MIXTURE PRINCIPAL COMPONENT ANALYSIS FOR DISTRIBUTION VOLUME PARAMETRIC IMAGING IN BRAIN PET STUDIES

Peng Qiu, Z. Jane Wang[2], and K. J. Ray Liu

Department of Electrical and Computer Engineering, Institute for Systems Research
University of Maryland, College Park
[2]Department of Electrical and Computer Engineering, University of British Columbia, Canada

ABSTRACT

In this paper, we present a mixture Principal Component Analysis (mPCA)-based approach for voxel level quantification of dynamic positron emission tomography (PET) data in brain studies. The parameters of the probabilistic mixture model are determined using an EM algorithm. The problem of interest here requires neither the accurate arterial blood measurements as the input function nor the existence of a reference region. The effects of mPCA are examined in two different ways on the basis of whether the compartmental model for tracer dynamics is considered. First, the mPCA approach itself is used to classify all voxels into the specific binding and non-specific binding groups, and the resulting power is used for revealing the underlying distribution volume (DV) image. Second, the proposed mPCA-based classification approach is incorporated as the clustering preprocessing into our earlier work [4] to simultaneously estimate the DV parametric image and the input function. The efficiency and superiority of the proposed scheme is demonstrated by real brain PET data.

1. INTRODUCTION AND MOTIVATION

Analysis of dynamic positron emission tomography (PET) data has been widely applied to determine neuroreceptors binding sites in vivo. Of particular interest in this paper is the problem of estimation of the underlying distribution volume (DV) parametric image of neuroreceptors in brain, which provides image-wide quantification of the concentration of neuroreceptor and thus can be used to track or identify dynamic physiological and biochemical (e.g. disease) processes.

For quantitative analysis of neuroreceptor PET studies, compartmental model-based approaches are the most widely used for tracer kinetic modeling [1]. Among these approaches, a reference region model has been shown valid and widely applied as a *noninvasive* approach to avoid arterial blood sampling [2], though it involves a nontrivial challenge of the manual definition of a region of interest (ROI) as reference region. Another noninvasive research direction with great interest is to estimate both the kinetic parameters and the input function simultaneously. Only a few works for this purpose have been reported and most have been ROI-based. Theoretically, quantitative analysis of receptor can be at either the ROI level or voxel level. However, due to the poor signal-to-noise-ratio (SNR) in the voxel time-activity curves (TACs), ROI level quantification is commonly studied while voxel level quantification (i.e. parametric image analysis) has been hindered in the past. Here we are mainly tackling two concerns. First, no input function or reference region is presumably available. Second, we are interested in analyzing the problem at the voxel level, i.e. the identification of the voxels of specific binding and non-specific binding.

The goal of identifying specific binding voxels and non-specific binding voxels can be achieved by estimating the DV parametric image from voxel TACs and visually inspecting the estimated DV image. The purpose of the present work is to validate the feasibility that no input function or reference region is needed to obtain the DV parametric images. Specifically, we propose an algorithm to automatically sketch out the voxel regions for specific binding and non-specific binding. We incorporate the model of mixture Principal Component Analysis (mPCA). Distinguishing specific binding and non-specific binding voxels can be regarded as identifying different voxel function activity patterns, where each activity pattern can be represented by a different underlying model. As demonstrated in many areas, the idea of mPCA is proved to be a promising framework to deal with such problems by modeling the underlying nonlinearity and complexity with a collection, or mixture, of local linear sub-models [6]. Because patterns of observed TACs of specific binding voxels and non-specific binding voxels are different as characterized by different kinetic parameters, motivated by the successes of mPCA in areas such as image analysis, we proposed to apply mPCA to model the voxel TACs. One probabilistic PCA is used to describe the principal components of TACs from specific binding voxels; another probabilistic PCA is used to describe the principal components of TACs from non-specific binding voxels. In addition, as reported in the literature, cluster analysis (e.g. k-means-like method, hierarchical linkage method) has been used to improve the determination of TACs of reference tissue regions [3] and can be used as a prepro-

cessing step to improve the accuracy of voxel level quantification [5]. This further motivates us to accommodate the mPCA idea into our earlier work regarding voxel quantitative PET analysis [4] as a clustering preprocessing step.

The main contributions of this paper are as follows:

- Present an mPCA-based algorithm to sketch out the voxel regions for specific binding and non-specific binding. The mPCA model is able to classify all voxels into two groups in a Bayesian fashion, where an estimation and maximization (EM) algorithm is applied to iteratively estimate mPCA parameters.
- Incorporate the proposed mPCA-based classification approach into our earlier work [4] where both the DV parametric image and the blood input function are simultaneously estimated. The real PET data analysis demonstrates that the proposed method can improve the estimation accuracy.

2. FORMULATION AND METHODS

2.1. Formulation under mPCA framework

In this section, we formulate the PET problem of interest in the framework of mPCA. In [6], the mixture of probabilistic principal component analyzers is proposed. A probabilistic PCA (PPCA) model is introduced by associating a probability density with the conventional PCA model. A set of prior probabilities is applied to combine several PPCA models into a mixture model.

The concepts in [6] is related with our PET parametric imaging problem as follows. Suppose the observed TAC y_n for voxel n can be described by one PPCA model, i.e. the i^{th} PPCA model,

$$y_n = W_i x + \mu_i + \epsilon_i, \tag{1}$$

where y_n is a d dimensional vector, and the dimension of x is assumed to be q. The principal components are the columns of the matrix W_i. x is assumed to be independent Gaussian vector with unit variance, $x \sim N(0, I)$. The principal components are not necessarily unitary, so the energy of each component can be taken cared of in the W_i matrix. The parameter μ_i represents the mean vector, and ϵ_i represents measurement noise.

For the case of isotropic noise, $\epsilon_i \sim N(0, \sigma_i^2 I)$, the conditional probability of observed TAC y_n can be written as follows,

$$p(y_n|x,i) = (2\pi\sigma_i^2)^{-d/2} exp\{-\frac{1}{2\sigma_i^2} \parallel y_n - W_i x - \mu_i \parallel^2\}. \tag{2}$$

Associated with the distribution of x, we obtain the distribution of observation y_n given PPCA model parameters,

$$\begin{aligned} p(y_n|i) &= \int p(y_n|x,i)p(x|i)dx \\ &= (2\pi)^{-d/2}|C|^{-1/2} exp\{-\frac{1}{2}(y_n-\mu_i)^T C^{-1}(y_n-\mu_i)\} \end{aligned} \tag{3}$$

where $C = \sigma_i^2 I + W_i W_i^T$.

Given the prior probabilities $p(i)$ of a set of K PPCA models, the marginal probability of observation TAC y_n is,

$$p(y_n) = \sum_{i=1}^{K} p(y_n|i)p(i), \tag{4}$$

and the posterior probability of the i^{th} PPCA model can be expressed as

$$p(i|y_n) = \frac{p(y_n|i)p(i)}{p(y_n)}. \tag{5}$$

Therefore, the posterior probability can be used for the classification purpose.

As in [6], an EM algorithm of mPCA is derived. In the E-step, given the observed TACs and model parameters from last iteration, the posterior probability of the i^{th} PPCA model can be calculated by equation (5).

In the M-step, the update of model parameters can be summarized as follows. Suppose there are in total N voxels under consideration.

$$\widetilde{p}(i) = \frac{1}{N}\sum_{n=1}^{N} p(i|y_n) \tag{6}$$

$$\widetilde{\mu}_i = \frac{\sum_{n=1}^{N} p(i|y_n) y_n}{\sum_{n=1}^{N} p(i|y_n)} \tag{7}$$

$$\widetilde{W}_i = S_i W_i (\sigma_i^2 I + M_i^{-1} W_i^T S_i W_i)^{-1} \tag{8}$$

$$\widetilde{\sigma}_i^2 = \frac{1}{d} tr(S_i - S_i W_i M_i^{-1} \widetilde{W}_i^T) \tag{9}$$

where, $\widetilde{p}(i)$, $\widetilde{\mu}_i$, $\widetilde{W}_i$, $\widetilde{\sigma}_i^2$ are the updated model parameters for the i^{th} PPCA model in the mixture, and

$$S_i = \frac{1}{\widetilde{p}(i)N}\sum_{n=1}^{N} p(i|y_n)(y_n - \widetilde{\mu}_i)(y_n - \widetilde{\mu}_i)^T \tag{10}$$

$$M_i = \sigma_i^2 I + W_i^T W_i \tag{11}$$

2.2. Methods

mPCA-based classification approach to identify specific binding voxels

In PET parametric image, other than specific binding voxels and non-specific binding voxels, there are some irrelevant voxels which do not correspond to the whole brain region. In order to sketch out the regions of specific binding and non-specific binding, we propose the following processing steps:

- A simple masking step is applied to roughly determine the whole brain region by discarding irrelevant voxels (i.e. voxels with small TAC observation powers). A simple threshold based on the overall power of the voxel TACs is employed as masking criteria.
- Apply the mPCA approach to refine the rough brain region determined in the simple masking step. Voxels in the rough brain region are classified into two classes. One class corresponds to voxels in the real brain region; the other corresponds to the voxels outside. An

Expectation Maximization (EM) algorithm is applied to iteratively estimate mPCA parameters, which is summarized in the Appendix.

- For the refined brain region, the mPCA approach is applied again, in order to distinguish specific binding voxels from non-specific binding voxels. So that, regions of specific binding and non-specific binding can be sketched out.

- For voxels labeled as specific binding class, calculate the intensity of each voxel based on the class posterior probability and the projection coefficients in the mPCA model. This intensity value is expected to reveal the underlying DV value for each voxel.

Such generated voxel-wise intensity power image is proposed for representing the underlying DV spatial pattern.

mPCA-based approach as clustering precessing step to improve noninvasive voxel quantitative analysis

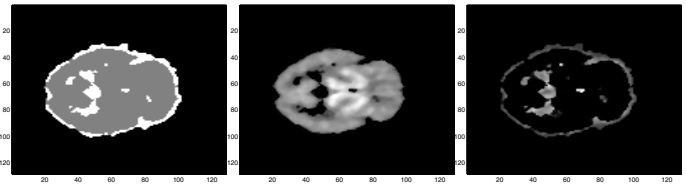
In our earlier work [4], the basic idea is to estimate the integral of the input function $c_p(t)$ by exploring the intersections of spaces, each of which is spanned by two vectors representing the voxel cluster TACs and their integrals. Based on the estimated input function, we then apply approaches which require the knowledge of the input function to estimate the DV parametric image. In [4], a clustering method is required as a preprocessing step, where the popular Gaussian clustering method is employed. The choice of clustering scheme may affect the overall estimation performance in [4]. As each PPCA model represents a different underlying pattern, it is naturally to apply the presented mPCA approach for the clustering purpose.

Therefore, in this study, the proposed mPCA approach can also serve as a clustering preprocessing step in the algorithm proposed in [4]. The voxels giving a sufficient large posterior probability of the i^{th} PPCA model are chosen to represent the i^{th} voxel cluster. Then we apply the space-intersection-based algorithm in [4] to estimate both the input function and the DV parametric image. In section 3, we will demonstrate the estimation performance improvement from incorporating the proposed mPCA approach with [4].

3. RESULTS

We apply mPCA to examine the PET studies of healthy control subjects obtained after intravenous injection of C-11 labeled DASB, a radioligand used for imaging the serotonin transporter (SERT). The experimental details are the same as in [7]. Totally 10 subjects were tested. For each subject, 18 serial dynamic PET images were acquired during the experiment. All PET scans were reconstructed in a 128x128 matrix. The proposed method is applied on all slices. Due to the space limitation, we illustrate the proposed method by one example.

First, we evaluate its classification performance on identifying specific binding voxels. As mentioned in subsection 2.2, the rough brain region is obtained by discarding voxels with small TACs observation powers. Then, the mPCA approach is applied to refine the rough brain region. In Figure 1(a), the union of white and gray areas is the rough brain region obtained in Step 1 in subsection 2.2. In Step 2, by applying the mPCA, the gray area is obtained as the refined brain region. The brain region and non-brain region is shown separately in Figure 1 (b) and (c). Figure 1(b) corresponds to the refined brain region. Figure 1(c) corresponds to non-brain region, which is of little interest. The intensity of each voxels is proportional to the class posterior probability and the projection coefficient in the mPCA model. Intuitively, we expect the intensity value to be highly correlated with the underlying voxel-wise DV value. Because, class posterior probability describes how likely a voxels belongs to an PCA model, e.g. brain region or non-brain region; and mPCA projection coefficient represents how much power the mPCA model supports the observed TACs.



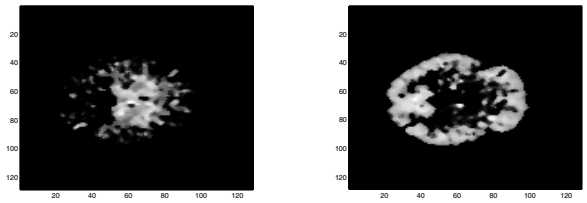
(a) (b) (c)

Fig. 1. The identified brain region in PET image. The union of white and gray areas in (a) is the rough brain region obtained by Step 1 in subsection 2.2. The gray area in (a) and Fig (b) is the obtained as the refined brain region in Step 2. The white area in (a) and Fig (c) does not correspond to brain voxels.

Based on the refined brain region, Figure 1(b), the mPCA approach is applied again, distinguishing specific binding voxels from non-specific binding voxels. Shown in Figure 2(a) are the voxels for specific binding, while Figure 2(b) corresponds to the voxels for non-specific binding. The intensity of each voxels is defined the same with that in Figure 1. In this step, class posterior probability describes how likely a voxels belongs specific binding or non-specific binding. Figure 3(a) shows the DV image estimated by the traditional multivariate analysis with the known input function in [8], where the bright region corresponds to specific binding voxels with higher DV values. Figure 2(a) appears similar to the bright region in Figure 3(a), which indicates that, the proposed method is able to sketch out the regions for specific binding voxels.

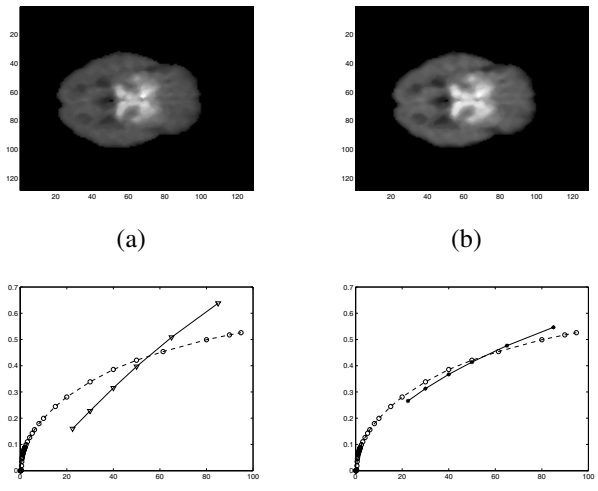
Further, we examine the proposed mPCA method as a clustering algorithm, which is incorporated with [4]. Given the specific binding voxels and non-specific binding voxels obtained by the proposed mPCA model, we estimate the plasma input function and DV image simultaneously as in [4]. Fig-

ure 3(b) is the estimated DV image, which is almost identical with Figure 3(a), the DV image estimated from known experiment measured input function. Figure 3(c) shows the integral of the measured and estimated input functions in [4]. Figure 3(d) shows the estimated input function by incorporating the proposed mPCA model. The scale is normalized, because in the proposed method, the shape is important for the estimated input function, which the scale does not affect the final parametric image. From these figures, we can see that, the proposed approach yields improvement in estimating the input function, because the proposed approach can cluster voxels in a way with physiological meaning, specific binding and non-specific binding.



(a) (b)

Fig. 2. The specific binding regions and non-specific binding regions sketched out by the mPCA model. Figure (a) corresponds to specific binding, while Figure (b) corresponds to non-specific binding.



(a) (b)

(c) (d)

Fig. 3. Figure (a) is the DV parametric image estimated with the knowledge of input function, as in [8]. Figure (b) is the estimated DV image by combining the mPCA approach and [4], without the knowledge of input function. In (c), the dashed line shows the integral of the normalized measured input function. The solid line is the normalized estimated input functions in [4]. The solid line in Figure (d) shows the normalized estimated input function by the proposed method.

4. CONCLUSION

An mPCA-based framework is presented for the voxel level quantification of dynamic PET data in brain studies. Real brain PET data were studied to examine the performance of the proposed scheme. We have demonstrated the feasibility that no input function or reference region is needed to obtain the DV parametric images. The proposed mPCA approach is able to sketch out specific binding regions. Further more, incorporating the proposed scheme with [4] yields improvement of the estimation of DV parametric images. Future work will focus on two directions: one is to improve the mPCA approach within a framework of hidden Markov model since the adjacent voxels more likely belong to the same hidden state (i.e. specific binding or non-specific binding); the other is to extend the proposed 3D PET analysis (i.e. the current analysis is based on a slice-by-slice manner) to 4D PET analysis by jointly considering multiple slices.

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