Published in final edited form as:

IEEE Trans Radiat Plasma Med Sci. 2018 September ; 2(5): 470–482. doi:10.1109/TRPMS.2018.2844559.

Spatially-Compact MR-Guided Kernel EM for PET Image Reconstruction

James Bland, Martin A. Belzunce, and Sam Ellis

King's College London, St Thomas' Hospital, London, U.K.

Colm J. McGinnity and Alexander Hammers

King's College London & Guy's and St Thomas' PET Centre, St Thomas' Hospital, London, U.K.

Andrew J. Reader

King's College London, St Thomas' Hospital, London, U.K.

Abstract

Positron emission tomography (PET) is a highly sensitive functional and molecular imaging modality which can measure picomolar concentrations of an injected radionuclide. However, the physical sensitivity of PET is limited, and reducing the injected dose leads to low count data and noisy reconstructed images. A highly effective way of reducing noise is to reparameterise the reconstruction in terms of MR-derived spatial basis functions. Spatial basis functions derived using the kernel method have demonstrated excellent noise reduction properties and maintain shared PET-MR detailed structures. However, as previously shown in the literature, the MR-guided kernel method may lead to excessive smoothing of structures that are only present in the PET data. This work makes two main contributions in order to address this problem: first, we exploit the potential of the MR-guided kernel method to form more spatially-compact basis functions which are able to preserve PET-unique structures, and secondly, we consider reconstruction at the native MR resolution. The former contribution notably improves the recovery of structures which are unique to the PET data. These adaptations of the kernel method were compared to the conventional implementation of the MR-guided kernel method and also to MLEM, in terms of ability to recover PET unique structures for both simulated and real data. The spatially-compact kernel method showed clear visual and quantitative improvements in the reconstruction of the PET unique structures, relative to the conventional kernel method for all sizes of PET unique structures investigated, whilst maintaining to a large extent the impressive noise mitigating and detail preserving properties of the conventional MR-guided kernel method. We therefore conclude that a spatially-compact parameterisation of the MR-guided kernel method, should be the preferred implementation strategy in order to obviate unnecessary losses in PET-unique details.

Index Terms

image reconstruction; PET-MR; positron emission tomography

I Introduction

Positron emission tomography (PET) image quality is predominately determined by the level of noise present in the measured projection data. The widespread reconstruction methodology of maximum likelihood expectation maximisation (MLEM) [1], [2], is an iterative algorithm that models the projection data as a set of Poisson random variables. In routine use, MLEM is terminated prior to convergence, with post reconstruction smoothing applied to reduce the impact of noise. However, this simultaneously decreases the contrast recovery and resolution of the reconstructed image. Through the inclusion of prior information into the reconstruction process via maximum *a posteriori* expectation maximisation (MAPEM) [3]–[5] or penalised maximum likelihood (PML) [6] the impact of noise in the reconstructed image can also be reduced. These penalized reconstruction methods can include anatomical information into the penalty term, to encourage similar structures in the reconstructed image. The assumption of structural similarity generally holds in [¹⁸F]FDG brain PET, where the uptake is strongly delineated between the central nervous system's white and grey matter. Recently developed simultaneous PET-MR systems [7] provide a simple workflow for acquiring co-registered MR images which have excellent soft tissue contrast and resolution. Many algorithms have been proposed for exploiting this anatomical information in PET reconstruction including aligning vector gradients between PET and MR data [8], sparsity-based PET reconstruction from MRI learned dictionaries [9], anatomically weighted quadratic penalties (e.g. Bowsher) [10], and maximising the joint entropy or mutual information between the PET and MR data [11], [12], to name but a few. However, these regularization-based methods are highly sensitive to the value of the hyperparameter, which weights the relative importance of the data fidelity term and the penalty term in the objective function. There is no straightforward way for determining the value of the hyperparameter. The appropriate hyperparameter value is also dependent on the count level of the data, and therefore no fixed value can be easily determined for real data.

MR anatomical information has also shown utility in the determination of the attenuation correction image for PET-MR [13]. Multiple methods have been proposed, including segmenting the MR image into tissue types [14], [15], fitting the MR image to an atlas [16], [17], or weighting the contribution between an MR determined value and a joint estimation value in accordance to the MR signal strength [18], [19].

Another means of including prior anatomical information into PET reconstruction is to extract an alternative set of spatial basis functions from the anatomical image, to reparametrise the emission image and the expectation maximisation update equation. The inclusion of prior anatomical information in the form of spatial basis functions has been implemented using dictionary learning [20], supervoxels [21] and the kernel method [22]–[25], all of which have shown excellent noise reduction and detail retention properties. In comparison to other methods, the kernel method (originating from the field of machine learning [26]) is simple to implement, has shown improved ROI quantification performance in comparison to Bowsher [24], and is becoming increasingly popular in the current literature.

The kernel method has shown a wide range of applications for the reconstruction of tomographic data, including static PET [24], [25], dynamic PET [22], [23], [27], reduced dose PET [28], diffuse optical tomography [29] and fluorescence molecular tomography [30], [31]. The kernel method, based on the non-local means filter [32] in image denoising, uses a k nearest neighbour (kNN) search of a specified feature space to determine the voxels which contribute to a given basis function. The feature vectors have previously been derived from either a co-registered MR image [23], [24], [28], or reconstructed images of re-binned PET data [22] (in the case of dynamic data). For dynamic PET reconstruction, a hybridized kernel matrix [27] has also been developed, based on a similarity measure between both PET and MR feature vectors, to reduce the risk of smoothing structures unique to the PET data. More recently the kernel method has been implemented based on the HYPR denoising method [33] for dynamic PET reconstruction [34] with the kernel calculated using the total time frame reconstructed image as a composite image, and for static PET OSEM reconstruction [35] with the composite image derived from the sum of each subset's reconstructed image at the previous iteration.

Of particular focus in this work is the non-local means based MR-guided kernel method, which reparametrises the reconstructed image into spatial basis functions derived from an anatomical MR image. Like the majority of anatomically-guided methods, the MR-guided kernel method is susceptible to over smoothing (suppression) of structures which are unique to the PET data [24], [28]. In this work, two developments for the MR-guided kernel method are presented to improve the recovery of unique PET structures whilst retaining the noise reduction and detail preserving properties. Firstly, the kernel method is adapted to produce more spatially-compact basis functions in uniform MR regions (the very regions that have potential to result in suppression of PET-unique features). These spatially-compact basis functions are comprised of the k nearest neighbour voxels in a composite feature space. The composite feature space is composed of an MR voxel or patch intensity vector and a spatial vector term. This differs to previous MR-guided kernel implementations [23]–[25], [28] that select voxels based purely on the MR voxel or patches intensity vector. The inclusion of the spatial vector leads to the preferential selection of spatially local voxels to contribute to a given voxel's basis function, in particular for regions which have little variation in the MR intensity features. This encourages the formation of more compact basis functions in uniform MR regions (in comparison to the conventional kernel implementation). Secondly, the basis functions are constructed at MR resolution.

This proposed spatially compact kernel method is compared to MLEM, and to multiple implementations of the conventional kernel method with parameters selected to improve its recovery of unique PET structures. This is to assess the proposed kernel methods suppression of unique PET features relative to MLEM, and whether the proposed kernel methods results are achievable through an alternative parameter selection using the conventional kernel. These methods were evaluated for a simulated and real patient dataset (augmented with simulated tumours).

II Theory

MLEM is an iterative algorithm that seeks to maximise the Poisson log likelihood of the parameterised representation of the emission image ($\mathbf{x}$) given the PET projection data ($\mathbf{m}$):

$$L(\mathbf{q}(\mathbf{x}); \mathbf{m}) = \sum_i m_i \log(q_i(\mathbf{x})) - q_i(\mathbf{x}) \quad (1)$$

where

$$\mathbf{q}(\mathbf{x}) = \mathbf{A}\mathbf{x} + \mathbf{r} + \mathbf{s} \quad (2)$$

and $\mathbf{A}$ is the system matrix, $\mathbf{r}$ is a model of the randoms, $\mathbf{s}$ is a model of the scatters and $\mathbf{q}$ is the modelled expectation of the projection data. The Poisson log likelihood is maximised through a reformulation of the problem in terms of a complete data set [2]. Using a surrogate objective function for the complete data log likelihood, a simple voxel-based update equation can be derived that is guaranteed to converge to the maximum of the likelihood:

$$\mathbf{x}^{n+1} = \frac{\mathbf{x}^n}{\mathbf{A}^T \mathbf{1}} \mathbf{A}^T \left(\frac{\mathbf{m}}{\mathbf{A}\mathbf{x}^n + \mathbf{r} + \mathbf{s}} \right) \quad (3)$$

where vector-by-vector division and multiplication are elementwise. Alternatively to using the expectation maximization algorithm to find the maximum likelihood estimation, other methods such as Quasi-Newton algorithms can be selected to achieve faster convergence rates [36]–[39]. The expectation maximization algorithm was employed due to its simplicity and well-established status in the PET reconstruction literature.

A Conventional kernel method

The kernel method [22] is used to reparametrise the voxel based emission image into an alternative set of basis functions. Generally, the emission image can be expressed as a non-linear function (Γ) acting on a set of low dimensional feature vectors ($\mathbf{f}$) associated with each voxel:

$$x_j = \Gamma(\mathbf{f}_j) \quad (4)$$

The conventional kernel method in this work refers to the MR-guided kernel method [23]–[25], [28], for which the feature vectors are formed from the MR voxel values, or patches of MR voxel values. Through transforming the feature vectors to a higher dimensional space, the emission image can be described as a linear function of these higher dimension features [22], [26]:

$$x_j = \mathbf{w}^T \phi(f_j) \quad (5)$$

where $\phi(f_j)$ maps the feature vector to the higher dimensional space. The weighting function $\mathbf{w}$ can also be expressed in this higher dimensional space:

$$\mathbf{w} = \sum_l \alpha_l \phi(f_l) \quad (6)$$

$$x_j = \sum_l \alpha_l \phi^T(f_l) \phi(f_j) = \sum_l \alpha_l \kappa(f_l, f_j) \quad (7)$$

where κ is a kernel, and α is the linear weighting coefficient. The inner product of the high dimension feature vector representation, means that the high dimensional transform does not need to be explicitly defined. The voxel intensities are now expressed as a linear combination of the higher dimensional kernel representation. The matrix representation of (7) is given by

$$\mathbf{x} = \mathbf{K} \boldsymbol{\alpha} \quad (8)$$

where $\mathbf{K}$ is a matrix containing the kernels for all feature vector combinations, the columns of $\mathbf{K}$ are a set of basis functions of the emission image vector ($\mathbf{x}$), which are weighted in accordance with $\boldsymbol{\alpha}$. If the orthogonality between the set of basis functions is reduced, the possible solution space is restricted to a subspace of the full dimensional space, constraining the emission image. There are multiple choices for the kernel, such as the radial Gaussian kernel [22]:

$$\kappa(f_j, f_l) = \exp\left(-\frac{\|f_j - f_l\|^2}{2\sigma_f^2}\right) \quad (9)$$

σ_f is a standard deviation parameter that alters the sharpness of the Gaussian kernel, dependent on the similarity between two feature vectors. The radial Gaussian kernel can be extended to include a positional (z) dependence of the voxels [25]:

$$\kappa(f_j, f_l, z_j, z_l) = \exp\left(-\frac{\|f_j - f_l\|^2}{2\sigma_f^2}\right) \times \exp\left(-\frac{\|z_j - z_l\|^2}{2\sigma_s^2}\right) \quad (10)$$

σ_s is a standard deviation parameter that alters the sharpness of the Gaussian kernel due to the similarity between two positional vectors (z). The kernel matrix is sparsified to remove

dissimilar voxels and disregard long-range voxel correlations. Sparsification is implemented at two levels: the first level of sparsification restricts the voxels that contribute to the basis function of x_j to lie within a chosen spatial neighbourhood (N) of x_j . In the second level of sparsification, each basis function is defined to only contain the k nearest neighbours in feature space. The Euclidean distance between feature vectors f_j and f_l (where the l^{th} voxel lies within the neighbourhood of j) is used to determine the k nearest neighbours in feature space:

$$K_{jl} = \begin{cases} \kappa(f_j, f_l), & f_l \in \text{kNN of } f_j \\ 0, & \text{otherwise} \end{cases} \quad (11)$$

For the conventional kernel method, the feature vector for a given voxel consists of MR intensity values, either from a patch or a single voxel. Each basis function for a given voxel is formed by selecting the voxel's k nearest neighbours in this MR intensity feature space, within a limited spatial neighbourhood. The weighting of each selected voxel contributing to a basis function is calculated by (10). The conventional kernel method will be referred to as the kNN kernel method. This produces basis functions comprised of voxels with similar MR voxel values (or patches values), highlighting structural features present in the prior MR image, within a given neighbourhood. The modelled PET projection data is re-expressed in terms of the kernel matrix and coefficients:

$$q(\alpha) = AK\alpha + r + s \quad (12)$$

This reparameterised image vector is incorporated into the maximum likelihood objective function, producing a reparameterised update equation, referred to as kernelised expectation maximisation (KEM):

$$\alpha^{n+1} = \frac{\alpha^n}{K^T A^T \mathbf{1}} K^T A^T \left(\frac{m}{AK\alpha^n + r + s} \right) \quad (13)$$

The positive constraint enforced by the KEM algorithm further restricts the possible solution space, as only positive combinations of basis functions are permitted, therefore the reconstructed image is further constrained.

B Proposed Kernel Method Implementation

While the conventional implementation of the kernel method shows improved noise reduction and detail preserving properties, it is susceptible to over smoothing unique PET structures. For the recovery of unique PET structures which are situated within a uniform MR region, spatially-compact basis functions are desirable as they can be more readily combined to construct the structures unique to the PET data. However, all previous implementations of the MR-guided kernel method to date [23]–[25], [28] have only used MR intensity patches or single voxels in the feature vector formation, and have failed to

exploit spatial information in the feature vectors. The lack of spatial information in the feature vector description produces diffuse basis functions in uniform MR regions (Fig. 1), which hinders the reconstruction of unique PET structures. While the diffuse nature of the basis functions can be limited by reducing the size of the neighbourhood or by applying a spatial Gaussian kernel to modulate the kernel values (10) (shown in Fig. 1), this undermines the noise and detail preserving benefits of the kernel method for the shared PET-MR structures.

Alternatively, as proposed here, through including a positional term into the feature vector, the voxels contributing to each basis function will be selected based on their spatial location in addition to their MR intensity values. The proposed kernel method differs to all previous implementations of the MR-guided kernel method, in that previous implementations select the voxels that contribute to each basis functions based on the MR intensity values only. In contrast, the proposed implementation includes both MR intensity values and positional information in the selection of voxels for each basis function. For both the proposed and the conventional implementation the weighting of the selected voxels contributing to a given basis function is calculated using (10).

The proposed kernel method's voxel selection encourages more spatially-compact basis functions in uniform MR regions, whilst still producing basis functions with similar structures to the conventional kernel method in detailed MR regions (as shown in Fig. 1). The incorporation of positional information into the basis function formation process can be accomplished through either modifying the sparsification process or by modifying the choice of feature-vector. Both methods are addressed here, with an alternative sparsification process (using the largest kernel values) and a composite intensity-spatial feature vector proposed.

The composite intensity-spatial feature vector is formed through the amalgamation of the original intensity feature vector and positional vector, weighted in accordance to their own standard deviations:

$$X = \begin{bmatrix} \frac{f}{\sqrt{2}\sigma_f} \\ \frac{z}{\sqrt{2}\sigma_s} \end{bmatrix} \quad (14)$$

The standard deviation enables the relative importance between the voxels' spatial and intensity similarities to be varied. The k nearest neighbours of this composite feature space are the k voxels with the shortest Euclidean distance in X vector space. This is equivalent to finding the k voxels with the lowest value of:

$$\frac{1}{2\sigma_f} \left\| f_j - f_k \right\|_2^2 + \frac{1}{2\sigma_s} \left\| z_j - z_k \right\|_2^2 \quad (15)$$

Therefore, voxels with similar feature vectors and positional locations are more likely to contribute to a given basis function. This encourages the formation of more spatially-compact basis functions, especially in uniform MR regions. This contrasts with the conventional (MR intensity only) kNN sparsification method where contributing voxels are selected based solely on feature vectors calculated from MR intensity values, with no spatial component.

Another means for implementing the proposed spatially compact kernel method is to employ a different sparsification procedure with the conventional (MR intensity only) feature space. The basis functions are instead sparsified by selecting the k voxels with the largest kernel values (10), which is dependent on both the voxels spatial location and intensity based feature vector. The combined argument of both exponentials in the kernel value equation (10) is the negative of the composite vectors' inner product (15), hence the largest kernel value corresponds to the smallest Euclidean distance in the composite vector $\mathbf{X}$ space. Therefore the largest value sparsification method and the composite intensity-spatial feature vector method are equivalent in the resultant sparsification of the basis functions. In this paper, the method of largest kernel values sparsification (LVS) was employed to implement the spatially-compact kernel method, the results of which are equivalent to using the composite vector space implementation.

To recap, the conventional kernel method constructs basis functions through selecting each central voxel's kNN of the MR intensity only feature space, within a spatial neighbourhood. The conventional kernel method is referred to as kNN for the remainder of the paper. The proposed kernel method constructs basis functions through selecting each central voxel's largest kernel values (10), within a given spatial neighbourhood. The feature vector used in (10) also refers to the MR intensity only feature space. The proposed method is referred to as LVS throughout the remainder of the paper. Both the proposed and the conventional kernel implementations weight the voxels selected to contribute to a given basis function with (10).

The second implementation modification of the MR-guided kernel method was to construct the kernel matrix at the native resolution of the MR image, leading to an MR resolution image vector. The MR resolution image (in 3D) is resampled to PET resolution via a tri-linear resampling operator (R) that determines each MR resolution voxel's contribution to the 8 neighbouring PET resolution voxels. The resampling operator is applied to the MR resolution emission image vector to produce a PET resolution image [21], which is projected (A) into sinogram space:

$$q(\alpha) = ARK\alpha + r + s \quad (16)$$

The update equation is then also appropriately reparameterised in terms of the MR resolution modelled image vector:

$$\alpha^{n+1} = \frac{\alpha^n}{K^T R^T A^T \mathbf{1}} K^T R^T A^T \left(\frac{\mathbf{m}}{A R K \alpha^n + \mathbf{r} + \mathbf{s}} \right) \quad (17)$$

III Methods

In this work, several kernel EM implementations are analysed, the parameters of which are stated in Table 1. The parameter variation allows the resolution and sparsification changes to be systematically assessed, stratifying their individual and combined effects on the recovery of PET unique structures. Both single-voxel [23] and patch-based feature vectors [24] (patch length of 3) are investigated for simulated data, with the real data only being investigated using single-voxel feature vectors. For example, a feature vector $\mathbf{f}_j$ with a patch length (p) of 3, is a $3 \times 3 \times 3$ cubic patch of MR voxel intensities centered on voxel j , from which a 27×1 vector of MR voxel intensities is extracted. The feature vectors are normalised by their standard deviation, where $\sigma_m(\mathbf{f})$ is the standard deviation for the m^{th} element of each feature vector, over all voxels:

$$\bar{f}_{j,m} = \frac{f_{j,m}}{\sigma_m(\mathbf{f})} \quad (18)$$

For the calculation of the kernel values (10), the spatial and feature space standard deviations (σ_s & σ_f) are both set to large fixed values, in line with what was previously reported in the literature for the conventional kernel method [24], [28]. These same standard deviation parameter values are used for both the conventional and proposed kernel methods, allowing a comparison which at least ensures that the performance of the conventional kernel method is fairly represented. Alternative parameter values for the proposed kernel method could improve its performance still further. The kernel matrix is also row normalised as described in [22].

The different kernel EM implementations are assessed for the recovery of PET unique structures, using both a simulated phantom and real PET-MR data. The kNN kernel basis function with only 2 contributing voxels is included to allow comparison with the kNN kernel methods in the limit of very small basis functions. The MLEM reconstruction algorithm is included as a benchmark for the accurate recovery of PET unique structures, which all proposed methods ideally need either to match or surpass.

The following error metrics of normalised root mean square error (NRMSE) and region of interest (ROI) mean ($\bar{x}_{ROI}$) and standard deviation (σ_{ROI}) were calculated, where $\mathbf{x}^{GT}$ is the voxel value of the ground truth image. Images reconstructed at PET resolution were resampled to MR resolution through linear interpolation for the calculation of the error metrics. All reconstructed images in this paper are shown at MR resolution.

The normalised root mean square error, mean and standard deviation are defined as:

$$NRMSE(\%) = \sqrt{\frac{\sum_j^N (x_j - x_j^{GT})^2}{\sum_k (x_k^{GT})^2}} \times 100 \quad (19)$$

$$\bar{x}_{ROI} = \frac{1}{N_{ROI}} \sum_j^{N_{ROI}} x_j \quad (20)$$

$$\sigma_{ROI} = \sqrt{\sum_j^{N_{ROI}} (x_j - \bar{x}_{ROI})^2} \quad (21)$$

IV Simulation Studies

A 3D PET-MR phantom was constructed from the Brain-Web [40] segmented T1 MR phantom. Both the PET and MR phantoms were constructed at MR resolution with a grid size of $688 \times 688 \times 254$ and a voxel size of $1.0431 \text{ mm} \times 1.0431 \text{ mm} \times 1.0156 \text{ mm}$. High intensity lesions (A, B and C) Fig. 2 were added to the white matter of the PET phantom (not present in the MR) with intensities varying between that of the grey matter to twice the grey matter intensity. The PET phantom (constructed at MR resolution) was projected into a span 11 sinogram, and rescaled to a high count level with a total prompts count of 1×10^8 , and a lower count level with a total prompts count of 1×10^7 . Images reconstructed at PET resolution have a voxel size of $2.08626 \text{ mm} \times 2.08626 \text{ mm} \times 2.03125 \text{ mm}$ and a matrix size of $344 \times 344 \times 127$, equivalent to the specifications of the standard reconstruction from the Siemens Biograph mMR scanner.

All kernel EM implementations were initially investigated for noise free data, to assess their intrinsic deviation from the ground truth in comparison to the MLEM reconstruction, as shown in Fig. 3 and Fig. 4. A tumour containing slice is dissected along its vertical profile containing the two tumours located on the left-hand side of the brain. For the kernels constructed at PET resolution (Fig. 3), there appears to be only minor differences between the kernel implementations investigated and MLEM for regions of shared PET-MR structure. However, for the two high intensity tumour regions unique to the PET data (the two largest peaks of the ground truth profile) the conventional kernel method leads to a clear suppression of the peaks, showing the lowest intensity values, and the largest difference in voxel intensity to MLEM. The reconstruction of the tumour regions for the kNN kernel method is slightly improved with patch based feature vectors, which support the formation of more spatially-compact basis functions in comparison to single voxel feature vectors. However, patch-based feature vectors are still susceptible to the noise and shallow spatial gradients in the MR image, as illustrated in Fig. 1, limiting their effectiveness in recovering PET unique structures. Through using the LVS kernel method (in particular for single voxel feature vectors) the peak height tends closer to the MLEM and ground truth peaks. The

conventional kernel method can attain similar reconstruction of the noise free tumour regions to the LVS method through reducing the neighbourhood size and number of contributing voxels, however this severely limits its noise reduction and detail preserving properties over the remainder of the data. The LVS method limits the suppressing impact of the kernel method on PET unique features, whilst retaining its noise reducing and detail preserving properties to a greater extent.

The reconstruction of the noise free data with either MLEM or the kernel method at MR resolution (Fig. 4) leads to problematic Gibbs ringing artefacts [41], [42] along the profile, with large over and undershoots in intensity in comparison to the ground truth. This is due to the use of the smaller voxel sizes, which are effectively seeking to recover spatial frequencies beyond those that are measured by the PET scanner. It is possible to recover spatial frequencies up to a limit, and then no more – and this sudden cut off in the ability to recover spatial frequencies manifests as a Gibbs ringing effect. This issue could be overcome with additional regularization. Despite the images of the noise free data being visually clearer and more detailed when reconstructed at MR resolution, their quantitative value is limited. This also applies for the reconstruction of the tumour regions, which are more clearly defined using the MR resolution kernel method, but the PET resolution counterpart is a more faithful interpretation of the true radiation distribution.

The noisy simulated data (with a randoms and scatters fraction of 20%) was reconstructed up to 500 iterations using MLEM and the kernel implementations stated in Table 1. The NRMSE (19) and mean values (20) were calculated for the three tumour regions to assess the ability of each kernel EM implementation to accurately recover PET unique regions. In addition, whole brain NRMSE was used to indicate the noise reduction properties of all methods. Initially both the single voxel and patch based feature vectors are implemented and investigated.

Figure 5 shows the improved whole brain denoising properties of the conventional k-nearest neighbours PET resolution kernel method in comparison to MLEM, for the high count data. The conventional kernel method achieves a lower whole brain NRMSE in comparison to MLEM for all iterations, for both single voxel and patch based feature vectors. The noise reduction impact of the kernel method is furthered (at lower iterations) through constructing the basis functions at MR resolution, due to greater recovery of detailed structures present in the ground truth, that are blurred at PET resolution. However, the kNN based kernel method demonstrates an increased error for the recovery of all PET unique structures, relative to MLEM. The kNN kernel method's error in reconstructing tumour regions can be reduced through decreasing the neighbourhood size and number of contributing voxels, but this is at the expense of increased whole brain NRMSE. The NRMSE of the tumour regions can also be reduced relative to the conventional kernel method, through using the LVS kernel method. At PET resolution, the LVS kernel method reconstructs the tumour regions with a comparable NRMSE to MLEM, whilst providing a reduced whole brain NRMSE. The LVS kernel method clearly outperforms the conventional kernel method in accurately reconstructing the tumour regions, although the whole brain NRMSE is notably lower for the conventional kNN kernel method. The LVS kernel method at MR resolution leads to the

lowest tumour NRMSE for all tumours in comparison to all other kernel methods, however the value is highly iteration number dependent.

The NRMSE curves of the reduced count data (1×10^7), Fig. 6, further demonstrates the improvement of the proposed LVS kernel method at PET resolution relative to the conventional kernel method and MLEM. The increased noise present in this simulated dataset heightens the importance of the kernel method's noise suppression, leading to the LVS kernel method outperforming MLEM for all tumours in terms of NRMSE for both the single voxel and patch based feature vectors. However, at MR resolution, all kernel and MLEM reconstructions are shown to be highly susceptible to noise and tend further away from the ground truth at high iterations. Both the single voxel and patch based feature vector kernel methods return similar results for the reconstruction of the PET unique structures, in terms of NRMSE, with single voxel feature vectors attaining a lower whole brain NRMSE (for the higher count data). The remainder of this work focuses on the single voxel feature vector implementation of the kernel method.

Figure 7 shows the tumour mean value with respect to the spatial standard deviation of a chosen white matter background region, for the higher count simulated data. The MR resolution kernel reconstructions are shown to overshoot the ground truth mean value. Therefore, although the MR resolution LVS kernel method produces the lowest background noise level for a given mean value of tumour A, the kernel MR resolution reconstruction methods are of little utility for quantitative reconstructions. A comparison of the PET resolution reconstruction methods, shows that for a given noise level the proposed PET resolution LVS kernel method outperforms the conventional kernel method, and MLEM, for all three tumours. In addition, its tumour mean value tends to a very similar value to that achieved from MLEM, for all three tumours.

Visually the LVS method produces reconstructions of the tumour regions that are similar to the MLEM reconstruction in terms of shape and intensity, as shown in Fig. 8 at equal noise levels for the high count level data. In comparison, the kNN kernel method leads to notable blurring and distortion of the tumour regions, resulting in tumour regions that are visually dissimilar to the MLEM reconstructions. The reconstructed images are shown in Fig. 9 (high count data) and Fig. 10 (low count data), at a fixed iteration number for a tumour containing slice. In Fig. 10, attention should be paid to tumour C which is still clearly visible for the proposed LVS kernel method at PET resolution, which is not the case for the majority of other methods compared. In particular for the MLEM reconstruction tumour C is difficult to distinguish from the background noise. The MLEM reconstruction at MR resolution suffers from noise to a greater extent than the PET resolution reconstruction, as shown in Fig. 10. This highlights the potential risk of using an unconstrained reconstruction method at MR resolution, with the increased high intensity noise causing greater uncertainty in tumour detection.

The proposed LVS kernel method at PET resolution reconstructs the PET unique structures with a reduced deviation from the ground truth (for noise free simulations) and a lower NRSME (for noisy data), in comparison to the conventional kernel method. Whilst at the same time the proposed LVS kernel method retains, to a large extent, the denoising

properties and cortical detail present in the images reconstructed with the conventional kernel method. The mean value of the PET unique structures achieved for a given noise level can be further enhanced at MR resolution, however the mean values are larger than the predicted ground truth.

V Real Data Studies

An [^{18}F]FDG scan was undertaken on a Siemens Biograph mMR PET-MR with a total prompt count of 4.69×10^9 and a scan duration of 23 minutes. The tracer activity at time of injection (81 minutes prior to start of image acquisition) was 229 MBq. A T1 MPRAGE scan provided the anatomical image, from which the kernel basis functions were derived at the native MR resolution ($1.055 \text{ mm} \times 1.055 \text{ mm} \times 1.1 \text{ mm}$) over the PET field of view, or resampled to the PET resolution ($2.08626 \text{ mm} \times 2.08626 \text{ mm} \times 2.03125 \text{ mm}$). The span 11 projection data was augmented with simulated tumours, of equal size and shape to those used in the simulated data. The simulated tumours were projected into sinogram space from which a set of Poisson random variables is calculated to produce a noisy sinogram of the tumours that is added to the prompts data after accounting for normalisation and attenuation factors. The real data was reconstructed for MLEM and the (single voxel feature vector) kernel EM implementations stated in Table 1, for up to 500 iterations.

Figure 11 shows similar trends between the simulated and real data are observed with the PET resolution LVS kernel method attaining the highest tumour mean value for a given standard deviation, in comparison to all other PET resolution reconstruction methods. Its tumour mean value is also similar to that attained by MLEM for tumours A and B. The ground truth mean values were calculated from the real data through summing the simulated tumours mean to the mean value of the white matter background region from the MLEM reconstructed image at 500 iterations. The ground truth values are only approximate, due to the large spatial standard deviation of the white matter background region (approximately 0.06) that the measured value is subject to. Conversely to the simulated results, the mean value of the MLEM reconstructed image is higher than the PET resolution LVS method for tumour region C. This demonstrates the shortcomings of the LVS kernel method for reconstructing small high intensity PET unique regions. These small high intensity PET unique regions would be better reconstructed using MLEM, although due to the noise present in MLEM reconstructions these regions could be confused with noise spikes, or blurred by post reconstruction smoothing. Further investigation and developments (e.g. inclusion of PET data) to the MR guided kernel method are required to make it impervious to all sizes and shapes of PET-MR mismatches. The mean value of the tumour regions reconstructed with the MR resolution LVS kernel method in Fig. 11 outperforms the other kernel implementations and MLEM, however the quantitative accuracy of these values is uncertain. It should be noted that the tumour mean values by the MR resolution LVS kernel method are larger than the ground truth estimate for all regions.

The conventional kNN kernel method at PET and MR resolution visually suppresses the tumour regions, as shown in Fig. 12 at matched noise levels. The tumour regions reconstruction using the LVS kernel method at PET resolution are visually closer to those reconstructed using MLEM. The LVS kernel method results in a better recovery of PET

unique structures both visually and numerically in comparison to the other kernel implementations, whilst retaining the noise reduction and detail preserving properties of the kernel method in comparison to MLEM. This is illustrated by the reconstructed images, Fig. 13, for the tumour containing slice at a fixed iteration number.

Both the simulated and real data results demonstrate the benefit of the spatially compact LVS kernel method for the reconstruction of PET unique structures, relative to the conventional kernel method. In both datasets, there is a clear trade-off between the spatially compact and conventional kernel methods, with the former achieving more accurate reconstruction of PET unique structures, and the latter achieving further reduction in whole brain NRMSE.

Future work should investigate the proposed kernel method on real data which has genuine PET-MR mismatches (e.g. tumours only present in the PET), to assess the full utility of this work. In addition, further developments to the kernel method are required to make it robust to all forms of PET-MR mismatches, these include MR structures not present in the PET, and structures in both the PET and MR which do not match. The kernel method is practically insensitive to MR structures in uniform PET regions, as the incorrectly shaped basis functions will be correctly weighted using the PET data only. However, differing PET and MR structures will lead to distortion of the PET structure in accordance to that of the MR. The scope of this present work only concerns the specific case of PET-MR mismatches in the form of PET unique structures situated within uniform MR regions. To accurately reconstruct contradicting PET-MR structures requires further investigation and development of the kernel method.

VI Summary

The conventional MR-guided kernel method suffers from poor recovery of structures unique to the PET data. The proposed developments to the implementation of the kernel method produce spatially compact basis functions that have demonstrated clear improvements in the recovery of PET unique structures compared to the conventional kernel method for both simulated and real data. For all sizes of PET unique structures evaluated, the spatially compact kernel method showed quantitative and visual improvement in comparison to the conventional kernel method whilst maintaining to a large extent the kernel method's improved noise reduction properties relative to MLEM. This provides an improved balance between noise reduction, and recovery of PET unique structures. Further developments to the MR-guided kernel method are required to eliminate the bias introduced by the kernel method in the reconstruction of PET unique structures, in particular for very small high intensity regions. Extending the kernel method to MR resolution resulted in notable Gibbs ringing artefacts for noise free data at high iterations.

Acknowledgements

This work was funded by the King's College London & Imperial College London EPSRC Centre for Doctoral Training in Medical Imaging (EP/L015226/1), and supported by the Wellcome EPSRC Centre for Medical Engineering at King's College London (WT 203148/Z/16/Z) and by the EPSRC grant number EP/M020142/1. According to the EPSRC's policy framework on research data, figures and data supporting this study are openly available at [10.5281/zenodo.1120311](https://doi.org/10.5281/zenodo.1120311)

References

- [1]. Shepp LA, Vardi Y. Maximum Likelihood Reconstruction for Emission Tomography. *IEEE Trans Med Imaging*. 1982
- [2]. Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data via the EM algorithm. *J R Stat Soc Ser B Methodol*. 1977; 39(1):1–38.
- [3]. Mumcuoglu EU, Leahy RM, Cherry SR. Bayesian reconstruction of PET images: methodology and performance analysis. *Phys Med Biol Phys Med Biol*. 1996; 41(41):1777–1807. [PubMed: 8884912]
- [4]. Green PJ. Bayesian Reconstructions From Emission Tomography Data Using a Modified EM Algorithm. *IEEE Trans Med Imaging*. 1990; 9
- [5]. Levitan E, Herman GT. A Maximum a Posteriori Probability Expectation Maximization Algorithm for Image Reconstruction in Emission Tomography. *IEEE Trans Med Imaging*. 1987 Sep; 6(3): 185–192. [PubMed: 18244020]
- [6]. Green PJ. On Use of the EM Algorithm for Penalized Likelihood Estimation. *J R Stat Soc*. 1990; 52(3):443–452.
- [7]. Delso G, Furst S, Jakoby B, Ladebeck R, Ganter C, Nekolla SG, Schwaiger M, Ziegler SI. Performance Measurements of the Siemens mMR Integrated Whole-Body PET/MR Scanner. *J Nucl Med*. 2011; 52(12):1914–1922. [PubMed: 22080447]
- [8]. Ehrhardt MJ, Thielemans K, Pizarro L, Atkinson D, Ourselin S, Hutton BF, Arridge SR. Joint reconstruction of PET-MRI by exploiting structural similarity. *Inverse Probl*. 2014; 31(1)
- [9]. Chen S, Liu H, Shi P, Chen Y. Sparse representation and dictionary learning penalized image reconstruction for positron emission tomography. *Phys Med Biol*. 2015; 60
- [10]. Bowsher JE, Yuan H, Hedlund LW, Turkington TG, Akabani G, Badea A, Kurylo WC, Wheeler CT, Cofer GP, Dewhirst MW, Johnson GA. Utilizing MRI Information to Estimate F18-FDG Distributions in Rat Flank Tumors. *IEEE Symp Conf Rec Nucl Sci* 2004; 2004. 2488–2492.
- [11]. Tang J, Rahmim A. Bayesian PET image reconstruction incorporating anato-functional joint entropy. *Phys Med Biol*. 2009 Dec; 54(23):7063–75. [PubMed: 19904028]
- [12]. Nuyts J. The use of mutual information and joint entropy for anatomical priors in emission tomography. 2007 IEEE Nuclear Science Symposium Conference Record; 2007. 4149–4154.
- [13]. Mehranian A, Arabi H, Zaidi H. Quantitative analysis of MRI-guided attenuation correction techniques in time-of-fl brain PET/MRI. *Neuroimage*. 2016 Apr.(130):123–133.
- [14]. Hofmann M, Pichler B, Schölkopf B, Beyer T. Towards quantitative PET/MRI: a review of MR-based attenuation correction techniques. *Eur J Nucl Med Mol Imaging*. 2009 Mar; 36(S1):93–104.
- [15]. Martinez-Moller A, Souvatzoglou M, Delso G, Bundschuh RA, Ched'hotel C, Ziegler SI, Navab N, Schwaiger M, Nekolla SG. Tissue Classification as a Potential Approach for Attenuation Correction in Whole-Body PET/MRI: Evaluation with PET/CT Data. *J Nucl Med*. 2009 Mar; 50(4):520–526. [PubMed: 19289430]
- [16]. Hofmann M, Steinke F, Scheel V, Charpiat G, Farquhar J, Aschoff P, Brady M, Scholkopf B, Pichler BJ. MRI-Based Attenuation Correction for PET/MRI: A Novel Approach Combining Pattern Recognition and Atlas Registration. *J Nucl Med*. 2008 Oct; 49(11):1875–1883. [PubMed: 18927326]
- [17]. Rota Kops E, Herzog H. Alternative methods for attenuation correction for PET images in MR-PET scanners. 2007 IEEE Nuclear Science Symposium Conference Record; 2007. 4327–4330.
- [18]. Nuyts J, Dupont P, Stroobants S, Bennisck R, Mortelmans L, Suetens P. Simultaneous maximum a posteriori reconstruction of attenuation and activity distributions from emission sinograms. *IEEE Trans Med Imaging*. 1999 May; 18(5):393–403. [PubMed: 10416801]
- [19]. Ahn S, Cheng L, Shanbhag DD, Qian H, Kaushik SS, Jansen FP, Wiesinger F. Joint estimation of activity and attenuation for PET using pragmatic MR-based prior: application to clinical TOF PET/MR whole-body data for FDG and non-FDG tracers. *Phys Med Biol*. 2018
- [20]. Tahaei MS, Reader AJ. Patch-based image reconstruction for PET using prior-image derived dictionaries. *Phys Med Biol*. 2016; 61(18):6833–6855. [PubMed: 27581747]

- [21]. Jiao J, Markiewicz P, Burgos N, Atkinson D, Hutton B, Arridge S, Ourselin S. Detail-preserving PET reconstruction with sparse image representation and anatomical priors. *Inf Process Med Imaging*. 2015;540–551. [PubMed: 26221701]
- [22]. Wang G, Qi J. PET image reconstruction using kernel method. *IEEE Trans Med Imaging*. 2015; 34(1):61–71. [PubMed: 25095249]
- [23]. Novosad P, Reader AJ. MR-guided dynamic PET reconstruction with the kernel method and spectral temporal basis functions. *Phys Med Biol*. 2016
- [24]. Hutchcroft W, Wang G, Chen KT, Catana C, Qi J. Anatomically-aided PET reconstruction using the kernel method. *Phys Med Biol*. 2016; 61(18):6668–6683. [PubMed: 27541810]
- [25]. Ellis S, Reader AJ. Kernelised EM image reconstruction for dual-dataset PET studies. 2016 IEEE Nuclear Science Symposium, Medical Imaging Conference; 2016. 1–3.
- [26]. Hofmann T, Schölkopf B, Smola AJ. Kernel methods in machine learning. *Ann Stat*. 2008; 36(3): 1171–1220.
- [27]. Gong K, Cheng-Liao J, Wang G, Chen KT, Catana C, Qi J. Direct Patlak Reconstruction from Dynamic PET Data Using the Kernel Method with MRI Information Based on Structural Similarity. *IEEE Trans Med Imaging*. 2017; 62(1):1–11.
- [28]. Bland J, Mehranian A, Belzunce MA, Ellis S, McGinnity CJ, Hammers A, Reader AJ. MR-Guided Kernel EM Reconstruction for Reduced Dose PET Imaging. *IEEE Trans Radiat Plasma Med Sci*. 2017 in press.
- [29]. Baikejiang R, Zhang W, Li C. Gaussian kernel based anatomically-aided diffuse optical tomography reconstruction. *Proc SPIE 10059, Optical Tomography and Spectroscopy of Tissue XII*; 2017. 1005912
- [30]. Baikejiang R, Zhao Y, Fite BZ, Ferrara KW, Li C. Anatomical image-guided fluorescence molecular tomography reconstruction using kernel method. *J Biomed Opt*. 2017; 22(5)
- [31]. Zhao Y, Baikejiang R, Li C. Application of kernel method in fluorescence molecular tomography. *Proc SPIE 10057, Multimodal Biomedical Imaging XII*; 2017.
- [32]. Buades A, Coll B. A non-local algorithm for image denoising. *Comput Vis Pattern*. 2005; 2(0): 60–65.
- [33]. Christian BT, Vandehey NT, Floberg JM, Mistretta CA. Dynamic PET denoising with HYPR processing. *J Nucl Med*. 2010; 51(7):1147–1154. [PubMed: 20554743]
- [34]. Spencer B, Qi J, Badawi RD, Wang G. Dynamic PET Image reconstruction for parametric imaging using the HYPR kernel method. 2017 SPIE Med Imaging Proc; 2017.
- [35]. Cheng J-C (Kevin)Matthews J, Sossi V, Anton-Rodriguez J, Salomon A, Boellaard R. Incorporating HYPR de-noising within iterative PET reconstruction (HYPR-OSEM). *Phys Med Biol*. 2017; 62
- [36]. Matthies H, Strang G. The solution of nonlinear finite element equations. *Int J Numer Methods Eng*. 1979; 14(11):1613–1626.
- [37]. Nocedal J. Updating Quasi-Newton Matrices with Limited Storage. *Math Comput*. 1980 Jul. 35(151):773.
- [38]. Andrew G, Gao J. Scalable Training of L1-Regularized Log-Linear Models. 2007 Jan 01.
- [39]. Tsai YJ, Bousse A, Ehrhardt MJ, Stearns CW, Ahn S, Hutton B, Arridge S, Thielemans K. Fast Quasi-Newton Algorithms for Penalized Reconstruction in Emission Tomography and Further Improvements via Preconditioning. *IEEE Trans Med Imaging*. 2017; 62(c):1–11.
- [40]. Cocosco C, Kollokian V, Kwan RK, Pike GB, Evans AC. BrainWeb?: Online Interface to a 3D MRI Simulated Brain Database. 3-rd Int Conf Funct Mapp Hum Brain; 1997. S425
- [41]. Nuyts J. Unconstrained image reconstruction with resolution modelling does not have a unique solution. *EJNMMI Phys*. 2014; 1
- [42]. Stute S, Comtat C. Practical considerations for image-based PSF and blobs reconstruction in PET. *Phys Med Biol*. 2013; 58(11):3849–70. [PubMed: 23681172]

Fig. 1.

Basis functions derived using either the conventional kernel method, or the proposed spatially compact kernel method. The impact of the different implementations on basis function shape is shown for a uniform (left) and structured (right) MR region. The method developed by Hutchcroft [17] is also shown for comparison. The parameters for each method are, unless otherwise indicated in each sub-figure: $\sigma_f = 5$, $\sigma_s = 30$, $N = 9$, $p = 3$, $k = 10$. Only the proposed spatially compact kernel method can deliver compact basis functions in uniform MR regions and also structured basis functions in detail containing MR regions for the same parameters.

Fig. 2.
PET phantom (left), MR phantom (centre) constructed from the BrainWeb MR phantom.
The added PET unique structures are high intensity lesions labelled A, B and C (right). The
PET phantom is constructed at MR resolution.

Fig. 3.

Vertical line profiles of the reconstructed noise free simulated data after 500 iterations, through a tumour containing slice. The two largest peaks of the ground truth correspond to the top and bottom tumours on the left side of the brain, shown in Fig. 2. The top graph (a) shows the intensity profile for the single-voxel feature vector kernels with the images reconstructed at PET resolution. The corresponding T1 profile is also shown, scaled to fit into the PET range. The middle (b) and bottom (c) graph shows the difference between the MLEM profile and the stated profile for single voxel (b) and patch (c) based feature vectors

respectively, at PET resolution. The difference is calculated through subtracting the stated method from the MLEM profile.

Fig. 4.

Vertical line profiles of the reconstructed noise free simulated data after 500 iterations, through a tumour containing slice. The top graph (a) shows the intensity profile for the single-voxel feature vector kernels with the images reconstructed at MR resolution. The bottom graph (b) shows the difference between the MLEM profile and the stated method for single voxel feature vectors, at MR resolution. The difference is calculated through subtracting the stated method from the MLEM profile.

Fig. 5.

NRMSE vs iteration number for the kernel variations stated in Table 1, for the higher count data (1×10^8). Figures shown for the three tumour regions of the simulated data shown in Fig. 2, and the whole brain region. The first two columns (a, b, d, e) use single voxel feature vectors in the kernel matrix formation, the last column (c, f) uses patch based feature vectors.

Fig. 6.

NRMSE vs iteration number for the kernel variations stated in Table 1, for the lower count data (count level of 1×10^7). Figures shown for the three tumour regions of the simulated data shown in Fig. 2, and the whole brain region. The first two columns (a, b, d, e) use single voxel feature vectors in the kernel matrix formation, the last column (c, f) uses patch based feature vectors.

Fig. 7.

Mean value of tumour regions A, B and C (shown in Fig. 2) vs the standard deviation of white matter region for the simulated high count (1×10^8) data. Ground truth mean values are labelled for reference.

Fig. 8.

Reconstructions of the three tumour regions for high count (1×10^8) simulated data, shown for each of the kernel methods (single voxel feature vectors) stated in Table 1, at a fixed noise level. Ground truth of the tumour regions are shown in the first column. The noise free reconstructions are shown at different colour thresholds to the other images.

Fig. 9.

Reconstructed images of the high count (1×10^8) simulated data for a tumour containing slice, for each of the kernel implementations (single voxel feature vectors) stated in Table 1. All images are shown at a fixed iteration number of 100. Red arrows are centred on the tumour regions.

Fig. 10.

Reconstructed images of the low count (1×10^7) simulated data for a tumour containing slice, for each of the kernel implementations (single voxel feature vectors) stated in Table 1. All images are shown at a fixed iteration number of 100. Red arrows are centred on the tumour regions.

Fig. 11.

Mean value of tumours A, B and C vs the standard deviation of white matter region for the real data. The ground truth mean values were calculated from the real data through summing the simulated tumours mean to the mean value of the MLEM reconstruction of the white matter background region at 500 iterations. The ground truth values are only approximate, due to the large spatial standard deviation of the white matter background region (approximately 0.06) that the measured value is subject to.

Fig. 12.

Reconstructions of the three tumour regions for real data, shown for each of the kernel methods stated in Table 1, at a fixed noise level. The shape of each of the tumour regions are shown in the first column.

Fig. 13.

Reconstructed images of the real data with the augmented tumours, for the tumour containing slice. All images are shown at 100 iterations. Red arrows are centred on the tumour regions.

Table I

Algorithm and parameters of the reconstruction methods investigated, for both the simulated and real data. A reduced neighbourhood size and number of contributing voxels were used for the PET resolution kernel methods due to their larger voxel size.

Algorithm	Voxel Size	kNN or LVS	Neighbourhood	Patch Size	Number of Voxels
MLEM	PET	N/A	N/A	N/A	1
KEM	PET	kNN	5	1, 3	6
KEM	PET	LVS	5	1, 3	6
KEM	PET	kNN	3	1, 3	3
KEM	MR	kNN	7	1, 3	16
KEM	MR	LVS	7	1, 3	16