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Abstract: Whole-body parametric PET imaging along with Patlak graphical analysis has the potential to provide improved diagnosis. However, a voxel-based fitting approach for a short dynamic scan protocol results in high statistical noise in the parametric images. The objective of our study is to present the framework of a novel multiple clustering realizations (MCR) method for estimating parametric images with improved image quality. The method relies primarily on using standard k-means clustering for segmenting the time-activity curves within the whole-body volume. In addition, in order to obtain improved accuracy without increasing noise, multiple realizations of clustering were performed. During each realization, cluster centers were selected from a unique ordered set of time-activity curves within the whole-body volume. All the remaining data were classified into the cluster centers based on minimum Euclidean distance measure. Patlak analysis was performed on the cluster average to form the slope and intercept images. Parametric images thus obtained for all realizations were averaged. An XCAT phantom based simulations for the torso were performed using dynamic time-activity curves to model FDG uptake. Five dynamic images each representing 1 min scan time with 7 min intervals were created starting 60 minutes post injection. In addition, 5 whole-body dynamic FDG patient datasets with image-derived blood input function and whole-body dynamic data measurements were also used. All dynamic data were reconstructed using OSEM applying corrections for image-degrading factors. Slope and intercept parametric images were obtained for the voxel-fitting and MCR method. Noise in a liver region of interest increased as a function of the number of clusters for the simulated data. On the other hand, bias decreased with increasing number of clusters. However, as number of clustering realizations increased, noise reduced and $K_i$ estimates stabilized. The parametric images obtained with MCR method showed better image quality compared to voxel-based fitting method for the patient and simulated datasets. Multiple clustering realizations method has the potential to provide improved parametric image quality for short scan whole-body parametric PET imaging.

I. INTRODUCTION

Quantitative whole-body (WB) parametric PET imaging has been proposed to improve diagnostic capability as well as prognostication and assessment of response to therapy with 18F-FDG PET. Several studies with dynamic single-bed PET imaging along with compartment modelling have shown promise over conventional SUV based static PET measurements. These studies include discrimination of hepatic lesions [1], differentiation of tumor subtype for breast cancer imaging [2] as well as assessment of aggressiveness of pancreatic tumors [3]. Nevertheless, all these studies not only were restrained to the limited axial field of view of a single bed but also involved relatively long scan durations (~60 – 90 minutes) which can be prone to patient discomfort and motion. Recent studies have also investigated the potential of using dynamic PET imaging for the WB volume [4 – 8]. Karakatsanis et al have proposed a clinically feasible protocol whereby WB dynamic PET data may be collected for about 30 minutes following a single bed 10 minutes dynamic PET scan over a blood pool region right after the tracer injection to obtain the initial peak of the blood input function [4, 5]. The WB volumes for each dynamic frame were independently reconstructed and Patlak graphical analysis was later used to fit time-activity curves derived from each voxel, which is referred to as the indirect WB parametric imaging approach. The slope images, expressing the 3D distribution of the metabolic glucose rate $K_i$ estimates, from 30 min dynamic PET data were found to be quantitatively similar to those obtained from 60 minutes total scan duration.

In this study we investigated a more recent WB dynamic PET scan protocol whereby total scan duration was again 30 minutes but starting 50 minutes post-injection (p.i.) in order to facilitate within the same session the use of standard clinical SUV based static images alongside parametric images [9, 10]. A population-based model was employed to estimate the missing early section of the input function for the first 50min p.i. [11]. However, in this case the indirect voxel based fitting approach resulted in noisy slope parametric images [12, 13]. In order to suppress noise, the use of 4D direct reconstruction of parametric images was found to produce more robust images with less noise [12 - 14]. However, the use of direct 4D reconstruction has an inherent positivity constraint and may result in artifacts surrounding regions with a large negative slope.

Our objective in this work was to develop a clustering based method for the indirect parametric image formation to suppress noise while maintaining quantitative accuracy. In this paper we present the framework of the novel multiple clustering realizations method for whole-body parametric
PET. The method was validated with XCAT phantom based simulations and 5 whole-body dynamic clinical datasets.

II. METHODS

Standard k-means clustering belongs to the family of unsupervised segmentation techniques and has been used previously for region-of-interest delineation in dynamic PET and dynamic cardiac SPECT imaging [15, 16]. Here, voxels with similar temporal characteristics are grouped together into clusters so as to maximize the inter-cluster distance and minimize the intra-cluster distance. The members belonging to each cluster are averaged and the resulting time-activity curve is used to represent all members of the cluster. Time-activity curves for all clusters are then fit to the desired model in order to obtain the parametric images. The accuracy of the parametric images depends upon the number of clusters chosen. When few clusters are chosen, the resulting parametric images have less noise but may be biased. On the other hand, as the number of clusters increases, noise in the parametric images may increase. Our clustering based approach utilizes few clusters to limit noise while employing multiple realizations to improve quantitative accuracy of the parametric images. In particular, the following workflow describes our proposed multiple clustering realization (MCR) method:

1. A uniformly spaced grid is computed for the WB volume consisting of \( N \) points where 
   \[ N = \text{number of seeds for cluster initialization (} N_s) \times \text{number of realizations} \]
   During each realization, a set of uniformly spaced seeds \( N_s \) (~ 0.01% of total number of image voxels) are selected to form the seed pool.

2. The Euclidean distance metric is computed for all seed pairs:
   \[ d_{ab} = \sqrt{\sum_{i=1}^{n} (x_{ai} - x_{bi})^2} \text{ where } x_a \neq x_b \]
   where \( n \) is the number of temporal samples and \( x_a \) and \( x_b \) are time-activity curves for seeds \( a \) and \( b \).

3. The seed pair distances are histogrammed such that the bin width equals \( \frac{\text{sum of distance measures}}{N_c^2} \) where \( N_c \) is the number of clusters. The pair of seeds with a distance corresponding to the center of each bin is selected. The time-activity curves corresponding to the selected seeds serve as the initial cluster centers.

4. Now the Euclidean distance for time-activity curves from the whole-body volume with respect to each cluster center are computed and classified based on a minimum distance. Upon classification, an average of all curves belonging to a cluster is obtained followed by reclassification of the curves.

5. Assuming that the blood input function is known, Patlak graphical analysis is performed on each cluster average. An estimate of the slope \( K_i \) and intercept \( V_1 \) for a tissue time-activity curve of \( C(t) \) and plasma input function \( C_p(t) \) is obtained by fitting the data to the linear standard Patlak model by
   \[ \frac{C(t)}{C_p(t)} = \frac{\int_0^t C_p(\tau)d\tau}{C_p(t)} - K_i + V_1 \]
   The fits obtained for each cluster average are then assigned to its members’ spatial locations which in turn results in the slope and intercept parametric images.

6. Steps 2 – 5 are repeated using the set of seeds for the next realization and the resulting parametric image is averaged with the previous realization respective image estimate.

A. XCAT simulations

An XCAT phantom was used to simulate WB dynamic FDG data acquisition of the torso [17]. Time-activity curves for different tissue types in the torso were generated using a two tissue compartment model [1, 4]. In addition, a 1 cm diameter spherical lesion with FDG dynamics representative of a hepatic tumor was also simulated. Respiratory and cardiac motion was also modeled for the XCAT phantom excluding the liver lesion.

Five dynamic image frames each representing activity estimates for a 1 minute scan duration with 7 minutes inter-frame interval were generated starting 60 minutes p.i. Decay correction and scanner calibration factors corresponding to measurements from a PET/CT scanner (mCT Biograph, Siemens) were applied to the images. Each dynamic image was forward projected along with modelling of image degradation factors such as attenuation, scatter, randoms and point spread function (PSF) to create a realistic sinogram [18]. Poisson noise was added to the simulated prompts as well as randoms sinograms. PSF reconstruction using Siemens tools of each dynamic frame was performed using 3 iterations of time-of-flight (TOF) based OSEM with 21 subsets.

The reconstructed images were further processed to obtain parametric images with the indirect approach using two methods. First, voxel-based parametric images were estimated by fitting time-activity curves from each voxel to the Patlak model. The fits were obtained using linear regression curve fitting technique. Next, MCR method was used to obtain parametric images by varying the number of clusters (2 – 20 in steps of 2) and the number of realizations (1 – 10). A volume of interest in the liver was used to obtain estimates of noise in the slope image. The noise was quantified as

\[ \text{Noise} = \frac{\text{std dev (liver ROI)}}{\text{mean (liver ROI)}} \]

B. Patient data

Five WB patient datasets acquired with a dynamic acquisition on the Biograph mCT PET/CT scanner were used for evaluation. Each study consisted of a WB CT followed by a PET scan. The PET acquisition for each dataset started with a single bed list-mode scan over the torso for the first 6 minutes p.i., so as to capture the early peak of the blood input function, directly followed by 15 dynamic WB acquisitions of 45sec per bed to track the FDG kinetics across ~7 beds. The single bed list-mode data was histogrammed in order to obtain
a series of sinograms consisting of twelve 10 sec frames and twelve subsequent 20 sec frames. Further details on the acquisition workflow can be found in Karakatsanis et al [4]. All sinogram data were reconstructed using TOF based OSEM (3 iterations and 21 subsets) correcting for attenuation, scatter and the measured scanner PSF resolution response.

An image derived blood input function was obtained from a manually drawn ROI in the center of the heart left ventricle. A subset of the dynamic PET data consisting of the last six frames, i.e. ~50 min p.i was used for parametric image formation. In addition static PET images were obtained by summing the 3 consecutive dynamic frames following ~50 min p.i. Finally, the indirect voxel-based fitting and MCR method were used to obtain the WB parametric images.

The noise in indirect voxel-based parametric images was found to be equivalent between the simulated and patient datasets. The number of clusters is the main determining factor for noise in the slope image estimated with the MCR method. Consequently, a baseline number of clusters was selected for simulated data and later applied to the clinical data. The baseline number of clusters and realizations were selected such that the resulting image quality was comparable to that from a standard static PET image. The mean histogram bin width for the seed pair distances corresponding to the baseline number of clusters for simulated data was used to obtain the histogram bin width for a patient dataset. This estimated histogram bin width can be expressed as

\[
\text{Hist. bin width} = \frac{\text{baseline hist bin width}}{\text{number of voxels in clinical data}} \times \frac{\text{baseline number of voxels}}{\text{number of voxels in clinical data}}
\]

The number of clusters was then computed as

\[
\text{Number of clusters} = 2 \times \frac{\text{sum of distance measures for clinical data}}{\text{Hist. bin width}}
\]

III. RESULTS

Noise and \( K_i \) metrics in the liver ROI for the simulated data as a function of number of clusters is shown in Fig. 1. It can be observed that noise increased with larger number of clusters. However, as the number of realizations increased, the noise reduces and stabilizes as a function of number of clusters. Similarly, \( K_i \) estimates in liver were found to get closer to the true value as the number of clusters were increased. At the same time, as the number of realizations were increased the \( K_i \) estimates were found to be more stable for larger number clusters with some increase in bias. In particular, it was found that as number of clusters became greater than 14, the slope images got noisier, hence 14 was chosen as the baseline number of clusters. In addition, it was observed that as number of realizations increased from 1 to 5, liver noise decreased, whereas beyond 5 realizations improvement in noise was minimal. Hence, 5 realizations were chosen as baseline.

Fig. 2 shows the parametric \( K_i \) images (a, c and d) and the static SUV PET image (b) for the simulated data. The \( K_i \) parametric image with MCR was obtained with 14 clusters and 5 realizations and was found to have noise equivalent to that of the static PET image. Moreover, it can be visually observed that the overall image quality as well as the signal-to-noise ratio for the liver lesion is improved compared to the voxel-based \( K_i \) image.

Fig. 3 shows the static and parametric images for two patient studies. The number of clusters for each study was different and dependent upon the seed pair distances measured. The use of multiple clustering realizations method was found to give good noise suppression without affecting lesion contrast.

The measured noise in a liver ROI for static, voxel-based \( K_i \) and MCR-based \( K_i \) is shown in Fig. 4. It can be observed that noise is reduced with MCR method compared to voxel-based fitting. However, the lowest noise levels are still found in the static PET images. The use of post-smoothing Gaussian filter may be used to further suppress noise in the parametric images as shown in Fig. 3.
developed to improve parametric image quality by suppressing noise using least squares or ridge regression in the context of weighted correlation coefficient quality. This technique, while not validated completely, was found to give good noise suppression for all clinical datasets. Alternate methods of using information theoretic criteria such as Akaike and Schwarz criterion for number of clusters selection have been used previously by others [12] but were not explored in this work.

Future work will involve investigation with different dynamic acquisition protocols in terms of scan durations and post-injection time windows. In addition the use of non-linear compartment models to obtain parametric images will also be investigated [20]. We hypothesize that robust parametric images with more complex non-linear models may be obtained with MCR method due to its nature of grouping curves with similar temporal behavior while obtaining fits for an average curve in a repetitive fashion.

IV. DISCUSSION

The use of indirect voxel-based fitting for short dynamic WB PET scan durations results in noisy parametric images. The introduction of 4D direct reconstruction methods, whereby parametric images are reconstructed directly incorporating the Patlak model in the reconstruction framework, has been shown to provide an improvement [12 - 14]. On the other hand, a hybrid method for Patlak model has been investigated in order to improve parametric image quality with the indirect approach [19]. In this method, weighted correlation coefficients of the Patlak model fits were used to discriminate between voxels in order to select ordinary least squares or ridge regression fitting technique and obtain images with improved contrast to noise ratio while suppressing noise. Our clustering based approach was also developed to improve parametric image quality for the indirect approach. While each of the methods mentioned above aim at achieving improved image quality for parametric images, a comparison between their performances was not done in this work.

One of the main factors in using the MCR method is the number of clusters selection which in turn determines the quality of the parametric image. In this work we proposed a method in order to facilitate the number of clusters selection for the clinical data by establishing a baseline metric using the simulated data. This technique, while not validated completely, was found to give good noise suppression for all clinical datasets. Alternate methods of using information theoretic criteria such as Akaike and Schwarz criterion for number of clusters selection have been used previously by others [12] but were not explored in this work.

Future work will involve investigation with different dynamic acquisition protocols in terms of scan durations and post-injection time windows. In addition the use of non-linear compartment models to obtain parametric images will also be investigated [20]. We hypothesize that robust parametric images with more complex non-linear models may be obtained with MCR method due to its nature of grouping curves with similar temporal behavior while obtaining fits for an average curve in a repetitive fashion.

V. REFERENCES


