Development of a Recursive Finite Difference Pharmacokinetic Model from an Exponential Model: Application to a Propofol Bolus

GLEN M. ATLAS,[1,2,3] SUNIL DHAR[4]

[1]Department of Anesthesiology, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, 185 S. Orange Avenue MSB E-538, Newark, New Jersey 07103

[2]Department of Biomedical Engineering, Rutgers University, Piscataway, New Jersey

[3]Department of Chemical, Biomedical Engineering, and Materials Engineering, Stevens Institute of Technology, Hoboken, New Jersey

[4]Department of Mathematical Sciences and Center for Applied Mathematics and Statistics, New Jersey Institute of Technology, Newark, New Jersey

Received 28 November 2005; revised 14 December 2005; accepted 20 December 2005

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20579

ABSTRACT: Propofol is commonly administered, as a single bolus dose, for the induction of general anesthesia. The purpose of this study was to mathematically assess the ability to model propofol induction-dose serum levels with a recursive finite difference equation (RFDE). Using data obtained from a prior published study, propofol induction pharmacokinetics were accurately modeled, on a subject-specific basis, with a third-order homogeneous finite difference equation with constant coefficients: $P_{(k+3)} = AP_{(k+2)} + BP_{(k+1)} + CP_{(k)}$. Furthermore, each RFDE model is derived directly from the coefficients of a traditional three-compartment pharmacokinectic exponential equation. Based on this study, third-order RFDE models can have identical accuracy as three-compartment exponential models. In this particular application, it should be noted that each RFDE model required only three coefficients whereas each exponential model required six. Also, there was overall less patient-to-patient variability of the coefficients of the RFDE models. In general, it appears that RFDE models uniquely allow for predicting subsequent drug levels from preexisting ones. However, RFDE models require initial conditions whereas exponential models do not. Additional studies and applications of exponentially-derived RFDE pharmacokinetic models may be warranted. J Pharm Sci 95:810–820, 2006

Keywords: recursive finite difference equation; propofol; pharmacokinetic; modeling

INTRODUCTION

Finite difference equations have been used in modeling such diverse topics as economics and human behavior.[1–3] Because of their recursive properties, they may be useful in pharmacokinetic modeling as well. Therefore, ongoing metabolism, elimination, and redistribution can be taken into effect when modeling sequential serum levels of a single bolus.

Propofol is an ultra-short acting sedative-hypnotic which is commonly used for the induction of general anesthesia. Propofol allows for rapid awakening from anesthesia and has few adverse effects. Small doses of propofol are also used for

Glen M. Atlas is an Associate Professor, Adjunct Member of the Graduate Faculty, and Adjunct Associate Professor; Sunil Dhar is an Associate Professor.

Correspondence to: Glen M. Atlas (Telephone: 973-972-5006/5254; Fax: 973-972-4172; E-mail: atlasgm@umdnj.edu)

Journal of Pharmaceutical Sciences, Vol. 95, 810–820 (2006)

brief episodes of sedation. Continuous infusions are frequently employed for longer periods of sedation. Propofol infusions are also employed as adjuncts for general anesthesia and in "total intravenous anesthesia."[4]

The purpose of this study was to assess the utility of recursive finite difference equations (RFDEs) as a tool for modeling serum propofol levels following a single induction dose. In addition, this modeling scheme is derived directly from a traditional three-compartment exponential equation.

Figure 1 illustrates how an RFDE may be useful in pharmacokinectic modeling. After the initial bolus of propofol is administered through an intravenous catheter, the drug is then "pumped" through the heart into the arterial tree. Following metabolism, redistribution, and elimination, from the arterial circulation, these processes are then repeated after the remaining propofol reenters the venous circulation.

Thus, following the administration of a propofol bolus, serum levels are noted to be monotonically decreasing. Average serum levels, for the 16 subjects examined in this study, are illustrated in Figure 2.[5]

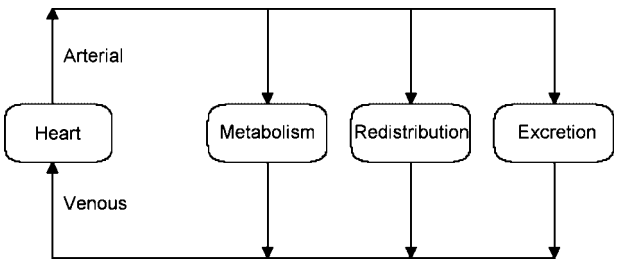

Figure 1. Conceptual diagram illustrating the recursive nature of pharmacokinetics. Arterial propofol blood levels are metabolized, excreted, and redistributed. After passing through the heart, the venous drug concentrations become the subsequent arterial drug concentrations. Ultimately, the remaining propofol is again passed to the venous system. Thus, RFDEs may be useful for modeling this recursive pharmacologic phenomena.

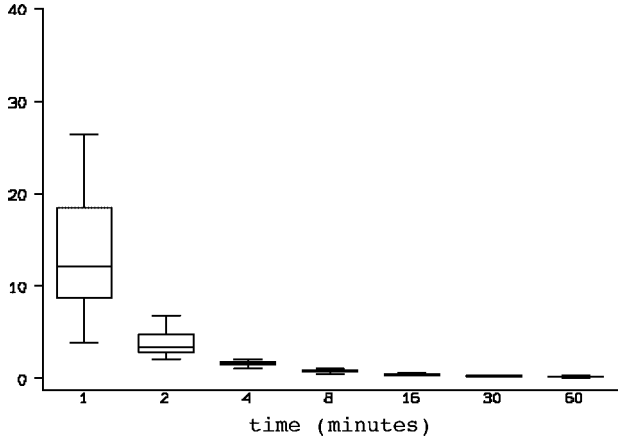

Figure 2. The above graph documents the mean and standard deviation of propofol serum levels, over time, for the 16 subjects. Note that these measured levels monotonically decreased.

A BRIEF OVERVIEW OF RFDEs IN PHARMACOKINETIC MODELING OF A BOLUS

The familiar concepts, of zero and first order pharmacokinetics, can be represented with RFDEs. As an example of modeling first order pharmacokinetics of a bolus, a constant fraction, C_1, of a serum concentration, $P_{(k)}$, may be metabolized, eliminated, and/or redistributed every k^{th} unit of time. With $0 < C_1 < 1$, this would be represented as:

$$P_{(k+1)} = C_1 P_{(k)} \qquad k = 1, 2, 3 \ldots \tag{1}$$

Whereas, with zero order pharmacokinetics, a constant amount of a serum level, C_2, may be removed every kth unit of time. With $0 < C_2 < P_{(k)}$, this could be modeled as:

$$P_{(k+1)} = P_{(k)} - C_2 \qquad k = 1, 2, 3 \ldots \tag{2}$$

Using RFDEs, these two pharmacokinetic properties can also be modeled simultaneously:

$$P_{(k+1)} = C_1 P_{(k)} - C_2 \qquad k = 1, 2, 3 \ldots \tag{3}$$

Assuming that $P_{(k)}$ represents a monotonically decreasing serum level, then a solution to Equation (3) can be shown:[2]

$$P_{(k+1)} = C_1^k (P_1 - P^*) + P^* \qquad k = 1, 2, 3 \ldots \tag{4}$$

It should also be noted that the recursive relationship, in Equation (4), can also be expressed as:

$$P_{(k)} = C_1^{(k-1)} (P_1 - P^*) + P^* \qquad k = 1, 2, 3 \ldots \tag{4.1}$$

Where P_1 represents the initial serum level of medication and $P^* = C_2/(1 - C_1)$. Assuming only first order pharmacokinetics, then $C_2 = 0$ and consequently $P^* = 0$. Under this circumstance, $P_{(k+1)}$ is then:

$$P_{(k+1)} = C_1^k P_1 \qquad k = 1, 2, 3 \ldots \tag{5}$$

This can also be similarly expressed as:

$$P_{(k)} = C_1^{(k-1)} P_1 \qquad k = 1, 2, 3 \ldots \tag{5.1}$$

It should be noted that this would represent a single-compartment model. A more complex situation, analogous to a three-compartment model, can be represented as:

$$P_{(k+3)} = AP_{(k+2)} + BP_{(k+1)} + CP_{(k)} \qquad k = 1, 2, 3 \ldots \tag{6}$$

The general solution to the above RFDE, assuming the stated characteristics as before, (see Appendix A) is:[1–3]

$$P_{(k)} = \alpha\beta^k + \gamma\delta^k + \varepsilon\zeta^k \tag{7}$$

Similarly, using a traditional three-compartment exponential model, serum levels of a pharmaceutical are typically represented as:

$$Q_{(k)} = a\mathrm{e}^{-bk} + c\mathrm{e}^{-dk} + f\mathrm{e}^{-gk} \tag{8}$$

For third-order RFDEs, as in Equation (6), it is necessary to determine their initial conditions: P_1, P_2, and P_3 from either their general solution or their parent exponential equation. With these, each RFDE can then determine its respective subsequent values.

It is frequently necessary to calculate area under the concentration versus time curve, or AUC, when determining pharmacologic clearance. This can be done by evaluating the integral:

$$\mathrm{AUC} = \int_1^n P_{(k)}\, \mathrm{d}k \tag{8.1}$$

Where n represents the total number of serum levels modeled. In determining Equation (8.1), numerical approximation techniques can be readily used as well as common integration methods.

Pharmacologic half-life, for first-order RFDEs such as Equation (4.1), can be found by solving the following equation for k:

$$\frac{P_1}{2} = C_1^{(k-1)}(P_1 - P^*) + P^* \tag{8.2}$$

For higher-ordered RFDEs, half-life can be determined using numerical or graphical techniques.

As will be shown later, values computed from either the RFDE model or exponential model, will be identical on a subject-specific basis. This applies not only to the modeled serum values, $P_{(k)}$ and $P_{(k+3)}$, but also to AUC and half-life values as well. This occurs since the coefficients of RFDE models are derived directly from those of their respective parent exponential model.

NOMENCLATURE

$P_{(k+3)}$ refers to the values generated from the RFDE:

$$P_{(k+3)} = AP_{(k+2)} + BP_{(k+1)} + CP_{(k)} \qquad k = 1, 2, 3 \ldots \tag{9}$$

Whereas $P_{(k)}$ is the general solution to Equation (9):

$$P_{(k)} = \alpha\beta^k + \gamma\delta^k + \varepsilon\zeta^k \tag{10}$$

It should be noted that the solution to Equation (9), $P_{(k+3)}$, and the solution to Equation (10), $P_{(k)}$, are numerically equivalent. The term: $k = 1, 2, 3 \ldots$ denotes that values obtained from a RFDE must be calculated sequentially. This sequential process is unnecessary when using the general solution.

$Q_{(k)}$ refers to solutions obtained for the three-compartment exponential model:

$$Q_{(k)} = a\mathrm{e}^{-bk} + c\mathrm{e}^{-dk} + f\mathrm{e}^{-gk} \tag{11}$$

Deriving Each RFDE Model From its Respective Parent Exponential Model

A traditional three-compartment exponential model is based on the following equation:

$$Q_{(k)} = a\mathrm{e}^{-bk} + c\mathrm{e}^{-dk} + f\mathrm{e}^{-gk} \tag{12}$$

Equating Equation (12) to the general solution of the finite difference model:

$$\alpha\beta^k + \gamma\delta^k + \varepsilon\zeta^k = a\mathrm{e}^{-bk} + c\mathrm{e}^{-dk} + f\mathrm{e}^{-gk} \tag{13}$$

The above equality is valid under the following conditions:

$$\alpha = a,\ \gamma = c,\ \text{and}\ \varepsilon = f \tag{14}$$

and

$$\beta = \mathrm{e}^{-b},\ \delta = \mathrm{e}^{-d},\ \zeta = \mathrm{e}^{-g} \tag{15}$$

Substituting the above relations, into the RFDE model from Appendix A, yields:

$$P_{(k+3)} = AP_{(k+2)} + BP_{(k+1)} + CP_{(k)} \qquad k = 1, 2, 3 \ldots \tag{16}$$

 DOI 10.1002/jps

Where

$$A = (\beta + \zeta + \delta) = (e^{-b} + e^{-g} + e^{-d}) \quad (17)$$

$$\begin{aligned} B &= -(\beta\zeta + \beta\delta + \delta\zeta) \\ &= -(e^{-b} \cdot e^{-g} + e^{-b} \cdot e^{-d} + e^{-d} \cdot e^{-g}) \\ &= -(e^{-(b+g)} + e^{-(b+d)} + e^{-(d+g)}) \end{aligned} \quad (18)$$

and

$$C = (\beta\delta\zeta) = (e^{-b} \cdot e^{-d} \cdot e^{-g}) = e^{-(b+d+g)} \quad (19)$$

Thus, A, B, C, the coefficients of each RFDE model, are obtained *directly* from those of their respective parent exponential models. Therefore, each RFDE model will have the same accuracy as the "curve-fitted" parent exponential model from which it was derived.

In this particular application, each RFDE was based on three coefficients. Whereas each exponential model, as well as the general solution of each RFDE, required six. Thus, the RFDE model is a more "compact" representation.

However, it is necessary to determine the initial conditions: P_1, P_2, and P_3 for each RFDE. These can be obtained from either their general solution or their respective parent exponential model. With these initial values, each RFDE can then determine subsequent subject-specific propofol serum levels.

A numerical example of this process is illustrated in Appendix B.

METHODS: DATA ACQUISITION AND ANALYSIS

The propofol serum levels, for this analysis, were obtained from prior research and supplied directly to the authors from Astra-Zeneca pharmaceuticals. In the initial IRB-approved study, volunteers, age 19 through 65, who had received informed consent, had been given an intravenous propofol bolus of 2 mg/kg. Venous serum levels of propofol were then measured sequentially at: 1, 2, 4, 8, 16, 30, and 60 min.[5] These data are shown in Table 1.

These same subjects had later received continuous IV propofol infusions. The original study obtained serum levels, during this infusion, which were not analyzed in the present study.

In addition, the original study examined older subjects age >65 years as well. These subjects received a smaller intravenous induction dose of 1 mg/kg. These results were also not assessed in the present study.

Furthermore, the purpose of the original study was to compare propofol pharmacokinetics with, versus without, disodium edetate (EDTA). The addition of EDTA has been shown to significantly

Table 1. Measured Serum Propofol Levels, for Each of the 16 Subjects, at the Specified Times

	Subject 101	105	202	207	102	108	201	205
Propofol level min 1	18.0000	18.8000	34.5000	26.4000	9.8000	3.8900	8.8600	8.5900
2	3.6200	4.5100	6.8400	5.1000	2.9500	2.1200	3.5500	2.4000
4	1.3300	1.7500	2.0400	2.0900	1.2500	1.7700	1.6500	1.0200
8	0.6760	0.8620	0.8620	0.9720	0.5830	1.1400	0.9490	0.4140
16	0.3380	0.4430	0.4480	0.4230	0.5920	0.5770	0.4830	0.2460
30	0.2040	0.2710	0.2700	0.2770	0.1730	0.3080	0.2850	0.1370
60	0.1100	0.1120	0.2040	0.1910	0.1190	0.2500	0.1540	0.1160
	Subject 103	106	204	208	104	107	203	206
Propofol level min 1	14.4000	5.3600	18.1000	8.4400	16.8000	9.0700	19.2000	9.6200
2	3.1500	2.6100	4.8800	2.7000	4.9200	3.3900	4.2600	3.2600
4	1.7900	1.3200	1.9800	1.5200	1.6300	1.5200	1.7500	1.8700
8	0.8500	0.7590	0.7140	0.8490	0.6970	0.9090	1.0600	0.9850
16	0.5250	0.3860	0.1800	0.4140	0.3690	0.4150	0.3980	0.4690
30	0.3430	0.2560	0.1300	0.2130	0.2730	0.3800	0.2050	0.2350
60	0.2440	0.2010	0.0804	0.1410	0.1510	0.1830	0.1370	0.1310

reduce bacterial growth within the commercial formulation of propofol. It should be noted that propofol is prepared as an emulsion which requires this, or a similar, antimicrobial additive.[4]

Our data are based on an analysis of only those subjects, age 19–65 years, who had received a single induction dose of 2 mg/kg intravenous propofol with EDTA as an additive. Currently, this formulation is in clinical use in the United States.

This retrospective analysis, of existing data, was deemed exempt from requiring IRB approval at both authors' institutions. Data from a total of the 16 original subjects met inclusion criteria for this present analysis.

Curve fitting was performed using MATHCAD (Mathsoft Cambridge, MA). For each parent exponential model, this was based upon (see Appendix B):

$$Q_{(k)} = a\mathrm{e}^{-bk} + c\mathrm{e}^{-dk} + f\mathrm{e}^{-gk} \qquad (20)$$

Specifically, a minimum error function, predicated upon the Levenberg–Marquardt algorithm, was used.[6,7] Iterations were performed until the mean sum of the squared error (MSSE) was on the order of 10^{-3} or less:

$$\mathrm{MSSE} = \frac{1}{n}\sum_{j=1}^{n}\left(s_j - \{a\mathrm{e}^{-bj} + c\mathrm{e}^{-dj} + f\mathrm{e}^{-gj}\}\right)^2 \quad (21)$$

Where s_j represents each *measured* propofol serum level and $n = 7$ for each subject's seven measurements. This process was repeated for each subject-specific parent exponential model.

Following the determination of the exponential coefficients, those coefficients, for each RFDE model, were then calculated using the method described in Equation (12) through Equation (19). *(See: Deriving each RFDE model from its respective parent exponential model.)* The flowchart in Figure 3 summarizes these processes.

Note that curve fitting could also have been done with respect to the coefficients of the general solution of the finite difference equation, $P_{(k)}$. This technique would have ultimately yielded identical results for the coefficients of the RFDEs.

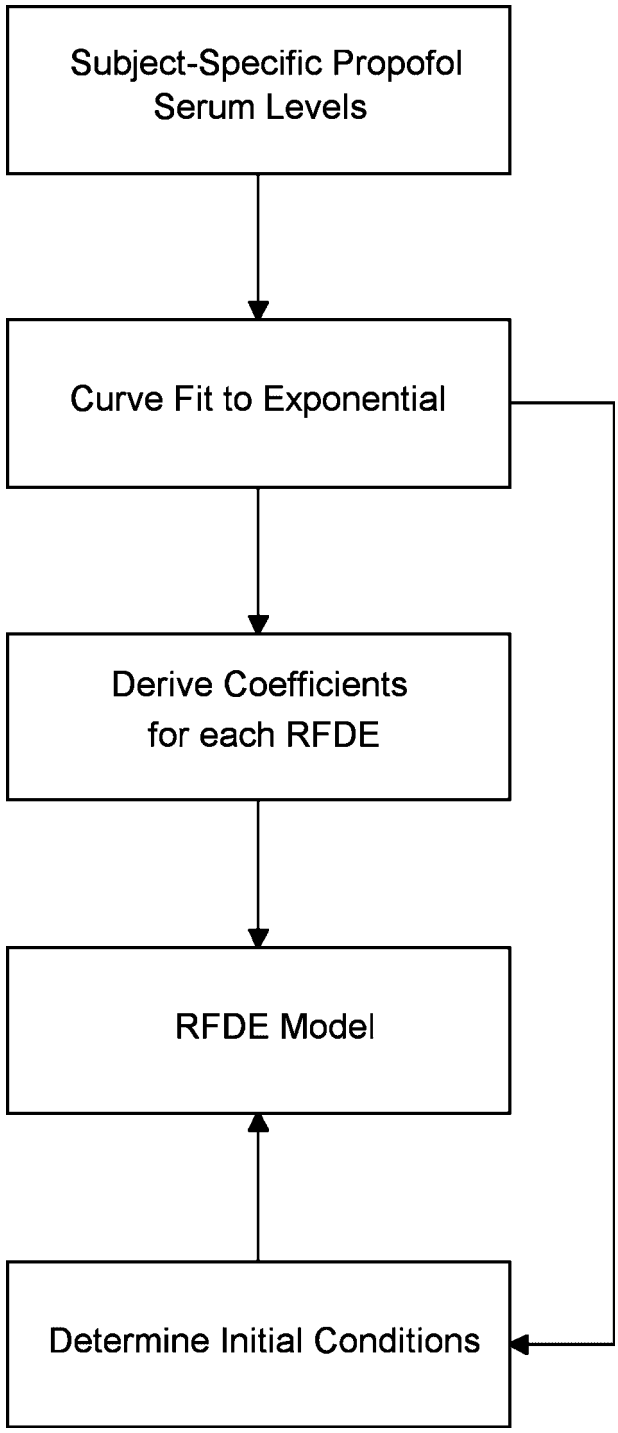

Figure 3. This flowchart depicts how the RFDE models were derived from their respective parent exponential equations.

RESULTS

The coefficients, for each of the 16 subject-specific exponential and RFDE models, are shown in Table 2. These coefficients are also displayed graphically in Figures 4A and 4B. On initial inspection, each RFDE model required only three coefficients whereas each exponential model required six. Thus, the RFDE models, in general, may be thought of as being "more straightforward" than their respective parent exponential

 DOI 10.1002/jps

Table 2. The Mean Sum of the Squared Error (MSSE) is Identical for Each Subject-Specific Exponential Model and its Corresponding RFDE

	Subject 101	105	202	207	102	108	201	205
Coefficient *a*	146.157	130.332	259.421	266.498	108.114	152.671	28.434	65.868
b	2.24	2.139	2.155	2.479	3.016	4.613	1.491	2.391
c	0.424	0.663	0.508	0.43	0.837	0.241	0.506	0.285
d	0.023	0.03	0.017	0.014	0.038	0.0001177	0.02	0.017
f	2.625	3.802	5.411	4.732	7.139	2.409	2.374	3.304
g	0.261	0.302	0.318	0.26	0.658	0.121	0.19	0.371
Coefficient *A*	1.854	1.828	1.827	1.838	1.53	1.896	2.032	1.765
B	−0.939	−0.919	−0.914	−0.905	−0.571	−0.905	−1.217	−0.832
C	0.08	0.085	0.083	0.064	0.024	0.00879	0.183	0.062
Mean SSE	1.74E-05	3.21E-07	3.55E-04	1.71E-05	4.85E-03	4.48E-04	9.99E-07	2.51E-04
	Subject 103	106	204	208	104	107	203	206
Coefficient *a*	498.72	12.388	125.081	57.026	77.943	32.487	138.296	70.211
b	3.856	1.278	2.219	2.251	1.776	1.578	2.12	2.4
c	0.613	0.299	0.163	0.357	0.478	0.493	0.176	0.537
d	0.016	0.006607	0.011	0.016	0.019	0.015	0.004219	0.025
f	4.507	1.919	5.818	2.526	4.404	2.309	2.811	3.423
g	0.329	0.175	0.292	0.192	0.342	0.208	0.148	0.228
Coefficient *A*	1.725	2.111	1.845	1.915	1.861	2.004	1.978	1.862
B	−0.744	−1.345	−0.927	−1.003	−0.983	−1.171	−1.082	−0.937
C	0.015	0.232	0.08	0.086	0.118	0.165	0.103	0.07
Mean SSE	3.35E-04	9.33E-08	4.09E-05	1.14E-04	2.10E-06	1.19E-03	2.95E-04	1.54E-04

A, *B*, and *C* represent the coefficients for the RFDE models. Whereas *a*, *b*, *c*, *d*, *f*, and *g* are the coefficients for the exponential models.

models. However, the RFDE models required the specification of their initial conditions. These were readily obtained from either their parent exponential model or their general solution.

The coefficients, of each RFDE model, were derived directly from each of their respective parent exponential models. Thus, the MSSE, for each RFDE model, is identical to that of the exponential model from which it was derived.

Furthermore, on graphical inspection, of the coefficients of both models, there is less overall patient-to-patient variation of the three coefficients: *A*, *B*, and *C*, comprising the RFDE models.

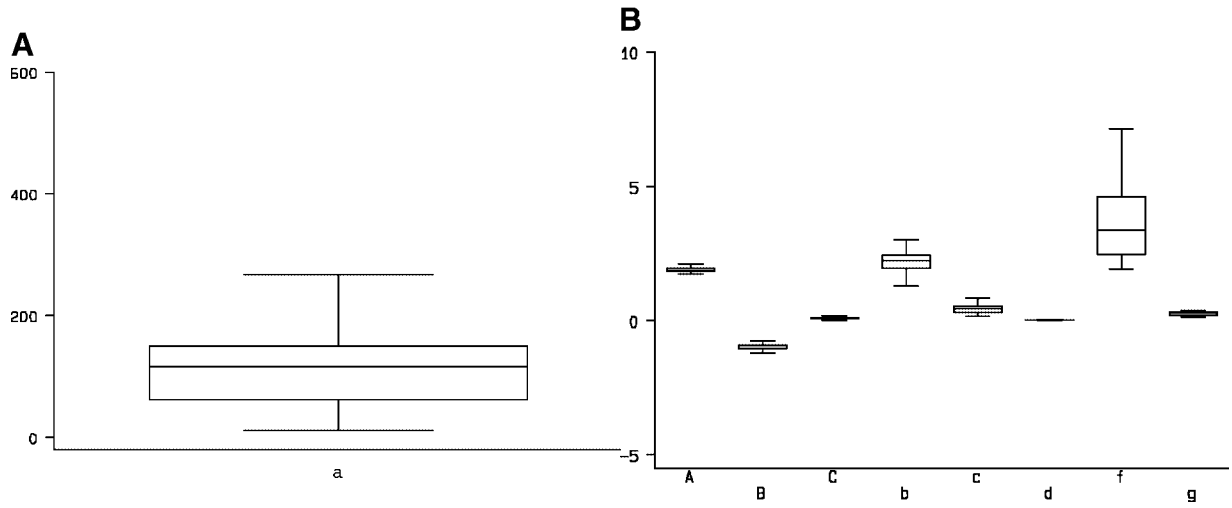

Figure 4. (A) represents coefficient *a* of the exponential models. Whereas (B) represents coefficients *A*, *B*, and *C* of the RFDE models as well as coefficients *b*, *c*, *d*, *f*, and *g* of the exponential models. Overall, there is less patient-to-patient variability of *A*, *B*, and *C* of the RFDE models.

Table 3. Minimum and Maximum Values of the Partial Derivatives for Equations (22–24)

	$\frac{\partial A}{\partial b}$	$\frac{\partial A}{\partial d}$	$\frac{\partial A}{\partial g}$
Minimum	-0.2786	-0.9999	-0.8860
Maximum	-9.922×10^{-3}	-0.9630	-0.5180
	$\frac{\partial B}{\partial b}$	$\frac{\partial B}{\partial d}$	$\frac{\partial B}{\partial g}$
Minimum	0.0187	0.546	0.5240
Maximum	0.5106	1.1107	1.0678
	$\frac{\partial C}{\partial b} = \frac{\partial C}{\partial d} = \frac{\partial C}{\partial g}$		
Minimum	-0.2323		
Maximum	-8.7902×10^{-3}		

These explain the overall reduction, in patient-to-patient variability, seen in the coefficients of the RFDEs. This is in comparison to the coefficients of their respective parent exponential models. It should be noted that, for negative values, *minimum* refers to the negative value with the greatest magnitude. Whereas for positive values, *maximum* refers to the greatest positive value.

This general decrease in patient-to-patient variability, of the coefficients of the RFDE models, is explained by use of the chain rule (see Appendix C):[8]

$$\mathrm{d}A = \frac{\partial A}{\partial b}\mathrm{d}b + \frac{\partial A}{\partial d}\mathrm{d}d + \frac{\partial A}{\partial g}\mathrm{d}g \tag{22}$$

$$\mathrm{d}B = \frac{\partial B}{\partial b}\mathrm{d}b + \frac{\partial B}{\partial d}\mathrm{d}d + \frac{\partial B}{\partial g}\mathrm{d}g \tag{23}$$

$$\mathrm{d}C = \frac{\partial C}{\partial b}\mathrm{d}b + \frac{\partial C}{\partial d}\mathrm{d}d + \frac{\partial C}{\partial g}\mathrm{d}g \tag{24}$$

It should be noted that A, B, and C are derived from only b, d, and g of the exponential models.

Table 4. A Comparison of the RFDE and Exponential Modeling Schemes in This Application

	RFDE Model	Exponential Model
Number of coefficients	3	6
Patient-to-patient coefficient variability	Lesser	Greater
Ability to predict "present" levels from "past"	Yes	No
Mean sum of the square error	Identical	Identical
Need to specify initial conditions	Yes	No

The "maximum patient-to-patient change" of each coefficient of the RFDEs, can be summarized with the triangle inequality:[9]

$$|\mathrm{d}A| < \{|\mathrm{d}b| + |\mathrm{d}d| + |\mathrm{d}g|\} \tag{25}$$

$$|\mathrm{d}B| < 2\{|\mathrm{d}b| + |\mathrm{d}d| + |\mathrm{d}g|\} \tag{26}$$

$$|\mathrm{d}C| < \{|\mathrm{d}b| + |\mathrm{d}d| + |\mathrm{d}g|\} \tag{27}$$

More importantly, on numerical evaluation, the patient-to-patient variability of coefficients A, B, and C was found to be considerably smaller than what the above inequalities "allow." This is demonstrated, in Table 3, by evaluating the numerical values for the partial derivatives in Equations (22), (23), and (24).

As an example, using Table 1 subject 101, Equations (22–24) establish dA, dB, and dC, respectively for this case:

$$\mathrm{d}A = (-0.106)\mathrm{d}b + (-0.977)\mathrm{d}d + (-0.77)\mathrm{d}g \tag{28}$$

Table 5. A Numerical Comparison of the Measured Serum Propofol Concentrations to Those of Their RFDE, General Solution, and Exponential Models

	Measured Serum	RFDE $P_{(k+3)}$	General Solution $P_{(k)}$	Exponential $Q_{(k)}$
Propofol level min 1	18.0000	17.9960	17.9960	17.9960
2	3.6200	3.6190	3.6190	3.6190
4	1.3300	1.3300	1.3300	1.3300
8	0.6760	0.6790	0.6780	0.6780
16	0.3380	0.3340	0.3340	0.3340
30	0.2040	0.2140	0.2140	0.2140
60	0.1100	0.1070	0.1070	0.1070

This is based upon subject 101.

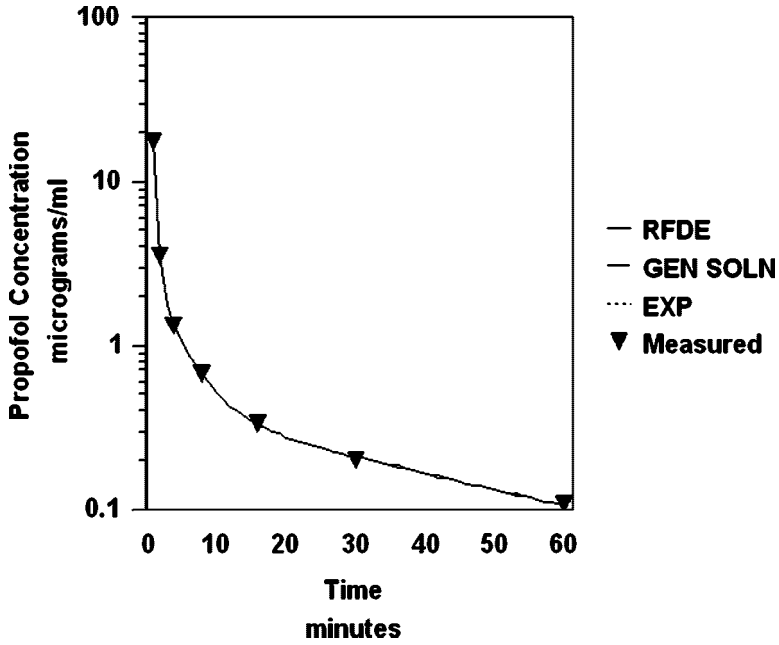

Figure 5. A graphical representation of the measured propofol concentrations as well as the RFDE, general solution, and exponential models. Note that the lines for the models overlap. This is from subject 101.

$$dB = (-0.186)db + (-0.857)dd + (-0.835)dg \quad (29)$$

$$dC = (-0.08)[db + dd + dg] \quad (30)$$

By using the triangle inequality, absolute values for dA, dB, and dC can then be assessed:

$$|dA| \leq (0.106)|db| + (0.977)|dd| + (0.77)|dg| \quad (31)$$

$$|dB| \leq (0.186)|db| + (0.857)|dd| + (0.835)|dg| \quad (32)$$

$$|dC| \leq (0.08)[|db| + |dd| + |dg|] \quad (33)$$

This exemplifies why coefficients A, B, and C, from the RFDE models, have overall less patient-to-patient variation than the coefficients from the exponential models.

In addition, the changes in the patients' initial conditions, of the RFDE models, contributes to the decreased patient-to-patient variability observed in coefficients A, B, and C.

This study has also shown that RFDE modeling also has the unique property that "present" propofol serum levels can be determined from their "past" levels.

Table 4 summarizes and compares the different characteristics of the exponential and RFDE modeling schemes.

DISCUSSION

The recursive nature of finite difference equations seems to make them well-suited for modeling pharmacokinetics.[1–3] This appears to be particularly appropriate in the unique situation of single induction-dose propofol serum levels.

It should be noted that the exponential models, and the general solutions of the finite difference equations, are both summations of power functions. In addition, both the general solution of the finite difference equations and the RFDEs, are derived directly from their respective parent exponential models.

RFDE modeling has demonstrated that "present" serum levels of propofol can be determined from their "previous" levels in a sequential manner. Each RFDE model is also more "compact" in that fewer coefficients are needed. This is in comparison to those of their general solution and parent exponential models.

The MSSE has shown that both of these models are reasonably accurate. Furthermore, since the

coefficients, of each RFDE, are derived directly from their respective parent exponential models, both modeling schemes yield identical accuracy on a subject-specific basis.

Perhaps the most striking aspect of the RFDE models is the overall decreased patient-to-patient variability of their coefficients. This is in comparison to those of the exponential models. An analysis using the chain rule and triangle inequality explains and supports this observation.

Furthermore, the decrease in patient-to-patient variability, of RFDE modeling, may make this technique desirable in comparing pharmacokinectics across different agents and/or different patient populations.

Furthermore, slightly different RFDEs, such as those based on *inhomogeneous* difference equations, may be useful for modeling infusion-based pharmacokinetics. Whereas this present study used *homogeneous* RFDEs to model bolus-based pharmacokinetics. It should be noted that inhomogeneous difference equations have the form:[1]

$$P_{k+n} + A_n P_{k+n-1} + \ldots + A_1 P_{k+1} = R \qquad (34)$$

Where R is non-zero. This is in contradistinction to homogeneous difference equations were R is zero.

Therefore, RFDE models may be useful in computer-controlled infusions as well as simula-tions.

However, RFDE models cannot "stand alone." They require the specification of their initial conditions. Whereas both the exponential and general solution do not. Nonetheless, these values can be obtained directly from their parent exponential model or general solution.[1–3]

CONCLUSION

A technique to model induction-dose propofol pharmacokinetics, with exponentially-derived RFDEs, has been presented. Additional assessment and comparisons, of RFDE pharmacokinetic modeling, would be necessary to further establish this technique. Other "single dose" medications, including additional anesthesia induction agents, may possibly be modeled with similar RFDE techniques.

As stated, the coefficients of the RFDEs have been derived directly from their respective parent exponential models. Thus, the MSSE is identical for both the RFDE and exponential modeling schemes.

The apparent "benefit" to RFDEs is that these pharmacokinetic models may be more "compact" as compared to traditional exponential models. Furthermore, there appears to be overall less patient-to-patient variability, when comparing the coefficients of the RFDEs, to those of their parent exponential models.

However, RFDEs require the specification of their initial conditions. These can be determined from either their respective parent exponential model or their general solution. Additional research and applications of this modeling technique appear warranted. Further comparisons, of RFDEs to exponential models, may promote more insight into their potential utility.

APPENDIX A

A case-specific solution, to a third-order homogeneous finite difference equation, with constant coefficients, can be obtained. In this particular application, it is assumed that propofol serum levels are monotonically decreasing. Thus, there is no oscillatory behavior noted as these levels consistently diminish.

The RFDE is defined with the following form:

$$P_{(k+3)} = AP_{(k+2)} + BP_{(k+1)} + CP_{(k)} \qquad k = 1, 2, 3 \ldots \qquad (1A)$$

It should be noted that a solution to a first-order homogeneous finite difference equation:

$$z_{(k+1)} = C_1 z_{(k)} \qquad k = 1, 2, 3 \ldots \qquad (2A)$$

has a solution which has the form:[1,2]

$$z_{(k+1)} = C_2 C_1^k \qquad k = 1, 2, 3 \ldots \qquad (3A)$$

The particular solutions we are modeling would require that $C_2 > 0$ and $0 < C_1 < 1$ for a monotonically decreasing function with all values of $z_{(k)} \geq 0$.

Therefore, the general solution to Equation (1A) will have a form consisting of a superposition of solutions resembling Equation (3A):[1–3]

$$P_{(k)} = \alpha\beta^k + \gamma\delta^k + \varepsilon\zeta^k \qquad (4A)$$

The solution to Equation (1A), using the form of Equation (4A), requires the definition of a third-order auxiliary or characteristic equation:[1–3]

$$(M - \beta)(M - \delta)(M - \zeta) = 0 \qquad (5A)$$

 DOI 10.1002/jps

Expanding (5A) and collecting terms yields:

$$M^3 + (-\beta - \zeta - \delta)M^2 + (\beta\zeta + \beta\delta + \delta\zeta)M - \beta\delta\zeta = 0 \tag{6A}$$

Rearranging:

$$M^3 = (\beta + \zeta + \delta)M^2 - (\beta\zeta + \beta\delta + \delta\zeta)M + \beta\delta\zeta \tag{7A}$$

The solution will then take on the requisite form as:

$$P_{(k+3)} = (\beta + \zeta + \delta)P_{(k+2)} - (\beta\zeta + \beta\delta + \delta\zeta)P_{(k+1)} + (\beta\delta\zeta)P_{(k)}. \qquad k = 1, 2, 3 \ldots \tag{8A}$$

Therefore, by defining:

$$A = (\beta + \zeta + \delta) \tag{9A}$$

and

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

and

$$C = (\beta\delta\zeta) \tag{11A}$$

Equation (8A) will then take on the form of Equation (1A):

$$P_{(k+3)} = AP_{(k+2)} + BP_{(k+1)} + CP_{(k)} \qquad k = 1, 2, 3 \ldots \tag{12A}$$

APPENDIX B

The following is a numerical example, which is based upon Table 1 subject 101. Using the exponential model from Equation (8):

$$Q_{(k)} = a\mathrm{e}^{-bk} + c\mathrm{e}^{-dk} + f\mathrm{e}^{-gk} \tag{1B}$$

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 conditions Equations (14) and (15):

$$P_{(k)} = \alpha\beta^k + \gamma\delta^k + \varepsilon\zeta^k \tag{2B}$$

Where

$$\alpha = a,\ \gamma = c,\ \text{and}\ \ \varepsilon = f\ \text{and}\ \beta = \mathrm{e}^{-b},\ \delta = \mathrm{e}^{-d},\ \zeta = \mathrm{e}^{-g} \tag{3B}$$

The coefficients, for the RFDE, $P_{(k+3)}$, can then be determined by first calculating A, B, and C from Equations (9A), (10A), and (11A), respectively using Equation (15):

$$\begin{aligned} A &= (\beta + \zeta + \delta) = (\mathrm{e}^{-b} + \mathrm{e}^{-g} + \mathrm{e}^{-d}) \\ &= (\mathrm{e}^{-2.24} + \mathrm{e}^{-0.261} + \mathrm{e}^{-0.023}) = 1.854 \end{aligned} \tag{4B}$$

$$\begin{aligned} B &= -(\beta\zeta + \beta\delta + \delta\zeta) \\ &= -(\mathrm{e}^{-(b+g)} + \mathrm{e}^{-(b+d)} + \mathrm{e}^{-(d+g)}) \\ &= -(\mathrm{e}^{-2.501} + \mathrm{e}^{-2.263} + \mathrm{e}^{-0.284}) = -0.939 \end{aligned} \tag{5B}$$

$$\begin{aligned} C &= (\beta\delta\zeta) = (\mathrm{e}^{-b} \cdot \mathrm{e}^{-d} \cdot \mathrm{e}^{-g}) \\ &= \mathrm{e}^{-(b+d+g)} = \mathrm{e}^{-(2.24+0.023+0.261)} = 0.08 \end{aligned} \tag{6B}$$

The RFDE is then expressed as in Equation (12A):

$$P_{(k+3)} = (1.854)P_{(k+2)} - (0.939)P_{(k+1)} + (0.08)P_{(k)} \qquad k = 1, 2, 3 \ldots \tag{7B}$$

It should be noted that the initial conditions: $P_{(3)}$, $P_{(2)}$, and $P_{(1)}$ are determined from either Equations (1B) or (2B). Thus, Equations (1B), (2B), and (7B) yield numerically identical results for the entire time period. This is illustrated in both Table 5 and Figure 5. Minor numerical differences are attributable to rounding.

The initial conditions, for this case, are: $P_1 = 17.996$, $P_2 = 3.619$, and $P_3 = 1.772$.

APPENDIX C

In order to assess the decrease in patient-to-patient variability, of the coefficients of the RFDE models, as compared to those of the exponential models from which they are derived, it is important to first note that coefficients b, d, and g are all numerically nonnegative and nonzero. Therefore:

$$\begin{aligned} &0 < \left|-\mathrm{e}^{-b}\right| < 1 \quad \text{and} \\ &0 < \left|-\mathrm{e}^{-d}\right| < 1 \quad \text{and}\ 0 < |-\mathrm{e}^{-g}| < 1 \end{aligned} \tag{1C}$$

The variation in coefficient A, expressed as $\mathrm{d}A$, can then be stated using the chain rule:[8]

$$\mathrm{d}A = \frac{\partial A}{\partial b}\mathrm{d}b + \frac{\partial A}{\partial d}\mathrm{d}d + \frac{\partial A}{\partial g}\mathrm{d}g \tag{2C}$$

Realizing that: $\frac{\partial A}{\partial b} = -\mathrm{e}^{-b}$, $\frac{\partial A}{\partial d} = -\mathrm{e}^{-d}$, and $\frac{\partial A}{\partial g} = -\mathrm{e}^{-g}$. Equation (2C) can then be expressed as:

$$\mathrm{d}A = [-\mathrm{e}^{-b}]\mathrm{d}b + [-\mathrm{e}^{-d}]\mathrm{d}d + [-\mathrm{e}^{-g}]\mathrm{d}g \tag{3C}$$

Under these circumstances, the triangle inequality will be such that the absolute value of the sum will be less than the sum of the absolute values.[9] This and Equation (1C) therefore yield the following valid expression:

$$|\mathrm{d}A| \leq \{\left|\mathrm{e}^{-b}\mathrm{d}b\right| + \left|\mathrm{e}^{-d}\mathrm{d}d\right| + |\mathrm{e}^{-g}\mathrm{d}g|\} \qquad (4\mathrm{C})$$

Therefore:

$|\mathrm{d}A| < \{|\mathrm{d}b| + |\mathrm{d}d| + |\mathrm{d}g|\}$.

Similarly, the patient-to-patient variation, in coefficient B, is:

$$\mathrm{d}B = \frac{\partial B}{\partial b}\mathrm{d}b + \frac{\partial B}{\partial d}\mathrm{d}d + \frac{\partial B}{\partial g}\mathrm{d}g \qquad (5\mathrm{C})$$

In this case: $\frac{\partial B}{\partial b} = \mathrm{e}^{-(b+g)} + \mathrm{e}^{-(b+d)}$ and $\frac{\partial B}{\partial d} = e^{-(b+d)} + \mathrm{e}^{-(d+g)}$ and $\frac{\partial B}{\partial g} = \mathrm{e}^{-(b+g)} + \mathrm{e}^{-(d+g)}$. Equation (5C) can then be expressed as:

$$\begin{aligned}\mathrm{d}B = {} & \mathrm{e}^{-b}\{[\mathrm{e}^{-d}] + [\mathrm{e}^{-g}]\}\mathrm{d}b + \mathrm{e}^{-d}\{[\mathrm{e}^{-b}] \\ & + [\mathrm{e}^{-g}]\}\mathrm{d}d + \mathrm{e}^{-g}\{[\mathrm{e}^{-b}] + [\mathrm{e}^{-d}]\}\mathrm{d}g\end{aligned} \qquad (6\mathrm{C})$$

Again, use of the triangle inequality yields:

$$\begin{aligned}|\mathrm{d}B| \leq \{ & \left|\mathrm{e}^{-b}\{[\mathrm{e}^{-d}] + [\mathrm{e}^{-g}]\}\mathrm{d}b\right| + \left|\mathrm{e}^{-d}\{[\mathrm{e}^{-b}] + \right. \\ & \left. [\mathrm{e}^{-g}]\}\mathrm{d}d\right| + \left|\mathrm{e}^{-g}\{[\mathrm{e}^{-b}] + [\mathrm{e}^{-d}]\}\mathrm{d}g\right|\}\end{aligned} \qquad (7\mathrm{C})$$

Equation (7C) can then be expressed as:

$$|\mathrm{d}B| < 2\{\left|\mathrm{e}^{-b}\mathrm{d}b\right| + \left|\mathrm{e}^{-d}\mathrm{d}d\right| + |\mathrm{e}^{-g}\mathrm{d}g|\} \qquad (8\mathrm{C})$$

So that: $|\mathrm{d}B| < 2\{|\mathrm{d}b| + |\mathrm{d}d| + |\mathrm{d}g|\}$.

Also,

$$\mathrm{d}C = \frac{\partial C}{\partial b}\mathrm{d}b + \frac{\partial C}{\partial d}\mathrm{d}d + \frac{\partial C}{\partial g}\mathrm{d}g \qquad (9\mathrm{C})$$

In this case: $\frac{\partial C}{\partial b} = \frac{\partial C}{\partial d} = \frac{\partial C}{\partial g} = \mathrm{e}^{-(b+d+g)}$ so that:

$$\mathrm{d}C = -\mathrm{e}^{-(b+d+g)}[\mathrm{d}b + \mathrm{d}d + \mathrm{d}g] \qquad (10\mathrm{C})$$

Similarly,

$$|\mathrm{d}C| \leq \{\left|\mathrm{e}^{-(b+d+g)}\right| \cdot [|\mathrm{d}b| + |\mathrm{d}d| + |\mathrm{d}g|]\} \qquad (11\mathrm{C})$$

Therefore: $|\mathrm{d}C| < \{|\mathrm{d}b| + |\mathrm{d}d| + |\mathrm{d}g|\}$.

Thus, the magnitude, of the patient-to-patient variation in coefficient A, will be less than the sum of: $|\mathrm{d}b|$, $|\mathrm{d}d|$, and $|\mathrm{d}g|$. 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: $|\mathrm{d}b|$, $|\mathrm{d}d|$, and $|\mathrm{d}g|$.

Furthermore, Equations (2C), (5C), and (9C) can be summarized as:

$$\begin{bmatrix}\mathrm{d}A \\ \mathrm{d}B \\ \mathrm{d}C\end{bmatrix} = \begin{bmatrix}\frac{\partial A}{\partial b} & \frac{\partial A}{\partial d} & \frac{\partial A}{\partial g} \\ \frac{\partial B}{\partial b} & \frac{\partial B}{\partial d} & \frac{\partial B}{\partial g} \\ \frac{\partial C}{\partial b} & \frac{\partial C}{\partial d} & \frac{\partial C}{\partial g}\end{bmatrix}\begin{bmatrix}\mathrm{d}b \\ \mathrm{d}d \\ \mathrm{d}g\end{bmatrix} \qquad (12C)$$

REFERENCES

1. Mickens R. 1990. Difference equations theory and applications, 2nd edn. New York: Van Nostrand Reinhold.
2. Goldberg S. 1986. Introduction to difference equations. New York: Dover Publications.
3. Levy H, Lessman F. 1992. Finite difference equations. New York: Dover Publications.
4. Sneyd JR. 2004. Recent advances in intravenous anesthesia. Br J Anesth 93:725–736.
5. Schnider TW, et al. 1998. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 88:1170–1182.
6. Levenberg K. 1944. A method for the solution of certain problems in least squares. Quart Appl Math 2:164–168.
7. Marquardt D. 1963. An algorithm for least-squares estimation of nonlinear parameters SIAM. J Appl Math 11:431–441.
8. Edwards CH, Penney DE. 2002. Calculus. New Jersey: Prentice Hall.
9. Apostol T. 1974. Mathematical analysis, 2nd edn. Boston: Addison-Wesley.