Logan Plot

Zeyu Zhou (zeyu.zhou@emory.edu)

November 16, 2023

Contents

1 Intro

The Logan plot [2] is a graphical tool for analyzing pharmacokinetics of tracers with reversible binding/uptake. The main result is the following equation:

$$\frac{\int_0^t ROI(\tau)\,\mathrm{d}\tau}{ROI(t)} = \left(-U_n^T K^{-1} Q + V_p\right) \frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{ROI(t)} + \frac{U_n^T K^{-1} \boldsymbol{A}(t)}{U_n^T \boldsymbol{A}(t) + V_p C_p(t)}\,. \tag{1}$$

The notation follow that in the setup of Patlak plot ([3], also see Zeyu's academic diary on 2023-10-13). For convenient, we re-iterate them here:

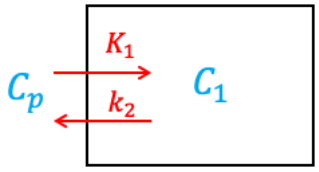
- K, a $n \times n$ matrix, the rate constant matrix for the reversible compartments in tissue/ROI. Note that by assumption, there is no irreversible compartment.
- Q is a $n \times 1$ vector of the rate constants from the plasma to the reversible compartments.
- $C_p(t)$ is the plasma concentration at time t.
- V_p is the plasma volume in the sampled tissue.
- $\boldsymbol{A}(t)$ is a $n \times 1$ vector of the tracer concentration in the n reversible compartments.
- $ROI(t) = U_n^T \boldsymbol{A}(t) + V_p C_p(t)$, is the total concentration measured in the ROI/tissue.

Patlak et al. [3] showed that for $t > t^*$, when the reversible compartments reach a steady-state with the blood plasma, $\boldsymbol{A}(t) = -K^{-1} Q C_p(t)$. With this, Eq. 1 can be written as (for $t > t^*$):

$$\frac{\int_0^t ROI(\tau)\,\mathrm{d}\tau}{ROI(t)} = \left(-U_n^T K^{-1} Q + V_p\right) \frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{ROI(t)} + \frac{-U_n^T K^{-2} Q}{-U_n^T K^{-1} Q + V_p}\,. \tag{2}$$

If we plot $\frac{\int_0^t ROI(\tau)\,\mathrm{d}\tau}{ROI(t)}$ vs. $\frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{ROI(t)}$, we can obtain the slope $-U_n^T K^{-1} Q$ and the intercept $\frac{-U_n^T K^{-2} Q}{-U_n^T K^{-1} Q + V_p}$.

1.1 Examples: 1TCM and 2TCM

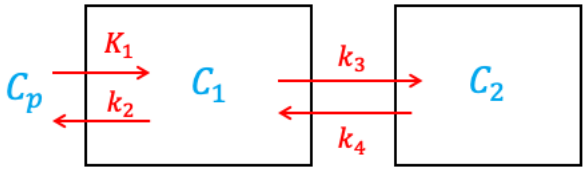


For 1-Tissue Compartment Model, $K = [-k_2]$, $Q = [K_1]$. So

$$\text{slope} = -U_n^T K^{-1} Q + V_p = \frac{K_1}{k_2} + V_p = V_D + V_p$$

$$\text{intercept} = \frac{-U_n^T K^{-2} Q}{-U_n^T K^{-1} Q + V_p} = \frac{-K_1/k_2^2}{K_1/k_2 + V_p} = -\frac{1}{k_2\left(1 + \frac{V_p}{V_D}\right)}$$

V_D is the distribution volume of the (only) tissue compartment and is equal to $\frac{C_1}{C_p}$ at equilibrium.



For 2-Tissue Compartment Model, $K = \begin{bmatrix} -(k_2+k_3) & k_4 \\ k_3 & -k_4 \end{bmatrix}$ and $K^{-1} = \frac{1}{k_2 k_4}\begin{bmatrix} -k_4 & -k_4 \\ -k_3 & -(k_2+k_3) \end{bmatrix}$, $Q = \begin{bmatrix} K_1 \\ 0 \end{bmatrix}$. So

$$\text{slope} = -U_n^T K^{-1} Q = \frac{K_1(k_3+k_4)}{k_2 k_4} = V_D\left(1 + \frac{k_3}{k_4}\right),$$

where V_D is the distribution volume of compartment C_1. $BP = \frac{k_3}{k_4}$. For the intercept in this case, let us consider the more general form in Eq. 1, but ignoring the $V_p C_p(t)$ term, i.e. $\frac{U_n^T K^{-1} \boldsymbol{A}(t)}{U_n^T \boldsymbol{A}(t)}$. First, $U_n^T \boldsymbol{A}(t) = C_1(t) + C_2(t)$. Second,

$$U_n^T K^{-1} \boldsymbol{A}(t) = \begin{bmatrix} 1 & 1 \end{bmatrix} \frac{1}{k_2 k_4}\begin{bmatrix} -k_4 & -k_4 \\ -k_3 & -(k_2+k_3) \end{bmatrix}\begin{bmatrix} C_1(t) \\ C_2(t) \end{bmatrix}.$$

We can work out the math and get

$$\text{intercept} = \frac{U_n^T K^{-1} \boldsymbol{A}(t)}{U_n^T \boldsymbol{A}(t)} = -\frac{k_3+k_4}{k_2 k_4} - \frac{1}{k_4}\frac{C_2(t)}{C_1(t)+C_2(t)}.$$

2 Derivation

We start with the DEs describing the rate of tracer transport among the reversible compartments and the blood plasma:

$$\frac{\mathrm{d}\boldsymbol{A}}{\mathrm{d}t} = K\boldsymbol{A} + QC_p(t).$$

Take integral on both sides:

$$\boldsymbol{A}(t) = \int_0^t K\boldsymbol{A}(\tau)\,\mathrm{d}\tau + Q\int_0^t C_p(\tau)\,\mathrm{d}\tau\,.$$

Multiplying both sides by $U_n^T K^{-1}$ and noting that $U_n^T\boldsymbol{A}(t) = A(t)$, we have

$$U_n^T K^{-1}\boldsymbol{A}(t) = \int_0^t A(\tau)\,\mathrm{d}\tau + U_n^T K^{-1} Q\int_0^t C_p(\tau)\,\mathrm{d}\tau\,.$$

Plug in $A(t) = ROI(t) - V_p C_p(t)$ and re-arrange, we have

$$\int_0^t ROI(\tau)\,\mathrm{d}\tau = \left(-U_n^T K^{-1} Q + V_p\right)\int_0^t C_p(\tau)\,\mathrm{d}\tau + U_n^T K^{-1}\boldsymbol{A}(t)\,.$$

Dividing both sides by $ROI(t) = U_n^T\boldsymbol{A}(t) + V_p C_p(t)$ gives Eq. 1.

2.1 Direct derivation for 1TC

Let us try to derive the operational Logan plot equation for 1TC directly from the fundamental differential equation. This is helpful for us in understanding the condition under which the Logan plot equation holds. That is, we want to derive from

$$\frac{\mathrm{d}C_1}{\mathrm{d}t} = K_1 C_p(t) - k_2 C_1(t)$$

and

$$ROI(t) = C_1(t) + V_p C_p(t)$$

to

$$\frac{\int_0^t ROI(\tau)\,\mathrm{d}\tau}{ROI(t)} = \left(\frac{K_1}{k_2} + V_p\right)\frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{ROI(t)} - \frac{1}{k_2\left(1 + \frac{V_p}{K_1/k_2}\right)}\,.$$

Starting from the DE, we take integration on both sides:

$$C_1(t) = K_1\int_0^t C_p(\tau)\,\mathrm{d}\tau - k_2\int_0^t C_1(\tau)\,\mathrm{d}\tau\,.$$

Replacing the $C_1(t)$ on the RHS in the integral with $ROI(t) - V_p C_p(t)$, and re-arranging, we have

$$C_1(t) = (K_1 + k_2 V_p)\int_0^t C_p(\tau)\,\mathrm{d}\tau - k_2\int_0^t ROI(\tau)\,\mathrm{d}\tau\,.$$

Moving the $ROI(t)$ term to the LFS and the $C_1(t)$ term to the RHS, and dividing both sides by $k_2 ROI(t)$, we get

$$\frac{\int_0^t ROI(\tau)\,\mathrm{d}\tau}{ROI(t)} = \left(\frac{K_1}{k_2} + V_p\right)\frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{ROI(t)} - \frac{C_1(t)}{k_2 ROI(t)}\,.$$

Everything matches our target, except the intercept. But since $ROI(t) = C_1(t) + V_p C_p(t)$, we have

$$\text{intercept} = -\frac{C_1(t)}{k_2(C_1(t) + V_p C_p(t))}\,.$$

The intercept reaches a constant when $\frac{C_1}{C_p} \to$ constant. That is also the condition under which the operational equation becomes linear. If we solve the DE directly, we obtain

$$C_1(t) = K_1 e^{-k_2(t)} \otimes C_p(t)\,.$$

When $C_p(t)$ satisfies the slow-decaying tail condition and then t is large enough, i.e. $t > t^*$, we have

$$C_1(t) \approx K_1 C_p e^{-k_2(t)} \otimes u(t) \to \frac{K_1}{k_2} C_p\,.$$

Thus, the intercept becomes

$$\text{intercept} = -\frac{C_1/C_p}{k_2(C_1/C_p + V_p)} = -\frac{K_1/k_2}{k_2(K_1/k_2 + V_p)} = -\frac{1}{k_2}\frac{1}{1+\frac{V_p}{K_1/k_2}}\,.$$

2.2 Direct derivation for 2TC

Fundamental DEs:

$$\begin{aligned}\frac{\mathrm{d}C_1}{\mathrm{d}t} &= K_1 C_p(t) - (k_2+k_3)C_1(t) + k_4 C_2(t)\\ \frac{\mathrm{d}C_2}{\mathrm{d}t} &= k_3 C_1(t) - k_4 C_2(t)\,.\end{aligned}$$

Taking integration on both sides of both DEs, we get

$$\begin{aligned}C_1(t) &= K_1 \int_0^t C_p(\tau)\,\mathrm{d}\tau - (k_2+k_3)\int_0^t C_1(\tau)\,\mathrm{d}\tau + k_4 \int_0^t C_2(\tau)\,\mathrm{d}\tau\\ C_2(t) &= k_3 \int_0^t C_1(\tau)\,\mathrm{d}\tau - k_4 \int_0^t C_2(\tau)\,\mathrm{d}\tau\end{aligned}$$

Writing these two equations in matrix form, we have

$$\begin{bmatrix}C_1(t)\\ C_2(t)\end{bmatrix} = K \begin{bmatrix}\int_0^t C_1(\tau)\,\mathrm{d}\tau\\ \int_0^t C_2(\tau)\,\mathrm{d}\tau\end{bmatrix} + \begin{bmatrix}K_1\\ 0\end{bmatrix}\int_0^t C_p(\tau)\,\mathrm{d}\tau\,,$$

where

$$K = \begin{bmatrix}-(k_2+k_3) & k_4\\ k_3 & -k_4\end{bmatrix}\,.$$

Let us denote

$$\boldsymbol{A}(t) = \begin{bmatrix}C_1(t)\\ C_2(t)\end{bmatrix} \quad \text{and} \quad Q = \begin{bmatrix}K_1\\ 0\end{bmatrix}\,.$$

Multiplying both sides by $U_n^T K^{-1}$, we get

$$U_n^T K^{-1}\boldsymbol{A}(t) = \int_0^t (C_1(\tau) + C_2(\tau))\,\mathrm{d}\tau + U_n^T K^{-1} Q \int_0^t C_p(\tau)\,\mathrm{d}\tau\,.$$

Writing $C_1(\tau) + C_2(\tau)$ as $ROI(\tau) - V_p C_p(\tau)$, we have

$$U_n^T K^{-1}\boldsymbol{A}(t) = \int_0^t ROI(\tau)\,\mathrm{d}\tau + \left(U_n^T K^{-1} Q - V_p\right)\int_0^t C_p(\tau)\,\mathrm{d}\tau\,.$$

Re-arranging and dividing both sides by $ROI(t)$, we obtain

$$\frac{\int_0^t ROI(\tau)\,\mathrm{d}\tau}{ROI(t)} = \left(-U_n^T K^{-1} Q + V_p\right) \frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{ROI(t)} + \frac{U_n^T K^{-1} \boldsymbol{A}(t)}{ROI(t)}$$

We can work out that,

$$-U_n^T K^{-1} Q = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right),$$

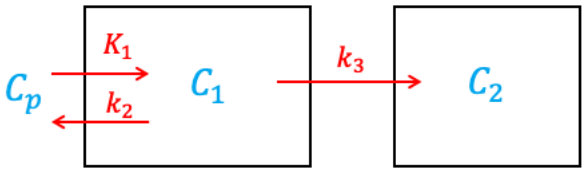
and for the intercept, if we ignore the blood fraction, i.e. $ROI(t) = C_1(t) + C_2(t)$, we find that

$$\text{intercept} = \frac{U_n^T K^{-1} \boldsymbol{A}(t)}{U_n^T \boldsymbol{A}(t)} = -\frac{k_3 + k_4}{k_2 k_4} - \frac{1}{k_4}\frac{C_2(t)}{C_1(t) + C_2(t)}.$$

For some time $t > t'$ when $(C_1 + C_2) \propto C_p$ and $C_2 \propto C_p$, the intercept becomes a constant. In many cases the intercept becomes constant even before t'. See [1] for discussion and examples.

3 Comparison to Patlak plot

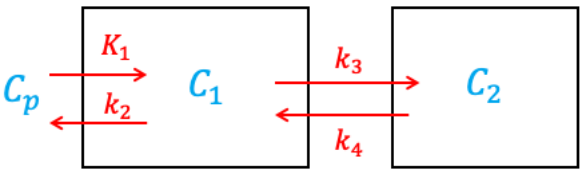
Patlak plot:



$$\frac{ROI(t)}{C_p(t)} = K\frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{C_p(t)} + V,$$

where K is the overall uptake rate from plasma to the irreversible compartment C_2 and $V = V_0 + V_p$, where V_p is the fraction of blood plasma in the sampled tissue and V_0 is a fraction of the distribution volume of the reversible compartment (ZEYU: the interpretation of V_0 needs care. See discussion in Zeyu's Patlak plot diary.)

Logan plot:



$$\frac{\int_0^t ROI(\tau)\,\mathrm{d}\tau}{ROI(t)} = a\frac{\int_0^t C_p(\tau)\,\mathrm{d}\tau}{ROI(t)} + b,$$

For 1TCM, $a = \frac{K_1}{k_2} + V_p = V_D + V_p$, $b = -\frac{1}{k_2(1+V_p/V_D)}$. For 2TCM, $a = \frac{K_1(k_3+k_4)}{k_2 k_4} = V_D(1 + BP)$.

Note what are plotted in the two plots.

4 Appendix B

Derivation of Eq. B3. To make it clearer to see, let $\alpha_1 = \alpha_+$, $\alpha_2 = \alpha_-$, and $\rho = \rho_+$.

$$\begin{aligned}
C_1 + C_2 &= K_1 \left(\gamma_1 e^{\alpha_1 t} + \gamma_2 e^{\alpha_2 t}\right) \otimes C_p(t) \\
&= K_1 \left(\frac{k_3 + k_4 + \alpha_1}{\alpha_1 - \alpha_2} e^{\alpha_1 t} \otimes C_p(t) - \frac{k_3 + k_4 + \alpha_2}{\alpha_1 - \alpha 2} e^{\alpha_2 t} \otimes C_p(t) \right) \\
&= \frac{K_1}{\alpha_1 - \alpha_2} \left((k_3 + k_4 + \alpha_1) \left(e^{\alpha_1 t} \rho - \frac{C_p}{\alpha_1 + \beta_q} \right) - (k_3 + k_4 + \alpha_2) \cdot (-1) \cdot \frac{C_p}{\alpha_2 + \beta_q} \right) \\
&= \frac{K_1}{\alpha_1 - \alpha_2} (k_3 + k_4 + \alpha_1) e^{\alpha_1 t} \rho + \frac{K_1 C_p}{\alpha_1 - \alpha_2} \left(\frac{k_3 + k_4 + \alpha_2}{\alpha_2 + \beta_q} - \frac{k_3 + k_4 + \alpha_1}{\alpha_1 + \beta_q} \right) \\
&= \underbrace{\frac{K_1}{\alpha_1 - \alpha_2} (k_3 + k_4 + \alpha_1) e^{\alpha_1 t} \rho}_{A} + \underbrace{K_1 C_p \frac{(k_3 + k_4 - \beta_q)}{(\alpha_1 + \beta_q)(\alpha_2 + \beta_q)}}_{B}
\end{aligned} \tag{3}$$

Now, consider the RHS of Eq. B3.

$$\frac{k_1 k_4 (1 + B_{\max}/K_d)}{(\alpha_1 + \beta_q)(\alpha_2 + \beta_q)} = \frac{K_1 (k_3 + k_4)}{(\alpha_1 + \beta_q)(\alpha_2 + \beta_q)} \,. \tag{4}$$

$$\omega \left(\frac{\alpha_1}{k_3 + k_4} + 1 \right) = \frac{e^{\alpha_1 t} \rho}{C_p} \frac{(\alpha_1 + \beta_q)(\alpha_2 + \beta_q)}{\alpha_1 - \alpha_2} \frac{k_3 + k_4 + \alpha_1}{k_3 + k_4} \,. \tag{5}$$

Therefore

$$\frac{k_1 k_4 (1 + B_{\max}/K_d)}{(\alpha_1 + \beta_q)(\alpha_2 + \beta_q)} \cdot \omega \left(\frac{\alpha_1}{k_3 + k_4} + 1 \right) = \frac{K_1}{\alpha_1 - \alpha_2} (k_3 + k_4 + \alpha_1) e^{\alpha_1 t} \rho \frac{1}{C_p} = \frac{A}{C_p} \,, \tag{6}$$

and

$$\frac{k_1 k_4 (1 + B_{\max}/K_d)}{(\alpha_1 + \beta_q)(\alpha_2 + \beta_q)} \cdot \left(1 - \frac{\beta_q}{k_3 + k_4} \right) = \frac{K_1 (k_3 + k_4 - \beta_q)}{(\alpha_1 + \beta_q)(\alpha_2 + \beta_q)} = \frac{B}{C_p} \,. \tag{7}$$

Thus Eq. B3 is validated.

The validation of Eq. B4 is similar. It requires finding the coefficients θ_1 and θ_2 such that $C_2 = k_1(\theta_1 e^{\alpha_1 t} + \theta_2 e^{\alpha_2 t}) \otimes C_p(t)$. The process is a little tedious. We skip it.

More comments. In Eq. B5, C_p is dominated by $e^{-\beta_q t}$, which decays much slower than $e^{\alpha_1 t}$. So $\omega \to 0$.

In Eq. B3, β_q is typically much smaller than $k_3 + k_4$. So

$$\frac{C_1 + C_2}{C_p} \to \frac{k_1 (k_3 + k_4)}{(\alpha_1 + \beta_q)(\alpha_2 + \beta_q)} \approx \frac{k_1 (k_3 + k_4)}{\alpha_1 \alpha_2} \,. \tag{8}$$

But because α_1 and α_2 are the solutions of $x^2 + (k_2 + k_3 + k_4)\lambda + k_2 k_4 = 0$, $\alpha_1 \alpha_2 = k_2 k_4$. Therefore

$$\frac{C_1 + C_2}{C_p} \to \frac{k_1 (k_3 + k_4)}{k_2 k_4} = \lambda \left(1 + \frac{k_3}{k_4} \right) \,. \tag{9}$$

Similarly,

$$\frac{C_2}{C_p} \to \frac{k_1 k_3}{k_2 k_4} \,. \tag{10}$$

References

[1] Jean Logan. Graphical analysis of pet data applied to reversible and irreversible tracers. *Nuclear medicine and biology*, 27(7):661–670, 2000.

[2] Jean Logan, Joanna S Fowler, Nora D Volkow, Alfred P Wolf, Stephen L Dewey, David J Schlyer, Robert R MacGregor, Robert Hitzemann, Bernard Bendriem, S John Gatley, et al. Graphical analysis of reversible radioligand binding from time—activity measurements applied to [n-11c-methyl]-(-)-cocaine pet studies in human subjects. *Journal of Cerebral Blood Flow & Metabolism*, 10(5):740–747, 1990.

[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.