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Testing Computer-controlled Infusion Pumps by Simulation

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The pharmacokinetic behavior of intravenous anesthetic drugs can be described by two- or three-compartment models. Rapid achievement and maintenance of steady plasma concentrations of these drugs requires a complicated delivery scheme, perhaps best controlled by a computer. The authors developed a method of simulating the performance of a computer-controlled infusion pump from the differential equations describing drug transfer between compartments. They also derived a mathematically simple and flexible approximate solution to these equations using Euler's numerical method. They incorporated this approximate solution into a computer-controlled infusion pump for intravenous drugs. They tested their pump by simulating the administration of fentanyl to a hypothetical patient whose fentanyl pharmacokinetics were described by a three-compartment model. The exact analytical solution served as the standard of comparison. The approximation technique, using a 15-s interval between model updates, had a maximum error of 0.35 ng · ml^{-1}, and rapidly converged on the exact solution. The simulations revealed oscillations in the system. The authors suggest that such simulations be used to evaluate computer-controlled infusion pumps prior to clinical trials of these devices. (Key words: Anesthesia: computer-assisted. Anesthetics, intravenous: fentanyl; infusion. Equipment, infusion pump: simulations. Pharmacokinetics.)

USEFUL PROPERTIES OF some intravenous anesthetic drugs include rapid onset, cardiovascular stability, and, for narcotics, postoperative analgesia. For an intravenous drug to be titrated with precision, a method must be sought by which the anesthesiologist can rapidly achieve and maintain a steady plasma concentration.

The most common method of administering these drugs, *via* iv bolus, results in either an initial overdose of drug, or in a plasma concentration which rapidly declines below the desired concentration.[1] Administration by continuous infusion will eventually produce a steady state, but only after four to five elimination half-lives (*e.g.*, nearly 15 h for fentanyl). A more sophisticated technique is to give an initial bolus to "fill up" the central compartment, and follow with a steady infusion to replace drug as it is eliminated from the central compartment. This technique works well for drugs described by one-compartment pharmacokinetics; however, the plasma concentrations of the intravenous anesthetics are best described by two- or three-compartment models.[2] In these cases, an exponentially decreasing infusion rate is required to maintain a steady plasma concentration, because drug is distributed from the central compartment to the peripheral compartments.[3] Since the multicompartmental behavior of the intravenous drugs precludes achieving a steady concentration within the usual duration of an anesthetic with simple dosing regimens,[4] numerous investigators are currently developing computer-controlled infusion pumps.[5-8]

In theory, pumps programmed from multicompartmental models can maintain steady plasma drug concentrations and can adjust the infusion rate to achieve and maintain a higher or lower plasma drug concentration as desired. Although pharmacokinetic variability will prevent the anesthesiologist from precisely knowing the plasma drug concentration, the ability to achieve rapidly and maintain a steady state will allow the anesthesiologist to make proportional adjustments in plasma drug concentration to achieve a stable anesthetic depth.

We developed a computer-controlled infusion pump and a method for testing the pump with simulations. We investigated the accuracy of the specific implementation of the pharmacokinetic model and tested the overall accuracy of the computer-controlled infusion pump.

Materials and Methods

HARDWARE AND SOFTWARE CONFIGURATION

The computer-controlled infusion pump consisted of an IMED 929® pump connected to an Apple II® computer through an RS-232 interface. The software was a highly modified version of the original CACI software developed by Reves *et al.*[9] and Alvis *et al.*[10,11] in Pascal using the UCSD p-system. The software used the three-compartment model for fentanyl with elimination from the central compartment (fig. 1). The rate constants

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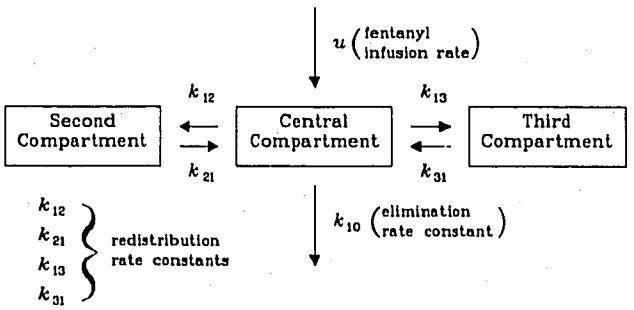

FIG. 1. Three-compartment model with an infusion into and elimination from the central compartment.

describing the transfer of drug between compartments were those of McClain and Hug.[12]

PHARMACOKINETIC ALGORITHM

In a linear pharmacokinetic model, the rate of transfer of drug from one compartment to another is proportional to the amount of drug in the first compartment. The system is linear because the proportionality factor is constant at all times for all amounts of drug (*i.e.*, the system is not saturable). For the three-compartment model, the rate of drug crossing from compartment 1 (the central compartment) to compartment 2 will be a rate constant (k_{12}) multiplied by the amount of drug in compartment 1. The rate of drug crossing from compartment 2 to compartment 1 will be a different rate constant (k_{21}) multiplied by the amount of drug in compartment 2. The *net* rate of drug transfer from compartment 1 to compartment 2 will be the absolute rate of transfer from compartment 1 to compartment 2, less the absolute rate of transfer from compartment 2 to compartment 1.

For the three-compartment model shown in figure 1, the rate of change in the amount of drug in each compartment is:[13]

$$\frac{da_1(t)}{dt} = k_{21}a_2(t) + k_{31}a_3(t) - (k_{10} + k_{12} + k_{13})a_1(t) + u(t) \quad (1)$$

$$\frac{da_2(t)}{dt} = k_{12}a_1(t) - k_{21}a_2(t) \quad (2)$$

$$\frac{da_3(t)}{dt} = k_{13}a_1(t) - k_{31}a_3(t) \quad (3)$$

where $a_1(t)$ = amount of drug in compartment 1 at time t; $a_2(t)$ = amount of drug in compartment 2 at time t; $a_3(t)$ = amount of drug in compartment 3 at time t; $\frac{da_1(t)}{dt}$ = rate of change in compartment 1 at time t; $\frac{da_2(t)}{dt}$ = rate of change in compartment 2 at time t; $\frac{da_3(t)}{dt}$ = rate of change in compartment 3 at time t; k_{10} = rate constant for elimination from compartment 1; k_{12} = rate constant for drug transfer from compartment 1 to 2; k_{13} = rate constant for drug transfer from compartment 1 to 3; k_{21} = rate constant for drug transfer from compartment 2 to 1; k_{31} = rate constant for drug transfer from compartment 3 to 1; and u(t) = infusion rate into compartment 1 at time t.

Analytical Solution. Equations 1, 2, and 3 represent the instantaneous rate of drug transfer at time t. Implementation of these differential equations on a digital computer requires that we work in a discrete time system. We, therefore, analyzed the differential equations over discrete time intervals, which correspond to the interval between rate adjustments from the computer to the infusion pump. If T is the duration of the interval (and duration of the infusion), then t = nT where n represents the nth interval.

For n = 0, we define the initial conditions as: $a_1[0] = 0$, $a_2[0] = 0$, and $a_3[0] = 0$ (*i.e.*, there is no drug in the body). For all values of n, we can exactly define the amount of drug in each compartment at time nT as a function of $a_1[n-1]$, $a_2[n-1]$, $a_3[n-1]$, the duration of the interval, T, the infusion rate during the interval, $u[n-1]$, and the rate constants.[14] The equations describing the amount of drug in each compartment at time nT are listed in the appendix.

Approximate Solution. The analytic solution, described in the appendix, is difficult to manipulate mathematically and may be too computationally demanding for the small microprocessors which will drive dedicated pumps. We, therefore, analyzed the initial differential equations (1, 2, and 3) as first-order difference equations over an interval of length T. This method assumes that the rate of drug transfer between compartments at time (n − 1)T is the same as the rate of transfer at time nT. This is only an approximation as the rate of drug transfer changes during the interval, except when the amount in each compartment at (n − 1)T is the same as the amount at time nT (*i.e.*, steady state). The accuracy of this technique, Euler's numerical method,[15] increases as T becomes smaller. Euler's method is an approximation technique which sacrifices a small amount of accuracy for flexibility and mathematical simplicity. The equations for computing the approximate amount in each compartment at time nT are:

$$a_1[n] = a_1[n-1] + (k_{21}a_2[n-1] + k_{31}a_3[n-1] + u[n-1] - k_1a_1[n-1])T \quad (4)$$

$$a_2[n] = a_2[n-1] + (k_{12}a_1[n-1] - k_{21}a_2[n-1])T \quad (5)$$

$$a_3[n] = a_3[n-1] + (k_{13}a_1[n-1] - k_{31}a_3[n-1])T \quad (6)$$

where:

$$k_1 = k_{10} + k_{12} + k_{13}$$

From these equations, we can calculate the plasma concentration (C_p) of the drug at time nT:

$$C_p[n] = a_1[n]/V_1 \quad (7)$$

where $C_p[n]$ = plasma drug concentration at time nT; and V_1 = volume of compartment 1 (the central compartment).

We incorporated equations 4, 5, 6, and 7 into our pump software to predict the amount of drug in each compartment and the plasma drug concentration at each time nT.

The Infusion Rate. The computer-controlled infusion pump calculates a new infusion rate at each time nT. The equation for pump rate is:

$$u[n] = (k_1a_1[n] - k_{21}a_2[n] - k_{31}a_3[n]) + (C_d[n + 1]V_1 - a_1[n])/(3T) \quad (8)$$

where $C_d[n + 1]$ = desired drug concentration at time $(n + 1)T$.

The first term in this calculation ($k_1a_1[n] - k_{21}a_2[n] - k_{31}a_3[n]$) represents the rate of drug leaving compartment 1 at time nT. The second term ($C_d[n + 1]V_1 - a_1[n]$) represents the difference between the desired amount in compartment 1 ($C_d[n + 1]V_1$) and the amount currently in compartment 1 ($a_1[n]$). This difference is divided by the time interval over which we intend to infuse this difference. We empirically found that the pump oscillated dramatically if we tried to make up the difference between current amount and desired amount in a single interval T. The pump appears properly damped if we attempt to make up the difference over an interval of 3T; hence, the division of the difference by 3T. This represents a trade-off between smooth damping, which is favored by a longer interval, and rapid response, which is favored by a shorter interval.

We used a T of 15 s in our computer-controlled infusion pump. As discussed below, the approximation method, with T = 15 s, introduced only a minimal error when compared to the exact solution.

Simulations

We designed the following simulations to test our computer-controlled infusion pump. We simulated infusion of undiluted fentanyl (50 $\mu g \cdot ml^{-1}$) into a 70-kg patient for 1 h except as specifically noted. We tested the following.

A. The ability to maintain a steady plasma fentanyl concentration for three clinically useful plasma concentrations: 2, 5, and 10 $ng \cdot ml^{-1}$.
B. The ability to increase the plasma fentanyl concentration from 5 to 10 $ng \cdot ml^{-1}$.
C. The ability to decrease the plasma fentanyl concentration from 10 to 5 $ng \cdot ml^{-1}$.
D. The ability to return to the appropriate plasma fentanyl concentration after a 10-min pump malfunction (*e.g.*, air in line, line occlusion, etc).
E. The ability to maintain a steady plasma fentanyl concentration using diluted fentanyl (10 $\mu g \cdot ml^{-1}$).
F. The ability to maintain a steady plasma fentanyl concentration in a 10-kg pediatric patient.
G. The ability to maintain a steady plasma fentanyl concentration of 10 $ng \cdot ml^{-1}$ for 24 h.
H. The ability to model accurately the decline over 24 h in plasma concentration after a 500-μg fentanyl bolus.
I. The ability to alternate as rapidly as pharmacokinetically possible between a concentration of 10 $ng \cdot ml^{-1}$ and 5 $ng \cdot ml^{-1}$ for 24 h.
J. The original CACI pump[8–11] and our pump for the ability to alternate the plasma fentanyl concentration between 5 and 10 $ng \cdot ml^{-1}$ every 10 min.

Analysis of Simulations

For simulations A through F, the computer controlled infusion pump (an Apple II® computer driving an IMED 929® pump) was instructed to maintain the plasma concentration required by the simulations. The infusion pump's rate and volume infused was recorded on disk at each time nT (T = 15 s). This disk file was then read by the simulation analysis program, which used the time, pump rate, and volume infused information to recreate the infusion regimen. The simulation analysis program then predicted the precise plasma drug concentration at each time nT by applying the exact solution (equations 9, 10, and 11) to the infusion regimen. These equations precisely simulated the hypothetical three-compartment patient specified by the model.

After the pump reached the target plasma fentanyl concentration, we identified the maximum deviation from this target concentration. We report the magnitude of this deviation, as a percentage of the target concentration, as the percent maximum error.

Simulations A, B, C, D, E, and F evaluated the overall performance of the infusion pump, the controlling software, and the pump-computer interface. Simulations G, H, and I demonstrate the behavior over time of our approximation technique (Euler's method). Since we were exclusively interested in evaluating the accuracy of the approximation technique (as opposed to evaluating the accuracy of the specific pumping and computing

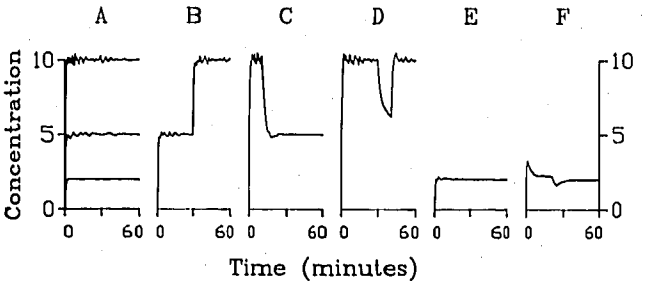

FIG. 2. Six simulations of the computer controlled infusion pump. *A.* Ability to maintain 2, 5, and 10 ng·ml^{-1}. *B.* Ability to increase from 5 to 10 ng·ml^{-1}. *C.* Ability to decrease from 10 to 5 ng·ml^{-1}. *D.* Ability to recover after a 10-min "air-in-line" pump error. *E.* Ability to maintain 2 ng·ml^{-1} while infusing diluted fentanyl (10 μg·ml^{-1}). *F.* Ability to maintain 2 ng·ml^{-1} in a 10-kg pediatric patient.

hardware), the software simulated perfect performance by the IMED 929® infusion pump for these three simulations. The use of a simulated infusion pump allowed the software to focus on the intrinsic accuracy of the algorithms by assuming that the pump delivered exactly the amount of drug requested over the interval from (n − 1)T to nT. These simulations computed the concentration of drug at each time nT (T = 15 s).

Results

Figure 2 shows the results of simulations A–F. The computer-controlled infusion pump had a maximum error of 3% when maintaining a plasma fentanyl concentration of 10 ng·ml^{-1}, of 6% when maintaining a concentration of 5 ng·ml^{-1}, and of 3% when maintaining a concentration of 2 ng·ml^{-1} (simulation A). The software was able to increase the plasma concentration to 10 ng·ml^{-1} and maintain that level within 3% (simulation B). The software was able to decrease the concentration to 5 ng·ml^{-1} and maintain that level within 4% (simulation C).

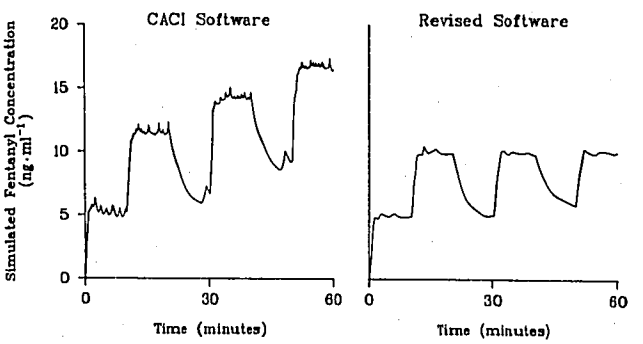

FIG. 3. Simulation of the original CACI software and our software ("revised software"): the program was instructed to vary the concentration between 5 and 10 ng·ml^{-1} every 10 min in a 70-kg patient.

After a simulated 10-min pump malfunction (simulation D), the software returned to the target concentration within 2.25 min. The software maintained the target concentration within 3% after an initial overshoot of 5%.

The software's performance was not significantly affected when infusing dilute fentanyl. The intrinsic oscillations in the software were exacerbated in a simulated pediatric patient, which resulted in a 23% overshoot in initial plasma fentanyl concentration.

When compared to the exact solution, the maximum error in the predicted fentanyl concentration with Euler's numerical approximation was 0.28 ng·ml^{-1} when we simulated the maintenance of a steady concentration of 10 ng·ml^{-1} (simulation G). The maximum error occurred 1 min into the infusion. The maximum error when the pump attempted to alternate the concentration between 10 and 5 ng·ml^{-1} as rapidly as pharmacokinetically possible (simulation I) was also 0.28 ng·ml^{-1}, and this also occurred 1 min into the infusion. The maximum error during the simulated decline from a bolus injection of 500 μg was 0.35 ng·ml^{-1}, which occurred at 2 min (simulation H).

In all three simulations, the difference between the numerical approximation and the exact solution decreased with time. The error at the end of 24 h was .0021 ng·ml^{-1} for the simulated alternating concentration (simulation I), and was less than .0001 ng·ml^{-1} both for the simulated maintenance of a steady concentration and for the simulated decline from a bolus (simulations G and I). Thus, Euler's method converged on the exact solution with time. The greatest error occurred during periods of rapidly changing plasma fentanyl concentration.

Figure 3 shows the results of attempting to step between concentrations of 5 and 10 ng·ml^{-1} in a 70-kg patient with the original CACI software and with our computer-controlled infusion pump. At the end of the simulation, the original CACI pump maintained a plasma fentanyl concentration 74% higher than the target concentration.

Note that the plasma fentanyl concentration achieved with the revised software did not decline to 5 ng·ml^{-1} prior to the last increase to 10 ng·ml^{-1} in simulation J. This is because the fentanyl which accumulated in peripheral compartments delayed the decline in plasma fentanyl concentration so that the concentration could not reach 5 ng·ml^{-1} by 50 min, when the desired concentration was again adjusted to 10 ng·ml^{-1}.

Discussion

The exact solution (equations 9, 10, and 11) to the differential equations describing a three-compartment pharmacokinetic model could be used by the software

of a computer-controlled infusion pump. However, the exact equations are not easy to manipulate, and may be too demanding for the small microprocessors used in commercial pumps. However, the exact equations provide a method for evaluating the performance of computer-controlled infusion pumps in simulations.

Simulations G, H, and I demonstrate that Euler's simple numerical solution (equations 4, 5, and 6) is an acceptable approximation of the exact equations. There is a small error during the initial rapid infusion; however, this error rapidly decreases with time as the computed amount in each compartment converges on the exact solution.

These simulations provided insight into the overall performance of the computer-controlled infusion pump. For example, it is clear that our pump oscillates (fig. 2, simulation A). This oscillation is exacerbated by small patient size (fig. 2, simulation F). Further analysis has revealed that the IMED 929® pump does not accurately infuse at the requested rate when the rate of infusion changes rapidly. When the infusion rate changes by large amounts every 15 s, the IMED 929® only infuses about 85% of the anticipated volume. The software's response to the inaccurate infusion is compounded by the IMED 929® computer interface, which only reports to the computer the integer portion of the volume infused (*e.g.*, if 3.7 ml have been infused, the IMED 929® will report 3 ml to the computer). Therefore, the software is forced to make inferences about the actual quantity of drug infused when calculating the infusion rate. The software's adjustments to the infusion rate, in response to these inferences, produced the observed oscillation. The inferences become more accurate, and the oscillations decrease, when dilute fentanyl is infused.

Simulation J (fig. 3) also demonstrates how this simulation methodology can generate useful insight into pharmacokinetically controlled pumps. Several problems with the original CACI software have been reported,[16,17] and since corrected. The results we present concerning the original CACI pump are not clinically relevant, since the CACI software has since been corrected. We have included these results to illustrate the importance of testing computer-controlled infusion pumps in simulations. This approach would have revealed significant problems prior to the clinical tests[8-11] performed with the original CACI software.

The exact solution to the three-compartment model makes these simulations computationally easy. However, Euler's method of approximating the differential equations as first-order difference equations over a 15-s interval is simple and sufficiently accurate for implementation in a computer-controlled infusion pump when using the fentanyl model of McClain and Hug.[12] The maximum error for Euler's method depends both on T (the time interval) and on the rate constants of the model. It is quite possible that a shorter time interval may be required for different drugs, or when infusing fentanyl according to a different set of rate constants.

Even if computer-controlled infusion pumps can obtain perfect accuracy in simulations, the accuracy in the clinical setting will be compromised by the large pharmacokinetic variability of intravenous anesthetics. There will almost inevitably be a bias between the patient's blood level and the predicted blood level. This does not reduce the utility of the pump, however, because the pump can still provide a method of making controlled, proportional adjustments in the patient's plasma drug concentration.

Recent advances in pharmacokinetic statistical analysis, such as those employed by Maitre *et al.*,[18] will allow an estimate of the influence of patient specific factors (*e.g.*, weight, age, and sex) on intravenous drug pharmacokinetics, as well as an estimate of the remaining interindividual variability. The impact of these individual factors on the pharmacokinetic model can be incorporated into the design of computer-driven infusion pumps.

Pharmacokinetically controlled pumps do not account for the pharmacodynamic variability (the variability between plasma drug concentration and response). Currently the pharmacokinetic and pharmacodynamic variability must be handled by the anesthesiologist, who can use the pump to increase or decrease the plasma drug concentration in response to a subjective assessment of anesthetic requirement. In the future, computer-controlled infusion pumps may use a direct measurement of pharmacodynamic effect, such as computerized EEG analysis, as part of a feedback control system.

Addendum

The software incorporating the exact solution (equations 9, 10, and 11) for the analysis of infusion pumps controlled by compartmental models is available at no charge from the author (Steven L. Shafer, M.D.). The programs are written in C, and run on an 80286 processor under MS-DOS. The C source code is also available to those interested in compiling the programs into another environment.

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Appendix

The analytic solution for the amount of drug in each compartment at time nT, adapted from Maitre *et al.*,[14] is:

$$\alpha_1[n] = \sum_{j=1}^{3} \frac{e^{-\lambda_j T}\left(\left(\alpha_1[n-1] - u[n-1]\frac{(1-e^{\lambda_j T})}{\lambda_j}\right)(k_{21}-\lambda_j)(k_{31}-\lambda_j) + a_2[n-1]\,k_{21}(k_{31}-\lambda_j) + a_3[n-1]k_{31}(k_{21}-\lambda_j)\right)}{d_j} \quad (9)$$

$$\alpha_2[n] = \sum_{j=1}^{3} \frac{e^{-\lambda_j T}\left(\left(\alpha_1[n-1] - u[n-1]\frac{(1-e^{\lambda_j T})}{\lambda_j}\right)(k_{31}-\lambda_j) + a_3[n-1]k_{31})k_{12} + a_2[n-1]((k_1-\lambda_j)(k_{31}-\lambda_j) - k_{13}k_{31})\right)}{d_j} \quad (10)$$

$$\alpha_3[n] = \sum_{j=1}^{3} \frac{e^{-\lambda_j T}\left(\left(\alpha_1[n-1] - u[n-1]\frac{(1-e^{\lambda_j T})}{\lambda_j}\right)(k_{21}-\lambda_j) + a_2[n-1]k_{21})k_{13} + a_3[n-1]((k_1-\lambda_j)(k_{21}-\lambda_j) - k_{12}k_{21})\right)}{d_j} \quad (11)$$

where $d_1 = (\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)$; $d_2 = (\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)$; $d_3 = (\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)$; n = nth interval; $a_1[n]$ = amount of drug in compartment 1 at time nT; $a_2[n]$ = amount of drug in compartment 2 at time nT; $a_3[n]$ = amount of drug in compartment 3 at time nT; $a_1[n-1]$ = amount of drug in compartment 1 at time (n − 1)T; $a_2[n-1]$ = amount of drug in compartment 2 at time (n − 1)T; $a_3[n-1]$ = amount of drug in compartment 3 at time (n − 1)T; $u[n-1]$ = infusion rate from time (n − 1)T to nT; $k_1 = k_{10} + k_{12} + k_{13}$; $\lambda_1, \lambda_2, \lambda_3$ = the roots of the following equation:

$$X^3 + (k_{10} + k_{12} + k_{13} + k_{21} + k_{31})X^2 + (k_{10}k_{31} + k_{21}k_{31} + k_{21}k_{13} + k_{10}k_{21} + k_{31}k_{12})X + k_{10}k_{21}k_{31} = 0$$

λ_1, λ_2 and λ_3 may be more easily recognized as the exponential coefficients which describe the plasma concentration-time curve following a bolus dose according to the standard pharmacokinetic equation:

$$C_p(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t} + A_3e^{-\lambda_3 t}.$$