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Review Article

Major Trends in Nuclear Medicine, a Critical Technology in Research and Treatment of Neurological Disorders

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Abstract

Nuclear medicine has established an irreplaceable role in biomedical research and disease management. Its unique capacity to visualize molecular events in vivo as they unfold provides diagnostic clarity into functional performance and the option for precise intervention in therapy. Over the last several decades nuclear medicine has evolved from a functional imaging modality using a handful of radioligands, into a modern specialty with the potential for molecular systems imaging. Driving this evolution has been a growing recognition of the need for a systemic understanding tailored to patient need that can support treatment decisions. Developments in radiochemistry, scanning capabilities, and targeted delivery have dominated the toolkit for imaging and treatment of a wide range of molecular processes and gene expressions in domains once considered 'undruggable'. Key innovations in technology include multimodal imaging systems like PET/MRI, advanced scintillator materials, and reconstruction free algorithms. Radioprobes and radiopharmaceuticals have also benefitted, both from enhanced radiochemical methodology for under-utilized radioligands and large molecules and from novel methods for cellular tracking and intracellular access. This review will explore the dominant pathways of this evolution and their potential for molecular systems imaging.

Key Words: radiopharmaceuticals; PET/MRI; radiogenomics; reporter genes; nanoparticles; antisense oligonucleotides; SPECT/CT; click reactions

Introduction

Over several decades, nuclear medicine has evolved from a functional imaging modality using a handful of radionuclides into a modern specialty that can be described more accurately as molecular imaging. Innovation in equipment and radiopharmaceuticals has yielded a wide array of advances significantly increasing the number and range of diagnostic and therapeutic applications and propelling clinical management [1-4]. As of 2021, for example, the World Nuclear Association documented more than 40 million procedures conducted each year worldwide, with a frequency in developing countries roughly 1/10 that of developed nations [5].

Underlying its growing clinical use is the ability of nuclear medicine to offer an unparalleled, non-invasive view of unlimited depth into intracellular processes, providing diagnostic clarity into cellular processes affecting functional performance and the option for precise intervention in therapy. Molecular imaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), notably provide for the spatiotemporal monitoring of biomarkers associated with key cellular processes in disease and tissue dysfunctions. By directly combining medium and long-range positron or gamma-emitting radionuclides to molecular markers it is possible to assess not only the distribution and concentration of biomarker molecules, but also the performance of the function associated with a given biomarker. In cases, the combination of such radionuclides with short range radioisotopes (alpha- or beta-particle emission) can transform the imaging radioligand into a therapeutic tool, a process termed theranostics [3, 6]

Affecting the growth of nuclear medicine is an increasing recognition of the multi-layered and heterogeneous nature of tissue dysfunctions [6]. Advances in genetic methods, gene sequencing and single cell transcriptomics, for example, clearly show the complexity and interconnectivity of tumor microenvironments and their molecular changes as cancer progresses. Dysfunctional heart conditions and degeneration of brain tissue present cases of even greater complexity [3,7,8]. To adequately assess such complex environments requires continual monitoring directed to a spectrum of processes and conducted optimally over various regions and time [6].

The need to monitor multiple processes has been a chief factor driving the current evolution in scanning technology and radiopharmaceutical procedures. Key to the acquisition of such multisource information is the ability to detect unique biomarkers with adequate spatial and temporal precision in a specific tissue domain of interest. This has placed a focus on the development of radiochemical procedures that can generate probes

uniquely associated with and targeted to a specific molecular process of interest together with the scanning technology needed to detect them. Imaging techniques, however, have been traditionally difficult to multiplex and hence incapable of probing large numbers of different biomarkers, posing a major obstacle to assessing multiple processes. While this obstacle has been addressed in part by technologies that measure other radionuclide features [9,10], it has also shifted developmental efforts to technologies that are capable of multi-modal data acquisition, such as hybrid MRI and PET scanners [11,12].

Together, such influences have shaped the advances that are heralding a coming era of molecular systems imaging. These advances have generally proceeded along three pathways: in the evolution of radiochemical probes and pharmaceuticals - from crude tools for assessing physiological function to probes for imaging previously inaccessible molecular processes; in the development of methods for precise cellular delivery and molecular targeting; and in the pursuit of multimodal scanners with increasingly refined spatiotemporal accuracy and computational proficiency (Figure 1).

This review will take up the innovations emerging along each of these routes and their contribution to systemic imaging and therapy.

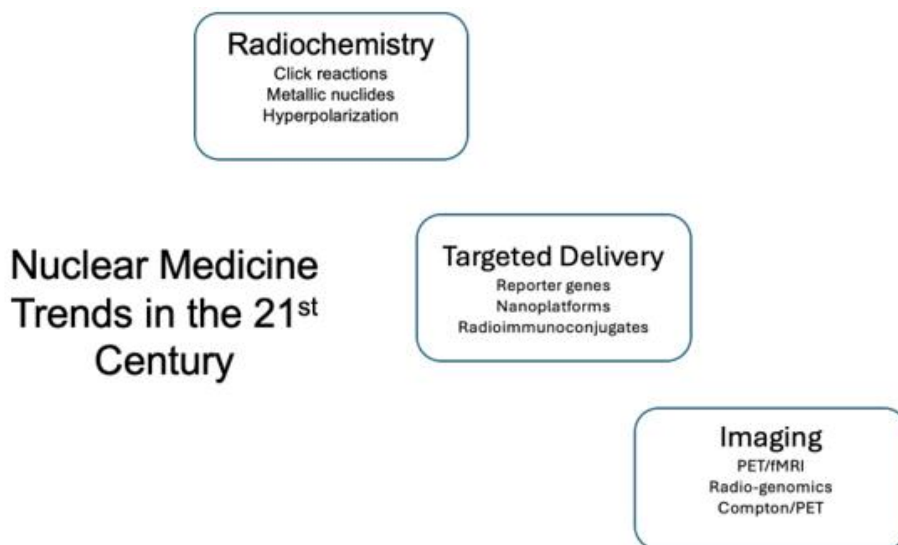

Figure 1: Major trends in nuclear medicine in the 21st century. Advances in nuclear medicine encompass three complementary pathways: radiochemical procedures for under-utilized radio nuclides and large molecules, targeting methods for delivery of radioligands to specific cells and tissues and to intracellular domains, and advances in imaging technology for multimodal and multiprobe monitoring.

[2] Radiochemistry for Probes and Pharmaceuticals

Early radiopharmaceuticals were dominated chiefly by small molecule radioligands [13]. This focus kept to a general conceptual model that viewed medicinal procedures in terms of accessibility and functionality. Small drugs could be made to ‘fit’ molecular pockets corresponding to binding or active sites of receptors and enzymes, thereby modulating the activity of these key proteins and affecting cellular function. By selectively binding to such site’s radiopharmaceuticals could quantify receptor distribution as well as influence relevant activity and provide for targeted therapy. Under this model, the so-called ‘druggable’ space was thus chiefly extracellular and/or limited to membrane bound extracellular receptors, leaving many other components of cellular processes, notably intracellular molecules, unexamined.

By contrast, many new types of molecular pharmaceuticals have become available in the last two decades, expanding the pharmaceutical repertoire and enabling the penetration of the ‘undruggable’ space. Included in this repertoire are various antibodies, peptides, and RNA molecules such as antisense oligonucleotides that are increasingly used to assess or modulate heretofore unmonitored and unmodulated processes and or molecular species [14,15]. Antisense oligonucleotides, for example, are increasingly used for silencing gene expression.

In contrast to small molecular drugs, these new molecular entities typically require new, i.e., previously unused or underused, radionuclides. Whereas classical approaches for radiolabeling of small molecule, drug candidates employed long lived isotopes, e.g., 14C (t1/2 5,730 yrs) and tritium-3H (t1/2 12.3 yrs), molar activities of these radionuclides were too low for large molecules like peptides, proteins, or antibodies. This resulted in the use of short-lived radionuclides like 11C (t1/2 of 20 minutes) and 18F (t1/2 of 110 minutes), which provided higher activity. Additionally, short lived radionuclides more closely matched biological half-life [13], thereby permitting live tracking of novel molecular species.

Increasingly, metallic radionuclides are being employed for labeling of larger molecules [16]. 68Ga (t1/2 of 68 minutes), for example, is employed for radiolabeling of peptides, since its half-life is even closer to the biological half-life of these molecules than radionuclides like 11C and 18F. For monoclonal antibodies, 89Zr and 64Cu are most often used, while for nucleic acid medicines 99mTc is usually preferred.

Peptides

Introducing a radionuclide such as 68Ga into a specific peptide typically proceeds via bifunctional chelating agents or prosthetic groups [6, 13]. Bifunctional chelators are metal-binding chelators that are first bound to a desired peptide and subsequently complexed with the radioactive metal. Early bifunctional chelators of 68Ga were made from 1,4,7,10-tetraaza-cyclododecane-1,4,7,10-tetraacetic acid, termed DOTA, which had also been developed for use with the radionuclide’s yttrium-90, copper-64/67, and later lutetium-177. Besides their use in diagnostic procedures, they have also been employed in theranostics. The peptide radiotherapeutic Lutathera, for example, is complexed with 68Ga as a diagnostic radionuclide, and subsequently bound to 177Lu, which functions therapeutically [13]. Besides DOTA, new bifunctional chelators have been developed that are amenable to kit labeling, such as NOTA (- 1,4,7-triazacyclononane-N, N′, N ″-triacetic acid - derivatives and their phosphate analogues) and acyclic (HBED - N, N′-Di(2-hydroxybenzyl) ethyle- nediamine-N, N′-diacetic acid, THP – tris (hydroxypyri- dinone)) chelators.

Due to the low molar activity attained in peptides with 14C, radio iodide is a frequently used alternate radionuclide, which binds to prosthetic groups and yields higher specific activities. Among the iodine isotopes most often used are: 123I (t1/2: 13 h; SPECT), 124I (t1/2: 4 days; PET), 125I (t1/2: 59 days; SPECT, in vitro bioassays), 131I (t1/2: 8 days; SPECT, radiotherapy). Radiolabeling with iodine is usually carried out on tyrosine (Tyr) or histidine (His) residues, where an aromatic Tyr or His proton is replaced by the electrophilic radioiodine (I+). Occasionally, 18F is used to label peptides and small protein-based tracers, due to its appropriate half-life and favorable economics. Because the chemical procedures for labeling are difficult to carry out, however, it is a less frequently used option.

Antibodies and antibody fragments

Various labeling procedures have been used to bind radionuclides to antibodies [17,18]. Among these are radiometals complexed with chelators or binding to prosthetic groups with Iodine, procedures similar to methods used for peptides. In cases, dual labeling with radionuclides and fluorescent probes is reported [3]. For radiolabeling of monoclonal antibodies, 89Zr (t1/2: 78 h) and 64Cu (t1/2: 13 h) (for PET) and 111In (t1/2: 168 h) (for SPECT) are often employed in diagnostic imaging. Tritium labeling is also frequently used to monitor the pharmacokinetic behavior of candidate antibodies preclinically.

Complicating the use of radiolabeled antibodies, however, is a complex pharmacokinetic pattern, which is due to their large size, long circulating half-life, and immunogenic responses. These complications make accurate predictions about the distribution of monoclonal antibodies difficult to achieve [13]. Additionally, candidate antibodies have the potential for generating immunogenic responses, resulting in the production of anti-drug antibodies. Such antibodies, when generated to the candidate antibody drug, reduce the drug's efficacy and may in cases completely neutralize its intended therapeutic effects. Nonetheless, the ability of radioimmunotherapies to deliver high radiation doses with precision make them attractive therapeutic options.

Oligonucleotides

Oligonucleotides are increasingly used therapeutically to modify intracellular processes or gene products, frequently through gene silencing, but also by gene activation or modulating splicing assembly stages [14,19]. For nucleic acid- based medicines, radiolabeling requires that several factors be considered to optimize signal level and selectivity.

Each of the three isotopes primarily used for radiolabeling of oligonucleotides, 3H, 14C, 35S, present difficulties for imaging [13], which need to be considered in the selection of radio nuclide. For instance, the relatively long terminal elimination half-life of oligonucleotides, in some cases 30–60 days or even longer, poses a significant disadvantage affecting considerations of metabolic stability. Additionally, 14C typically needs to be incorporated in the C2 pyrimidine position to achieve sufficient activity for detection. In the case of tritium, the C-8 position of purines may undergo tritium-hydrogen back-exchange with the resulting formation of tritiated water, especially under alkaline conditions.

Besides long-lived radionuclides, short life span radionuclides have also been used for radiolabeling of oligonucleotide pharmaceuticals. Among these 99mTc (t1/2: 6 h) is the most frequently used radionuclide for diagnostic applications, particularly for applications using SPECT- based imaging. Binding methods for 99mTc employ either bifunctional chelators or prosthetic groups, as with peptides.

Specialized reactions

The development of biorthogonal reactions known as click reactions [13,20-23], which minimally disrupt cellular processes, has enabled the selective, rapid, and relatively straightforward binding of radiolabel to biological compounds. The earliest of these reactions, known as the Staudinger reaction, involved the reaction of an azide with a phosphine. However, its slow reaction kinetics led to the current inverse electron-demand Diels–Alder (IEDDA) ligation between tetrazine (Tz) derivatives and trans-cyclooctene (TCO). Current developments continue to search for an optimal balance between stability and reaction rate, as more rapidly binding reactions are also more prone to decomposition.

[3] Targeting and Delivery

The development of novel methods for precisely targeting drug delivery or selectively monitoring cellular processes have greatly expanded the domain accessible to diagnosis and therapy. Targeted radiopharmaceutical delivery with imaging has thus become a pillar for therapeutic intervention and key to obtaining critical in vivo data on the functional well-being of specific molecular processes altered by disease. In principle, such precision contains the latent possibility for monitoring and treating multiple processes affected by disease and hence of attaining to a systemic and personalized level of care.

Targeting methods can vary widely to accommodate a range of objectives and can include procedures for overcoming physical and chemical barriers, identifying and tracking select cells, accessing and monitoring intracellular processes, and modulating genetic expression, among others.

Overcoming physical barriers

Among the new methods are procedures for accessing specific tissues, which have been shown to successfully surmount physical and/or biochemical barriers to the entry of radiolabeled compounds. For example, a fundamental limit on the use of radioligands in the brain is the blood brain barrier (BBB). Accordingly, radioligands must be designed to incorporate features enabling the ligand to overcome this barrier. For many such compounds this can be achieved by using radioligands of small molecular weight, generally not exceeding 500 daltons. Because many of the new radiopharmaceuticals are larger than this, however, novel procedures are required for the radioligand to bypass the BBB.

Recent developments in nanotechnology, particularly, afford platforms that can cross the BBB and can carry larger molecular weight radioligands [24]. By manipulating the physical and chemical properties of these nanoparticles (NPs), radiopharmaceutical agents can be attached or loaded. For example, organically modified amino- functionalized silica NPs have been used to carry the gene encoding GDNF to striatal cells [24]. Currently, there is a large and growing number of different NP platforms, which have been used to treat such diseases or dysfunctions as pancreatic cancer, diabetic nephropathy, and myocardial infarction [24,25].

Besides nanoparticles, viral vectors are also increasingly used to deliver radioligands. Viral vectors for neurological tissue now include a broad spectrum of vehicles that have been derived from multiple viral classes. Among these are included retrovirus, lentivirus, adenovirus, herpes simplex virus type 1(HSV-1) and AAV vectors, with recombinant adeno-associated virus (rAAV) vectors generally finding more frequent use [26,27]. Recombinant AAV vectors feature numerous advantages. They are nonreplicable, non-pathogenic, and do not integrate into the host genome [14]. Pre-clinical in vivo AAV gene therapy studies, for example, have been carried out for Huntington's Disease that have utilized both shRNA and miRNA approaches [27].

Cell Specific Identification and Tracking

Radioimmuno-diagnostic or radioimmuno-therapeutic tracers afford the opportunity to pinpoint molecular and cellular species and are typically constructed from monoclonal antibodies and their derivatives. When combined with radionuclides, it is possible to obtain critical information on antigen quantitation, heterogeneity, and kinetics in real time. A wide variety of radionuclides are currently available, including actinium-225 (225Ac), astatine-211 (211At), bismuth-213 (213Bi), indium-111 (111In), iodine-123 (123I), iodine-124 (124I), iodine-131 (131I), lead-

212 (212Pb), lutetium-177 (177Lu), technetium-99m (99mTc), copper-64 (64Cu), gallium-68 (68Ga), yttrium-86 (86Y), yttrium-90 (90Y), and zirconium-89 (89Zr). The choice of radionuclide is based on several properties that are dictated by need and objective, which can include emitter type, energetics, and half-life, as well as tissue characteristics. Efficient radiolabeling is often carried out by binding the radionuclide to a bifunctional chelator, which possesses a binding site for the radionuclide and a linker that can attach a nucleophilic group to a carrier antibody [6,13,28].

Targeting extracellular proteins

Extracellular proteins can, in cases, precipitate disease symptoms. For example, much evidence reveals the involvement of mutant huntingtin protein (mHTT) in extracellular events that influence the severity, symptomatology, and propagation of Huntington's Disease across cell systems. Among the various mechanisms proposed for influencing these features are effects on brain related immunogenicity, a seeding pathology that amplifies mHTT mobilization, and prion like activity [12]. The extracellular antibody targeting of these aspects has the advantage of requiring simpler protocols than those needed for cell entry, such as directly exposing the immune system to the mutant form of HTT, which makes it a desirable protocol objective.

Targeting free/extracellular mHTT can be carried out by passive or active immunization. In active immunization the immune system is exposed to an exogenous antigen to elicit an adaptive immune response. This process has the advantage of generating an acquired immune response that is relatively long lasting. In passive immunization exogenous antibodies are introduced to suppress antigenicity. While passive immunization generates a relatively rapid response, the introduction of exogenous antibodies lasts for a much shorter interval than active immunization.

In vivo cell tracking using direct cell labeling

Radioligand imaging using single photon emission computed tomography (SPECT) or positron emission tomography (PET) has several advantages over other imaging modalities for cell tracking because of its high sensitivity and whole-body quantitative imaging capability with clinically available scanners. For cell tracking, ex vivo direct cell radiolabeling, that is, radiolabeling cells before their administration, is the simplest and most robust method, allowing labeling of any cell type without the need for genetic modification [29].

Cells are usually radiolabeled ex vivo by incubation with a radiotracer, followed by injection of the radiolabeled cells into the imaging subject. In vivo PET or SPECT imaging can then be performed over time to assess the distribution of the cells. The radiolabeling mechanism can vary depending on the type of probe. Cells can either be radiolabeled using radiotracers designed to bind to the cell membrane or specifically designed to penetrate the membrane where they become trapped intracellularly. A limitation of direct cell labeling is that the imaging time window of this technique is restricted by the half-life of the radionuclide used, with progressive loss of signal strength. Direct cell labeling can also be affected by the efflux of the radiotracer from the radiolabeled cells in vivo. Hence, ideal, direct cell labeling agents should facilitate fast, efficient (high yield) cellular uptake, with high cellular retention of the radionuclide, while not affecting cell viability. Furthermore, they should allow imaging over relatively long periods of time if needed for a given imaging application. Accordingly, long-lived radionuclides (such as 111In, 89Zr) are usually preferred.

Most compounds used for direct cell radiolabeling are "radiometal−ionophore" complexes, which consist of a radio- metal and an ionophore, a ligand which binds to a metal ion reversibly for transport across lipid membranes [30] The resulting radiometal complex is sufficiently hydrophobic to allow passage across cell membranes but insufficiently stable to remain intact within the cell. Once inside the cell, the radiometal can be captured by intracellular proteins or other macromolecules [31] resulting in trapping of the radionuclide−and generation of a radiolabeled cell. Despite the successful use of ionophore ligands for transport of label into cells, the potential radiotoxicity associated with delivery of ionizing radiation intracellularly can pose a danger to cell health and viability. One approach to mitigating this danger is by radiolabeling cells on the cell membrane, further away from the nucleus, with the prospect of reducing Auger-electron toxicity originating from some nuclides.

Accessing and monitoring intracellular processes

Reporter genes

A key question has been that of which sets of protein interactions mediate particular cellular processes and how these become dysfunctional in disease. Increasingly, reporter gene imaging has been used for introducing radiolabeled imaging agents into cells to assay the activity of specific cell processes. When introduced into target cells, reporter genes produce a protein receptor or enzyme that binds, transports, or traps a subsequently injected imaging radioprobe, which becomes the contrast agent [29,32]. Currently, recombinant adeno-associated viral (AAV) vectors are the most frequently used delivery method for effective cell transduction and stable expression of a modified gene.

Several gamma-emitting radionuclides are available for radiolabeling injected agents, ranging from small molecules and peptides to antibodies, nanoparticles, and cells. In the clinic, the most widely used radionuclide is 99mTc, which has a moderately short half-life (6 hours). This is long enough for convenient synthesis of radiotracers (while not imposing prolonged radiation exposure to the subject), offers favorable emission properties, and has convenient production methods. Because of its metallic character, 99mTc radiotracers employ coordination complexes to bind the radionuclide with a chelating agent [6,13].

Despite significant limitations initially with the biodistribution and specificity of reporter gene products, there is a growing repertoire of available reporter genes that could be used for tracking cellular processes and protein-protein interactions within them. Following the advent of standardized genetic editing techniques, researchers have isolated a large collection of reporter and modifier proteins (RPs and MPs, respectively) from a variety of species that have since been instrumental in characterizing a wide range of biological processes [32]. For example, RPs are frequently used to tag endogenous proteins or to track the behavior of individual cells in vivo.

Antibody fragments

An especially promising avenue employs radiolabeled antibody fragments as reporter probes [32,33]. Antibody fragments retain the ability to target specific protein domains that may be critical in mediating protein-protein interactions and are more accessible to restricted sites than whole antibodies due to their smaller size. Their mode of action is to suppress protein activity by directly binding to functional domains, thereby interfering with the ability of aberrant proteins to interact with binding partners; or to redirect the pathogenic protein to clearance processes.

Research with intrabodies has been conducted for several decades. The first intrabodies for functional sites on huntingtin protein, for example, were generated from a human spleen, single- chain variable fragment (scFv) phage library [34]

Modulating genetic expression

Nucleic acid therapies for chronic diseases typically adopt one of two approaches, interference with protein specific, RNA translation mechanisms or direct modification of the genes of protein products. RNAi approaches employ short-interfering RNAs (siRNA) or microRNAs (miRNA) [35]. These molecules target mature mRNA in the cytosol, triggering degradation through the RNA-induced silencing complex and

eventually reducing protein expression [36]. Gene therapy, on the other hand, entails the use of altered genes (termed transgenes) to treat and prevent disease [37]. Nucleic acid-based approaches have employed gapmer anti-sense oligonucleotides (ASO) and anti-sense oligonucleotides [14,38]. The former are a string of nucleotides with a central unmodified region flanked by modified nucleotides. Such radiolabeled drug oligonucleotide probes can provide a reliable quantitative tool for distribution, mass balance, and metabolite profiling studies [39].

To induce expression, several cancers and/or tumor-specific promoter's systems have been developed. Tumor-specific promoters that are over-expressed in the tumor can induce specific therapeutic genes, enhancing their localized activity [40].

[4] Advances in Technology

Despite the current plethora of candidates, imaging procedures for nuclear medicine have proven difficult to multiplex, making the development of scanners capable of imaging molecular systems an ongoing effort. Recent studies into the use of energy resolution for distinguishing radionuclides have achieved only limited success, typically with two or three nuclides. Complicating these efforts are inherent limits on signal resolution, particularly in cases in which the ratio of dose to target object is small and where contamination from other tracers and Compton scattering significantly impact signal resolution [9,10,41].

Accordingly, most innovation in scanning technology to date has occurred in the domain of multimodal instrumentation, where various information modes are combined with that of nuclear imaging, as in hybrid PET and MRI. One outcome of this focus, for example, has been the emergence of radiogenomics [42,43]. In this methodology magnetic resonance spectroscopy (MRS) and PET imaging data are correlated with data from genome sequencing to yield correlation matrices used to guide personalized treatments without the need for pathology specimens.

Besides such multimodal scanners, improved characterization of cellular processes has helped to clarify areas where advances in nuclear medicine technology can assist diagnosis and therapy, including enhanced monitoring of the dynamics and quantitation of radioligand probes and radiopharmaceutical delivery. Among these are improvements in signal acquisition and system sensitivity and stability, as well as computational proficiency.

Multimodal technologies

PET/MRI

Combining PET and MRI into a single device that can acquire both datasets simultaneously has been an objective for several decades [11,12,44,45]. Simultaneous acquisition provides for the temporal correlation of data sets, which, given the dynamic nature of PET measurements, can undergo substantial change during the interval between dataset readings and must be accurately adjusted for in co-registration procedures.

The techniques of PET and MRI provide complementary types of information [11,12]. On the one hand, PET can yield insight into the physiological and metabolic features of patient tissue by tracking the distribution of molecules in vivo using radionuclide positron emission. Because of the nature of the emission, however, spatial resolution is limited, restricting the ability of PET to localize events that radio-tracers are illuminating. MRI, on the other hand, can yield precise anatomical and structural imagery that has superior contrast in soft tissue. The evolution in modern

MRI techniques has additionally exploited other sources of endogenous contrast to monitor function (functional MRI), physiology (diffusion tensor MRI), and composition (magnetic resonance spectroscopy) [46,47], expanding the available repertoire of hybrid instrumentation.

For multimodal imaging, significant changes in instrumental design have been required. A chief obstacle in PET imaging has involved magnetic field interference on the performance of photomultiplier tubes. In early modifications this obstacle was addressed by integrating PET detectors in specialized MRI scanners such as split- magnet or field-cycled units [48,49]. Later and more successful modifications have been achieved with the development of MRI-compatible photon detectors that could be placed inside the magnet's bore. Avalanche photodiodes, for example, were capable of functioning in the presence of even ultra-high magnetic fields [12] allowing their use with MRI in brain imaging. Solid-state photomultipliers (SSPM), silicon photomultipliers (SiPMs) or multi-photon pixel counters (MPPC)) are now the photon detectors of choice for hybrid units. Most PET systems use lutetium oxyorthosilicate (LSO) or lutetium yttrium oxyorthosilicate (LYSO) as scintillator materials [3]. For MRI imaging, a major hurdle to combined modalities involved the maintenance of magnetic field homogeneity with the placement of PET components inside the MRI scanner bore. To overcome this hurdle only non-magnetic versions of working components are currently used. Additionally, electromagnetic interference in the radiofrequency range is minimized and the shielding designed to avoid currents that occur due to changes in the magnetic field gradient during scanning.

MRI as a structural framework for PET in combined systems

Improved spatiotemporal accuracy of PET estimates has been achieved through the use of MRI data to provide a structural framework on which the simultaneously recorded PET signal is distributed. Combining these with adjunct computational analyses such as time of flight localization and principal components analysis has been shown to further enhance spatial resolution.

Time of flight localization: Time of flight information (TOF) narrows the spatial location of positron emission, thereby improving the spatial resolution of emitted signals by compensating for positron travel time. In principle, time of flight computations rest on the detection of the physical annihilation of the positron and the generation of two 511 kEV photons that are separated by 180 degrees. The computational steps are straightforward and use the following equation:

$$D1 - D2 = (t1 - t2) \times c$$

where c is the speed of light and t1 and t2 are the recorded detection times. Uncertainty in the time measurements is incorporated in computations by use of TOF probability distributions.

Time of flight technology has undergone a significant improvement in localization capability due to the evolution in silicon photomultiplier tubes and the use of scintillators with improved performance [3,4], such as those containing lutetium oxyorthosilicate or lutetium yttrium oxyorthosilicate. With these materials, the current coincidence time resolution is listed at 200 pico-seconds, while experimental systems have been able to achieve nearly double that at 100 pico-seconds. Given ongoing developments, time of flight determinations may eventually prove sufficient for clinical localization, obviating the need for reconstruction algorithms [3,50].

Quantitative evaluation of PET data using MRI

Attenuation correction: Attenuation correction in procedures such as PET/CT scanning can be directly carried out based on photon attenuation in the tissue medium and its conversion via 512 keV linear attenuation coefficients. MRI based attenuation correction in combined PET/MRI, however, is challenging due to MRI datasets that are based on proton density and relaxation rates rather than on electron density. The latter must therefore be inferred to provide for PET attenuation. Accordingly, several methods have been developed to correct for tissue attenuation in PET/MRI [51–53].

One class of methods employs PET emission data to estimate attenuation data via iterative joint estimation, based on maximum likelihood (ML)

[51]. Other procedures derive attenuation data from MRI based information. These may use precompiled atlas pairing, which relates MRI and PET images via an algorithm, or direct imaging using Dixon, ultra-short echo (UTE) or zero echo time (ZTE) methods that avoid use of complex imaging registration and processing procedures. In the direct method, individual patient MR images are segmented into several tissue classes with individual tissue classes assigned a constant or continuous attenuation factor value. In the direct 2-point Dixon method [52] two different echo times are used based on the different precession rates of fat and water molecules.

This method, however, does not compensate for lung and bone readings, which thus distorts the attenuation correction. An alternative and frequently employed approach is the use of an ultra-short time echo (UTE) sequence, with acquisition times approximately 100-fold shorter than echo times typically used in T1-weighted MR images [53]. Using these techniques, for example, a recent region of interest analysis of inflammation in Huntington’s Disease with the tracer 11C-PBR28, showed statistically significant differences between manifest patients and controls in the pallidum and putamen regions of the brain [46].

Principle Components: Objective methods for PET typically treat voxels as if they represented independent or uniformly correlated measures throughout the brain, an unwarranted presumption given the brain’s known structural variation. Principal components analysis assists in accounting for this variation, reducing the original dimensionality of imaging data to a suite of low dimensional contributing features. The magnitude of a feature’s contribution to signal variation within a PET image can then be assigned to individual component axes.

In practice, data are typically transformed into a (n x v) data matrix where n is the number of image observations and v is the number of voxels. Principal components and their variance are obtained from the eigenvectors and eigenvalues, respectively, which are determined from the correlation matrix of the data matrix [54]. One of the important features of PCA is to provide quantitative coordinates for the observations on uncorrelated axes. The coordinates are then quantitatively related to attributes of the individuals. In a principal components study of Huntington’s disease subjects, for example, atrophy of the caudate was found to be a significant contributor to the total correlation as a function of the stage of disease progression [46]. The identification of this component - along a first PCA axis - was sufficient to classify HD subjects according to their disease status.

Image-based radiotracer AIF estimation and radiotracer delivery quantitation: Accurate PET quantification requires an input function to compartment models used for estimating parameters of interest for normal and pathologic changes in tissue function or metabolism. For example, a plasma time–activity curve of tracer delivery to the tissue is typically derived from a radiotracer arterial input function (AIF) [12]. Because the determination of the AIF involves radial artery catheterization, however, its use is limited in routine PET studies. Accordingly, noninvasive image-based techniques have been proposed.

One such method is a derivation of the AIF determined from blood vessel, regions of interest, obtained after administering a tracer. Correctly defining the region of interest over a vessel together with confounding effects can be challenging using PET images only, however. This drawback has been addressed and circumvented in a combined scanner, where coregistered and simultaneous MRI anatomic images can be used to accurately measure the position and size of the vessels of interest. With coadministration of both MRI contrast and PET tracers, MRI can also provide information about the dynamics of bolus delivery to the tissue of interest and assess any local changes in blood flow, thereby reducing the effects of bolus delay and dispersion in the AIF estimate [55].

Dynamic acquisition of uptake and elimination of tracer over time additionally allows for kinetic analysis of data sets, which may be clinically relevant. With combined PET/MRI systems, kinetic models can be developed that use both dynamic PET and dynamic MRI data for parameter estimation. These systems also provide for non-invasive estimation of the input function, which is needed for kinetic modelling.

MRI based PET motion correction

Simultaneous PET/MRI enables spatial and temporal correlation not accessible by sequential or parallel methods. This is significant in neurologic and psychiatric diagnoses, where MRI is typically a firstline modality and many brain PET tracers are now available. Typical cross correlation can correct spatial and temporal changes that are due to physiological or subject motion, anatomical variability, or dynamical event transitions [47]. However, most of these methods require a relatively unobstructed view of the optical sensors from outside the scanner—which is difficult to achieve in an integrated PET/MRI scanner due to the presence of the radiofrequency coils.

For more conventional acquisition methods, motion estimates with very high temporal resolution (e.g., every 20 ms) can be obtained using embedded navigator pulses. Their use to correct PET data in very short frames are especially important for performing motion correction in the early phases of a dynamic PET study, when frames as short as 1 s are often used to sample the radiotracer AIF.

PET/fMRI

Functional magnetic resonance imaging (fMRI) evolved to capture dynamic brain events with high spatial precision. Recent combined sensing using fMRI with PET have begun to link molecular and subcellular information to functional, systems level dynamics, with the prospect of offering novel perspectives into the brain’s function and dysfunction [56]. In Parkinson’s disease, for example, simultaneous PET and MRI signaling can relate complex dopamine mechanistic responses such as the rates of release or transport (PET) with neuronal activation (fMRI) [57].

PET/Task based and resting state fMRI

Increasingly, non-invasive, task-based regimes are employed to monitor the functional consequences of perturbing the brain’s network organization, including repetitive transcranial magnetic or direct-current stimulation, that could be used to activate or inhibit select areas of the cortex, in conjunction with PET imaging [56].

From its origins in the 1990’s, resting state fMRI has evolved into a powerful and spatially accurate tool for assessing the functional organization of the brain. The early detection of resting state networks by Biswal et al. [58] used a standard 1.5 T clinical scanner equipped with a three-axis head gradient coil that obtained images every

250 ms. Under these relatively moderate scanning conditions, they showed the presence of a high degree of temporal correlation in brain activity of the sensorimotor cortex and several other regions associated with motor function in resting patients. Current procedures typically employ 3.0 T for better spatial resolution and use parallel imaging for fast data access. In special cases, high strength magnetic fields (7 T) and big data acquisition procedures are used [59]. Use of resting state fMRI has revealed, for example, that brain connectivity of the left middle frontal and pre- central gyrus, and right post central gyrus with the medial visual network is reduced in premanifest and manifest HD as compared to controls [60].

PET/MRS

Magnetic resonance spectroscopy (MRS) is a non-invasive technique used for in vivo measurement of levels of unique molecular species, such as total choline (tCho), a marker of neoplastic proliferation [61,62]. In MRS the magnetic field experienced by a particular nucleus is affected by the motions of its nearby electrons, in contrast to MRI where the magnetic moments of nuclei become oriented relative to the direction of the applied field. Hence, differently sited nuclei experience slightly different applied

fields and resonate at slightly different frequencies, generating unique fingerprints for different compounds. Single-voxel MRS methods have been used to compare levels of such compounds in tumors and in adjacent or contralateral normal brain tissue in neurodegeneration.

PET/MRS combined modalities offer the prospect of simultaneous molecular assessment by two independent signal sources. The use of MRS imaging (MRSI), however, has generally been hampered by its low sensitivity in vivo. Recent developments using hyperpolarized MRS have addressed this obstacle, enabling wider use of combined

PET/MRS. With hyperpolarization signal strength can be increased by many orders of magnitude. PET/MRS studies with a combined hyperpolarized, 13C-labeled pyruvate substrate have confirmed its capability for imaging tumor metabolism [63,64].

Multiple hyperpolarization technologies have been developed for biomedical applications [65], including dissolution Dynamic Nuclear Polarization (d-DNP), Parahydrogen Induced Polarization, Signal Amplification by Reversible Exchange (SABRE), and Spin Exchange Optical Pumping. The chief objective of the hyperpolarization process is to yield sufficient hyperpolarized contrast agent (HCA) having an adequate lifetime, i.e., long T1, for in vivo distribution and metabolism. Because protons typically have low T1 values - on the order of only a few seconds - most HCA include a low-γheteronucleus (129Xe, 13C, 15N, 3He, etc.) for hyperpolarization storage and detection.

In cases where sensitivity is sufficient, various nuclear signatures can be used in PET/MRS for detection of a wide range of metabolite markers of functional integrity [66]. Use of 31P-MRS, for example, enables detection of phosphorylated metabolites, such as adenosine diphosphate (ADP), adenosine triphosphate (ATP), or phosphocreatine.

PET/MRS and radiogenomics

Radiogenomics is a novel approach to combined PET/MRS nuclear isotopic and nuclear moment modalities that interrogates large scale relationships, termed association maps, among imaging phenotypes and molecular data sets, such as those from specific gene and microRNA expression signatures. Association maps can identify high dimensional, correlation relationships, using either simple discrete measurements or complex combinatorial data, such as those between high dimensional image features and large scale molecular or genomic elements. Such relationships constitute putative biomarkers of disease, and the information has the potential for guiding treatments in the absence of new pathologic specimens [42,43].

PET/OI

PET and optical imaging (OI) dual modalities have developed chiefly in the context of surgical guidance. Optical imaging methods currently available employ a range of optical modalities [3], including fluorescent protein molecules, Cherenkov luminescence imaging, near-infrared light, and quantum dots composed from Cd/Te or Cd/Se materials. For surgical guidance, the radioactive signal enables identification and localization of a lesion by means of its radioactive signature, whereas the optical feedback allows direct visualization of the lesion in exposed tissue.

Multiprobe technologies

Dual probe scanners are chiefly an evolution of SPECT imaging, although research into multi-tracer PET has also been performed. Research on dual probe scanners has demonstrated their feasibility for radionuclides having widely separated energy profiles [9,10], based on the detection of energy differences in gamma ray emission, such as that between Tc-99m and I-123. A drawback of multi-tracer imaging is crosstalk from other gamma rays, which affects reconstruction of the image and requires scattering correction methods to lessen background caused by energy overlap.

Due to the lack of energy difference in the measured photons, PET has traditionally relied on detection of one radio- nuclide at a time, making multiple PET scans for different radionuclides a necessity. Since multi-nuclide detection cannot be achieved via energy resolution differences, efforts to differentiate signals have explored several alternative methods including differences in half-life, staggered dose injections, and prompt gamma [67, 68]

A recent development has been that of combining PET and SPECT modalities, since these are inherently complementary [67,69]. Traditionally, this combination has been difficult to achieve due to the presence of the collimator in SPECT scanners. One proposal to overcome this difficulty is the use of Compton imaging with PET, using technology taken from astrophysical applications [69]. Absorbers, such as scintillator or semiconductor detectors, surround the subject as in PET. Additionally, there are scatterers that surround the subject inside the absorber ring. Gamma source localization is based on the coincidence between a scattered gamma ray and an absorbed gamma ray, which enables localization of the gamma source.

Computational and technology advances

Enhanced signal acquisition

Important improvements in sensitivity and resolution of PET technology have included more rapidly responding and brighter scintillators that are based on materials like lutetium oxyorthosilicate (LSO), gadolinium oxyorthosilicate, and lutetium yttrium oxyorthosilicate [4,70]. Coupled with the development of solid-state read-out detectors, new scintillators now enable 3-dimensional data acquisition and use detector material composed from cadmium zinc telluride (CZT).

Small-field planar gamma cameras

Over recent decades, small hand-held, planar gamma cameras designed for use in surgery have increased in use. Given the need for genetic therapies treatment, the smaller cameras are likely to see more frequent use in these procedures, which require targeted delivery of probe material [11]. Several groups have developed CZT-based intra-surgical systems for which a range of cameras are now commercially available. In contrast to probes, the use of cameras enables more precise viewing of a region of interest and can be combined with optical cameras for visualization.

Reconstruction software

Developments in image reconstruction continue to play an integral role in achieving optimal image quality for both SPECT and PET. In most cases iterative reconstruction [70] is used, since the contribution from attenuation, motion, and detector resolution are sufficiently large as to appreciably lessen image quality. In other case's reconstruction can be performed more rapidly by filtered back-projection techniques.

Since all such approaches require significant computational tasking, albeit at different scales, recent proposals have advanced the concept of reconstruction free PET imaging [50]. Reconstruction free imaging is based on the hypothesis that with sufficient improvement in time-of-flight information, the need for reconstruction will be eliminated. A recent demonstration of an imaging system based on the detection of Cherenkov photons in two collimated detectors, in fact, had a coincidence TOF resolution of 32 ps3, i.e., nearly sufficient to eliminate the need for reconstruction [50].

Conclusion

Nuclear medicine has confirmed its place as a versatile and powerful technique for in vivo diagnosis and therapy. Recent decades have amplified these capabilities. Advances in radiochemistry, targeted delivery, and technological innovation have broadened access to domains once thought 'undruggable', laying the groundwork for transitioning from molecular imaging to molecular systems imaging. Radiochemical techniques are no longer limited to labeling small compounds only but now include a wide range of radio nuclides that can be attached to various large molecules with enhanced speed and simplicity. Major intracellular

functions, including clearance, energetics, transport, gene transcription, and protein processing, are increasingly accessible for interrogation. Targeting has also improved, with natural and synthetic nano platforms that can be combined with radioimmunoconjugates, reporter genes, and antibody fragments. Importantly, technological developments like hybrid scanning systems are providing multimodal information sourcing that is yielding insight into tissue and cellular physiology and molecular dynamics, as well as improved spatiotemporal resolution. Time of flight determinations, moreover, are increasingly rapid, bringing reconstruction free imaging within reach.

Despite these successes, difficulties in multiplexing multiple radionuclides continue to be significant obstacles to systems molecular imaging. The inability of PET to discriminate energy levels, notably, is a major drawback to multinuclide monitoring that is only beginning to be addressed in hybrid PET/gamma counters or SPECT dual detection systems.

Molecular systems imaging promises to attain a comprehensive level of diagnostic interrogation, informing treatment decisions that are unique to individual patients. This will require the accumulation of large data sets, encompassing multiple candidates and tissue features over time and requiring large scale computational resourcing, analogous to methods currently evolving for radiogenomics. Computational and statistical resources will also need to be developed for resolving small signal differences. Protein complexes mediating key intracellular functions constitute important targets for monitoring disease states, as in the case of the huntingtin protein [8]. In many cases, the functional features of these complexes remain to be unraveled prior to the development of candidate probes. Significantly, technological developments for multiprobe monitoring are increasingly needed driving research in this key area.

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