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Event-by-event respiratory motion correction for PET with 3D internal-1D external motion correlation

Chung Chan
Department of Diagnostic Radiology, Yale PET Center, School of Medicine, Yale University, New Haven, Connecticut 06520

Xiao Jin and Edward K. Fung
Department of Diagnostic Radiology, Yale PET Center, School of Medicine, Yale University, New Haven, Connecticut 06520 and Department of Biomedical Engineering, Yale University, New Haven, Connecticut 06520

Mika Naganawa and Tim Mulnix
Department of Diagnostic Radiology, Yale PET Center, School of Medicine, Yale University, New Haven, Connecticut 06520

Richard E. Carson and Chi Liu
Department of Diagnostic Radiology, Yale PET Center, School of Medicine, Yale University, New Haven, Connecticut 06520 and Department of Biomedical Engineering, Yale University, New Haven, Connecticut 06520

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Purpose: Respiratory motion during PET/CT imaging can cause substantial image blurring and underestimation of tracer concentration for both static and dynamic studies. In this study, the authors developed an event-by-event respiratory motion correction method that used three-dimensional internal-one-dimensional external motion correlation (INTEX3D) in listmode reconstruction. The authors aim to fully correct for organ/tumor-specific rigid motion caused by respiration using all detected events to eliminate both intraframe and interframe motion, and investigate the quantitative improvement in static and dynamic imaging.

Methods: The positional translation of an internal organ or tumor during respiration was first determined from the reconstructions of multiple phase-gated images. A level set (active contour) method was used to segment the targeted internal organs/tumors whose centroids were determined. The mean displacement of the external respiratory signal acquired by the Anzai system that corresponded to each phase-gated frame was determined. Three linear correlations between the 1D Anzai mean displacements and the 3D centroids of the internal organ/tumor were established. The 3D internal motion signal with high temporal resolution was then generated by applying each of the three correlation functions to the entire Anzai trace (40 Hz) to guide event-by-event motion correction in listmode reconstruction. The reference location was determined as the location where CT images were acquired to facilitate phase-matched attenuation correction and anatomical-based postfiltering. The proposed method was evaluated with a NEMA phantom driven by a QUASAR respiratory motion platform, and human studies with two tracers: pancreatic beta cell tracer \([^{18}\text{F}]\text{FP}(+)\text{DTBZ}\) and tumor hypoxia tracer \([^{18}\text{F}]\text{fluormisonidazole}\) (FMISO). An anatomical-based postreconstruction filter was applied to the motion-corrected images to reduce noise while preserving quantitative accuracy and organ boundaries in the patient studies.

Results: The INTEX3D method yielded an increase of 5%–9% and 32%–40% in contrast recovery coefficient on the hot spheres in the NEMA phantom, compared to the reconstructions with only 1D motion correction (INTEX1D) and no motion correction, respectively. The proposed method also increased the mean activities of the pancreas and kidney by 9.3% and 11.2%, respectively, across three subjects in the FPDTBZ studies, and the average lesion-to-blood ratio by 20% across three lesions in the FMISO study, compared to the reconstructions without motion correction. In addition, the proposed method reduced intragate motion as compared to phase-gated images. The application of the anatomical-based postreconstruction filter further reduced noise in the background by >50% compared to reconstructions without postfiltering, while preserving quantitative accuracy and organ boundaries. Finally, the measurements of the time-activity curves from a subject with FPDTBZ showed that INTEX3D yielded 18% and 11% maximum increases in tracer concentration in the pancreas and kidney cortex, respectively.
1. INTRODUCTION

Respiratory motion is one of the major degrading factors in PET/CT imaging. Typical diaphragm motion amplitude due to respiration is 11 mm on average in the superior-inferior (SI) direction.1, 2 The motion is more complicated for organs in the thorax and lower abdomen because the chest and abdomen also expand/contract in the anterior-posterior (AP) and left-right (LR) directions during respiration. These motions can cause substantial image blurring and reduced contrast and accuracy in disease detection and radiotracer quantification for both static and dynamic studies.

Many methods have been proposed to correct for respiratory motion in the literature.3–6 The most common approach is respiratory gated PET/CT, which divides PET data into different gates based on either temporal phase or respiratory displacement information.7, 8 However, this method suffers from a substantial increase in image noise as only a fraction of the detected coincidence events is used, leading to potentially reduced signal-to-noise ratios (SNR).9 In order to use all events to correct for motion, methods were proposed to obtain motion vectors from respiratory gated CT or PET, and incorporate them into image reconstruction10–12 or postprocessing.9, 13 However, these methods do not account for intragate motions due to intercycle and intracycle motion variations.5 In addition, most of the existing respiratory motion correction methods rely on retrospective binning for the entire data acquisition, thus can only be applied in static imaging, but not in dynamic imaging, which requires challenging motion correction for each time point.

To correct for intragate motion and to correct motion for dynamic PET imaging, internal motion information with high temporal resolution is required, and the most desirable motion correction should be able to correct individual lines of response (LOR) on an event-by-event basis during reconstruction.10, 14, 15 However, obtaining internal organ motion information with high temporal resolution is very challenging. Previously, we proposed to convert external respiratory chest/abdomen motion, which was recorded at high temporal resolution in the AP direction, into internal organ movement in the SI direction. This was achieved by a linear correlation established between the mean displacement of the external motion trace and the center of mass of the internal tumor for each respiratory gate.16 However, the previous study only corrected motion in the SI direction in sinogram space with finely rebinned sinograms (1 s per frame). Therefore, the motion correction may be suboptimal if the patient has large breathing amplitude in the AP and LR directions. In addition, the 1-s sinogram rebinning in the previous study reduced intragate motion by eliminating intercycle variations, but is still subject to minor intracycle variations.

In this study, we extended the internal-external motion correlation method (INTEX) (Ref. 16) to three-dimensions (3D) and incorporated the estimated motion parameters in the Motion compensation OSEM List-mode Algorithm for Resolution recovery reconstruction (MOLAR) with time-of-flight (TOF) capability for event-by-event motion correction.15, 17, 18 The reference location was determined as the location where CT images were acquired to facilitate phase-matched attenuation correction and anatomical-based postfiltering. We also investigated its applicability to dynamic studies. A preliminary report of this work was previously presented in Ref. 19. The proposed method was first evaluated with a moving NEMA phantom driven by a real patient respiratory motion trace, and four human subjects with two tracers: [18F]FDG and [18F]fluoromisonidazole (FMISO) for assessing the hypoxia level in lung lesions.21 All studies were acquired on a Siemens Biograph mCT PET/CT scanner with TOF capability. For patient studies, we also applied a 3D anatomical-based median nonlocal means (AMNLM) filter22, 23 to the motion-corrected images that incorporate the accurately aligned CT information to suppress noise while preserving quantitative accuracy and organ boundaries.

2. METHODS

2.A. The Biograph mCT scanner

In this study, all the data were acquired on a Biograph mCT scanner. The scanner consists of four rings of 48 blocks, each of which contains 13 × 13 crystals (4.01 × 4.01 × 20 mm). The TOF information of the detected events is measured with 78 ps time bins, and rebinned into 13 time bins with 312 ps bin width and 580 ps FWHM.24

2.B. Respiratory signal analysis and processing

Studies have shown that a linear correlation between rigid internal organ or tumor motion and measured external motion signal that characterizes chest/lower abdomen movement can be established.16, 25–30 This can be done by measuring the mean displacement of the external motion trace and the center of mass of the internal organ/tumor for each phase gated image. In this study, the external respiratory motion in the AP direction was monitored by the Anzai belt system (Anzai Medical, Tokyo, Japan), which was attached to the patient’s lower abdomen, and the respiratory trace was recorded at
40 Hz. The trace was first phase-binned into eight gates based on the triggers registered at each inspiration peak. The mean displacements of the Anzai trace that corresponded to each phase gate were determined. Due to the fact that inspiration peaks were determined prospectively by the Anzai system, baseline variation may produce some missing triggers at the inspiration peaks. In such cases, the data acquired without inspiration triggers were discarded in both the trace and the initial gated reconstructions to establish a more accurate linear correlation that will be introduced in Sec. 2.C. Note that these missing data were included in the final INTEX reconstructions as the motion field of the internal organ was converted from the entire respiratory trace.

2.C. 3D internal-1D external motion correlation

To determine the positional translation of an internal structure, i.e., organ or lesion, during respiration, the listmode data acquired on the mCT scanner were binned into eight phase gates. Then, a scout reconstruction using OSEM with three iterations, 21 subsets with point-spread-function (PSF) and TOF was performed on these rebinned raw data with the manufacturer’s algorithm. A level-set (active contour) segmentation method was used to segment the targeted internal manufacturer’s algorithm. A level-set (active contour) segmentation method was used to segment the targeted internal organ/lesion during respiration, the listmode data from the entire respiratory trace.

Missing data were included in the final INTEX reconstructions as the motion field of the internal organ was converted from the entire respiratory trace.

2.D. Reference frame and matched attenuation correction

In this study, the reference frame was chosen at the end-expiration period, at which CT images were acquired for attenuation correction to minimize any attenuation correction mismatch. By monitoring the subject respiratory traces on the Anzai system, the subject was directed to hold their breath at end-expiration when CT data were acquired.

2.E. Motion compensation and postprocessing

The transformation matrix was incorporated into TOF-MOLAR reconstruction in listmode notation as described in Eq. (1)

\[ \lambda_{j_{n+1}} = \frac{\lambda_{j_{n}}}{Q_j} \sum_{k=1}^{K} T(\sum_{j'} C_{i_{n},t_j,j} L_{i_{n},t_j} A_{i_{n},t_j} N_{i_{n},t_j} \xi_{i_{n},t_j,t_k,j}^n + R_{i_{n},t_j,t_k} + S_{i_{n},t_j,t_k}), \]

where

\[ Q_j = \frac{1}{n_T} \sum_{t_1}^{n_T} \sum_{t_2}^{n_T} \sum_{t_3}^{n_T} C_{i_{n},t_j,j} L_{i_{n},t_j} A_{i_{n},t_j} N_{i_{n},t_j} \xi_{i_{n},t_j,t_k,j}, \]

\[ i_{k} = \delta_{k}(i_{k}), \]

and the system matrix that represents the contribution of voxel \( i_{k} \) to LOR \( i_{k}^n \) inside the CT, accounting for geometry, resolution, and solid angle effects. \( L_{i_{n}} \) is the decay factor, \( A_{i_{n}} \) is the attenuation factor, \( N_{i_{n}} \) is the sensitivity (normalization) term, \( R_{i_{n},t_j,t_k} \) is the randoms rate estimate, and \( S_{i_{n},t_j,t_k} \) is the scatter rate estimate. Each time frame of duration \( T \) (s) is divided into \( n_T \) sub-bins of duration \( t \) in seconds. \( n_T \) represents the total number of TOF bins (\( n_T = 13 \) for the mCT). \( \xi_{i_{n},t_j,t_k,j}^n \) is the TOF kernel indicating the contribution of image voxel \( j \) to time bin \( t_k \) on LOR \( i_{k}^n \). To perform event-by-event motion correction, as illustrated in Fig. 1, the position of each LOR was first corrected by a
constructed human studies with motion correction.\textsuperscript{22, 23} While nonlocal means filter (AMNLM) was also applied to the re-
was aligned accurately at end-expiration location after res-
was used to model the point-spread function. As PET and CT
els. A spatially invariant Gaussian kernel with 4-mm FWHM
at three iterations and 21 subsets using 2
rection is summarized in Fig. 2.
transformation matrix $\mathbf{T}$ that transforms the endpoint coordi-
nates of LOR $i_k$, to $i_k'$, the comparable LOR in the reference
position, such as at the end-expiration phase where the attenu-
ation CT was acquired. In this application, the transformation
matrix consisted of time-dependent translations in $x$, $y$, and $z$, but no rotations. A motion-dependent sensitivity image $Q$
was computed from a subset of randomly selected LORs. The
details of TOF-MOLAR implementation can be found in Refs.\textsuperscript{17 and 18. The workflow of the proposed motion cor-
rection is summarized in Fig. 2.

In this study, the images were reconstructed with MOLAR
at three iterations and 21 subsets using $2 \times 2 \times 2$ mm vox-
els. A spatially invariant Gaussian kernel with 4-mm FWHM
was used to model the point-spread function. As PET and CT
were aligned accurately at end-expiration location after res-
piration motion correction, an anatomically guided median
nonlocal means filter (AMNLM) was also applied to the re-
constructed human studies with motion correction.\textsuperscript{22, 23} While
details can be found in Refs.\textsuperscript{22 and 23, a brief description
of AMNLM filter is given here. To suppress noise, this filter
computes the weighted average of voxels based on a simi-
larity measurement between 2D patches of voxels within a
3D search window in the image. Anatomical knowledge ob-
tained from the accurately aligned attenuation CT was incor-
porated through a segmentation-free approach to preserve or-
gan boundaries. This filter has been demonstrated to suppress
noise effectively while preserving signal and boundaries for
whole body PET/CT images, thus leading to improved SNR.
In this study, the dimension of the 3D search window $N$ and
the 2D patch $M$ were set to $11 \times 11 \times 3$ and $3 \times 3$, respecti-
vively, as previously proposed.\textsuperscript{22} The smoothing parameter $h$
was determined as $\sqrt{2} \sigma$, where $\sigma$ was the standard deviation
in a region-of-interest (ROI) that was expected to have uni-
form uptake, such as in the liver region for the FPDTBZ and
lung region for the FMISO studies, respectively.

3. EXPERIMENTS AND EVALUATIONS

3.A. Phantom experiment

A phantom experiment was performed to evaluate the
proposed INTEX3D for respiratory motion correction. The
NEMA IEC Body phantom filled with 74 MBq of $[^{18}F]$FDG
was placed on the QUASAR programmable respiratory
motion platform (Modus Medical Devices, Inc., London,
Canada). Four hot spheres (10, 13, 17, 22 mm in diameter)
had a contrast of 4:1 to the background, and two cold spheres
(28, 37 mm in diameter) were filled with water. A static PET
scan without motion was first acquired to serve as the ground
truth. To create motion in the AP and LR directions, we raised
the platform by $\sim 2.5$ cm and tilted it by $\sim 7^\circ$ as shown in
Fig. 3(a). The movement of the platform was driven by a typ-
ical patient’s respiratory trace as shown in Fig. 3(b). This trace
was rescaled in mm, thus the displacement of the motion plat-
form in the SI direction matches with the magnitude of the
rescaled motion trace. Data were acquired on the Siemens Bi-
ograph mCT PET/CT scanner for 10 min. The attenuation CT
was acquired at the end-expiration position where the mo-
tion of the platform was suspended. To assess the effective-
ness of 3D motion correction, these data were reconstructed
with no motion correction (NMC), motion correction in one-
dimensional superior-inferior direction only (INTEX1D), and
3D motion correction (INTEX3D). For quantitative evalua-
tion, contrast recovery coefficient (CRC) was computed as
\[
\text{CRC} = \frac{M_{\text{hot}}/M_{\text{bkg}} - 1}{C_{\text{true}} - 1},
\]
where $M_{\text{hot}}$ and $M_{\text{bkg}}$ are the mean values in the hot spheres
and in the background regions, respectively. The volumes of interest (VOI) of the hot spheres were defined from the
CT images, i.e., they encompassed the entire sphere, and the
background VOIs were defined as four spheres with diameter
30 mm in the background. $C_{\text{true}} = 4$ is the true contrast value
between the hot spheres and the background, measured by
samples counted in a gamma counter.

3.B. Human studies: $[^{18}F]$FP$\text{(+)}$DTBZ

The proposed method was applied to scans from
three healthy control human subjects with approval of
our institutional review board (IRB) and injected with
$[^{18}F]$FP$\text{(+)}$DTBZ.\textsuperscript{20} This tracer binds to the VMAT2 site,
which is expressed in beta cells in the pancreas and can be

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{An illustration of event-by-event motion correction during recon-
struction. LOR $i_k$ generated at $(x,y,z)$ during inspiration, is transformed to a
reference location, i.e., end-expiration $(x_1,y_1,z_1)$ where the attenuation CT
was acquired, as LOR $i_k'$.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{The work flow of INTEX3D and MOLAR reconstruction.}
\end{figure}
used to study patients with diabetes. An average of 248 MBq was injected and the first 10 min of the 2-h scan was analyzed. The Anzai system was attached to the subject’s lower abdomen to record the respiratory motion. Since kidney cortex has been used as the reference region in kinetic modeling, it is crucial to correct respiratory motion of both pancreas and kidney. As will be shown in Sec. 4.B, the motion amplitude and internal-external correlations of pancreas and kidney were consistent for all the subjects, therefore the transformation matrices were generated from the pancreas and applied to the entire FOV. INTEX3D was applied to a 10-min acquisition with simulated respiratory motion are shown in Figs. 4(b)–4(e), respectively. The motion platform yielded an average motion of ∼18 mm in the SI direction, and ∼3 mm motion in the AP and LR directions, as measured from the mean displacements of the centroid of the 22 mm hot sphere. The correlation coefficients in the LR, AP, and SI directions were 0.77, 0.72, and 0.92, respectively. It can be observed that the moving phantom acquisition without motion correction caused substantial blurring of the hot spheres. The 10- and 13-mm spheres were smeared into the background, as seen in the coronal and sagittal views, respectively. The cold sphere (28 mm) was also blurred in the SI direction as seen in the sagittal view. The phase gating compensated for motion and restored all the hot spheres at the expense of substantial increase in image noise, which led to reduced image quality visually. INTEX1D corrected the motion in the SI direction, and restored the shape of the cold

3.D. Quantitative evaluations in human studies

The quantitative evaluations were assessed by measuring mean activity concentrations (Bq/ml) in pancreas and kidney for the FPDTBZ studies, and lesion-to-blood ratio (L/B) was computed to assess the level of hypoxia of the lesions for the FMISO study. The organ/lesion VOIs were defined by applying the level set segmentation on the reconstructed images with INTEX3D motion correction. The same VOI was also applied to the gated images at end-expiration phase. For NMC and INTEX1D images, the VOIs were shifted according to the average organ displacement. To evaluate image noise levels, we also computed the standard deviations in the background VOIs (i.e., liver/soft tissue) using a sphere with 20 mm diameter. For the FMISO study, since the normoxic tissues have tissue-to-blood ratio of almost 1, the activity in blood was measured as the mean value from a large VOI (a sphere with 30 mm diameter) in the heart that consists of both blood pool and myocardium where the radiotracer uptake was uniform.

4. RESULTS

4.A. NEMA phantom study

The reconstructions of the NEMA phantoms are shown in Fig. 4. The central slices that cut through the 10-mm sphere in the transaxial and coronal views, and the 13-mm sphere in the sagittal view are displayed in each column. The images shown in Fig. 4(a) were reconstructed from the static acquisition. The images reconstructed with NMC, the end-expiration gate of eight-bin phase gating, INTEX1D, and INTEX3D from the acquisition with simulated respiratory motion are shown in Figs. 4(b)–4(e), respectively. The motion platform yielded an average motion of ∼18 mm in the SI direction, and ∼3 mm motion in the AP and LR directions, as measured from the mean displacements of the centroid of the 22 mm hot sphere. The correlation coefficients in the LR, AP, and SI directions were 0.77, 0.72, and 0.92, respectively. It can be observed that the moving phantom acquisition without motion correction caused substantial blurring of the hot spheres. The 10- and 13-mm spheres were smeared into the background, as seen in the coronal and sagittal views, respectively. The cold sphere (28 mm) was also blurred in the SI direction as seen in the sagittal view. The phase gating compensated for motion and restored all the hot spheres at the expense of substantial increase in image noise, which led to reduced image quality visually. INTEX1D corrected the motion in the SI direction, and restored the shape of the cold

3.C. Human studies: FMISO

We further evaluated the proposed method on a nonsmall cell lung cancer (NSCLC) patient study with approval of our IRB and injected with FMISO, a PET tracer used to measure tumor hypoxia. Due to the low contrast of this tracer, it is critical to correct for respiratory motion to achieve higher lesion-to-blood contrast and quantitative results. The patient was injected with 180 MBq FMISO and a 30-min scan was acquired 2.5 h after the injection. Similarly, the Anzai system was attached to the patient’s lower abdomen, and the images were reconstructed with NMC, the end-expiration phase of eight-bin phase gating, INTEX1D, and INTEX3D.

FIG. 3. (a) Illustration of the NEMA phantom setup placed on the QUASAR motion platform. The bold arrows indicate the displacement in each direction. (b) The respiratory trace used to drive the QUASAR motion platform. The first 180 s data are shown here.
FIG. 4. Reconstructed images of the NEMA phantom in transaxial, coronal, and sagittal views. Images in each row are the central slices that cut through the smallest sphere in that view. The axis in the first row indicates the directions of the respiration motion in that view. (a) The static acquisition. The acquisition with motion and reconstructed with (b) NMC, (c) The end-expiration gate of eight-bin phase gating, (d) INTEX1D, and (e) INTEX3D.

sphere. However, the hot spheres were slightly blurred in the horizontal direction when compared to the static acquisition visually. INTEX3D corrected the motion in all directions and yielded similar image quality to the static scan visually.

Table I presents the CRC of each sphere from all reconstructions; the % bias between each reconstruction and the static scan are shown in parentheses. Respiratory motion caused $-54.0\%$, $-49.5\%$, $-43.3\%$, and $-36.1\%$ bias in CRC on the 10, 13, 17, and 22 mm hot spheres, respectively. Phase gating yielded $8.7\%$ overestimation in CRC on the 10 mm hot sphere due to the increased noise, and reduced the bias to $-8\%$, $-4.9\%$, and $-6.5\%$ on the 13, 17, and 22 mm hot spheres, respectively. Although INTEX1D recovered the CRC to some extent, there were still $-14.6\%$ and $-13.9\%$ biases in CRC on the smaller hot spheres (10 and 13 mm), and $-10.2\%$ and $-7.4\%$ biases on the larger hot spheres (17 and 22 mm). By correcting the motion in all directions, INTEX3D further reduced the bias in CRC to $4\%$–$5\%$ for the smaller spheres and $2\%$ for the larger spheres as compared to the static scan.

4.B. Human studies: $[^{18}F]FP(+)-DBZ$

The segmentation results of the pancreas and kidney across eight gates from a sample subject are shown in Fig. 5. The horizontal lines above and under each organ indicate the highest and lowest positions of the objects across eight respiratory gates to illustrate the magnitude of organ displacements, where gate 4 and 8 correspond to the end-expiration and inspiration gates, respectively.

The motion amplitudes measured from the centroids of the segmented pancreas in SI, AP, and LR axis, between the peak inspiration gate and end-expiration gate, for all three subjects are shown in Table II. It can be seen that the organ displacement in the LR direction was negligible compared to the intrinsic resolution of the PET scanner ($\sim 4\text{ mm}$) and voxel dimension (2 mm) for all subjects. However, the motion in the AP direction was relatively large for subject 1. Table II also showed that the variation of motion amplitudes across subjects can be substantial, thus motion correction may significantly reduce intersubject variation in quantitative outcome measures.

The correlations between the centroids of the pancreas and kidney with the Anzai trace of a sample subject in the LR, AP, and SI directions are shown in Fig. 6. The means and standard deviations of the correlation coefficient for the pancreas of all the subjects were $0.43 \pm 0.35$, $0.85 \pm 0.15$, and $0.93 \pm 0.05$ for LR, AP, and SI, respectively. This shows high correlation was obtained in the SI and AP directions, but not in the LR direction. As the motion in the LR direction was negligible (Table II) and its correlation with the external trace was poor, we therefore applied INTEX3D in the AP and SI directions only for these subjects. The summary of the slopes of the regression lines for both pancreas and kidneys in the

Table I. CRC of the NEMA phantom study. The percentage changes compared to the static acquisition are shown in the parentheses.

<table>
<thead>
<tr>
<th>Sphere (mm)</th>
<th>Static</th>
<th>NMC</th>
<th>End-expiration gate</th>
<th>INTEX1D</th>
<th>INTEX3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.65</td>
<td>0.30 (−54.0%)</td>
<td>0.71 (8.7%)</td>
<td>0.56 (−14.6%)</td>
<td>0.62 (−4.9%)</td>
</tr>
<tr>
<td>13</td>
<td>0.88</td>
<td>0.45 (−49.5%)</td>
<td>0.81 (−8.0%)</td>
<td>0.76 (−13.9%)</td>
<td>0.85 (−3.8%)</td>
</tr>
<tr>
<td>17</td>
<td>0.91</td>
<td>0.53 (−43.3%)</td>
<td>0.87 (−4.9%)</td>
<td>0.82 (−10.2%)</td>
<td>0.89 (−2.0%)</td>
</tr>
<tr>
<td>22</td>
<td>0.96</td>
<td>0.61 (−36.1%)</td>
<td>0.90 (−6.5%)</td>
<td>0.89 (−7.4%)</td>
<td>0.94 (−2.0%)</td>
</tr>
</tbody>
</table>

Table II. Motion amplitudes of three subjects for $[^{18}F]FP(+)-DBZ$ measured from the centroids of the pancreas.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>LR (mm)</th>
<th>AP (mm)</th>
<th>SI (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>9.1</td>
<td>17.4</td>
</tr>
<tr>
<td>2</td>
<td>1.3</td>
<td>3.8</td>
<td>8.3</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>3.7</td>
<td>7.4</td>
</tr>
<tr>
<td>Mean</td>
<td>0.9</td>
<td>5.5</td>
<td>11.0</td>
</tr>
</tbody>
</table>
FIG. 6. The linear correlations between the center of mass (COM) of the (a) pancreas and (b) kidney with Anzai mean displacement derived from eight respiratory gates of a sample human study. The correlation in the LR direction was small since the motion in that direction was negligible and its correlation with the external trace was poor. The numbers denote the corresponding gating phase where gates 5 and 8 were the end-expiration and inspiration gates, respectively.

AP and SI directions is shown in Table III. The consistency of the slopes reveals that pancreas and kidney moved together, so the same regression line and thus the same transformation matrix were applied to both organs in the reconstruction.

The sample reconstructed slices of pancreas and kidney of all the subjects are shown in Figs. 7 and 8, respectively. As can be seen in the NMC images, the pancreas and the fine structures on the kidney cortex (denoted by arrows) were blurred due to respiratory motion. Although the single gated reconstruction at end-expiration phase compensated for respiratory motion, it yielded substantially increased image noise due to the fact that only a portion of the counts was used in the reconstruction. INTEX1D recovered the fine structures to some extent; however, it can be observed that some blurring still remained in the image, as compared to INTEX3D, that was caused by the motion in the AP direction. As the INTEX methods preserved all the events in the reconstruction, both images with 1D and 3D motion correction showed similar noise level to the NMC images. Finally, the application of the AMNLM to the INTEX3D reconstructions suppressed noise effectively, preserved sharp organ boundaries, and yielded lower noise images than other methods.

Figure 9 presents the images reconstructed using eight-bin phase gating with and without incorporating INTEX3D at both end-expiration and inspiration phases. This comparison demonstrates the effectiveness of correction for intragate motion achieved by the event-by-event approach at high temporal resolution. It can be seen that, at end-expiration, the visual differences between gated reconstruction without intragate motion correction and gated INTEX3D reconstruction are subtle. This is because the end-expiration phase is generally motion free, consistent with our previous observations.35 In contrast, the gated images at inspiration phase show more pronounced differences in the pancreas, fine structures of kidney cortex, and the liver domes, as denoted by the arrows. These objects are more blurred than in the images at end-expiration phase. This was due to larger intragate motion during inspiration phase. Indeed, the standard deviations of the displacement measured from the Anzai trace for three subjects were $11.1 \pm 3.4$ and $6.2 \pm 1.8$ at inspiration and end-expiration phases, respectively. The bigger variation of the displacement value (unitless) also reveals the larger intragate motion during inspiration phase. In contrast, these objects appear with similar resolution in both inspiration and end-expiration phases of the images reconstructed with INTEX3D due to the intragate motion correction.

Tables IV and V summarize the percentage changes of the activity in pancreas and kidney, respectively, as compared to

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Pancreas</th>
<th>Kidney</th>
<th>Pancreas</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AP</td>
<td>SI</td>
<td>AP</td>
<td>SI</td>
</tr>
<tr>
<td>1</td>
<td>$-0.0789$</td>
<td>$-0.1937$</td>
<td>$-0.0799$</td>
<td>$-0.2013$</td>
</tr>
<tr>
<td>2</td>
<td>$-0.1278$</td>
<td>$-0.2388$</td>
<td>$-0.1229$</td>
<td>$-0.2359$</td>
</tr>
<tr>
<td>3</td>
<td>$-0.0682$</td>
<td>$-0.1482$</td>
<td>$-0.0688$</td>
<td>$-0.1532$</td>
</tr>
</tbody>
</table>
the images without motion correction. It can be seen that the gated reconstruction led to an average of 9.9% and 11.8% increase of radioactivity concentration in pancreas and kidney, respectively. INTEX1D improved the concentration by 6.8% and 6.4% in pancreas and kidney, respectively. INTEX3D further improved these increments to 9.3% and 11.2%, which is similar to the percentage improvements achieved by the gating method. These tables also show that the correction of motion in the AP direction can be critical for the subjects with large breathing magnitudes in three dimensions, such as subject 1, who had ~9 mm AP motion. INTEX1D only improved the uptake concentration by 10.6% in the kidney cortex while INTEX3D achieved 17.1% increase. The INTEX3D reconstruction with AMNLM postfiltering yielded similar improvement to the mean radiotracer concentration as INTEX3D.

Table VI presents the standard deviation of a VOI within the liver, where the uptake was relatively uniform, to reveal the noise level. As expected, the standard deviations in gated images are about twofold that of NMC and reconstructions with INTEX due to the fact that only a fraction of the events were used to reconstruct a single gated image. In contrast, the INTEX approach used all the counts and thus yielded similar noise level as NMC images. The application of the AMNLM filter on INTEX3D images suppressed the image noise effectively and led to an average of 64% reduction in standard deviation as compared to INTEX3D while preserving the mean activity (as shown in Tables IV and V), and thus led to improved SNR.

The pancreas and kidney TACs of subject 1 from the first 10 min are shown in Fig. 10. Compared to the NMC
reconstruction, INTEX3D yielded 18% and 11% maximum increases in the radioactivity in pancreas and kidney cortex, respectively. The shape of TAC also changed slightly due to motion correction. These corrections may lead to more accurate parameter estimation and need further investigation. Note the activity increase in the organs was not uniform across time. The maximum activity increase was obtained at 10-min in the pancreas and 2-min in the kidney, due to the dynamic changes of tracer concentration in these organs.

4.C. FMISO patient results

Figure 11 presents the results of the FMISO study. Three lung lesions (L1–L3) can be identified in the PET images as denoted by the arrows. The largest lesion L1 measured from CT images was \( \sim 37 \) (vertical direction) \( \times \) 32 mm (horizontal direction). This lesion was used to generate the INTEX correlation and transformation matrix. The correlation coefficients \( r \) between the Anzai mean displacement and mean displacement of L1 were 0.001, 0.38, and 0.94 in LR, AP, and SI directions, respectively. The motion amplitude measured from the centroid of the lesion in the LR, AP, and SI directions were 1.6, 2.9, and 6 mm, respectively. Similar to the FPDTBZ studies, INTEX1D was applied to correct motion in the SI direction, and INTEX3D was used to correct for motion in the AP and SI directions only, as the motion in the LR direction was negligible compared to the intrinsic spatial resolution (~4 mm) and the correlation was poor. It can be seen that in the NMC images, the lesion boundaries appear blurred visually in both transaxial and coronal views. The smaller lesions L2 and L3 appear to be stretched in the SI direction compared to other images. Although the gated reconstruction yielded sharper lesion boundaries, the substantial increase in image noise led to degradation of lesion detection visually, particularly for smaller lesions L2 and L3. INTEX1D corrected motion in SI direction and yielded sharper lesion boundaries such that lesion L3 appeared to be more compact. In contrast to the FPDTBZ studies, INTEX3D yielded slightly blurrier boundaries on lesions L2 and L3 than INTEX1D. This may be due to the small correlation in the AP direction for this case, which may have yielded worse performance on motion correction. Thus, the AMNLM was applied to the INTEX1D image to reduce image noise while preserving the lesions and organ boundaries.

The quantification of the FMISO patient is shown in Table VII. The L/B ratio was used to assess the level of hypoxia of the lesions relative to the normoxic tissues.\(^{36}\) It can be seen that, although the gated images yielded an average of 16% increase in L/B ratio, the noise in the background measured as the standard deviation in the blood pool also

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**TABLE IV.** Percentage change of the mean activity in the pancreas compared to NMC.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>End-expiration</th>
<th>INTEX1D (%)</th>
<th>INTEX3D (%)</th>
<th>INTEX3D-AMNLM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.4</td>
<td>15.5</td>
<td>16.8</td>
<td>16.3</td>
</tr>
<tr>
<td>2</td>
<td>5.8</td>
<td>2.5</td>
<td>5.3</td>
<td>5.1</td>
</tr>
<tr>
<td>3</td>
<td>6.6</td>
<td>2.2</td>
<td>5.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Mean</td>
<td>9.9</td>
<td>6.8</td>
<td>9.3</td>
<td>8.7</td>
</tr>
</tbody>
</table>

**TABLE V.** Percentage change of the mean activity in the kidneys compared to NMC.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>End-expiration</th>
<th>INTEX1D (%)</th>
<th>INTEX3D (%)</th>
<th>INTEX3D-AMNLM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.8</td>
<td>10.6</td>
<td>17.1</td>
<td>16.0</td>
</tr>
<tr>
<td>2</td>
<td>11.1</td>
<td>4.4</td>
<td>9.6</td>
<td>9.2</td>
</tr>
<tr>
<td>3</td>
<td>9.5</td>
<td>4.2</td>
<td>6.8</td>
<td>5.2</td>
</tr>
<tr>
<td>Mean</td>
<td>11.8</td>
<td>6.4</td>
<td>11.2</td>
<td>10.1</td>
</tr>
</tbody>
</table>
TABLE VI. Percentage change of the noise level (standard deviation) in the liver VOI compared to NMC.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>End-expiration gate (%)</th>
<th>INTEX1D (%)</th>
<th>INTEX3D (%)</th>
<th>INTEX3D-AMNLM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>102.2</td>
<td>−3.8</td>
<td>−3.7</td>
<td>−56.3</td>
</tr>
<tr>
<td>2</td>
<td>85.1</td>
<td>−2.8</td>
<td>−1.1</td>
<td>−56.5</td>
</tr>
<tr>
<td>3</td>
<td>143.4</td>
<td>8.7</td>
<td>−1.3</td>
<td>−78.6</td>
</tr>
<tr>
<td>Mean</td>
<td>110.2</td>
<td>−0.7</td>
<td>−2.0</td>
<td>−63.8</td>
</tr>
</tbody>
</table>

increased substantially by 149%. INTEX1D and INTEX1D + AMNLM yielded nearly equivalent improvement in L/B contrast over NMC by 20% on average for three lesions, with the larger increases for the smaller lesions. INTEX3D yielded the same amount of improvement for L1, however, the increase was smaller for L2 and L3 due to the less effective motion correction as described above. INTEX1D and INTEX3D yielded similar standard deviation in the blood pool as the NMC images, while AMNLM reduced the standard deviation in the blood pool by 55%.

5. DISCUSSION

This study extended the previously developed INTEX method to correct for respiratory motion in three-dimensions. In contrast to the original INTEX, motion correction was carried out in an event-by-event manner with high temporal resolution (40 Hz). Thus, the proposed method can uniquely correct for intragate respiratory motion and facilitate respiratory motion correction for dynamic studies that, to the best of our knowledge, has not yet been realized for internal organs in whole-body PET.

The effectiveness of 3D and intragate motion corrections was assessed using the NEMA phantom driven by a real patient respiratory trace, and four patient studies with targeted tracers of FPDTBZ and FMISO. Both NEMA and FPDTBZ results demonstrate that, although the respiratory motion was the largest in the superior-inferior direction, motion in other directions can still lead to considerable blurring and underestimation in quantification of small objects. In the NEMA study, INTEX1D corrected motion in the SI direction effectively. However, there was still an average of ~14% and ~9% underestimation in the smaller spheres (10 and 13 mm) and bigger spheres (17 and 22 mm), respectively, compared to the static acquisition, mainly due to the remaining motions in LR and AP directions. By correcting motion in all directions, INTEX3D further reduced the relative bias to ~4% in the smaller spheres, and nearly recovered the contrast for the bigger spheres to the level of the static acquisition (2% relative bias). Note, we consistently observed higher CRC on the bigger spheres than the smaller spheres for all the methods due to the partial volume effect of PET image. Similarly, the FPDTBZ human studies also showed that INTEX1D achieved comparable quantifications to INTEX3D for large organs, such as the pancreas (the difference of the mean percentage improvement was 2.5% as shown in Table IV), but the difference can be substantial in the fine structures, such as in the kidney (the difference was 4.8% as shown in Table V). In those cases, INTEX3D yielded superior performance over INTEX1D both visually and quantitatively. Therefore, as state-of-the-art PET/CT scanners can achieve high spatial resolution (typically ~4 mm FWHM) and the variation of motion in different directions between subjects can be substantial, it is essential to correct motion in all directions to achieve optimal image quality and to minimize inter-subject variation in quantitative outcome measures.

On the other hand, the incorporation of poor correlation into event-by-event motion correction can lead to reduced quality in motion correction. One example is the FMISO study, INTEX3D was applied to correct the motion in both the AP and SI directions, where the correlation coefficient between the AP direction and the external trace was relatively poor at 0.38. INTEX3D yielded lower lesion-to-blood ratio than INTEX1D on the smaller lesions L2 and L3 in the FMISO study. The poor correlation may be caused by several factors. First, the internal landmarks that are not substantially influenced by respiratory motion and thus exhibiting small motion amplitude, e.g., apex and sternum, are more likely to have poor internal-external correlation as demonstrated in the

![TAC of pancreas](image1)

![TAC of kidney](image2)

FIG. 10. Time-activity-curves measured in the pancreas and kidney of subject 1 from the first 10 min scan with NMC and INTEX3D. It can be seen that the tracer concentration increased by 18% in the pancreas and 11% in the kidney at the maximum of the curves after correcting for respiratory motion using INTEX3D.
previous studies.\textsuperscript{25, 28, 30} Second, the positioning of the respiratory monitoring devices can also have substantial impact on the correlation, such that a worse correlation was observed when the external tracking devices were placed between the chest and the abdominal region,\textsuperscript{30} which had little motion externally. Third, the determination of the centroids from inaccurate segmentations may also lead to worse correlation due to the noise in the gated PET images. The worse performance of INTEX3D compared to INTEX1D may be caused by a combination of all these factors. Therefore, we suggest applying INTEX only in the directions with high correlation coefficient, e.g., \( r > 0.6 \), and with motion magnitude that is discernible with the intrinsic spatial resolution and voxel dimension, e.g., \( > 2 \text{ mm} \), for more effective motion correction.

An eight-bin phase gating was used in this study to correlate the 3D internal organ motion and the 1D external respiratory trace. With these settings, we observed consistent high correlation (i.e., \( r > 0.9 \)) in the SI direction in both phantom and patient studies. Increasing the number of phase bins may lead to improved correlations, especially in the AP and LR directions. This is because the intragate motion may affect the segmentation outcomes and hence the estimation of the centroids. However, the number of events within each gate will decrease correspondingly and may impact the accuracy of segmentation, and hence the estimation of the centroids. The optimal number of gates depends on numerous factors that affect the segmentation outcomes on the gated images including the scanner, injection dose, acquisition duration, reconstruction parameters, the organ size/shape, etc. Therefore, the number of gates needs to be determined to optimize the tradeoff between the effect of intragate motion and number of counts per gate, which requires future investigation.

In this study, the measurement of the centroid of the organ/tumor was based on an assumption that the target organ does not deform across the respiratory gates and that motion mainly involves rigid transformation as the diaphragm moves and chest/abdomen expands during inspiration.\textsuperscript{32, 33} Thus, a constraint was applied to preserve the volume of the segmented organ across all the gates to obtain a reliable measurement of the internal organ displacement. Although this can be applied to most of the lesions and small organs such as pancreas and kidney, studies have shown that the motion of other larger organs, such as the heart, due to respiration also includes rotational and deformable motions in some patients.\textsuperscript{38} Future development is needed for these types of organs to include nonrigid motion estimation in the voxel-by-voxel correlation model and to perform event-by-event nonrigid motion correction, and some “weights” need to be determined for regions/organs with poor correlations.

In addition, the FPDTBZ studies revealed that the pancreas and kidneys displacements were consistent in all the patients, such that the slopes of the regression lines of pancreas and kidney had less than 5% difference in both AP and SI directions (Table III). As the internal-external correlation was similar for both organs, one motion correction file applied to the entire FOV could effectively correct the motions for both organs. Although this approach did not show any artifact here, for whole-body imaging that involves multiple bed positions and multiple organs/lesions with different motion profiles, multiple sets of INTEX correlations and reconstructions may be required for each individual bed position or specific organ.

In this study, the attenuation correction mismatch was minimized by using the end-expiration phase as the reference frame where the CT images were acquired. In addition, the

![Image](image-url)

**Fig. 11.** Sample slices of the FMISO study in transaxial (top) and coronal (bottom) views. The arrows indicate three lesions (L1–L3) in the lung. All images are displayed in the same intensity scale.

**TABLE VII.** The L/B ratio and standard deviation in the blood pool comparing to NMC of the FMISO study. The percentage changes comparing to NMC are shown in the parentheses.

<table>
<thead>
<tr>
<th></th>
<th>NMC</th>
<th>End-expiration gate (%)</th>
<th>INTEX1D (%)</th>
<th>INTEX3D (%)</th>
<th>INTEX1D + AMNLM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1/B ratio</td>
<td>2.2</td>
<td>2.3 (4%)</td>
<td>2.4 (9%)</td>
<td>2.4 (9%)</td>
<td>2.4 (9%)</td>
</tr>
<tr>
<td>L2/B ratio</td>
<td>2.4</td>
<td>2.9 (21%)</td>
<td>2.8 (17%)</td>
<td>2.6 (8%)</td>
<td>2.8 (17%)</td>
</tr>
<tr>
<td>L3/B ratio</td>
<td>2.7</td>
<td>3.3 (22%)</td>
<td>3.6 (33%)</td>
<td>3.3 (20%)</td>
<td>3.6 (33%)</td>
</tr>
<tr>
<td>Mean</td>
<td>2.4</td>
<td>2.8 (16%)</td>
<td>2.9 (20%)</td>
<td>2.7 (12%)</td>
<td>2.9 (20%)</td>
</tr>
<tr>
<td>Std dev in blood pool</td>
<td>795.0</td>
<td>1982.9 (149%)</td>
<td>771.2 (−3%)</td>
<td>751.8 (−5%)</td>
<td>355.0 (−55%)</td>
</tr>
</tbody>
</table>

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accurately aligned PET and CT images also facilitate the use of anatomical knowledge to suppress noise while preserving organ boundaries. As demonstrated in both FPDTBZ and FMISO studies, the application of AMNLM to the motion corrected images reduced the background noise by >50% while preserving the quantitative accuracy (as shown in Tables IV–VI) in the targeted organs, and organ boundaries. Without accurately aligned PET and CT images, the use of the anatomical based filter may cause artifacts due to mismatched boundaries, and preserve artifacts caused by respiratory motion.

One of the goals of this study was to correct for intragate motion. The standard deviation of the Anzai respiratory displacements obtained from the FPDTBZ studies revealed that the intragate motion at inspiration phase can be substantially larger than the end-expiration phase for some subjects. By comparing the gated reconstructions with and without INTEX3D at both end-expiration and inspiration phases, the results demonstrated that the use of the external motion trace with high temporal resolution in the event-by-event motion correction effectively eliminated intragate motion in both phases, and thus led to reduced image blurring in the final reconstructed images.

Finally, to demonstrate the feasibility of respiratory motion correction for dynamic studies, we compared the TACs for both pancreas and kidney before and after motion correction. As expected, the proposed method increased the values of the TACs for both organs. However, without knowing the ground truth, it remains unclear what the impact of event-by-event motion correction is on kinetic modeling. Therefore, the application of INTEX motion correction on tracer kinetic parameter estimation warrants comprehensive investigation in the future using simulations similar to the previous study.39

6. CONCLUSIONS

This study showed that the proposed INTEX3D method with matched attenuation correction can effectively compensate for respiratory motion while preserving all the counts, leading to improved image quality and contrast recovery of the target organs. The proposed framework of event-by-event motion correction can uniquely correct intragate motion and can be applied to dynamic imaging that may lead to improved tracer kinetic modeling. With aligned PET and CT, this method also facilitates the use of anatomical knowledge to suppress noise while preserving organ boundaries and quantitative accuracy.

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Electronic addresses: Chung.Chan@yale.edu and Chi.Liu@yale.edu; Telephone: +12037375481.


