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Model equations for reference tissue compartmental models

This document describes the mathematical equations needed to simulate the PET time-radioactivity concentration curves in reference tissue compartmental models [Blomqvist et al 1989, Cunningham et al 1991], and to solve them using multilinear regression methods. The approach of Kuwabara et al. (1993) is used for partial solutions of the differential equations.

Compartmental model for reversible tracer binding to receptors

The two-tissue compartmental model, commonly applied in tracer receptor studies, is described with the following equations (1-4), where $C_T(t)$ is the tracer concentration in the region of interest, consisting of the free and receptor-bound components, $C_F(t)$ and $C_B(t)$, $C_R(t)$ is the tracer concentration in a reference region (assumed to show no specific binding of tracer), $C_P(t)$ is the concentration of authentic tracer in arterial plasma; K_1 and k_2 are the transport rates between compartments for plasma and free tracer in region of interest, K'_1 and k'_2 are the transport rates in reference region, and k_3 and k_4 are the rate constants between free and receptor-bound compartments.

$$C_T(t) = C_F(t) + C_B(t) \quad (1)$$

$$dC_F(t)/dt = K_1 C_P(t) - (k_2 + k_3) C_F(t) + k_4 C_B(t) \quad (2)$$

$$dC_B(t)/dt = k_3 C_F(t) - k_4 C_B(t) \quad (3)$$

$$dC_R(t)/dt = K'_1 C_P(t) - k'_2 C_R(t) \quad (4)$$

The integrated forms of equations (2-4) are:

$$C_F(T) = K_1 \int_0^T C_P(t)dt - (k_2 + k_3) \int_0^T C_F(t)dt + k_4 \int_0^T C_B(t)dt \quad (5)$$

$$C_B(T) = k_3 \int_0^T C_F(t)dt - k_4 \int_0^T C_B(t)dt \quad (6)$$

$$C_R(T) = K'_1 \int_0^T C_P(t)dt - k'_2 \int_0^T C_R(t)dt \quad (7)$$

Original reference tissue compartment model (RTCM)

In reference tissue models the concentration in plasma is not measured. Instead, it is assumed that K_1/k_2 is the same in all brain regions, including the reference region, and thus $K_1/k_2 = K'_1/k'_2$. The ratios of transport rates between the regions can be represented with R_1:

$$R_1 = \frac{K_1}{K'_1} = \frac{k_2}{k'_2} \quad (8)$$

Substitution of Eq. (8) into Eq. (4) with rearrangement gives the unknown $C_P(t)$ as a function of the measured time course of tracer in the reference region:

$$K_1 C_P(t) = R_1 \frac{dC_R(t)}{dt} + k_2 C_R(t) \qquad (9)$$

By applying linear interpolation, the integral of compartments radioactivity concentration can be represented as in Eq. (10) for receptor bound tracer, where Δt is the PET frame length:

$$\int_0^T C_B(t)dt = \int_0^{T-\Delta t} C_B(t)dt + \frac{\Delta t}{2} C_B(T-\Delta t) + \frac{\Delta t}{2} C_B(T) \qquad (10)$$

Substitution of Eq. (10) into Eq. (6) gives the equation for $C_B(t)$:

$$C_B(T) = \frac{k_3 \int_0^T C_F(t)dt - k_4 \left(\int_0^{T-\Delta t} C_B(t)dt + \frac{\Delta t}{2} C_B(T-\Delta t) \right)}{1 + \frac{\Delta t}{2} k_4} \qquad (11)$$

Substitutions of Eq. (6) and Eq. (11) into Eq. (5), and applying for $C_F(T)$ the same method as for $C_B(T)$ in Eq. (10), $C_F(T)$ can be solved as:

$$C_F(T) = \left\{ \begin{array}{c} R_1\left(1+\frac{\Delta t}{2}k_4\right)C_R(T) \\ + k_2\left(1+\frac{\Delta t}{2}k_4\right)\int_0^T C_R(t)dt \\ + k_4\left(\int_0^{T-\Delta t} C_B(t)dt + \frac{\Delta t}{2} C_B(T-\Delta t) \right) \\ -\left(k_2+k_3+\frac{\Delta t}{2}k_2k_4\right)\left(\int_0^{T-\Delta t} C_F(t)dt + \frac{\Delta t}{2} C_F(T-\Delta t) \right) \end{array} \right\} \Big/ \left(1+\frac{\Delta t}{2}\left(k_2+k_3+k_4+\frac{\Delta t}{2}k_2k_4\right)\right) \qquad (12)$$

To solve the parameters using linear regression methods, as proposed by Blomqvist [4], $dC_T(t)/dt$ is as a first step derived from the sum of Eqs. (2) and (3), and $K_1C_P(t)$ is substituted from Eq. (9). The resulting Eq. (13) is then reorganized and derivated to solve $C_F(t)$ and $dC_F(t)/dt$ in Eqs (14) and (15):

$$\frac{dC_T(t)}{dt} = R_1 \frac{dC_R(t)}{dt} + k_2 C_R(t) - k_2 C_F(t) \qquad (13)$$

$$C_F(t) = \left(\frac{R_1}{k_2}\right)\frac{dC_R(t)}{dt} + C_R(t) - \left(\frac{1}{k_2}\right)\frac{dC_T(t)}{dt} \qquad (14)$$

$$\frac{dC_F(t)}{dt} = \left(\frac{R_1}{k_2}\right) d\left(\frac{dC_R(t)}{dt}\right) \Big/ dt + \frac{dC_R(t)}{dt} - \left(\frac{1}{k_2}\right) d\left(\frac{dC_T(t)}{dt}\right) \Big/ dt \qquad (15)$$

The Eqs. (1), (14) and (15) are substituted into Eq. (2), and after rearrangement and two integrations, the tissue activity can be represented as a function of measured concentrations in tissue and in reference region, or their integrals:

$$C_T(T) = R_1 C_R(T) + R_1\left(\frac{k_2}{R_1} + k_3 + k_4\right)\int_0^T C_R(t)dt + k_2(k_3+k_4)\int_0^T\left[\int_0^T C_R(t)du\right]dt - (k_2+k_3+k_4)\int_0^T C_T(t)dt - k_2k_4\int_0^T\left[\int_0^T C_T(t)du\right]dt \quad (16)$$

However, this function is over-determined and the parameters can not be solved by using any simple unconstrained "six-dimensional" linear regression.

Reduced reference tissue model (RRTM)

If the binding of tracer is irreversible, i.e. $k_4=0$, the reference tissue model can be applied by removing the terms containing k_4 in equations (11), (12) and (16); instead of binding potential, $BP=k_3/k_4$, the rate constant k_3 is then determined.

The unconstrained linear regression method cannot be applied, because the function is still overdetermined.

Simplified reference tissue model (SRTM)

In the simplified reference tissue model [Lammertsma & Hume, 1996] it is assumed that the time-radioactivity curve of the region of interest can be fitted satisfactorily to a single tissue compartment model with plasma input. In this case the Eqs. (1-3) can be replaced by a single equation (17), where k_{2a} is the apparent rate constant for transfer from compartment of specific binding to plasma.

$$dC_T(t)/dt = K_1 C_P(t) - k_{2a} C_T(t) \quad (17)$$

The total volume of distribution is the same as that derived from Eqs (1-3):

$$\frac{K_1}{k_{2a}} = \frac{K_1}{k_2}(1+BP) \quad (18)$$

When Eq (18) is substituted into Eq (17), and then the Eq. (9) is substituted into it, Eq. (19) can be derived:

$$\frac{dC_T(t)}{dt} = R_1\frac{dC_R(t)}{dt} + k_2 C_R(t) - \frac{k_2}{1+BP}C_T(t) \quad (19)$$

Integrating the Eq (15) and applying the same method for $C_T(T)$ as for $C_B(T)$ in Eq. (10), the Eq. (20) for $C_T(T)$ can be derived:

$$C_T(T) = \frac{R_1 C_R(T) + k_2\int_0^T C_R(t)dt - \frac{k_2}{1+BP}\left(\int_0^{T-\Delta t} C_T(t)dt + \frac{\Delta t}{2}C_T(T-\Delta t)\right)}{1+\left(\frac{\Delta t}{2}\right)\frac{k_2}{1+BP}} \quad (20)$$

With nonlinear optimization methods this equation can be used to estimated the model parameters. As an alternative, a multidimensional regression method can be applied to solve the parameters of the integrated form of Eq. (19):

$$C_T(T) = R_1 C_R(T) + k_2 \int_0^T C_R(t)dt - \left(\frac{k_2}{1+BP}\right)\int_0^T C_T(t)dt \qquad (21)$$

From Eq. (8) we can notice that $k_2=R_1k'_2$, where k'_2 was the k_2 of the reference region. Therefore, Eq. (21) can be represented in a form with parameters R_1, BP and k'_2 in Eq. (22). Because the reference region is the same for all image pixels, it can be constrained to a median value of all brain pixels to reduce the noise in parametric image [Wu & Carson, 2002].

$$C_T(T) = R_1 C_R(T) + R_1 k'_2 \int_0^T C_R(t)dt - R_1\left(\frac{k'_2}{1+BP}\right)\int_0^T C_T(t)dt \qquad (22)$$

To estimate BP directly without unstable division calculations, both sides of equation (21) can be multiplied by $(1+BP)/k_2$ and then rearranged to give Eq. (23) [Zhou et al., 2003].

$$\int_0^T C_T(t)dt = (1+BP)\int_0^T C_R(t)dt + R_1\left(\frac{1+BP}{k_2}\right)C_R(T) - \left(\frac{1+BP}{k_2}\right)C_T(T) \qquad (23)$$

To reduce the noise and the bias caused by the noise, a spatial smoothing filter can be applied to C_T, but smoothing is not necessary for C_R, which is an average from a large reference region, or for the integral of C_T [Zhou et al., 2003].

Transport limited reference tissue model (TRTM)

In the transport limited reference tissue model for irreversible binding, first proposed by Herholz et al. (2001), it is assumed that the binding in reference region is fast (high) enough that the second term in Eq. (4) can be ignored, and the kinetics can be described with Eq. (24):

$$dC_R(t)/dt = K'_1\, C_P(t) \qquad (24)$$

The Eqs. (1-3) for region of interest are still valid, except that $k_4=0$. Substituting Eq. (8) into Eq. (24) and rearranging, a reduced form of the Eq. (9) can be derived:

$$K_1 C_P(t) = R_1 \frac{dC_R(t)}{dt} \qquad (25)$$

Substitution of this equation into Eq. (2), still assuming that $k_4=0$, gives Eq. (26):

$$\frac{dC_F(t)}{dt} = R_1 \frac{dC_R(t)}{dt} - (k_2 + k_3)C_F(t) \qquad (26)$$

Integration of it using the above mentioned methods gives equation for $C_F(T)$, and for irreversible binding, the $C_B(T)$ can be represented by setting $k_4=0$ in Eq. (11):

$$C_F(T) = \frac{R_1 C_R(T) - (k_2 + k_3)\left(\int_0^{T-\Delta t} C_F(t)dt + \frac{\Delta t}{2} C_F(T-\Delta t)\right)}{1 + \frac{\Delta t}{2}(k_2 + k_3)} \quad (27)$$

$$C_B(T) = k_3 \int_0^T C_F(t)dt \quad (28)$$

To solve the parameters using linear regression methods, $dC_T(t)/dt$ is as a first step derived from the sum of Eqs. (26) and (3), assuming that $k_4=0$. The resulting Eq. (29) is then reorganized and derivated to solve $C_F(t)$ and $dC_F(t)/dt$ in Eqs (30) and (31):

$$\frac{dC_T(t)}{dt} = R_1 \frac{dC_R(t)}{dt} - k_2 C_F(t) \quad (29)$$

$$C_F(t) = \left(\frac{R_1}{k_2}\right)\frac{dC_R(t)}{dt} - \left(\frac{1}{k_2}\right)\frac{dC_T(t)}{dt} \quad (30)$$

$$\frac{dC_F(t)}{dt} = \left(\frac{R_1}{k_2}\right) d\left(\frac{dC_R(t)}{dt}\right) \Big/ dt - \left(\frac{1}{k_2}\right) d\left(\frac{dC_T(t)}{dt}\right) \Big/ dt \quad (31)$$

Eqs. (30) and (31) are substituted into Eq. (26). After rearrangement and two integrations, the tissue activity can be represented as a function of only measured concentrations in tissue and in reference region, or their integral:

$$C_T(T) = R_1 C_R(T) + R_1 k_3 \int_0^T C_R(t)dt - (k_2 + k_3)\int_0^T C_T(t)dt \quad (32)$$

The resulting Eq. (32) can be solved using multidimensional regression. For non-linear parameter estimation, the same method for $C_T(t)$ as previously for $C_B(t)$ in Eq. (11) can be applied, resulting into the Eq. (33):

$$C_T(T) = \frac{R_1 C_R(T) + R_1 k_3 \int_0^T C_R(t)dt - (k_2 + k_3)\left(\int_0^{T-\Delta t} C_T(t)dt + \frac{\Delta t}{2} C_T(T-\Delta t)\right)}{1 + \frac{\Delta t}{2}(k_2 + k_3)} \quad (33)$$

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