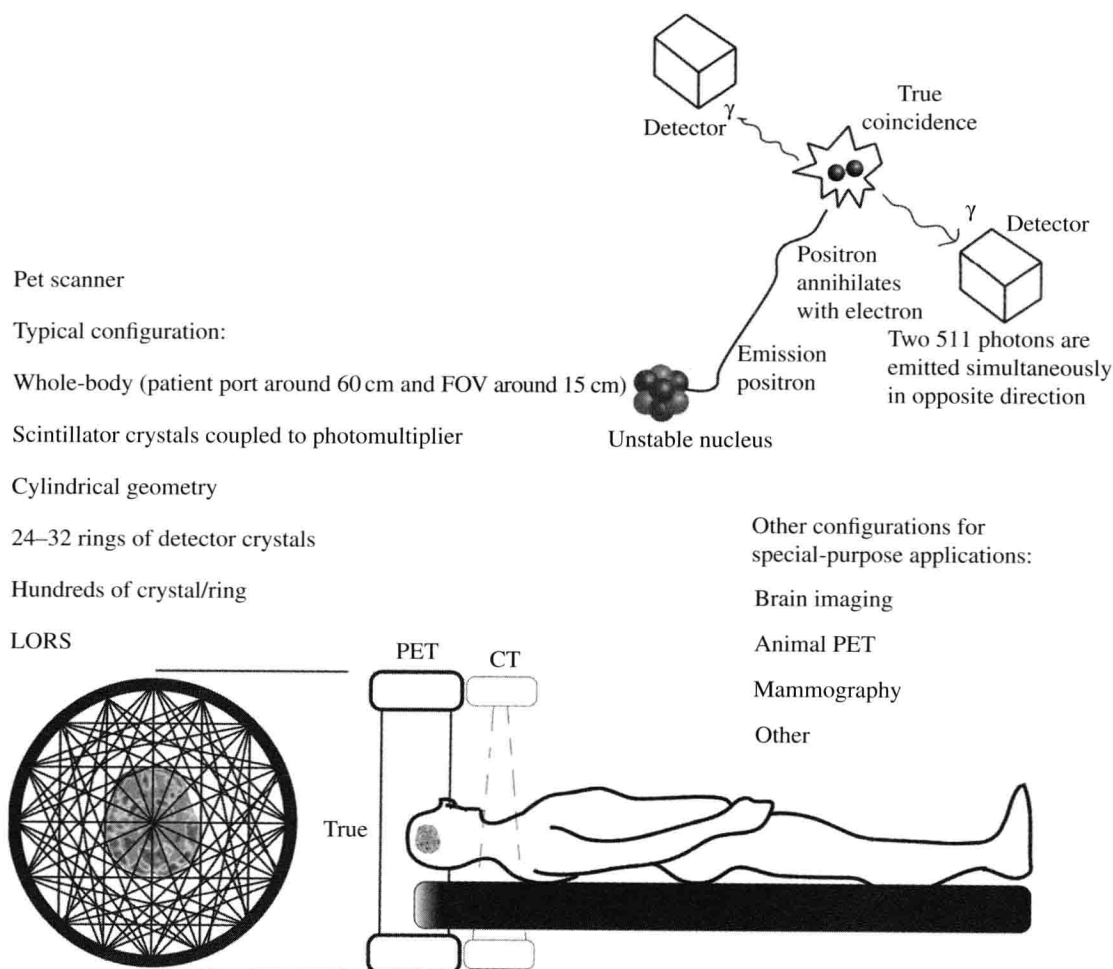


FIGURE 1.5 Typical configuration of a PET scanner.