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List-mode Reconstruction for the Biograph mCT with Physics Modeling and Event-by-Event Motion Correction

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Abstract

Whole-body PET/CT scanners are important clinical and research tools to study tracer distribution throughout the body. In whole-body studies, respiratory motion results in image artifacts. We have previously demonstrated for brain imaging that, when provided accurate motion data, event-by-event correction has better accuracy than frame-based methods. Therefore, the goal of this work was to develop a list-mode reconstruction with novel physics modeling for the Siemens Biograph mCT with event-by-event motion correction, based on the MOLAR platform (Motion-compensation OSEM List-mode Algorithm for Resolution-Recovery Reconstruction). Application of MOLAR for the mCT required two algorithmic developments. First, in routine studies, the mCT collects list-mode data in 32-bit packets, where averaging of lines of response (LORs) by axial span and angular mashing reduced the number of LORs so that 32 bits are sufficient to address all sinogram bins. This degrades spatial resolution. In this work, we proposed a probabilistic assignment of LOR positions (pLOR) that addresses axial and transaxial LOR grouping in 32-bit data. Second, two simplified approaches for 3D TOF scatter estimation were developed to accelerate the computationally intensive calculation without compromising accuracy. The proposed list-mode reconstruction algorithm was compared to the manufacturer's point spread function + time-of-flight (PSF+TOF) algorithm. Phantom, animal, and human studies demonstrated that MOLAR with pLOR gives slightly faster contrast recovery than the PSF+TOF algorithm that uses the average 32-bit LOR sinogram positioning. Moving phantom and a whole-body human study suggested that event-by-event motion correction reduces image blurring caused by respiratory motion. We conclude that list-mode reconstruction with pLOR positioning provides a platform to generate high quality images for the mCT, and to recover fine structures in whole-body PET scans through event-by-event motion correction.

Keywords

Motion correction; TOF; event-by-event; list-mode; scatter; mCT

1. Introduction

Whole body PET/CT scanners are important clinical and research tools to study tracer distribution throughout the body. The Siemens Biograph mCT (Siemens Medical Solutions USA, Inc.) is a state-of-the-art time-of-flight (TOF) PET/CT tomograph targeted for whole body PET studies (Jakoby *et al.*, 2011).

Respiratory motion in whole-body scans blurs reconstructed images and generates inaccurate activity quantification. One way to address such motion is to track subject motion using an external device, such as the Anzai system (Anzai Medical, Tokyo, Japan) (Seppenwoolde *et al.*, 2007), and bin the scan data into individual gates using the respiratory traces based on either phase of amplitude information (Dawood *et al.*, 2007). Each frame is reconstructed and possibly registered to a reference position (Dawood *et al.*, 2006). However, even with gated data, respiratory motion in whole-body studies is of sufficient magnitude that noticeable image blurring occurs due to intra-gate motion (Nehmeh *et al.*, 2003). On the contrary, event-by-event motion correction (Daube-Witherspoon *et al.*, 1990; Bloomfield *et al.*, 2003; Buhler *et al.*, 2004; Zhou *et al.*, 2009; Menke *et al.*, 1996) can eliminate intra-gate motion, and is the most direct method to achieve minimal motion-induced blurring in PET data.

In brain PET studies, we have previously demonstrated that event-by-event motion correction is able to reduce image blurring due to the intra-frame motion in brain PET studies (Jin *et al.*, 2009). The goal of this work was to develop list-mode reconstruction with event-by-event motion correction for the mCT, based on MOLAR (Motion-compensation OSEM List-mode Algorithm for Resolution-Recovery Reconstruction) (Carson *et al.*, 2003) in order to correct for respiratory motion on a continuous basis. Motion data were tracked with the Anzai device, and an internal-external motion correlation technique (INTEX) (Liu *et al.*, 2011) was employed to convert the externally measured motion into the movements of the internal organs in the axial direction.

The MOLAR implementation of event-by-event motion correction involves reassigning the endpoints of each line-of-response (LOR), i.e., the pair of detector locations, based on the motion information. This approach was not straightforward for the Biograph mCT. In its routine clinical operating mode, the mCT is designed to save list-mode data in 32-bit packets, in which the event coordinates of each detected LOR are stored as the address of a sinogram bin. Axial span of 11 and in-plane grouping (mashing) of 2 adjacent angles reduce the number of LORs, so that the addresses of all possible sinogram bins can be stored in 32 bits. This introduces uncertainty in the locations of the detected events and thus some blurring of the reconstructed images. This design choice is suitable for typical clinical imaging studies; however, given the structure of MOLAR, it was of interest to explore if higher resolution could be achieved. To reduce the effect of LOR grouping, we propose a probabilistic assignment of LOR (pLOR) positions, in which the position of each event is selected from all of the possible sub-LORs within each sinogram bin.

The mCT scanner has TOF capability, so the TOF information must be incorporated into the image reconstruction, with appropriate adjustments for the physical correction terms. Specifically, scatter correction should address the addition of TOF data (Watson, 2007). It has been shown that scatter calculation using TOF data is much more computationally intensive than using non-TOF data. In this work, two techniques are proposed to reduce the computational demand in fully 3D TOF scatter calculation.

Static phantom studies as well as human and animal brain studies were performed to compare the proposed reconstruction method to the manufacturer's reconstruction methods. Moving phantom and whole-body human PET studies were performed to evaluate the effectiveness of the event-by-event motion correction algorithm.

2. Methods

2.1. The Biograph mCT scanner

The Biograph mCT scanner consists of four rings of 48 blocks, each of which contains 13×13 crystals ($4.01 \text{ mm} \times 4.01 \text{ mm} \times 20 \text{ mm}$). The TOF information of the detected events is measured with 78 psec time bins, and rebinned into 13 time bins with 312 psec bin width and 580 psec FWHM. Images can be reconstructed using the manufacturer's software, which includes an analytic algorithm (filtered back-projection (FBP)) and an iterative algorithm (OP-OSEM with point spread function (PSF) model). TOF information can be incorporated into each of the reconstruction methods.

2.2. The MOLAR algorithm

MOLAR was originally designed for list-mode reconstruction for the HRRT (Carson *et al.*, 2003), and has been adapted for the microPET scanner FOCUS-220 (Jin *et al.*, 2012). The theoretical framework remains essentially the same when MOLAR was adapted for the mCT, with additions for TOF in the projection model, as follows:

$$E(Y_{i,t,\tau}^{(n)}) = \Delta t \left(\sum_j c_{i,t,j} \zeta_{i,t,\tau,j} L_{i,t} A_{i,t} N_j \lambda_j^{(n)} + R_{i,t,\tau} + S_{i,t,\tau} \right) \quad (1)$$

To account for motion and other time-varying effects, each time frame of duration T (sec) is divided into n_T sub-bins indexed by t of duration Δt (sec). The expected value for the number of counts $Y_{i,t}$ along each LOR i in time bin t for TOF bin τ is calculated by forward projecting through the voxel grid (Eq. 1). $c_{i,t,j}$ the system matrix, represents the contribution of pixel j to LOR i at time t , accounting for geometry, resolution, solid angle, and motion effects. $\zeta_{i,t,\tau,j}$ the TOF kernel, is a new addition to the MOLAR algorithm, and defines the contribution of pixel j to TOF bin τ of LOR i at time t . This function is expressed as a Gaussian with FWHM based on the TOF resolution. $L_{i,t}$ is the dimensionless product of decay factor at time t , livetime at time t , and positron branching fraction. N_j is a sensitivity (normalization) factor, in units of (counts/sec)/(Bq/mL $\times$ mm), which converts the forward projection through the image grid (Bq/mL) to units of counts/sec. A component-based model (Casey *et al.*, 1995) was used to compute the normalization factor. $A_{i,t}$ is the dimensionless attenuation factor. The attenuation map was generated from the CT image by translating Hounsfield units to attenuation coefficient. $R_{i,t,\tau}$ is the estimated random coincidence rate in counts per second in TOF bin τ of LOR i at time t . $S_{i,t,\tau}$ is the estimated scatter coincidence rate in counts per second in TOF bin τ of LOR i at time t . Compared to the non-TOF system model of MOLAR, TOF information is included as an additional factor to the calculation of system matrix, and the estimated random and scattered coincidence rates.

2.3. Probabilistic line-of-response positioning technique

In routine studies, the list-mode data of the mCT scanner are recorded in 32-bit packets. Two bits are used for packet identification, thus leaving 30 available bits to represent the coordinates of each event. For the mCT, the full 3D data sinogram contains 400 radial bins, 336 angular bins, 3025 axial bins (55 direct axial planes). When TOF information is included, there are 13 TOF bins and one bin for delayed events for each of the full 3D sinograms. This would require 33 bits to represent all detector pairs and TOF information, exceeding the 30-bit limit. Transverse mashing ($\times 2$) and axial span of 11, as used in earlier scanner models, were adapted to reduce the number of sinogram bins. For example, as shown in Fig. 1, each LOR Y_i (Fig. 1B) represents the sum of counts (dotted lines) from individual detector pairs (sub-LORs) (Fig. 1A) j in sinogram bin i . The coordinates

associated with each sinogram bin is the average location of all the sub-LORs within the sinogram bin. Naturally, this grouping introduces uncertainty in the location of each detected event and results in blurring of the reconstructed images. One way to account for the effect of such LOR grouping is to incorporate the grouping information into the PSF of the resolution model (Panin *et al.*, 2006).

Alternatively, a probabilistic LOR positioning technique is proposed in this work. In this method, the position of each event Y_i is selected among all possible sub-LORs for LOR i , based on a probability density function (Eq. 2). Here, $P_{i,l}$ represents the probability that an event assigned to LOR i originated in sub-LOR l . $N_{i,l}$ is the normalization (efficiency) factor for sub-LOR l in LOR i , and n is the total number of sub-LORs within sinogram bin i . Axial and transaxial grouping of LORs is thus avoided. The probability of LOR assignment is weighted by the normalization factor $N_{i,l}$ for each sub-LOR within a sinogram bin to account for the variation in detection efficiencies among sub-LORs. Normally, such variation in detector efficiencies is accounted for by the normalization correction. However, when 32-bit list-mode data are used in the reconstruction, the normalization factor for each event is derived from the summed efficiencies of all sub-LORs in each sinogram bin. Therefore, when an individual sub-LOR is selected from all possible sub-LORs, it is necessary to account for each sub-LOR's relative efficiency, determined from the components of the normalization model. As one example, a random number P between 0 and 1 is generated for each LOR assignment. If the six sub-LORs in Fig. 1 had relative efficiencies of 0.1, 0.2, 0.2, 0.2, 0.2 and 0.1, corresponding to cumulative probabilities of 0.1, 0.3, 0.5, 0.7, 0.9, and 1. A value of P of 0.4 would assign the LOR to the third sub-LOR, and a P value of 0.85 would assign the LOR to fifth sub-LOR. Other factors such as attenuation were not used in the weighting (see Discussion).

$$P_{i,l} = \frac{N_{i,l}}{\sum_{k=1}^n N_{i,k}} \quad (2)$$

2.4. TOF-based scatter estimation

2.4.1. Extension of the single scatter simulation model (scatter method 1)—In

the non-TOF reconstruction, the expected scattered coincidence rate is estimated using the single scatter simulation (SSS) model (Watson *et al.*, 1996). This model has been extended by Watson for TOF-based reconstruction (Watson, 2007) to include the distribution of scattered events across TOF bins. The details of the implementation can be found in Eqs. 2 and 3 in Watson's work (Watson, 2007).

A major difference in scatter estimation between TOF and non-TOF reconstructions is the addition of the TOF probability function $\phi(s)$ (Eq. 3 in (Watson, 2007)) that is unique for each point along the path connecting a scatter point and a virtual detector. Consequently, the computation time rises significantly compared to the non-TOF scatter calculation, in which the integrated emission intensities between each detector-scatter point pair are calculated once and reused.

To accelerate this TOF SSS calculation, a simplified approach has been developed in this work. This approach reduces the computation time in calculating the Gaussian function $\phi(s)$, which contributes to the major increase in computation time for TOF SSS calculation. It was noticed that $\phi(s)$ depends on the path length difference between two *emitter-detector* pairs (s) and the TOF bin t , instead of any specific *scatter point-detector* pair. To avoid calculation of the Gaussians, a look-up table for $\phi(s)$ may be pre-computed and stored, as a function of s and t . Strictly speaking, s takes continuous values between $-L/2$ and $+L/2$, where L , in units of mm, is the maximum distance between any two

detectors. In this simplified approach, s is rounded to the closest integer in mm, so that the total number of possible s is L . Let n be the number of TOF bins. A look-up table (s, n) with dimension (L, n) can be pre-computed and stored. The computation demand and storage requirement for this look-up table is trivial, as L (in mm) is in the range of 1000 for typical whole-body PET scanners, and n is 13 for the Biograph mCT. Compared to the original implementation of TOF SSS (Watson, 2007), the computation time using this approach is reduced by a factor of 3, accounting for the overhead involved in the scatter simulation and scaling.

In the MOLAR implementation of SSS, scatter is estimated 3 times at sub-iterations 1, 4, and 10 of iteration 1. In each case, the scatter simulation is based on the image at that sub-iteration. In the simulation step of SSS, scattered coincidences were simulated in 3D mode with an isotropic average scatter point spacing of 12 mm (~ 600 sample scatter points per liter). Line integrals are estimated from ray sums sampled at 4 mm intervals. Axial detector sample space was 12 mm, and 100 azimuthal detector positions per ring were used in the simulation. The energy resolution used to determine the probability of detection of a scattered coincidence was 18%. The energy window for prompt coincidences is 435 – 650 keV. Following the simulation step of the SSS, the simulated scatter profile was scaled to match the detected scattered coincidences, determined by the difference between the prompt coincidences and the delayed coincidences, outside the object. A single scale factor was used for the entire 3D volume to enhance statistics in the scatter simulation and scaling. To minimize the effect of outside FOV activity on scatter estimation, only the scattered coincidences that intersect with a narrow band just outside of the object were used to for scaling.

2.4.2. SSS Approximation using the true+scattered coincidences (scatter method 2)—Even with the implementation approaches for TOF SSS calculation described in the previous section, computation of the TOF SSS method is still considerably slower than the non-TOF SSS calculation, as the line integrals I can no longer be pre-calculated for each combination of scatter points and one detector. Instead, TOF SSS requires calculation of I_{τ}^A and I_{τ}^B for each combination of scatter point S and detectors A and B as a function of TOF bin τ . A second method was explored to estimate the relative scatter distribution across TOF bins. This method assumes that, for each LOR, the TOF scatter distribution is the same as the true+scatter coincidence distribution, as described in Eq. 3.

$$S_{i,\tau} = \frac{P_{i,\tau} - D_{i,\tau}}{\sum_{\tau} (P_{i,\tau} - D_{i,\tau})} S_i \quad (3)$$

Here, S_i is the expected scattered coincidence rate for TOF bin τ along LOR i , $P_{i,\tau}$ is the prompt coincidence rate for TOF bin τ along LOR i , $D_{i,\tau}$ is the delayed coincidence rate for TOF bin τ along LOR i , assuming that the distribution of delayed coincidences is uniform across TOF bins, S_i is the scattered coincidence rate estimated using the non-TOF SSS model (Watson *et al.*, 1996), and distributed to each TOF bin using the TOF distribution of the true+ scatter (i.e., prompts-delays) coincidence rate. Using this method, the total computation time is comparable to non-TOF scatter calculation. The reduction in the total image reconstruction time depends on the count level in the list mode reconstruction. For a high-count frame of 80M events, the computation time using scatter method 2 is reduced by a factor of 2.5 compared with the scatter method 1, described in section 2.4.1. For a frame with 8M events, the reduction factor increases to 5, due to the smaller overhead in the image reconstruction in a low-count frame.

In summary, the original TOF scatter calculation method (Watson, 2007) calculates the contribution (Gaussian function) of each emitter to each TOF bin. The first proposed method

in this work reads the value of the Gaussian function from a pre-computed look-up table. The second proposed method calculates this contribution based on the TOF bin distribution of the true coincidences.

2.5. Image reconstruction

Images were reconstructed with MOLAR (Eq. 4), using the pLOR positioning technique. In Eq. 4, k represents the index of each detected event, i_k represents the LOR index of event k , t_k represents the time stamp for event k , k represents the TOF bin for event k . When motion data are available, event-by-event motion correction was carried out by transforming the locations of the endpoints of the LOR of each detected event to the reference position. Attenuation (A), scatter (S), system matrix (c) and TOF kernel () incorporate the motion-corrected LOR, as denoted by the tilde sign () in Eq. 4. For example, $\tilde{A}_{i_k, t_k}$ represents the attenuation factor for the motion-corrected event k detected on LOR i_k at time t_k . Each LOR is mapped back to the reference position, defined as the orientation of the subject during the CT scan. Therefore, motion correction maps each LOR back to where the subject was during the CT scan, thus correctly aligning the attenuation map to the emission scan. In this way, both attenuation and scatter correction incorporates event-by-event motion correction. For each frame, a motion-dependent sensitivity image Q is computed from a subset of randomly selected LORs. The TOF kernel is included in the forward and back-projection in the same way as reported in the literature (Conti *et al.*, 2005; Wang *et al.*, 2006). TOF random coincidence rate is estimated from the product of the singles rates of the two detectors for each LOR, assuming that the random coincidences are uniformly distributed across all TOF bins. The scattered coincidence rate was estimated in 3D mode using the TOF extension of the SSS model (Watson, 2007), as detailed in section 2.4.1, except in the cases in which two scatter correction methods are compared.

$$\lambda_j^{(n+1)} = \frac{\lambda_j^n}{Q_j} \sum_{k=1}^K \frac{\tilde{c}_{i_k, t_k, j} L_{i_k, t_k} \tilde{A}_{i_k, t_k} N_{i_k} \tilde{\zeta}_{i_k, t_k, \tau_k, j}}{\left(\sum_{j'} \tilde{c}_{i_k, t_k, j'} L_{i_k, t_k} \tilde{A}_{i_k, t_k} N_{i_k} \tilde{\zeta}_{i_k, t_k, \tau_k, j'} \lambda_j^{(n)} + R_{i_k, t_k, \tau_k} + \tilde{S}_{i_k, t_k, \tau_k} \right)} \quad (4)$$

$$Q_j = \frac{1}{n_T} \sum_{t=1}^{n_T} \sum_{i=1}^I \sum_{\tau=1}^{n_\tau} \tilde{c}_{i, t, j} \tilde{\zeta}_{i, t, \tau, j} L_{i, t} \tilde{A}_{i, t} N_i$$

In addition, the manufacturer's TrueX reconstruction algorithm (PSF+TOF) was included for comparison. As described earlier, in TrueX for 32-bit data, the coordinates of each detected LOR is the average position of all sub-LORs within each sinogram bin, and the PSF kernels were implemented based on empirical point source measurements (Panin *et al.*, 2006). The FWHM of the PSF kernel used in MOLAR was set to the FWHM at the center of the FOV in the point source measurements. The image pixel dimension was 2 mm × 2 mm × 2 mm for both reconstruction algorithms. For MOLAR, 1-mm pixels were also used to reconstruct the mini-Derenzo phantom to better resolve the fine structures. Both reconstruction algorithms used 21 subsets and 3 iterations for routine studies. For MOLAR, the subsets are defined by the order of arrival of the events. For TrueX, the subsets are defined by groupings of transverse angles of the sinogram. Larger numbers of iterations were also performed to evaluate the contrast recovery in the static NEMA phantom and the mini-Derenzo phantom.

2.6. Phantom studies

2.6.1. Contrast phantom study—A NEMA IEC body phantom (Data Spectrum, Hillsborough NC, USA) was filled with 74 MBq of [¹⁸F]FDG. The hot sphere inserts had a contrast of 6.2:1 to the warm background, measured by samples counted in a gamma counter. The phantom was positioned at the center of the FOV and was scanned for 30 minutes following a CT scan for attenuation correction. The emission data had 600M events

with 12% random coincidences and 29% scattered coincidences. The primary purpose of this phantom scan was to compare the consistency of the physical correction terms (scatter and TOF) in different reconstruction algorithms by calculating the contrast recovery coefficients (CRC) in the hot and cold regions as a function of effective iteration (iteration $\times$ subsets) (Eq. 5). H is the average pixel intensity in the hot region, B is the average pixel intensity in the warm background, C is the average pixel intensity in the cold region, and T is the true contrast ratio (6.2).

$$\begin{aligned} CRC_{Hot} &= \frac{H-B}{T-1} \\ CRC_{Cold} &= \frac{C}{B} \end{aligned} \quad (5)$$

2.6.2. Comparison of scatter estimation methods—A phantom study was performed to examine the validity of the assumptions in the second scatter calculation method (section 2.4.2), i.e., to compare the TOF distribution of true coincidence rates to that of scattered coincidence rates. As shown in Fig. 2, two cylindrical phantoms (20 cm diameter), one cold and one hot, were positioned back-to-back axially and were scanned for 4 hours to collect sufficient counts. The axial border between the two phantoms was positioned in the middle of the scanner axial FOV. In this configuration, events detected in slices that just intersect the cold phantom should contain only random and scattered coincidences, while events detected in slices that intersect the hot phantom should contain true, random and scattered coincidences.

Two transverse slices, one intersecting the cold phantom and the other one intersecting the hot phantom, were selected in the middle of both phantoms. The delayed coincidences were subtracted from the prompt coincidences, so that the cold phantom data should contain only scattered events and the hot phantom data should contain both true and scattered coincidences. Sinograms were summed over all transverse angles, as the phantoms were positioned along the central z-axis of the scanner, producing a matrix of dimension equal to the number of radial bins (336) by the number of TOF bins (13). For each radial bin, the mean TOF bin ($\bar{\tau}_r$, calculated as a “center of mass”) and the standard deviation (σ_r) of the TOF bin distribution were calculated using Eq. 6. Here, r is the radial bin index, $C_{\tau,r}$ is the number of counts in radial bin r and TOF bin τ , summed over transverse angles. If the assumption in this scatter calculation method is valid, i.e., if the TOF distribution of the trues and scattered counts are the same, then the mean and the standard deviation of the TOF bin distribution for the scattered coincidences should be the identical to that for the true +scatter coincidences.

$$\begin{aligned} \bar{\tau}_r &= \frac{1}{\sum_{\tau=1}^N C_{\tau,r}} \sum_{\tau=1}^N C_{\tau,r} \tau \\ \sigma_r &= \sqrt{\frac{1}{\sum_{\tau=1}^N C_{\tau,r}} \sum_{\tau=1}^N C_{\tau,r} (\tau - \bar{\tau}_r)^2} \end{aligned} \quad (6)$$

2.6.3. Mini-Derenzo phantom study—To evaluate the spatial resolution with an object with fine structures, a mini-Derenzo phantom (Data Spectrum, Hillsborough NC, USA) with rod diameters ranging from 1.2 mm to 4.8 mm was filled with 37 MBq of [^{18}F]FDG, and was scanned for 10 min at 5 cm radial offset from the center of the FOV, following a CT scan for attenuation correction. PET scan data were divided into 10 sequential frames of equal counts to examine noise properties across the 10 replicates. To examine spatial resolution, two line profiles were drawn through the 3.2-mm rod structures, as shown in Fig. 3.

The CRC was calculated using Eq. 7. Here, I_H is the intensity of each hot insert along the line profile, and I_C is the intensity of each cold region between the hot inserts along the line profile. To calculate the intensities in the hot and cold regions, the line profile was divided into 7 equally-spaced segments ($n_H=4$ is the number of the hot regions and $n_C=3$ is the number of the cold regions between the hot regions), each having a width of 3.2 mm, which is the true width of the rod diameter and rod separation. If a pixel was shared between the hot and cold regions, the intensity of the pixel was divided based on the relative width of the pixel in each region. Therefore, the ratio of n_H to n_C is 4:3. The CRCs for the two line profiles and the 10 replicates were averaged to provide a CRC value at each iteration.

$$CRC = \frac{\frac{1}{n_H} \sum_{H=1}^{n_H} I_H - \frac{1}{n_C} \sum_{C=1}^{n_C} I_C}{\frac{1}{n_H} \sum_{H=1}^{n_H} I_H} \quad (7)$$

The coefficient of variation (COV) across the replicates was calculated using Eq. 8. Here, K denotes the set of pixels that correspond to all the hot inserts, and $\bar{\lambda}_k$ and σ_k represent the mean and standard deviation of pixel k across the replicates, respectively.

$$COV = \frac{\sum_{k \in K} \sigma_k}{\sum_{k \in K} \bar{\lambda}_k} \quad (8)$$

2.7. Motion tracking and correction

In order to perform event-by-event motion correction, the motion of the target internal organ needs to be obtained in high temporal resolution. This was achieved by using the internal external correlation (INTEX) technique (Liu *et al.*, 2011), as described below. In the whole-body human studies, the respiratory movement was tracked by the Anzai system (Chan *et al.*, 2012). A pressure sensing belt was attached to the subject's abdomen, and the respiratory trace was recorded at 40 Hz. A linear correlation was established between the measured external motion and the rigid internal organ movement in the superior-inferior direction. Transformation matrices that describe the internal organ movement were then generated by converting the entire Anzai trace into internal organ motion using the linear correlation. The coordinates of each LOR were motion-corrected according to the transformation matrices as a continuous function of time in the MOLAR reconstruction algorithm.

To assess the accuracy of motion tracking and the motion correction method, a moving NEMA phantom study was performed. The phantom was filled with 74 MBq of [^{18}F]FDG, with approximately 4:1 contrast ratio between the hot sphere and the warm background. A CT scan was followed by 1) a 10-min static scan, and 2) a 10-min scan in which the phantom was placed on the QUASAR respiratory motion platform (Modus Medical Devices, London, Canada) driven by a respiratory motion trace of a human subject (Chan *et al.*, 2012). The average magnitude of motion across all cycles was ~15 mm in the superior-inferior direction. The static NEMA phantom scan was used as a reference to assess the accuracy of motion correction in the moving phantom. The CRC, defined as (Hot-Cold)/Hot in this case, was used to examine the resolution in the hot spheres and the effectiveness of motion correction. To avoid partial volume effect, the hot and cold regions were defined on the hot and cold spheres as circles, whose diameters were 2 pixels smaller than the true diameters of the spheres.

2.8. Human and animal studies

For each of the human and animal studies described below, list-mode data were acquired for 2 hours, each following a CT scan for attenuation correction.

2.8.1. Brain studies—A human brain study was performed with a bolus injection of 459 MBq of [^{11}C]PE2I, a dopamine transporter ligand (Halldin *et al.*, 1998). An anesthetized baboon brain study was performed using a bolus injection of 115 MBq of [^{18}F]CFPYPB, a glycine transporter ligand (Williams *et al.*, 2008). No motion tracking or correction was performed on the brain studies. It should be noted that the human brain study was performed when the subject was awake. Head motion, though kept minimal, was unavoidable. In the baboon brain study, head motion was eliminated with anesthesia. Images were reconstructed using both MOLAR and PSF+TOF with 21 subsets and 3 iterations.

2.8.2. Whole-body human study—To evaluate the accuracy of motion correction, a whole-body human study was performed using bolus injection of 306 MBq of [^{18}F]FP-(+)-DTBZ, a pancreatic beta cell tracer (Normandin *et al.*, 2012). Motion tracking and correction for this study is described in section 2.7. Images were reconstructed using both MOLAR and PSF+TOF with 21 subsets and 3 iterations.

3. Results

3.1. Contrast phantom study

Fig. 4 shows the reconstructed image of a static NEMA phantom, used for comparison of the CRC performance of the two reconstruction algorithms. The hot, warm and cold ROIs, defined on the 37-mm sphere, background, and 28-mm spheres, are shown as the red, yellow and blue circles, respectively.

The CRC values, defined in Eq. 5, are plotted as a function of effective iteration (iteration $\times$ subsets) in Fig. 5. The 2 reconstruction algorithms (MOLAR and PSF+TOF) are included for comparison. Across all effective iterations, the CRC values in the hot and cold regions are comparable between the two algorithms. This experiment suggested that the two reconstruction algorithms give consistent results with regard to the physical correction terms, such as scatter and TOF.

3.2. Comparison of scatter estimation methods

Two scatter calculation methods were used here, 1) the full TOF version (Watson, 2007) and 2) a simplified version. In method 2, an important assumption is that the TOF bin distribution of the scattered coincidences is the same as the TOF bin distribution of the true coincidences. Fig. 6 shows the mean (Fig. 6A) and the standard deviation (Fig. 6B) of the TOF bins as a function of radial offset in the dual-phantom scan (Fig. 2) for scattered coincidences (solid curve) and the sum of true+scattered coincidences (dashed curve). Only the radial bins that intersect the phantom (20 cm diameter) are shown, and the center of the phantom is represented by radial bin 0. Across different radial bins, the mean TOF bin is similar between the scattered coincidence and true+scatter (Fig. 6A). The mean TOF bin is slightly below 0, due to the offset of 0.125 of a TOF bin width between the center of the gantry and the center of TOF bin 0. For the standard deviation (Fig. 6B), near the center of the FOV (radial bins -30 to $+30$), the standard deviation of TOF bins for scattered coincidences is close to that for the sum of true and scattered coincidences, indicating that approximating the TOF bin distribution of the scattered coincidence with the TOF bin distribution of the true coincidences is appropriate. Towards the edge of the object (radial bin approaching -50 and $+50$), the standard deviation of the TOF bin for the scattered coincidences is higher than that for the true+scattered coincidences, indicating that the TOF

bin distribution for the scattered coincidences is broader than that of true+scattered coincidences. These data suggest that the assumption in scatter method 2 is generally valid, especially towards the center of the object.

The contrast NEMA phantom scan was reconstructed with MOLAR using both scatter estimation methods, and with the manufacturer's PSF+TOF method to compare the two scatter correction methods. The intensities in the hot, warm and cold regions are shown in Fig. 7. In the warm region (Fig. 7B), the intensities are comparable for all image reconstructions method, and are close to the true intensity, since calibration was performed with a large and uniform region for each scatter correction method. In the hot region (Fig. 7A), MOLAR with the scatter method 2, which approximates the TOF bin distribution of the scattered coincidences using the TOF bin distribution of the true+scatter coincidences, gives slightly higher intensities than both PSF+TOF and MOLAR with the first scatter correction method, which was implemented based on the TOF-extension of the SSS method. In the cold region (Fig. 7C), MOLAR with scatter method 2 gives higher intensity values than PSF+TOF and MOLAR with scatter method 1. These findings suggest that the scatter method 2 may under-correct scatter. MOLAR with the scatter method 1 gives slightly lower intensity values than PSF+TOF in the cold region, whereas the intensity values are similar in the warm and hot regions. Unless otherwise noted, all MOLAR reconstruction throughout the rest of this manuscript employed scatter method 1.

3.3. Mini-Derenzo phantom study

The reconstructed images of the mini-Derenzo phantom are shown in Fig. 8. The top row shows the images reconstructed with PSF+TOF, and the bottom row shows the images reconstructed with MOLAR for different effective iterations. The last column shows the MOLAR image using 1-mm pixels. The intensity for each column is individually scaled. At 630 effective iterations, the 3.2 mm rods are clearly resolved using both reconstruction algorithms. However, at 63 effective iterations, which is the routine operating range, MOLAR with pLOR better resolves the 3.2-mm rod structures than PSF+TOF. With 1-mm pixels, MOLAR is also able to resolve the 2.4 mm rods (last column).

3.4. Tradeoff between contrast recovery and noise

In the mini-Derenzo study, the CRC was plotted as a function of COV in Fig. 9. Each data point represents an iteration with 21 subsets. MOLAR and PSF+TOF have a highly similar relationship between CRC and COV. However, at the same number of iteration, MOLAR gives slightly higher CRC than PSF+TOF, as the data points on the dashed curve (MOLAR) progress faster than the data points on the solid curve (PSF+TOF). The data points for the 3rd, 10th and 30th iterations, which correspond to the same effective iteration numbers in Fig. 8, are labeled on the plot for illustration. MOLAR at the 3rd iteration gives similar contrast and noise level as PSF+TOF at the 4th iteration. At very large number of iterations, MOLAR and PSF+TOF give comparable contrast, as the gap between MOLAR and PSF+TOF for the same iteration shrinks towards iteration 30.

3.5. Human brain study

The reconstructed images of a human brain study injected with [¹¹C]PE2I are shown in Fig. 10. The images were reconstructed with 10 min of data (68M counts) at 40 min post-injection using PSF+TOF (Fig. 10A) and MOLAR (Fig. 10B). Visually, the contour of the body of the caudate (arrows) is slightly better delineated with MOLAR. However, MOLAR with pLOR gives higher noise than PSF+TOF, which is consistent with the CRC-COV plot in Fig. 9.

3.6. Animal brain study

The reconstructed images of a [^{18}F]CFPYPB baboon brain study are shown in Fig. 11. The images were reconstructed with 5 min of data (78M counts) at 5 min post injection using PSF+TOF at the 3rd iteration (Fig. 11A), PSF+TOF at the 4th iteration (Fig. 11B), MOLAR with the scatter method 1 (Fig. 11C), and MOLAR with scatter method 2 (Fig. 11D). All MOLAR images were reconstructed for 3 iterations. The MR images (Fig. 11E) are displayed to identify the brain structures. The shape of the cingulate ROI (arrows) is more clearly delineated by MOLAR than PSF+TOF at the 3rd iteration. Also, the cortical gray and white matter structures are more clearly resolved by MOLAR than PSF+TOF, as shown in the bottom row. Visually, PSF+TOF at the 4th iteration gives comparable contrast as MOLAR at the 3rd iteration, as predicted by Fig. 9. Intensity profiles at the level indicated by the horizontal bars in Fig. 11A are shown in Fig. 12 for PSF+TOF and MOLAR. The middle peak represents the cingulate, and the two peaks on the side represent the cortex. At the same iteration, MOLAR with the scatter method 1 gives higher contrast recovery than PSF+TOF. The contrasts between the 4th iteration of PSF+TOF and the 3rd iteration of MOLAR are similar. This agrees with the finding in Fig. 9. Comparing the two scatter correction methods for MOLAR, method 2 shows noticeable differences in intensities in the high and low-uptake regions.

3.7. Moving NEMA phantom study

In the moving NEMA phantom study, the respiratory motion of ~ 15 mm amplitude was generated in the axial direction, and the INTEX algorithm was used to generate 1D motion transformation matrices. The translational components in the axial direction of the motion trace in the first minute are shown in Fig. 13.

Fig. 14 shows the sagittal view of the reconstructed images of the moving NEMA phantom without motion correction (Fig. 14A) to show the degrading effect of motion on image quality, the moving phantom with motion correction (Fig. 14B), and the static NEMA phantom (Fig. 14C), all reconstructed with MOLAR. Without motion correction, the hot spheres (13-mm diameter) were blurred due to the motion. The CRC of the hot sphere is 0.80 in the motion-corrected image (B), comparable to the static image (0.79), and is better than the no motion correction case (0.70), indicating the accuracy of the motion tracking method and motion correction algorithm.

3.8. Whole-body human study

In the whole-body [^{18}F]FP-(+)-DTBZ human study, the first 10 min of list-mode data (190M counts) after injection were reconstructed using MOLAR without motion correction (Fig. 15A), and with event-by-event motion correction (Fig. 15B). The kidneys are shown on the top row, and the pancreas is shown on the bottom row. Image intensities were individually scaled within each row. Subject motion was tracked with the Anzai device and was converted to 1D motion transformation matrices in the axial direction using the INTEX algorithm. As denoted by the arrows, noticeable blurring of the kidney cortical structures (top) and the pancreas (bottom) is observed without motion correction (Fig. 15A). Event-by-event motion correction (Fig. 15B) is able to substantially reduce image blurring caused by the respiratory motion.

4. Discussion

In this work, we developed an OP-OSEM based list-mode reconstruction algorithm with TOF capability for the Biograph mCT. The primary motivation for developing list-mode reconstruction for the whole-body PET scanner was to perform event-by-event motion correction, which is clearly advantageous over the frame-based motion correction methods

since continuous respiratory and cardiac motion is present in whole-body studies. Gating of data addresses some motion effects but frame-based gated motion correction methods do not correct for intra-gate motion. We performed initial evaluations using phantom and whole-body human studies, and demonstrated that image blurring can be substantially reduced using event-by-event motion correction with motion data measured with a motion tracking device and converted to the motion transformation matrices at a rate of 40 Hz using the INTEx algorithm.

In the development of this algorithm, two issues arose. The first issue that was addressed here was image reconstruction with 32-bit list-mode data. We demonstrated with phantom, animal and human studies that the probabilistic LOR (pLOR) technique increases the speed of contrast recovery in comparison to using the average LOR position for each sinogram bin. Secondly, two 3D TOF scatter calculation methods based on SSS were described and examined with phantom and real studies. While the scatter method 1 was more precise in simulating the TOF bin distribution of the scattered coincidences, the scatter method 2 substantially improved the speed of scatter calculation, albeit with some loss of accuracy.

4.1. Probabilistic LOR positioning

The pLOR technique improves the speed of resolution recovery compared with the PSF+TOF method, in which sub-LORs are assigned to the average position within each sinogram bin, and a wider and spatially variant resolution kernel (Panin *et al.*, 2006) is used to account for the grouping (mashing). For MOLAR with pLOR, since grouping of sub-LORs is avoided, a spatially invariant resolution kernel is used. The same kernel width was used for both methods at the center of the FOV to match the two resolution kernels. In Fig. 9, it was shown that MOLAR converges slightly faster than PSF+TOF. It is likely that the difference in convergence rate reflects the small differences between the PSF kernels used by MOLAR and PSF+TOF. To fully evaluate the effect of pLOR on convergence, it would require implementing MOLAR without LOR, i.e. assigning each event to the average position within each sinogram bin. Our preliminary tests with MOLAR without pLOR showed some artifacts although it is likely that careful optimization of LOR position and PSF would have eliminated these artifacts.

In the implementation of pLOR the location of each event is selected from one of the possible sub-LORs in each sinogram bin based on the relative normalization factor for each sub-LOR (Eq. 2). Strictly speaking, other factors, such as attenuation should also be included to account for the difference in path length of the sub-LORs within each sinogram bin. However, the relative attenuation factor were not considered in the implementation, as the difference in the intersection of sub-LORs and the attenuation map is trivial, so the attenuation correction factor for each sub-LOR within a sinogram bin is expected to be very similar.

In clinical applications, 32-bit list-mode data reduces the requirement for data storage and facilitates faster image reconstruction due to the reduced number of sinogram bins. Alternatively, in preclinical research studies where higher image resolution is desirable and the statistical quality of the data can support higher resolution, 64-bit list-mode data acquisition is preferred. In this case, the exact coordinates of all events are stored. We would expect that 64-bit list mode would provide a further improvement in the noise/resolution curve compared to pLOR. To fully investigate the effect of pLOR, our future work will directly compare 1) the current pLOR method with 32-bit data, 2) MOLAR with 32-bit data but without pLOR, i.e. with the average LOR positioning technique and a wider PSF, and 3) MOLAR using full 64-bit data.

4.2. Event-by-event motion correction

In this work, event-by-event motion data were generated using the INTEX algorithm that correlates the externally tracked motion with the locations of the centroid of the internal organ. Motion transformation matrices (1D) along the axial direction were generated using the INTEX algorithm. Initially, this includes translational motion information in three dimensions (Chan *et al.*, 2012). Based on that work, axial motion is the predominant source of motion for normal respiration. It should be noted that the INTEX algorithm assumes rigid motion of the internal organs with no relative motion among internal organs. In our previous study (Liu *et al.*, 2011), it was demonstrated that a linear correlation can be established between the external respiratory trace and rigid internal tumor movement in the superior-inferior (SI) directions. In this study, we applied this method to correct the rigid motion of the internal organs in the SI direction. For the patient study, as the pancreas and kidney were the organs of interest, the internal-external motion correlations were established for both of the organs. The INTEX correlation coefficient r was 0.87 and 0.86 for the pancreas and kidney, respectively. The slopes of the regression lines were 0.238 and 0.236 for the pancreas and kidney, respectively. This shows that the movements of the pancreas and kidney were highly correlated and thus one motion profile was applied to the entire FOV to correct motions on both organs. Ongoing research (Chan *et al.*, 2012) is extending the algorithm to 3D rigid motion, with eventual extension to the non-rigid case. While this assumption is expected to be valid in tumor imaging and organs with rigid motion, cardiac motion involves twisting and deformation of the myocardium. Also, relative motion among organs and arms generates deformed attenuation map that cannot be modeled by the rigid-body motion correction used here. This leads to inaccurate attenuation correction and scatter correction, as the misaligned attenuation map may result in erroneous scatter profile simulation and scaling. Therefore, it is strictly necessary to apply a non-rigid model for such motion. A possible solution is to simultaneously reconstruct the attenuation map and the emission activity (Nuyts *et al.*, 1999; Rezaei *et al.*, 2011). Ideally, this can generate an attenuation map whenever there is new motion. Then the attenuation map at the reference orientation can be non-linearly transformed to the orientation for each motion. In this way, an attenuation map of the correct shape at the correct orientation can be used for attenuation and scatter corrections.

A potential solution is to estimate the motion field of each pixel and correct the position of the detected event, based on the estimated motion field for each image pixel along the path of the detected event. Such motion fields may be estimated from 4D CT datasets (Lamare *et al.*, 2007), which have higher statistics than gated PET reconstruction. In this reported method, non-rigid transformation parameters for each pixel may be derived using B-spline basis functions. As reported by Lamare *et al.*, the motion data are incorporated in the system matrix, the attenuation and normalization corrections in the reconstruction process. This method involves a 4D CT scan that increases the radiation dose. The motion field may also be determined from gated PET frames using the an elastic model (Klein and Huesman, 2002) or through rigid-body transformation of list-mode projection data (Jin *et al.*, 2012). Alternatively, with the advent of the integrated PET/MR scanners (Delso *et al.*, 2011), the MR images can be used to estimate the motion field of each image pixel (Tsoumpas *et al.*, 2010). It should be noted that fast MR sequences are required to accurately measure the respiratory motion field.

4.3. Comparison between the scatter estimation methods

Scatter estimation for TOF PET introduces significant computational demands, as the contribution of image intensity to each TOF bin must be integrated along the path of the scattered coincidence. Additional parameters in the scatter algorithm that are common to TOF and non-TOF versions include the total number of scatter points and the number of

pseudo-detectors in the simulation. Previously, Watson (Watson, 2007) reported that the addition of TOF information in scatter simulation increases computation time by a factor of ~ 7 compared to the conventional SSS in whole-body studies. Including the overhead due to the image reconstruction, the total increase in computation time is about threefold. Compared with the conventional non-TOF SSS, the increased computation time for the TOF SSS calculation depends on several factors, such as the number of TOF bins, the size of the subject, and the step size s used in integrating between each scatter point and detector pair. While the number of TOF bins and the size of the subject are independent of the scatter calculation algorithm, a large s causes the fine structures in the intensity image to be lost, and a small s increases the computation time. Watson reported that ray sums were sampled at 17.5 mm intervals, and the scatter points were separated by 22.5 mm (Watson, 2007). Ideally, the choice of the step size should be application dependent. Regions with uniform intensities require less finely sampled integration steps and scatter points than regions with high contrast and fine structures. In this work, a fine step size of 4 mm and 12-mm separation between scatter points were used as an initial setting to eliminate potential inaccuracies in scatter simulation, at the price of larger computation time. One potential method to reduce the overall scatter computation time and to minimize the possible adverse effect of averaging intensity values in high contrast regions is to adapt variable step sizes when scatter is calculated iteratively. Specifically, the ratio of the interval sizes might be 4:2:1 if scatter calculation is iterated three times. At early iterations, the image contrast is low and a coarse sampling is justified. As the contrast of the image increases and the fine structures in the image are recovered, a finer sampling is favorable. In addition, both TOF and non-TOF scatter computation time depends on the number of pseudo-detectors. Similar detector spacing for TOF scatter calculation was used as the non-TOF version. Optimization of detector spacing may reduce computation time without introducing inaccuracy in TOF scatter calculation.

Two TOF scatter calculation approaches were evaluated in this work. The first method was based on the idea proposed by Watson (Watson, 2007), and the second method was based on the assumption that the TOF distribution of the scattered coincidence rate along an LOR is the same as the TOF distribution of the true coincidence rate (Jakoby *et al.*, 2011). While the first method accurately models the TOF bin distribution of the scattered coincidences, the second method substantially improves the speed of the computation, since its computation time is identical to that for non-TOF scatter. Practically, the choice between the two scatter estimation methods depends on the specific situation. For list mode reconstruction, if many short and low-count frames are reconstructed, the fraction of time dedicated to scatter computation will be very high, since the computation time for scatter is independent of the total counts within a frame, and the relative overhead in list mode image iteration is low. In such cases, it may be better to perform faster scatter calculation using the second scatter calculation method. On the contrary, for list-mode reconstruction of long and high-count frames, the first method is recommended, since the relative fraction of time for scatter computation will be less.

The two scatter calculation methods described in this work performed 3D scatter simulation using the SSS model, as compared with 2D scatter simulation followed by inverse single slice rebinning to generate the 3D scatter profiles in many other works reported in the literature (de Jong *et al.*, 2007; Watson, 2000). While the 2D approach has been shown to be very computationally efficient, a recent study reported that a negative bias of 5% was observed at the center of the FOV using 2D scatter simulation, but not in 3D scatter simulation (Sibomana *et al.*, 2012). The reported work was performed on a brain PET scanner (HRRT), which does not have TOF capability. Therefore, the discrepancy between 2D and 3D TOF scatter calculation deserves further investigation.

4.4. Applicability to other PET scanners

While this work was based on the Siemens Biograph mCT scanner, the image reconstruction and the novel physics modeling techniques may be applied to other PET scanners. For example, the proposed scatter correction method for TOF PET data can be conveniently adapted for any TOF PET scanners. Also, the pLOR technique is not scanner-specific, and may be applied to other PET scanners whose scan data are grouped (mashed) for reduced storage.

4.5. Resolution vs. noise

In the mini-Derenzo phantom study (Fig. 8), 1-mm voxels were used to demonstrate the potential of achieving the highest possible resolution. It was shown that the 2.4-mm rod structures were resolved at high iterations using MOLAR with 1-mm voxels, but not with 2-mm voxels. This result implies that 1-mm voxels are useful to achieve the highest possible resolution on the Biograph mCT, and that motion may be the dominating factor for resolution degradation. Therefore, accurate motion correction gives a more accurate system model, suggesting that the images can potentially have higher resolution. This would require more iterations, with the resultant higher noise. As some researchers reported (Blume *et al.*, 2010; Tsoumpas *et al.*, 2013; Chun and Fessler, 2013), regularization methods may be an important approach to increase resolution without an undue increase in noise. This will be a future direction of our investigation.

4.6. Summary of studies

In this work, instead of limiting the studies to simulations or phantoms, we performed a wide range of real data comparisons to evaluate the novel physics modeling and event-by-event motion correction. The phantom studies (Figs. 8 and 9) were useful in demonstrating the characteristics of the new techniques, e.g., pLOR and TOF scatter correction. The mini-Derenzo study (Fig. 8) was valuable in examining the extent to which the spatial resolution of the Biograph mCT images may be improved. This result also stresses the importance of accurate motion correction in whole-body PET studies. However, the phantom studies are not definitive, due to the physiologically unrealistic contrast. Therefore, we also performed a human brain study (Fig. 10), an anesthetized animal brain study (Fig. 11), a moving phantom study with real patient motion (Fig. 14) and a human whole-body study (Fig. 15). The animal study is essential because it allows us to compare image resolution in real data without the degrading effect of possible motion. The human brain study is important to demonstrate the feasibility of the techniques in clinical studies. However, there is no gold standard in real human studies, and the apparent higher resolution in Fig. 10 could, in part, be caused by correlated noise. Although head motion is of lower magnitude and frequency than motion of the organs in whole-body studies, we feel that the brain studies are essential, as many brain regions have high tracer uptakes and local contrast. Such fine structures are helpful in examining the image resolution in real-world situations. Finally, the human whole-body study with event-by-event motion correction shows highly encouraging results, as the image blurring due to the respiratory motion was substantially reduced, indicating the potential of our methods for whole-body studies with motion correction. As discussed in section 4.2, motion tracking and correction in whole-body PET studies is highly complex. The results of our initial study show the feasibility of performing event-by-event motion correction in whole-body studies to substantially reduce motion artifacts, and substantiate the necessity of future work to develop robust algorithms of motion correction in whole-body PET studies. Ultimately, the utility of these methods will be demonstrated by their application to cohorts of human data, where they demonstrate less variation and/or higher accuracy in assessing disease severity, progression, or for monitoring therapies.

5. Conclusion

This work demonstrated the successful development of list-mode image reconstruction for the Biograph mCT with event-by-event motion correction. In these initial studies, we have demonstrated that list-mode reconstruction with the pLOR positioning technique gives faster resolution recovery for fine structures than the PSF+TOF algorithm. Novel algorithms for TOF scatter calculation were proposed and evaluated to improve the speed of scatter calculation. The event-by-event motion correction method using the INTEX algorithm is able to substantially reduce image blurring due to the subject motion in the whole-body studies. The improvement in spatial resolution in routine studies and the capability of performing list-mode motion correction has great potential in improving the quantification of high-resolution PET studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Bloomfield PM, Spinks TJ, Reed J, Schnorr L, Westrip AM, Livieratos L, Fulton R, Jones T. The design and implementation of a motion correction scheme for neurological PET. *Phys. Med. Biol.* 2003; 48:959–78. [PubMed: 12741495]
- Blume M, Martinez-Moller A, Keil A, Navab N, Rafecas M. Joint reconstruction of image and motion in gated positron emission tomography. *IEEE transactions on medical imaging.* 2010; 29:1892–906. [PubMed: 20562034]
- Buhler P, Just U, Will E, Kotzerke J, van den Hoff J. An accurate method for correction of head movement in PET. *IEEE Trans. Med. Imag.* 2004; 23:1176–85.
- Carson RE, Barker W, Liow J-S, Adler S, Johnson C. Design of a motion-compensation OSEM List-mode Algorithm for Resolution-Recovery Reconstruction of the HRRT. *IEEE Nucl. Sci. Symp. Conf. Rec.* 2003; M16-6
- Casey ME, Gadagkar H, Newport D. A component based method for normalization in volume PET. *Three-Dimensional Image Reconstruction in Radiology and Nuc. Med.* 1995:66–71.
- Chan C, Jin X, Fung EK, Naganawa M, Mulnix T, Carson RE, Liu C. Event-by-event Respiratory Motion Correction for PET with 3-Dimensional Internal-external Motion Correlation. *IEEE NSS/MIC Conference Record.* 2012
- Chun SY, Fessler JA. Noise properties of motion-compensated tomographic image reconstruction methods. *IEEE transactions on medical imaging.* 2013; 32:141–52. [PubMed: 22759442]
- Conti M, Bendriem B, Casey M, Chen M, Kehren F, Michel C, Panin V. First experimental results of time-of-flight reconstruction on an LSO PET scanner. *Physics in medicine and biology.* 2005; 50:4507–26. [PubMed: 16177486]
- Daube-Witherspoon ME, Yan YC, Green MV, Carson RE, Kempner KM, Herscovitch P. Correction for motion distortion in PET by dynamic monitoring of patient motion. *J. Nuc. Med.* 1990; 31:816.
- Dawood M, Buther F, Lang N, Schober O, Schafer KP. Respiratory gating in positron emission tomography: a quantitative comparison of different gating schemes. *Med Phys.* 2007; 34:3067–76. [PubMed: 17822014]

- Dawood M, Lang N, Jiang X, Schafers KP. Lung motion correction on respiratory gated 3-D PET/CT images. *IEEE Trans. Med. Imag.* 2006; 25:476–85.
- de Jong HW, van Velden FH, Kloet RW, Buijs FL, Boellaard R, Lammertsma AA. Performance evaluation of the ECAT HRRT: an LSO-LYSO double layer high resolution, high sensitivity scanner. *Phys. Med. Biol.* 2007; 52:1505–26. [PubMed: 17301468]
- Delso G, Furst S, Jakoby B, Ladebeck R, Ganter C, Nekolla SG, Schwaiger M, Ziegler SI. Performance measurements of the Siemens mMR integrated whole-body PET/MR scanner. *J Nucl Med.* 2011; 52:1914–22. [PubMed: 22080447]
- Halldin C, Guilloteau D, Okubo Y, Lundkvist C, Olsson H, Karlsson P, Chalon S, Emond P, Swahn CG, L. F. PET-characterization of [C-11] PE2I binding to dopamine receptors in the monkey brain. *J. Nuc. Med.* 1998; 39
- Jakoby BW, Bercier Y, Conti M, Casey ME, Bendriem B, Townsend DW. Physical and clinical performance of the mCT time-of-flight PET/CT scanner. *Phys. Med. Biol.* 2011; 56:2375–89. [PubMed: 21427485]
- Jin X, Jian Y, Mulnix T, Sandiego CM, Yao R, Carson RE. List-mode image reconstruction for the FOCUS-220 with motion correction and spatially-variant probability density functions: Application to awake monkey imaging. *IEEE NSS/MIC Conference Record.* 2012
- Jin X, Mulnix T, Planeta-Wilson B, Gallezot JD, Carson RE. Accuracy of head motion compensation for the HRRT: comparison of methods. *IEEE Nucl. Sci. Symp. Conf. Rec.* 2009; 2009:3199–202.
- Klein GJ, Huesman RH. Four-dimensional processing of deformable cardiac PET data. *Med. Image Anal.* 2002; 6:29–46. [PubMed: 11836133]
- Lamare F, Ledesma Carbayo MJ, Cresson T, Kontaxakis G, Santos A, Le Rest CC, Reader AJ, Visvikis D. List-mode-based reconstruction for respiratory motion correction in PET using non-rigid body transformations. *Physics in medicine and biology.* 2007; 52:5187–204. [PubMed: 17762080]
- Liu C, Alessio AM, Kinahan PE. Respiratory motion correction for quantitative PET/CT using all detected events with internal-external motion correlation. *Med. Phys.* 2011; 38:2715–23. [PubMed: 21776808]
- Menke M, Atkins MS, Buckley KR. Compensation methods for head motion detected during. PET imaging *IEEE Trans. Med. Imag.* 1996; 43:310–7.
- Nehmeh SA, Erdi YE, Rosenzweig KE, Schoder H, Larson SM, Squire OD, Humm JL. Reduction of respiratory motion artifacts in PET imaging of lung cancer by respiratory correlated dynamic PET: methodology and comparison with respiratory gated PET. *J. Nucl. Med.* 2003; 44:1644–8. [PubMed: 14530480]
- Normandin MD, Petersen KF, Ding YS, Lin SF, Naik S, Fowles K, Skovronsky DM, Herold KC, McCarthy TJ, Calle RA, Carson RE, Treadway JL, Cline GW. In vivo imaging of endogenous pancreatic beta-cell mass in healthy and type 1 diabetic subjects using 18F-fluoropropyl-dihydrotetrabenazine and PET. *J Nucl Med.* 2012; 53:908–16. [PubMed: 22573821]
- Nuyts J, Dupont P, Stroobants S, Benninck R, Mortelmans L, Suetens P. Simultaneous maximum a posteriori reconstruction of attenuation and activity distributions from emission sinograms. *IEEE transactions on medical imaging.* 1999; 18:393–403. [PubMed: 10416801]
- Panin VY, Kehren F, Michel C, Casey M. Fully 3-D PET reconstruction with system matrix derived from point source measurements. *IEEE transactions on medical imaging.* 2006; 25:907–21. [PubMed: 16827491]
- Rezaei A, Nuyts J, Defrise M, Bal G, Michel C, Conti M, Watson C. Simultaneous reconstruction of activity and attenuation in Time-of-Flight PET. *Nuclear Science Symposium and Medical Imaging Conference Conference Record.* 2011:2375–82.
- Seppenwoolde Y, Berbeco RI, Nishioka S, Shirato H, Heijmen B. Accuracy of tumor motion compensation algorithm from a robotic respiratory tracking system: a simulation study. *Med. Phys.* 2007; 34:2774–84. [PubMed: 17821984]
- Sibomana M, Keller SH, Stute S, Comtat C. Benefits of 3D scatter correction for the HRRT – a large axial FOV PET scanner. *IEEE NSS/MIC Conference Record.* 2012:2954–7.

- Tsoumpas C, Mackewn JE, Halsted P, King AP, Buerger C, Totman JJ, Schaeffter T, Marsden PK. Simultaneous PET-MR acquisition and MR-derived motion fields for correction of non-rigid motion in PET. *Ann Nucl Med*. 2010; 24:745–50. [PubMed: 20842466]
- Tsoumpas C, Polycarpou I, Thielemans K, Buerger C, King AP, Schaeffter T, Marsden PK. The effect of regularization in motion compensated PET image reconstruction: a realistic numerical 4D simulation study. *Physics in medicine and biology*. 2013; 58:1759–73. [PubMed: 23442264]
- Wang W, Z. H, Gualtieri EE, Parma MJ, Walsh ES, Sebok D, Hsieh Y-L, Tung C-H, Song X, Griesmer JJ, Kolthammer JA, Popescu LM, Werner M, Karp JS, Gagnon D. Systematic and Distributed Time-of-Flight List Mode PET Reconstruction. *IEEE Conference Record*. 2006; 3:1715–22.
- Watson CC. New, Faster, Image-Based Scatter Correction for 3D PET. *IEEE Trans Nucl Sci*. 2000; 47:1587–94.
- Watson CC. Extension of Single Scatter Simulation to Scatter Correction of Time-of-Flight PET. *IEEE Trans Nucl Sci*. 2007; 54
- Watson CC, Newport D, Casey ME. A single scatter simulation technique for scatter correction in 3D PET. *Three-Dimensional Image Reconstruction in Radiology and Nuclear Medicine*. 1996:255–68.
- Williams DL, Jennings A, Lewis R, Street L, Paten S, Wisnoski DD, Wolkenberg SE. A novel glycine transporter-1 PET tracer: from discovery to clinic. *Neurosci*. 2008; 885:15.
- Zhou VW, Kyme AZ, Meikle SR, Fulton R. A scheme for PET data normalization in event-based motion correction. *Phys Med Bio*. 2009; 54

Fig.1.

With 32-bit list-mode data, to reduce the number of unique LORs, individual sub-LORs (A) are grouped within a sinogram bin (B). The coordinates of all the sub-LORs in (A) are thus recorded as the sinogram bin address in (B), which is the average location of all possible sub-LORs within the sinogram bin.

Fig. 2. Cold phantom (white) was placed flush against a ^{68}Ge phantom (dark). Phantom positioning was coaxial with the scanner z-axis.

Fig. 3. Two line profiles were drawn through the 3.2-mm rod structures to compute the contrast recovery coefficients.

Fig. 4. Contrast phantom. Hot, warm and cold ROIs are shown as red, yellow and blue circles, respectively. The hot and cold contrast recovery coefficients are computed using Eq. 5.

Fig. 5. CRC values for the hot and cold ROIs as a function of effective iteration (iteration $\times$ subsets) for the contrast phantom. The two reconstruction algorithms (MOLAR and PSF +TOF) give comparable CRC in the hot and cold ROIs.

Fig. 6.

Mean (A) and standard deviation (B) of the TOF bin locations for scattered coincidences (solid curve) and true+scattered coincidences (dashed curve) from the phantom shown in Figure 2. The mean TOF bin is comparable for the scatter coincidences and true+scatter across all radial bins. Near the center of the FOV (radial bins between -30 and +30), the standard deviation of TOF bin for the scattered coincidences is close to that for the true +scattered coincidences, indicating that the assumption in scatter method 2 is appropriate. Towards the edge of the object, where (radial bins approaches -50 and +50), some discrepancy is observed between the two curves, indicating that the TOF bin distribution for the scattered coincidences is broader than that of the true+scattered coincidences.

Fig.7.

Intensities of the contrast phantom in the hot (A), warm (B) and cold (C) regions as a function of effective iteration (iteration $\times$ subsets). While comparable intensities are observed for all reconstruction methods in the hot and warm regions, MOLAR with the second scatter correction method gives higher intensities in the cold region than both PSF+TOF and MOLAR with the first scatter correction method.

Fig. 8.

Reconstructed images of a mini-Derenzo phantom. Top: images reconstructed with PSF +TOF. Bottom: images reconstructed with MOLAR for various effective iterations. The last column shows the MOLAR image using 1-mm pixels. While the 3.2 mm rods are clearly resolved at 630 iterations for both methods, MOLAR gives higher contrast in the 3.2-mm rods at 63 iterations than PSF+TOF. The 2.4 mm rods are also visible using MOLAR with 1 mm pixels.

Fig. 9.

Contrast recovery is plotted a function of noise, represented by the COV across 10 replicates of the mini-Derenzo phantom. Molar and PSF+TOF follow a similar trend. However, the convergence of Molar is slightly faster than PSF+TOF.

Fig. 10. Reconstructed images of a human brain study injected with [^{11}C]PE2I shown in sagittal orientation on a common intensity scale. The body of the caudate (arrows) shows slightly better delineation with MOLAR (B) than PSF+TOF (A). However, MOLAR gives higher noise level than PSF+TOF, due to the probabilistic LOR assignment.

Fig. 11.

An anesthetized baboon [^{18}F]CFPYPB brain study, reconstructed with PSF+TOF at the 3rd iteration (A), PSF+TOF at the 4th iteration (B), MOLAR using the scatter method 1 (C), and MOLAR using scatter method 2 (D). Images were reconstructed with 21 subsets. All MOLAR images were reconstructed for 3 iterations. The MR images (E) are included in the last column for identification of the brain regions. Top and bottom rows are coronal and transverse orientations, respectively. PET images were scaled to the same intensity level within each row. As denoted by the arrows, at the same iteration, the cingulate ROI is better delineated by MOLAR than PSF+TOF. Also, the cortical gray and white matter structures are more clearly resolved by MOLAR than PSF+TOF (bottom row). MOLAR at the 3rd iteration gives similar contrast as PSF+TOF at the 4th iteration, as predicted by Fig. 9.

Fig. 12.

Intensity profiles at the level indicated by the horizontal bars in Fig. 11A. At the same number of iterations, MOLAR with the scatter method 1 gives higher contrast than PSF +TOF. The contrasts between the 3rd iteration of MOLAR and the 4th iteration of PSF+TOF are comparable, as suggested by Fig. 9. Differences in intensities in the high and low uptake regions are observed between the two scatter

Fig. 13.
Motion trace of the moving NEMA phantom in the axial direction. The first minute of motion data is shown here.

Fig. 14.

NEMA phantom with hot and cold inserts in sagittal view (A) Moving phantom scan reconstructed without motion correction (B) Moving phantom scan reconstructed with list-mode motion correction and (C) static scan. For the moving case, the direction of motion was vertical in this image view. Images were reconstructed using MOLAR with 21 subsets and 3 iterations, and were scaled to the same intensity level. Event-by-event list-mode motion correction for image B generates comparable image contrast to the static scan.

Fig. 15.

Reconstructed images in coronal view of a whole-body human [^{18}F]FP-(+)-DTBZ study using MOLAR without motion correction (A) and with event-by-event motion correction (B). Images were scaled to the same intensity level within each row. Subject motion was tracked with the Anzai device, and converted to 1D motion transformation matrices in the axial direction using the INTEX algorithm at a frequency of 40 HZ. As indicated by the arrows, substantial image blurring of the cortical structures in the kidney (top) and the pancreas (bottom) is observed without motion correction (A). Event-by-event correction (B) is able to reduce the image blurring caused by the respiratory motion.