

Supplement to: On the reduction of imaging time-points for dosimetry in radionuclide therapy

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The bi-exponential case

Consider a bi-exponential TAC, *i.e.*,

$$A(t) = a_1 \exp(-[\lambda_1 + \lambda_{\text{phys}}]t) + a_2 \exp(-[\lambda_2 + \lambda_{\text{phys}}]t) \quad (\text{S1})$$

corresponding to the parameter vector $\mathbf{p} = [a_1, \lambda_1, a_2, \lambda_2]^T$.

The Jacobian for the fitting problem to the n data points is

$$\mathbf{J} = \begin{bmatrix} \exp(-[\lambda_1 + \lambda_{\text{phys}}]t_1) & -t_1 a_1 \exp(-[\lambda_1 + \lambda_{\text{phys}}]t_1) & \exp(-[\lambda_2 + \lambda_{\text{phys}}]t_1) & -t_1 a_2 \exp(-[\lambda_2 + \lambda_{\text{phys}}]t_1) \\ \exp(-[\lambda_1 + \lambda_{\text{phys}}]t_2) & -t_2 a_1 \exp(-[\lambda_1 + \lambda_{\text{phys}}]t_2) & \exp(-[\lambda_2 + \lambda_{\text{phys}}]t_2) & -t_2 a_2 \exp(-[\lambda_2 + \lambda_{\text{phys}}]t_2) \\ \vdots & \vdots & \vdots & \vdots \\ \exp(-[\lambda_1 + \lambda_{\text{phys}}]t_n) & -t_n a_1 \exp(-[\lambda_1 + \lambda_{\text{phys}}]t_n) & \exp(-[\lambda_2 + \lambda_{\text{phys}}]t_n) & -t_n a_2 \exp(-[\lambda_2 + \lambda_{\text{phys}}]t_n) \end{bmatrix} \quad (\text{S2})$$

and the covariance matrix of the parameter vector becomes

$$\Sigma_{\mathbf{p}} = r^2 \begin{bmatrix} Q_1 & -a_1 Q_1 \bar{t}_1 & Q_{12} & -a_2 Q_{12} \bar{t}_{12} \\ -a_1 Q_1 \bar{t}_1 & a_1^2 Q_1 (s_1^2 + \bar{t}_1^2) & -a_1 Q_{12} \bar{t}_{12} & a_1 a_2 Q_{12} (s_{12}^2 + \bar{t}_{12}^2) \\ Q_{12} & -a_1 Q_{12} \bar{t}_{12} & Q_2 & -a_2 Q_2 \bar{t}_2 \\ -a_2 Q_{12} \bar{t}_{12} & a_1 a_2 Q_{12} (s_{12}^2 + \bar{t}_{12}^2) & -a_2 Q_2 \bar{t}_2 & a_2^2 Q_2 (s_2^2 + \bar{t}_2^2) \end{bmatrix}^{-1} \quad (\text{S3})$$

where $Q_1 = \sum_{i=1}^n q_1^2(t_i)$, $Q_2 = \sum_{i=1}^n q_2^2(t_i)$, and $Q_{12} = \sum_{i=1}^n q_1(t_i)q_2(t_i)$ with $q_1(t) = \exp(-[\lambda_1 + \lambda_{\text{phys}}]t)/A(t)$ and $q_2(t) = \exp(-[\lambda_2 + \lambda_{\text{phys}}]t)/A(t)$; $\bar{t}_1$, $\bar{t}_2$, and $\bar{t}_{12}$ are the weighted averages $\bar{t}_1 = \sum_{i=1}^n q_1^2(t_i)t_i/Q_1$, $\bar{t}_2 = \sum_{i=1}^n q_2^2(t_i)t_i/Q_2$ and $\bar{t}_{12} = \sum_{i=1}^n q_1(t_i)q_2(t_i)/Q_{12}$; and s_1^2 , s_2^2 , and s_{12}^2 are the weighted variances $s_1^2 = \sum_{i=1}^n q_1^2(t_i)(t_i - \bar{t}_1)^2/Q_1$, $s_2^2 = \sum_{i=1}^n q_2^2(t_i)(t_i - \bar{t}_2)^2/Q_2$, and $s_{12}^2 = \sum_{i=1}^n q_1(t_i)q_2(t_i)(t_i - \bar{t}_{12})^2/Q_{12}$.

Denote

$$\Delta_1 = \begin{bmatrix} Q_1 & -a_1 Q_1 \bar{t}_1 \\ -a_1 Q_1 \bar{t}_1 & a_1^2 Q_1 (s_1^2 + \bar{t}_1^2) \end{bmatrix}, \quad (\text{S4})$$

$$\Delta_2 = \begin{bmatrix} Q_2 & -a_2 Q_2 \bar{t}_2 \\ -a_2 Q_2 \bar{t}_2 & a_2^2 Q_2 (s_2^2 + \bar{t}_2^2) \end{bmatrix}, \quad (\text{S5})$$

and

$$\mathbf{K} = \begin{bmatrix} Q_{12} & -a_2 Q_{12} \bar{t}_{12} \\ -a_1 Q_{12} \bar{t}_{12} & a_1 a_2 Q_{12} (s_{12}^2 + \bar{t}_{12}^2) \end{bmatrix} \quad (\text{S6})$$

such that

$$\begin{aligned} \Sigma_{\mathbf{p}} &= r^2 \begin{bmatrix} \Delta_1 & \mathbf{K} \\ \mathbf{K}^T & \Delta_2 \end{bmatrix}^{-1} = \\ &= r^2 \begin{bmatrix} \Delta_1^{-1} + \Delta_1^{-1} \mathbf{K} (\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \mathbf{K}^T \Delta_1^{-1} & -\Delta_1^{-1} \mathbf{K} (\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \\ -(\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \mathbf{K}^T \Delta_1^{-1} & \Delta_2^{-1} + \Delta_2^{-1} \mathbf{K}^T (\Delta_1 - \mathbf{K} \Delta_2^{-1} \mathbf{K}^T)^{-1} \mathbf{K} \Delta_2^{-1} \end{bmatrix} = \\ &= r^2 \begin{bmatrix} \Delta_1^{-1} & \mathbf{0} \\ \mathbf{0} & \Delta_2^{-1} \end{bmatrix} + r^2 \begin{bmatrix} \Delta_1^{-1} \mathbf{K} (\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \mathbf{K}^T \Delta_1^{-1} & \mathbf{0} \\ \mathbf{0} & \Delta_2^{-1} \mathbf{K}^T (\Delta_1 - \mathbf{K} \Delta_2^{-1} \mathbf{K}^T)^{-1} \mathbf{K} \Delta_2^{-1} \end{bmatrix} + \\ &= r^2 \begin{bmatrix} \mathbf{0} & -\Delta_1^{-1} \mathbf{K} (\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \\ -(\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \mathbf{K}^T \Delta_1^{-1} & \mathbf{0} \end{bmatrix}. \end{aligned} \quad (\text{S7})$$

The Jacobian for the integration is

$$\mathbf{Y} = [\mathbf{Y}_1 \quad \mathbf{Y}_2], \quad (\text{S8})$$

where

$$\mathbf{Y}_1 = [\tilde{\alpha}_1 a_1^{-1} \quad -\tilde{\alpha}_1 \tau_1] \quad (\text{S9})$$

and

$$\mathbf{Y}_2 = [\tilde{\alpha}_2 a_2^{-1} \quad -\tilde{\alpha}_2 \tau_2] \quad (\text{S10})$$

with $\tilde{\alpha}_1 = a_1 \lambda_1^{-1}$, $\tilde{\alpha}_2 = a_2 \lambda_2^{-1}$, $\tau_1 = \lambda_1^{-1}$, and $\tau_2 = \lambda_2^{-1}$.

The variance of the TIA becomes

$$\begin{aligned} V(\tilde{A}) &= \mathbf{Y} \Sigma_{\mathbf{p}} \mathbf{Y}^T = r^2 \mathbf{Y}_1 \Delta_1^{-1} \mathbf{Y}_1^T + r^2 \mathbf{Y}_2 \Delta_2^{-1} \mathbf{Y}_2^T + \\ &+ r^2 \mathbf{Y}_1 \Delta_1^{-1} \mathbf{K} (\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \mathbf{K}^T \Delta_1^{-1} \mathbf{Y}_1^T + \\ &+ r^2 \mathbf{Y}_2 \Delta_2^{-1} \mathbf{K}^T (\Delta_1 - \mathbf{K} \Delta_2^{-1} \mathbf{K}^T)^{-1} \mathbf{K} \Delta_2^{-1} \mathbf{Y}_2^T - \\ &- r^2 \mathbf{Y}_1 \Delta_1^{-1} \mathbf{K} (\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \mathbf{Y}_2^T - \\ &- r^2 \mathbf{Y}_2 (\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \mathbf{K}^T \Delta_1^{-1} \mathbf{Y}_1^T. \end{aligned} \quad (\text{S11})$$

Noting that $V(\tilde{A})$, and hence all constituent terms, are scalar in combination with $(\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1}$ being symmetric, $\mathbf{Y}_2 (\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \mathbf{K}^T \Delta_1^{-1} \mathbf{Y}_1^T = [\mathbf{Y}_1 \Delta_1^{-1} \mathbf{K} (\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \mathbf{Y}_2^T]^T = \mathbf{Y}_1 \Delta_1^{-1} \mathbf{K} (\Delta_2 - \mathbf{K}^T \Delta_1^{-1} \mathbf{K})^{-1} \mathbf{Y}_2^T$ and defining

$$D_1 = \mathbf{Y}_1 \Delta_1^{-1} \mathbf{Y}_1^T, \quad (\text{S12})$$

$$D_2 = \mathbf{Y}_2 \Delta_2^{-1} \mathbf{Y}_2^T, \quad (\text{S13})$$

$$C_1 = \mathbf{Y}_1 \mathbf{\Delta}_1^{-1} \mathbf{K} (\mathbf{\Delta}_2 - \mathbf{K}^T \mathbf{\Delta}_1^{-1} \mathbf{K})^{-1} \mathbf{K}^T \mathbf{\Delta}_1^{-1} \mathbf{Y}_1^T, \quad (\text{S14})$$

$$C_2 = \mathbf{Y}_2 \mathbf{\Delta}_2^{-1} \mathbf{K}^T (\mathbf{\Delta}_1 - \mathbf{K} \mathbf{\Delta}_2^{-1} \mathbf{K}^T)^{-1} \mathbf{K} \mathbf{\Delta}_2^{-1} \mathbf{Y}_2^T, \quad (\text{S15})$$

and

$$\rho = \mathbf{Y}_1 \mathbf{\Delta}_1^{-1} \mathbf{K} (\mathbf{\Delta}_2 - \mathbf{K}^T \mathbf{\Delta}_1^{-1} \mathbf{K})^{-1} \mathbf{Y}_2^T \quad (\text{S16})$$

leads to

$$V(\tilde{A}) = r^2 (D_1 + D_2 + C_1 + C_2 - 2\rho), \quad (\text{S17})$$

where, in analogy with the mono-exponential case,

$$D_1 = \tilde{\alpha}_1^2 \frac{1}{a_1^2 Q_1} \left[1 + \frac{(\bar{t}_1 - \tau_1)^2}{s_1^2} \right], \quad (\text{S18})$$

and

$$D_2 = \tilde{\alpha}_2^2 \frac{1}{a_2^2 Q_2} \left[1 + \frac{(\bar{t}_2 - \tau_2)^2}{s_2^2} \right]. \quad (\text{S19})$$

There are straight-forward interpretations of the different terms in (S17) with D_1 and D_2 representing the propagation of dispersion for the two phases individually; C_1 and C_2 represent corrections to D_1 and D_2 ; and ρ represent the correlation between the two phases.