Engineering Pharmacology: Pharmacokinetic Models Using Recursive Finite Difference Equations

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Abstract: - Pharmacokinetic models have typically been developed using traditional exponential equations. This paper summarizes a mathematical technique of transforming multi-compartment models, for both bolus and infusion data, into recursive finite difference equations (RFDEs). Specifically, a bolus can be represented as homogenous RFDE whereas an infusion can be represented as inhomogenous RFDE. In addition to being identically as accurate as traditional exponential equations, RFDE pharmacokinetic models have fewer coefficients. The coefficients of the RFDE also appear to have an overall reduction in patient-to-patient variability when compared to those of the traditional exponential models from which they were derived. However, initial conditions for RFDEs have to be specified. Pharmacokinetic modeling, using RFDEs, is feasible and may offer advantages over traditional exponential equations.

Key-Words: - recursive finite difference equation, propofol, pharmacokinetic, modeling

1 Introduction

The application of recursive finite difference equations (RFDEs) in pharmacokinetics may offer advantages for modeling, simulation and situations requiring automatic control.

This paper demonstrates how RFDE models, of both bolus and infusions of medications, can be derived directly from traditional exponential equations.

2 Bolus Model

A typical three compartment pharmacokinetic model, for a single bolus, is represented as a summation of exponential equations:

$$Q_{(k)} = ae^{-bk} + ce^{-dk} + fe^{-gk} \quad . \qquad (1)$$

The associated homogeneous RFDE for this would be [1]:

$$P_{(k+3)} = A \cdot P_{(k+2)} + B \cdot P_{(k+1)} + C \cdot P_{(k)} \quad . \qquad (2)$$

Note that P represents measured blood or plasma levels of the given medication each k^{th} unit of time starting from $k = 1$.

The general solution for equation (2) is [3] [4] [5]:

$$P_{(k)} = \alpha\beta^k + \gamma\delta^k + \varepsilon\zeta^k \quad . \qquad (3)$$

2.1 Solution for the bolus model

The solution for the bolus model is first determined by equating (1) with (3) [1]:

$$\alpha\beta^k + \gamma\delta^k + \varepsilon\zeta^k = ae^{-bk} + ce^{-dk} + fe^{-gk} \quad . \qquad (4)$$

The above equality is valid if:

$$\alpha = a,\ \gamma = c, \text{ and } \varepsilon = f\ , \tag{5}$$

and

$$\beta = e^{-b},\ \delta = e^{-d},\ \zeta = e^{-g}\ . \tag{6}$$

2.1.1 Development of the RDFE bolus model

The solution of the RFDE (2) is then determined using the third-order auxiliary or characteristic equation:

$$(M - \beta)(M - \delta)(M - \zeta) = 0. \tag{7}$$

This is expanded as:

$$M^3 + (-\beta - \zeta - \delta)M^2 + (\beta\zeta + \beta\delta + \delta\zeta)M - \beta\delta\zeta = 0\ . \tag{8}$$

Rearrangement yields:

$$M^3 = (\beta + \zeta + \delta)M^2 - (\beta\zeta + \beta\delta + \delta\zeta)M + \beta\delta\zeta\ . \tag{9}$$

The RFDE (2) will then take on the above form if:

$$A = (\beta + \zeta + \delta)\ , \tag{10}$$

$$B = -(\beta\zeta + \beta\delta + \delta\zeta)\ , \tag{11}$$

and

$$C = (\beta\delta\zeta)\ . \tag{12}$$

3 Infusion Model

The traditional exponential equation for a third order infusion model is:

$$Q_{(k)} = h - (ae^{-bk} + ce^{-dk} + fe^{-gk})\ . \tag{13}$$

The associated inhomogeneous RFDE is then [2]:

$$P_{(k+3)} = A \cdot P_{(k+2)} + B \cdot P_{(k+1)} + C \cdot P_{(k)} + R\ . \tag{14}$$

3.1 Solution for the infusion model

The solution for (14) represents the superposition of the homogeneous and particular solutions [3], [4], [5].

Thus, the homogeneous solution is determined with $h = 0$ and using the method shown in (7) through (12).

The particular solution is then used to determine the value for the constant R.

3.1.1 The particular solution for the infusion model

The particular solution is found by algebraic rearrangement of (14) [2]:

$$P_{(k+3)} - A \cdot P_{(k+2)} - B \cdot P_{(k+1)} - C \cdot P_{(k)} = R\ . \tag{15}$$

It should be noted that as $k \longrightarrow \infty$:

$$P_{(k+3)} = P_{(k+2)} = P_{(k+1)} = P_{(k)} = h\ . \tag{16}$$

Thus, the infusion model is assumed to eventually reach a steady-state, or plateau, with an established value of h.

Substituting (16) into (15) yields:

$$h - A \cdot h - B \cdot h - C \cdot h = R\ \ . \tag{17}$$

Thus:

$$R = h \cdot [1 - (A + B + C)]\ . \tag{18}$$

It should be noted that this represents an application of the *method of undetermined coefficients*.

4 Patient-to-patient variability

The decrease in patient-to-patient variability, of the coefficients of the RFDE models, as compared to those of the exponential models, can be assessed by first noting that coefficients b, d, and g are all numerically nonnegative and nonzero:

$$0 < \left| -e^{-b} \right| < 1\ \ , \tag{19}$$

$$0 < \left| -e^{-d} \right| < 1\ \ , \tag{20}$$

$$\text{and} \quad 0 < \left| -e^{-g} \right| < 1\ \ . \tag{21}$$

The patient-to-patient variability of coefficients A, B, or C of either the bolus (homogeneous) or infusion (inhomogeneous) models can then be examined using the chain rule and the total differential. For coefficient A this is:

$$\Delta A = \frac{\partial A}{\partial b}\Delta b + \frac{\partial A}{\partial d}\Delta d + \frac{\partial A}{\partial g}\Delta g \quad . \qquad (22)$$

Examination of (10) shows:

$$\frac{\partial A}{\partial b} = -e^{-b} \quad , \qquad (23)$$

$$\frac{\partial A}{\partial d} = -e^{-d} \quad , \qquad (24)$$

and

$$\frac{\partial A}{\partial g} = -e^{-g} \quad . \qquad (25)$$

Substituting (23) through (25) into (22) yields:

$$\Delta A = (-e^{-b})\Delta b + (-e^{-d})\Delta d + (-e^{-g})\Delta g \quad . \qquad (26)$$

Use of the triangle inequality will be such that the absolute value of the sum will less than, or equal to, the sum of the absolute values:

$$|\Delta A| \leq \left(\left|-e^{-b}\Delta b\right| + \left|-e^{-d}\Delta d\right| + \left|-e^{-g}\Delta g\right|\right) \quad . \qquad (27)$$

Therefore:

$$|\Delta A| < \left(|\Delta b| + |\Delta d| + |\Delta g|\right) \quad . \qquad (28)$$

Similarly, the patient-to-patient variability of coefficient *B* can be found:

$$\Delta B = \frac{\partial B}{\partial b}\Delta b + \frac{\partial B}{\partial d}\Delta d + \frac{\partial B}{\partial g}\Delta g \quad . \qquad (29)$$

Examination of (11) shows:

$$\frac{\partial B}{\partial b} = e^{-(b+g)} + e^{-(b+d)} \qquad (30)$$

$$\frac{\partial B}{\partial d} = e^{-(b+d)} + e^{-(d+g)} \qquad (31)$$

and

$$\frac{\partial B}{\partial g} = e^{-(b+g)} + e^{-(d+g)} \quad . \qquad (32)$$

Equation (29) can then be expressed as:

$$\Delta B = e^{-b}\{[e^{-d}] + [e^{-g}]\}\Delta b + e^{-d}\{[e^{-b}] + [e^{-g}]\}\Delta d + e^{-g}\{[e^{-b}] + [e^{-d}]\}\Delta g \; . \qquad (33)$$

Use of the triangle rule then shows:

$$|\Delta B| \leq \{|e^{-b}\{[e^{-d}] + [e^{-g}]\}\Delta b| + |e^{-d}\{[e^{-b}] + [e^{-g}]\}\Delta d| + |e^{-g}\{[e^{-b}] + [e^{-d}]\}\Delta g|\} \; . \qquad (34)$$

Therefore:

$$|\Delta B| < 2\{|e^{-b}\Delta b| + |e^{-d}\Delta d| + |e^{-g}\Delta g|\} \; . \qquad (35)$$

Thus:

$$|\Delta B| < 2\{|\Delta b| + |\Delta d| + |\Delta g|\} \; . \qquad (36)$$

The variation in *C* can be determined as well:

$$\Delta C = \frac{\partial C}{\partial b}\Delta b + \frac{\partial C}{\partial d}\Delta d + \frac{\partial C}{\partial g}\Delta g \qquad (37)$$

Examination of (12) shows that:

$$\frac{\partial C}{\partial b} = \frac{\partial C}{\partial d} = \frac{\partial C}{\partial g} = -e^{-(b+d+g)} \quad . \qquad (38)$$

Thus:

$$\Delta C = -e^{-(b+d+g)}[\Delta b + \Delta d + \Delta g] \; . \qquad (39)$$

Therefore:

$$|\Delta C| \leq \{|e^{-(b+d+g)}| \bullet [|\Delta b| + |\Delta d| + |\Delta g|]\} \quad . \qquad (40)$$

Thus:

$$|\Delta C| < \{|\Delta b| + |\Delta d| + |\Delta g|\} \; . \qquad (41)$$

To summarize, the patient-to-patient variation in coefficient *A* will be less than the sum of: $|\Delta b|$, $|\Delta d|$,and $|\Delta g|$. This also applies to *C* .

Whereas the magnitude, observed in the patient-to-patient variation of coefficient *B*, will be less than twice the sum of: $|\Delta b|$, $|\Delta d|$, and $|\Delta g|$.

Note that this analysis of the variability of *A*, *B*, and *C* applies to both the bolus (homogeneous) and infusion (inhomogeneous) models. Figure 1 illustrates the range of the coefficients for both the bolus RFDE and traditional exponential equations from clinically-acquired data.

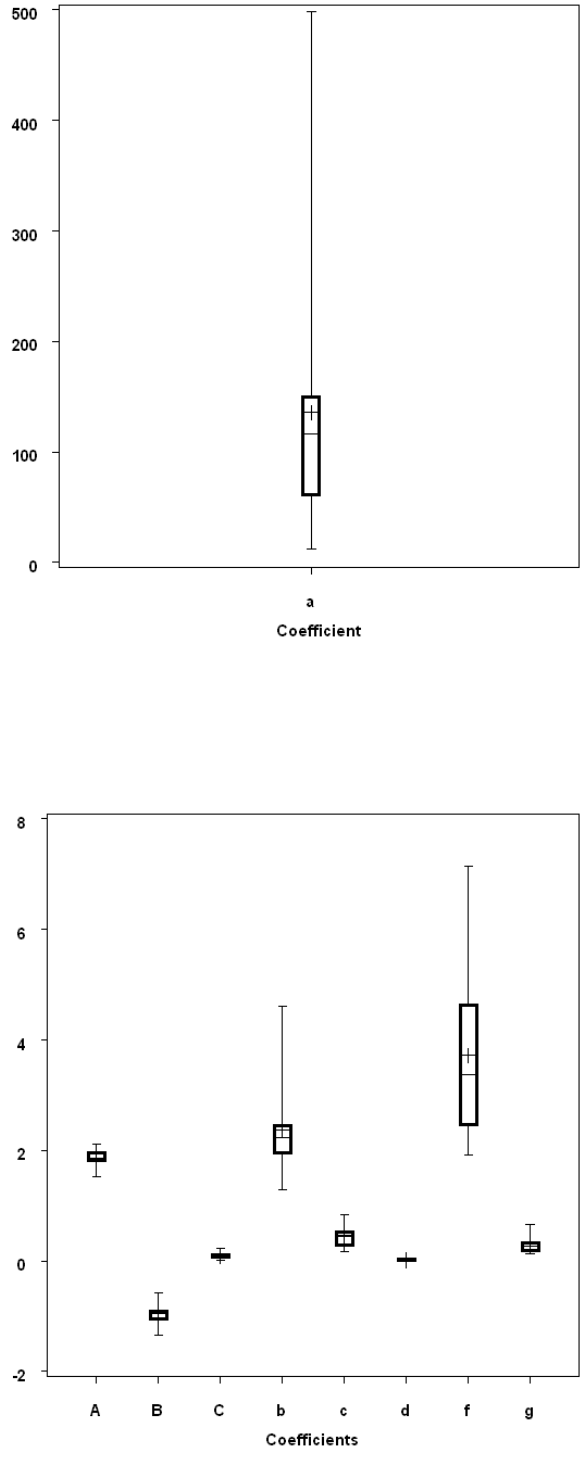

Figure 1. Box-plots of coefficients A, B, and C, of the bolus RFDE model, show less patient-to-patient variability than those coefficients of the traditional exponential model.

4.1 Patient-to-patient variability for the particular solution

The patient-to-patient variability of the constant R for the infusion (inhomogeneous) model can also be assessed.

Substituting the definitions of coefficients *A*, *B*, and *C* from equations (10), (11), and (12) yields:

$$R = h\cdot[1 - (\{e^{-b} + e^{-g} + e^{-d}\} - \{e^{-(b+g)} + e^{-(b+d)} + e^{-(d+g)}\} + \{e^{-(b+d+g)}\})]. \quad (42)$$

Each partial derivative is then obtained:

$$\frac{\partial R}{\partial b} = h\cdot e^{-b}\left(1-e^{-g}\right)\left(1-e^{-d}\right) \quad , \quad (43)$$

$$\frac{\partial R}{\partial d} = h\cdot e^{-d}\left(1-e^{-b}\right)\left(1-e^{-g}\right) \quad , \quad (44)$$

$$\frac{\partial R}{\partial g} = h\cdot e^{-g}\left(1-e^{-b}\right)\left(1-e^{-d}\right) \quad , \quad (45)$$

and

$$\frac{\partial R}{\partial h} = \left(1-e^{-b}\right)\left(1-e^{-g}\right)\left(1-e^{-d}\right) \quad . \quad (46)$$

Combining (43) through (46):

$$\Delta R = \frac{\partial R}{\partial b}\Delta b + \frac{\partial R}{\partial d}\Delta d + \frac{\partial R}{\partial g}\Delta g + \frac{\partial R}{\partial h}\Delta h \quad . \quad (47)$$

Note inequalities (19) through (21) as well as the following inequalities:

$$0 < \left|1-e^{-b}\right| < 1 \quad , \quad (48)$$

$$0 < \left|1-e^{-d}\right| < 1 \quad , \quad (49)$$

$$\text{and} \quad 0 < \left|1-e^{-g}\right| < 1 \quad . \quad (50)$$

Equation (47) can then be expressed as an inequality:

$$|\Delta R| < h(|\Delta b| + |\Delta d| + |\Delta g|) + |\Delta h| \quad . \quad (51)$$

Therefore, small changes in *R* are less than a value which is proportional to the sum of the small changes in *b*, *d*, *g*, and *h*.

If $m = \max(|h|, 1)$ then :

$$|\Delta R| < m\{|\Delta b| + |\Delta d| + |\Delta g| + |\Delta h|\} \quad . \quad (52)$$

Figure 2 illustrates the range of the coefficients for both the infusion RFDE and traditional exponential equations from clinically-acquired data.

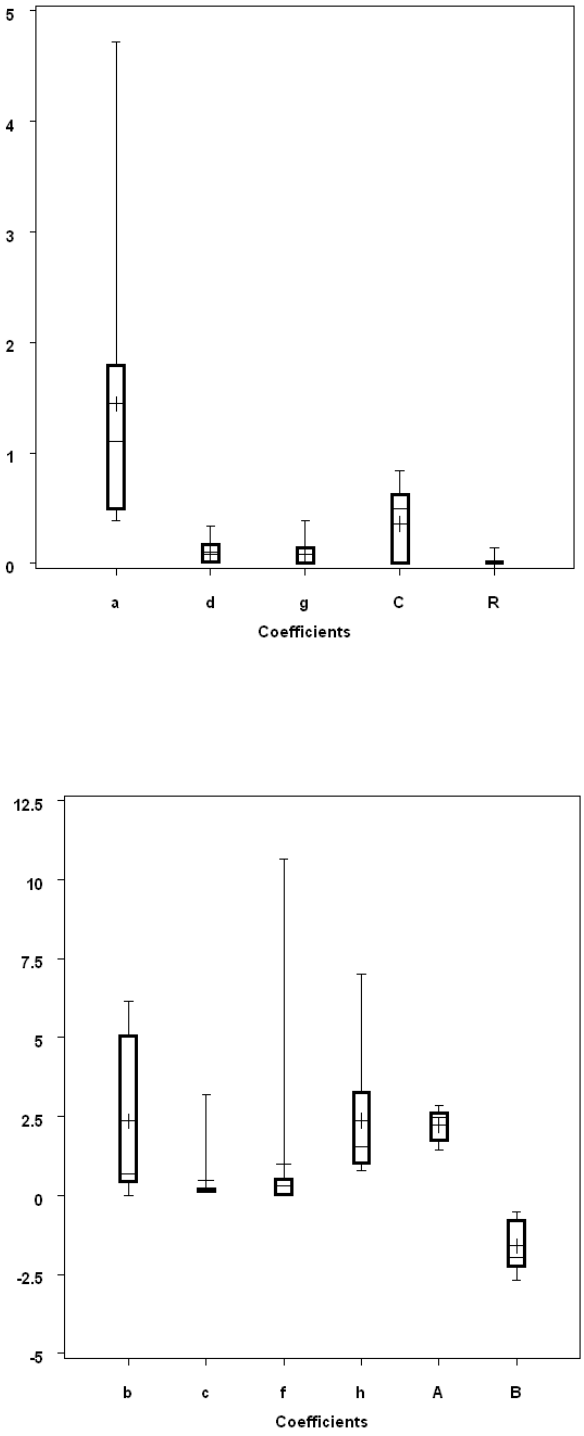

Figure 2. Box-plots of Coefficients A, B, C, and R of the infusion RFDE model, show less patient-to-patient variability than those coefficients of the traditional exponential model.

5 Example: Bolus RFDE

The following is a numerical example, of a bolus, which is based upon a single patient. Using the exponential model from (1) :

$$Q_{(k)} = ae^{-bk} + ce^{-dk} + fe^{-gk}. \quad (53)$$

Based on non-linear curve fitting, coefficients for the above equation were found to be: a = 146.157, b = 2.24, c = 0.424, d = 0.023, f = 2.625, g = 0.261.

The general solution, $P_{(k)}$, is then determined from equation (3):

$$P_{(k)} = \alpha\beta^k + \gamma\delta^k + \varepsilon\zeta^k. \quad (54)$$

Where: $\alpha = a$, $\gamma = c$, and $\varepsilon = f$ and $\beta = e^{-b}$, $\delta = e^{-d}$, $\zeta = e^{-g}$.

The coefficients, for the RFDE, can then be determined by first calculating A, B, and C from (10), (11), and (12) :

$$A = (\beta + \zeta + \delta) = (e^{-b} + e^{-g} + e^{-d}) = (e^{-2.24} + e^{-0.261} + e^{-0.023}) = 1.854, \quad (55)$$

$$B = -(\beta\zeta + \beta\delta + \delta\zeta) = -(e^{-(b+g)} + e^{-(b+d)} + e^{-(d+g)}) = -(e^{-2.501} + e^{-2.263} + e^{-0.284}) = -0.939, \quad (56)$$

$$C = (\beta\delta\zeta) = (e^{-b} \bullet e^{-d} \bullet e^{-g}) = e^{-(b+d+g)} = e^{-(2.24 + 0.023 + 0.261)} = 0.08. \quad (57)$$

The RFDE is then expressed as in (2):

$$P_{(k+3)} = (1.854)P_{(k+2)} - (0.939)P_{(k+1)} + (0.08)P_{(k)}. \quad (58)$$

It should be noted that the initial conditions: $P_{(3)}$, $P_{(2)}$, and $P_{(1)}$ are determined from either (53) or (54). Thus, (53), (54) and (58) yield numerically identical results for the entire time period. This is illustrated in Figure 1. Minor numerical differences are attributable to rounding.

The initial conditions, for this case, are: P_1=17.996, P_2 = 3.619, and P_3 = 1.772 μg/ml. Figure 3 illustrates the serum levels of propofol modeled using both techniques.

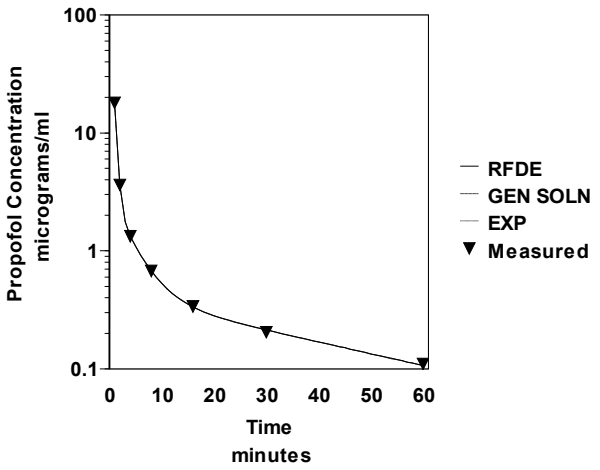

Figure 3. A graphical representation of the measured propofol bolus concentrations as well as the RFDE, general solution, and exponential models. Note that the lines for the models overlap. This is from a single subject.

5 Example: Infusion RFDE

The following is a numerical example, of an infusion, which is also based upon a single subject. Using the exponential model from (13):

$$Q_{(k)} = h - (ae^{-bk} + ce^{-dk} + fe^{-gk}). \quad (59)$$

Based on non-linear curve fitting, coefficients for the above equation were found to be: a = 0.463, b=0.493, c = 0.13, d = 0.012, f = 0.359, g = 0.013, and h = 1.048.

The general solution, $P_{(k)}$, is then determined from using the same form as (3) :

$$P_{(k)} = h - (\alpha\beta^k + \gamma\delta^k + \varepsilon\zeta^k). \quad (60)$$

Where: $\alpha = a$, $\gamma = c$, and $\varepsilon = f$ and $\beta = e^{-b}$, $\delta = e^{-d}$, $\zeta = e^{-g}$.

The coefficients, for the RFDE, can then be determined by calculating A, B, and C from (10), (11), and (12) in a manner similar to the bolus:

$$A = (\beta + \zeta + \delta) = (e^{-b} + e^{-g} + e^{-d}) = (e^{-0.493} + e^{-0.013} + e^{-0.012}) = 2.586 , \quad (61)$$

$$B = -(\beta\zeta + \beta\delta + \delta\zeta) = -(e^{-(b+g)} + e^{-(b+d)} + e^{-(d+g)}) = -(e^{-0.506} + e^{-0.505} + e^{-0.025}) = -2.181 , \quad (62)$$

$$C = (\beta\delta\zeta) = (e^{-b} \bullet e^{-d} \bullet e^{-g}) = e^{-(b+d+g)} = e^{-(0.493 + 0.012 + 0.013)} = 0.596 . \quad (63)$$

The homogeneous RFDE is then expressed as in (2):

$$P_{(k+3)} = (2.586)P_{(k+2)} - (2.181)P_{(k+1)} + (0.596)P_{(k)} . \quad (64)$$

The constant R is then determined using the *method of undetermined coefficients*:

$$R = h\cdot[1 - (A + B + C)]. \quad (65)$$

$$R = 1.048\cdot[1 - (2.586 - 2.1826 + 0.596)] = 6.24\cdot10^{-5} . \quad (66)$$

Thus, the complete solution is the superposition, or sum, of equations (64) and (66):

$$P_{(k+3)} = (2.586)P_{(k+2)} - (2.181)P_{(k+1)} + (0.596)P_{(k)} + 6.24\cdot10^{-5}. \quad (67)$$

The initial conditions, for this case, are: P_1 = 0.096, P_2 = 0.283, and P_3 = 0.399 μg/ml.

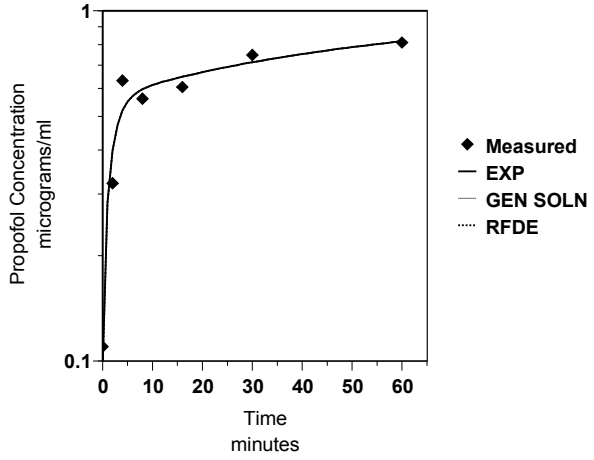

Figure 4. A graphical representation of the measured propofol infusion concentrations as well as the RFDE, general solution, and exponential models. Note that the lines for the models overlap. This is from a single subject.

6 Conclusion

Recursive finite difference equations can be applied in pharmacokinetic modelling. Further research and applications, to determine their utility and limitations, appears indicated.

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