An Approximate Bootstrap Technique for Variance Estimation in Parametric Images

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Abstract
Parametric imaging procedures offer the possibility of comprehensive assessment of tissue metabolic activity. Estimating variances of these images is important for the development of inference tools in a diagnostic setting. However, these are not ready to obtain because the complexity of the radio-tracer models used in the generation of a parametric image makes analytic variance expressions intractable. On the other hand, a natural extension of the usual bootstrap resampling approach is infeasible because of the expanded computational effort. This paper suggests a computationally practical, approximate simulation strategy to variance estimation. Results of experiments done to evaluate the approach in a simplified model one-dimensional problem are very encouraging. Diagnostic checks performed on a single real-life PET image to test for the feasibility of applying the procedure in a real-world PET setting also show some promise. The suggested methodology is evaluated here in the context of parametric images extracted by mixture analysis; however, the approach is general enough to extend to other parametric imaging methods.

Keywords: variance estimation, parametric image, positron emission tomography, bootstrap, resampling methods

1. INTRODUCTION
The ability to assess quantitatively the biologic status of tissue from a sequence of dynamic Positron Emission Tomography (PET) scans is one of the most powerful features of this radiologic tool. The most common approach in this regard is a technique called ROI analysis. Here, the reconstructed pixel values in each scan are averaged over a given region (ROI) to yield a time series, called the time-activity curve (TAC), and then the regional biologic parameter values are estimated by fitting non-linear models to the resulting time series. There are concerns regarding image registration while drawing these regions with the help of other imaging modalities such as X-ray Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), as well as the potential for inaccurate metabolic parameter estimation because of the possible selection of inhomogeneous regions (O’Sullivan, 1994). From a practical standpoint however, the most important concern is that outside the selected regions, the reconstructed PET data are only interpreted qualitatively, thus not fully utilizing the quantitative potential of this expensive technology.

An alternative methodology is provided by parametric imaging whose goal is to provide comprehensive pixel-wise assessments of tissue metabolic activity. The technique builds on fitting radio-tracer models to the time-course reconstructed PET data at each pixel. However, the presence of noise and heterogeneity between the reconstructed pixel values make direct fitting of models inappropriate (Herholz and Patlak, 1991; Schmidt et al., 1991) and underlines the need for more refined approaches (Blomqvist et al., 1984; Cunningham and Jones, 1993; Gjedde, 1981; Gjedde, 1982; Herholz, 1988; Patlak et al., 1983; O’Sullivan, 1993; O’Sullivan, 1994).

1.1. An Illustration
Figure 1 displays a time-course sequence of images of [C-11]-glucose uptake in a subject. The images reveal that there is very little activity in the first few minutes after injection of the dose while the radio-tracer is being transported through
Figure 1. Time-course sequence of reconstructed PET images of [C-11]-glucose radio-tracer uptake. The time-points were (i) at injection, and (ii) 1 minute, (iii) 80 seconds, (iv) 2 minutes, (v) 160 seconds, (vi) 200 seconds, and (vii) 4, (viii) 5, (ix) 6, (x) 7, (xi) 8, (xii) 11, (xiii) 14, (xiv) 17, (xv) 20, (xvi) 25, (xvii) 30, (xviii) 35, (xix) 40, (xx) 45, (xxi) 50, (xxii) 55, (xxiii) 60, (xxiv) 65, (xxv) 70, (xxvi) 75, (xxvii) 80, (xxviii) 85, (xxix) 128.5, and (xxx) 129.5 minutes, after injection of the radio-tracer.
the circulatory system and then the brain starts taking up the radio-tracer differentially. The rate of emissions increases as more and more of the radio-tracer is taken up, till around the time-point of 20 minutes which corresponds to the half-life of the radio-tracer. After this the rate of emissions decrease and this is again differential over pixels. The spatio-temporal dynamics are illustrated in the study. At any one time-point, the uptake is differential over pixels. On the other hand, at any pixel, the uptake varies over time. The power of the PET radiologic tool is that it attempts to provide quantitative summaries of tissue biologic parameters from such image sequences. Performing a ROI analysis on this image would imply defining a few regions (ROIs) and then fitting a radio-tracer model to the resulting time series of average uptake over the region. This would deprive the radiologist of useful information on the spatial behavior of the metabolic parameter of interest. At the same time, he would have to be content with qualitative assessments of tissue metabolic parameters for regions outside the selected ROIs.

Parametric imaging, on the other hand, maps a metabolic parameter of interest at each pixel of the image. The basic approach is to fit a metabolic parameter to the underlying time series of radio-tracer uptake (also called time-activity curve) at each pixel (Figure 2a). Doing so over all pixels and imaging the resulting pixel-wise fitted biologic parameter values would give us a parametric image such as that displayed in Figure 2b which is an estimate of the glucose metabolic rate in the brain of the patient scanned in the study presented in Figure 1. It is seen that the glucose metabolic rate is high in the peripheral regions of the brain where most of the gray matter is present. The pixel-wise estimates of the parameter are also somewhat high in the lower left-of-central region of the brain where the patient was known to have a tumor.

1.2. Variance Estimation in Parametric Images

The full quantitative potential of PET can be realized if it is possible to draw scientific inferences from these parametric images. To this end, in recent years, there has been considerable attention directed to the analysis of multi-subject cerebral activation studies using [O-15]-water (Friston et al., 1991; Worsley et al., 1992). Such studies are interesting in order to determine, for instance, how the brain processes different cognitive tasks and functions. In a clinical setting however, there is a practical need for inference tools to guide diagnostic decisions from single-patient studies (Heiss, et al., 1993; Heiss, et al., 1993). In this context, Blomqvist et al. (1995) noted the desirability of developing methodology to estimate variances in parametric images. Such mechanisms will permit the evaluation of hypotheses related not only to the mean parameter over regions but also regional heterogeneity measures. As an illustration, consider the case of the glucose metabolic rate of the patient displayed in Figure 2b. As noted, the patient’s estimated glucose metabolic rate is high both in the gray matter as also in the tumor region. In order to aid the radiologist as a diagnostic for his clinical decisions, it may be useful to assess the statistical significance of these estimated values for glucose metabolic rate. The statistical significance of any hypothesis test is based on the assumption that under the null hypothesis, the behavior of the test statistic can be explained in terms of purely random variation. In setting up such a test, estimates of dispersion are needed. Unfortunately however, the numerical methods used to solve the nonlinear formulations in the construction of parametric images make analytic variance formulae intractable. The simulation approach of Haynor and Woods (1989) could theoretically be extended to develop a variation of the bootstrap method of Efron (1982). This would involve simulating inhomogeneous Poisson processes, independent over time, in the observation (sinogram) domain with (time-dependent) mean intensities estimated by the count data, applying image reconstruction and parametric image generation to obtain an ensemble of simulated functional images. The re-sampled parametric images could then be used to estimate the dispersions. This is the natural extension of the parametric bootstrap technique in this setting. Unfortunately however, the cumulative computational burden of the number of reconstruction steps needed in the simulation makes such an approach impractical.

This paper suggests a synthetic simulation approach via the parametric bootstrap executed in the imaging domain. Under idealized projection conditions, each reconstructed PET scan is well approximated by a multivariate Gaussian distribution. The mean of this distribution is estimated by the
reconstructed image. Computationally feasible and accurate dispersion estimates developed in Maitra and O’Sullivan (1995; 1998) and Maitra (1996; 1997) are exploited and the result validated for a realistic range of total expected counts. This model is used to simulate dynamic PET sequences, from each of which biologic parameters are extracted. This yields a bootstrap sample of the functional images, which can be used to assess variability. The advantage of this approach over the one that extends the strategy in Haynor and Woods (1989) is that it eliminates the computationally expensive reconstruction step when simulating from the observation process.

The main contributions of this paper are presented in two sections. Section 2 develops the methodology used in the simulation of dispersion estimates. Section 3 reports on the experiments done to validate the approximate Gaussian distributional assumption of reconstructed PET scans, as well as those done to assess the performance of the suggested methodology. Since the latter is very tedious to evaluate extensively in a two-dimensional PET setup, the suggestions are evaluated on experiments performed on a model one-dimensional problem with reconstruction characteristics similar to PET. Results for a set of diagnostic checks performed in a real-life PET model that incorporates correction factors are also reported. Finally, Section 4 summarizes the contributions of this paper and poses questions for future research.

2. THEORY AND METHODS

2.1. Distribution of a Time-course Reconstructed PET Sequence

The standard reconstruction algorithm in PET for the distribution of radio-tracer in tissue at a fixed time-point is the filtered backprojection algorithm:

\[
\hat{h}_i^b = \sum_{\theta=1}^{n_\theta} \sum_{d=1}^{n_d} e_h(u_i \cos \theta + v_i \sin \theta - d) \gamma_{d,\theta}.
\] (1)

Here \( \gamma_{d,\theta} \) is the reconstruction filter with resolution size \( \text{FWHM} \), \( \lambda = \{ \lambda_i; i = 1, 2, \ldots, I \} \) is the source distribution and \( \hat{h}_i^b \) the corresponding reconstruction.

Theoretically, it can be shown that the asymptotic distribution of the reconstructed PET scan at a fixed time-point under idealized projection conditions is multi-Gaussian (Maitra, 1996; Maitra, 1997). The mean of this distribution is given by,

\[
\hat{\lambda}_i^b = \sum_{\theta=1}^{n_\theta} \sum_{d=1}^{n_d} e_h(u_i \cos \theta + v_i \sin \theta - d) \gamma_{d,\theta}.
\] (2)

which can be estimated unbiasedly by the reconstructed image. Unbiased estimates of the variances can be obtained accurately by applying the methods outlined in Maitra and O’Sullivan (1995; 1998). The building block for this methodology is to first recognize that the convolution step in the filtered backprojection algorithm in Equation (1) given by

\[
\sum_{d=1}^{n_d} e_h(u_i \cos \theta + v_i \sin \theta - d) \gamma_{d,\theta}.
\] (3)

is implemented discretely via Fast Fourier Transforms. To achieve this, the corrected data \( y_{\theta,\theta} \) in each projection angle are convolved with the discrete periodic sequence \( \{ e_i^* \} \), defined by the function \( e_h(\cdot) \) evaluated on a regular-spaced grid in the distance domain, followed by interpolation to obtain the value of (3) at the point \( x = u_i \cos \theta + v_i \sin \theta \). To obtain the interpolated value at \( x \), denote \( \bar{x} \) as the smallest integer less than or equal to \( x \). Then (3) is approximated by the following equation:

\[
\sum_{d=1}^{n_d} e_h(x - d) \gamma_{d,\theta} = (1 - x + \bar{x}) e_i^* \gamma_{\bar{x},\theta} + (x - \bar{x}) e_i^* \gamma_{\bar{x} + 1,\theta}.
\] (4)

Here, \( e_i^* \gamma_{\bar{x},\theta} \) denotes the convolution of the discrete sequence \( e_i^* \) and \( \gamma_{\bar{x},\theta} \) evaluated at \( k \). Incorporating (4) in (1) gives

\[
\hat{\lambda}_i^b = \sum_{\theta} \left\{ (1 - x + \bar{x}) e_i^* \gamma_{\bar{x},\theta} + (x - \bar{x}) e_i^* \gamma_{\bar{x} + 1,\theta} \right\}.
\] (5)

In the above expression, the \( \bar{x} \)'s depend on \( i \) as well as \( \theta \). For notational simplicity, we have suppressed this dependence. Furthermore, the interpolation steps discussed here arise due to discrete convolution used in the reconstruction procedure. They are separate from the interpolation that is used to correct for irregularities in the detector grid. These detector interpolation effects are accounted for by re-weighting raw event data (see O’Sullivan and Pawitan, 1996 for details).

Ignoring the interpolation step in calculating the variances, as done in Alpert et al. (1982), leads to some errors. This is because the interpolation introduces correlations between the filtered data at adjacent distance-bins, for each projection angle. More accurate variance calculations can be obtained by incorporating these effects. To do this in a computationally practical framework, Maitra and O’Sullivan (1995, 1998)
suggest writing the reconstruction filter as a weighted sum of a few Gaussian kernels:

\[ e_h(x) \approx \tilde{e}_h(x) = a_1\phi_{h_1}(x) + a_2\phi_{h_2}(x) + \ldots + a_L\phi_{h_L}(x), \quad (6) \]

where \( \phi_{h_i}(x) \) are mean-zero Gaussian kernels and \( a_1, a_2, \ldots, a_L \) are so chosen that \( \tilde{e}_h(0) = e_h(0) \) and \( \sum_{x} \tilde{e}_h(x) = \sum_{x} e_h(x) = 1 \). The experiments reported there indicate that no more than four Gaussian kernels are needed to accurately produce such a representation of the PET reconstruction filter. This reduces the expressions for the \( \tau \) here, to variance calculations to the sum of a few convolution backprojection-type calculations:

\[
\tau_i^2 = \sum_\theta (1 - x + y)^2 \sigma_i^2 \theta [\xi] + \sum_\theta (x - y)^2 \sigma_i^2 \theta [\xi + 1] \\
+ 2(x - y)(1 - x + y) \\
\times \sum_{l,l',m=1} a_l a_{l'} \phi_{h_{l,l'}} \left[ \frac{1}{2} \right] \phi_{h_{l,l'}} \sigma_{l,l'}^2 [\xi + h_{l,l'}^2]. 
\]

Here, \( \tau_i^2 \) is the variance of the \( i \)th reconstructed pixel value, \( h_{l,l'} = \frac{\sigma_i^2}{h_{l,l'}^2 + h_{l,l'}^2} \), \( h_{l,l'}^{-1} = \sqrt{\frac{1}{h_{l,l'}^2} + \frac{1}{h_{l,l'}^2}} \), \( \tilde{h}_{l,l'} = \sqrt{h_{l,l'}^2 + h_{l,l'}^2} \), and \( \sigma_{l,l'}^2 \) is the variance of the corrected projection data, \( y_{d,\theta} \). Under idealized projection characteristics, and using the Poisson characteristics of the observed counts data, unbiased variances for the reconstructed pixel values can be obtained by replacing the \( \sigma_{l,l'}^2 \) in the above expression by its unbiased estimate, \( \tilde{y}_{d,\theta} \).

The inter-pixel correlation structure is computed by combining the assumption of relative uniformity of the variances of the observed bins with the properties of the Radon transform. This technique, developed in Maitra (1996, 1997) and Maitra and O’Sullivan (1998) is a computationally elegant implementation of the spatially invariant correlation structure of Carson et al. (1993).

The above results can be used to suggest an approximate distribution for a dynamic sequence of reconstructed PET scans. The data recorded by the detector over time are independent. Further, the reconstruction of the radio-tracer uptake at any one time-point, does not involve the observations at any other; hence, the reconstructions are themselves independent over time. This gives

**Result 1** The asymptotic distribution of the time-course reconstructed PET sequence \( \{ \tilde{L}^t(t); t = 1, 2, \ldots, T \} \) is a Gaussian random field.

### 2.2. Synthetic Simulation Approach to Estimating Dispersions

Result 1 implies that for high expected total emissions, the distribution of the time-course reconstructed PET sequence can be approximated by a Gaussian random field. This is used to construct a practical modification to the re-sampling scheme outlined earlier. The exact implementation is as follows:

1. Obtain a time-course reconstructed image sequence of radio-tracer uptake from the PET study. Also, obtain the variance estimates of the reconstructed pixel values for each of these scans. Approximate the correlations between the reconstructed pixel values in each scan by the spatially invariant correlation structure developed in Maitra (1996, 1997) or in Maitra and O’Sullivan (1998). From this reconstructed PET sequence, obtain a functional image of the estimated pixel-wise tissue biologic parameters.

2. Simulate from a Gaussian random field with mean estimated by the above reconstructed time-course sequence. The spatially invariant correlation structure means that Fourier methods can be used in the simulation of correlated multivariate Gaussian realizations (see appendix for details). From each simulated PET sequence, obtain pixel-wise simulated images of the desired biologic parameters.

3. Estimate dispersion of the estimated functional image from this bootstrap sample. This approach is practical because it eliminates the cumulative computational overhead of performing many reconstruction steps while obtaining bootstrap estimates of variability.

### 3. Evaluation of Suggested Strategy

#### 3.1. Diagnostic Checks

Diagnostic checks were performed to evaluate the approximation of the distribution of a reconstructed PET scan by the multivariate Gaussian distribution and a spatially invariant correlation structure at realistic total expected emissions rates. There are two levels of approximation here: these are (1) the asymptotic Gaussian distributional assumption for a typical PET scan, and (2) the assumption of a spatially invariant Fourier correlation structure. Both these assumptions need to be tested. To this end, experiments were performed on a set of simulation PET experiments.

#### 3.1.1. Experiments

The model chosen in the diagnostic checks was a version of the Shepp-Vardi-Kaufmann phantom (Vardi, et al., 1985) digi-
The diagnostic checks were performed by comparing the distribution of this statistic with that obtained by summing the reference distribution for the range of counts. The plots in Figure 4a and 4b are generally linear and, as expected, the quality of the linear fit improves with increasing count. However, the slope is lower than unity with increasing count rate. This can be explained by the fact that for higher total expected emissions, the optimal bandwidth required in smoothing the reconstructions for consistency is lower and as reported in several studies (Carson, et al., 1993; Maitra, 1996; Maitra and O’Sullivan, 1998), the dispersions are under-approximated at lower smoothing levels.

To further our understanding of the performance of the diagnostic evaluations, the two-dimensional PET experiments were repeated by fixing the total expected emissions at the highest level ($10^6$) and varying the bandwidth over the range of nine corresponding values used in the previous experiments. The plots (Figure 4b) were generally similar to those in Figure 4a. However, at higher bandwidths, the upper quantiles of $W_2$ were slightly heavier. The slope of the plot went down, away from unity with decreasing bandwidth, thus strengthening our view that it is the under-approximated dispersions for lower bandwidths that made the diagnostic suspect in the previous experiments. These experiments again underline the need for improved schemes for approximating dispersions in reconstructed PET scans; however, the multi-Gaussian distributional approximation to a reconstructed PET scan seems reasonable.

3.2. Variance Estimation in Parametric Images

3.2.1. Mixture Models

The mixture analysis approach (O’Sullivan, 1993; O’Sullivan 1994) to parametric imaging is one of many methods suggested in the literature. Let $\lambda_i(t)$ represent the true source distribution in the $i$'th time-bin at the $i$'th pixel in the PET imaging domain. The vector $\lambda_i(.) = \{\lambda_i(t); t = 1, 2, \ldots, T\}$ is called the true time-activity curve (TAC) at the $i$'th pixel. A $K$-component mixture model represents the $i$'th pixel TAC as a weighted average of $K$ underlying curves (sub-TACs) $\xi_k$, $k = 1, 2, \ldots, K$.

$$\lambda_i(t) = \sum_{k=1}^{K} \pi_{ik} \xi_k(t) \tag{9}$$
For functional imaging, those of the theoretical model are on the abscissa (where the mixing proportions $\pi$'s) correspond to the different tissue types represented in the image and the underlying $\pi$'s indicate the anatomic tissue composition of the underlying pixel.

Parametric imaging maps the metabolic parameter of interest, $\bar{\vartheta}$, at each pixel in the image. The mixture analysis approach fits the metabolic parameter $\vartheta^{(k)}$ to each tissue sub-TAC $\tilde{\xi}_k(\cdot)$ and following (9) regards each pixel biologic parameter as a composition of the component tissue parameters, $\bar{\vartheta}_t = \sum_{k=1}^{K} \pi_k\vartheta^{(k)}$.

### 3.2.1.1. Estimation Algorithms

For functional imaging, the data are a time-course sequence of reconstructed PET scans $\hat{\lambda}^h = \{\hat{\lambda}^h(t); t = 1, 2, \ldots, T\}$. The number of tissue types, $K$, the sub-TACs $\tilde{\xi}_k(\cdot)$, and the mixing proportions $\pi_k$'s have to be determined. $K$ is obtained from anatomic considerations or through clustering or other sophisticated algorithms (O’Sullivan, 1993; O’Sullivan, 1994). Estimation of $\xi$’s and $\pi$’s is usually done alternately to fit the model,

$$\hat{\lambda}^h(t) \sim \sum_{k=1}^{K} \pi_k\tilde{\xi}_k(t); \quad t = 1, 2, \ldots, T. \quad (11)$$

The problem of estimating $\xi$’s, given the $\pi$’s, is a low-dimensional problem and usually robust to the choice of the estimation method. On the other hand, the dimensionality of the $\pi_k$’s is high and so the estimation problem is delicate. Many methods have been proposed: among them is a quadratic (weighted) least-squares algorithm which constrains $\pi_k$’s to belong to the $K$-dimensional simplex.

Figure 4. Quantile-quantile plots of the empirical distribution of $W_2$ generated from the reference distribution against those obtained from simulations obtained from the model. The asymptotic fit is tested (a) for a range of total expected counts, and (b) for a range of bandwidths at the same total expected counts ($10^6$). For both sets of plots, the quantiles of the empirical distribution of $W_2$ are on the ordinate ($y$-axis) while those of the theoretical model are on the abscissa ($x$-axis).
The tissue metabolic parameters $\hat{\vartheta}^{(k)}$'s are estimated from the $\xi_k(t)$'s and the pixel metabolic parameters are estimated following (10):

$$\hat{\theta}_k = \sum_{k=1}^{K} \hat{\pi}_m \hat{\vartheta}^{(k)}$$

(12)

3.2.1.2. Comment Constraining $\pi_m$'s to belong to the $K$-dimensional simplex means that the solutions to $\pi$'s and consequently $\vartheta$'s are numerical in nature. Analytic expressions for the variances are clearly intractable, and even approximate bounds (exploiting, for example, the Cramer-Rao approach) such as those used in non-linear situations are impossible to obtain.

3.2.2. Experiments

Experiments were conducted to assess the performance of the suggested approach for estimating the pixel-wise variances of the functional parameters, $\vartheta$'s. Since it is tedious to perform an extensive performance evaluation in a two-dimensional PET frame-work, evaluations were done in a simplified one-dimensional deconvolution setting with projection characteristics as described in O'Sullivan, et al. (1993). A 6-component mixture model was specified. Since as explained earlier, most of the variability is in the estimation of the mixing proportions, the component sub-time activity curves $\xi$'s (and hence $\vartheta^{(k)}$'s) were known. The relationship between $\xi$'s and $\vartheta^{(k)}$'s was specified by the equation

$$\xi_k(t) = \vartheta(t) \exp \{-h_k t\}; \quad k = 1, 2, \ldots, 6.$$  

(13)

This implies that $\vartheta^{(k)} = \xi_k(0)$. This is called the “amplitude parameter”, $h_k$ is another functional parameter (the “half-life”) but this parameter was not of interest in this experiment. The source distribution $\lambda(\cdot)$ (Figure 5a) was specified using (9) with mixing proportions ($\pi_m$'s) that were blurred step functions (Choudhury and O'Sullivan, 1995). The target functional parameter was defined using the $\pi$'s and the $\vartheta^{(k)}$'s in (10).

Time activity curves over 60 time-points were reconstructed at 216 bins (pixels) from realizations of an inhomogeneous Poisson process in the observation domain (Choudhury and O'Sullivan, 1995). The reconstructions were smoothed by a Gaussian kernel with bandwidth preset to correspond to smoothing parameters that are reasonable for the given total expected emissions. The $\pi_m$'s were estimated from $\hat{\lambda}(\cdot)$ and used to obtain $\hat{\vartheta}$'s.

1000 simulated reconstructions of the TAC were obtained by simulating the observed process and $\hat{\vartheta}$'s were extracted from each $\hat{\lambda}(\cdot)$. Sample pixel-wise standard deviations of these $\hat{\theta}$'s were assumed to be the “ground truth” in our performance evaluations.

Realizations were simulated from the approximate multivariate Gaussian model for the estimated TACs $\hat{\lambda}(\cdot)$. Bootstrap samples of $\hat{\vartheta}$'s were obtained as outlined in Section 2.2 and standard deviations calculated. The experiment was done with bootstrap sample sizes $m=10$, 30 and different total expected emissions and replicated 500 times in order to study the distributional properties of these bootstrapped standard deviations.

The above experiment was performed using an extension of the simulation approach in Haynor and Woods (1989). Sample data sets were simulated in the observation domain followed by reconstruction and mixture analysis to obtain sample parametric data sets from where variances of the parameters were estimated. This simulation strategy is impractical to implement in the two-dimensional PET context; however, in the one-dimensional experiments, it can be used as a benchmark for our synthetic re-sampling scheme, indicating the performance of our strategy when applied to PET.

The suggested modified simulation method for estimating dispersions was also evaluated for estimating the covariances. This was done in terms of the ability to estimate the variances of the mean functional parameter in 40 homogeneous regions of sizes that ranged from 6 to 36 pixels. The locations of these regions are shown in Figure 5b. The true intensity of the source distribution at the fifth time-point is shown in the background. As before, the experiments were performed for different ranges of counts as well as different bootstrap sample sizes.

3.2.3. Results

The results of the experiments conducted to evaluate the modified bootstrap approach are presented here. Figure 6a is a plot of the functional parameter — the “amplitude” — along with a sample estimate obtained using mixture analysis. The suggested method was evaluated in terms of its ability to assess the variance of this estimate. The percent relative absolute bias, averaged over pixels ranged from around 4–5% for all count rates and bootstrap sample sizes. Figure 6b shows a set of pixel-wise bootstrapped standard deviation estimates (points). Here the bootstrap sample size, $m=10$. The “true” standard deviation is shown by means of the broken line in Figure 6b. This was estimated from replicating the experiment 1000 times. The standard deviations were high in regions where the value of the parameter was high. The bootstrapped standard deviation estimates were post-processed by smoothing with the variable-span smoother of Friedman (1984) which uses a local cross-validation scheme to adaptively estimate the resolution size of the smoothing filter. The smoothed estimate (Figure 6b, bold line) gave a better fit. Variability of the estimates was measured by
Figure 5. (a) Perspective plot of the source distribution $\lambda(\cdot)$ used in the experiments. (b) The selected regions (ROI) (shaded bars) and the true source distribution at the fifth time-point (broken line). Size of the shaded bars is proportional to the ROI size.

Figure 6. (a) true amplitude (broken line) and a sample estimate (bold line); (b) true pixel-wise standard deviation (broken line) of the estimated amplitude and its unsmoothed (points) and smoothed (bold line) estimates (10 bootstrap replications).
the average, over pixels, of the mean percent absolute error in estimated standard deviation. Table 1 summarizes the bias and the variability measures of the estimated bootstrap standard deviations for both the synthetic re-sampling approach (left block) as well as the usual re-sampling strategy (right block). There is virtually no difference between either method, suggesting good performance of our approximate re-sampling scheme for variance estimation of parametric images. Further, the percent relative absolute biases are not altered appreciably as a result of the smoothing; however, the variability measures are considerably improved. The bias and variability rates do not differ appreciably for different total expected counts, for the unsmoothed estimates. This points suggests that the unsmoothed estimators. As expected, the error rates decrease with increasing bootstrap sample size.

The errors in estimating standard deviations of the estimated mean functional parameter over the 40 homogeneous regions are presented in Table 2. The variability measures decreased with increasing size of region; a corresponding, albeit slight, phenomenon was also reported for the bias measures. Since summing over larger regions tends to have a smoothing effect, this is expected. However, since the variability measures are still high, this suggests the need for post-processing the estimates.

### 3.3. Incorporating Correction Factors

In our experimental evaluations, we have assumed idealized projection conditions. In other words, the corrected projection data \( \{ y_{d, \theta}; d = 1, 2, \ldots, n_d; \theta = 1, 2, \ldots, n_\theta \} \) is the same as the observed sinogram projection data \( \{ p_{d, \theta}; d = 1, 2, \ldots, n_d; \theta = 1, 2, \ldots, n_\theta \} \). In a real-life PET setting, there are several factors that degrade the observed data in the sinogram domain. As a result, correction factors have to be applied to the data in order to apply the filtered backprojection algorithm in (1). In this section, the performance of the approximation of the distribution of the reconstructed time-course sequence by a Gaussian random field is evaluated through a set of diagnostic checks on a highly realistic PET data set, which includes correction factors for attenuation.

In this setting, the corrected projection data are given by, \( y_{d, \theta} = p_{d, \theta}/A_{d, \theta} \) where \( A_{d, \theta} \) is the correction factor for attenuation in the sinogram bin corresponding to the distance-angle bin \((d, \theta)\). The attenuation correction factors are obtained by carrying out a transmission scan in which the subject under study is surrounded by a ring source containing radio-isotope and then imaged in the tomograph. Relative to the variability in the emission data from the Poisson statistics, the variability on account of estimating these attenuation correction factors is negligible, and so these may be considered to be constant.

### Table 1. Bias and variability measures for smoothed bootstrap standard deviation estimates over different total expected counts and bootstrap sample sizes. The bias measure is the percent relative bias averaged over pixels and the variability measure is the mean relative percent absolute error in estimating standard deviations averaged over pixels. Corresponding measures for unsmoothed estimates are in parenthesis.

<table>
<thead>
<tr>
<th>Counts ((\times 10^5))</th>
<th>Bias</th>
<th>Variability</th>
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<tbody>
<tr>
<td></td>
<td>10 rep</td>
<td>30 rep</td>
</tr>
<tr>
<td>1.02</td>
<td>4.6</td>
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<td>5.1</td>
<td>5.1</td>
</tr>
<tr>
<td>4.10</td>
<td>5.1</td>
<td>4.9</td>
</tr>
<tr>
<td>(5.6)</td>
<td>(3.7)</td>
<td>(27.7)</td>
</tr>
</tbody>
</table>

### Table 2. Bias and variability measures for estimated standard deviations of mean estimated functional parameters over regions and different bootstrap sample sizes. Bias and variability measures are similar to those in Table 1. The reported percentages are averaged over regions of the same size.

<table>
<thead>
<tr>
<th>ROI size ((\text{pixels}))</th>
<th>Bias</th>
<th>Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 rep</td>
<td>20 rep</td>
</tr>
<tr>
<td>6</td>
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<td>2.19</td>
</tr>
<tr>
<td>36</td>
<td>3.18</td>
<td>2.02</td>
</tr>
</tbody>
</table>
for the patient.

In this framework, the pixel-wise variances of the reconstructed PET values can be obtained by using,

$$\sigma_{d,\theta}^2 = \frac{\text{Var}(p_{d,\theta})}{A_{d,\theta}^2}$$

in equation (7). In particular, unbiased variance estimates can be obtained by estimating $\sigma_{d,\theta}^2$ by the corresponding corrected projection data $y_{d,\theta}$ scaled by the appropriate correction factor $A_{d,\theta}$. Since the spatially invariant correlation structure assumes relative uniformity of the variances of the corrected projection data, it remains unchanged.

To test the validity of the assumption that the distribution of the reconstructed time-course sequence can be approximated by a Gaussian random field, a modest set of diagnostic checks similar to those in Section 3.1 were carried out. The ground truth here was the fluoro-deoxyglucose [FDG]-18 uptake image presented in Figure 7a. This was projected onto the sinogram domain. The transmission scan for the same patient presented in Figure 7b was projected onto the sinogram domain to obtain the negative of the logarithm of the attenuation correction factors. Sample realizations were obtained by generating pseudo-random Poisson deviates with mean intensities that were proportional to the product.
the observation domain is displayed in Figure 7c. The data
attenuation correction factors. The total expected counts of
the observed image was set at $2 \times 10^6$. A sample dataset in
the observation domain is displayed in Figure 7d. The data
were then scaled by the attenuation correction factors. The
corrected projection dataset is shown in Figure 7d. For the
given counts, a bandwidth (FWHM) of 3.4 pixels was found
to be reasonable for the reconstruction filter. The reconstruc-
tion corresponding to the sinogram data in Figure 7c is shown
in Figure 7e. 1000 sample realizations were generated in this
way and the pixel-wise variances for the reconstructed
pixel values were computed. These pixel-wise variance
estimates, shown in Figure 7f served as the “ground truth”,
against which the performance of our variance approximation
formula was evaluated. The 1000 realizations were also
used to generate the reference distribution of $W_2$, as defined
in equation (8). Next, the suggested variance formulae in
equation (7) was used after incorporating the changes for the
correction factors to assess the pixel-wise variances. Figure 8a is a plot of the variances obtained using the formula
against that obtained using simulation. The plots indicate
good performance of the approximation formula. Figure 8b
plots the quantiles of the reference distribution of $W_2$ against
the quantiles of the reference distribution obtained by sum-
ning up the corresponding squared coordinates of sample re-
alizations generated from a multi-Gaussian distribution with
zero-mean and unit variance and correlation structure given
by the spatially invariant structural assumption. The plot
indicates linearity; however, the slope is considerably lower
than 1. This indicates good performance of the approximate

of the sinogram projection of the FDG-18 uptake with the
attenuation correction factors. The total expected counts of
the observed image was set at $2 \times 10^6$. A sample dataset in
the observation domain is displayed in Figure 7c. The data
were then scaled by the attenuation correction factors. The corrected projection dataset is shown in Figure 7d. For the
given counts, a bandwidth (FWHM) of 3.4 pixels was found to be reasonable for the reconstruction filter. The reconstruction corresponding to the sinogram data in Figure 7c is shown in Figure 7e. 1000 sample realizations were generated in this way and the pixel-wise variances for the reconstructed pixel values were computed. These pixel-wise variance estimates, shown in Figure 7f served as the “ground truth”, against which the performance of our variance approximation formula was evaluated. The 1000 realizations were also used to generate the reference distribution of $W_2$, as defined in equation (8). Next, the suggested variance formulae in equation (7) was used after incorporating the changes for the correction factors to assess the pixel-wise variances. Figure 8a is a plot of the variances obtained using the formula against that obtained using simulation. The plots indicate good performance of the approximation formula. Figure 8b plots the quantiles of the reference distribution of $W_2$ against the quantiles of the reference distribution obtained by summing up the corresponding squared coordinates of sample realizations generated from a multi-Gaussian distribution with zero-mean and unit variance and correlation structure given by the spatially invariant structural assumption. The plot indicates linearity; however, the slope is considerably lower than 1. This indicates good performance of the approximate

Gaussian distributional assumption. As before, the fact that the slope is considerably less than unity (0.84) makes the spatially invariant correlation structural assumption suspect. The fact that its performance is poorer at a higher bandwidth than it is at the lower bandwidths in Figure 4 points to the possibility that the approximation to the correlation structure worsens with the inclusion of correction factors: however, the variance approximations and the Gaussian distributional assumptions seem reasonable.

4. DISCUSSION

The main contribution of this paper is a practical approach
to variability assessment in parametric images obtained from
dynamic sequences of reconstructed Positron Emission To-
mography (PET) scans. The approach hinges on the approxi-
mation of the distribution of the reconstructed PET sequence
by a Gaussian random field. The dispersions are specified by
the Fourier methods outlined in Maitra (1996) and Maitra and
O’Sullivan (1997). Diagnostic checks were performed to test
the validity of our suggestion, in the context of simulation
PET experiments. These were also done for a model which
incorporated correction factors for attenuation. Further, a
one-dimensional analogue of the PET reconstruction problem
was used to evaluate the performance of the approach in
estimating the variances of the estimated parameters, with
encouraging results. Though the focus has been the estima-
tion of pixel-wise variances of parametric images using the
mixture analysis of O’Sullivan (1993, 1994), the technique
is general enough to be applied to variance assessment in
parametric images obtained by approaches other than mixture
analysis.

A number of issues remain to be addressed. As seen in the
experiments, the estimation process can be improved by post-
processing the estimated variances. The crude smoothing
algorithm we have used does not perform well in the presence
of correlated coordinates, which is very likely in our case.
Hence, the obtained error rates may potentially be decreased
by a more sophisticated choice of smoothing parameter.
Another question of interest is determining the number of
bootstrap samples. Further, the diagnostic tests indicate that
there is need for better dispersion estimation procedures,
especially at lower bandwidths. An attraction of the Fourier
method of estimating correlations is the computational effi-
ciency in generating correlated data — such an approach is
not necessarily possible even in the one-dimensional model
where we have accurate correlation computation procedures
(Maitra, 1995; 1996). Hence, there is need for developing
better dispersion estimation procedures, and also efficient
simulation procedures that can generate data with similar
correlation structures. Moreover, the synthetic variance esti-
mation strategy was evaluated here within the frame-work of a one-dimensional model. It is tedious and perhaps computationally impractical to perform extensive evaluations using a two-dimensional PET phantom. However, it may be possible to evaluate the method in a limited frame-work on real-life PET scans, and this remains an issue for further work. Finally, with the increasing use of three-dimensional scanners, modest moves are beginning to be made in the direction of using these reconstructions for quantitative purposes. Extending the suggested technique to such settings would be invaluable for diagnosis. Thus, while this seems a promising new technique towards variability estimation in functional images, a number of questions remain to be investigated. To this end, a promising beginning with tremendous potential can be said to have been made.

ACKNOWLEDGEMENTS

This research was supported in part by the National Institutes of Health grant CA-57903 at the University of Washington, Seattle, USA. I thank Professor Alex Spence and Mr Mark Muzi at the University of Washington Medical Center, Seattle, USA for providing the datasets in Sections 1 and 3.3. These came from a study supported by NIH under the grant CA-42045. In addition, I thank Professor Finbarr O’Sullivan, my dissertation advisor in the Department of Statistics at the University of Washington, for introducing me to the problem and for the many hours of helpful advice and invaluable insights that I have received from him. Some of the routines used in the one-dimensional experimental evaluations were written by Kingshuk Roy Choudhury of the Department of Statistics at the University of Washington: his help is gratefully acknowledged.

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A. APPENDIX: FOURIER SIMULATION METHODS

In matrix notation, the reconstruction equation can be expressed as

\[ \hat{\lambda}^h = S_h(K'K)^{-1}K'y \]  

(14)

where \( y \) is the corrected projection data, \( K \) is the discretized version of the Radon transform, and \( S_h \) represents the smoothing operation of resolution size (FWHM) \( h \) that is applied to the raw reconstructions in order to obtain acceptable solutions (O’Sullivan, et al., 1993). Under the assumption of relative uniformity of variances of the observed \( y \)'s, it can be shown (Maitra, 1996; Maitra 1997; Maitra and O’Sullivan, 1997) that the reconstruction \( \hat{\lambda}^h \) has a spatially invariant correlation structure given by

\[ \text{Corr}(\hat{\lambda}_i^h, \hat{\lambda}_j^h) = \frac{\Psi_h(i-j)}{\Psi_h(0)}, \]  

(15)

where \( \Psi = \{C_h(0),C_h(1),\ldots,C_h(I)\} \) is the first row of the approximately Fourier matrix \( S_h(K'K)^{-1}S_h \).

Let \( Z = \{Z_1, Z_2, \ldots, Z_I\} \) be independent standard Gaussian random variables. Denote \( \hat{Z} \) and \( \hat{\Psi} \) as the corresponding Fast Fourier transforms of \( Z \) and \( \Psi \), respectively. \( \hat{\Psi} \) is real-valued and positive, and so is \( \hat{\Psi} = \sqrt{\hat{\Psi}} \). Defining \( B_h \) as the the matrix formed by the rows obtained by permuting the inverse Fourier transform of \( \Psi \), we get \( B_hB_h^T = S_h(K'K)^{-1}S_h \). Let \( X = \{X_1, X_2, \ldots, X_I\} = B_hZ \). Then \( X \) can be readily obtained from \( Z \) by discrete convolution with \( \hat{\Psi} \). This step can be achieved via Fast Fourier transforms. Further, \( X \) forms a set of correlated zero-mean, unit-variance Gaussian variables with the desired correlation structure. Let \( R_i = \hat{\lambda}_i^h + \hat{\tau}_iX_i \), where \( \hat{\tau}_i \) is the variance estimate of \( \hat{\lambda}_i^h \) as detailed in this paper. Then \( R = \{R_1, R_2, \ldots, R_I\} \) is a realization from the asymptotic distribution of \( \hat{\lambda} \). The realizations are readily simulated because of the Fast Fourier Transforms used in obtaining correlated realizations.