# A Reliable Unbiased Parametric Imaging Algorithm for Noisy Clinical Brain PET Data

Dagan Feng[1,2], Weidong Cai[1,2], and Roger Fulton[1,3]

[1] Center of DSP for Multimedia Applications,

Dept. of Electronic & Information Engineering, Hong Kong Polytechnic University

[2] Biomedical and Multimedia Information Technology (BMIT) Group,

Basser Dept. of Computer Science, The University of Sydney, Australia

[3] Dept. of PET and Nuclear Medicine, Royal Prince Alfred Hospital, Australia

Address correspondence to Prof. Dagan Feng

Professor & Deputy Director,

Center of DSP for Multimedia Applications

The Hong Kong Polytechnic University

Director, Biomedical & Multimedia Information Technology (BMIT) Group

The University of Sydney

NSW 2006, Australia

Telephone: (+61-2) 9351-2103

Facsimile: (+61-2) 9351-3838

E-mail: feng@cs.usyd.edu.au or enfeng@polyu.edu.hk

Running Title: A Reliable Parametric Imaging Algorithm for Clinical Brain PET

# ABSTRACT

The generalized linear least squares (GLLS) algorithm for parameter estimation of non-uniformly sampled biomedical systems is a computationally efficient and statistically reliable way to generate parametric images for tracer dynamic studies with positron emission tomography (PET). However, for very noisy clinical PET data, parameter estimation using GLLS may not converge for every pixel. In this paper, we proposed an improved GLLS algorithm which can guarantee that the estimation converges for noisy pixel curves and the parameters estimated are within the physiological and pathological ranges. It has been investigated via clinical FDG-PET studies. The results showed that the parametric image generated by the improved GLLS is more smooth and reliable than that by the GLLS algorithm. Therefore, this new algorithm can provide more accurate parametric images in dynamic clinical brain PET studies.


# I. INTRODUCTION

Biomedical parametric imaging, which requires the estimation of parameters for certain bio-systems on a pixel-by-pixel basis, is an important technique providing image-wide quantification of physiological and biochemical function and visualization of the distribution of these functions corresponding to anatomic structures. A number of parametric imaging algorithms have been developed previously [1]-[7]. The steady-state method [5] uses a constant input of tracer allowing the radioactivity concentrations in blood and tissue to reach an equilibrium. The autoradiographic approach (ARA) [3] has the advantage of using only one tissue concentration measurement although still requires a fully sampled arterial input

function to estimate usually one parameter. In both the steady state and the ARA methods, parameter estimation is based on some assumptions which reduce the estimation accuracy, particularly when abnormal pathology is present. In the dynamic protocols, more than one unknown parameter can be estimated from a Single Input / Single Output (SISO) experiment. The nonlinear least squares (NLLS) algorithm [2] can provide parameter estimates of optimum statistical accuracy. However, this NLLS method requires considerable computation time and good initial parameter values (without a good initial guess, NLLS will not converge). Therefore it is impractical for estimation of image-wide parameter estimates. Several alternative rapid parameter estimation schemes for certain specific dynamic PET data or model types have been proposed. For example, the integrated projection method can simultaneously estimate cerebral blood flow and distribution volume from the decay uncorrected and corrected PET data in a very efficient way [7]. The well-known Patlak graphical approach (PGA) can estimate the combination of the model rate constants, which allows for the determination of cerebral metabolic rate of glucose, when a uni-directional transfer process is dominant during the experimental period, i.e., the returning rate constant for the model used must be assumed to be zero [3]. Among these schemes, the weighted integration method (WIM) [1] algorithm is more generally applicable. However, to increase the estimation reliability by predetermining the optimal sets of weighting functions for every pixel in the functional image is difficult. A generalized linear least squares (GLLS) algorithm [8] has been proposed by our research group and is useful in image-wide parameter estimation to generate parametric images with PET. We have found that, compared with the existing algorithms, the GLLS algorithm: (1) can directly estimate continuous model parameters; (2) does not require initial parameter values; (3) is generally applicable to a variety of models with

different structures; (4) can estimate individual model parameters as well as physiological parameters; (5) requires very little computing time; and (6) can produce unbiased estimates [8]. However, like most of the other parameter estimation algorithms (e.g., NLLS [2]), due to the very noisy clinical PET data, parameter estimation using the GLLS may not converge to reasonable values within the expected physiological and pathological ranges for every pixel (noisy curve). Therefore, in this paper, we proposed an improved GLLS algorithm which can guarantee that the estimation converges for all pixels (noisy pixel curves) and the parameters estimated are within the physiological and pathological ranges.

# II. MATERIALS AND METHODS

## A. *The Improved GLLS Algorithm*

For simplicity and clarity, we developed the new algorithm using dynamic PET *[18F]-2-fluoro-2-deoxy-D-glucose* (FDG) images as a motivative example, although the algorithm can be used for other biomedical functional imaging. In this paper, the algorithm is based on an optimal image sampling schedule involving smaller number of image frames with a five-parameter FDG model [9]. The GLLS estimator can be derived as:

$$\hat{\theta} = [\mathbf{Z}']^{-1}\mathbf{r}' \tag{1}$$

where

$$\mathbf{r}' = [\psi_1 \otimes C_i^*(t_1'), \psi_1 \otimes C_i^*(t_2'), \psi_1 \otimes C_i^*(t_3'), \psi_1 \otimes C_i^*(t_4'), \psi_1 \otimes C_i^*(t_5')]^{\mathbf{T}} \tag{2}$$

$$\mathbf{Z}' = \begin{bmatrix} \psi_1 \otimes C_p^*(t_1') & \psi_2 \otimes C_p^*(t_1') & \frac{1}{\lambda_1\lambda_2}\int_0^{t_1'} C_p^*(\tau)d\tau + \psi_3 \otimes C_p^*(t_1') & \psi_2 \otimes C_i^*(t_1') & \frac{1}{\lambda_1\lambda_2}\int_0^{t_1'} C_i^*(\tau)d\tau + \psi_3 \otimes C_i^*(t_1') \\ \psi_1 \otimes C_p^*(t_2') & \psi_2 \otimes C_p^*(t_2') & \frac{1}{\lambda_1\lambda_2}\int_0^{t_2'} C_p^*(\tau)d\tau + \psi_3 \otimes C_p^*(t_2') & \psi_2 \otimes C_i^*(t_2') & \frac{1}{\lambda_1\lambda_2}\int_0^{t_2'} C_i^*(\tau)d\tau + \psi_3 \otimes C_i^*(t_2') \\ \psi_1 \otimes C_p^*(t_3') & \psi_2 \otimes C_p^*(t_3') & \frac{1}{\lambda_1\lambda_2}\int_0^{t_3'} C_p^*(\tau)d\tau + \psi_3 \otimes C_p^*(t_3') & \psi_2 \otimes C_i^*(t_3') & \frac{1}{\lambda_1\lambda_2}\int_0^{t_3'} C_i^*(\tau)d\tau + \psi_3 \otimes C_i^*(t_3') \\ \psi_1 \otimes C_p^*(t_4') & \psi_2 \otimes C_p^*(t_4') & \frac{1}{\lambda_1\lambda_2}\int_0^{t_4'} C_p^*(\tau)d\tau + \psi_3 \otimes C_p^*(t_4') & \psi_2 \otimes C_i^*(t_4') & \frac{1}{\lambda_1\lambda_2}\int_0^{t_4'} C_i^*(\tau)d\tau + \psi_3 \otimes C_i^*(t_4') \\ \psi_1 \otimes C_p^*(t_5') & \psi_2 \otimes C_p^*(t_5') & \frac{1}{\lambda_1\lambda_2}\int_0^{t_5'} C_p^*(\tau)d\tau + \psi_3 \otimes C_p^*(t_5') & \psi_2 \otimes C_i^*(t_5') & \frac{1}{\lambda_1\lambda_2}\int_0^{t_5'} C_i^*(\tau)d\tau + \psi_3 \otimes C_i^*(t_5') \end{bmatrix} \quad (3)$$

$\theta = [P_1, P_2, P_3, P_4, P_5]^{\mathrm{T}}$, and $C_p^*(t)$ is the FDG concentration in plasma represented by the plasma time-activity curve (PTAC), $C_i^*(t)$ is the total FDG concentration in tissue, or tissue time activity concentration curve (TTAC). Once estimates of the macro-parameters are obtained, the micro-parameters, i.e. the rate constants for the FDG model, can be calculated as

$$\hat{k}_1^* = \frac{P_1P_4 + P_2}{1 - P_1}, \qquad \hat{k}_2^* = -\frac{P_1P_5 + P_3}{P_1P_4 + P_2} - P_4,$$

$$\hat{k}_3^* = -(\hat{k}_2^* + \hat{k}_4^* + P_4), \qquad \hat{k}_4^* = -\frac{P_5}{\hat{k}_2^*}, \qquad \hat{k}_5^* = P_1 \quad (4)$$

Then the local cerebral metabolic rate of glucose (LCMRGlc) in the human brain can be calculated from

$$LCMRGlc = \left(C_p / LC\right)\left(k_1^* k_3^*\right)/\left(k_2^* + k_3^*\right) \quad (5)$$

where $LC$ denotes the lumped constant, and $C_p$ is the "cold" glucose concentration in plasma [6]. Details of the GLLS can be found in [8][9].

In this new algorithm, a clustering technique [10] was employed to determine the lower / upper bounds of parameter estimation at various pixels. Many clustering algorithms have been developed [11][12], which can be divided into direct (constructive) or indirect (optimization) ones, depending on whether a criterion measure is used during cluster analysis. The direct algorithms perform clustering

without the necessity of a criterion measure, whereas indirect algorithms use the criterion measure to optimize clustering. Clustering algorithms can be further classified as agglomerative or divisive, according to whether classification is in a top-down or bottom-up direction. In this paper, we use an indirect agglomerative clustering algorithm based on the traditional Euclidean distance criterion measure. In general, a time activity curve (TAC) can be obtained from each pixel. However, many TACs have similar kinetics. The clustering technique can be used to classify image-wide TACs, $C_i(t)$ (where $i$=1,2,…,R, and R is the total number of image pixels), into S cluster groups $C_j$ (where j=1,2,…,S, and S<<R) by measurement of the magnitude of natural association (similarity characteristics). It is expected that TACs with high degrees of natural association will belong to the same cluster groups, and conversely, TACs with low degrees will belong to different groups [8][9]. For clustering to be valid, each TAC must be assigned uniquely to a cluster group (i.e., no TAC is allowed to belong to two different groups. The indexed image will map each pixel into a particular cluster. The respective temporal information for each cluster group will be contained in a look-up table (LUT). The LUT will be sequentially indexed by cluster group and each index will contain the mean TAC cluster values for that group. For each TAC group, the maximum and minimum values of parameter estimates can be pre-calculated according to certain rules based on the mean TAC, including the consideration of the physiological and pathological ranges. For each pixel parameter within the group, the estimation is forced to be converged within the upper and lower bounds.

B. *Clinical FDG-PET Studies*

Clinical dynamic FDG-PET studies were carried out at the National PET/Cyclotron Center, Taipei Veterans General Hospital, Taiwan, using a PC4096-15WB PET

scanner (GE / Scanditronix) which has eight detector rings and fifteen slices. This scanner contains 4096 detectors with axial and transaxial resolutions of 6.5mm full width at half maximum (FWHM). Between 200 and 400MBq (approximately 0.5mg) of FDG was injected intravenously and serial arterial blood samples (each 2-3 ml) were taken at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 7, 10, 15, 20, 30, 60, 90 and 120 minutes post-injection. These samples were immediately placed on ice and the plasma was separated for the determination of plasma FDG and glucose concentrations. PET scanning was performed according to a schedule which consisted of 22 temporal frames: 10×0.2, 2×0.5, 2×1, 1×1.5, 1×3.5, 2×5, 1×10 and 3×30 minute scans. The scanning was completed within 120 minutes of tracer injection. The PET data were corrected for attenuation and decay-corrected to the time of injection and then reconstructed using filtered back-projection with a Hanning filter. The reconstructed images were 128×128 with pixel size of 2mm×2mm.

## III. RESULTS AND DISCUSSION

The parametric image of the local cerebral metabolic rates of glucose (LCMRGlc) generated by the improved GLLS algorithm was compared with that by the GLLS. The resultant physiological parametric images for six different planes from three clinical FDG-PET studies are shown in Fig.1. From the images, we can see the parametric images generated by the improved GLLS algorithm are more smooth and reliable that those by the GLLS algorithm, in which there are some pixels with diverged estimates. In contrast with other kinds of images, dynamic PET images have a consistent general structure consisting of and approximately oval region containing almost all of the information of interest. In our new algorithm, background pixels

were neglected, which greatly reduced computing time of parameter estimation, and removed background noise. Therefore, this new algorithm can provide more accurate parametric images in dynamic clinical brain PET studies.

# IV. CONCLUSIONS

An improved generalized linear least squares (GLLS) algorithm, which can generate more smooth and reliable parametric images, has been presented. It has been investigated via clinical FDG-PET studies. Our results demonstrated that this new parametric imaging algorithm can provide more accurate parametric images and is potentially very useful in dynamic clinical brain PET studies.

# ACKNOWLEDGMENTS

This research is supported by the RGC and ARC Grants. The authors are grateful to the National PET /Cyclotron Center, Taipei Veterans General Hospital Taiwan for their kind assistance.

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Fig.1. Illustration of the difference between the parametric image of local cerebral metabolic rates of glucose (LCMRGlc) generated from the GLLS algorithm and from the new algorithm. The unit of LCMRGlc is mg/min/100ml.