Patlak Plot

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October 20, 2023

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1 Introduction

Patlak plot is a graphical tool for analyzing relevant parameters in the uptake process of an irreversible radioactive tracer. The original model is general (Fig. 1). The tissue is modeled as two kinds of compartments: reversible and irreversible. The n reversible compartments can freely communicate with each other and the plasma. The irreversible compartment models the lumped irreversible regions in the tissue, which the tracer can enter into (from plasma and the reversible compartments) but cannot leave from.

Let $A_m(t)$ (unit: mCi) be the total amount of tracer in the tissue measured by PET at time t. $A_m(t)$ includes amount both in the reversible and irreversible compartments. Let $C_p(t)$ (unit: mCi/ml) be the tracer concentration in the plasma at time t. The goal is to find the relationship between $A_m(t)$ and $C_p(t)$.

Result: there exists sufficiently large t^* such that for $t > t^*$,

$$A_m(t) = K_i \int_0^t C_p(\tau)\mathrm{d}\tau + (V_0 + V_p)C_p(t)\,, \tag{1}$$

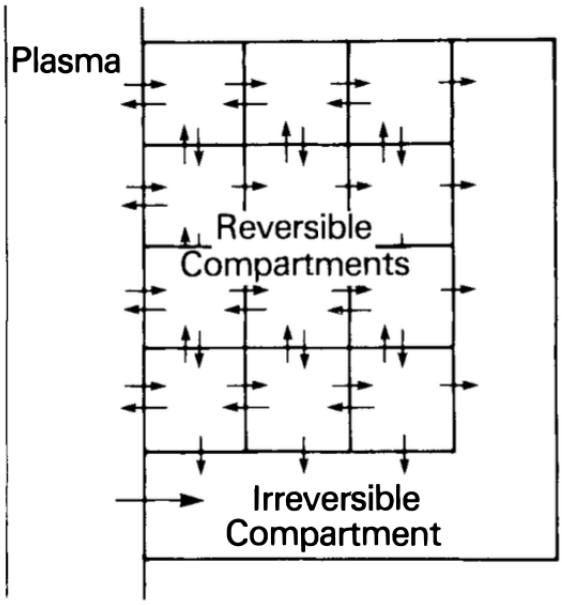

Figure 1: The original model considered in [3].

where K_i is rate constant of the overall uptake (into the irreversible compartment), V_p is the volume of the plasma in the tissue sampled. Simple unit analysis shows that the units of K_i, V_p and V_0 are $\mathrm{ml} \cdot \mathrm{min}^{-1}$, ml and ml.

The meaning and interpretation of V_0 is more involved:

- The original paper [3] defines V_0 mathematically through Eq. 22, but doesn't give it a direct physical interpretation. However, it does say that V_0 is $\leq$ the "steady-state space" (i.e. volume) of the exchangeable/reversible region, which by definition is the ratio of $\sum_i A_i$, the total amount of tracer in the exchangeable region relative to (i.e. divided by) C_p, a constant plasma concentration level, i.e. $\frac{\sum_i A_i}{C_p}$. It is suspected by Zeyu that the "steady-state volume" is the same as the volume of distribution, a more commonly used terminology now.
- According to a second paper [2], $V_0 = fV_e$, where V_e is the steady-state volume of the reversible compartments and f is fraction of the amount in the reversible compartments that goes back into the blood plasma and leaves the system. f is always ≤ 1. This is consistent with the point above.
- According to Wikipedia, V_0 is the volume of distribution of the tracer in the central/reversible compartment.
- According to PMOD, V_0 is the volume of distribution of the reversible compartment.
- According to [1] (Page 146), V_0 is the *initial* volume of distribution. Zeyu: I am not sure what "initial" means here.
- To summarize: I (Zeyu) think Wikipedia and PMOD made a mistake there. V_0 is not the distribution volume of the reversible compartment, but a fraction of it.

If we re-arrange Eq. (1), we get

$$\frac{A_m(t)}{C_p(t)} = K_i \frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{C_p(t)} + (V_0 + V_p)\,. \tag{2}$$

If you plot $\frac{A_m(t)}{C_p(t)}$ versus $\frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{C_p(t)}$, for $t > t^*$, we expect to see a straight line with slope K_i and intercept $V_0 + V_p$.

1.1 Notes

We make a special note about two things: *units* and *irreversibility*.

First, it is more common to replace A_m with C_m now, i.e. not the amount, but the concentration. The equation will look similar:

$$C_m(t) = K_i \int_0^t C_p(\tau)\mathrm{d}\tau + (V_0 + V_p)C_p(t)\,, \tag{3}$$

except the units need update. The unit of K_i is min^{-1} and V_0 and V_p are unitless. Note that In this context, it makes more sense to compare V_0 with the distribution volume of the reversible compartment, which is a unitless quantity. V_p is the plasma volume fraction, also unitless.

Second, Patlak plot applies generally to uptake, transport, and metabolism processes as long as there is a last irreversible step.

2 Notation and basic equations

- A or $A(t)$, an $n \times 1$ vector of the amounts of tracer in each of the reversible compartments.
- $K = [k_{ij}]$, a $n \times n$ matrix of the rate constants among the n reversible compartments. For $i \neq j$, k_{ij} is the transport rate constant from compartment j to compartment i (note that it is not the natural direction, but it will be clear why it is so in an example below.) k_{ii} is a negative term and is a sum of all the rate constants *out of* (i.e. leaving) compartment i.
- $Q = [k_{1p} \cdots k_{np}]^T$, an $n \times 1$ vector of the rate constants from the plasma to each of the reversible compartments. k_{ip} is the rate constant from plasma to reversible compartment i.
- $C_p(t)$, scaler, the tracer concentration in the plasma at time t.
- $G = \mathrm{diag}(k_{b1}, \cdots, k_{bn})$, an diagonal matrix of the rate constants from the reversible compartments to the irreversible/bound compartment. 'b' for bound.
- k_{bp}, scaler, the rate constant for the direct movement of tracer from the plasma to the bound compartment.
- $U_n^T = [1 \cdots 1]$, a $1 \times n$ row vector.
- $T(t)$, the amount of tracer in the irreversible compartment at time t.
- V_p, the volume of the plasma in the tissue sampled, unit ml.
- $A_m(t)$, the total amount of tracer measured in the sampled tissues at time t, including the reversible and irreversible compartments and the amounts contributed by blood/plasma.

The measurables of the system are $C_p(t)$ and $A_m(t)$. The basic mathematical relationships are:

$$\frac{\mathrm{d}A(t)}{\mathrm{d}t} = KA(t) + QC_p(t)\,, \tag{4}$$

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} = U_n^T G A(t) + k_{bp} C_p(t)\,, \tag{5}$$

and

$$A_m(t) = U_n^T A(t) + T(t) + V_p C_p(t)\,. \tag{6}$$

2.1 Example

To be concrete, for the example model shown in Fig 2, the notation are specified as follows. $K = \begin{bmatrix} -(k_{p1}+k_{b1}+k_{21}) & k_{12} \\ k_{21} & -(k_{p2}+k_{b2}+k_{12}) \end{bmatrix}$, $Q = \begin{bmatrix} k_{1p} \\ k_{2p} \end{bmatrix}$, $G = \begin{bmatrix} k_{b1} & 0 \\ 0 & k_{b2} \end{bmatrix}$, $k_{bp} = k_{bp}$. The equations become

$$\begin{aligned}
\frac{\mathrm{d}A(t)}{\mathrm{d}t} &= \begin{bmatrix} -(k_{p1}+k_{b1}+k_{21}) & k_{12} \\ k_{21} & -(k_{p2}+k_{b2}+k_{12}) \end{bmatrix} \begin{bmatrix} A_1(t) \\ A_2(t) \end{bmatrix} + \begin{bmatrix} k_{1p} \\ k_{2p} \end{bmatrix} C_p(t)\,, \\
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= \begin{bmatrix} 1 & 1 \end{bmatrix} \begin{bmatrix} k_{b1} & 0 \\ 0 & k_{b2} \end{bmatrix} \begin{bmatrix} A_1(t) \\ A_2(t) \end{bmatrix} + k_{bp} C_p(t)\,, \\
A_m(t) &= (A_1(t) + A_2(t)) + T(t) + V_p C_p(t)\,.
\end{aligned}$$

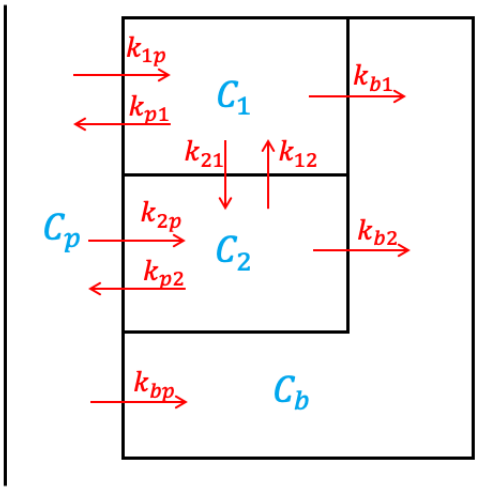

Figure 2: An example model to illustrate the notation.

3 Derivation

We go through the derivation steps in the paper in detail. The solution of Eq. 4 is

$$\underbrace{A(t)}_{n\times 1} = \underbrace{e^{Kt}}_{n\times n} \int_0^t \underbrace{C_p(\tau)}_{1\times 1} \underbrace{e^{-K\tau}}_{n\times n} \mathrm{d}\tau \underbrace{Q}_{n\times 1}\,. \tag{7}$$

For intuition of Eq. 7, suppose K is a scaler. Laplace transform of Eq. 1 gives $s\bar{A}(s) = K\bar{A}(s) + Q\bar{C_p}(s)$, thus $\bar{A}(s) = \bar{C_p}(s)\frac{Q}{s-K}$. So $A(s) = C_p(t) \otimes e^{Kt}Q = \int_0^t C_p(\tau) e^{K(t-\tau)}\,\mathrm{d}\tau Q$.

Then, consider Eq. 5 and note that the RHS does not have T. So we can directly integrate both sides to obtain $T(t)$:

$$\begin{aligned} T(t) &= U_n^T G \int_0^t A(\tau)\,\mathrm{d}\tau + k_{bp}\int_0^t C_p(\tau)\,\mathrm{d}\tau \\ &= U_n^T G \underbrace{\int_0^t e^{K\tau}\int_0^\tau C_p(\theta)e^{-K\theta}\,\mathrm{d}\theta\mathrm{d}\tau}_{I=\int_0^t u'(\tau)v(\tau)\,\mathrm{d}\tau} Q + k_{bp}\int_0^t C_p(\tau)\,\mathrm{d}\tau\,, \end{aligned}$$

where $u'(\tau) = e^{K\tau}$ and $v(\tau) = \int_0^\tau C_p(\theta)e^{-K\theta}\,\mathrm{d}\theta$. Thus $u(\tau) = K^{-1}e^{K\tau}$ and $v'(\tau) = C_p(\tau)e^{-K\tau}$. It follows that

$$\begin{aligned} I &= u(\tau)v(\tau)\Big|_{\tau=0}^t - \int_0^t u(\tau)v'(\tau)\,\mathrm{d}\tau \\ &= K^{-1}e^{K\tau}\int_0^\tau C_p(\theta)e^{-K\theta}\,\mathrm{d}\theta\Big|_{\tau=0}^t - \int_0^t K^{-1}e^{K\tau}C_p(\tau)e^{-K\tau}\,\mathrm{d}\tau \\ &= K^{-1}e^{Kt}\int_0^t C_p(\tau)e^{-K\tau}\,\mathrm{d}\tau - K^{-1}\int_0^t C_p(\tau)\,\mathrm{d}\tau \end{aligned}$$

Note that

$$\begin{aligned} IQ &= K^{-1}\underbrace{e^{Kt}\int_0^t C_p(\tau)e^{-K\tau}\,\mathrm{d}\tau\cdot Q}_{=A(t)} - K^{-1}\int_0^t C_p(\tau)\,\mathrm{d}\tau\cdot Q \\ &= K^{-1}A(t) - K^{-1}\int_0^t C_p(\tau)\,\mathrm{d}\tau\cdot Q\,. \end{aligned}$$

So

$$\begin{aligned} T(t) &= U_n^T G I Q + k_{bp}\int_0^t C_p(\tau)\,\mathrm{d}\tau \\ &= U_n^T G K^{-1}A(t) - U_n^T G K^{-1}\int_0^t C_p(\tau)\,\mathrm{d}\tau\cdot Q + k_{bp}\int_0^t C_p(\tau)\,\mathrm{d}\tau \\ &= U_n^T G K^{-1}A(t) + (-U_n^T G K^{-1}Q + K_{bp})\int_0^t C_p(\tau)\,\mathrm{d}\tau\,. \end{aligned} \tag{8}$$

Note: K is a negative definite matrix; in case K is 1×1, it is a negative scaler. So in the second line of Eq. 8, term 1 is negative, term 2 is positive. Plugging Eq. 8 into Eq. 6, we get

$$\begin{aligned} A_m(t) &= (-U_n^T G K^{-1}Q + K_{bp})\int_0^t C_p(\tau)\,\mathrm{d}\tau + (U_n^T G K^{-1}A(t) + U_n^T A(t)) + V_p C_p(t) \\ &= (-U_n^T G K^{-1}Q + K_{bp})\int_0^t C_p(\tau)\,\mathrm{d}\tau + U_n^T(K+G)K^{-1}A(t) + V_p C_p(t)\,. \end{aligned} \tag{9}$$

If $C_p(t)$ is constant over time, $A(t)$ will approach a finite limit as $t\to\infty$. In that case,

$$A_m(t) \overset{t\to\infty}{=} (-U_n^T G K^{-1}Q + K_{bp})C_p t\,.$$

The overall uptake rate constant K_i is defined as such that $K_i C_p$ is the average uptake rate in the limit as $t\to\infty$, that is, $\lim_{t\to\infty}\frac{A_m(t)}{t}$. Therefore,

$$K_i = -U_n^T G K^{-1}Q + k_{bp}\,. \tag{10}$$

Thus, $A_m(t)$ can be written as

$$A_m(t) = K_i \int_0^t C_p(\tau)\,\mathrm{d}\tau + U_n^T(K+G)K^{-1}A(t) + V_p C_p(t)\,. \tag{11}$$

Next, we try to simplify the expression of $A(t)$ as a function of $C_p(t)$. We diagonalize matrix K by

$$PKP^{-1} = D = \begin{bmatrix} d_1 & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & d_n \end{bmatrix}.$$

The real parts of the eigenvalues of K are negative (Hearon, 1963, Zeyu: try to understand). For illustration, let $d_1, \cdots, d_n$ be negative values arranged in decreasing order, for example $d_1 = -1, \cdots, d_n = -100$. We have

$$K = P^{-1}DP, \quad e^{Kt} = P^{-1}e^{Dt}P, \quad e^{-Kt} = P^{-1}e^{-Dt}P\,.$$

Plugging in these into the general solution of $A(t)$ in Eq. 7, we have

$$A(t) = P^{-1}\underbrace{e^{Dt}\left[\int_0^t C_p(\tau)e^{-D\tau}\,\mathrm{d}\tau\right]}_{=J}PQ\,. \tag{12}$$

Consider the case where $C_p(t)$ can be expressed in terms of a series of exponentials, i.e.,

$$C_p(t) = \sum_{i=1}^m b_i e^{-\beta_i t} = b_1 e^{-\beta_1 t} + b_2 e^{-\beta_2 t} + \cdots + b_m e^{-\beta_m t}\,,$$

where $\beta_1, \beta_2, \cdots, \beta_m$ are real, non-negative values arranged in decreasing order. For example, $\beta_1 = 50, \beta_2 = 20, \cdots, \beta_m = 0.1$. Hence, $C_p(t)$ is dominated by latter terms which decay slowly. For large t, $C_p(t)$ is dominated by $b_m e^{-\beta_m t}$. It follows that

$$\begin{aligned}
J &= e^{Dt}\int_0^t \sum_{i=1}^m b_i e^{-\beta_i \tau} e^{-D\tau}\,\mathrm{d}\tau \\
&= e^{Dt}\sum_{i=1}^m \int_0^t e^{-(\beta_i I + D)\tau}\,\mathrm{d}\tau \\
&= e^{Dt}\sum_{i=1}^m b_i\,(\beta_i I + D)^{-1}\left(I - e^{-(\beta_i I + D)t}\right) \\
&= \sum_{i=1}^m b_i\,(\beta_i I + D)^{-1}\left(e^{Dt} - e^{-\beta_i I t}\right) \\
&= -\sum_{i=1}^m b_i\,(\beta_i I + D)^{-1}\left(e^{-\beta_i I t} - e^{Dt}\right)\,.
\end{aligned}$$

(Eq. 13 in the original paper [3] missed the negative sign here.d) We now assume that there exists a $q \le m$ such that $\beta_q \ll |\text{real part of}\, d_1|$, where d_1 is the eigenvalue of K with the minimum absolute

real component. For example, $q = m$, $\beta_m = 0.1$, $d_1 = -1$. Then there exists a t^* such that, for $t > t^*$,

$$
\begin{aligned}
e^{-\beta_q I t} &\gg \left| e^{Dt} \right| \\
D + \beta_q I &\approx D \\
\sum_{i=1}^{q-1} b_i e^{-\beta_i t} &\ll \sum_{i=q}^{m} b_i e^{-\beta_i t} \,. \quad (C_p(t) \text{ is dominated by slow decaying terms})
\end{aligned}
$$

For example and illustration,

$$
e^{-\beta_q I t} = \begin{bmatrix} e^{-0.1t} & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & e^{-0.1t} \end{bmatrix} \gg \begin{bmatrix} e^{-t} & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & e^{-100t} \end{bmatrix} = e^{Dt} \,,
$$

$$
D + \beta_q I = \begin{bmatrix} -1 & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & -100 \end{bmatrix} + \begin{bmatrix} 0.1 & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & 0.1 \end{bmatrix} \approx \begin{bmatrix} -1 & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & -100 \end{bmatrix} .
$$

It follows that for $t > t^*$,

$$
\begin{aligned}
J &\approx -\sum_{i=q}^{m} b_i (\beta_i I + D)^{-1} \left(e^{-\beta_i I t} - e^{Dt} \right) \\
&\approx -\sum_{i=q}^{m} b_i D^{-1} e^{-\beta_i I t} \\
&= -D^{-1} \sum_{i=q}^{m} b_i e^{-\beta_i I t} \\
&= -D^{-1} \sum_{i=q}^{m} b_i e^{-\beta_i t} \quad \text{(because everything is diagonal)} \\
&\approx -D^{-1} C_p(t) \,.
\end{aligned}
$$

Substituting J in Eq. 12, we have, for $t > t^*$,

$$
\begin{aligned}
A(t) &= -P^{-1} D^{-1} C_p(t) P Q \\
&= -K^{-1} Q C_p(t) \,.
\end{aligned} \tag{13}
$$

Dimension check: $A : n$, $K^{-1} : n \times n$, $Q : n \times 1$. Reminder: the condition for Eq. 13 is that, the change in the blood plasma concentration $C_p(t)$ eventually becomes slow enough. Plugging Eq. 13 into Eq. 11, we get

$$
A_m(t) = K_i \int_0^t C_p(\tau) \, \mathrm{d}\tau + \left(-U_n^T (K + G) K^{-2} Q + V_p \right) C_p(t) \tag{14}
$$

$A_m(t)$ is the total amount of tracer in the tissue. The first term involving $\int_0^t C_p(\tau) \, \mathrm{d}\tau$ is due to tracer accumulation in the irreversible compartment. Part of the second term, $-U_n^T K K^{-2} Q C_p(t) = -U_n^T K^{-1} Q C_p(t) = U_n^T A(t)$, is due to tracer in the reversible compartments.

The authors went on to give an interpretation of the term $U_n^T (K + G) K^{-1} A(t)$ in Eq. 11. As illustrated by an example before, $U_n^T K$ is a row vector whose components are the sums of the

columns of K, with the ith component being $-(k_{pi} + k_{bi})$. Since the ith component of $U_n^T G$ is k_{bi}, the ith component of $U_n^T(K+G)$ is $-k_{pi}$. Since A and K^{-1} consist of positive and negative elements, respectively, $U_n^T(K+G)K^{-1}A$ is positive. Since $K+G$ is less negative than K alone,

$$U_n^T(K+G)K^{-1}A \leq U_n^T K K^{-1} A = U_n^T A\,.$$

The steady-state space of A is defined as $\frac{U_n^T A}{C_p}$. If we define V_0 by (for $t > t^*$)

$$U_n^T(K+G)K^{-1}A = V_0 C_p\,, \tag{15}$$

then

$$V_0 \leq \text{steady-state space of } A\,.$$

Plugging in Eq. 15 into Eq. 11, we have

$$A_m(t) = K_i \int_0^t C_p(\tau)\,\mathrm{d}\tau + (V_0 + V_p)C_p(t)\,. \tag{16}$$

4 Reflection

4.1 Simplification of $A(t)$

We have shown that, if the change in the plasma concentration $C_p(t)$ eventually becomes slow enough, for $t > t^*$,

$$A(t) = e^{Kt}\int_0^t C_p(\tau)e^{-K\tau}\,\mathrm{d}\tau \cdot Q = -K^{-1}QC_p(t)\,.$$

To provide intuition for this, suppose $C_p(t)$ is constant over time, which satisfies the assumption trivially with $C_p(t) = C_p e^{-0t}$. Then, with diagonolization $PKP^{-1} = D$,

$$\begin{aligned}
A(t) &= C_p e^{Kt}\int_0^t e^{-K\tau}\,\mathrm{d}\tau \cdot Q \\
&= C_p P^{-1}e^{Dt}P\int_0^t P^{-1}e^{-D\tau}P\,\mathrm{d}\tau \cdot Q \\
&= C_p P^{-1}e^{Dt}\int_0^t e^{-D\tau}\,\mathrm{d}\tau \cdot PQ \\
&= C_p P^{-1}e^{Dt}(-1)D^{-1}e^{-D\tau}\Big|_{\tau=0}^{t} \cdot PQ \\
&= -C_p P^{-1}e^{Dt}D^{-1}(e^{-Dt} - I)PQ \\
&= -C_p P^{-1}D^{-1}(I - e^{Dt})PQ\,. \quad \text{(because everything is diagonal)}
\end{aligned}$$

Since D is a diagonal matrix with negative elements, as $t \to \infty$, $e^{Dt} \to 0$. So

$$A(t) \to -C_p P^{-1}D^{-1}PQ = -C_p K^{-1}Q\,.$$

4.2 The necessity of irreversibility

The key condition for the analysis and and the Patlak plot is the existence of an irreversible compartment in which the tracer gets trapped. Recall the final result:

$$A_m(t) = K_i \int_0^t C_p(\tau)\,\mathrm{d}\tau + (V_0 + V_p)C_p(t)\,.$$

It is $\frac{A_m(t)}{C_p(t)}$ versus $\frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{C_p(t)}$ that will be plotted. Because of the irreversible compartment, tracer eventually accumulates there and never leaves (ideally), therefore $A_m(t)$ will continue growing. However, if the irreversibility assumption does not hold, as the plasma concentration vanishes in the long run, $A_m(t)$ will eventually become zero. Therefore, without the irreversibility assumption, Patlak plot does not apply.

The case with reversible binding is dealt with by the Logan plot.

5 Example: 2TCM

We apply Patlak plot and the analysis to a simple and practical model: 2-Tissue Compartment Model.

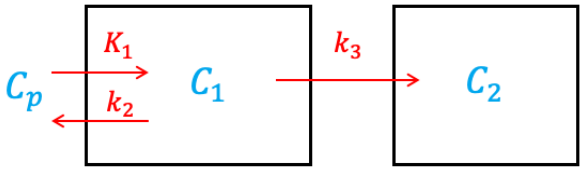

Figure 3: 2-Tissue compartment model with an irreversible compartment.

5.1 Using Patlak's general result

Based on the setup in [3], for this particular model,

$$K = [-(k_2 + k_3)], \quad Q = [K_1], \quad G = [k_3], \quad k_{bp} = 0\,.$$

Suppose $C_p(t)$ satisfies the condition that its decay eventually becomes slow enough. More specifically, if $C_p(t)$ is dominated by a term $be^{-\beta t}$, such that $0 < \beta \ll (k_2 + k_3)$. Then for $t > t^*$,

$$C_1(t) = A(t) = -K^{-1}QC_p(t) = \frac{K_1}{k_2 + k_3}C_p(t)\,,$$

and

$$\begin{aligned} C_2(t) = T(t) &= U_n^T G K^{-1} A(t) + (-U_n^T G K^{-1} Q + k_{bp}) \int_0^t C_p(\tau)\,\mathrm{d}\tau \\ &= -\frac{k_3}{k_2 + k_3}C_1(t) + \frac{K_1 k_3}{k_2 + k_3}\int_0^t C_p(\tau)\,\mathrm{d}\tau \\ &= -\frac{K_1 k_3}{(k_2 + k_3)^2}C_p(t) + \frac{K_1 k_3}{k_2 + k_3}\int_0^t C_p(\tau)\,\mathrm{d}\tau\,. \end{aligned}$$

The total tissue concentration is

$$C(t) = C_1(t) + C_2(t) = \frac{K_1 k_2}{(k_2 + k_3)^2}C_p(t) + \frac{K_1 k_3}{k_2 + k_3}\int_0^t C_p(\tau)\,\mathrm{d}\tau\,.$$

So

$$K_i = \frac{K_1 k_3}{k_2 + k_3} \quad \text{and} \quad V_0 = \frac{K_1 k_2}{(k_2 + k_3)^2}\,.$$

5.2 Direct derivation

We can also derive results for this model directly. The differential equations are:

$$\begin{aligned}\frac{\mathrm{d}C_1}{\mathrm{d}t} &= K_1 C_p - k_2 C_1 - k_3 C_1 \\ \frac{\mathrm{d}C_2}{\mathrm{d}t} &= k_3 C_1 \,.\end{aligned}$$

The solution for $C_1(t)$ can be written in several different forms, all equivalent:

$$\begin{aligned}C_1(t) &= K_1 e^{-(k_2+k_3)t} \int_0^t C_p(\tau) e^{(k_2+k_3)\tau}\,\mathrm{d}\tau = K_1 \int_0^t C_p(\tau) e^{-(k_2+k_3)(t-\tau)}\,\mathrm{d}\tau \\ &= K_1 C_p(t) \otimes e^{-(k_2+k_3)t}\,.\end{aligned}$$

If $C_p(t)$ is constant, it is easy to calculate that

$$C_1(t) = \frac{K_1 C_p}{k_2+k_3}\left(1 - e^{-(k_2+k_3)t}\right) \overset{t\to\infty}{\to} \frac{K_1 C_p}{k_2+k_3}\,.$$

Suppose $C_p(t) = be^{-\beta t}$, where $\beta \ll (k_2+k_3)$, then

$$\begin{aligned}C_1(t) &= K_1 \int_0^t b e^{-\beta\tau} e^{-(k_2+k_3)(t-\tau)}\,\mathrm{d}\tau \\ &= K_1 e^{-(k_2+k_3)t} b \int_0^t e^{(k_2+k_3-\beta)\tau}\,\mathrm{d}\tau \\ &= K_1 e^{-(k_2+k_3)t} \frac{b}{k_2+k_3-\beta}\left(e^{(k_2+k_3-\beta)t} - 1\right) \\ &= K_1 \frac{be^{-\beta t}}{k_2+k_3-\beta}\left(1 - e^{-(k_2+k_3-\beta)t}\right) \\ &\approx K_1 \frac{be^{-\beta t}}{k_2+k_3}\left(1 - e^{-(k_2+k_3-\beta)t}\right) \\ &\to K_1 \frac{be^{-\beta t}}{k_2+k_3} = \frac{K_1 C_p(t)}{k_2+k_3}\,.\end{aligned}$$

Next, we show that

$$C_2(t) = \frac{K_1 k_3}{k_2+k_3} C_p(t) \otimes \left(1 - e^{-(k_2+k_3)t}\right)\,.$$

One way to show this is to work out the following compound integral by integral-by-parts (see the beginning of Section 3 in this notes):

$$\begin{aligned}C_2(t) &= k_3 \int_0^t C_1(\tau)\,\mathrm{d}\tau \\ &= k_3 \int_0^t K_1 \int_0^\tau C_p(\theta) e^{-(k_2+k_3)(\tau-\theta)}\,\mathrm{d}\theta\mathrm{d}\tau \\ &= K_1 k_3 \int_0^t e^{-(k_2+k_3)\tau} \int_0^\tau C_p(\theta) e^{(k_2+k_3)\theta}\,\mathrm{d}\theta\,\mathrm{d}\tau\,.\end{aligned}$$

An easier and cleaner way is to realize that $\int_0^t x(\tau)\,\mathrm{d}\tau = x(t) \otimes u(t)$, where $u(t) = 1$ for $t \geq 0$. Then

$$\begin{aligned} C_2(t) &= k_3 C_1(t) \otimes u(t) \\ &= K_1 k_3 \left(C_p(t) \otimes e^{-(k_2+k_3)t} \right) \otimes u(t) \\ &= K_1 k_3 C_p(t) \otimes \left(e^{-(k_2+k_3)t} \otimes u(t) \right) \\ &= K_1 k_3 C_p(t) \otimes \int_0^t e^{-(k_2+k_3)\tau}\,\mathrm{d}\tau \\ &= \frac{K_1 k_3}{k_2+k_3} C_p(t) \otimes \left(1 - e^{-(k_2+k_3)t} \right) . \end{aligned}$$

The third equality above used the associativity of convolution, i.e. $(x(t) \otimes y(t)) \otimes z(t) = x(t) \otimes (y(t) \otimes z(t))$, which can be proved through the associativity of multiplication in Fourier space.

Adding $C_1(t)$ and $C_2(t)$, we have

$$\begin{aligned} C(t) &= C_p(t) \otimes \left(\frac{K_1 k_3}{k_2+k_3} + \frac{K_1 k_2}{k_2+k_3} e^{-(k_2+k_3)t} \right) \\ &= \frac{K_1 k_3}{k_2+k_3} \int_0^t C_p(\tau)\,\mathrm{d}\tau + \frac{K_1 k_2}{k_2+k_3} C_p(t) \otimes e^{-(k_2+k_3)t} . \end{aligned}$$

When $C_p(t)$ satisfies the slow decay condition discussed above, we have that, for $t > t^*$,

$$C(t) \approx \frac{K_1 k_3}{k_2+k_3} \int_0^t C_p(\tau)\,\mathrm{d}\tau + \frac{K_1 k_2}{(k_2+k_3)^2} .$$

Again, we obtain

$$K_i = \frac{K_1 k_3}{k_2+k_3} \quad \text{and} \quad V_0 = \frac{K_1 k_2}{(k_2+k_3)^2} .$$

5.3 Interpretation of K_i and V_0

$$K_i = K_1 \cdot \frac{k_3}{k_2+k_3} .$$

K_1 is the uptake rate constant from the plasma to the reversible compartment. $\frac{k_3}{k_2+k_3}$ is the fraction of tracer that reaches the irreversible compartment once it enters the reversible compartment. So K_i is the overall uptake rate constant from the plasma to the irreversible compartment.

$$V_0 = \frac{K_1}{k_2+k_3} \cdot \frac{k_2}{k_2+k_3} .$$

$\frac{K_1}{k_2+k_3} = V_e$ is the distribution volume of the reversible compartment (the ratio of the reversible compartment concentration and plasma concentration at equilibrium). $\frac{k_2}{k_2+k_3}$ is the fraction of tracer that goes back to plasma after it enters the reversible compartment. The overall interpretation: ???

6 Alternative Derivation

Patlak et al. [2] wrote a second paper two years after [3], in which they provided an alternative derivation to the same result. This deviation avoids the forward analysis and starts with an overall

process to define K_i. (In [2]), the symbol K is used in placement of K_i. Here, in order to be consistent with our previous discussion, we still use K_i.) The overall uptake constant K_i is defined by:

$$A_m(\infty) = K_i \int_0^\infty C_p(t)\,\mathrm{d}t\,, \tag{17}$$

where $A_m(\infty)$ is the amount of tracer in the whole tissue region at infinite time, i.e. trapped forever.

Interpretation: it is easier to use C_m instead of A_m in explaining this. Suppose $C_p(t)$ is constant over time. Since the only source of the tracer is the plasma, $C_m(\infty) = \lim_{t\to\infty} K_i C_p t$. Verify that the units make sense. Now, if $C_p(t)$ is not constant, this equation becomes $C_m(\infty) = K_i \int_0^t C_p(t)\,\mathrm{d}t$.

Consider an imagined experiment in which $C_p(t)$ becomes zero for time $> t$. Then (key equation):

$$A_m(\infty) = A_m(t) - V_p C_p(t) - f(t) A_e(t)\,, \tag{18}$$

where $A_e(t)$ is the amount of tracer in the reversible compartments at time t, i.e. $A_e(t) = U_n^T A(t)$, $f(t)$ is the fraction of the amount of tracer in the reversible compartments that goes back into the blood plasma and leaves the system.

Interpretation: At time t, the amount of tracer as detected by PET in the tissue is $A_m(t)$. Note that $A_m(t)$ includes amounts in the plasma, $V_p C_p(t)$. After time t, the no more tracer coming from the plasma source, only tracer leaving. So

$$A_m(\infty) = A_m(t) - (\text{tracer that leaves from } A_m(t) \text{ from time } t \text{ to } \infty)\,.$$

How can a tracer leave after time t? (1) If the tracer is in plasma, it will leave with blood flow. This part is $V_p C_p(t)$. (2) A fraction of tracer will flow back to blood from the reversible compartments and leaves the system; by definition, this is $f(t)A_e(t)$.

If $C_p(t)$ satisfies the slow decay condition, then after some time t^*, the reversible compartments will be in effective steady state (Zeyu: now we call it equilibrium) with the blood plasma. Then according to [3], for $t > t^*$, we have

$$A_e(t) = V_e C_p(t)\,, \tag{19}$$

where V_e is the steady-state volume (Zeyu: i.e. distribution volume) of the reversible compartments. By [3], we know that $V_e = -U_n^T K^{-1} Q$ (here, since we didn't even define K and Q, it is not relevant.) In this situation (equilibrium in reversible compartments), $f(t)$ becomes a constant, f.

Combining Eqs. 17, 18 and 19, we have, for $t > t^*$,

$$A_m(t) = K_i \int_0^t C_p(\tau)\,\mathrm{d}\tau + (fV_e + V_p) C_p(t)\,. \tag{20}$$

This is the same with the result from [3] (Eq. 16. We avoided the hassle of defining matrices K, Q, G, etc. and the complicated math. Moreover, we see that $V_0 = fV_e$, giving a physical interpretation to V_0.

7 Patlak reference model

The purpose of a reference model is to avoid resorting to blood/plasma measurements. Suppose there is a reference tissue, which only has the reversible compartments. Recall that in Eq. 20, the term $K_i \int_0^t C_p(t)\,\mathrm{d}t$ is solely due to the irreversible compartment. So, for the reference tissue, this term disappears. Also, since there is no irreversible compartment, all tracer in the reversible

compartment will eventually goes back to the blood in the reference tissue, so $f' = 1$. Thus, for the reference tissue, for $t > t^*$,

$$A'_m(t) = (V'_e + V'_p)C_p(t)\,. \tag{21}$$

Our goal is to combine Eqs. 20 and 21 so that we don't have any terms involving $C_p(t)$. However, we realize that we cannot cancel $\int_0^t C_p(\tau)\,\mathrm{d}\tau$ here. That fact that we have $A'_m(t) = (V'_e + V'_p)C_p(t)$ for $t > t^*$ doesn't imply that $\int_0^t A'_m(\tau)\,\mathrm{d}\tau = \int_0^t (V'_e + V'_p)C_p(\tau)\,\mathrm{d}\tau$ for $t > t^*$, because the integration involves time periods before t^*.

We seek for another equation next (this is in [2] Appendix). For the reference tissue,

$$\frac{\mathrm{d}A'}{\mathrm{d}t} = K'A' + Q'C_p(t)\,,$$

where K', A', Q' are the counterparts of K, A, Q in the reference tissue. Taking integral on both sides, and using the fact that the is no tracer in the reference tissue at the beginning of time, we have

$$A'(t) = \int_0^t K'A'(\tau)\,\mathrm{d}\tau + Q'\int_0^t C_p(\tau)\,\mathrm{d}\tau\,. \tag{22}$$

Note that $A'(t)$ is a column vector., so the above is a system of equations. Remember our goal is to relate $\int_0^t C_p(\tau)\mathrm{d}\tau$ to $A'_m(t)$. By our previous analysis for the target tissue, the following are readily available for $t > t^*$,

$$\begin{aligned} A'(t) &= -(K')^{-1}Q'C_p(t) \\ A'_e(t) &= U_n^T A'(t) = V'_e C_p(t) \\ V'_e &= -U_n^T(K')^{-1}Q'\,. \end{aligned}$$

Also,

$$A'_m(t) = A'_e(t) + V'_p C_p(t)\,.$$

We are ready to manipulate Eq. 22 now. First, multiply both sides by $U_n^T(K')^{-1}$ to make A'_e in the integral:

$$U_n^T(K')^{-1}A'(t) = \int_0^t A'_e(\tau)\,\mathrm{d}\tau - V'_e\int_0^t C_p(\tau)\,\mathrm{d}\tau\,.$$

(NOTE: $A'_e(t) = V'_e C_p(t)$ for $t > t^*$ doesn't mean $\int_0^t A'_e(\tau)\mathrm{d}\tau = V'_e\int_0^t C_p(\tau)\mathrm{d}\tau$ for $t > t^*$! Because the integral involves a time period before t^*.)

Next, replace $A'(t)$ by $-(K')^{-1}Q'C_p(t)$, and replace $A'_e(\tau)$ by $A'_m(t) - V'_p C_p(t)$, we have

$$-U_n^T(K')^{-2}Q'C_p(t) = \int_0^t A'_m(\tau)\,\mathrm{d}\tau - (V'_e + V_p)\int_0^t C_p(\tau)\,\mathrm{d}\tau\,.$$

Finally, replace $C_p(t)$ by $\frac{1}{V'_e+V'_p}A'_m(t)$ and define $D' = \frac{U_n^T(K')^{-2}Q'}{V'_e+V'_p}$, we get

$$\int_0^t A'_m(\tau)\,\mathrm{d}\tau = (V'_e + V'_p)\int_0^t C_p(\tau)\,\mathrm{d}\tau - D'A'_m(t)\,. \tag{23}$$

Eq. 21 allows us to write $C_p(t)$ in terms of $A'_m(t)$. Eq. 23 allows us to write $\int_)^t C_p(\tau)\mathrm{d}\tau$ in terms of $A'_m(t)$. Substituting all these into Eq. 20, we obtain the following relationship without involving C_p: for $t > t^*$,

$$\frac{A_m(t)}{A'_m(t)} = \frac{K_i}{V'_e + V'_p}\frac{\int_0^t A'_m(\tau)\,\mathrm{d}\tau}{A'_m(t)} + \frac{fV_e + V_p + KD'}{V'_e + V'_p}\,. \tag{24}$$

Recall that $K_i = \frac{K_1 k_3}{k_2+k_3}$, $V_e' = \frac{K_1'}{k_2'}$ is the distribution volume of the tissue compartment in the reference tissue. Suppose $\frac{K_1}{k_2} = \frac{K_1'}{k_2'}$. Ignore V_p'. Then the slope is

$$\frac{K_i}{V_e'} = \frac{\frac{K_1 k_3}{k_2+k_3}}{K_1/k_2} = \frac{k_2 k_3}{k_2+k_3}\,.$$

References

[1] Richard E Carson. Tracer kinetic modeling in pet. In *Positron emission tomography: basic sciences*, pages 127–159. Springer, 2005.

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[3] Clifford S Patlak, Ronald G Blasberg, and Joseph D Fenstermacher. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *Journal of Cerebral Blood Flow & Metabolism*, 3(1):1–7, 1983.