Two Tissue Compartment Model for Radioligand Kinetics

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1 Model setup

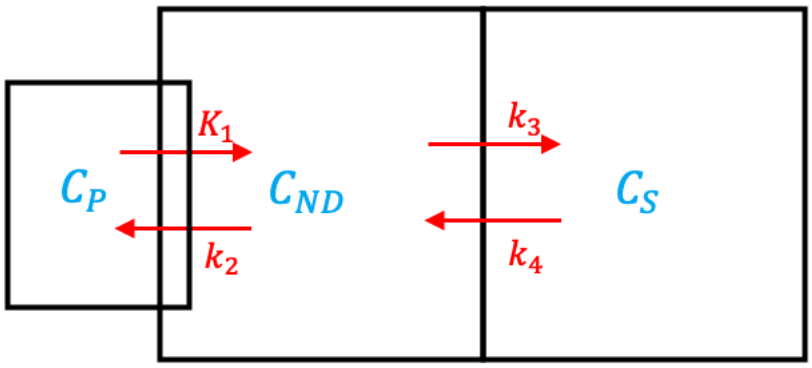

Figure 1: Two-tissue compartment model. P: plasma (including free plus protein bound). ND: nondisplaceable tissue update (including free and non-specifically bound radioligands in tissue). S: specific bound radioligand.

This document is based on [2] Appendix A and the nomenclature in [1].

The diagram above illustrates the two-tissue compartment model for radioligand kinetics. The relating differential equations are:

$$\frac{\mathrm{d}C_{\mathrm{ND}}(t)}{\mathrm{d}t} = K_1 C_P(t) - k_2 C_{\mathrm{ND}}(t) - k_3 C_{\mathrm{ND}}(t) + k_4 C_S(t)\,, \tag{1}$$

$$\frac{\mathrm{d}C_S(t)}{\mathrm{d}t} = k_3 C_{\mathrm{ND}}(t) - k_4 C_S(t)\,, \tag{2}$$

where

- C_P: metabolite-corrected plasma concentration (kBq/ml).

- C_{ND}: concentration of radioligand in the nondisplaceable compartment (i.e. free plus non-specifically bound) (kBq/ml).
- C_S: concentration of specifically bound radioligand (kBq/ml).
- K_1: rate constant for transfer from arterial plasma to tissue ($\mathrm{ml} \cdot \mathrm{ml}^{-1} \cdot \mathrm{min}^{-1}$).
- k_2: rate constant for transfer from ND compartment to plasma compartment (min^{-1}).
- k_3: rate constant for transfer from ND compartment to specifically bound compartment (min^{-1}).
- k_4: rate constant for transfer from specifically bound to ND compartment (min^{-1}).

In practice, only C_T, the total concentration in the tissue, can be measured by PET. That is,

$$C_T(t) = C_{\mathrm{ND}}(t) + C_S(t)\,. \tag{3}$$

2 Solution

The goal is to express the output signal $C_T(t)$ as a function of the input signal $C_P(t)$. To do that, we re-write Equations (1-3), with the following symbol replacement for better exposition: $C_P \to P$, $C_{ND} \to F$, $C_S \to S$, $C_T \to T$, and we have

$$\frac{\mathrm{d}F(t)}{\mathrm{d}t} = K_1 P(t) - (k_2 + k_3)F(t) + k_4 S(t)\,, \tag{4}$$

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = k_3 F(t) - k_4 S(t)\,, \tag{5}$$

$$T(t) = F(t) + S(t)\,. \tag{6}$$

The the Laplace transform of Equations (4) and (5), along with initial conditions $F(0) = 0$ and $S(0) = 0$, we have

$$s\bar{F}(s) = K_1 \bar{P}(s) - (k_2 + k_3)\bar{F}(s) + k_4 \bar{S}(s)\,, \tag{7}$$

$$s\bar{S}(s) = k_3 \bar{F}(s) - k_4 \bar{S}(s)\,, \tag{8}$$

$$\bar{T}(s) = \bar{F}(s) + \bar{S}(s)\,, \tag{9}$$

where $\bar{F}(s)$, $\bar{S}(s)$ and $\bar{T}(s)$ are the Laplace transforms of $F(t), S(t)$ and $T(s)$ respectively. Solving (7) and (8) as two linear equations with two unknowns $\bar{F}(s)$ and $\bar{S}(s)$, we obtain

$$\bar{F}(s) = \frac{K_1(s + k_4)}{s^2 + (k_2 + k_3 + k_4)s + k_2 k_4}\bar{P}(s)\,, \tag{10}$$

and

$$\bar{S}(s) = \frac{K_1 k_3}{s^2 + (k_2 + k_3 + k_4)s + k_2 k_4}\bar{P}(s)\,. \tag{11}$$

So

$$\bar{T}(s) = \frac{K_1 s + K_1(k_3 + k_4)}{s^2 + (k_2 + k_3 + k_4)s + k_2 k_4}\bar{P}(s)\,. \tag{12}$$

The goal next is to do algebraic manipulation to obtain

$$\frac{K_1 s + K_1(k_3 + k_4)}{s^2 + (k_2 + k_3 + k_4)s + k_2 k_4} = \frac{a}{s + c} + \frac{b}{s + d} \tag{13}$$

for some a, b, c, d. Denote $g \triangleq k_2 + k_3 + k_4$ ([2] uses s instead of g) and $q \triangleq 4k_2k_4$. The quadratic equation $s^2 + (k_2 + k_3 + k_4)s + k_2k_4 = s^2 + gs + q = 0$ has two roots

$$s_1 = \frac{-g + \sqrt{g^2 - q}}{2} \quad \text{and} \quad s_2 = \frac{-g - \sqrt{g^2 - q}}{2}\,.$$

Denote $p \triangleq \sqrt{g^2 - q}$. c and d are the negative of the two roots, i.e.

$$c = -s_1 = \frac{g - p}{2} \quad \text{and} \quad d = -s_2 = \frac{g + p}{2}\,.$$

Thus (13) becomes

$$\frac{K_1 s + K_1(k_3 + k_4)}{(s + c)(s + d)} = \frac{a}{s + c} + \frac{b}{s + d} = \frac{(a + b)s + (ad + bc)}{(s + c)(s + d)}\,.$$

Thus we have

$$\begin{cases} K_1 & = a + b \\ K_1(k_3 + k_4) & = ad + bc \end{cases}$$

Let c and d be given, then solve for a and b, we get

$$a = \frac{K_1}{p}(k_3 + k_4 - c) \quad \text{and} \quad b = \frac{K_1}{p}(d - k_3 - k_4)\,,$$

or

$$a = r(k_3 + k_4 - c) \quad \text{and} \quad b = r(d - k_3 - k_4)\,,$$

where $r = \frac{K_1}{p}$. It follows that

$$\bar{T}(s) = \left(\frac{a}{s + c} + \frac{b}{s + d}\right)\bar{P}(s)\,. \tag{14}$$

Inverse Laplace transform takes us back to the time domain:

$$T(t) = aP(t) \otimes e^{-ct} + bP(t) \otimes e^{-dt}\,. \tag{15}$$

Using the original symbols, this can be written as

$$C_T(t) = aC_P(t) \otimes e^{-ct} + bC_P(t) \otimes e^{-dt}\,. \tag{16}$$

To summarize the notations:

$$\begin{aligned} a &= r(k_3 + k_4 - c) \\ b &= r(d - k_3 - k_4) \\ c &= \frac{g - p}{2} \\ d &= \frac{g + p}{2} \\ p &= \sqrt{g^2 - q} \\ q &= 4k_2k_4 \\ r &= \frac{K_1}{p} \\ g &= k_2 + k_3 + k_4\,. \end{aligned}$$

3 Curve-fitting

(In practice, the PET measurements also contain a non-negligible contribution from intravascular activity. Therefore an additional parameter V_b, the blood volume fraction, is usually taken into account. But for now, let us ignore it.)

For given $C_P(t)$ and specific values of (a, b, c, d), one can obtain an estimated total concentration in tissue $\widehat{C}_T(t)$. Curve fitting steps:

- Choose (a, b, c, d) so that the estimated $\widehat{C}_T(t)$ is close to measured $C_T(t)$ according to some criteria/principle (e.g. least square estimation). Next, we solve for (K_1, k_2, k_3, k_4) from (a, b, c, d).
- Given c and d, solve for g and p: $g = d + c$, $p = d - c$.
- Solving $a = r(k_3 + k_4 - c)$ and $b = r(d - k_3 - k_4)$ and treating r and $k_3 + k_4$ as unknowns. Obtain r and $k_3 + k_4$.
- Since $r = K_1/p$ and we have obtained r and p. We get K_1.
- Since $g = k_2 + k_3 + k_4$ and we have obtained g and $k_3 + k_4$, we get k_2.
- Since $p = \sqrt{g^2 - q}$ and we have obtained g and p, we get q.
- Since $q = 4k_2k_4$ and we have obtained k_2 and q, we get k_4.
- Finally, since we know $k_3 + k_4$ and k_4, we get k_3.

References

[1] Robert B Innis, Vincent J Cunningham, Jacques Delforge, Masahiro Fujita, Albert Gjedde, Roger N Gunn, James Holden, Sylvain Houle, Sung-Cheng Huang, Masanori Ichise, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *Journal of Cerebral Blood Flow & Metabolism*, 27(9):1533–1539, 2007.

[2] AA Lammertsma, CJ Bench, SP Hume, S Osman, K Gunn, DJ Brooks, and RSJ Frackowiak. Comparison of methods for analysis of clinical [11c] raclopride studies. *Journal of Cerebral Blood Flow & Metabolism*, 16(1):42–52, 1996.