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Improved quantification for local regions of interest in preclinical PET imaging

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Abstract

In Positron Emission Tomography, there are several causes of quantitative inaccuracy, such as partial volume or spillover effects. The impact of these effects is greater when using radionuclides that have a large positron range, e.g., ⁶⁸Ga and ¹²⁴I, which have been increasingly used in the clinic. We have implemented and evaluated a local projection algorithm (LPA), originally evaluated for SPECT, to compensate for both partial-volume and spillover effects in PET. This method is based on the use of a high-resolution CT or MR image, co-registered with a PET image, which permits a high-resolution segmentation of a few tissues within a volume of interest (VOI) centered on a region within which tissue-activity values need to be estimated. The additional boundary information is used to obtain improved activity estimates for each tissue within the VOI, by solving a simple inversion problem. We implemented this algorithm for the preclinical Argus PET/CT scanner and assessed its performance using the radionuclides ¹⁸F, ⁶⁸Ga and ¹²⁴I. We also evaluated and compared the results obtained when it was applied during the iterative reconstruction, as well as after the reconstruction as a postprocessing procedure. In addition, we studied how LPA can help to reduce the “spillover contamination”, which causes inaccurate quantification of lesions in the immediate neighborhood of large, “hot” sources. Quantification was significantly improved by using LPA, which provided more accurate ratios of lesion-to-background activity concentration for hot and cold regions. For ¹⁸F, the contrast was improved from 3.0 to 4.0 in hot lesions (when the true ratio was 4.0) and from 0.16 to 0.06 in cold lesions

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(true ratio = 0.0), when using the LPA postprocessing. Furthermore, activity values estimated within the VOI using LPA during reconstruction were slightly more accurate than those obtained by post-processing, while also visually improving the image contrast and uniformity within the VOI.

Keywords

Positron Emission Tomography; Partial Volume Correction; Positron range

1. Introduction

In Positron Emission Tomography (PET), there are several causes of quantitative inaccuracy (Erlandsson et al. 2012, Soret et al. 2007, Barrett and Myers 2004, Hutton and Lau 1998), such as random- and scatter-coincidence events or excess background attributable to positron-gamma events from non-pure positron emitters (Laforest *et al* 2002, Lubberink and Herzog 2011, Cal-González *et al* 2015a). Another cause of quantitative inaccuracy, related to the limited spatial resolution of the system, is the partial volume effect (PVE), which can be defined as the loss in apparent activity of a given structure due to the limited spatial resolution of the system and the sampling (voxelization) of the image (Erlandsson et al. 2012).

The principal PVE in emission tomography results in a cross-contamination between different regions due to the finite resolution of the system (i.e., the finite point-spread function (PSF)). When focusing on one region in which the activity concentration needs to be quantified, the PVE can often be viewed as the combined result of two related effects: spill-in (counts from the surrounding media that are incorrectly assigned to the tissue of primary interest) and spill-out (counts from the tissue of interest which are incorrectly assigned to the surrounding media). Another type of PVE is the sampling effect; this is related to the finite voxel size and, as a consequence, the fact that each individual voxel might in principle contain contributions from two or more different tissue types. This can occur in the boundary region of different tissue types, where a voxel may contain a mixture of tissues coming from a few subregions, each of which contains a single tissue type. This type of PVE is also known as the tissue-fraction effect (Erlandsson et al. 2012).

Iterative reconstruction algorithms such as the Maximum Likelihood Expectation Maximization (MLEM) method (Shepp and Vardi 1982), and its accelerated variant, the Ordered Subsets Expectation Maximization (OSEM) (Hudson and Larkin 1994), may incorporate an accurate model of all the main factors that contribute to image blurring and compensate for the PVE to a large extent (Herraiz *et al* 2006). Unfortunately, the noise amplification and edge artifacts seen when using a large number of iterations (as required for a substantial PVE correction) can outweigh the improvement brought about by accurate modeling.

As summarized by (Soret et al. 2007) and by (Erlandsson et al. 2012), many different approaches have been proposed to compensate for partial volume and spillover effects in nuclear medicine. These techniques can be divided into two different categories: post-

reconstruction and within-reconstruction methods. Among the proposed post-reconstruction methods in the literature, there are region-based methods, such as the recovery-coefficient correction (Hoffman et al. 1979), the geometric transfer-matrix (GTM) method (Rousset et al, 1998), or a modified GTM-based algorithm that is more appropriate when used jointly with non-linear reconstruction algorithms (Du et al. 2005). Other post-reconstruction corrections consist of voxel-based methods, such as the extensively used MGM method (Müller-Gärtner *et al* 1992), image deconvolution (Teo et al. 2007) and the “region-based voxel-wise correction” (RBV) proposed by Thomas *et al* 2011. Some within-reconstruction methods are, for example, Carson’s region-based MLEM (Carson 1986), as well as Bayesian approaches which incorporate region-dependent penalties (Baete et al. 2004). The majority of the methods mentioned above require the co-registration and segmentation of a CT or MR anatomical image (Bai et al. 2013) and may, therefore, be affected by any errors in tissue segmentation (Meltzer et al. 1999).

In this work we implemented and evaluated for PET imaging a local projection algorithm (LPA), that was originally proposed and implemented for SPECT quantification by (Moore et al. 2012, Southekal et al. 2012) who, at that time, called this the “local VOI” method of compensating for partial-volume and spillover effects. The approach takes advantage of a higher resolution image co-registered with the PET data, which makes possible a high-resolution segmentation of, typically, a few tissues within a volume of interest centered on the lesion that needs to be quantified. This additional information can be used to obtain improved activity estimates for each tissue within the small volume of interest (VOI), by seeking consistency of the raw projection data acquired by the scanner and the high-resolution segmentation. The approach requires an accurate model of the scanning system, and in principle it can be implemented during iterative reconstruction of the PET images.

As mentioned, the evaluation of the LPA method for a multiple-pinhole micro-SPECT system (Moore et al. 2012) and for a clinical SPECT system (Southekal et al. 2012) was presented in previous work. In this paper we discuss the implementation and evaluation of this method when it is applied, along with the positron range correction described in (Cal-González et al. 2011), for high-resolution PET imaging. The preclinical Argus PET/CT scanner (Wang et al. 2006) and three radionuclides -- ^{18}F , ^{68}Ga (Hoffend et al. 2005, Breeman and Verbruggen 2007) and ^{124}I (Pentlow et al. 1991, Herzog et al. 2002, Belov et al. 2011) -- were evaluated in our study. We also evaluated the imaging results obtained when the LPA-estimated mean activity for each tissue within the VOI was fed back into the iterative reconstruction algorithm. While the typical values of spatial resolution for micro-SPECT and micro-PET imaging are not the same (SPECT: ~ 0.8 mm FWHM; PET: ~ 1.3 mm FWHM), the most important consideration for the ability of any PV-correction method to improve quantitative accuracy is the correctness of the underlying system-matrix model used for the correction, assuming that the standard corrections for other systematic effects (e.g., randoms, scatter, attenuation) have also been implemented correctly. The differences in spatial resolution and systematic effects between PET and SPECT, in fact, provided the main motivation for our study to see how accurately the LPA method could correct for PV effects in the setting of preclinical PET/CT imaging.

2. Methods

Simulated and real acquisitions for the preclinical ARGUS PET/CT system (Wang *et al* 2006) were reconstructed with our iterative PR-OSEM algorithm (Cal-González et al. 2011, Herraiz et al. 2006). The Argus small-animal PET/CT system (Sedecal) (Wang *et al* 2006) consists of 36 detector modules, each one coupled to a dual layer array of 13×13 cerium - doped lutetium - yttrium orthosilicate (LYSO) and cerium - doped gadolinium orthosilicate (GSO) scintillation crystals. Each crystal has a size of $1.45 \times 1.45 \text{ mm}^2$ and is separated by 0.1 mm of white reflector. The length of LYSO and GSO layers is 7 and 8 mm respectively. The 36 modules are arranged in two rings of 18 modules each, with a diameter of 11.8 cm. The transaxial Field of View (FOV) is 67 mm and the axial FOV is 48 mm.

The reconstruction code was modified to incorporate the local-projection algorithm (LPA), using the same system model as the one employed for the reconstructions. In this paper, we use the label “IMG” to indicate reference images obtained using the standard PR-OSEM iterative reconstruction without using any type of LPA correction. In this work we evaluated several methods for incorporating the LPA into the image reconstruction and image-analysis workflow.

2.1. LPA as a post-processing step (LPA)

Consider a reconstructed image with a detected lesion (for instance, a tumor that shows high uptake of the administered radiotracer). Our goal is to improve the quantification of the activity concentration in that lesion by introducing information taken from a high-resolution segmentation, and removing background activity from neighbouring tissues. The lesion will be surrounded by one or more different tissues, which would be identified in the high-resolution image. The activity concentration in every different tissue will be represented by the average value inside each tissue.

We can identify J different tissue compartments, including the lesion of interest, within a volume of interest (VOI) delineated in the object as shown in figure 1A (for $J=2$). The remaining object outside the VOI is considered globally. If we have a precise segmentation of organs and tissues, we can take advantage of this information and improve PET quantification based on (Moore et al. 2012):

- It is reasonable to assume that voxels belonging to the same tissue have a more similar activity than voxels belonging to different tissues.
- Voxels from different tissues would be represented by different average values of activity within the VOI. This is equivalent to what is done in the clinical or preclinical evaluation of the quantification in tumours.
- We can also estimate the PET counts assigned to the inside of the VOI which actually originated from outside the VOI.

With these assumptions, the measured data, λ_i , can be modeled as the sum of the projection counts from each of the J segmented tissue compartments (each with a mean activity concentration A_j), plus the background counts coming from the region outside the VOI, as shown in Eq. 1:

$$\lambda_i \equiv \sum_{j=1}^J A_j P_{ij} + g_{out,i} \quad (1)$$

where λ_i are the expected counts per line of response (LOR), A_j the activity for each tissue, P_{ij} is the system matrix for tissue j along the LOR i and $g_{out,i}$ represents the background counts coming from the region outside the VOI. The activity within the J compartments A_j is represented by an average value inside the compartment that can be determined by fitting the measured projection data to the model in Eq. 1, as explained in (Southekeal et al. 2012). Taking into account that the joint likelihood of measuring an entire projection data set is given by the product of the Poisson probability density function for each measured projection ray, the vector A can be determined by maximizing the log likelihood for the expected value λ_i :

$$\sum_{j'=1}^J A_{j'}^{(k)} \left[\sum_i \frac{P_{ij'} P_{ij}}{\lambda_i^{(k)}} \right] = \sum_i \frac{P_{ij} (n_i - g_{out,i}^{(k)})}{\lambda_i^{(k)}} \quad (2)$$

where n_i are the measured counts per LOR. Note that the equations in Eq. 2 cannot be solved analytically for the unknown A_j . Instead, an iterative solution for these equations is sought (Moore et al. 2012). Note that the values of λ_i , $g_{out,i}$ and A_j are updated in each iteration (k).

In this work we obtain A_j by using the following procedure:

- Step 1: Segment a VOI (containing the lesions of interest) from the registered anatomical image.
- Step 2: Project these segmented volumes, with unity activity voxel values, through an accurate forward model incorporating all physical effects to obtain P_{ij} matrix elements which represent the contribution of segmented tissue j (with unit activity concentration) to the i 'th PET line-of-response.
- Step 3: Mask (zero) the segmented VOI from the reconstructed image, using the anatomical segmentation performed in step 1, and re-project through the same forward model to obtain g_{out} .
- Step 4: Compute all of the necessary matrix elements, D_j and $H_{jj'}$, which are simply short-hand expressions for collections of terms that arise from maximization of the log-likelihood (Moore et al., 2012). In fact, the H-matrix is related to the Fisher information matrix for this estimation problem, while the D-matrix describes a weighted linear vector product of the “system matrix” for each region, applied to the sinogram elements which traverse the VOI, after subtracting an estimate of the counts arising from outside the VOI.

$$H_{jj'}^{(k)} = \sum_i \frac{P_{ij'} P_{ij}}{\lambda_i^{(k)}} \quad (3)$$

$$D_j^{(k)} = \sum_i \frac{P_{ij}(n_i - g_{out,i}^{(k)})}{\lambda_i^{(k)}} \quad (4)$$

- Step 5: From the matrix elements calculated previously, estimate the values of tissue activities by inverting the matrix H to solve equation 1, obtaining:

$$A_j^{(k)} = \sum_{j'=1}^J \left[H_{jj'}^{(k)} \right]^{-1} D_{j'}^{(k)} \quad (5)$$

- Step 6: The procedure above is repeated from step 4 using new estimates of the $A_j^{(k)}$ to compute new elements of matrices H and D, and after that, improved estimates of the $A_j^{(k)}$ in step 2. This procedure is repeated until the estimates change by less than a very small amount in a single iteration (typically less than 0.1%).

Steps 1 and 2 can be performed *prior* to the image reconstruction procedure, while steps 3 to 6 must be done during or after the image reconstruction. The convergence of the LPA iterative procedure is very fast, i.e., just 2 or 3 iterations were enough in the majority of the cases. The system response matrix employed to produce the projections was the same as the one used in the iterative image reconstruction procedure (Herraiz *et al* 2006). It included non-collinearity effects plus photon penetration in the detectors, with complete modeling of intra- and inter-crystal scatter. Positron-range effects had been already incorporated and corrected during the image reconstruction with the PR-OSEM procedure, as described in (Cal-González et al. 2011).

2.2. LPA in the image reconstruction (LPAR)

Compensating for partial volume effects within a volume of interest using the local projection algorithm can not only be implemented as a post-processing step on reconstructed images (as described in the previous section), but it can also be used to “feed” the activity values back into the image-reconstruction procedure, to provide improved estimates of the updated image (LPA reconstruction, or LPAR, method). In this case, the local projection algorithm is applied to the images obtained after each iteration. Using this algorithm, the activity estimates from each tissue within the VOI are computed, after which the activity values in the reconstructed images are replaced by the tissue-activity obtained using the LPA processing (i.e. corrected for PVE) at the end of each iteration; these more accurate activity values are then used in the following iteration, and the same process is repeated for all subsequent iterations. With this procedure, we expect to introduce some of the consistency recovered by using equations (1) to (5) into the reconstructed image and, in this manner, obtain better quantification of activity values in the different tissues inside the VOI.

As shown schematically in Figure 1B, we first compute the system-matrix values (P_{ij}) for each tissue j within the VOI (Step 0). This operation is performed only once right before the first iteration of the PR-OSEM iterative reconstruction. Then, after each iteration of the PR-OSEM algorithm (Step 1), we compute the global background $g_{out,i}^{(k)}$ that comes from

outside the VOI (Step 2) and the LPA activities for each tissue within the VOI (Step 3). Finally, using the masks obtained from the segmentation of the CT image, we replace the estimated activity in each voxel within the VOI by the tissue activities obtained by LPA (Step 4), and proceed with a new iteration of the PR-OSEM (Step 5).

2.3. LPA in the image reconstruction and as post-processing step (LPAR + LPA)

We can also apply LPA as a post-processing step on the images already reconstructed with the LPAR method. The assumption here is that any remaining PVE can be further corrected. Note that the difference between LPAR and LPAR+LPA is that for LPAR alone, we obtain the activity estimates for each tissue in the VOI by simple averaging of the voxel values within the VOI, whereas for LPAR+LPA, we use the LPA correction for partial-volume and spillover to obtain the activity estimates after each iteration of LPAR.

2.4. Additional corrections: background subtraction and positron range correction

In order to obtain optimal quantification values, attenuation correction and background subtraction of scattered and random counts should be performed during image reconstruction.

The attenuation correction was performed following the standard bilinear method for PET/CT systems, described in Kinahan *et al* 1999. Regarding the background subtraction, several methods have been proposed in the literature to correct for scatter and random coincidence events in PET (Cherry et al. 2003). The background due to prompt emissions has been also studied and corrected by several authors (Lubberink and Herzog 2011, Liu and Laforest 2009, Laforest and Liu 2008). In this work we followed a straightforward but accurate method to estimate the background counts in our acquisitions. First, we obtain a PR-OSEM image without any background subtraction. Using the CT information, we set to zero the activity values in all voxels where there is no material, because no activity distribution should be present there. We perform a Monte Carlo simulation with the same settings of each acquisition, but using the image obtained in the previous PR-OSEM reconstruction as the activity source distribution for the simulation. We store scattered, random and positron-gamma counts in the LOR histogram obtained from the MC simulation. Finally, we can either subtract the MC-estimated background from the data or include it during the reconstruction procedure. The resulting images in both cases are very similar, although not identical. In this work we decided to subtract the MC-estimated background from the data prior to the reconstruction procedure.

In addition, for ^{68}Ga and ^{124}I radionuclides positron range is the most significant factor that limits PET image resolution and must be also corrected for (Blanco 2006, Levin and Hoffman 1999). To correct for positron range (Cal-González et al. 2015b, 2011) we introduced an analytical expression for the positron range blurring kernel, obtained from fits to MC simulations of positron range (Cal-González et al. 2013). This kernel is employed to deconvolve the image for the blurring attributable to positron range during reconstruction. The spatially-variant blurring kernel is computed taking into account the voxel to which it is applied and the surrounding media. This correction requires a co-registered CT image, and it

is expected to work well everywhere, even near tissue boundaries, as reported in Cal-González et al. 2015b.

2.5. Simulation and acquisition settings

2.5.1. Simulated acquisitions: IQ phantom—Acquisitions of the NEMA NU4 IQ phantom (NEMA NU-4 2008) filled with ^{18}F , ^{68}Ga or ^{124}I radionuclides were simulated with the PeneloPET Monte Carlo code (España et al. 2009). In these simulated acquisitions, the five capillary rods and the cylindrical cavity were filled with a uniform activity concentration of 500 kBq/mL (background). One of the two small cavities was filled with a “hot” activity concentration, 4 times higher than that of the “warm” background, and the other small cavity was filled with non-radioactive water, so no activity should be present there (“cold” region). We included attenuation, scatter and random coincidences in the simulations. The main parameters of the simulated acquisitions were:

- Energy window: 400 – 700 keV
- Theoretical hot-to-warm background ratio: 4.0
- Theoretical cold-to-warm background ratio: 0.0
- Background subtraction: Yes
- Iterative reconstruction: 5 iterations, 20 subsets per iteration.
- Voxels in the image: $175 \times 175 \times 61$ voxels
- Voxel size: $0.3886 \times 0.3886 \times 0.775$ mm³

In order to evaluate the performance of the LPA method, quantification of the hot and cold regions of the simulated IQ phantoms was assessed. The LPA post-processing results were also compared with those obtained directly from the reconstructed image.

2.5.2. Simulated acquisitions: Small lesions close to large hot sources—An extreme case of spillover may take place for lesions in the direct neighborhood of large hot sources, e.g., areas with high tracer uptake such as a tumor, myocardium, urinary bladder or kidneys (Liu 2012). If the lesion of interest is close enough to a hot source, the quantification may be invalid and misleading, and must be corrected. In order to evaluate the LPA performance in cases where “spillover contamination” can be relevant, acquisitions of a modified NEMA NU4 IQ phantom (NEMA NU-4 2008) filled with ^{18}F were simulated with PeneloPET (España *et al* 2009). As in the previous cases, the background activity was 500 kBq/mL, and one of the two cavities was filled with an activity concentration 9 times higher than that of the background (hot region). In addition, we added a small spherical hot source (4 mm diameter), close to the hot cylindrical cavity. The activity in this small sphere was 3 times higher than the background activity. The energy window was 400 – 700 keV, and the reconstruction parameters were the same as for the NEMA IQ simulations.

2.5.3. Simulated acquisitions: IQ phantom with small spherical lesions—In order to evaluate the performance of the LPA method for lesions with different sizes we simulated a modified NEMA NU4 IQ phantom (NEMA NU-4 2008) filled with ^{18}F . For this case, the cylindrical hot and cold lesions (see section 2.5.1) were substituted by spherical hot

and cold lesions of diameters between 2 and 5 mm. The background activity, as in the previous cases, was 500 kBq/mL. The hot lesion was filled with an activity concentration 4 times higher than the background, and the cold lesion was filled with non radioactive water.

In order to evaluate the performance of the LPA method at different levels of noise in the image, we simulated different acquisition times for the phantom with 5mm spherical lesions. The total number of simulated events was: 40, 100, 200 and 300 million coincidences.

2.5.4. Acquisitions of real phantoms—In addition, several acquisitions of a phantom made from gels, including several hot and cold lesions (diameters approximately 4 mm) were obtained at Brigham and Women's Hospital (Boston, MA). The settings for these acquisitions were:

- Background activity at the start of the acquisition: 1.6 ± 0.1 MBq / cm³ (measured in a well-counter).
- Energy window: 250 – 700 keV
- Theoretical hot/uniform background ratio: 4.25
- Theoretical cold/uniform background ratio: 0.0

The reconstruction parameters were the same as in the previous cases. The evaluation of the LPA post-processing results was performed by comparing the LPA results with those obtained directly from the reconstructed image.

3. Results

3.1. Simulated NEMA IQ phantom (¹⁸F)

Figure 2 shows transverse and sagittal views of the simulated NEMA IQ phantom, filled with ¹⁸F and reconstructed with the PR-OSEM procedure using 5 iterations and 20 subsets per iteration. In addition, we show the hot and cold regions which were used for the evaluation of the quantification methods previously explained.

In figure 3 we plot the evolution of the hot/uniform and cold/uniform activity ratios for different numbers of iterations, for the four quantification methods studied in this work (IMG and LPAR in red, LPA and LPAR + LPA in blue). In the upper part of the figure we show a transverse view of the reconstructed image, using the standard PR-OSEM reconstruction with positron range correction (left), LPA reconstruction using the LPA values for the HOT region as prior (LPAR, center), and LPA reconstruction using LPA values for the COLD region (LPAR, right).

As demonstrated in figure 3, the quantification in both hot and cold regions was significantly improved when LPA post-processing was applied. We can also see that the use of LPA activities during image reconstruction (LPAR) improved the quantification within the VOI, obtained both from the image and from the LPA post-processing. For example, regarding the quantification within the VOI which includes the hot region, the hot/uniform ratio (within the VOI) obtained from the image was about 3.0, while the same ratio from the LPA post-processing improved this up to 4.0, which was the expected (true) value, based on the

activities used to prepare the phantom. Furthermore, the quantification was even better when LPAR was used (ratio of 3.2 from the image and 4.0 from the LPA post-processing).

Regarding the quantification within the VOI which includes the cold region, similar results were obtained. The cold *versus* uniform ratio values were 0.16 from the standard PR-OSEM image and 0.12 from the image obtained by means of the LPAR. In this case, the quantification obtained from the LPA post-processing was ~ 0.06 (where the theoretically expected value for this case would be 0.0).

The effect of using LPA post-processing after LPAR was a slight improvement in the quantification of the lesion of interest. This improvement was greater for the cold lesion.

3.2. Small lesions close to large hot sources

Figure 4 shows the transverse views of the simulated phantom after a reconstruction with 5 iterations and 20 subsets per iteration. On the left, we show the image with the mask employed for each tissue (3 tissues: hot cavity, hot sphere and background). The standard PR-OSEM reconstruction is depicted in the center, and the LPA reconstruction using the LPA values for each tissue on the right (LPAR). The activity ratios (hot/background) obtained for each “hot” region are presented in table 1.

As seen in figure 4 and in table 1, the quantification in both regions was better when the LPA method was used after reconstruction. Also, the image contrast of the small lesion was much better when using the LPA reconstruction. The LPAR+LPA estimated activity values in the small sphere overestimated the actual activity by $\sim 13\%$, and underestimated the activity of the large cylinder by $\sim 2\%$. On the other hand, the PR-OSEM values underestimated the activity in the hot sphere by $\sim 40\%$ and in the large cylinder by $\sim 28\%$.

3.3. Results for acquisitions of real phantoms

In this section we present the results obtained for the phantom acquisitions performed with the preclinical Argus PET/CT at Brigham and Women’s Hospital (Boston, MA). Figure 5 shows the reconstructed images of the phantom and the three hot and cold lesions considered.

In addition, figure 6 shows the reconstructed images of the phantom, using the standard PR-OSEM procedure (left) and the LPA reconstruction with LPA values of the HOT1 mask and with LPA values of the COLD1 mask. In the same figure, we also plot the evolution of hot/uniform and cold/uniform ratios of activities for each lesion. As in the previous subsection, we plot the results obtained with the four quantification methods: IMG and LPAR in red, LPA and LPAR + LPA in blue.

Table 2 shows the absolute quantification values in the hot and cold lesions and in the background, obtained from the standard reconstruction (PR-OSEM) and with the LPAR method (LPAR). These values are compared with that obtained from the LPA postprocessing, performed on PR-OSEM and LPAR-reconstructed images. The errors in these estimates were computed as the weighted sum of the error in the activity calibration and the standard deviation between the quantification values of all hot and cold lesions.

For the real acquisitions (figure 6), a significant improvement in the quantification was observed when LPA post-processing or LPAR was employed, for all hot and cold lesions analyzed. The lesions were also better delineated and quantified when the LPA activities were used (for tissues within the VOI) during reconstruction.

Regarding the quantification of hot lesions, the mean hot-uniform ratio values obtained from the images were about 2.9 and 3.0 for LPAR. With the LPA post-processing we obtained a significant improvement, with hot /uniform ratios above 4.0 in all cases, while the theoretically expected value was 4.25.

For cold lesions, the quantification was also improved when LPA post-processing was used. The estimated cold-uniform ratios were close to the theoretically expected value (0.0) with the LPA post-processing. The ratios obtained from the image were ~0.4 in all cases. When LPA-estimated activities were used during reconstruction, the cold/background ratios were decreased further to ~0.3. Absolute quantification values also showed the trend observed for the ratios. In particular, cold lesions with no activity were quantified properly, within error bars, for the LPA+LPAR method. Background and hot regions were also well quantified, within the expected error of the absolute calibration factor.

3.4. Results with ^{68}Ga and ^{124}I

In this section, we analyze the performance of the LPA post-processing and LPA reconstruction method for simulated acquisitions of the NEMA IQ phantom filled with ^{68}Ga (with a large positron range and no additional prompt emissions) and with ^{124}I (with a large positron range and additional prompt emissions) radionuclides. The masks employed for the hot and cold regions were the same used for the simulated acquisitions with ^{18}F (see figure 2).

Figures 7 and 8 show the evolution of the hot/uniform and cold/uniform activity ratios with the number of iterations, for the four quantification methods studied in this work (IMG and LPAR in red, LPA and LPAR+LPA in blue), when applied to the acquisitions with ^{68}Ga (figure 7) and with ^{124}I (figure 8). In the upper part of the figures we plot the images reconstructed using the standard PR-OSEM method (i.e. with positron range correction) (left), LPA reconstruction using the LPA values for the HOT region (center) and LPA reconstruction using LPA values for the COLD region (right).

As was the case for the standard radionuclides, for these non-standard radionuclides we observed a significant improvement in the quantification of hot and cold regions when the LPA post-processing or reconstruction were applied (see figures 7 and 8). However, for these long positron-range radionuclides, we were not able to fully recover the expected (true) values for hot/uniform and cold/uniform ratios (4.0 and 0.0 respectively). As one can see in the figures, maximum values of hot/uniform ratios of ~3.7 were obtained using LPA postprocessing, while from the images, we obtained 3.0 (standard PR-OSEM reconstruction) and 3.5 (LPA reconstruction). For cold regions, cold/uniform ratios of ~0.12 with LPA postprocessing, ~0.25 from the image (PR-OSEM reconstruction) and ~0.20 from the LPA reconstruction were obtained.

The reconstructed images (figures 7 and 8) show that the PR-OSEM images (with positron range correction and background subtraction) obtained for these radionuclides were of better quality (better spatial resolution and quantitative accuracy) than the images obtained without positron range correction and without background subtraction. In addition, a significant improvement (better lesion-of-interest delineation and quantification within the chosen VOI) was seen when LPA activities were used during reconstruction.

3.5. Dependence of LPA results on VOI size and radionuclide

In table 3 we present a summary of the results obtained with the simulated acquisitions of the NEMA IQ phantom, filled with ^{18}F , ^{68}Ga and ^{124}I , respectively. Quantification in the hot and cold lesions and in the background, obtained from the standard reconstruction (PR-OSEM) and with the LPAR method (LPAR), is compared with that obtained from the LPA post-processing, performed on PR-OSEM and LPAR-reconstructed images. These values and their respective errors were obtained from 5 statistically independent images of the same IQ phantom simulation, reconstructed with 5 iterations and 20 subsets each, and using slightly different VOIs to perform the quantification in each case.

In addition, in table 4 we present the dependence of the LPA results on the size of the VOI used for quantification. The sizes of these volumes, always larger than the region to be quantified (0.75 cm^3 for both hot and cold lesions in the IQ phantom), varied from 1.8 cm^3 (VOI 1) to 3.1 cm^3 (VOI 5). It is obvious that the VOIs employed in the LPA algorithm should be larger than the region of interest, so that the entire area that could be affected by spill-over (spill-out and spill-in) is considered in the algorithm. But, on the other hand, if the VOI is too large, then the estimate of the background contribution from the remainder of the image would be inaccurate. A slight dependence of the LPA quantification on the size of the 3D VOI was observed, particularly for the radionuclides with larger positron range, for which we obtained converged results (with almost no dependence of quantification on the size of the VOI) when using VOIs significantly larger than the size of the lesion to be quantified. This effect was greater for radionuclides with larger positron range.

3.6. Dependence of LPA results on lesion size and noise in the image

Figure 9 shows the reconstructed images for the IQ phantom with spherical hot and cold lesions. On the top of the figure we show the standard and LPA reconstructions with 5 mm spherical lesions; below we show the images with 2 mm lesions. On the bottom of the figure we show the LPA results for all the lesion diameters (from 2 to 5 mm). In the figure we present the lesion-to-background ratios for all the lesions, obtained from the image and from the LPA method. The images were reconstructed with the standard and the LPA reconstruction procedures. The LPA results (blue curves in the figure) do not show a significant dependence on the lesion size for diameters larger than 2 mm. However, the quantification values obtained from the PR-OSEM and LPAR images are strongly dependent on the lesion size, especially for the smaller lesions.

Table 5 shows the dependence of the LPA results on the noise in the image, for the phantom with 5 mm spherical lesions and simulated acquisitions of 40, 100, 200 and 300 million counts. All the values in the table and their respective errors were obtained from 3

statistically independent images of the same simulation, and using slightly different VOIs to perform the quantification in each case. As we can see in the table, the LPA results are not significantly affected by the noise in the images, giving better performance of the method and more accurate quantification values for images with lower levels of noise.

4. Discussion

The simple method used for background subtraction is expected to be valid if we assume that the distribution of scattered, random and positron-gamma events is smooth across the FOV of the system, and if the number of these events is relatively small in comparison with the number of true coincidences, so that the initial estimate of activity can be used reasonably in the MC simulation of the background. These assumptions are usually valid and indeed, for the acquisitions used in this work they were appropriate because the activity was relatively small in all cases (yielding a small number of randoms) and, furthermore, the percentage of scattered events was ~10% for the IQ phantom simulations (400–700-keV) and less than 20% for the phantom acquisitions. For the non-pure emitter studied here (^{124}I), the number of positron-gamma events at the activity simulated was about 20% of the total number of coincidences. For cases in which these assumptions are not valid, this procedure can be applied iteratively, i.e., using the reconstructed activity distribution after the background counts are estimated from the first MC simulation as input for a second MC simulation employed to compute a better estimate of background counts. Although the proposed method for background subtraction increases the noise in the image, this does not substantially affect the overall performance of the LPA method, as we can see in table 5. In order to reduce the noise in the image with background subtraction, longer simulation times or variance reduction techniques can be used. As this was not the goal of this work and the noise in the image does not strongly affect the overall performance of the LPA method, we used this straightforward method for the background subtraction without utilizing longer simulation times or variance-reduction techniques.

For the NEMA IQ simulations and phantom acquisitions with the standard radionuclide (^{18}F), quantification improved significantly when the LPA post-processing or LPA reconstruction were used, yielding hot/uniform and cold/uniform ratios much closer to the theoretically expected values than those obtained from the images reconstructed with the PR-OSEM procedure.

Similarly, for the simulated acquisitions with ^{68}Ga and ^{124}I , we also observed a significant improvement in the quantification within small volumes of interest when LPA was applied as a post-processing method or during the reconstruction. We also noted that better images of local VOIs (with better identification of the lesion of interest) should be obtained when LPA values are employed during reconstruction. For these radionuclides, while the images were not as good as those obtained with ^{18}F , using positron-range correction and LPA reconstruction provided acceptable images, with good spatial resolution and improved quantitative accuracy. For the radionuclides with a large positron range, the loss of quantitative accuracy was probably due to the larger spatial spread of annihilations caused by the positron range, which was not completely recovered by the positron range-correction

algorithm. For these cases, larger VOIs should be used around each lesion of interest, in order to recover completely the effects of spill-in and spill-out within the VOI.

For ^{68}Ga and ^{124}I acquisitions, we observed a significant improvement in the quantification of lesions of interest when positron range correction and background subtraction were applied during image reconstruction. This improvement was enhanced when the LPAR method was employed. For example, for ^{124}I , the hot-to-background ratio was ~ 2.0 in the reconstructed image (5 iterations, 20 subsets) without positron range correction and background subtraction. When these corrections were applied during reconstruction, the ratio was ~ 3.0 . Finally, when reconstructing the image using the LPAR method, the hot-to-background ratio was 3.5.

Generally speaking, for hot lesions we obtained similar results using the LPA postprocessing of images reconstructed with the PR-OSEM and LPAR methods. A slightly better quantification of cold lesions was obtained using LPA post-processing of images reconstructed using the LPAR method. In summary, we have seen that LPA+LPAR is the best choice for obtaining better image quality and quantification. By using the LPA method during the reconstruction we improve the visual aspect of the image in the local region of interest (better delineation of the segmented tissues and improved detectability and quantification of small lesions). The LPA post-processing allows for further improvement in the quantification of each segmented tissue. The execution time of the LPA method is the time needed to perform a whole projection from the image space to the data space. On a single 3 GHz i7 CPU this required around 15 minutes. This procedure can be easily accelerated with a version of the code running in parallel simultaneously on several CPUs (Herraiz et al 2006).

Regarding the performance of the LPA method under challenging conditions, such as with small lesions or mixed masks with several tissues, we have seen that the LPA method performs well, providing improved quantification accuracy of the lesions of interest. Mixed 3-tissue masks, with a hot and cold lesions and background, were also evaluated, obtaining similar quantification performance as when using 2 different VOI with 2-tissue segmentations. We also expect to obtain good quantification for more complex segmentations of 4 or more tissues, if an accurate segmentation of the tissues of interest is provided, as was demonstrated for SPECT in Moore *et al* 2012 and Southekal *et al* 2012. Regarding the performance of the LPA method for small lesions, we have seen (figure 9) that the method remains accurate down to lesions sizes that satisfy the Nyquist sampling condition (lesion sizes bigger than 3 voxels in each spatial direction).

4.1. Potential applicability of the LPA method in small animal studies

While we have evaluated the performance of the LPA approach for the Sedecal Argus system, the method should be easily extendable to other preclinical PET imaging systems, as long as the necessary conditions are met; the requirements for achieving good performance using the LPA method are the following:

1. - A segmentation of the J compartments can be obtained from a co-registered high-resolution anatomical image (in this work we used a CT image, but other modalities such as MRI or US could be used as well).
2. - The radiotracer uptake for the different tissues within the VOI can be considered as uniform.
3. - No significant motion effects are present in the VOI, or motion-compensation was previously obtained in the image reconstruction procedure.
4. - An accurate model of the system matrix must be available. That is, the projections of the individual compartments can be separately computed for unit-activity tissue templates and an accurate and low noise projection from all the activity coming from outside of the VOI can be obtained from the reconstructed images.

Note that if one of these requisites is not met, the LPA method could still be used, although in this case the same degree of performance and accuracy of the method could not be guaranteed. For example, although our approach requires an accurate model of the scanning system, good results can be also obtained even if the model of the system is not very accurate. Good quantification values, both for hot and cold lesions, have been obtained using approximate system models. On other hand, it must be mentioned that the approach can also be extended to incorporate models of non-uniform radiotracer uptake into the fitting procedure (e.g., Southekal *et al* 2011) or to incorporate the LPA method in combination with motion-compensated image reconstruction techniques as the ones published by Tsoumpas *et al* 2013. The applicability of the LPA method for preclinical data and for cases of nonuniform uptake, or for additional sub-tumoral soft-tissue regions that might not be well segmented from a CT scan, or areas affected by motion will be matters for further investigation.

5. Conclusion

In this paper we described and evaluated a method to improve the quantification within small volumes of interest. The LPA procedure may be applied either as a post-reconstruction method (LPA) or within the reconstruction (LPA-R). This algorithm is easy to implement and extensible enough to be used for other preclinical or clinical scanners, provided that a relatively accurate system response matrix is available for the scanner under consideration.

Quantification was significantly improved by using LPA, which provided more accurate ratios of lesion-to-background activity concentration for both hot and cold lesions. Further, using activities obtained with LPA during the reconstruction improves the quantification within the VOI, especially in cold regions.

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Figure 1.

A: Illustration of a basic model with $J=2$ compartments. The VOI includes the lesion of interest (in black) and a soft-tissue background (in dark gray). The two segmented compartments are forward projected with unit-activity concentration to obtain P_j , while $g_{out}^{(k)}$ is obtained by forward projecting the reconstructed image at iteration k , with all the voxels within the VOI set to zero. This approach is easily extendable to $J > 2$ compartments.

B: Illustration of the procedure employed to improve the quantification of the reconstructed image within the VOI using the activities computed with the LPA processing.

Figure 2. Transverse and sagittal views of the IQ phantom (simulated acquisition) filled with ^{18}F , 5 iterations and 20 subsets. The hot and cold regions are shown in the figure.

Figure 3.

Top: Reconstructed images of the IQ phantom: left: PR-OSEM, center: LPA reconstruction using LPA values from hot VOI, right: LPA reconstruction using LPA values from cold VOI. Bottom: hot/uniform and cold/uniform activity ratios. The number of image updates (abscissa) is equal to the product of the number of iterations and the number of subsets. The precision of these estimates is provided in tables 2 and 3.

Figure 4.

Left: Segmentation of 3 tissues (background, hot cylinder and hot sphere within a cylindrical VOI inside a larger cylinder) obtained from the CT, center: PR-OSEM reconstruction, right: LPA reconstruction. Note that the VOI actually corresponds to a $20 \times 20 \times 12$ - voxel region of the phantom which includes both hot lesions, as well as part of the uniform background.

Figure 5.

Transverse, coronal and sagittal views of the real phantom filled with ^{18}F , after reconstruction with 5 iterations and 20 subsets. The three hot and cold regions analyzed in this work are depicted in the figure. The transverse and axial FOVs of these images were 68 and 47 mm, respectively.

Figure 6.

Top: Transverse views of reconstructions of the real phantom (filled with ^{18}F) shown in Fig. 5. From left to right: PR-OSEM reconstruction (2 views), LPA reconstruction using LPA values from HOT1 region and from COLD1 region. Hot/uniform and cold/uniform activity ratios for each lesion studied in this work. The number of image updates (abscissa) is equal to the product of the number of iterations and the number of subsets.

Figure 7.

Top: Reconstructed images of the simulated IQ phantom filled with ^{68}Ga . From left to right: OSEM reconstruction without positron range correction, PR-OSEM reconstruction, LPA reconstruction using LPA values from HOT region, and LPA reconstruction using LPA values from COLD region. Bottom: hot/uniform and cold/uniform activity ratios. The number of image updates (abscissa) is equal to the product of the number of iterations and the number of subsets. The precision of the estimates is provided in tables 2 and 3.

Figure 8. Same as figure 7, except for this case, the radionuclide simulated was ^{124}I .

Figure 9.

Top: Reconstructed images of the ^{18}F IQ phantom with spherical lesions of 5 mm diameter. Middle: Images of the IQ phantom with 2 mm spherical lesions. From left to right: PR-OSEM reconstruction, LPA reconstruction using LPA values from the HOT lesion, and LPA reconstruction using LPA values from the COLD lesion. Bottom: hot/uniform and cold/uniform activity ratios for different diameter of the spherical lesions.

Table 1

Activity ratios for the hot cylinder and the small sphere, after 5 iterations and 20 subsets per iteration.

Region	Quantification method			
	PR-OSEM	LPA	PR-OSEM + LPA	LPA + LPA
Hot sphere	1.73 ± 0.10	2.05 ± 0.12	3.30 ± 0.10	3.39 ± 0.10
Hot cylinder	6.5 ± 0.2	7.0 ± 0.2	8.7 ± 0.2	8.8 ± 0.2

Quantification obtained with the methods studied in this work for the acquisitions of the real phantom filled with ¹⁸F. The expected values, obtained from independent dose calibrator measurements, are shown as “EXP”.

Table 2

Region	Quantification values (kBq/cm ³)				
	PR-OSEM	LPAR	PR-OSEM + LPA	LPAR + LPA	EXP
Hot1	5200 ± 300	5300 ± 300	7400 ± 500	7300 ± 500	6800 ± 400
Hot2	5100 ± 300	5300 ± 300	6900 ± 400	6900 ± 500	6800 ± 400
Hot3	5100 ± 300	5300 ± 300	6900 ± 400	6900 ± 400	6800 ± 400
Cold1	670 ± 70	560 ± 40	10 ± 40	-20 ± 20	0.0
Cold2	790 ± 80	600 ± 50	50 ± 40	10 ± 20	0.0
Cold3	740 ± 80	540 ± 40	110 ± 40	2 ± 20	0.0
Bckg	(1.78 ± 0.11) 10 ³	(1.78 ± 0.11) 10 ³	(1.71 ± 0.11) 10 ³	(1.71 ± 0.11) 10 ³	(1.6 ± 0.1) 10 ³

Table 3

Absolute quantification values obtained with the methods studied in this work for simulated acquisitions of a NEMA IQ phantom filled with ^{18}F , ^{68}Ga and ^{124}I . The simulated “reference” values are shown as “EXP”.

Isotope	Region	Quantification values (kBq/cm ³)				
		PR-OSEM	LPAR	PR-OSEM + LPA	LPAR + LPA	EXP
^{18}F	Hot	1650 ± 40	1760 ± 20	2059 ± 19	2058 ± 10	2000
	Cold	90 ± 4	67 ± 3	45 ± 2	43 ± 2	0
	Bckg	508 ± 5	511 ± 5	511 ± 4	512 ± 4	500
^{68}Ga	Hot	1430 ± 60	1720 ± 30	1740 ± 20	1790 ± 30	2000
	Cold	119 ± 4	85 ± 3	60.9 ± 0.9	56.5 ± 1.7	0
	Bckg	486 ± 6	495 ± 5	476 ± 4	480 ± 4	500
^{124}I	Hot	1500 ± 60	1820 ± 30	1830 ± 20	1850 ± 30	2000
	Cold	135 ± 5	93 ± 4	73 ± 3	67 ± 4	0
	Bckg	510 ± 6	516 ± 4	494 ± 4	492 ± 4	500

Dependence of quantification on the size of the VOI, which was always larger than the volume of the hot and cold regions (0.75 cm^3).

Table 4

Isotope	Region	PR-OSEM + LPA: Quantification values (kBq/cm ³)				
		$V_1 = 1.82 \text{ cm}^3$	$V_2 = 1.98 \text{ cm}^3$	$V_3 = 2.26 \text{ cm}^3$	$V_4 = 2.54 \text{ cm}^3$	$V_5 = 3.10 \text{ cm}^3$
¹⁸ F	Hot	2030 ± 20	2070 ± 20	2070 ± 20	2070 ± 20	2060 ± 20
	Cold	42 ± 2	43 ± 2	45 ± 2	47 ± 2	47 ± 2
⁶⁸ Ga	Hot	1710 ± 20	1720 ± 20	1730 ± 20	1750 ± 20	1770 ± 20
	Cold	60.0 ± 0.9	60.0 ± 0.9	61.5 ± 0.9	62.0 ± 0.9	60.9 ± 0.9
¹²⁴ I	Hot	1800 ± 20	1820 ± 20	1830 ± 20	1850 ± 20	1840 ± 20
	Cold	68 ± 3	71 ± 3	74 ± 3	75 ± 3	76 ± 3

Table 5

Dependence of the quantification values on the noise in the image for the modified NEMA IQ phantom with spherical lesions of 5 mm in diameter.

Counts	Noise (%) (wo BCKG sub)	Noise (%) (w BCKG sub)	PR-OSEM + LPA: Quantification values (kBq/cm ³)	
			Hot lesion (5 mm)	Cold lesion (5 mm)
40M	12 ± 2	14 ± 3	1901 ± 21	82 ± 12
100M	8.9 ± 1.0	9.2 ± 1.0	1973 ± 21	52 ± 7
200M	7.0 ± 0.9	8.3 ± 1.1	1970 ± 25	65 ± 7
300M	6.4 ± 0.6	7.6 ± 0.8	1979 ± 19	56 ± 5
EXP	-	-	2000	0