Full Reference Tissue Model for Radioligand Kinetics

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1 Model setup

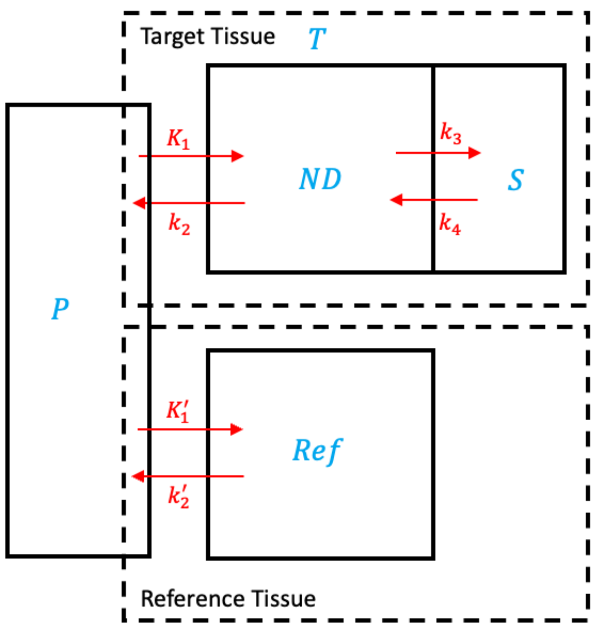

Figure 1: Reference tissue model. P: plasma (including free plus protein bound). ND: nondisplaceable tissue uptake in target tissue. S: specific bound radioligand in target tissue. Ref: total concentration in the reference tissue.

This document is based on [3] Appendix C and the nomenclature in [2]. Also see [1] for the first time the reference tissue model is proposed (in rat for diprenorphine).

For simplicity, we use the following symbols: $C_P \to P$, $C_{\mathrm{ND}} \to N$, $C_S \to S$, $C_T \to T$, $C_{\mathrm{Ref}} \to F$.

Differential equations are:

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = K_1 P(t) - k_2 N(t) - k_3 N(t) + k_4 S(t)\,, \tag{1}$$

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = k_3 N(t) - k_4 S(t)\,, \tag{2}$$

$$T(t) = N(t) + S(t)\,, \tag{3}$$

$$\frac{\mathrm{d}F(t)}{\mathrm{d}t} = K_1' P(t) - k_2' F(t)\,. \tag{4}$$

where

- P: metabolite-corrected plasma concentration (kBq/ml).
- N: concentration of radioligand in the nondisplaceable compartment in the target tissue (kBq/ml).
- S: concentration of specifically bound radioligand in target tissue(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_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}).
- K_1':
- k_2':

2 Assumptions

- Same plasma input to target and reference tissues.
- None or little specific receptors in the reference tissue.
- $\frac{K_1'}{k_2'} = \frac{K_1}{k_2}$.

3 Solution

The reference tissue equation can be re-arranged to get

$$K_1 P(t) = \frac{K_1}{K_1'} \frac{\mathrm{d}F(t)}{\mathrm{d}t} + \frac{k_2' K_1}{K_1'} F(t)\,. \tag{5}$$

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

$$K_1 P(t) = R_1 \frac{\mathrm{d}F(t)}{\mathrm{d}t} + k_2 F(t)\,. \tag{6}$$

Substitute the expression of $K_1 P(t)$ in (6) to Eq. (1), we obtain

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = R_1 \frac{\mathrm{d}F(t)}{\mathrm{d}t} + k_2 F(t) - k_2 N(t) - k_3 N(t) + k_4 S(t)\,. \tag{7}$$

Now we can combine (7) and (2) to derive a solution without the blood input. Taking the Laplace Transform of these two equations, we obtain

$$\begin{cases} s\bar{N} = sR_1\bar{F} + k_2\bar{F} - (k_2 + k_3)\bar{N} + k_4\bar{S} \\ s\bar{S} = k_3\bar{N} - k_4\bar{S}\,, \end{cases} \tag{8}$$

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

$$\bar{N} = \frac{(sR_1 + k_2)(s + k_4)}{s^2 + (k_2 + k_3 + k_4)s + k_2 k_4}\bar{F} \quad \text{and} \quad \bar{S} = \frac{(sR_1 + k_2)k_3}{s^2 + (k_2 + k_3 + k_4)s + k_2 k_4}\bar{F}\,.$$

Therefore

$$\begin{aligned} \bar{T} = \bar{N} + \bar{S} &= \frac{(sR_1 + k_2)(s + k_3 + k_4)}{s^2 + (k_2 + k_3 + k_4)s + k_2 k_4}\bar{F} \\ &= R_1 \frac{(s + r)(s + k_3 + k_4)}{s^2 + (k_2 + k_3 + k_4)s + k_2 k_4}\bar{F} \\ &= R_1 \left[1 + \frac{(-k_2 + r)s - k_2 k_4 + r(k_3 + k_4)}{s^2 + (k_2 + k_3 + k_4)s + k_2 k_4}\right]\bar{F}\,, \end{aligned}$$

where $r \triangleq \frac{k_2}{R_1}$. Solving the quadratic equation in the denominator, we can obtain

$$s^2 + (k_2 + k_3 + k_4)s + k_2 k_4 = (s + c)(s + d)\,,$$

where $c \triangleq \frac{g+p}{s}$, $d \triangleq \frac{g-p}{2}$, $p \triangleq \sqrt{(g^2 - q)}$, $q \triangleq 4k_2 k_4$, and $g \triangleq k_2 + k_3 + k_4$. Next, we try to find $a.b$ such that

$$\frac{(-k_2 + r)s - k_2 k_4 + r(k_3 + k_4)}{s^2 + (k_2 + k_3 + k_4)s + k_2 k_4} = \frac{a}{s + c} + \frac{b}{s + d} = \frac{(a + b)s + (ad + bc)}{(s + c)(s + d)}\,.$$

This leads to the following system of two linear equations

$$\begin{cases} a + b = r - k_2 \\ ad + bc = -k_2 k_4 + r(k_3 + k_4)\,. \end{cases} \tag{9}$$

Solving the equations involves a little trick. We can easily obtain that $pb = k_2 d - k_2 k_4 - r(d - k_3 - k_4)$. Recall that $-d$ is the root of $s^2 + (k_2 + k_3 + k_4)s + k_2 k_4 = 0$. Therefore $d^2 - (k_2 + k_3 + k_4)d + k_2 k_4 = 0$. Thus, $k_2 d - k_2 k_4 = d^2 - (k_3 + k_4)d = d(d - k_3 - k_4)$. Thus, $pb = (d - k_3 - k_4)(d - r)$, hence

$$b = \frac{(d - k_3 - k_4)(d - r)}{p},$$

which matches the result in [3] Appendix C. Similarly, we can obtain that

$$a = \frac{(k_3 + k_3 - c)(c - r)}{p}.$$

To summarize,

$$\bar{T} = R_1 \left[1 + \frac{a}{s + c} + \frac{b}{s + d} \right] \bar{F}, \tag{10}$$

where a, b, c, d are defined above. Take the inverse Laplace transform to the time domain, we get

$$T(t) = R_1 \left(F(t) + aF(t) \otimes e^{-ct} + bF(t) \otimes e^{-dt} \right). \tag{11}$$

4 Additional

$$C_T(t) = R_1 \left(C_{\mathrm{Ref}}(t) + aC_{\mathrm{Ref}}(t) \otimes e^{-ct} + bC_{\mathrm{Ref}}(t) \otimes e^{-dt} \right). \tag{12}$$

where

$$
\begin{aligned}
a &= \frac{(k_3 + k_3 - c)(c - r)}{p} \\
b &= \frac{(d - k_3 - k_4)(d - r)}{p} \\
c &= \frac{g + p}{2} \\
d &= \frac{g - p}{2} \\
p &= \sqrt{(g^2 - p)} \\
q &= 4k_2 k_4 \\
g &= k_2 + k_3 + k_4 \\
r &= \frac{k_2}{R_1} \\
R_1 &= \frac{K_1}{K_1'}
\end{aligned}
$$

References

[1] Vincent J Cunningham, Susan P Hume, Gary R Price, Randall G Ahier, Jill E Cremer, and Anthony KP Jones. Compartmental analysis of diprenorphine binding to opiate receptors in the rat in vivo and its comparison with equilibrium data in vitro. *Journal of Cerebral Blood Flow & Metabolism*, 11(1):1–9, 1991.

[2] 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.

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