Simplified Reference Tissue Model for Radioligand Kinetics

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1 Model setup

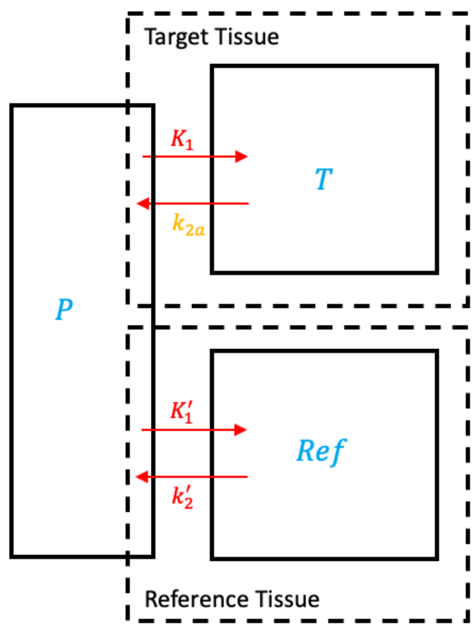

Figure 1: Simplified reference tissue model. P: plasma (including free plus protein bound). T: total concentration in target tissue. Ref: total concentration in the reference tissue.

This document is based on [1].

For simplicity, we use the following symbols: $C_P \to P$, $C_T \to T$, $C_{\text{Ref}} \to F$.

Differential equations are:

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} = K_1 P(t) - k_{2a} T(t)\,, \tag{1}$$

$$\frac{\mathrm{d}F(t)}{\mathrm{d}t} = K_1' P(t) - k_2' F(t)\,. \tag{2}$$

where

- P: metabolite-corrected plasma concentration (kBq/ml).
- F: concentration in reference tissue (kBq/ml).
- T: total concentration in target tissue (kBq/ml).
- K_1: rate constant for transfer from arterial plasma to tissue ($\mathrm{ml} \cdot \mathrm{ml}^{-1} \cdot \mathrm{min}^{-1}$).
- k_{2a}: apparent rate constant for transfer from ND compartment to plasma compartment (min^{-1}).
- K_1':
- k_2':

2 Relationship between k_2 and k_{2a}

For the two-tissue compartment model for the target tissue,

$$\begin{aligned} \frac{\mathrm{d}N(t)}{\mathrm{d}t} &= K_1 P(t) - k_2 N(t) - k_3 N(t) + k_4 S(t) \\ \frac{\mathrm{d}S(t)}{\mathrm{d}t} &= k_3 N(t) - k_4 S(t)\,. \end{aligned}$$

At equilibrium,

$$\begin{aligned} (k_2 + k_3)N - k_4 S &= K_1 P \\ k_3 N &= k_4 S\,. \end{aligned}$$

This leads to $\frac{N}{P} = \frac{K_1}{k_2}$ and $\frac{S}{P} = \frac{K_1}{k_2}\frac{k_3}{k_4}$. So the total volume of distribution

$$V_T = \frac{T}{P} = \frac{N+S}{P} = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right)\,.$$

For the simplified reference tissue model, if we assume that the total volume of distribution is the same, then

$$\frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right) = \frac{K_1}{k_{2a}}\,.$$

Thus

$$k_{2a} = \frac{k_2}{1 + k_3/k_4} = \frac{k_2}{1 + BP}\,.$$

3 Assumptions

- Same plasma input to target and reference tissues.
- None or little specific receptors in the reference tissue.
- $\frac{K_1'}{k_2'} = \frac{K_1}{k_2}$. The distribution of volume of the non-specifically bound tracer in both tissues is the same. (ZEYU: why this, but not $\frac{K_1'}{k_2'} = \frac{K_1}{k_{2a}}$?)

4 Solution

The reference tissue equation can be re-arranged to get

$$K_1 P(t) = \frac{K_1}{K_1'} \frac{\mathrm{d}F(t)}{\mathrm{d}t} + \frac{k_2' K_1}{K_1'} F(t)\,. \tag{3}$$

Denote $R_1 \triangleq \frac{K_1}{K_1'}$. By assumption, $\frac{k_2' K_1}{K_1'} = k_2$. Thus the above equation can be re-written as

$$K_1 P(t) = R_1 \frac{\mathrm{d}F(t)}{\mathrm{d}t} + k_2 F(t)\,. \tag{4}$$

Substitute the expression of $K_1 P(t)$ in (4) to Eq. (1), we obtain

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} = R_1 \frac{\mathrm{d}F(t)}{\mathrm{d}t} + k_2 F(t) - k_{2a} T(t)\,. \tag{5}$$

Now we can combine (5) and (2) to derive a solution without the blood input. Taking the Laplace Transform of these two equations, we obtain

$$s\bar{T} = sR_1 \bar{F} + k_2 \bar{F} - k_{2a} \bar{T}\,. \tag{6}$$

where $\bar{T}$ and $\bar{F}$ are the Laplace transforms of $T(t)$, and $F(t)$. Solving them, we obtain

$$\bar{T} = \frac{sR_1 + k_2}{s + k_{2a}} \bar{F} = \left(R_1 + \frac{k_2 - k_{2a} R_1}{s + k_{2a}} \right) \bar{F}\,.$$

In time domain,

$$\begin{aligned} T(t) &= R_1 F(t) + (k_2 - k_{2a} R_1) F(t) \otimes e^{-k_{2a} t} \\ &= R_1 F(t) + \left(k_2 - \frac{k_2 R_1}{1 + BP} \right) F(t) \otimes e^{-\frac{k_2}{1+BP} t}\,. \end{aligned} \tag{7}$$

The fitting parameters are (R_1, k_2, BP).

5 Alternative solution

Alternatively, Eq. (3) can be written as

$$K_1 P(t) = R_1 \frac{\mathrm{d}F(t)}{\mathrm{d}t} + k_2' R_1 F(t)\,. \tag{8}$$

Plugging this $K_1 P(t)$ to Eq. (1), we obtain

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} = R_1 \frac{\mathrm{d}F(t)}{\mathrm{d}t} + k_2' T_1 F(t) - k_{2a} T(t)\,. \tag{9}$$

We skip the derivation process. The solution is

$$\bar{T} = R_1 \left(1 + \frac{k_2' - k_{2a}}{s + k_{2a}}\right) \bar{F}\,. \tag{10}$$

In time domain, that is

$$T(t) = R_1 \left(F(t) + (k_2' - k_{2a})F(t) \otimes e^{-k_{2a}t}\right)\,. \tag{11}$$

The fitting parameters are (R_1, k_2', k_{2a}).

In order to obtain BP, recall that

$$\frac{K_1}{k_2}(1 + BP) = \frac{K_1}{k_{2a}} \quad \text{and} \quad \frac{K_1}{k_2} = \frac{K_1'}{k_2'}\,. \tag{12}$$

So

$$BP = \frac{K_1/k_{2a}}{K_1/k_2} - 1 = \frac{K_1/k_{2a}}{K_1'/k_2'} - 1 = R_1 \frac{k_2'}{k_{2a}} - 1\,. \tag{13}$$

In some papers (such as [2]), the symbol k_{2a} is replaced with k_2, but it actually means k_{2a}.

References

[1] Adriaan A Lammertsma and Susan P Hume. Simplified reference tissue model for pet receptor studies. *Neuroimage*, 4(3):153–158, 1996.

[2] Yanjun Wu and Richard E Carson. Noise reduction in the simplified reference tissue model for neuroreceptor functional imaging. *Journal of Cerebral Blood Flow & Metabolism*, 22(12):1440–1452, 2002.