Non-invasive Estimation of Cerebral Metabolic Rate of Glucose Using Simultaneous Estimation and Cluster Analysis: A Feasibility Study

Koon-Pong Wong[1,2] **Dagan Feng**[2,3] **Steven R. Meikle1** **Michael J. Fulham**[1,4]

[1]Department of PET and Nuclear Medicine, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia
[2]Basser Department of Computer Science, The University of Sydney, NSW 2006, Australia
[3]Department of Electronic and Information Engineering, The Hong Kong Polytechnic University, Hong Kong
[4]Faculty of Medicine, The University of Sydney, NSW 2006, Australia

kpong@cs.usyd.edu.au

Abstract

Quantitative PET studies usually require invasive blood sampling from a peripheral artery to obtain an input function for accurate modelling. However, blood sampling is impractical in clinical PET studies. We recently proposed a non-invasive modelling approach that can simultaneously estimate parameters which describe both the input and output functions using two or more regions of interest (ROIs). However, this approach is still limited by manual delineation of ROIs which is subjective and time-consuming. In this work, we present an extension to our method where ROI delineation is performed automatically by cluster analysis so that subjectivity is reduced while at the same time ensuring that the extracted time-activity curves have distinct kinetics. Our aim was to investigate the feasibility of using the kinetics extracted by cluster analysis for non-invasive quantification of physiological parameters. The estimates and the fitted curves obtained by simultaneous estimation are in good agreement with those obtained by model fitting with the measured input function (*gold standard* method). We conclude that cluster analysis is able to identify distinct kinetics and hence can be used for the non-invasive quantification of physiological parameters.

Keywords: Input function, impulse response function, cerebral metabolic rate of glucose, simultaneous estimation, cluster analysis, positron emission tomography (PET).

1 Introduction

Quantitative PET studies usually require invasive blood sampling at the peripheral artery to form a input function (IF) for accurate modelling. However, blood sampling is impractical in routine studies due to various reasons. A number of approaches have been proposed to reduce the need for blood sampling. We recently proposed a simultaneous estimation (SIME) approach to estimate the IF and the kinetic model parameters from two or more ROIs, making use of one or more late venous blood samples for calibration (Feng *et al*., 1997). We modified the method to improve the reliability of parameter estimation (SIMEP) and our results with *in vivo* PET data are promising (Wong *et al*., 1999). However, the method is still limited by the requirement to select ROIs whose time-activity curves (TACs) must have distinct kinetics so that the physiological parameters in the impulse response functions (IRFs) obtained by SIME are numerically identifiable. The ROIs are usually drawn manually on the PET images but they may not be reproducible due to subjectivity and the process of ROI delineation is time-consuming. This work presents a further extension to the method whereby the tissue TACs are extracted automatically from dynamic PET data by cluster analysis which is used to segment tissues of different kinetics based on the time-activity behaviour. Our aim is to investigate the feasibility of using the kinetics extracted by cluster analysis for non-invasive quantification of physiological parameters.

2 Materials and Methods

2.1 Simultaneous Estimation of Physiological Parameters and Input Function

We have previously reported the Monte-Carlo simulations (Feng *et al*., 1997) and the *in vivo* [^{18}F]fluorodeoxy-D-glucose (FDG) PET studies that validate our method (Wong *et al*., 1999). Only a brief summary of the method is presented here. Multiple tissue TACs can be obtained by defining different ROIs on the dynamic PET images. These TACs are the convolution of the IF with the physiological IRFs corresponding to the ROIs. The IRF parameters and the IF may thus be estimated simultaneously from two or more tissue TACs. In order to improve the numerical identifiability of the parameters to be estimated, two late venous blood samples are taken to calibrate the estimated IF. Nonlinear least squares (NLLS) is used to optimise the IF and the IRF parameters.

Although precise parameter estimates can be obtained theoretically with SIME, we found that the estimation of the standard deviations for the parameter estimates are usually very poor even though the values of the parameter estimates are accurate (Wong *et al*., 1999). This may be because a large number of noisy data are fitted simultaneously and the information matrix may be poorly-conditioned since the stability of its Jacobian matrix is disrupted by noise. Another possibility could be the high nonlinearity of the parameter space. We have developed a technique that is applied after SIME for the above situations and we refer to this method as post-estimation (SIMEP) (Wong *et al*., 1999) in which the parameters in the IRFs are estimated separately by using the estimated IF from SIME and the individual tissue

TACs as input-output pairs. The standard deviations of the parameters can be greatly improved due to the reduction in dimensionality of parameter space.

2.2 Automatic Extraction of Tissue TACs

Cluster analysis is used to extract the different kinetics present in dynamic PET data (Wong *et al*., 2000). The method is similar to the one proposed by Ashburner *et al.* (1996) in that there is a finite number of kinetics present in the dynamic PET data. The difference is that the latter algorithm maximises the probability of an arbitrary selected TAC from the data belonging to a specified cluster while the method used in this work minimises the weighted sum of squared residuals for an arbitrary selected TAC to its cluster centroid (Wong *et al*., 2000).

2.3 Computer Simulations

A slice of numerical Hoffman brain phantom (Hoffman *et al*., 1990) was modified using a template consisting of five different kinetics (grey matter, white matter, thalamus, tumour in white matter and an adjacent hypometabolic region in right middle temporal gyrus). The activities in grey matter and white matter were generated using a 5-parameter 3-compartment FDG model (Hawkins *et al*., 1986) with a measured arterial IF obtained from a patient, and the kinetics present in the hypometabolic region, thalamus and tumour were set to 0.7, 1.1 and 2.0 times the activity in grey matter, respectively. The kinetics were then assigned to each brain region and a dynamic sequence of sinograms was obtained by forward projecting the images. Appropriate Poisson noise and blurring were also added to simulate realistic sinograms acquired on an ECAT 951R whole body tomograph (CTI/Siemens, Knoxville, TN). Dynamic images were reconstructed using filtered back-projection. Five cluster images were generated by applying cluster analysis to the noisy dynamic images and their associated TACs were extracted. Three (grey matter, white matter and tumour) out of five TACs were selected as they have very different kinetics. The selected TACs were then used by SIME and SIMEP for non-invasive estimation of the physiological parameters. Model fitting to the three TACs with the measured IF was also performed in order to compare the agreement between the parameter estimates obtained from different methods.

3 Results and Discussion

The three TACs and the corresponding fitted curves by SIME are shown in Figure 1, while the estimated physiological parameters, $K = k_1k_3/(k_2+k_3)$, in the three TACs using different methods are shown in Table 1. It is seen that the fitted curves and the estimates are in good agreement with the corresponding kinetic curves extracted by cluster analysis. The coefficients of variation (CVs) obtained by SIMEP are reasonable and are much better than those obtained from using SIME despite the fact that they are relatively larger than those obtained from model fitting. It is as expected because the only information available are the tissue kinetics and the two late venous blood samples which is in contrary to the model fitting approach in which the whole measured IF is available in addition to the tissue kinetics. Given the very limited information the CVs obtained by SIMEP are acceptable.

Since the tissue TACs are extracted by cluster analysis automatically, the subjectivity of manual ROI delineation can be reduced and thus it is feasible that cluster analysis can be used to segment tissues of different kinetics in PET data and that it can be used as an alternative to manual ROI delineation for the non-invasive quantification of physiological parameters as in our previous work (Wong *et al*., 1999).

Table 1: Estimates for the physiological parameter, *K*, in the three TACs using different methods. Values are estimates ± %CV.

	Gold standard	SIME	SIMEP
Grey Matter	0.0109±3.2	0.0102±1001.9	0.0113±8.7
White Matter	0.0075±10.6	0.0076±1223.5	0.0075±29.6
Tumour	0.0219±19.5	0.0203±1228.8	0.0201±15.3

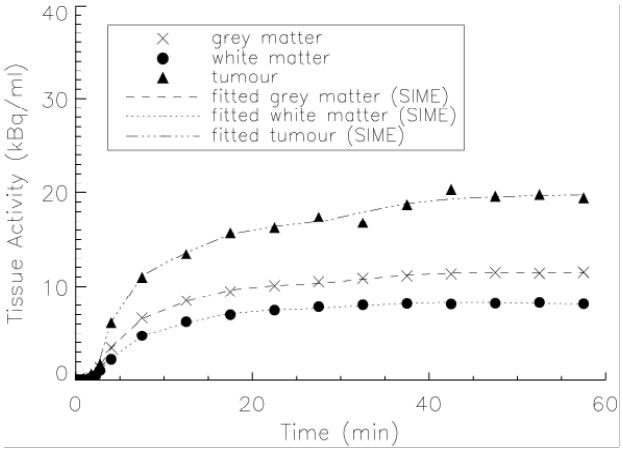

Figure 1: Extracted tissue TACs corresponding to grey matter, white matter and tumour bycluster analysis and the fitted curves obtained by SIME

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4 Conclusions

Our results show that it is feasible to estimate the physiological parameters with SIME (and SIMEP) using the TACs extracted automatically by cluster analysis. The physiological parameters in different TACs estimated by SIME and SIMEP are comparable to those obtained from model fitting to the TACs with the measured input function (*gold standard*). The results have encouraged us to investigate the applicability of the combined approach to clinical PET study. Although this work used FDG-PET as an example for illustration, it is expected that the methodologies can be applied to PET studies with other tracers.

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