
Abstract

Positron emission tomography (PET) is a nuclear medicine-technique that provides tomographic images of the distribution of positron-emitting radioactively labeled pharmaceutical. The most commonly used isotopes for PET are ^{15}O , ^{11}C , and ^{18}F . This paper deals with the brain PET images obtained using 2-deoxy-2- ^{18}F -fluoro-D-glucose (FDG). FDG is utilized for regional cerebral metabolic rate of glucose (rCMRGlu). FDG-PET images are useful in diagnosis of tumor and Alzheimer's disease that are associated with abnormal metabolic activity.

This paper focuses on the brain FDG-PET images obtained by dynamic scan. Dynamic scan is a scan with frames collected sequentially in time. The dynamic PET images are assumed to consist of radioactivity in plasma and in tissue. The time courses of the radioactivity in plasma and in tissue are termed as plasma time-activity curve (pTAC) and tissue time-activity curve (tTAC), respectively. The dynamic PET images are described as

$$\mathbf{X} = [\mathbf{c}_p \ \mathbf{c}_t][\mathbf{s}_p \ \mathbf{s}_t]^T + \mathbf{N}, \quad (1)$$

where \mathbf{X} represents dynamic PET image matrix. The row of the matrix describes the voxel values of the scanned image and the column of the matrix describes the time curve of the radioactivity in a single voxel. The column vectors of \mathbf{c}_p and \mathbf{c}_t represent the pTAC and the tTAC, respectively, and the column vectors of \mathbf{s}_p and \mathbf{s}_t represent the contribution ratio of blood vessels and brain tissue to a single voxel, respectively. \mathbf{s}_p is named as blood volume image and \mathbf{s}_t a tissue image. The matrix of \mathbf{N} is a noise matrix. The blood volume image can be measured using ^{15}O -CO by PET scan. The contribution ratio of the blood vessels to a single voxel of a PET image is extremely small, and the radioactivity in blood is considered as outliers in dynamic PET images, accordingly.

The relation between pTAC and tTAC can be described using the compartment model. pTAC is an input function of the compartment model, and tTAC an output function. The model is described by one or more first order differential

equations with kinetic parameters. The kinetic parameters denotes the transfer rate constants between compartments. Functional parameters such as $rCMRGlu$ can be calculated by solving the differential equations. Parametric images can be also generated by voxel-by-voxel kinetic parameters estimation. An input function, $pTAC$, is required for the estimation. Serial arterial sampling via an inserted catheter into the radial artery is the gold standard method for measuring the $pTAC$. However, insertion of the catheter is painful for patients. Also, the procedure requires superfluous operators and processing time. In addition to them, arterial sampling also exposes operators to the risks associated with the handling of patients' blood. Therefore, it is of clinical interest to eliminate serial arterial blood sampling. This thesis proposes the methods for extracting blood vessel-related component, such as $pTAC$ and blood volume image, from dynamic PET images using statistical signal processing based on factor analysis model. The outline of each chapter is presented as below.

In Chapter 1, the role of serial arterial sampling in kinetic analysis of dynamic PET images is explained. The problems that serial arterial sampling causes are also described. Several existing methods and the new proposed methods for eliminating serial arterial blood sampling are introduced briefly.

In Chapter 2, first, the principle of PET measurement and properties of radiopharmaceuticals are explained. Next, the compartment model and kinetic analysis are overviewed. The methods for estimating $rCMRGlu$ and regional cerebral blood volume ($rCBV$) are described. Additionally, procedures of serial arterial blood sampling and the existing methods to eliminate the serial arterial sampling are explained in detail. Their practical disadvantages are also considered.

Chapter 3 introduces the algorithms of ICA and EL. ICA is a method for estimating components by maximizing the independency among components. The cost function that evaluates the independency is optimized in ICA. EL derives an approximate posteriors by assuming a prior on each component, and estimates the components by minimizing Kullback-Leibler divergence between the posteriors and the approximate posteriors.

Chapter 4 proposes the algorithm of the extraction of the $pTAC$ using ICA (EPICA). EPICA assumes that the spatial distribution of blood volume image and tissue image are spatially independent with respect to each other. If the standard spatial ICA is simply applied, the $pTAC$ cannot be estimated properly. Therefore, preprocessing of data and design of the cost function are proposed. EPICA, first, appends negative images to the original PET images and forces the distribution of PET images to be symmetric. Second, a time-activity curve of each voxel is standardized by its time integral. The standardization locates the voxel values of the tissue image near to 1 or -1 and transforms the distribution of the blood volume image into heavy-tailed distribution. The series of preprocessing steps have the effect that enhance the difference between two distributions. EPICA adopts FastICA (deflation approach). The algorithm is similar to projection pursuit, and performs one-by-one estimation. The estimation er-

ror is accumulated along the estimation in contrast to simultaneous estimation. Therefore, in case that the components to be estimated are determined in advance, one-by-one estimation has an advantage that the estimation error of the “privileged” components are small. Generally speaking, the robust cost functions that are not influenced by outliers are proposed as a good function of ICA. However, in EPICA, the nonlinear cost function is designed to be sensitive to the distribution with heavy tails. The cost function of EPICA consists of two terms. The first term evaluates the outliers and the second term penalizes too much concentration of voxels near zero. The shape of the cost function is determined by two parameters. For the evaluation of EPICA, three experiments were performed using noise-added simulated data and clinical data. First, the influence of choice of a cost function on an extracted pTAC was investigated. The deviation in the tails of the estimated pTAC increased when the cost function is less sensitive to the tails of distributions. Next, the relation between the parameters of the cost function and the estimated pTAC was investigated. As the contribution of the penalty term to the cost function increases, the tail of the estimated pTAC decreases more rapidly. Finally, EPICA was applied to the computer-generated data and clinical PET data. The pTAC was extracted successfully in both data. Although the estimated blood volume image included negative values, its spatial distribution was still very similar to the measured blood volume image. ROIs were placed on the clinical PET images and the influx parameter of each ROI are estimated using the measured pTAC and the EPICA-estimated pTAC. The parameters using the EPICA-estimated pTAC correlated well with those estimated using the measured pTAC.

Chapter 5 proposes the algorithm of the extraction of the pTAC using EL (EPEL). The EPICA-estimated blood volume image included negative values. To overcome the problem, maximization of independency between images with nonnegative constraint is performed using EL. The rectified Gaussian and exponential are assumed as the priors of the pTAC and the blood volume image, respectively. These priors enforces the nonnegativity on the estimates. In order to evaluate EVAM, three experiments were performed using the same data as used in Chapter 4. First, the effect of a prior on the extracted pTAC was investigated. When Gaussian prior is assumed on the pTAC or blood volume image, the estimation result included negative values. EL has a flexibility about the number of sources, whereas the standard ICA requires to reduce the dimension of data to the number of sources to be estimated. EPEL was applied to data assuming the number of sources to be two or five. The estimates included the vessel-related component and the tissue-related component in either case, and the remaining three components had small variance in case of assuming five components. Finally, EPEL was applied the same data used in Chapter 4. The pTAC and the blood volume image were estimated correctly and the blood volume image was nonnegative. The influx parameters of the time-activity curves averaged over ROIs are estimated using the measured pTAC and the EPEL-estimated pTAC.

The parameters using the EPEL-estimated pTAC correlated well with those estimated using the measured pTAC as in the case with EPICA.

Chapter 6 compares the estimation results using the factor analysis methods. Existing methods, FADS and NMF, were applied to dynamic PET images for the estimation of the pTAC. The shape of the FADS-estimated pTAC was greatly different from that of the measured pTAC, and the tail of the NMF-estimated pTAC was deviated from that of the measured pTAC. FADS and EPICA estimate components using oblique rotation. FADS determines the oblique rotation using nonnegative constraints. The nonnegative constraints are not sufficient to determine the oblique rotation. Also, the data after dimension reduction include little information on the pTAC in FADS. Although both NMF and EPEL utilize the loglikelihood of the model, NMF does not assume the specific statistical distribution for each factor TAC and factor image, and thereby fails in estimation.

In Chapter 7, the parametric images were generated using the EPICA-estimated pTAC and the EPEL-estimated pTAC, and these images were compared with the estimated parametric images using the measured pTAC. From clinical stand point of view, it is not important if the shape of the estimated pTAC resembles that of the measured pTAC or not. What is important is that the kinetic parameters can be estimated successfully using the estimated pTAC. Kinetic analysis is performed using the estimated pTACs to clinical PET images in order to introduce application examples. The EPICA-estimated pTAC generated more reliable parametric images than the EPEL-estimated pTAC.

Chapter 8 summarizes the results of this work. The estimated pTACs using EPICA and EPEL have an ambiguity in its scale and the absolute value of the estimated pTACs is determined by one-point arterial sampling. The timing for one-point arterial sampling is also described. From the results of this thesis, we conclude that EPICA and EPEL are practical methods for estimating the pTAC.