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Improved Regional Activity Quantitation in Nuclear Medicine using a New Approach to Correct for Tissue Partial Volume and Spillover Effects

Stephen C. Moore, Sudeepti Southeikal, Mi-Ae Park, Sarah J. McQuaid, Marie Foley Kijewski, and Stefan P. Müller*

Department of Radiology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts USA

*Klinik für Nuklearmedizin, Universitätsklinikum Essen, Germany

Abstract

We have developed a new method of compensating for effects of partial volume and spillover in dual-modality imaging. The approach requires segmentation of just a few tissue types within a small VOI surrounding a lesion; the algorithm estimates simultaneously, from projection data, the activity concentration within each segmented tissue inside the VOI. Measured emission projections were fitted to the sum of resolution-blurred projections of each such tissue, scaled by its unknown activity concentration, plus a global background contribution obtained by reprojection through the reconstructed image volume outside the VOI. The method was evaluated using multiple-pinhole μ SPECT data simulated for the MOBY mouse phantom containing two spherical lung tumors and one liver tumor, as well as using multiple-bead phantom data acquired on μ SPECT and μ CT scanners. Each VOI in the simulation study was 4.8 mm (12 voxels) cubed and, depending on location, contained up to four tissues (tumor, liver, heart, lung) with different values of relative ^{99m}Tc concentration. All tumor activity estimates achieved $<3\%$ bias after ~ 15 OSEM iterations ($\times 10$ subsets), with better than 8% precision ($\sim 25\%$ greater than the Cramer-Rao lower bound). The projection-based fitting approach also outperformed three SUV-like metrics, one of which was corrected for count spillover. In the bead phantom experiment, the mean $\pm$ standard deviation of the bias of VOI estimates of bead concentration were $0.9 \pm 9.5\%$, comparable to those of a perturbation geometric transfer matrix (pGTM) approach ($-5.4 \pm 8.6\%$); however, VOI estimates were more stable with increasing iteration number than pGTM estimates, even in the presence of substantial axial misalignment between μ CT and μ SPECT image volumes.

Keywords

Partial-volume effect; count spillover; resolution recovery; PET; SPECT; OSEM

I. INTRODUCTION

In tomographic imaging, there are several causes of quantitative inaccuracy, including sampling phenomena due to the continuous-to-discrete mapping from the “object” to the “image” [1] and aperture effects (blurring). The *partial-volume* effect, also called the “tissue-fraction” effect, stems from the inclusion of more than one structure or tissue type in the same image voxel. For example, in transmission computed tomography (CT), the apparent CT-number of a voxel near the spine may include partial contributions of 30% from bone and 70% from adjacent soft tissue. However, there are other phenomena, related to resolution blurring by the imaging system, which also contribute to the mixing of image properties among different voxels. In nuclear medicine imaging, for example, the term,

count spillover, is used to refer to the three-dimensional blurring of counts from inside a structure to outside (*spill-out*), or vice versa (*spill-in*). These count spillover contributions arise primarily from the limited spatial resolution of nuclear medicine imaging systems, as well as from photon scatter that is not adequately corrected during reconstruction. While some practitioners have conflated the different resolution and sampling phenomena and simply referred to them collectively as the “partial-volume effect”, we and others have preferred to maintain the semantic distinctions described above. For example, Soret *et al.* [2] have addressed these issues in their comprehensive review article.

SPECT or PET images are generally reconstructed using iterative approaches such as the maximum-likelihood expectation maximization (MLEM) method [3], or an accelerated variant of MLEM, e.g., the ordered-subsets expectation maximization (OSEM) algorithm [4]. Because accurate models of photon scatter and resolution blurring can be incorporated within these types of iterative reconstruction algorithms, it is possible for such methods to recover resolution to some extent, thereby diminishing the impact of tissue spillover effects. To attain a significant improvement in quantitative accuracy, however, it is often necessary to reconstruct the emission data for many more iterations than can normally be used in actual clinical practice. In addition, under such conditions, the reconstructed image noise will be greatly amplified, potentially leading to only a small improvement in the accuracy of VOI activity estimates but greatly degraded precision. Furthermore, even the accuracy may be limited by Gibbs artifacts; these arise at higher numbers of iterations when the recovered resolution approaches a value that can no longer be supported by the underlying image sampling. For these reasons, most nuclear medicine practitioners first reconstruct tomographic images using fewer than 4 or 5 iterations, with a modest number of subsets per iteration. Following this, they may utilize a simple quantitation approach to estimate radioactivity values, most often within two-dimensional regions-of-interest (ROI) drawn manually over lesions or tissues of interest. The most common metrics computed from the reconstructed count values in these ROIs are various types of *standardized uptake values* (SUV) [5]. One of these, *SUV-average*, is computed from the mean of the counts within the ROI, while another, *SUV-max*, is based on the maximum pixel value within the ROI. Such metrics are simple to compute if the appropriate software tools are available on the imaging workstation; unfortunately, for small lesions in particular, they often yield estimates that are inaccurate and/or imprecise, unless an additional correction for resolution blurring is used [6].

As summarized by Rousset *et al.* [7] and Soret *et al.* [2], many different approaches have been proposed to compensate for partial-volume and spillover effects in nuclear medicine. These techniques can be broadly divided into two categories: post-reconstruction methods, and within-reconstruction methods. One class of post-reconstruction approaches consists of region-based methods, such as the recoverycoefficient correction [8] and the geometric transfer-matrix (GTM) method [9], as well as a similar perturbation-based GTM approach which is more appropriate to use in conjunction with nonlinear iterative reconstruction algorithms [10], [11]. Some authors (e.g., [12], [13]) have advocated including a voxel-noise model within an ROI-based correction procedure. Although it can be challenging to include the full noise covariance of the reconstructed images, Barrett *et al.* [14] and Qi [15] have described covariance estimation procedures. Other post-reconstruction corrections consist of voxel-based methods which utilize, for example, image deconvolution (e.g., [16]) or a partition-based approach [17]. Reconstruction methods that include compensation for resolution blurring include, for example, Carson’s region-based MLEM [18], as well as Bayesian approaches which incorporate region-dependent penalties [19], [20].

With any correction method, there are several challenges inherent in compensating for partial-volume and spillover effects. First, it is often necessary to delineate one or more

tissue boundaries in order to define relevant regions or volumes-of-interest (VOI) for activity quantitation. An important issue is the accuracy with which these boundaries can be determined by segmenting tumors or organs from higher resolution morphologic images. Boundary accuracy depends on how well the morphologic and functional images can be registered, the number of structures that must be segmented, and how well the structures of interest can be segmented into discrete regions. Furthermore, when working directly on reconstructed images, there is a question of how the spatially correlated reconstruction noise will affect the accuracy and/or precision of the correction approach, and another consideration is whether or not the lesion of interest contains uniform, or non-uniform tracer uptake. Finally, some of the methods require segmentation of tissues into many different VOIs that span the entire cross-sectional extent of the subject being imaged. Zaidi and colleagues [21] compared different methods for segmenting brain MR images for partial-volume compensation in PET, and pointed out many challenges of such methods. Even when only a single structure, such as the diaphragm, has to be accurately delineated on body CT images, a manual segmentation procedure can take an experienced clinician a half-day or more; an automatic algorithm has been shown to speed up this procedure to approximately 15 minutes, but it still failed in ~20% of cases [22]. Because of such challenges, explicit corrections for partial-volume and/or spillover effects are almost never utilized today in the clinic; instead, practitioners mostly just use implicit compensation by system-response modeling during iterative reconstruction, along with simple 2D, ROI-based activity measurements, as discussed above.

Our aim in the work reported here was to develop and evaluate a new method of compensating for tissue partial-volume and spillover, requiring segmentation of only a few (typically 2 to 4) tissue types within a small VOI surrounding a lesion seen on CT or MR images, as well as on spatially registered emission tomographic images. We use a model-based fitting method which operates in projection space, where the statistical noise is spatially uncorrelated, as opposed to reconstruction space, where the voxel noise is correlated and nonstationary -- and, hence, more challenging to incorporate in the fitting procedure. The algorithm estimates simultaneously the activity concentration within each tissue of interest defined inside the small VOI, while also compensating for the partial-volume and spillover effects. The approach requires an accurate mathematical model of the forward-projection operation, which should include all factors contributing to the spatial resolution of the system, and the method is currently based on the assumption of uniform activity concentration within each different segmented tissue type inside the VOI, like most other region-based approaches.

It should be noted that Huesman [23] was the first to describe a method for computing region-of-interest values directly from projection measurements. This calculation utilized a forward-projection of an ROI template, convolved with the same filter kernel that would be used for reconstructing a filtered-backprojection image. Muzic and colleagues [24] later extended this approach by including a 2D inverse filtering operation to compensate for local blurring, but this method did not explicitly correct for cross-talk from, or among, surrounding tissues. Least-squares fitting approaches have also been used; Formiconi developed [25], and Vanzi *et al.* [26] evaluated, a 2D projection-space method based on segmenting an entire slice into ROIs, while Chen *et al.* [27] used a 3D local least-squares fit in image space. Despite the fact that this method did not include a model of the local noise covariance, it has nevertheless proven to be effective [6].

In the remainder of this paper, we will describe the new correction algorithm, as well as the Cramer-Rao lower bound (CRB) on the variance of tissue activity estimates achievable with an ideal unbiased, linear estimator based on the task of fitting projection data for multiple tissue-activity values within a small VOI. Using simulated microSPECT imaging data, we

then compare the performance (bias and variance) of the VOI estimator for 2-, 3-, and 4-tissue activity estimation tasks to that of simple SUV estimators, as well as to a spillover-corrected SUV metric (for the 2-tissue VOI only) using the perturbation-based approach. All of these methods make use of identical segmented tumor regions, as well as the same underlying OSEM reconstruction algorithm, which incorporates an accurate model of collimator and detector resolution. The realized variance of VOI tissue activity estimates will also be compared to the best possible variance predicted by the CRB. Finally, we evaluate the algorithm's performance under more realistic conditions in a SPECT-CT phantom experiment.

II. METHODS

A. Algorithm

Consider a tumor located within lung tissue, but very close to the myocardium and to other tissue types. In this case, a relatively small parallelepiped-shaped VOI (illustrated by the yellow square in Fig. 1) might contain four segmented tissues of interest, e.g., tumor, lung, myocardium, and soft tissue. (In practice, we assume that the tissue boundaries within the VOI would be obtained by application of a suitable segmentation algorithm to a spatially registered volume of high-resolution morphologic images, e.g., acquired using a SPECT-CT, PET-CT, or SPECT- or PET-MR system.) To obtain estimates of each tissue's activity concentration, we consider only those projection rays that traverse the VOI. For example, Fig. 1 shows such a set of parallel projection rays for just one of many angular-projection views. Although this example is illustrated with parallel projection rays, our approach is general, in the sense that the forward-projection operation could be modeled for PET, or for SPECT with any other type of collimator and detector geometry.

The joint likelihood of measuring a given projection data set is given by the product, over all rays traversing the volume-of-interest, of the Poisson probability density function for each measured projection ray, i :

$$L = \prod_{i \in \text{VOI}} \frac{\lambda_i^{n_i} e^{-\lambda_i}}{n_i!}, \quad (1)$$

where λ_i is the expected value of the i^{th} projection-ray traversing the VOI, while n_i is its actual measured value. We seek to maximize the log of this joint likelihood,

$$\ln(L) = \sum_{i \in \text{VOI}} n_i \ln \lambda_i - \lambda_i - \ln(n_i!), \quad (2)$$

and we define the projection model for projection-ray, i , as

$$\lambda_i^{(k)} = \sum_{j=1}^J A_j p_{ij} + g_{\text{out},i}^{(k)}. \quad (3)$$

Thus, we model $\lambda_i^{(k)}$, the expected value of the i^{th} projection ray through the VOI (re-projected following the k^{th} iteration of a suitable iterative reconstruction algorithm) as the sum of two terms; the first term is obtained by modeling the sum of the contributions from each of the J tissue types occupying the VOI, while the second term is a “nuisance term” computed by forward-projection over the rest of the (unsegmented) image volume outside the VOI. In formula (3), A_j is the unknown activity concentration of the j^{th} tissue type within the VOI, p_{ij} is the “system matrix” contribution from the j^{th} tissue type within the VOI to the

i^{th} resolution-blurred estimated projection ray, and $g_{\text{out},i}^{(k)}$ is the global background contribution to the same projection ray, after the k^{th} iteration of the image reconstruction algorithm, obtained by summing over the contributions to this ray from all voxels outside the VOI (e.g., by reprojection over the image volume, with all voxels inside the VOI set to zero). The p_{ij} are equivalent to a weighted sum of the conventional system matrix elements over all source voxels falling either partially or entirely within the segmented volume corresponding to tissue-type j for projection-ray i . The weighting factors in this sum are unity for source voxels that are entirely within the segmented tissue volume; however, other source voxels, particularly those around the tissue's boundary, contain only fractional contributions that were computed based on the number of much smaller voxels from the higher resolution "anatomic" image that were located within the segmented tissue volume. Note that the p_{ij} only need to be calculated once, by separately forward-projecting each of the J segmented tissue volumes within the VOI, whereas the global background reprojections, $g_{\text{out},i}^{(k)}$, must be computed after every iteration because the voxel values outside the VOI change with each iteration.

We now seek to estimate simultaneously the J different values of tissue activity concentration ($A_j; 1 \leq j \leq J$) that will maximize the log-likelihood in equation 2. By taking derivatives of $\ln(L)$ with respect to each of the J values of A_j , and setting the results to zero, one can obtain the following J equations which can be solved by inverting a $J \times J$ matrix.

$$\sum_{j'=1}^J A_{j'} \left[\sum_i \frac{p_{ij'} p_{ij}}{\lambda_i^{(k)}} \right] = \sum_i \frac{p_{ij} (n_i - g_{\text{out},i}^{(k)})}{\lambda_i^{(k)}}, j=1, J. \quad (4)$$

Note that these equations are not, strictly speaking, linear in the A_j because the $\lambda_i^{(k)}$ in the denominators of the factors on both sides of the equation also depend on the A_j . However, for simplicity, we choose to solve the set of equations (4) for the A_j by using the following very fast iterative procedure. (N.B. This should not be confused with the iterative reconstruction algorithm; the fast iterative procedure described here for estimating the J unknown values of activity concentration is carried out after each iteration, k , of the image reconstruction.)

Step 1 We first compute all of the matrix elements,

$$\begin{aligned} H_{jj'}^{(k)} &= \sum_i \frac{p_{ij} p_{ij'}}{\lambda_i^{(k)}}, \\ \text{and} \quad D_j^{(k)} &= \sum_i \frac{p_{ij} (n_i - g_{\text{out},i}^{(k)})}{\lambda_i^{(k)}}. \end{aligned} \quad (5)$$

For the first iteration of this activity-estimation procedure, we approximate the $\lambda_i^{(k)}$ in the denominator by simply using the corresponding measured projection data values, i.e., $\lambda_i^{(k)} \sim n_i$. For each subsequent iteration, we update these $\lambda_i^{(k)}$ by using the most recently computed estimates of A_j (for $j=1, J$) in equation 3.

Step 2 From the matrix elements computed using equation 5, we estimate the required J values of tissue activity concentration, $\tilde{A}_j^{(k)}$, by inverting the matrix, H , to solve equation 4:

$$\tilde{A}_j^{(k)} = \sum_{j'=1}^J H_{jj'}^{-1(k)} D_{j'}^{(k)}. \quad (6)$$

Step 3 The procedure above is repeated from step 1 using the new estimates of the $A_j^{(k)}$ to compute new elements of matrices H and D and, in turn, improved estimates of the $A_j^{(k)}$ in step 2; this is continued until the estimates change by less than a very small amount from one iteration to the next. In practice, for the imaging examples shown later in the paper, convergence of this fast iterative calculation was always achieved (to better than 0.001%) in just a few iterations; however, to provide a safety margin, 10 iterations were always used.

B. Calculation of Cramer-Rao bounds

The CRB is a lower bound on the minimum parameter variance achievable by an ideal, linear, unbiased estimator [28]. The CRB for each different tissue-activity concentration is given by the appropriate diagonal matrix element of the inverse of the Fisher information matrix, F. For our problem, F is a $J \times J$ matrix whose elements are given by

$$F_{jj'} = \sum_{i \in VOI} \frac{1}{\text{var}(\lambda_i)} \frac{\partial \lambda_i}{\partial A_j} \frac{\partial \lambda_i}{\partial A_{j'}}, \quad (7)$$

where λ_i is the expected (noise-free) value of the i^{th} modeled projection ray. Because the derivative of the model with respect to the j^{th} tissue's activity concentration is just p_{ij} , and since the variance of a Poisson random variable equals its expected mean value, the Fisher matrix elements become

$$F_{jj'} = \sum_{i \in VOI} \frac{p_{ij} p_{ij'}}{\lambda_i}, \quad (8)$$

and the CRB on the variance of the j^{th} tissue activity concentration is then given by,

$$CRB_{jj} = F_{jj}^{-1}. \quad (9)$$

When computing these CRB, λ_i was set equal to the value of the i^{th} simulated noise-free projection ray which traverses the VOI, while p_{ij} was defined as the j^{th} tissue's contribution to the i^{th} projection ray, obtained by forward-projection of a unit-activity template of the j^{th} segmented tissue region.

C. Evaluation

To evaluate the accuracy and precision of the new algorithm for activity estimation with correction for the partial volume and spillover effects, we used projection data simulated for Harvard Medical School's triple-detector, 6-pinhole microSPECT imaging system [29], [30]. The system matrix was computed by using numerical ray-tracing to sample the pinhole apertures, as well as a Gaussian blurring function to model the intrinsic camera resolution. Data from 90 projection views were simulated for MOBY (Fig. 2), the digital mouse phantom described by Segars and colleagues [31]. We placed three mathematical tumors inside MOBY, and defined three VOIs, one for each tumor. Each cubic VOI contained $12 \times 12 \times 12$ voxels (with a voxel size of 0.4 mm), and contained a centered spherical tumor, 4 voxels (1.6-mm) in diameter.

This first VOI, centered on a hepatic tumor, also contained a partial-organ contribution from the surrounding higher-activity liver tissue within VOI 1. The second VOI contained three tissue types: a centered lung tumor, plus partial contributions from liver and lung. And the third VOI contained a different centered lung tumor, surrounded by liver, lung, and myocardial tissue. Data were simulated for a one-hour acquisition, following a 2.6 mCi (98 MBq) injection of an experimental ^{99m}Tc -labeled melanoma imaging agent [32]. Resolution blurring by the six simulated 1.2-mm-diameter pinholes and by the intrinsic resolution of the gamma cameras were both modeled, yielding a combined system resolution of ~ 1.4 mm (3.5 voxels) near the center of rotation; this FWHM resolution value is 87.5% of the diameter of the simulated tumors. Photon scatter and attenuation were not simulated for this study because these are both small effects at ^{99m}Tc energies in microSPECT mouse studies. Moreover, a small amount of photon scatter could be corrected quite well by independent means, e.g., by using an energy-based technique such as the TEW correction method [33]. Photon attenuation does not contribute at all to the partial-volume or tissue spillover effects, yet attenuation could also be corrected, if necessary, by energy-scaling the same well-registered CT attenuation map that would also be used for defining the high-resolution morphologic tissue boundaries within a VOI. The relative activity-concentration values in the tumor, liver, heart, and lung were simulated in the proportions 139:176:32:8, based on the average relative uptake values measured previously by tissue well counting in mouse experiments with this imaging agent. The other relative organ activity-concentration values included for the same agent were intestines (253), bladder (220), testes (120), kidneys (71), pancreas (52), stomach (46), thyroid (40), bones (30), spleen (14), blood (9), soft tissue (8), and brain (4).

After each iteration of OSEM (with 10 subsets), the mean estimation bias and variance were determined from noisy simulated data (over 30 statistically independent noise realizations), and the CRB lower bound on variance of the tissue activity estimates was calculated from noise-free projections. The bias and variance of more conventional activity estimation metrics, SUV-average and SUV-center, were also computed over the different Poisson noise realizations, for comparison with the performance of the VOI parameter fitting approach. SUV-center was defined as the average of a $2 \times 2 \times 2$ voxel region, exactly centered within the simulated tumor; this metric is similar to the ‘SUVpeak’ metric [34] in that both measures should be somewhat less noisy in comparison to SUV-max, which is based on just a single voxel value. We used SUV-center, rather than SUV-peak, because in our simulation study, we knew the exact location of the spheres.

D. Perturbation correction

For the simplest case, i.e., VOI #1 in Fig. 2, for which there were only two tissues inside the VOI, we also computed a local, image-based, spillover-corrected tumor activity estimate by modifying the global perturbation geometric transfer matrix (pGTM) method described by Du and colleagues [10], [11], as follows. Suppose that the SUV-average measurements of total tumor and total background counts within the VOI are T_m and B_m , respectively. If f_{TB} is the fraction of tumor counts that are blurred into the background region of the VOI, and f_{BT} is the fraction of background counts from inside the VOI that are blurred into the tumor, then T_m and B_m can be expressed in terms of the true (unknown) underlying tumor and background counts, T and B , as:

$$\begin{aligned} T_m &= T(1 - f_{TB}) + B f_{BT}, \\ B_m &= B(1 - f_{BT}) + T f_{TB}. \end{aligned} \quad (10)$$

The second of these two equations is exactly correct only if the background tissue inside and outside the VOI can be considered to be in a “steady-state equilibrium”, such that the

number of background tissue counts which are blurred from inside to outside the VOI is equal to the number of background counts blurred from outside to inside. For VOI 1 in Fig. 2, this is not an unreasonable approximation, because this VOI is entirely surrounded on all sides by normal background liver tissue, whereas for VOIs 2 and 3, which contain, respectively, three and four different tissue types, with widely disparate values of activity concentration, this steady-state background equilibrium assumption is badly violated. Therefore, for these two VOIs, a purely local image-based spillover correction approach like this would not be reasonable and, in any case, cannot be derived without using additional, more questionable approximations.

By eliminating B in equations (10), we can solve for the true (corrected) number of counts in the tumor,

$$T = [T_m (1 - f_{BT}) - B_m f_{BT}] / [1 - f_{TB} - f_{BT}]. \quad (11)$$

The perturbation method was used to determine the two spillover fractions. To compute f_{TB} , we added a small perturbation (10% of the tumor counts), to the segmented tumor region. This tumor-only perturbation was then forward projected, and the resulting projections were added to the original measured projections from the entire phantom. These perturbed projections were then reconstructed by OSEM for 50 iterations ($\times 10$ subsets). The tumor-to-background spill-out fraction, f_{TB} , at each iteration was defined as the fraction of perturbed tumor counts blurred into the background tissue region within the VOI. The spill-in fraction, f_{BT} , was computed analogously, but for this case, we perturbed only the background region within the VOI, rather than the tumor region.

E. Experimental multiple-bead phantom study of VOI and global pGTM performance

Finally, to assess real-world activity estimation performance with spillover corrections, we compared the VOI estimation method to the full global pGTM method [10], [11] using data from a multiple-bead phantom acquired on the HMS scanner. Six molecular-sieve beads, ~ 1.8 mm in diameter, were soaked for 15 minutes in a high specific-activity solution of $^{99m}\text{TcO}_4^-$. The beads were then sealed with epoxy and, after measuring each bead's activity in a dose calibrator, the bead activity was allowed to decay overnight; this yielded a mean ($\pm$ standard deviation of) bead activity-concentration values of 12.22 ± 1.27 kBq/ μL at the beginning of SPECT data acquisition. The beads were affixed to a thin (~ 0.5 mm) plastic sheet, embedded in a 2.0-cm diameter cylindrical gel phantom (inside a plastic 2.3-cm-diameter syringe) containing a uniform background activity concentration of 1.67 kBq/ μL at the start of scanning. After a one-hour SPECT acquisition on the HMS μSPECT scanner, utilizing six 1.6-mm-diameter pinholes with a radius-of-rotation of 3.0 cm, the phantom was then scanned on a μCT scanner (Bioscan NanoSPECT/CTTM).

The μCT reconstructed image volume was rigidly registered to the μSPECT reconstruction using a normalized cross-correlation objective function, with tri-linear interpolation providing four-fold higher CT sampling (0.1 mm voxels) compared to the SPECT image array (0.4 mm voxels). The registered μCT image volume was segmented into three materials -- beads, gel, and plastic sheet -- before down-sampling the high-resolution segmented CT images to the SPECT voxel size.

The forward-projection blurring operation, used for OSEM reconstruction as well as for VOI activity estimates, included the magnified 1.6-mm-diameter pinhole resolution along with a crystal depth-of-interaction model, as well as the minified intrinsic camera resolution. The system resolution near the center of the phantom was ~ 1.8 mm (4.5 voxels) FWHM. Because the fraction of scattered photons is small in μSPECT imaging, we did not correct

for scatter. Photon attenuation, though also small, was corrected using a Chang approach [35]. Attenuation-correction factors at the locations of the six beads ranged from 0.985 to 1.011 with respect to the mean correction factor over the entire phantom background.

The performance of the local VOI fitting method was compared with that of the global pGTM approach [10, 11]. For the VOI fitting method, local cubic VOI, 6.4 mm (16 SPECT voxels) on each side, were defined around each bead, where each VOI contained the three segmented materials. For the global pGTM method, eight segmented regions were defined over the entire phantom (6 beads, background, and plastic sheet). Estimates of bead and background activity obtained by both methods were compared with “gold-standard” values obtained from dose-calibrator measurements during phantom preparation.

Finally, to provide an initial assessment of the robustness of both partial-volume correction approaches to errors in the spatial registration of the μ SPECT and μ CT images, we deliberately shifted the CT image volume by 2 SPECT voxels (0.8 mm) in the axial direction, and then repeated all activity estimates by both methods.

III. RESULTS

A. Two-tissue activity estimation

The two-tissue VOI estimation bias and precision values are shown vs. OSEM iteration number in Fig. 3 for the hepatic tumor in VOI #1, which is surrounded only by liver tissue. Both tissue activity estimates stabilized at about 15 iterations, where they achieved very low values of bias that continued to improve with increasing iteration number. After the same number of iterations, the relative standard deviation of both estimates exceeded predictions from the Cramer-Rao lower bound (CRB) by ~25%, and continued to increase slowly with iteration number. This noise increase with respect to the CRB is attributable to an unavoidable property of MLEM and OSEM algorithms whereby the reconstructed voxel noise continues to increase with increasing iteration number. Because of this behavior, the noise on rays that are re-projected across the global background outside the specified VOI, i.e., the terms, $g^{(k)}_{\text{out},i}$ in formula (3), also increases correspondingly, although the reprojected noise increases more slowly than the underlying voxel noise because re-projection averages the noise over many voxels.

For this lower-activity hepatic tumor estimation task, the SUV-average and SUV-center metrics were positively biased compared to VOI estimation (Fig. 4). Beyond ~15 iterations, the precision of the SUV metrics degraded at a much faster rate than that of the VOI estimator. The perturbation correction yielded improved bias but worse precision than SUV-average, and (asymptotically) slightly less bias than SUV-center, but with much better precision.

B. Three-tissue activity estimation

The estimation performance for the three tissues in VOI #2 exhibited similarly low-bias and stable behavior with increasing iteration number, but with worse estimation precision for the low-activity lung tissue component (Fig. 5).

It may seem surprising that, at relatively low iteration numbers, the values of precision of the tissue activity estimates from VOI fitting were better than those predicted from the CRB on variance. It is important to recall, however, that the CRB represents a lower bound on the variance of an unbiased, linear estimator. For the lower iteration numbers, i.e., before the OSEM reconstruction has begun to converge, the estimates of tissue activity concentration values can still be significantly biased, and it is well known that biased estimators can outperform a lower bound on variance. It is interesting to note that the variance of lung

activity estimates does not exceed the CRB until ~28 iterations, which is approximately the number of iterations where the relative bias of the lung activity estimates begins to exhibit convergent behavior.

For VOI #2, the SUV-average metric (Fig. 6) underestimated the tumor's activity by about 36 percent, while SUV-center overestimated it by more than 40%; however, the precision of SUV-average was slightly better than that of the VOI estimator, while the precision of the SUV-center metric was significantly worse.

C. Four-tissue activity estimation

The estimation performance for the four tissues in VOI #3 (Fig. 7) followed the same general trends seen above for the other VOI estimates, although the absolute values of bias and precision were somewhat worse for this case. Two of the four tissue types in VOI 3, lung and heart, contain low activity values, which leads to increased noise of the estimates. Moreover, the requirement of fitting for four unknown activity concentration values further worsens precision of the estimates. The rank order of precision by tissue type remains well predicted by the CRB, and the activity estimates of all tissues appear to be stable, i.e., converging towards low bias values with increasing iteration number.

As we saw above for VOI #2, the SUV-average metric for tumor-activity estimation within VOI #3 (Fig. 8) significantly underestimated the tumor's activity, while SUV-center overestimated it, also by a large amount; however, the precision of the SUV-average metric remained slightly better than that of the VOI estimator, with the precision of the SUV-center metric significantly worse.

Overall, by 15 iterations, the VOI fitting method yielded very accurate tumor activity estimates (Table 1), and was only slightly less precise than the SUV-average metric, despite the fact that the new approach requires multiple-parameter estimation. In contrast, the SUV-center and SUV-average metrics were both significantly biased, as expected, and SUV-center exhibited worse precision than either SUV-average or VOI-fit. Although activity estimation from the small regions of surrounding organs which partially occupy the VOI is generally not of primary clinical interest, even these estimates were seen to be biased less than ~9% at 15 iterations.

D. Performance of VOI and pGTM estimates from the multiple-bead phantom

Spatially registered images of the beads segmented from the μ CT image volume and reconstructed μ SPECT images are shown in Fig. 9.

Table 2 lists the percent errors in the estimates of bead activity concentration values produced by both correction methods. In addition to the bead activity, the VOI method estimated the counts per voxel within the local background gel around each of the six beads. The mean and standard deviation of these background count values were 2.89 ± 0.05 , for the VOI fitting method, while the pGTM estimate of the global background was 2.85 counts per voxel. Because the uniform gel activity concentration was independently measured to be 1.67 kBq/ μ L, we used the estimated background count density of each method to define a linear transformation for converting the estimated count density within the beads to activity-concentration values, in order to compute the errors in bead activity values shown in Table 2.

The minimum % root-mean squared error was found after 2 iterations $\times$ 10 subsets of OSEM (Fig. 10). (The first-iteration's update cannot be properly corrected using the VOI fitting approach, so this data point is not shown in the plots.) After 2 iterations, the bias and precision of the estimates were similar for both methods. (See Fig. 10, and the average

values in Table 2.) As the number of iterations increased, the errors in VOI activity estimates remained quite stable, whereas those of the pGTM method worsened.

After deliberately shifting the CT image volume axially by 2 SPECT pixels (0.8mm), both methods underestimated the bead activity values by ~25% at 2 iterations (Fig. 11), and again, at increasing iteration numbers, the bias of the pGTM method continued to degrade.

IV. DISCUSSION

In conclusion, we have described a new compensation approach that requires tissue segmentation of a registered CT or MR image volume only within a small VOI, which could easily be defined interactively on a computer screen by a knowledgeable operator, such as a radiologist. The estimates of activity concentration are obtained by a straightforward and robust fit to an image model in projection space, where the statistical noise is approximately “white” (spatially uncorrelated); this offers a significant advantage in comparison with image-space correction approaches. Even though most image-based methods published previously for partial-volume and spillover correction are deterministic approaches, in the sense that they do not incorporate knowledge of the underlying voxel noise properties within the correction process, this information is in any case challenging to include in image space, where the image noise is both nonstationary and correlated by the reconstruction algorithm.

The new method compensates simultaneously for tissue partial-volume and spillover effects, and the bias of tumor-activity estimates appeared to converge with increasing OSEM iteration number. Convergence was somewhat slower for the partial organ contributions to the VOI although, in our study, even the activity estimates of the multiple partial-organ contributions to the VOI were accurate to better than 10%. For the three- and four-tissue VOI examples, the tissues with the lowest values of activity concentration, lung and heart, converged most slowly. We believe that this is a reflection of the convergence properties of the underlying OSEM reconstruction, i.e., the high-count features of the image volume converge most rapidly, while it can take many more iterations for the low-count regions to achieve comparable accuracy. This, in turn, implies that reprojected rays through regions of the lungs and heart that are outside of our defined VOI will require more iterations until their bias no longer dominates the relative error of the lower activity tissue estimates within the VOI. On the other hand, at higher iteration numbers, as the OSEM reconstruction attempts to recover better resolution than can be supported by the underlying image sampling (i.e., thereby violating the Nyquist sampling theorem), there is clear evidence of Gibbs artifacts appearing near high-contrast boundaries of various organs. This can be noted, for example, in the noise-free reconstruction of the MOBY phantom after just 10 iterations $\times$ 10 subsets (Fig. 2c). In fact, we believe that such artifacts in regions outside the local VOI lead to inaccuracies in the calculation of the g_{out} contributions to the estimated model projections; these errors, in turn, are likely responsible for the small residual bias of VOI estimates that is often seen, despite the use of perfectly matched projectors used for simulation and OSEM reconstruction of the simulated data.

At earlier iteration numbers, the variances of these tissue activity estimates were less than those predicted by the CRB. As described in section III.B, biased estimators can often outperform lower bounds on variance, so this is not surprising behavior. In fact, on the contrary, this property may provide an advantage for certain low-count imaging tasks, e.g., when estimating tissue activity parameters from short, dynamic frames of data. Under such count-limited conditions, it may be desirable to achieve very good precision of activity estimates, while accepting a modest degree of bias. Whether this approach is ultimately useful depends on the details of the imaging task in question, and the parameters which need to be estimated.

It is also not surprising that the VOI fitting approach generally outperformed the simple volume-of-interest estimators. Even though these SUV-like estimators were applied to images reconstructed with OSEM using an accurate forward-projection model, nevertheless, after 50 iterations, the extent of resolution recovery and spillover corrections reflected in the SUV-average measurements remained poor. The SUV-center metric exhibited better bias, but significantly worse precision than SUV-average. When SUV-average was corrected using the perturbation approach, the corrected bias was substantially less than that of SUV-average, and the corrected precision was also much better than that of the SUV-center metric. Overall, the perturbation-correction method provided performance in between that of the two simpler methods, but it was still inferior to the VOI fitting approach in both bias and precision. The residual bias in the corrected SUV measurements may be due to some inaccuracy of the “steady-state” approximation mentioned earlier, i.e., the number of counts blurred from the liver tissue inside the VOI to the liver tissue outside the VOI is not exactly equal to the number blurred from outside to inside. And the improved precision of the VOI estimates may arise from the fact that this method incorporates knowledge of the Poisson statistical noise of the projection data within the fitting procedure, whereas the perturbation-based spillover correction is deterministic. For the case when even more tissues are located in close proximity to the primary tissue of interest (e.g., a tumor), it becomes increasingly difficult to handle the various spillover contributions, which is why we applied the local perturbation correction only to VOI #1 that contained two different tissues, liver and tumor. To extend this approach to the case of more tissues, it would probably be necessary to use the full global pGTM method [10], [11], which requires segmenting many more tissues.

In our experimental comparison of the local VOI method and the global pGTM method using data acquired on the HMS μ SPECT system from the multiple-bead and gel phantom, we observed that, while both methods provided comparable accuracy and precision of bead activity estimates near the minimum rMSE condition (at 2 iterations $\times$ 10 subsets), the bias and precision of VOI estimates were more stable than those of pGTM with increasing iteration numbers. This behavior was observed even when the μ CT image boundaries were deliberately shifted by 2 SPECT voxels (0.8 mm) in the axial direction with respect to the μ SPECT image volume, in order to provide an initial assessment of the robustness of the partial-volume correction approaches to errors in the spatial registration of the μ SPECT and μ CT images.

We also observed that the reconstructed activity distribution within some of the beads was non-uniform. It is possible that the less stable behavior of the pGTM method might be related to a violation of the assumption of uniform uptake underlying both methods. For the pGTM method, each of the uniform region masks -- which were defined for eight different segmented regions -- is scaled appropriately and added to the reconstructed image as a uniform perturbation, before reprojection and reconstruction to compute the geometric transfer matrix elements. If the reconstructed activity distribution within one or more of these regions becomes increasingly nonuniform at higher and higher iteration numbers, then the shape of the perturbation within those regions will diverge more and more from the shape of the underlying region distribution, which could lead to unstable behavior of the pGTM bead activity estimates with increasing iteration number. Because the VOI estimator, on the other hand, fits the activity distribution within a local VOI to a highly constrained segmented-tissue model, this calculation yields estimates of activity concentration within each tissue type that rapidly converge towards the mean value of the activity concentration over the tissue's volume; this suggests that the VOI estimator may be more robust to violations of the assumption of uniform uptake in each segmented region.

We used a Chang approach for attenuation correction during the VOI estimation procedure. In a recent paper, Wu *et al.* [37] reported an absolute accuracy of $\sim 2\%$ for Tc-99m

microSPECT phantom imaging when using Chang post-correction approaches. This is consistent with our observation that attenuation factors varied little with bead location, i.e., they were all within a few percent of each other and within $\pm 1.5\%$ of the mean background attenuation factor. For these reasons, we believe that the first-order Chang method is quite reasonable to use for attenuation compensation in microSPECT imaging, despite the fact that it is theoretically not as rigorous as the approach of incorporating attenuation factors within the iterative reconstruction procedure by pre-computing line integrals over the CT-based attenuation map. It should be noted in this regard that there are additional factors, e.g., the transformation relating Hounsfield units from a low-kVp CT scan to linear attenuation coefficients at 140 keV, which may in any case limit the accuracy of even superior attenuation-correction approaches to a few percent.

Implementation of the VOI fitting method requires an accurately registered morphologic image volume, e.g., from CT or MR. This can be especially challenging for cases where the functional or metabolic tissue boundaries do not correspond well to the morphologic boundaries (see, e.g., [36]). Furthermore, the different tissue types included within the VOI also need to be accurately segmented, ideally using the higher resolution morphologic images to define the boundaries between the different tissues within the VOI. For our simulation study, we assumed perfect knowledge of all tissue boundaries; these were all defined using a factor of 10 oversampling in each direction, compared to the 0.4-mm microSPECT voxels. For the multiple-bead phantom study, on the other hand, we used very high-resolution μ CT images to help define and register “anatomic” boundaries to the μ SPECT images, and we additionally performed a preliminary assessment of the robustness of the VOI and pGTM correction methods to inaccuracy in the spatial registration of the μ SPECT and μ CT images. In future work, we will explore in greater detail the robustness of correction methods to errors in both image segmentation and registration -- both of which lead to inaccuracies in the assumed boundaries. We will also examine the possible effects of high-activity structures located outside the VOI on the tissue activity estimates inside the boundary.

Another approach to quantitative imaging is based on reconstruction of highly sampled voxels within regions of primary interest, while reconstructing only a single average value within regions of no particular interest [38], [39]. This method has been studied using uniform background regions, where it was shown to yield bias values less than $\sim 10\%$ in the structures of interest. Because the approach is voxel-based, as opposed to model-based, it compensates implicitly for partial-volume and spillover effects by recovering resolution during the iterative reconstruction; however, it does not require the assumption of uniform uptake within the targeted region(s). One way of relaxing the uniform-uptake assumption of the VOI model-based method is to modify the model by incorporating higher-order radial and/or other spatially varying terms when fitting underlying tumor activity distributions; this approach will also be investigated in future work.

Finally, we note that the VOI fitting approach should be easily extendable to humanscale SPECT imaging, as well as to micro-PET or human PET imaging. To implement the method, one needs to obtain or develop (1) tools for defining accurately segmented tissue regions within one or more small VOI containing potential tumors or lesions of interest, (2) an accurate iterative reconstruction algorithm with complete corrections for all physical effects, and (3) a forward-projector which accurately models the relevant physical phenomena. We are currently investigating this approach for human SPECT imaging with parallel-hole collimation.

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Fig. 1.

All measured projection rays that traverse the three-dimensional VOI (shown here for just one angular view) are used for estimating activity concentration values within each of the small number of segmented tissue types occupying the VOI. The VOI should be approximately centered on the tissue of primary interest, e.g., the lung tumor. The other tissues within the VOI shown here are myocardium, soft tissue, and lung.

Fig. 2.

A coronal slice through MOBY, the digital mouse phantom [31], showing the three magnified cubic VOIs used for testing the new activity quantitation algorithm. The VOIs are displayed with different color mappings to permit better visualization of the different structures within each VOI. (a) VOI 1 (blue border) includes two tissues: normal liver tissue (light orange), plus a hepatic tumor (darker orange). VOI 2 (green border) includes three tissues: a lung tumor (mostly yellow), normal liver tissue (mostly white), and normal lung tissue (mostly black). VOI 3 (red border) includes four tissues: a lung tumor (mostly yellow), normal liver (mostly white), lung (mostly black), and myocardial tissue (mostly blue in lower right-hand corner); (b) initial ^{99m}Tc source map, showing the relative activity concentration in various organs and tumors in different colors; (c) OSEM reconstruction (10 iterations $\times$ 10 subsets) of simulated noise-free data from HMS 6-pinhole micro-SPECT scanner; (d) OSEM reconstruction (10 iterations $\times$ 10 subsets) of data from one of many Poisson noise realizations. The “Fire” color scale shown in (b), (c), and (d) ranges from 0 (black) on the left, to 255 (white) on the right.

Fig. 3. (left) percent bias and (right) percent precision of tumor and liver background activity-concentration estimates from VOI #1, computed over 30 independent Poisson noise realizations. Also shown are the square-root of the Cramer-Rao lower bounds on variance for both tissues.

Fig. 4. (left) percent bias and (right) percent precision for different metrics related to the activity concentration of the hepatic tumor in VOI #1, computed over 30 independent Poisson noise realizations. In addition to the VOI-fit estimates, we show three SUV-related metrics: the average SUV over the tumor, the SUV in the central $2 \times 2 \times 2$ voxel region, and the average SUV, corrected using the perturbation approach described in Methods section D.

Fig. 5. (left) percent bias and (right) percent precision of lung tumor, liver, and lung activity-concentration estimates from VOI #2, computed over 30 independent Poisson noise realizations. Also shown are the square-root of the Cramer-Rao lower bounds on variance for these tissues.

Fig. 6. (left) percent bias and (right) percent precision for three metrics related to the activity concentration of the lung tumor in VOI #2, computed over 30 independent Poisson noise realizations.

Fig. 7. (left) percent bias and (right) percent precision of lung tumor, liver, lung, and myocardial activity-concentration estimates from VOI #3, computed over 30 independent Poisson noise realizations. Also shown are the square-root of the Cramer-Rao lower bounds on variance for these tissues.

Fig. 8. (left) percent bias and (right) percent precision for the various metrics related to the activity concentration of the lung tumor in VOI #3, computed over 30 independent Poisson noise realizations.

Fig. 9. Coronal reprojction through six ~1.8-mm-diameter molecular-sieve beads, **(top)** segmented from a high-resolution μ CT image of the bead-in-gel phantom that was spatially registered to a μ SPECT reconstruction of the phantom **(bottom)**.

Fig. 10.

Mean of the errors in bead activity estimates for the VOI and pGTM correction methods vs. OSEM iteration number; error bars show the standard deviation computed over all beads. Overall % root-mean-squared error (% rMSE) values are also shown. (Data points were offset horizontally for improved visual discrimination of error bars.)

Fig. 11.

Mean bias in bead activity estimates introduced by a deliberate shift of 2 pixels (0.8 mm) in the axial direction between the μ CT and μ SPECT image volumes for the VOI and pGTM correction methods; error bars indicate the standard deviation computed over all beads. (Data points were offset horizontally for improved visual discrimination of error bars.)

Table 1

Overall performance range at 15 iterations.

Method	Tissue	Bias (%)	Std. Dev. (%)
SUVcen	tumors	7.9 -> 36.2	7.9 -> 12.8
SUVave	tumors	-34.3 -> 13.5	2.3 -> 6.6
VOI fit	tumors	-2.8 -> 1.1	3.2 -> 7.8
VOI fit	organs	-5.4 -> 8.8	0.9 -> 11.7

Table 2

Activity estimates of all beads by both methods (at 2 iterations, 10 subsets)

	activity conc. (kBq/ μ L)	% error in activity estimate (VOI)	% error in activity estimate (pGTM)
bead 1	13.64	-14.1 %	-19.4 %
bead 2	12.61	1.6 %	-5.8 %
bead 3	10.30	-6.4 %	-11.0 %
bead 4	13.48	8.8 %	0.1 %
bead 5	11.67	4.1 %	-0.7 %
bead 6	11.64	11.3 %	4.3 %
average	12.22	0.9 ± 9.5 %	-5.4 ± 8.6 %