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Simultaneous Emission-Transmission Tomography in an MRI Hardware Framework

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Abstract

Multi-modality imaging is essential for diagnosis and therapy in challenging cases. A Holy Grail of medical imaging is a hybrid imaging system combining computed tomography (CT), nuclear imaging, and magnetic resonance imaging (MRI) to deliver registered morphological, functional, and cellular/molecular information simultaneously and quantitatively for precision medicine. Recently, a unique imaging approach was demonstrated that combines nuclear imaging with polarized radiotracers and MRI-based spatial encoding. The detection scheme exploits the directional preference of γ -rays emitted from the polarized nuclei, and the result is a concentration image with resolution that can outperform standard nuclear imaging at a sensitivity significantly higher than that of MRI. However, the method does not calculate the attenuation image. Here we propose to obtain MRI-modulated γ -ray data for simultaneous image reconstruction of emission and transmission parameters, which could serve as a stepping stone toward simultaneous CT-SPECT-MRI. This method acquires synchronized datasets to provide insight into morphological features and molecular activities with accurate spatiotemporal registration. We present a complete overview of the system design and the formulation for tomographic reconstruction when the distribution of polarized radiotracers is either global or limited to a region of interest (ROI). Numerical results support the feasibility of our approach and suggest further research topics.

Keywords

Single photon emission computed tomography (SPECT); polarized radiotracer; computed tomography (CT); magnetic resonance imaging (MRI); multimodality imaging

I. INTRODUCTION

Multi-modal/hybrid systems that combine positron emission tomography (PET) with either CT or MRI have greatly benefitted the medical imaging field. PET-CT provides functional information co-registered with structural images from CT [1]. PET-MRI delivers complementary functional and morphological information with high-sensitivity and rich soft tissue contrast [2]. The synergy between nuclear and magnetic imaging techniques has enabled significant advancements in diagnostics and therapy [3], [4]. Thus far, simultaneous PET-CT-MRI in one system remains unrealized despite detailed investigations on the topic [5].

A recent study in *Nature* reported a system to perform nuclear imaging in an MRI hardware framework [6]. The method is called “polarized nuclear imaging” (PNI), and experimental demonstrations delivered a two-dimensional concentration image of a polarized radioactive tracer. A novel detection scheme is made possible by the nuclear polarization and magnetic manipulation of the radiotracer. The polarized tracer creates anisotropic emission of γ -rays with a known and controllable directional preference. An MRI-type perturbation strategy for spatial encoding is employed to collect the emitted γ -ray signals for tomographic reconstruction. Gradient magnetic fields and an RF pulse sequence “activate” a specific region of pixels or voxels so that γ -rays from only those regions are directed into the transverse direction for measurement by a detector pair. The principles of PNI imply three key advantages: (1) better image resolution than that of classical nuclear imaging, (2) higher signal sensitivity than that of advanced MRI, and (3) closer and easier integration of three major imaging modalities (CT, SPECT and MRI), provided that practical polarizable tracers can be eventually produced.

A key component missing from the PNI work is attenuation background imaging. Previously, methods were designed to reconstruct attenuation coefficients directly from emission data, but their success is limited [7]–[9]. These techniques rely on consistency conditions or maximum likelihood algorithms, but the ill-posedness of the problem and poor quality of raw data leads to errors and artifacts in the reconstructed images. For example, time-of-flight (TOF) information in PET can be used to estimate attenuation coefficients, but the values are only determined up to a constant term [10].

Here we present a novel acquisition process that improves upon the reported PNI work by reconstructing both the concentration and attenuation images from the same γ -ray dataset. Our imaging approach is for simultaneous emission-transmission tomography (SET), and has the potential to be extended for MRI with the hardware framework in place. SET is both a structural and functional tomographic imaging method that uses polarized radiotracers as a novel medium to probe cellular and molecular targets and measure the attenuation background at the same time.

Initial versions of this work were presented at two conferences [11],[12], which demonstrated the preliminary system design and feasibility of SET. We explored cases when the radiotracer accumulates over a significant amount everywhere in the field of view and simulated interior tomography-based SET reconstruction in cases where the radiotracer is localized to a small region of interest (ROI). This paper expands upon the ideas from both studies to present a holistic description and analysis of SET with improvements to the physical model and reconstruction scheme that can now address noise in global and interior imaging cases. Specifically, we explore a new activation and reconstruction technique that uses half-voxel offset to double sampling resolution. In section II, we describe the system with an emphasis on the data acquisition and image formation over an ROI. Also, we review basic knowledge of the radioisotopes. In section III, we present numerical results to demonstrate the feasibility of global and interior SET in numerical simulation with a head phantom. Finally, in section IV we discuss next steps toward a physical SET prototype and beyond, with an emphasis on the need for suitable radiotracers.

II. METHODOLOGY

A. Imaging system

The proposed SET system employs polarized radioactive tracers as the source for tomographic imaging in a main magnetic field B_0 . Polarization of the radiotracer is known to be feasible using the spin-exchange optical pumping technique to rearrange electrons with an infrared laser [13]. More efficient and effective methods may be further developed once the need for polarized tracers is recognized. The imaging process requires the nuclear spins to be substantially polarized; for example, at least 60% in the perpendicular axis. Fig. 1(a) depicts a simplified polar plot of the angular emission probability with and without nuclei polarization.

Once the nuclei are polarized along the direction of the main magnetic field, a $\pi/2$ RF pulse at the Larmor frequency can tilt the polarization axes of nuclei along a transverse direction within a selected section. B_1 gradient fields generated by gradient coils can alter the B_0 field along the y -direction (or x -direction) to perform spatial encoding by activating a line of pixels parallel to the x -direction (or y -direction) in the selected plane. Then, detectors in the selected plane can measure γ -rays along the lines perpendicular to the y -direction (or the x -direction) in the plane through regions where significant signals are emitted.

Detectors can be positioned parallel to the y -axis to measure photons emitted from voxels, as shown in Fig. 1(b). Any section can be scanned in this way, since the transverse and longitudinal directions are specified by users. The selection of a section, a line in the section, and even a pixel in the line can be specifically activated using an appropriate RF pulse sequence. For example, if a particular voxel or an ROI needs to be activated, we can use the x -, y -, and z -gradients as sketched in Fig. 2. This means that only the nuclei within the active voxel emit γ -rays within a preferred planar slab towards a collimated detector pair. For more efficient data acquisition, the whole field of view can be modulated by sinusoidal or other basis functions, which is similar to k -space imaging for MRI but with an attenuation background (also see the Discussion section).

This data acquisition process can be performed with mechanical collimator grids or without them, as in a full-body SET system (see Discussion). With metallic collimators, the imaging process is much easier to visualize and analyze. If no metallic collimators are used, the radioactive tracers must be flipped into more orientations to unravel projective entanglements in raw data. In principle, the PNI mode can be enabled only through magnetic flipping of polarized tracers. This is essentially a magnetic collimation scheme, in addition to the well-known mechanical collimation (for CT and SPECT), electronic collimation (for PET) and temporal collimation (optical imaging with early photons) schemes.

A stationary system design for global SET imaging is shown in Fig. 3(a). In Fig. 3(b), we propose a rotating SPECT gantry to highlight the working principle of interior SET. In this pilot study, we assume the use of 2D mechanical collimator grids with 0.5mm^2 holes and a thin wall of γ -ray blocking material between each hole. Collimators are used at the cost of a compromised detection efficiency (note that the most efficient utilization of emitted γ -rays will be achieved in the whole body SET design that assumes the full detection coverage of the patient without mechanical collimation; Fig. 12 in the Discussion section).

B. Radiotracers

The pioneering PNI feasibility study utilized hyperpolarized $^{131\text{m}}\text{Xe}$. Although it was suitable for demonstration, the half-life of the tracer is 12 days, which is too long for clinical/preclinical tasks. As a result, polarization had to be refreshed multiple times before the data acquisition process was finished. Ideally, the preferred characteristics of a radiotracer should be as follows.

First, the tracer with nuclei spin number of $> \frac{1}{2}$ must be cost-effectively polarized up to a majority percentage, between 60–90%. In addition to the spin-exchange optical pumping method that is particularly suited to polarize noble gases, there are multiple other hyperpolarization methods that work better for condensed state molecules. For example, dynamic nuclear polarization can be utilized to polarize frozen solutes (Fig. 4) followed by rapid dissolution at room temperature [14]. Also, the anti-parallel spin-order in para-hydrogen (with ~99% purity) is able to hyperpolarize nuclei magnetization through double-bond addition reaction [15]. When H_2 is frozen to solids, its constituting hydrogen atoms tend to have anti-parallel nuclear spins, due to the lower rotational energy of this spin isomer. After para-hydrogen is thawed, this spin order can be maintained for hours at room temperature, which is long enough for vascular delivery inside the body. Once the para-hydrogen reacts with a molecule containing an asymmetric double bond, the spin order of para-hydrogen can be transformed into hyperpolarized hydrogen in the reaction product. More impressively, para-hydrogen can also achieve Signal Amplification by Reversible Exchange (SABRE) *in situ* (Fig. 5), via transient interaction with the test molecule through a metallic coordination center [16].

Second, both the half-life of the tracer's radioactivity and the half-life of the tracer's polarity need to be on the scale of minutes to hours. This is to make sure that in an imaging session of a reasonable length we can collect sufficient data. For a given level of data sufficiency, the data acquisition time should be minimized to accommodate the half-lives of radioactivity and polarity of the tracer. Additionally, the isotope should have a favorable γ -ray branching

ratio, say >20%. This is to maximize the signal-to-noise ratio (SNR) for the given half-lives for radioactivity and polarity of the tracer. The emission efficiency of the isotope greatly affects the flux of γ -ray radiation.

Finally, the toxicity of the tracer must be minimal. From this perspective, the half-life of the tracer's radioactivity should not be too long either. If a generic tracer is not biocompatible, some compounds could be designed to cover up tracer molecules. Table 1 summarizes a few candidate materials. For example, $^{127\text{m}}\text{Xe}$ has a half-life of 69 seconds and a good biocompatibility similar to $^{131\text{m}}\text{Xe}$. Its branching ratio is at 38%, which is much greater than 2% for $^{131\text{m}}\text{Xe}$. Another option is $^{79\text{m}}\text{Kr}$, with a half-life and a branching ratio similar to that of $^{127\text{m}}\text{Xe}$. Both $^{127\text{m}}\text{Xe}$ and $^{79\text{m}}\text{Kr}$ isotopes were clinically used [17], [18]. The emitted photons are easily measurable using a conventional gamma camera at a high efficiency. However, for SET imaging, isotope half-lives on the order of a few minutes would be too short to finish a complete data acquisition session. Our research into alternate isotopes is ongoing, including $^{132\text{m}}\text{I}$ and $^{81\text{m}}\text{Rb}$, with the target half-life between 30 minutes and 12 hours. Before moving to a physical SET system, the most important key is to find promising radioisotope candidates and produce them for initial investigation.

C. Mathematical basis

Our SET method reconstructs the radiotracer distribution and the attenuation background quantitatively and simultaneously from the same dataset. The pair of gamma cameras detect γ -rays along the paths defined by the collimators. Hence, the attenuation background must be compensated to perform quantitative SPECT imaging. Furthermore, the attenuation background is exactly what we need for the same purpose of CT scanning. Fortunately, the distributions of emission intensities and attenuation coefficients can be decoupled mathematically. Let us assume that γ -rays from radioactive molecules at position r are recorded by a pair of detectors on the left and right, $m_l(r)$ and $m_r(r)$, respectively:

$$\begin{aligned} m_l(r) &= \Phi(r) \exp \left(- \int_{-\infty}^r \mu(r') dr' \right) \\ m_r(r) &= \Phi(r) \exp \left(- \int_r^{\infty} \mu(r') dr' \right) \end{aligned} \quad (1)$$

where $\Phi(r)$ is the intensity of γ -rays at position r directly proportional to the concentration $\lambda(r)$ of a radioactive tracer, and $\mu(r)$ is the corresponding linear attenuation coefficient. Supposing that $\Phi(r) > 0$, and the measured intensity of γ -rays has a sufficient SNR, the dual integral equations in Eq. (1) can be converted to:

$$\sqrt{m_l(r)m_r(r)} = \phi(r) \exp \left(- \frac{1}{2} \int_{-\infty}^{\infty} \mu(r') dr' \right) \quad (2)$$

Then, we rearrange to obtain a formula with respect to γ -ray emission intensity $\Phi(r)$,

$$\phi(r) = \sqrt{m_l(r)m_r(r)} \exp \left(\frac{1}{2} \int_{-\infty}^{\infty} \mu(r') dr' \right) \quad (3)$$

From Eq. (1–2), we obtain a formula with respect to attenuation coefficient $\mu(r)$,

$$m_l(r) = m_r(r) \exp \left(\int_r^{-\infty} \mu(r') dr' - \int_{-\infty}^r \mu(r') dr' \right) \quad (4)$$

Once the attenuation background is known, the tracer concentration can be readily estimated from Eq. (3). Then, Eq. (4) can be discretized into a linear equation, which is solved using an inverse method or compressive sensing-based image reconstruction. The cutting-edge compressive sensing (CS) method can achieve a high quality result from fewer measurements than what the Nyquist sampling criterion demands.

D. Half-voxel activation

A further look at the simplified pixel-/voxel-oriented activation suggests that the solution is not unique if the attenuating effect within a pixel/voxel cannot be ignored. Indeed, in the case of a single pixel there are two independent unknowns (attenuation and concentration) and two dependent measurements (the flux from both sides is the same). This problem can be addressed by activating not only pixels/voxels individually but also mixed/halved pixels/voxels, creating new independent measurements as shown in Fig. 6. With the half-pixel/voxel offset activation, data become sufficient for the unique solution.

Half-voxel activation for interior tomography also enables the concentration image to be reconstructed without injecting a known radiotracer at a point. In that case, we would need to know the line integral of attenuation coefficients along the line of active emission, which can be externally measured with a method such as radiography. Once we know the line integral, we can determine the source concentration (the natural logarithm of the product of measurements from a detector pair would be proportional to the line integral of attenuation coefficients).

If external measurement is not available, it would still be helpful to computationally estimate the line integral based on an elastically deformed CT atlas. This process can be iteratively performed, and regularized with the reconstructed attenuation map of the ROI and other prior knowledge.

E. Tomographic reconstruction

The above-derived formulas and algorithms are physically valid and easily understandable if $\Phi(r) > 0$ holds everywhere in the field of view. The most interesting scenario we address in this paper is when $\Phi(r) > 0$ holds only within one or multiple ROIs well inside the patient body, as explained more in this subsection. A discrete model can be formulated for the active

half of a given pixel/voxel, $\frac{a}{2}$, as shown in Fig. 6. Then, the intensity measurements at each detector from the active side of the pixel/voxel can be expressed as follows:

$$J = \int_0^{\frac{a}{2}} \lambda \exp(-\mu(a-r)) dr \quad (5)$$

$$= \frac{\lambda}{\mu} \exp(-\mu a) \left(\exp\left(\frac{\mu a}{2}\right) - 1 \right)$$

$$K = \exp\left(-\frac{\mu a}{2}\right) * J \quad (6)$$

The measurements J and K will be different when each half of the voxel is activated due to different paths of attenuation. The four measurements can be represented by the following:

$$m_{J_1} = \frac{a\lambda}{2} x \quad (7)$$

$$m_{K_1} = \frac{a\lambda}{2} \left(1 - \frac{a\mu}{2}\right) y \quad (8)$$

$$m_{J_2} = \frac{a\lambda}{2} \left(1 - \frac{a\mu}{2}\right) x \quad (9)$$

$$m_{K_2} = \frac{a\lambda}{2} y \quad (10)$$

The outside attenuation effects, x and y , can be divided out by taking the ratio of the consecutive half-voxel measurements in a detector. This allows an expression for attenuation of the active pixel:

$$\frac{m_{J_2}}{m_{J_1}} = \left(1 - \frac{a\mu}{2}\right) \quad (11)$$

$$\mu = 2 \left(\frac{1}{a} - \frac{m_{J_2}}{am_{J_1}} \right)$$

An equation to determine the concentration at a given pixel is given below:

$$\ln(m_{J_1} m_{K_2}) - a\mu = 2 \ln\left(\frac{a\lambda}{2}\right) - \text{LineIntegral} \quad (12)$$

where the *LineIntegral* can be determined by either global reconstruction of the attenuation background, or by radiography in the case of interior reconstruction. The further propagation/attenuation process towards a detector element can be simply modeled according to a discretized Beer–Lambert law. In this way, the system matrix A can be constructed to solve the $Ax = b$ inverse problem. The imaging geometry during data acquisition is illustrated in Fig. 7, and the pseudocodes describing the reconstruction process are listed below:

Reconstruct the attenuation coefficients

- Do the following for each half of the pixel (row, column) assuming that each measured intensity is non-zero:
  - Set the component of vector b corresponding to the active half-pixel to the logarithmic ratio of measurements from detectors 1 and 2 (Eqs. (7–10));
  - Construct the corresponding rows and columns of system matrix A . The coefficients contained in A depend on pixel positions relative to the active half-pixel (each of which determines the contribution of a particular attenuating pixel to the normalized measurement);
- Solve the inverse problem to recover attenuation coefficients (the solution will be unique if the pixel is sufficiently small).

Recover the radiotracer concentration distribution

- Do the following for each pixel along the row direction:
  - Find flux escaping each side of the pixel using the Beer-Lambert law in a reverse order in terms of the reconstructed attenuation coefficients and known intensity measurements from each detector
  - Compute the average of the two flux estimates
  - Solve for the concentration of the pixel (Eq. (12))

Under ideal circumstances, the radiotracer will be widely distributed in the subject being imaged with high SNR so that the tissue attenuation can be accurately reconstructed from γ -ray signals everywhere. However, in practical cases where extensive perfusion of the tracer does not occur, a different reconstruction method is needed. Hence, interior tomography must be formulated here to reconstruct the attenuation coefficients in an ROI where the tracer concentration is significant [19], according to our continuous model. Then, to recover the tracer concentration within the ROI, effects of the object attenuation outside the tracer ROI must be estimated.

A source point can be introduced into the tracer ROI by an injection containing a small volume of radiotracer with a known concentration, as illustrated in Fig. 8 (inner light region). The detectors will then measure the emitted γ -ray intensities along a line through the ROI, and the attenuation effects can be calculated on both sides of the entire path length using the Beer-Lambert Law.

The attenuated measurements will cover both the light inner ROI and the light blue path segments intersection the active pixel. Since the attenuation coefficients in the tracer ROI have already been calculated, the attenuation of the non-tracer path section can be estimated from the difference. After that, the tracer concentrations along the line inside the ROI can be recovered. Additional pixels in the ROI can be activated to determine attenuation effects of other segments (light blue) outside the ROI to eventually recover the entire concentration distribution within the ROI.

III. NUMERICAL SIMULATION

The γ -ray intensity measurements were simulated based on our discretized forward model Eqs. (5–6). For simplicity, the simulation was not tailored to a specific radionuclide or decay time. The pixel size was set to 0.5 mm. The image matrix was 128×128 pixels. From m_l and m_r measurements of each active half-pixel, the attenuation and concentration images were reconstructed. A brain phantom was generated from a brain CT image (courtesy of Dr. Frank Gaillard, *Radiopaedia.org*) to demonstrate SET numerically according to Eqs. (5–12). The half-voxel activation technique was simulated for two different phantom cases.

The first case assumed that a radiotracer was distributed in the whole phantom with a background concentration of 0.05 MBq/ml, and that it became more significantly concentrated in ROIs [20], [21]. Specifically, eight ROIs were defined with concentrations ranging from 0.150 to 0.325 MBq/ml. The second case assumed that radiotracer was isolated to one ROI and was not widely distributed outside. When radiotracers are limited to ROIs, our interior SET method must be used to calculate the attenuation coefficients in the tracer regions. Then, the remaining background attenuation effects were found by one of two ways. First, we demonstrated the method of probing the phantom with a tracer point source of known concentration as described in Fig. 8. Second, we showed that a known tracer injection is not necessary if the line integrals along one dimensional can be determined as prior knowledge. This can be achieved by a simple radiograph.

A. Global reconstruction

The case of the phantom containing widely distributed tracer activities is presented in Fig. 9. The ground truth and noise-free reconstructed images of the attenuation are shown along with the corresponding difference image in Fig. 9(a–c). The mean reconstruction error of the attenuation map (Fig. 9(c)) was 2.58% in the brain region, with the largest errors in attenuation coefficient occurring at the edges. Fig. 9(f–h) shows the ground truth and noise-free reconstructed images of the radiotracer distribution along with the difference image. The concentration images calculated from the estimated attenuation values show good agreement with the ground truth, as the mean concentration errors in the ROIs range between 0.0007% and 0.0028%, as noted in Fig. 9(h).

A Poisson distribution of the measurements was then used to simulate noise when the photon counts were set to 10^8 . This estimate is based on the measurement of 5×10^5 photon counts per second of $^{131\text{m}}\text{Xe}$ as reported by the PNI methods. Over a several minute acquisition, the total photons would be approximately 10^8 . Note that this is a conservative case. In the future, a much higher emission efficiency could be expected of a polarizable tracer. Fig. 9(d,e) shows the attenuation image reconstructed from simulated noisy data, along with the difference compared to ground truth. Fig. 9(i,j) shows the noisy reconstruction of the radiotracer concentration image and the difference image. Noise increased the errors in both images.

B. Interior reconstruction

The second numerical experiment is to test our interior SET method noise-free and with Poisson noise added. Using the same brain phantom, a small region of radiotracer was defined slightly off-center. The ground truth attenuation and concentration maps corresponding to the ROI are shown in Fig. 10(a) and (f) respectively. Measurements were obtained from the ROI. Then, interior SET was used to reconstruct the attenuation coefficients and lumped effects inside and outside the ROI respectively.

Next, a known concentration of tracer was “injected” inside the ROI to allow estimation of attenuation effects outside the ROI along a line of emission. Using this information, the concentration was calculated for each pixel along the line. Note that after this step, all the concentration values along the lines intersecting the pixels with known concentrations inside the ROI can be considered known, without any additional need to introduce a known concentration point into the ROI. Using each solved “active” pixel along the same line as the known concentration point, the process can be repeated for other lines to recover the entire ROI radiotracer distribution (also see the whole-body SET scanner described in the Discussion). Fig. 10(b,c,g,h) displays the reconstructions and difference maps obtained using the interior SET method without noise. The mean error within the ROI of the attenuation image was 9.5% and the mean error in the concentration image was 0.38%. Fig. 10(d,e,i,j) display the reconstructions and difference images with Poisson noise added. The mean error in the attenuation image was 11.3% and the mean error in the concentration image was 0.42%.

Fig. 11 presents our results of the half-voxel activation scheme for interior SET with the assumption of known line integrals outside the ROI. For the noise-free case, the mean error within the ROI of the attenuation image was 12.66%, while the error within the concentration image was 9.78%. The largest errors are seen at the boundaries of each tracer concentration ring. With Poisson noise added to the measurements, the reconstruction error was 13.49% in the attenuation image and 9.81% in the concentration image.

IV. DISCUSSION

This work provides a holistic system design and mathematical formulation to perform global and interior simultaneous emission-transmission tomography (SET) in a novel way. Reconstruction results obtained from numerical simulation in both ideal and non-ideal cases demonstrate the imaging capabilities of our method. The tissue attenuation and

concentration images are determined simultaneously with high accuracy from γ -ray data. With noise added, the reconstruction method is able to handle the random variation. For interior SET, iterative reconstruction methods would further reduce effects from noise and artifacts in the images. Physical experiments are needed on a prototype SET system in order to assess the imaging performance and reconstruction scheme under realistic conditions.

The acquisition method of activating pixels line-by-line demonstrates the feasibility of high accuracy reconstruction in terms of both attenuation coefficients and tracer concentrations, but for practical purposes a more efficient method is certainly feasible, and indeed there is a great potential along this direction. For example, instead of activating one line of pixels each time, we can disable this line and detect the emission of all other pixels. In this way, only photons from the disabled pixel are “wasted”. More generally, the activation and detection scheme can be easily controlled by the gradient magnetic field, and more advanced reconstruction methods can be designed in the compressed sensing framework. Furthermore, by extending the field of view over the entire body surface, nearly all emitted photons can be captured by a cylindrical detector assembly. Whole-body PET is a promising research tool currently under development [22], [23], and this principle could be adapted for our SET approach to perform whole-body SPECT-CT in the MRI framework. If it is made successful and practical, this technology would allow a significant increase in image sensitivity, potentially for whole body cancer screening [23]. Fig. 12 illustrates an idealized SET system design.

The data acquisition methods or activation schemes we have described above are used to show the feasibility of the technology and the uniqueness of the solution. Alternative acquisition strategies can be more efficient and effective. In particular, a series of dynamic gradient magnetic fields can be used to modulate polarized signals in a sinusoidal fashion at different frequencies. The measurements will be the results of performing an attenuated Fourier transform, similar to magnetic particle imaging [24]. A sinusoidal excitation method should have a faster acquisition time than pixel-by-pixel activation, and needs to take the directional emission probability into account as a function of space and time. More advanced compressed sensing and machine learning techniques can be applied to improve the reconstruction quality.

Regarding the magnet subsystem of a SET prototype, there are several technologies available. A Helmholtz coil design with a field strength of less than 0.1 T would be the most straightforward. However, inhomogeneity in the field can be an issue, similar to the case of MRI. The addition of shimming coils could help improve field homogeneity in the imaging region. One alternative is an emerging technology called superconducting fibers that can achieve more efficient generation of the magnetic field [25]. These fibers are made with an iron core and fused silica cladding, and are capable of exhibiting superconductivity for an extended period of time after injection with liquid helium [26]. The fiber can be wound into coils to achieve a homogeneous main magnetic field with less power consumption.

Attenuation-based imaging tasks are currently performed with x-rays from an external radiation source, the x-ray tube. In our proposed SET scheme, polarized radiotracers are used to serve as internal sources for attenuation-based imaging via γ -rays, which have an

energy spectra close to that of x-rays. The internal source of signal means a shorter source-to-detector distance that greatly reduces the attenuation path length, and thus lowers the requisite radiation dose. This could be an out of box way to perform low-dose CT, as for a given imaging task, fewer photons would be needed compared to conventional CT methods. There is also an opportunity for a trinity system capable of CT-MRI-SPECT given that the SET system can be equipped for MRI as well. This would enable higher level synergy relative to two-modality scanners, such as PET-CT, PET-MRI, and CT-MRI reported in other papers [5], [27].

V. CONCLUSION

In conclusion, our SET method presents a unique way to acquire simultaneous emission and transmission data from γ -ray measurements of a polarized radionuclide activated by MRI hardware, with the potential for MR imaging in synchrony. The combined information, perfectly co-registered, provides insight into morphological features and molecular activity in an ROI. Numerical simulation shows the accurate reconstruction scheme for global and interior imaging. A physical prototype with this capability would be particularly useful to analyze many types of biomedical problems in diagnostic settings and beyond. In order to achieve this goal, an appropriate radioisotope must be identified/developed that meets the polarization and half-life needs for clinically relevant imaging. Previous studies explored xenon isotopes for *in vivo* biosensors [28]–[30], and the SET idea provides a novel platform for us to brainstorm for more techniques and applications.

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Fig. 1.

(a) Angular plot of γ -ray emission probability at varying levels of nuclei polarization. Without polarization (solid inner circle – red), the probability is equal in every direction. As polarization approaches 100% (dashed inner ellipses – green), the emission probability significantly favors the axis perpendicular to the nuclei orientation, resulting in high count rates in a transverse detector. (b) Any pixel/voxel can be magnetically turned on or off and γ -rays are simultaneously emitted and attenuated by this pixel/voxel. Transverse detectors on both sides of the voxel measure the emitted photons.

Fig. 2.

Three RF pulses combined with gradients in the x-, y-, and z-directions can be used to activate any cross section, any line in the active section, and even any single voxel along the line. The entire pulse sequence targeting a single voxel or a region of interest is known as point-resolved spectroscopy. Only nuclei within the intersection region of the gradient pulses will undergo refocusing (small central cube – purple), and thus only these nuclei emit γ -rays along the line of detection. Note that if a section (or a line in the section) is to be activated, only one (or two) gradient(s) should be applied, and must be timed differently for best focusing.

Fig. 3.

Simplified SET system designs for demonstration of the working principle. (a) System containing Helmholtz coils (outer rings: gray – 0.56 m in diameter and spaced 0.2 m apart), gradient coils (inner ring sections: red and green), RF coils (inner transparent cylinder – 0.1 m in diameter and 0.2 m long), and γ -ray detectors with collimators (orange and blue blocks – 0.2 m by 0.2 m). (b) A simplified system with an emphasis on interior SET. Signals are collected by a pair of collimated γ -ray detectors (red collimators in front of green scintillator layer). An ROI for interior SET is highlighted within the mouse. Adapted from [11], [12].

Fig. 4.

Illustration of dynamic nuclear polarization. When a nucleus is surrounded by coupled electron spins, irradiation of a particular electron at a certain frequency causes other coupled electron spins to flip. If the spins at other resonance frequencies have slightly different energies, the energy difference can be made up with a coupled nuclear spin. As a result, the nuclear polarization can be enhanced under microwave irradiation at the electron resonance frequency $\pm$ the nuclear frequency.

Fig. 5.

Diagram of the SABRE technique. Para-hydrogen can hyperpolarize another substrate when it transiently interacts with the substrate via reversible binding to a coordination center $[\text{M}]$. Polarization is transferred from H_2 to the substrate (this process is labelled by the darker circles – red).

Fig. 6.

Half-voxel offset activation enables doubling of sampling resolution. In a single voxel case, the γ -ray signals (J and K) measured by the left (L) and right (R) collimated detectors are different when each half of the voxel is activated separately.

Fig. 7.

Imaging geometry showing detector positions relative to numerical phantom during measurement of emitted γ -rays.

Fig. 8.

Interior SET aided by a single measurement with a known source point. The tracer ROI is shown in the light region (yellow) and the remaining object region is darker (purple). A probe needle with a known tracer concentration can be inserted to establish a reference point (shaded pixel – red), and the γ -ray intensities are measured by the collimated detector pair, represented by vertical slabs.

Fig. 9.

SET reconstruction from half-voxel activation measured by detectors on each side of the head phantom. (a) The ground truth attenuation image (cm^{-1}), (b) the reconstruction result without noise, and (c) the difference; (d) the reconstruction result with noise added, and (e) the difference compared to ground truth; (f) The ground truth concentration image (MBq/ml), (g) the reconstruction result without noise, and (h) the difference image with mean error percentages for each ROI shown; (i) The reconstructed radiotracer concentration image with noise added and (j) the difference compared to the ground truth.

Fig. 10.

Interior SET reconstruction results measured by detectors on each side of the head phantom in the vertical and horizontal directions. A known source point of radiotracer was injected to facilitate calculation of the concentration map. (a) The ground truth ROI attenuation image (cm^{-1}), (b) the reconstructed attenuation image without noise, and (c) the difference compared to ground truth; (d) The reconstructed attenuation image with noise added and (e) the difference compared to the ground truth; (f) The ground truth ROI radiotracer concentration image (MBq/ml), (g) the reconstructed concentration image without noise, and (h) the difference; (i) The reconstructed radiotracer concentration image with noise and (j) the difference compared to the ground truth.

Fig. 11.

Interior SET reconstruction results using the half-voxel activation scheme. Attenuation line integrals along the horizontal direction were assumed to be known outside the ROI to facilitate calculation of the concentration map. (a) The ground truth ROI attenuation image (cm^{-1}), (b) the reconstructed attenuation image without noise, and (c) the difference; (d) The reconstructed attenuation image with noise added and (e) the difference compared to the ground truth; (f) The ground truth ROI radiotracer concentration image (MBq/ml), (g) the reconstructed concentration image without noise, and (h) the difference; (i) The reconstructed radiotracer concentration image with noise added and (j) the difference compared to the ground truth.

Fig. 12.

System design for whole-body SPECT-CT containing Helmholtz coils (gray), gradient coils (red and green), a cylindrical γ -ray detector array (orange), and a patient table. Note that for clarity only a top portion of MR components are shown for the whole-body SPECT-CT system rendering.

TABLE 1

Characteristics of some radioisotopes that are the best known candidates for SET at this time. However, these would not be practical for clinical imaging.

Isotope	Half-life	Spin number	γ -ray Emission (keV)	γ -ray Branching Ratio
^{131m}Xe	12 days	11/2	164	2%
^{127m}Xe	69 sec	9/2	124.8–172.5	38%
^{79m}Kr	50 sec	7/2	130	27%