Reconstruction of linear kinetic parameters directly from projection PET data

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Abstract. Dynamic Positron Emission Tomography (PET) data provide functional information. Usually, this is measured in the form of pharmacokinetic parameters derived from the temporal response of each region. Recent trends have shown that when pharmacokinetic parameters are estimated directly from the projection data, they are less affected by noise. This work investigates an existing parametric maximum likelihood expectation maximization algorithm applied to [18F]DOPA data using reference-tissue input function. The study reveals how direct reconstruction of pharmacokinetic parameters from the measured data can be performed optimally. It explains how to optimize the speed of the standard iterative algorithm and it compares the results with the existing FBP method. The improvement of the quality of the parametric images preserving quantification suggests the usefulness of direct estimation of the kinetic parameters. This algorithm is freely available within the open-source library STIR 2.1.

1. Introduction
Dynamic PET data can provide physiologically meaningful parameters about the biological process of interest. This is done by independently reconstructing all dynamic frames and then applying an appropriate kinetic model to the time-activity curve (TAC) of a region of interest (ROI). However, it is desirable to measure parameters at very small regions (e.g. voxels) in order to detect functional heterogeneity. Nevertheless, it is difficult to perform voxel-wise parametric images since they tend to be noisy. Additionally, the kinetic modelling requires appropriate weights in order to model the noise distribution in the reconstructed images, which is very difficult, because noise depends on multitude of parameters [1].

However, these limitations can be eliminated when the kinetic model is incorporated within the reconstruction algorithm and the kinetic parameters are estimated directly from the measured data. In this case, the noise distribution in the measured data can be accurately modelled, since it is well approximated by Poisson statistics, leading to statistically improved parameter estimation [2].
Recently, it has been clearly demonstrated that particularly for FDG brain studies, direct parametric reconstruction, using the Parametric Ordered Subsets Expectation Maximization (POSEM) algorithm, outperforms conventional post reconstruction methods using standard Patlak analysis [3]. However, as pointed out by Tsoumpas et al. [4], POSEM usually demonstrates impractically slow convergence rates.

In this paper, we apply POSEM to [18F]DOPA brain studies to estimate the tracer uptake in the striatal region and attempt to optimize the convergence rate. In order to do that, we employed a progressively decreasing subset scheme during the reconstruction, which allowed faster and more accurate parameter estimation compared to the original POSEM algorithm.

2. Materials and methods
The reference-region Patlak plot [5] was applied to clinical datasets related to striatal dopaminergic activity studies. The data were acquired using the Siemens ECAT® EXACT™ 3D, which operates in fully 3D acquisition mode storing all measured PET data in list-mode. List-mode data were rebinned into sinograms according to the scan protocol. The bilinear Patlak plot was incorporated within an ordinary Poisson algorithm, allowing the acquisition of two parametric images representing the tracer influx in the tissue of interest and the tracer free fraction. The reference tissue TAC was extracted from cerebellum using a ligand specific template image and an ad-hoc atlas.

The open-source software package STIR (release 2.1) [6] was used to process PET data and reconstruct dynamic and parametric images. The post reconstruction parametric maps were acquired in two steps; First, the dynamic image was reconstructed using FBP-3DRP algorithm, and then the Patlak plot was applied to the last 8 frames (5 minutes each).

For POSEM, three different subset schemes were investigated: (a) “6-6-1”: 6 subsets for 460 iterations and then 260 iterations of PMLEM; (b) “18-6-1”: 18 subsets for 230 iterations then 6 subsets for another 230 iterations and finally 260 PMLEM iterations; and (c) “18-1-1”: 18 subsets for 230 iterations and then 520 PMLEM iterations. All reconstruction schemes were initialized by the post reconstruction FBP image and let run approximately for 750 iterations. The different multi-subsets schemes were evaluated in terms of convergence rate of the mean ROI value on striatum which were automatically delineated using the CIC atlas [7]. The post reconstruction parametric maps, obtained with POSEM were quantitatively compared to FBP using a voxel-wise Bland-Altman for all voxels located in the area of interest (i.e. striatum). To reduce noise for this specific comparison, both parametric images were post-filtered with a 3 mm FWHM Gaussian kernel.

| Table 1. Mean ROI and standard deviation values on striatum for the final Patlak slope images of each POSEM scheme and the FBP image. |
|---------------------------------------------------------------|
| Uptake (10^4 s^{-1}) | Patient Mean | Patient Std. Dev | Normal Mean | Normal Std. Dev |
|----------------------|--------------|------------------|-------------|----------------|
| FBP                  | 2.21 ± 1.70  |                  | 1.76 ± 1.42 |                 |
| POSEM (6-6-1)        | 2.06 ± 1.86  | 2.07 ± 1.97      | 1.79 ± 1.61 | 1.79 ± 1.70     |
| POSEM (18-6-1)       | 2.07 ± 1.94  | 2.07 ± 1.97      | 1.79 ± 1.61 | 1.79 ± 1.70     |
| POSEM (18-1-1)       | 2.07 ± 1.94  | 2.07 ± 1.97      | 1.79 ± 1.61 | 1.79 ± 1.70     |

3. Results
A comparison among the descending-subset schemes under investigation is presented in table 1 and figure 1. All schemes appear to converge to the same ROI value for both parameters, but those employing more subsets (i.e. 18) converge faster. A quantitative comparison between FBP and POSEM (scheme 18-6-1) for all voxels in striatum of a normal study is presented in figure 2 using the Bland-Altman plot for both parameters. Both cases indicate better visual quality for POSEM compared to the indirect FBP. Finally, in figure 3 a qualitative comparison of the Patlak slope sagittal and
transaxial views of the striatum between the indirect FBP and POSEM is presented for one normal volunteer and one patient.

Figure 1. Mean ROI values for the slope (up); and intercept (bottom) on striatum with schemes: 6-6-1, 18-6-1 and 18-1-1.

Figure 2. Voxel-wise Bland Altman plots comparing the voxel values in striatum for the slope (up) and intercept (bottom) parameters.

4. Discussion
The results obtained from different subset combinations showed that there is no practical difference in the final estimated values (figure 1). However, schemes started with more subsets showed higher speed-up compared to those started with smaller subsets. Therefore, it is recommended to start the reconstruction using a large number of subsets, in order to take advantage of the fast convergence rate and then switch to a smaller number of subsets, or even to PMLEM in an attempt to avoid the limit subset cycle and achieve better accuracy in the finally estimated parameter. However, there is trade-off between faster convergence and increased standard deviation in the reconstructed images (table 1).

Voxel-wise Bland-Altman plots were employed in order to investigate the quantitative agreement between the parametric maps of the proposed method (i.e. POSEM; scheme 18-6-1) and the well-established post-reconstruction FBP method (figure 2). The results showed good quantitative agreement between the two methods for both parameters (i.e. slope and intercept), since the linear regression line (black line) is almost horizontal, crossing the zero of the vertical axis. However, bias is observed for low parametric values due to the non-negativity constraint induced by POSEM. This bias is high in low-uptake regions, e.g. cerebellum, where the effect of non-negativity is prominent.
Finally, visual inspection of the reconstructed images (figure 3) indicates that POSEM produces parametric images of better quality than the conventional indirect FBP. Nevertheless, the images are still noisy. Regularization approaches are expected to be advantageous and may also reduce bias if the penalty terms are carefully selected [8].

5. Conclusions
The results of this work indicate that POSEM is applicable to $^{18}$F-DOPA brain studies, producing images with better visual quality compared to the conventional indirect methods and preserving quantification. Convergence has been optimized by gradual reduction of the number of subsets over iterations, though the computational demand is still very high [9].

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