

Equations for graphical analysis of irreversible tracers (Gjedde-Patlak plot)

This document derives from three-compartment model the mathematical equations for Gjedde-Patlak plot with plasma and reference region input [1, 2].

Gjedde-Patlak plot with plasma input

For the two-tissue compartment model the equations for tracer concentration in tissue, $ROI(t)$, are given in Eqs. (1a-1b), where K_1 , k_2 and k_3 are the rate constants, $C_P(t)$ is the concentration of authentic tracer in arterial plasma (input), $C_B(t)$ is the total radioactivity concentration in tissue vasculature, and V_B is the volume fraction of blood in tissue. $C_1(t)$ and $C_2(t)$ are the concentrations of non-metabolized and metabolized tracer in tissue.

$$\left\{ \begin{array}{l} \frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t) \quad (1a) \\ \frac{dC_2(t)}{dt} = k_3 C_1(t) \quad (1b) \\ ROI(t) = C_1(t) + C_2(t) + V_B C_B(t) \quad (1c) \end{array} \right.$$

Rearranging Eq. (1a) gives an equation for $C_1(t)$, which is substituted into Eq. (1b) to solve $dC_2(t)/dt$:

$$\left\{ \begin{array}{l} C_1(t) = \frac{K_1}{k_2 + k_3} C_P(t) - \left(\frac{1}{k_2 + k_3} \right) \frac{dC_1(t)}{dt} \quad (2a) \\ \frac{dC_2(t)}{dt} = \frac{K_1 k_3}{k_2 + k_3} C_P(t) - \left(\frac{k_3}{k_2 + k_3} \right) \frac{dC_1(t)}{dt} \quad (2b) \end{array} \right.$$

In integrated form this gives solution for $C_2(t)$:

$$C_2(T) = \frac{K_1 k_3}{k_2 + k_3} \int_0^T C_P(t) dt - \frac{k_3}{k_2 + k_3} C_1(t) \quad (3)$$

With substitution of Eq. (3) into the expression for $ROI(t)$ in Eq. (1c), we get Eq. (4):

$$ROI(T) = \frac{K_1 k_3}{k_2 + k_3} \int_0^T C_P(t) dt + \frac{k_2}{k_2 + k_3} C_1(t) + V_B C_B(t) \quad (4)$$

Dividing Eq. (4) by $C_p(t)$ gives Eq. (5). The $ROI(t)/C_p(t)$ is then plotted on y axis and integral of $C_p(t)$ over $C_p(t)$ on x axis.

$$\frac{ROI(t)}{C_p(t)} = \left(\frac{K_1 k_3}{k_2 + k_3} \right) \frac{\int_0^T C_p(t) dt}{C_p(t)} + \left(\frac{k_2}{k_2 + k_3} \right) \frac{C_1(t)}{C_p(t)} + \frac{V_B C_B(t)}{C_p(t)} \quad (5)$$

The condition for linearity of the plot based on Eq. (5) is that the intercept $k_2/(k_2+k_3)(C_1(t)/C_p(t)) + V_B C_B(t)/C_p(t)$ is constant. After some time $t > t'$, the reversible compartment concentration follows the plasma concentration so that $C_1(t)/C_p(t)$ and $C_B(t)/C_p(t)$ are constant, which ensures that the intercept is constant [3]. The slope of the linear phase of plot equals then the tracer net uptake K_i :

$$K_i = Slope = \frac{K_1 k_3}{k_2 + k_3} \quad (6)$$

This method can be used even when tissue data is measured only after time t' , if plasma samples have been collected from the beginning.

Gjedde-Patlak plot with reference tissue input

Plasma sampling may be omitted, if there exists a tissue where the tracer is not accumulated because of specific binding or metabolism, i.e. $k_3^{REF} = 0$. The impact of vascular radioactivity to the total tissue and reference tissue radioactivity content is assumed negligible, and omitted from the equations ($V_B = V_B^{REF} = 0$). Equation for the tracer concentration in reference tissue, $REF(t)$, can thus be described with Eq. (7):

$$\frac{dREF(t)}{dt} = K_1^{REF} C_p(t) - k_2^{REF} REF(t) \quad (7)$$

The arterial input is assumed to be the same for all tissue regions. Its integral is solved from the integrated form of Eq. (7),

$$\int_0^T C_p(t) dt = \frac{1}{K_1^{REF}} REF(T) + \frac{k_2^{REF}}{K_1^{REF}} \int_0^T REF(t) dt \quad (8)$$

and substituted into Eq. (4), with assumption $V_B = 0$, after which the equation is divided by $REF(t)$ to produce the Gjedde-Patlak plot with reference region input:

$$\frac{ROI(T)}{REF(T)} = \left[\left(\frac{K_1}{K_1^{REF}} \right) \frac{k_2^{REF} k_3}{k_2 + k_3} \right] \frac{\int_0^T REF(t) dt}{REF(T)} + \left(\frac{K_1}{K_1^{REF}} \right) \frac{k_3}{k_2 + k_3} + \left(\frac{k_2}{k_2 + k_3} \right) \frac{C_1(T)}{REF(T)} \quad (9)$$

If we make the assumption $K_1/k_2 = K_1^{REF}/k_2^{REF}$, common to all reference tissue models, the net uptake rate can be represented as:

$$K_i^{REF} = Slope = \frac{k_2 k_3}{k_2 + k_3} \quad (10)$$

This plot becomes linear after some time $t > t'$, when the tracer concentrations in tissue's reversible compartment, $C_1(t)$, and in reference tissue, $REF(t)$, follow the plasma concentration so that their ratio is constant [3].

Reference tissue curve has been known from the beginning of the study. Thus the Gjedde-Patlak method with reference input can not be used if PET scanning is not started at the injection time.

Linear fitting of the Gjedde-Patlak plots

Graphical methods are easy to perform and are generally considered more robust than kinetic analysis with (full) compartmental models, especially for noisy data sets. The traditional linear regression model takes into account only the errors in the Y variable. The bias in the (reference input) Gjedde-Patlak slope may be diminished by using a linear regression model that accounts for errors in both variables [4, 5, 6]. This method can take into account also separate weights for both variables.

References

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