Wavelet denoising in voxel-based parametric estimation of small animal PET images: a systematic evaluation of spatial constraints and noise reduction algorithms

To cite this article: Yi Su and Koresh I Shoghi 2008 Phys. Med. Biol. 53 5899

View the article online for updates and enhancements.
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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Received 27 March 2008, in final form 14 August 2008
Published 3 October 2008
Online at stacks.iop.org/PMB/53/5899

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 with 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.

1. Introduction

Positron emission tomography 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 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 phenomena 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 is 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. 2001, 2002, 2003).

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 datasets, including small animal image datasets. Specifically, noise suppression techniques such as wavelet denoising, image space smoothing filters or clustering techniques are combined with algorithms which constrain kinetic estimates spatially. Various versions of the above-
Table 1. Kinetic parameter sets used in the simulation study. $V_f$ is the vasculature component. Parameter sets 1 and 2 correspond to myocardial tissue, and sets 3 and 4 correspond to brain tissue. The values for $K_1 \sim k_3$ were taken from the literature (Wu et al 2007). The $V_f$ value for myocardial tissue was 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).

<table>
<thead>
<tr>
<th></th>
<th>$K_1$ (mL min$^{-1}$ g$^{-1}$)</th>
<th>$k_2$ (min$^{-1}$)</th>
<th>$k_3$ (min$^{-1}$)</th>
<th>$V_f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.36</td>
<td>0.22</td>
<td>0.16</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>0.07</td>
<td>0.13</td>
<td>0.10</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>0.13</td>
<td>0.29</td>
<td>0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>4</td>
<td>0.10</td>
<td>0.21</td>
<td>0.05</td>
<td>0.02</td>
</tr>
</tbody>
</table>

mentioned 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, the 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 there of (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 rates 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 three-compartment model reported in the literature (Wu et al 2007) (table 1). 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 × 0.25 × 0.75 mm is created (figure 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 × 0.2 × 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 1. Gaussian random noise with 5% standard deviation is then applied to the parameter values in each voxel, followed by spatial smoothing with a 1.7 mm FWHM 3D Gaussian filter consistent with the spatial resolution of the microPET® Focus system (Siemens Medical Solutions USA, Inc.) for a $^{18}$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 (figure 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 the differential equations of a
three-compartment model (Phelps 2004), with $k_4$ equal to zero and with a vasculature component $V_f$:

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

where $C_p$ is the blood input function, and $\otimes$ indicates convolution. The first two terms correspond 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 μl of blood is removed for each sample (Laforest et al 2005). The simulated data have 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 figure 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 three and ten 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.
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 three and ten times that for NL1.

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 maximum (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 are 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):

\[
\text{Threshold} = \left( \frac{\text{MAD}}{0.6745} \right) \times \sqrt{2 \log M},
\]

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:

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

$$\hat{I}_i = F(\beta; t_i),$$  \hspace{1cm} (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 $\beta$, $I_i$ is the voxel intensity of the dynamic image sequence, $\Delta_i$ is the frame duration, and $\bar{I}_i$ is the mean voxel intensity in frame $i$, i.e. we assume that 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:

$$Q = \sum_{i=1}^{T} \left[ (\hat{I}_i - I_i)^2 \cdot \frac{\Delta_i}{T} \right] + \sum_{j=1}^{P} \left[ w_j (\beta_j - \beta^s_j) \right]^2,$$  \hspace{1cm} (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), $\beta^s_j$ is the reference parameter value used as spatial constraints, and $w_j$ is the weighting factor for the corresponding parameter. The value of $\beta^s_j$ 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 $2 \times 10^7$ for $K_1$, $1.5 \times 10^8$ for $k_2$, $3 \times 10^7$ for $k_3$ and $7 \times 10^6$ 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 that the regulatory portion of $Q$ equation (5) is set to 10% of the least-square term based on one set of the simulation data. Then, 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 (Zhou et al 2001):

$$w_j = \frac{WSS_0}{T \left( \beta_j - \beta^s_j \right)},$$  \hspace{1cm} (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.
Table 2. Summary of compartmental model parametric imaging methods.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Preprocessing</th>
<th>Initial estimation methods</th>
<th>Spatial constraint filter</th>
<th>Weighting factors estimation</th>
<th>SCWNLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>None</td>
<td>WNLS</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>M2</td>
<td>Gaussian filter</td>
<td>WNLS</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>M3</td>
<td>None</td>
<td>WNLS</td>
<td>Lowpass</td>
<td>Empirical</td>
<td>Yes</td>
</tr>
<tr>
<td>M4</td>
<td>Gaussian filter</td>
<td>WNLS</td>
<td>Lowpass</td>
<td>Empirical</td>
<td>Yes</td>
</tr>
<tr>
<td>M5</td>
<td>Gaussian filter</td>
<td>WNLS</td>
<td>Lowpass</td>
<td>Automatic</td>
<td>Yes</td>
</tr>
<tr>
<td>M6</td>
<td>Gaussian filter</td>
<td>WNLS</td>
<td>Neighborhood</td>
<td>Empirical</td>
<td>Yes</td>
</tr>
<tr>
<td>M7</td>
<td>Wavelet denoising</td>
<td>WNLS</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>M8</td>
<td>Wavelet denoising</td>
<td>WNLS</td>
<td>Lowpass</td>
<td>Empirical</td>
<td>Yes</td>
</tr>
<tr>
<td>M9</td>
<td>Wavelet denoising</td>
<td>WNLS</td>
<td>Lowpass</td>
<td>Automatic</td>
<td>Yes</td>
</tr>
<tr>
<td>M10</td>
<td>Wavelet denoising</td>
<td>WNLS</td>
<td>Neighborhood</td>
<td>Empirical</td>
<td>Yes</td>
</tr>
<tr>
<td>M11*</td>
<td>None</td>
<td>Clustering</td>
<td>Lowpass</td>
<td>Automatic</td>
<td>Yes (Gauss–Newton)</td>
</tr>
<tr>
<td>M12</td>
<td>None</td>
<td>Clustering</td>
<td>Lowpass</td>
<td>empirical</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* This parametric imaging algorithm is a re-implementation of Zhou et al (2002), with a different optimization approach from the rest.

To obtain the spatial constrained parameter estimation, SCWNLS is applied iteratively. In each iteration, the weighting factors \( w \) and the reference parameters \( \beta^s \) 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 is used for fitting as opposed to the denoised dataset. For both the WNLS and SCWNLS a bounded nonlinear least-square algorithm implemented in the MATLAB™ function lsqnonlin is used. The lower bounds of the parameters are set to zero, and the upper bounds of the parameters are set to infinity to ensure that the estimated kinetic parameters are positive. In the initial WNLS step, \( K_1 = 0.16 \text{ mL min}^{-1} \text{ g}^{-1} \), \( k_2 = 0.21 \text{ min}^{-1} \), \( k_3 = 0.09 \text{ min}^{-1} \) 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 2) 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 re-implementation 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) (equation (7)) of the relative difference between the calculated parameter and the ground truth is computed:

\[
\text{RMSE} = \sqrt{\frac{\sum_{i=1}^{50} \sum_{s=1}^{N} \left( \frac{\hat{p}_{is} - p_i}{p_i} \right)^2}{50 \times N}}.
\]  

In equation (7), \( \hat{p}_{is} \) 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. Note that 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 min 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 the factor analysis based approach with two blood samples as constraints (Su et al 2007). Three-dimensional 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 15408 0.2 × 0.2 × 0.8 mm voxels for the rat data, and 5 slices with 2908 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 12051 voxels for the rat data and 5 slices with 2076 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 figures 3(a)–(e). The overall RMSEs and SDs of the relative difference of the estimated kinetic parameters using these methods are reported in table 3. Noise reduction techniques alone, such as spatial filtering (M2) or wavelet-based approaches (M7), improve the parameter estimation by reducing the RMSE compared 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 compared 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 compared to M1. The best results in terms of smallest RMSE are obtained by combining denoising techniques and the SCWNLS (M4, M5, M8 and M9), compared with the other methods. The neighborhood filter (M6 or M10) similar to those used in (Zhou et al 2002) generates higher RMSEs compared 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 \( K_i \), 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.
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 2. M13 is Patlak analysis applied to original data. Plots (a)–(e) show the parameters $K_1$ through $K_6$, respectively.

(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 ($\approx 0.02$) in some of the
Figure 4. Linear correlation of the estimated $K_i$ values using the M9 compared 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.

Table 3. RMSEs and SDs of the relative difference of estimated kinetic values using different methods. See table 2 for the different parameter estimation methods. M13 is Patlak analysis of the original datasets and wavelet denoised datasets.

<table>
<thead>
<tr>
<th>Methods</th>
<th>$K_i$ RMSE/SD</th>
<th>$k_2$ RMSE/SD</th>
<th>$k_3$ RMSE/SD</th>
<th>$V_f$ RMSE/SD</th>
<th>$K_i$ RMSE/SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>0.0854/0.0850</td>
<td>0.187/0.185</td>
<td>0.0877/0.0874</td>
<td>0.222/0.222</td>
<td>0.0151/0.0151</td>
</tr>
<tr>
<td>M2</td>
<td>0.0418/0.0403</td>
<td>0.0409/0.0404</td>
<td>0.0352/0.0285</td>
<td>0.112/0.095</td>
<td>0.0511/0.0453</td>
</tr>
<tr>
<td>M3</td>
<td>0.0343/0.0333</td>
<td>0.0774/0.0731</td>
<td>0.0352/0.0345</td>
<td>0.0927/0.0926</td>
<td>0.0100/0.0092</td>
</tr>
<tr>
<td>M4</td>
<td>0.0178/0.0166</td>
<td>0.0288/0.0283</td>
<td>0.0200/0.0166</td>
<td>0.0613/0.0589</td>
<td>0.0092/0.0090</td>
</tr>
<tr>
<td>M5</td>
<td>0.0179/0.0176</td>
<td>0.0329/0.0320</td>
<td>0.0200/0.0183</td>
<td>0.0928/0.0925</td>
<td>0.0076/0.0073</td>
</tr>
<tr>
<td>M6</td>
<td>0.0542/0.0540</td>
<td>0.0678/0.0661</td>
<td>0.0435/0.0355</td>
<td>0.222/0.192</td>
<td>0.0272/0.0213</td>
</tr>
<tr>
<td>M7</td>
<td>0.0546/0.0536</td>
<td>0.0356/0.0348</td>
<td>0.0585/0.0576</td>
<td>0.134/0.127</td>
<td>0.0843/0.0829</td>
</tr>
<tr>
<td>M8</td>
<td>0.0177/0.0174</td>
<td>0.0206/0.0254</td>
<td>0.0257/0.0254</td>
<td>0.0858/0.0857</td>
<td>0.0177/0.0108</td>
</tr>
<tr>
<td>M9</td>
<td>0.0175/0.0174</td>
<td>0.0311/0.0309</td>
<td>0.0256/0.0254</td>
<td>0.116/0.116</td>
<td>0.0087/0.0081</td>
</tr>
<tr>
<td>M10</td>
<td>0.0057/0.0054</td>
<td>0.0673/0.0652</td>
<td>0.0432/0.0382</td>
<td>0.219/0.189</td>
<td>0.0257/0.0204</td>
</tr>
<tr>
<td>M11</td>
<td>0.0697/0.0697</td>
<td>0.1388/0.138</td>
<td>0.0750/0.0749</td>
<td>0.214/0.214</td>
<td>0.0146/0.0144</td>
</tr>
<tr>
<td>M12</td>
<td>0.0666/0.0638</td>
<td>0.1410/0.134</td>
<td>0.0520/0.0520</td>
<td>0.0929/0.0901</td>
<td>0.0132/0.0116</td>
</tr>
<tr>
<td>M13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0251/0.0251</td>
</tr>
</tbody>
</table>

regions, hence leads to high level of relative difference. The estimated parameters correlate well with the ground truth values (figure 4) as the correlation between estimated $K_i$ using M9 and the ground truth $K_i$ is essentially 1.00. Patlak analysis (M13) estimated that $K_i$ has a RMSE of 0.0251, which is higher than M5 and M9, but lower than M2 and M7. The wavelet denoising based approach (M9) gives smaller RMSE at higher noise levels in comparison to the spatial filtering based technique (M5) (figure 5).
Figure 5. Kinetic parameter estimation error (RMSE) as a function of noise level in the dataset of two estimation methods 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 three and ten times that for NL1. See figure 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.

### 3.2. Animal study

Figure 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: $K_1 = 1.108 \pm 0.161 \text{ mL min}^{-1} \text{ g}^{-1}$, $k_2 = 3.855 \pm 0.179 \text{ min}^{-1}$, $k_3 = 0.375 \pm 0.095 \text{ min}^{-1}$ and $V_f = 0.202 \pm 0.056$. Figure 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
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.

original data rather than wavelet denoised data. A correlation coefficient of 0.92 was observed between the two sets of results. Figure 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 $K_1 = 0.154 \pm 0.077 \text{ mL min}^{-1} \text{ g}^{-1}$, $k_2 = 0.184 \pm 0.124 \text{ min}^{-1}$, $k_3 = 0.036 \pm 0.014 \text{ min}^{-1}$ and $V_f = 0.405 \pm 0.133$. Figure 9 compares estimated $K_i$ value using M9 and the result obtained from Patlak analysis. A correlation coefficient of 0.84 is observed between
Wavelet denoising in voxel-based parametric estimation of small animal PET images

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 $k_4 = 0$.

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 above-mentioned 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 \( K_i = K_i k_3/(k_2 + k_3) \) for FDG or irreversible tracer studies, and the Logan plot is used to extract distribution volumes \( DV = (K_i/k_2)(1 + k_3/k_4) \) 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 the 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 \( V_f \) compared 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 are removed, and further improved results are obtained for all parameters including \( K_i \).

When comparing the modeling \( K_i \) and Patlak \( K_i \) estimates, it appears that the correlation is less variable in the simulation, in particular, when comparing the mouse data \( K_i \) correlation to the simulation. Several factors may contribute to this observation. First, the simulated data do not fully account for scatter and other random events seen in real PET images, which needless to say would add variability to real data parameter estimates. Secondly, due to partial volume effects, 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. 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 spatial constraint was applied in the modeling approach which penalizes the difference of the kinetic parameters from its neighboring region; therefore, voxels with distinct kinetic behavior will be penalized. In the Patlak analysis, voxels are analyzed individually. Based on our observation, most of the voxels that have 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 potentially contributing 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 a 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 domains. 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 the wavelet denoising technique. We observed similar improvements in parameter estimation compared 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 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.

Acknowledgments

This project is supported primarily by internal funding to KIS and partly by funding from the NIH/NHLBI grant 5-PO1-HL-13851 and the Washington University Small Animal Imaging Resource (WUSAIR) R24-CA83060.

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