APPENDIX B: APPLICATIONS OF COMPUTERS IN PHARMACOKINETICS: INTRODUCTION

The availability of computers and improvements in bioanalytical chemistry have greatly accelerated the development of pharmacokinetics. Computer software programs now allow for the rapid solution of complicated pharmacokinetic equations and rapid modeling of pharmacokinetic processes. Computers simplify tedious calculations and allow more time for the development of new approaches to data analysis and pharmacokinetics modeling. In addition, computer software is used for the development of experimental study designs, statistical data treatment, data manipulation, graphical representation of data, pharmacokinetic model simulation, and projection or prediction of drug action. Furthermore, computers are used frequently for written reports, documentation, and archiving.

A variety of computers are now available. Personal computers (PCs) may be used independently or linked together into local networks (LANs) that share many application software packages. Each type of computer has an operating system (OS), which is a collection of programs that allocates resources and enables algorithms (well-defined rules or processes for solving a problem in a finite number of steps) to be processed. UNIX, Windows, and more recently, LINUX, are examples of commonly used operating systems. Windows NT is used mostly in network systems that link many PCs. Most PCs today are equipped with a modem to allow access to remote information. Netscape and Microsoft Internet Explorer are browsers that allow PCs to access remote information at various sites on the Internet referred to as Websites.

A program of instructions known as a computer package or software is written in a computer language. This software is needed to run the computer. The computer operating system must support the computer language of the software. In the past, computer users needed to be competent in computer programming and usually had knowledge of at least one computer language such as Pascal, C, or Basic. As a result of the availability of various commercial and noncommercial pharmacokinetic applications and spreadsheets, such as Excel, very little computer programming is required for many applications in pharmacokinetics. Some examples are given below.

PHARMACOKINETIC SOFTWARE

Pharmacokinetic software consists of computer programs designed for computation and easy solution of pharmacokinetic problems. Not all computer programs satisfy the user's full requirements, but many provide the following.

1. Fitting drug concentration-versus-time data to a series of pharmacokinetic models, and choosing the one that best describes the data statistically

Typically, a least-squares program is employed, in which the sum of squared differences between observed data points and theoretic prediction is minimized. Usually, a mathematical procedure is used iteratively (repetitively) to achieve a minimum in the sum of squares (convergence). Some data may allow easier convergence with one procedure rather than another. The mathematical method employed should be reviewed before use.

2. Fitting data into a pharmacokinetic or pharmacodynamic model defined by the user

This method is by far the most useful, because any list of prepared models is often limited. The flexibility of user-defined models allows continuous refinement of the model as new experimental information becomes available. Some software merely provides a utility program for fitting the data to a series of polynomials. This utility program provides a simple, quantitative way of relating the variables, but offers little insight into the underlying pharmacokinetic processes.

3. Simulation

Some software programs generate data based on a model with parameter input by the user. When the parameters are varied, new data are generated based on the model chosen. The user is able to observe how the simulated model data matches the experimental observed data. Because pharmacokinetic processes are conveniently described by systems of differential equations, the simulation process involves a numerical solution of the equation with predefined precision.

4. Experimental design

To estimate the parameters of any model, the experimental design of the study must have points appropriately spaced to allow curve description and modeling. Although statisticians stress the need for proper experimental design, little information is generally available for experimental design in pharmacokinetics when a study is performed for the first time. For the first pharmacokinetic study, an empirical or a statistical experiment design is necessarily based on assumptions that may later prove to be wrong.

5. Clinical pharmacokinetic applications

Some software programs are available for the clinical monitoring of narrow-therapeutic-index drugs (ie, critical-dose drugs) such as the aminoglycosides, other antibiotics, theophylline, or antiarrythmics. These programs may include calculations for creatinine clearance using the Cockcroftâ€"Gault equation (see), dosage estimation, pharmacokinetic parameter estimation for the individual patient, and pharmacokinetic simulations.

6. Computer programs for teaching

Software applications for teaching have been reviewed by . These authors taught a course in which students used (download free ware). Pharmacalc and PharmaSim may be used for pharmacokinetic computations. SAAM II or Stella and ModelMaker may be used for "system dynamics." The latter takes into account stochastic processes in the simulation and may be more suitable when variability is considered to be an important factor in a clinical situation. Other software reviewed includes ADAPT for use in parameter estimation, simulation, and experimental (sample schedule) design.

VALIDATION OF SOFTWARE PACKAGES

Software used for data analysis such as statistical and pharmacokinetic calculations should be validated with respect to the accuracy, quality, integrity, and security of the data. One approach for determining the accuracy of the data analysis is to compare the results obtained from two different software packages using the same set of data (). Because software packages may have different functionalities, different results (eg, pharmacokinetic parameter estimates) may be obtained.

PHARMACOKINETIC SOFTWARE

Various pharmacokinetic programs (software) are available on the Internet. These programs may not have been validated by the programmer. Thus, the user is responsible for validating the program. Other programs are available from commercial suppliers. Dr. David Bourne of the University of Oklahoma has compiled a listing of pharmacokinetic programs, general references in pharmacokinetics, pharmacodynamics, and other information, available at www.boomer.org. The Website http://www.boomer.org/pkin/soft.html lists numerous pharmacokinetic software packages with user comments. Students should consult the site for updated information.

Popular Programs

Some popular commercially available computer software programs are listed below. The descriptions may not represent the latest versions. New features are often added or old features improved. The user should contact the program vendor directly for more information. See below for information about Internet resources, including user evaluations of software packages.

PCNONLIN

PCNonlin is a powerful least-squares program for parameter estimation. Both a user-defined model and a library of over 20 compartmental models are available. The program accepts both differential and regular (analytical) equations. Users may select the Hartley-modified or Levenberg-type Gaussâ€"Newton algorithm or the (Nelder and Mead) simplex algorithm for minimizing the sum of squared residuals. Some training is needed. Until its commercial release, Nonlin was installed mostly on mainframe computers. PCNonlin includes additional features and was designed to run on PCs. PCGRAPH (Version 4) was bundled to improve the quality of the plots from previous versions of Nonlin. Compartmental models, curve fitting, and simulations are specially designed for pharmacokinetics.

WINNONLIN

Pharsight Corporation Main

800 W. El Camino Real, Suite 200

Mountain View, CA 94040

(650) 314-3800

www.pharsight.com/products/winnonlin

WinNonlin is Windows-based software for pharmacokinetic, pharmacodynamic, and noncompartmental analysis. It is designed for easy interfacing and secure data management with PkS Suite. WinNonlin can calculate individual bioequivalences for all of the common replicated crossover designs. WinNonMix is associated software for population pharmacokinetic analysis. WinNonlin has an improved user interface that makes it easier to use and to interface with other Windows applications. WinNonlin is relatively easy to use for modeling or noncompartmental analysis of data files and handles large numbers of subjects or profiles. WinNonlin's input and output data may be managed via Excel (Microsoft)-compatible spreadsheet files. The Noncompartmental Analysis module computes derived pharmacokinetic parameters ($AUC_{t\to 0}$, $AUC_{0\to \hat{a}\hat{z}}$, C_{max}, cumulative excretion, etc). PCNonlin's extensive library of models for nonlinear regression and parameter estimation are included in this software. Standard descriptive statistics and confidence intervals are determined from datasets.

SAS

SAS Institute, Inc.

Cary, NC 27511

(919) 677-8000

www.sas.com

An all-purpose data analysis system with a flexible application-development language, SAS Graph allows for multidimension plots, for bar, pie, and contour charts, and for all sorts of other graphs. Over 5000 SAS products are reported to be available. Various "procs" (subroutines) are available for statistics as well as general linear and nonlinear regression models. There are over 80 procedures for univariate descriptive statistics; *t*-test, chi-square, correlation, autoregression, multidimensional scaling, nonparametric test, factor analysis, and discriminant and stepwise analysis. SAS runs in many user environments, including PCSAS for personal computers. A special startup interface, ASSIST, facilitates beginners who are unfamiliar with the default batch data entry.

The U.S. Code of Federal Regulations, 21CFR Part 11, requires all datasets to be provided in special format for review and inspection. SAS Institute published the SAS XPORT format (Version 5) for electron data submission for regulatory purposes. Details about SAS EXPORT can be found at www.sas.com/fda-esub. *Guidance for Industry: Providing regulatory submissions in electronic formatâ€"General considerations 1999*.

RSTRIP

MicroMath Research

1710 South Brentwood Blvd.

Saint Louis, MO 63144

www.micromath.com

RSTRIP is menu-driven and very suitable for student use; it fits data to models, mono-, bi-, and tri-exponentials based on model selection criteria (Akaike Information Criteria). A good statistics menu is available for AUC, C_{max}, T_{max}, and mean residence time. The program gives initial parameter estimates and final parameters after iteration. However, the program does not handle differential equations or user-defined models. Plot outputs are available, as are pharmacokinetic curve stripping, and least-squares parameter optimization. The original software was written for PC DOS but has now been replaced by a Windows version with additional features.

SCIENTIST FOR WINDOWS

Scientist for Windows V2.01 is a general mathematical modeling application from MicroMath, www.micromath.com. It can perform nonlinear least-squares minimization and simulation. Models can consist of both analytic and differential equations. The software has many functions with pharmacokinetic applications.

PKANALYST FOR WINDOWS

MicroMath Scientific Software

PO Box 21550

Salt Lake City, UT 84121

PKAnalyst is a bundled pharmacokinetic software incorporating many features of RSTRIP but with more statistics and mathematical functions. The program operates under Windows and is generally easy to use. It is very user-friendly for routine data analysis in pharmacokinetics.

DIFFEQ AND DIFFEQ PHARMACOKINETICS LIBRARY

MicroMath Scientific Software

PO Box 21550

Salt Lake City, UT 84121

DIFFEQ is a nonlinear least-squares program for PCs. Model entry uses a generic language with syntax similar to Basic; it may be used with DIFFEQ Pharmacokinetic Library, which includes many models used in pharmacokinetics. The original version was updated under a different name.

P-STAT

P-Stat Inc.

Princeton, NJ 08540

(609) 924-9100

This program supplies statistical data handling for mainframe computers.

STELLA

High Performance Systems

Lyme, NH 03755

(603) 643-9636

STELLA is a structural thinking experimental learning laboratory with animation, available for Windows-based PCs. The program was developed on the MAC. STELLA solves differential equations and simulates pharmacokinetic models and other physiologic systems. The software is particularly suitable for teaching because of its animation and learning simulation by drawing the model.

NONMEM

NONMEM Project Group, C255

University of California

San Francisco, CA 94143

NONMEM (Nonlinear Mixed Effects Model), developed by S. L. Beal and L. B. Sheiner, is a statistical program used for fitting parameters in population pharmacokinetics. The NONMEM program first appeared in 1979. It is useful in evaluating relationships between pharmacokinetic parameters and demographic data such as age, weight, and disease state. Average population

parameters and intersubject variance are estimated. The program fits the data of all the subjects simultaneously and estimates the parameters and their variances. The parameters are useful in estimating doses for individuals based on population pharmacokinetics with calculated risks. A regression program is written in ANSI (American National Standards Institute) Fortran 77 for mainframe computers.

The current version of NONMEM (Version IV) consists of several parts. The NONMEM program itself is a general (noninteractive) regression program which can be used to fit many different types of data. PREDPP consists of subroutines that can be used by NONMEM to compute predictions for population pharmacokinetics. NM-TRAN is a preprocessor, allowing control and other needed inputs and error messages to NONMEM/PREDPP.

MKMODEL

Biosoft

PO Box 10398

Ferguson, MO

MKMODEL, by N. Holford, is a pharmacokinetic program from the National Institutes of Health-supported PROPHET system. The program, available for the PC, performs nonlinear least-squares regression and includes both pharmacokinetic and pharmacodynamic models (effect compartment).

ADAPT II

D. Z. D'Argenio and A. Schumitzky

Biomedical Simulation Resource

University of Southern California

Los Angeles, CA

Supplied as Fortran code for various operating systems, this program performs simulations, nonlinear regression, and optimal sampling, and includes extended least-squares and Bayesian optimization. Models can be expressed as integrated or differential equations ().

USC*PACK PC PROGRAMS

USC Laboratory of Applied Pharmacokinetics

2250 Alcazar St, CSC 134B

Los Angeles, CA 90033

www.lapk.org/software.php

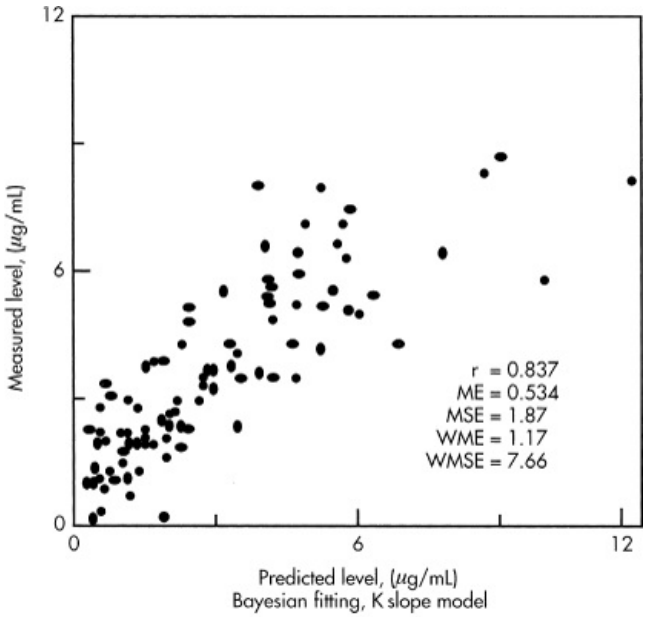
This software package consists of various pharmacokinetic programs bundled for clinical pharmacokinetic applications and model parameter estimation. The program NPEM2 (Version 3) is an improved version of the nonparametric expectation maximization algorithm that is well adapted for population pharmacokinetics. The program is now available for a three-compartment model with various routes of dosing. Lahey Fortran F77EM32 and its associated package is used in this program.

Clinical programs include related routines in which past therapy data for individual patients are entered into files along with parameter and dose-prediction programs for various drugs (eg, aminoglycosides, other antibiotics, and drugs of special interest). Bayesian fitting procedures are included to fit a selected drug population model to a patient's data of doses and serum concentrations and to adaptive control of the individual dose regimen. Some program selections include:

- Amikacin (Amik)
- Gentamicin (Gent)
- Netilmicin (Net)
- Tobramycin (Tob)
- Bayesian General Modeling (MB)
- Least-Squares General Modeling (MLS)

Many patient-oriented programs for adaptive dosing based on pharmacokinetics and pharmacodynamic are featured in the package. Maximum Aposteriori Probability (MAP) Bayesian fitting is useful in individual dosing; an example is shown in for gentamicin dose prediction. This method yields better prediction than conventional clinical methods even in patients with unstable renal function.

Figure B-1.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

An example of gentamicin dosing prediction in patients using MAP Bayesian fitting and K slope method (one compartment): Predicted versus measured serum gentamicin. (r = correlation coefficient, ME = mean error, MSE = mean squared error, WME = mean weighted error. WMSE = weighted mean squared error.)

()

S-PLUS

S-plus is a versatile package that can be used for analyzing data using the included software, and also includes its own programming language, which can be used to write your own routines. S is a statistical package developed at AT&T's Bell Laboratories. S-Plus is an extension of this statistical language produced by the StatSci Division of MathSoft in Seattle. The software is used extensively by many pharmacokinetics and statisticians for model analysis.

MATHCAD

www.mathcad.com

MathCAD 11 has many general mathematical and statistical functions which can be easily adaptable for data analysis or fitting data to probability distribution models. Differential equation solvers support ordinary differential equations, systems of differential equations, and boundary-value problems both at the command line and in Solve blocks that use natural notation to specify the differential equations and constraints.

CYBER PATIENT

Cyber Patient is a Windows-based multimedia pharmacokinetic simulation program that can be used for development and presentation of problem-solving case studies from Michael B. Bolger, USC School of Pharmacy. This program is suitable for simulations in pharmacy courses and research in development of pharmacokinetic drug models.

GASTROPLUS

GastroPlus is a computer simulation program that predicts the rate and extent of drug absorption from the gastrointestinal tract. This innovative program was developed by a team of scientist-programmers under the direction of Dr. Michael B. Bolger at Simulations Plus, Inc., in collaboration with Dr. Gordon L. Amidon.

INSTRUCTIONAL PROGRAMS

The **Modern Biopharmaceutics Version 6** Computer Based Training Software provides a complete information base for both university biopharmaceutics courses and continuing education courses. The program teaches both basic principles and important applications. Course material is available in modules on CD for individualized learning. For more information see www.tsrlinc.com/mbindex.htm or www.simulations-plus.com.

Other Pharmacokinetic Programs

ACSL BioMed Software based on the ACSL language that is used to simulate clinical trials of drugs. Pharsight Corporation, www.pharsight.com.

BIOPAK A pharmacokinetic program for bioavailability/bioequivalence studies, available from SCI Software.

BOOMER/MULTI-FORTE A simulation program by D. W. A. Bourne, College of Pharmacy, University of Oklahoma.

PCDCON A convolution/deconvolution program by W. R. Gillespie ().

FUNFIT A parameter estimation regression program.

Kinetica 4.0 A pharmacokinetic/pharmacodynamic analysis and simulation program that supports nonlinear mixed-effect model fitting. Available at www.innaphase.com.

LAGRAN A parameter estimation regression program.

MATLAB A powerful program that handles complex models, mostly in chemical engineering but found useful in pharmacokinetics.

NCOMP An Excel-based program for noncompartmental analysis of pharmacokinetic data, by Paul B. Laub. For integration of AUC and other uses, with choice of splines obtained from Lagrange polynomials or the hybrid method recommended by . J Pharm Sci 85:393â€"395, 1996.

NPEM A nonparametric expectation maximization program by . It is part of the USC*PACK collection (see above).

Pharsight Trial Simulator A comprehensive computer-assisted trial simulation software system by Pharsight Corporation, www.pharsight.com/products/prod_pts_home.php.

PDx-Pop Integrates with NONMEM and other software to expedite population modeling and analysis. UNIX version published by GloboMax LLC.

SAAM A program for pharmacokinetics and other biological models that was developed at the National Institutes of Health (NIH).

SAAM/CONSAM Performs nonlinear regression in batch (SAAM) or conversational mode (CONSAM). The SAAM/CONSAM programs are provided by the NIH. Available from L. A. Zech and P. C. Greif, Laboratory of Mathematical Biology, NIH, zech@ncifcrf.gov.

P-PHARM A population pharmacokinetic-dynamic data modeling program from InnaPhase, science@innaphase.com.

PK-Sim A whole-body physiology-based pharmacokinetic (PBPK) simulation software by Bayer Technology Services GmbH, www.pk-sim.com.

PopKinetics A population pharmacokinetics analysis program. It is a companion application to SAAM II that uses parametric algorithms, Standard Two-Stage and Iterated Two-Stage, to compute population parameters. Available from the SAAM Institute, info@saam.com.

TOPFIT A PC-based pharmacokinetic program with both data fitting and clinical application, available from Gustav Fischer ().

WinNonMix A program for nonlinear mixed-effects modeling provided in an interactive and easy-to-use Windows application. By Pharsight Corporation, www.pharsight.com.

WinSAAM A Windows version of the original interactive biological modeling program, CONSAAM, developed in 1980 at the NIH. WinSAAM adds Windows features and enhances application environment and is maintained by Peter C. Grief.

ELECTRONIC SPREADSHEETS

For general computation, many programs, such as electronic spreadsheets, are very adaptable to calculation and pharmacokinetic curve plotting. Spreadsheet software programs such as Quattro and Microsoft Excel are easy to use. Data are entered in columns (referred to alphabetically as A, B, C, . . .) and rows (referred to numerically as 1, 2, 3, . . .). Manuals are generally displayed on screen and can be selected by moving the arrow keys followed by pressing the Return or Enter key. An example of a Microsoft Excel worksheet used to generate time-versus-concentration data after *n* doses of a drug given orally according to a one-compartment model is given in . The parameter inputs are in column B, time is in column D, and concentration is in column E.

Figure B-2.

	A	B	C	D	E	F
1	D	100000		0	0.00	
2	KA	2		0.1	1.78	
3	K	0.4		0.2	3.16	
4	V	10000		0.3	4.23	
5	TAU	4		0.4	5.04	
6	F	1		0.5	5.64	
7	N	1		0.6	6.07	
8	EXP(-KA*TAU)	0.00033546		0.7	6.36	
9	EXP(-K*TAU)	0.20189652		0.8	6.55	
10	FKAD	200000		0.9	6.65	
11	V(K-KA)	-16000		1	6.69	
12	AA	1		1.1	6.67	
13	BB	1		1.2	6.60	
14				1.3	6.50	
15	FD/VK	25	AUC	1.4	6.38	
16				1.5	6.24	
17	FD/V...	8.86435343	Cmax-ss	1.6	6.08	
18				1.7	5.92	
19				1.8	5.74	
20	TMAX	1.0058987	tmax-1	1.9	5.57	
21				2	5.39	
22				2.1	5.21	
23	TMAX-SS	0.86516026	tmax-ss	2.2	5.03	
24				2.3	4.86	
25				2.4	4.68	
26				2.5	4.51	
27				2.6	4.35	
28				2.7	4.19	
29				2.8	4.03	
30				2.9	3.88	
31				3	3.73	
32				3.1	3.59	
33				3.2	3.45	
34				3.3	3.32	
35				3.4	3.19	
36				3.5	3.07	
37				3.6	2.95	
38				3.7	2.84	
39				3.8	2.73	
40				3.9	2.62	
41			tmin	4	2.52	Cmin
42						
43						
44						
45						
46						
47	PARAMETER	PARAM. VAL	PHARM-TERM	TIME (HRS)	CONC (MCG/ML)	

Example of a Microsoft Excel spreadsheet used to calculate timeâ€"concentration data according to an oral one-compartment model after *n* doses.

Example 1

From a series of timeâ€"concentration data (, rows A and B), determine the elimination rate constant using the regression feature of MS Excel.

Figure B-3.

A sample spreadsheet showing a set of timeâ€"concentration data (Time and Conc) being analyzed to obtain the slope or the elimination constant. Note: Only four points from the terminal part of the curve were regressed [*t* versus ln (conc)].

Solution

a. Type in the time and concentration data shown in columns A and B ().

b. Convert in column C all concentration data to ln concentration. Data point #1 may be omitted because ln of zero cannot be determined.

c. From the main menu, select Insert:

Select function

SLOPE

Y data range (select last 4 value)

X data range (select last 4 value)

The slope, given in is â€"0.1. In this case, the ln concentration is plotted versus time, and the slope is simply the elimination

rate constant.

Note: To check this result, students may be interested in simulating the data with dose = 10,000 µg/kg, V_D = 1000 mL/kg, k_a = 0.8 hr$^{â€“1}$, and k = 0.1 hr$^{â€“1}$.

Example 2

Generate some data for a two-compartment model using two differential equations. Initial conditions are dose = 1, V = 1, and k_{12} = 0, k_{21} = 1, and k = 3.

Solution

The data may be generated with MathCAD (). Note that k_{12} is abbreviated as k_1, k_{21} is abbreviated as k_2, and k is abbreviated at k_3 in the program for simplicity. Also, $dC_p/dt = F(t, x, y)$; $x = C_p$; $y = C_t$; t = time; and $dC_t/dt = G(t, x, y)$.

Figure B-4.

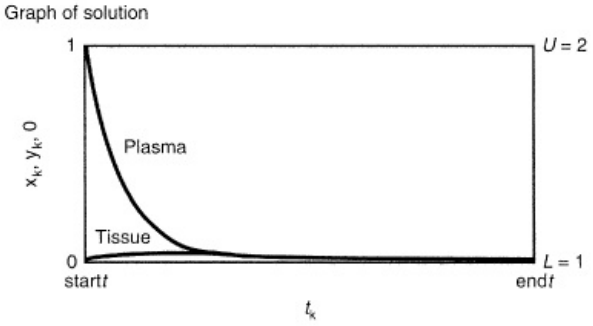
SOLVING A SYSTEM OF DIFFERENTIAL EQUATIONS $k_1 = 0.2$ $k_2 = 1$ $k_3 = 3$

x and y are functions of the time variable t, and F and G are the derivatives dx/dt and dy/dt.

$F(t,x,y) = k_2 \cdot y - [k_3 + k_1] \cdot x$

$G(t,x,y) = k_1 \cdot x - k_2 \cdot y$

startt = 0 endt = 4 n = 100 intervals initx = 1 inity = 0



k	x_k	y_k
0	1	0
1	0.88	0.007
2	0.775	0.014
3	0.682	0.019
4	0.601	0.023
5	0.53	0.027
6	0.467	0.029
7	0.412	0.032
8	0.364	0.033
9	0.321	0.035
10	0.284	0.036

Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

A sample of the MathCAD application program used to solve the two-differential equation for a two-compartment model after IV bolus dose. (The first 10 data points are shown.)

Model Fitting

An example of a set of oral plasma data was fitted to a one-compartment model by RSTRIP (). The software makes an initial estimate as well as a final parameter after several iterations. An example of some oral plasma data was generated with PCNonlin (, ,).

Figure B-5.

Summary of Least Squares for dataset oral absorption

computation time:	1.04 secs	A[1]= 12.801	k[1]= 0.40724
calculated lag time:	0.00000	k[2]= -12.800	k[2]= 1.9428
sum of squared residuals:	0.0048572		
Model Selection Criterion:	8.1157		
Weighting Factor:	0.00000		

time	y-obs	y-calc	resid	wt*res-sq
0.00000	0.00000	0.00051906	-0.00051906	2.694E-007
0.40000	5.0000	4.9919	0.0080675	6.509E-005
0.80000	6.5000	6.5363	-0.036276	0.0013160
1.2000	6.6600	6.6087	0.051306	0.0026323
2.0000	5.3900	5.4062	-0.016228	0.00026334
2.4000	4.6800	4.6961	-0.016060	0.00025791
2.8000	4.0300	4.0373	-0.0072648	5.278E-005
3.2000	3.4500	3.4520	-0.0020411	4.166E-006
3.6000	2.9500	2.9431	0.0069157	4.783E-005
4.0000	2.5200	2.5053	0.014746	0.00021745

press any key to continue

Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Sample output from RSTRIP pharmacokinetic software showing a good fit of the theoretical data to actual data (columns 2 and 3). The parameters estimated are given in the top right-hand corner.

Figure B-6A.

```
LISTING OF INPUT COMMANDS

MODEL 3, 'ONE'
MODEL 3
REMARK   ONE COMPARTMENT MODEL - FIRST ORDER INPUT AND OUTPUT
REMA
REMA     NO.     PARAMETER         CONSTANT         SECONDARY PARM.
REMA     ---     ---------         --------         ---------------
REMA     1        VOLUME             DOSE               AUC
REMA     2         K01                                 K01 HALF LIFE
REMA     3         K10                                 K10 HALF LIFE
REMA     4                                               TMAX
REMA     5                                               CMAX
REMA*****************************************************************
REMA              I----------------------I
REMA              I                      I
REMA    K01   --> I    COMPARTMENT 1     I   ---> K10
REMA              I                      I
REMA              I----------------------I
REMA*****************************************************************
COMM
NPARM 3
NCON 1
MSEC 5
PNAMES 'VOLUME', 'K01', 'K10'
SNAMES 'AUC', 'K01-HL', K10-HL', 'TMAX', 'CMAX'
END
TEMP
D=CON(1)
V=P(1)
K01=P(2)
K10=P(3)
T=X
END
FUNC1
COEF=D*K01/(V*(K01-K10))
F=COEF*(DEXP(-K10*T)-DEXP(-K01*T))
END
SECO
S(1)=D/V/K10
S(2)=-DLOG(.5)/K01
S(3)=-DLOG(.5)/K10
TMAX=(DLOG(K01/K10)/(K01-K10))
S(4)=TMAX
S(5)=(D/V)*DEXP(-K10*TMAX)
END
EOM
CONS 250
INIT 100.7, 1.03, .13
NOBS 9
DATA
BEGIN

PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION WEIGHTED SS       VOLUME        K01           K10
   0       1.34180           100.7        1.030          .1300
                  TAU  = .1583E-04   RANK = 3   COND = 1049.
   1       .136818           100.7         .5689         .1706
                  TAU  = .1108E-04   RANK = 3   COND = 1701.
   2       .358976E-01       100.7         .4396         .1788
                  TAU  = .1008E-04   RANK = 3   COND = 2489.
   3       .357194E-01       100.7         .4439         .1795
                  TAU  = .1005E-04   RANK = 3   COND = 2451.
   4       .357049E-01       100.7         .4442         .1791
                  TAU  = .1008E-04   RANK = 3   COND = 2447.
   5       .356635E-01       99.63         .4392         .1816
                  TAU  = .9998E-05   RANK = 3   COND = 2473.
   6       .356553E-01       99.63         .4383         .1815
                  TAU  = .1000E-04   RANK = 3   COND = 2481.

CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN        .000100
    6      .356533E-01       99.57         .4377         .1817
```


Sample output from PCNONLIN showing data fitted to Model 3, a one-compartment model with first-order absorption and first-order elimination.

Figure B-6B.

PARAMETER	ESTIMATE	STANDARD ERROR	95% CONFIDENCE LIMITS		
VOLUME	99.568030	19.182331	52.630524	146.505537	UNIVARIATE
			24.795837	174.340224	PLANAR
K01	.437738	.117793	.149508	.725969	UNIVARIATE
			-.021417	.896894	PLANAR
K10	.181749	.043746	.074706	.288792	UNIVARIATE
			.011228	.352271	PLANAR

*** SUMMARY OF NONLINEAR ESTIMATION ***

FUNCTION 1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARDIZED RESIDUAL
1.000	.7000	.8085	-.1085	1.000	.4987E-01	-1.847
2.000	1.200	1.196	.3927E-02	1.000	.4740E-01	.6460E-01
3.000	1.400	1.334	.6581E-01	1.000	.4034E-01	1.002
4.000	1.400	1.330	.7008E-01	1.000	.4253E-01	1.090
6.000	1.100	1.132	-.3226E-01	1.000	.4620E-01	-.5228
8.000	.8000	.8737	-.7371E-01	1.000	.4000E-01	-1.119
10.00	.6000	.6435	-.4349E-01	1.000	.3919E-01	-.6552
12.00	.5000	.4624	.3760E-01	1.000	.4469E-01	.5986
16.00	.3000	.2305	.6954E-01	1.000	.4888E-01	1.167

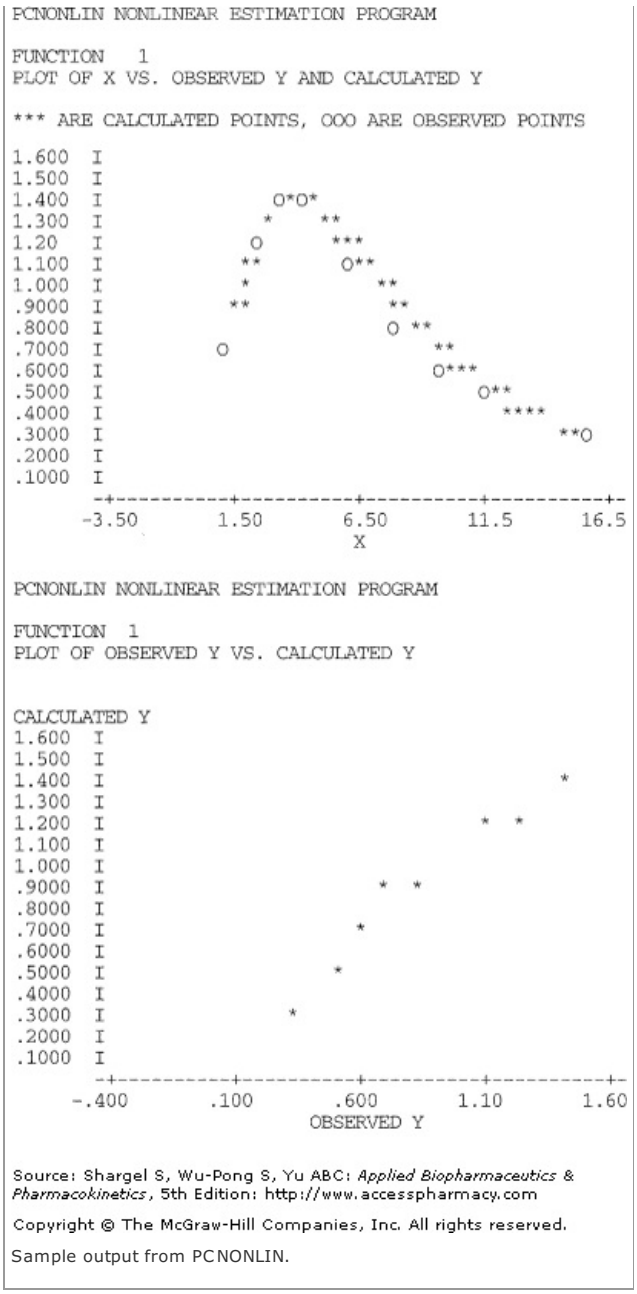
CORRECTED SUM OF SQUARED OBSERVATIONS = 1.28889
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 1.28889
SUM OF SQUARED RESIDUALS = .356533E-01
SUM OF WEIGHTED SQUARED RESIDUALS = .356533E-01
S = .770857E-01 WITH 6 DEGREES OF FREEDOM

SUMMARY OF ESTIMATED SECONDARY PARAMETERS

PARAMETER	ESTIMATE	STANDARD ERROR
AUC	13.814898	.847009
K01-HL	1.583474	.425680
K10-HL	3.813757	.917038
TMAX	3.433715	.217994
CMAX	1.345203	.040455

Sample output from PCNONLIN.

Figure B-6C.



Sample output from PCNONLIN.

Example 3

After a drug is administered orally, a series of plasma drug concentrationâ€"time data may be fitted to a one-compartment model, to estimate the absorption rate constant, elimination rate constant, and volume of distribution. Other pharmacokinetic parameters of interest may also be calculated using the NONLIN program, as shown in , , . Three parameters were estimatedâ€"*V*, k_{01}, and k_{10}â€"representing volume of distribution, k_a, and *k* (see model). Initial estimates were derived from either curve stripping or feathering. Dose is CON (1). In this case, NOBS = 9, showing that there are 9 data points. There is only one function that describes the model FUNC 1. S(1) represents the calculation of AUC, S(2) the calculation of absorption, and S(3) the calculation of elimination half-life.

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