Developments in Positron Emission Tomography (PET) scanning

KATE KONSEWICZ
James Scholar Honors Project
Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801 USA

MAGDI RAGHEB
Department of Nuclear, Plasma and Radiological Engineering, University of Illinois at Urbana-Champaign, 216 Talbot Laboratory, 104 South Wright Street, Urbana, Illinois 61801, USA.
mragheb@illinois.edu, http://www.mragheb.com

ABSTRACT: Nuclear medicine provides functional imaging in vivo. PET scanning detects photon coincidence resulting from an interaction between a positron and electron from Beta-plus decay. PET is most beneficial when paired with CT or MRI systems to provide functional imaging with anatomical structure. Recent advancements in PET include algorithms to enhance spatial resolution and limit of detection in order to provide earlier detection of lesions and disease. Much research is being conducted in developing radiotracers to target specific tissues and diseases. PET provides an attractive imaging technique to detect and monitor disease and cancer therapies.

INTRODUCTION

Positron emission tomography (PET) scanning allows imaging of function in-vivo with increased sensitivity and attenuation via biological aspects of radioactive pharmaceuticals. A positron-tagged biochemical is administered to the patient intravenously, and when the radionuclide decays and an annihilation event occurs, a positron camera is used to detect the radiation emitted in coincidence to produce a three-dimensional image of the distribution of the biochemical in the body.

PET is highly beneficial in oncology in diagnosis, staging, and follow-up. Images displayed via PET scanning facilitate the detection of tumors as well as monitoring cancer therapy progress.

PHYSICS

A positron is the antimatter equivalent of an electron; the detection of the gamma photons emitted after a positron undergoes an annihilation reaction with an electron is the underlying premise of PET. The four radionuclides most commonly used in PET are Fluorine[18], Carbon[11], Nitrogen[13], and Oxygen[15] because those positron emitting radiopharmaceuticals have short half-lives. Radionuclides with lower positron energy are preferred because positron energy is proportional to positron range, the distance a positron can travel in tissue before coming into contact with an electron, which reduces spatial resolution. The radionuclides are paired with a molecule that result in stable covalent bonds that make-up the tracer. These tracers are produced at cyclotrons. The most common tracer used in PET is ^{18}F-FDG, a radiolabeled sugar (glucose) molecule, because of its ability to detect metabolic activity. Abnormal glucose metabolic rates are detected from images using ^{18}F-FDG, which can be used to localize tumors and monitor progression of disease or cancer therapies.

Table 1. Typical positron emitters and their properties.[2]

Radio nuclide	Half-life $T_{1/2}$/min	Decay mode (%)	Positron energy (max)/keV	Nuclear reaction	Target material	Product after irradiation
^{11}C	20.4	β^+ (99.8) EC (0.2)	960	$^{14}N(p,\alpha)^{11}C$	$N_2(O_2)$	$[^{11}C]CO_2$ ($[^{11}C]CO$)
^{13}N	10.0	β^+ (100)	1199	$^{16}O(p,\alpha)^{13}N$	H_2O	$[^{13}N]NO_3^-$, $[^{13}N]NO_2^-$
^{15}O	2.0	β^+ (99.9) EC (0.1)	1732	$^{14}N(d,n)^{15}O$ $^{15}N(p,n)^{15}O$	$N_2(O_2)$	$[^{15}O]O_2$
^{18}F	109.8	β^+ (97) EC (3)	634	$^{18}O(p,n)^{18}F$	$H_2{}^{18}O$	$[^{18}F]fluoride_{aq.}$

Certain types of the nucleus of the radioactive atom emit gamma rays when they decay, which is detected by gamma cameras to make images. The mechanisms of radioactive decay, process in which an unstable atomic nucleus loses energy via radiation, occurs most typically via alpha decay, beta-minus decay, and beta-plus decay in relation to nuclear medicine. Beta-plus decay is the mechanism of

radioactive decay observed in PET scanning. Beta-plus decay, also known as positron emission, occurs with radionuclides that have an excess number of protons compared to neutrons. As seen in Equation 1, a proton in an atom is converted into a neutron and a neutrino and positron are emitted.

$$ {}^{A}_{Z}X \rightarrow {}_{Z-1}{}^{A}Y + B^{+} + \nu + energy \qquad (1) $$

Where B^{+} is a positron, ν is a neutrino, and X,Y are the radioactive atoms.

Interactions between positrons at rest and free electrons result in annihilation and emission of photons (gamma rays).

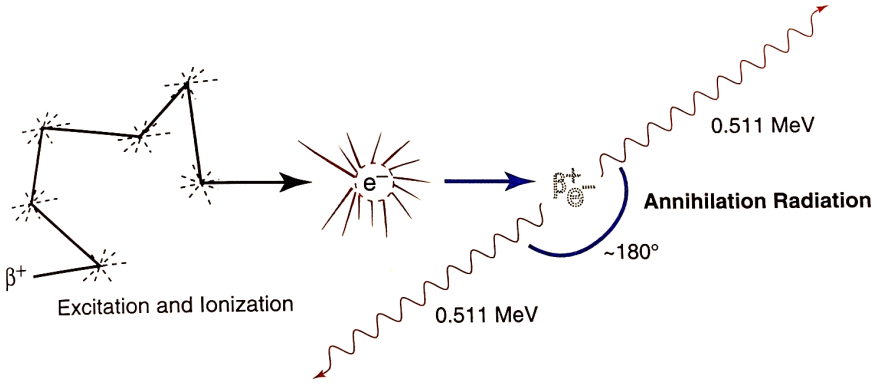

Figure 1. Annihilation Radiation

The rest mass of both particles, positron and electron, instantaneously convert to energy (511 keV for each positron/electron) and emit gamma rays in opposite directions as depicted in Figure 1. PET uses annihilation coincidence detection (ACD) to obtain projections of the interactions to create images. True coincidence is a single nuclear transformation resulting in a simultaneous interaction with the detectors of emission. Scatter coincidence occurs when one or both of the photons emitted from a single annihilation are scattered and detected. Random coincidence mimics a true coincidence in that emissions from different nuclear transformations are detected simultaneously. Random and scatter coincidence result in image degradation and misrepresent annihilation interactions.

PET IMAGER/POSITRON CAMERA

Unlike conventional gamma cameras, where the photomultiplier tubes (PMTs) are interconnected to generate positional signals, the typical positron camera consists of a dual headed gamma camera, where each photomultiplier tube in each head is its own entity. The array of photomultiplier tubes is coupled to scintillation crystals which work to detect the annihilation photons. PMTs collect signals from the source of the nuclear interaction and represent the signals in energy and time-of-flight (TOF). TOF can minimize detection from random coincidence when the time difference is smaller than 4-12 ns. To enhance the likelihood of detecting true coincidence, scintillators need to be able to emit light very promptly. Radionuclides with lower energy result in better spatial resolution since there is minimal distance traveled by the positrons before annihilation. The development of the combination of PET and x-ray CT (computed tomography) enhances this imaging modality by providing anatomical reference making PET more versatile and applicable to medicine. PET is most commonly paired with CT, but also magnetic resonance imaging (MRI) in order to provide cross-sectional anatomical information. The main advantage of PET/CT systems is the ability to localize increased activity (typically metabolic) to specific anatomic locations resulting in detecting abnormalities.

Common methods for assessing the uptake of the radiotracer by different tissues is Standardized uptake value (SUV) and visual comparison.

$$SUV = \frac{tracer\ activity\ in\ tissue}{radiotracerdose/patientweight} \qquad (2)$$

The respective units are $\mu Ci/g$ (microcurie/g) for tracer activity in tissue, mCi for radiotracer dose, and kg for patient's weight. Malignant tumors often range in SUV values from 2.5-3.0 or greater, while reference organs of normal tissues like liver and marrow range from 0.5-2.5. SUV values are useful in monitoring treatment response and assess tumor grade when the initial SUV of a tumor is measured. SUV values are taken at a specific time point, so that needs to be accounted for when assessing the SUV values to healthy tissue SUV values.

IMAGING RECONSTRUCTION AND DETECTABILITY

In conventional PET/CT scanners, detected coincidences are stored in a computer and used for image reconstruction via backprojection. Different from CT and SPECT, the detectors used in PET collect projection data simultaneously from all angles around the patient, while the detectors in CT or SPECT would need to revolve around the patient to collect projections from all angles. In PET, the primary limitations in spatial resolution of the scanners stem from the intrinsic spatial resolution of the detectors (typically PMTs coupled with scintillation crystals), distances traveled by the positrons before annihilation, and the fact that annihilation photons are not emitted perfectly 180° in opposite directions.

Point-spread-function (PSF) modelling regarding tomographic reconstruction likely implemented in a PET/CT system, improves spatial resolution by reducing spatial noise. This reconstruction enhancement has an improved ability to detect smaller tumors and abnormal objects, but needs further research supporting that it does not increase Deauville score (DS), a five-point scale used in clinical trials involving FDG PET/CT indicating FDG uptake in reference to two organs: mediastinum and liver.

Silicon photomultiplier (SiPM) tubes have been studied to improve sensitivity and detection of small lesions. This technology utilizes a matrix reconstruction (1 mm or 1 mm_{PSF}) via a PET camera coupled with small SiPMs that are crystal coupled 1-to-1. The matrix reconstruction increases the tumor/background, which enhances sensitivity and specificity. In comparison to PMTs, SiPMs in the same scanners were able to detect smaller lesions that conventional PET/CT scanners were unable to identify. The max Standardized Uptake Value (SUV) measurements were higher in tumors detected via SiPM.

DEVELOPMENTS IN RADIOTRACERS

Radiotracer selection is very important because the molecule tagged with a positron-emitting radionuclide needs to bind to their target of interest with a binding affinity ($K_d < 50$ nM), while not binding with other proteins or small molecules in the body. There needs to be high specificity of target binding, so the

uptake sites represent molecular pathology and not a normal process in the body. It is beneficial for the radiotracer to progress and exit the body quickly to minimize radiation exposure to patients. As previously mentioned, the most common tracer is ^{18}F-FDG due to its ability to localize many types of tumors based off of glucose metabolism. Other radiotracers are being developed to increase specificity of targets in different diseases.

Bromodomain and extra-terminal domain (BET) proteins are involved in the development of many diseases such as cancer and neurodegeneration. BET proteins are a good therapeutic target, but there is still a need for a radiotracer that specifically targets BET proteins to be able to visualize and quantify them via PET. The molecule ^{11}C-CH_3I has been clinically studied in assessing the potential of a BET PET radiotracer, but more support is needed to have a promising effect in epigenetic imaging via PET.

Translocator protein (TSPO), also known as peripheral benzodiazepine receptor, is the primary index in neuropsychiatric and neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, multiple sclerosis (MS), and more. Radioligands ^{18}F15 and ^{11}CJNJ717 TSPO have been studied, but due to the lack of understanding in how TSPO binds to ligands and standard values for upregulation of TSPO in response to brain injury and inflammation, a radiotracer that targets TSPO to track glial cell activation and monitor neuroinflammation needs to be further studied.

CONCLUSIONS

Nuclear medicine is a great advancement in identifying disease and disease progression. PET is best optimized when utilized with CT or MRI systems since paired together, the system provides visualization and quantification of specific functions in vivo as well as anatomical representation to help localize. The future of PET involves improving detection to higher sensitivity and resolution via computer algorithms in image reconstruction as well as clinical developments in radiotracers specific to diseases affecting certain tissues. More improvements rely on decreasing scan speed and limiting radiotracer dose to minimize radiation to patients and provide more efficient and effective imaging.

REFERENCES

1. Ragheb, M. (n.d.). *Chapter 11: Positron Emission Tomography*. Retrieved March 3, 2022, from https://mragheb.com/NPRE%20402%20ME%20405%20Nuclear%20Power%20Engineering/Positron%20Emission%20Tomography.pdf.
2. Enderle, J., Bronzino, J., & Szabo, T. (2011). *Introduction to biomedical engineering*. *ScienceDirect*. Elsevier Science. Retrieved March 20, 2022, from https://reader.elsevier.com/reader/sd/pii/B9780123749796000162?token=60CFB6EE1A6829473D617B574D4E70BEB4EC218EAD77F0795172E4F0D09A4130CA77666549F68084794665FC2A109E54&originRegion=us-east-1&originCreation=20220501180914.
3. Aide, Nicolas et al. "New PET technologies - embracing progress and pushing the limits." *European journal of nuclear medicine and molecular imaging* vol. 48,9 (2021): 2711-2726. doi:10.1007/s00259-021-05390-4
4. Kinahan, Paul E, and James W Fletcher. "Positron emission tomography-computed tomography standardized uptake values in clinical practice and assessing response to therapy." *Seminars in ultrasound, CT, and MR* vol. 31,6 (2010): 496-505. doi:10.1053/j.sult.2010.10.001
5. Kapoor, V., McCook, B. M., & Torok, F. S. (2004). An introduction to PET-CT imaging. *RadioGraphics*, *24*(2), 523–543. https://doi.org/10.1148/rg.242025724
6. Song, Pengfei. "Lecture 8: Nuclear Medicine Imaging". PowerPoint, 8 April. 2022, https://courses.grainger.illinois.edu/ece380/fa2021/index.html.
7. Lau, Joseph et al. "Insight into the Development of PET Radiopharmaceuticals for Oncology." *Cancers* vol. 12,5 1312. 21 May. 2020, doi:10.3390/cancers12051312
8. Bai, P., Lan, Y., Wang, H., Chen, Z., Fiedler, S., Striar, R., Lu, X., & Wang, C. (2020). Development of a novel Positron Emission Tomography (PET) Radiotracer targeting bromodomain and extra-terminal domain (BET) family proteins. *Frontiers in Molecular Biosciences*, *7*. https://doi.org/10.3389/fmolb.2020.00198
9. Zhang, L., Hu, K., Shao, T., Hou, L., Zhang, S., Ye, W., Josephson, L., Meyer, J. H., Zhang, M.-R., Vasdev, N., Wang, J., Xu, H., Wang, L., & Liang, S. H. (2021). Recent developments on pet radiotracers for TSPO and

their applications in neuroimaging. *Acta Pharmaceutica Sinica B*, *11*(2), 373–393. https://doi.org/10.1016/j.apsb.2020.08.006