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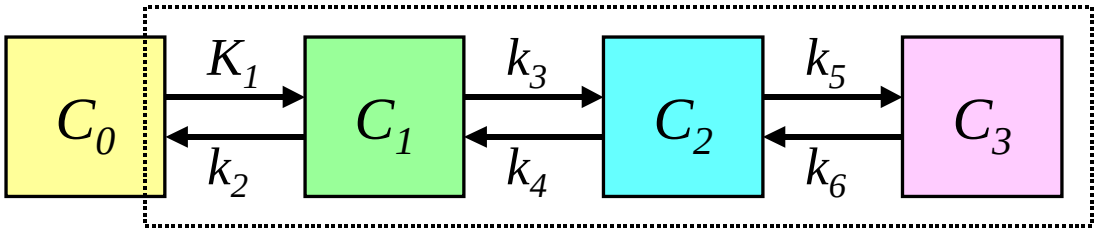
Multilinear solution for 4-compartment model: I. Tissue compartments in series

The compartmental models presently used in the analysis of positron emission tomography data lead into similar systems of differential equations. Usually, the unknown model rate constants are solved with iterative non-linear least-squares methods. Blomqvist (1984) proposed a linear algorithm for solution of two-compartment and irreversible three-compartment models. The same method has been extended to reversible three-compartment model with vascular contribution to the total radioactivity concentration (Gjedde 1990). This document extends further the method by applying it to compartmental model with three tissue compartments in series.

Compartmental model



The measured radioactivity concentration of the parent tracer in arterial plasma, $C_0(t)$, is the input to tissue compartments $C_1(t)$, $C_2(t)$ and $C_3(t)$. The total tissue concentration that is measured with PET, $C_T(t)$, is defined as the sum of separate tissue compartments and the product of vascular volume fraction in tissue, V_0, and radioactivity concentration in vascular volume:

$$C_T(t) = V_0 C_0(t) + C_1(t) + C_2(t) + C_3(t) \quad (1)$$

The contribution of vascular radioactivity is included in the model in a way that is valid only if the radioactivity concentration in vascular volume can be assumed to be equal to concentration of parent tracer in plasma; this is the case usually in [^{18}F]FDG studies. Another possibility is to assume that V_0 represents only arterial volume fraction, and that the radioactivity concentration in venous blood is similar or at least proportional to the sum of radioactivity concentrations in tissue compartments. All radioactivities are corrected for physical decay, and they are therefore proportional to the concentration of tracer molecules.

The total distribution volume, DV_T, equals the sum of distribution volumes of separate tissue compartments:

$$DV_T = DV_1 + DV_2 + DV_3 = \frac{K_1}{k_2} + \frac{K_1}{k_2}\frac{k_3}{k_4} + \frac{K_1}{k_2}\frac{k_3}{k_4}\frac{k_5}{k_6} =$$
$$\frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\left(1 + \frac{k_5}{k_6}\right)\right) = \frac{K_1\left(k_3k_5 + k_3k_6 + k_4k_6\right)}{k_2k_4k_6}$$

Differential equations

$$\frac{dC_1(t)}{dt} = K_1C_0(t) - \left(k_2 + k_3\right)C_1(t) + k_4C_2(t) \quad (2)$$
$$\frac{dC_2(t)}{dt} = k_3C_1(t) - \left(k_4 + k_5\right)C_2(t) + k_6C_3(t) \quad (3)$$
$$\frac{dC_3(t)}{dt} = k_5C_2(t) - k_6C_3(t) \quad (4)$$

Solution to the full model

The sum of equations 2-4 is substituted into differential format (differentiation with respect to time) of equation 1, giving equation 5.

$$\frac{dC_T(t)}{dt} = V_0\frac{dC_0(t)}{dt} + K_1C_0(t) - k_2C_1(t) \quad (5)$$

The concentration of the first tissue compartment is solved from it (Eq. 6) and its first, second and third order differential equations are represented in equations 7-9.

$$k_2C_1(t) = V_0\frac{dC_0(t)}{dt} + K_1C_0(t) - \frac{dC_T(t)}{dt} \quad (6)$$
$$k_2\frac{dC_1(t)}{dt} = V_0\frac{ddC_0(t)}{dt\,dt} + K_1\frac{dC_0(t)}{dt} - \frac{ddC_T(t)}{dt\,dt} \quad (7)$$
$$k_2\frac{ddC_1(t)}{dt\,dt} = V_0\frac{dddC_0(t)}{dt\,dt\,dt} + K_1\frac{ddC_0(t)}{dt\,dt} - \frac{dddC_T(t)}{dt\,dt\,dt} \quad (8)$$
$$k_2\frac{dddC_1(t)}{dt\,dt\,dt} = V_0\frac{ddddC_0(t)}{dt\,dt\,dt\,dt} + K_1\frac{dddC_0(t)}{dt\,dt\,dt} - \frac{ddddC_T(t)}{dt\,dt\,dt\,dt} \quad (9)$$

Concentration of the third tissue compartment can be solved from the equation 3 (Eq. 10), and differentiated with respect to time (Eq. 11):

$$k_6C_3(t) = \frac{dC_2(t)}{dt} - k_3C_1(t) + \left(k_4 + k_5\right)C_2(t) \quad (10)$$
$$k_6\frac{dC_3(t)}{dt} = \frac{ddC_2(t)}{dt\,dt} - k_3\frac{dC_1(t)}{dt} + \left(k_4 + k_5\right)\frac{dC_2(t)}{dt} \quad (11)$$

These can be substituted into equation 4, which gives, after rearrangement:

$$\frac{ddC_2(t)}{dt\,dt} + (k_4 + k_5 + k_6)\frac{dC_2(t)}{dt} + k_4 k_6 C_2(t) = k_3 \frac{dC_1(t)}{dt} + k_3 k_6 C_1(t) \quad (12)$$

Similarly, concentration of the second tissue compartment can be solved from the equation 2 (Eq. 13), and differentiated twice with respect to time (Eqs. 14 and 15):

$$k_4 C_2(t) = \frac{dC_1(t)}{dt} - k_1 C_0(t) + (k_2 + k_3) C_1(t) \quad (13)$$

$$k_4 \frac{dC_2(t)}{dt} = \frac{ddC_1(t)}{dt\,dt} - k_1 \frac{dC_0(t)}{dt} + (k_2 + k_3)\frac{dC_1(t)}{dt} \quad (14)$$

$$k_4 \frac{ddC_2(t)}{dt\,dt} = \frac{dddC_1(t)}{dt\,dt\,dt} - k_1 \frac{ddC_0(t)}{dt\,dt} + (k_2 + k_3)\frac{ddC_1(t)}{dt\,dt} \quad (15)$$

Equations 13-15 can be substituted into equation 12, which gives, after rearangement:

$$\begin{aligned} &\frac{dddC_1(t)}{dt\,dt\,dt} + (k_2 + k_3 + k_4 + k_5 + k_6)\frac{ddC_1(t)}{dt\,dt} + \\ &[k_2 k_4 + k_5(k_2 + k_3) + k_6(k_2 + k_3 + k_4)]\frac{dC_1(t)}{dt} + k_2 k_4 k_6 C_1(t) \\ &= K_1 \frac{ddC_0(t)}{dt\,dt} + K_1(k_4 + k_5 + k_6)\frac{dC_0(t)}{dt} + K_1 k_4 k_6 C_0(t) \end{aligned} \quad (16)$$

Equations 6-9 are substituted into equation 16. Rearrangement, and three integrations over the time interval *(0,T)* and using the initial conditions
$C_T(0)=C_1(0)=C_2(0)=C_3(0)=0$
and
$dC_T(0)/dt=dC_1(0)/dt=dC_2(0)/dt=dC_3(0)/dt=0$, gives

$$\begin{aligned} &C_T(T) = \\ &[K_1(k_3k_5 + k_3k_6 + k_4k_6) + V_0 k_2 k_4 k_6]\int_0^T\left[\int_0^T\left[\int_0^T C_0(t)dv\right]du\right]dt + \\ &[K_1(k_3 + k_4 + k_5 + k_6) + V_0(k_2k_4 + k_5(k_2 + k_3) + k_6(k_2 + k_3 + k_4))]\int_0^T\left[\int_0^T C_0(t)du\right]dt + \\ &[K_1 + V_0(k_2 + k_3 + k_4 + k_5 + k_6)]\int_0^T C_0(t)dt + \\ &V_0 C_0(T) - \\ &k_2k_4k_6\int_0^T\left[\int_0^T\left[\int_0^T C_T(t)dv\right]du\right]dt - \\ &[k_2k_4 + k_5(k_2 + k_3) + k_6(k_2 + k_3 + k_4)]\int_0^T\left[\int_0^T C_T(t)du\right]dt - \\ &(k_2 + k_3 + k_4 + k_5 + k_6)\int_0^T C_T(t)dt \end{aligned} \quad (17)$$

After numerical integration of the measured plasma and tissue concentrations, the coefficients can be estimated with any least-squares method, e.g. NNLS (Lawson and Hanson, 1974). The model parameters can then be solved from these coefficients. If the coefficients are represented with P_1, ..P_7, the equations for model parameters are:

$$\begin{cases} V_0 = P_4 \\ K_1 = P_3 - P_4 * P_7 \\ k_2 = P_7 - (P_2 - P_4 * P_6) / K_1 \\ k_3 = P_7 - k_2 - (P_6 - (P_1 - P_4 * P_5) / K_1) / k_2 \\ k_4 = P_7 - k_2 - k_3 - ((P_1 - P_4 * P_5) / K_1 - P_5 / k_2) / k_3 \\ k_6 = P_5 / (k_2 * k_4) \\ k_5 = P_7 - k_2 - k_3 - k_4 - k_6 \end{cases} \quad (18)$$

Total volume of distribution could be calculated as $DV_T=P_1/P_5-P_4$. However, if DV_T is the only parameter of interest, it may be preferable to get an estimate for it directly without division. For that purpose, equation 17 can divided by $k_2k_4k_6$ and rearranged to give

$$\begin{aligned} &\int_0^T \left[\int_0^T \left[\int_0^T C_T(t)dv \right] du \right] dt = \\ &\left[\frac{K_1(k_3k_5 + k_3k_6 + k_4k_6)}{k_2k_4k_6} + V_0 \right] \int_0^T \left[\int_0^T \left[\int_0^T C_0(t)dv \right] du \right] dt + \\ &\left[\frac{K_1(k_3 + k_4 + k_5 + k_6) + V_0(k_2k_4 + k_5(k_2 + k_3) + k_6(k_2 + k_3 + k_4))}{k_2k_4k_6} \right] \int_0^T \left[\int_0^T C_0(t)du \right] dt + \\ &\left[\frac{K_1 + V_0(k_2 + k_3 + k_4 + k_5 + k_6)}{k_2k_4k_6} \right] \int_0^T C_0(t)dt + \\ &\frac{V_0}{k_2k_4k_6} C_0(T) - \\ &\left[\frac{k_2k_4 + k_5(k_2 + k_3) + k_6(k_2 + k_3 + k_4)}{k_2k_4k_6} \right] \int_0^T \left[\int_0^T C_T(t)du \right] dt - \\ &\left(\frac{k_2 + k_3 + k_4 + k_5 + k_6}{k_2k_4k_6} \right) \int_0^T C_T(t)dt - \\ &\frac{1}{k_2k_4k_6} C_T(T) \end{aligned} \quad (19)$$

, where the first coefficient equals DV_T+V_0.

Solution to the model when $V_0=0$

If the contribution of vascular concentration to the total tissue radioactivity can be assumed negligible, then V_0 can be set to zero in the equation 17, giving

$$
\begin{aligned}
&C_T(T) = \\
&K_1(k_3k_5 + k_3k_6 + k_4k_6)\int_0^T\left[\int_0^T\left[\int_0^T C_0(t)dv\right]du\right]dt + \\
&K_1(k_3 + k_4 + k_5 + k_6)\int_0^T\left[\int_0^T C_0(t)du\right]dt + \\
&K_1\int_0^T C_0(t)dt - \\
&k_2k_4k_6\int_0^T\left[\int_0^T\left[\int_0^T C_T(t)dv\right]du\right]dt - \\
&[k_2k_4 + k_5(k_2 + k_3) + k_6(k_2 + k_3 + k_4)]\int_0^T\left[\int_0^T C_T(t)du\right]dt - \\
&(k_2 + k_3 + k_4 + k_5 + k_6)\int_0^T C_T(t)dt
\end{aligned}
\tag{20}
$$

, where, if the coefficients are represented with P_1, ..P_6, the equations for solving model parameters are:

$$
\begin{cases}
K_1 = P_3 \\
k_2 = P_6 - P_2 / K_1 \\
k_3 = P_6 - k_2 - (P_5 - P_1 / K_1) / k_2 \\
k_4 = P_6 - k_2 - k_3 - (P_1 / K_1 - P_4 / k_2) / k_3 \\
k_6 = P_4 /(k_2 * k_4) \\
k_5 = P_6 - k_2 - k_3 - k_4 - k_6
\end{cases}
\tag{21}
$$

Solution to the model when $k_6=0$

If there is irreversible uptake in the tissue, then k_6 must be set to zero in the equation 17, giving

$$
\begin{aligned}
&C_T(T) = \\
&K_1k_3k_5\int_0^T\left[\int_0^T\left[\int_0^T C_0(t)dv\right]du\right]dt + \\
&[K_1(k_3 + k_4 + k_5) + V_0(k_2k_4 + k_5(k_2 + k_3))]\int_0^T\left[\int_0^T C_0(t)du\right]dt + \\
&[K_1 + V_0(k_2 + k_3 + k_4 + k_5)]\int_0^T C_0(t)dt + \\
&V_0C_0(T) - \\
&[k_2k_4 + k_5(k_2 + k_3)]\int_0^T\left[\int_0^T C_T(t)du\right]dt - \\
&(k_2 + k_3 + k_4 + k_5)\int_0^T C_T(t)dt
\end{aligned}
\tag{22}
$$

, where, if the coefficients are represented with P_1, ..P_6, the equations for solving model parameters are:

$$\begin{cases} V_0 = P_4 \\ K_1 = P_3 - P_4 * P_6 \\ k_2 = P_6 - (P_2 - P_4 * P_5) / K_1 \\ k_3 = P_6 - k_2 - (P_5 - P_1 / K_1) / k_2 \\ k_5 = P_1 /(K_1 * k_3) \\ k_4 = P_6 - k_2 - k_3 - k_5 \end{cases} \quad (23)$$

Equation (22) coeld be rearranged to a form that was previously given by Gjedde (1991). Because the model is irreversible, the total volume of distribution cannot be calculated, but instead the influx rate constant, K_i, can be solved as $K_i = P_1/P_5$. In this four-compartmental model setting

$$K_i = \frac{K_1 k_3 k_5}{k_2 k_4 + k_2 k_5 + k_3 k_5}$$

If K_i is the only parameter of interest, it may be preferable to get an estimate for it directly without division. For that purpose, equation 23 can divided by $k_2k_4+k_2k_5+k_3k_5$ and rearranged to give

$$\begin{aligned} &\int_0^T \left[\int_0^T C_T(t)du \right] dt = \\ &\frac{K_1 k_3 k_5}{k_2 k_4 + k_2 k_5 + k_3 k_5} \int_0^T \left[\int_0^T \left[\int_0^T C_0(t)dv \right] du \right] dt + \\ &\left[\frac{K_1 (k_3 + k_4 + k_5)}{k_2 k_4 + k_2 k_5 + k_3 k_5} + V_0 \right] \int_0^T \left[\int_0^T C_0(t)du \right] dt + \\ &\left[\frac{K_1 + V_0 (k_2 + k_3 + k_4 + k_5)}{k_2 k_4 + k_2 k_5 + k_3 k_5} \right] \int_0^T C_0(t)dt + \\ &\frac{V_0}{k_2 k_4 + k_2 k_5 + k_3 k_5} C_0(T) - \\ &\left(\frac{k_2 + k_3 + k_4 + k_5}{k_2 k_4 + k_2 k_5 + k_3 k_5} \right) \int_0^T C_T(t)dt - \\ &\frac{1}{k_2 k_4 + k_2 k_5 + k_3 k_5} C_T(T) \end{aligned} \quad (24)$$

Solution to the model when $k_6=0$ and $V_0=0$

If there is irreversible uptake in the tissue and vascular volume can be ignored, then k_6 and V_0 can be set to zero in the equation 17, giving

$$
\begin{aligned}
&C_T(T) = \\
&K_1 k_3 k_5 \int_0^T \left[\int_0^T \left[\int_0^T C_0(t)dv \right] du \right] dt + \\
&K_1 (k_3 + k_4 + k_5) \int_0^T \left[\int_0^T C_0(t)du \right] dt + \\
&K_1 \int_0^T C_0(t)dt - \\
&[k_2 k_4 + k_5 (k_2 + k_3)] \int_0^T \left[\int_0^T C_T(t)du \right] dt - \\
&(k_2 + k_3 + k_4 + k_5) \int_0^T C_T(t)dt
\end{aligned}
\qquad (25)
$$

, where, if the coefficients are represented with P_1, ..P_5, the equations for solving model parameters are:

$$
\begin{cases}
K_1 = P_3 \\
k_2 = P_5 - P_2 / K_1 \\
k_3 = P_5 - k_2 - (P_4 - P_1 / K_1) / k_2 \\
k_5 = P_1 / (K_1 * k_3) \\
k_4 = P_5 - k_2 - k_3 - k_5
\end{cases}
\qquad (26)
$$

Solution to the reversible model with only two tissue compartments

If the third tissue compartment does not exist, then k_5 and k_6 can be set to zero in the equation 17, giving

$$
\begin{aligned}
&C_T(T) = \\
&[K_1 (k_3 + k_4) + V_0 k_2 k_4] \int_0^T \left[\int_0^T C_0(t)du \right] dt + \\
&[K_1 + V_0 (k_2 + k_3 + k_4)] \int_0^T C_0(t)dt + \\
&V_0 C_0(T) - \\
&k_2 k_4 \int_0^T \left[\int_0^T C_T(t)du \right] dt - \\
&(k_2 + k_3 + k_4) \int_0^T C_T(t)dt
\end{aligned}
\qquad (27)
$$

, which is the same equation that has been previously formed from the two-tissue compartment model (Gjedde and Wong, 1990). If the coefficients are represented with P_1, ..P_5, the equations for solving model parameters are:

$$\begin{cases} V_0 = P_3 \\ K_1 = P_2 - P_3 * P_5 \\ k_2 = P_5 - (P_1 - P_3 * P_4) / K_1 \\ k_4 = P_4 / k_2 \\ k_3 = P_5 - k_2 - k_4 \end{cases} \quad (28)$$

Total volume of distribution in this model setting is

$$DV_T = DV_1 + DV_2 = \frac{K_1}{k_2} + \frac{K_1}{k_2}\frac{k_3}{k_4} = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right)$$

It can be calculated from the coefficients as $DV_T = P_1/P_4 - P_3$. However, if DV_T is the only parameter of interest, it may be preferable to get an estimate for it directly without division. For that purpose, equation 17 can divided by $k_2k_4k_6$ and rearranged to give

$$\begin{aligned} &\int_0^T \left[\int_0^T C_T(t)du \right] dt = \\ &\left[\frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right) + V_0 \right] \int_0^T \left[\int_0^T C_0(t)du \right] dt + \\ &\left[\frac{K_1 + V_0(k_2 + k_3 + k_4)}{k_2 k_4} \right] \int_0^T C_0(t)dt + \\ &\frac{V_0}{k_2 k_4} C_0(T) - \\ &\left(\frac{k_2 + k_3 + k_4}{k_2 k_4} \right) \int_0^T C_T(t)dt - \\ &\frac{1}{k_2 k_4} C_T(T) \end{aligned} \quad (29)$$

If also vascular volume is ignored ($V_0=0$), then the following equations can be formed:

$$\begin{aligned} &C_T(T) = \\ &K_1(k_3 + k_4) \int_0^T \left[\int_0^T C_0(t)du \right] dt + \\ &K_1 \int_0^T C_0(t)dt - \\ &k_2 k_4 \int_0^T \left[\int_0^T C_T(t)du \right] dt - \\ &(k_2 + k_3 + k_4) \int_0^T C_T(t)dt \end{aligned} \quad (30)$$

$$\begin{cases} K_1 = P_2 \\ k_2 = P_4 - P_1 / K_1 \\ k_4 = P_3 / k_2 \\ k_3 = P_4 - k_2 - k_4 \end{cases} \quad (31)$$

Total volume of distribution could be calculated directly without division using the following equation (instead of equation 30):

$$\begin{aligned} &\int_0^T \left[\int_0^T C_T(t)du \right] dt = \\ &\frac{K_1}{k_2}\left(1+\frac{k_3}{k_4}\right)\int_0^T \left[\int_0^T C_0(t)du \right] dt + \\ &\frac{K_1}{k_2 k_4}\int_0^T C_0(t)dt - \\ &\left(\frac{k_2+k_3+k_4}{k_2 k_4}\right)\int_0^T C_T(t)dt - \\ &\frac{1}{k_2 k_4} C_T(T) \end{aligned} \quad (30)$$

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