Research article

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Multi-molecule imaging and inter-molecular imaging in nuclear medicine

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Abstract: Multi-molecule imaging and inter-molecular imaging are not fully implemented yet, however, can become an alternative in nuclear medicine. In this review article, we present arguments demonstrating that the advent of the Compton positron emission tomography (Compton-PET) system and the invention of the quantum chemical sensing method with double photon emission imaging (DPEI) provide realistic perspectives for visualizing inter-molecular and multi-molecule in nuclear medicine with MeV photon. In particular, the pH change of InCl₃ solutions can be detected and visualized in a three-dimensional image by combining the hyperfine electric quadrupole interaction sensing and DPEI. Moreover, chemical states, such as chelating, can be detected through angular correlation sensing. We argue that multi-molecule and chemical sensing could be a realistic stream of research in future nuclear medicine.

Keywords: Compton PET, chemical sensing, double photon emission imaging (DPEI), double photon emission imaging, Single Photon Emission CT (SPECT), medical imaging, pH, multi-photon imaging, hyperfine interaction.

Introduction

In conventional nuclear medicine imaging, the accumulation of radioactive tracers is implemented to diagnose diseases, such as cancers or Alzheimer by combining the design of molecules having an affinity to the target biological phenomena. For example, positron emission tomography (PET) [1-4] and single photon emission tomography (SPECT) [5,6] are both valid because of their high sensitivity (better than 10⁻¹² molar) in medical diagnosis. In contrast, fluorescence imaging is extensively used in molecular biological studies with cells because of its high spatial resolution and multi-molecule imaging capability. Moreover, fluorescence resonance energy transfer technology (FRET) [7] enables the detection of inter-molecular interaction by using energy transfer, which nuclear medicine does not consider. Recently, quantum-sensing methods using nitrogen-vacancy centers have been proposed [8] to sense pH [9], temperature, and magnetic field in vivo. However, as fluorescence imaging cannot be applied to medical imaging due to its low penetration of visible light, inter-molecule or multi-molecule imaging in the nuclear medicine regime is a promising alternative. This communication reviews recent developments in multi-molecule imaging based on Compton PET imaging and describe a possible pathway to inter-molecular imaging with double photon coincidence imaging (DPEI) and perturbed angular correlation (PAC) as a quantum sensing method in nuclear medicine.

This communication is structured as follows. The following section reviews the multi-molecule imaging research currently implemented in nuclear medicine. After that, we present the advancement of Compton-PET imaging and double photon emission imaging (DPEI) in nuclear medicine. Subsequently, the possibility of inter-molecular imaging and chemical
sensing is discussed. Finally, the conclusions of the review are presented.

Multi-molecule imaging in nuclear medicine

Multi-molecule imaging has not been fully implemented in clinical situations might be because of its unmatured technology and cross-talk between nuclides. Until now, medical diagnosis has been conducted by manual eye-based comparison of multiple scanned images, such as \(^{18}\)F-FDG PET scan and \(^{111}\)In-octreotide SPECT. In particular, dual imaging is essential to diagnose cancer progression by comparing the accumulation of different radioactive nuclides and molecules. For example, in a neuro-endocrine tumor, the accumulation of \(^{18}\)F and \(^{111}\)In depends on the tumor progression grade [10]. Because the scan timing differs for PET and SPECT, a possible movement of organs or even tumor progression exists between the two scans. The simultaneous scan using the same coordinates can provide a more accurate diagnosis in future nuclear medicine. Moreover, with the recent development of total body PET [11,12], multi-molecule imaging within a reduced time scale can provide practical insights into the molecular dynamics in the body. In several studies, simultaneous imaging has been investigated using SPECT and Compton imaging [13-24]. In both imaging modalities, the cross-talk between nuclides has been a challenge; thus, several studies have focused on reducing the cross-talk using energy information [25,26] and timing information [27].

Several studies have used PET with multi-photon detection, and the main challenge has been the cross-talk effect for discriminating the two nuclides [28,29].

In particular, combining PET scanner with Compton scanner remained open until [30]. The combination of PET and Compton imaging is preferable due to its high sensitivity without a collimator-less design for multi-nuclide imaging.

Compton PET scanner

PET imaging provides extremely highly sensitive molecular imaging, while collimator-less Compton imaging provides higher sensitivity than mechanical collimation systems. Moreover, the collimator-less Compton imaging can be combined with a PET instrument by inserting a thin scatterer layer inside the PET absorber.

Note that the word “Compton PET” has been used in several ways; for instance, as a method to increase the sensitivity of PET by using Compton imaging [31] or PET imaging combined with Compton imaging with three gamma-ray emissions [32,33]. However, we refer to “Compton PET” to indicate the simultaneous imaging of Compton imaging and PET imaging to realize the multi-molecule and multi-isotope imaging [30].

In the advancement of Compton imaging, we have demonstrated multi-molecule imaging with the developed Compton PET scanner with \(^{111}\)In SPECT nuclides and \(^{18}\)F-FDG PET nuclides [30]. The concept is shown in Figure 1. In particular, the capability of multi-molecule imaging was demonstrated for the first time in an in-vivo experiment with simultaneous PET imaging and Compton imaging [34]. Furthermore, the developed Compton PET can be applied to imaging PET and SPECT nuclide and the therapeutic nuclide [35], such as \(^{131}\)I and \(^{211}\)At, which is crucial for future radio-theranostics applications [36].

Double Photon Emission Imaging (DPEI)

PET and SPECT imaging relies on the tomography system, which relies on the Radon transform image reconstruction using the line of response. In particular, tomography requires 360-degree projections, while SPECT system requires rotations to acquire the data. We proposed a method relying on multi-photon emission cascade nuclides and coincidence detection to localize the position of the radioisotope with a single coincidence
event. The concept is shown in Figure 2. The coincidence detection of multi-photons by angular resolving detectors can localize the position by intersecting two lines. We have two options to perform the angular resolving detectors: Compton imaging and mechanical collimation imaging, as illustrated in Figure 3.

![Figure 2: Concept of double photon emission imaging (DPEI) compared with positron emission.](image)

![Figure 3: DPEI methods using Compton imaging, electron tracking Compton imaging, and mechanical collimation imaging as angular resolving detectors. The intersection of two Compton cones can result in a complicated projection. ET-Compton imaging and collimation imaging exhibit an improved projection with reduced background.](image)

In Compton imaging-based DPEI, the signal-to-background ratio significantly improved in simulation and experiment by reducing the effect of artifacts due to Compton cones. For example, SNR was improved approximately five times in a GEANT4 Monte Carlo simulation [37] and approximately two times experimentally [38]. Furthermore, combining the time-of-flight (TOF) information with DPEI improved the image quality to that of a TOF-PET system [39]. In addition, coincidence detection can provide an improved cross-talk reduction for multi-nuclide imaging because coincidence detection can reject random events, as shown in [27]. In future systems, adopting silicon detectors as scatters will be preferable to improve the angular resolution in an image [40]. Moreover, more advanced Compton imaging called electron tracking Compton (ET-Compton) imaging measuring the direction of Compton electron are preferable for achieving approximately a two times higher signal-to-noise ratio [41,42]. Several studies have been performed on electron tracking in Compton scatterer using silicon pixel detectors. tomography (PET) and single photon emission CT (SPECT). In ET-Compton based DPEI, obtaining the coincidence between gamma1 and gamma2 enables localizing the projection to ideally one point.

In mechanical collimation DPEI, the first demonstration is performed by combining parallel hole-parallel hole collimators [43]. In particular, several clinically used nuclides emitting two cascade photons exist for therapeutic application, such as 111In for SPECT and 177Lu. Moreover, both nuclides can be simultaneously visualized with a static DPEI system.

In both cases, Compton DPEI and collimation DPEI, the detection efficiency is significantly decreased; however, the signal-to-background ratio is improved more than four times, as reported in [44]. The detailed comparison between the single-photon method and DPEI should be investigated in future work. Another advantage of DPEI is the reduction of cross-talks between nuclides. Because of the coincidence detection of cascade photons, the cross-talk is substantially reduced, as shown in [44].

Some authors have proposed combining multi-pinhole with slit collimation in DPEI to improve detection efficiency [45].

Our recent experiments showed that the combination of slit-parallel collimators increased the efficiency approximately five times compared with the parallel-parallel collimators.

**Inter-molecular imaging and chemical sensing**

In nuclear medicine, the possibility of inter-molecular sensing has rarely been investigated. As mentioned in the previous section, multi-molecule or multi-nuclide imaging with Compton PET or energy-resolving SPECT can provide an “indirect” correlation of molecules the time and space. However, the direct measurement of inter-molecule can provide useful information, such as the chemical state of target molecules. Owing to the feature of relatively solid decay with the MeV energy range, the direct use of the gamma-ray to detect chemical...
information in nuclear medicine might be challenging. However, several methods can be used in chemical analysis with the particle physics technology. One example is the positronium lifetime spectroscopy to detect defects or nanostructure in the crystal or materials [46,47]. Currently, this technology has been successfully investigated as positronium imaging in nuclear medicine for oxygen sensing, representing an excellent example of chemical sensing. The cost-effective total-body PET concepts and the first multi-photon PET images discussed in [48,49] also have the capability of providing multi-photon and multi-nuclide imaging in nuclear medicine.

Another possibility is the use of the angular correlation of cascade photons. The cascade decay nuclides have the angular correlation between the first gamma-ray photon and the second gamma-ray photon that originates from its nuclear spin state [50]. In particular, external electric and magnetic fields can perturb the angular correlation if the nuclide has a relatively long intermediate half-life and the gamma-ray distribution is changed, called PAC. This PAC is typically used to determine the magnetic moment, electric quadrupole moment, and decay scheme. Therefore, we have considered implementing PAC as a chemical sensing method in the nuclear medicine regime.

![Figure 4: Concept of quantum chemical sensing using the DPEI method. The electromagnetic hyperfine interaction with nuclear spins, including the chemical structure, can be detected through the gamma-ray emission time-space correlation.](image)

Traditional research focused on sensing parameters such as viscosity, pH, and temperature. In this regard, we have made a pixel detector array to measure precisely the angle from the cascade nuclides to determine the emission of gamma rays. Specifically, $^{111}$In decay starts with the electron capture and nuclear spin changes from $7/2$ (initial state), $5/2$ (intermediate state) to $1/2$ and emits two gamma-rays with the energy of 171 and 245 keV, which are generally used in SPECT scanner. The spatial distribution between 171 keV and 245 keV changes depending on the external field perturbation.

The pH information can be extracted through the hyperfine interaction between the $^{111}$In nucleus and the external electric field gradient, especially the change around pH 3-5. Moreover, by combining the DPEI method with chemical sensing, we can simultaneously visualize the accumulation of radioactive sources and their surrounding environment, such as pH in the pico-mole concentration range [51].

The study demonstrated the imaging of pH change from three to five. However, the target pH range in humans changes approximately from six to seven. Therefore, chemical sensing in nuclear medicine still requires further improvement, such as the dedicated design of molecules. Another possibility is to use the chelating state detection demonstrated in the [51].

We have also demonstrated that ultrasound irradiation can change the angular correlation through the quadrupole hyperfine interaction [52]. This finding indicates that combining ultrasound and nuclear medical imaging can be a potential future study.

![Figure 5 shows the proof-of-concept experimental setup of two-dimensional pH imaging using mechanical collimators. The prototype consists of eight 8 x 8 arrays (512 channels) of Ce:GAGG scintillator (4 mm thickness) individually coupled to SiPMs. Energy and positions were recorded all the time as list-mode data. The right-top panel shows the typical energy spectrum from $^{111}$In nuclide. In particular, 171 and 245 keV were used in the angular correlation measurement. After selecting the gamma1 and gamma2 energy, the timing histogram was generated from the recorded timestamps, as shown in the right-bottom panel of the figure. The time window extracting the correlated photons (from -50 to 200 ns) was set for calculating the angular correlation. The angular resolution corresponds to approximately 4–5 deg from the geometry in this configuration. The detector with an 8 x 8 parallel-hole collimator (Pb thickness 15 mm and hole size 2 mm) was used to identify the two-dimensional position of the accumulation imaging and pH sensing source. The angular correlation depending on the pH value was also measured.](image)

Figure 6 shows the measured angular correlation with different pH settings. The results indicate a significant decrease in counts at around 90 deg. In contrast, the results show an increase in counts close to 0 and 180 deg of more than 5% with the transition
Figure 5: Geometry setup for measuring the angular correlation with two-dimensional imaging. A 3.2 mm pitch 8 x 8 array of GAGG scintillator coupled to an MPPC was used. The energy and timing selections were applied to extract the correlated cascade photon in one nuclear decay.

Figure 6: Angular correlation and two-dimensional imaging of the InCl₃ liquid with different pH states. By combining the collimation imaging, the accumulation and pH information are simultaneously acquired during imaging. The right panel shows the accumulation and pH imaging results.

The angular correlation change corresponds to the change of molecular state in different pH values. Figure 7 shows the estimated and calculated molecule state of InCl₃ depending on pH by adding NaOH. Although the effect of relatively large time window (250 ns) to random events and the method of sensitivity correction should be investigated in the future study, the concept of chemical sensing with MeV gamma-rays is proved in this study.

Figure 7: Calculated chemical state of InCl₃ depending on pH value by PHREEQC.
Conclusions

This communication discussed various prospects of multi-molecule and inter-molecular imaging for nuclear medicine. We presented arguments indicating that the newly demonstrated Compton PET might be effective for high-sensitivity PET/SPECT simultaneous imaging. Moreover, DPEI can be used for chemical sensing combined with nuclear medical imaging. Future work should be focused on increasing the sensitivity and validation studies in vivo for practical application.

List of abbreviations

DPEI: Double photon emission imaging
SPECT: Single Photon Emission CT
PET: Positron emission tomography
PAC: Perturbed angular correlation
TOF: Time-of-flight

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References


