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Wavelet Denoising in Voxel Based Parametric Estimation of Small Animal PET Images: A Systematic Evaluation of Spatial Constraints and Noise Reduction Algorithms

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Abstract

Voxel based estimation of PET images, generally referred to as parametric imaging, can provide invaluable information about the heterogeneity of an imaging agent in a given tissue. Due to high level of noise in dynamic images, however, the estimated parametric image is often noisy and unreliable. Several approaches have been developed to address this challenge, including spatial noise reduction techniques, cluster analysis, and spatial constrained weighted nonlinear least square (SCWNLS) methods. In this study, we develop and test several noise reduction techniques combined with SCWNLS using simulated dynamic PET images. Both spatial smoothing filters and wavelet based noise reduction techniques are investigated. In addition, 12 different parametric imaging methods are compared using simulated data. With the combination of noise reduction techniques and SCWNLS methods, more accurate parameter estimation can be achieved than either of the two techniques alone. A less than 10% relative root-mean-square-error is achieved with the combined approach in the simulation study. The wavelet denoising based approach is less sensitive to noise and provides more accurate parameter estimation at higher noise levels. Further evaluation of the proposed methods is performed using actual small animal PET datasets. We expect that the proposed method would be useful for cardiac, neurological and oncologic applications.

Keywords

parametric imaging; small animal imaging; PET; wavelet denoising

1. Introduction

Positron emission tomography (PET) is a quantitative imaging technique capable of measuring the spatial and temporal distribution of an injected radiopharmaceutical in vivo. Due to the recent technological advances, PET has been brought into biological and preclinical animal research with the development of dedicated small animal scanners (Tai *et al.*, 2005; Missimer *et al.*, 2004; Seidel *et al.*, 2003; Knoess *et al.*, 2003). The improved spatial resolution at approximately 1.5 mm (Tai and Laforest, 2005) enables the study of

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small animals such as rats and mice using a wide variety of positron-emitting tracers. This noninvasive imaging technique allows the investigation of normal as well as pathological processes in real time and over an extended period for the same animal (Tai and Laforest, 2005). Combined with kinetic modeling, quantitative measurements can be made in vivo for a variety of physiological and/or biological phenomenon including glucose metabolism (Weber *et al.*, 2000), receptor binding (Alexoff *et al.*, 2004; Bremner *et al.*, 2000), as well as oncological problems (Castell and Cook, 2008).

When kinetic analysis is performed on a voxel by voxel basis, micro parameters that characterize the delivery, transport and biochemical processes can be estimated for each voxel to yield what's known as parametric images. The noisy nature of PET images, however, presents a major challenge for the accurate estimation of parametric images. As such, a direct voxel by voxel kinetic modeling will generate large variations in the estimated parameter values which do not reflect the true spatial distribution of the physiological and/or biochemical behavior of the tissue (Alpert *et al.*, 2006; Kimura *et al.*, 2006; Layfield and Venegas, 2005; Zhou *et al.*, 2002). While simple smoothing in the parameter space can alleviate noise, it is achieved with the loss of spatial resolution. Region-of-interest (ROI) based kinetic analysis also reduces the impact of noise, nevertheless, the heterogeneity within the selected ROI is lost, and there is always the question of how to define the ROI objectively. Traditionally, graphical approaches such as Patlak analysis (Patlak *et al.*, 1983), for irreversible tracer studies, and Logan plot (Logan *et al.*, 1990), for reversible binding tracers, have been applied at the voxel level. These approaches, however, are limited to the estimation of uptake rates or distribution volumes and neglect the estimation of physiologically-motivated micro-parameters. To improve the parametric image estimation, Zhou *et al.* proposed to include a constraint based on ridge regression theory (Hoerl and Kennard, 1970, 2000) that penalizes the spatial variations in micro-parameters (Zhou *et al.*, 2003; Zhou *et al.*, 2002; Zhou *et al.*, 2001).

The application of denoising techniques may further facilitate parametric imaging. In particular, wavelet transform (Ingrid, 1988; Mallat, 1989) is a powerful mathematical tool which has been applied to several aspects of biomedical imaging research (Unser *et al.*, 2003) including image denoising (Weaver *et al.*, 1991; Pizurica *et al.*, 2003) and PET imaging applications (Turkheimer *et al.*, 1999; Millet *et al.*, 2000; Alpert *et al.*, 2006; Shidahara *et al.*, 2007; Shih *et al.*, 2005). Clustering, a technique that groups voxels together based on their time activity curves, has also been applied to suppress noise for kinetic analysis (Kimura *et al.*, 1999; Zhou *et al.*, 2002; Layfield and Venegas, 2005). This approach can be further improved by introducing a component representation model (CRM) (O'Sullivan, 1994), which assumes that each voxel can be expressed linearly in terms of the components, therefore, the parameter values for each voxel can be approximated by the linear combination of the parameter values for the components defined by the clustering procedure (Zhou *et al.*, 2002). In addition, spatial smoothing based techniques can also reduce the noise in the estimated kinetic parameters, and can potentially be integrated into the parametric imaging procedure.

While considerable work has been done to improve parametric image estimation, in particular in large animal and human PET imaging, limited work has been done to validate

voxel-wise kinetic analysis of rodent small animal PET images. In this work, we develop and validate a robust parametric imaging approach which can be applied to a variety of data sets, including small animal image datasets. Specifically, noise suppression techniques such as wavelet denoising, image space smoothing filters or clustering technique are combined with algorithms which constrain kinetic estimates spatially. Various versions of the abovementioned techniques are implemented and validated using simulated datasets. In doing so, we select the method that produced optimal parametric images for a given set of criteria. It should be noted that, in the simulation study, the blood input function is assumed to be known. In practice, blood input function can be obtained by invasive techniques such as arterial blood sampling or some image based techniques such as factor analysis (Laforest *et al.*, 2005; Su *et al.*, 2007) or a combination thereof (Shoghi and Welch, 2007). Finally, we apply our selected methods for parametric imaging to small animal PET datasets.

2. Methods and Materials

2.1. Data simulation

Monte Carlo simulations are performed to generate multiple sets of dynamic image sequences. The simulation starts from four sets of distinct kinetic parameters (i.e. K_1 and k_2 for the rate of inward and outward transportation of FDG across the capillary membrane, respectively; k_3 for the rate of phosphorylation; and k_4 for the rate of dephosphorylation) calculated based on mouse FDG studies using a 3-compartment model reported in literature (Wu *et al.*, 2007) (Table I). The k_4 values are set to zero for all four sets of kinetic parameters, allowing for objective comparisons between $K_i = K_1 k_3 / (k_2 + k_3)$ obtained from Patlak analysis (Patlak *et al.*, 1983) and parametric imaging. The K_i value characterizes the uptake rate of the radiotracer in the tissue compartment. Therefore in the simulation study described below, only K_1 , k_2 , k_3 and the vasculature component V_f are estimated for each voxel. A digital parametric map of 128 by 128 by 32 with a voxel size of $0.25 \times 0.25 \times 0.75$ mm is created (Fig. 1). The voxel size is comparable to small animal PET images. For example, in mouse FDG studies performed at our lab the images are commonly reconstructed to a voxel size of $0.2 \times 0.2 \times 0.8$ mm. In order to generate a general purpose simulation rather than simulating a particular anatomy, a cubic phantom is created. Four quadrants of the phantom are initialized with the four sets of kinetic parameters listed in Table I. Gaussian random noise with 5% standard deviation is then applied to the parameter values in each voxel, followed by spatial smoothing with a 1.7mm FWHM 3D Gaussian filter consistent with the spatial resolution of the microPET® Focus system (Siemens Medical Solutions USA, Inc.) for ^{18}F based tracer. This smoothed parametric map is used as the basis for generating the dynamic image sequence as well as the ground truth for evaluation of the parametric image estimation accuracy (Fig. 1). From a specific set of parametric values of a particular voxel, the corresponding time activity curve can be calculated using the equation below, derived from differential equations of a 3-compartment model (Phelps, 2004), with k_4 equal to zero and with a vasculature component V_f .

$$C(t) = K_i \cdot \int_0^t C_p(\tau) d\tau + \frac{K_1 k_2}{k_2 + k_3} e^{-(k_2 + k_3)t} \otimes C_p(t) + V_f C_p(t) \quad (1)$$

where C_p is the blood input function, and $\otimes$ indicates convolution. The first two terms corresponds to the tissue compartment tracer concentration and the last term corresponds to the vasculature component. In the simulation, a blood input function obtained from an actual mouse FDG study is used. The blood samples are obtained from the carotid artery at regular intervals, and approximately 5 μ l of blood is removed for each sample (Laforest *et al.*, 2005). The simulated data has a unit of nCi/cc.

To simulate the statistical noise in the image data, Monte Carlo simulations were performed with Poisson random noise applied in the sinogram space. Details of the noise simulation have been previously described (Su *et al.*, 2007). Three levels of noise have been added to the sinogram. The first level, which we refer to as NL1, is calibrated so that the noise level in the simulated dynamic images resembles the noise level in a typical mouse FDG PET study. An example of the time activity curve in a given voxel of the simulated dataset and a small animal PET dataset is shown in Fig. 2 for visual comparison of the noise level. Fifty sets of simulated dynamic image sequences are created at noise level NL1 using Monte Carlo simulation. In order to evaluate the performance of parametric image estimation algorithms at higher noise levels, 50 sets of dynamic image sequences each are also created at 3 and 10 times (NL2 and NL3, respectively) of the noise level of NL1. Validation at higher noise level is important because noise level is dependent upon the type of animals and the radioactive tracer used. In general, rat data have lower signal to noise ratio due to smaller dose per unit mass at similar injection dose level.

2.2. Algorithms

The parametric image estimation process can be separated into two steps. The first step generates initial estimates and the second step performs the spatial constrained weighted nonlinear least square (SCWNLS) fit starting from values derived in the first step while using the original dataset. To obtain the initial parametric estimation, three methods are implemented in this study: weighted nonlinear least square (WNLS) fit applied to the spatially filtered dynamic image data, WNLS fit applied to the wavelet denoised data, or a clustering based technique. A Gaussian filter is applied as the spatial smoothing filter for the first method in this study. The full-width-half-max (FWHM) of the Gaussian filter is empirically determined to be 1.0 mm based on one set of simulation data. For wavelet denoising of the dynamic image datasets, each frame of the dynamic dataset is transformed into the wavelet space using a 3D dual-tree discrete wavelet transform (DTWT) (Kingsbury, 2000; Selesnick *et al.*, 2005). The wavelet denoising MATLAB™ code was obtained from <http://taco.poly.edu/WaveletSoftware/index.html> (using the real 3DTWT version) (Selesnick and Li, 2003). Since dynamic PET data is irregularly sampled in time, with much higher frequencies at the early frames and longer frame durations in later frames, 3D DTWT was applied in the spatial domain. While there might be some concerns about applying 3D DTWT to non-cubic data with a larger slice thickness than in plane voxel size, we chose to do so for additional noise reduction while maintaining smoothness in the z direction. Three levels of wavelet decomposition are performed which generates 84 subbands, and soft thresholding (Weaver *et al.*, 1991) is applied to the wavelet coefficients. The threshold for each band of the wavelet coefficients is calculated individually using the following formula (Shih *et al.*, 2005):

$$\text{Threshold} = (MAD/0.6745) \times \sqrt{2 \log M} \quad (2)$$

where, MAD is the median absolute deviation from zero, M is the size of the matrix. In addition, the first level wavelet coefficients are set to zero due to the fact that the voxel size usually encountered in small animal PET imaging is much smaller than spatial resolution of the scanner, therefore first level wavelet coefficients contain mainly noise. The thresholded wavelet coefficients are then transformed back to the image space to obtain the denoised dynamic image sequence. In the clustering based technique, hierarchical clustering with average linkage is used to obtain components as the basis for the CRM analysis (Zhou *et al.*, 2002).

In the WNLS process, the weighted sum of squares (WSS) is minimized to obtain the parameters for each voxel:

$$WSS = \sum_{i=1}^T \left(\hat{I}_i - I_i \right)^2 \cdot \frac{\Delta_i}{I_i}, \quad (3)$$

$$\hat{I}_i = F(\beta; t_i), \quad (4)$$

where, T is the total number of frames in the dynamic image sequence; $\hat{I}_i$ is the estimated voxel intensity of the i th frame based on the kinetic model F and estimated parameter set β ; I_i is the voxel intensity of the dynamic image sequence; t_i is the frame duration and Δ_i is the mean voxel intensity in frame i , i.e. we assume the variance of the voxel intensity is proportional to the mean voxel intensity in the corresponding frame and inversely proportional to the frame duration.

In the SCWNLS step, a penalizing term similar to what was used in (Zhou *et al.*, 2002) is added to the cost function to regularize the optimization process:

$$Q = \sum_{i=1}^T \left[\left(\hat{I}_i - I_i \right)^2 \cdot \frac{\Delta_i}{I_i} \right] + \sum_{j=1}^P \left[w_j \left(\beta_j - \beta_j^s \right) \right]^2 \quad (5)$$

where, the first term is the weighted sum of squares as defined in equation (3), and the second term is the regularization term. In equation (5), β_j^s is the reference parameter value used as spatial constraints; w_j is the weighting factor for the corresponding parameter. The value of β_j^s is determined by applying a spatial smoothing filter to the current estimation of the parametric image, and P is the number of parameters to be estimated in the kinetic model. The regularization term penalizes the local spatial variation in the parameter space. Two types of spatial smoothing filters are compared in this study: a 3D lowpass finite impulse response (FIR) filter with empirically determined cutoff frequency; and a $5 \times 5 \times 3$ neighborhood filter with each element inversely weighted by its distance from the center. The empirically determined cutoff for the 3D lowpass FIR filter is 1.75 mm. To determine the weighting factor (w_j) for each parameter, two approaches are taken. In the first approach, the weighting factors are determined empirically to be $2e7$ for K_1 , $1.5e8$ for k_2 , $3e7$ for k_3

and $7e6$ for V_f . A fixed weighting factor is used for each parameter regardless of the spatial location. The empirical weighting factors are determined in an iterative fashion using simulated data testing a wide range of values. The initial weighting factors are set in such a way so that the regulatory portion of Q eq. 5 is set to 10% of the least square term based on one set of the simulation data. Then the each weighting factor is varied while keeping others unchanged to choose the best weighting factor. This process is iterated several times, and the final weighting factors (listed above) are selected. In the second approach, the weighting factor was calculated automatically based on the following equation similar to what was used in ref (Zhou *et al.*, 2001):

$$w_j = \frac{WSS_0}{T(\beta_j - \beta_j^s)^2} \quad (6)$$

where, WSS_0 is the weighted sum of squares of direct WNLS for the corresponding voxel. In this second approach, the weighting factor is estimated for each voxel and each parameter individually followed by spatial smoothing of the weighting factors.

To obtain the spatial constrained parameter estimation, SCWNLS is applied iteratively. In each iteration, the weighting factors w and the reference parameters β^s are updated and Q is minimized individually for each voxel and summed over the entire volume. The stopping criterion for the optimization is when the change in total sum of cost over the entire volume is less than 0.1% between two iterations. As noted above, in the SCWNLS step, the original dataset are used for fitting as opposed to the denoised dataset. For both the WNLS and SCWNLS a bounded nonlinear least square algorithm implemented in the MATLABTM function LSQNONLIN is used. The lower bounds of the parameters are set to 0, and the upper bounds of the parameters are set to infinity to ensure the estimated kinetic parameters are positive. In the initial WNLS step, $K_1 = 0.16$ mL/min/g, $k_2 = 0.21$ min⁻¹, $k_3 = 0.09$ min⁻¹ and $V_f = 0.11$ are used to initialize the least square fit.

2.3. Simulation Studies

In the simulation study, 12 different versions of parametric image estimation algorithms (summarized in Table II) are applied to the simulated dynamic image sequences at noise level NL1. The calculated parameters are compared with the ground truth. It should be noted that M11 is essentially a reimplement of Zhou's algorithm (Zhou *et al.*, 2002) in 3D for comparison purpose. In addition, Patlak analysis is applied to the original datasets (M13) to obtain the parameter K_i for each voxel for comparison. To quantify the performance of these different parameter estimation methods, the root-mean-square-error (RMSE) (eq. 7) of the relative difference between the calculated parameter and the ground truth are computed.

$$RMSE = \sqrt{\frac{\sum_{s=1}^N \sum_{i=1}^N \left(\frac{\hat{p}_{si} - p_i}{p_i} \right)^2}{50 \times N}} \quad (7)$$

In eq. 7, $\hat{p}_{si}$ is the estimated parameter p for the i th voxel and the s th simulation; p_i is the corresponding true parameter value; and N is the total number of voxels in the image. Notice the RMSE is defined in a relative sense. The RMSE is calculated for the entire simulation

datasets and all the voxels modeled, therefore s corresponds to the number of simulation datasets generated.

To investigate the parameter estimation accuracy at different noise levels, two algorithms (M5 and M9) are applied to the simulated dynamic image sequences at the higher noise levels (NL2 and NL3) and again compared with ground truth.

2.4. Animal study

In addition to the simulation study, validation of the parametric imaging algorithm is also performed on 60-minute rat and mouse dynamic microPET® (Siemens Medical Solutions USA, Inc.) FDG datasets. Images are reconstructed using the filtered back-projection (FBP) algorithm with a total of 40 frames per dataset. In the animal study, the blood input function is determined using factor analysis based approach with 2 blood samples as constraints (Su *et al.*, 2007). 3D ROI of the cardiac region is defined based on the summed image and parametric image analysis is applied to the myocardium region which is defined based on the factor images obtained from the factor analysis. The 3D ROI for factor analysis is defined on 12 slices with 15,408 $0.2 \times 0.2 \times 0.8$ mm voxels for the rat data, and 5 slices with 2,908 voxels for the mouse data. The maximum diameter of the ROI at the central slice is approximately 9.6 mm for the rat data and 6.4 mm for the mouse data. The 3D myocardial ROI for parametric image estimation contains 12 slices with 12,051 voxels for the rat data, and 5 slices with 2,076 voxels for the mouse data; at the central slice, the outer diameter is approximately 9.6 mm for the rat and 6.4 mm for the mouse, and the inner diameter is approximately 4.8 mm for the rat and 2.8 mm for the mouse. M5 and M9 are then applied to the animal datasets to obtain the parametric images. For fair comparison with Patlak results, we assume the k_4 values to be zero in the modeling process; thus only K_1 , k_2 , k_3 and V_f are estimated.

3. Results

3.1. Simulation studies

Distributions of relative kinetic parameters estimation error using different methods are illustrated using error bars in Fig. 3(a-e). The overall RMSEs and SDs of the relative difference of the estimated kinetic parameters using these methods are reported in Table III. Noise reduction techniques alone, such as spatial filtering (M2) or wavelet based approaches (M7), improve the parameter estimation by reducing the RMSE comparing to direct voxel wise kinetic modeling (M1). However, it is observed that denoising in the absence of SCWNLS (M2, M7) makes the estimation of K_i less accurate in terms of RMSE comparing to direct kinetic modeling for each voxel (M1). SCWNLS alone (M3) also improves the parameter estimation as can be observed by reducing the RMSE, and SCWNLS (M3) does not have a negative impact on the K_i estimation and generates smaller RMSE comparing to M1. The best results in terms of smallest RMSE are obtained by combining denoising techniques and the SCWNLS (M4, M5, M8 and M9), comparing with the other methods. The neighborhood filter (M6 and M10) similar to those used in (Zhou *et al.*, 2002) generates higher RMSEs comparing to lowpass filtering based spatial (M4) constraints. Combining denoising techniques with SCWNLS (M4, M5, M8 and M9) also generates lower RMSEs

and reduced variability (smaller SD) than starting from clustering based approaches (M11 and M12). It is observed that the estimated k_2 and k_3 have larger variances than K_1 , and K_i in terms of the relative difference. The difference between M4, M8 and M5, M9 is the use of an automatic weighting factor estimation approach (M5, M9) instead of an empirical set of weighting factors (M4, M8). Although the results are similar, M5 and M9 have the advantage of being adaptive to noise and can be applied directly across datasets with different noise levels. On the other hand, the empirical weighting factors have to be recalibrated for datasets with different noise levels for optimal results for M4 and M8. Therefore, only M5 and M9 are applied in the noise study and to real animal datasets. Overall, the RMSEs for the kinetic parameters are well within 5% except for V_f , for which the relatively high level of error is partly due to its small absolute value (≈ 0.02) in some of the regions, hence leads to high level of relative difference. The estimated parameters correlate well with the ground truth values (Fig. 4) as the correlation between estimated K_i using M9 and the ground truth K_i is essentially 1.00. Patlak analysis (M13) estimated K_i has a RMSE of 0.0251, which is higher than M5 and M9, but lower than M2 and M7. Wavelet denoising based approach (M9), gives smaller RMSE at higher noise levels in comparison to spatial filtering based technique (M5) (Fig. 5).

3.2. Animal Study

Fig. 6 illustrates a transverse slice of the parametric images obtained using M9 on a FDG rat study. The average estimated parameters for the cardiac region are: $K_1 = 1.108 \pm 0.161$ mL/min/g, $k_2 = 3.855 \pm 0.179$ min⁻¹, $k_3 = 0.375 \pm 0.095$ min⁻¹, $V_f = 0.202 \pm 0.056$. Fig. 7 compares estimated K_i value using M9 and the result obtained from Patlak analysis. The K_i values for the patlak analysis in these animal studies are all based on original data rather than wavelet denoised data. A correlation coefficient of 0.92 was observed between the two sets of results. Fig. 8 illustrates one transverse slice of the parametric images obtained using M9 on an FDG mouse study, the estimated parameters for the cardiac region are: $K_1 = 0.154 \pm 0.077$ mL/min/g, $k_2 = 0.184 \pm 0.124$ min⁻¹, $k_3 = 0.036 \pm 0.014$ min⁻¹, $V_f = 0.405 \pm 0.133$. Fig. 9 compares estimated K_i value using M9 and the result obtained from Patlak analysis. A correlation coefficient of 0.84 is observed between the two sets of results. The kinetic parameters estimated using M5 are in agreement with M9, therefore the result is not presented here.

4. Discussion

Quantitative imaging of physiological parameters using PET and kinetic analysis provides invaluable insight about the underlying functional and biochemical processes in the target tissue. ROI based analysis is a simple way of extracting abovementioned parameters; however, it only provides a global measure of kinetics and neglects the spatial heterogeneity within the region. On the other hand, the metabolic and physiologic behavior of the target region can be quite different from area to area within itself (Henriksson *et al.*, 2007; Wyss *et al.*, 2006; Zhao *et al.*, 2005). In addition, most kinetic models generally assume homogeneous tracer distribution within the volume from where the time activity curve was extracted. When heterogeneity exists, the estimated parameter could be biased (Herholz and Patlak, 1987; Wu *et al.*, 1995; Schmidt *et al.*, 1992). Performing kinetic analysis on a voxel

by voxel basis avoids these shortcomings and generates a set of physiologically-motivated parameters for each voxel. Graphical analysis based approaches (Patlak *et al.*, 1983; Logan *et al.*, 1990; Logan, 2000) have been applied to dynamic PET data at the voxel level, and have the advantage of being relatively simple and computationally inexpensive. They are however, limited to certain macro-parameters. For example, the Patlak analysis is generally used to extract uptake rate constant ($K_i = K_1 k_3 / (k_2 + k_3)$) for FDG or irreversible tracer studies, and the Logan plot is used to extract distribution volumes ($DV = (K_1 / k_2) (1 + k_3 / k_4)$) for reversible ligand-receptor binding studies. Voxel based kinetic modeling, on the other hand, estimates all parameters in the model, with individual parameter each having its own physiological meaning, therefore it provides more detailed information about the underlying physiology and/or biochemistry.

In this work, we demonstrate that noise reduction algorithms such as spatial filtering and wavelet transform improve the robustness of spatially constrained parametric imaging algorithms, in particular SCWNLS. The wavelet based approach is more robust at higher noise level in comparison to Gaussian filtering with a fixed FWHM. When the weighting factors are calculated automatically using equation (6), only the cutoff parameter for the lowpass FIR spatial constraint filter is potentially in need of adjustments. Compared to clustering and CRM based approaches (M11) for initial guesses as used in Zhou *et al.*'s work (Zhou *et al.*, 2002), both the spatial filtering based approach (M4, M5) and wavelet based approach (M8, M9) give lower RMSE and SD. They also avoid the need for choosing a certain number of clusters for clustering and CRM analysis. The drawback is the need to perform WNLS for each voxel, which is more time consuming. In the spatial smoothing based noise reduction approach implemented in this study, the cutoff parameter for the Gaussian smoothing filter is empirically determined at the lowest noise level (NL1) and may need to be adjusted for better results at higher noise levels. The spatial smoothing based noise reduction approach may cause loss of resolution and potentially could provide less accurate initial guesses. In contrast, wavelet based approaches preserve image detail (Unser *et al.*, 2003) and as such are the method of choice in denoising PET images. It is interesting to observe that while denoising techniques alone (M2 and M7) improve the estimation of individual kinetic parameters (K_1 , k_2 , k_3 and V_f) comparing to direct voxel-wise WNLS (M1), they actually result in higher levels of error in the estimated K_i values, and the RMSE values are also higher than the K_i values obtained from Patlak analysis (M13). The increased RMSE in K_i is mainly caused by the bias introduced by the denoising techniques, either Gaussian filtering (M2) or wavelet denoising (M7). Also, K_i estimation is not sensitive to noise; therefore, direct NLS (M1) generated reasonably accurate K_i values. It should be noted that in the SCWNLS step, the original dataset was used instead of the denoised dataset, consequently the biases introduced by denoising is removed, and further improved results are obtained for all parameters including K_i .

Based on this study, it might appear that there is a discrepancy between the close to perfect correlation between estimated K_i values and Patlak analysis observed in simulation study and a less perfect correlation between the two in the small animal studies especially the mouse study. Several factors may contribute to this discrepancy. The simulation data were generated using exactly the same kinetic model used for parameter estimation, the only

difference between simulated TAC and model TAC is noise and K_i is not sensitive to noise. This is most likely the primary reason for the perfect correlation between kinetic modeling based K_i and Patlak based K_i . On the other hand, for real data, the kinetic model is only a simplified model of the truth. In addition, due to the partial volume effect, surrounding tissues which might have different kinetic behavior could contribute to the TAC. This difference of the actual kinetic behavior from the assumed kinetic model used for the modeling process may have led to the less than perfect correlation between K_i values estimated from the two approaches. Also, it should be mentioned that the simulation process may not fully account for scatter and other random events seen in real PET images. A third factor that could contribute to the difference and may explain those points that are far away from the line of identity especially in the mouse study is the fact that a spatial constraint was applied in the modeling approach which penalize the difference of the kinetic parameters from its neighboring region, therefore voxel with distinct kinetic behavior will be penalized, while this effect does not exist in the Patlak analysis voxels are analyzed individually. Based on our observation, most of the voxels that has a large difference in model based K_i and Patlak based K_i are from in the inner boundary of the myocardium. There is a large portion of the signal contributed from blood for this region and the proportion of tissue contribution is relatively low. The higher blood contribution led to higher noise levels in the TACs especially at the earlier portion of the curve. This may also contribute to the difference of the K_i values, since the modeling procedure analyzes the entire TAC curve while the Patlak analysis only fits the later linear portion of the curve.

In this study, we adopt the approach which is evaluated in (Shih *et al.*, 2005) to determine the subband threshold for its simplicity, and we set all of the first level wavelet coefficients to zero since the PET images are reconstructed to a considerably finer voxel size than the spatial resolution of typical scanner. The wavelet technique applied in this study is used as a preprocessing step to reduce the spatial noises in the images with further analysis performed in the image space. Simulation based validation has been performed to establish the threshold value for wavelet denoising in (Alpert *et al.*, 2006), in which wavelet transform is applied to both spatial and temporal domain. In addition, theoretical work exists in developing more advanced wavelet denoising techniques such as (Sendur and Selesnick, 2002). While more sophisticated wavelet denoising techniques may improve the noise reduction, it should be kept in mind that further fine tuning of the kinetic parameters is achieved using the SCWNLS based approach in this study, and WNLS applied to wavelet denoised images only generates the initial guess for the SCWNLS step.

In a very recent work, Shidahara *et al.* applied a parametric imaging technique combining wavelet denoising with nonlinear least square fitting for voxel-wise kinetic modeling of human brain images (Shidahara *et al.*, 2008) and observed improved K_1 and binding potential estimation. This approach is essentially M7 of this study, with some variation in the details of wavelet denoising technique. We observed similar improvements in parameter estimation comparing to direct estimation (M1). It should be emphasized that, the integration of SCWNLS with the wavelet denoising based technique for parametric image estimation (M9) further improved the results in comparison to wavelet denoised (M7) or SCWNLS alone (M3). In addition, due to the improved robustness to noise as we mentioned

earlier, we consider wavelet denoising combined with SCWNLS (M9) to be the optimal approach for parametric image estimation, in particular for small animal PET imaging.

5. Conclusion

In this work we combine noise reduction algorithms and SCWNLS to improve the performance of parametric imaging algorithms for small animal imaging. The combined approach improves the parametric estimation accuracy compared to noise reduction or SCWNLS alone. The wavelet based noise reduction technique is especially favorable at higher noise levels, characteristic of pre-clinical PET scanners. The proposed methods are validated using simulated small animal PET datasets and applied to animal data. Given the robustness of the method, it is applicable to preclinical data and should also be applicable to clinical PET images, although only the former has been validated within.

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Figure 1.

An example slice of the ground truth parameters used in the simulation study.

Figure 2.

Demonstration of animal data voxel level time activity curve (a) and the simulation data voxel level time activity curve (b). It can be seen that due to the vascular fraction, there is a peak at the beginning of the time activity curve. NL1, NL2 and NL3 correspond to the three noise levels in the simulation study from low to high. The magnitude of noise for NL2 and NL3 was 3 and 10 times that for NL1.

Figure 3.

Distributions of relative kinetic parameters estimation error using different methods are illustrated using error bars. A summary of the compared methods is described in Table II. M13 is Patlak analysis applied to original data. Plots (a)-(e) show the parameters K_1 through K_i respectively.

Figure 4. Linear correlation of the estimated K_i values using the M9 comparing to ground truth K_i , r is the correlation coefficient. The noise level for this plot is NL1 which is the lowest noise level in the simulated datasets.

Figure 5.

Kinetic parameter estimation error (RMSE) as a function of noise level in the dataset of two estimation method M5 and M9. (a) K_1 ; (b) k_2 ; (c) k_3 ; and (d) V_f . NL1, NL2 and NL3 correspond to the three noise levels in the simulation study from low to high. The magnitude of noise for NL2 and NL3 was 3 and 10 times that for NL1. See Fig. 2 for visual comparison of the noise level.

Figure 6. Parametric images estimated from a rat FDG study. M9 was used to obtain the result demonstrated here.

Figure 7.

a) K_i images of the rat myocardium using M9 and Patlak analysis. b) Linear correlation of the estimated K_i values using the two methods, r is the correlation coefficient. The K_i parametric image in this figure is obtained using M9 while assuming $k_4 = 0$.

Figure 8.
Parametric images estimated from a mouse FDG study. M9 was used to obtain the result demonstrated here.

(a)

(b)

Figure 9.

a) K_i images of the mouse myocardium using M9 and Patlak analysis. b) Linear correlation of the estimated K_i values using the two methods, r is the correlation coefficient. The K_i parametric image in this figure is obtained using M9 while assuming $k_4 = 0$.

Table I

Kinetic parameter sets used in the simulation study, V_f is the vasculature component. Parameter sets 1 and 2 corresponds to myocardial tissue, and sets 3 and 4 corresponds to brain tissue. The values for $K_I \sim k_3$ were taken from literature (Wu *et al.*, 2007). The V_f value for myocardial tissue were chosen to be within the range of what was used in other studies (0.1 (Sitek *et al.*, 2002) to 0.25 (El Fakhri *et al.*, 2005)); the V_f values for brain tissue were also chosen to be similar to what was used in published studies (Zhou *et al.*, 2002).

	K_I (mL/min/g)	k_2 (min ⁻¹)	k_3 (min ⁻¹)	V_f
1	0.36	0.22	0.16	0.2
2	0.07	0.13	0.10	0.2
3	0.13	0.29	0.07	0.02
4	0.10	0.21	0.05	0.02

Table II

Summary of compartmental model parametric imaging methods.

Methods	Preprocessing	initial estimation methods	Spatial constraint filter	Weighting factors estimation	SCWNLS
M1	none	WNLS	N/A	N/A	No
M2	Gaussian filter	WNLS	N/A	N/A	No
M3	none	WNLS	lowpass	empirical	Yes
M4	Gaussian filter	WNLS	lowpass	empirical	Yes
M5	Gaussian filter	WNLS	lowpass	automatic	Yes
M6	Gaussian filter	WNLS	neighborhood	empirical	Yes
M7	wavelet denoising	WNLS	N/A	N/A	No
M8	wavelet denoising	WNLS	lowpass	empirical	Yes
M9	wavelet denoising	WNLS	lowpass	automatic	Yes
M10	wavelet denoising	WNLS	neighborhood	empirical	Yes
M11 [*]	none	Clustering	lowpass	automatic	Yes (Gauss-Newton)
M12	none	Clustering	Lowpass	empirical	Yes

^{*} This parametric imaging algorithm is a reimplementation of Zhou et al. (Zhou *et al.*, 2002), with different optimization approach from the rest.

Table III

RMSEs and SDs of the relative difference of estimated kinetic values using different methods. See Table II for the different parameter estimation methods. M13 is Patlak analysis of the original datasets.

Kinetic parameters	K_1	k_2	k_3	V_f	K_i
Methods	RMSE/SD	RMSE/SD	RMSE/SD	RMSE/SD	RMSE/SD
M1	0.0854/0.0850	0.187/0.185	0.0877/0.0874	0.222/0.222	0.0151/0.0151
M2	0.0418/0.0403	0.0409/0.0404	0.0352/0.0285	0.112/0.095	0.0511/0.0453
M3	0.0343/0.0333	0.0774/0.0731	0.0352/0.0345	0.0927/0.0926	0.0100/0.0092
M4	0.0178/0.0166	0.0288/0.0283	0.0200/0.0166	0.0613/0.0589	0.0092/0.0090
M5	0.0179/0.0176	0.0329/0.0320	0.0200/0.0183	0.0928/0.0925	0.0076/0.0073
M6	0.0542/0.0540	0.0678/0.0661	0.0435/0.0355	0.222/0.192	0.0272/0.0213
M7	0.0546/0.0536	0.0356/0.0348	0.0585/0.0576	0.134/0.127	0.0843/0.0829
M8	0.0177/0.0174	0.0206/0.0254	0.0257/0.0254	0.0858/0.0857	0.0177/0.0108
M9	0.0175/0.0174	0.0311/0.0309	0.0256/0.0254	0.116/0.116	0.0087/0.0081
M10	0.0557/0.0549	0.0673/0.0652	0.0432/0.0382	0.219/0.189	0.0257/0.0204
M11	0.0697/0.0697	0.138/0.138	0.0750/0.0749	0.214/0.214	0.0146/0.0144
M12	0.0666/0.0638	0.141/0.134	0.0520/0.0520	0.0929/0.0901	0.0132/0.0116
M13					0.0251/0.0251