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Extraction of an input function from dynamic micro-PET images using wavelet packet based sub-band decomposition independent component analysis

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ABSTRACT

Positron emission tomography (PET) can be used to quantify physiological parameters. However to perform quantification requires that an input function is measured, namely a plasma time activity curve (TAC). Image-derived input functions (IDIFs) are attractive because they are noninvasive and nearly no blood loss is involved. However, the spatial resolution and the signal to noise ratio (SNR) of PET images are low, which degrades the accuracy of IDIFs. The objective of this study was to extract accurate input functions from microPET images with zero or one plasma sample using wavelet packet based sub-band decomposition independent component analysis (WP SDICA). Two approaches were used in this study. The first was the use of simulated dynamic rat images with different spatial resolutions and SNRs, and the second was the use of dynamic images of eight Sprague–Dawley rats. We also used a population-based input function and a fuzzy c-means clustering approach and compared their results with those obtained by our method using normalized root mean square errors, area under curve errors, and correlation coefficients. Our results showed that the accuracy of the one-sample WP SDICA approach was better than the other approaches using both simulated and realistic comparisons. The errors in the metabolic rate, as estimated by one-sample WP SDICA, were also the smallest using our approach.

Introduction

Positron emission tomography (PET) is a nuclear medicine imaging modality. Its dynamic images with attenuation and scatter corrections can be acquired and processed to allow quantitative analysis. After quantitative analysis, it is possible to obtain physiological parameters that can be used to improve classification accuracy with respect to various types of disease. For example, ^{18}F-FDG-PET can be used to quantify the local metabolic rate of glucose, which is changed in patients with several neurological diseases such as epilepsy (La Fougere et al., 2009; Liew et al., 2009) and Alzheimer's disease (Mosconi et al., 2009, 2010; Nordberg et al., 2010). Other studies have used various small animal models for investigating pathophysiological mechanisms (Lancelot and Zimmer, 2010; Maeda et al., 2007; O'Brien and Jupp, 2009). To calculate physiological parameters requires the measurement of an input function. A plasma time activity curve (TAC) is referred to as an input function because it serves as an input for the tracer kinetic model, which describes arterial blood plasma delivery of the tracer to all tissues. Therefore, an accurate determination of the input function is important when carrying out a kinetic analysis.

The gold standard for input function determination is an invasive arterial blood sampling procedure that allows the measurement of ^{18}F-FDG activity in the arterial plasma (Lammertsma and Hume, 1996; Phelps et al., 1979; Terry et al., 2005). This technique has several drawbacks, including the fact that arterial puncture is uncomfortable, that the blood sampler is exposed repeatedly to radiation, that there is a need for frequent sampling, and that there is a need for centrifugation. The approach is labor intensive and all these steps affect the accuracy of the input function because they may potentially create major errors. Furthermore, arterial puncture and arterial blood sampling are challenging in small animal studies due to the subject's small arteries and limited blood volume. In addition, large blood loss can affect the accuracy of the physiological parameters. These problems have led several groups to investigate alternative methods.

One alternative is often called the population-based method and is able to reduce the number of plasma samples taken from one individual (Eberl et al., 1997; Takikawa et al., 1993). First, a template of the input function is calculated by averaging the input functions from a sample population. Second, only one or two plasma samples are taken from each individual. Finally, the estimated input function can be obtained by scaling the template using the actual plasma activity of the individual. The population-based method has been found to

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be high accuracy when estimating physiological parameters and require only one or two plasma samples for calibration, which reduces the radiation exposure to the blood sampler (Eberl et al., 1997; Takikawa et al., 1993). In this study, we used the population-based method and compared it with our method.

Another attractive method is categorized as an approach that uses image-derived input functions (IDIFs). Herein, the image based input function is determined from the region of interest (ROI) within the left ventricle, the left atrium or the ascending aorta (Gambhir et al., 1989; Hoekstra et al., 1999, 2000; Li et al., 1998; Ohtake et al., 1991; Rechavia, 1997; Richard et al., 2005; van der Weerdt et al., 2001; Wahl et al., 1999). This method is attractive because it is nearly noninvasive, and involves a simpler protocol than manual blood sampling. Chen et al. (1998) used the method to manually draw ROIs at the carotid artery to generate an IDIF and corrected the partial volume and spillover effects (PVE) of the IDIF using three venous plasma measurements. This method can reduce the PVE and provide accurate IDIFs. However, this method still needs three venous plasma samples manually to calculate the coefficients for the PVE correction. Furthermore, the ROIs for the PVE correction need to be determined manually. This is subjective and prone to man-made errors. As a result more objective methods such as cluster analysis (Arai and Barakbah, 2007; Bezdek and Ehrlich, 1984; Hartigan and Wong, 1979) or independent component analysis (ICA) (Hyvarinen, 1999; Hyvarinen and Oja, 1997) have been used. For cluster analysis, the boundaries between the blood pool and the other tissue can be treated as another cluster in order to minimize the PVE. It has been report that cluster analysis is able to provide accurate input functions without the need for manual delineation of the ROI in human studies (Liptrot et al., 2004; Murase et al., 2004). When the ICA method is used, dynamic PET images are treated as mixed signals that are spatial distributions across several tissues (Ahn et al., 2001; Chen et al., 2007; Lee et al., 2001; Naganawa et al., 2005; Richard et al., 2005; Su et al., 2005). ICA can estimate the tissues that are spatially independent by a maximization of their non-Gaussian nature (Hyvarinen, 1999; Hyvarinen and Oja, 1997). However, the spatial resolution and signal to noise ratio (SNR) of PET images are poor and the independence property of the different tissue distributions does not always hold. A poor SNR, the presence of cardiac motion, and the presence of respiratory motion all affect the independence property of the different tissue distributions. A poor spatial resolution can make tissue distributions move towards a Gaussian distribution that cannot be directly solved by ICA. Kopriva and his colleagues developed a wavelet packet based sub-band decomposition independent component analysis (WP SDICA) in order to increase the accuracy of such ICA estimated results (Kopriva and Sersic, 2008). When source signals are dependent, WP SDICA assumes that there exist some frequency sub-bands that are independent. Then WP SDICA extends applicability of standard ICA by making the source signals more independent and extracts the sub-band with the least-dependent components. It has been shown that WP SDICA is able to provide accuracy and robustness when separating mixtures of images of human faces with Gaussian noise (Kopriva and Sersic, 2008). In this study, we used WP SDICA to extract input functions.

^{18}F-FDG is widely used to quantify metabolic rate of glucose and microPET has been used to investigate neuronal metabolism, for the most part in rats (Lancelot and Zimmer, 2010). Therefore we used WP SDICA to extract the ^{18}F-FDG TACs in rats. In order to derive a truly unsupervised approach to extract input function, an artificial neural network (ANN) was used to select a whole blood TAC from the WP SDICA-estimated TACs. Finally, we transferred the image-derived whole blood TAC to plasma using a two-exponential correction. If one plasma sample is available, the one-sample WP SDICA-estimated input function was obtained by scaling the WP SDICA-estimated input function with the plasma activity. The method was validated by comparing the WP SDICA-estimated input function with a cluster analysis estimated input function, a population-based input function and a manual sampled input function.

Material and methods

Digital dynamic rat phantom

We designed a digital dynamic rat cardiac phantom to validate and evaluate our method. Three tissues, the ventricle, the myocardium and the rat body, were manually delineated in the last frame of a realistic rat PET image (Fig. 1a). The TAC of the ventricle was a manually sampled whole blood TAC. The blood-sampled TAC was acquired from a realistic rat study. The sampling time points were 0 s, 8 s, 15 s, 30 s, 45 s, 1 min, 2 min, 3 min, 5 min, 7.5 min, 10 min, 15 min, 25 min, 35 min, 45 min and 60 min. The tissue TACs of the myocardium and the rat body were computed using the three-compartment model (Phelps et al., 1979) and ^{18}F-FDG with given flux constants K_1–k_4 values; these were calculated from a realistic study and the manually sampled input function (Fig. 1d). Digital dynamic image sequences were simulated using the 0 s, 8 s, 15 s, 30 s, 45 s, 1 min, 2 min, 3 min, 5 min, 7.5 min, 10 min, 15 min, 25 min, 35 min, 45 min and 60 min frames. The time points of the dynamic images were created according to the manual blood sampling protocol. This is able to avoid considering errors that occur due to interpolation of the whole blood TAC to fit the same time points as the image frames and can evaluate each image based method directly. The original cardiac phantom is noise-free without PVE. In order to simulate more realistic PET dynamic images, we included the following steps:

(A) *Radon transform was performed on the images to acquire noise-free sinograms.* In PET imaging, images are reconstructed from sinograms. Thus we forward projected images to the sinogram domain using Radon transformation (Deans, 1983). The computed noise-free sinograms were regarded as the mean values of the detector counts.

(B) *The total event counts of the computed sinogram were changed and random numbers were generated using a Poisson distribution and the mean counts of each pixel.* After generating random numbers from the Poisson distribution of the sinogram, the SNR of each pixel in the sinogram is the square root of the mean value of the pixel in the sinogram. Thus, there is a spatial-variant noise distribution in our simulated sinograms and images. We also simulated images with different SNRs by changing the total counts of the sinogram.

(C) *The sinograms were convoluted using 1-D Gaussian blurring filters.* In PET imaging, the high energy γ-ray might penetrate several detectors instead of interacting with a single detector. The detector blurring factor degrades image quality and causes PVE. In order to evaluate the efficiency of ICA at different spatial resolutions, the sinogram was convoluted using different 1-D Gaussian filters.

(D) *Sinograms were reconstructed using filtered back-projection (FBP) to form a set of dynamic images.* After FBP, we can obtain a set of dynamic images with the dimensions $256\times256\times16$.

The SNR of each total count was computed over the rat body. The SNR of the image was then estimated by the following equation:

$$SNR = mean(\mathbf{x})/std(\mathbf{x}), \tag{1}$$

where $\mathbf{x}$ belongs to a manually delineated region in the rat body. In order to determine the spatial resolution (the full-width-at-half-maximum, FWHM) of the simulated image, we fitted the point spread function to the reconstructed image using the Gaussian model. The FWHM is calculated using the following equation:

$$\mathrm{FWHM} = 2\sqrt{2\ln(2)}\sigma, \tag{2}$$

where σ is the standard deviation of the point spread function. The SNR of our realistic rat image is about 4, and the FWHM of our PET is about 2.5 mm. In order to evaluate the robustness of our methods under