MRTM0, MRTM, MRTM2

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1 Review on Logan plot [3]

Logan plot can be used to analyze tracers with reversible binding/update. The operational equation for Logan plot is, for $t > t^*$,

$$\frac{\int_0^t T(\tau)\,\mathrm{d}\tau}{T(t)} = V\frac{\int_0^t P(\tau)\,\mathrm{d}\tau}{T(t)} + b\,, \tag{1}$$

where

- $T(t)$ is the total concentration measured by PET in the target tissue,
- $P(t)$ is the plasma concentration,
- V is the macro-parameter of the model and is the total distribution volume of the tissue.
- b is the intercept on the vertical axis.

Logan plot does not assume any particular compartment model. But for a specific model, the parameters have specific forms.

- For 1TCM, $V = \frac{K_1}{k_2} + v_B = V_D + v_B$, and $b = -\frac{1}{k_2(1+v_B/V_D)}$ where v_B is the blood volume fraction in the tissue. In this document, for simplicity, we ignore v_B as it is usually small. Then we have $V = \frac{K_1}{k_2}$ and $b = -\frac{1}{k_2}$.
- For 2TCM, $V = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right) = \frac{K_1}{k_2}(1+BP)$. b is a function of micro-parameters K_1, k_2, k_3, k_4 can be complicated.

2 MRTM0 [1]

MRTM0 assumes the existence a reference tissue devoid of the specific biding receptors. Because of the assumption, the reference tissue can be modeled by 1TCM along with the following equation:

$$\frac{\int_0^t T'(\tau)\,\mathrm{d}\tau}{T'(t)} = V'\frac{\int_0^t P(\tau)\,\mathrm{d}\tau}{T'(t)} - \frac{1}{k_2'}\,, \tag{2}$$

Combining Eq. 1 and Eq. 2 to cancel the plasma term and after re-arranging, we obtain, for $t > t^*$,

$$\frac{\int_0^t T(\tau)\,\mathrm{d}\tau}{T(t)} = \frac{V}{V'}\frac{\int_0^t T'(\tau)\,\mathrm{d}\tau}{T(t)} + \frac{V}{V'k_2'}\frac{T'(t)}{T(t)} + b\,. \tag{3}$$

Three parameters can be estimated by a multilinear regression analysis: $\beta_1 = \frac{V}{V'}, \beta_2 = \frac{V}{V'k_2'}$ and $\beta_3 = b$.

- Suppose the target tissue can be modeled by 2TC and the non-displaceable distribution volume of the target tissue and reference tissue are the same, i.e. $\frac{K_1}{k_2} = \frac{K_1'}{k_2'}$, then

$$\beta_1 = \frac{V}{V'} = \frac{K_1/k_2}{K_1'/k_2'}(1 + BP) = 1 + BP\,.$$

  Thus BP can be estimated by $BP = \beta_1 - 1$.

- Suppose the target tissue can be modeled by 1TC. Then $\beta_3 = b = -\frac{1}{k_2}$. Then

$$\frac{\beta_2}{\beta_3} = \frac{K_1/k_2}{K_1'/k_2'}\frac{1}{k_2'}(-k_2) = -\frac{K_1}{K_1'} = -R_1\,,$$

  where R_1 is the relative tracer delivery. Then R_1 can be calculated by $R_1 = -\frac{\beta_2}{\beta_3}$. Note that in this case, $t^* = 0$, i.e. Eq. 3 is linear from the beginning of time.

3 MRTM [2]

The major drawback of MRTM0 is that it produces biased estimates. Two factors contribute to this bias (observing Eq. 3):

1. Ordinary least-square parameter estimation assumes that independent variables (RHS of the equation) are noise-free. However, the RHS of Eq. 3 contains a noisy term $T(t)$.
2. The noise in the dependent variable (LHS) and the independent variables (RHS) are correlated through $T(t)$.

MRTM1 is simply a re-arrangement of Eq. 3:

$$T(t) = -\frac{V}{V'b}\int_0^t T'(\tau)\,\mathrm{d}\tau + \frac{1}{b}\int_0^t T(\tau)\,\mathrm{d}\tau - \frac{V}{V'k_2'b}T'(t)\,. \tag{4}$$

Compared with Eq. 3, in Eq. 4, the noisy term $T(t)$ is no longer present in the independent variables on the RHS, although the integral of $T(t)$ is present. However, integrals of noisy data typically have much lower percent variation than the data themselves. The correlation of the noise in the dependent and independent variables is dramatically reduced.

MRTM1 produces three parameters $\gamma_1 = -\frac{V}{V'b}$, $\gamma_2 = \frac{1}{b}$ and $\gamma_3 = -\frac{V}{V'k_2'b}$.

- If the target tissue has 2TC kinetics, BP can be calculated as $BP = -\left(\frac{\gamma_1}{\gamma_2} + 1\right)$. To verify:

$$-\left(\frac{\gamma_1}{\gamma_2} + 1\right) = -\left(-\frac{V}{V'} + 1\right) = \frac{V}{V'} - 1 = BP\,.$$

- If the target tissue has 1TC kinetics, $R_1 = \gamma_3$ and $k_2 = -\gamma_2$. To verify:

$$\gamma_3 = -\frac{V}{V'k_2'b} = \frac{V}{V'}\frac{k_2}{k_2'} = \frac{K_1}{K_1'} = R_1$$
$$-\gamma_2 = -\frac{1}{b} = k_2\,.$$

4 MRTM2 [2]

Eq. 4 also allows estimation of k_2' by $k_2' = \frac{\gamma_1}{\gamma_3}$. However, a different value of k_2' is estimated for each voxel, although k_2' refers to the clearance rate from tissue to the plasma in the reference tissue, which should only one true value. The idea of MRTM2 is to first do a preliminary analysis by MRTM using Eq. 4, then fix k_2' to one value (more details to be discussed later). Then use a re-arranged two-parameter version of Eq. 4:

$$T(t) = -\frac{V}{V'b}\left(\int_0^t T'(\tau)\,\mathrm{d}\tau + \frac{1}{k_2'}T'(t)\right) + \frac{1}{b}\int_0^t T(\tau)\,\mathrm{d}\tau\,. \tag{5}$$

This equations enables us to estimate two parameters: $\gamma_1 = -\frac{V}{V'b}$ and $\gamma_2 = \frac{1}{b}$ for $t > t^*$.

- For 2TC kinetics, $BP = -(\gamma_1/\gamma_2 + 1)$.
- For 1TC kinetics, $R_1 = \gamma_1/k_2'$ and $k_2 = -\gamma_2$.

MRTM2 is more stable than MRTM because it estimates fewer parameters.

Zeyu: careful consideration may be needed in how to obtain a single value for k_2' from many values across the pixels or ROIs.

References

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