Nonlinear spatio-temporal filtering of dynamic PET data using a four-dimensional Gaussian filter and expectation-maximization deconvolution

This content has been downloaded from IOPscience. Please scroll down to see the full text.
(http://iopscience.iop.org/0031-9155/58/4/1151)

View the table of contents for this issue, or go to the journal homepage for more

Download details:

IP Address: 128.104.3.118
This content was downloaded on 09/12/2013 at 15:45

Please note that terms and conditions apply.
Nonlinear spatio-temporal filtering of dynamic PET data using a four-dimensional Gaussian filter and expectation-maximization deconvolution

J M Floberg and J E Holden

Department of Medical Physics, University of Wisconsin-Madison, 1111 Highland Avenue, Madison, WI 53705 USA

E-mail: jfloberg@wisc.edu

Received 7 September 2012, in final form 2 December 2012
Published 31 January 2013
Online at stacks.iop.org/PMB/58/1151

Abstract

We introduce a method for denoising dynamic PET data, spatio-temporal expectation-maximization (STEM) filtering, that combines four-dimensional Gaussian filtering with EM deconvolution. The initial Gaussian filter suppresses noise at a broad range of spatial and temporal frequencies and EM deconvolution quickly restores the frequencies most important to the signal. We aim to demonstrate that STEM filtering can improve variance in both individual time frames and in parametric images without introducing significant bias. We evaluate STEM filtering with a dynamic phantom study, and with simulated and human dynamic PET studies of a tracer with reversible binding behaviour, [C-11]raclopride, and a tracer with irreversible binding behaviour, [F-18]FDOPA. STEM filtering is compared to a number of established three and four-dimensional denoising methods. STEM filtering provides substantial improvements in variance in both individual time frames and in parametric images generated with a number of kinetic analysis techniques while introducing little bias. STEM filtering does bias early frames, but this does not affect quantitative parameter estimates. STEM filtering is shown to be superior to the other simple denoising methods studied. STEM filtering is a simple and effective denoising method that could be valuable for a wide range of dynamic PET applications.

Online supplementary data available from stacks.iop.org/PMB/58/1151/mmedia

1. Introduction

The interpretation and analysis of dynamic positron emission tomography (PET) data are limited by noise because of the finite duration of time-series image frames and the amount of radiation that can be tolerably given to patients. A number of data filtering techniques have been developed to reduce noise present in PET data, including a variety of filters applied in
the spatial and frequency domains (King et al 1983, 1988, Herholz 1988), as well as filters applied in the wavelet domain (Turkheimer et al 2000, 2003, Lin et al 2001, Alpert et al 2006). Noise has also been controlled in the time domain by a number of methods, including the direct reconstruction of parametric images from sinogram data (Carson and Lange 1985, Meikle et al 1998, Kamasak et al 2005), principal component analysis (Wernick et al 1999), basis function methods (Gunn et al 1997, 2002), and four-dimensional (4D) reconstruction techniques (Lalush and Tsui 1998, Kadrmas and Gullberg 2001, Nichols et al 2002, Walledge et al 2004, Li et al 2007, Verhaeghe et al 2007, Reader et al 2006). These methods have provided possible means of obtaining high resolution parametric images of quantitative physiologic parameters, but are still limited to varying degrees by the complexity of their implementation, and \textit{a priori} assumptions that may not be true, for example the imposition of a limit on the degree to which neighbouring voxels can vary in space and time or the assumption of a model that is valid for the entire imaged object.

The purpose of this work is to introduce a simple nonlinear spatio-temporal filtering process, which we term spatio-temporal expectation-maximization (STEM) filtering, that can be applied to a wide range of dynamic PET tracer studies that couples two established image processing methods: 4D Gaussian filtering followed by expectation-maximization (EM), or Richardson–Lucy, deconvolution (Richardson 1972, Lucy 1974). In principle, the initial 4D filter suppresses noise at a broad range of spatial and temporal frequencies and subsequent deconvolution recovers the frequencies most important to the signal after only a few iterations. EM deconvolution is chosen as it is simple to implement, its properties are well understood, and its implementation does not require the definition and optimization of regularization parameters. The degree and rate of signal recovery will be dependent on the data being filtered. This approach is similar to early termination of EM reconstruction, which improves noise at the cost of degraded spatial resolution. However it provides significantly more noise reduction because the filtering process is 4D, and as we aim to demonstrate it does so while introducing little bias.

In this work we develop the STEM filtering methodology, and aim to illustrate the improvements in variance relative to introduced bias obtained with the method. Its properties are demonstrated both in individual time frames and in parametric images generated with various kinetic analysis methods, using phantom data, and data from simulated and actual human [C-11]raclopride and [F-18]FDOPA studies. STEM filtering is compared to more traditional filtering methods applied in both three and four dimensions.

2. Theory

2.1. Initial filtering

The goal of STEM filtering is to suppress both spatial and temporal noise in the initial filtering step, and then to restore the spatial and temporal frequencies most important to the signal using EM deconvolution. The initial filtering step can be described as:

\[ g_{i,j} = (f \otimes' S)_{i,j} \]

where \( f_{i,j} \) is the original 4D dataset, denoted by the spatial dimension, \( i \), and the image frame (as opposed to time) dimension, \( j \), \( S_{i,j} \) is the 4D filter, \( g_{i,j} \) is the filtered result, and \( \otimes' \) is a modified, shift-variant convolution process.

The temporal component of the convolution takes place in the image frame, not time, domain (figures 1(a) and (b)). Dynamic PET studies typically have non-uniform frames, and filtering in the frame domain is more practical than interpolating to uniform time frames. It is
also potentially advantageous as dynamic tracer studies are sampled more finely at early time points to capture rapid tracer kinetics, and more coarsely at later time points to maximize noise suppression as a tracer reaches equilibrium. Such a sampling scheme facilitates STEM filtering by limiting the change in tracer activity from one frame to the next, making the restoration of the signal by EM deconvolution easier. It also provides the maximum possible degree of noise averaging.

The convolution process we employ is distinct from standard convolution in that the filtering kernel is truncated at the beginning and end of the frame domain, and is hence shift-variant. This approach is required as PET time activity curves (TACs) are not periodic and not compactly supported. The filter is truncated by simply ignoring the elements of the kernel that fall outside the frame domain during the convolution, (figure 1(c)). Any kernel that is truncated must be normalized only by the area falling within the image frame domain. This modified convolution between the dynamic PET data $f_{i,j}$ with $M$ frames indexed by $j = 1, 2 \ldots M$, and the filtering kernel $S_i^j$ with $2N+1$ elements in the image frame domain indexed by $j = -N, -N + 1 \ldots 0 \ldots N - 1, N$, and $2P+1$ elements in the spatial domain indexed by $i = -P, P + 1 \ldots 0 \ldots P - 1, P$, can be represented as:

\[
(f \otimes' S)_{i,j} = \frac{\sum_{i'=-P}^{P} \sum_{j'=-N}^{N} f_{i-i'-j} S_{i',j}}{\sum_{i'=-P}^{P} \sum_{j'=-N}^{N} S_{i',j}^j} \tag{2a}
\]

for $j = 1$ to $N$

\[
(f \otimes' S)_{i,j} = \frac{\sum_{i'=-P}^{P} \sum_{j'=-N}^{N} f_{i+i'-j} S_{i',j}}{\sum_{i'=-P}^{P} \sum_{j'=-N}^{N} S_{i',j}^j} \tag{2b}
\]

for $j = N + 1$ to $M - N$

\[
(f \otimes' S)_{i,j} = \frac{\sum_{i'=-P}^{P} \sum_{j'=-N}^{N} f_{i-i'-j-M} S_{i',j}}{\sum_{i'=-P}^{P} \sum_{j'=-N}^{N} S_{i',j}^j} \tag{2c}
\]

for $j = M - N + 1$ to $M$

The modified convolution is performed with a flipped kernel (the same as standard convolution), as the kernel is symmetric and truncated in the exact same manner at the beginning (equation 2a) and end (equation 2c) of the study. As PET images are typically compactly supported in space, no special normalization in the spatial domain is included in equation (2), though it could easily be done if required.
2.2. EM deconvolution

After the initial filtering step, EM deconvolution is performed to recover the frequencies most important to the signal:

\[ y_{n+1}^{i,j} = y_{n}^{i,j} \left( \frac{g_{i,j}}{(y^n \otimes S)_{i,j}} \otimes S_{i,j} \right) \]

where \( y_{n}^{i,j} \) is the STEM filtered result after \( n \) iterations, and \( g_{i,j} \) is the dynamic data after the initial filtering as defined above (equation (1)).

The reduction in noise from the initial filtering step is sustained by terminating EM deconvolution after only a few iterations. Because the initial filter is 4D, it can be made relatively small to limit the degradation of the signal and still reduce noise to a substantial degree. A few EM deconvolution iterations are thus all that is needed to largely restore the temporal and spatial frequencies that dominate the signal, while noise is still largely suppressed.

2.3. STEM filtering parameters

The factors most important to the adequate recovery of signal are the size of the initial filter and the number of EM iterations performed. The selection of the filter’s size can be informed by the temporal and spatial frequencies present in the study being filtered. For most PET tracer studies, the frequencies needed to represent frame activity curves are relatively low (figures 1(b) and 2(b)). We therefore make the size of the 4D filters used in this work relatively large in the frame domain, with a four frame full width at half maximum (FWHM). However, the spatial frequencies present in PET images are relatively high (figures 2(c) and (d)). We therefore limit the spatial dimensions of the 4D filters used in this work to a FWHM approximately equal to the spatial resolution of the scanner being studied (two voxels in the \( x \) and \( y \) dimensions, and an equivalent spatial distance in the \( z \) dimension).

Using kernels of this size, we have found that relatively few iterations are required to largely restore the temporal and spatial frequencies most important to the signal. Example frequency spectra from a from a noise-free [C-11]raclopride study before and after STEM filtering show that most temporal and spatial frequencies are recovered after ten iterations (figure 2). Note that in this case we have left the first frame unfiltered to improve the temporal frequency spectra. This is not done for the studies below to illustrate the high bias that can be introduced into the earliest frames by STEM, but it is recommended as a possible way to minimize bias. More iterations can be performed to recover even more signal, but this will
come at the cost of increased noise. Likewise, fewer iterations can be performed to reduce noise at the cost of slightly degraded spatial and temporal resolution. This is explored in more detail below.

Different filter sizes can be used for STEM, and this will impact the number of iterations required to obtain a given level of bias (i.e. spatial and temporal resolution) and variance. Fewer iterations will be required to restore the signal if a smaller kernel is used, but the potential degree of noise suppression will not be as great as with larger kernels. Likewise, larger kernels will provide a greater degree of initial noise suppression, but more iterations will be required to restore the signal. The effects of kernel size on STEM filtering are explored in supplemental results. The optimal filter size and number of iterations required will likely ultimately be task dependent.

It is also important to note that the effectiveness of the proposed method arises primarily from the temporal filtering. The fact that the spatial filtering serves primarily to condition the data for the temporal filtering allows the use of minimal spatial filtering, which is thus easily restored in a small number of iterations. Our study of the method with spatial filtering alone showed it to perform little better than simpler more traditional filtering methods.

In the following work, we aim to demonstrate that STEM filtering achieves results that cannot be obtained with more conventional means of filtering. For example, we show that 3 and 4D Gaussian and median filters introduce more bias for an equivalent or lesser degree of noise suppression. These comparisons are meant to put STEM filtering in context in this introductory work. Comparisons to more sophisticated methods are not included here.

3. Methods

3.1. Dual-isotope phantom

A dynamic phantom study was used to characterize the effects of STEM filtering on noise variance, and spatial and temporal resolution. A NEMA IEC body phantom with sphere inserts 10, 13, 17, 22, and 28 mm in diameter was filled with a background of F-18 and spheres were filled with C-11. A PET/CT study was acquired on a Discovery VCT (GE Healthcare), with radionuclide concentrations at the start of the emission scan of 13.1 kBq ml$^{-1}$ for F-18 and 96.4 kBq ml$^{-1}$ for C-11. Emission data were acquired for 150 min and reconstructed into 30 × 5 min frames with filtered back-projection (FBP) using two different filters: a 2D (two-dimensional) ramp filter with a frequency cut-off of 0.104 mm$^{-1}$, and a 3D Hann filter with a frequency cut-off 0.065 mm$^{-1}$. FBP reconstruction was used as it is an analytical method, and bias in the filtered datasets will therefore be due to the filtering methods alone. Corrections for deadtime, normalization, and scatter were applied using the system software, and attenuation correction was applied using the CT data. All reconstructions used an image matrix of 128 × 128 × 47 with voxel sizes of 3.125 × 3.125 × 3.27 mm$^3$ for each frame.

STEM filtering was applied to the ramp reconstruction, the highest resolution images. A 4D Gaussian filter with a FWHM in of four frames in the temporal dimension and a FWHM in each of the three spatial dimensions of 6.25 mm was used for STEM filtering. Twenty EM deconvolution iterations were performed. STEM filtering was compared to four more traditional filtering methods: the Hann filter reconstruction, a 3 × 3 × 3 3D median filter, a 3 × 3 × 3 × 3 4D median filter, and a 4D Gaussian with a FWHM of 3.12 frames in the temporal dimension and 4.88 mm in each spatial dimension. The 4D Gaussian was applied using equations (1) and (2), and its size was empirically determined such that it gives nearly the same noise variance as STEM filtering with ten iterations. The median filters were included in the comparison as they preserve sharper changes in the signal in space and time.
To study the effects of filter size on STEM, two other 4D filters were studied, a filter with a FWHM of 4.69 mm in each spatial dimension and a FWHM of three frames in the temporal dimension, and a filter with a FWHM of 7.81 mm in each of the spatial dimensions and a FWHM of four frames in the temporal dimension. Comparisons between the STEM filters are included as supplemental data (supplementary data are available from http://stacks.iop.org/PMB/58/1151/mmedia).

Bias in both spatial and temporal resolution was assessed using the per cent contrast of the 13 mm sphere to the background at each frame in the study using a volume of interest (VOI) drawn on the CT image and impressed onto the co-registered PET image (57 voxels):

$$\text{Contrast (\%)} = \frac{13 \text{ mm Sphere (Bq/ml)} - \text{Background (Bq/ml)}}{\text{Background (Bq/ml)}} \times 100.$$  (4)

Bias in spatial resolution was evaluated by summing the first 60 min of the study, before and after applying the various filters, and finding the FWHM of a Gaussian fit to the profile of the 10 mm diameter sphere. The coefficient of variation (COV) was assessed at each frame in a large VOI (5471 voxels) drawn in the F-18 background:

$$\text{COV (\%)} = \frac{\sigma_{\text{Background}}}{\mu_{\text{Background}}}.$$  (5)

where $\sigma_{\text{Background}}$ is the standard deviation and $\mu_{\text{Background}}$ is the mean of the large background VOI.

Bias in temporal resolution was evaluated by finding the half-life of [C-11] in a VOI drawn in the 28 mm diameter sphere. The VOI was made small enough to minimize volume averaging effects (31.9 mm$^3$). The half-life of a decay curve averaged over the VOI was calculated by fitting it to a mono-exponential function (equation (6)) using a trust-region-reflective nonlinear least-squares algorithm:

$$C(t) = C_0 \exp(-\lambda t)$$  (6)

where $C(t)$ is the radioactivity concentration at time $t$, $C_0$ is the initial radioactivity concentration of the voxel, and $\lambda$ is the radioactive decay constant.

3.2. [C-11]raclopride and [F-18]FDOPA simulations

3.2.1. Creation of simulated data. Simulated dynamic image datasets for [C-11]raclopride and [F-18]FDOPA were created using a previously published methodology (Floberg et al 2012). Briefly, TACs of the caudate nucleus, putamen, thalamus, white matter, and the frontal, parietal, temporal, and occipital cortex were derived from human studies of patients with Parkinson’s disease and impressed onto the Zubal brain phantom (Zubal et al 1994). The [C-11]raclopride TACs were obtained from a 60 min study with 16 frames of 4 × 1, 3 × 2, 8 × 5, and 1 × 10 min duration. [F-18]FDOPA TACs were obtained from a 90 min study with 18 frames of 2 × 30 s, 3 × 1, 3 × 2, 4 × 5, and 6 × 10 min duration. As is shown below, these sampling schemes are not ideal as the early frames will be biased by STEM filtering. However, we chose the merits of using TACs derived from real human studies with adequate signal-to-noise ratios as opposed to resampling to get noisier, less reliable data, or simulating TACs with model derived rate constants.

Simulated PET images of the phantom were created using published performance information of the Siemens HR+ scanner (Brix et al 1997, Herzog et al 2004). Namely, the phantom was spatially resampled to voxel sizes of 2.2 × 2.2 × 2.45 mm$^3$, smoothed with a 4.39 × 4.39 × 5.10 mm$^3$ Gaussian to approximate spatial resolution, and voxel values were converted from activity concentrations to detected counts. Image frames were then forward projected at 160 different angles spaced at 1.125 degrees using the 2D radon
Nonlinear spatio-temporal filtering of dynamic PET data

The resulting sinograms were multiplied by attenuation sinograms derived from the Zubal phantom and by additional factors accounting for the published sensitivity of the scanner and the expected scatter fraction for the amount of activity used in the simulation. While this does not accurately model scatter, it will reduce the counts in the sinograms to a similar degree as a scatter correction algorithm so that count-dependent Poisson noise is appropriately scaled. Forty noisy realizations of both the [C-11]raclopride and [F-18]FDOPA sinograms were then created by giving each position in the sinograms values drawn from a Poisson distribution scaled by the values at each position in the noise-free sinograms. Noisy sinograms were then reconstructed with either ordered-subset EM (OSEM) ([C-11]raclopride) or FBP ([F-18]FDOPA), after being corrected for attenuation, sensitivity, and scatter fraction. OSEM was performed with eight subsets and either three or eight iterations. FBP was performed with either a ramp filter with a frequency cut-off of 0.171 mm\(^{-1}\), or a Hann filter with a frequency cut-off of 0.227 mm\(^{-1}\). Noise-free sinograms were also reconstructed to serve as standards.

STEM filtering was performed on the eight iteration OSEM reconstruction of the [C-11]raclopride data, and the ramp reconstruction of the [F-18]FDOPA data, as these images will have the best initial spatial resolution. STEM filtering was performed up to 20 iterations using a 4D Gaussian with a FWHM of four frames in the temporal dimension and 4.40 mm in each of the spatial dimensions. STEM filtering was compared to the 3-iteration OSEM reconstruction of the [C-11]raclopride data, the FBP reconstruction with the Hann filter of the [F-18]FDOPA data, and the same 4D median and 4D Gaussian filters used in the dual-isotope phantom study. In this case, the 4D Gaussian filter had a FWHM of 3.43 mm in each spatial dimension, making its width in terms of number of voxels the same as that of the 4D Gaussian used for the dual-isotope phantom. The 3D median filter was not included based on the results of the dual-isotope phantom data.

As with the phantom data, the effects of filter size on STEM were evaluated with two other 4D Gaussian filters, a filter with a FWHM of 3.3 mm in each spatial dimension and a FWHM of three frames in the temporal dimension, and a filter with a FWHM of 5.5 mm in each spatial dimension and a FWHM of four frames in the temporal dimension. The comparisons between the different STEM filters are also included as supplemental data (supplementary data are available from http://stacks.iop.org/PMB/58/1151/mmedia).

3.2.2. Kinetic analysis of the simulated data. Parametric images were generated from the simulated datasets using multiple kinetic analysis methods. Parametric images of the non-displaceable binding potential (BP\(_{ND}\)) were generated from the [C-11]raclopride simulations with the data driven reference region Logan graphical method (Logan et al 1996), and the model-based simplified reference tissue model (SRTM) (Lammertsma and Hume 1996). SRTM was applied using basis functions, a method frequently referred to as receptor parametric mapping (RPM) (Gunn et al 1997). RPM was also used to generate parametric images of R1, the relative delivery of tracer to the tissue versus the reference region. Logan plots were fit from 30 to 60 min with no weighting scheme. Calculation of the abscissa values did not include the term involving the reference region efflux rate constant \(k_2^{REF}\) as it is known to be unimportant for [C-11]raclopride data (Logan 2000). RPM was performed using a fixed \(k_2^{REF}\) (RPM2), determined by a SRTM fit to a TAC averaged over a VOI encompassing the entire striatum (Wu and Carson 2002). The range of the efflux rate constant, \(k_2\), used in RPM2 was 0.035 to 0.2 min\(^{-1}\), with 50 possible values (i.e. 50 basis functions). The minimum and maximum \(k_2\) values were derived from nonlinear least-squares SRTM fits to the TACs used to create the numerical phantom. RPM2 was applied with frames weighted by the square of their duration divided by the number of counts in the frame (Gunn et al 1997). A TAC from a
large cerebellar VOI, obtained prior to STEM filtering, was used as the reference tissue TAC for both the reference region Logan graphical method and RPM2. Parametric images of the normalized uptake rate constant, $K_I^*$, were generated from the [F-18]FDOPA simulations with the reference region Patlak method, using a reference region TAC averaged over both occipital lobes (Patlak and Blasberg 1985, Brooks et al 1990).

3.2.3. Evaluation of simulated data. Bias and variance were measured in the same way for both the simulated time-frame and parametric images. The bias of each voxel in the filtered images was taken as the per cent difference between the mean of that voxel over the 40 noise realizations, $\mu$, and that voxel’s value in the noise-free OSEM or FBP reconstruction, or the noise-free parametric image, $x$:

$$\text{bias} (\%) = \frac{\mu_x - x}{x} \times 100.$$  \hspace{1cm} (7)

Variance was assessed using the COV at each voxel:

$$\text{COV} = \frac{\sigma_x}{\mu_x}$$  \hspace{1cm} (8)

where $\sigma_x$ is the standard deviation of each voxel. The mean bias and variance of voxels in the caudate nucleus (442 voxels) were evaluated. The caudate nucleus was used as it is typically a structure of interest in [C-11]raclopride and [F-18]FDOPA scans, and its relatively small size should help identify bias introduced by the various filtering methods.

3.2.4. Effect of temporal sampling. Simulated data were also used to study the effect of temporal sampling on bias introduced by STEM. Ideally, a study should be sampled such that the per cent change in activity from frame to frame should be similar throughout the study. If TACs have not been sampled at an adequate rate, STEM will have difficulty fully restoring them. As mentioned above and demonstrated below, the human study-derived TACs used in the simulations, particularly those used in the [F-18]FDOPA simulations, are not sufficiently sampled to prevent significant bias in the early frames. In order to illustrate how an increased sampling rate at early frames might reduce bias, the first 2 min of the noise-free [F-18]FDOPA study were effectively resampled by interpolating to 10 s frames. Bias in the original and resampled TACs were then compared after STEM filtering. While the interpolation is an oversimplification of the true behaviour of the [F-18]FDOPA TAC at early frames, it nevertheless illustrates the impact of sampling on the ability of STEM filtering to recover the temporal signal.

3.3. Human [C-11]raclopride and [F-18]FDOPA scans

The performance of STEM filtering on PET studies in humans was evaluated using anonymized archived dynamic image data from two separate research protocols. [C-11]raclopride scans of Parkinson disease patients were acquired on a High Resolution Research Tomograph (HRRT, Siemens Healthcare) scanner at the University of British Columbia. Data were acquired in list-mode over 60 min and reconstructed with 3D ordinary Poisson (OP) OSEM into 16 frames with durations of $4 \times 1$, $3 \times 2$, $8 \times 5$, and $1 \times 10$ min with matrix sizes of $256 \times 256 \times 205$ and voxel sizes of $1.2 \times 1.2 \times 1.23$ mm. [F-18]FDOPA scans, also of patients with Parkinson’s disease, were acquired on an ECAT HR+ scanner (Siemens Healthcare) at the University of Wisconsin-Madison. Data were acquired over 90 min and reconstructed with FBP into 18 frames with durations of $2 \times 30$ s, $3 \times 1$, $3 \times 2$, $4 \times 5$, and $6 \times 10$ min with matrix sizes of $128 \times 128 \times 63$ and voxel dimensions of $2.57 \times 2.57 \times 2.45$ mm. In both cases
Nonlinear spatio-temporal filtering of dynamic PET data

The dual-isotope phantom used to evaluate spatial and temporal resolution and noise variance. (a)–(e) An example frame showing the original FBP ramp reconstruction and the various filters studied. (f) The contrast and (g) the COV over the entire time course for the original reconstruction, the 4D median filter, the 4D Gaussian, and STEM filtering. (h) The per cent bias in the contrast of the 13 mm sphere and (i) the FWHM of the 10 mm sphere in an image averaged from 0–60 min. Both are compared to the average COV of the frames in the first 60 min. The number of STEM iterations performed in (h) and (i) is indicated by the shading (unshaded = 3, vertical shading = 6, horizontal shading = 10, and full shading = 20).

The data were acquired in accordance with human subjects research protocols approved by the respective local institutional review boards, and in accordance with the declaration of Helsinki.

STEM filtering was implemented with up to ten iterations using a 4D Gaussian with a FWHM of four frames in the frame domain, and a FWHM of 2.4 mm in each spatial dimension for the HRRT data and 5.2 mm in each spatial dimension for the HR+ data. All human data were compared to 4D Gaussian smoothing and the 4D median filter, as these methods performed best relative to STEM filtering in the simulation results. The frame and voxel dimensions of the 4D Gaussian were the same as those used in the dual-isotope and simulation studies, giving it a FWHM in the spatial dimensions of 1.9 mm for the HRRT data, and 4.0 mm for the ECAT HR+ data.

Parametric images of the human data were created with the same methods used for the simulated data. Bias in the time-series data was assessed by examining the residuals of filtered TACs relative to the original TACS from large VOIs. Bias in the parametric images was assessed by comparing BPND or $K'_i$ values obtained from TACs averaged over VOIs with BPND or $K'_i$ values obtained from parametric images averaged over the same VOIs. VOIs were drawn on PET images temporally summed over the entire course of the study over the right and left caudate nucleus, the right and left putamen, the thalamus, the frontal cortex, and the temporal cortex. VOIs ranged from 172 voxels for the caudate nucleus from the HR+ image to 8925 voxels for the temporal cortex from the HRRT image (average 2591).

4. Results

4.1. Dual-isotope phantom

The effects of STEM filtering on spatial and temporal resolution and noise variance were evaluated with the dual-isotope phantom. STEM filtering reduced noise substantially and its effects on spatial and temporal resolution were relatively small. It also compares favourably to the other filtering methods studied (figures 3(a)–(e)). Bias of the contrast of the 13 mm sphere...
Table 1. The calculated half-life for each filter of a small VOI drawn in the 28 mm diameter \([^{11}\text{C}]\) filled sphere of the dual-isotope phantom.

<table>
<thead>
<tr>
<th>Filter</th>
<th>Filter</th>
<th>3D Median</th>
<th>4D Median</th>
<th>4D Gaussian</th>
<th>STEM (number of iterations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramp</td>
<td>Hann</td>
<td>20.41</td>
<td>20.62</td>
<td>20.45</td>
<td>21.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20.68</td>
</tr>
</tbody>
</table>

sphere was measured to assess spatial and temporal resolution. When the entire time series is considered, the contrast in the images filtered with 6 STEM iterations is closer to that in the original ramp reconstruction, and is better than that in the images filtered with the 4D median and the 4D Gaussian (figure 3(f)). The COV is lowest following STEM filtering at every frame (figure 3(g)). The contrast bias in an image averaged over the first 60 min of the study and the average COV of individual frames in this time period are lower with STEM after three iterations than with any of the other filters. More STEM iterations can be performed to further reduce bias at the cost of increased noise (figure 3(h)).

When spatial resolution is considered separately, the spatial resolution of the STEM filtered images is not as good as that of the images filtered with the 3D and 4D median filters, but the COV is significantly better. STEM filtering also compares favourably to the 4D Gaussian. After six iterations, the spatial resolution of the STEM filtered image is slightly better than that of the 4D Gaussian filtered image, and the COV is better (figure 3(i)). With regard to temporal resolution, the calculated half-life of TACs from the 28 mm sphere demonstrates that STEM filtering preserves temporal resolution relatively well compared to the other 4D filters studied (table 1). As more STEM iterations are performed, the calculated half-life grows closer to the true half-life.

The size of the kernel used in STEM filtering affects the degree to which noise is suppressed and signal is recovered after a given number of iterations. A smaller kernel will result in less bias in the spatial and temporal resolution of the phantom after fewer iterations, but the maximum possible noise suppression will be less. Likewise, a larger kernel will provide a greater possible degree of noise suppression, but will require more iterations to fully recover the signal (supplemental figure 1 and supplemental table 1 (supplementary data available from http://stacks.iop.org/PMB/58/1151/mmedia)).

4.2. Simulated data results

4.2.1. Simulated time-frame images. The results from the simulated data largely confirm that STEM filtering provides substantial reductions in variance for little introduced bias in the context of PET tracer data. Example voxel TACs from the caudate nucleus of the \([^{11}\text{C}]\)raclopride and \([^{18}\text{F}]\)FDOPA simulations show that the STEM filtered TAC falls closer to the underlying truth than either the original noisy TAC or the 4D Gaussian filtered TAC (figures 4(a) and (d)). With the exception of the earliest frames, the bias in the caudate nucleus of the STEM filtered images is lower than that in the images created with the other filters (figures 4(b) and (e)). Bias is very high in the first frames of the STEM filtered data, is still relatively high in the subsequent 2–3 frames, and diminishes after that. This bias is likely due to inadequate temporal sampling at the earliest frames. Importantly, it does not significantly bias the kinetic parameters studied here, as demonstrated below. The COV in the images filtered with STEM is lower than that achieved with any other filter (figures 4(c) and (f)).

STEM filtering compares favourably to the 4D median and 4D Gaussian filters in the simulated time-frame data. STEM filtering introduces less bias than either of these filters, and provides a greater reduction in the COV than the 4D median filter and a nearly equivalent
Nonlinear spatio-temporal filtering of dynamic PET data

Figure 4. Evaluation of STEM filtering in the simulated data. (a) An example voxel TAC from the caudate nucleus of a [C-11]raclopride simulation shows that the STEM filtered TAC falls much closer to the underlying truth than the original noisy TAC or the TAC filtered with the 4-D Gaussian. (b) For the [C-11]raclopride data, the bias introduced by STEM is lower than that introduced by the other filters, with the exception of the earliest frames. (c) STEM filtering reduces noise as much or more than the other filters at all frames. (d)–(f) The results from the [F-18]FDOPA simulations are consistent with the [C-11]raclopride results. Bias and COV are averaged over voxels in the caudate nucleus.

reduction as the 4D Gaussian. The bias-variance trade-off seen with STEM filtering is even more favourable compared to the spatial denoising methods (OSEM with three iterations and FBP with the Hann filter). An example image slice (t = 50–60 min) from the [C-11]raclopride study showing the bias at each voxel demonstrates the bias introduced by the various filters (figure 5).

4.2.2. Effect of temporal sampling on bias. Resampling the first 2 min of the noise-free [F-18]FDOPA simulation by interpolating to 10 s frames reduces the bias in these frames (figure 6). The early peak in activity better preserved by STEM filtering in the resampled data, and STEM introduces less bias into both the TAC and the Fourier spectrum of the curve.

4.2.3. Simulated parametric images. STEM filtering likewise improves parametric images created from the simulated data, and compares favourably to the other filtering methods studied. In the RPM2 BP\textsubscript{ND} images, STEM provides the greatest reduction of COV relative to bias introduced (table 2). An example slice from the [C-11]raclopride RPM2 images showing the bias in each voxel illustrates that the bias introduced by STEM with ten iterations is less than that introduced by the other filters (figure 5). STEM filtering also compares relatively favourably to the other filters for the RPM2 R1 images, with the exception of the 4D Gaussian, which performs comparably. For the Logan BP\textsubscript{ND} images, STEM filtering gives the greatest reductions in the COV and provides the greatest improvement in the noise-dependent Logan bias (table 2). Finally, for the Patlak $K_t$ images of the [F-18]FDOPA data, STEM filtering reduces noise to a greater degree than all the other filtering methods studied and introduces less bias than all of them but the 4D median filter (table 3).
As more iterations are performed, the bias introduced by STEM is reduced, and the COV of the parameters increases. Interestingly, it appears that for some of the parameters studied (R1 and $K_i$), performing an excessive number of iterations can actually positively bias the data. The number of iterations required to obtain a given trade-off between bias and variance will depend on kernel size. A smaller kernel will achieve a lower level of bias with fewer iterations, but the degree of variance reduction that is possible when fewer iterations are used will be less. Likewise, a larger kernel can provide a greater degree of variance reduction, but will require more iterations to achieve a low level of bias (supplemental tables 2 and 3 (supplementary data available from http://stacks.iop.org/PMB/58/1151/mmedia)).

4.3. Human [C-11]raclopride and [F-18]FDOPA data

The human results largely verify the simulated results. STEM filtering visually appears to blur data less than a 4D Gaussian for a very similar level of noise reduction (figure 7). Likewise,
Figure 7. (a)–(c) Example images from the human [C-11]raclopride study ($t = 30–35$ min) showing the original reconstruction, 4-D Gaussian filtering, and STEM with 10 iterations. (d) Residuals of filtered [C-11]raclopride caudate nucleus TACs relative to the original TAC. (e)–(g) Example slices from the [F-18]FDOPA study ($t = 50–60$ min), and (h) residuals of filtered [F-18]FDOPA caudate nucleus TACs.

Table 2. The average bias and COV of all voxels in the caudate nucleus of the [C-11]raclopride simulated parametric images for the various filtering methods studied. Parametric images of both BP$_{ND}$ and R1 were created with RPM2.

<table>
<thead>
<tr>
<th>Filter</th>
<th>OSEM 8 Iterations</th>
<th>OSEM 3 Iterations</th>
<th>4D Median</th>
<th>4-D Gaussian</th>
<th>STEM (number of iterations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPM2 BP$_{ND}$</td>
<td>1.62</td>
<td>−9.09</td>
<td>−14.9</td>
<td>−6.92</td>
<td>−6.64</td>
</tr>
<tr>
<td>Bias (%)</td>
<td>16.5</td>
<td>9.33</td>
<td>6.53</td>
<td>5.20</td>
<td>3.03</td>
</tr>
<tr>
<td>COV (%)</td>
<td>−5.11</td>
<td>−8.43</td>
<td>−10.0</td>
<td>−4.83</td>
<td>−9.17</td>
</tr>
<tr>
<td>RPM2 R1</td>
<td>15.6</td>
<td>8.09</td>
<td>5.99</td>
<td>4.16</td>
<td>2.78</td>
</tr>
<tr>
<td>Bias (%)</td>
<td>−25.7</td>
<td>−20.7</td>
<td>−16.6</td>
<td>−7.63</td>
<td>−8.60</td>
</tr>
<tr>
<td>COV (%)</td>
<td>21.2</td>
<td>14.9</td>
<td>12.2</td>
<td>8.12</td>
<td>3.78</td>
</tr>
</tbody>
</table>

with the exception of the earliest frames it introduces less bias than either the 4D Gaussian or 4D median filter, shown here with the residuals of caudate nucleus TACs (figures 7(d) and (h)).
The human parametric images likewise show improvements following STEM filtering (figure 8). STEM filtering with ten iterations significantly improves noise over the original reconstructions, and for both RPM2 and Patlak graphical analysis it introduces very little bias into the quantitative kinetic parameters. STEM filtering also largely compares favourably to the other 4D filtering methods studied. The parametric images of the STEM filtered data visually appear to have a similar level of variance as the parametric images of the 4D Gaussian filtered data, and the $B_{\text{PND}}$ and $K_\text{P}$ values obtained from the RPM2 and Patlak parametric images are less biased following STEM filtering than following 4D Gaussian and 4D median filtering (figures 8(d) and (l)).

The Logan parametric images created from the 4D filtered data have a small but noticeable number of voxels with $B_{\text{PND}}$ values that are either very high or negative (figures 8(f) and (g)). As a result, although the 4D filters globally increase the $B_{\text{PND}}$ values in the Logan parametric images, indicating a reduction in the noise-dependent Logan bias, the $B_{\text{PND}}$ values from these images are still biased (figure 8(h)). This is likely due to the very high noise in the HRRT data, which causes some $[C-11]$raclopride curves to trend positive at the end of the study. The 4D filters exacerbate this trend and skew the slopes of the Logan plots (figure 9).
5. Discussion and conclusions

We have introduced a simple but effective nonlinear spatio-temporal filtering method for reducing noise in dynamic PET data. This method, which we term STEM filtering, combines an initial 4D filtering step with subsequent EM deconvolution. The initial filter suppresses noise at a wide range of spatial and temporal frequencies, and the subsequent deconvolution restores the frequencies most important to the signal. This method relies on the fact that the temporal frequencies, and to a lesser extent the spatial frequencies, required to adequately represent a dynamic PET study are relatively low. We have empirically demonstrated that there is thus relatively little loss of spatial and temporal resolution even after only a few EM deconvolution iterations, but substantial reductions in noise.

The effects of STEM filtering on spatial and temporal resolution and noise variance were assessed using a dual-isotope dynamic phantom study (figure 3 and table 1). STEM filtering provides substantial reductions in noise, but it does result in some loss of spatial and temporal resolution. These effects are diminished if more iterations are performed, at the cost of increased noise. STEM filtering compares favourably to the more traditional filters evaluated. For a nearly equivalent level of noise (after ten iterations EM iterations), it degrades the accuracy of the contrast, the spatial resolution, and the estimated [C-11] half-life less than the 4D Gaussian and 3D Hann filters. The 3D and 4D median filters do not degrade the spatial resolution as much as STEM filtering, but they do degrade the contrast to a greater degree, and they do not provide as much of a reduction in noise.

The simulated and human data show that STEM filtering can significantly reduce noise without introducing a great degree of bias in the context of dynamic PET tracer studies. Compared to the other filters studied, STEM filtering with ten iterations provides a nearly equivalent reduction in variance as the 4D Gaussian filter and a greater reduction in variance than the other denoising methods. STEM introduces less bias than all other methods studied at all but the earliest frames (figures 4, 5, and 7).

The bias in early study frames is largely due to inadequate temporal sampling. As a result, there is a large degree of averaging between early frames in the initial filtering process, making it difficult for EM deconvolution to restore the signal. This bias could be reduced if a finer sampling scheme was used, demonstrated here by simply interpolating to a finer temporal
sampling scheme (figure 6). While this is an oversimplification, it nevertheless demonstrates how bias might be reduced with finer sampling. It is important to note that finer sampling of early frames would come at the cost of increased noise in the shorter frames. Additionally, in spite of the bias in early frames seen with coarser sampling, STEM does not significantly bias the quantitative parameters studied here. Alternatively, the original reconstructions of the first one or more frames could simply be restored after STEM filtering.

STEM filtering substantially improves the parametric images studied here (tables 2 and 3, figures 5 and 8). STEM filtering provides significant reductions in the variance of kinetic parameters while introducing less bias than nearly all of the other simple filtering methods studied here. This includes the relative tracer delivery parameter, R1. This implies that although STEM filtering may bias early frames, it does not significantly bias the fits used to obtain kinetic parameters. As with individual time frames, as more iterations are performed the bias introduced by STEM is reduced at the cost of increased variance. For some parameters it does appear as if there is a point at which additional iterations are no longer beneficial in terms of bias reduction, and simply increase variance. While this work has demonstrated that STEM filtering can improve aggregate parameters like BP_{ND} and \( K_i \), these parameters may be relatively insensitive to subtle shift in TACs (e.g. the Logan method is relatively insensitive to the behaviour of the early frames). The potential of STEM to improve the estimation of individual rate constants has not been explored here.

Interestingly, the Logan parametric images created from the filtered [C-11]raclopride human images show a small but noticeable number of voxels with either very high or very negative values. This is likely due to the very high noise in the HRRT data and the tendency of some TACs to either flatten out or increase at the end of the study following STEM filtering (figure 9(a)). Positive bias in low count frames from the OSEM reconstruction may also contribute. These filtered TACs thus no longer follow reversible binding kinetics, and while the resulting Logan plots have less variability between data points, the fitted slopes have either very high or even negative values (figure 9(b)). The other 4D filters have a similar effect. The simulated results show that this effect should not be as pronounced in studies acquired on more conventional PET scanners where the noise is not as extreme (table 2). It would also likely be less significant for tracers whose activity falls more rapidly at the end of the study than [C-11]raclopride.

As a post-processing technique, STEM is very easy to implement, and it is relatively fast. Our implementation of STEM filtering using MATLAB (version 2011b, the MathWorks, Inc.) on a 64-bit Linux workstation with two dual core AMD 270 2 GHz processors and 8 GB of RAM takes 698 s to filter a 128 × 128 × 63 × 18 dynamic dataset with ten iterations. It should also be emphasized that the same implementation of STEM improved variance while introducing little bias for tracers with both reversible and irreversible behaviours, using multiple analysis methods, and for two different reconstructions (FBP and OSEM). STEM filtering may thus prove to be a useful tool for analysing a wide range of dynamic PET data from different imaging centres, acquired with different scanners, and reconstructed with different algorithms.

In this introductory work, we have aimed to illustrate the general bias-variance properties of STEM filtering for typical PET tracer studies. We have therefore focused on a relatively simple implementation of STEM, primarily using one kernel size and the basic EM deconvolution algorithm. Different sized kernels can be used, and the size of the kernel will determine the number of iterations required to achieve a given trade-off between bias and variance (supplemental figure and tables (supplementary data are available from http://stacks.iop.org/PMB/58/1151/mmedia)). The optimal filter size and number of iterations performed will likely be application dependent. Likewise, a more sophisticated deconvolution
algorithm could be used that applies some form of regularization. However, the implementation of STEM studied here using basic EM deconvolution is very simple to implement, and for the data studied here appears to be effective.

We have also shown that STEM filtering compares relatively favourably to simple 3D and 4D denoising methods. In the future, STEM filtering must be considered more fully in the context of the variety of other 4D denoising methods (Rahmim et al 2009). STEM filtering may have some advantages over other 4D methods as it imposes no explicit limits on the degree to which voxels neighbouring each other in space and time are allowed to vary (e.g. a Gibbs prior used in MAP reconstructions or predetermined temporal basis functions). The size of the initial filter and the number of iterations performed in STEM filtering do impose an implicit limit on voxel variability in space and time. However, the use of EM deconvolution will make the effective filter applied by STEM dependent on the data, potentially making it a more data-driven method. STEM filtering may therefore require less optimization for a given dataset or application. Although its performance relative to more sophisticated 4D denoising methods must still be demonstrated, STEM filtering is a simple and effective means of reducing noise in dynamic PET data, and it could prove valuable in a number of imaging applications.

Acknowledgments

We are grateful to Dr Vesna Sossi of the Pacific Parkinson’s Research Centre, University of British Columbia, and Dr Catherine Gallagher of the Department of Neurology, University of Wisconsin-Madison, for access to the image data used in this evaluation. We are also grateful to Christine Jaskowiak, Mark McNall, and Brooke Peters for their assistance in acquiring the phantom data, and to Todd Barnhart and the UW Cyclotron Group for providing the isotopes used in that study. JF gratefully acknowledges the support of the NIH Radiological Sciences Training grant, T32 CA009206, and the University of Wisconsin Medical Scientist Training Program, NIH grant T32 GM008692.

References

Alpert N M, Reilhac A, Chio T C and Selesnick I 2006 Optimization of dynamic measurement of receptor kinetics by wavelet denoising NeuroImage 30 444–51


Logan J 2000 Graphical analysis of PET data applied to reversible and irreversible tracers Nucl. Med. Biol. 27 661–70
Lucy L B 1974 An iterative technique for the rectification of observed distributions Astron. J. 79 745–54
Patlak C S and Blasberg R G 1985 Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data: Generalizations J. Cereb. Blood Flow Metab. 5 584–90
Rahmim A, Tang J and Zaidi H 2009 Four-dimensional (4D) image reconstruction strategies in dynamic PET: beyond conventional independent frame reconstruction Med. Phys. 36 3654–70