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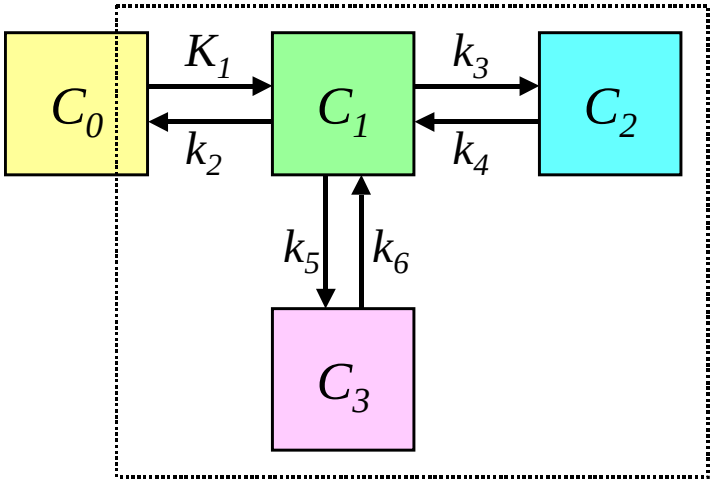
Multilinear solution for 4-compartment model: II. Two parallel tissue compartments

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 further extends the method with an additional tisue compartment in parallel to the second one.

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:

$$DV_T = DV_1 + DV_2 + DV_3 = \frac{K_1}{k_2} + \frac{K_1}{k_2}\frac{k_3}{k_4} + \frac{K_1}{k_2}\frac{k_5}{k_6} = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4} + \frac{k_5}{k_6}\right) = \frac{K_1\left(k_3k_6 + k_5k_4 + k_4k_6\right)}{k_2k_4k_6}$$

Differential equations

$$\frac{dC_1(t)}{dt} = K_1C_0(t) - \left(k_2 + k_3 + k_5\right)C_1(t) + k_4C_2(t) + k_6C_3(t) \quad (2)$$

$$\frac{dC_2(t)}{dt} = k_3C_1(t) - k_4C_2(t) \quad (3)$$

$$\frac{dC_3(t)}{dt} = k_5C_1(t) - k_6C_3(t) \quad (4)$$

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 and second order differential equations are represented in equations 7-8.

$$k_2C_1(t) = V_0\frac{dC_0(t)}{dt} + K_1C_0(t) - \frac{dC_T(t)}{dt} \quad (6)$$

$$k_2\frac{dC_1(t)}{dt} = V_0\frac{ddC_0(t)}{dt\,dt} + K_1\frac{dC_0(t)}{dt} - \frac{ddC_T(t)}{dt\,dt} \quad (7)$$

$$k_2\frac{ddC_1(t)}{dt\,dt} = V_0\frac{dddC_0(t)}{dt\,dt\,dt} + K_1\frac{ddC_0(t)}{dt\,dt} - \frac{dddC_T(t)}{dt\,dt\,dt} \quad (8)$$

Concentration of the second tissue compartment can be solved from the equation 1 and substituted into equation 2. After rearrangement this gives equation 9, which is differentiated with respect to time in equation 10:

$$(k_6 - k_4)C_3(t) = \frac{dC_1(t)}{dt} + (k_2 + k_3 + k_4 + k_5)C_1(t) - k_4 C_T(t) - (K_1 - V_0 k_4)C_0(t) \quad (9)$$

$$(k_6 - k_4)\frac{dC_3(t)}{dt} = \frac{ddC_1(t)}{dt\,dt} + (k_2 + k_3 + k_4 + k_5)\frac{dC_1(t)}{dt} - k_4\frac{dC_T(t)}{dt} - (K_1 - V_0 k_4)\frac{dC_0(t)}{dt} \quad (10)$$

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

$$\frac{ddC_1(t)}{dt\,dt} + (k_2 + k_3 + k_4 + k_5 + k_6)\frac{dC_1(t)}{dt} + [k_5 k_4 + k_6(k_2 + k_3 + k_4)]C_1(t) = (K_1 - V_0 k_4)\frac{dC_0(t)}{dt} + k_6(K_1 - V_0 k_4)C_0(t) + k_4\frac{dC_T(t)}{dt} + k_4 k_6 C_T(t) \quad (11)$$

Equations 6-8 are substituted into equation 11. 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

$$\begin{aligned} C_T(T) = {} & [K_1(k_3k_6 + k_5k_4 + k_4k_6) + V_0k_2k_4k_6]\int_0^T\left[\int_0^T\left[\int_0^T C_0(t)dv\right]du\right]dt + \\ & [K_1(k_3 + k_4 + k_5 + k_6) + V_0(k_4k_6 + k_4(k_2 + k_5) + k_6(k_2 + k_3))]\int_0^T\left[\int_0^T C_0(t)du\right]dt + \\ & [K_1 + V_0(k_2 + k_3 + k_4 + k_5 + k_6)]\int_0^T C_0(t)dt + \\ & V_0C_0(T) - \\ & k_2k_4k_6\int_0^T\left[\int_0^T\left[\int_0^T C_T(t)dv\right]du\right]dt - \\ & [k_4k_6 + k_4(k_2 + k_5) + k_6(k_2 + k_3)]\int_0^T\left[\int_0^T C_T(t)du\right]dt - \\ & (k_2 + k_3 + k_4 + k_5 + k_6)\int_0^T C_T(t)dt \end{aligned} \quad (12)$$

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). Lets use symbols P_1, ..P_7 to represent the coefficients. Because in this model structure the two parallel tissue compartments are similar, the model parameters k3, k4, k5 and k6 are not identifiable. Only the the following model parameters can be solved:

$$\begin{cases} V_0 = P_4 \\ k_2 = P_7 - (P_2 - P_4 * P_6) / K_1 \\ k_4 k_6 = P_5 / k_2 \end{cases} \quad (13)$$

Although the individual rate constants cannot be determined, the 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 12 can divided by $k_2k_4k_6$ and then rearranged to give

$$\begin{aligned} &\int_0^T \left[\int_0^T \left[\int_0^T C_T(t)dv \right] du \right] dt = \\ &\left[\frac{K_1(k_3k_6 + k_5k_4 + k_4k_6)}{k_2k_4k_6} + V_0 \right] \int_0^T \left[\int_0^T \left[\int_0^T C_0(t)dv \right] du \right] dt + \\ &\left[\frac{K_1(k_3 + k_4 + k_5 + k_6) + V_0(k_4k_6 + k_4(k_2 + k_5) + k_6(k_2 + k_3))}{k_2k_4k_6} \right] \int_0^T \left[\int_0^T C_0(t)du \right] dt + \\ &\left[\frac{K_1 + V_0(k_2 + k_3 + k_4 + k_5 + k_6)}{k_2k_4k_6} \right] \int_0^T C_0(t)dt + \\ &\frac{V_0}{k_2k_4k_6} C_0(T) - \\ &\left[\frac{k_4k_6 + k_4(k_2 + k_5) + k_6(k_2 + k_3)}{k_2k_4k_6} \right] \int_0^T \left[\int_0^T C_T(t)du \right] dt - \\ &\left(\frac{k_2 + k_3 + k_4 + k_5 + k_6}{k_2k_4k_6} \right) \int_0^T C_T(t)dt - \\ &\frac{1}{k_2k_4k_6} C_T(T) \end{aligned} \quad (14)$$

, 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 12, giving

$$
\begin{aligned}
&C_T(T) = \\
&K_1\left(k_3k_6 + k_5k_4 + k_4k_6\right)\int_0^T\left[\int_0^T\left[\int_0^T C_0(t)dv\right]du\right]dt + \\
&K_1\left(k_3 + k_4 + k_5 + k_6\right)\int_0^T\left[\int_0^T C_0(t)du\right]dt + \\
&K_1\int_0^T C_0(t)dt - \\
&k_2k_4k_6\int_0^T\left[\int_0^T\left[\int_0^T C_T(t)dv\right]du\right]dt - \\
&\left[k_4k_6 + k_4\left(k_2 + k_5\right) + k_6\left(k_2 + k_3\right)\right]\int_0^T\left[\int_0^T C_T(t)du\right]dt - \\
&\left(k_2 + k_3 + k_4 + k_5 + k_6\right)\int_0^T C_T(t)dt
\end{aligned}
\tag{15}
$$

To solve DVT directly without division of coefficients, the equation can again be divided by $k_2k_4k_6$ and then rearranged to give

$$
\begin{aligned}
&\int_0^T\left[\int_0^T\left[\int_0^T C_T(t)dv\right]du\right]dt = \\
&\frac{K_1\left(k_3k_6 + k_5k_4 + k_4k_6\right)}{k_2k_4k_6}\int_0^T\left[\int_0^T\left[\int_0^T C_0(t)dv\right]du\right]dt + \\
&\frac{K_1\left(k_3 + k_4 + k_5 + k_6\right)}{k_2k_4k_6}\int_0^T\left[\int_0^T C_0(t)du\right]dt + \\
&\frac{K_1}{k_2k_4k_6}\int_0^T C_0(t)dt - \\
&\left[\frac{k_4k_6 + k_4\left(k_2 + k_5\right) + k_6\left(k_2 + k_3\right)}{k_2k_4k_6}\right]\int_0^T\left[\int_0^T C_T(t)du\right]dt - \\
&\left(\frac{k_2 + k_3 + k_4 + k_5 + k_6}{k_2k_4k_6}\right)\int_0^T C_T(t)dt - \\
&\frac{1}{k_2k_4k_6}C_T(T)
\end{aligned}
\tag{16}
$$

Solution to the model when $k_6=0$

If the uptake in one of the parallel tissue compartments is irreversible, the subsequant efflux parameter can be set to zero in the equation 12. Here we set $k_6=0$, giving

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

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

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

Because the model is irreversible, the total volume of distribution cannot be calculated, but instead the influx rate constant, K_i, can be calculated as $K_i = P_1/P_5$. In this model setting

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

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 17 can divided by $k_4(k_2+k_5)$ and rearranged to give

$$\int_0^T \left[\int_0^T C_T(t)du \right] dt =$$
$$\frac{K_1 k_5}{k_2 + k_5} \int_0^T \left[\int_0^T \left[\int_0^T C_0(t)dv \right] du \right] dt +$$
$$\left[\frac{K_1(k_3 + k_4 + k_5)}{k_4(k_2 + k_5)} + V_0 \right] \int_0^T \left[\int_0^T C_0(t)du \right] dt +$$
$$\left[\frac{K_1 + V_0(k_2 + k_3 + k_4 + k_5)}{k_4(k_2 + k_5)} \right] \int_0^T C_0(t)dt + \quad (19)$$
$$\frac{V_0}{k_4(k_2 + k_5)} C_0(T) -$$
$$\left(\frac{k_2 + k_3 + k_4 + k_5}{k_4(k_2 + k_5)} \right) \int_0^T C_T(t)dt -$$
$$\frac{1}{k_4(k_2 + k_5)} C_T(T)$$

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 12, giving

$$C_T(T) =$$
$$K_1 k_4 k_5 \int_0^T \left[\int_0^T \left[\int_0^T C_0(t)dv \right] du \right] dt +$$
$$K_1(k_3 + k_4 + k_5) \int_0^T \left[\int_0^T C_0(t)du \right] dt +$$
$$K_1 \int_0^T C_0(t)dt - \quad (20)$$
$$k_4(k_2 + k_5) \int_0^T \left[\int_0^T C_T(t)du \right] dt -$$
$$(k_2 + k_3 + k_4 + k_5) \int_0^T C_T(t)dt$$

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

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

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 12, giving

$$
\begin{aligned}
&C_T(T) = \\
&\left[K_1(k_3+k_4)+V_0k_2k_4\right]\int_0^T\left[\int_0^T C_0(t)du\right]dt + \\
&\left[K_1+V_0(k_2+k_3+k_4)\right]\int_0^T C_0(t)dt + \\
&V_0C_0(T) - \\
&k_2k_4\int_0^T\left[\int_0^T C_T(t)du\right]dt - \\
&(k_2+k_3+k_4)\int_0^T C_T(t)dt
\end{aligned}
\qquad (22)
$$

, which is the same equation that has been previously formed from the two-tissue compartment model (Gjedde and Wong, 1990; TPCMOD0023).

References

1. Blomqvist G. On the construction of functional maps in positron emission tomography. *J. Cereb. Blood Flow Metab.* 1984; 4: 629-632.
2. Gjedde A, Wong DF. Modeling neuroreceptor binding of radioligands *in vivo*. In: *Quantitative Imaging: Neuroreceptors, Neurotransmitters, and Enzymes.* (Eds. Frost JJ, Wagner HN Jr). Raven Press, Ltd., New York, 1990, 51-79.
3. Lawson CL, Hanson RJ. *Solving least squares problems.* Prentice-Hall, Englewood Cliffs, New Jersey, 1974.