Short Communications

Investigation of the Effect of Data Error on the Determination of Physiological Parameters by Means of Compartmental Analysis

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The determination of physiological parameters by observing tracer kinetics in a steady-state system usually involves two stages. The first consists of fitting exponential functions of the form:

$$a = \sum X_i \cdot \exp(-\lambda_i t)$$

(where $i = 1, 2, \dots, n$) to values of specific activity, or relative specific activity, at times t . By performing a non-linear regression of a on t the parameters X_i and λ_i are estimated. Usually the physiological parameters of interest are transfer rates (R_{ij}) or rate constants (k_{ij}), and these are algebraic functions of the first set of parameters. The form of these functions is determined by the model of the system being studied. The second stage calculates the physiological parameters from the parameters of the exponential functions by using these algebraic functions.

For the first stage, Myhill (1967, 1968) has produced extensive data to illustrate how error in the tracer specific activities affects the precision of estimating the parameters of the exponential functions. However, since this stage is only part of the process, the present communication is concerned with determining the effect of error in the data on the precision of estimating the physiological parameters.

For this study the three two-compartment models shown in Fig. 1 were used. Assuming that tracer is injected into compartment 1, the relative specific activity in this compartment at later times t is given by the two-exponential function:

$$a = X_1 \cdot \exp(-\lambda_1 t) + X_2 \cdot \exp(-\lambda_2 t)$$

The relationships between the constants of this two-exponential function and the physiological parameters of the three models can be determined by standard methods (e.g. Atkins, 1969). The results are: For model A:

$$X_1 = (k_{21} - \lambda_2) / (\lambda_1 - \lambda_2)$$

$$X_2 = (\lambda_1 - k_{21}) / (\lambda_1 - \lambda_2)$$

$$(\lambda_1 + \lambda_2) = k_{02} + k_{12} + k_{21}, \quad \lambda_1 \lambda_2 = k_{02} \cdot k_{21}$$

For model B:

$$X_1 = (\lambda_1 - k_{12}) / (\lambda_1 - \lambda_2)$$

$$X_2 = (k_{12} - \lambda_2) / (\lambda_1 - \lambda_2)$$

$$(\lambda_1 + \lambda_2) = k_{01} + k_{12} + k_{21}, \quad \lambda_1 \lambda_2 = k_{01} \cdot k_{12}$$

For model C:

$$X_1 = (\lambda_1 - k_{01} - k_{12}) / (\lambda_1 - \lambda_2)$$

$$X_2 = (\lambda_1 - k_{01} - k_{21}) / (\lambda_1 - \lambda_2)$$

$$(\lambda_1 + \lambda_2) = 2k_{01} + k_{12} + k_{21},$$

$$\lambda_1 \lambda_2 = k_{01} (k_{01} + k_{12} + k_{21})$$

Model A

Model B

Model C

Fig. 1. The three two-compartment models used in this study

a_i is the specific activity of tracer in compartment i , k_{ij} is the rate constant for transport of material to compartment i from compartment j , and R_{10} is the rate of input of unlabelled material into compartment 1.

Fig. 2. Comparison of error in data with that of the calculated parameters

The coefficients of variation of the calculated parameters (X_1 , λ_1 , k_{ij}) are plotted against the coefficients of variation of the pseudo-random numbers used to generate the simulated data. Logarithmic scales are used for convenience.

Simulated data were generated by a method described elsewhere (Atkins, 1971). The function:

$$a = 4.0 \exp(-0.4t) + 1.0 \exp(-0.1t)$$

was used to calculate perfect values for a . These values were multiplied by sets of pseudo-random numbers with a mean of 1.00 and standard deviations respectively of 0.01, 0.02, 0.05 and 0.10. Twelve sets of simulated data were generated at each standard deviation. Each set was analysed graphically to provide initial estimates of X_1 , X_2 , λ_1 and λ_2 . The function:

$$a = X_1 \cdot \exp(-\lambda_1 t) + X_2 \cdot \exp(-\lambda_2 t)$$

was then fitted to each simulated data set, with the data points equally weighted, to calculate precise values for the parameters. The non-linear regression program (Atkins, 1971) always converged to a minimum. The physiological parameters (k_{ij}) were calculated for each set of parameters (X_1 , X_2 , λ_1 , λ_2). For each parameter at each standard deviation of the data error 12 values were thus obtained, and their

means and coefficients of variation were calculated. All the mean values were unbiased.

Fig. 2, in the form of a double-logarithmic plot for convenience, compares the coefficients of variation of the estimated parameters with the coefficients of variation of the pseudo-random numbers used to generate the data.

The major conclusion is that the uncertainty in determining the physiological parameters is about the same as that in estimating the parameters of the exponential function. For both types of parameter the variation in their estimation is much greater than the error in the simulated data.

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