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New Parametric Imaging Algorithm for Quantification of Binding Parameter in non-reversible compartment model: MLAIR

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1. Introduction

Parametric imaging allows us analysis of the entire brain or body image. Graphical approaches are commonly employed to generate parametric imaging through linear or multilinear regression [1, 2, 3]. However, this linear regression method has limited accuracy due to bias in high level of noise data [4, 5]. Several methods have been proposed to reduce bias for linear regression estimation [4, 6] especially in reversible model.

In this study, we focus on generating a net accumulation rate (K_i), which is related to binding parameter in brain receptor study, parametric imaging in an irreversible compartment model using multiple linear analysis. The reliability of a newly developed multiple linear analysis method (MLAIR) was assessed through the Monte Carlo simulation, and we applied it to a [^{11}C]MeNTI PET for opioid receptor.

2. Methods and Results

2.1 Theory (Multiple Linear Analysis with Irreversible Binding Radioligands: MLAIR)

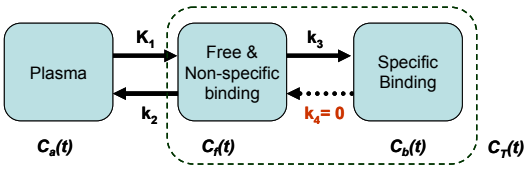


Figure 1. Three compartment model in brain

General differential equation of three compartment model with irreversible binding (Fig. 1) are described by

$$\frac{dC_f(t)}{dt} = K_1 C_a(t) - k_2 C_f(t) - k_3(t) C_f(t) \quad (1)$$

$$\frac{dC_b(t)}{dt} = k_3(t) C_f(t) \quad (2)$$

$$C_T(t) = C_f(t) + C_b(t) + V_a C_a(t) \quad (3)$$

Where the rate constants K_1, k_2, k_3 and V_a are defined as those of delivery (ml/min/g), washout (min^{-1}), the forward receptor-ligand reaction (min^{-1}), and plasma volume fraction. The concentration of the radioligand in tissue is obtained from summation concentrations of free or nonspecifically bound radioligand in brain (C_f, μCi/g), specifically bound radioligand to receptors (C_b, μCi/g), and concentration of the radioligand in plasma (C_a, μCi/ml). Using equation (1), (2) and (3), we can obtain changing rate in tissue concentration with plasma concentration as following equation.

$$\frac{d^2 C_T(t)}{dt^2} = V_a \frac{d^2 C_a(t)}{dt^2} + \left(K_1 + k_2 V_a + k_3 V_a\right) \frac{dC_a(t)}{dt} - (k_2 + k_3) \frac{dC_T(t)}{dt} + K_1 k_3 C_a(t)$$

In MLAIR method, double integration of this equation and division both sides by $(k_2 + k_3)$ was performed to obtain the binding parameter (K_i) directly from macro parameter using Linear Least Square (LLS) method using following equation.

$$\hat{\theta}_{LLS} = \left(X^T X\right)^{-1} X^T y$$

Where

$$y \equiv \begin{bmatrix} \int_0^{t_1} C_T(\tau) d\tau & \int_0^{t_2} C_T(\tau) d\tau & \int_0^{t_n} C_T(\tau) d\tau \end{bmatrix}$$

$$X \equiv \begin{bmatrix} \int_0^{t_1}\int_0^{\tau} C_a(s) ds d\tau & \int_0^{t_1} C_a(\tau) d\tau & C_a(t_1) & C_T(t_1) \\ \int_0^{t_2}\int_0^{\tau} C_a(s) ds d\tau & \int_0^{t_2} C_a(\tau) d\tau & C_a(t_2) & C_T(t_2) \\ \int_0^{t_n}\int_0^{\tau} C_a(s) ds d\tau & \int_0^{t_n} C_a(\tau) d\tau & C_a(t_n) & C_T(t_n) \end{bmatrix}$$

$$\theta \equiv \begin{bmatrix} P_1 & P_2 & P_3 & P_4 \end{bmatrix}$$

2.2 Monte Carlo simulation

Noiseless C_b, C_f and C_T time-activity curves were generated with irreversible three compartment model. K_1, k_2 and blood volume fraction were fixed at 0.24 ml/min/g, 0.028 min^{-1}, and 5% respectively. Binding parameter k_3 was varied between 0.5~2.0 times the value of k_2. Gaussian noise with zero mean and variance $\sigma^2 = \alpha C_T(t_i) \exp(0.693 t_i / \lambda) / \Delta t_i$ was added to each frame i of the C_T in order to simulate the noisy measurements, where λ is the physical half life, t_i is the midtime of frame i, Δt_i is time duration of frame i. α is varied from 0 to 6.0 for different noise level. One thousand

realizations were produced for all the simulations at each noise level. The K_i was estimated using MLAIR and PGA method, and the coefficient of variation (CV), bias and error in the estimation were calculated. The CV, bias and error are defined as

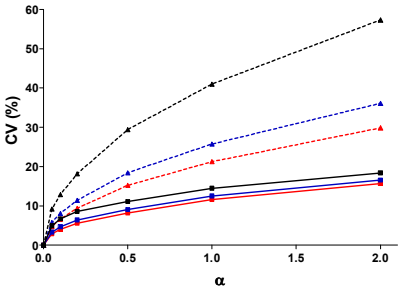
$$CV = \frac{\sigma(\hat{K}_i)}{\overline{K}_i} \times 100 \ (\%), \quad Error = \frac{\left[\sum_{i=1}^{n} \frac{|\hat{K}_i - K_i|}{K_i}\right]}{n} \times 100 \ (\%)$$

$$Bias = \frac{\left[\sum_{i=1}^{n} \frac{\hat{K}_i - K_i}{K_i}\right]}{n} \times 100 \ (\%)$$

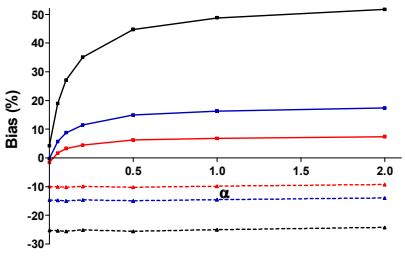
Where $\hat{K}_i$ is estimated parameter, K_i is true value, $\overline{K}_i$ is mean value, and n is the number of realization.

2.3 Result

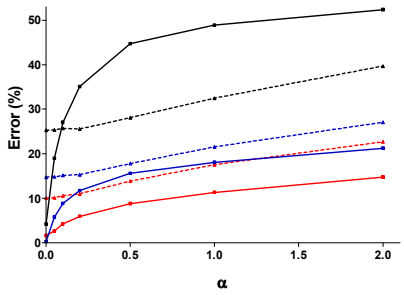
Figure 2 shows CV (%), Error (%) and Bias (%) of estimates at different noise levels in three regions, which are low, intermediate and high receptor density region. Regardless of region, MLAIR reveal that CV is significantly lower than those of PGA at all noise level. It means that the new method is not sensitive to noise level and region. MLAIR shows lower error and bias than PGA except for low receptor density site with noise. PGA reveals error even when there is no noise data because of mismatching assumptions. And it causes bias. The bias of K_i estimated is converged to constant value by increasing noise level. The K_i was underestimated by 10% in PGA, while, MLAIR overestimate 5% than true value in high receptor density region. Figure 3 shows parametric imaging of K_i in [^{11}C]MeNTI PET using MLAIR and PGA. The new method is successful in generating good quality images than PGA.



(a)

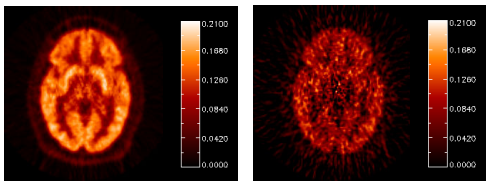


(b)



(c)

Figure 2. CV, Bias and Error of estimates at different noise levels with MLAIR (line) and PGA (dot line) in three regions, which are low (k3 = 0.5 x k2: black), intermediate (k3 = k2: blue) and high receptor density region (k3=1.5xk2: red).



(a) (b)

Figure 3. Parametric Imaging of Ki using MLAIR (a) and PGA (b) method

3. Conclusion

In this study, the results showed that MLAIR improved statistical reliability in the estimation of K_i compared to the PGA and would be useful for the generation of parametric images in radioligands with irreversible uptake or specific binding. It is expected that this new method will be a good alternative to PGA for the radiotracers with irreversible three compartment model.

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