Technical Note

Analysis of Kinetic Rate Constants in [^{18}F]Fluorodeoxyglucose Model Using a Least Square Fitting Package SALS (Statistical Analysis with Least Squares)[†]

Shuzo UEHARA, Yasuo KUWABARA*, Yuichi ICHIYA*, Makoto OTSUKA*,
Yoshiharu AYABE*, Yoshinori MIYAKE*, Koji MASUDA*
and Atsushi YOSHIMURA**

Laboratory of Physics, School of Health Sciences,

*Department of Radiology, Faculty of Medicine,

**Radioisotope Center, Kyushu University

3-1-1, Maidashi, Higashi-ku, Fukuoka 812, Japan

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The analysis of kinetic rate constants in the compartment model for [^{18}F]fluorodeoxyglucose (FDG) was undertaken. Four kinetic rate constants were determined with a least square fitting package SALS (Statistical Analysis with Least Squares), using the measured data of ^{18}F activity as a function of time. SALS calculations were found to be easy and quick with high precision. The rate constants and the curves fitted by the k_3^ and the k_4^* models were compared in situations with various degree of cerebral glucose metabolism during positron emission tomography (PET) studies. The k_4^* model in the determination of cerebral metabolic rate for glucose (CMR_{glu}) was much superior than the k_3^* model in any given situation as it always underestimates the metabolic rate. However, the k_3^* model produces less variation when the cerebral radioactivity curve shows steady rising pattern.*

Key Words: statistical analysis with least squares, cerebral glucose metabolism, kinetic rate constants, fluorodeoxyglucose, positron emission tomography

1. Introduction

An accurate and easy determination of kinetic rate constants ($k_1^* - k_4^*$) in PET study using FDG model is important in the diagnosis of cerebral disorders¹⁾. Several fitting methods to determine the kinetic rate constants have been adopted by many authors. Reivich et al. used the function minimization procedure of Fletcher-Powell²⁾. Wienhard et al. used the MINUIT

system³⁾. Sasaki et al. developed a table storage and look up method for the function minimization⁴⁾.

Although many general-purpose packages for the statistical analysis including the least square fitting method are available, they cannot be applied easily due to the complexity of equations used for FDG studies. While, the package SALS is a suitable one because it has aimed to analyse exclusively physical and chemical data⁵⁾. SALS made the analysis based on the k_4^* model ($k_4^* \neq 0$) and the k_3^* model ($k_4^* = 0$) and it is possible to execute in the program, simultaneously.

We compared the results for each model by observing the degree of deviation from the true cerebral radioactivity, at a given time.

[†] 最小二乗法パッケージSALSを用いた[^{18}F]Fluorodeoxyglucose モデルにおける速度定数の解析。上原周三, 桑原康雄*, 一矢有一*, 大塚 誠*, 綾部善治*, 三宅義徳*, 増田康治*, 吉村 厚**: 九州大学医療技術短期大学部, *同大学医学部放射線科, **同大学アイソトープ総合センター, 812 福岡市東区馬出3-1-1。

2. Methods

PET studies were done on subjects including 2 volunteers and patients with cerebral disorders. Arterial blood plasma activities ($C_p^*(t)$) were obtained at every 15 sec for 2 min, every 30 sec for 4 min, every 1 or 2 min for 10 min and every 10 min for 90 min following ^{18}F FDG administration. The cerebral radioactivities ($C_i^*(t)$) were obtained at every 2 min for 20 min, every 4 min for 60 min, and at 70 and 90 min using PET (Shimadzu HEADTOME III) section scans. The mean values in the region of interest (ROI) (14×18 mm) set on the cortical regions were used for calculation. Correction for the intravascular radioactivity was not performed.

Program package SALS was executed by feeding a few control parameters to solve problems and the model function. The model function and its partial derivatives with respect to each k^* were prepared in the user-coded subroutine 'MODEL D'. The model function F corresponding to $C_i^*(t)$ is represented by rewriting the original operational equation of the compartment model as follows:

$$F = k_1^*(p_1 S_1 + p_2 S_2) / (2f) \quad (1)$$

in which

$$f = \sqrt{(k_2^* + k_3^* + k_4^*)^2 - 4k_2^*k_4^*}$$

$$p_1 = f - k_2^* + k_3^* + k_4^*$$

$$p_2 = f + k_2^* - k_3^* - k_4^*$$

$$S_1 = \int_0^t e^{-\alpha_1(t-s)} C_p^*(s) ds$$

$$S_2 = \int_0^t e^{-\alpha_2(t-s)} C_p^*(s) ds.$$

Notations α_1 and α_2 are identical to those given by Phelps et al. The residual function R is defined by

$$R = C_i^*(t) - F. \quad (2)$$

Analytical expressions of partial derivatives are easily derived from Eq. (1). For k_2^* , k_3^* and k_4^* , the representation lying at the second line of Eq. (3) is commonly used except for explicit forms of f' , p_1' and p_2' as follows:

$$\frac{\partial F}{\partial k_1^*} = F / k_1^* \quad (3)$$

$$\begin{aligned} \frac{\partial F}{\partial k^*} = & k_1^* \{ (f p_1' - f' p_1) S_1 + (f p_2' - f' p_2) S_2 \\ & + f [(f' - 1) p_1 T_1 \\ & - (f' + 1) p_2 T_2] / 2 \} / (2f^2) \end{aligned}$$

in which

$$f' = (k_2^* + k_3^* - k_4^*) / f$$

$$p_1' = f' - 1 \quad p_2' = f' + 1 \text{ for } k_2^*$$

$$f' = (k_2^* + k_3^* + k_4^*) / f$$

$$p_1' = f' + 1 \quad p_2' = f' - 1 \text{ for } k_3^*$$

$$f' = (-k_2^* + k_3^* + k_4^*) / f$$

$$p_1' = f' + 1 \quad p_2' = f' - 1 \text{ for } k_4^*$$

$$T_1 = \int_0^t (t-s) e^{-\alpha_1(t-s)} C_p^*(s) ds$$

$$T_2 = \int_0^t (t-s) e^{-\alpha_2(t-s)} C_p^*(s) ds.$$

Using the analytical expression for $C_p^*(t)$ estimated by linear equations between the actual data points, integrals were evaluated by the subroutine AQC8 adopting the Clenshaw-Curtis

Fig. 1 Comparisons of tissue radioactivity between observed (•) and calculated by the k_4^* model (solid line) and by the k_3^* model (dashed line). Curves are principally characterized by the rising pattern after 60 min.

Table 1 Comparison of calculated rate constants in the k_4^* and the k_3^* model for typical data as shown in Fig. 1. D was evaluated by Eq. (4)

Model	(min $^{-1}$)				D	$A = \frac{k_1^* k_3^*}{k_2^* + k_3^*}$	Ratio
	k_1^*	k_2^*	k_3^*	k_4^*			
(a)	k_4^*	0.075	0.105	0.073	0.0064	72.2	0.0306
	k_3^*	0.069	0.072	0.044	—	102.6	0.0261
(b)	k_4^*	0.056	0.081	0.061	0.0098	77.6	0.0238
	k_3^*	0.048	0.043	0.025	—	97.9	0.0178
(c)	k_4^*	0.072	0.124	0.088	0.0130	67.1	0.0302
	k_3^*	0.055	0.041	0.023	—	135.2	0.0199

method documented in the Scientific Subroutine Library (SSL II)[®]. Numerical evaluations for Eqs. (1)–(3) were carried out for each measuring time t for given k^* , those were set initially as 0.1. The iterative procedure based on the Gauss-Newton method was repeated until the variation of the sum of R^2 decreases less than a given factor of 10^{-4} . The convergence was obtained usually in 10–20 iterations. Calculations were performed on a FACOM VP-100 computer, in which the SALS package is installed.

3. Results and Discussion

Figure 1 shows a comparison of the cerebral tissue activities in the frontal cortices between observed and calculated by using k_4^* or k_3^* models, in which typical curves having the following characteristics are given: (a) steady rising pattern over after 60 min, (c) a plateau after 60 min with higher washout rate of radiotracer and (b) an intermediate situation. Table 1 compares corresponding calculated rate constants, together with the factor $A (=k_1^* k_3^* / (k_2^* + k_3^*))$ relevant to the local cerebral metabolic rate for glucose (CMR_{glu}) and their ratios.

The standard deviations (D) listed in Table 1 give a quantitative evaluation of the fitting grade. That is defined by

$$D = \sqrt{\sum R^2 / (N_{\text{data}} - N_{\text{para}})} \quad (4)$$

in which R is given by Eq. (2), and N_{data} and N_{para} represent the number of data and parameters, respectively. It is reasonable that the curves fitted by the k_4^* model are almost in agreement with the observed or the true cerebral tissue activity and the k_3^* model shows much

Fig. 2 Distributions of the factor $A (=k_1^* k_3^* / (k_2^* + k_3^*))$ by the k_3^* model corresponding to various A by the k_4^* model at three ROIs of 19 patients.

variation especially in situations with a higher rate of clearance of tracer as is seen in (c). However, the k_3^* model shows less variation when there is a steady rise of radioactivity after 60 min as is seen in (a).

Taking into account the better fitting of the k_4^* model, it is assumed that the kinetic rate constants and A by the k_4^* model are more plausible than those by the k_3^* model. The deviation of A by the k_3^* model (A_3) from that by the k_4^* model (A_4) was examined for a common data set. Figure 2 presents distributions of A_3 corresponding to various A_4 at three ROIs, those are frontal cortex, whole brain and white matter, of randomly sampled 19 patients. If the marked point lies on a diagonal line, both A coincide. Therefore, the fact that all the points exist below the line shows underestima-

tion of A values by the k_3^* model, thus producing an error in the calculation of CMR_{glu} . On an average, the points are distributed around the line of $A_3=0.75A_4$, and which is consistent with the ratio of 0.748 for an intermediate example (b) in Table 1.

This study shows an important factor in the accurate determination of the CMR_{glu} using k_3^* or k_4^* model, as the k_4^* model is far more superior and compatible with the true cerebral tissue activity especially over the area with high metabolic activity and rapid clearance of radio-tracer when the k_3^* and the corresponding k_4^* values are also larger. In contrast, the k_3^* model is applicable to area with delayed clearance of tracer. The computing time is shorter by a factor of 2 than the k_4^* model analysis which consumes about 4 sec for a ROI.

In this study we have two problems. First, we used the mean values in a ROI as $C_1^*(t)$ which includes heterogenous tissues because of the limited resolution of the PET scan. Therefore, k^* values in this study were obtained for these tissues. Second, we did not correct intravascular radioactivity. It should not be neglected in tissue with large vascular space. ROI in the frontal region is estimated to contain 3–4% of blood volume. It may produce variation of $\sim 10\%$ in metabolic rate. We gave notice that our results included both uncertainties.

4. Conclusions

Package SALS has not been used before for the analysis of FDG dynamic scan data and our study shows it is easier and quicker in the determination of rate constants and compare the

k_4^* and k_3^* models with the cerebral time activity. The following conclusions can be deduced:

- (1) The k_4^* model fitting was more plausible than the k_3^* model.
- (2) The k_3^* model gives smaller A values compared to the k_4^* model and the magnitude of error becomes larger especially on the area with hypermetabolism, and it should be in mind.
- (3) The k_3^* model fitting is applicable in such a situation as a steady rising pattern of the radioactivity.

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