Fast Determination Method of Cerebral Metabolic Rate Images of Glucose Using Dynamic PET Data

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Abstract
Measurement of the rate constant parameters of the tracer 18F–FDG, used with positron emission tomography (PET) to determine the cerebral metabolic rate of glucose (CMRGlc), can provide a clear understanding of the physiological processes in the human brain. At present, the methods that are widely used to obtain CMRGlc, such as nonlinear least squares (NLS), first require the reconstruction of a time sequence of images. The reconstruction of these images requires a large amount of computation, especially in 3D Depth-of-Interaction PET (DOI–PET), and the nonlinear based methods also require a large amount of computation. In this paper, we propose a fast parametric image reconstruction method for 18F–FDG dynamic PET studies. In our method a deconvolving process is first employed on the time sequential projection data to remove the effect of the measured plasma time activity. The deconvolved terms are integrated over three different time intervals and the parameters for determining CMRGlc can be obtained analytically. Our method requires only three reconstructing processes and reduces the computational demand to estimate CMRGlc. The algorithm performance is evaluated using a digital phantom and a clinical data set and the results show that the proposed method produces images with the same or better quality as the images from the NLS method, with much less computation compared to the NLS method.

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1. Introduction

Parametric images are very useful to show spatial and temporal changes and differences between regions of tracer. For example measurement of the rate constant parameters of the tracer $^{18}$F–FDG, used with positron emission tomography (PET) to determine the cerebral metabolic rate of glucose (CMRGlc), can provide a clear understanding of the physiological processes in the human brain. In general approaches to estimate the rate constants, the time activities of tissue (TAC) are first obtained from each pixel of a reconstructed image using dynamic PET data. Then the rate constants are estimated from the time activity curves of total tissue (tTAC) in conjunction with the plasma time activity curve of FDG (pTAC) and CMRGlc is calculated from the estimated rate constants. At present, a variety of methods, including nonlinear least squares (NLS), the weighted integration method (WIM)\textsuperscript{1–3}, the generalized least squares method\textsuperscript{4} etc.\textsuperscript{5,6} are used for this aim. However, reconstructing a large number of sequential images takes a long time and this tendency increases dramatically in 3D Depth–of Interaction PET (DOI–PET). Moreover, since the NLS method, known as the most accurate method\textsuperscript{7,8}, uses a recursive algorithm, the time to estimate the rate constants will increase in a high resolution PET. We can find alternative approaches such as direct calculation methods using ML reconstruction\textsuperscript{9,10} though they require an iterative approach to solve the reconstruction problem or a special assumption for describing a linear combination of TACs. So, there would be significantly less computation for a method not requiring a reconstruction process for the time sequential images and an iterative estimation technique but instead using an analytical direct parametric image reconstruction technique from PET projection data.

In this paper, we propose a fast CMRGlc estimation method for $^{18}$F–FDG dynamic studies. In our method the effect of the pTAC is removed from the time sequential projection data and the updated projection data are integrated over three different temporal intervals. Then the proposed method requires only three reconstructing processes and CMRGlc and the rate parameters are given analytically in a short time.

2. Method

2.1. Formulation of the FDG model

The FDG model\textsuperscript{11} consists of three compartments which describe the tracer distribution in the brain as shown in Figure 1. Our method assumes the 3–compartment, 3–parameter model ($k_4$ is assumed to be zero in our study). Then the set of differential equations of the FDG model is given by

\[
\begin{align*}
\frac{d}{dt} C_e(t) &= K_1 C_p(t) - (k_2 + k_3) C_e(t) \\
\frac{d}{dt} C_m(t) &= k_3 C_e(t)
\end{align*}
\]

\text{(1)}
where \( C_p(t) \) denotes pTAC, \( C_e(t) \) and \( C_m(t) \) are TAC of FDG and FDG–6P in tissue respectively, \( C_i(t) = C_e(t) + C_m(t) \) denotes tTAC, and \( k_1, k_2, k_3 \) are rate constants.

After the rate constants have been estimated, CMRGl, denoted by \( R \), is given by

\[
R = \frac{1}{LC} \times C_p^g,
\]

where \( LC \) denotes the lumped constant \(^{12}\), \( C_p^g \) is the concentration of non–tracer glucose in the plasma and \( \times \) is a combination parameter called \( K–complex \) which is defined as

\[
\times = \frac{k_1/k_3}{k_2 + k_3}.
\]

This parameter is also used in FDG studies and it is easy to obtain CMRGl from this one. Therefore we use \( K–complex \) to evaluate methods instead of using CMRGl in this paper.

To begin with, the projection data of PET are formulated. In a dynamic study the radioactivity distribution will be changing temporally and spatially. Moreover, the rate constants are also distinct for different positions. Therefore by solving equation (1), the total radioactivity distribution in tissue described as a function of time and position is expressed \(^{12,14}\) by

\[
C_i(r, t) = C_p(t) \times \frac{K_1(r)}{k_2(r) + k_3(r)} (k_3(r) + k_2(r) \exp \{- (k_2(r) + k_3(r)t)\}),
\]

in which \( t \) denotes a time, \( r \) indicates a position in the object space and \( \times \) represents convolution.

If the sensitivity function of the \( j–th \) pair of detectors is denoted by \( h_j(r) \), the projection data for the \( j–th \) bin, \( g_j(t) \), obtained at a certain time \( t \) is given by

\[
g_j(t) = \int h_j(r) C_i(r, t) \, dr = C_p(t) \times L_j(t) \quad (j = 1, \cdots, M),
\]

where

\[
L_j(t) = \int h_j(r) \frac{K_1(r)}{k_2(r) + k_3(r)} \times (k_3(r) + k_2(r) \exp \{- (k_2(r) + k_3(r)t)\}) \, dr,
\]

and \( M \) denotes the number of projection data. We mention here that the sensitivity functions, which are calculated from the scanner geometry and other factors such as the attenuation and detector efficiency, are independent of the time activities.

The integration of equation (5) can be approximated by a convolving sum and the measured data are rewritten as

\[
g_j(n \Delta t) = \sum_{i=1}^{n} C_p(i \Delta t) L_j(n \Delta t - i \Delta t) \Delta t,
\]

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where $\Delta t$ is the duration of each time frame of the measured data and $n$ represents a frame number in the sequence. From equation (7), $L_j(t)$ can be calculated by achieving deconvolution of $g_j(t)$ numerically as follows.

$$L_j(0) = g_j(\Delta t) \times \frac{1}{C_p(\Delta t) \Delta t},$$  \hspace{2cm} (8)

$$L_j(n \Delta t) = \left[ g_j((n+1) \Delta t) - \sum_{i=0}^{n-1} C_p [(n-i+1) \Delta t] L_j(i \Delta t) \Delta t \right] \times \frac{1}{C_p(\Delta t) \Delta t} \quad (n \geq 1)$$

Before the deconvolution, equal interval data are required so we have to interpolate the original data and the random, scatter and deadtime corrections must be applied to the original data. Those sequential terms of equation (8), $L_j(t)$, only depend on the three parameters, $K_1$, $k_2$, $k_3$. However we need a reconstruction of the sequential terms and we have to use a nonlinear estimation approach to obtain those parameters in this stage.

2.2. Parameter estimation

The basic approach of our method involves a reconstruction process using an integration of sequential data obtained by equation (8), followed by a useful trick to obtain the rate constants analytically in a short time.

At first, we note that there are three unknown parameters at each point in an object, so, we integrate the updated terms of equation (8) over three temporal intervals from 0 to $T_i \ (i=1,2,3)$. The integral values, $Q^j_i$, can be approximated using a summation over the sequences again as,

$$Q^j_i = \int_0^{T_i=n \Delta t} L_j(t) dt \approx \sum_{n=1}^{n} L_j(i \Delta t) \Delta t \quad i=1,2,3.$$  \hspace{2cm} (9)

Then the reconstruction technique which is used for equation (5) as the forward problem, for example the filtered back projection (FBP) or the natural pixel based reconstruction, is employed on the vector $Q^j$ which is a column vector of $M$ elements $Q^j_i$, to obtain the reconstructed images $S_i(r)$ as follows [see equation (6)].

$$S_i(r) = \text{Reconstruction} [Q^j].$$

$$= \int_0^{T_i} \frac{K_1(r)}{k_2(r)+k_3(r)} (k_3(r)+k_2(r)\exp \left\{ -(k_2(r)+k_3(r)t) \right\}) dt$$

$$= T_i \ x_1(r) + x_2(r) - x_2(r) \exp \left\{ -T_i \ x_3(r) \right\} \quad \text{[see equation (6)]} \hspace{2cm} (10)$$

where $x_1(r)$, $x_2(r)$ and $x_3(r)$ are secondary parameters defined by

$x_1(r) = K_1(r)k_3(r) / \{k_2(r)+k_3(r)\} = \kappa(r)$

$x_2(r) = K_1(r)k_2(r) / \{k_2(r)+k_3(r)\}^2, \hspace{2cm} (11)$

$x_3(r) = k_2(r)+k_3(r)$
Then we apply a useful trick to equation (10). If we carefully choose the three temporal intervals, $T_i \ (i=1,2,3)$ which are related by $T_3 = 2T_2 = 4T_1$, the exponential terms of equation (10) can be expressed by

$$\exp\{-T_2x_3(r)\} = \exp\{-2T_1x_3(r)\} = (\exp\{-T_1x_3(r)\})^2$$ (12)

$$\exp\{-T_2x_3(r)\} = \exp\{-2T_2x_3(r)\} = (\exp\{-T_2x_3(r)\})^2$$ (13)

Subsequently using equation (10), the relation described in equation (12) becomes

$$(\exp\{-T_1x_3(r)\})^2 = \left[ \frac{T_1x_1(r) + x_2(r) - S_1(r)}{x_2(r)} \right]^2 = \frac{2T_1x_1(r) + x_2(r) - S_2(r)}{x_2(r)} = \exp\{-T_2x_3(r)\}$$

Then it can be simplified as

$$(S_1(r) - T_1x_1(r))^2 = (2S_1(r) - S_2(r))x_2(r)$$ (14)

Also the following equation can be derived from equations (10) and (13) as

$$(S_1(r) - 2T_1x_1(r))^2 = (2S_2(r) - S_3(r))x_2(r)$$ (15)

From equations (14) and (15), eliminating $x_2(r)$, a quadratic equation for $x_1(r)$ can be derived as,

$$(4\alpha T_1^2 - T_1^2)x_1(r)^2 - 2T_1(2\alpha S_2(r) - S_1(r))x_1(r) + \alpha S_2^2(r) - S_1^2(r) = 0$$ (16)

where $\alpha = (2S_1(r) - S_2(r))/(2S_2(r) - S_3(r))$.

Finally solving this equation, $x_1(r)$ is given by

$$x_1(r) = \frac{(2\alpha S_2(r) - S_1(r)) - \sqrt{\alpha (2S_1(r) - S_2(r))}}{(4\alpha - 1)T_1}$$ (17)

Also from equations (10) and (15), $x_2(r)$ and $x_3(r)$ are derived as

$$x_2(r) = \frac{(S_2(r) - 2T_1x_3(r))^2}{2S_2(r) - S_3(r)}$$ (18)

$$x_3(r) = -\frac{1}{4T_1}\log\left[ \frac{x_2(r) + 4T_1 - S_3(r)}{x_2(r)} \right]$$ (19)

Once the secondary parameters have been calculated, the K–complex and the rate constants can be obtained from equation (11) using a simple calculation. The estimation of these parameters uses the following equations.
The proposed method is simpler than nonlinear techniques because it only requires the solution of a quadratic equation for the 3-compartment, 3-parameter model of FDG, even though it requires the extra processing of deconvolution and summation. Consequently, our method provides a considerable reduction in computational time for estimating parameters compared with other methods.

3. Computer Simulation Using The Digital Brain Phantom

Numerical simulation was carried out to confirm the effectiveness of the proposed method. The measurement system assumed a 2D PET system and a 2D Hoffman digital brain phantom (256 pixels by 256 pixels) containing white matter and gray matter regions [Figure 2(a)] was used for the evaluation. The measurement data for the digital phantom were sinograms of 256 bins x 256 views simulating dynamic $^{18}$F-FDG flow with 40 frames per 60 minutes (12 frames of 30s, 4 frames of 60s and 24 frames of 120s). Only for the deconvolution process of the proposed method were the projection data interpolated to 120 frames of 30 seconds each over a 60 minute period. The kinetic parameters used were known rate constants (for gray matter $K_1 = 0.102$ (ml/g/min), $k_2 = 0.130$ (min$^{-1}$) and $k_3 = 0.062$ (min$^{-1}$), for white matter $K_1 = 0.054$ (ml/g/min), $k_2 = 0.109$ (min$^{-1}$) and $k_3 = 0.042$ (min$^{-1}$)). A pTAC function proposed by Phelps et al. was used to generate an input function [Figure 2(b)]. Scattered and attenuated photons were neglected here though the projection data included the effects of the Poisson statistics. In the simulation to take account of the lifetime of the radioisotope, the ideal projection data were divided by the decay correction factor, the Poisson noise was added and the result was multiplied by the decay correction factor again for parameter estimation processing.

The noise level mentioned in our results was based on the last frame of the projection data, $g_{\text{noise}}$.
Figure 3 shows examples of the time count curves of the projection data at various noise levels.

In our phantom and clinical studies, the reconstruction technique employed was FBP because of its easy implementation though our method can be used with any reconstruction techniques. The cut-off frequency of FBP was 0.375 of the Nyquist frequency in the phantom study. The NLS was used with the 0.1% convergence criterion and its maximum iteration number was 50.

Figure 4 (a) and (b) show the estimated images of K-complex using respectively, the proposed method and the NLS which is based on the modified Marquardt method 17, 18) at the same noise level (13%). In this study the total time of the dynamic study was sixty minutes, so the proposed method was used with the integration period $T_1 = 15\text{min}$. The integration period has an effect on the accuracy of the results and longer integration period will reduce the estimation errors, so we chose as long a period as possible.

The rate constants of some pixels for the NLS did not converge due to noise. Those points are shown as isolated black points in the figure for evaluating the methods objectively, though an interpolation technique is usually applied to the estimated images to help in visualization. We also clipped estimated values for $K_1 < 0.5$, $k_2 < 0.5$ and $k_3 < 0.2$. The results illustrated that our method is stable and that those methods provide similar results except for the above issues.

Figures 5 and 6 compare results of comparisons of the proposed method, the NLS and the weighted integral method (WIM) for a range of noise levels. In this study we compared the accuracy versus noise behavior of the estimation techniques. The performance of the algorithms was evaluated using the the mean absolute difference (MAD) and the standard deviation (SD) 17). The MAD and SD are defined as

$$\text{Noise level} = \frac{\sum_{i=0}^{M} |g_{i,\text{noise add}} - g_{i,\text{true}}|}{\sum_{i=0}^{M} g_{i,\text{true}}} \times 100\%$$
Figure 5. Mean absolute differences of digital phantom for parameters. (a) K-complex, (b) $K_1$, (c) $k_2$, (d) $k_3$.

Figure 6. Standard deviations of digital phantom for parameters. (a) K-complex, (b) $K_1$, (c) $k_2$, (d) $k_3$. 
\[ \text{MAD} = \frac{1}{N} \sum_{i=0}^{N} \left| \frac{\hat{p}_i - p_i}{p_i} \times 100 \% \right) \]

\[ \text{SD} = \sqrt{\frac{1}{N} \sum_{i=0}^{N} (\hat{p}_i - \bar{p})^2 / N \times \frac{100}{\bar{p}}} \% \]

where \( p_i \) is an ideal value and \( \hat{p}_i \) is an estimated value of rate constants of \( i \)-th pixel, \( \bar{p} \) is an average of the estimated values in the region of the same matter and \( N \) denotes a total number of pixels in the region. These values were calculated for white and gray matter separately. The proposed method had almost the same accuracy as the NLS for the rate constants and the K-complex respectively. The fact that the difference of K-complex was smaller than the differences of other rate constants confirmed that the estimation of K-Complex is generally stable. Moreover estimated results provided by the WIM had a tendency to be biased; this was clearly shown in the gray matter estimation results.

The correlations of the estimated K-complex obtained by the proposed method and the NLS at noise free and the 13% noise level are shown in Figure 7. Points in the graph represent each value estimated by the NLS and the proposed method with the NLS estimates as the horizontal coordinate and the proposed one as the vertical coordinate. In the noise free case the result showed that the two methods correlated perfectly and most of the points were gathered around the true values; a few points were scattered because of the unavoidable systematic error caused by the FBP. The true values of K-complex were 0.016 for the white matter and 0.033 for the gray matter and averages of estimated values of both methods were 0.016 (\( C_1 \) in Figure 7(a)) and 0.032 (\( C_2 \) in Figure 7(a)) respectively. In the noise added case the points were clearly shown to make two clusters with center points that were almost the true values. Averages of estimated values of both methods were 0.017 (\( C_1 \) in Figure 7(b)) and 0.031 (\( C_2 \) in Figure 7(b)) respectively. Those clusters were located on the same diagonal line. We could clearly see the difference between the two methods was small enough to be neglected, so our method had the same accuracy as NLS, which can be considered as a gold standard.

![Figure 7. Correlation between K-complex estimated by the NLS and the proposed method on the phantom study. (a) Noise free. (b) 13% noise added.](https://example.com/figure7.png)

<table>
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<th>Reconstruction(s)</th>
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Table 1 shows the computation time for the reconstruction step and the estimation step on a Gateway Intel Celeron 500 MHz personal computer. The estimation time of the proposed method included the times needed for the deconvolution and summation. The computation time of NLS varied according to the noise level and it was clearly seen that the proposed approach was faster than the WIM and much faster than the NLS.

These results indicate that the proposed method has the same accuracy as NLS and our method can replace the NLS method because of its computational efficiency.

4. Clinical Study

Data from a clinical study were used to assess the proposed method. The clinical PET data were acquired using an Shimadzu HEADTOME IV (Kyoto, Japan) with the 2D acquisition mode. A 45-min dynamic scan was performed and the measured sinogram data were 256 bins x 256 views x 7 slices with 18 frames (two time frames of 30 s, four frames of 60 s, four frames of 120 s and eight frames of 240 s). Only for the deconvolution process of the proposed method were the projection data interpolated to 80 frames of 45s each. The cut-off frequency of FBP was 0.25 of the Nyquist frequency in the clinical study and the maximum iteration number for NLS was 50.

At first we applied the Karhunen–Loève (K–L) transform to the dynamic projection data to achieve a reduction in noise because it is difficult to know the noise properties of the PET data. The projection data consisted of selecting the first 5 components in the K–L space. Then applying our method with $T_1 = 12\text{ min}$ and the NLS to the 5-component projection data, the K–complex, $K_1$, $k_2$, and $k_3$ images were estimated.
The estimated K-complex images are shown in Figure 8. In these images, we noted some non-convergence points, which we also saw in the simulation result of the NLS. Usually some visualization techniques are applied to erase the non-convergence points, but for easy understanding we left those points in the images. Apart from them, there was little difference between the two methods.

The correlations of the estimated K-complex obtained by the two methods are shown in Figure 9. The points were almost all on the same diagonal line, though the estimated values of the proposed method were slightly different from the values of the NLS method. The difference between the two methods was small enough to be neglected, so our method had almost the same accuracy as NLS.

Table 2 shows the computation time of the comparisons between the NLS and our method in the clinical study. The reconstruction time of the proposed method included the time for the K-L transform and the pre-processing. The computation time of the proposed method was about 70 times faster than that of the NLS. This showed high efficiency, consistent with our previous phantom study.

5. Discussion And Conclusion

We have developed a new fast method for estimating kinetic parameter images from dynamic PET data. Our phantom and clinical studies for FDG confirm that the proposed approach provides a considerable improvement in estimation time as compared to the NLS-based method. The computation time is clinically practical even on a general-purpose computer, while the accuracy of the rate constants is similar to that of the NLS method.

Our method can be considered to be similar in its approach to the weighted integral method (WIM)\(^1\)\(^-\)\(^3\). However, compared with our method, the WIM has to do an optimization of weighting factors\(^2\) for each of the target tracer studies and this process is not practical for clinical use. Moreover estimated results provided by the WIM have a tendency to be biased, which is not seen with our method. However in the proposed method we have to use short time frames for deconvolution. In this study we used 30s intervals, but the computational time of the deconvolution represents 90% of the estimation time so it is important to define an optimal time interval for deconvolution.

And also a method for defining the integration period \(T_1\) is a needed because reducing examination time is a subject of general interest to medical doctors.

Another problem of our method is that the deconvolution has the possibility to enhance the noise. But we can try another approach to apply our method to the sequential reconstructed images if the reconstruction method which can estimate a smooth TAC is developed. Recently some methods\(^13\) have been proposed to use the smooth basis functions representing the tTAC as

\[
C_i(r, t) = C_p(t)**R(r,t) = \sum_{l=1}^{L} a_i(r) \varphi_l(t) \tag{27}
\]
where

\[ R(r, T) = \frac{K_1(r)}{k_2(r) + k_3(r)} (k_3(r) + k_2(r)\exp\{-(k_2(r) + k_3(r))t\}), \]

and \( \phi(t) \) are basis functions.

Applying those methods with our method the deconvolution process works well because the TAC, which is expressed by a linear combination of the smooth basis functions given a priori, will be smooth.

Once the coefficients \( a_i(r) \) are estimated using a 4-D reconstruction method, we can apply the deconvolution process to the basis functions like

\[ R(r, t) = \sum_{i=1}^{L} a_i(r) \cdot \text{Deconv} \{ \phi_i(t) \} = \sum_{i=1}^{L} a_i(r)R_i(r), \tag{28} \]

and can obtain the integral images \( S_i(r) \) in equation (10) as

\[ S_i(r) = \int_0^T R(r, t)dt. \tag{29} \]

Unfortunately we do not have a concrete plan here, so this approach remains a subject of future work.

The proposed method can be extended to other tracers like MP4A \(^{21}\) which is used to find the activity of acetylcholinesterase (AChE), whose behavior is also described using the 3-compartment, 3-parameter model. Our present simulation results show that our method will provide a stable estimation of the rate constants. However for extending our method to MP4A studies, we have to develop more quantitative evaluation tests for the estimated values of \( K_1 \) and \( k_3 \), in clinical cases because these values are important for knowing the activity of AChE in the brain tissue and these parameters are greatly influenced by the measurement noise even if applying the NLS method.

Although the method has been validated only for 2D acquisitions here, the theory can apply equally well to the 3D acquisition mode. Also our approach can be applied with any reconstruction algorithm even those belonging to the class of iterative methods. It would be practical to use an iterative method with our approach because the computation time to estimate the parameters is significantly reduced, compared to the standard approach.

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