

## Equations for graphical analysis of reversible tracers (Logan plot)

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

### *Logan 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  $K_1$ ,  $k_2$ ,  $k_3$  and  $k_4$  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 free and bound tracer in tissue. Contrary to the Logan's original model, vascular radioactivity concentration  $C_B(t)$  is not assumed to be equal to arterial plasma  $C_A(t)$ .

$$\left\{ \begin{array}{l} \frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3)C_1(t) + k_4 C_2(t) \quad (1a) \\ \frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t) \quad (1b) \\ ROI(t) = C_1(t) + C_2(t) + V_B C_B(t) \quad (1c) \end{array} \right.$$

The sum of Eqs. (1a) and (1b) can be rearranged to give  $C_1(t)$  and the Eq. (1a) to give  $C_2(t)$ :

$$C_1(t) = \frac{K_1}{k_2} C_P(t) - \frac{1}{k_2} \left( \frac{dC_1(t)}{dt} + \frac{dC_2(t)}{dt} \right) \quad (2a)$$

$$C_2(t) = \left( \frac{1}{k_4} \right) \frac{dC_1(t)}{dt} - \frac{K_1}{k_4} C_P(t) + \left( \frac{k_2 + k_3}{k_4} \right) C_1(t) \quad (2b)$$

With substitution of Eq. (2b) into the expression for  $ROI(t)$  in Eq. (1c), we get Eq. (3):

$$ROI(t) = \left( 1 + \frac{k_2 + k_3}{k_4} \right) C_1(t) + \left( \frac{1}{k_4} \right) \frac{dC_1(t)}{dt} + V_B C_B(t) - \frac{K_1}{k_4} C_P(t) \quad (3)$$

and then with substitution of Eq. (2a), after rearrangements:

$$ROI(t) = \frac{K_1}{k_2} \left( 1 + \frac{k_3}{k_4} \right) C_P(t) - \frac{1}{k_2} \left( 1 + \frac{k_3}{k_4} \right) \left[ \frac{dC_1(t)}{dt} + \frac{dC_2(t)}{dt} \right] - \left( \frac{1}{k_4} \right) \frac{dC_2(t)}{dt} + V_B C_B(t) \quad (4)$$

The integrated form of this equation is:

$$\int_0^T ROI(t)dt = \frac{K_1}{k_2} \left(1 + \frac{k_3}{k_4}\right) \int_0^T C_p(t)dt - \frac{1}{k_2} \left(1 + \frac{k_3}{k_4}\right) [C_1(t) + C_2(t)] - \left(\frac{1}{k_4}\right) C_2(t) + V_B \int_0^T C_B(t)dt \quad (5)$$

Dividing Eq. (5) by  $ROI(t)$  gives Eq. (6), which can be rearranged to Eq. (7), assuming that  $ROI(t)=C_1(t)+C_2(t)$  (neglecting  $V_B$ ):

$$\frac{\int_0^T ROI(t)dt}{ROI(T)} = \left(\frac{K_1}{k_2} \left(1 + \frac{k_3}{k_4}\right)\right) \frac{\int_0^T C_p(t)dt}{ROI(T)} \quad (6)$$

$$- \frac{1}{k_2} \left(1 + \frac{k_3}{k_4}\right) \frac{[C_1(t) + C_2(t)]}{ROI(T)} - \left(\frac{1}{k_4}\right) \frac{C_2(t)}{ROI(T)} + V_B \frac{\int_0^T C_B(t)dt}{ROI(T)}$$

$$\frac{\int_0^T ROI(t)dt}{ROI(T)} = \left(\frac{K_1}{k_2} \left(1 + \frac{k_3}{k_4}\right)\right) \frac{\int_0^T C_p(t)dt}{ROI(T)} - \frac{1}{k_2} \left(1 + \frac{k_3}{k_4}\right) - \left(\frac{1}{k_4}\right) \frac{C_2(t)}{C_1(t) + C_2(t)} + V_B \frac{\int_0^T C_B(t)dt}{ROI(T)} \quad (7)$$

The condition for linearity of Eq. (7) is that the intercept  $-(1/k_2)(1+k_3/k_4) - (1/k_4)(C_2(t)/(C_1(t)+C_2(t)))$  is constant (assuming here that the last term containing the blood volume fraction can be neglected, or included in the slope as in Logan's original model). After some time  $t > t'$ , the compartment concentrations follow the plasma concentration so that  $(C_1(t)+C_2(t))/C_p(t)$  and  $C_2(t)/C_p(t)$  are constant, which ensures that the intercept is constant since  $C_p(t)$  cancels. In many cases the intercept becomes constant even before  $(C_1(t)+C_2(t))/C_p(t)$  becomes constant so that the graphical method can be applied before the steady-state condition becomes valid.

If distribution volume  $DV=(K_1/k_2)(1+k_3/k_4)$ , and the intercept is marked with  $Int$ , the Logan plot can be represented as:

$$\frac{\int_0^T ROI(t)dt}{ROI(T)} = DV \frac{\int_0^T C_p(t)dt}{ROI(T)} + Int \quad (8)$$

The slope of the linear phase of plot equals the distribution volume of tracer.

#### *Logan plot with reference tissue input*

The Logan plot a reference region with no specific binding ( $k_3^{REF}=k_4^{REF}=0$ ) can be represented with Eq. (9). For reference region, the distribution volume  $DV^{REF} = K_1^{REF}/k_2^{REF}$ . When using reference region input, we assume that the vascular radioactivity can be neglected ( $V_B=0$ ).

$$\frac{\int_0^T REF(t)dt}{REF(T)} = DV^{REF} \frac{\int_0^T C_p(t)dt}{REF(T)} + \frac{1}{k_2^{REF}} \quad (9)$$

The integral of arterial plasma concentration can be solved as:

$$\int_0^T C_p(t)dt = \frac{1}{DV^{REF}} \left( \int_0^T REF(t)dt + \frac{REF(T)}{k_2^{REF}} \right) \quad (10)$$

and then substituted into the Eq. (8) for region of interest. Here is introduced a new term, distribution volume ratio, as  $DVR = DV/DV^{REF}$ , giving Eq. (11).

$$\frac{\int_0^T ROI(t)dt}{ROI(T)} = DVR \left( \frac{\int_0^T REF(t)dt + REF(t)/k_2^{REF}}{ROI(T)} \right) + Int' \quad (11)$$

The slope of the linear phase of plot equals the distribution volume ratio. Note, that the term containing  $k_2^{REF}$  must be included in the computation of x axis values, unless there is a good reason to neglect it. However,  $k_2^{REF}$  is probably relatively constant between subjects, and using a population mean may often be appropriate.

### *Linear fitting of the Logan 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. However, it has been shown with simulated data that the slope obtained from the Logan plot with the traditional linear regression model is biased, when noise is introduced to the simulated data curves [2]. The traditional linear regression model takes into account only the errors in the *Y* variable. The bias in the Logan slope can be diminished by using a linear regression model that accounts for errors in both variables [3]. This method [4, 5, 6] can take into account also separate weights for both variables.

### *References*

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