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Quantitative Accuracy of HRRT List-mode Reconstructions: Effect of Low Statistics

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Abstract

Previous studies showed that iterative image reconstruction algorithms may produce overestimations of activity in low-activity regions in low-count frames. The purpose of this study was (1) to evaluate the quantitative accuracy of the MOLAR list-mode iterative reconstruction method in the context of ligand-receptor PET studies in low counts, and (2) to determine the minimum noise equivalent counts (NEC) per frame to avoid bias. Evaluation of clinical data was performed for 4 tracers using dynamic brain PET studies. True activity was estimated from high-statistics frames (300s) and ROI analysis was performed to evaluate bias in low-activity regions in short acquisition frames (10-30s) from matching times. Bias in the ROI mean values was analyzed as function of NEC. In addition, accuracy was assessed using Hoffman phantom data and simulated list mode data based on human data, but without scatter and randoms.

Unlike previous results, small biases of $-3\pm 3\%$ for low statistics region across the 4 tracers were found for NEC >100K in each frame. Very similar results were found in the phantom and simulation data. We conclude that the MOLAR iterative reconstruction method provides accurate results even in very low-count frames. This improved performance may be attributed to some of the unique characteristics of MOLAR including randoms estimation from singles, iterative estimation of scatter within the algorithm, component-based normalization, and incorporation of a line-spread function model in the reconstruction.

I. INTRODUCTION

The High Resolution Research Tomograph (HRRT) is a brain-dedicated, three-dimensional (3D) PET scanner with an axial field of view of 25 cm and resolution better than 3 mm [1]. Previous studies in this and other scanners have shown that iterative reconstruction methods are biased in the presence of low statistics frames [2-5]. For example, in [3], white matter regions had positive bias of > 10% for NEC below 3M counts. The goal of this study is to evaluate the magnitude of low-statistics bias when using our list mode reconstruction, MOLAR [6]. Evaluation was performed with human and animal HRRT data by comparing reconstructed values from “long” frames to the average value obtained by reconstructions of the same list mode data into multiple shorter frames. Evaluation was also performed with simulated list-mode data using MOLAR as well as Hoffman brain phantom data.

II. METHODS

All emission and transmission data were acquired using the HRRT scanner. This 3D-only scanner has approximately 4.5×10^9 lines-of-response (LOR) in the field-of-view (FOV) of 252 mm in axial and 312 mm in transaxial directions.

A. Dynamic human and non-human measurements

Clinical evaluation was performed using three human and one monkey 3D quantitative dynamic brain PET studies. Using [^{11}C]AFM (serotonin transporter), [^{11}C]MRB (norepinephrine transporter), [^{11}C]P943 (serotonin-1B receptor), and [^{11}C]MKAP (kappa opiate receptor). Acquisition of list mode data began shortly before each injection. Injected dose was ~740 MBq for human studies and 78 MBq for monkey. List mode data were acquired for a total duration of 120 minutes.

B. Reconstruction method

Dynamic list mode data from 60-120 min postinjection were reconstructed with 3 different frame durations into 12×300 sec, 120×30 sec and 360×10 sec. Reconstruction was performed with MOLAR, a cluster-based iterative list-mode OSEM (2 iteration, 30 subsets) algorithm [6]. MOLAR directly reconstructs list-mode prompts (i.e., OP-OSEM) using a full system model including exact reprojection of each line-of response (LOR); system matrix computed from voxel-to-LOR distances (radial and axial); distribution of events to processors and to subsets based on order of arrival; removal of voxels and events outside a reduced field-of-view defined by the attenuation map; no pre-corrections to Poisson data, i.e., all physical effects are defined in the model; randoms estimation from singles; model-based single scatter simulation incorporated into the iterations; component-based normalization; and event-by-event motion correction measured with the Yicra (NDI Systems, human studies only). The current data were reconstructed with an isotropic Gaussian line spread function with FWHM of 2.5 mm. Final image dimensions were 256×256×207 with voxel size of 1.2 mm.

For each frame, NEC was calculated with prompts in the subject field-of-view (defined by the transmission scan) determined from the list mode data, randoms estimated from singles, and scatter estimated by the single-scatter-simulation method. In these data, randoms fractions were low: 0.04-0.06 (human data) and 0.05 (monkey) and scatter fraction was estimated as 0.32-0.36 (human data) and 0.27 (monkey).

C. Image analysis

Summed images from 0-10 min postinjection were created and registered to the subject's MR 3T anatomical image (6-parameter affine registration) which was then registered to an MR template using a 12-parameter linear transform using a mutual-information algorithm [7] and the FLIRT software (www.fmrib.ox.ac.uk/fsl/flirt). Automatic regions-of-interest [8] were then applied to generate time-activity curves (TAC). As the largest bias effects have been reported in low-activity regions, the selected regions were cerebellum for AFM, P943, and MKAP and occipital cortex for MRB.

Percent bias in the ROI mean values was calculated by comparing the average ROI value in the short reconstructions to the matching value in the 300-sec images. Bias was analyzed as function of NEC for each ROI.

D. Hoffman Phantom

A 3D anthropomorphic human brain phantom (Hoffman phantom, Data Spectrum, Hillsborough, NC, USA) [10] was filled with ^{18}F -FDG in water solution so that the activity

concentration at start was 18.5 MBq and list mode data were acquired for 120 min. The list mode scan was reconstructed using MOLAR algorithm into 5, 10, 30, 60, 300 and 1800 s frames using the same corrections and parameters as human data, but motion. Five minute transmission scan, used for attenuation and scatter correction purposes, was acquired after activity had decayed to background levels.

True activity was estimated from high-statistics frames (300s) and ROI analysis was performed to evaluate bias in low-activity regions in short acquisition frames (5-60s) from matching times as described for the subject data.

Two 3D ROIs were identified on the first 1800-s frame using MEDx (MEDx, Sensor Systems, Inc. Sterling, VA, USA) region growing segmentation tool. Large gray matter (GM; volume: 91 ml) and white matter (WM; volume: 79 ml) regions were used to study bias in GM, WM and the contract between OM and WM, following the approach described in [5].

In Hoffman phantom data, randoms fraction was 0.04 and scatter fraction was estimated as 0.39.

E. Simulation

Using the MOLAR software, 4D PET list-mode data (500M events) were simulated for a brain phantom derived from a subject's measured data. This simulation uses the same forward model used in the MOLAR reconstruction to determine the expected value of counts in a LOR, and then Poisson replicates are simulated. The simulation had regions representing ROIs for cerebellum, thalamus and cortical areas. TACs were simulated with one-tissue model over 120 minutes post injection, with a real subject's [^{11}C]AFM arterial input function corrected for metabolites and parameters (volume of distribution (V_T) and delivery rate (K_1)) typical for each region [11]. List mode data were created with MOLAR's forward projection model including detector resolution, normalization, attenuation, deadtime, but without randoms, scatter or motion. These data were reconstructed, TACs were computed for low-activity regions in the manner described for the real data, and the bias was assessed.

To ensure sufficient convergence of MOLAR algorithm, the 120×30 sec frames were reconstructed with various iterations (30 subsets). No effects were seen of increased iterations. Comparing results at 5 iterations to that at 2 iterations, the mean differences were less than 1% for both low-activity (cerebellum) and high-activity (thalamus) regions.

III. RESULTS AND DISCUSSIONS

A. Subject studies

Figure 1 shows % bias vs. NEC across different tracers in 10- and 30-s frames. Each point represents a different time point comparison in a different study. A bias of $-3\pm 3\%$ ($\text{NEC} > 100\text{K}$) and -1 ± 1 ($\text{NEC} > 200\text{K}$) was observed for low statistics region across 4 tracers. The NEC of the 300-sec scans was $2.8\text{M} \pm 2.0\text{M}$.

B. Hoffman Phantom

Results obtained for the anthropomorphic brain phantom are shown in Figure 2. A bias of $-4\pm 2\%$ and $+4\pm 5\%$ (for NEC between 160K and 3500K) was observed for GM and WM regions respectively. The negative bias in gray matter region is consistent with the real and simulated data. The white matter region shows a positive bias for NEC values less than 3500K.

The differences in the activity concentration distribution as a function of NEC in the GM and WM contrast ratio between long and short duration frames is shown in Figure 3. There was a bias of $-7 \pm 6\%$ observed in the GM/WM ratio in 5, 10, 30 and 60s frames compared to 300s frames.

C. 4D Simulation

The simulation provided similar results to those obtained with the clinical data. Simulation results showed bias of $-4 \pm 3\%$ ($\text{NEC} > 100\text{K}$) and $-3 \pm 2\%$ ($\text{NEC} > 200\text{K}$) in 10-30s frames for $[^{11}\text{C}]\text{AFM}$. Figure 4 shows % bias vs. NEC in 10 and 30-sec frames for 2 iterations. NEC of the 300-sec scans was $3400\text{K} \pm 300\text{K}$ counts.

IV. DISCUSSION

The MOLAR reconstruction algorithm provides minimum bias, even in very low-count frames in simulation, phantom, and subject data.

These results differ substantially from other studies which showed bigger bias in low-activity regions at substantially higher NEC. In [2], the differences in estimated activities were as high as 70% in case of a low statistic region (cerebellum) with various iterative reconstruction methods (e.g. attenuation and normalization weighted OSEM 3D algorithm). Our results showed larger bias for the Hoffman phantom compared with subject data but the bias was significantly smaller than in other publications. For example, a large positive bias in WM (28%) and negative bias in OM (14%) for the Hoffman phantom was reported in [5] at NEC greater than 1M counts. Also, considerably larger biases of gray to white matter contrast ratio (up to 88%) were shown in [5]. Other HRRT brain phantom studies [4] showed large under- and overestimation of 20 and 50% in gray and white matter areas, respectively, in case of short acquisition frames (10-30s). In [3], white matter regions had positive bias of $> 10\%$ for NEC below 3M counts; these findings are somewhat more consistent with our results.

It is worth mentioning that our “long” frames (300-sec) have considerably lower NEC (for example $3.2 \pm 2.5\text{M}$ counts in the subject data) compared to other publications [3], [5]. To expand a range of NEC values, we additionally calculated bias for NEC greater than 1M counts using the subject data. For this purpose, dynamic list mode data from 60-120 min postinjection were reconstructed into $6 \times 600\text{-sec}$ frames. TACs were computed for low-activity regions (cerebellum for AFM, P943, and MKAP and occipital cortex for MRB) in the manner described for the subject data, and then compared to the matching value in the 300-sec frames. The percentage difference across 4 tracers was $1 \pm 1\%$ at NEC between 1.3M and 21M counts.

Although the exact basis for the superior performance of MOLAR is not clear, a number of unique characteristics of MOLAR should be considered in that the other results were obtained with data that were histogrammed and then reconstructed with a sinogram based OP-OSEM. These include: 1) estimation of randoms (from singles), 2) estimation of 3D scatter (estimated iteratively within the algorithm), 3) use of component-based normalization [9], 4) use of original list mode data instead of binned data, and 5) incorporation of line-spread function model in the reconstruction. However, it is not clear why any one of these features should limit the bias.

In the simulation and the clinical data, low-activity regions were negatively biased at low NEC ($< 200\text{K}$). If even lower NEC were used, more substantial negative bias was found (data not shown). This effect is due to insufficient counts in each subset. Specifically, the OSEM algorithm only backprojects along LORs found in the list mode stream. When there

are very few events, “holes” are left in the backprojection which are set to 0, due to the multiplicative nature of the OSEM algorithm.

V. CONCLUSION

An experimental comparison of the quantitative accuracy of MOLAR iterative reconstruction method for HRRT was performed in this study to assess the bias of low-activity frames. For the ROI analysis, MOLAR reconstruction provides robust estimates of the activity in regions with very low statistics. Small overestimation was seen in low-activity regions in the Hoffman phantom, below 500K NEC. Such error was not seen in the simulation or the subject data. Based on our clinical, phantom and simulated measurements, count statistics should exceed 200K NEC in each frame to effectively eliminate bias.

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Fig. 1. BIAS (%) in low activity regions of the measured 3D brain data as a function of NEC in 10 and 30s frames compared to 300s frames.

Fig. 2. BIAS (%) in low activity regions of the Hoffman phantom data as a function of NEC in 5, 10, 30 and 60s frames compared to 300s frames for the (a) GM and (b) WM.

Fig. 3.
GM to WM contrast ratio as a function of NEC in 5, 10, 30 and 60s frames compared to 300s frames.

Fig. 4. BIAS (%) in low activity regions of the simulated 3D brain data as a function of NEC in 10 and 30s frames compared to 300s frames.