University of Southern California

ADAPT 5

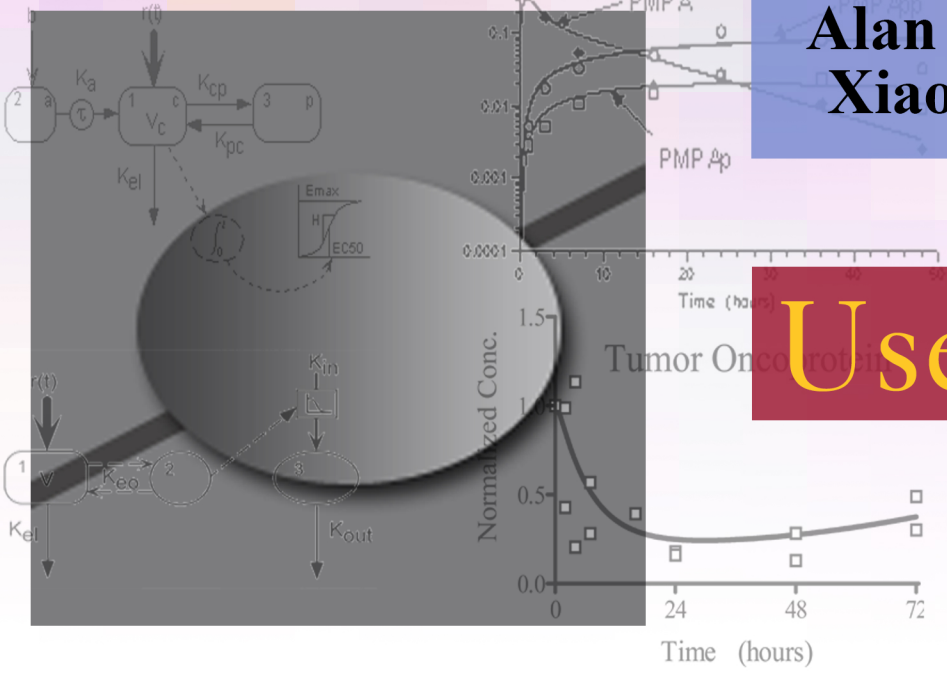
Pharmacokinetic/Pharmacodynamic Systems Analysis Software

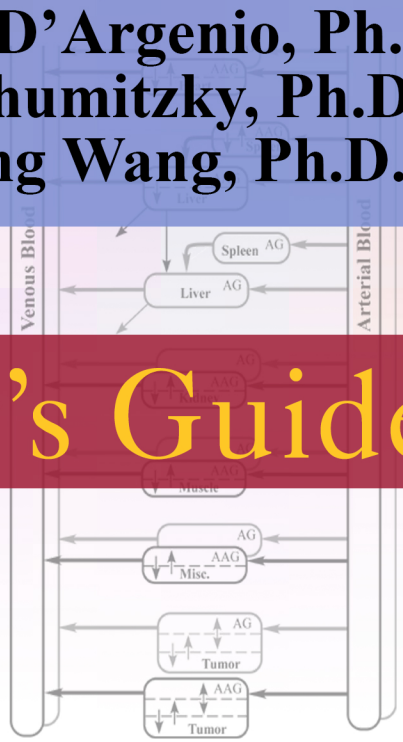
Biomedical Simulations Resource (BMSR)

by

David Z. D'Argenio, Ph.D.
Alan Schumitzky, Ph.D.
Xiaoning Wang, Ph.D.

User's Guide





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ADAPT User's Guide Series

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Preface to ADAPT 5

ADAPT 5 represents a major new version of ADAPT and includes the addition of population modeling capabilities. In accomplishing these additions and enhancements we have worked to maintain the programs generality, flexibility and computational robustness.

We would like to thank some current and former graduate students and postdoctoral fellows who have contributed to the testing and evaluation of ADAPT 5: Phyllis Chan, Joy Hsu, Ritesh Jain, Dongwoo Kang, Brittany Kay, Tong Lu, Gabriela Mallen-Ornelas, Kyung-Soo Park, Min-Hyung Park, Nathalie Poupin, Linh Van, Jian Wang, Xiaoning Wang, Lu Xu, Zexun Zhou, and Rui Zhu. We also acknowledge Ashutosh Gandhi for programming the ADAPT 5 interface, Amy Joe for help with the ADAPT Library, and Andrew Bae and Christine Lee for their work on this User's Guide and the BMSR web site. We gratefully express our appreciation to BMSR collaborators and other colleagues for their suggestions and for providing stimulating applications: Edward Acosta, Michael Amentea, Kyun-Seop Bae, Robert Bauer, Stacey Berg, Paul Berringer, Jan Beumer, Richard Brundage, Jurgen Bulitta, George Drusano, Murray Ducharme, Laszlo Endrenyi, Merrill Egorin, Julie Eiseman, Courtney Fletcher, Alan Forrest, Iztok Grabnar, Mathew Hsu, Shasha Jumbe, William Jusko, Wojciech Krzyzanski, Jean Lavigne, Jian-Feng Lu, Donald Mager, Daniel Maneval, Giovanni Pacini, Carl Panetta, Mark Ratain, Mary Relling, Keith Rodvold, Gary Rosner, Thomas Sun, Jurgen Venitz, Davide Verotta, Paolo Vicini, Jon Wakefield, and Michael Weiss.

The feedback and advice we continue to receive from many users (far too many to list here) have served as an important impetus for the significant enhancements included in ADAPT 5; we greatly appreciate your contributions. As always, please contact us with any questions, suggestions and comments about ADAPT, as well as corrections and suggestions for this User's Guide.

ADAPT has been developed by the Biomedical Simulations Resource at the University of Southern California, under support from the National Institute for Biomedical Imaging and Bioengineering (NIBIB) at the National Institutes of Health. (P41-RR01861). We gratefully acknowledge the advice and support of Dr. Grace Peng, Program Director at NIBIB over the past years. Over the past 10 years the BMSR has been the fortunate beneficiary of the expert administrative skills of Marcos Briano – thank you Marcos!

It is with great pleasure and immense gratitude that we dedicate this User's Guide to Roger W. Jelliffe and to the memory of John Rodman.

Los Angeles
July 2009

David Z. D'Argenio
Alan Schumitzky
Xiaoning Wang

Preface to the Fourth Release

Release 4 of ADAPT is a continuation of our efforts to develop, distribute and support computational software for use in pharmacokinetic/pharmacodynamic systems analysis. A number of enhancements to ADAPT are incorporated in Release 4, including expanded capabilities for modeling pharmacokinetic/pharmacodynamic processes, an extensive library of models and an expanded User's Guide. Chapter 1 of the User's Guide reviews these and other new features included in Release 4. Versions of Release 4 of ADAPT are available for several computing environments as listed in Chapter 1.

ADAPT is developed as part of the Service function of the Biomedical Simulations Resource at the University of Southern California, with support from the Biomedical Technology Program of the National Center for Research Resources at the National Institutes of Health (P41-RR01861). We are also grateful to our colleagues Alan Forrest, Darryl Katz and John Rodman for their continued contributions to the development of ADAPT. In addition we would like to acknowledge the programming efforts of Jun Chen, Dilip Jain and Qiuyan Zhang. We would also like to thank Jocelyn De Guzman for her expert help in preparing the User's Guide, and Lisa Bartoli and Nicole Smith for their assistance in preparing the examples illustrated in the User's Guide.

The feedback we have received from many users has contributed significantly to Release 4 of ADAPT. We would like to especially thank the following people who have generously shared with us their suggestions and ideas: William Bachman, Robert Bauer, Alan Boddy, Richard Brundage, George Drusano, William Ebling, Merrill Egorin, Tom Hennessy, Paul Hutson, Paul Laub, Daniel Maneval, Soren Rasmussen, Gerard Sirois, Lloyd Whitfield, Yuri Yanishevski. We appreciate receiving questions, suggestions and comments from ADAPT users and will do our best to respond to your requests.

Los Angeles
March 1997

David Z. D'Argenio
Alan Schumitzky

Preface to the Third Release

ADAPT II is now available for the following three computing environments: VAX/VMS; DOS; SUN/UNIX. Appendices A, B, and C of this manual provide information concerning installation, system requirements and program execution of the VAX/VMS, DOS and SUN/UNIX versions of ADAPT II, respectively. Before installing Release 3 of ADAPT II please consult the relevant appendix for specific instructions. All ADAPT Model Files and Data Files created with previous releases of ADAPT II are compatible with Release 3. The examples included in this revision of the User's Guide have been obtained using the DOS version of the program.

Release 3 of ADAPT II includes a SUN/UNIX version of the package (new with this release), and incorporates significant enhancements to the graphics capabilities of the DOS version (see Appendix B), as well as a number of corrections, modifications and additions to the programs (see Chapters 4.5.3 and 4.5.4 of the User's Guide). The ADAPT Driver for the DOS version of the programs has also been redesigned and rewritten as a DOS batch program (see Chapters 1.2, 1.3 and Appendix B.4 of the User's Guide). The UNIX version of the package is supported for Sun Microsystems hardware and requires the Sun Fortran Compiler version 1.3 or higher. It can be run from Sun Workstations via SunView or X Windows, or from a terminal capable of VT100 and Tektronix emulation. While the UNIX version of ADAPT II is only supported for the Sun Fortran Compiler, we expect that it can be readily ported to other UNIX environments. User's interested in installing ADAPT II on other UNIX machines are welcome to contact us for advice.

As always, we appreciate receiving questions, suggestions and comments from ADAPT II users and will do our best to respond to your requests. We would ask that the use of ADAPT II be acknowledged in research publications, as appropriate, by citing this user's guide: D. Z. D'Argenio and A. Schumitzky. ADAPT II User's Guide. Biomedical Simulations Resource, University of Southern California, Los Angeles, 1992. The contributions of the following people to the programming effort for Release 3 of ADAPT II are gratefully acknowledged: Nicolas Rouquette, Tarun Jain, Qiuyan Zhang.

Los Angeles
February 1992

David Z. D'Argenio
Alan Schumitzky

Preface to the Second Release

The Second Release of ADAPT II includes implementations for the DOS as well as the VAX/VMS environments. Specific details concerning installation, system requirements and program execution are provided in Appendix A (VAX/VMS version) and Appendix B (DOS version). Both of these versions have identical capabilities, with the exception of some differences in the graphics options. In response to suggestions and comments from current users of ADAPT II, several revisions and enhancements have also been made to this new release. These include: improved capability for analysis of population simulation results; additional error analysis for statistical estimators; file storage option for program results. This User's Guide has also been expanded with more discussion of model specification, and with additional examples illustrating various features of the programs. All model and data files created with the previous release of ADAPT II are compatible with Release 2.

Users of ADAPT II are most welcome to communicate to us any questions, suggestions or comments they may have concerning the package. We also ask that the use of ADAPT II be acknowledged in research publications, as appropriate, by citing this user's guide. (D.Z. D'Argenio and A. Schumitzky. ADAPT II User's Guide. Biomedical Simulations Resource, University of Southern California, Los Angeles, 1990.) Finally, we gratefully acknowledge Kamesh Kothuri of the BMSR scientific programming staff for his significant contributions in the development of the DOS version of ADAPT II.

Los Angeles
April 1990

David Z. D'Argenio
Alan Schumitzky

Preface to the First Release

ADAPT II is distributed as part of the Biomedical Simulations Resource's effort to develop, disseminate and support software designed for the advanced modeling and data analysis applications of the biomedical research community. The programs in ADAPT II have been developed mainly for pharmacokinetic and pharmacodynamic modeling applications. This user's guide describes the capabilities and illustrates the use of ADAPT II. We encourage users of ADAPT II to communicate to us any questions, comments or suggestions concerning the package. We also ask that the use of ADAPT II be acknowledged in research publications, as appropriate, by citing this user's guide. (D.Z. D'Argenio and A. Schumitzky. ADAPT II User's Guide. Biomedical Simulations Resource, University of Southern California, Los Angeles, 1988.)

An early version of ADAPT II was tested and evaluated by J.H. Rodman and his colleagues at the Biomedical Modeling Laboratory, Center for Pediatric Pharmacokinetics and Therapeutics, University of Tennessee. D.C. Maneval of the Department of Biomedical Engineering at the University of Southern California has also tested early versions of these programs. We are especially grateful for their efforts which have contributed significantly to the development of ADAPT II.

We would like to acknowledge the contributions of the BMSR scientific programmers who have been involved with the development of ADAPT II (C.S. Lam, C.C. Tong, A.W. Yueh and V. Krishnan). Some of the numerical analysis software used in ADAPT II was developed by others and is generally available (e.g. LINPACK, EISPACK, LSODA); we would like to thank the developers of these high quality numerical software packages. We would also like to thank T.J. Pearsons of the California Institute of Technology for allowing us to use and distribute the graphics software contained in ADAPT II. Finally, we gratefully acknowledge the contributions of R.W. Jelliffe and W. Wolf in the development of the original version of ADAPT.

Los Angeles
September, 1988

David Z. D'Argenio
Alan Schumitzky

Contents

CHAPTER 1

Introduction

1.1 Overview

The ADAPT software has been developed for pharmacokinetic and pharmacodynamic modeling and data analysis applications and includes tools for individual analysis (simulation - SIM, parameter estimation – ID, sample schedule design - SAMPLE) and for population analysis (parametric maximum likelihood via the EM algorithm - MLEM, iterated two stage - ITS, standard two stage – STS, and naïve pooled data - NPD). It is intended for basic and clinical research scientists and is designed to facilitate the discovery, exploration and application of the underlying pharmacokinetic and pharmacodynamic properties of drugs. ADAPT is also suitable for use in introductory and advanced courses in pharmacokinetics and pharmacodynamics, and includes a library of fundamental models used in teaching drug kinetic and dynamic concepts.

Three principles continue to guide our development of ADAPT. First, the dynamic systems modeling, estimation and control framework of engineering systems theory used widely for physical system applications continues to inform our development efforts. Second, ADAPT is designed to be general and flexible, so that only minimal restrictions are placed on the type of pharmacokinetic/pharmacodynamic model that the user can implement. Third, the software incorporates numerically robust and proven algorithms to perform the program's computations. The generality of ADAPT also makes it a useful tool for dynamic system modeling applications involving sparse data systems that arise in other biomedical research areas such as systems biology, metabolism, endocrinology, biochemistry, toxicology, pharmacology and others.

Since 1985, ADAPT has been developed and supported by the Biomedical Simulations Resource (BMSR) in the Department of Biomedical Engineering at the University of Southern California, under support from the National Institute for Biomedical Imaging and Bioengineering (P41-EB001978) and the National Center for Research Resources (P41-RR01861) of the National Institutes of Health. It is distributed by the BMSR at no charge to the user, under the terms of a Release Agreement.

1.2 Comments on the Benefits of Source Code Distribution

ADAPT was developed initially as an in-house modeling tool for the challenging clinical pharmacokinetic applications of Drs. Roger Jelliffe and John Rodman in the Laboratory of Applied Pharmacokinetics at the University of Southern California. Since that time, we have made the source code for ADAPT freely available to interested researchers [1]. This open-source policy has allowed numerous users to customize the software for use at their own institutions and companies. We appreciate the many users that have informed us of their efforts.

In addition, others have used ADAPT as a platform to implement and test various PK/PD modeling and analysis methods. For example, Dr. Alan Forrest and J. Hawtoff, working in the laboratory of Dr. Merrill Egorin, implemented a general iterated two stage population estimation algorithm based on ADAPT. Dr. Robert Bauer at XOMA (US) wrote a script-based interface for ADAPT (for use within XOMA) and subsequently incorporated population parametric maximum likelihood and Bayesian analysis into this program (currently distributed by the BMSR as S-ADAPT). The experiences derived from the work of Drs. Forrest and Bauer, with their modifications and extensions of ADAPT, have in-turn contributed to the further development of ADAPT as reflected in this current version. Also, methods and algorithms evaluated using the ADAPT platform have then been incorporated into other software (e.g., PDx-MCPEM developed by Dr. Surge Guzy and distributed by ICON Development Solutions), thereby providing an expanded array of tools for use by PK/PD researchers. At this writing, Dr. Bauer is also incorporating the EM and Bayesian parametric population methods, initially implemented and evaluated in the ADAPT platform, into NONMEM for release by ICON Development Solutions.

Thus, beyond the contribution that ADAPT has made to the research of its users, the availability of the source code for the ADAPT platform has benefited other method and software developers, thereby further amplifying its impact on the PK/PD scientific enterprise.

1.3 New Features in ADAPT 5

ADAPT 5 represents a major new version of ADAPT with expanded capabilities and other enhancements, including:

- Parametric population PK/PD modeling using maximum likelihood estimation via the EM algorithm with sampling, as introduced by Schumitzky (1995) and Walker (1996). The program allows for general user defined second stage covariate models and first stage error variance models.
- Iterated two-stage (ITS) analysis as proposed by Prevost (1977) and Steimer, Mallet and colleagues (1984), with general covariate and error variance models.
- Convenient standard two-stage (STS) and naive pooled data (NPD) modeling, each with WLS, ML and MAP estimators.
- ADAPT library of common PK/PD models, each of which is also available as a stand-alone executable program (no compiler required) via the BMSR web site.

With this release we are adopting the now conventional software version numbering scheme (ADAPT 5 is the successor version to ADAPT II, Release 4).

It is with great pleasure that we also welcome Dr. Xiaoning Wang to the ADAPT development effort. Her work on EM methods and population modeling has contributed significantly to ADAPT 5.

1.4 System Requirements

ADAPT 5 is supported for the following platforms:

HARDWARE	COMPILER	OPERATING SYSTEM
PC	Intel Visual Fortran 11.1 (distribution includes version with MVS[1] 2008 Shell and Libraries integrated and the version for MVS 2008/2005 installed separately)	Windows XP/ Server 2003/Vista
PC	Intel Visual Fortran 11.0 (distribution includes version with MVS[2] 2005 integrated and the version for MVS 2008/2005 installed separately)	Windows XP/ Server 2003/Vista
PC	Intel Visual Fortran 10.1 (distribution includes version with MVS[2] 2005 integrated and the version for MVS 2008/2005 installed separately)	Windows XP/ Server 2003/Vista
PC	Intel Visual Fortran 10.0 (distribution includes version with MVS[2] 2005 integrated and the version for MVS 2005 or MVS .NET 2003 installed separately)	Windows XP/ Server 2003/Vista
PC	Intel Visual Fortran 9.1 (MVS 2005 or MVS .NET 2003 must be installed separately)	Windows 2000/XP/ Server 2003
PC	Compaq 6.6c	Windows 2000/XP/Vista

[1]Microsoft Visual Studio.

Alas, the issue of compatible Fortran compilers has been rather confused as the above table reflects - not to mention past migrations from Microsoft to Digital Equipment Corporation to Compaq to Hewlett Packard. Perhaps more stable development and support will result now that Intel has fully transitioned the Fortran compiler into its compiler development efforts. The platforms listed in the above table are the only environments on which ADAPT 5 has been tested and validated.

1.5 Installing ADAPT and Validating the Installation

ADAPT 5 can be downloaded from the BMSR the web site http://bmsr.usc.edu and installed by clicking on the installation icon (one of the above listed compilers must be installed first). The installation can be validated by running the Validation program in the ADAPT Program Group. The pdf file for this User's Guide is accessed via the ADAPT Program Group after installation. The default path for installation of ADAPT is `C:\Program Files\BMSR\ADAPT 5`. The installation folder also includes the subfolder, `\Validation`, that contains all the model, data, parameter and control input files used to validate the ADAPT 5 installation, as well as a subfolder, `\Example`, that includes the files used for the examples in this User's Guide. Another subfolder, `\Library`, contains all the model files that are available in the ADAPT Library.

1.6 About this User's Guide

This User's Guide is intended as the complete reference to ADAPT. It includes chapters on:

How to run ADAPT for new users.

Chapter 2 is a tutorial introduction to ADAPT for those who have had no prior experience with program. It provides a step-by-step introduction illustrating how to write model equations and prepare data for use with ADAPT, and how to construct new models, enter data and run some of the programs. Detailed examples are presented illustrating the basic features ADAPT.

All the details.

Chapters 3-5 document the mathematical and computational methods incorporated in ADAPT for individual and population analysis. Chapter 6 provides specifics on model implementation and program output.

Examples, examples and more examples.

Chapters 7-10 provide examples illustrating almost all of the options in ADAPT. These chapters present pharmacokinetic examples, pharmacokinetic/pharmacodynamic examples, and include examples illustrating individual and population analyses.

Library of models.

Chapter 11 is a library of over 30 different models that are provided with the ADAPT distribution. The Model Files include some common pharmacokinetic and pharmacokinetic/pharmacodynamic models that can be customized for user applications.

1.7 Using and Contributing Library Model Files

All the library models are also available as standalone, executable programs bundled with each of the ADAPT high-level programs. Interested users can download any of these executable programs, together with a sample run, from the BMSR web site. Do you have a model file that can be shared with other ADAPT users? If so, we strongly encourage you to contact the BMSR and we will work with you to publish your model on our web site for others to download.

1.8 Citing ADAPT in Publications

Our ability to further develop and support ADAPT depends on the degree to which it is used by the research community. This is measured in part by the number of scientific publications that use and reference ADAPT. Accordingly, we ask that you acknowledge use of ADAPT in your research publications, as appropriate, by citing this user's guide:

D'Argenio, D.Z., A. Schumitzky and X. Wang. ADAPT 5 User's Guide: Pharmacokinetic/ Pharmacodynamic Systems Analysis Software. Biomedical Simulations Resource, Los Angeles, 2009.

1.9 Learning About the Research Contributions of other ADAPT Users

How do other researchers use ADAPT? The BMSR web site includes a chronological compilation of citations of published journal articles that have referenced ADAPT. If we have missed any of your publications please let us know and we will add them to the list.

1.10 Getting Help and Staying Current

If you have problems installing or using ADAPT you can contact the BMSR:

- E-mail: marcos@bmsr.usc.edu
- Phone: (213) 740-0342
- Fax: (213) 740-0343

Also, from the BMSR Web site (http://bmsr.usc.edu) you can:

- Download ADAPT updates
- Download the complete User's Guide
- Submit questions or suspected program bugs.
- Download stand alone library models
- Get a current list of ADAPT Users' publications

CHAPTER 2

Tutorial Introduction with Examples

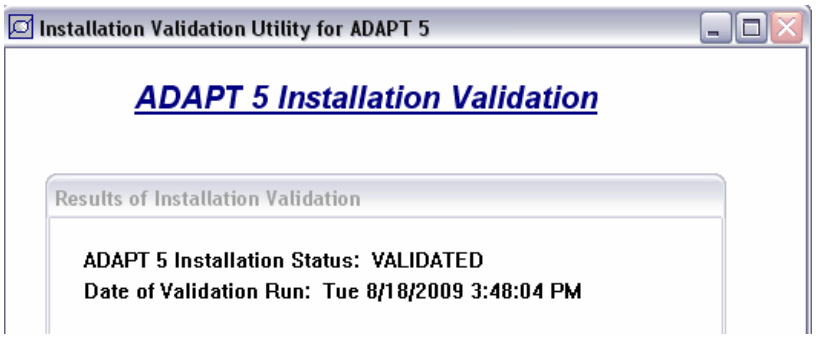
This chapter provides a brief introductory tutorial on the use of ADAPT, including: how to write pharmacokinetic/pharmacodynamic model equations for use with ADAPT; how to code the model equations in a Model File; how to prepare data to be used in ADAPT; how to run ADAPT, with examples illustrating the simulation program SIM and the individual estimation program ID. Experienced ADAPT users often recommend this chapter to other PK/PD researchers and students as a quick introductory overview of ADAPT. Numerous additional examples illustrating the range of PK/PD models that can be implemented in ADAPT, as well as the capabilities of all the ADAPT programs (for individual and population analysis) are given later in the User's Guide. The complete mathematical and computational details for all the methods used in ADAPT as well as the details on the use of the programs are presented in Chapters 3-6 and of this User's Guide. (We gratefully acknowledge the contributions of Brittany Kay and Rui Zhu in preparing this chapter.)

2.1 Installing ADAPT

One of the Fortran compilers described in Chapter 1.4 must first be fully installed on your system (see Chapter 1.4). The Intel Visual Fortran compilers 10.x -11.x are distributed with and without Microsoft Visual Studio components included, and you will need to install the correct version for your system.

After downloading ADAPT 5 from the BMSR the web site click on the ADAPT installation icon. If a previous version of ADAPT 5 has been installed you will be prompted to remove it. The default path for installation of ADAPT is `C:\Program Files\BMSR\ADAPT 5`, which also contains several subfolders including user's guide examples and library models as noted in Chapter 1.5. After successful installation, the installation can be validated by running the Validation program in the ADAPT 5 Program Group as indicated shown below. (On Vista machines it may be necessary to first change the Properties of the ValidateADAPT.exe program in the ADAPT 5 folder as follows: Compatibility Mode – Windows XP (Service Pack 2); Privilege Level – Administrator.)

This process will run over 25 examples invoking various features of all of the ADAPT programs, and will compare the results obtain from the user's installation to the set of results distributed with ADAPT. If these two sets of results are in agreement the window shown below will be displayed. The full set of results from the validation (all files created by ADAPT) are archived in the validation folder. ADAPT 5 has been validated for all of the platforms listed in Chapter 1.4.



If ADAPT is uninstalled, all the files in the installation director will be removed, including those in the `\Validation`, `\Example` and `\Library` folders and any files created by the user. Thus the user should not place his or her project files in the ADAPT installation folder. The `globals.inc` file, however, with any changes made by the user will be retained and used on reinstallation of ADAPT 5 (see Appendix A).

2.2 The ADAPT Interface

When ADAPT is launched (via the ADAPT 5 shortcut in the in the ADAPT 5 Program Group) the window shown below in Figure 2.1 will open. Through its five menus, this interface is used to perform the following tasks: Program – select one of the ADAPT programs (SIM, ID, SAMPLE or MLEM, ITS, STS, NPD); Model – define a model (new, previously created, select one form the library); Data – specify all problem data (new, edit an existing data file, open an existing data file); Parameter – specify parameter values or initial guesses (new, edit an existing parameter file, open an existing parameter file); Batch – specify a command input file (used in program run). These steps are illustrated in the tutorial examples presented below.

Also in the interface window, the Link bottom will compile the model file and link it to the selected ADAPT program. The Run button will then execute the task (program plus model) using the specified data and parameter files.

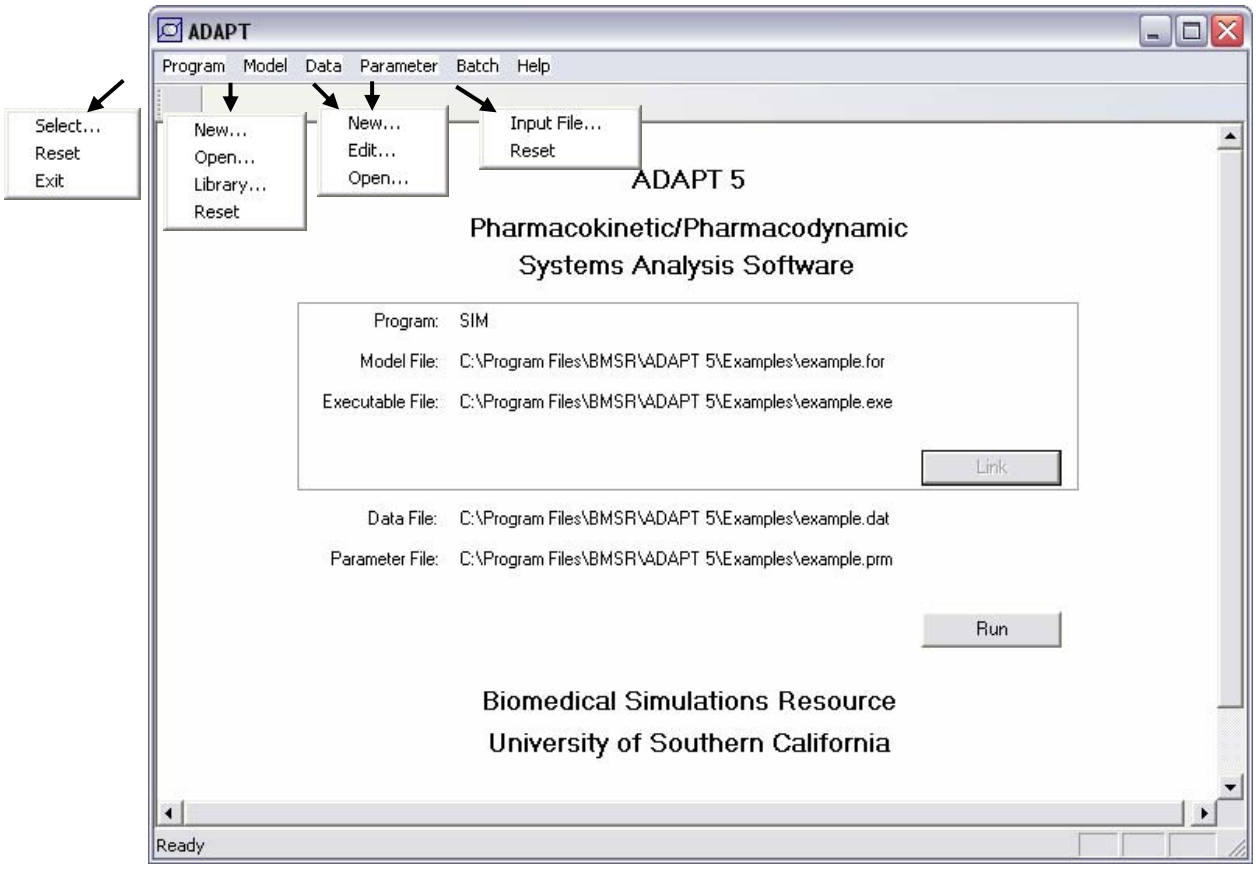
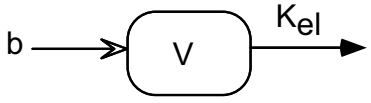


Figure 2.1 ADAPT interface.

2.3 Formulating the Model

2.3.1 Model Equations

Models to be used with ADAPT are written as sets of first-order differential equations, sets of algebraic equations, or both (as described in detail in Chapter 3). This is best illustrated by considering the simplest of pharmacokinetic models, a one compartment model with first-order elimination and bolus injection.



If we let $x(t)$ represent the amount of drug in the compartment at time t, then the following differential equation describes the rate of change of the amount of drug with respect to time:

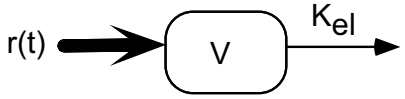
$$\frac{dx(t)}{dt} = -K_{el}x(t) \qquad (2.1)$$

The associated concentration of drug at time t, denoted by $y(t)$, is given by the following output equation:

$$y(t) = x(t)/V \tag{2.2}$$

Note that the bolus input b is not included in either the differential (Eq. (2.1)) or the output (Eq. (2.2)) equations. It is instead specified in an ADAPT Data File, including the dose times at which the bolus is given and the corresponding values for the bolus doses. In the above model equations there are two parameters, K_{el} and V; these are referred to as the system parameters in ADAPT.

How do the above model equations change if, instead of a bolus administration, the drug is administered as an intravenous infusion?



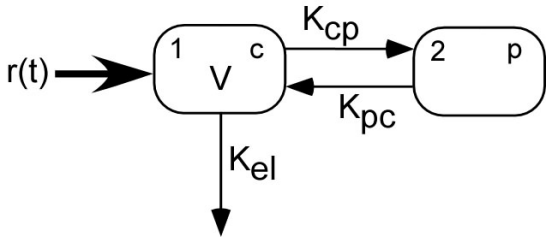
In the case of an infusion input, the variable $r(t)$ appears explicitly in the differential equation, resulting in the following model equations:

$$\frac{dx(t)}{dt} = -K_{el}x(t) + r(t) \tag{2.3}$$

$$y(t) = x(t)/V \tag{2.4}$$

The particular details of the infusion regimen are supplied in an ADAPT Data File. The symbol $r(t)$ is referred to as a model input and, in addition to representing infusion of a drug into a compartment, it can also be used to represent a measured covariate.

Instead of a one-compartment model, suppose the kinetics of the drug under study are to be described by the following linear two-compartment model with intravenous drug infusion:



If we let $x_1(t)$ and $x_2(t)$ represent the amount of drug in compartments 1 and 2, respectively, and let $y(t)$ represent drug concentration in compartment 1, the following differential and output equations describe the model depicted above:

$$\frac{dx_1(t)}{dt} = -\left(K_{el} + K_{cp}\right)x_1(t) + K_{pc}x_2(t) + r(t) \tag{2.5}$$

$$\frac{dx_2(t)}{dt} = K_{cp}x_1(t) - K_{pc}x_2(t) \tag{2.6}$$

$$y(t) = x_1(t)/V \tag{2.7}$$

When using differential equation models, it is necessary to specify the initial condition for each of the differential equation variables. For example $x_1(t=0)$ (`IC(1)`) and $x_2(t=0)$ (`IC(2)`) in the above two-compartment model. These values, along with values (or initial guesses) for the other model parameters, are provided in an ADAPT Parameter File.

The use of both differential and output equations is the most general way to define a model for use with ADAPT. The differential equation variables $x_1(t), \cdots x_n(t)$, can be used to represent: compartment amounts (as in the examples above); tissue concentrations; cellular concentrations; effect site concentrations; physiological variables; ligand concentrations; biomarkers; disease states; etc. The output variables $y_1(t), \cdots, y_l(t)$, can represent any quantities to be measured or predicted including: plasma concentrations; drug exposure; drug effects; etc. The model inputs, $r_1(t),\ldots,r_k(t)$, can represent: drug infusion (of one or more compounds); covariates (e.g., body weight, creatinine clearance, etc.). Chapter 11 describes a number of models supplied with ADAPT, and illustrates how to write the model equations for a broad class of pharmacokinetic and pharmacokinetic/pharmacodynamic models. After reading the current chapter, you should look through the models presented in Chapter 11 as they will provide you with a better understanding of how ADAPT can be used to model a variety of pharmacokinetic and pharmacodynamic processes.

2.3.2 Measurement Model

For some of the options in ADAPT, it is necessary to specify a model for the additive error variance associated with observed data (i.e., error variance model). Observations are collected at discrete times, t_j, and assumed to include additive error as follows:

$$z(t_j) = y(t_j) + e(t_j),\ j = 1,\ldots,m \tag{2.8}$$

In this equation, $z(t_j)$ represents the observed value of the model output $y(t_j)$ at time t_j, and $e(t_j)$ is the associated error. A portion of $e(t_j)$ is attributable to errors in the measurement process.

In ADAPT, $e(t)$ is assumed to be normally distributed, with zero mean and variance given by the user defined variance model. A commonly used error variance model relates the variance of $e(t)$ $\left(\text{var}\{e(t)\}\right)$ to the model output $y(t_j)$ as follows:

$$\text{var}\left\{e(t)\right\} = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2 \tag{2.9}$$

As an example assume $\sigma_{inter} = 0.0$ and $\sigma_{slope} = 0.1$ in Eq. (2.9). Then the variance model represents an error process with a standard deviation of 10% of the measured quantity (i.e., 10% coefficient of variation). Another error variance model is the power model, which can be written:

$$\text{var}\left\{e(t)\right\} = \sigma_0^2 y(t)^{\gamma} \tag{2.10}$$

The parameters appearing in the variance models (σ_{inter} and σ_{slope} in Eq. (2.9) and σ_0 and γ in Eq. (2.10)) are referred to as the variance model parameters. For models with multiple responses, each output can be defined by a unique error variance model.

2.3.3 Secondary Parameters

ADAPT allows for the definition of secondary parameters that can be written as functions of the model system parameters. As an example, the following secondary parameters can be defined for the two-compartment model shown above (Eqs. (2.5)-(2.7)).

$$CL_t = K_{el} \cdot V \tag{2.11}$$

$$CL_d = K_{cp} \cdot V \tag{2.12}$$

$$V_P = V_C \cdot K_{cp} / K_{pc} \tag{2.13}$$

In this example the model is parameterized using rate constants with the secondary parameters used to provide the corresponding clearance parameterization.

2.4 Implementing the Model

The equations for the two compartment model (for example) given above are entered into an ADAPT Model File as follows: 1) from the ADAPT interface, select the Model menu and the New entry in the menu; 2) provide a Model File name and indicate the location for the file that will be created, as illustrated in the screen shot shown in Figure 2.2 below. After saving the Model File, the installed Fortran compiler's development environment will open allowing the user to enter the model equations.

The Model File contains several Fortran subroutines into which you must enter the Fortran code for the parameter symbols, model differential equations, output equations, any error variance model equations, as well as any secondary model parameters and equations. To do this you must follow the syntax rules of the Fortran language and of ADAPT. As shown in the remainder of this section, it is relatively straight forward to translate model equations into Fortran code. (See Chapter for some additional discussion regarding Fortran syntax.)

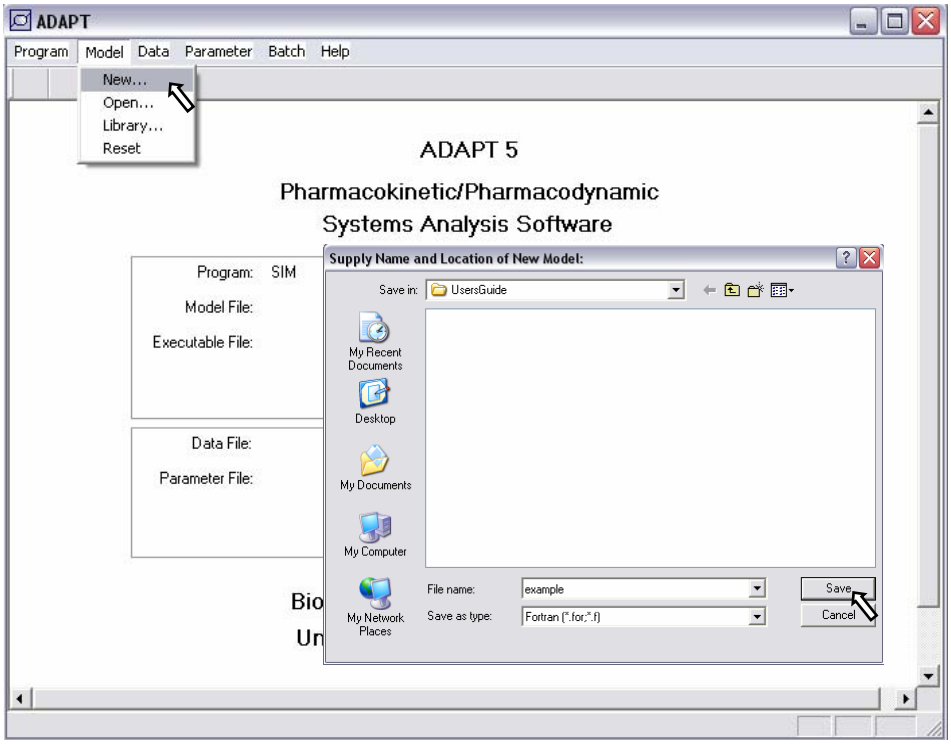


Figure 2.2 Selecting new file from the Model File menu.

To illustrate how to create an ADAPT Model File, consider the two-compartment model presented above as an example. The first step is to relate the algebraic symbols used to define the model differential and output equations in Eqs. (2.5)-(2.7), the variance model equation in Eq. (2.9), and the secondary parameter equations in Eqs. (2.11)-(2.13), to the appropriate Fortran symbols as indicated in the Tables 2.1 and 2.2 below.

Table 2.1 Model Equation Variables

Model Variable	Code
$x_1(t)$	X(1)
$x_2(t)$	X(2)
$y(t)$	Y(1)

Model Variable	Code
$dx_1(t)/dt$	XP(1)
$dx_2(t)/dt$	XP(2)
$r(t)$	R(1)

Table 2.2

System Parameters

Model Variable	Code
K_{el}	P(1)
V	P(2)
K_{cp}	P(3)
K_{pc}	P(4)

Error Variance Model

Model Variable	Code
$\mathrm{var}\{e(t)\}$	V(1)
σ_{inter}	PV(1)
σ_{slope}	PV(2)

Secondary Parameters

Model Variable	Code
CL_t	PS(1)
CL_d	PS(2)
V_p	PS(3)

Figure 2.3 shows the initial portion of the new Model File as it appears in the edit window of the Fortran compiler's development environment. The figure indicates user entries made in Subroutine SYMBOL for: the number of differential equations; the number of system parameters; the number of error variance parameters; the number of secondary parameters; the equation solver method; and a text description of the model.

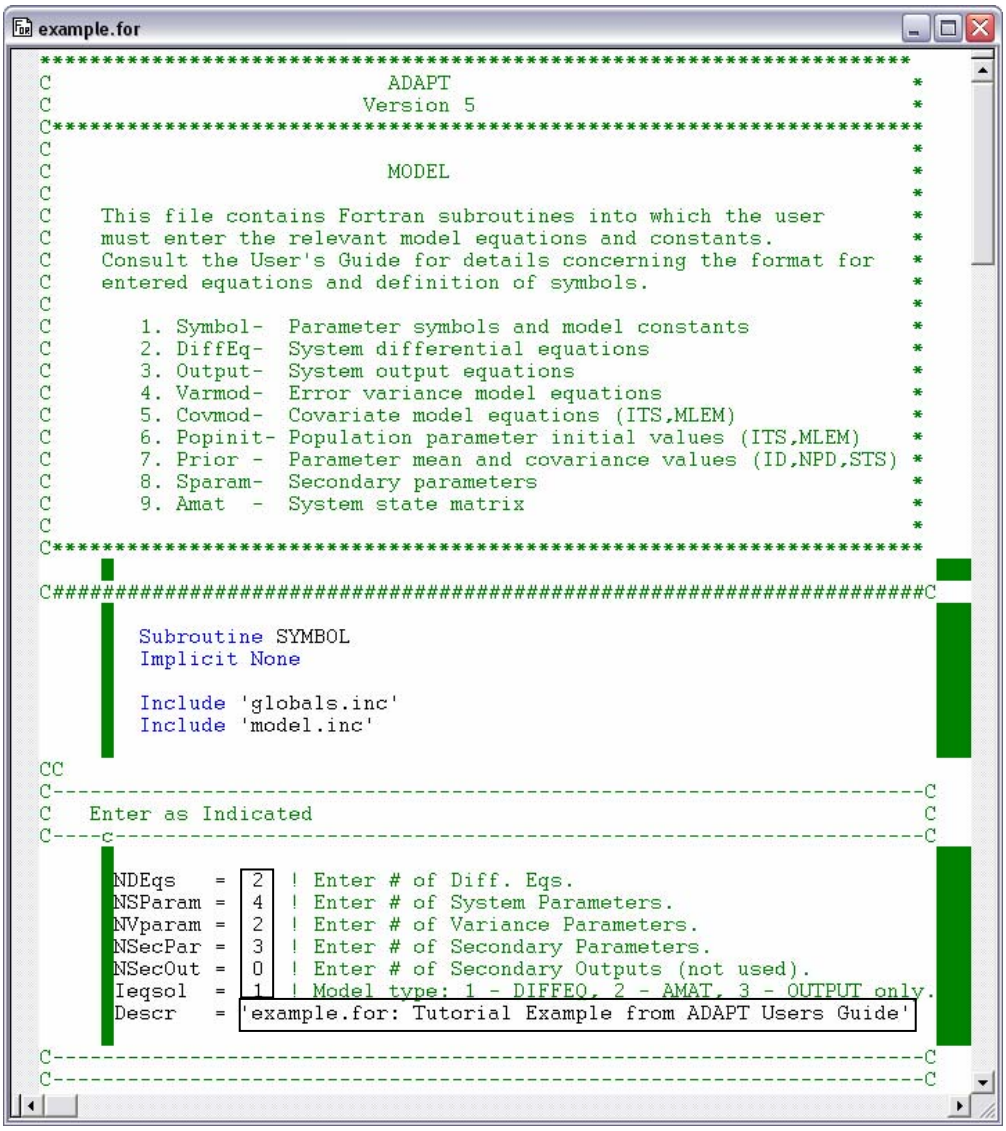


Figure 2.3 A portion of Subroutine SYMBOL from Model File example.for. The entries made by the user are indicated.

The remaining user entries in Subroutine SYMBOL include the symbols for the system parameters, as well as symbols for any error variance model and secondary model parameters. This is illustrated in Figure 2.4 for the example defined above.

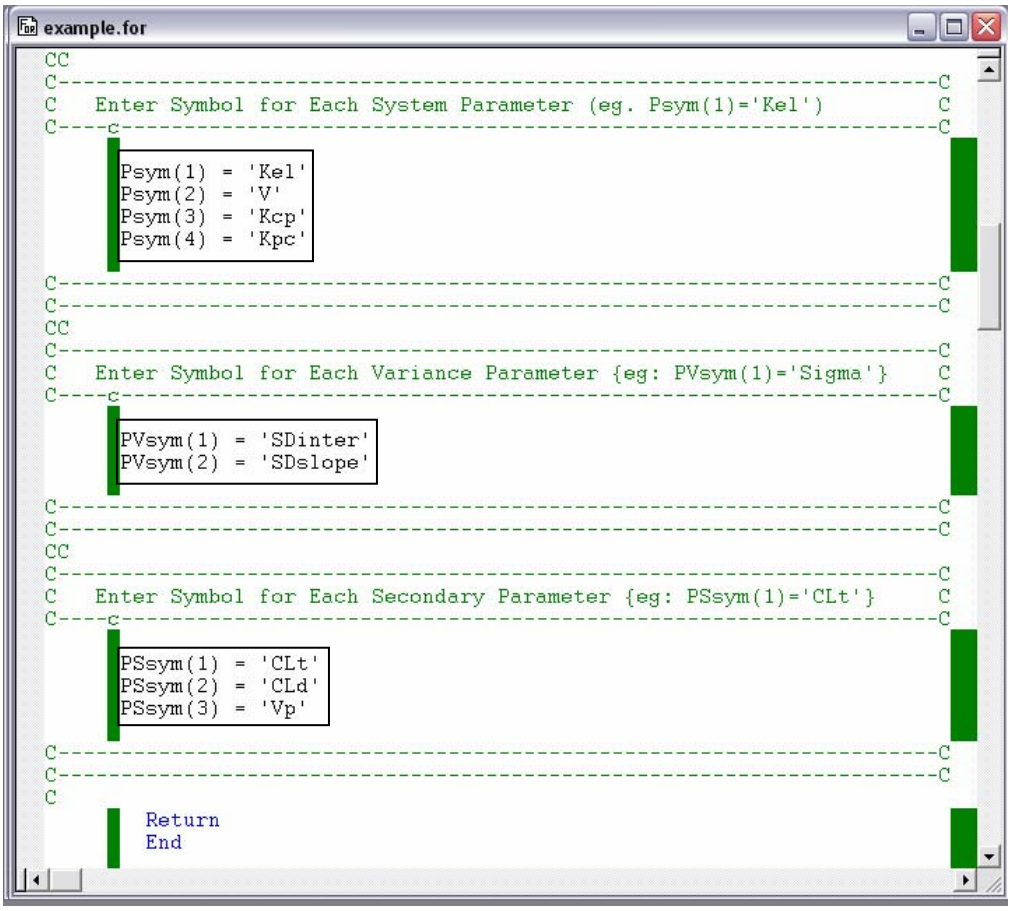


Figure 2.4 The second part of Subroutine SYMBOL from Model File example.for.

Figure 2.5 shows a portion of Subroutine DIFFEQ showing the coded model differential equations. Each equation is entered on a separate line, beginning in column 7 or after, and extending no further than column 72. (To continue an equation on a second line see the examples in Chapter 7.) The Fortran symbols can be entered as either upper case or lower case characters. Figure 2.6 shows a portion of Subroutine OUTPUT illustrating the coded model output equations.

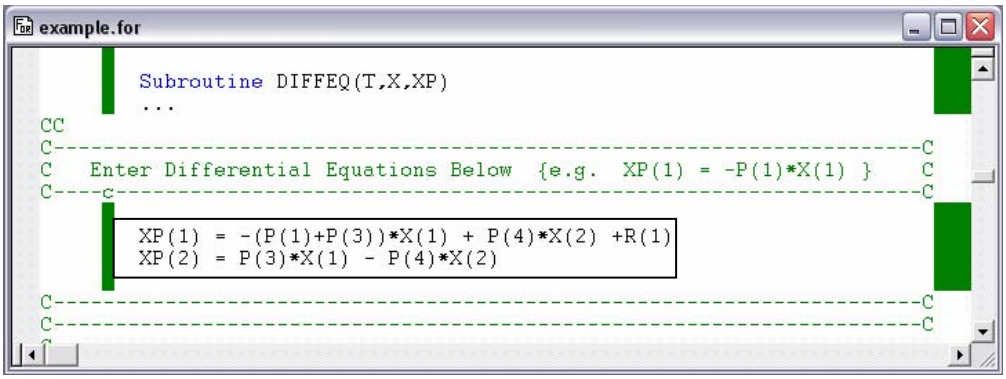


Figure 2.5 Excerpt from Subroutine DIFFEQ illustrating how to code the model differential equations from the Mode File example.for.

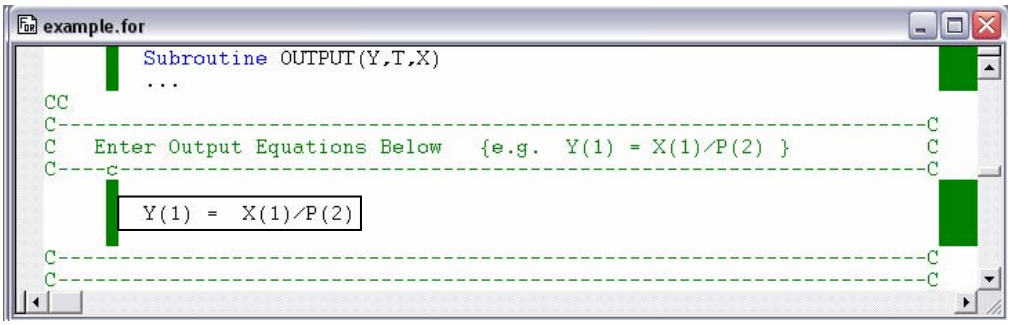


Figure 2.6 Excerpt from Subroutine OUTPUT illustrating how to code model output equations.

Using the above Fortran symbol correspondence, the error variance model given in Eq. (2.9) is coded in Subroutine VARMOD as illustrated in Figure 2.7. Figure 2.8 shows an excerpt from Subroutine SPARAM defining the secondary parameters.

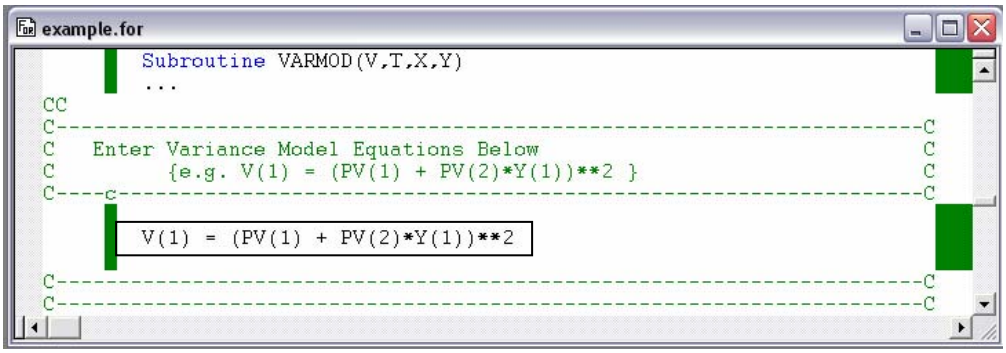


Figure 2.7 Excerpt from Subroutine VARMOD illustrating how to code the variance model

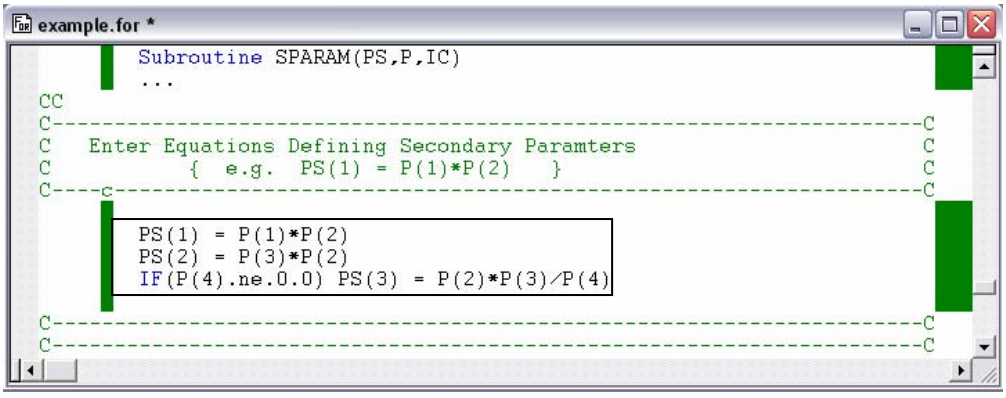


Figure 2.8 Excerpt from Subroutine SPARAM illustrating how to code the secondary parameter equations. Note the code that skips the evaluation of V_P if $K_{pc} = 0$.

2.5 Preparing Data to be used with ADAPT

2.5.1 Model Input Information

To illustrate how to arrange dose regimen information for use with ADAPT, assume a drug is administered as an intravenous infusion and also as an intravenous bolus, with the dose regimen shown in Figure 2.9. To enter the dose regimen in ADAPT it must be supplied as a spreadsheet as illustrated in Table 2.3. In this example, there are five input events. An input event is defined as any time at which one of the model inputs or bolus inputs changes. For each input event, you must supply the associated input event time and the values for any of the model and bolus inputs. (For further details on defining model input information see the examples later in the User's Guide.)

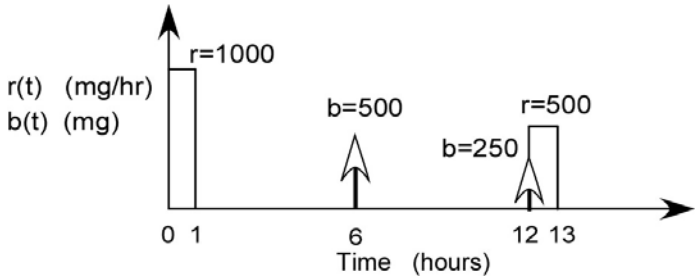


Figure 2.9 Diagram showing the dose regimen for both the intravenous and bolus administration of the drug. In this example there is one model input and one bolus input.

Table 2.3 Model Input Information

Input Event Number	Input Event Time (hr)	Infusion Rate (mg/hr)	Bolus Amount(mg)
1	0.0	1000	0.0
2	1.0	0.0	0.0
3	6.0	0.0	500
4	12.0	500	250
5	13.0	0.0	0.0

2.5.2 Model Output Information

Model output information includes the number of output equations, the number of observations, the observation times and the measured data (when appropriate) for each output. For the two compartment model defined above consider as an example the output information given in Table 2.4.

Table 2.4 Model Output Information

Observation Number	Observation Time (hr)	Measurements (μg/ml)
1	1.0	70.
2	3.0	20.
3	6.0	5.0
4	6.1	50.
5	7.0	30.
6	12.0	5.0
7	13.0	50.
8	15.0	15.
9	17.0	10.
10	20.0	5.0
11	24.0	3.0
12	36.0	1.0

2.5.3 Creating an ADAPT Data File

Given this model input information, a new ADAPT Data File can be created via the ADAPT interface by selecting the Data menu and the New entry in the menu. The entries are made in the appropriate locations as illustrated in Figure 2.10. For the SIM and SAMPLE programs, the entries

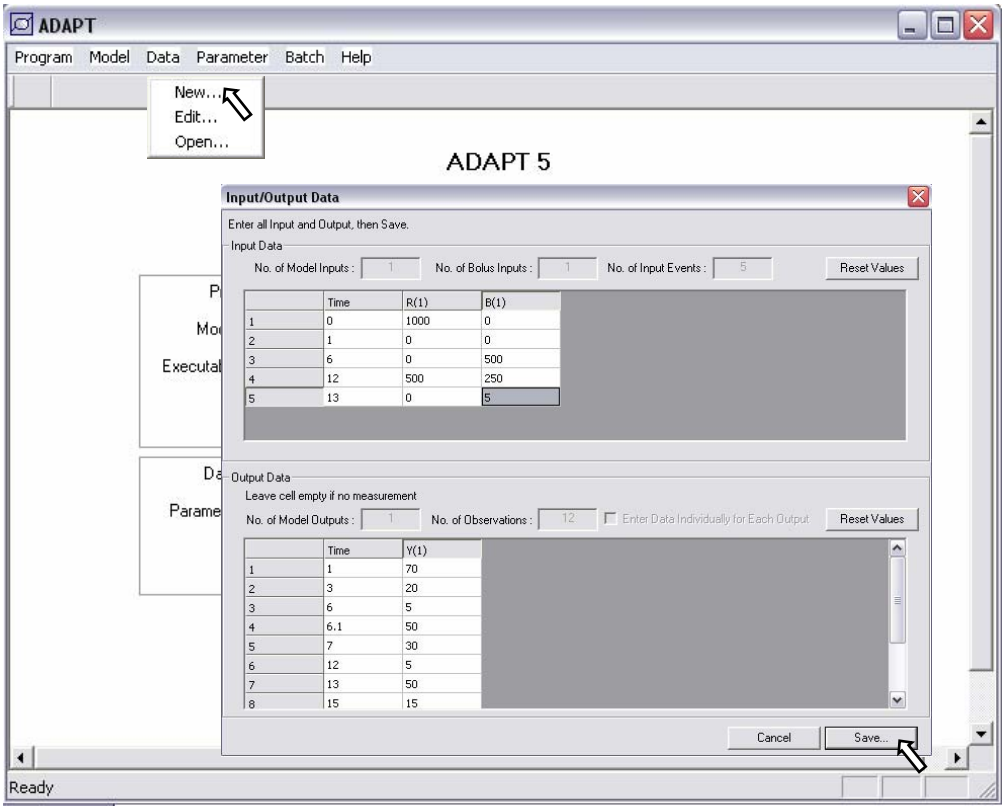


Figure 2.9 Screen shot illustrating how to create an ADAPT Data File.

in the measurement column would be left blank. Finally, name and save the Data File to the same directory that contains the Model File. In this example, the Data File is named “example1.dat” and it will be used below to illustrate the ID program. A Data File without the measurements has been saved in a file named “example.dat” and it will be used below to illustrate the SIM program.

2.6 Creating an ADAPT Parameter File

The ADAPT Parameters File includes values (or initial guesses) for all system parameters including any initial conditions for differential equations, as well as any error variance model parameters. Figure 2.10 illustrate the construction of a Parameter File using the values given in Table 2.5 (a file example.prm is created).

Table 2.5 Parameter values for the two compartment model example.

System Parameters	
K_{el}	0.5
V	10
K_{cp}	0.2
K_{pc}	0.1

Initial Conditions	
IC(1)	0
IC(2)	0

Variance Parameters	
σ_{inter}	0.5
σ_{slope}	0.1

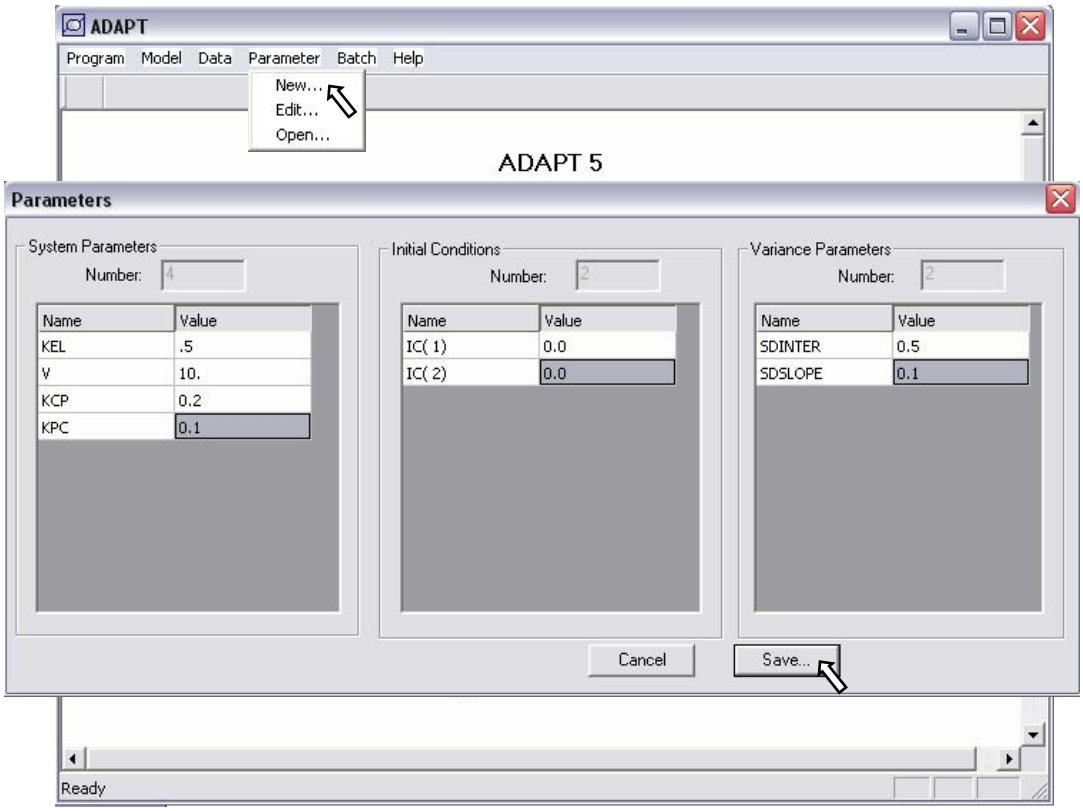


Figure 2.10 Screen shot illustrating how to create an ADAPT Parameter File.

2.7 Sample Run of SIM

To illustrate the SIM program, consider the two-compartment model defined by Eqs. (2.5)-(2.7) above and coded in the Model File example.for. After selecting the program SIM and creating model, data and parameter files through the ADAPT interface, the program and model file can be linked and saved as an executable file and then run as indicated in Figure 2.11. Figure 2.12 shows an overview of the resulting run of the SIM program, with the detailed SIM command, results and plot windows shown in Figures 2.13-2.15.

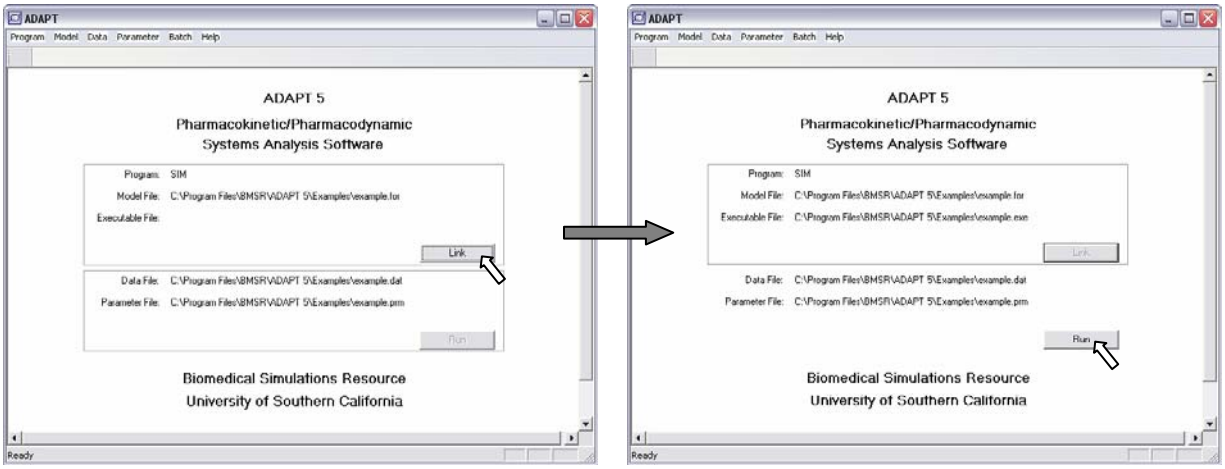


Figure 2.11 Linking (including compiling) and running via the ADAPT interface.

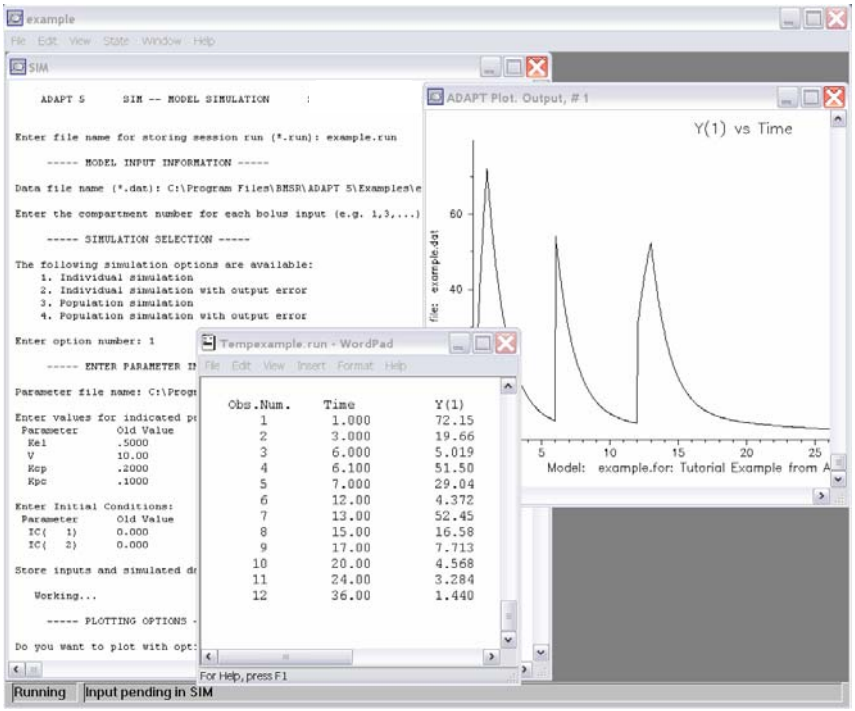


Figure 2.12 Overview of program run via the ADAPT interface, showing the command window (left, background), plot window (right) and results window (center, foreground).

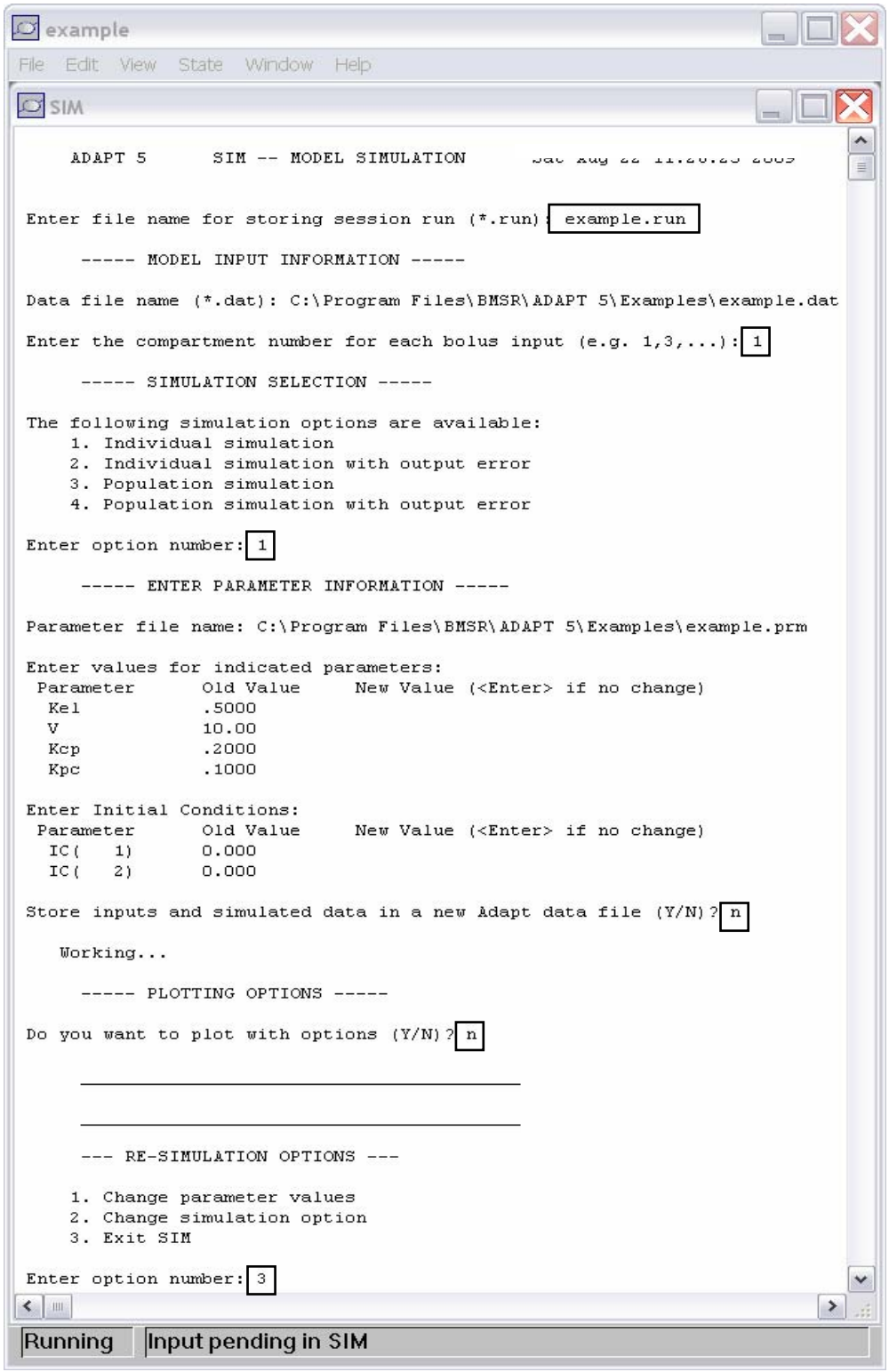


Figure 2.13 SIM program command window with the user's input indicated.

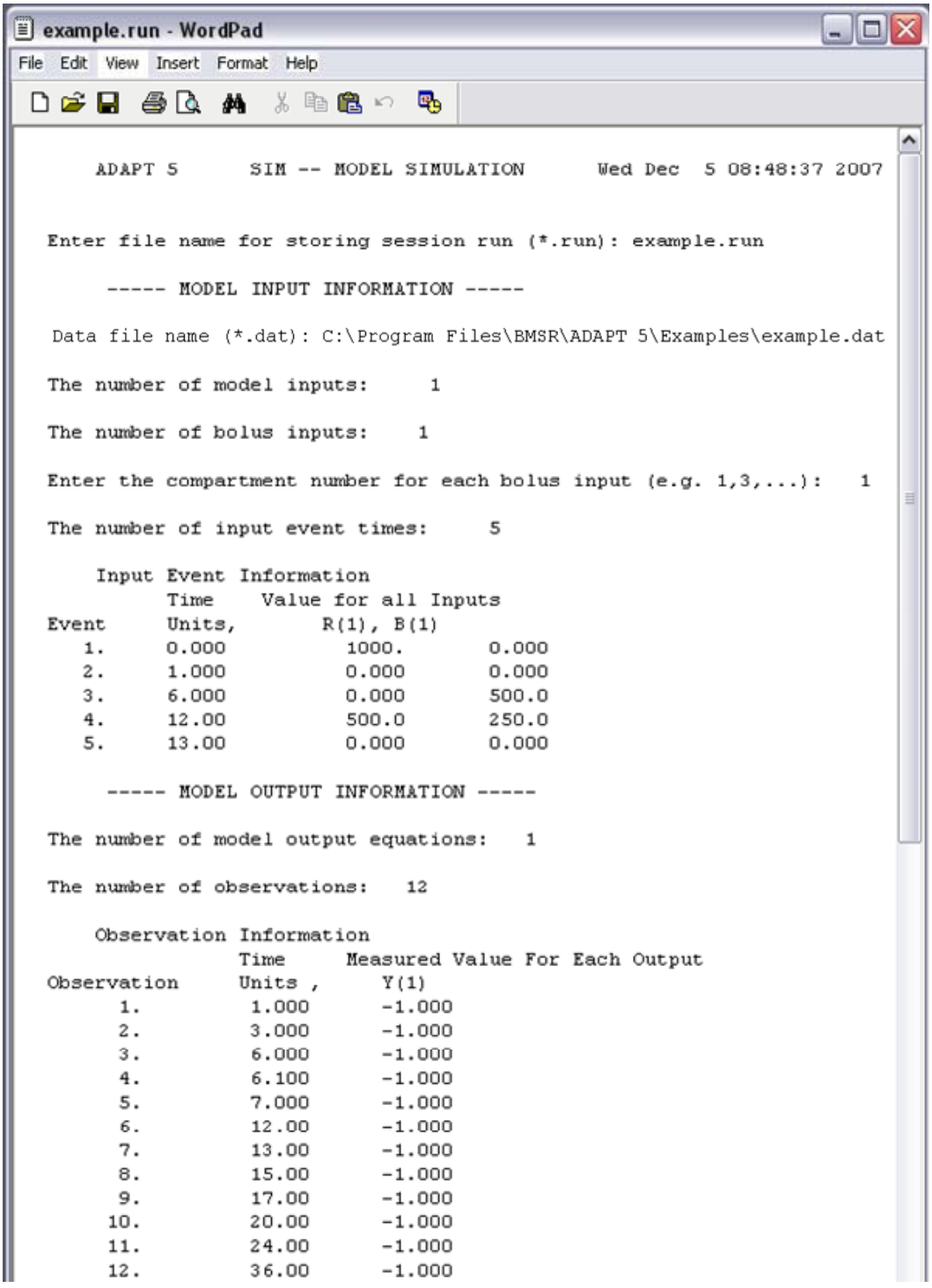


Figure 2.14 A section of the SIM program results window. After exiting the program the complete record of the program dialogue and the results are saved in the named run file (example.run). During the run these results are contained in a temporary file.

```
     ----- ENTER PARAMETER INFORMATION -----

Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\example.prm

Enter values for indicated parameters:
 Parameter      Old Value     New Value (<Enter> if no change)
  Kel           .5000
  V             10.00
  Kcp           .2000
  Kpc           .1000

Enter Initial Conditions:
 Parameter      Old Value     New Value (<Enter> if no change)
  IC(   1)      0.000
  IC(   2)      0.000

Store inputs and simulated data in a new Adapt data file (Y/N)?  n

     ----- RESULTS -----

     --- A. Parameter Summary ---

Wed Dec  5 08:48:51 2007

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\example.dat

Model: example.for: Tutorial Example from ADAPT Users Guide

Individual simulation

Parameter       Value
 Kel           0.5000
 V              10.00
 Kcp           0.2000
 Kpc           0.1000
 IC(  1)        0.000
 IC(  2)        0.000


 CLt            5.000
 CLd            2.000
 Vp             20.00


     --- B. Simulation Summary ---

Wed Dec  5 08:48:51 2007

Data file name: C:\UsersGuide\example.dat

Model: example.for: Tutorial Example from ADAPT Users Guide

Individual simulation

 Obs.Num.     Time          Y(1)
     1         1.000        72.15
     2         3.000        19.66
     3         6.000        5.019
     4         6.100        51.50
     5         7.000        29.04
     6         12.00        4.372
     7         13.00        52.45
     8         15.00        16.58
     9         17.00        7.713
    10         20.00        4.568
    11         24.00        3.284
    12         36.00        1.440
```

Figure 2.14 (Continue)

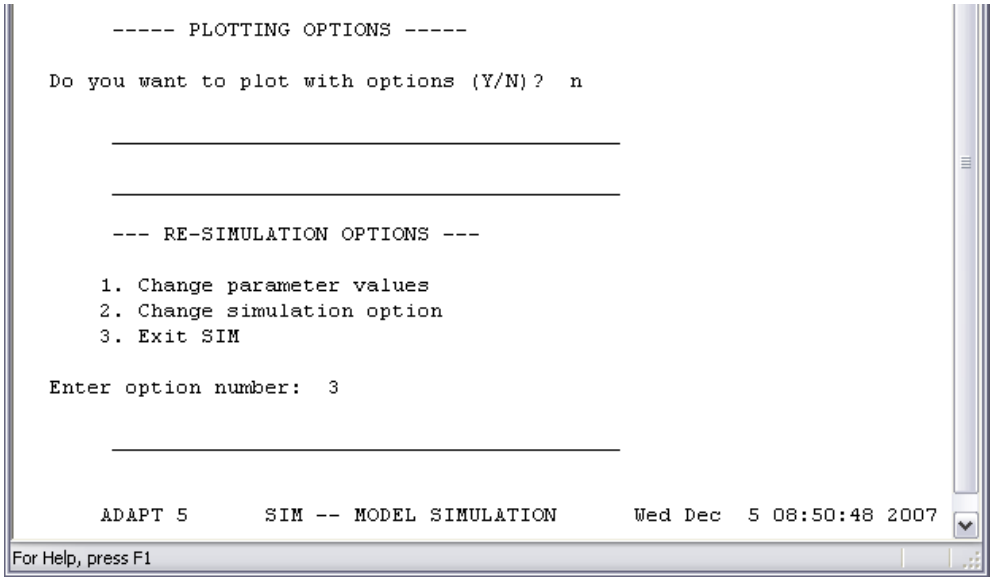


Figure 2.14 (Continue)

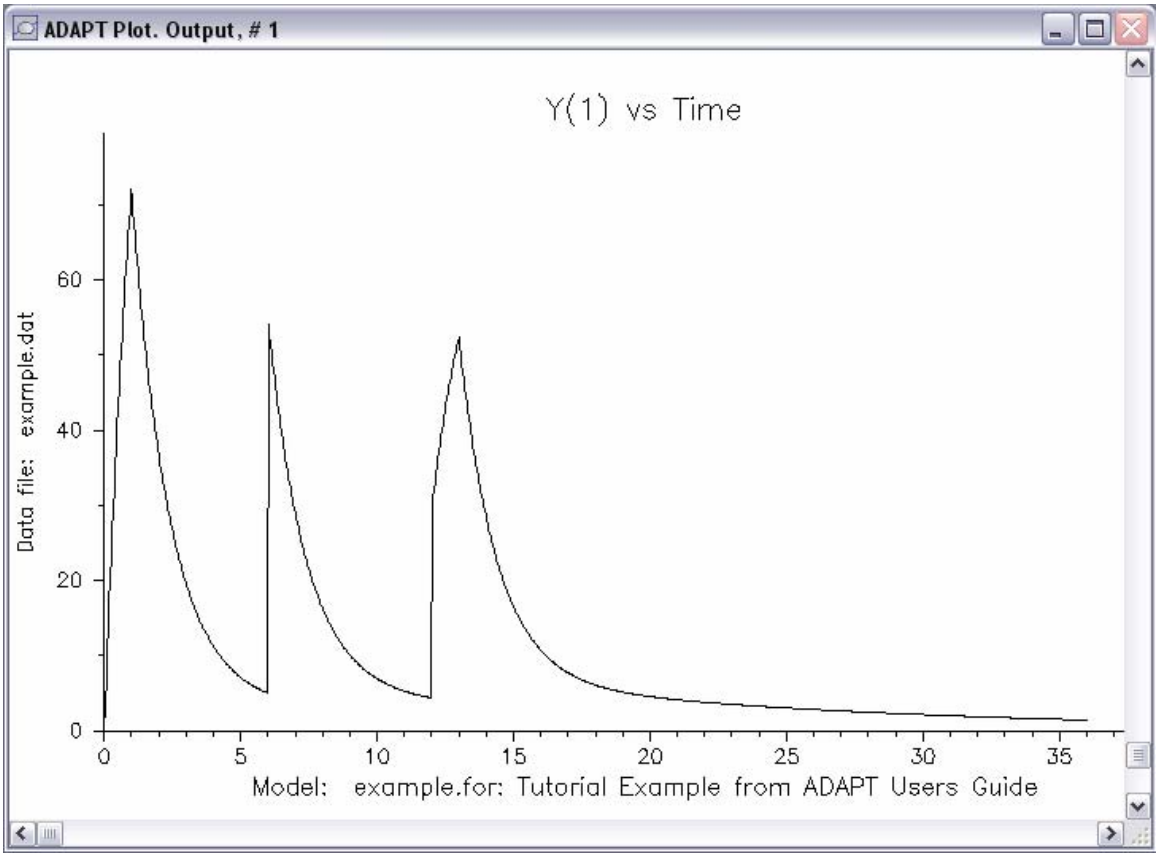
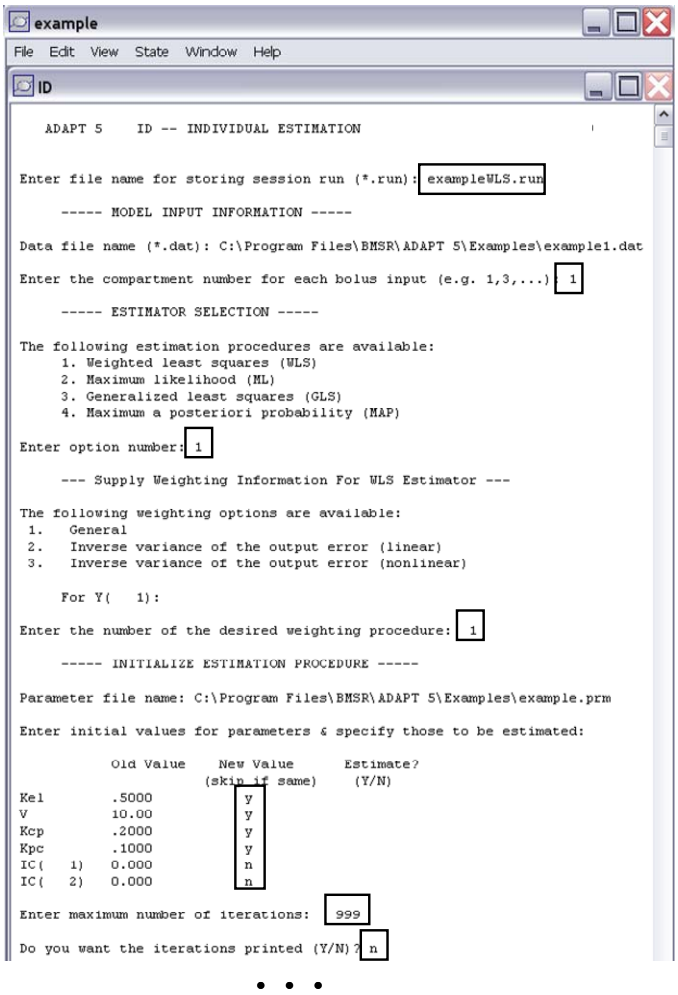


Figure 2.15 A SIM program plot window. After exiting the graph shown in the plot window is also stored as an eps file (example.eps).

2.8 Sample Runs of ID

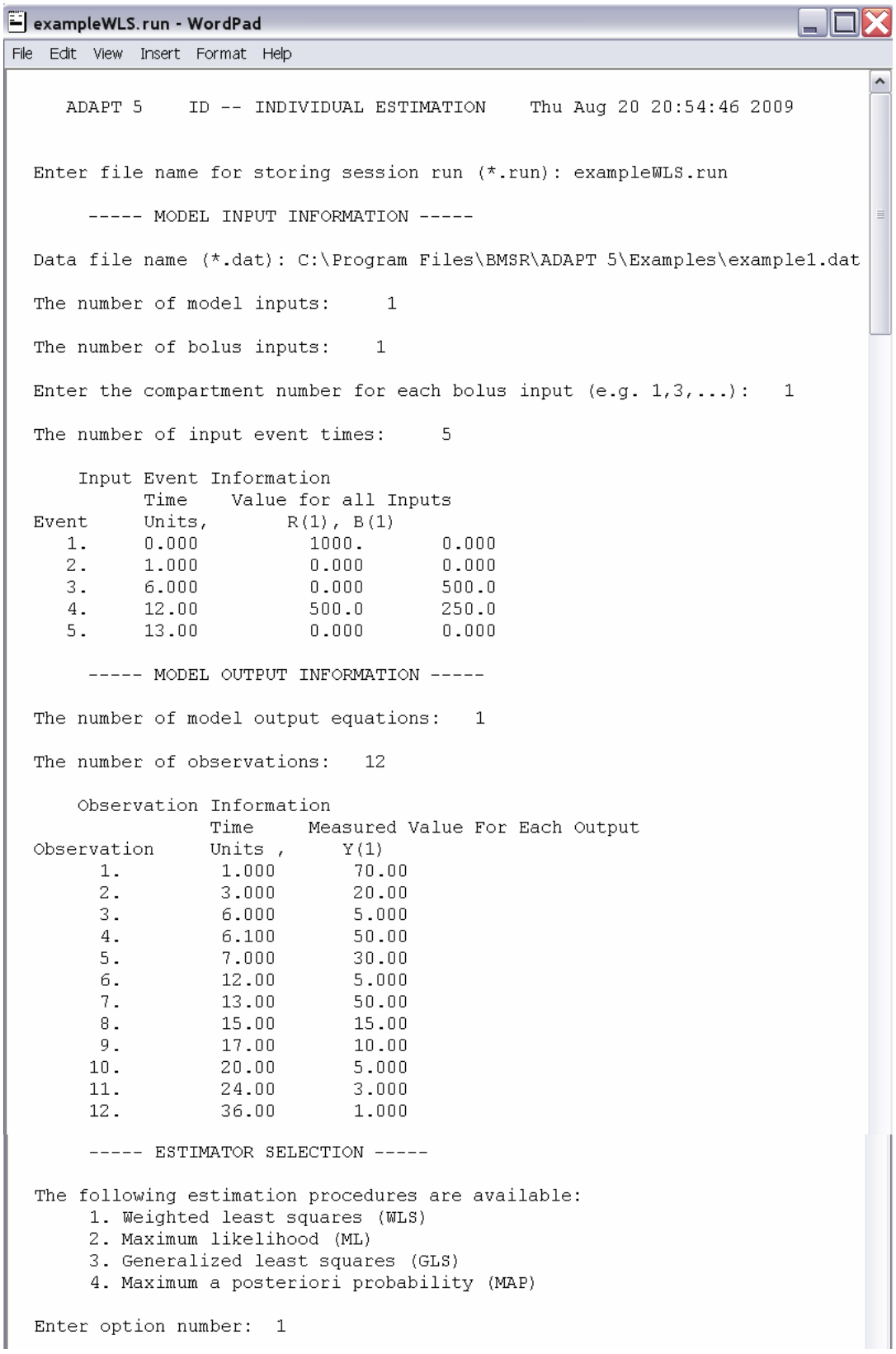
The two-compartment model defined above and encoded in the Model File example.for is used to illustrate the use of the individual subject estimation program, ID. The measured data stored in the file example1.dat (see Table 2.4 above) is used along with the initial guesses for model parameters stored in file example.prm. Examples are presented illustrating both the weighted least squares (WLS) and the maximum likelihood (ML) estimation options of ID. The program, model, data and parameter files are selected via the ADAPT interface (screen shot not shown) as illustrated previously.

Figure 2.16 shows the ID program command window for the WLS run, with sections of the corresponding ID results and plot windows shown in Figures 217 and 2.18. For the WLS estimation example, ordinary least squares is selected (General weighting option). See Chapter 3 for a discussion of the WLS weighting options.



• • •

Figure 2.16 ID program command window for the WLS example.



exampleWLS.run - WordPad

File Edit View Insert Format Help

```
   ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Thu Aug 20 20:54:46 2009


Enter file name for storing session run (*.run): exampleWLS.run

     ----- MODEL INPUT INFORMATION -----

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\example1.dat

The number of model inputs:     1

The number of bolus inputs:    1

Enter the compartment number for each bolus input (e.g. 1,3,...):   1

The number of input event times:     5

    Input Event Information
          Time    Value for all Inputs
Event     Units,       R(1), B(1)
   1.     0.000          1000.       0.000
   2.     1.000          0.000       0.000
   3.     6.000          0.000       500.0
   4.     12.00          500.0       250.0
   5.     13.00          0.000       0.000

     ----- MODEL OUTPUT INFORMATION -----

The number of model output equations:   1

The number of observations:   12

    Observation Information
                Time     Measured Value For Each Output
Observation     Units ,     Y(1)
      1.         1.000       70.00
      2.         3.000       20.00
      3.         6.000       5.000
      4.         6.100       50.00
      5.         7.000       30.00
      6.         12.00       5.000
      7.         13.00       50.00
      8.         15.00       15.00
      9.         17.00       10.00
     10.         20.00       5.000
     11.         24.00       3.000
     12.         36.00       1.000

     ----- ESTIMATOR SELECTION -----

The following estimation procedures are available:
     1. Weighted least squares (WLS)
     2. Maximum likelihood (ML)
     3. Generalized least squares (GLS)
     4. Maximum a posteriori probability (MAP)

Enter option number:  1
```

Figure 2.17 The ID program results window (and run file) for the WLS example.

```
     --- Supply Weighting Information For WLS Estimator ---

The following weighting options are available:
 1.   General
 2.   Inverse variance of the output error (linear)
 3.   Inverse variance of the output error (nonlinear)

     For Y(   1):

Enter the number of the desired weighting procedure:   1

     ----- INITIALIZE ESTIMATION PROCEDURE -----

Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\example.prm

Enter initial values for parameters & specify those to be estimated:

           Old Value    New Value      Estimate?
                       (skip if same)    (Y/N)
Kel        .5000            y
V          10.00            y
Kcp        .2000            y
Kpc        .1000            y
IC(   1)   0.000            n
IC(   2)   0.000            n

Enter maximum number of iterations:       999

Do you want the iterations printed (Y/N)?  n

            ----- RESULTS -----

            --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      Kel        =   0.5000
      V          =    10.00
      Kcp        =   0.2000
      Kpc        =   0.1000

    Weighted Least Squares =  22.4894


             ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =    42
    Number of function calls  =   174

     Fitted Parameters
      Kel        =   0.4999
      V          =    10.41
      Kcp        =   0.2004
      Kpc        =   0.1468

    Weighted Least Squares =  10.1794
```

Figure 2.17 (continued)

```
            --- C. WLS Estimation Summary---

Thu Aug 20 20:55:37 2009

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\example1.dat

Model:  example.for: Tutorial Example from ADAPT Users Guide

Weighting Information
  Option for Y( 1):  1

Convergence achieved
  Number of iterations:          42
  Number of function calls:     174
Weighted Least Squares:    10.1794


                              Weighted
 Output        R-squared    Sum of Squares   Sum of Squares
 Y( 1)        0.998           10.1794          10.1794

 Model Selection Criteria
  AIC:          35.8444
  BIC:          37.7841


                Initial      Final
 Parameter       Value      Estimate    SE (CV%)    Confidence interval (95%)

 Kel            0.5000      0.4999       5.385      [ 0.4378    ,  0.5620    ]
 V               10.00       10.41       1.910      [  9.952    ,   10.87    ]
 Kcp            0.2000      0.2004       15.72      [ 0.1278    ,  0.2731    ]
 Kpc            0.1000      0.1468       37.01      [ 0.2151E-01,  0.2721    ]
 IC(   1)        0.000      Not estimated
 IC(   2)        0.000      Not estimated


 CLt             5.000       5.204       4.758      [  4.633    ,   5.775    ]
 CLd             2.000       2.087       14.97      [  1.366    ,   2.807    ]
 Vp              20.00       14.21       40.07      [  1.081    ,   27.35    ]


 Correlation Matrix

          Kel       V         Kcp       Kpc
Kel         1.00
V          -0.49      1.00
Kcp        -0.17     -0.44      1.00
Kpc         0.76     -0.17      0.01      1.00


 Covariance Matrix

          Kel       V         Kcp       Kpc
Kel       0.725E-03
V        -.261E-02 0.395E-01
Kcp      -.141E-03 -.278E-02 0.992E-03
Kpc       0.110E-02 -.183E-02 0.181E-04 0.295E-02
```

Figure 2.17 (continued)

```
          --- D. WLS Estimation Model Prediction and Data Summary ---

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\example1.dat

Model:  example.for: Tutorial Example from ADAPT Users Guide

Y( 1)
 Obs.Num.   Time         Data       Model Est.     Residual      Weight
     1       1.000        70.00        69.39        0.6068        1.000
    ** 2-11 NOT Shown
    12       36.00        1.000       0.9455        0.5454E-01    1.000

Y( 1) (Continued)                  Std. Err.   Standardized
          Obs.Num.   Model Est.   Model Est.   Residual
              1       69.39        0.8955       0.5379
    ** 2-11 NOT Shown
             12      0.9455       0.5825       0.4835E-01

     ----- PLOTTING OPTIONS -----

Do you want to plot with options (Y/N)?  n

     ------------------------------------------

     ----- RE-ESTIMATION OPTIONS -----

    1. Change initial parameter values
    2. Select a different estimator
    3. Exit ID

Enter option:  3

     ------------------------------------------

   ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Thu Aug 20 20:55:54 2009
```

Figure 2.17 (continued)

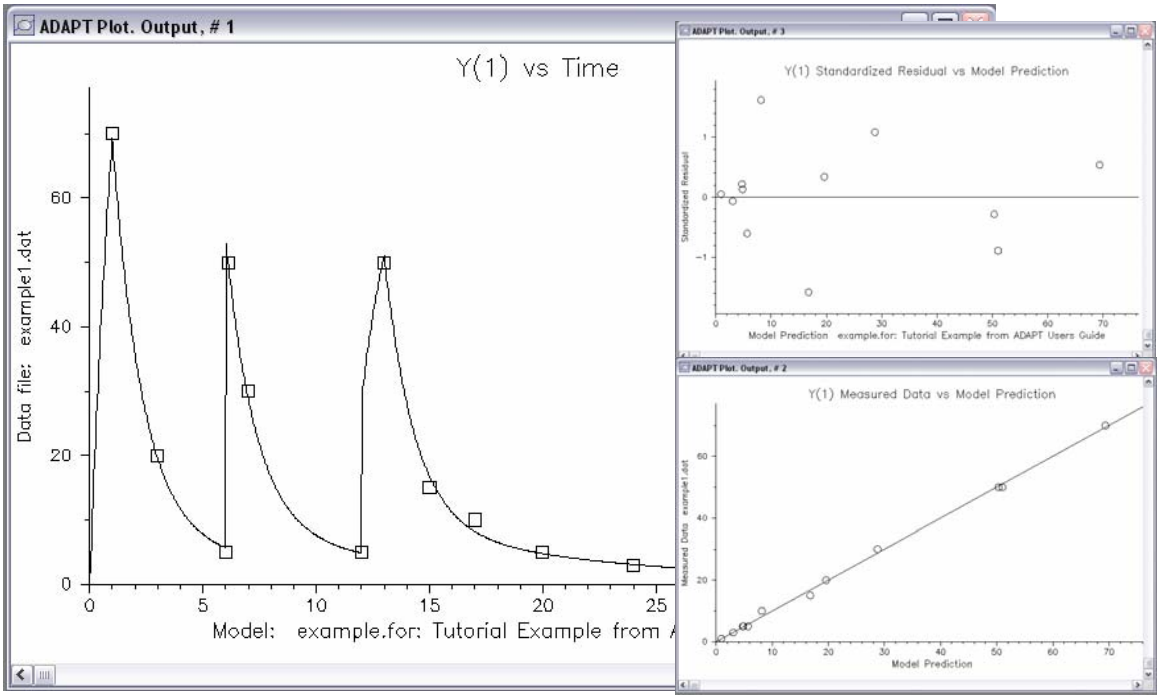


Figure 2.18 Screen shot of ID program plot windows (3 of 4) for the WLS example.

Figure 2.19 shows the ID program command window for the ML run, with sections of the corresponding ID results and plot windows shown in Figures 2.20 and 2.21. In Figure 2.19, the four PK parameters are selected to be estimated as is the *SDslope* parameter of the error variance model, while the *SDinter* parameter is fixed at a value of 0.5.

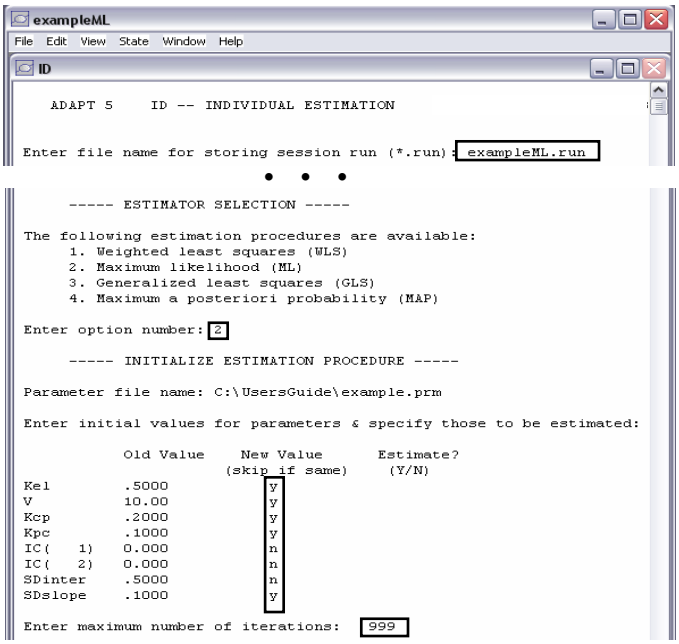


Figure 2.19 Sections of ID program command window for the ML example.

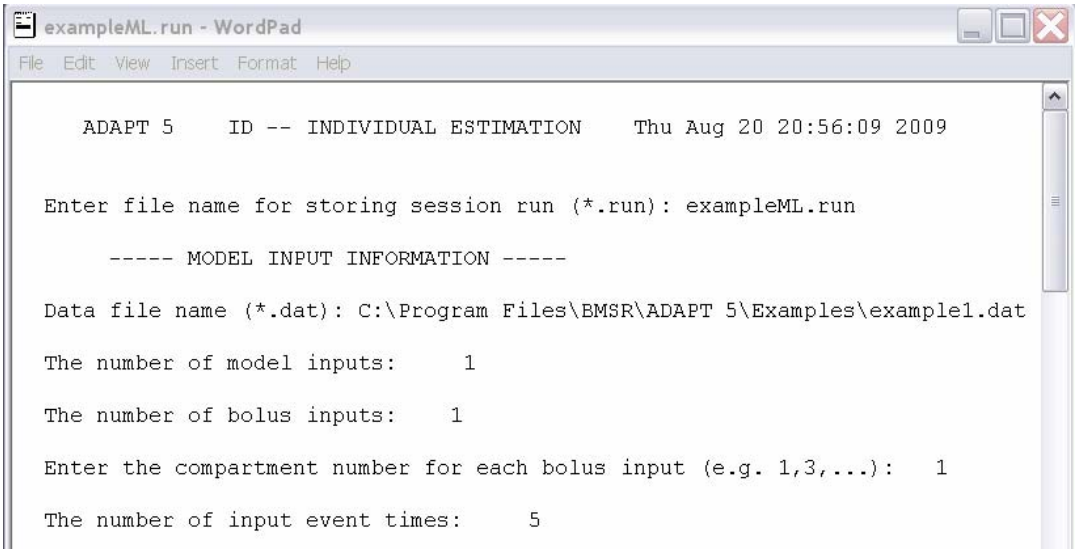


Figure 2.20 The ID program results window for the ML example.

```
    Input Event Information
          Time    Value for all Inputs
Event     Units,       R(1), B(1)
   1.     0.000          1000.       0.000
   2.     1.000          0.000       0.000
   3.     6.000          0.000       500.0
   4.     12.00          500.0       250.0
   5.     13.00          0.000       0.000

     ----- MODEL OUTPUT INFORMATION -----

The number of model output equations:   1

The number of observations:   12

    Observation Information
                Time     Measured Value For Each Output
Observation     Units ,     Y(1)
      1.         1.000       70.00
      2.         3.000       20.00
      3.         6.000       5.000
      4.         6.100       50.00
      5.         7.000       30.00
      6.         12.00       5.000
      7.         13.00       50.00
      8.         15.00       15.00
      9.         17.00       10.00
     10.         20.00       5.000
     11.         24.00       3.000
     12.         36.00       1.000

     ----- ESTIMATOR SELECTION -----

The following estimation procedures are available:
     1. Weighted least squares (WLS)
     2. Maximum likelihood (ML)
     3. Generalized least squares (GLS)
     4. Maximum a posteriori probability (MAP)

Enter option number:  2

     ----- INITIALIZE ESTIMATION PROCEDURE -----

Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\example.prm

Enter initial values for parameters & specify those to be estimated:

           Old Value    New Value      Estimate?
                      (skip if same)     (Y/N)
Kel        .5000            y
V          10.00            y
Kcp        .2000            y
Kpc        .1000            y
IC(   1)   0.000            n
IC(   2)   0.000            n
SDinter    .5000            n
SDslope    .1000            y

Enter maximum number of iterations:       999

Do you want the iterations printed (Y/N)?  n
```

Figure 2.20 (continued)

```
            ----- RESULTS -----

            --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      Kel         =   0.5000
      V           =    10.00
      Kcp         =   0.2000
      Kpc         =   0.1000
      SDslope     =   0.1000

    Negative Log Likelihood =  21.6713


             ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =    43
    Number of function calls  =   225

     Fitted Parameters
      Kel         =   0.4958
      V           =    10.40
      Kcp         =   0.2136
      Kpc         =   0.1493
      SDslope     =   0.2524E-01

    Negative Log Likelihood =  16.5698

            --- C. ML Estimation Summary---

Thu Aug 20 20:58:16 2009

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\example1.dat

Model:  example.for: Tutorial Example from ADAPT Users Guide

Convergence achieved
  Number of iterations:          43
  Number of function calls:     225
Negative Log Likelihood:    16.5698

 Output        R-squared    Sum of Squares
 Y( 1)          0.998          10.4502

 Model Selection Criteria
  AIC:          43.1395
  BIC:          45.5641


               Initial      Final
 Parameter      Value      Estimate    SE (CV%)    Confidence interval (95%)

 Kel           0.5000      0.4958       3.966      [ 0.4493    ,  0.5423    ]
 V              10.00       10.40       2.761      [  9.725    ,   11.08    ]
 Kcp           0.2000      0.2136       11.53      [ 0.1553    ,  0.2718    ]
 Kpc           0.1000      0.1493       22.60      [ 0.6947E-01,  0.2291    ]
 IC(   1)       0.000      Not estimated
 IC(   2)       0.000      Not estimated
```

Figure 2.20 (continued)

```
 SDslope       0.1000      0.2524E-01   43.15      [-0.5180E-03,  0.5099E-01]
 SDinter       0.5000      Not estimated


 CLt            5.000       5.158       2.943      [  4.799    ,   5.517    ]
 CLd            2.000       2.222       10.55      [  1.668    ,   2.777    ]
 Vp             20.00       14.89       21.54      [  7.304    ,   22.47    ]


 Correlation Matrix

          Kel       V         Kcp       Kpc
Kel         1.00
V          -0.67      1.00
Kcp         0.33     -0.46      1.00
Kpc         0.65     -0.16      0.34      1.00


 Covariance Matrix

          Kel       V         Kcp       Kpc
Kel       0.387E-03
V         -.379E-02 0.825E-01
Kcp       0.160E-03 -.326E-02 0.607E-03
Kpc       0.434E-03 -.158E-02 0.285E-03 0.114E-02

           --- D.  ML Estimation Model Prediction and Data Summary ---

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\example1.dat

Model:  example.for: Tutorial Example from ADAPT Users Guide


Y( 1)
 Obs.Num.   Time         Data       Model Est.     Residual     Variance
     1       1.000        70.00        69.19        0.8122        5.045
     2       3.000        20.00        19.43        0.5651       0.9810
     3       6.000        5.000        5.794       -0.7944       0.4176
     4       6.100        50.00        50.43       -0.4257        3.142
     5       7.000        30.00        28.75         1.247        1.502
     6       12.00        5.000        5.042       -0.4212E-01   0.3934
     7       13.00        50.00        51.01        -1.012        3.195
     8       15.00        15.00        16.84        -1.842       0.8556
     9       17.00        10.00        8.380         1.620       0.5062
    10       20.00        5.000        4.985        0.1509E-01   0.3916
    11       24.00        3.000        3.252       -0.2523       0.3388
    12       36.00        1.000        1.010       -0.1015E-01   0.2761

Y( 1) (Continued)                Std. Err.   Standardized
          Obs.Num.   Model Est.   Model Est.   Residual
               1       69.19        1.401       0.3616
               2       19.43       0.7574       0.5705
               3       5.794       0.3796       -1.229
               4       50.43        1.148      -0.2401
               5       28.75       0.4863        1.017
               6       5.042       0.3202      -0.6716E-01
               7       51.01       0.8710      -0.5660
               8       16.84       0.4944       -1.991
               9       8.380       0.3427        2.277
              10       4.985       0.3300       0.2411E-01
              11       3.252       0.3640      -0.4335
              12       1.010       0.3388      -0.1931E-01
```

Figure 2.20 (continued)

```
      ----- PLOTTING OPTIONS -----

 Do you want to plot with options (Y/N)?  n

      ---------------------------------------

      ----- RE-ESTIMATION OPTIONS -----

     1. Change initial parameter values
     2. Select a different estimator
     3. Exit ID

 Enter option:  3

      ---------------------------------------

    ADAPT 5     ID -- INDIVIDUAL ESTIMATION     Thu Aug 20 20:58:23 2009
```

For Help, press F1

Figure 2.20 (continued)

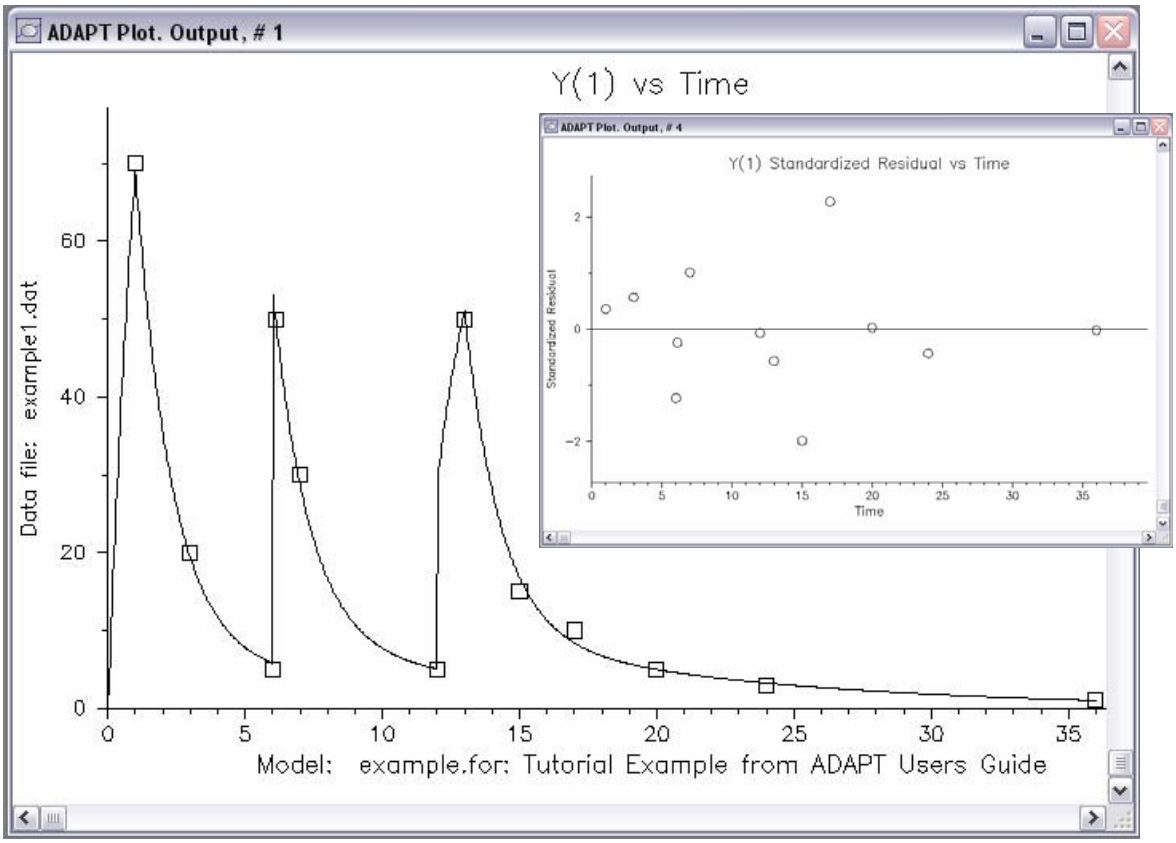


Figure 2.21 Screen shot of ID program plot windows (2 of 4) for the WLS example. All plots also stored in the file exampleML.eps

CHAPTER 3

Modeling Framework and Statistical Methods: Individual Analysis

3.1 System Model

It is assumed that the process under study (i.e. the system) is described by the following set of differential and/or output equations:

$$\frac{dx(t)}{dt} = f\left(x(t), \alpha, r(t), t\right), \;\; x(0) = c \tag{3.1}$$

$$y(t) = h\left(x(t), \alpha, r(t), t\right) \tag{3.2}$$

Equations (3.1) and (3.2) are referred to as the state and output equations. The symbols introduced in the above equations are defined in Table 3.1. The vector θ will be used to represent the collection of model parameters α and initial conditions c. To emphasize the dependence of the model output on the parameters θ, the solution of Eqs. (3.1) and (3.2) will be represented by $y(\theta, t)$.

3.2 Model Inputs, Bolus Inputs and Others

The elements of the vector $r(t)$ represent inputs to the model that are explicitly included in the model equations. For example, $r(t)$ is used to represent a drug infusion regimen in which the rates of infusion remain constant between input times t_i (i.e., piece-wise constant inputs):

$$r_j(t) = r_{i-1}, \; dt_{i-1} < t \le dt_i, \; i = 2, ..., nd+1 \tag{3.3}$$

Each element of the vector $r(t)$ (i.e., $r_j(t)$) is used to represent the dose regimen of a specific

compound. The elements are also used to represent measured covariates that are included in the model differential and output equations, as well as in covariate model equations (see Chapter 4). These covariates are also assumed to be piece-wise constant as defined in Eq. (3.3).

Table 3.1 Model Equation Definitions

Symbol	Definition	Dimension
x	state vector, $x(t) = \left[x_1(t) \ldots x_n(t) \right]^T$	n
α	model parameter vector	p_m
r	input vector, $r(t) = \left[r_1(t) \cdots r_k(t) \right]^T$	k
c	initial condition vector	n
y	output vector, $y(t) = \left[y_1(t) \cdots y_l(t) \right]^T$	l
t	time	scalar
$dx(t)/dt$	derivative of state vector	n
b	bolus vector, $b(t) = \left[b_1(t) \ldots b_n(t) \right]^T$	n
θ	system parameter vector, $\theta = \left[\alpha \mid c \right]^T$	$p = p_m + n$

A second class of inputs used in ADAPT is bolus inputs. These inputs do not appear explicitly in the model equations, but are defined when the programs are run. Bolus-type inputs are simulated as producing instantaneous changes in model states in the following manner:

$$x\left(dt_i^+\right) = x\left(dt_i^-\right) + b\left(dt_i\right), \quad i = 1, ..., nd \tag{3.4}$$

where $b(t)$ is the bolus input vector $(b(t) = \left[b_1(t) \ldots b_n(t) \right]^T)$ and the $-$ and $+$ indicate times immediately before and after bolus administration. The input event times, dt_i, appearing in Eqs. (3.3) and (3.4), are defined as any time at which any element of the input vectors $r(t)$ or $b(t)$ changes value (e.g., administration of a new bolus or changing of an infusion rate or covariate value - see below).

Finally, input functions that are not piece-wise constant or boluses are entered explicitly in the model equations. This includes inputs represented by sums of exponentials, trigonometric functions, piece-wise linear functions and others. See the ADAPT Model Library in Chapter 11 for examples that illustrate the definition of such model inputs.

3.3 Measurement Model

Data to be used in parameter estimation are generally collected at discrete times and subject to additive output error as follows:

$$z(t_j) = y(\theta, t_j) + e(t_j),\ j = 1,...,m \tag{3.5}$$

where $y(\theta, t_j)$ represents the model output vector at time t_j (from Eqs. (3.1) and (3.2)) and $e(t_j)$ is the vector of additive output error terms. A portion of the output error is generally attributed to errors in the measurement process. In Eq. (3.5) $e(t_j)$ represents all sources of uncertainty (including measurement error) that can be modeled as a random process added (directly or by transformation) to the true model output.

In Eq. (3.5) it is assumed that $E\{e(t_j)\} = 0$, $j = 1,...,m$, $e_j(t)$ and $e_k(t)$ are independent for $j \neq k$, and $e(t_j)$ and $e(t_k)$ are independent for $j \neq k$. Under these assumptions, ADAPT allows the user to supply a model for the variance of the additive error $e(t)$ in the following form:

$$\text{var}\{e_i(t_j)\} = g_i(x(t_j), \theta, t_j, \beta),\ j = 1,...,m,\quad i = 1,...,l \tag{3.6}$$

The vector β represents additional parameters that are unique to the error variance model. See Table 3.2 for Definitions of all symbols. As a convenience, the function g in Eq. (3.6) may also be defined directly in terms of the model outputs.

$$\text{var}\{e_i(t_j)\} = g_i(y_i(\theta, t_j), \beta),\ j = 1,...,m,\quad i = 1,...,l \tag{3.7}$$

Table 3.2 Observation and Error Variance Model Symbols

Symbol	Definition	Dimension
$z(t_j)$	observation vector at time t_j $z(t_j) = [z_1(t_j) \dots z_l(t_j)]^T$	l
$e(t_j)$	error vector at time t_j $e(t_j) = [e_1(t_j) \dots e_l(t_j)]^T$	l
$g(t_j)$	error variance model vector at time t_j $g(t_j) = [g_1(y_1(\theta,t_j),\beta) \dots g_l(y_l(\theta,t_j),\beta)]^T$	l
β	error variance parameter vector	q

3.4 Parameter Model

ADAPT allows for two types of system parameters θ: θ constant, either known or unknown; θ random vector, with density function $p(\theta)$. Depending on the particular program and option selected, the following density functions for θ can be defined:

$$p(\theta) = N(\mu, \Sigma) \quad \text{(multivariate Normal - SIM, ID, NPD, STS, ITS, MLEM)}$$
$$p(\theta) = LN(\mu, \Sigma) \quad \text{(multivariate lognormal - SIM, ID NPD, STS, ITS, MLEM)}$$
$$p(\theta) = U(0, \theta^{\max}) \quad \text{(independent uniform - SIM)}$$
$$p(\theta) = NI \quad \text{(noninformative, } \theta > 0 \text{ -ID, NPD, STS)} \qquad (3.8)$$

where μ (dimension $p \times 1$) and Σ (dimension $p \times p$) represent the prior mean vector and covariance matrix, respectively, of the model parameters θ.

Table 3.3 Parameter Model Symbols

Symbol	Definition	Dimension
μ	mean of $p(\theta)$	p
Σ	covariance of $p(\theta)$	$p \times p$

The system parameter vector θ can also be partitioned into two independent components θ_1 and θ_2 (i.e., $\theta = \left[\theta_1^T \middle| \theta_2^T\right]^T$). In this case, θ_1 is assumed to be either multivariate Normal or lognormal with mean μ_1 and covariance Σ_1 ($\theta_1 \sim N(\mu_1, \Sigma_1)$ or $\theta_1 \sim LN(\mu_1, \Sigma_1)$). The elements of θ_2 are assumed to be independent uniform random variables in SIM ($\theta_2 \sim U(0, \theta^{\max})$) or to come from a noninformative prior distribution in ID, NPD and STS ($\theta_2 \sim NI$ with $\theta_2 > 0$).

3.5 Secondary Parameters

The user can also specify a collection of secondary parameters, represented by the vector γ, that are defined as functions of the parameters θ as follows:

$$\gamma = w(\theta) \qquad (3.9)$$

Any variable written as an algebraic function of θ can be defined as a secondary parameter.

3.6 The Simulation Program – SIM

Four simulation options are available through the program SIM. Option 1 constructs the model output vector ($y(\theta, t)$ in Eq. (3.2)) for an individual given values for all system parameters θ (including initial conditions). With option 2, the error corrupted output vector at each observation time ($z(t_j)$ in Eq. (3.5)) is simulated for a given value of the model parameters. This is repeated a specified number of times by repeated generation of random deviates to construct the output error. With this option the equation for the variance of the output error must be coded in subroutine VARMOD of the Model File. Option 3 provides the capability for performing a population simulation. SIM performs a specified number of simulations of the

model, with values for the system parameters randomly selected from either a Normal or lognormal distribution with mean vector and covariance matrix as given in subroutine PRIOR of the Model File. As discussed in Chapter 3.4, θ can be partitioned into a Normal or lognormal component, θ_1, and a component, θ_2, consisting of parameters assumed to come from independent uniform distributions. In this case, the upper limits of the uniform distributions for each element of θ_2 are requested by the program. Finally, option 4 allows for a population simulation with output error.

When either option 2, 3 or 4 is selected, the summary of the simulation results is generated that includes the mean, standard deviation and minimum and maximum values for each output at each observation time. For the case of options 3 and 4 (population simulations) a summary of the parameters is also provided with the same statistical analysis. The plots displayed with options 2, 3 and 4 show for each observation time, the average output with standard deviation bars. A continuous curve is also displayed for each model output, that is obtained using the entered parameter values (option 2) or the population mean parameter values (options 3 and 4).

3.7 The Estimation Program – ID

This section defines the four statistical estimation options available in ID; it is not intended as an introduction to the general problem of nonlinear parameter estimation in pharmacokinetic/pharmacodynamic data analysis. For background on the analysis of kinetic/dynamic data using parametric methods and nonlinear regression in general, the user is referred to references ([3]-[9]).

3.7.1 Weighted Least Squares (WLS)

The WLS objective function is

$$O_{WLS}(\theta) = \sum_{i=1}^{l}\sum_{j=1}^{m} w_{ij}\left(z_i(t_j) - y_i(\theta, t_j)\right)^2 \tag{3.20}$$

The weighted least squares estimate (denoted $\hat{\theta}$) is the value of θ that minimizes $O_{WLS}(\theta)$. In Eq. (3.20), $y_i(\theta, t_j)$ represents the solution of the i^{th} model equation at time t_j (from Eqs. (3.1) and (3.2)). The weights for each observation, w_{ij}, are specified by the user. This is done by entering the weights to be attached to each model output ($o_i, i = 1,...,l$), and the weights for each of the observations (w'_{ij}, $j = 1,...,m$) of each output ($w_{ij} = o_i w'_{ij}$). Three options are available in ID for specifying the observation weights w'_{ij}. In option 1, the weights are all set initially to 1, and the user specifies which if any are non unity and the value for the weight for that observation (i.e. w'_{ij} entered directly). In options 2 and 3, the observation weights are set equal to the inverse of the variance of the output error ($w'_{ij} = 1/\sigma^2_{ij}$). In option 2, σ_{ij} is approximated as a linear function of the measured data ($\sigma_{ij} = a z_i(t_j) + b$). To define this function, the user enters two points on this standard deviation – measurement line. All the values of σ_{ij} must be entered by the

user when option 3 is selected.

Included in the WLS estimation summary are approximate values for the standard errors (as coefficients of variation) of the parameter estimates ($\hat{\theta}$), which are obtained from the asymptotic covariance matrix of the estimated parameters ($\widehat{\mathrm{cov}}\left(\hat{\theta}\right)$). The asymptotic covariance matrix of the estimates, which can also be listed in the WLS estimation summary, is calculated as follows:

$$\widehat{\mathrm{cov}}\left(\hat{\theta}\right) = \left(P^T W P\right)^{-1}\left(P^T W G W P\right)\left(P^T W P\right)^{-1} \tag{3.21}$$

where P is the $m \cdot l \times p$ Jacobian matrix obtained from

$$P = \frac{\partial y\left(\hat{\theta}\right)}{\partial \theta},\ y\left(\theta\right) = \left(y_1\left(\theta, t_1\right) \quad y_1\left(\theta, t_2\right) \quad \cdots \quad y_l\left(\theta, t_m\right)\right)^T \tag{3.22}$$

and W is the $m \cdot l \times m \cdot l$ matrix of weights used in Eq. (3.21),

$$W = diag\left\{w_{11} \quad w_{12} \quad \cdots \quad w_{lm}\right\} \tag{3.23}$$

For weighting option 1, the $m \cdot l \times m \cdot l$ matrix R contains estimates of the error variance for each output:

$$G = diag\left\{\sigma_1^2 \quad \cdots \quad \sigma_1^2 \quad \sigma_2^2 \quad \cdots \quad \sigma_l^2\right\} \tag{3.24}$$

where

$$\sigma_i^2 = \frac{1}{df_i}\sum_{j=1}^{m} w_{ij}\left(z_i\left(t_j\right) - y_i\left(\hat{\theta}, t_j\right)\right)^2 \tag{3.25}$$

and

$$df_i = m_i - \left(p/l\right),\ i = 1,...,l \tag{3.26}$$

In this last equation defining the degrees of freedom for the i^{th} output, m_i represents the number of non-missing, non-zero weight observations for the i^{th} output. For observation weighting options 2 and 3,

$$G = diag\left\{\sigma_{11}^2 \quad \cdots \quad \sigma_{1m}^2 \quad \cdots \quad \sigma_{lm}^2\right\} \tag{3.27}$$

When different weighting options are selected for the different model outputs, the corresponding blocks in the matrix G are constructed using the appropriate error variance (σ_i^2 or σ_{ij}^2) from above. The approximate standard errors of the estimated parameters, σ_{θ_i}, $i = 1,..., p$ are obtained from the covariance matrix in Eq. (3.21). The corresponding coefficients of variation are calculated as $CV_{\hat{\theta}_i} = 100\sigma_{\theta_i} / \hat{\theta}_i$.

The WLS estimation summary provides, for each model output, values of the final sum of squares (SS_i), weighted sum of squares (WSS_i) and coefficient of determinations (R_i^2) as defined below:

$$SS_i = \sum_{j=1}^{m} \left(z_i\left(t_j\right) - y_i\left(\hat{\theta}, t_j\right) \right)^2 \tag{3.28}$$

$$WSS_i = \sum_{j=1}^{m} w_{ij} \left(z_i\left(t_j\right) - y_i\left(\hat{\theta}, t_j\right) \right)^2 \tag{3.29}$$

$$R_i^2 = \frac{\left(\sum_{j=1}^{m} \left(y_i\left(\hat{\theta}, t_j\right) - \overline{y}_i\left(\hat{\theta}\right) \right) \left(z_i\left(t_j\right) - \overline{z}_i \right) \right)^2}{\sum_{j=1}^{m} \left(y_i\left(\hat{\theta}, t_j\right) - \overline{y}_i\left(\hat{\theta}\right) \right)^2 \sum_{j=1}^{m} \left(z_i\left(t_j\right) - \overline{z}_i \right)^2}, \; i = 1, \ldots, l \tag{3.30}$$

where $\overline{y}_i\left(\hat{\theta}\right)$ and $\overline{z}_i$ represent the average values of the model predictions and observations for each output. For each estimated parameter, $\hat{\theta}_i$, a 95% confidence interval is calculated as follows:

$$\hat{\theta}_i \pm \sqrt{\hat{\mathrm{cov}}\left(\hat{\theta}\right)_{ii}}\, t_{0.975}\left(df\right) \tag{3.31}$$

where $\widehat{\mathrm{cov}}\left(\hat{\theta}\right)_{ii}$, $i = 1, \ldots, p$ are the diagonal elements from Eq. (3.21), and the total degrees of freedom used to determine the appropriate value of the Student's t distribution is $ml - p$.

The resulting estimates of the secondary parameters are calculated by evaluating Eq. (3.9) at the least squares estimates for $\hat{\theta}$. The approximate covariance matrix of the estimates for the secondary parameters, $\hat{\mathrm{cov}}\left(\hat{\gamma}\right)$) ($\dim s \times s$), is calculated as follows:

$$\widehat{\mathrm{cov}}\left(\hat{\gamma}\right) = \left(\frac{\partial w\left(\hat{\theta}\right)}{\partial \theta} \right) \widehat{\mathrm{cov}}\left(\hat{\theta}\right) \left(\frac{\partial w\left(\hat{\theta}\right)}{\partial \theta} \right)^T \tag{3.32}$$

The standard errors of the secondary parameters and the corresponding 95% confidence intervals are calculated as described above.

3.7.2 Maximum Likelihood (ML)

When the additive error is normally distributed, and given the independence assumptions in Section 3.3, the ML estimates for both the system and variance model parameters (θ and β) can be estimated by maximizing the likelihood function:

$$L(\theta,\beta)=\prod_{i=1}^{l}\prod_{j=1}^{m}\ell\left(\theta,\beta\mid z_i\left(t_j\right)\right)=(2\pi)^{-l\cdot m/2}\left|G(\theta,\beta)\right|^{-1/2}e^{-\frac{1}{2}\sum_{i=1}^{l}\sum_{j=1}^{m}\left(\frac{\left(z_i(t_j)-y_i(\theta,t_j)\right)^2}{g_i\left(y_i(\theta,t_j),\beta\right)}\right)} \tag{3.33}$$

This is done by minimizing, over θ and β, the negative of the log of the likelihood:

$$O_{NLL}(\theta,\beta)=l\cdot m\cdot\ln(2\pi)/2+\frac{1}{2}\sum_{i=1}^{l}\sum_{j=1}^{m}\left(\frac{\left(z_i\left(t_j\right)-y_i\left(\theta,t_j\right)\right)^2}{g_i\left(y_i(\theta,t_j),\beta\right)}+\ln g_i\left(y_i(\theta,t_j),\beta\right)\right) \tag{3.34}$$

The resulting ML estimates are denoted $\hat{\theta}$ and $\hat{\beta}$. For the ML estimation option, it is not required to estimate variance model parameters. (The case when observations exceed quantitation limits is described below.)

The approximate covariance matrix for the ML parameter estimates $\hat{\theta}$ and $\hat{\beta}$ is calculated as detailed below.

$$\widehat{\mathrm{cov}}\left(\hat{\theta},\hat{\beta}\right)=\left(M_{\theta,\beta}\right)^{-1} \tag{3.35}$$

The elements of the matrix $M_{\theta,\beta}=\left\{m_{jk}\right\}$, $j=1,\ldots,p+q$, $k=1,\ldots,p+q$, are defined in the following equations and evaluated at $\left(\hat{\theta},\hat{\beta}\right)$.

$$m_{jk}=\sum_{i=1}^{n_r}\frac{1}{g_i}\left(\frac{\partial y_i}{\partial\theta_j}\right)\left(\frac{\partial y_i}{\partial\theta_k}\right)+\frac{1}{2}\sum_{i=1}^{n_r}\frac{1}{g_i^2}\left(\frac{\partial g_i}{\partial\theta_j}\right)\left(\frac{\partial g_i}{\partial\theta_k}\right) \tag{3.36}$$

$$j=1,\ldots,p\ ;\ k=1,\ldots,p$$

$$m_{jk}=\frac{1}{2}\sum_{i=1}^{n_r}\frac{1}{g_i^2}\left(\frac{\partial g_i}{\partial\beta_{j'}}\right)\left(\frac{\partial g_i}{\partial\beta_{k'}}\right) \tag{3.37}$$

$$j=p+1,\ldots,p+q\ ;\ k=p+1,\ldots,p+q\ ;\ j'=j-p\ ;\ k'=k-p$$

$$m_{jk}=\frac{1}{2}\sum_{i=1}^{n_r}\frac{1}{g_i^2}\left(\frac{\partial g_i}{\partial\theta_j}\right)\left(\frac{\partial g_i}{\partial\beta_{k'}}\right) \tag{3.38}$$

$$j=1,\ldots,p\ ;\ k=p+1,\ldots,p+q\ ;\ k'=k-p$$

$$m_{jk}=m_{kj}\qquad j=p+1,\ldots,p+q\ ;\ k=1,\ldots,p \tag{3.39}$$

where y_i are the elements of the vector $y(\theta)$ (see Eq. (3.22)), g_i are the elements of the vector $g(\theta,\beta)\equiv\left[g_1\left(y_1(\theta,t_1),\beta\right)\cdots g_l\left(y_l(\theta,t_m),\beta\right)\right]$, and n_r is the number of non missing observations. When no variance parameters are estimated, Eq. (3.36) defines the covariance matrix and is denoted $\widehat{\mathrm{cov}}\left(\hat{\theta}\right)$. We also define the matrix $G(\theta,\beta)$ (dim n_rxn_r) for latter use: $G(\theta,\beta)=diag\left\{g_1\left(y_1(\theta,t_1),\beta\right)\cdots g_l\left(y_l(\theta,t_m),\beta\right)\right\}$

The standard errors and the confidence intervals for the parameter estimates are calculated as described for the case of the least square parameter estimates. Also the secondary parameters and their statistics can be calculated by applying Eqs. (3.9) and (3.32) using the ML estimates of the parameters and the associated covariance matrix (upper $p \times p$ block of $\widehat{\mathrm{cov}}\left(\hat{\theta},\hat{\beta}\right)$ from Eq. (3.35)).

If any of the observations are below the quantitation limit (BQL) or above the of quantitation limit (AQL), then those observations are treated as censored and their likelihoods are defined as follows:

$$l\left(\theta,\beta \mid z_i\left(t_j\right)\right) = \Phi\left(\frac{\left(LLQ_i - y_i\left(\theta,t_j\right)\right)}{\sqrt{g_i\left(y_i(\theta,t_j),\beta\right)}}\right) \quad \text{or} \quad l\left(\theta,\beta \mid z_i\left(t_j\right)\right) = 1 - \Phi\left(\frac{\left(ULQ_i - y_i\left(\theta,t_j\right)\right)}{\sqrt{g_i\left(y_i(\theta,t_j),\beta\right)}}\right)$$

where LLQ_i and ULQ_i denote the values of the lower limit of quantitiation and upper limit of quantitation, respectively, for the ith output. In these equations, $\Phi(\cdot)$ denotes the cumulative Normal distribution function. The negative of the log of the likelihood in Eq. (3.34) is adjusted accordingly. This is method M3 as suggested by Beal [10].

3.7.3 Generalized Least Squares (GLS)

The GLS method implemented in ID uses the following algorithm to estimate θ and β:

$$\begin{aligned}
&i) \quad \hat{\theta} = \arg\left\{\min_{\theta} O_{LS}\right\} \\
&ii) \quad \hat{\beta} = \arg\left\{\min_{\beta} O_{NLL}\right\}, \qquad \text{given } \hat{\theta} \\
&iii) \quad \hat{\theta} = \arg\left\{\min_{\theta} O_{WLS}\right\}, \qquad \text{given } \hat{\beta} \\
&iv) \quad \text{go to } ii \text{ or stop.}
\end{aligned} \tag{3.40}$$

The three objective functions introduced in this algorithm are given below.

$$O_{LS}\left(\theta\right) = \sum_{i=1}^{l}\sum_{j=1}^{m}\left(z_i\left(t_j\right) - y_i\left(\theta,t_j\right)\right)^2 \tag{3.41}$$

$$O_{NLL}\left(\beta\right) = l \cdot m \cdot \ln\left(2\pi\right)/2 + \frac{1}{2}\sum_{i=1}^{l}\sum_{j=1}^{m}\left(\frac{\left(z_i\left(t_j\right) - y_i\left(\hat{\theta},t_j\right)\right)^2}{g_i\left(y_i(\hat{\theta},t_j),\beta\right)} + \ln g_i\left(y_i(\hat{\theta},t_j),\beta\right)\right) \tag{3.42}$$

$$O_{WLS}\left(\theta\right) = \sum_{i=1}^{l}\sum_{j=1}^{m} w_{ij}\left(z_i\left(t_j\right) - y_i\left(\theta,t_j\right)\right)^2, \qquad \text{where } w_{ij} = \frac{1}{g_i\left(y_i(\hat{\theta},t_j),\hat{\beta}\right)} \tag{3.43}$$

In defining w_{ij} in Eq. (3.43), $\hat{\theta}$ and $\hat{\beta}$ are set at their values at the start and end of step *ii*, respectively. The asymptotic error analysis defined above for the WLS estimator is also provided when the GLS estimation option is selected. For this case, the elements of W in Eq. (3.23) are defined by the w_{ij} in Eq. (3.42). The diagonal elements of the matrix G in Eq. (3.24) are defined by the output error variance model $g_i\left(y_i(\hat{\theta},t_j),\beta\right)$. The $\widehat{\mathrm{cov}}\left(\hat{\theta}\right)$ in Eq. (3.21), therefore, reduces to $\left(P^T G^{-1} P\right)^{-1}$. The secondary parameters and their statistics are calculated as described above.

3.7.4 Bayesian (MAP)

Incorporating prior information about unknown system parameters can be useful in certain pharmacokinetic/pharmacodynamic estimation problems. One Bayesian point estimator which can be calculated in a computationally straightforward manner (given certain distributional assumptions) is the mode of the posterior parameter density (i.e. the maximum *a posteriori* probability (MAP) estimator). For Normally distributed output error (as defined in Chapter 3.3) and with $\theta \sim N\left(\mu,\Sigma\right)$), the MAP estimates of the system and error variance parameters, assuming a noninformative prior for the latter, are obtained by maximizing the posterior distribution:

$$p\left(\theta,\beta \mid z\right) = L\left(\theta,\beta\right) p\left(\theta \mid \mu,\Sigma\right) / c \tag{3.44}$$

where z denotes the vector of all the observations $\left[z_1\left(t_1\right) \ldots z_l\left(t_m\right)\right]$, $L\left(\theta,\beta\right)$ is the likelihood function defined in Eq. (3.33), $p\left(\theta \mid \mu,\Sigma\right)$ is the Normal density, and c is constant. The MAP estimates that maximize $p\left(\theta,\beta \mid z\right)$ can be obtained by minimizing the negative of Eq. (3.44), which is equivalent to minimizing the following objective function:

$$O_{MAP}\left(\theta,\beta\right) = \sum_{i=1}^{l}\sum_{j=1}^{m}\left(\frac{\left(z_i\left(t_j\right) - y_i\left(\theta,t_j\right)\right)^2}{g_i\left(y_i(\theta,t_j),\beta\right)} + \ln g_i\left(y_i(\theta,t_j),\beta\right)\right) + \left(\theta-\mu\right)^T \Sigma^{-1}\left(\theta-\mu\right) \tag{3.45}$$

If θ is partitioned into informative and non-informative parts (i.e. $\theta = \left[\theta_1^T \mid \theta_2^T\right]^T$, with $\theta_1 \sim N\left(\mu_1,\Sigma_1\right)$), then θ_1, μ_1 and Σ_1 replace θ, μ and Σ in Eq. (3.45).

For the case when $\theta \sim LN\left(\mu,\Sigma\right)$, the objective function becomes:

$$O_{MAP}\left(\theta,\beta\right) = \sum_{i=1}^{l}\sum_{j=1}^{m}\left(\frac{\left(z_i\left(t_j\right) - y_i\left(\theta,t_j\right)\right)^2}{g_i\left(y_i(\theta,t_j),\beta\right)} + \ln g_i\left(y_i(\theta,t_j),\beta\right)\right)$$

$$+\left[\ln\theta-\nu\right]^T\Phi^{-1}\left[\ln\theta-\nu\right]+2\sum_{i=1}^{p}\ln\theta_i \tag{3.46}$$

where $\nu=\{\nu_i\}$, $i=1,...,p$ and $\Phi=\{\phi_{ij}\}$, i, $j=1,...,p$. The elements of ν and Φ are defined in terms of the elements of μ and Σ as follows:

$$\nu_i=\ln\mu_i-\phi_{ii}/2,\ i=1,...,p \tag{3.47}$$

$$\phi_{ij}=\ln\left(\frac{\sigma_{ij}}{\mu_i\mu_j}+1\right),\ i,j=1,...,p \tag{3.48}$$

Approximate statistics are also provided for the MAP estimates ($\hat{\theta}$ and $\hat{\beta}$), when the prior distribution for θ is either Normally or lognormally distributed. The approximation used to calculate the standard errors of $\hat{\theta}$ and $\hat{\beta}$ are given in Eq. (3.49) for the case of $\theta\sim N(\mu,\Sigma)$ and in Eq. (3.50) for the case of $\theta\sim LN(\mu,\Sigma)$.

$$\widehat{\mathrm{cov}}\left(\hat{\theta},\hat{\beta}\right)=\left(M_{\theta,\beta}+\begin{bmatrix}\Sigma^{-1} & 0\\ 0 & 0\end{bmatrix}\right)^{-1} \tag{3.49}$$

$$\widehat{\mathrm{cov}}\left(\hat{\theta},\hat{\beta}\right)=\left(M_{\theta,\beta}+\begin{bmatrix}E\left(\Phi^{-1}-D-I\right)E & 0\\ 0 & 0\end{bmatrix}\right)^{-1} \tag{3.50}$$

where $E=diag\left\{1/\hat{\theta}_1\ \cdots\ 1/\hat{\theta}_p\right\}$ and I is the $p\times p$ identity matrix. The matrix D is defined as follows: $D=diag\left\{d_1\ \cdots\ d_p\right\}$, where $d=\left[d_1\ \cdots\ d_p\right]^T=\Phi^{-1}\left[\ln\hat{\theta}-\nu\right]$ (Σ and ν given above).

The standard errors and the confidence intervals for the parameter estimates are calculated as described for the case of the least square parameter estimates. Also the secondary parameters and their statistics can be calculated by applying Eqs. (3.9) and (3.32) using the MAP estimates of the parameters and the associated covariance matrix (upper $p\times p$ block of $\widehat{\mathrm{cov}}\left(\hat{\theta},\hat{\beta}\right)$ from Eqs. (3.49) or (3.50).

If any of the observations are below the quantitation limit (BQL) or above the of quantitation limit (AQL), then those observations are treated as censored and their likelihoods are defined as described above for the ML estimates. The objective function in Eq. (3.45) or (3.46) is then adjusted accordingly.

3.7.5 Prediction Variance and Residual Analysis

The Prediction and Data Summary Table printed for each of the estimators lists the predicted values of the model outputs and their corresponding standard errors, along with the standardized residuals for each output at each observation time. The standard errors of the predictions are calculated from

$$\widehat{\text{var}} y_i\left(\hat{\theta}, t_j\right) = \frac{\partial y_i\left(\hat{\theta}, t_j\right)}{\partial \theta} \widehat{\text{cov}}\left(\hat{\theta}\right) \left(\frac{\partial y_i\left(\hat{\theta}, t_j\right)}{\partial \theta} \right)^T, \; j = 1, ..., m, \; i = 1, .., l \tag{3.51}$$

where $\widehat{\text{cov}}\left(\hat{\theta}\right)$ is given above for each of the four estimators. For the case of the ML and MAP estimates $\widehat{\text{cov}}\left(\hat{\theta}\right)$ represents the upper $p \times p$ block of the complete covariance matrix $\widehat{\text{cov}}\left(\hat{\theta}, \hat{\beta}\right)$ as given in Eqs. (3.35) and (3.49 or 3.50). The data summary table also lists the standardized residual calculated as indicated below for each of the estimators. For the WLS estimators the standardized residuals are

$$\frac{z_i\left(t_j\right) - y_i\left(\hat{\theta}, t_j\right)}{\sqrt{\sigma_{ij}}}, \; j = 1, ..., m, \; i = 1, .., l \tag{3.52}$$

For the ML, GLS and MAP estimators the standardized residuals are given by

$$\frac{z_i\left(t_j\right) - y_i\left(\hat{\theta}, t_j\right)}{\sqrt{g_i\left(y_i(\hat{\theta}, t_j), \hat{\beta}\right)}}, \; j = 1, ..., m, \; i = 1, .., l \tag{3.53}$$

3.7.6 Model Selection Criteria

For each of the estimators, model selection information criteria are evaluated (see [11]). For the WLS and GLS estimators, the Akiake Information Criterion (AIC) and the Bayesian Information Criterion due to Schwarz are calculated as follows:

$$AIC = l \cdot m \cdot \ln O_{WLS} + 2p \tag{3.54}$$

$$BIC = l \cdot m \cdot \ln O_{WLS} + \ln\left(l \cdot m\right) p \tag{3.55}$$

The objective function, O_{WLS} given in Eq. (3.20) and evaluated at the least squares estimates, $\hat{\theta}$.

For the ML estimator, AIC and BIC are:

$$AIC = 2O_{NLL} + 2\left(p + q\right) \tag{3.56}$$

$$BIC = 2O_{NLL} + \ln\left(l \cdot m\right)\left(p + q\right) \tag{3.57}$$

The objective function, O_{NLL}, is given in Eq. (3.34) and evaluated at the maximum likelihood estimates, $\hat{\theta}$ and $\hat{\beta}$.

For the MAP estimator, the generalized information criterion is calculated:

$$GEN - IC = O_{MAP} + \frac{2\left(p+q\right)}{l \cdot m} \tag{3.58}$$

In this equation, the MAP objective function given in Eq. (3.45) or Eq. (3.46) is evaluated at the MAP estimates $\hat{\theta}$ and $\hat{\beta}$.

3.8 The Sample Schedule Design Program – SAMPLE

3.8.1 D- and C-Optimality

The sample schedule design program (see [12]) calculates the vector of sampling times $d = \left[t_1 \quad t_2 \quad \cdots \quad t_m\right]$, based on one of the following design criteria:

$$\text{D – optimality: } d^* = \arg\min_d \left\{-\left|M_\theta\left(d\right)\right|\right\} \tag{3.59}$$

$$\text{C – optimality: } d^* = \arg\min_d \left\{\sum_{i=1}^{p} \frac{\tilde{m}_{ii}\left(d\right)}{\theta_i^{*2}}\right\} \tag{3.60}$$

The matrix $M_\theta\left(d\right)$ above (Fisher information matrix) has dimension $p \times p$ and the elements of the matrix $M_\theta\left(d\right) = \left\{m_{jk}\right\}$, $j = 1,..., p$, $k = 1,..., p$, are as follows:

$$m_{jk} = \sum_{i=1}^{n_r} \frac{1}{g_i}\left(\frac{\partial y_i}{\partial \theta_j}\right)\left(\frac{\partial y_i}{\partial \theta_k}\right) + \frac{1}{2}\sum_{i=1}^{n_r} \frac{1}{g_i^2}\left(\frac{\partial g_i}{\partial \theta_j}\right)\left(\frac{\partial g_i}{\partial \theta_k}\right) \tag{3.61}$$

where y_i and g_i are defined in Section 3.7.2 and are functions of $d = \left[t_1 \quad t_2 \quad \cdots \quad t_m\right]$); they are evaluated at the nominal values for the model parameters (θ^*) and variance model parameters (β^*) provided by the user. In Eq. (3.60), $\tilde{m}_{ii}\left(d\right)$ is the i^{th} diagonal element of M_θ^{-1}.The sampling interval, $\left[t_1, t_m\right]$, can be constrained to $\left[t_L, t_U\right]$.

3.8.2 Partially Optimized Designs

The user is given the option in SAMPLE to fix selected design times while optimizing the remaining times using either the D-optimality or C-optimality criteria.

CHAPTER 4

Modeling Framework and Statistical Methods: Population Analysis

4.1 A Brief Perspective

One of the significant contributions of modeling to pharmaceutical research and clinical pharmacology is the work of Sheiner, Rosenberg and Melmon reported in 1972 [13], proposing the nonlinear mixed effects (NLME) modeling framework for quantifying both within and between individual variability in pharmacokinetic data analysis (population pharmacokinetics). This idea has had a conceptually profound impact on how pharmacokinetic (and pharmacodynamic) variability is quantified and studied, and on the identification of important pathophysiological and other factors associated with kinetic/dynamic variability in patients. The implementation of this framework in the versatile software package NONMEM developed by Beal and Sheiner [14], has provided researchers with a widely available tool for population PK/PD data analysis that has become an integral component of most drug development efforts. Under the expert direction of Thomas Ludden of ICON Development Solutions, enhancements are continually added to the NOMEM software.

The past 30 years has witnessed rigorous statistical contributions to the solution of the nonlinear mixed effects problem, as well as important extensions to this framework. A few notable advances include: the work of Lindstrom and Bates in 1990 on a first-order conditional (FOCE) approximation to the parametric NLME problem [15]; the creative 1986 contributions of Mallet in defining and solving the nonparametric maximum likelihood problem [16]; the smooth nonparameteric maximum likelihood method developed by Davidian and Gallant [17]; the Bayesian formulation of the NLME problem and its computational solution by Wakefield, Smith, Racine-Poon and Gelfand [18]-[19]. A review of these and other significant contributions is beyond the scope of this User's Guide - although we will return to a few more later in this chapter. The interested reader is referred to the indispensable 1995 monograph of Davidian and Giltinan [20] for or a more detailed, unified exposition of methods for population PK/PD, as well as to the 2003 update by these authors [21]. In addition, Pillai, Mentre and Steimer provide an informative historical account (through 2005) of the developments in population PK/PD [22]. Finally, for the serious user of these methods the monograph by Bonate [] is essential reading.

In the following sections of this chapter, the parametric population problem is defined and its maximum likelihood solution is presented as implemented in the MLEM program of ADAPT 5. In addition, the iterated two-stage (ITS), standard two-stage (STS) and naïve pooled data (NPD) programs are presented.

4.2 The Population Model and Estimation Problem

The dynamic systems model framework for the individual presented in Chapter 3 is extended to the case of a population of N individuals. For simplicity, the system and measurement models given in Eqs. (3.1), (3.2) and (3.5) are combined as follows:

$$Y_i = h_i(\theta_i) + e_i, \quad i = 1, ..., N \tag{4.1}$$

where θ_i represents the vector of system parameters for the i^{th} individual (dim p), $h_i(\theta_i)$ is the vector of model outputs for the i^{th} individual (constructed from the solution of Eqs. (3.1) and (3.2), dim $m_i = m \cdot l$), e_i is the vector of associated output errors, and Y_i is the vector of all measurements for the i^{th} individual. Following the assumptions noted in Section 3.3 regarding the independence of the output error, it is further assumed that $e_i \sim N(0, G_i\left(h_i(\theta_i), \beta\right))$, where β represents the vector of parameters (dim q) that are unique to the error variance model (assumed common across individuals) and $G_i\left(h_i(\theta_i), \beta\right)$ is a positive definite covariance matrix whose structure was discussed earlier. For convenience $G_i\left(\theta_i, \beta\right) \equiv G_i\left(h_i(\theta_i), \beta\right)$.

To account for the differences between individuals, the system parameters θ_i are assumed to be independent, identically distributed random vectors as follows:

$$\theta_i \sim_{i.i.d.} N(\mu, \Sigma) \text{ or } LN(\mu, \Sigma) \tag{4.2}$$

This basic parametric population model can be extended to incorporate subject specific measured covariates to explain some of the inter-individual variability as follows:

$$\theta_i \sim_{i.i.d.} N(\mu_i, \Sigma) \text{ or } LN(\mu_i, \Sigma) \quad \text{where } \mu_i = v(c, r_i) \tag{4.3}$$

In Eq. (4.3), $v(c, r_i)$ is a general (linear or nonlinear in r_i) user defined covariate model relating any measured covariates from the i^{th} individual to the population mean for the i^{th} individual (μ_i). The vector r_i is the collection of known, time-invariant covariates for the i^{th} individual. The vector c (dim p_c) represents the covariate model parameters (assumed common across individuals).

The population model can be summarized as follows using the hierarchical modeling framework:

Stage 1 - PK/PD system and observation model (intra-individual variation):

$$Y_i = h_i(\theta_i) + e_i, \quad i = 1, ..., N$$
$$e_i \sim N\left(0,\, G_i\left(\theta_i, \beta\right)\right)$$

Stage 2 - Parameter model (inter-individual variation):

$$\theta_i \sim_{i.i.d.} N(\mu, \Sigma) \text{ or } LN(\mu, \Sigma) \quad \text{without covariates}$$
$$\theta_i \sim_{i.i.d.} N(v(c, r_i), \Sigma) \text{ or } LN(v(c, r_i), \Sigma) \quad \text{with covariates}$$

The population estimation problem involves estimating the parameters (μ, Σ, β) or (c, Σ, β), as well as $(\theta_i,\ i = 1, ..., N)$, given all the population data $\{Y_1, \ldots, Y_N\}$.

In the next section, the maximum likelihood solution to this population estimation problem (via the EM algorithm) is presented as implemented in the MLEM program. The last three sections of this chapter present the details of the ITS, STS and NPD programs.

4.3 Maximum Likelihood Solution via the EM Algorithm (MLEM)

The expectation-maximization (EM) algorithm introduced in 1977 by Dempster, Laird and Rubin [24] to solve an important class of maximum likelihood problems, has been applied widely to solve linear mixed effects models. In 1995, Schumitzky applied the EM algorithm to solve the nonlinear mixed effects maximum likelihood estimation problem and suggested the use of sampling-based methods (including importance sampling) to calculate the required integrals [25]. In a seminal 1996 paper, Walker also applied the EM algorithm to this problem and extended it to including the case of linear covariate models. In addition he provided an error analysis for the maximum likelihood estimates and illustrated its application [26]. More recently, Bauer et al. [27] extended the EM solution to include general error variance models, arbitrary nonlinear covariance models (stationary covariate case) and inter-occasion variability. He also tackled the problem of calculating the conditional mean and covariance required in the EM algorithm (see below), and showed that the importance sampling algorithm represents a practical solution to this computationally challenging step in the algorithm even for complex PK/PD population modeling problems (see Ng, et al., [28]). Most recently, the EM solution to the nonlinear mixed effects maximum likelihood problem with the population modeled as mixtures of Normals has been derived by Wang et al. [29].

The EM algorithm with importance sampling has now been tested extensively through its implementation by Bauer in S-ADAPT [30]. The EM with sampling algorithm is also contained in the commercial PK/PD modeling software PDx-MCPEM developed by Guzy and distributed by GloboMax, LLC. A stochastic approximation EM implementation using Markov chain Monte Carlo sampling has been applied to the nonlinear mixed effects maximum likelihood modeling problem by Kuhn and Lavielle [31]-[32], and a general purpose PK/PD population modeling program implementing this method is freely available in the MATLAB-based MONOLIX program (developed and distributed by the MONOLIX group, chaired by M. Lavielle and F.

Mentre).

The use of the EM algorithm with sampling-based methods now provides a powerful and computationally practicable method for solving the parametric maximum likelihood population PK/PD modeling problem, without recourse to model linearization or analytic likelihood approximation (and thus without the resulting estimator bias). This is the approach implemented in the MLEM program of ADAPT 5 as detailed below.

Following the definition of the population PK/PD maximum likelihood estimation problem, the sections below present the MLEM program implementation details including: the EM algorithm; importance-sampling calculations; covariate models; standard error analysis; lognormal parameter model; model selection criteria.

4.3.1 The Likelihood Function and the Estimation Problem

Given the problem statement above define:

$$p\left(Y_i \mid \theta_i, \beta\right) = N\left(h_i\left(\theta_i\right), G_i\left(\theta_i, \beta\right)\right)$$
$$p\left(\theta_i \mid \mu, \Sigma\right) = N\left(\mu, \Sigma\right)$$

The case when the systems parameters are distributed log normally is handled by transformation internally within the MLEM program as described below. If any of the observations exceed the quantitation limits, then those observations are treated as censored and their likelihoods are defined as described for the individual ML estimation in Chapter 3.7.2.

From the independence of the $\{Y_1, \ldots, Y_N\}$, the overall data likelihood function is then given by:

$$L\left(\mu, \Sigma, \beta\right) = \prod_{i=1}^{N} \int p\left(Y_i \mid \theta_i, \beta\right) p\left(\theta_i \mid \mu, \Sigma\right) d\theta_i \tag{4.4}$$

Defining $\phi = \left(\mu, \Sigma, \beta\right)$, the maximum likelihood estimator of ϕ is then: $\phi_{ML} = \arg\max L(\phi)$.

4.3.2 The EM Algorithm Solution

As shown by Schumitzky [25] and also by Walker [26], the EM algorithm given below solves (locally) the maximum likelihood estimation problem defined above.

Given initial guesses for the population, error variance and individual subject parameters ($\mu^{(0)}$ $\Sigma^{(0)}$ $\beta^{(0)}$ $\theta_i^{(0)}$), the EM algorithm proceeds in two steps. In Step 1 (estimation or E step) the conditional mean and covariance for each individual's parameters are estimated, while Step 2 (Maximization-M step) updates the population mean, covariance and error variance parameters. These two steps, defined below for the k^{th} iteration, are then iterated until convergence.

Step 1

$$\bar{\theta}_i^{(k)} = E\left[\theta_i \mid Y_i,\ \phi^{(k)}\right] \tag{4.5}$$

$$\bar{\Omega}_i^{(k)} = E\left[\left(\theta_i - \bar{\theta}_i^{(k)}\right)\left(\theta_i - \bar{\theta}_i^{(k)}\right)^T \mid Y_i,\ \phi^{(k)}\right] \tag{4.6}$$

$$i = 1,\ \ldots,\ N$$

Step 2

$$\mu^{(k+1)} = \frac{1}{N}\sum_{i=1}^{N} \bar{\theta}_i^{(k)} \tag{4.7}$$

$$\Sigma^{(k+1)} = \frac{1}{N}\sum_{i=1}^{N}\left\{\left(\bar{\theta}_i^{(k)} - \mu^{(k+1)}\right)\left(\bar{\theta}_i^{(k)} - \mu^{(k+1)}\right)^T + \bar{\Omega}_i^{(k)}\right\} \tag{4.8}$$

$$\beta^{(k+1)} = \beta^{(k)} - H\left(\phi^{(k)}\right)^{-1}\frac{\partial\left(-\log L\left(\phi^{(k)}\right)\right)}{\partial\beta} \tag{4.9}$$

Letting $H(\phi^{(k)}) = \left\{h_{j1,j2}\right\},\ j1, j2 = 1,\ldots,q$ and $\partial\left(-\log L\left(\phi^{(k)}\right)\right)/\partial\beta = \left\{L_{\beta_{j1}}\right\},\ j1 = 1,\ldots,q$ and also defining $Y_i = \left\{y_{ij}\right\},\ h_i(\theta_i) = \left\{h_{ij}(\theta_i)\right\}$ and $G_i(\theta_i,\beta) = diag\left\{g_{ij}(\theta_i,\beta)\right\},\ j = 1,\ldots,m_i$ (m_i is the total number of observations for the i^{th} subject), then terms in Eq. (4.9) are constructed from:

$$h_{j1,j2} = \frac{1}{2}\sum_{i=1}^{N} E\left[\sum_{j=1}^{m_i}\frac{1}{g_{ij}^2(\theta_i,\beta)}\left(\frac{\partial g_{ij}(\theta_i,\beta)}{\partial\beta_{j1}}\right)\left(\frac{\partial g_{ij}(\theta_i,\beta)}{\partial\beta_{j2}}\right)\mid Y_i,\ \phi^{(k)}\right]$$

$$L_{\beta_{j1}} = \frac{1}{2}\sum_{i=1}^{N} E\left[\sum_{j=1}^{m_i}\frac{1}{g_{ij}^2(\theta_i,\beta)}\left(\frac{\partial g_{ij}(\theta_i,\beta)}{\partial\beta_{j1}}\right)\left(g_{ij}(\theta_i,\beta) - \left(y_{ij} - h_{ij}(\theta_i)\right)^2\right)\mid Y_i,\ \phi^{(k)}\right]$$

The required partial derivatives are calculated by finite difference approximation as described in Chapter 3.5. (See also Bauer [26].)

An argument similar to the one given in Dempster et al. [24] shows that the resulting sequence $\{\phi^{(k)}\}, k = 1,\ldots$ has the likelihood improving property $L(\phi^{k+1}) \geq L(\phi^k)$. Wu [33] and Tseng [34] give sufficient conditions for the convergence of ϕ^k to a local maximum of the likelihood function in Eq. (4.4).

When the user constrains some or all of the intersubject covariances to zero (structured covariance), then the corresponding elements of $\Sigma^{(k+1)}$ are set to zero after their calculation in Eq. (4.8).

The population mean ($\bar{\gamma}$) and population covariance (Σ_γ) of any secondary parameters ($\gamma = w(\theta)$) are approximated as follows:

$$\bar{\gamma} \approx w(\mu) \quad \text{and} \quad \Sigma_\gamma \approx \left(\frac{\partial w(\mu)}{\partial \theta}\right) \Sigma \left(\frac{\partial w(\mu)}{\partial \theta}\right)^T$$

with the partial derivatives are calculated by finite difference approximation. Model predictions based on the population mean are approximated as $h_i(\mu),\ i = 1, ..., N$.

Individual Estimates. At the maximum likelihood solution, the conditional means in Eq. (4.5) serve as estimates for each individual's parameter values, while the conditional covariances in Eq. (4.6) provide the standard errors of these estimates. Also for each individual, the conditional means and covariances for the model predictions, the conditional residuals, the conditional error variances, the conditional standardized residuals, as wells as the conditional means and covariances for any secondary parameters are calculated and denoted (in turn) as follows:

$$\overline{h_i} = E\left[h_i(\theta_i) \mid Y_i,\ \phi\right]$$

$$\operatorname{cov}(h_i \mid \phi) = E\left[\left(h_i(\theta_i) - \overline{h_i}\right)\left(h_i(\theta_i) - \overline{h_i}\right)^T \mid Y_i,\ \phi\right]$$

$$\overline{e_i} = Y_i - E\left[h_i(\theta_i) \mid Y_i,\ \phi\right]$$

$$\overline{g_{ij}} = E\left[g_{ij}(\theta_i, \beta_{ML}) \mid Y_i,\ \phi\right],\ \ j = 1, \ldots, m_i$$

$$stdres_{ij} = E\left[\frac{y_{ij} - h_{ij}(\theta_i)}{\sqrt{g_{ij}(\theta_i, \beta_{ML})}} \mid Y_i,\ \phi\right],\ \ j = 1, \ldots, m_i$$

$$\overline{\gamma_i} = E\left[w(\theta_i) \mid Y_i,\ \phi\right]$$

$$\operatorname{cov}(\gamma_i \mid \phi) = E\left[\left(w(\theta_i) - \overline{\gamma_i}\right)\left(w(\theta_i) - \overline{\gamma_i}\right)^T \mid Y_i,\ \phi\right]$$

During the EM iterations these quantities are evaluated at $\phi = \phi^{(k)}$ and for the maximum likelihood solution at $\phi = \phi_{ML}$.

4.3.3 The Conditional Mean and Covariance

The conditional mean and covariance in Eq. (4.5) and (4.6), as well as all of the other expectations required above, are defined by the conditional distribution for θ_i :

$$p(\theta_i \mid Y_i,\ \mu,\ \Sigma,\ \beta) = \frac{p(Y_i \mid \theta_i,\ \beta)\, p(\theta_i \mid \mu,\ \Sigma)}{\int p(Y_i \mid \theta_i,\ \beta)\, p(\theta_i \mid \mu,\ \Sigma)\, d\theta_i}, \quad i = 1, \ldots, N \tag{4.12}$$

We note that all of the expectations required in the EM algorithm outlined above have the form $E\left[f\left(\theta_i\right)\right] = \int f\left(\theta_i\right) p\left(\theta_i \mid Y_i,\, \mu,\, \Sigma,\, \beta\right) d\theta_i$. Numerical approximation of these *p*-dimensional integrals is accomplished in ADAPT using sampling based methods as discussed in Chapter 5.

4.3.4 The EM Algorithm with Covariates

The solution to the nonlinear random effects modeling problem via the EM algorithm for the case of a linear stage 2 covariate model ($\mu_i = C \cdot r_i$) was presented in Walker [26]. Bauer gives the solution for the general nonlinear covariate model case defined above ($\mu_i = v(c, r_i)$) [27].

Defining $p\left(\theta_i \mid c,\, r_i,\, \Sigma\right) = N\left(v(c, r_i),\, \Sigma\right)$ and $\phi = \left(c,\, \Sigma,\, \beta\right)$, the maximum likelihood estimator of ϕ maximizes the function

$$L\left(c,\, \Sigma,\, \beta\right) = \prod_{i=1}^{N} \int p\left(Y_i \mid \theta_i,\, \beta\right) p\left(\theta_i \mid c,\, r_i,\, \Sigma\right) d\theta_i \tag{4.13}$$

The EM solution to this problem follows the algorithm defined above, with Step 1 identical to that given in Eqs. (4.5) and (4.6) while the Step 2 update for the population mean in Eq. (4.7) is replaced by the following:

$$\begin{aligned} c^{(k+1)} &= \arg\min_{c} \sum_{i=1}^{N} \left\{ \left(\overline{\theta}_i^{(k)} - v(c,\, r_i)\right)^T \left(\Sigma^{(k)}\right)^{-1} \left(\overline{\theta}_i^{(k)} - v(c,\, r_i)\right) \right\} \\ \mu_i^{(k+1)} &= v(c^{(k+1)},\, r_i) \end{aligned} \tag{4.14}$$

No constraints are placed on the covariate model parameters c (i.e., they can any real number). In the implementation, only those parameters modeled via covariates are used in Eq. (4.14), while the remaining parameter means are updated using Eq. (4.7). The updating formula for Σ is identical to that given in Eq. (4.8), but with μ_i replacing μ. All the other calculations in Section 4.2.2 (the individual estimates section) proceed as indicated above. The relatively straight-forward numerical solution to the nonlinear function minimization in Eq. (4.14) is solved in ADAPT using the Nelder-Mead simplex algorithm (see Chapter 5).

4.3.5 Standard Errors of the Estimates

This section presents an asymptotic analysis of the EM estimates. Given the regularity conditions from Philppou and Roussas [35] for the maximum likelihood estimate of independent but not identically distributed random variables, it can be shown that asymptotically as $N \to \infty$,

$$Cov\left(\phi_{ML}\right) \approx \left(\sum_{i=1}^{N} V_i\left(\phi_{ML}\right) \right)^{-1} \tag{4.15}$$

where

$$V_i\left(\phi\right) = \left(\frac{\partial}{\partial \phi} \log p\left(Y_i \mid \phi\right) \right) \left(\frac{\partial}{\partial \phi} \log p\left(Y_i \mid \phi\right) \right)^T$$

and $p(Y_i \mid \phi) = \int p(Y_i \mid \theta_i, \beta) p(\theta_i \mid c, r_i, \Sigma) d\theta_i$ (c.f., Eq. (4.13)).

The components of $\partial \log p(Y_i \mid \phi) / \partial \phi$ (for the case where $\phi = (c, \Sigma, \beta)$) are constructed as outlined below for each individual using the following notation: $sc_i = \partial \log p(Y_i \mid \phi) / \partial c$, $s\Sigma_i = \partial \log p(Y_i \mid \phi) / \partial \Sigma$ and $s\beta_i = \partial \log p(Y_i \mid \phi) / \partial \beta$.

$$sc_i = \left(\frac{\partial v(c, r_i)}{\partial c} \right)^T \Sigma^{-1} \left(\bar{\theta}_i - v(c, r_i) \right) \tag{4.16}$$

$$s\Sigma_i = -\frac{1}{2} \Sigma^{-1} \left(\Sigma - \left(\left(\bar{\theta}_i - \mu_i \right) \left(\bar{\theta}_i - \mu_i \right)^T + \bar{\Omega}_i \right) \right) \Sigma^{-1} \tag{4.17}$$

$$s\beta_i = \left\{ -L_{\beta_i} \right\}, \quad i = 1, \ldots q \tag{4.18}$$

where the elements of Eq. (4.18) are defined in the EM algorithm (see Section 4.3.2). All quantities are evaluated at their converged values from the EM algorithm. Also, since Σ is symmetric, we only need the gradient with respect to the lower triangular part of Σ, which is constructed as follows: let

$$s\Sigma_i^* = \left(2s\Sigma_i - \text{diag}\left(s\Sigma_i(1,1) \cdots s\Sigma_i(p,p) \right) \right)$$

$$\widetilde{s\Sigma}_i = \left\{ s\Sigma_i^*(j,k) \right\}, \; j = 1, \ldots, k, \; i = 1, \ldots, p$$

The $p(p+1)/2$ vector $\widetilde{s\Sigma}_i$, together with the vectors sc_i and $s\beta_i$ defined above, can then be used to form the vector $s_i = (sc_i, s\beta_i, \widetilde{s\Sigma}_i)$ for each individual. Equation (4.15) becomes:

$$Cov\left(\phi_{ML} \right) \approx \left(\sum_{i=1}^{N} s_i s_i^T \right)^{-1} \tag{4.19}$$

We note that the components in Eqs. (4.16)-(4.18) are already calculated during the course of the EM algorithm computations, with the exception of $\partial v(c, r_i) / \partial c$ in Eq. (4.16) which is determine easily via a finite difference approximation.

The square roots of the diagonal elements of Eq. (4.19) are then the standard errors $(se_c, se_\beta, se_\Sigma)$ for the maximum likelihood estimates $(c_{ML}, \beta_{ML}, \Sigma_{ML})$. The standard errors se_Σ are displayed in the program output for the corresponding (lower diagonal) elements of the population covariance Σ_{ML}, while the standard errors se_c and se_β are shown as a percent of their correspond maximum likelihood estimates (%RSE). In addition, the standard errors are also listed for the maximum likelihood estimates of the population standard deviations (i.e, $\sqrt{\Sigma_{ML}(i,i)}$, $i = 1, \ldots, p$), also as a %RSE (i.e., $100 se_\Sigma(i(i+1)/2)) / \left(2\Sigma_{ML}(i,i) \right)$, $i = 1, \ldots, p$).

Notes: 1) The standard error calculations include the case when the population mean model for some of the parameters does not depend on covariates. For these parameters, then $v_j(c, r_i) = c_j = \mu_j$. 2) If there are no subject specific covariates, in the above error analysis $c \to \mu$ and $sc_i \to s\mu_i$, where $s\mu_i = \Sigma^{-1}(\bar{\theta}_i - \mu)$. 3) In the case of a structured covariance, the matrix $\widetilde{s\Sigma}_i$ above only includes those elements of $s\Sigma_i^*$ that are estimated.

4.3.6 Lognormal Parameter Model

For the case when the Stage 2 parameter model is assumed to be lognormal, all Stage 1 parameters θ_i (original parameterization) are replaced with e^{θ_i} (transformed parameterization), and then the EM algorithm is implemented as presented in Sections 4.2.1 – 4.2.6 (this transformation occurs internally within the program).

The following expressions are then used to convert the results obtained based on this transformed parameterization back to the original parameters. The conditional mean and conditional covariance for the i^{th} individual are (approximately):

$$e^{\bar{\theta}_i} \quad \text{and} \quad \left[e^{\bar{\theta}_i}\right]\overline{\Omega}_i\left[e^{\bar{\theta}_i}\right]^T, \quad i = 1, \ldots, N \tag{4.20}$$

The population mean and population covariance (case with no covariates) are calculated as follows:

$$e^{\mu} \quad \text{and} \quad \text{diag}\left(e^{\mu_1} \ldots e^{\mu_p}\right)\left(\sum\right)\text{diag}\left(e^{\mu_1} \ldots e^{\mu_p}\right)^T \tag{4.21}$$

In addition, the matrix Σ in the last expression is also displayed (i.e., population covariance for $\ln(\theta)$ of the original parameterization). For the case when Stage 2 parameters are modeled as functions of covariates, then only Σ in expression (4.21) is presented.

4.3.7 Model Selection and Hypothesis Testing

The AIC and BIC criteria for use in model selection are calculated as follows:

$$AIC = -2\log L(\phi_{ML}) + 2(p^*) \tag{4.22}$$

$$BIC = -2\log L(\phi_{ML}) + (p^*)\ln(m^*) \tag{4.23}$$

where $L(\phi_{ML})$ is given in Eq. (4.4), p^* represents the total number of parameters estimated (population means, elements of the population covariance matrix, error variance parameters and covariate model parameters), and m^* is the total number of observations ($m^* = \sum_{i=1}^{N} m_i$).

For hypothesis testing involving nested models, the program also displays the value of the quantity $-2\log L(\phi_{ML})$.

4.4 Iterated Two-Stage (ITS)

In 1977, motivated by the problem of estimating the dispersion of properties of a biomaterial, Guy Prevost reported algorithms for density estimation from noisy data [36]. (This work was done at the process engineering consulting company ADERSA located at the time in Velizy, France, which was founded by the applied mathematician/control systems engineer and originator of the field of model-based predictive control Jaques Richalet.) Recognizing the relevance of Prevost's work to population PK, Jean-Louis Steimer, Alain Mallet and their colleagues formulated and presented the global two-stage (GLS) and iterated two-stage (ITS) methods for NLME modeling applications in 1984 [37].

Despite the well-known limitations of the ITS algorithm, it remains an efficient approach for exploratory population PK/PD modeling and is included in ADAPT 5. We present below the details of the ITS implementation for the case with covariate models as defined in Section 4.2. The reader is also referred to the discussion in Schumitzky [25] on the relation between the ITS and MLEM algorithms.

Given initial guesses for the population, error variance and individual subject parameters ($c^{(0)}$ $\Sigma^{(0)}$ $\beta^{(0)}$ $\theta_i^{(0)}$), the ITS algorithm proceeds in two steps. In Step 1, the MAP estimates are determined for each subject along with their approximate covariances (see also Chapter 3.7.4), while in Step 2 the covariate model, population covariance and error variance parameters are updated. These two steps, defined below for the k^{th} iteration, are then iterated until convergence.

Step 1

$$\hat{\theta}_i^{(k)} = \arg\min O_{MAP}\left(\theta_i\right) \tag{4.24}$$

$$\hat{\Omega}_i^{(k)} = \left(M_{\theta_i} + \left(\Sigma^{(k)}\right)^{-1}\right)^{-1} \tag{4.25}$$

$$i = 1, \ldots, N$$

where

$$O_{MAP}\left(\theta_i\right) = \sum_{j=1}^{m_i}\left(\frac{\left(y_{ij} - h_{ij}\left(\theta_i\right)\right)^2}{g_{ij}\left(\theta_i, \beta^{(k)}\right)} + \ln g_{ij}\left(\theta_i, \beta^{(k)}\right)\right) + \left(\theta_i - v(c^{(k)}, r_i)\right)^T \left(\Sigma^{(k)}\right)^{-1}\left(\theta_i - v(c^{(k)}, r_i)\right)$$

and the elements of the matrix $M_{\theta_i} = \left\{m_{j1,j2}\right\}$, $j1, j2 = 1, ..., p$ are

$$m_{j1,j2} = \sum_{j=1}^{m_i}\frac{1}{g_{ij}\left(\hat{\theta}_i, \beta^{(k)}\right)}\left(\frac{\partial h_{ij}\left(\hat{\theta}_i\right)}{\partial \theta_{j1}}\right)\left(\frac{\partial h_{ij}\left(\hat{\theta}_i\right)}{\partial \theta_{j2}}\right) + \frac{1}{2}\sum_{j=1}^{m_i}\frac{1}{g_{ij}^2\left(\hat{\theta}_i, \beta^{(k)}\right)}\left(\frac{\partial g_{ij}\left(\hat{\theta}_i, \beta^{(k)}\right)}{\partial \theta_{j1}}\right)\left(\frac{\partial g_{ij}\left(\hat{\theta}_i, \beta^{(k)}\right)}{\partial \theta_{j2}}\right)$$

Step 2

$$c^{(k+1)} = \arg\min_{c} \sum_{i=1}^{N} \left\{ \left(\hat{\theta}_i^{(k)} - v(c,\, r_i) \right)^T \left(\Sigma^{(k)} \right)^{-1} \left(\hat{\theta}_i^{(k)} - v(c,\, r_i) \right) \right\} \tag{4.26}$$

$$\Sigma^{(k+1)} = \frac{1}{N} \sum_{i=1}^{N} \left\{ \left(\hat{\theta}_i^{(k)} - v\left(c^{(k+1)},\, r_i \right) \right) \left(\hat{\theta}_i^{(k)} - v\left(c^{(k+1)},\, r_i \right) \right)^T + \widehat{\Omega}_i^{(k)} \right\} \tag{4.27}$$

$$\beta^{(k+1)} = \arg\min \sum_{i=1}^{N} -\log p\left(Y_i \mid \hat{\theta}_i^{(k)}, \beta \right) \tag{4.28}$$

The function minimizations in Eqs. (4.26) and (4.28) are performed using the Nelder-Mead simplex algorithm.

Notes: 1) When the Stage 2 parameter model does not depend on covariates, then $v(c, r_i) \to \mu$ and Eq. (4.26) is replaced by: $\mu^{(k+1)} = \sum_{i=1}^{N} \hat{\theta}_i^{(k)} / N$. 2) For the case when the Stage 2 parameter model is assumed to be lognormal, all Stage 1 parameters θ_i (original parameterization) are replaced with e^{θ_i} (transformed parameterization), and then the ITS algorithm proceeds as given in Eqs. (4.24)-(4.28) (this transformation occurs internally within the program). The transformation back to the original parameterization follows Eqs. (4.20) and (4.21). 3) The individual subject model predictions, individual standard errors and residual analysis are calculated as given in Chapter 3.7.6. 4) For hypothesis testing and model selection the overall likelihood is approximated as $L\left(\theta_{ITS_i}, \beta_{ITS} \right) = \prod_{i=1}^{N} p\left(Y_i \mid \theta_{ITS_i}, \beta_{ITS} \right)$ and the criteria *AIC* and *BIC* are given by Eqs. (4.22) and (4.23) with the term $L\left(\phi_{ML} \right)$ in those equations replaced by $L\left(\theta_{ITS_i}, \beta_{ITS} \right)$. The term $-2 \log L\left(\theta_{ITS_i}, \beta_{ITS} \right)$ is also displayed.

4.5 Standard Two Stage (STS)

The calculations for each individual in the STS program proceed as presented in Chapter 3 depending on the estimation option selected WLS, ML or MAP. The resulting individual subject estimates $\hat{\theta}_i$, $i = 1, \ldots, N$ are then used to approximate the population mean and covariance (μ, Σ) as follows:

$$\mu = \frac{1}{N} \sum_{i=1}^{N} \hat{\theta}_i \tag{4.29}$$

$$\Sigma = \frac{1}{N} \sum_{i=1}^{N} \left(\hat{\theta}_i - \mu \right) \left(\hat{\theta}_i - \mu \right)^T \tag{4.30}$$

Other sample statistics are also calculated (e.g., standard deviations, medians). The mean and standard deviation for the estimates of $\widehat{\beta}_i$, $i = 1, \ldots, N$ are also calculated for the ML and MAP estimators.

4.6 Naïve Pooled Data (NPD)

Although not a population analysis approach, a program to conveniently calculate naïve pooled data estimates is included in ADAPT 5 because of its relevance to certain types of experiments. As with the MLEM, ITS and STS programs, data from each individual can arise from a different experiment design. The NPD program includes WLS, ML and MAP estimation options. The calculations are as defined in the sections of Chapter 3 describing each of these estimators (Eq. (3.20) for WLS, Eq. (3.34) for ML, Eqs. (3.45) and (3.46) for MAP), but now the respective objective functions include an additional summation over all individuals in the population data set.

CHAPTER 5

Computational Methods

5.1 Solving Model Equations

5.1.1 General Differential Equation Solver

When the model differential equations are defined by Eq. (3.1), ADAPT uses the differential equation solver LSODA (Livermore Solver for Ordinary Differential equations with Automatic method switching for stiff and nonstiff problems). This powerful general purpose differential equation solver was developed by Linda Petzold and Alan Hindmarsh ([38] and [39]), and uses variable order, variable step size formulations of Adam's method and Gear's method as the nonstiff and stiff equation solvers, respectively. The most recent (November 2003) version of LSODA is included in ADAPT.

The most important computational component of any general purpose software system for PK/PD modeling is the ability to solve the model differential equations accurately, robustly and efficiently. We have discussed previously [1] some of the difficulties associated with the numerical solution of ordinary differential equations when imbedded in any iterative estimation algorithm. In past versions of this user's guide we have emphasized the ability of LSODA to detect stiffness and switch between Adam's and Gear's methods, which together with its capability to control the step size and order of the selected method make this program the most robust and efficient software we know of to solve imbedded estimation applications. No other software that we have evaluated recently has caused us to change this view. While there are solvers that can handle either non-stiff or stiff systems efficiently (including the excellent SUNDIALS differential/algebraic equation solver suite [40] from Lawrence Livermore National Labs), it is not always evident when nonlinear differential equations are stiff versus non-stiff and, most importantly, the same system can exhibit either stiff or non-stiff behavior depending on the particular parameter values encountered in the course of the iterative estimation calculations. Thus the often cited recommendation to select either a stiff or non-stiff solver depending on the problem is at best inefficient for imbedded iterative estimation applications.

After installation of ADAPT, certain LSODA options can be set through parameters in the globals.inc file. The version of this file received with ADAPT has these options set to allow for the most general implementation of LSODA with the minimum user input. For example, the parameter which indicates how the Jacobian is to be determined when the stiff solver is used has been set so that the Jacobian is calculated internally by finite difference approximation. The other setting for this option requires the user to supply a subroutine to be used to compute this Jacobian matrix. In addition to these options, the relative and absolute error tolerances (RTOL, ATOL) used by LSODA to control the local solution error (i.e. at each observation time) are supplied as parameters via the globals.inc file. LSODA controls its estimate of the local errors (e_i) in the states ($x_i(t_j)$, $i=1,...,n$), such that the maximum of $e_i \Big/ \left(RTOL \left| x_i(t_j) \right| + ATOL \right)$, $i=1,...,n$ is less than 1.0. The parameter RTOL has been set rather conservatively at 10^{-6} recognizing that the tolerance parameters control only the local error, that can accumulate into global error. The value of ATOL has also been set to 10^{-6}, which should be considered when selecting the scale for the state variables.

5.1.2 Linear Differential Equations

For systems that can be modeled as a set of linear homogeneous differential equations, the following state equation may be used in place of Eq. (3.1):

$$\frac{dx(t)}{dt} = A(\alpha)\,x(t), \quad x(0) = c \tag{5.1}$$

The state matrix $A(\alpha)$ has dimensions *n* x *n*.

If linear model differential equations are defined by their state matrix in Eq. (5.1), then the solution is obtained using the exponential of the matrix A (see [41]). This matrix exponential is approximated using an eigenvalue decomposition of A. The method computes $x(t_i)$ as

$$x(t_j) = \mathbf{V} \exp\left(\mathbf{D}(t_j - t_0)\right)\mathbf{y}_0, \quad j = 1,...,m \tag{5.2}$$

where $\mathbf{D}$ is the diagonal matrix of eigenvalues and $\mathbf{V}$ is the matrix of eigenvectors calculated from a $\mathbf{QR}$ decomposition of the matrix following the suggestion in [42]. In the above equation, $\mathbf{V}$ is calculated as $\mathbf{QR}$, and $\mathbf{y}_0$ is computed by solving

$$\mathbf{R}\mathbf{y}_0 = \mathbf{Q}^T\mathbf{x}_0 \tag{5.2}$$

where $\mathbf{x}_0 = \mathbf{x}(t_0)$. The eigenvalue-eigenvector decomposition approach, as we have implemented it, is restricted to the case where the matrix $\mathbf{A}$ is diagonalizable, as determined in our program from the condition number of $\mathbf{R}$. If $\mathbf{A}$ cannot be diagonalized, a message to this effect is printed. In such a case it would be necessary to re–code the model in DIFFEQ, using LSODA to solve the model equations.

We have reported previously [43] on the efficiency of this matrix exponential approach for

solving linear differential equations, relative to a second matrix exponential approximation algorithm and to LSODA. For the two examples considered, the approach summarized above reduced the CPU time required to solve a parameter estimation problem by a factor of 10 over that needed when the model equations were solved using LSODA. Also in [43], a state augmentation procedure is illustrated which allows one to convert a linear model with infusion inputs into the form shown in Eq. (3.10), thus allowing the matrix exponential solution algorithm in ADAPT to be used for this important class of problems. However, we have used this technique only infrequently in recent years, preferring instead the ease of use of the general differential equation solver LSODA.

5.2 Function Minimization

In the programs ID, SAMPLE, NPD, STS, ITS and MLEM it is necessary to minimize functions of several variables (used in MLEM to solve the covariate model optimization problems). Function minimization is accomplished in ADAPT using the Nelder-Mead Simplex algorithm as described originally in [44] (see also [1]). To initiate the Nelder-Mead search procedure for minimization a function of p parameters, it is necessary to define the vertices of the starting simplex (e.g., in ID this requires specifying $p+1$ sets of parameters and in SAMPLE $m+1$ sets of sample times are required). In ID (as well as NPD, STS and ITS), the starting simplex $(\theta^1, \theta^2, ..., \theta^{p+1})$ is constructed from the user-entered initial parameter vector $\theta^o = \left[\theta_1^o ... \theta_p^o\right]$ as follows:

$$\begin{aligned}
\theta^1 &= \left[\theta_1^0 \quad \theta_2^0 \quad \cdots \quad \theta_p^0\right]^T \\
\theta^2 &= \left[\theta_1^0 - 0.2\theta_1^0 \quad \theta_2^0 \quad \cdots \quad \theta_p^0\right]^T \\
\theta^3 &= \left[\theta_1^0 \quad \theta_2^0 - 0.2\theta_2^0 \quad \cdots \quad \theta_p^0\right]^T \\
&\vdots \\
\theta^{p+1} &= \left[\theta_1^0 \quad \theta_2^0 \quad \cdots \quad \theta_p^0 - 0.2\theta_p^0\right]^T
\end{aligned} \tag{5.3}$$

The starting simplex for the sample schedule design vector is similarly constructed in SAMPLE and for covariate model parameters in MLEM.

The stopping rule used to terminate the Nelder-Mead iterative procedure is

$$\text{Stop if : } \left| \frac{O\left(\theta_{(i)}\right)}{O\left(\theta_{(i-1)}\right) - 1} \right| \leq \text{ REQMIN} \tag{5.4}$$

where $O\left(\theta_i\right)$ is the function to be minimized evaluated at the parameter vector for the i^{th} iteration, $\theta_{(i)}$. The value of the stopping tolerance in the above equation REQMIN, is specified in the file globals.inc and. The default value of REQMIN is set at 10^{-6}.

In the function minimizations in ID, NPD and STS, model parameters are constrained to be positive as are measurement times in SAMPLE. This is accomplished using a square transformation within ADAPT.

5.3 Finite Difference Approximations

The error analyses provided in ID, NPD, STS, ITS and MLEM and the design criteria implemented in SAMPLE, all require calculations of the derivation of a function with respect to model parameters. This is accomplished in ADAPT using a central difference approximation as illustrated below for the case of a function *f* of a single parameter θ

$$\frac{df(\theta)}{d\theta} \approx \frac{f(\theta+h)-f(\theta-h)}{2h} \tag{5.5}$$

In this approximation, *h* is determined as

$$h = \sqrt{RTOL} \cdot \max\left(|\theta|, ATOL\right) \tag{5.6}$$

for the case when the model is defined using differential equations. When the model equations are solved using the matrix exponential algorithm or when the analytic solution is given, RTOL, ATOL in the previous equation are both replaced by the machine epsilon. The error in the central difference approximation is of the order h^2.

5.4 Calculating Conditional Means and other Expectations in MLEM

As noted in the discussion of the EM algorithm in Chapter 4, the conditional mean and covariance in Eq. (4.5) and (4.6), as well as all of the other expectations, are defined by the conditional distribution for θ_i given in Eq. (4.12) and repeated below:

$$p(\theta_i \mid Y_i, \mu, \Sigma, \beta) = \frac{p(Y_i \mid \theta_i, \beta)\, p(\theta_i \mid \mu, \Sigma)}{\int p(Y_i \mid \theta_i, \beta)\, p(\theta_i \mid \mu, \Sigma) d\theta_i}, \quad i = 1, \ldots, N$$

All the expectations required in the EM algorithm and indicated in Chapter 4.3 have the form $E\left[f(\theta_i)\right] = \int f(\theta_i)\, p(\theta_i \mid Y_i, \mu, \Sigma, \beta) d\theta_i$. Numerical approximation of these *p*-dimensional integrals is accomplished in ADAPT using importance sampling, as introduced by Kloeck and Van Dijk in 1978 for econometric applications [45] and following the suggestions in Geweke [46].

Let $I(\theta_i)$ denote a *p*-dimensional importance function and let $\theta_i^{(1)}, \ldots, \theta_i^{(M)}$ represent M independent, identically distributed samples (importance sample) generated from $I(\theta_i)$. The importance sampling approximation to $E\left[f(\theta_i)\right]$ is given by:

$$E\left[f\left(\theta_i\right)\right] \approx \sum_{j=1}^{M} f\left(\theta_i^{(j)}\right) w_i^{(j)} \tag{5.7}$$

where

$$w_i^{(j)} = \frac{p\left(Y_i \mid \theta_i^{(j)},\, \beta\right) p\left(\theta_i^{(j)} \mid \mu,\, \Sigma\right) / I\left(\theta_i^{(j)}\right)}{\sum_{k=1}^{M}\left(p\left(Y_i \mid \theta_i^{(k)},\, \beta\right) p\left(\theta_i^{(k)} \mid \mu,\, \Sigma\right) / I\left(\theta_i^{(k)}\right)\right)} \tag{5.8}$$

Thus the conditional mean and covariance for a subject for the k^{th} iteration in Step 1 of the EM algorithm (Eqs. 4.5 and 4.6 in Chapter 4) are approximated as follows:

$$\bar{\theta}_i^{(k)} = \sum_{j=1}^{M} \theta_i^{(j)} w_i^{(j)}$$

$$\bar{\Omega}_i^{(k)} = \sum_{j=1}^{M}\left(\theta_i^{(j)} - \bar{\theta}_i^{(k)}\right)\left(\theta_i^{(j)} - \bar{\theta}_i^{(k)}\right)^T w_i^{(j)}$$

While the numerical approximation in Eq. (5.7) improves as $M \to \infty$, the precision of this approximation depends critically on the choice of the sampling function $I\left(\theta_i\right)$ which in turn is dictated by model complexity and data informativeness (see Geweke [46] for the seminal discussion of these issues). In the MLEM algorithm in ADAPT, an importance function based the multivariate Normal density $N\left(\hat{\theta}_i, \gamma\hat{\Omega}_i\right)$ is used, where $\hat{\theta}_i$ and $\hat{\Omega}_i$ are the mode of the posterior distribution its approximate covariance calculated using MAP estimation (see Chapter 3.7) with the prior distribution defined based on the population mean and covariance from the previous EM iteration ($\mu^{(k-1)}$, $\Sigma^{(k-1)}$) (also $\gamma = 1.2$). This importance function was first suggested by Geweke (section 4 of [45]) and adopted in a modified form by Bauer [30] for use in S-ADAPT. The user must supply the value of M (see population modeling examples in Chapter 10 for further discussion).

This importance sampling calculation is the most computationally intensive component of the MLEM algorithm in ADAPT, requiring *M* evaluations of the likelihood ($p\left(Y_i \mid \theta_i,\, \beta\right)$) for each individual. Once calculated to determine the conditional means and covariances, however, these same likelihood values are used to evaluate all the other expectations listed above, as well as those associated with standard error calculations presented below. In addition, they are used to approximate the overall data likelihood function in Eq. (4.4) as follows:

$$L\left(\phi\right) \approx \prod_{i=1}^{N}\left(\frac{1}{M}\sum_{j=1}^{M}\left(p\left(Y_i \mid \theta_i^{(j)},\, \beta\right) p\left(\theta_i^{(j)} \mid \mu,\, \Sigma\right) / I\left(\theta_i^{(j)}\right)\right)\right) \tag{5.9}$$

The overall data likelihood is used in model selection and hypothesis testing.

5.5 Random Number Generation

To implement the importance sampler in the MLEM program, and for several options in the program SIM, it is necessary to generate random samples from a multivariate density, which requires generation of pseudorandom random samples from a univariate uniform density on the interval [0, 1] ($U(0,1)$). This is accomplished in ADAPT 5 using the Mersenne Twister as proposed by Matsumoto and Nishimura [47] (Fortran implementation by Tsuyoshi Tada [48]). The Mersenne Twister was designed for use in Monte Carol simulations and among its desirable properties is negligible serial correlation between successive values in the output sequence (in contrast to linear congruential generators). It passes numerous tests for statistical randomness and is the default option in programs such as MATLAB, Maple and R. To produce $N(0,1)$ pseudorandom deviates from the $U(0,1)$ pseudorandom random numbers generated from the Mersenne Twister, the Box-Muller method is used.

To generate random samples from a multivariate Normal distribution (e.g., $\theta \sim N(\mu,\Sigma)$) as needed in SIM and MLEM, the covariance matrix Σ (dim p x p) is factored: $LL^T = \Sigma$ (L is lower triangular). The elements of a vector z (dimension p) are then filled with $N(0,1)$ random deviates. A sample vector from the specified multivariate Normal distribution is then generated as follows:

$$\theta = \mu + Lz \tag{5.10}$$

Only random vectors whose elements are greater than zero are used in the population simulation.

If θ is assumed to come from a lognormal distribution (i.e. $\theta \sim LN(\mu,\Sigma)$), then a random vector λ (dim p) is generated, where $\lambda \sim N(\nu,\Phi)$. The elements of the desired random vector θ are obtained from the elements of the random vector λ as $\theta_j = e^{\lambda_j}$, $j = 1, \ldots, p$. The elements of the mean vector ν and covariance matrix Φ are defined in terms of the elements of μ and Σ. as indicated below:

$$\nu_i = \ln \mu_i - \phi_{ii}/2, \quad i = 1,..., p \tag{5.11}$$

$$\phi_{ij} = \ln\left(\frac{\sigma_{ij}}{\mu_i \mu_j} + 1\right), \quad i, j = 1,..., p \tag{5.12}$$

In the program SIM, the user enters the seed for the random number generator. For the MLEM program the seed is fixed in the program, except for continuation runs (using previously created *IND.csv and *IT.csv files) where a seed is then selected based on the system clock.

CHAPTER 6

Model Implementation and Program Results

The tutorial introduction in Chapter 2 provides the basic information needed to implement a model in ADAPT and to prepare the required data and parameter files. This chapter gives complete details on model implementation and data preparation, as well as on the results generated by the ADAPT programs following the methods presented in Chapters 3-5. (Raise your hand if you skipped Chapters 3 through 5.)

6.1 Implementing the Model Equations

All model equations and associated model information are entered into an ADAPT Model File (*.for), including model constants and symbols (in SYMBOL), model differential equations (in DIFFEQ), model output equations (in OUTPUT), error variance models (in VARMOD), covariate models and initial values for population analysis (in COVMOD and in POPINIT), prior parameter values (in PRIOR), and secondary parameter equations (in SPARAM). Entries into the Model File must follow the rules of the Fortran language. For most model specifications this involves a direct specification of the user's PK/PD model equations. (See below for a discussion of some basic Fortran syntax that may be of use for some problems.)

6.1.1 Model Constants and Symbols (in SYMBOL)

The values for certain model constants are entered in subroutine SYMBOL using the code indicated in Table 5.1. In addition, the variable `Ieqsol` is also set in subroutine SYMBOL to either 1, 2 or 3 depending on how the model is defined: 1 - differential equations in DIFFEQ; 2 - matrix equation formulation in AMAT; 3 - algebraic equations only in OUTPUT. (Several library models use built-in analytic solutions to the model differential equations; this is indicated by a different unique value for `Ieqsol` in that library model file that should not be changed.) The code symbol `Descr` can be assigned a text string (60 characters or less) and is used to describe the model in program results. Finally, symbols (10 characters or less) can be provided to represent model parameters (`Psym(1)`, …), error variance model parameters (`PVsym(1)`, …), and any secondary model parameters (`PSsym(1)`, …).

Table 6.1 Model Constants and Symbols

Code	Definition
`NDEqs`	number of differential equations
`NSParam`	number of system parameters
`NVParam`	number of error variance model parameters
`NSecPar`	number of secondary parameters
`Ieqsol`	model definition (1, 2 or 3)
`Descr`	model description text string
`Psym(1) … Psym(NSParam)`	symbol for each system parameter
`PVsym(1) … PVsym(NVParam)`	symbol for each error variance parameter
`PSsym(1) … PSsym(NSecPar)`	symbol for each secondary parameter

6.1.2 Model Differential (in DIFFEQ) and Output (in OUTPUT) Equations

Any model differential equations defined by Eq. (3.1) are entered in the subroutine DIFFEQ of the Model File, while the model output equations of Eq. (3.2) are entered in the subroutine OUTPUT. The symbols that are used in these two subroutines to represent the variables in these equations are given in Table 6.2. The model inputs, represented by $r(t)$ in Eqs. (3.1) and (3.2), are entered directly in the code for the model differential and output equations, using the symbols `R(1)`, ..., `R(NRI)` to represent each of the different inputs The number of model output equations (`NOEqs`), the number of model inputs (`NRI`), along with the number of bolus inputs (`NBI`) are all specified in the subject specific ADAPT data file as indicated below. The particular differential equations that are subject to each bolus input are indicated when running ADAPT. Thus symbols representing the bolus inputs ($b(t)$ in Eq (3.4)) do not appear explicitly in the differential equations.

Table 6.2 Model Differential and Output Equation Symbols for DIFFEQ and OUTPUT

Code	Definition
`X(1) … X(NDEqs)`	model state variables $x_1(t) \ldots x_n(t)$
`P(1) … P(NSParam)`	model system parameters
`R(1) … R(NRI)`	model inputs $r_1(t) \cdots r_k(t)$
`IC(1) … IC(NDEqs)`	initial conditions for state variables
`Y(1) … Y(NOEqs)`	model outputs $y_1(t) \cdots y_l(t)$
`T`	time
`XP(1) … XP(NDEqs)`	derivatives of the state variables $dx_1(t)/dt \ldots dx_n(t)/dt$

When the model differential equations are defined using the linear homogenous differential equation formulation given in Eq. (3.10), then each element of the state matrix is entered in subroutine AMAT using the code variable `A(I,J)` (e.g., `A(1,1)=-(P(1)+P(2))`. Only the non-zero elements of the state matrix are entered.

6.1.3 Error Variance Model (in VARMOD)

The functions used to model the error variance for each output or response, as indicated in Eq. (3.7), are entered in subroutine VARMOD. The symbols used to represent the equation variables are listed in Table 6.3. Any limits of quantitation are also specified in VARMOD.

Table 6.3 Error Variance Model Symbols for VARMOD

Code	Definition
`V(1) … V(NOEqs)`	error variance for each model output
`PV(1) … PV(NVParam)`	variance model parameters
`Y(1) … Y(NOEqs)`	model outputs $y_1(t) \cdots y_l(t)$
`LLQ(1) … LLQ(NOEqs)`	model outputs $LLQ_1 \cdots LLQ_l$
`ULQ(1) … ULQ(NOEqs)`	model outputs $ULQ_1 \cdots ULQ_l$

6.1.4 Stage 2 Covariate Model (in COVMOD)

User defined models relating parameter population mean values and subject specific measured covariates (as defined Eq. (4.3)) are entered in subroutine COVMOD, along with covariate model parameter symbols as listed in Table 5.3. This information is used in the MLEM and ITS programs.

Table 6.4 Covariate Model Symbols for COVMOD

Code	Definition
`NCparam`	number of covariate model parameters
`PCsym(1) … PCsym(NCparam)`	symbol for each covariate parameter
`Pmean(1) … Pmean(NSparam)`	covariate model equation for system parameters
`ICmean(1) … ICmean(NDEqs)`	covariate model equation for initial conditions
`R(1) … R(NRI)`	model inputs used to represent measured covariates

6.1.5 Initial Guesses for Population Parameters (in POPINIT)

Initial guesses for the population mean and covariance are provided in subroutine POPINIT along with initial guesses for any covariate model parameters using the symbols listed in Table 6.5. Values are needed only for parameters to be estimated. The selection of Normal or lognormal distribution option is made during the program run (MLEM or ITS), and all initial guesses entered in POPINIT are in the original units of the problem (i.e., not ln(parameter)). (Initial guesses for individual subject parameters values are obtained from the *.prm file.)

For the initial guess of the covariance matrix, only the lower triangular elements are entered (`PCovI(I,J)`, `ICCovI(I,J)` for $I \geq J$). The initial guesses of the diagonal elements of the covariance matrix (`PCovI(I,I)`, `ICCovI(I,I)`) must be entered as non-zero values. For the

off-diagonal elements of the covariance matrix (`PcovI(I,J)`, `ICcovI(I,J)`), the initial guess is taken to be zero unless an explicit value is entered. If a covariate model is provided for a parameter in subroutine COVMOD, then no initial guess is needed for that parameter's population mean (`PmeanI(I)`, `ICmeanI(I)`).

All off-diagonal elements of the covariance matrix can be constrained to zero in the population estimation when the program is run (MLEM or ITS) by selecting the "diagonal covariance matrix option". Individual covariance elements can be constrained to zero by entering an initial guess in POPINIT equal to the ADAPT missing data number (defaults -1) for that element of the covariance matrix (`PcovI(I,J)=-1`), then selecting the "full covariance matrix option" during the program run.

Table 6.5 Initial Guesses for Population Parameters in POPINIT

Code	Definition
`PmeanI(1) … PmeanI(NSparam)`	population mean - system parameters
`ICmeanI(1) … ICmeanI(NDEqs)`	population mean - initial conditions
`PcovI(1,1) … PcovI(NSparam,NSparam)`	population covariance - system parameters
`ICcovI(1,1) … ICcovI(NDEqs,NDEqs)`	population covariance - initial conditions
`PCI(1) … PCI(NCparam)`	covariate model parameters

6.1.6 Prior Parameter Model (in PRIOR)

For MAP estimation in ID, STS, NPD and for population simulation in SIM, the mean μ and the covariance Σ defining the prior density are entered in subroutine PRIOR. Table 6.5 provides the code symbols used to represent the mean and covariance of the prior densities.

Table 6.5 Prior Distribution Parameters in PRIOR

Code	Definition
`Pmean(1) … Pmean(NSparam)`	prior mean for system parameters
`ICmean(1) … ICmean(NDEqs)`	prior mean for initial conditions
`Pcov(1,1) … Pcov(NSparam,NSparam)`	prior covariance for system parameters
`ICcov(1,1) … ICcov(NDEqs,NDEqs)`	prior covariance for initial conditions

When entering the elements of the covariance matrices in subroutine PRIOR, only the lower triangular elements of the matrices are entered (i.e., the diagonal elements and below - `Pcov(I,J)`, `ICcov(I,J)` for $I \geq J$).

When θ is partitioned to include either uniformally distributed elements or elements subject to a noninformative prior, those elements are so indicated by assigning to either `Pmean` or `ICmean` the ADAPT missing data number (default -1). Finally, the $\theta^{\max}$ values are provided when SIM is run.

6.1.7 Secondary Parameter Model (in SPARAM)

The definitions of any secondary parameters are entered in subroutine SPARAM in the Model File. The symbols used in defining the secondary parameters are given in Table 6.6.

Table 6.6 Secondary Parameters in SPARAM

Code	Definition
PS(1) … PS(NSecPar)	secondary parameters
P(1) … P(NSParam)	system parameters
IC(1) … IC(NDEqs)	initial conditions

6.1.8 Other Variables Available in the Model File

In addition to the variables given in Tables 6.1 through 6.3, a number of additional variables are available in subroutines DIFFEQ, OUTPUT and VARMOD to use in defining the model. These are listed and defined in Table 6.7.

Table 6.7 Additional Variables Available to Define the Model

Code	Definition
NRI	# of model inputs
NBI	# of bolus inputs
NDos	# of input event times
dostim(I)	value for each input event time (I=1,…,NDos)
rates(I,J)	values for model inputs (I=1,…,NDos, J=1,…,NRI)
bolus(I,J)	values for bolus inputs (I=1,…,NDos, J=1,…,NBI)
NOEqs	# of output equations
NObs	# of composite observations per output
obstim(I)	value for each observation time (I=1,…,NObs)
obsdat(I,J)	values for observations (I=1,…,NObs, J=1,…,NOEqs)
bolusc(I)	compartment (state) # for each bolus (I=1,…,NBI)
curDN	input event # at current time T in the model solution
curON	measurement # at current time T in the model solution
simdat(I,J)	values for model predictions (I=1,…,NObs, J=1,…,NOEqs)
xstore(I,J)	values for states (I=1,…,NObs, J=1,…,NDEqs)
SubjID	identifier for the current individual
SubjInd	# of current individual (1, 2, …)

6.1.9 A Note on Model Definition for Population Analysis

For population modeling, the first stage PK/PD system and observation model may be different depending on the individual. For example: in a bioavailability study (non crossover)

some individuals may receive intravenous drug administration while others may receive the drug via extravascular administration; in a two drug interaction modeling study some individuals may receive only one of the two compounds while others may receive both; in a simultaneous PK/PD modeling effort only PK or PD data may be available in some individuals, while both PK and PD data may be available for other individuals.

To model data from such population studies in ADAPT, the user must specify a single composite model in the ADAPT Model File. Thus, in an oral bioavailability study with intravenous and oral administration, the complete model with the absorption portion should be specified in the model file and all subject data files would include both a bolus input for the oral dose and a model input representing the intravenous dose. For any subject receiving the oral administration, the model input representing the intravenous dose would be zero at all input times for that subject, while the bolus dose would be zero for any subject receiving the drug intravenously. For a two drug interaction study, the composite model should reduce to the appropriate single drug dose response model form when only one of the two compounds is present. In the case the simultaneous PK/PD model, the composite model must include all model outputs, but the PD data will be indicated as missing in the data files for those individuals with only PK data while the PK data will be denoted as missing for those individuals with only PD data.

6.2 Data and Parameter File Formats

6.2.1 Data File for Single Individual

The ADAPT Data File (*.dat)contains the number of model and bolus inputs, the number of input events, the input event times, and values for all model and bolus inputs at each input event time. It also includes the number of model outputs and observations, and the observation times and values for measured outputs or responses at each observation time. As illustrated in Chapter 2.4.3, the ADAPT Interface provides for the creation of a single individual data file. The general format for individual data file in ADAPT is shown in Table 6.8.

The user can also create an ADAPT Data File directly (e.g., via a text editor, spread sheet, data base or other special purpose software) by following the format in Table 6.8. When creating a data file outside of ADAPT save the file as a comma, space or tab delimited text file.

Table 6.8 ADAPT Data File Format - Individual

# model inputs						
# bolus inputs						
# input events						
event time 1	rates(1,1)	...	rates(1,NRI)	bolus(1,1)	...	bolus(1,NBI)
event time 2	rates(2,1)	...	rates(2,NRI)	bolus(2,1)	...	bolus(2,NBI)
•	•		•	•		•
•	•		•	•		•
•	•		•	•		•
event time NDos	rates(NDos,1)	...	rates(NDos,NRI)	bolus(NDos,1)	...	bolus(NDos,NBI)
# output eqs.						

# observations			
obs. time 1	obsdat(1,1)	...	obsdat(1,NOEqs)
obs. time 2	obsdat(2,1)		obsdat(2,NOEqs)
•	•		•
•	•		•
•	•		•
obs. time NObs	obsdat(NObs,1)	...	obsdat(NObs,NOEqs)

When entering the data via the ADAPT Interface for the case of multiple outputs, the user enters the times and observed data, either separately for each output or as a composite spreadsheet with all the unique observation times for all outputs representing the rows and the different outputs representing the columns. In the later case, if a particular output is not available at a given observation time, then the missing data number is entered as the value for the observation (default missing data number -1). Any measurements that are BQL are denoted by L and those AQL are indicated by H (see example pd3 in Chapter 8).

6.2.2 Population Data File

The data associated with each individual in a population data file follows the format presented above for individual data files. To construct a population data file, individual data files are simple concatenated, with each separated by a line containing a text string (20 characters or less) used to identify the individual. The overall format is illustrated in Table 6.9.

Table 6.9 ADAPT Data File Format - Population

individ. #1 ident.						
# model inputs						
# bolus inputs						
# input events						
event time 1	rates(1,1)	...	rates(1,NRI)	bolus(1,1)	...	bolus(1,NBI)
•	•		•	•		•
•	•		•	•		•
•	•		•	•		•
obs. time NObs	obsdat(NObs,1)	...	obsdat(NObs,NOEqs)			
individ. #2 ident.						
# model inputs						
# bolus inputs						
# input events						
event time 1	rates(1,1)	...	rates(1,NRI)	bolus(1,1)	...	bolus(1,NBI)
•	•		•	•		•
•	•		•	•		•
•	•		•	•		•
obs. time NObs	obsdat(NObs,1)	...	obsdat(NObs,NOEqs)			
individ. #3 ident.						
•	•		•	•		•
•	•		•	•		•
•	•		•	•		•

The ADAPT interface does not create population data files. For larger population data sets, these files are generally created via database programs or other specialized software that create a text file with comma, space or tab delimiters (formatted as per Table 6.9).

6.2.3 Parameter Files

ADAPT Parameter Files (*.prm) are created via the ADAPT interface and contain values for model parameters that are used in all of the programs. When ADAPT reads a specified Parameter File, it checks that the number of differential equations, number of system parameters, number of variance parameters and number of covariate model parameters (as appropriate) is consistent with the corresponding numbers specified in subroutines SYMBOL and COVMOD of the selected Model File. The Parameter Files follow the format given in Table 5.10. The user can also create an ADAPT Parameter File directly (e.g., via a text editor or spread sheet program saved as a comma, space or tab delimited text file) by following the format in Table 6.10.

Table 6.10 ADAPT Parameter File

# differential eqs.	# system params	# error variance params	# covariate params
P(1)			
P(2)			
•			
•			
•			
P(NSParam)			
IC(1)			
•			
•			
•			
IC(NDEqs)			
PV(1)			
•			
•			
•			
PV(NVParam)			

The STS, MLEM and ITS programs also can use other files (*IND.csv and *FIX.csv) that contain model parameter values, as described below.

6.3 Results Generated by the ADAPT Programs

All programs produce a *.run file (file name prefix supplied by the user) that contains a complete record of the program run as displayed during the program execution. The file name prefix supplied by the user for the run file is also used as the prefix for all other files created by ADAPT. The run file and all other files created by ADAPT (with the exception of graphics files) are text files (space delimited) that can be read by text editors and imported into spread sheet and graphing programs.

6.3.1 Files created by SIM

All plots displayed by SIM are saved as a single, multi-page encapsulated postscript file (name, *.eps). This file can be viewed or incorporated into documents using any program that can manipulate multi-page postscript files (e.g., Adobe Professional™, Ghostview) .

The raw data used to construct the plots displayed by the program SIM are also saved in a text file (name, *PLT.csv). This "comma separated variable" text file can then be imported into a spreadsheet or graphics program, allowing the user to construct customized plots. The format of the *PLT.csv file for Option 1 of the SIM program (individual simulation) is shown in Table 6.11. The second column contains the plot times used to construct the smooth graphs for the model outputs displayed during the program run and in the *.eps file; the corresponding simulated model output values are given in columns three through `NOEqs+2` of the *PLT.csv file. The remainder of the columns list the observations times specified in the *.dat file, followed by the corresponding simulated values for each model output (SIM Option 1) or the mean simulated output and their standard deviations (SIM Options 2-4).

Table 6.11 ADAPT Plot File (*PLT.csv). Format for SIM Option 1

Num	**Plot-Time**	**Y(1)**	···	**Y(NOEqs)**	•••
1	0.0	$y_1(0)$	···	$y_{NOEqs}(0)$	
2	t_2	$y_1(t_2)$	···	$y_{NOEqs}(t_2)$	
•	•	•		•	
•	•	•		•	
•	•	•		•	
MaxPLT	t_{MaxPLT}	$y_1(t_{MaxPLT})$	···	$y_{NOEqs}(t_{MaxPLT})$	

•••	**Observ.-Time**	**Y(1)**	···	**Y(NOEqs)**
	obs. time 1	simdat(1,1)	···	simdat(1,NOEqs)
	•	•		•
	•	•		•
	•	•		•
	obs. time NObs	simdat(NOBs,1)	···	simdat(NOBs,NOEqs)

Table 6.12 ADAPT Plot File (*PLT.csv). Format for SIM Options 2-4

Num	**Plot-Time**	**Y(1)**	···	**Y(NOEqs)**	•••
1	0.0	$y_1(0)$	···	$y_{NOEqs}(0)$	
2	t_2	$y_1(t_2)$	···	$y_{NOEqs}(t_2)$	
•	•	•		•	
•	•	•		•	
•	•	•		•	
MaxPLT	t_{MaxPLT}	$y_1(t_{MaxPLT})$	···	$y_{NOEqs}(t_{MaxPLT})$	

...	Observ.-Time	Y(1)-mean	Y(1)-SD	...	Y(NOEqs)-mean	Y(NOEqs)-SD
	obs. time 1	simdat(1,1)	$y_1 sd(t_1)$	...	simdat(1,NOEqs)	$y_{NOEqs} sd(t_1)$
	•	•	•		•	•
	•	•	•		•	•
	•	•	•		•	•
	obs. time NObs	simdat(NOBs,1)	$y_1 sd(t_{NOBs})$	...	simdat(NOBs,NOEqs)	$y_{NOEqs} sd(t_{NOBs})$

Options 2, 3, and 4 in SIM perform populations simulations for a specified number of simulated subjects (see Section 3.8). The simulation results for each of these subjects can be stored in a population simulation file (name, *POP.csv). This "comma separated variable" text file can be imported into a statistical analysis program for more detailed analysis of simulation results than is provided by ADAPT. Each row of the file presents the results for one simulated subject and the entire file is formatted as shown in Table 6.13

Table 6.13 ADAPT Population File (*POP.csv). Format for SIM.

Indiv.#	Psym(1)	...	Psym(NSparam)	IC(1)	...	IC(NDEqs)	...
1	θ_1	...	θ_{pm}	$IC(1)$	...	$IC(n)$	
2	θ_1	...	θ_{pm}	$IC(1)$	...	$IC(n)$	
•	•		•	•		•	
•	•		•	•		•	
•	•		•	•		•	
MaxSIM	θ_1	...	θ_{pm}	$IC(1)$	...	$IC(n)$	

...	Y1(1)	...	Y1(NOBs)	Y2(1)	...	Y2(NOBs)	...
	$y_1(t_1)$	...	$y_1(t_{NOBs})$	$y_2(t_1)$	...	$y_2(t_{NOBs})$	
	•		•	•		•	
	•		•	•		•	
	•		•	•		•	
	$y_1(t_1)$	...	$y_1(t_{NOBs})$	$y_2(t_1)$	...	$y_2(t_{NOBs})$	

The simulations results can also be stored in an ADAPT data file (name, *.dat). For the Simulation Option 1 the file format is as given above in Table 6.8, while for Option 2-4 the created data file follows the format given in Table 6.9.

6.3.2 Files created by ID

All plots displayed by the program ID are saved as a single, multi-page encapsulated postscript file (name, *.eps). This file can be viewed or incorporated into documents using any program that can manipulate multi-page postscript files (e.g., Adobe Professional™, Ghostview).

The raw data used to construct the plots displayed by the ID program are also saved in a text file (name, *PLT.csv). This "comma separated variable" text file can then be imported into a spreadsheet or graphics program, allowing the user to construct customized plots. The format of the *PLT.csv file for the ID program is shown in Table 6.14. The second column contains the plot times used to construct the smooth graphs for the model outputs displayed during the program run and in the *.eps file; the corresponding simulated model output values are given in columns three through `NOEqs+2` of the *PLT.csv file. The remaining columns contain the observations times, and for each output the model prediction, observed data, standard error of the prediction, residual and standardized residual.

Table 6.14 ADAPT Plot File (*PLT.csv). Format for ID.

Num	**Plot-Time**	**Y(1)**	···	**Y(NOEqs)**	•••
1	0.0	$y_1(0)$	···	$y_{NOEqs}(0)$	
2	t_2	$y_1(t_2)$	···	$y_{NOEqs}(t_2)$	
•	•	•		•	
•	•	•		•	
•	•	•		•	
MaxPLT	t_{MaxPLT}	$y_1(t_{MaxPLT})$	···	$y_{NOEqs}(t_{MaxPLT})$	

•••	**Observ.-Time**	**Z(1)**	**Y(1)**	**Y(1)-SE**	**Residual**	**Stand.Res.**	•••
	obs. time 1	obsdat(1,1)	$y_1(t_1)$	$y_1 sd(t_1)$	$y_1 res(t_1)$	$y_1 stdres(t_1)$	
	•	•	•	•	•	•	
	•	•	•	•	•	•	
	•	•	•	•	•	•	
	obs. time NObs	obsdat(NOBs,1)	$y_1(t_{NOBs})$	$y_1 sd(t_{NOBs})$	$y_1 res(t_{NOBs})$	$y_1 stdres(t_{NOBs})$	

The ID program also creates a separate file that includes the same information contain in the second part of the Table 6.14 but formatted differently. The format of this file (name, *RSD.csv) is described below in the discussion of the STS program output.

Finally the ID program creates an ADAPT Command Input file (name, *.aci) that can be edited and selected when ADAPT is run using the Batch run option via the ADAPT interface. It is also used when an executable ADAPT program is run via another program (see Section 6.4 below). The *.aci file contains the replies entered by the user during the run of ID.

6.3.3 Files created by SAMPLE

All plots displayed by SAMPLE are saved as a single, multi-page encapsulated postscript file (name, *.eps). This file can be viewed or incorporated into documents using any program that can manipulate multi-page postscript files (e.g., Adobe Professional™, Ghostview) .

The raw data used to construct the plots displayed by the program SIM are also saved in a text file (name, *PLT.csv). This space delimited text file can then be imported into a spreadsheet or graphics program, allowing the user to construct customized plots. The format of the *PLT.csv file for created by SAMPLE is the same as that created by Option 1 of the SIM program and shown in Table 6.11.

6.3.4 Files created by STS

All plots displayed by the program STS are saved as a single, multi-page encapsulated postscript file (name, *.eps). In addition, the file includes plots of the predicted model outputs shown with observed data for each individual that are not displayed during the run of STS. This file can be viewed or incorporated into documents using any program that can manipulate multi-page postscript files (e.g., Adobe Professional™, Ghostview).

The raw data used to construct all the predicted model output with data plots for each subject, as displayed in the *.eps file, are also saved in a text file (name, *PLT.csv). This file can then be imported into a spreadsheet or graphics program, allowing the user to construct customized plots. The format of this *PLT.csv file for the first individual is shown in Table 6.15, which is followed in subsequent rows by the plot data for each of the individuals in blocks as shown for the first subject in Table 6.15.

Table 6.15 ADAPT Plot File (*PLT.csv). Format for ID.

Individ#	IndividualID	Obser.#	Plot-Time	Y(1)	···	•••
1	individ. #1 ident.	1	0.0	$y_1(0)$	···	
1	individ. #1 ident.	2	t_2	$y_1(t_2)$	···	
•	•	•	•	•	•	
•	•	•	•	•	•	
•	•	•	•	•	•	
1	individ. #1 ident.	MaxPLT	t_{MaxPLT}	$y_1(t_{MaxPLT})$	···	

•••	Y(NOEqs)	Observ.-Time	Z(1)	···	Z(NOEQs)
	$y_{NOEqs}(0)$	obs. time 1	obsdat(1,1)	···	obsdat(1,1)
	$y_{NOEqs}(t_2)$	•	•	•	•
	•	•	•	•	•
	•	•	•	•	•
	•	obs. time NObs	obsdat(NOBs,1)	···	obsdat(NOBs,1)
	$y_{NOEqs}(t_{MaxPLT})$				

The data used to create the various residuals plots displayed by STS (also contained in the *.eps file) are stored in the residual file (name, *RSD.csv) following the format shown in Table 6.16.

Table 6.16 ADAPT Residual File (*RSD.csv). Format for STS.

Individ#	Individ.ID	Output#	Obser.#	Observ.Time	Data	...
1	individ.#1 ident.	1	1	obs. time 1	obsdat(1,1)	
1	individ. #1 ident.	1	2	obs. time 2	obsdat(2,1)	
•	•	•	•	•	•	
•	•	•	•	•	•	
•	•	•	•	•	•	
1	individ. #1 ident.	1	NOBs	obs. time NOBS	obsdat(NOBs,1)	
1	individ. #1 ident.	2	1	obs. time 1	obsdat(1,2)	
1	individ. #1 ident.	2	2	obs. time 2	obsdat(2,2)	
•	•	•	•	•	•	
•	•	•	•	•	•	
•	•	•	•	•	•	
1	individ. #1 ident.	2	NOBs	obs. time NOBS	obsdat(NOBs,2)	
•	•	•	•	•	•	
•	•	•	•	•	•	
•	•	•	•	•	•	

...	ModelPred.	SE-ModelPred.	Residual	Std.Resid.
	$y_1(t_1)$	$y_1sd(t_1)$	$y_1res(t_1)$	$y_1stdres(t_1)$
	$y_1(t_2)$	$y_1sd(t_2)$	$y_1res(t_2)$	$y_1stdres(t_2)$
	•	•	•	•
	•	•	•	•
	•	•	•	•
	$y_1(t_{NOBs})$	$y_1sd(t_{NOBs})$	$y_1res(t_{NOBs})$	$y_1stdres(t_{NOBs})$
	$y_2(t_1)$	$y_2sd(t_1)$	$y_2res(t_1)$	$y_2stdres(t_1)$
	$y_2(t_2)$	$y_2sd(t_2)$	$y_2res(t_2)$	$y_2stdres(t_2)$
	•	•	•	•
	•	•	•	•
	•	•	•	•
	$y_2(t_{NOBs})$	$y_2sd(t_{NOBs})$	$y_2res(t_{NOBs})$	$y_2stdres(t_{NOBs})$
	•	•	•	•
	•	•	•	•
	•	•	•	•

The parameter estimates obtained by STS for each individual are stored in the individual subject estimate file (name, *IND.csv) following the format shown in Table 5.17. The file also contains for each individual, values for any secondary parameters, the value for the weighted sum of squares, negative loglikelihood or MAP objective function (depending on the estimator selected), and the covariance matrix (lower triangular form) for the standard errors of the parameter estimates.

This *IND.csv file can also be used in place of an ADAPT parameter file (*.prm file) to provide the initial guesses for estimated model parameters. By supplying the name of the appropriate individual subject estimate file (*IND.csv) under the parameter menu in the ADAPT interface, the values stored in the *IND.csv for each individual will be used as the initial guesses for the estimated parameters for that individual. Those parameters not estimated will also be taken from the *IND.csv file. Thus a subsequent run of the STS program can use parameter values read from a previously created *IND.csv as the initial guesses for the model parameters to be estimated.

Table 6.17 ADAPT Individual Subject Estimate File (*IND.csv). Format for STS.

Created by:	STS				
Model Descript:	Descr				
Num of Diff. Eqs	**Num Sys. Param.**	**Num Var. Param.**			
NDEqs	NSParam	NVParam			
Number	**IndividID**	**Psym(1)**	···	**IC(NDEqs)**	•••
	ParamEstimated?	YorN	···	YorN	
1	individ.#1 ident.	θ_1	···	$IC(n)$	
2	individ.#2 ident.	θ_1	···	$IC(n)$	
•		•		•	
•		•		•	
•		•		•	

•••	**PVsym(1)**	···	**PSsym(1)**	···	**Est.Obj.Value**	•••
	YorN	···		···		
	β_1	···	γ_1	···	WLS/-LL/MAP	
	β_1	···	γ_1	···	WLS/-LL/MAP	
	•		•		•	
	•		•		•	
	•		•		•	

•••	**Psym(1)/Psym(1)**	**Psym(2)/Psym(1)**	**Psym(2)/Psym(2)**	•••
	Cov(1,1)	Cov(2,1)	Cov(2,2)	
	Cov(1,1)	Cov(2,1)	Cov(2,2)	
	•	•	•	
	•	•	•	
	•	•	•	

Another parameter file, created by the user, can be used to provide individual specific values for all parameters that will not be estimated (name, *FIX.csv). The format of this file containing the values for the parameters to be fixed for each subject is given in Table 6.18. (When the estimated model parameters are the same for each subject, then the *.prm file can be used to provide the values for each non estimated parameter.)

Table 6.18 ADAPT Fixed Parameter File (*FIX.csv). Format for STS.

Title of File				
# Fixed Params.				
Individ.#	**Individ.ID**	**Psym(1)**	**…**	**IC(NDEqs)**
1	individ.#1 ident.	θ_1		$IC(n)$
2	individ.#2 ident.	θ_1		$IC(n)$
•	•	•		•
•	•	•		•
•	•	•		•

Finally the STS program also creates an ADAPT Command Input file (name, *.aci) that can be edited and selected when ADAPT is run using the Batch run option via the ADAPT interface. It is also used when an executable ADAPT program is run via another program (see Section 6.4 below). The *.aci file contains the replies entered by the user during the run of STS.

6.3.5 Files created by NPD

All plots displayed by the program NPD are saved as a single, multi-page encapsulated postscript file (name, *.eps). In addition, the file includes plots of the predicted model outputs shown with observed data for each individual that are not displayed during the run of NPD. This file can be viewed or incorporated into documents using any program that can manipulate multi-page postscript files (e.g., Adobe Professional™, Ghostview).

The NPD program also produces a plot data file (name, *PLT.csv) and residual file (name, *RSD.csv) with formats identical those shown in Tables 6.15 and 6.16. An ADAPT Command Input file (name, *.aci) is also created containing the user's replies entered during the run of STS.

6.3.6 Files created by MLEM

All plots displayed by the program MLEM are saved as a single, multi-page encapsulated postscript file (name, *.eps). In addition, the file includes plots of the predicted model outputs shown with observed data for each individual that are not displayed during the run of MLEM. This file can be viewed or incorporated into documents using any program that can manipulate multi-page postscript files (e.g., Adobe Professional™, Ghostview).

The MLEM program produces a plot data file (name, *PLT.csv) and residual file (name, *RSD.csv) with formats identical to that produced by the STS program and shown Tables 6.15

and 6.16. For MLEM the *RSD.csv file also contains an additional column of the model predictions for each individual evaluated at the population mean. An ADAPT Command Input file (name, *.aci) is also created containing the replies entered by the user during the run of STS.

An individual subject estimate file (name, *IND.csv) is also created similar to the format shown in Table 6.17. For the MLEM program, the individual subject estimates are the conditional mean and conditional covariance defined in Section 4.3 (Eq. (4.5)-(4.6)). The *IND.csv file created by the MLEM program, however, includes the following columns in addition to those given in Table 6.17: all the model inputs for each subject whether they are used as covariates or not; conditional mean values for each subject minus the population mean values ($\bar{\theta} - \mu$); the conditional mode for each subject as calculated from the samples from the conditional density. The format of the trailing columns of the *IND.csv is shown in Table 6.19.

Table 6.19 ADAPT Individual Subject Estimate File (*IND.csv) Additional Columns for the Case of Covariate Model(s). Format for MLEM.

...	R(1)	...	R(NRI)	Psym(1)-mean	...	IC(NDEqs)-mean	...
		...			...		
	Rates(1,1)	...	Rates(1,NRI)	$\bar{\theta}_1 - \mu_1$	...	$\mu_{IC(n)}$	
	Rates(1,1)	...	Rates(1,NRI)	$\bar{\theta}_1 - \mu_1$	...	$\mu_{IC(n)}$	
	•		•	•		•	
	•		•	•		•	
	•		•	•		•	

...	modePsym(1)	...	modeIC(NDEqs)
	modeθ_1	...	mode$IC(n)$
	modeθ_1		mode$IC(n)$
	•		•
	•		•
	•	...	•

The MLEM program can also read a parameter file with individual specific fixed values for model parameters via the *FIX.csv file (see Table 6.18).

The MLEM program produces an iteration file (name, *IT.csv) that contains the estimated values for the population means and covariances, error variance parameters, as well as any covariate model parameters for each EM iteration (format as per Table 6.20). This *IT.csv file along with the corresponding *IND.csv file can also be used to continue an estimation, by selecting the individual subject estimate file (*IND.csv) from the ADAPT interface.

Table 6.20 ADAPT Iteration File (*IT.csv). Format for MLEM.

Created by:	MLEM			
ModelDescription:	Descr			
N/LN **Dist. Option**				
Iteration	**Psym(1)**	···	**IC(NDEqs)**	•••
1	μ_1	···	$\mu_{IC(n)}$	
2	μ_1	···	$\mu_{IC(n)}$	
•	•		•	
•	•		•	
•	•		•	

•••	**Psym(1)/Psym(1)**	**Psym(2)/Psym(1)**	**Psym(2)/Psym(2)**	•••
	σ_1^2	σ_{21}	σ_2^2	
	σ_1^2	σ_{21}	σ_2^2	
	•	•	•	
	•	•	•	
	•	•	•	

•••	**PVsym(1)**	···	**PCsym(1)**	···	**NegLogLikelihood**
	β_1	···	c_1	···	$L(\phi)$
	β_1	···	c_1	···	$L(\phi)$
	•		•		•
	•		•		•
	•		•		•

6.3.7 Files created by ITS

All the files created by the ITS program are similar in format to those created by the MLEM program. (In the *IND.csv file, the individual parameter estimates displayed are the MAP estimates.)

6.4 Running Previously Created ADAPT Executable Files

Once an ADAPT executable file is created via the ADAPT Interface (ADAPT program complied with user model file), the resulting executable file (model.exe) can be run directly without using the ADAPT Interface in one of two ways. The user can double click on the model.exe file to launch the file. When an ADAPT model.exe file is run in this manner, the user's interaction with the program is the same as if the program where run via the interface, except the program will query the user to supply the names of both the ADAPT Data and Parameter Files during the course of the program run. Alternately, the user can run the model.exe

file via the Windows Command Prompt or via some other program that allows Windows executable files to be launched, in which case the program is run in background or batch mode. Figure 6.1 shows an ADAPT executable file (pd1.exe, see Chapter 8) run from the Windows Command Prompt. As indicated in the figure, the names of a batch command input file (*.aci), a data file (*.dat) and a parameter file (*.prm) must be supplied as arguments.

Figure 6.1 Windows command line run of an ADAPT executable file.

ADAPT executable files can be distributed to others and run on machines in which ADAPT is not installed. In such cases two additional files need to be distributed with the executable program: grfont.dat and filedisp.exe. These two files are located in the ADAPT installation folder (default location: `C:\Program Files\BMSR\ADAPT 5`). When ADAPT is run through the Windows Commnad Prompt, even on machines in which ADAPT is installed, these two files must also reside in the folder containing the ADAPT executable file.

CHAPTER 7

Some Pharmacokinetic Examples

The examples in this and subsequent chapters are intended to illustrate many of the capabilities of ADAPT for a variety of PK/PD modeling tasks. The examples show the resulting run files and plot files created by the program, but do not show the associated ADAPT interface (illustrating model, data and parameter file definitions) or the program command windows. These aspects are illustrated in Chapter 2. The files used for all the examples in this User's Guide, as well as those created from the program runs, can be found in the `\Example` subfolder of the installation.

7.1 Example pk1: SIM – Individual Simulation

This example uses the analytic solution for the plasma concentration predicted by a one-compartment model with first-order absorption, following administration of a single bolus dose. The plasma concentration model equation is:

$$y(t) = \frac{D \cdot K_a}{(V/F)(K_a - K_e)}\left(e^{-K_e t} - e^{-K_a t}\right) \tag{7.1}$$

The code for this equation has been entered into subroutine OUTPUT of the Model File pk1.for. The variance model given below has also been coded and entered into subroutine VARMOD of the same Model File:

$$\text{var}\left\{e(t)\right\} = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2 \tag{7.2}$$

The appropriate entries have been made in subroutine SYMBOL of the Model File pk1.for. Figure 7.1 shows the sections of code in pk1.for from the subroutines OUTPUT, SYMBOL, and VARMOD.

For this example the model input consists of a single bolus dose of 500 mg in compartment 1 given at a time 0.0 hr. with ten observation times in the interval 0.0 to 14.0 hrs. (information

entered in data file pk1.dat). Values for the model parameters have been entered in parameter file pk1.prm (rate constant units hr^{-1}, volume units L). The resulting run and plot files for this example are shown in Figures 7.2 and 7.3. A file named pk1PLT.csv is also created as described in Chapter 6 and can be viewed in the \Example subfolder of the installation.

Figure 7.1 Excerpts from pk1.for showing the user entries for the model of example pk1.

```
    ADAPT 5      SIM -- MODEL SIMULATION    Sun Aug  5 12:49:04 2007

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk1.dat

      ----- MODEL INPUT INFORMATION -----

 Data file name (*.dat): pk1.dat

 The number of model inputs:     0

 The number of bolus inputs:    1

 The number of input event times:     1

     Input Event Information
           Time    Value for all Inputs
 Event     Units,       B(1)
    1.     0.000          500.0

      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   1

 The number of observations:   10

     Observation Information
                 Time     Measured Value For Each Output
 Observation     Units ,     Y(1)
       1.        0.5000       -1
       2.         1.000       -1
       3.         2.000       -1
       4.         3.000       -1
       5.         4.000       -1
       6.         5.000       -1
       7.         7.000       -1
       8.         9.000       -1
       9.         11.00       -1
      10.         14.00       -1

      ----- SIMULATION SELECTION -----

 The following simulation options are available:
     1. Individual simulation
     2. Individual simulation with output noise
     3. Population simulation
     4. Population simulation with output noise

 Enter option number: 1
```

Figure 7.2 Example pk1. Simulation of 1 compartment absorption model. Display of run file, pk1.run, with user entries indicated.

Figure 7.2 (continue)

```
     ----- ENTER PARAMETER INFORMATION -----

 Parameter file name: pk1.prm

 Enter values for indicated parameters:
  Parameter      Old Value     New Value (<Enter> if no change)
   KE            .2000
   KA            1.000
   V             30.00
   F             .9000

 Store inputs and simulated data in a new Adapt data file (Y/N)? n

      ----- RESULTS -----

      --- A. Parameter Summary ---

 Sun Aug  5 12:49:04 2007

 Data file name: pk1.dat

 Model: pk1.for - Example pk1 in ADAPT Users Guide

 Individual simulation

 Parameter       Value
  KE            0.2000
  KA             1.000
  V              30.00
  F             0.9000


      --- B. Simulation Summary ---

 Sun Aug  5 12:49:04 2007

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pk1.dat

 Model: pk1.for - Example pk1 in ADAPT Users Guide

 Individual simulation

  Obs.Num.    Time          Y(1)
      1       0.5000        5.593
      2        1.000        8.453
      3        2.000        10.03
      4        3.000        9.357
      5        4.000        8.081
      6        5.000        6.771
      7        7.000        4.607
      8        9.000        3.097
      9        11.00        2.077
     10        14.00        1.140
```

Figure 7.2 (continue)

```
     ----- PLOTTING OPTIONS -----

Do you want to plot with options (Y/N)? y

Options Menu for Output Y(  1)
  1. Supply labels & title     5. Plot to screen
  2. Log Y versus time         6. Save plots in a file
  3. Y-axis scaling            7. EXIT options
  4. Select symbols
* Enter option number :     1

        * Enter title:  Example pk1:  ADAPT User's Guide
        * Enter X-axis label:  Time   (hours)
        * Enter Y-axis label:  Concentration   (\gmg/ml)

Options Menu for Output Y(  1)
  1. Supply labels & title     5. Plot to screen
  2. Log Y versus time         6. Save plots in a file
  3. Y-axis scaling            7. EXIT options
  4. Select symbols
* Enter option number :     6

        * Enter file name (*.eps):  pk1label.eps

Options Menu for Output Y(  1)
  1. Supply labels & title     5. Plot to screen
  2. Log Y versus time         6. Save plots in a file
  3. Y-axis scaling            7. EXIT options
  4. Select symbols
* Enter option number :     7

Do you want to plot with options (Y/N)? n

     _____________________________________________

     _____________________________________________

     --- RE-SIMULATION OPTIONS ---

    1. Change parameter values
    2. Change simulation option
    3. Exit SIM

Enter option number:  3

     _____________________________________________

    ADAPT 5      SIM -- MODEL SIMULATION    Sun Aug  5 12:49:04 2007
```

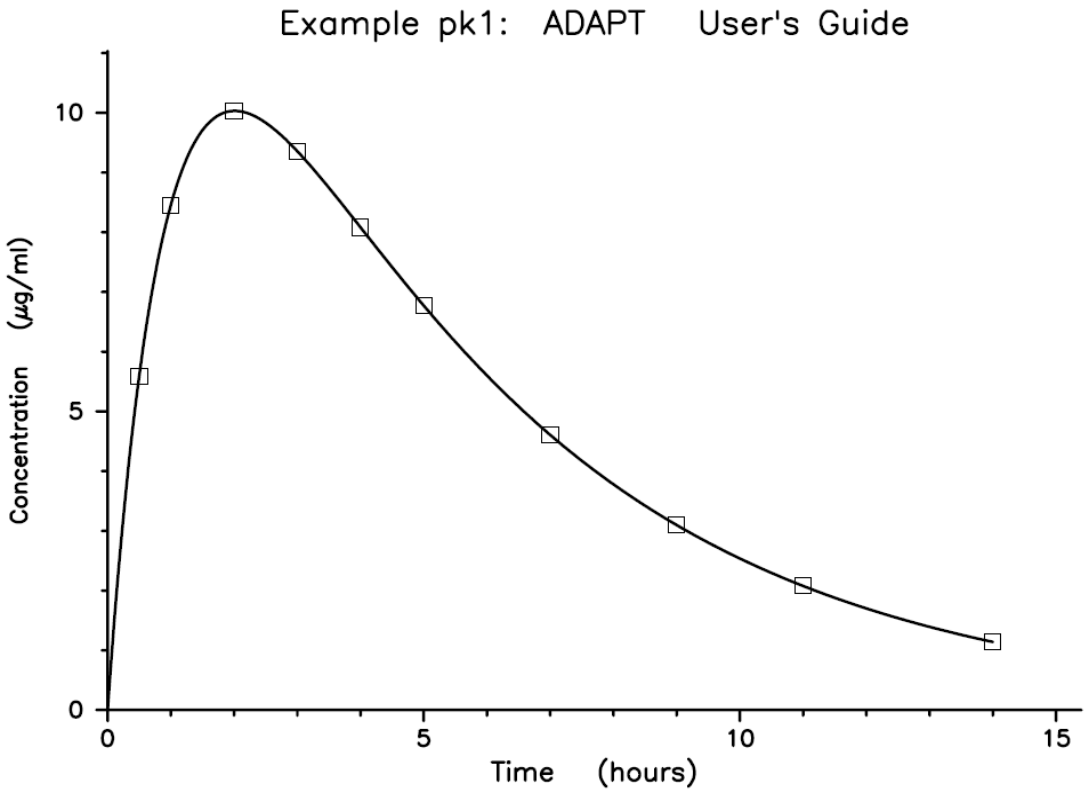


Figure 7.3 Example pk1. The resulting plot stored in file pk1.eps is similar to this graph but it will not include the open squares. This plot was created using a data file that included as observations the simulated model output values at each observation.

While not shown here, this model was re-simulated using the same parameter values but under simulation option 2, in order to simulate noisy observations. The parameters of the variance model (Eq. (5.2)) were set at $\sigma_{inter} = 0.1$ and $\sigma_{slope} = 0.1$. This error model results in an error coefficient of variation (CV) of approximately 20% at a concentration of 1.0 μg/ml and a CV of approximately 10% at a concentration of 10.0 μg/ml. The resulting simulated noisy data were stored in a data file and edited to round the observations to 2 significant figures (data file name 1compabs.dat). This data file is used in examples pk2, pk3, and pk4 to illustrate the WLS, ML and GLS estimation options in ID.

7.2 Example pk2: ID – WLS Estimation

Figure 7.4 shows an ID run file using the one compartment absorption model given in the previous example (recoded in file pk2) using the data in file 1compabs.dat. Initial guesses for the four model parameters are read from file pk2.prm. Weighted least squares estimation with weighting option 2 is selected. The parameter representing the fraction of the dose absorbed (F) fixed at 0.9 and not estimated. The resulting run and plot files are shown in Figures 7.5. Also, files named pk2PLT.csv, pk2RSD.csv and pk2.aci are created as described in Chapter 6 and can be viewed in the `\Example` subfolder of the installation.

```
   ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Tue Feb 12 15:27:40 2007

Enter file name for storing session run (*.run): pk2.run

     ----- MODEL INPUT INFORMATION -----

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\1compabs.dat

The number of model inputs:     0

The number of bolus inputs:    1

The number of input event times:     1

    Input Event Information
          Time    Value for all Inputs
Event     Units,       B(1)
   1.     0.000          500.0

     ----- MODEL OUTPUT INFORMATION -----

The number of model output equations:   1

The number of observations:   10

    Observation Information
                Time     Measured Value For Each Output
Observation     Units ,     Y(1)
      1.        0.5000       5.700
      2.         1.000       9.300
      3.         2.000       8.500
      4.         3.000       9.100
      5.         4.000       8.200
      6.         5.000       7.700
      7.         7.000       5.200
      8.         9.000       3.200
      9.         11.00       1.900
     10.         14.00       1.100

     ----- ESTIMATOR SELECTION -----

The following estimation procedures are available:
     1. Weighted least squares (WLS)
     2. Maximum likelihood (ML)
     3. Generalized least squares (GLS)
     4. Maximum a posteriori probability (MAP)

Enter option number:  1
```

Figure 7.4 Example pk2. WLS estimation with one-compartment absorption model. Display of run file, pk2.run, with user entries indicated.

Figure 7.4 (continue)

```
     --- Supply Weighting Information For WLS Estimator ---

 The following weighting options are available:
  1.   General
  2.   Inverse variance of the output error (linear)
  3.   Inverse variance of the output error (nonlinear)

     For Y(   1):

 Enter the number of the desired weighting procedure:   2

 Define the Linear Std. Dev. vs Output Curve:

                   Y( 1) Value, Std. Dev.
 Low Measurement                 1.000      0.2000
 High Measurement                10.00       1.000

     ----- INITIALIZE ESTIMATION PROCEDURE -----

 Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\pk2.prm

 Enter initial values for parameters & specify those to be estimated:

            Old Value    New Value      Estimate?
                       (skip if same)    (Y/N)
 KE          .6000            y
 KA          2.500            y
 V           20.00            y
 F           .9000            n

 Enter maximum number of iterations:       300

 Do you want the iterations printed (Y/N)?  n

             ----- RESULTS -----

             --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      KE         =   0.6000
      KA         =    2.500
      V          =    20.00

    Weighted Least Squares =  506.495
```

Figure 7.4 (continue)

```
          ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =    26
    Number of function calls  =   127

     Fitted Parameters
      KE         =   0.2027
      KA         =   0.9496
      V          =    29.47

    Weighted Least Squares =  6.90219


            --- C. WLS Estimation Summary---

Tue Feb 12 15:27:40 2007

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\1compabs.dat

Model:  pk2.for - Example pk2 in ADAPT Users Guide

Weighting Information
  Option for Y( 1):  2 with (1.000    ,.2000    ) and (10.00    ,1.000    )

Convergence achieved
  Number of iterations:          26
  Number of function calls:     127
Weighted Least Squares:    6.90219


                              Weighted
 Output        R-squared    Sum of Squares   Sum of Squares
 Y( 1)        0.950           6.90219          4.45241

 Model Selection Criteria
  AIC:          25.3184
  BIC:          26.2261


               Initial      Final
 Parameter      Value      Estimate    SE (CV%)    Confidence interval (95%)

 KE            0.6000      0.2027       8.641      [ 0.1613    ,  0.2441    ]
 KA             2.500      0.9496       16.65      [ 0.5756    ,   1.323    ]
 V              20.00       29.47       8.397      [  23.62    ,   35.32    ]
 F             0.9000      Not estimated
```

Figure 7.4 (continue)

```
 Correlation Matrix

          KE        KA        V
KE          1.00
KA         -0.78      1.00
V          -0.90      0.78      1.00


 Covariance Matrix

          KE        KA        V
KE        0.307E-03
KA        -.217E-02 0.250E-01
V         -.388E-01 0.305      6.12

           --- D. WLS Estimation Model Prediction and Data Summary ---

Tue Feb 12 15:27:40 2007

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\1compabs.dat

Model:  pk2.for - Example pk2 in ADAPT Users Guide


Y( 1)
 Obs.Num.   Time         Data       Model Est.     Residual     Weight
     1      0.5000        5.700        5.467        0.2330        2.620
     2       1.000        9.300        8.341        0.9593        1.137
     3       2.000        8.500        10.04        -1.537        1.331
     4       3.000        9.100        9.444       -0.3444        1.181
     5       4.000        8.200        8.195        0.5305E-02    1.417
     6       5.000        7.700        6.878        0.8219        1.580
     7       7.000        5.200        4.673        0.5273        3.042
     8       9.000        3.200        3.128        0.7166E-01    6.391
     9       11.00        1.900        2.088       -0.1876        12.76
    10       14.00        1.100        1.137       -0.3674E-01    22.92

Y( 1) (Continued)                Std. Err.   Standardized
          Obs.Num.   Model Est.   Model Est.   Residual
               1       5.467       0.4615       0.3771
               2       8.341       0.5203        1.023
               3       10.04       0.4391       -1.774
               4       9.444       0.4486      -0.3744
               5       8.195       0.4295       0.6315E-02
               6       6.878       0.3661        1.033
               7       4.673       0.2347       0.9197
               8       3.128       0.1797       0.1812
               9       2.088       0.1645      -0.6701
              10       1.137       0.1397      -0.1759

     ----- PLOTTING OPTIONS -----

  ...{Dialogue for plotting options and program exit not shown}...
```

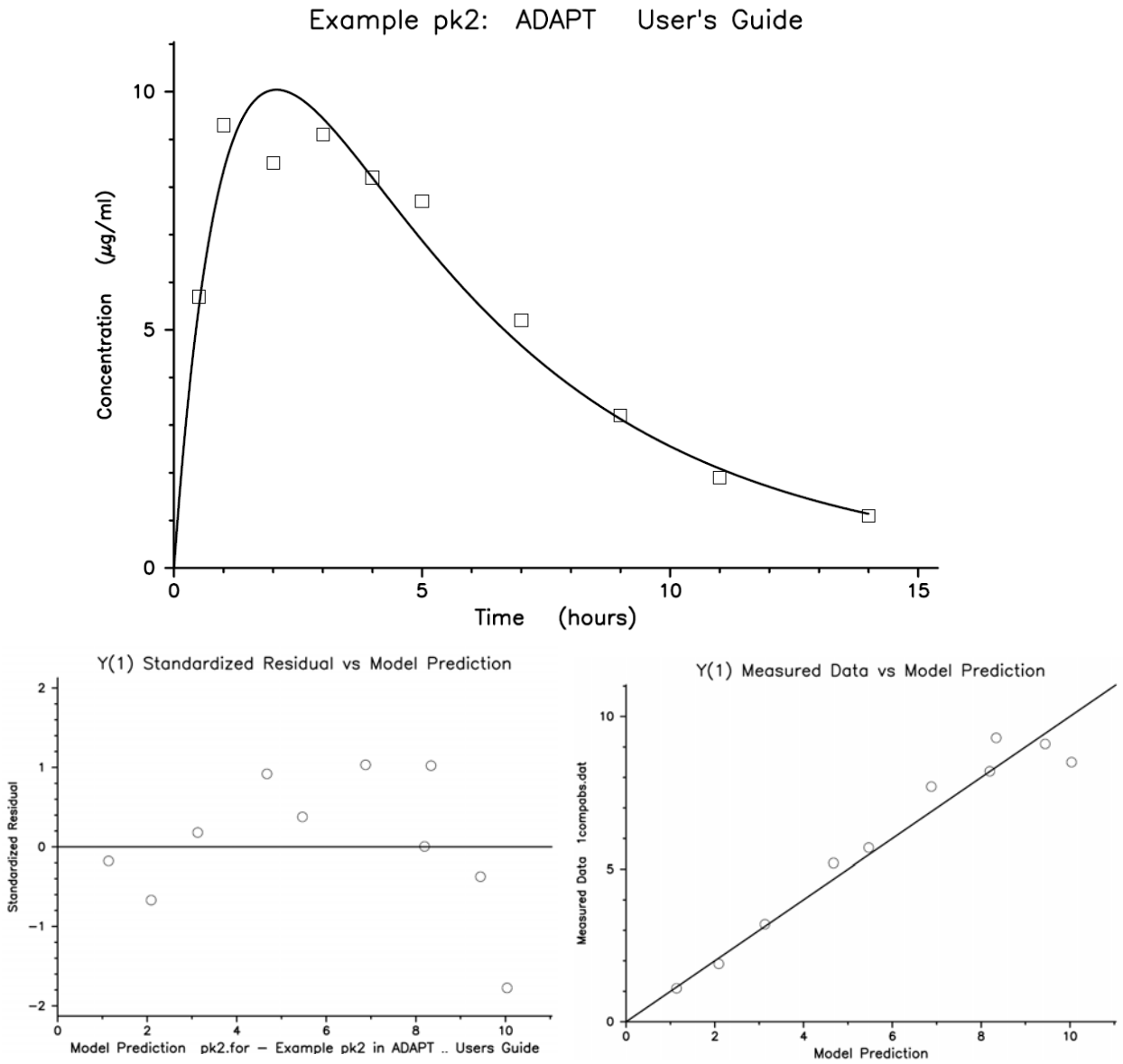


Figure 7.5 Example pk2. Resulting plots as stored in file pk2.eps.

7.3 Example pk3: ID – ML Estimation

Figure 7.6 shows an ID run file using the one compartment absorption model in Eq. (7.1) and the data in the file 1compabs.dat. The ML estimation option is selected with σ_{slope} fixed at 0.1 (i.e., not estimated) and σ_{inter} given an initial value of 0.1 and estimated. The resulting plots are shown in Figure 7.7. Also, files named pk3PLT.csv, pk3RSD.csv and pk3.aci are created as described in Chapter 6 and can be viewed in the `\Example` subfolder of the installation.

```
       ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Tue Feb 12 13:04:21 2007

Enter file name for storing session run (*.run): pk3.run

      ----- MODEL INPUT INFORMATION -----

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\1compabs.dat

 The number of model inputs:     0

 The number of bolus inputs:    1

 The number of input event times:     1

     Input Event Information
           Time    Value for all Inputs
 Event     Units,       B(1)
    1.     0.000          500.0

      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   1

 The number of observations:   10

     Observation Information
                 Time     Measured Value For Each Output
 Observation     Units ,     Y(1)
       1.        0.5000       5.700
       2.         1.000       9.300
       3.         2.000       8.500
       4.         3.000       9.100
       5.         4.000       8.200
       6.         5.000       7.700
       7.         7.000       5.200
       8.         9.000       3.200
       9.         11.00       1.900
      10.         14.00       1.100

      ----- ESTIMATOR SELECTION -----

 The following estimation procedures are available:
      1. Weighted least squares (WLS)
      2. Maximum likelihood (ML)
      3. Generalized least squares (GLS)
      4. Maximum a posteriori probability (MAP)

 Enter option number:  2

      ----- INITIALIZE ESTIMATION PROCEDURE -----

 Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\pk3.prm
```

Figure 7.6 Example pk3. ML estimation with one-compartment absorption model. Display of run file, pk3.run, with user entries indicated.

Figure 7.6 (continue)

```
Enter initial values for parameters & specify those to be estimated:

           Old Value    New Value      Estimate?
                      (skip if same)    (Y/N)
KE         .6000            y
KA         2.500            y
V          20.00            y
F          .9000            n
SDinter    .1000            n
SDslope    .1000            y

Enter maximum number of iterations:       300

Do you want the iterations printed (Y/N)?  n

             ----- RESULTS -----

             --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      KE          =   0.6000
      KA          =    2.500
      V           =    20.00
      SDslope     =   0.1000

    Negative Log Likelihood =  1598.94

              ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =    53
    Number of function calls  =   199

     Fitted Parameters
      KE          =   0.2061
      KA          =   0.9376
      V           =    28.66
      SDslope     =   0.7289E-01

    Negative Log Likelihood =  6.49368

             --- C. ML Estimation Summary---

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Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\1compabs.dat

Model:  pk3.for - Example pk3 in ADAPT Users Guide

Convergence achieved
```

Figure 7.6 (continue)

```
   Number of iterations:          53
   Number of function calls:     199
 Negative Log Likelihood:    6.49368

  Output        R-squared    Sum of Squares
  Y( 1)          0.950          4.76651

  Model Selection Criteria
   AIC:          20.9874
   BIC:          22.1977

                 Initial      Final
  Parameter       Value      Estimate    SE (CV%)    Confidence interval (95%)

  KE             0.6000      0.2061       7.364      [ 0.1690    ,  0.2433    ]
  KA              2.500      0.9376       13.36      [ 0.6310    ,   1.244    ]
  V               20.00       28.66       7.089      [  23.68    ,   33.63    ]
  F              0.9000      Not estimated

  SDslope        0.1000      0.7289E-01   28.98      [ 0.2120E-01,  0.1246    ]
  SDinter        0.1000      Not estimated

  Correlation Matrix

            KE        KA        V
 KE           1.00
 KA          -0.79      1.00
 V           -0.90      0.78      1.00

  Covariance Matrix

            KE        KA        V
 KE         0.230E-03
 KA         -.150E-02 0.157E-01
 V          -.278E-01 0.200      4.13

             --- D.  ML Estimation Model Prediction and Data Summary ---

 Tue Feb 12 13:04:21 2007

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\1compabs.dat

 Model:  pk3.for - Example pk3 in ADAPT Users Guide

Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1      0.5000        5.700        5.562        0.1382       0.2554
      2       1.000        9.300        8.498        0.8025       0.5175
      3       2.000        8.500        10.24        -1.742       0.7166
      4       3.000        9.100        9.637       -0.5374       0.6439
      5       4.000        8.200        8.352       -0.1525       0.5024
      6       5.000        7.700        6.996        0.7035       0.3721
      7       7.000        5.200        4.727        0.4729       0.1976
      8       9.000        3.200        3.145       0.5542E-01    0.1084
```

Figure 7.6 (continue)

```
     9       11.00        1.900        2.084       -0.1844       0.6347E-01
    10       14.00        1.100        1.123       -0.2346E-01   0.3308E-01

 Y( 1) (Continued)                  Std. Err.   Standardized
          Obs.Num.    Model Est.    Model Est.   Residual
                1         5.562        0.3716       0.2735
                2         8.498        0.4253        1.116
                3         10.24        0.3736       -2.058
                4         9.637        0.3802      -0.6697
                5         8.352        0.3592      -0.2151
                6         6.996        0.3033        1.153
                7         4.727        0.1942        1.064
                8         3.145        0.1531       0.1684
                9         2.084        0.1423      -0.7321
               10         1.123        0.1205      -0.1290

      ----- PLOTTING OPTIONS -----

...{Dialogue for plotting options and program exit not shown}...
```

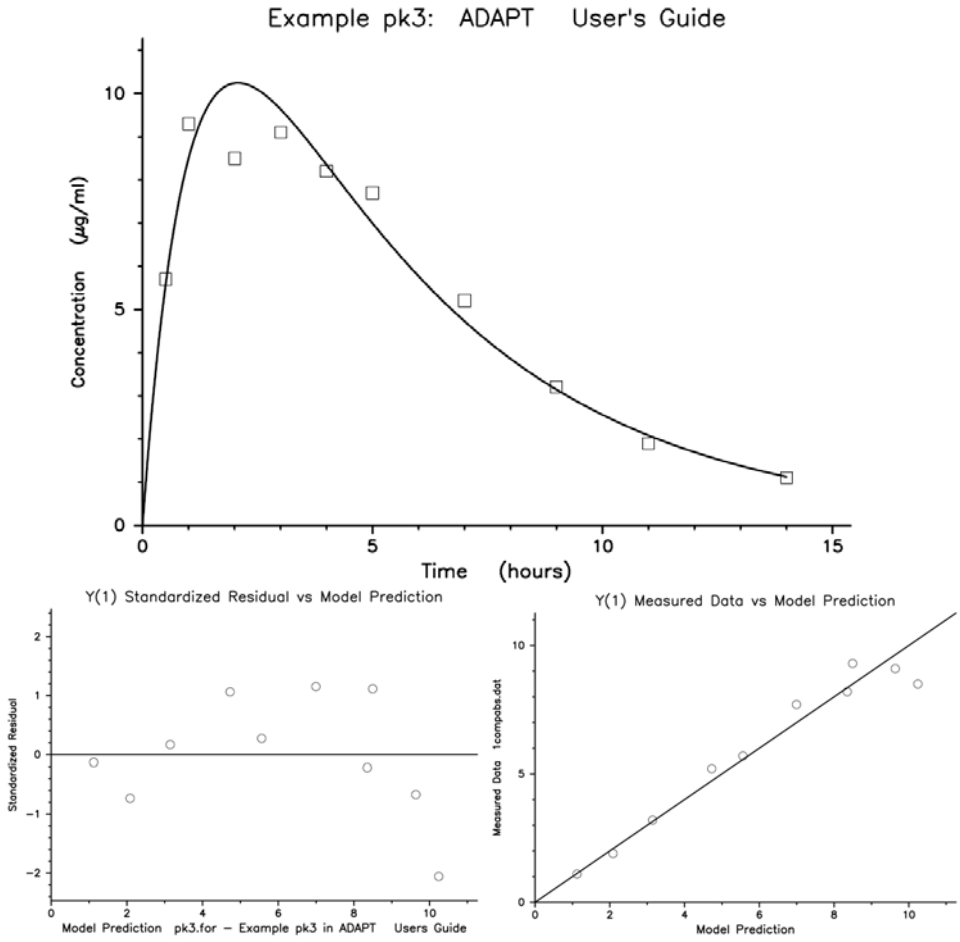


Figure 7.7 Example pk3. Resulting plots as stored in file pk3.eps.

7.4 Example pk4: ID – GLS Estimation

Figure 7.8 shows a run of ID using the one compartment absorption model in Eq. (7.1) and the data in the file 1compabs.dat. The GLS estimation option is selected with σ_{slope} fixed at 0.1 (i.e., not estimated) and σ_{inter} given an initial value of 0.1 and estimated. The resulting plots are shown in Figure 7.9. Also, files named pk4PLT.csv, pk4RSD.csv and pk4.aci are created as described in Chapter 6 and can be viewed in the \Example subfolder of the installation.

```
    ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Tue Feb 12 13:04:23 2007

 Enter file name for storing session run (*.run): pk4.run

      ----- MODEL INPUT INFORMATION -----

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\1compabs.dat

 The number of model inputs:     0

 The number of bolus inputs:    1

 The number of input event times:     1

     Input Event Information
           Time    Value for all Inputs
 Event     Units,       B(1)
    1.     0.000          500.0

      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   1

 The number of observations:   10

     Observation Information
                 Time     Measured Value For Each Output
 Observation     Units ,     Y(1)
       1.        0.5000       5.700
       2.         1.000       9.300
       3.         2.000       8.500
       4.         3.000       9.100
       5.         4.000       8.200
       6.         5.000       7.700
       7.         7.000       5.200
       8.         9.000       3.200
       9.         11.00       1.900
      10.         14.00       1.100
```

Figure 7.8 Example pk4. ML estimation with one-compartment absorption model. Display of run file, pk4.run, with user entries indicated.

Figure 7.8 (continue)

```
     ----- ESTIMATOR SELECTION -----

The following estimation procedures are available:
     1. Weighted least squares (WLS)
     2. Maximum likelihood (ML)
     3. Generalized least squares (GLS)
     4. Maximum a posteriori probability (MAP)

Enter option number:  3

     ----- INITIALIZE ESTIMATION PROCEDURE -----

Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\pk4.prm

Enter initial values for parameters & specify those to be estimated:

           Old Value    New Value      Estimate?
                      (skip if same)    (Y/N)
KE         .6000            y
KA         2.500            y
V          20.00            y
F          .9000            n
SDinter    .1000            n
SDslope    .1000            y

Enter maximum number of iterations:       300

Do you want the iterations printed (Y/N)?  n

Enter number of stage II -III cycles (e.g., 3 or 4):   4

            ----- RESULTS -----

  ----- STAGE I (OLS estimation of system parameters) -----

            --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      KE         =   0.6000
      KA         =    2.500
      V          =    20.00

    Ordinary Least Squares =  204.213

             ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =    23
    Number of function calls  =   104
```

Figure 7.8 (continue)

```
 Fitted Parameters
  KE         =   0.1732
  KA         =    1.136
  V          =    32.56

 Ordinary Least Squares =  3.93079


----- STAGE II (ML estimation of variance parameters) -----

         --- A. Iterations ---

 Number of iterations      =     0
 Number of function calls  =     1

 Fitted Parameters
  SDslope    =   0.1000

 Negative Log Likelihood =  8.98018

          ---B. Iteration Summary---

 Convergence has been achieved.

 Number of iterations      =     5
 Number of function calls  =    18

 Fitted Parameters
  SDslope    =   0.8672E-01

 Negative Log Likelihood =  8.86644


----- STAGE III (WLS estimation of system parameters) -----

         --- A. Iterations ---

 Number of iterations      =     0
 Number of function calls  =     1

 Fitted Parameters
  KE         =   0.1732
  KA         =    1.136
  V          =    32.56

 Weighted Least Squares =  10.7476

          ---B. Iteration Summary---

 Convergence has been achieved.

 Number of iterations      =    23
 Number of function calls  =    91
```

Figure 7.8 (continue)

```
   Fitted Parameters
    KE          =   0.2032
    KA          =   0.9484
    V           =    29.01

  Weighted Least Squares =  6.81160


----- STAGE II (ML estimation of variance parameters) -----

          --- A. Iterations ---

  Number of iterations      =     0
  Number of function calls  =     1

   Fitted Parameters
    SDslope     =   0.8672E-01

  Negative Log Likelihood =  6.70834


           ---B. Iteration Summary---

  Convergence has been achieved.

  Number of iterations      =     5
  Number of function calls  =    22

   Fitted Parameters
    SDslope     =   0.7264E-01

  Negative Log Likelihood =  6.51530


----- STAGE III (WLS estimation of system parameters) -----

          --- A. Iterations ---

  Number of iterations      =     0
  Number of function calls  =     1

   Fitted Parameters
    KE          =   0.2032
    KA          =   0.9484
    V           =    29.01

  Weighted Least Squares =  9.18259

           ---B. Iteration Summary---

  Convergence has been achieved.

  Number of iterations      =    13
  Number of function calls  =    91
```

Figure 7.8 (continue)

```
 Fitted Parameters
  KE         =   0.2042
  KA         =   0.9459
  V          =    28.87

 Weighted Least Squares =  9.15041


----- STAGE II (ML estimation of variance parameters) -----

         --- A. Iterations ---

 Number of iterations      =     0
 Number of function calls  =     1

 Fitted Parameters
  SDslope    =   0.7264E-01

 Negative Log Likelihood =  6.50151

          ---B. Iteration Summary---

 Convergence has been achieved.

 Number of iterations      =     0
 Number of function calls  =    20

 Fitted Parameters
  SDslope    =   0.7264E-01

 Negative Log Likelihood =  6.50151


----- STAGE III (WLS estimation of system parameters) -----

         --- A. Iterations ---

 Number of iterations      =     0
 Number of function calls  =     1

 Fitted Parameters
  KE         =   0.2042
  KA         =   0.9459
  V          =    28.87

 Weighted Least Squares =  9.15041

          ---B. Iteration Summary---

 Convergence has been achieved.

 Number of iterations      =     3
 Number of function calls  =    99
```

Figure 7.8 (continue)

```
 Fitted Parameters
  KE         =   0.2043
  KA         =   0.9451
  V          =    28.86

Weighted Least Squares =  9.14942


----- STAGE II (ML estimation of variance parameters) -----

         --- A. Iterations ---

Number of iterations      =     0
Number of function calls  =     1

 Fitted Parameters
  SDslope    =   0.7264E-01

Negative Log Likelihood =  6.50099



Convergence has been achieved.

Number of iterations      =     0
Number of function calls  =    20

 Fitted Parameters
  SDslope    =   0.7264E-01

Negative Log Likelihood =  6.50099


----- STAGE III (WLS estimation of system parameters) -----

         --- A. Iterations ---

Number of iterations      =     0
Number of function calls  =     1

 Fitted Parameters
  KE         =   0.2043
  KA         =   0.9451
  V          =    28.86

Weighted Least Squares =  9.14942


          ---B. Iteration Summary---

Convergence has been achieved.

Number of iterations      =     2
Number of function calls  =   102
```

Figure 7.8 (continue)

```
     Fitted Parameters
      KE         =   0.2043
      KA         =   0.9452
      V          =    28.86

    Weighted Least Squares =  9.14746


            --- C. GLS Estimation Summary---

 Tue Feb 12 13:04:23 2007

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\1compabs.dat

 Model:  pk4.for - Example pk4 in ADAPT Users Guide

 Number of stage II - III cycles:       4

                   Number of       Number of        Weighted
                  Iterations    Function Calls    Least Squares
 Last Stage  II:        0             20            6.50099
 Last Stage III:        2            102            9.14746


                              Weighted
  Output        R-squared    Sum of Squares   Sum of Squares
  Y( 1)        0.950           9.14746          4.67653

  Model Selection Criteria
   AIC:          28.1348
   BIC:          29.0425


                Initial      Final
  Parameter     Value      Estimate     SE (CV%)      Confidence interval (95%)

  KE            0.6000      0.2043       7.372      [ 0.1687    ,  0.2400    ]
  KA             2.500      0.9452       13.40      [ 0.6457    ,   1.245    ]
  V              20.00       28.86       7.067      [  24.03    ,   33.68    ]
  F             0.9000      Not estimated


  SDslope       0.1000      0.7264E-01
  SDinter       0.1000      Not estimated


  Correlation Matrix

           KE        KA        V
 KE          1.00
 KA         -0.79      1.00
 V          -0.90      0.78      1.00
```

Figure 7.8 (continue)

```
 Covariance Matrix

          KE        KA        V
KE        0.227E-03
KA        -.150E-02 0.160E-01
V         -.277E-01 0.202      4.16

            --- D. GLS Estimation Model Prediction and Data Summary ---

 Tue Feb 12 13:04:23 2008

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\1compabs.dat

 Model:  pk4.for - Example pk4 in ADAPT II Users Guide

Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Weight
      1      0.5000        5.700        5.561        0.1394        3.938
      2       1.000        9.300        8.487        0.8131        1.948
      3       2.000        8.500        10.22        -1.716        1.410
      4       3.000        9.100        9.610       -0.5097        1.570
      5       4.000        8.200        8.332       -0.1317        2.011
      6       5.000        7.700        6.985        0.7147        2.710
      7       7.000        5.200        4.732        0.4676        5.078
      8       9.000        3.200        3.158        0.4161E-01    9.214
      9       11.00        1.900        2.101       -0.2009        15.67
     10       14.00        1.100        1.138       -0.3832E-01    29.96

 Y( 1) (Continued)                Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
                1       5.561       0.3728       0.2765
                2       8.487       0.4250        1.135
                3       10.22       0.3724       -2.038
                4       9.610       0.3797      -0.6387
                5       8.332       0.3585      -0.1867
                6       6.985       0.3023        1.177
                7       4.732       0.1938        1.054
                8       3.158       0.1535       0.1263
                9       2.101       0.1432      -0.7951
               10       1.138       0.1217      -0.2098

      ----- PLOTTING OPTIONS -----

...{Dialogue for plotting options and program exit not shown}...
      ________________________________________________

    ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Tue Feb 12 13:04:23 2007
```

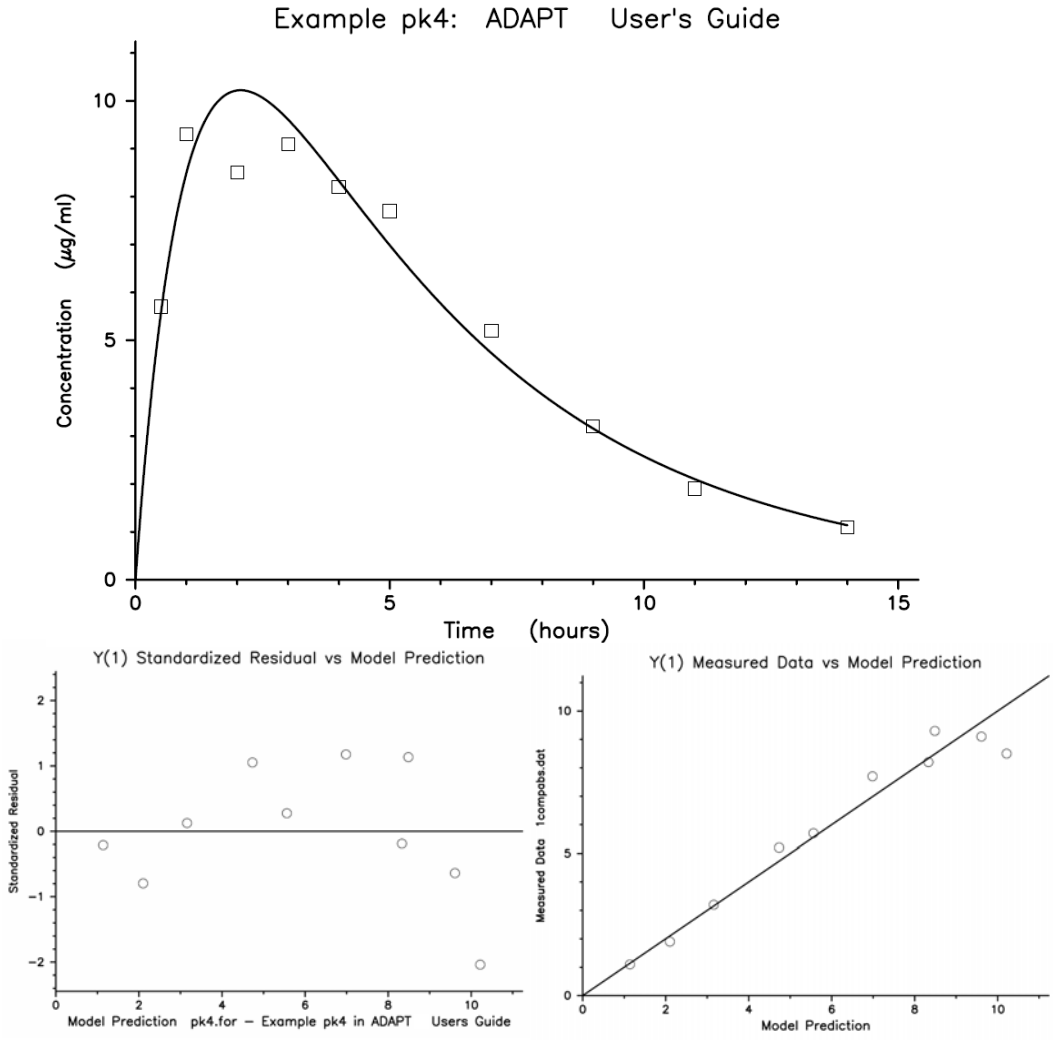


Figure 7.9 Example pk4. Resulting plots as stored in file pk4.eps.

7.5 Example pk5: SIM – Population Simulation

This example illustrates the use of SIM to perform a population simulation with output error for a one-compartment model with intravenous infusion. The library Model File 1compk.for (see Figure 7.10) is modified for this example to include the prior mean and covariance values for the model parameters V and K_e (K_a = 0.0 since an intravenous administration is used). The parameters V and K_e are assumed to come from a bivariate lognormal distribution with mean and covariance as listed in the caption of Figure 7.10. The variance model for the output error is given above in Eq. (7.2), with σ_{slope} = 0.0 and σ_{inter} = 1.0 (corresponds to constant output error variance). The dosage regimen is given in Table 7.1 and consists of a loading infusion followed by a maintenance dose designed to "achieve and maintain" a serum concentration of 10μg/ml for the mean parameters. After 24 hrs a steady-state infusion is given to achieve a concentration of 15 μg/ml given the mean parameters. Five observation times are considered, at 1.5, 10, 24, 48 and 72

hr. A total of 100 simulations will be preformed (i.e., 100 sets of model parameters selected randomly from the specified population distribution).

The complete run of SIM for this example is given in Figure 7.11. The population simulation option is selected (option 4). A statistical summary of the 100 sets of parameter values is displayed as well as a summary of the resulting simulated output. The plot (Figure 7.12) shows the response for the population mean parameter values (continuous curve), as well as the mean simulated output (indicated by X) and standard deviation bars at each observation time. Also, files named pk5PLT.csv, pk5POP.csv and pk5.aci are created as described in Chapter 5 and can be viewed in the `\Example` subfolder of the installation.

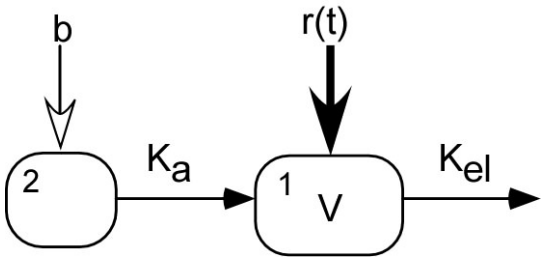


Figure 7.10 One compartment model used in Example pk5. Parameter means and variance as follows (see pk5.for): $V = 35 \pm 10.5\,(L)$; $Kel = 0.08 \pm 0.04\,(hr^{-1})$; $\sigma_{V-Kel} = -0.21$.

Table 7.1 Dosage Regimen for Example 7.5

Dose Event Time *dt* (hr)	Infusion Rate (mg/hr)
0	700
0.5	28
24	42

```
    ADAPT 5      SIM -- MODEL SIMULATION      Tue Feb 12 13:04:24 2007

Enter file name for storing session run (*.run): pk5.run

      ----- MODEL INPUT INFORMATION -----

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk5.dat

The number of model inputs:     1

The number of bolus inputs:    0
```

Figure 7.11 Example pk5. Population simulation of one-compartment infusion model. Display of run file, pk5.run, with user entries indicated.

Figure 7.11 (continue)

```
The number of input event times:     3

     Input Event Information
           Time    Value for all Inputs
 Event     Units,       R(1)
    1.     0.000          700.0
    2.    0.5000          28.00
    3.     24.00          42.00

      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   1

 The number of observations:    5

     Observation Information
                 Time     Measured Value For Each Output
 Observation     Units ,     Y(1)
       1.         1.500      -1.000
       2.         10.00      -1.000
       3.         24.00      -1.000
       4.         48.00      -1.000
       5.         72.00      -1.000

      ----- SIMULATION SELECTION -----

 The following simulation options are available:
     1. Individual simulation
     2. Individual simulation with output error
     3. Population simulation
     4. Population simulation with output error

 Enter option number:  4

      ----- ENTER PARAMETER INFORMATION -----

 Select distribution model (1-Normal, 2-Lognormal):  2

 Indicate if any system parameters are to be fixed:
                  Population     Fix?  If "Y" Enter
  Parameter          Mean       (Y/N)  Fixed Value (e.g. Y,7)
   Ke              0.8000E-01     n
   V                35.00         n

 Enter Non-Random Initial Conditions:
  Parameter      Value
   IC(   1)        0.000
   IC(   2)        0.000

 Enter values for variance model parameters:
  Parameter      Value
   SDinter         1.000
   SDslope         0.000
```

Figure 7.11 (continue)

```
 Enter number of simulations:         100

 Enter seed (positive integer) for random number generator:      123456

 Store inputs and simulated data in a new Adapt data file (Y/N)?  n

 Store individual subject simulation results in a file (Y/N)?  y

      ----- RESULTS -----

      --- A. Parameter Summary ---

 Tue Feb 12 13:04:24 2007

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk5.dat

 Model: pk5.for - Example pk5 in ADAPT Users Guide

 Population simulation with error:   100 simulations.  Seed =     123456

                       Population              Parameter Summary
 Parameter               Mean          Mean     Std.Dev.     Min         Max
  Ke          (LN)     0.8000E-01    0.8563E-01 0.4216E-01 0.2826E-01 0.2344
  V           (LN)      35.00         34.99      11.73      17.86      84.32

   Fixed
 Parameter               Value
  Ka                    0.000
  IC(   1)              0.000
  IC(   2)              0.000
  SDinter               1.000
  SDslope               0.000

 Secondary              Population     Sample
 Parameter                Mean          Mean
  CL                     2.800         2.997
  LAM1                  0.8000E-01    0.8563E-01
  t1/2-LAM1              8.664         8.094

 Parameter Correlation Matrix:

            Ke        V
 Ke           1.00
 V           -0.52      1.00

 Parameter Covariance Matrix:

            Ke        V
Ke        0.178E-02
 V         -.255      138.
```

Figure 7.11 (continue)

```
      --- B. Simulation Summary ---

 Tue Feb 12 13:04:24 2007

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk5.dat

 Model: pk5.for - Example pk5 in ADAPT Users Guide

 Population simulation with error:   100 simulations.  Seed =     123456

 Y(   1)             Output for          Summary of Simulation Results
  Obs.Num.  Time     Popul. Mean       Mean     Std.Dev.     Min        Max
      1      1.500       9.818         10.69      2.939      3.637      18.20
      2      10.00       9.908         10.40      2.812      3.487      18.07
      3      24.00       9.970         10.86      3.613      3.597      21.82
      4      48.00       14.26         15.97      5.162      6.711      30.67
      5      72.00       14.89         17.09      5.829      6.791      35.64

      ----- PLOTTING OPTIONS -----

...{Dialogue for plotting options and program exit not shown}...
```

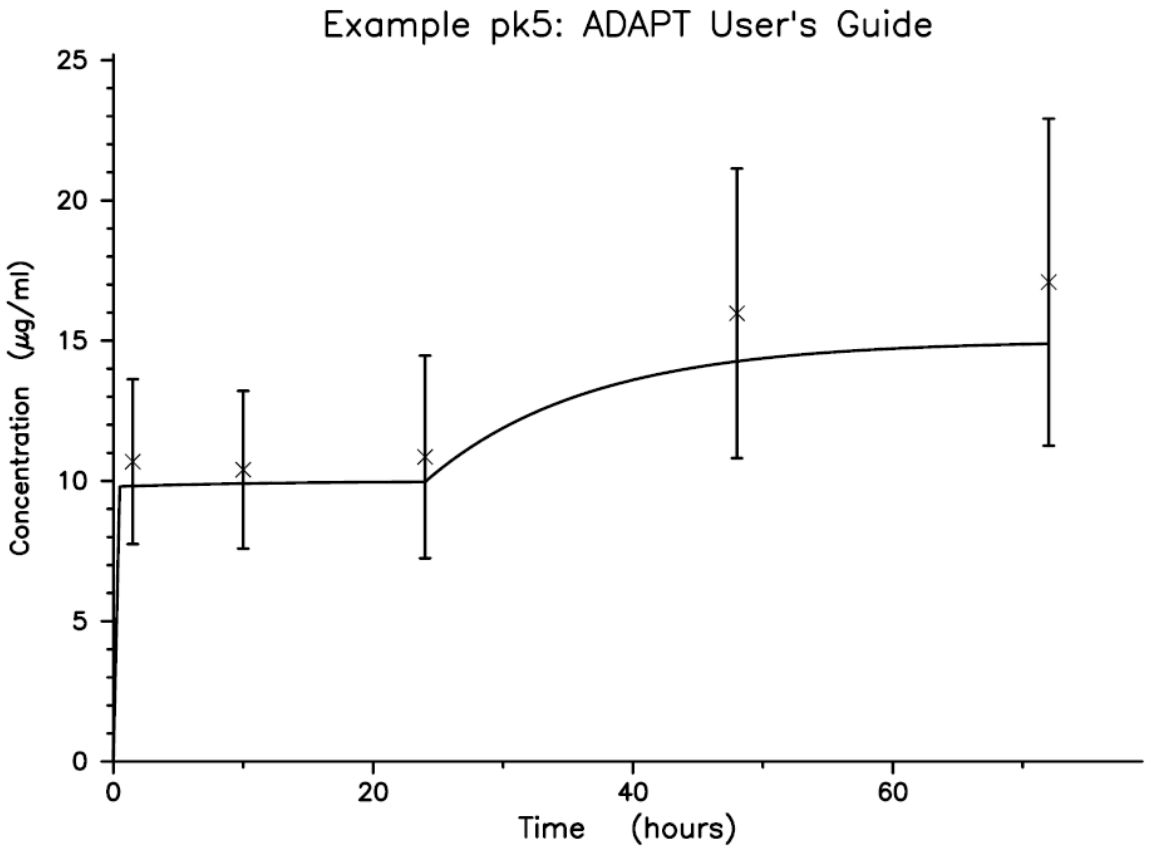


Figure 7.12 Example pk5. Resulting plot as stored in file pk5.eps.

7.6 Example pk6: ID – MAP Estimation

The one-compartment model from Example pk5 is also used in this example to illustrate the MAP estimation option in the ID program. A single simulated noisy data set was generated from the kinetic model, infusion input and variance model used in Example pk6, with three observations simulated at 1.5, 10 and 24 hours. Also, in this example, the distribution for the model parameters is assumed to be multivariate Normal with moments given in Figure 6.10. An ADAPT Data File was created (pk6.dat) from a run of SIM for this example (not shown, simulation option 4, 1 simulated subject), and used as input to the ID program. The resulting parameters values for the simulated subject are $V = 38.7$ L and $K_e = 0.037\ \text{hr}^{-1}$. The complete run of ID is given in Figure 6.13 and the plots shown in Figure 6.14. Also, files named pk6PLT.csv, pk6RSD.csv and pk6.aci are created as described in Chapter 5 and can be viewed in the Validation folder in the ADAPT Directory.

```
   ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Tue Feb 12 13:04:26 2007

Enter file name for storing session run (*.run): pk6.run

     ----- MODEL INPUT INFORMATION -----

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk6.dat

The number of model inputs:     1

The number of bolus inputs:    0

The number of input event times:     2

    Input Event Information
          Time    Value for all Inputs
Event     Units,       R(1)
   1.     0.000          700.0
   2.    0.5000          28.00

     ----- MODEL OUTPUT INFORMATION -----

The number of model output equations:   1

The number of observations:    3

    Observation Information
                Time     Measured Value For Each Output
Observation     Units ,     Y(1)
      1.         1.500       9.500
      2.         10.00       11.00
      3.         24.00       17.00

     ----- ESTIMATOR SELECTION -----
```

Figure 7.13 Example pk6. MAP estimation with one-compartment of model. Display of run file, pk6.run, with user entries indicated.

Figure 7.13 (continue)

```
The following estimation procedures are available:
      1. Weighted least squares (WLS)
      2. Maximum likelihood (ML)
      3. Generalized least squares (GLS)
      4. Maximum a posteriori probability (MAP)

 Enter option number:  4

      ----- INITIALIZE ESTIMATION PROCEDURE -----

 Parameter file name: pk6.prm

 Enter initial values for parameters & specify those to be estimated:

            Old Value    New Value      Estimate?
                       (skip if same)    (Y/N)
 Ke         .8000E-01        y
 V          35.00            y
 Ka         0.000            n
 IC(   1)   0.000            n
 IC(   2)   0.000            n
 SDinter    1.000            n
 SDslope    0.000            n

 Select prior distribution model (1 - Normal, 2 - Lognormal):  1

 Enter maximum number of iterations:       300

 Do you want the iterations printed (Y/N)?  n

             ----- RESULTS -----

             --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      Ke         =   0.8000E-01
      V          =    35.00

    MAP Objective Function =  50.7166

              ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =    14
    Number of function calls  =    54

     Fitted Parameters
      Ke         =   0.2628E-01
      V          =    41.37
```

Figure 7.13 (continue)

```
    MAP Objective Function =  4.11959

            --- C. MAP Estimation Summary---

Tue Feb 12 13:04:26 2007

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk6.dat

Model:  pk6.for - Example pk6 in ADAPT Users Guide

Convergence achieved
  Number of iterations:          14
  Number of function calls:      54
MAP Objective Function:    4.11959

 Output        R-squared    Sum of Squares
 Y( 1)          0.927          2.31011

 Model Selection Criteria
  GEN-IC:       5.45292

                Initial      Final
 Parameter      Value      Estimate    SE (CV%)    Confidence interval (95%)

Ke         (N)  0.8000E-01  0.2628E-01   32.81      [-0.8327E-01, 0.1358    ]
V          (N)   35.00       41.37       9.525      [ -8.697    ,  91.44    ]
Ka               0.000       Not estimated
IC(   1)         0.000       Not estimated
IC(   2)         0.000       Not estimated

SDinter          1.000       Not estimated
SDslope          0.000       Not estimated

CL               2.800       1.087       24.75      [ -2.332    ,  4.506    ]
LAM1            0.8000E-01  0.2628E-01   32.81      [-0.8327E-01, 0.1358    ]
t1/2-LAM1        8.664       26.38       32.81      [ -83.59    ,  136.3    ]

 Correlation Matrix

          Ke        V
Ke          1.00
V          -0.89      1.00

 Covariance Matrix

          Ke        V
Ke        0.743E-04
V         -.301E-01  15.5

           --- D. MAP Estimation Model Prediction and Data Summary ---

Tue Feb 12 13:04:26 2007

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk6.dat
```

Figure 7.13 (continue)

```
Model:  pk6.for - Example pk6 in ADAPT Users Guide

Y( 1)
  Obs.Num.    Time          Data        Model Est.      Residual      Variance
      1        1.500         9.500         8.855         0.6451         1.000
      2        10.00         11.00         12.24         -1.238         1.000
      3        24.00         17.00         16.40         0.6006         1.000

 Y( 1) (Continued)                  Std. Err.   Standardized
           Obs.Num.    Model Est.   Model Est.   Residual
               1        8.855        0.7638       0.6451
               2        12.24        0.5976       -1.238
               3        16.40        0.9516       0.6006

      ----- PLOTTING OPTIONS -----  {Dialogue for plotting not shown}...
```

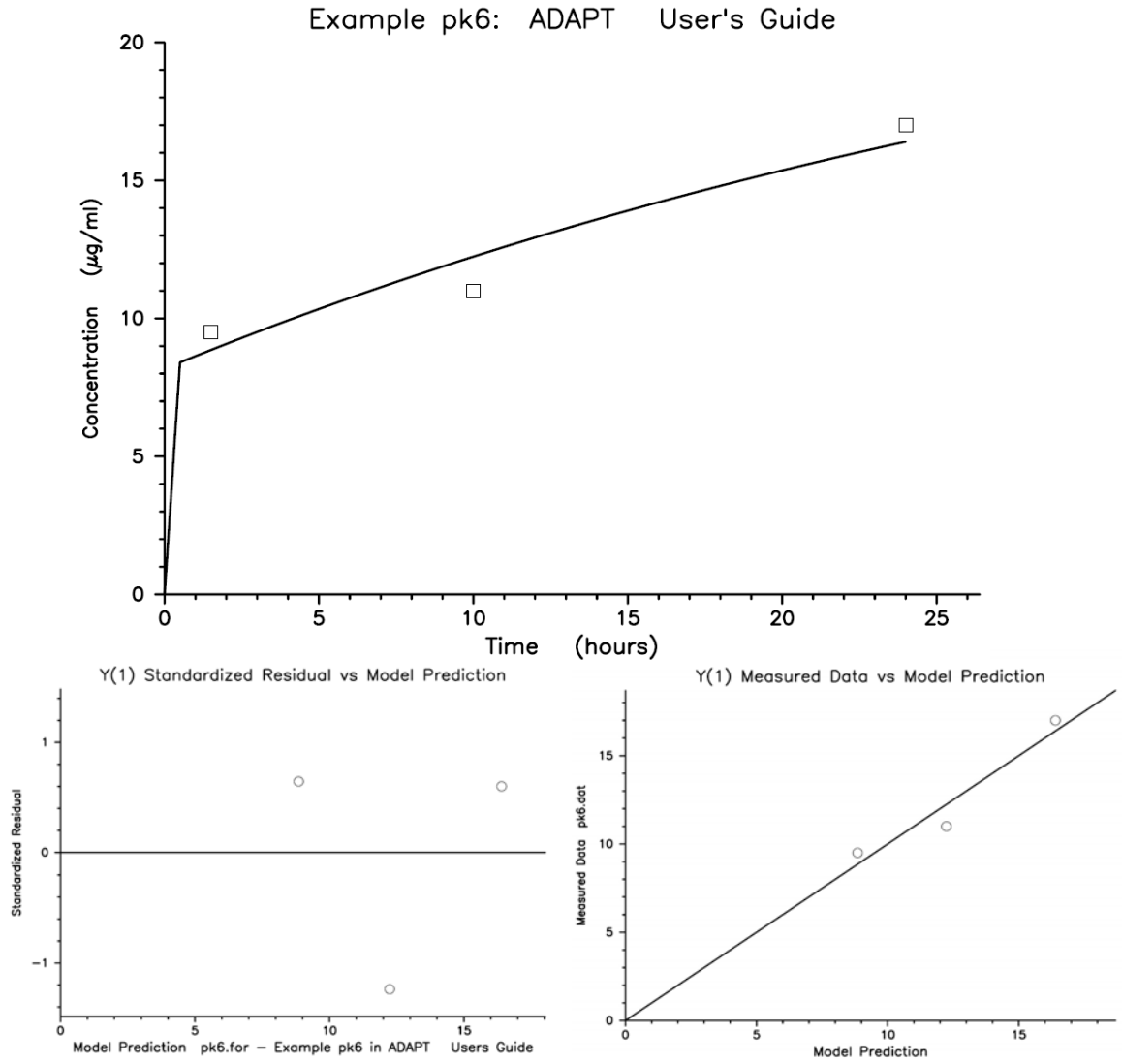


Figure 7.14 Example pk6. Resulting plot as stored in file pk6.eps.

7.7 Example pk7: Sample – D-Optimal Design

In this example the three compartment model shown in Figure 7.15 is used to illustrate the sample schedule design program SAMPLE. The model differential and output equations are given below:

$$\begin{aligned}
\frac{dx_1(t)}{dt} &= -(K_{10}+K_{12}+K_{13})x_1(t)+K_{21}x_2(t)+K_{31}x_3(t)\\
\frac{dx_2(t)}{dt} &= K_{12}x_1(t)-K_{21}x_2(t)\\
\frac{dx_3(t)}{dt} &= K_{13}x_1(t)-K_{31}x_3(t)\\
y(t) &= x_1(t)/V
\end{aligned} \tag{7.3}$$

Since the differential equations are linear and homogenous, the matrix exponential solution to the model equations can be used (see Chapter 5). This requires that the model differential equations be written as:

$$\begin{bmatrix} \frac{dx_1(t)}{dt} \\ \frac{dx_2(t)}{dt} \\ \frac{dx_3(t)}{dt} \end{bmatrix} = \begin{bmatrix} (K_{10}+K_{12}+K_{13}) & K_{21} & K_{31} \\ K_{12} & -K_{21} & 0 \\ K_{13} & 0 & -K_{31} \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} \tag{7.4}$$

Figure 7.16 is an excerpt for the Model File pk7.for showing subroutine AMAT in which the system matrix indicated in Eq. (7.4) is coded.

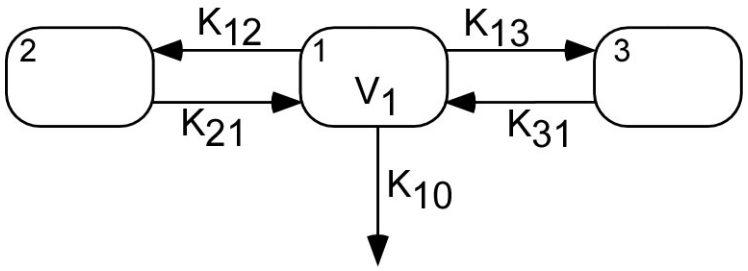


Figure 7.15 Three compartment model used in Example 6.7.

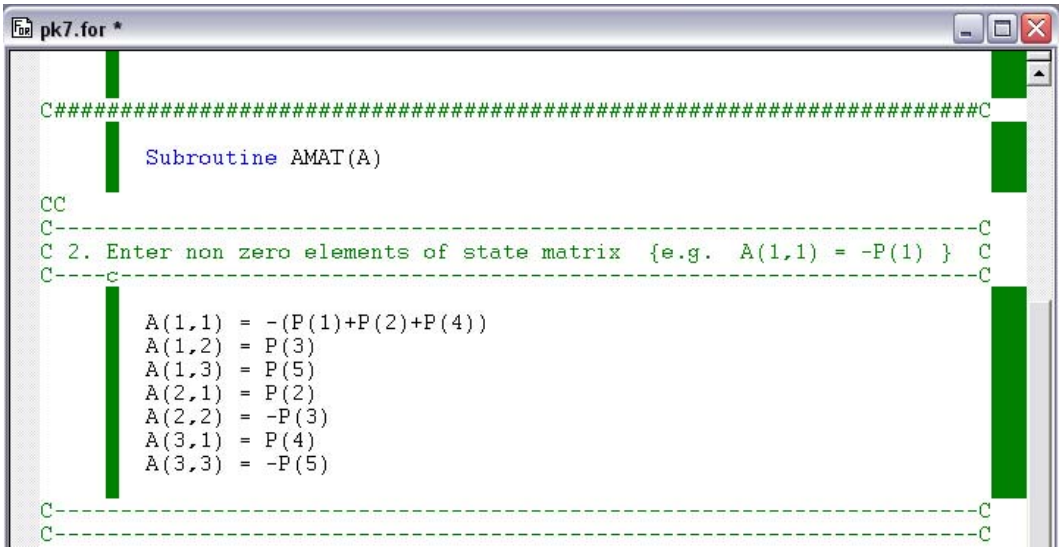


Figure 7.16 Excerpt from Subroutine AMAT of Model File pk7.for.

Figure 7.17 shows a complete run of SAMPLE for this example using the data file pk7.dat that includes the initial guesses for the sample times to be optimized. In the run, all six sample times are selected to be optimized (i.e., no fixed times). In addition, no time constraints are imposed on the sample times (selected by entering 0,0 as the lower and upper time limits). The error variance model for this example is $\text{var}\{e(t)\} = \sigma_0^2$. Nominal values for the model and variance parameters are stored in parameter file pk7.prm. A dose of 300 mg into compartment 1 is specified as an initial condition in file pk7.prm (i.e., IC(1)=300). The plot showing the optimal sample times on the concentration time profile is given in Figure 7.17. A file named pk6PLT.csv is created as described in Chapter 5 and can be viewed in the `\Example` subfolder of the installation.

```
ADAPT 5    SAMPLE -- SAMPLE SCHEDULE DESIGN    Tue Feb 12 13:04:28 2007

 Enter file name for storing session run (*.run): pk7.run

      ----- MODEL INPUT INFORMATION -----

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk7.dat

 The number of model inputs:     0

 The number of bolus inputs:    0

 The number of input event times:     0

      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   1

 The number of observations:    6
```

Figure 7.17 Example pk7. Sample schedule design for three compartment model.

Figure 7.17 (continue)

```
For each sample number enter as required:
                 Sample
 Sample Number   Time , Optimize (Y/N)?
      1.         2.0000     y
      2.         5.0000     y
      3.         10.000     y
      4.         20.000     y
      5.         75.000     y
      6.         240.00     y

 Enter lower and upper time constraints. (Lower, Upper)      2.000       300.0

      ----- ENTER PARAMETER INFORMATION -----

 Parameter file name: pk7.prm

Enter nominal values for parameters & specify those to be estimated:
                                       Estimated
            Old Nominal  New Nominal    in Design?
                       (skip if same)    (Y/N)
 K10        .9000E-01                     y
 K12        .3100                         y
 K21        .1500                         y
 K13        .2400                         y
 K31        .2000E-01                     y
 V          7.000                         y
 IC(   1)   300.0                         n
 IC(   2)   0.000                         n
 IC(   3)   0.000                         n

 Enter values for variance model parameters:
          Old Value     New Value (<Enter> if no change)
 Sigma0     .2000

         ----- SELECT OPTIMALITY CRITERION -----

 D or C optimality?   d

 Enter maximum number of iterations:       999

 Do you want the iterations printed (Y/N)?  n

 Store inputs, sample times & data in a new file (Y/N)?  n

            ------ RESULTS ------

             --- A. Iterations ---

  Number of iterations      =      0
  Number of function calls  =      7

    Time(   1) =   2.000
    Time(   2) =   5.000
    Time(   3) =   10.00
```

Figure 7.17 (continue)

```
    Time(   4) =   20.00
    Time(   5) =   75.00
    Time(   6) =   240.0

  Design criterion  = -0.958206E+18

              ---B. Iteration Summary---

  Convergence achieved

  Number of iterations       =     46
  Number of function calls   =   1631

    Time(   1) =   2.000
    Time(   2) =   3.204
    Time(   3) =   7.077
    Time(   4) =   19.93
    Time(   5) =   63.73
    Time(   6) =   279.2

  Design criterion  = -0.444502E+19

             --- C. Sample Schedule Design Summary ---

 Tue Apr 14 09:36:52 2009

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk7.dat

 Model:  pk7.for - Example pk7 in ADAPT Users Guide

Convergence achieved
   Number of iterations:          46
   Number of function calls:    1631
 D-optimal criterion value: -0.444502E+19


                 Initial      Final
 Sample Time      Value       Value
   Time(   1)    2.000       2.000
   Time(   2)    5.000       3.204
   Time(   3)    10.00       7.077
   Time(   4)    20.00       19.93
   Time(   5)    75.00       63.73
   Time(   6)    240.0       279.2


 Model Parameter Values used in the Design Calculations:

  System                      "Expected"
 Parameter       Value          SE (CV%)
  K10           .9000E-01        27.17
  K12           .3100            21.16
  K21           .1500            29.98
  K13           .2400            33.11
```

Figure 7.17 (continue)

```
 K31            .2000E-01        43.35
 V              7.000            12.91
 IC(   1)       300.0            Not estimated
 IC(   2)       0.000            Not estimated
 IC(   3)       0.000            Not estimated

Variance
Parameter        Value
 Sigma0         .2000

           --- D. Simulation Summary ---

Tue Apr 14 09:36:52 2009

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk7.dat

Model:  pk7.for - Example pk7 in ADAPT Users Guide

Y( 1)  Obs.Num.    Time         Model Simul.     Error Var.
            1       2.000          13.71           0.4000E-01
            2       3.204          8.328           0.4000E-01
            3       7.077          4.122           0.4000E-01
            4       19.93          2.429           0.4000E-01
            5       63.73          1.351           0.4000E-01
            6       279.2         0.4743           0.4000E-01

     ----- PLOTTING OPTIONS -----  {Dialogue for plotting not shown}...
```

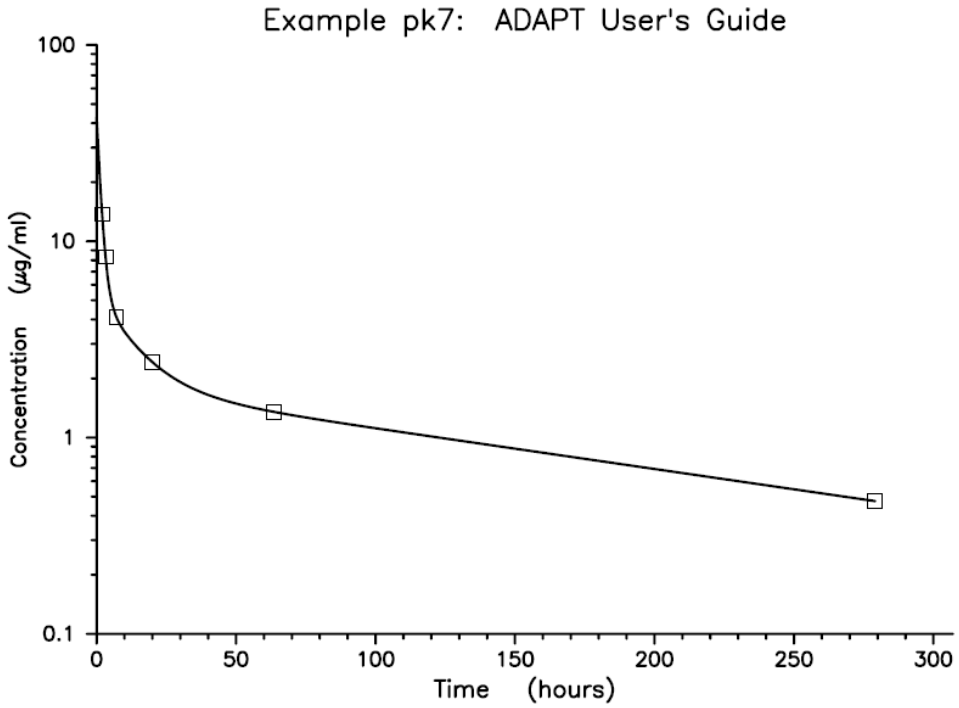


Figure 7.18 Example pk7. Resulting plot as stored in file pk7.eps.

7.8 Example pk8: ID – ML Estimation, Parent/Metabolite Model

This example, modified from [1], involves a pharmacokinetic model of a compound with an active metabolite formed by a saturable process. The compartment structure for this model is given in Figure 7.19.

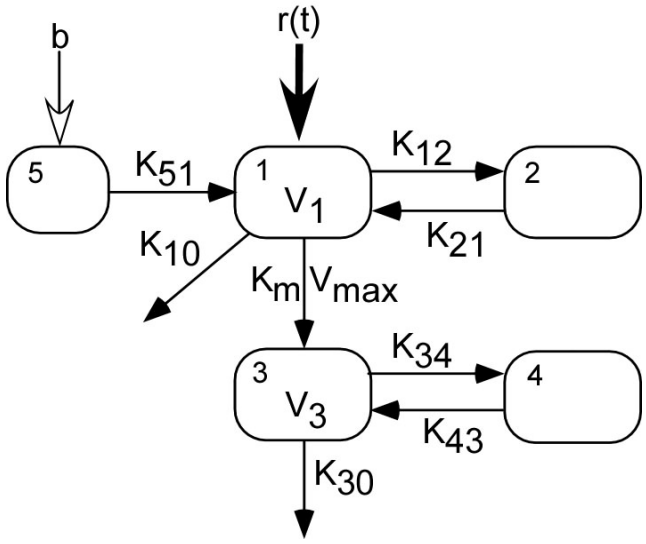


Figure 7.19 The drug-metabolite model of Example pk8.

The differential equations (representing compartment amounts) and the output equations (representing drug concentrations) for this model given below and have been used to create the model file pk8.for. (As noted below, the units used for V_{max} are mg/hr, while in [1] and in previous version of this guide units of $mg/L/hr$ were used for V_{max}.)

$$\frac{dx_1(t)}{dt} = -\left(\frac{V_{max}}{K_m + (x_1/V_1)}\right)\left(\frac{x_1(t)}{V}\right) - (K_{10} + K_{12})\,x_1(t) + K_{21}x_2 + K_{51}x_5 + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{12}x_1(t) - K_{21}x_2(t)$$

$$\frac{dx_3(t)}{dt} = \left(\frac{V_{max}}{K_m + (x_1/V_1)}\right)\left(\frac{x_1(t)}{V}\right) - (K_{30} + K_{34})\,x_3 + K_{43}x_4$$

$$\frac{dx_4(t)}{dt} = K_{34}x_3 - K_{43}x_4$$

$$\frac{dx_5(t)}{dt} = -K_{51}x_5$$

$$y_1(t) = x_1(t)/V_1$$

$$y_2(t) = x_3(t)/V_3 \qquad (7.6)$$

The parent compound is administered as two 1 hour intravenous infusions starting at time 0 (rate = 1000 mg/hr) and again at 12 hrs. (rate = 250 mg/hr). The parent drug is also given orally at 6 hrs. (amount = 500 mg) and at 12 hrs. (amount = 250 mg), and is assumed to be absorbed completely. A total of 14 blood samples are obtained, with both parent and metabolite serum concentrations determined at the following times: 0.5, 1, 2, 4, 6, 7, 8, 10, 12, 12.5, 13, 14, 16, 18, hrs. The parent drug concentration at t= 10 hrs is assuming missing.

Table 7.2 gives a list of the model parameters along with the corresponding Fortran symbols used in coding the model equations. The dosage regimen information is arranged in a spread-sheet format in Table 7.3. Data to be used in the estimation were generated by first simulating the response of this model with the parameter values given in Table 7.2, and then adding Normally distributed error to the simulated output. The random error added to the simulated parent concentration results had a standard deviation of 1.14μg/ml and that added to the metabolite concentration had a standard deviation of .06μg/ml. SIM was used to generate these simulated data, with the results stored in a data file (pk8.dat).

Table 7.2 Parameter Values for Example pk8

Parameter	Symbol	Parameter Value	(unit)
K_{10}	P(1)	0.04	(hr^{-1})
K_{12}	P(2)	0.6	(hr^{-1})
K_{21}	P(3)	0.10	(hr^{-1})
K_m	P(4)	10.	$(\mu g / ml)$
V_{max}	P(5)	1.00	(mg/hr)
K_{30}	P(6)	1.00	(hr^{-1})
K_{34}	P(7)	0.90	(hr^{-1})
K_{43}	P(8)	0.40	(hr^{-1})
K_{51}	P(9)	2.00	(hr^{-1})
V_1	P(10)	30.0	(L)
V_3	P(11)	15.0	(L)

Table 7.3 Dose Regimen for Example pk8

Dose Event Time *dt* (hr)	Infusion Rate *r* (mg/hr)	Bolus Amount (unit) *b* (mg)
0	1000	0
1	0	0
6	0	500
12	250	250
13	0	0

Figure 7.20 shows the run of ID for this example using the ML estimation option. For each bolus input, the user must interactively enter the compartment (or more generally the differential equation or state number) to receive the bolus input. In this example, the one bolus is into compartment 5 (see below). Inspection of the observation information, indicates that the eighth observation for the first output (i.e. $y_1(t_8)$) is missing (-1 is the missing data number). Also, files named pk8PLT.csv, pk8RSD.csv and pk8.aci are created as described in Chapter 6 and can be viewed in the \Example subfolder of the installation.

```
    ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Tue Feb 12 13:04:29 2007

Enter file name for storing session run (*.run): pk8.run

      ----- MODEL INPUT INFORMATION -----

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk8.dat

 The number of model inputs:     1

 The number of bolus inputs:    1

 Enter the compartment number for each bolus input (e.g. 1,3,...):   5

 The number of input event times:     5

     Input Event Information
           Time    Value for all Inputs
 Event     Units,        R(1), B(1)
    1.     0.000           1000.       0.000
    2.     1.000           0.000       0.000
    3.     6.000           0.000       500.0
    4.     12.00           250.0       250.0
    5.     13.00           0.000       0.000

      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   2

 The number of observations:   14

     Observation Information
                 Time     Measured Value For Each Output
 Observation     Units ,      Y(1), ... ,Y(   2)
       1.        0.5000        9.663      0.2038
       2.         1.000        17.67      0.6202
       3.         2.000        12.55      0.8137
       4.         4.000        9.536      0.6881
       5.         6.000        8.100      0.6293
       6.         7.000        10.94      0.7987
       7.         8.000        11.09      0.8339
```

Figure 7.20 Example pk8. ML estimation of parent-metabolite nonlinear model.

Figure 7.20 (continue)

```
      8.         10.00      -1.000      0.7633
      9.         12.00       4.611      0.6394
     10.         12.50       11.66      0.7446
     11.         13.00       13.16      0.8540
     12.         14.00       13.67      0.9928
     13.         16.00       8.353      0.9019
     14.         18.00       8.716      0.8510
     ----- ESTIMATOR SELECTION -----

The following estimation procedures are available:
     1. Weighted least squares (WLS)
     2. Maximum likelihood (ML)
     3. Generalized least squares (GLS)
     4. Maximum a posteriori probability (MAP)

Enter option number:  2

     ----- INITIALIZE ESTIMATION PROCEDURE -----

Parameter file name: pk8.prm

Enter initial values for parameters & specify those to be estimated:

           Old Value    New Value      Estimate?
                      (skip if same)    (Y/N)
K10        .4000E-01         n
K12        .6000             y
K21        .1000             n
Km         10.00             n
Vmax       30.00             y
K30        1.000             y
K34        .9000             n
K43        .4000             n
K51        2.000             n
V1         30.00             y
V3         15.00             n
IC(   1)   0.000              n
IC(   2)   0.000              n
IC(   3)   0.000              n
IC(   4)   0.000              n
IC(   5)   0.000              n
Sigma1     1.140              n
Sigma2     .6000E-01          n

Enter maximum number of iterations:       300

Do you want the iterations printed (Y/N)?  n

            ----- RESULTS -----

            --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1
```

Figure 7.20 (continue)

```
      Fitted Parameters
       K12        =   0.6000
       Vmax       =    30.00
       K30        =    1.000
       V1         =    30.00

     Negative Log Likelihood =  40.9242

             ---B. Iteration Summary---

     Convergence has been achieved.

     Number of iterations      =    39
     Number of function calls  =   199

      Fitted Parameters
       K12        =   0.2150
       Vmax       =    45.16
       K30        =    1.730
       V1         =    50.00

     Negative Log Likelihood = -.909939

             --- C. ML Estimation Summary---

 Tue Feb 12 13:04:29 2007

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk8.dat

 Model:  pk8.for - Example pk8 in ADAPT Users Guide

Convergence achieved
   Number of iterations:          39
   Number of function calls:     199
 Negative Log Likelihood:  -0.909939

  Output        R-squared    Sum of Squares
  Y( 1)          0.867          17.5046
  Y( 2)          0.935        0.376452E-01

  Model Selection Criteria
   AIC:          6.18012
   BIC:          11.3635

                Initial      Final
  Parameter      Value      Estimate    SE (CV%)    Confidence interval (95%)

  K12           0.6000      0.2150       18.08      [ 0.1346    ,  0.2955    ]
  Vmax           30.00       45.16       13.27      [  32.76    ,   57.56    ]
  K30            1.000       1.730       15.27      [  1.183    ,   2.277    ]
  V1             30.00       50.00       6.265      [  43.52    ,   56.48    ]
  K10           0.4000E-01  Not estimated
  K21           0.1000      Not estimated
  KM             10.00      Not estimated
```

Figure 7.20 (continue)

```
  K34           0.9000      Not estimated
  K43           0.4000      Not estimated
  K51            2.000      Not estimated
  V3             15.00      Not estimated
  IC(   1)       0.000      Not estimated
  IC(   2)       0.000      Not estimated
  IC(   3)       0.000      Not estimated
  IC(   4)       0.000      Not estimated
  IC(   5)       0.000      Not estimated
Sigma1          1.140      Not estimated
  Sigma2        0.6000E-01  Not estimated

  Correlation Matrix

           K12       VM        K30       V1
 K12         1.00
 Vmax       -0.62      1.00
 K30        -0.67      0.98      1.00
 V1         -0.86      0.39      0.40      1.00

  Covariance Matrix

           K12       VM        K30       V1
 K12       0.151E-02
 Vmax      -.144      35.9
 K30       -.689E-02  1.55      0.698E-01
 V1        -.104      7.35      0.332      9.81

            --- D.  ML Estimation Model Prediction and Data Summary ---

 Tue Feb 12 13:04:29 2007

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pk8.dat

 Model:  pk8.for - Example pk8 in ADAPT Users Guide

Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1      0.5000        9.663        9.268        0.3951        1.300
      2       1.000        17.67        17.36        0.3116        1.300
      3       2.000        12.55        13.28       -0.7313        1.300
      4       4.000        9.536        8.321         1.215        1.300
      5       6.000        8.100        5.800         2.300        1.300
      6       7.000        10.94        12.28        -1.343        1.300
      7       8.000        11.09        11.08        0.1452E-01    1.300
      8       10.00       -1.000        8.109       No Observation
      9       12.00        4.611        6.431        -1.820        1.300
     10       12.50        11.66        11.39        0.2657        1.300
     11       13.00        13.16        13.90       -0.7361        1.300
     12       14.00        13.67        12.18         1.493        1.300
     13       16.00        8.353        9.281       -0.9285        1.300
     14       18.00        8.716        7.652         1.064        1.300
```

Figure 7.20 (continue)

```
Y( 1) (Continued)                Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
                1       9.268       0.5093       0.3465
                2       17.36       0.8391       0.2733
                3       13.28       0.4010      -0.6415
                4       8.321       0.4329        1.066
                5       5.800       0.3985        2.017
                6       12.28       0.3613       -1.178
                7       11.08       0.3964       0.1274E-01
                8       8.109       0.4221       No Observation
                9       6.431       0.3437       -1.596
               10       11.39       0.3273       0.2331
               11       13.90       0.3996      -0.6457
               12       12.18       0.3815        1.310
               13       9.281       0.3968      -0.8145
               14       7.652       0.3385       0.9332

Y( 2)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1      0.5000       0.2038       0.2913       -0.8745E-01   0.3600E-02
      2       1.000       0.6202       0.5840        0.3619E-01   0.3600E-02
      3       2.000       0.8137       0.7451        0.6858E-01   0.3600E-02
      4       4.000       0.6881       0.7169       -0.2881E-01   0.3600E-02
      5       6.000       0.6293       0.6450       -0.1569E-01   0.3600E-02
      6       7.000       0.7987       0.8169       -0.1821E-01   0.3600E-02
      7       8.000       0.8339       0.8506       -0.1667E-01   0.3600E-02
      8       10.00       0.7633       0.7917       -0.2836E-01   0.3600E-02
      9       12.00       0.6394       0.7211       -0.8175E-01   0.3600E-02
     10       12.50       0.7446       0.7949       -0.5026E-01   0.3600E-02
     11       13.00       0.8540       0.8790       -0.2497E-01   0.3600E-02
     12       14.00       0.9928       0.9140        0.7883E-01   0.3600E-02
     13       16.00       0.9019       0.8560        0.4586E-01   0.3600E-02
     14       18.00       0.8510       0.7932        0.5783E-01   0.3600E-02

 Y( 2) (Continued)               Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
                1       0.2913       0.2549E-01   -1.458
                2       0.5840       0.3762E-01    0.6031
                3       0.7451       0.2832E-01     1.143
                4       0.7169       0.1827E-01   -0.4802
                5       0.6450       0.1743E-01   -0.2615
                6       0.8169       0.1883E-01   -0.3036
                7       0.8506       0.1832E-01   -0.2778
                8       0.7917       0.1884E-01   -0.4726
                9       0.7211       0.2086E-01    -1.362
               10       0.7949       0.1796E-01   -0.8377
               11       0.8790       0.1903E-01   -0.4162
               12       0.9140       0.2145E-01     1.314
               13       0.8560       0.2316E-01    0.7643
               14       0.7932       0.2529E-01    0.9639

      ----- PLOTTING OPTIONS -----  {Dialogue for plotting not shown}...
```

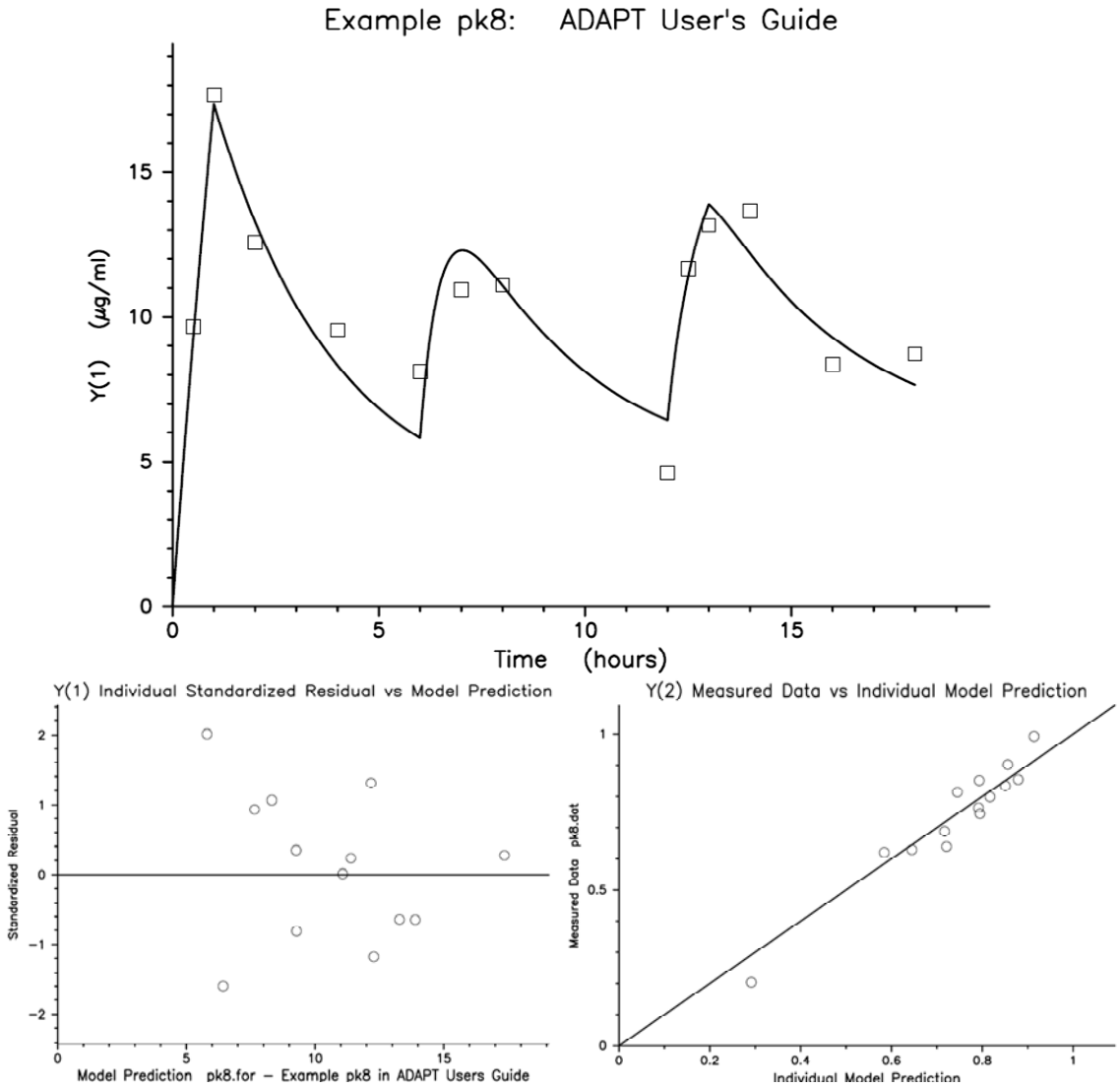


Figure 7.21a Example pk8. Resulting plot as stored in file pk8.eps.

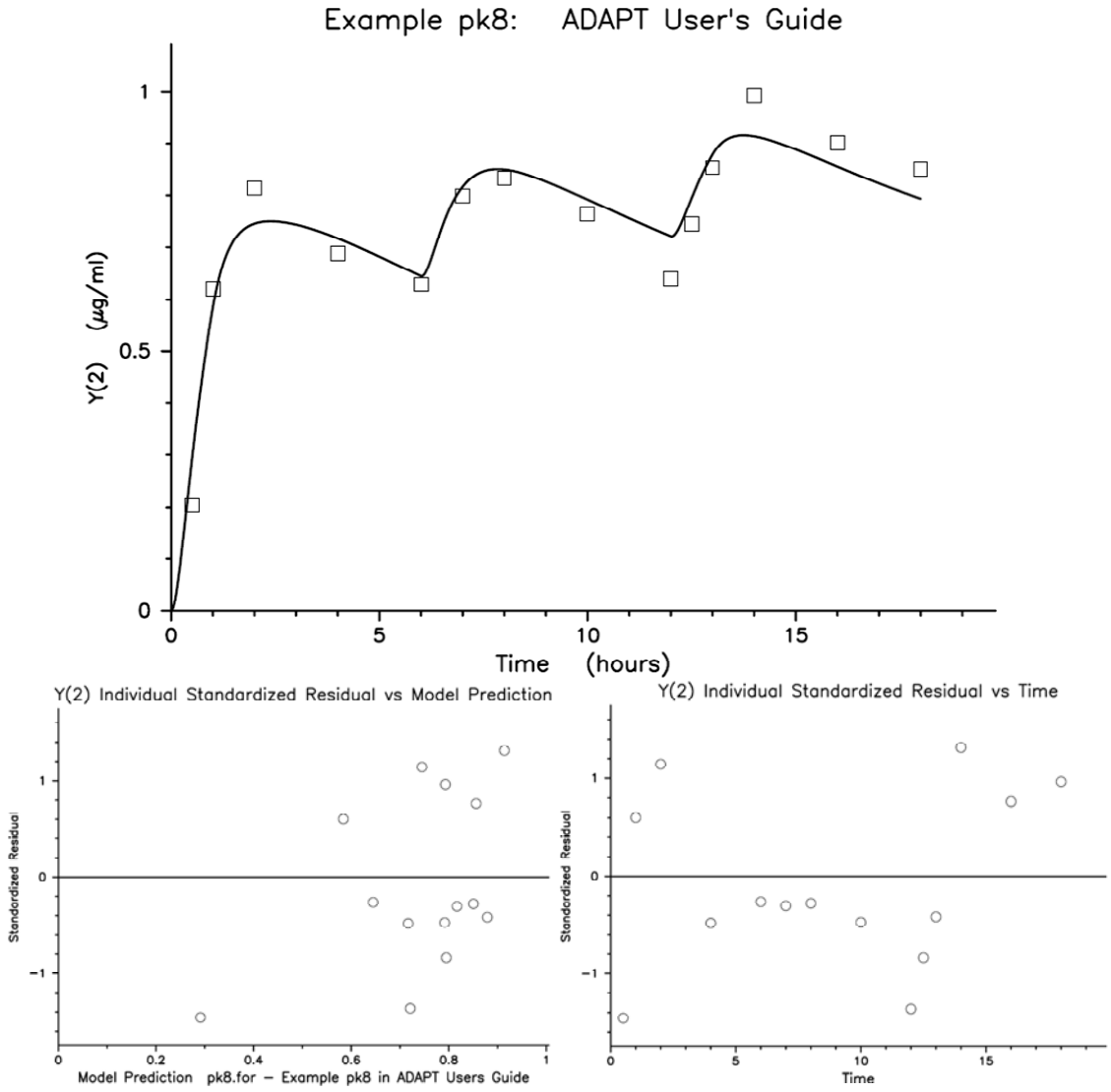


Figure 7.21b Example pk8. Resulting plot as stored in file pk8.eps.

CHAPTER 8

Some Pharmacokinetic/Pharmacodynamic Examples

This chapter illustrates the use of ADAPT with simultaneous pharmacokinetic/pharmacodynamic models. The first two examples presented are direct response models. In the first of these, the response is driven by plasma concentration, while in the second an effect compartment links plasma concentration to drug response. The third example implements an indirect response model. Consult the Model Library in Chapter 11 for other pharmacokinetic/pharmacodynamic examples.

8.1 Example pd1: ID – Direct Response Model

In this direct response model (see Figure 8.1) the pharmacokinetics of the drug are described by a linear two-compartment model (clearance parameterization) with intravenous drug administration. In the pharmacodynamic portion of the model, the drug's effect is related to its plasma concentration using a Hill-type model (*Emax* model). The following equations define the drug's plasma concentration and response, where $x_1(t)$ and $x_2(t)$ are compartment amounts, $y_1(t)$ is plasma concentration and $y_2(t)$ is drug response.

$$\frac{dx_1}{dt} = -\left(\frac{Clt}{V_C} + \frac{Cld}{V_C}\right)x_1(t) + \frac{Cld}{V_p}x_2(t) + r(t)$$
$$\frac{dx_2(t)}{dt} = \frac{Cld}{V_C}x_1(t) - \frac{Cld}{V_p}x_2(t)$$
$$y_1(t) = x_1(t)/V_C$$
$$y_2(t) = \frac{E_{max}y_1(t)}{EC_{50} + y_1(t)} \qquad (8.1)$$

These equations have been coded and entered in the Model File pd1.for along with linear variance models for each output and several secondary parameters.

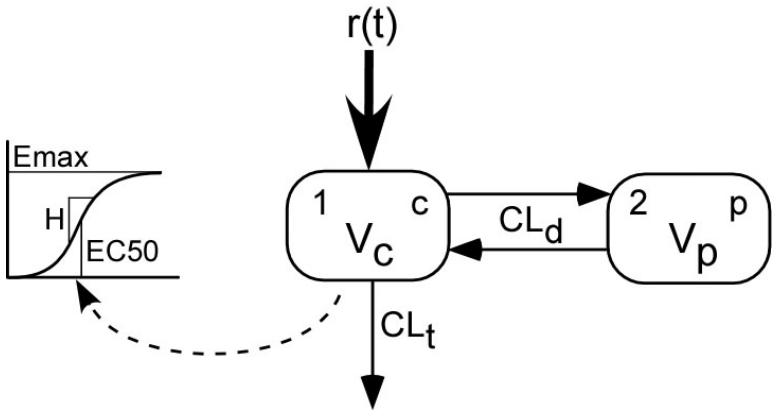


Figure 8.1 Model for Example pd1.

The data file pd1.dat contains dose regimen information along with measured values for both plasma concentration and drug response. Figure 8.2 shows a run of ID with the Model File pd1.for in which the maximum likelihood estimator is selected. Initial parameter values are read from the file pd1.prm. Also, files named pd1PLT.csv, pd1RSD.csv and pd1.aci are created as described in Chapter 6 and can be viewed in the \Example subfolder of the installation.

```
   ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Tue Sep  2 12:07:32 2008

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pd1.dat

      ----- MODEL INPUT INFORMATION -----

 Data file name (*.dat): pd1.dat

 The number of model inputs:     1

 The number of bolus inputs:    0

 The number of input event times:     2

     Input Event Information
           Time    Value for all Inputs
 Event     Units,       R(1)
    1.     0.000          100.0
    2.     1.000          0.000

      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   2

 The number of observations:   14
```

Figure 8.2 Example pd1. ML estimation results for a direct response model.

Figure 8.2 (continued)

```
    Observation Information
                Time     Measured Value For Each Output
Observation     Units ,     Y(1), ... ,Y(   2)
      1.         1.000       2.916       39.16
      2.         2.000       1.267       47.66
      3.         3.000      0.9619       69.25
      4.         4.000      0.9755       66.80
      5.         5.000      0.7909       39.29
      6.         6.000      0.5048       40.39
      7.         8.000      0.2741       38.79
      8.         10.00      0.3904       40.37
      9.         12.00      0.5752       30.37
     10.         16.00      0.2094       36.66
     11.         24.00      0.1885       18.78
     12.         30.00      0.1579       17.71
     13.         36.00      0.1219       12.74
     14.         48.00      0.4693E-01   8.041

     ----- ESTIMATOR SELECTION -----

The following estimation procedures are available:
     1. Weighted least squares (WLS)
     2. Maximum likelihood (ML)
     3. Generalized least squares (GLS)
     4. Maximum a posteriori probability (MAP)

Enter option number:  2

     ----- INITIALIZE ESTIMATION PROCEDURE -----

Parameter file name: pd1.prm

Enter initial values for parameters & specify those to be estimated:

           Old Value    New Value      Estimate?
                      (skip if same)    (Y/N)
CLt        6.000            y
Vc         30.00            y
CLd        12.00            y
Vp         60.00            y
Emax       100.0            y
EC50       25.00            y
IC(   1)   0.000              n
IC(   2)   0.000              n
SDinter1   .5000E-01         n
SDslope1   .1000              n
SDinter2   2.500              n
SDslope2   .1000              n

Enter maximum number of iterations:       500

Do you want the iterations printed (Y/N)?  n
```

Figure 8.2 (continued)

```
          ----- RESULTS -----

          --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      CLt         =    6.000
      Vc          =    30.00
      CLd         =    12.00
      Vp          =    60.00
      Emax        =    100.0
      EC50        =    25.00

    Negative Log Likelihood =  1262.13


           ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =   107
    Number of function calls  =   483

     Fitted Parameters
      CLt         =    6.328
      Vc          =    29.58
      CLd         =    10.34
      Vp          =    51.18
      Emax        =    68.77
      EC50        =   0.3415

    Negative Log Likelihood =  39.5548


          --- C. ML Estimation Summary---

 Tue Sep  2 12:07:32 2008

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pd1.dat

 Model:  pd1.for - Example pd1 in ADAPT Users Guide

 Convergence achieved
   Number of iterations:         107
   Number of function calls:     483
 Negative Log Likelihood:    39.5548

  Output        R-squared    Sum of Squares
  Y( 1)          0.950         0.366959
  Y( 2)          0.700          1298.82
```

Figure 8.2 (continued)

```
  Model Selection Criteria
   AIC:          91.1096
   BIC:          99.1028

                Initial      Final
  Parameter      Value      Estimate    SE (CV%)   Confidence interval (95%)

  CLt            6.000       6.328       7.749     [  5.311    ,   7.344    ]
  Vc             30.00       29.58       15.15     [  20.28    ,   38.87    ]
  CLd            12.00       10.34       21.62     [  5.702    ,   14.97    ]
  Vp             60.00       51.18       15.06     [  35.19    ,   67.17    ]
  Emax           100.0       68.77       12.15     [  51.44    ,   86.11    ]
  EC50           25.00      0.3415       33.86     [ 0.1017    ,  0.5812    ]
  IC(   1)       0.000      Not estimated
  IC(   2)       0.000      Not estimated

  SDinter1      0.5000E-01  Not estimated
  SDslope1      0.1000      Not estimated
  SDinter2       2.500      Not estimated
  SDslope2      0.1000      Not estimated

  Kel            0.2000      0.2139       15.59     [ 0.1448    ,  0.2831    ]
  V              30.00       29.58       15.15     [  20.28    ,   38.87    ]
  Kcp            0.4000      0.3495       30.59     [ 0.1278    ,  0.5713    ]
  Kpc            0.2000      0.2020       23.56     [ 0.1033    ,  0.3007    ]
  LAM1           0.7464      0.7041       23.03     [ 0.3678    ,   1.040    ]
  LAM2          0.5359E-01  0.6137E-01    15.27     [ 0.4194E-01,  0.8081E-01]
  t1/2-LAM1      0.9286      0.9845       23.03     [ 0.5143    ,   1.455    ]
  t1/2-LAM2       12.93       11.29       15.27     [  7.718    ,   14.87    ]

  Correlation Matrix

           CLt       Vc        CLd       Vp        Emax      EC50
CLt         1.00
 Vc          0.20      1.00
 CLd        -0.09     -0.36      1.00
 Vp         -0.39     -0.07      0.21      1.00
 Emax       -0.39      0.04      0.16      0.44      1.00
 EC50       -0.59      0.03      0.20      0.47      0.91      1.00


  Covariance Matrix

           CLt       Vc        CLd       Vp        Emax      EC50
CLt       0.240
 Vc        0.435      20.1
 CLd       -.103     -3.65      5.00
 Vp        -1.49     -2.41      3.68      59.4
 Emax      -1.60      1.60      2.97      28.2      69.9
 EC50     -.336E-01 0.173E-01 0.506E-01 0.416     0.875     0.134E-01

           --- D.  ML Estimation Model Prediction and Data Summary ---
```

Figure 8.2 (continued)

```
 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pd1.dat

 Model:  pd1.for - Example pd1 in ADAPT Users Guide

Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1       1.000        2.916        2.614        0.3019       0.9695E-01
      2       2.000        1.267        1.613       -0.3453       0.4463E-01
      3       3.000       0.9619        1.098       -0.1364       0.2555E-01
      4       4.000       0.9755       0.8262        0.1493       0.1759E-01
      5       5.000       0.7909       0.6747        0.1162       0.1380E-01
      6       6.000       0.5048       0.5840       -0.7912E-01   0.1175E-01
      7       8.000       0.2741       0.4806       -0.2065       0.9616E-02
      8       10.00       0.3904       0.4163       -0.2592E-01   0.8396E-02
      9       12.00       0.5752       0.3661        0.2091       0.7501E-02
     10       16.00       0.2094       0.2858       -0.7642E-01   0.6175E-02
     11       24.00       0.1885       0.1749        0.1363E-01   0.4555E-02
     12       30.00       0.1579       0.1210        0.3690E-01   0.3857E-02
     13       36.00       0.1219      0.8373E-01     0.3812E-01   0.3407E-02
     14       48.00      0.4693E-01   0.4009E-01     0.6841E-02   0.2917E-02

 Y( 1) (Continued)                  Std. Err.   Standardized
           Obs.Num.    Model Est.   Model Est.   Residual
                1        2.614       0.2846       0.9695
                2        1.613       0.1198       -1.635
                3        1.098      0.9313E-01    -0.8537
                4       0.8262      0.6775E-01     1.126
                5       0.6747      0.4987E-01    0.9893
                6       0.5840      0.4378E-01    -0.7300
                7       0.4806      0.4354E-01     -2.106
                8       0.4163      0.4098E-01    -0.2829
                9       0.3661      0.3672E-01     2.415
               10       0.2858      0.3013E-01    -0.9725
               11       0.1749      0.2519E-01    0.2019
               12       0.1210      0.2274E-01    0.5943
               13      0.8373E-01   0.1985E-01    0.6531
               14      0.4009E-01   0.1371E-01    0.1267

 Y( 2)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1       1.000        39.16        60.83        -21.67        73.66
      2       2.000        47.66        56.75        -9.098        66.84
      3       3.000        69.25        52.46         16.79        60.01
      4       4.000        66.80        48.66         18.14        54.26
      5       5.000        39.29        45.66        -6.373        49.93
      6       6.000        40.39        43.40        -3.010        46.78
      7       8.000        38.79        40.21        -1.413        42.52
      8       10.00        40.37        37.78         2.587        39.42
      9       12.00        30.37        35.58        -5.212        36.70
     10       16.00        36.66        31.33         5.323        31.74
     11       24.00        18.78        23.29        -4.516        23.32
     12       30.00        17.71        17.99       -0.2798        18.49
     13       36.00        12.74        13.54       -0.7996        14.86
     14       48.00        8.041        7.226        0.8154        10.39
```

Figure 8.2 (continued)

Y(2) (Continued)

Obs.Num.	Model Est.	Std. Err. Model Est.	Standardized Residual
1	60.83	5.338	-2.524
2	56.75	4.084	-1.113
3	52.46	3.152	2.167
4	48.66	2.611	2.463
5	45.66	2.332	-0.9018
6	43.40	2.254	-0.4401
7	40.21	2.342	-0.2167
8	37.78	2.381	0.4121
9	35.58	2.336	-0.8603
10	31.33	2.176	0.9450
11	23.29	1.977	-0.9352
12	17.99	1.947	-0.6508E-01
13	13.54	1.920	-0.2075
14	7.226	1.667	0.2530

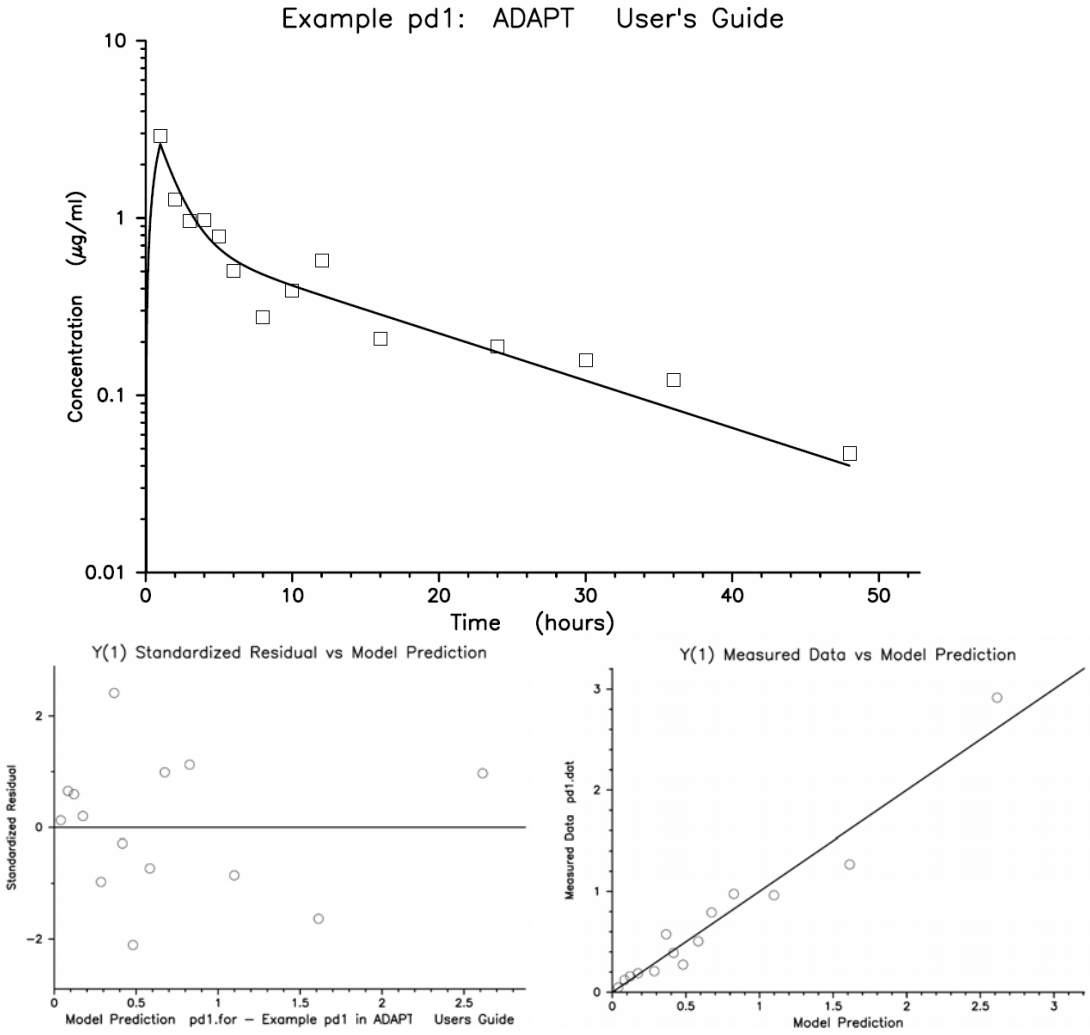


Figure 8.3a Example pd1. Resulting Plots as Stored in file pd1.eps.

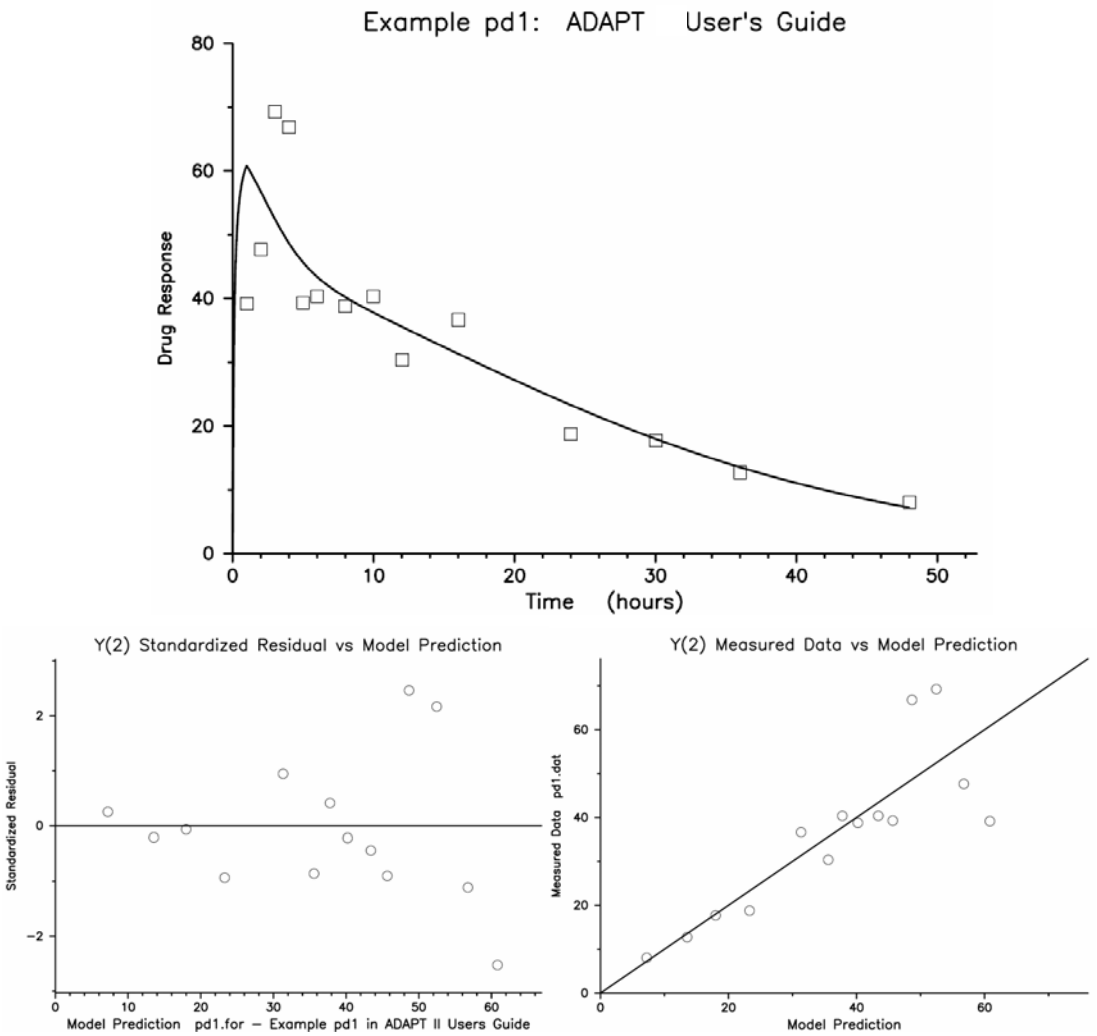


Figure 8.3b Example pd1. Resulting Plots as Stored in file pd1.eps.

8.2 Example pd2: ID – Direct Response/Effect Site Model

In this example an effect compartment is used to link the plasma concentration from the pharmacokinetic model to the Hill response model (see Figure 8.4). The following three differential and two output equations describe the model:

$$\frac{dx_1(t)}{dt} = -\left(\frac{Clt}{V_C} + \frac{Cld}{V_C}\right)x_1(t) + \frac{Cld}{V_P}x_2(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = \frac{Cld}{V_C}x_1(t) - \frac{Cld}{V_P}x_2(t)$$

$$\frac{dx_3(t)}{dt} = K_{eo}\left(x_1(t)/V_c - x_3(t)\right)$$

$$y_1(t) = x_1(t)/V_C$$
$$y_2(t) = \frac{E_{max} x_3(t)}{EC50 + x_3(t)} \qquad (8.2)$$

These equations have been coded and entered into the Model File pd2.for. The data file pd2.dat contains the same data as used for example pd1. Figure 8.5 shows a run of ID using the maximum likelihood estimator. Also, files named pd2PLT.csv, pd2RSD.csv and pd2.aci are created as described in Chapter 6 and can be viewed in the \Example subfolder of the installation.

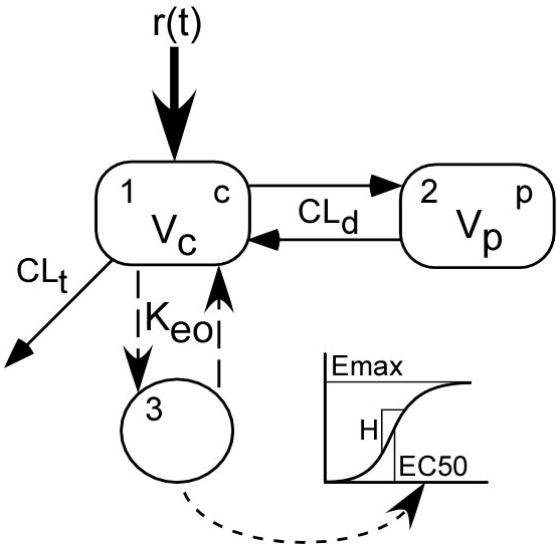


Figure 8.4 Model for Example pd2.

```
    ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Tue Sep  2 12:07:34 2008

Enter file name for storing session run (*.run): pd2.run

      ----- MODEL INPUT INFORMATION -----

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pd2.dat

 The number of model inputs:     1

 The number of bolus inputs:    0

 The number of input event times:     2

     Input Event Information
           Time    Value for all Inputs
 Event     Units,       R(1)
    1.     0.000          100.0
    2.     1.000          0.000
```

Figure 8.5 Example pd2. ML estimation results for an effect compartment model.

Figure 8.5 (continued)

```
     ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   2

 The number of observations:   14

    Observation Information
                Time     Measured Value For Each Output
 Observation    Units ,     Y(1), ... ,Y(   2)
      1.         1.000       2.916       39.16
      2.         2.000       1.267       47.66
      3.         3.000      0.9619       69.25
      4.         4.000      0.9755       66.80
      5.         5.000      0.7909       39.29
      6.         6.000      0.5048       40.39
      7.         8.000      0.2741       38.79
      8.         10.00      0.3904       40.37
      9.         12.00      0.5752       30.37
     10.         16.00      0.2094       36.66
     11.         24.00      0.1885       18.78
     12.         30.00      0.1579       17.71
     13.         36.00      0.1219       12.74
     14.         48.00     0.4693E-01    8.041

     ----- ESTIMATOR SELECTION -----

 The following estimation procedures are available:
     1. Weighted least squares (WLS)
     2. Maximum likelihood (ML)
     3. Generalized least squares (GLS)
     4. Maximum a posteriori probability (MAP)

 Enter option number:  2

     ----- INITIALIZE ESTIMATION PROCEDURE -----

 Parameter file name: pd2.prm

 Enter initial values for parameters & specify those to be estimated:

            Old Value    New Value      Estimate?
                       (skip if same)    (Y/N)
 CLt        6.000            y
 Vc         30.00            y
 CLd        12.00            y
 Vp         60.00            y
 Emax       100.0            y
 EC50       25.00            y
 Keo        .5000            y
 IC(   1)   0.000            n
 IC(   2)   0.000            n
 IC(   3)   0.000            n
 SDinter1   .5000E-01        n
 SDslope1   .1000            n
```

Figure 8.5 (continued)

```
SDinter2   2.500            n
SDslope2   .1000            n

Enter maximum number of iterations:       999

Do you want the iterations printed (Y/N)?  n

            ----- RESULTS -----

            --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      CLt         =    6.000
      Vc          =    30.00
      CLd         =    12.00
      Vp          =    60.00
      Emax        =    100.0
      EC50        =    25.00
      Keo         =   0.5000

    Negative Log Likelihood =  1259.85

             ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =   169
    Number of function calls  =   765

     Fitted Parameters
      CLt         =    5.812
      Vc          =    27.94
      CLd         =    12.39
      Vp          =    60.93
      Emax        =    100.9
      EC50        =   0.8940
      Keo         =   0.4786

    Negative Log Likelihood =  34.1450

            --- C. ML Estimation Summary---

Tue Sep  2 12:07:35 2008

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pd2.dat

Model:  pd2.for - Example pd2 in ADAPT Users Guide

Convergence achieved
  Number of iterations:         169
  Number of function calls:     765
```

Figure 8.5 (continued)

```
  Output        R-squared    Sum of Squares
  Y( 1)          0.960          0.304445
  Y( 2)          0.844           664.101

  Model Selection Criteria
   AIC:          82.2900
   BIC:          91.6155

                Initial      Final
  Parameter      Value      Estimate    SE (CV%)   Confidence interval (95%)

  CLt            6.000       5.812       8.479     [  4.787    ,   6.837    ]
  Vc             30.00       27.94       15.87     [  18.72    ,   37.16    ]
  CLd            12.00       12.39       19.39     [  7.395    ,   17.39    ]
  Vp             60.00       60.93       14.64     [  42.37    ,   79.49    ]
  Emax           100.0       100.9       29.89     [  38.17    ,   163.7    ]
  EC50           25.00      0.8940       52.08     [-0.7453E-01,   1.862    ]
  Keo           0.5000      0.4786       29.95     [ 0.1805    ,  0.7766    ]
  IC(   1)       0.000      Not estimated
  IC(   2)       0.000      Not estimated
  IC(   3)       0.000      Not estimated

  SDinter1      0.5000E-01  Not estimated
  SDslope1      0.1000      Not estimated
  SDinter2       2.500      Not estimated
  SDslope2      0.1000      Not estimated

  Kel           0.2000      0.2080       16.46     [ 0.1368    ,  0.2792    ]
  V              30.00       27.94       15.87     [  18.72    ,   37.16    ]
  Kcp           0.4000      0.4436       28.64     [ 0.1794    ,  0.7079    ]
  Kpc           0.2000      0.2034       22.38     [ 0.1087    ,  0.2981    ]
  LAM1          0.7464      0.8023       22.41     [ 0.4283    ,   1.176    ]
  LAM2          0.5359E-01  0.5274E-01   15.99     [ 0.3520E-01,  0.7027E-01]
  t1/2-LAM1     0.9286      0.8639       22.41     [ 0.4612    ,   1.267    ]
  t1/2-LAM2      12.93       13.14       15.99     [  8.773    ,   17.51    ]

  Correlation Matrix

           CLt       Vc        CLd       Vp        Emax      EC50
           Keo
CLt         1.00
 Vc          0.20      1.00
 CLd        -0.07     -0.31      1.00
 Vp         -0.46     -0.08      0.16      1.00
 Emax       -0.44     -0.08      0.29      0.45      1.00
 EC50       -0.52     -0.11      0.29      0.44      0.98      1.00
 Keo         0.08      0.36     -0.04     -0.23     -0.44     -0.40
             1.00
```

Figure 8.5 (continued)

```
  Covariance Matrix

           CLt       Vc        CLd       Vp        Emax      EC50
           Keo
CLt       0.243
 Vc        0.428      19.7
 CLd       -.833E-01 -3.33      5.78
 Vp        -2.03     -3.36      3.38      79.6
 Emax      -6.49     -10.3      20.9      120.      910.
 EC50      -.120     -.233     0.322      1.81      13.8     0.217
 Keo       0.549E-02 0.229     -.131E-01 -.288     -1.89     -.269E-01
           0.205E-01

            --- D.  ML Estimation Model Prediction and Data Summary ---

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pd2.dat

 Model:  pd2.for - Example pd2 in ADAPT Users Guide

 Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1       1.000        2.916        2.667        0.2482       0.1003
      2       2.000        1.267        1.546       -0.2791       0.4188E-01
      3       3.000       0.9619        1.026       -0.6393E-01   0.2328E-01
      4       4.000       0.9755       0.7754        0.2000       0.1627E-01
      5       5.000       0.7909       0.6469        0.1440       0.1315E-01
      6       6.000       0.5048       0.5740       -0.6913E-01   0.1153E-01
      7       8.000       0.2741       0.4916       -0.2175       0.9833E-02
      8       10.00       0.3904       0.4374       -0.4702E-01   0.8787E-02
      9       12.00       0.5752       0.3926        0.1826       0.7968E-02
     10       16.00       0.2094       0.3177       -0.1084       0.6687E-02
     11       24.00       0.1885       0.2084       -0.1985E-01   0.5018E-02
     12       30.00       0.1579       0.1518        0.6074E-02   0.4249E-02
     13       36.00       0.1219       0.1107        0.1120E-01   0.3729E-02
     14       48.00       0.4693E-01   0.5876E-01   -0.1183E-01   0.3122E-02

 Y( 1) (Continued)                Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
                1       2.667       0.2952       0.7837
                2       1.546       0.1230       -1.364
                3       1.026       0.9342E-01  -0.4190
                4      0.7754       0.6379E-01    1.568
                5      0.6469       0.4760E-01    1.255
                6      0.5740       0.4423E-01  -0.6437
                7      0.4916       0.4390E-01   -2.193
                8      0.4374       0.4024E-01  -0.5016
                9      0.3926       0.3589E-01    2.046
               10      0.3177       0.3019E-01   -1.325
               11      0.2084       0.2709E-01  -0.2802
               12      0.1518       0.2576E-01   0.9318E-01
               13      0.1107       0.2368E-01   0.1835
               14      0.5876E-01   0.1813E-01  -0.2118
```

Figure 8.5 (continued)

```
Y( 2)
  Obs.Num.    Time         Data       Model Est.     Residual     Variance
      1        1.000         39.16        40.44        -1.281        42.83
      2        2.000         47.66        56.30        -8.643        66.09
      3        3.000         69.25        57.17         12.08        67.52
      4        4.000         66.80        54.68         12.12        63.49
      5        5.000         39.29        51.22        -11.93        58.09
      6        6.000         40.39        47.69        -7.301        52.83
      7        8.000         38.79        41.69        -2.901        44.48
      8        10.00         40.37        37.32         3.051        38.84
      9        12.00         30.37        34.02        -3.651        34.84
     10        16.00         36.66        28.93         7.732        29.08
     11        24.00         18.78        20.95        -2.177        21.12
     12        30.00         17.71        16.18         1.537        16.96
     13        36.00         12.74        12.33        0.4179        13.93
     14        48.00         8.041        6.943         1.098        10.20

 Y( 2) (Continued)                 Std. Err.   Standardized
           Obs.Num.    Model Est.   Model Est.   Residual
                1        40.44        5.786      -0.1957
                2        56.30        4.414       -1.063
                3        57.17        4.150        1.470
                4        54.68        3.619        1.521
                5        51.22        3.182       -1.565
                6        47.69        2.954       -1.004
                7        41.69        2.801      -0.4349
                8        37.32        2.678       0.4896
                9        34.02        2.526      -0.6186
               10        28.93        2.236        1.434
               11        20.95        1.928      -0.4737
               12        16.18        1.849       0.3732
               13        12.33        1.782       0.1120
               14        6.943        1.534       0.3438

      ----- PLOTTING OPTIONS -----

 Do you want to plot with options (Y/N)?  y

 ...{Dialogue for plotting options not shown} ...

      ____________________________________________

      ----- RE-ESTIMATION OPTIONS -----

     1. Change initial parameter values
     2. Select a different estimator
     3. Exit ID

 Enter option:  3

      ____________________________________________

    ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Tue Sep  2 12:07:35 2008
```

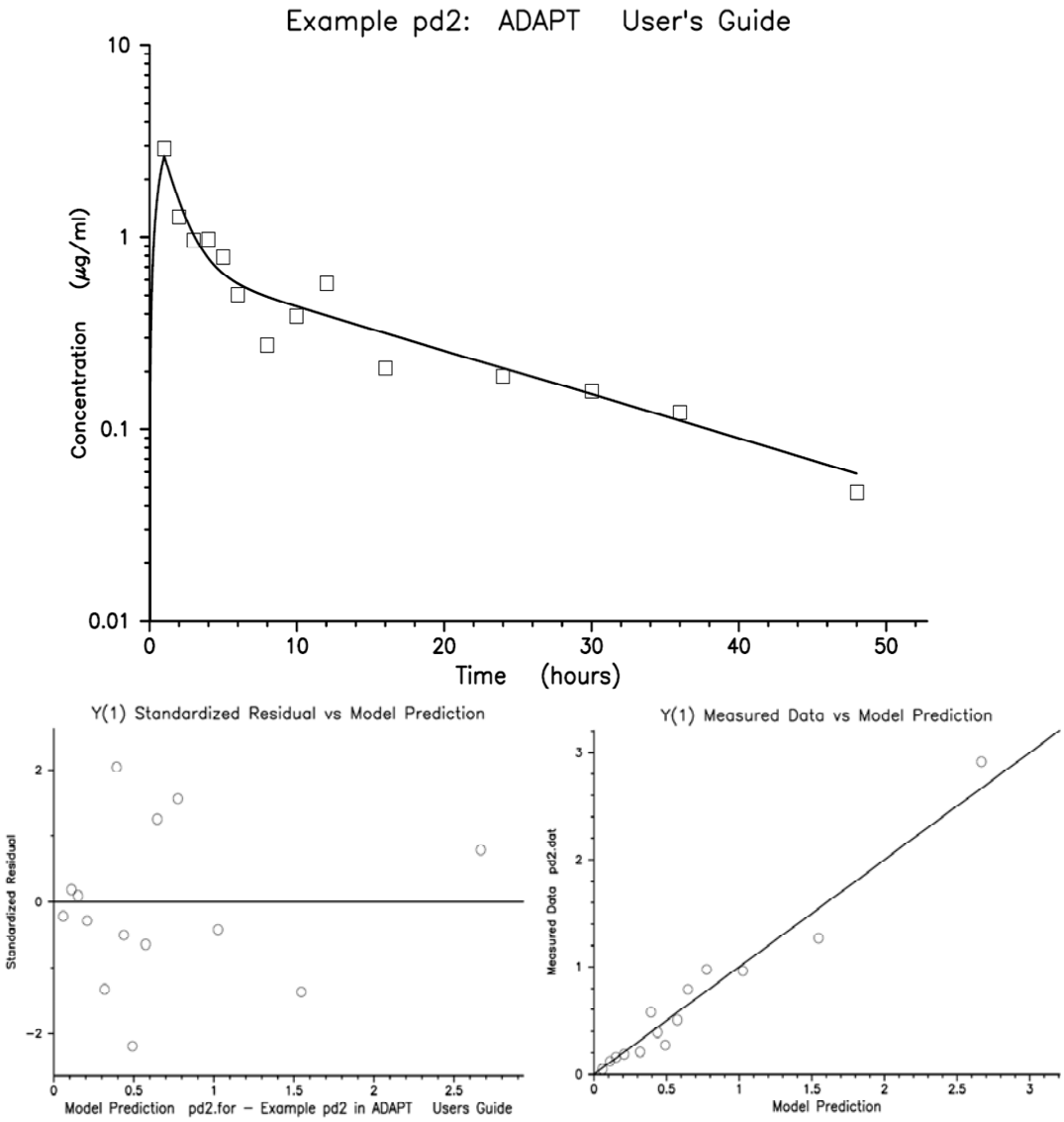


Figure 8.6a Example pd2. Resulting Plots as Stored in file pd2.eps.

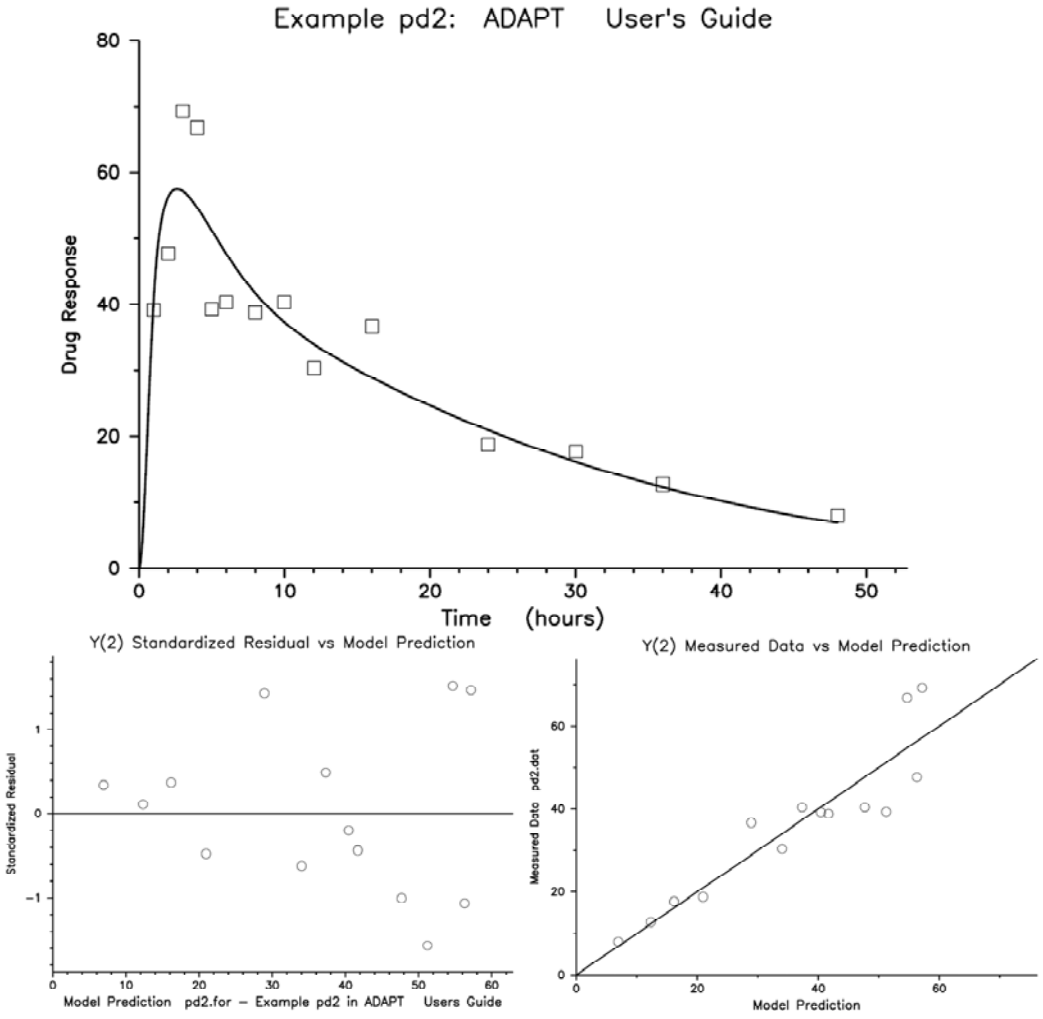


Figure 8.6b Example pd2. Resulting Plots as Stored in file pd2.eps.

8.3 Example pd3: ID – Indirect Response Model

In this example an indirect response model is used to describe drug response, together with a linear two compartment model for the drug's pharmacokinetics (see Figure 8.7). The model differential and output equations are given below.

$$\frac{dx_1}{dt} = -\left(\frac{Clt}{V_C} + \frac{Cld}{V_C}\right)x_1(t) + \frac{Cld}{V_P}x_2(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = \frac{Cld}{V_C}x_1(t) - \frac{Cld}{V_P}x_2(t)$$

$$\frac{dx_3(t)}{dt} = Kin\left(1 - \frac{x_1(t)/V_C}{IC50 + x_1(t)/V_C}\right) - \frac{Kin}{IC(3)}x_3(t)$$
$$y_1(t) = x_1(t)/V$$
$$y_2(t) = x_3(t) \qquad (8.3)$$

To insure a return to the pre-drug control value of the drug response variable after the drug is cleared completely, *Kout* is replaced by $Kin/IC(3)$ in the above equations. Figure 8.8a is an excerpt from the Model File pd3.for showing the coding of the model differential equations.

This example also involves measurements that exceed the limits of quantitation (BQL for plasma concentration $y_1(t)$ and AQL for response $y_2(t)$. Figure 8.8b also shows an excerpt from subroutine VARMOD were both the lower limit of quantitation and upper limit of quantitation are defined for the respective outputs. The data file indicates those measurements that exceed the quantitation limits as described in Chapter 6 (see also data tables in the program run below).

Figures 8.9 and 8.10 show the run of ID. Also, files named pd3PLT.csv, pd3RSD.csv and pd3.aci are created as described in Chapter 8 and can be viewed in the \Example.

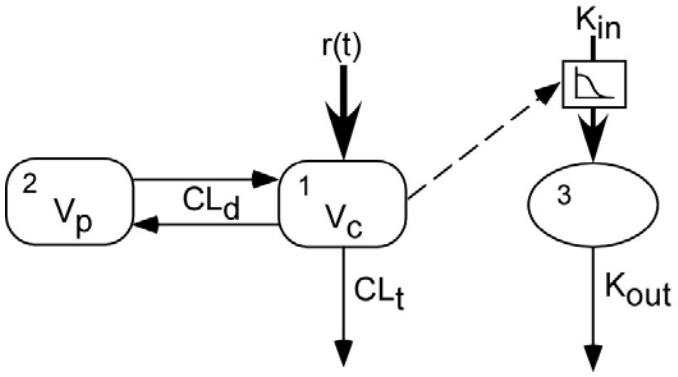


Figure 7.8 Model for Example pd3.

```
C-----------------------------------------------------------------------C
C 1. Enter Differential Equations Below {e.g. XP(1) = -P(1)*X(1) }     C
C----c------------------------------------------------------------------C

       XP(1) = -(P(1)+P(3))/P(2)*X(1) + P(3)/P(4)*X(2) + R(1)
       XP(2) = P(3)/P(2)*X(1) - P(3)/P(4)*X(2)
       XP(3) = P(5)*(1 - X(1)/P(2)/(P(6)+X(1)/P(2)))
      x                  - P(5)/IC(3)*X(3)

C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
```

Figure 8.8a Excerpt from Model File pd3 showing coding of the differential equations.

```
C-----------------------------------------------------------------------C
C       Enter Variance Model Equations Below                            C
C        {e.g. V(1) = (PV(1) + PV(2)*Y(1))**2 }                         C
C----c------------------------------------------------------------------C

        V(1) = (PV(1) + PV(2)*Y(1))**2
        V(2) = (PV(3) + PV(4)*Y(3))**2

        LLQ(1) = 0.10  ! LLQ for Plasma - Output Y(1)
        ULQ(2) = 90.0  ! ULQ for PD Response - Output Y(2)

C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
```

Figure 8.8b Excerpt from Model File pd3 showing the specification of the quantitation limits in routine VARMOD.

```
   ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Tue Sep  2 12:07:37 2008

 Enter file name for storing session run (*.run): pd3.run

      ----- MODEL INPUT INFORMATION -----

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pd3.dat

 The number of model inputs:     1

 The number of bolus inputs:    0

 The number of input event times:     2

     Input Event Information
           Time    Value for all Inputs
 Event     Units,       R(1)
    1.     0.000          100.0
    2.     1.000          0.000

      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   2

 The number of observations:   14

     Observation Information
                 Time     Measured Value For Each Output
 Observation     Units ,     Y(1), ... ,Y(   2)
       1.         1.000       2.853       84.43
       2.         2.000       1.332       63.86
       3.         3.000      0.9849       80.31
       4.         4.000      0.8997       75.07
       5.         5.000      0.7282       40.99
```

Figure 8.9 Example pd3. ML estimation for an indirect response model.

Figure 8.9 (continued)

```
       6.         6.000      0.5349       44.28
       7.         8.000      0.3797       47.98
       8.         10.00      0.4094       57.04
       9.         12.00      0.4649       46.94
      10.         16.00      0.2699       70.62
      11.         24.00      0.1967       60.60
      12.         30.00      0.1479       75.75
      13.         36.00      0.1080       79.13
      14.         48.00      L            H

      ----- ESTIMATOR SELECTION -----

 The following estimation procedures are available:
      1. Weighted least squares (WLS)
      2. Maximum likelihood (ML)
      3. Generalized least squares (GLS)
      4. Maximum a posteriori probability (MAP)

Enter option number:  2

     ----- INITIALIZE ESTIMATION PROCEDURE -----

 Parameter file name: pd3.prm

 Enter initial values for parameters & specify those to be estimated:

            Old Value    New Value      Estimate?
                        (skip if same)    (Y/N)
 CLt        6.000            y
 Vc         30.00            y
 CLd        12.00            y
 Vp         60.00            y
 Kin        20.00            y
 IC50       .5000            y
 IC(   1)   0.000            n
 IC(   2)   0.000            n
 IC(   3)   100.0            y
 SDinter1   0.000            n
 SDslope1   .1000            n
 SDinter2   10.00            n
 SDslope2   0.000            n

 Enter maximum number of iterations:       999

 Do you want the iterations printed (Y/N)?  n
```

Figure 8.9 (continued)

```
            ----- RESULTS -----

            --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      CLt         =    6.000
      Vc          =    30.00
      CLd         =    12.00
      Vp          =    60.00
      Kin         =    20.00
      IC50        =   0.5000
      IC( 3)      =    100.0

    Negative Log Likelihood =  30.9948

             ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =    36
    Number of function calls  =   234
     Fitted Parameters
      CLt         =    5.942
      Vc          =    28.94
      CLd         =    11.56
      Vp          =    59.35
      Kin         =    25.19
      IC50        =   0.4540
      IC( 3)      =    105.4

    Negative Log Likelihood =  30.4740

            --- C. ML Estimation Summary---

 Tue Sep  2 12:07:37 2008

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pd3.dat

 Model:  pd3.for - Example pd3 in ADAPT Users Guide

 Convergence achieved
   Number of iterations:          36
   Number of function calls:     234
 Negative Log Likelihood:    30.4740

  Output        R-squared    Sum of Squares
  Y( 1)          0.978         0.151697
  Y( 2)          0.561          1225.96

  Model Selection Criteria
   AIC:          74.9479
   BIC:          83.7546
```

Figure 8.9 (continued)

Parameter	Initial Value	Final Estimate	SE (CV%)	Confidence interval (95%)
CLt	6.000	5.942	3.169	[5.548 , 6.337]
Vc	30.00	28.94	12.22	[21.53 , 36.34]
CLd	12.00	11.56	12.47	[8.541 , 14.57]
Vp	60.00	59.35	7.159	[50.46 , 68.25]
Kin	20.00	25.19	30.06	[9.341 , 41.04]
IC50	0.5000	0.4540	33.42	[0.1364 , 0.7716]
IC(3)	100.0	105.4	10.86	[81.41 , 129.3]
IC(1)	0.000	Not estimated		
IC(2)	0.000	Not estimated		
SDinter1	0.000	Not estimated		
SDslope1	0.1000	Not estimated		
SDinter2	10.00	Not estimated		
SDslope2	0.000	Not estimated		
Kel	0.2000	0.2054	11.32	[0.1567 , 0.2540]
V	30.00	28.94	12.22	[21.53 , 36.34]
Kcp	0.4000	0.3994	19.25	[0.2385 , 0.5602]
Kpc	0.2000	0.1947	13.17	[0.1410 , 0.2484]
LAM1	0.7464	0.7458	14.95	[0.5125 , 0.9791]
LAM2	0.5359E-01	0.5361E-01	6.930	[0.4584E-01, 0.6139E-01]
t1/2-LAM1	0.9286	0.9294	14.95	[0.6386 , 1.220]
t1/2-LAM2	12.93	12.93	6.930	[11.05 , 14.80]
Kout	0.2000	0.2391	22.48	[0.1266 , 0.3516]

Correlation Matrix

	CLt	Vc	CLd	Vp	Kin	IC50	IC(3)
CLt	1.00						
Vc	0.41	1.00					
CLd	0.26	-0.22	1.00				
Vp	-0.09	-0.08	0.19	1.00			
Kin	-0.04	0.00	0.07	0.10	1.00		
IC50	-0.02	0.03	0.01	-0.11	-0.53	1.00	
IC(3)	-0.05	-0.04	0.02	0.09	0.79	-0.86	1.00

Covariance Matrix

	CLt	Vc	CLd	Vp	Kin	IC50	IC(3)
CLt	0.355E-01						
Vc	0.270	12.5					
CLd	0.699E-01	-1.10	2.08				
Vp	-.686E-01	-1.22	1.14	18.1			
Kin	-.514E-01	-.627E-01	0.781	3.25	57.3		
IC50	-.666E-03	0.137E-01	0.124E-02	-.687E-01	-.614	0.230E-01	
IC(3)	-.103	-1.55	0.341	4.54	68.5	-1.49	131.

Figure 8.9 (continued)

```
            --- D.  ML Estimation Model Prediction and Data Summary ---

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pd3.dat

 Model:  pd3.for - Example pd3 in ADAPT Users Guide

Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1       1.000        2.853        2.625        0.2284       0.6891E-01
      2       2.000        1.332        1.570       -0.2383       0.2465E-01
      3       3.000       0.9849        1.052       -0.6749E-01   0.1108E-01
      4       4.000       0.8997       0.7909        0.1088       0.6256E-02
      5       5.000       0.7282       0.6516        0.7659E-01   0.4246E-02
      6       6.000       0.5349       0.5711       -0.3629E-01   0.3262E-02
      7       8.000       0.3797       0.4817       -0.1020       0.2321E-02
      8       10.00       0.4094       0.4257       -0.1624E-01   0.1812E-02
      9       12.00       0.4649       0.3808        0.8410E-01   0.1450E-02
     10       16.00       0.2699       0.3069       -0.3704E-01   0.9420E-03
     11       24.00       0.1967       0.1999       -0.3165E-02   0.3994E-03
     12       30.00       0.1479       0.1449        0.3003E-02   0.2099E-03
     13       36.00       0.1080       0.1050        0.2991E-02   0.1103E-03
     14       48.00          L         0.5520E-01   BQL Observation

Y( 1) (Continued)                  Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
                1       2.625       0.2355       0.8702
                2       1.570       0.8774E-01   -1.518
                3       1.052       0.6157E-01  -0.6413
                4      0.7909       0.4278E-01    1.376
                5      0.6516       0.2914E-01    1.175
                6      0.5711       0.2350E-01  -0.6354
                7      0.4817       0.2217E-01   -2.118
                8      0.4257       0.2025E-01  -0.3815
                9      0.3808       0.1726E-01    2.209
               10      0.3069       0.1209E-01   -1.207
               11      0.1999       0.8225E-02  -0.1584
               12      0.1449       0.7876E-02   0.2073
               13      0.1050       0.7581E-02   0.2848
               14     0.5520E-01    0.6221E-02   BQL Observation
```

Figure 8.9 (continued)

```
Y( 2)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1       1.000        84.43        89.54        -5.108        100.0
      2       2.000        63.86        74.68        -10.82        100.0
      3       3.000        80.31        64.74         15.57        100.0
      4       4.000        75.07        58.49         16.58        100.0
      5       5.000        40.99        54.79        -13.80        100.0
      6       6.000        44.28        52.73        -8.455        100.0
      7       8.000        47.98        51.41        -3.429        100.0
      8       10.00        57.04        51.98         5.061        100.0
      9       12.00        46.94        53.50        -6.552        100.0
     10       16.00        70.62        57.83         12.79        100.0
     11       24.00        60.60        67.91        -7.311        100.0
     12       30.00        75.75        75.12        0.6296        100.0
     13       36.00        79.13        81.47        -2.346        100.0
     14       48.00          H          91.21       AQL Observation

 Y( 2) (Continued)                 Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
               1        89.54        7.153       -0.5108
               2        74.68        5.125        -1.082
               3        64.74        4.665         1.557
               4        58.49        4.549         1.658
               5        54.79        4.393        -1.380
               6        52.73        4.201       -0.8455
               7        51.41        3.959       -0.3429
               8        51.98        3.999        0.5061
               9        53.50        4.170       -0.6552
              10        57.83        4.460         1.279
              11        67.91        4.636       -0.7311
              12        75.12        4.903        0.6296E-01
              13        81.47        5.503       -0.2346
              14        91.21        7.241        AQL Observation


      ----- PLOTTING OPTIONS -----

 Do you want to plot with options (Y/N)?  y

...{Dialogue for plotting options not shown} ...
```

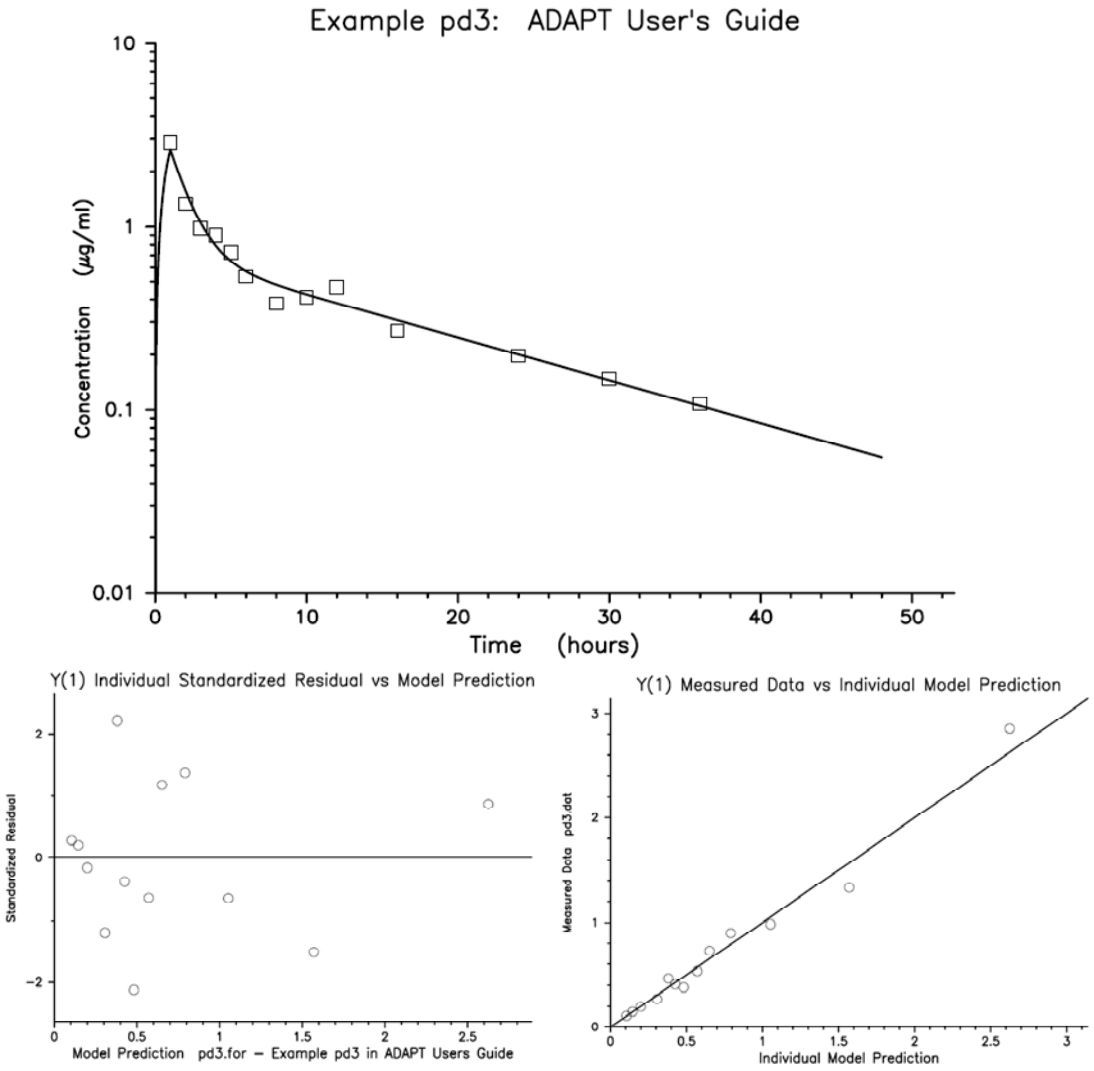


Figure 8.10a Example pd3. Resulting Plots as Stored in file pd3.eps.

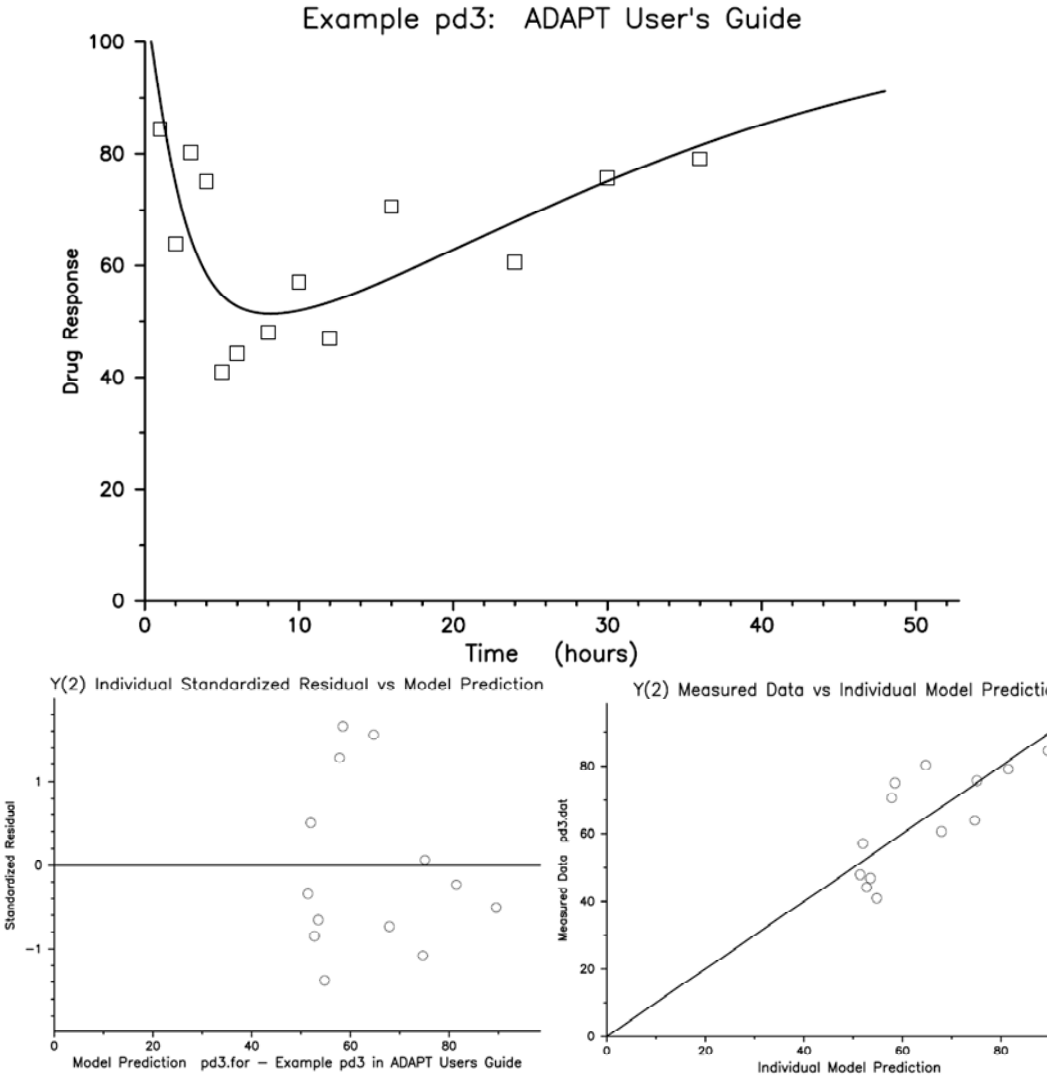


Figure 8.10b Example pd3. Resulting Plots as Stored in file pd3.eps.

CHAPTER 9

Some Other Examples

9.1 Example ivoral: NPD – Bioavailability Crossover Study

This example illustrates the use of the NPD program to model data from a single subject bioavailability crossover study. Drug disposition is described by a two-compartment linear model with oral administration modeled as a delayed first-order absorption process. It is assumed that plasma drug concentration measurements have been obtained following both oral drug administration and intravenous drug administration in a single individual. Both sets of data will be used to simultaneously estimate all model parameters. It is further assumed that the disposition kinetics are the same for the two routes of administration.

Figure 9.1 shows the composite model used to describe the plasma concentration for both routes of administration. In the data file shown in Table 9.1, the data from the IV administration is provided first (first individual) while the data from the oral administration is second (second individual). An excerpt from the model file for this example shows how Subroutine OUTPUT is

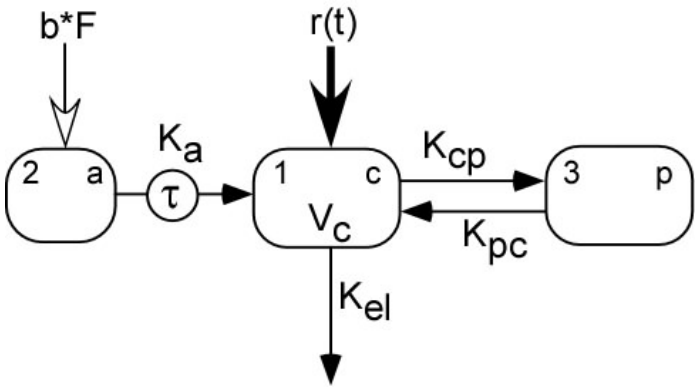


Figure 9.1 Model for example ivoral.

coded to define the output for each of the two individual data sets in the data file (see in Figure 9.2). As described in Chapter 6, the variable `SubjInd` indicates the number of the individual data set within the data file that is under analysis. Figures 9.3 and 9.4 show a complete run of the NPD program for this example. Also, files named oralivPLT.csv, oralivRSD.csv and oraliv.aci are created as described in Chapter 6 and can be viewed in the `\Example` subfolder of the installation.

Table 9.1 Portion of Data File ivoral.dat

IVData
1
1
2
0.0 100.0 0.0
1.0 0.0 0.0
1
12
0.0 0.0
0.50 3.21
• •
• •
• •
24.0 0.697

OralData
1
1
1
0.0 0.0 100.0
1
12
0.0 0.0
0.50 0.0
• •
• •
• •
24.0 0.636

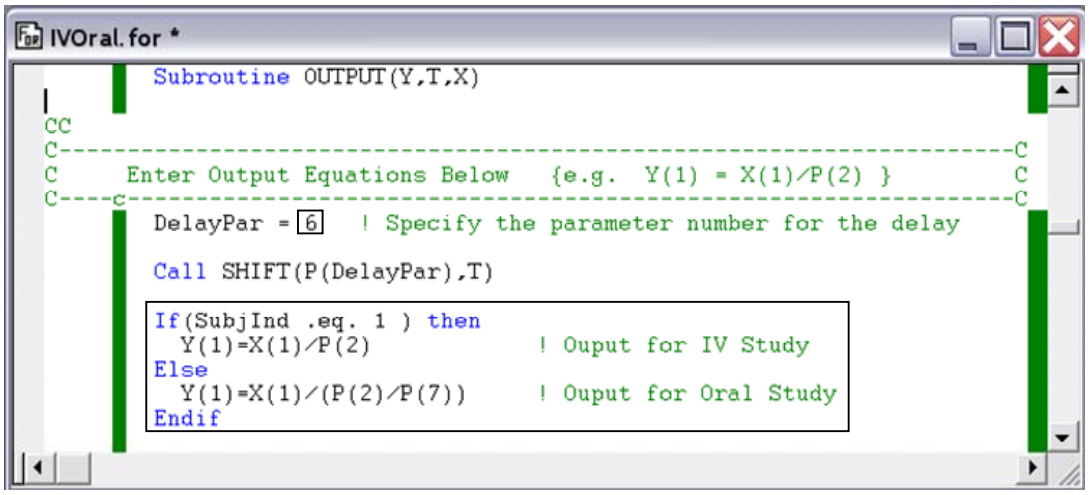


Figure 9.2 Excerpt from Subroutine OUPUT of model file ivoral.for. The code `P(2)` represents V, while `P(7)` represents the model parameter F (see complete model file). The code entered by the user is indicated. This model file was created by editing the modellag.for file stored in the ADAPT Library folder via the edit option in the ADAPT interface Model Menu.

```
 ADAPT 5  NPD -- NAIVE POOLED DATA POP. EST.  Fri Jan  2 12:09:11 2009

Enter file name for storing session run (*.run): IVOral.run

     ----- MODEL INPUT/OUTPUT INFORMATION -----

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\IVOral.dat

   - Successfully read all    2 subjects in the data file.

Enter the compartment number for each bolus input (e.g. 1,3,...):    2

     ----- ESTIMATOR SELECTION -----

The following estimation procedures are available:
     1. Weighted least squares (WLS)
     2. Maximum likelihood (ML)
     3. Maximum a posteriori probability (MAP)

Enter option number:  2

    ----- INITIALIZE ESTIMATION PROCEDURE -----

Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\IVOral.prm

Enter initial values for parameters & specify those to be estimated:

           Old Value    New Value      Estimate?
                      (skip if same)    (Y/N)
Kel        .2000            y
Vc         10.00            y
Ka         1.000            y
Kcp        1.000            y
Kpc        .5000            y
Tau        1.000            y
F          .8000            y
IC(   1)   0.000            n
IC(   2)   0.000            n
IC(   3)   0.000            n
SDinter1   .1000            n
SDslope1   .1000            n

Enter maximum number of iterations:       999

Do you want the iterations printed (Y/N)?  n

            ----- RESULTS -----

            --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1
```

Figure 9.3 NPD run for example ivoral.

Figure 8.3 (continued)

```
     Fitted Parameters
      Kel        =   0.2000
      Vc         =    10.00
      Ka         =    1.000
      Kcp        =    1.000
      Kpc        =   0.5000
      Tau        =    1.000
      F          =   0.8000

    Negative Log Likelihood =  2.40611

             ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =    91
    Number of function calls  =   485

     Fitted Parameters
      Kel        =   0.1883
      Vc         =    10.41
      Ka         =   0.9660
      Kcp        =   0.9392
      Kpc        =   0.4808
      Tau        =   0.9960
      F          =   0.7845

    Negative Log Likelihood =  2.02482

            --- C. ML Estimation Summary---

 Fri Jan  2 12:09:31 2009

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\IVOral.dat

 Model:  IVORAL.FOR: 2 comp., 1st Order Abs., Bioavail. Crossover

 Convergence achieved
   Number of iterations:          91
   Number of function calls:     485
 Negative Log Likelihood:    2.02482

  Output        R-squared    Sum of Squares
  Y( 1)          0.949          3.36153

  Model Selection Criteria
   AIC:          18.0496
   BIC:          26.2960

               Initial      Final
  Parameter      Value      Estimate    SE (CV%)   Confidence interval (95%)

  Kel           0.2000      0.1883       17.92     [ 0.1171    ,  0.2595    ]
  Vc             10.00       10.41       15.03     [  7.107    ,   13.71    ]
```

Figure 9.3 (continued)

Ka	1.000	0.9660	20.14	[0.5554 , 1.377]
Kcp	1.000	0.9392	32.21	[0.3009 , 1.577]
Kpc	0.5000	0.4808	24.99	[0.2273 , 0.7342]
Tau	1.000	0.9960	2.020	[0.9536 , 1.038]
F	0.8000	0.7845	8.524	[0.6434 , 0.9256]
IC(1)	0.000	Not estimated		
IC(2)	0.000	Not estimated		
IC(3)	0.000	Not estimated		
SDinter1	0.1000	Not estimated		
SDslope1	0.1000	Not estimated		
CLt	2.000	1.960	8.825	[1.595 , 2.325]
Vc	10.00	10.41	15.03	[7.107 , 13.71]
CLd	10.00	9.776	20.45	[5.557 , 14.00]
Vp	20.00	20.34	14.35	[14.18 , 26.49]
LAM1	1.639	1.550	26.90	[0.6702 , 2.430]
LAM2	0.6101E-01	0.5842E-01	15.45	[0.3937E-01, 0.7746E-01]
t1/2-LAM1	0.4229	0.4472	26.90	[0.1934 , 0.7011]
t1/2-LAM2	11.36	11.87	15.45	[7.997 , 15.73]

Correlation Matrix

	Kel	Vc	Ka	Kcp	Kpc	Tau	F
Kel	1.00						
Vc	-0.87	1.00					
Ka	-0.52	0.50	1.00				
Kcp	0.79	-0.87	-0.31	1.00			
Kpc	0.46	-0.38	0.10	0.70	1.00		
Tau	0.05	-0.06	0.21	0.09	0.08	1.00	
F	0.16	0.03	-0.54	-0.02	-0.18	-0.05	1.00

Covariance Matrix

	Kel	Vc	Ka	Kcp	Kpc	Tau	F
Kel	0.114E-02						
Vc	-.460E-01	2.45					
Ka	-.342E-02	0.152	0.379E-01				
Kcp	0.808E-02	-.413	-.183E-01	0.915E-01			
Kpc	0.186E-02	-.706E-01	0.231E-02	0.253E-01	0.144E-01		
Tau	0.333E-04	-.200E-02	0.833E-03	0.552E-03	0.196E-03	0.405E-03	
F	0.355E-03	0.288E-02	-.700E-02	-.410E-03	-.148E-02	-.681E-04	0.447E-02

Figure 9.3 (continued)

```
            --- D.  ML Estimation Model Prediction and Data Summary ---

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\IVOral.dat

 Number of subjects:    2

 Model:  IVORAL.FOR: 2 comp., 1st Order Abs., Bioavail. Crossover


IVData

 Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1       0.000        0.000        0.000         0.000       0.1000E-01
      2      0.5000        3.210        3.737       -0.5267       0.2244
      3       1.000        5.910        6.143       -0.2326       0.5102
      4       1.250        5.920        4.980        0.9400       0.3576
      5       1.500        4.830        4.179        0.6510       0.2682
      6       2.000        2.970        3.236       -0.2655       0.1794
      7       3.000        1.780        2.509       -0.7288       0.1231
      8       5.000        2.000        2.099       -0.9896E-01   0.9604E-01
      9       8.000        2.370        1.756        0.6144       0.7594E-01
     10       12.00        1.090        1.390       -0.2998       0.5711E-01
     11       20.00       0.8160       0.8709       -0.5491E-01   0.3500E-01
     12       24.00       0.6970       0.6894        0.7565E-02   0.2854E-01

 Y( 1) (Continued)                Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
                1       0.000        0.000        0.000
                2       3.737       0.3535       -1.112
                3       6.143       0.4145      -0.3257
                4       4.980       0.2883        1.572
                5       4.179       0.2798        1.257
                6       3.236       0.2410      -0.6269
                7       2.509       0.1792       -2.077
                8       2.099       0.1755      -0.3193
                9       1.756       0.1302        2.229
               10       1.390      0.9855E-01    -1.254
               11      0.8709      0.9493E-01   -0.2935
               12      0.6894      0.9557E-01    0.4478E-01


OralData

 Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1       0.000        0.000        0.000         0.000       0.1000E-01
      2      0.5000        0.000        0.000         0.000       0.1000E-01
      3       1.000        0.000      0.2898E-01   -0.2898E-01   0.1059E-01
      4       1.250        1.870        1.425        0.4453       0.5879E-01
      5       1.500        1.790        2.210       -0.4200       0.1030
      6       2.000        2.480        2.784       -0.3041       0.1432
      7       3.000        2.460        2.582       -0.1223       0.1283
      8       5.000        2.080        1.919        0.1609       0.8521E-01
```

Figure 9.3 (continued)

```
     9       8.000        1.370        1.516       -0.1463       0.6332E-01
    10       12.00        1.510        1.195        0.3155       0.4816E-01
    11       20.00       0.6530       0.7485       -0.9546E-01   0.3057E-01
    12       24.00       0.6360       0.5925        0.4350E-01   0.2536E-01

Y( 1) (Continued)                 Std. Err.   Standardized
          Obs.Num.   Model Est.   Model Est.   Residual
               1       0.000        0.000        0.000
               2       0.000        0.000        0.000
               3      0.2898E-01   0.9982E-01  -0.2816
               4       1.425       0.1582        1.836
               5       2.210       0.1991       -1.308
               6       2.784       0.2032      -0.8036
               7       2.582       0.1933      -0.3414
               8       1.919       0.1666       0.5514
               9       1.516       0.1320      -0.5812
              10       1.195       0.9453E-01    1.438
              11      0.7485       0.7931E-01  -0.5460
              12      0.5925       0.7866E-01   0.2732

    ____________________________________________

     --- RE-ESTIMATION OPTIONS ---

    1. Change initial parameter values
    2. Select a different estimator
    3. Exit ID

Enter option:  3

    ____________________________________________

List of Files Created

 Record of program run and all results:
   IVOral.run
 Table of predictions and residuals for each subject:
   IVOralRSD.csv
 Information for plotting model predictions for each subject:
   IVOralPLT.csv
 Composite residual and prediction vs measurements graphs and
 individual subject model prediction and measurement vs time graphs:
   IVOral.eps
 Command file for subsequent Batch runs:
   IVOral.aci


    ____________________________________________

 ADAPT 5  NPD -- NAIVE POOLED DATA POP. EST.  Fri Jan  2 12:09:36 2009
```

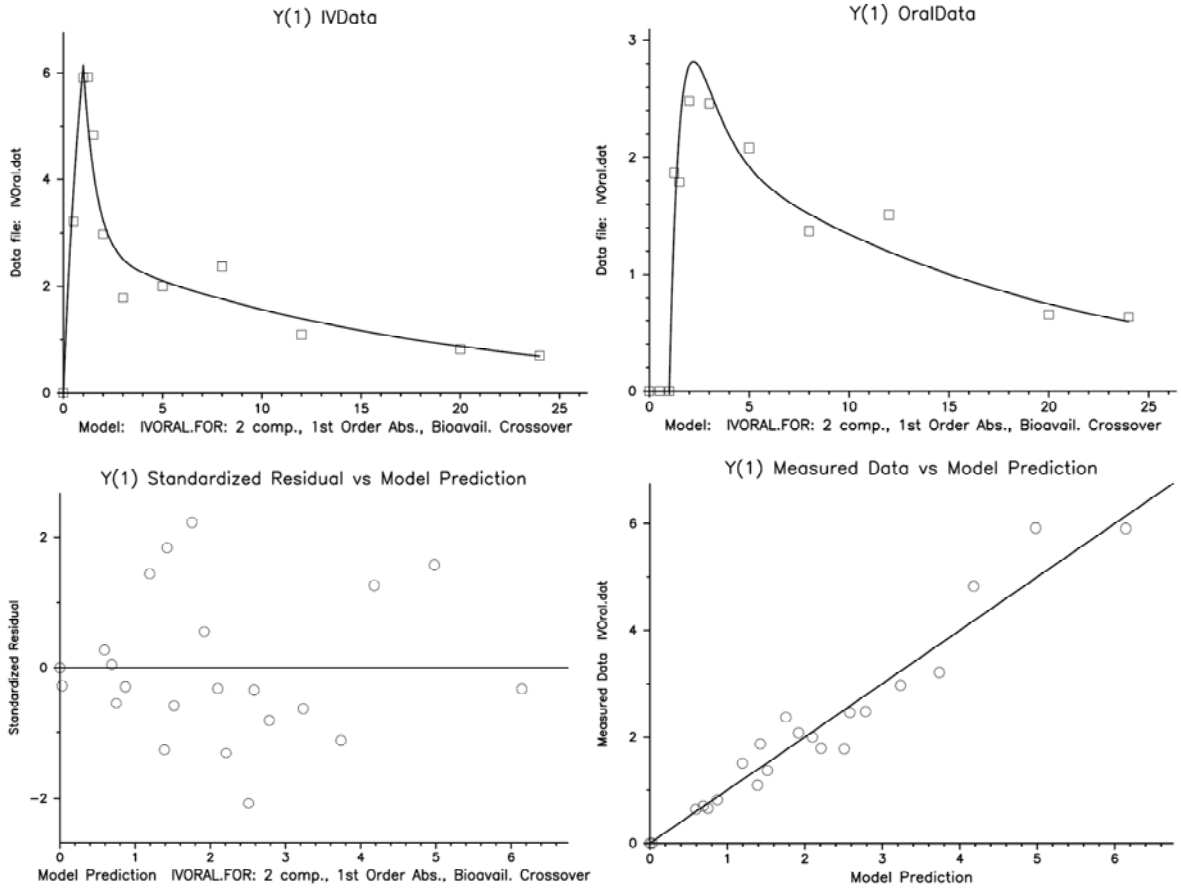


Figure 9.4 Example ivoral. Resulting plots for IV data as stored in file ivoral.eps. The residual plots include both the IV and oral predictions and data.

9.2 Example igabs: ID – Inverse Gaussian Absorption Model

After Weiss proposed the use of the inverse Gaussian (IG) function as a flexible empirical input function to describe drug delivery to the systemic circulation following oral administration, it has been used to model drug input for various extravascular administration routes. It is of interest to note that the IG is the first passage time distribution of a random walk with drift (first suggested by Schrödinger in 1915) and the solution of the convection-dispersion equation for pharmacokinetically relevant boundary conditions. The IG function has also been widely used to model the transit of drugs through organs and organ systems. See Wang, Weiss and D'Argenio [49] for further discussion, other references and applications using ADAPT.

This example illustrates the use of the IG function to model the oral absorption process of a delayed release compound. It is assumed that the plasma drug concentration following oral administration of the drug can be decomposed into an independent input process (representing

dissolution, transit and absorption processes) followed by the disposition process. It is further assumed that the parameters of a linear two compartment model used to describe the disposition process have been estimated following intravenous drug administration to an individual. The model shown in Figure 9.5 will then be used to describe the plasma kinetics of an oral formulation of the drug delivered to the individual.

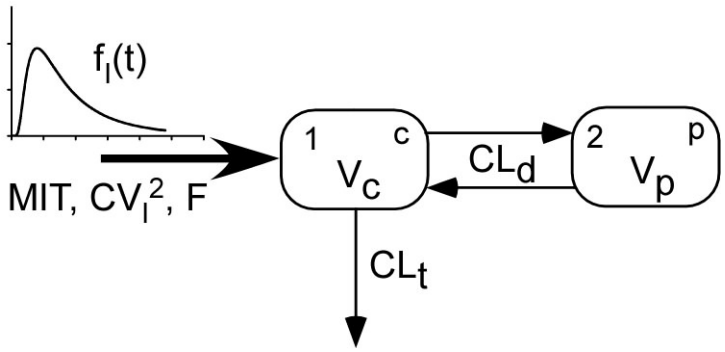


Figure 9.5 Example igabs. Two compartment disposition model with IG function input.

In the model above the systemic drug input function, $f_I(t)$, is assumed to be a single inverse Gaussian function defined as:

$$f_I(t) = D \cdot F \sqrt{\frac{MIT}{2\pi CV_I^2 t^3}} \exp\left[-\frac{(t - MIT)^2}{2CV_I^2 MIT t} \right], \qquad t > 0 \qquad (9.1)$$

where MIT represents the mean input time and CV_I^2 is a normalized variance (CV_I is the standard deviation of the density function $f_I(t)/(D \cdot F)$ divided by MIT, i.e., the relative dispersion of input times). The factor F is the bioavailability of the orally administered dose D. (Note at $f_I(0) = 0$.) One can also calculate, as a secondary parameter, the mode of the inverse Gaussian density as follows:

$$t_{I,\max} = MIT\left(\sqrt{1 + \frac{9}{4} CV_I^4} - \frac{3}{2} CV_I^2 \right) \qquad (9.2)$$

which is the time the input function achieves its maximum value.

Figure 9.6 shows a section of the model file igabs.for that implements this model. Figures 9.7 and 9.8 show a complete run of the ID program using ML estimation for this example. In the program run a fictitious compartment number (compartment 3) is used as the compartment number for the bolus input dose that is read from the data file. An additional plot created via SIM using the final parameter estimates is shown in Figure 9.8 that displays the estimated IG function $f_I(t)$.

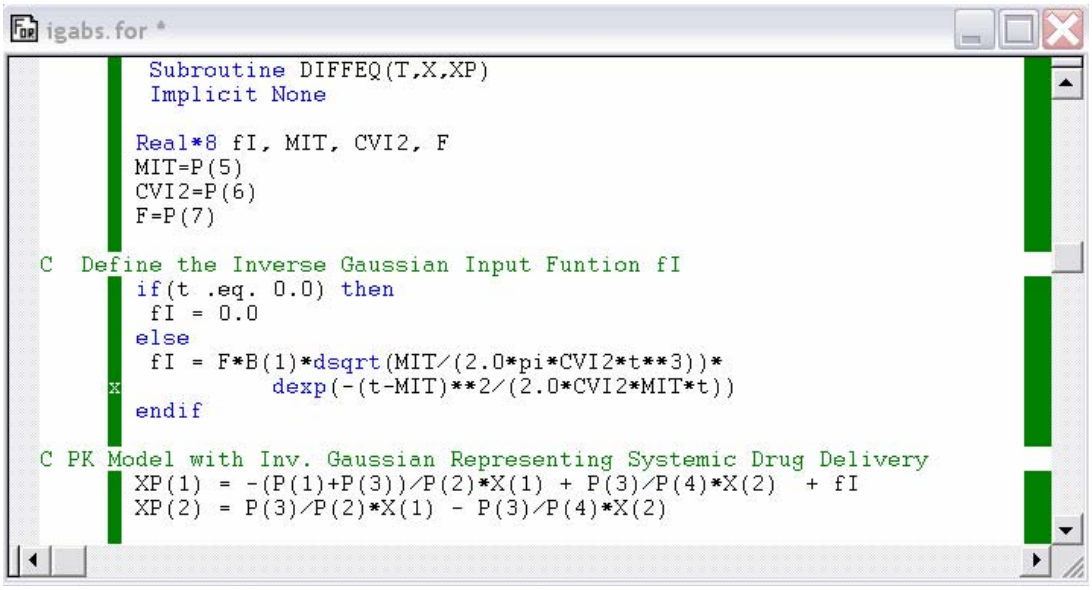


Figure 9.6 Excerpt from Subroutine DIFFEQ of model file igabs.for. For ease of coding, variables are used and defined to represent the three model parameters of the IG function as well as the function itself. Note the value of `fI` is defined explicitly for t=0.

```
    ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Sun Jan  4 10:11:24 2009

Enter file name for storing session run (*.run): igabs.run

      ----- MODEL INPUT INFORMATION -----

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\igabs.dat

 The number of model inputs:     0

 The number of bolus inputs:    1

 Enter the compartment number for each bolus input (e.g. 1,3,...):   3

 The number of input event times:     1

     Input Event Information
           Time    Value for all Inputs
 Event     Units,       B(1)
    1.     0.000          200.0

      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   1

 The number of observations:   14
```

Figure 9.7 ID run for example igabs.

Figure 9.7 (continued)

```
    Observation Information
                Time     Measured Value For Each Output
Observation     Units ,      Y(1)
      1.         15.00      0.7220E-02
      2.         30.00      0.5514
      3.         60.00       2.871
      4.         90.00       4.659
      5.         120.0       5.491
      6.         150.0       6.125
      7.         210.0       5.648
      8.         270.0       4.857
      9.         330.0       4.548
     10.         360.0       3.558
     11.         390.0       2.611
     12.         420.0       2.889
     13.         450.0       2.116
     14.         480.0       2.003

     ----- ESTIMATOR SELECTION -----

The following estimation procedures are available:
     1. Weighted least squares (WLS)
     2. Maximum likelihood (ML)
     3. Generalized least squares (GLS)
     4. Maximum a posteriori probability (MAP)

Enter option number:  2

     ----- INITIALIZE ESTIMATION PROCEDURE -----

Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\igabs.prm

Enter initial values for parameters & specify those to be estimated:

           Old Value    New Value      Estimate?
                      (skip if same)    (Y/N)
CLt        .7930E-01         n
V1         .6400             n
CL2        .2920             n
V2         9.630             n
MIT        190.0             y
CVI2       .6500             y
F          .9200             y
IC(   1)   0.000             n
IC(   2)   0.000             n
SDinter    0.000             n
SDslope    .1000             y

Enter maximum number of iterations:       999

Do you want the iterations printed (Y/N)?  n
```

Figure 9.7 (continued)

```
          ----- RESULTS -----

           --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      MIT        =    190.0
      CVI2       =   0.6500
      F          =   0.9200
      SDslope    =   0.1000

    Negative Log Likelihood = -4.39927


            ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =    35
    Number of function calls  =   156

     Fitted Parameters
      MIT        =    191.9
      CVI2       =   0.6554
      F          =   0.9060
      SDslope    =   0.7866E-01

    Negative Log Likelihood = -5.54229


            --- C. ML Estimation Summary---

 Sun Jan  4 10:11:47 2009

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\igabs.dat

 Model:  IGABS.FOR; 2CompCL w/ Inverse Gaussian Absorption

 Convergence achieved
   Number of iterations:          35
   Number of function calls:     156
 Negative Log Likelihood:   -5.54229

  Output        R-squared    Sum of Squares
  Y( 1)          0.980          1.03974

  Model Selection Criteria
   AIC:         -3.08457
   BIC:        -0.528342
```

Figure 9.7 (continued)

```
                Initial      Final
 Parameter       Value      Estimate    SE (CV%)   Confidence interval (95%)

 MIT             190.0       191.9       4.243     [  173.8    ,   210.1    ]
 CVI2           0.6500      0.6554       5.132     [ 0.5805    ,  0.7303    ]
 F              0.9200      0.9060       2.376     [ 0.8581    ,  0.9540    ]
 CLt           0.7930E-01  Not estimated
 V1             0.6400      Not estimated
 CL2            0.2920      Not estimated
 V2              9.630      Not estimated
 IC(   1)        0.000      Not estimated
 IC(   2)        0.000      Not estimated

 SDslope        0.1000      0.7866E-01   19.01     [ 0.4534E-01,  0.1120    ]
 SDinter         0.000      Not estimated

 tImax           80.11       80.45      0.9512     [  78.75    ,   82.16    ]

 Correlation Matrix

           MIT       CVI2      F
MIT          1.00
CVI2         0.98      1.00
F            0.34      0.28      1.00

 Covariance Matrix  {results not shown}

           --- D.  ML Estimation Model Prediction and Data Summary ---

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\igabs.dat

 Model:  IGABS.FOR; 2CompCL w/ Inverse Gaussian Absorption

Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1       15.00       0.7220E-02   0.7010E-02    0.2102E-03   0.3040E-06
      2       30.00       0.5514       0.5633       -0.1198E-01   0.1964E-02
      3       60.00        2.871        3.130       -0.2594       0.6061E-01
      4       90.00        4.659        4.752       -0.9275E-01   0.1397
      5       120.0        5.491        5.519       -0.2765E-01   0.1884
      6       150.0        6.125        5.777        0.3485       0.2065
      7       210.0        5.648        5.482        0.1653       0.1860
      8       270.0        4.857        4.721        0.1352       0.1379
      9       330.0        4.548        3.862        0.6860       0.9230E-01
     10       360.0        3.558        3.450        0.1080       0.7363E-01
     11       390.0        2.611        3.062       -0.4513       0.5802E-01
     12       420.0        2.889        2.705        0.1845       0.4526E-01
     13       450.0        2.116        2.379       -0.2631       0.3501E-01
     14       480.0        2.003        2.085       -0.8180E-01   0.2689E-01
```

Figure 9.7 (continued)

Y(1) (Continued) Obs.Num.	Model Est.	Std. Err. Model Est.	Standardized Residual
1	0.7010E-02	0.5174E-03	0.3812
2	0.5633	0.2091E-01	-0.2704
3	3.130	0.1157	-1.054
4	4.752	0.1679	-0.2481
5	5.519	0.1794	-0.6369E-01
6	5.777	0.1712	0.7670
7	5.482	0.1375	0.3833
8	4.721	0.1091	0.3641
9	3.862	0.9454E-01	2.258
10	3.450	0.9081E-01	0.3981
11	3.062	0.8818E-01	-1.874
12	2.705	0.8591E-01	0.8674
13	2.379	0.8356E-01	-1.406
14	2.085	0.8090E-01	-0.4988

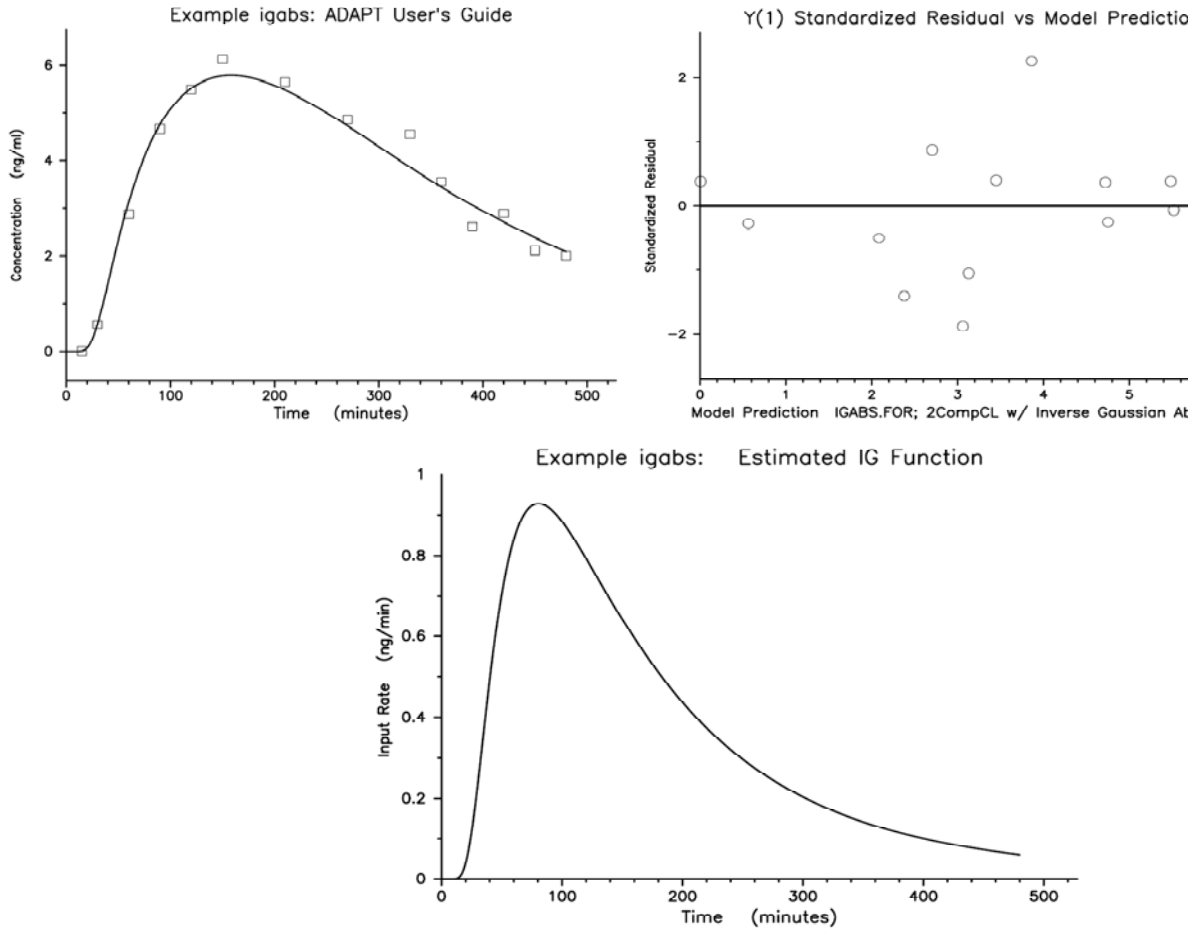


Figure 9.8 Example igabs. Selected plots for the plasma concentration and resdiduals (upper panels). The lower panel shows the estimated IG input function produced using SIM with the parameter values as estimated in the example.

9.3 Example pmetab: ID – Parent/Metabolite

Figure 9.9 shows the modeled used to describe the kinetics of a parent compound and its metabolite used in this example. Unlike the model in example pk8 in which the metabolism is saturable, the linear model in this example is not identifiable. The model relating dose of the parent compound to the plasma concentrations of parent drug and its metabolite can be rewritten in terms of the ratio Vm / fm along with the other model parameters Kp, Vp, K_{12}, K_{21} and Km. This reparameterized model is coded in model file pmetab.for (note: the second state now represents the amount of the metabolite divided by the fraction of drug metabolized, fm). Figures 9.10 and 8.11 show a run of ID using this model.

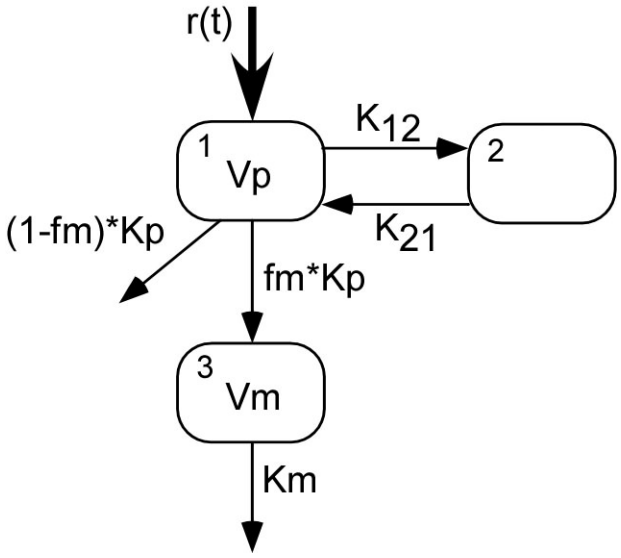


Figure 9.9 Model for example pmetab. *Kp* is the total elimination rate of the parent compound, while *fm* represent the fraction metabolized.

```
  ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Mon Jan  5 11:35:47 2009

Enter file name for storing session run (*.run): pmetab.run

     ----- MODEL INPUT INFORMATION -----

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pmetab.dat

The number of model inputs:     1

The number of bolus inputs:    0

The number of input event times:     2
```

Figure 9.10 ID run for example pmetab.

Figure 9.10 (continued)

```
    Input Event Information
          Time    Value for all Inputs
Event     Units,       R(1)
   1.     0.000          100.0
   2.     1.000          0.000

     ----- MODEL OUTPUT INFORMATION -----

The number of model output equations:   2

The number of observations:   10

    Observation Information
                Time     Measured Value For Each Output
Observation     Units ,     Y(1), ... ,Y(   2)
      1.        0.5000       3.602      0.1314
      2.         1.000       7.767      0.5882
      3.         3.000       2.599       1.457
      4.         5.000       1.083       1.317
      5.         7.000      0.5941      0.9595
      6.         9.000      0.3987      0.7223
      7.         12.00      0.2975      0.4448
      8.         16.00      0.2440      0.4333
      9.         20.00      0.2045      0.2252
     10.         24.00      0.1233      0.1239

     ----- ESTIMATOR SELECTION -----

The following estimation procedures are available:
     1. Weighted least squares (WLS)
     2. Maximum likelihood (ML)
     3. Generalized least squares (GLS)
     4. Maximum a posteriori probability (MAP)

Enter option number:  2

     ----- INITIALIZE ESTIMATION PROCEDURE -----

Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\pmetab.prm

Enter initial values for parameters & specify those to be estimated:

           Old Value    New Value      Estimate?
                      (skip if same)    (Y/N)
Kp         .4000            y
Vp         10.00            y
K12        .2000            y
K21        .1000            y
Km         .2000            y
Vm/fm      30.00            y
IC(   1)   0.000            n
IC(   2)   0.000            n
IC(   3)   0.000            n
```

Figure 9.10 (continued)

```
SDinter1   0.000           n
SDslope1   .1000           y
SDinter2   0.000           n
SDslope2   .1500           y

Enter maximum number of iterations:       999

Do you want the iterations printed (Y/N)?  n

            ----- RESULTS -----

            --- A. Iterations ---

    Number of iterations      =     0
    Number of function calls  =     1

     Fitted Parameters
      Kp          =   0.4000
      Vp          =    10.00
      K12         =   0.2000
      K21         =   0.1000
      Km          =   0.2000
      Vm/fm       =    30.00
      SDslope1    =   0.1000
      SDslope2    =   0.1500

    Negative Log Likelihood = -25.4353

             ---B. Iteration Summary---

    Convergence has been achieved.

    Number of iterations      =    46
    Number of function calls  =   327

     Fitted Parameters
      Kp          =   0.3836
      Vp          =    10.71
      K12         =   0.1788
      K21         =   0.1002
      Km          =   0.2096
      Vm/fm       =    28.60
      SDslope1    =   0.7706E-01
      SDslope2    =   0.1450

    Negative Log Likelihood = -27.3156

            --- C. ML Estimation Summary---

Mon Jan  5 11:36:08 2009

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pmetab.dat

Model:  PMETAB.FOR -Parent-Metab, 2 comp. parent, 1 comp. metab.
```

Figure 9.10 (continued)

```
Convergence achieved
   Number of iterations:          46
   Number of function calls:     327
 Negative Log Likelihood:   -27.3156

  Output        R-squared    Sum of Squares
  Y( 1)          0.991         0.596013
  Y( 2)          0.980         0.461970E-01

  Model Selection Criteria
   AIC:         -38.6312
   BIC:         -30.6653

                Initial      Final
  Parameter      Value      Estimate    SE (CV%)   Confidence interval (95%)
  Kp            0.4000      0.3836       5.092     [ 0.3411    ,  0.4262    ]
  Vp             10.00       10.71       5.902     [  9.334    ,   12.09    ]
  K12           0.2000      0.1788       8.877     [ 0.1442    ,  0.2134    ]
  K21           0.1000      0.1002       13.05     [ 0.7172E-01,  0.1287    ]
  Km            0.2000      0.2096       7.457     [ 0.1756    ,  0.2437    ]
  Vm/fm          30.00       28.60       8.784     [  23.12    ,   34.07    ]
  IC(   1)       0.000      Not estimated
  IC(   2)       0.000      Not estimated
  IC(   3)       0.000      Not estimated

  SDslope1      0.1000      0.7706E-01   22.49     [ 0.3929E-01,  0.1148    ]
  SDslope2      0.1500      0.1450       22.83     [ 0.7289E-01,  0.2171    ]
  SDinter1       0.000      Not estimated
  SDinter2       0.000      Not estimated

  CLp            4.000       4.109       3.286     [  3.815    ,   4.403    ]
  CLp-dist       2.000       1.915       8.633     [  1.555    ,   2.275    ]
  CLm/fm         6.000       5.994       4.904     [  5.354    ,   6.635    ]

  Correlation Matrix

           Kp        Vp        K12       K21       Km        Vm/fm
 Kp          1.00
 Vp         -0.83      1.00
 K12         0.66     -0.37      1.00
 K21         0.55     -0.17      0.56      1.00
 Km         -0.29      0.33     -0.03      0.02      1.00
 Vm/fm       0.38     -0.35      0.13      0.17     -0.83      1.00

  Covariance Matrix

           Kp        Vp        K12       K21       Km        Vm/fm
 Kp        0.382E-03
 Vp        -.103E-01 0.400
 K12       0.204E-03 -.374E-02 0.252E-03
 K21       0.141E-03 -.138E-02 0.115E-03 0.171E-03
 Km        -.874E-04 0.330E-02 -.753E-05 0.502E-05 0.244E-03
 Vm/fm     0.187E-01 -.560     0.527E-02 0.554E-02 -.326E-01  6.31
```

Figure 9.10 (continued)

```
           --- D.  ML Estimation Model Prediction and Data Summary ---

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\pmetab.dat

 Model:  PMETAB.FOR -Parent-Metab, 2 comp. parent, 1 comp. metab.

Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1      0.5000        3.602        4.072       -0.4700       0.9847E-01
      2       1.000        7.767        7.162        0.6053       0.3046
      3       3.000        2.599        2.515        0.8365E-01   0.3758E-01
      4       5.000        1.083        1.069        0.1391E-01   0.6788E-02
      5       7.000       0.5941       0.5949       -0.8170E-03   0.2101E-02
      6       9.000       0.3987       0.4188       -0.2006E-01   0.1041E-02
      7       12.00       0.2975       0.3094       -0.1184E-01   0.5684E-03
      8       16.00       0.2440       0.2331        0.1089E-01   0.3226E-03
      9       20.00       0.2045       0.1797        0.2475E-01   0.1918E-03
     10       24.00       0.1233       0.1389       -0.1562E-01   0.1146E-03

 Y( 1) (Continued)                 Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
                1       4.072       0.2201       -1.498
                2       7.162       0.3593        1.097
                3       2.515       0.1135       0.4315
                4       1.069       0.5443E-01   0.1688
                5      0.5949       0.2506E-01  -0.1782E-01
                6      0.4188       0.1851E-01  -0.6217
                7      0.3094       0.1447E-01  -0.4968
                8      0.2331       0.8773E-02   0.6062
                9      0.1797       0.7454E-02    1.788
               10      0.1389       0.8564E-02   -1.459

 Y( 2)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1      0.5000       0.1314       0.1477       -0.1632E-01   0.4590E-03
      2       1.000       0.5882       0.5228        0.6545E-01   0.5748E-02
      3       3.000        1.457        1.338        0.1189       0.3765E-01
      4       5.000        1.317        1.257        0.5995E-01   0.3324E-01
      5       7.000       0.9595        1.009       -0.4908E-01   0.2139E-01
      6       9.000       0.7223       0.7777       -0.5541E-01   0.1272E-01
      7       12.00       0.4448       0.5270       -0.8226E-01   0.5841E-02
      8       16.00       0.4333       0.3302        0.1031       0.2293E-02
      9       20.00       0.2252       0.2212        0.4051E-02   0.1029E-02
     10       24.00       0.1239       0.1562       -0.3226E-01   0.5130E-03

 Y( 2) (Continued)                 Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
                1      0.1477       0.1183E-01  -0.7616
                2      0.5228       0.4044E-01   0.8633
                3       1.338       0.8652E-01   0.6127
                4       1.257       0.6952E-01   0.3288
                5       1.009       0.5020E-01  -0.3356
                6      0.7777       0.3856E-01  -0.4913
```

```
                7      0.5270       0.3028E-01   -1.076
                8      0.3302       0.2274E-01    2.152
                9      0.2212       0.1613E-01   0.1263
               10      0.1562       0.1151E-01   -1.424

     ----- PLOTTING OPTIONS -----  {Dialogue for plotting not shown}...

     ----- RE-ESTIMATION OPTIONS -----

    1. Change initial parameter values
    2. Select a different estimator
    3. Exit ID

Enter option:  3
```

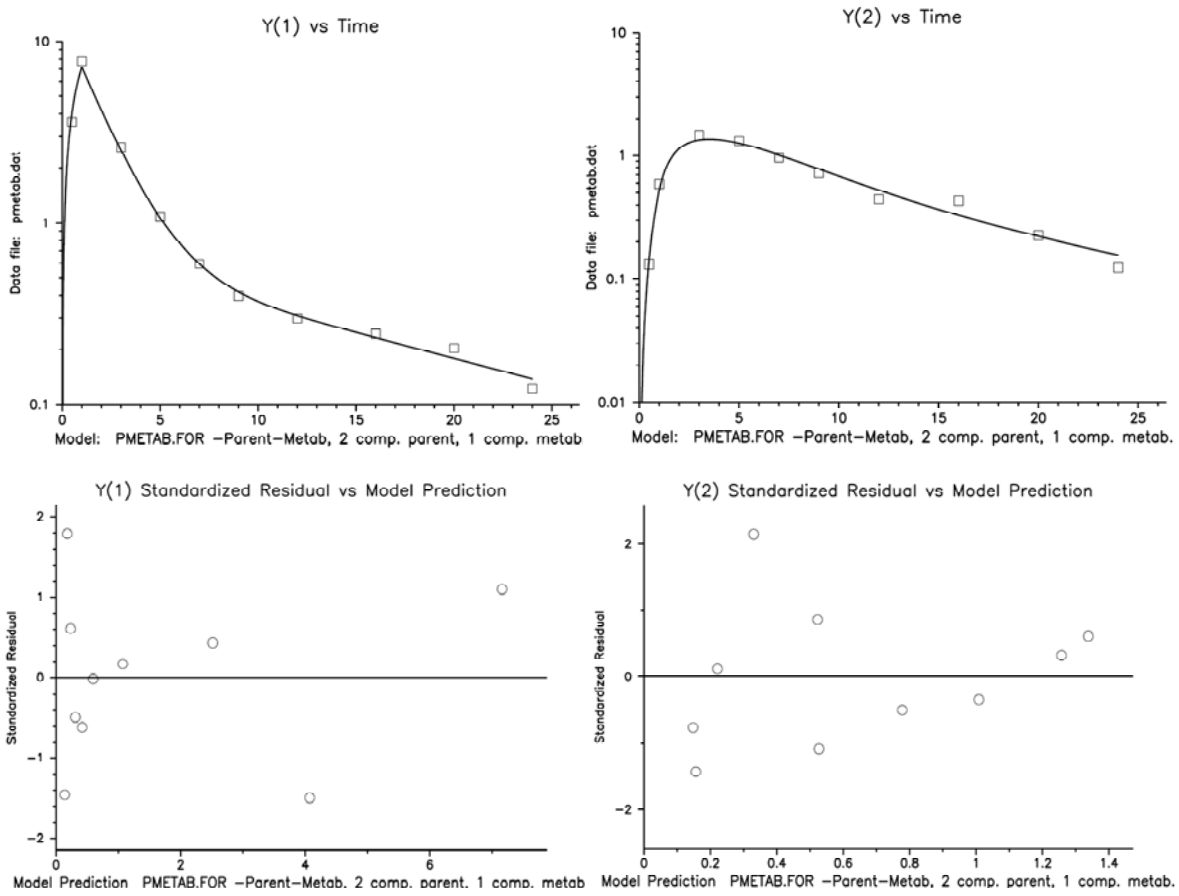


Figure 9.11 Example pmetab. Selected plots for the parent and metabolite concentrations.

9.4 Example plasmaurine: ID – Plasma and Urine Concentration Data

In this example plasma and urine drug concentration data are modeled. Figure 9.12 shows a one compartment first order absorption model, including a compartment representing amount of drug collected in the urine (x_3) and another representing urine volume (x_4). In the ADAPT model file (see Subroutine DIFFEQ in Figure 9.13) the urine compartment is used to define the amount of drug in the urine during each collection interval while the volume compartment defines the volume of urine formed during each collection interval. At the end of each collection interval, the states x_3 and x_4 are set to 0.0 by the code in the Subroutine OUTPUT of the model file. See the complete model file plasmaurine.for for additional description on the use of this model and its modification.

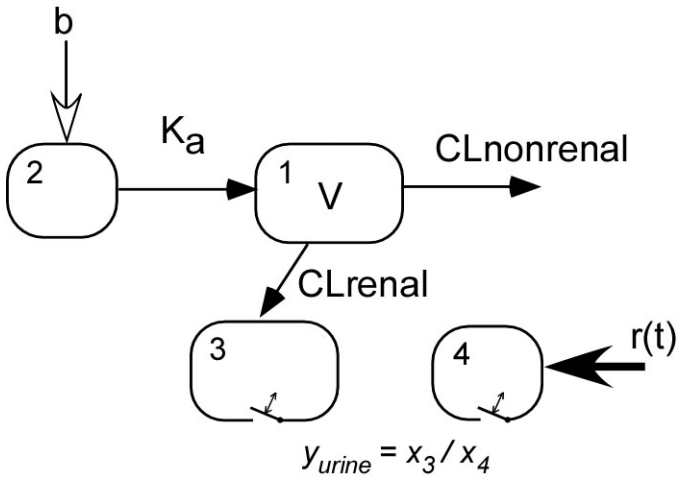


Figure 9.12 Model for example plasmaurine.

plasmaurine.for *

```
      Subroutine DIFFEQ(T,X,XP)
      Implicit None

C  Plasma and absorption compartments
      XP(1) = -(P(1)/P(3)+P(2)/P(3))*X(1) + P(4)*X(2)
      XP(2) = - P(4)*X(2)
c  Urine compartment amount and equation for volume of urine
C  (Two similar equations would need to be added to other models to
C   incorporate urine collection.)
      XP(3) = (P(2)/P(3))*X(1) ! X(3)-Drug amount in urine
      XP(4) = R(1)             ! X(4)-Volume of urine collected
```

Figure 9.13 Excerpt from Subroutine DIFFEQ of model file plasmaurine.for. The code `P(2)` represents CLrenal, while `P(3)` represents the model parameter V.

Figure 9.14 shows a section of Subroutine OUTPUT for this example. The routine COLLECT resides in ADAPT and controls resetting of states x_3 and x_4 at the collection times. This model file can be modified for other models by specifying the appropriate values for the symbols `RNumVol`, `XNumColl` and `XNumVol`, as well as defining any additional model outputs.

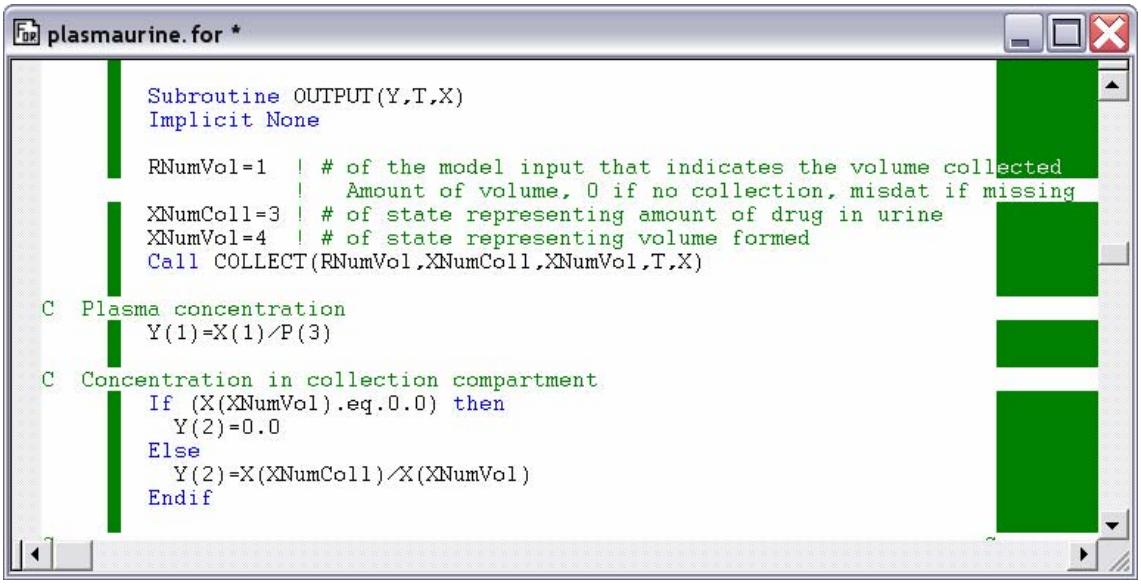


Figure 9.14 Excerpt from Subroutine OUTPUT of model file plasmaurine.for.

In addition to providing the bolus dose information and the measured plasma and urine concentration information in the data file, the user must also provide the urine volume information including the volume collected and the collection time. To provide this latter information, urine volume is treated as a model input (`R(1)` in the plasmaurine.for model file) and the urine volume collection times are included as model input times. In the example considered here, urine is collected at 1.0, 3.0, 5.0, 8.0 and 12.0 hours with volume 0.05, 0.1, 0.1, 0.15, and 0.25 L, respectively. The annotated data file plasmaurine.dat that incorporates this information is shown in Table 9.12. If no volume is collected at a model input time then 0 is entered for the value of volume (in this example the bolus does of 100 mg is administered at time 0 and therefore a value of 0.0 is entered for the collected urine volume at that time). In cases were the urine volume is collected but no measured value is available, the `misdat` number is entered for the volume (see input time 14 hr Table 8.x). All urine volume collection times must be specified as <u>both</u> model inputs times and model output times in the data file. (In routine COLLECT of the model file the entered urine volumes and collection times from the data file are converted to a rate of volume formation and stored in the variable `R(1),` which is used to define state x_4 of the model.)

A run of ID for this example is shown in Figures 9.15 and 9.16. An additional plot created via SIM using the final parameter estimates is shown in Figure 9.16 that displays the predicted cumulative amount of drug in the urine together with available measured values.

Table 9.12 Data file plasmaurine.dat

```
   1     # A model input is used to indicate amount of volume collected
   1     # Drug administered as a bolus dose
   7     # Input times: include both dose administration and collection times
# Time   Volume      Bolus Dose
 0.000   0.000000    100.000    # 0 indicates no urine collected
 1.000   0.050000    0.00000    # 0.05L is the volume collected at t=1.0
 3.000   0.100000    0.00000
 5.000   0.100000    0.00000
 8.000   0.150000    0.00000
12.000   0.250000    0.00000
14.000   -1          0.00000 # -1 indicates volume collected but not recorded
   2                           # Output 1-plasma, Output 2-urine conc.
   10
# Time   Plasma       Urine conc.
 0.000    -1            -1          # Neither plasma or urine measured
 1.000    5.47418       208.        # Both plasma & urine measured
 3.000    2.80660       180.        # Both plasma & urine measured
 4.000    2.07265       -1          # No urine since not a collection time
 5.000    1.23101       77.
 6.000   0.623901       -1
 7.000   0.317612       -1
 8.000   0.234898       29.
12.000   0.403408E-01   3.9
14.000   0.01           -1
```

```
    ADAPT 5    ID -- INDIVIDUAL ESTIMATION    Sat Jan  3 13:27:13 2009

 Enter file name for storing session run (*.run): plasmaurine.run

      ----- MODEL INPUT INFORMATION -----

Data file name (*.dat):C:\Program Files\BMSR\ADAPT 5\Examples\plasmaurine.dat

 The number of model inputs:     1

 The number of bolus inputs:    1

 Enter the compartment number for each bolus input (e.g. 1,3,...):   2

 The number of input event times:     7

     Input Event Information
           Time    Value for all Inputs
 Event     Units,       R(1), B(1)
    1.     0.000          0.000       100.0
    2.     1.000         0.5000E-01   0.000
    3.     3.000          0.1000      0.000
    4.     5.000          0.1000      0.000
    5.     8.000          0.1500      0.000
    6.     12.00          0.2500      0.000
    7.     14.00          -1.000      0.000
```

Figure 9.15 ID run for example plasmaurine.

Figure 9.15 (continued)

```
      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   2

 The number of observations:   10

     Observation Information
                 Time     Measured Value For Each Output
 Observation     Units ,     Y(1), ... ,Y(   2)
       1.         0.000      -1.000      -1.000
       2.         1.000       5.474       208.0
       3.         3.000       2.807       180.0
       4.         4.000       2.073      -1.000
       5.         5.000       1.231       77.00
       6.         6.000      0.6239      -1.000
       7.         7.000      0.3176      -1.000
       8.         8.000      0.2349       29.00
       9.         12.00      0.4034E-01   3.900
      10.         14.00      0.1000E-01  -1.000

      ----- ESTIMATOR SELECTION -----

 The following estimation procedures are available:
      1. Weighted least squares (WLS)
      2. Maximum likelihood (ML)
      3. Generalized least squares (GLS)
      4. Maximum a posteriori probability (MAP)

 Enter option number:  2

      ----- INITIALIZE ESTIMATION PROCEDURE -----

Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\plasmaurine.prm

 Enter initial values for parameters & specify those to be estimated:

            Old Value    New Value      Estimate?
                       (skip if same)    (Y/N)
 CLnonrenal 2.500            y
 CLrenal    2.500            y
 Vc         10.00            y
 Ka         2.000            y
 IC(   1)   0.000            n
 IC(   2)   0.000            n
 IC(   3)   0.000            n
 IC(   4)   0.000            n
 SDinter1   0.000            n
 SDslope1   .1000            y
 SDinter2   0.000            n
 SDslope2   .1000            y

Enter maximum number of iterations:       999

 Do you want the iterations printed (Y/N)?  n
```

Figure 9.15(continued)

```
             ----- RESULTS -----

             --- A. Iterations ---

     Number of iterations      =     0
     Number of function calls  =     1

      Fitted Parameters
       CLnonrenal =    2.500
       CLrenal    =    2.500
       Vc         =    10.00
       Ka         =    2.000
       SDslope1   =   0.1000
       SDslope2   =   0.1000

     Negative Log Likelihood =  8.51487

              ---B. Iteration Summary---

     Convergence has been achieved.

     Number of iterations      =    58
     Number of function calls  =   312

      Fitted Parameters
       CLnonrenal =    3.021
       CLrenal    =    2.307
       Vc         =    10.82
       Ka         =    1.892
       SDslope1   =   0.1447
       SDslope2   =   0.8639E-01

     Negative Log Likelihood =  2.72072

             --- C. ML Estimation Summary---

 Sat Jan  3 13:27:29 2009

Data file name (*.dat):C:\Program Files\BMSR\ADAPT 5\Examples\plasmaurine.dat

 Model:  PLASMAURINE.FOR - 1 comp. plasma & urine,CL param.

 Convergence achieved
   Number of iterations:          58
   Number of function calls:     312
 Negative Log Likelihood:    2.72072

  Output        R-squared    Sum of Squares
  Y( 1)          0.993         0.224552
  Y( 2)          0.982          652.086

  Model Selection Criteria
   AIC:          17.4414
   BIC:          21.2758
```

Figure 9.15 (continued)

```
                Initial      Final
  Parameter      Value      Estimate    SE (CV%)   Confidence interval (95%)

  CLnonrenal     2.500       3.021       7.382     [  2.507    ,   3.535    ]
  CLrenal        2.500       2.307       6.504     [  1.961    ,   2.653    ]
  Vc             10.00       10.82       7.201     [  9.026    ,   12.62    ]
  Ka             2.000       1.892       13.55     [  1.301    ,   2.484    ]
  IC(   1)       0.000      Not estimated
  IC(   2)       0.000      Not estimated
  IC(   3)       0.000      Not estimated
  IC(   4)       0.000      Not estimated

  SDslope1      0.1000      0.1447       24.06     [ 0.6440E-01,  0.2249    ]
  SDslope2      0.1000      0.8639E-01   31.86     [ 0.2292E-01,  0.1499    ]
  SDinter1       0.000      Not estimated
  SDinter2       0.000      Not estimated

  Knon-ur       0.2500      0.2791       3.414     [ 0.2571    ,  0.3011    ]
  Kurine        0.2500      0.2132       5.286     [ 0.1872    ,  0.2392    ]
  LAM1          0.5000      0.4923       2.339     [ 0.4658    ,  0.5189    ]
  t1/2-LAM1      1.386       1.408       2.339     [  1.332    ,   1.484    ]

  Correlation Matrix

           CLnonrenalCLrenal   Vc        Ka
 CLnonrenal  1.00
 CLrenal     0.45      1.00
 Vc          0.89      0.71      1.00
 Ka         -0.11     -0.09      0.11      1.00

  Covariance Matrix

 CLnonrenal0.497E-01
 CLrenal   0.149E-01 0.225E-01
 Vc        0.155     0.827E-01 0.607
 Ka        -.629E-02 -.340E-02 0.220E-01 0.658E-01

            --- D.  ML Estimation Model Prediction and Data Summary ---

Data file name (*.dat):C:\Program Files\BMSR\ADAPT 5\Examples\plasmaurine.dat

 Model:  PLASMAURINE.FOR - 1 comp. plasma & urine,CL param.

 Y( 1)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1       0.000       -1.000        0.000       No Observation
      2       1.000        5.474        5.751       -0.2765       0.6920
      3       3.000        2.807        2.809       -0.2163E-02   0.1651
      4       4.000        2.073        1.736        0.3362       0.6310E-01
      5       5.000        1.231        1.064        0.1667       0.2370E-01
      6       6.000       0.6239       0.6510       -0.2708E-01   0.8868E-02
      7       7.000       0.3176       0.3980       -0.8034E-01   0.3314E-02
      8       8.000       0.2349       0.2432       -0.8348E-02   0.1238E-02
```

Figure 9.15 (continued)

```
      9       12.00       0.4034E-01   0.3395E-01    0.6391E-02   0.2412E-04
     10       14.00       0.1000E-01   0.1268E-01   -0.2683E-02   0.3366E-05

Y( 1) (Continued)                Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
                1       0.000        0.000       No Observation
                2       5.751       0.4327      -0.3323
                3       2.809       0.1794      -0.5324E-02
                4       1.736       0.1047        1.338
                5       1.064       0.5893E-01    1.083
                6      0.6510       0.3335E-01  -0.2875
                7      0.3980       0.1955E-01   -1.396
                8      0.2432       0.1206E-01  -0.2373
                9      0.3395E-01   0.2467E-02    1.301
               10      0.1268E-01   0.1154E-02   -1.462

Y( 2)
  Obs.Num.   Time         Data       Model Est.     Residual     Variance
      1       0.000       -1.000        0.000       No Observation
      2       1.000        208.0        196.5         11.53        288.1
      3       3.000        180.0        201.7        -21.67        303.5
      4       4.000       -1.000        103.0       No Observation
      5       5.000        77.00        83.21        -6.210        51.67
      6       6.000       -1.000        38.80       No Observation
      7       7.000       -1.000        31.27       No Observation
      8       8.000        29.00        25.68         3.322        4.921
      9       12.00        3.900        3.924       -0.2390E-01   0.1149
     10       14.00       -1.000        0.000       No Observation

 Y( 2) (Continued)               Std. Err.   Standardized
           Obs.Num.   Model Est.   Model Est.   Residual
                1       0.000        0.000       No Observation
                2       196.5        15.20        0.6793
                3       201.7        9.124       -1.244
                4       103.0        5.343       No Observation
                5       83.21        4.231       -0.8640
                6       38.80        1.826       No Observation
                7       31.27        1.452       No Observation
                8       25.68        1.186        1.498
                9       3.924       0.2273      -0.7052E-01
               10       0.000        0.000       No Observation

      ----- PLOTTING OPTIONS -----  {Dialogue for plotting not shown}...

      ----- RE-ESTIMATION OPTIONS -----

     1. Change initial parameter values
     2. Select a different estimator
     3. Exit ID

 Enter option:  3
```

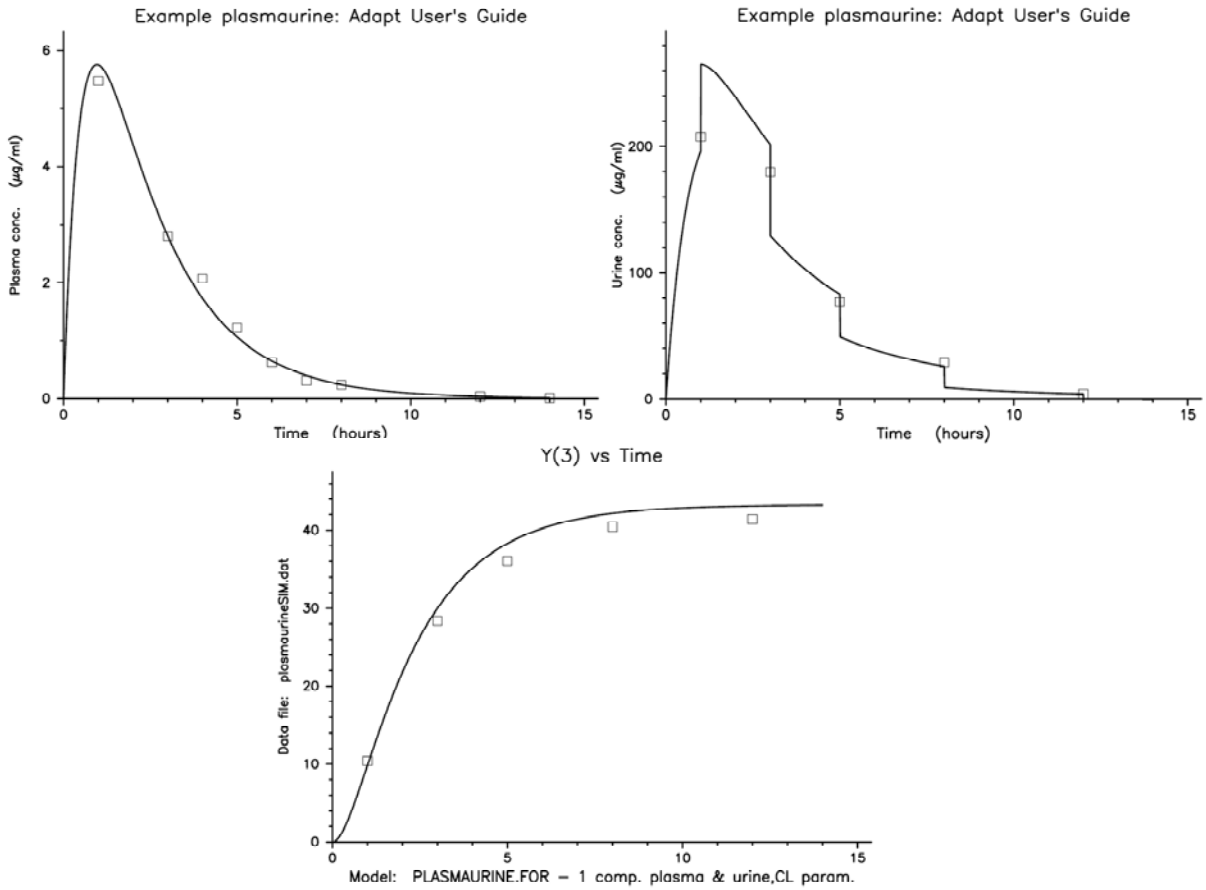


Figure 9.16 Example plasmaurine. Resulting plots for the plasma and urine concentrations (upper panels). The lower panel shows the predicted cumulative amount in the urine along with the urine amount as produced using SIM with the parameter values as estimated in the example.

9.5 Example 2compsamp: SAMPLE – Partial D-Optimal Design

This example illustrates the partial design feature of SAMPLE using the two-compartment pharmacokinetic model shown in Figure 9.17. A two dose intravenous regimen is used with two sample times fixed at the end of each of the two infusions. Four other sample times are then selected to estimate the four model parameters CLt, Vc, CLd, and Vp. Figures 9.18 and 9.19 show the run of SAMPLE for this example.

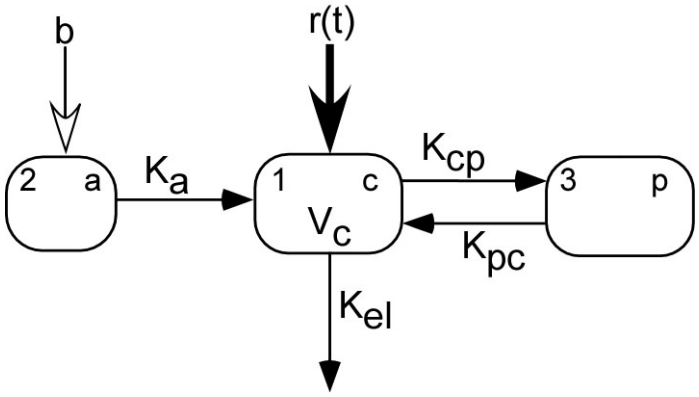


Figure 9.17 Model for example 2compsamp.

```
ADAPT 5    SAMPLE -- SAMPLE SCHEDULE DESIGN    Tue Feb 17 10:13:30 2007

 Enter file name for storing session run (*.run): 2compcl.run

      ----- MODEL INPUT INFORMATION -----

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\2compsamp.dat

 The number of model inputs:     1

 The number of bolus inputs:    0

 The number of input event times:     4

     Input Event Information
           Time    Value for all Inputs
 Event     Units,       R(1)
    1.     0.000          100.0
    2.     1.000          0.000
    3.     12.00          100.0
    4.     13.00          0.000

      ----- MODEL OUTPUT INFORMATION -----

 The number of model output equations:   1

 The number of sample times:    6

 For each sample number enter as required:
                 Sample
 Sample Number   Time , Optimize (Y/N)?
      1.        1.0000     n
      2.        6.0000     y
      3.        12.000     y
      4.        13.000     n
      5.        18.000     y
      6.        24.000     y
```

Figure 9.18 Sample run for 2compsamp

Figure 9.18 (continued)

```
Enter lower and upper time constraints. (Lower, Upper)    0.000     0.000

         ----- ENTER PARAMETER VALUES -----

 Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\2compsamp.prm

 Enter nominal values for parameters & specify those to be estimated:
                                          Estimated
            Old Nominal  New Nominal    in Design?
                       (skip if same)    (Y/N)
 CLt        3.000            y
 Vc         10.00            y
 CLd        5.000            y
 Vp         15.00            y
 IC(   1)   0.000            n
 IC(   2)   0.000            n

 Enter values for variance model parameters:
          Old Value     New Value (<Enter> if no change)
 SDinter    .2500
 SDslope    0.000

         ----- SELECT OPTIMALITY CRITERION -----

 D or C optimality?   d

 Enter maximum number of iterations:       500

 Do you want the iterations printed (Y/N)?  n

 Store inputs, sample times & data in a new file (Y/N)?  n

             ------ RESULTS ------

             --- A. Iterations ---

  Number of iterations      =      0
  Number of function calls  =      5

    Time(   1) =   1.000
    Time(   2) =   6.000
    Time(   3) =   12.00
    Time(   4) =   13.00
    Time(   5) =   18.00
    Time(   6) =   24.00

  Design criterion  = -0.241248E-02

              ---B. Iteration Summary---

  Convergence achieved
```

Figure 9.18 (continued)

```
 Number of iterations       =     63
 Number of function calls   =   1305

   Time(   1) =   1.000
   Time(   2) =   4.235
   Time(   3) =   13.00
   Time(   4) =   13.86
   Time(   5) =   17.49
   Time(   6) =   26.53

 Design criterion  =  -7.91296

            --- C. Sample Schedule Design Summary ---

 Tue Feb 17 10:13:30 2007

 Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\2compsamp.dat

 Model:  s2compcl.for: - 2 compart., CL param. - linear variance

 Convergence achieved
   Number of iterations:          66
   Number of function calls:    1300
 D-optimal criterion value:  -7.86040

                  Initial      Final
 Sample Time       Value       Value
   Time(   1)     1.000       1.000
   Time(   2)     6.000       4.235
   Time(   3)     12.00       13.00
   Time(   4)     13.00       13.86
   Time(   5)     18.00       17.49
   Time(   6)     24.00       26.53

Model Parameter Values used in the Design Calculations:

  System                       "Expected"
 Parameter       Value          SE (CV%)
  CLt           3.000            9.145
  Vc            10.00            6.936
  CLd           5.000            23.85
  Vp            15.00            28.96
  IC(   1)      0.000            Not estimated
  IC(   2)      0.000            Not estimated

Secondary                     "Expected"
 Parameter       Value          SE (CV%)
  Kel           .3000            11.87
  V             10.00            6.936
  Kcp           .5000            29.61
  Kpc           .3333            35.33
  LAM1          1.037            23.67
  LAM2          .9644E-01        27.33
  t1/2-LAM1     .6685            23.67
```

Figure 9.18 (continued)

```
 t1/2-LAM2     7.187            27.33

Variance
Parameter       Value
 SDinter       .2500
 SDslope       0.000

           --- D. Simulation Summary ---

Tue Feb 17 10:13:30 2007

Data file name (*.dat): C:\Program Files\BMSR\ADAPT 5\Examples\2compsamp.dat

Model:  s2compcl.for: - 2 compart., CL param. - linear variance

Y( 1)  Obs.Num.    Time        Model Simul.     Error Var.
           1       1.000         7.058           0.6250E-01
           2       4.235         1.920           0.6250E-01
           3       13.00         7.813           0.6250E-01
           4       13.86         4.821           0.6250E-01
           5       17.49         2.091           0.6250E-01
           6       26.53        0.8561           0.6250E-01

     ----- PLOTTING OPTIONS -----{Dialogue and program exit not shown}.
```

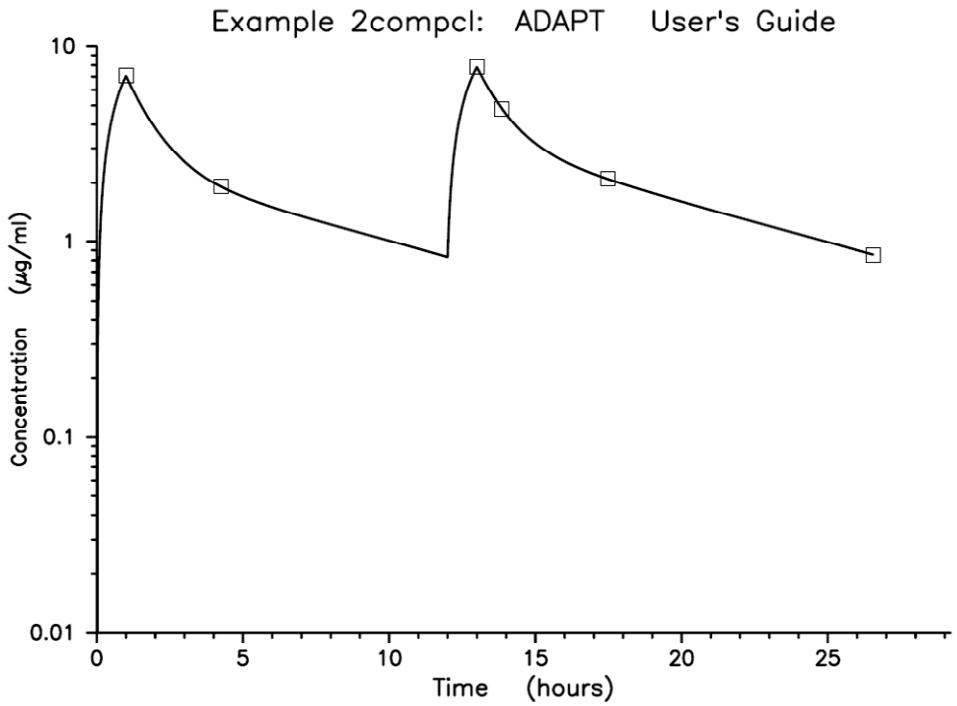


Figure 9.19 Example 2compsamp. Resulting plot show the fixed and optimized sample points.

CHAPTER 10

Some Population Modeling Examples

10.1 Example pop1: MLEM – PK Base Model

This example illustrates the use of the MLEM program to perform a population analysis using simulated plasma concentration data from 50 individuals following oral drug administration using the model shown in Figure 10.1. The population data file pop1.dat (not shown) contains the simulated data for each individual for an oral bolus dose of 100 mg along with six plasma concentration values ($\mu g / ml$) at 0.5, 1.0, 3.0, 5.0, 8.0 and 14.0 hours. The model file for this example was constructed by editing the 1compcl.for file in the ADAPT Library to include the initial guesses for the population model parameters. Figure 10.2 shows an excerpt from the edited model file (saved as pop1.for) showing subroutine POPINIT and the initial guesses entered for the population mean (`PmeanI(.)` code) and population covariance matrix (`PcovI(.,.)` code) (also see the discussion in Chapter 6.1). The initial guess for the variance elements of the population covariance matrix are set at a standard deviation of 40% of the mean initial guess. Since no off diagonal elements of the population covariance matrix are entered, the initial guesses for these three elements are taken to be 0.0. (Note that off-diagonal elements will be estimated even an initial guess of zero. To constrain selected, or all, off-diagonal elements to zero see discussion in Chapter 6.1). No other changes to the original 1compcl.for library model file are required. All ADAPT Library model files are available to be edited in this manner so they can be used with the population analysis programs MLEM and ITS.

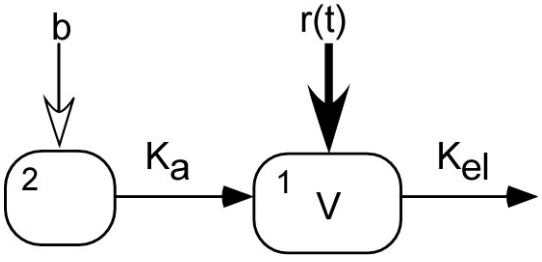


Figure 10.1 Model for example pop1.

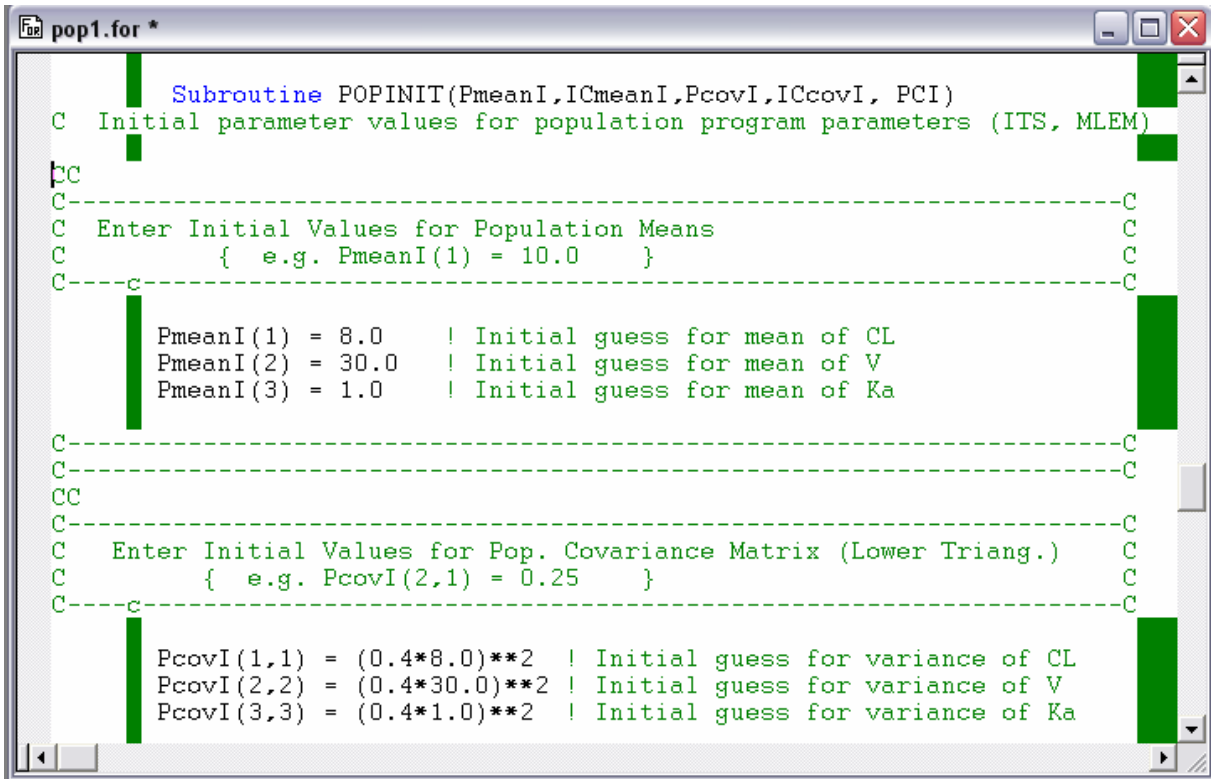


Figure 10.2 Excerpt from Subroutine POPINIT of model file pop1.for. This model file was created by editing the 1compcl.for file stored in the ADAPT Library folder via the edit option in the ADAPT interface Model Menu.

Figure 10.3 shows a portion of the run of the MLEM program for this example. In the program run, the Lognormal distribution option was selected for the model parameters and the Full population covariance matrix was selected to be estimated (versus assuming a diagonal population covariance matrix – see Chapter 6.1 for further discussion on specifying a structured covariance matrix). Finally, 1000 samples/EM iteration and 30 EM iterations were specified. As discussed in Chapter 5.3, the number of samples/EM iterations (M) determines the accuracy of the importance sampler numerical approximation used in the MLEM algorithm and a value of 1000 is generally large enough to produce two digits of accuracy in the estimates for the examples in the ADAPT library. More complicated models with more parameters may require a larger value for M in the importance sampler. If the `-logLikehood` value displayed in the MLEM command window at each iteration during the course of the run (not shown here) shows an increasing trend over several iterations, this may indicate that the value of M needs to be larger. The MLEM algorithm will perform the number of iterations specified and convergence is assessed by the user, in part via inspection of the parameter estimate versus iteration plots displayed in the MLEM plot window during the course of the program run (also see discussion regarding the created *IT.csv file below).

The last portion of the pop1.run file is shown in Figure 10.3 and provides a summary of the population analysis. The table in section A gives the estimates for the population mean of the

parameters and the interindividual standard deviation along with their respective relative standard errors (see Chapter 4). The full population covariance matrix estimates are given in section B of the MLEM final population summary, while section D gives the estimates for the error variance model parameters. At the end of the run is a list of all the files created by the program, which have been discussed in general in Chapter 5. The middle portion of the pop1.run file (not sown in Figure 10.3) provides the conditional estimation results for each of the 50 individuals at the last EM iteration.

```
 ADAPT 5  MLEM -- MAXIMUM LIKELIHOOD EM POP. EST.  Fri Jan  9 10:16:00 2009

Enter file name for storing session run (*.run): pop1.run

     ----- MODEL INPUT/OUTPUT INFORMATION -----

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop1.dat

   - Successfully read all   50 subjects in the data file.

Enter the compartment number for each bolus input (e.g. 1,3,...):    2

    ----- INITIALIZE PARAMETERS -----

Parameter file name: D:\AdaptV5\usersguide\Examples\pop1.prm

Indicate which parameters are to be estimated:

              Value     Estimate? (Y/N)
CL           8.000           y
V            30.00           y
Ka           1.000           y
IC(   1)     0.000           n
IC(   2)     0.000           n
SDinter     0.1000           y
SDslope     0.1000           y

Fix non estimated parameters to subject specific values (Y/N)?  n

Select parameter distribution model (1 - Normal, 2 - Lognormal):  2

Select full or diagonal covariance matrix (1 - Full, 2 - Diagonal):  1

Enter number of samples/EM iteration (1000 - 3000):      1000

Enter number of EM iterations:        30

     _____________________________________________

     ----- INDIVIDUAL SUBJECT RESULTS    {Output not shown}-----
```

Figure 10.3 MLEM run for example pop1.

Figure 10.3 (continued)

```
     ----- MLEM FINAL POPULATION PARAMETER ESTIMATES -----

 Fri Jan  9 10:17:32 2009

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop1.dat

 Model:  POP1.FOR: - 1 comp. pop. example base model

 Number of data sets analyzed successfully:    50

 Importance Sampler with number samples/iteration:    1000

 Total number of EM iterations:   30

 Lognormal distribution option

-2logLikelihood:   -258.991

 Model Selection Criteria
  AIC:       -236.991
  BIC:       -196.249

        --- A. Population Mean & Population Standard Deviation ---

 Parameter     Mean        %RSE         Std.Dev.   SD as CV%     %RSE
  CL           8.10        3.81          1.99        24.6        16.2
  V            30.8        4.14          7.44        24.2        19.4
  Ka           1.02        4.23         0.207        20.4        18.4
  IC(   1)     0.00      Not estimated
  IC(   2)     0.00      Not estimated

        --- B. Full Population Covariance of Estimated Parameters ---

  As Covariance Matrix:

           CL        V         Ka
 CL         3.97
 V         -3.32      55.4
 Ka        -.223E-01 0.164     0.429E-01

  As Covariance Matrix for ln(parameters):

           CL        V         Ka
 CL        0.604E-01
 V         -.133E-01 0.584E-01
 Ka        -.271E-02 0.524E-02 0.415E-01

  As Correlation Matrix:

           CL        V         Ka
 CL          1.00
 V          -0.22      1.00
 Ka         -0.05      0.11      1.00
```

Figure 10.3 (continued)

```
  Standard Errors of Estimated Covariance Matrix for ln(parameters):

           CL        V         Ka
CL        0.197E-01
 V         0.122E-01 0.227E-01
 Ka        0.120E-01 0.131E-01 0.159E-01

       --- D. Error Variance Model Parameters ---

Parameter     Estimate    %RSE
  SDinter     0.167E-02   141.
  SDslope     0.105       2.25

        --- E. Secondary Parameters: Pop. Mean & Pop. Std. Dev. ---

 Parameter     Mean       Std.Dev.
  Kel         0.263      0.100
  LAM1        0.263      0.100
  t1/2-LAM1    2.63       1.00

        --- F. Population Mean and Covariance (ADAPT Format) ---

       Pmean(  1) =   8.103535         ! CL
       Pmean(  2) =   30.80188         ! V
       Pmean(  3) =   1.016579         ! Ka

       Pcov(  1,  1) =   3.969320      ! CL         & CL
       Pcov(  2,  1) =  -3.317430      ! V          & CL
       Pcov(  2,  2) =   55.37318      ! V          & V
       Pcov(  3,  1) = -0.2230249E-01  ! Ka         & CL
       Pcov(  3,  2) =  0.1641737      ! Ka         & V
       Pcov(  3,  3) =  0.4292971E-01  ! Ka         & Ka

     ____________________________________________

List of Files Created

  Record of program run and all results:
    pop1.run
  Summary of population estimates at each iteration:
    pop1IT.csv
  Individual subject estimates at final iteration:
    pop1IND.csv
  Table of predictions and residuals for each subject:
    pop1RSD.csv
  Information for plotting model predictions for each subject:
    pop1PLT.csv
  Composite residual and prediction vs measurements graphs and
  individual subject model prediction and measurement vs time graphs:
    pop1.eps
  Command file for subsequent Batch runs:
    pop1.aci

     ____________________________________________
```

Figure 10.4 below shows several of the plots stored in the pop1.eps file. Additional plots in the file that are not shown in Figure 10.4 include all the plots used to assess convergence and displayed in the ADAPT plot window during the program run, additional residual plots, as well as the concentration-time curves for all of the individuals constructed using the conditional mean estimates for the subjects.

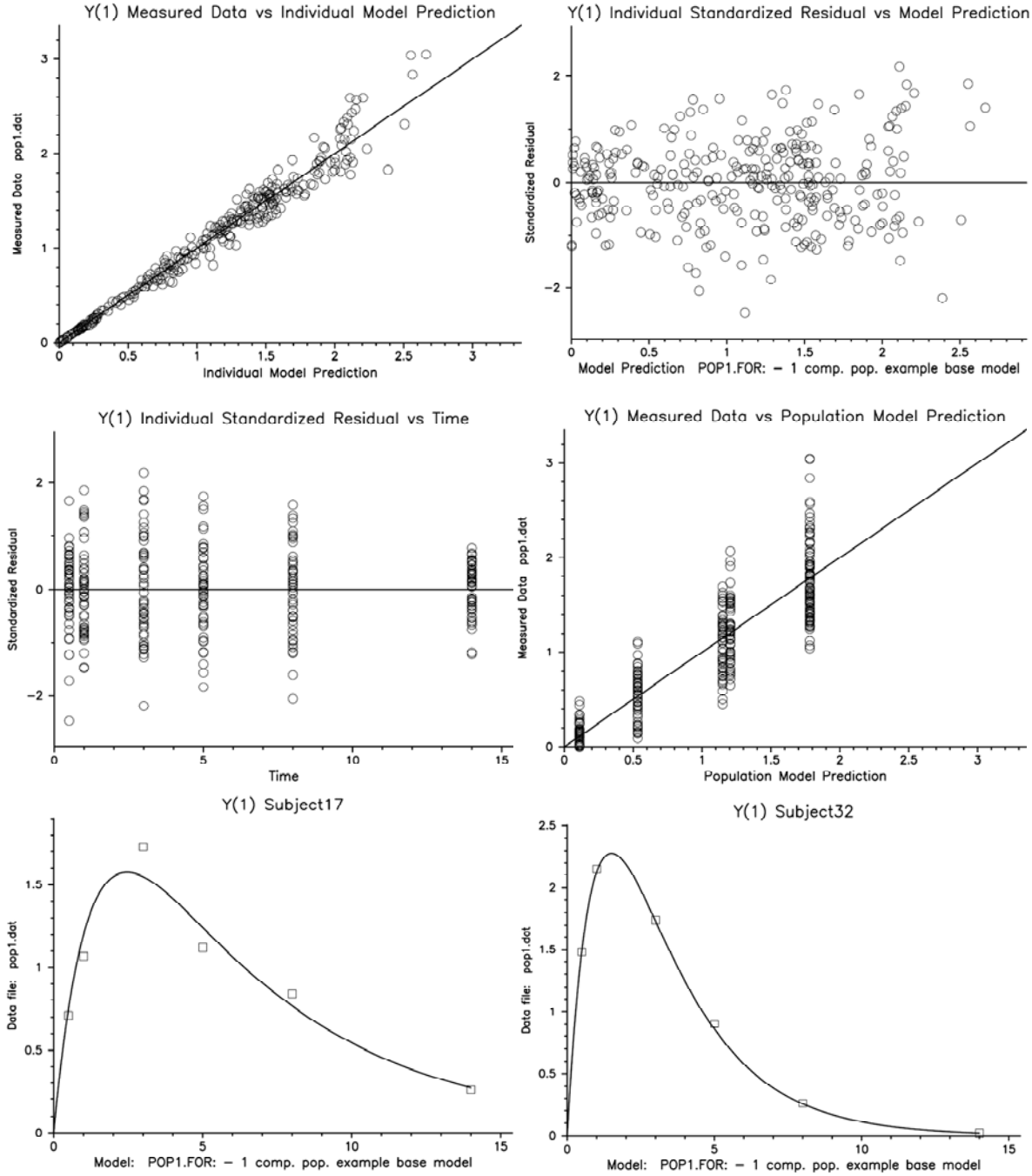


Figure 10.4 Example pop1. Selected plots from the file pop1.eps. Concentrations in $\mu g / ml$.

The estimation results for each of the individuals are stored in the file pop1IND.csv, a portion of which is shown in Table 10.1 (all results are defined in Chapter 4). For each individual, the table gives for the values for all model parameters (estimated conditional means and non estimated values - $CL\,(L/hr)$, $V\,(L)$, $Ka\,(hr^{-1})$, $IC(1)\,(mg)$, $IC(2)\,(mg)$), as well as values of the error variance parameters (estimated and non estimated - SDinter, $SDslope$). Subsequent columns in the table give, for each individual, the values for any secondary parameters (Kel, $LAM1$, $t1/2-LAM1$), the negative loglikelihood ($NegLogLike$), the conditional covariance values (CL/CL, V/CL, V/V, Ka/CL, Ka/V, Ka/Ka), values for any model inputs from the data file ($R(1)$, $R(2)$) values for the conditional mean minus the population mean for all estimated model parameters ($CL-\mu_{CL}$, $V-\mu_V$, $Ka-\mu_{Ka}$), and values for the conditional modes (not shown). This file can be used to perform more detailed analyses and visual display of individual subject results.

Table 10.1 Example pop1. Section of file pop1IND.csv.

```
Created by:        MLEM
Model Description: POP1.FOR: - 1 comp. pop. example base model
Num of Diff. Eqs. # Sys. Params # Var. Params # of Covariate Params
         2                3               2                0
Individ.# Individ.ID    'CL'       'V'      'Ka'    'IC(1)'   'IC(2)'   •••
          Estimated?     Y          Y        Y       N         N
1         'Subject1'  5.83810   23.6576   1.32678    0.00000   0.00000
2         'Subject2'  12.0612   32.7264   1.10975    0.00000   0.00000
3         'Subject3'  9.03042   37.8750   0.783812   0.00000   0.00000
                                   •••
50        'Subject50' 10.1362   37.1951   0.975136    0.00000   0.00000

•••'Sdinter'      'Sdslope'    'Kel'     'LAM1'  't1/2-LAM1'   'NegLogLike'•••
       Y            Y
   0.162406E-02   0.104733   0.247587    0.247587    2.80757    3.81014
   0.162406E-02   0.104733   0.369555    0.369555    1.87984    -4.68287
   0.162406E-02   0.104733   0.239648    0.239648    2.90756    -2.11896
                                   •••
   0.162406E-02   0.104733   0.273657    0.273657    2.54197    -4.72100

•••  'CL/CL'        'V/CL'          'V/V'         'Ka/CL'        'Ka/V'•••
   0.182010E-02   0.227279E-02   0.556469E-02   0.144243E-02   0.582041E-02
   0.230858E-02   0.280849E-02   0.555330E-02   0.144243E-02   0.582041E-02
   0.203119E-02   0.191045E-02   0.703263E-02   0.535889E-03   0.582041E-02
                                   •••
   0.201808E-02   0.263949E-02   0.683308E-02   0.163348E-02   0.717409E-02

••• 'Ka/Ka'       'R( 1)'    'R( 2)'    'CL-mean'   'V-mean'    'Ka-mean'•••
   0.158254E-01   0.00000    47.730     -2.26543    -7.14429    0.310198
   0.155714E-01   0.00000    103.910     3.95763    1.92449     0.931757E-01
   0.160259E-01   0.00000    70.5300     0.926888   7.07315     -0.232767
                                   •••
   0.162418E-01   0.00000    104.110     2.03267    6.39317     -0.414422E-01
```

The program also creates an iteration summary file (pop1IT.csv, not shown) containing the population estimates at each iteration of the EM algorithm (1 – 30 for this example). The pop1IND.csv file along with the pop1IT.csv file are used when continuing the EM algorithm for additional iterations. This is accomplished by selecting the the pop1IND.csv file in the parameter menu of the ADAPT Interface (the program will retrieve the population parameters estimates at the last iteration in the corresponding *IT.csv file – pop1IT.csv in this case).

The remaining files created by the program run include the iteration file pop1IT.csv shown in Table 10.2, as well as the residual file pop1RSD.csv, the raw data plot file pop1PLT.csv, and the command input file pop1.aci (the latter three are not shown.). The pop1RSD.csv file can be used to create customized residual plots. The complete contents of all files created can be viewed in the `\Example` subfolder of the installation.

Table 10.2 Example pop1. Section of file pop1IT.csv.

```
Created by:         MLEM
Model Description: POP1.FOR: - 1 comp. pop. example base model
LognormalPopulationOption
Iteration       'CL'       'V'       'Ka'       'CL/CL'       'V/CL'     •••
    0           8.00000    30.0000   1.00000    0.160000      0.00000
    1           8.26889    30.8460   0.998223   0.651266E-01  -0.717103E-02
    2           8.09862    30.4296   1.00536    0.614439E-01  -0.126448E-01
                                     •••
    30          8.10353    30.8019   1.01658    0.604459E-01  -0.132908E-01

•••'V/V'          'Ka/CL'        'Ka/V'         'Ka/Ka'        'SDinter'  •••
   0.160000       0.00000        0.00000        0.160000       0.100000
   0.770847E-01   0.703480E-03   0.280941E-01   0.945759E-01   0.125441E-01
   0.703618E-01   -0.202568E-02  0.211628E-01   0.710464E-01   0.748325E-02
                                    •••
   0.583640E-01   -0.270731E-02  0.524307E-02   0.415409E-01   0.166726E-02

•••'SDslope'      'NegLogLikelihood'
   0.100000
   0.768214E-01
   0.928054E-01   -110.013
            •••
   0.104527       -129.495
```

10.2 Example pop2: MLEM – PK Model with Covariates

In the previous example, the data file also included each individual's CrCl (ml/min) as a model input (model input 2). (In the library model file 1compcl.for from which the model file pop1.for was created, model input 1, `R(1)`, is reserved for any IV infusion.) As shown in Table 10.1, all model inputs (`R(1)` and `R(2)` in this case) from the data file are also listed in the pop1IND.csv file created by MLEM. Thus the pop1IND.csv file can be used to explore possible covariate models by plotting the conditional mean estimates versus covariates. Figure 10.5 is a plot constructed from pop1IND.csv showing the conditional mean of CL versus CrCl (`R(2)`) for

each of the 50 individuals analyzed in example pop1. The plot in Figure 10.5 suggests a linear covariate model for the mean CL in the Stage 2 population model.

Figures 10.6 and 10.7 shows the modifications needed to the model file of example pop1 to incorporate a Stage 2 covariate model for CL. Subroutine COVMOD shown in Figure 10.6 includes specification of the total number of parameters in the covariate models (one in this case), symbols for each of the covariate model parameters, and each of the covariate models (in this case a linear model relating mean CL to CrCl model input `R(2)`). Subroutine POPINIT is modified from that used in example pop1 and shown in Figure 10.2 by adding the initial guess for the covariate model parameter.

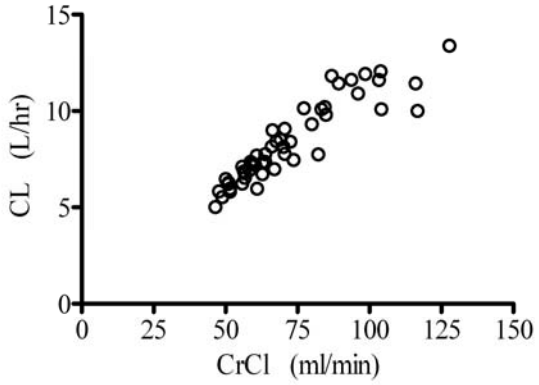


Figure 10.5 Conditional mean of CL versus CrCl constructed from the pop1IND.csv file.

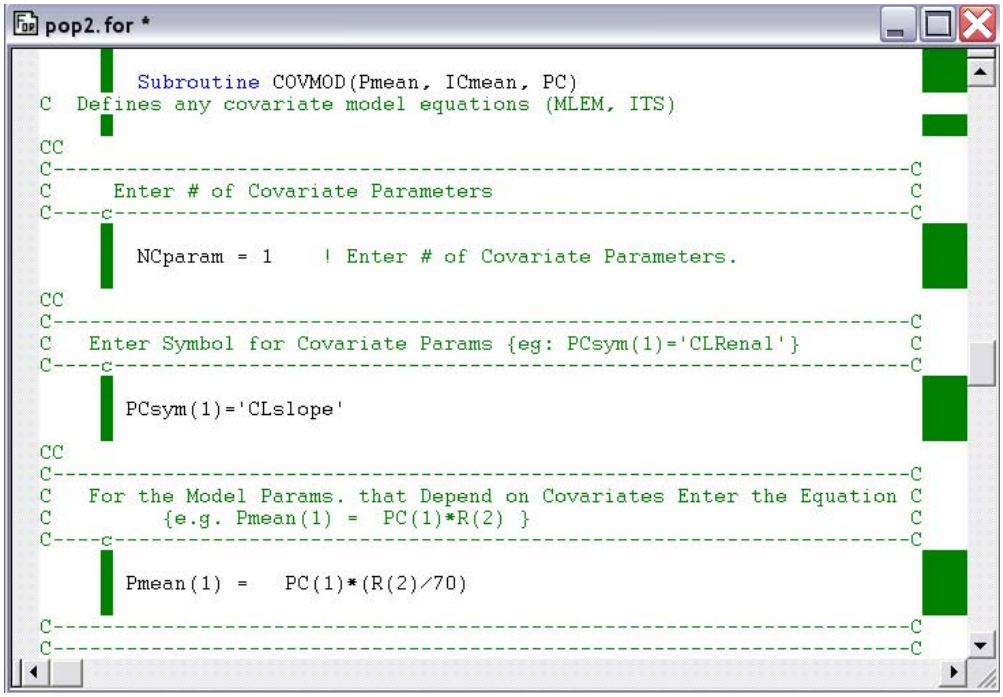


Figure 10.6 Excerpts from Subroutine COVMOD of model file pop2.for.

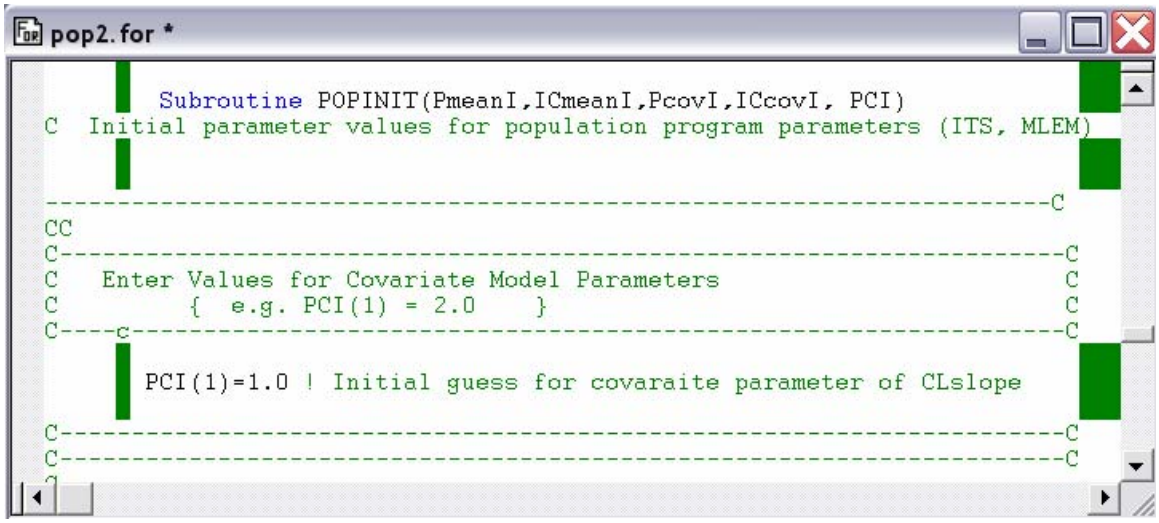


Figure 10.7 Excerpts from Subroutine COVMOD of model file pop2.for.

Figure 10.8 shows a portion of the run of the MLEM program for this example. Compare the resulting estimation results with those from the base model shown in Figure 10.3.

```
  ADAPT 5  MLEM -- MAXIMUM LIKELIHOOD EM POP. EST.  Thu Jan  8 11:57:19 2009

Enter file name for storing session run (*.run): pop2.run

      ----- MODEL INPUT/OUTPUT INFORMATION -----

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop2.dat

    - Successfully read all   50 subjects in the data file.

 Enter the compartment number for each bolus input (e.g. 1,3,...):    2

     ----- INITIALIZE PARAMETERS -----

 Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop2.prm

 Indicate which parameters are to be estimated:

               Value     Estimate? (Y/N)
 CLt          8.000           y
 Vc           30.00           y
 Ka           1.000           y
 IC(   1)     0.000           n
 IC(   2)     0.000           n
 SDinter     0.1000           y
 SDslope     0.1000           y
```

Figure 10.8 MLEM run for example pop2.

Figure 10.8 (continued)

```
 Fix non estimated parameters to subject specific values (Y/N)?  n

 Indicate which covariate model parameters are to be estimated:

              Value     Estimate? (Y/N)
 CLslope      1.000          y

 Select parameter distribution model (1 - Normal, 2 - Lognormal):  2

 Select full or diagonal covariance matrix (1 - Full, 2 - Diagonal):  1

 Enter number of samples/EM iteration (1000 - 3000):      1000

 Enter number of EM iterations:        30

      ____________________________________________


      ----- MLEM FINAL POPULATION PARAMETER ESTIMATES -----

 Thu Jan  8 11:58:46 2009

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop2.dat

 Model:  POP2.FOR: - 1 comp. pop. example w/ covariate

 Number of data sets analyzed successfully:    50

 Importance Sampler with number samples/iteration:    1000

 Total number of EM iterations:   30

 Lognormal distribution option

 -2logLikelihood:   -354.709

 Model Selection Criteria
  AIC:       -332.709
  BIC:       -291.968

        --- A. Population Mean & Population Standard Deviation ---

 Parameter     Mean        %RSE         Std.Dev.    SD as CV%     %RSE
  CL            --          --            --         8.27         14.9
  V            30.8        4.13          7.40        24.0         18.1
  Ka           1.02        4.26         0.205        20.2         18.0
  IC(   1)     0.00      Not estimated
  IC(   2)     0.00      Not estimated
```

Figure 10.8 (continued)

```
       --- B. Full Population Covariance of Estimated Parameters ---

  As Covariance Matrix for ln(parameters):

           CLt       Vc        Ka
 CL        0.685E-02
 V         -.457E-03 0.575E-01
 Ka        -.870E-03 0.466E-02 0.408E-01

  As Correlation Matrix:

           CLt       Vc        Ka
 CL          1.00
 V          -0.02      1.00
 Ka         -0.05      0.10      1.00

  Standard Errors of Estimated Covariance Matrix for ln(parameters):

           CLt       Vc        Ka
 CL        0.205E-02
 V         0.423E-02 0.210E-01
 Ka        0.380E-02 0.133E-01 0.151E-01

             --- C. Covariate Model Parameters ---

Parameter     Estimate    %RSE
  CLslope      8.13       1.64

        --- D. Error Variance Model Parameters ---

Parameter     Estimate    %RSE
  SDinter     0.171E-02   135.
  SDslope     0.105       2.20

      ____________________________________________

List of Files Created

  Record of program run and all results:
    pop2.run
  Summary of population estimates at each iteration:
    pop2IT.csv
  Individual subject estimates at final iteration:
    pop2IND.csv
  Table of predictions and residuals for each subject:
    pop2RSD.csv
  Information for plotting model predictions for each subject:
    pop2PLT.csv
  Composite residual and prediction vs measurements graphs and
  individual subject model prediction and measurement vs time graphs:
    pop2.eps
  Command file for subsequent Batch runs:
    pop2.aci
      ____________________________________________
```

10.3 Example pop3: MLEM – PK/PD Sequential Analysis

This example involves population parameter estimation using the indirect response model illustrated in Figure 10.9. The pharmacokinetic portion of the model consists of a two compartment linear model (clearance parameterization) with intravenous drug administration (100.0 mg/hr over 1.0 hr). The complete equations defining this PK/PD model have been introduced previously for example pd3 in Chapter 8.3.

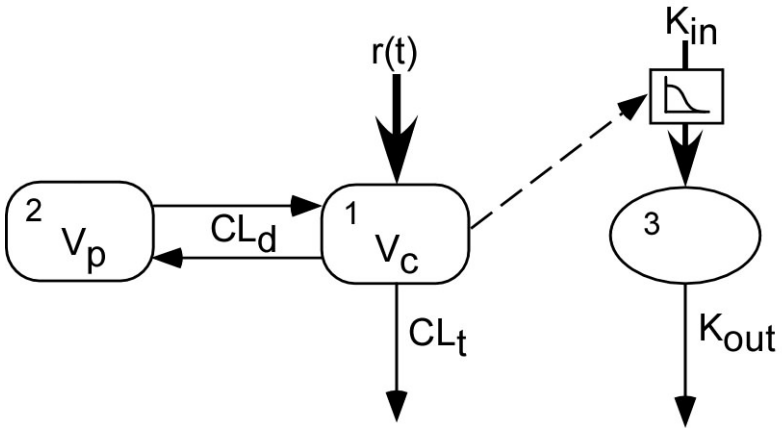


Figure 10.9 Model for example pop3.

Both PK (plasma concentration) and PD (response variable) measurements are available from 50 simulated subjects, which will be used to perform a sequential population analysis. First a population PK analysis will be performed using the plasma concentration data alone, which will yield a population PK model as well as estimates for the PK parameters for each of the 50 subjects. Next, each individual's estimated PK parameters (conditional means) will then be used to perform a population analysis using the PD response data only, resulting in a population model for the indirect response portion of the model.

The two equations for the PK portion of the model have been coded and entered into the model file pop3PK.for. Initial guesses for all population mean and population covariance parameters are entered in the POPINIT subroutine in the model file pop3PK.for. Figure 10.10 shows a portion of the run of the MLEM program for this example using data file pop3PK.dat and parameter file pop3PK.prm. In the program run, the Lognormal distribution option was selected for the model parameters and the Diagonal population covariance matrix was selected. Figure 10.11 shows several of the plots stored in the pop3PK.eps file, including selected composite residual plots as well as concentration-time curves for selected individuals constructed using the conditional mean estimates for the subjects. The conditional mean estimates for each of the 50 subjects are store in the file pop3PK.ind and will be used as described below in modeling of the PD response.

```
ADAPT 5  MLEM -- MAXIMUM LIKELIHOOD EM POP. EST.  Sun Jan 18 09:58:13 2009

 Enter file name for storing session run (*.run): pop3PK.run

      ----- MODEL INPUT/OUTPUT INFORMATION -----

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop3PK.dat

    - Successfully read all   50 subjects in the data file.

     ----- INITIALIZE PARAMETERS -----

 Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop3PK.prm

 Indicate which parameters are to be estimated:

               Value     Estimate? (Y/N)
 CLt          6.000           y
 Vc           30.00           y
 CLd          12.00           y
 Vp           60.00           y
 IC(   1)     0.000           n
 IC(   2)     0.000           n
 SDinterPK    0.000           n
 SDslopePK   0.1000           y

 Fix non estimated parameters to subject specific values (Y/N)?  n

 Select parameter distribution model (1 - Normal, 2 - Lognormal):  2

 Select full or diagonal covariance matrix (1 - Full, 2 - Diagonal):  2

 Enter number of samples/EM iteration (1000 - 3000):      1000

 Enter number of EM iterations:        25

      ------------------------------------------

      ----- MLEM FINAL POPULATION PARAMETER ESTIMATES -----

 Sun Jan 18 10:05:28 2009

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop3PK.dat

 Model:  POP3PK.for - 2 comp CL, PK part of PK/PD pop modeling

 Number of data sets analyzed successfully:    50

 Importance Sampler with number samples/iteration:    1000

 Total number of EM iterations:   25

 Lognormal distribution option

 -2logLikelihood:   -1862.36
```

Figure 10.10 MLEM run for example pop3 – PK portion.

Figure 10.10 (continued)

```
 Model Selection Criteria
  AIC:       -1844.36
  BIC:       -1803.40

        --- A. Population Mean & Population Standard Deviation ---

 Parameter     Mean        %RSE         Std.Dev.   SD as CV%     %RSE
  CLt          5.58        4.72          1.74        31.2        13.5
  Vc           30.2        5.64          9.22        30.5        17.4
  CLd          11.8        4.91          3.41        29.0        15.1
  Vp           57.5        4.32          15.5        27.0        11.8
  IC(   1)     0.00      Not estimated
  IC(   2)     0.00      Not estimated

        --- B. Full Population Covariance of Estimated Parameters ---

  As Covariance Matrix:

           CLt       Vc        CLd       Vp
 CLt        3.04
 Vc         0.00      85.0
 CLd        0.00      0.00       11.6
 Vp         0.00      0.00       0.00       241.

  As Covariance Matrix for ln(parameters):

           CLt       Vc        CLd       Vp
 CLt       0.976E-01
 Vc         0.00     0.930E-01
 CLd        0.00      0.00     0.839E-01
 Vp         0.00      0.00      0.00     0.729E-01

  Standard Errors of Estimated Covariance Matrix for ln(parameters):

           CLt       Vc        CLd       Vp
 CLt       0.233E-01
 Vc        -1.00     0.259E-01
 CLd       -1.00     -1.00     0.227E-01
 Vp        -1.00     -1.00     -1.00     0.181E-01

        --- D. Error Variance Model Parameters ---

Parameter     Estimate    %RSE
  SDslopePK   0.979E-01   3.28
  SDinterPK    0.00      Not estimated

        --- F. Population Mean and Covariance (ADAPT Format) ---
... {Not Shown}

List of Files Created ... {Not Shown}


  ADAPT 5  MLEM -- MAXIMUM LIKELIHOOD EM POP. EST.  Sun Jan 18 10:05:30 2009
```

Figure 10.10 (continued)

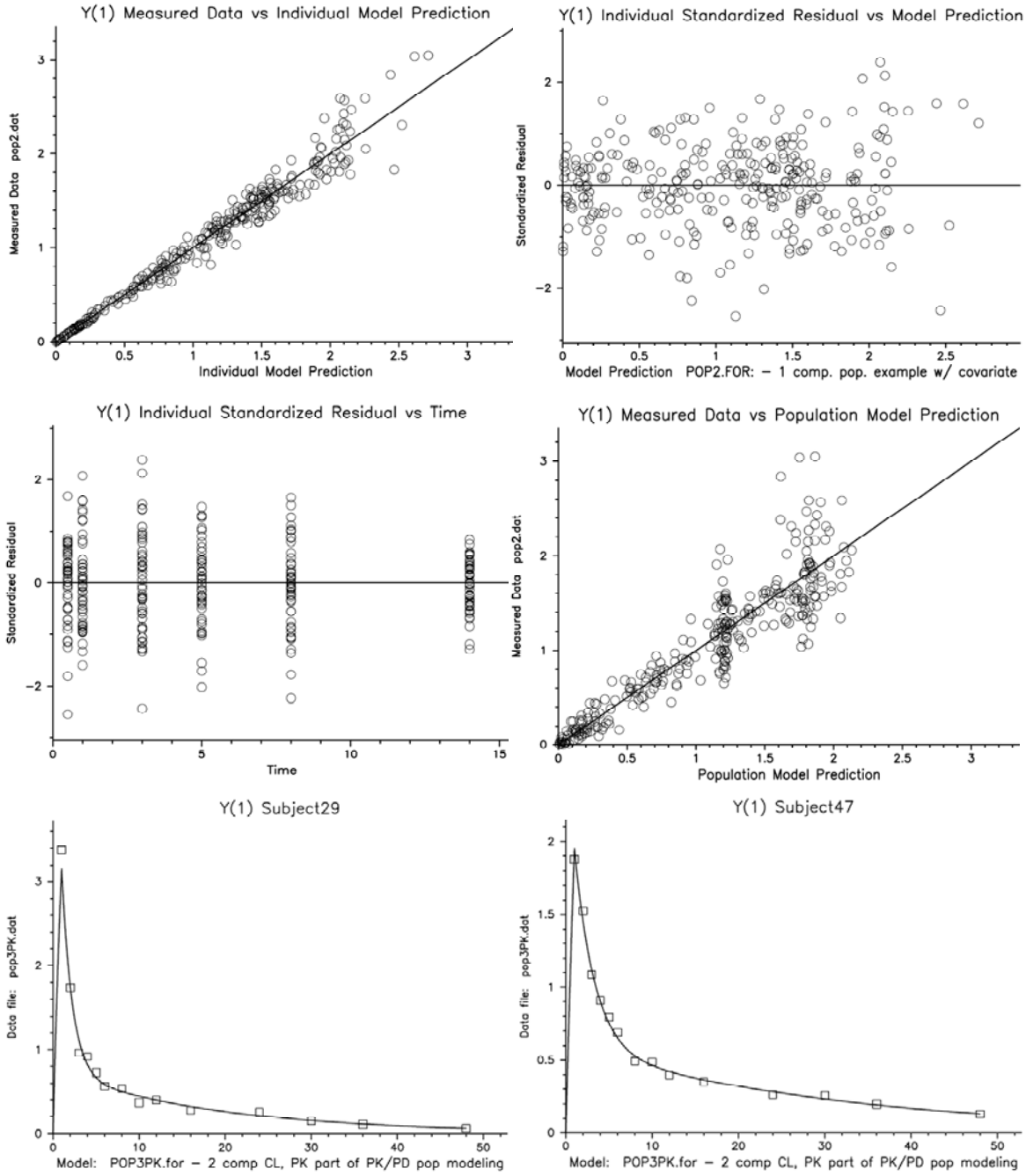


Figure 10.11 Example pop3 – PK portion. Selected plots from the file pop3PK.eps.

The equations for the complete PK/PD model have been coded and entered into the model file pop3PD.for with the PD response as the single output. Initial guesses for only those

population mean and population covariance PD parameters to be estimated K_{in}, $IC50$ and $IC(3)$ are entered in subroutine POPINIT of the model file pop3PD.for. Using the pop3PK.ind file created from the PK analysis above, a file name pop3PKFIX.csv containing the estimated PK parameters from each of the 50 subjects has been created as shown in Table 10.3.

Table 10.3 Example pop3. Section of file pop3PKFIX.csv created from pop3PKIND.csv.

```
pop3PKFIX.csv - For example pop3
6
Num  IndividID   'CLt'     'Vc'      'CLd'     'Vp'     'IC(   1)' 'IC(   2)'
1    'Subject1'   8.28365   29.2557   7.60259   40.069   0          0
2    'Subject2'   8.77795   42.0821   8.97461   48.624   0          0
3    'Subject3'   5.03366   33.9735   16.7842   45.5373  0          0
                                    •••
50   'Subject50'  4.60157   33.2455   10.5916   47.5017  0          0
```

Figure 10.11 shows a portion of the run of the MLEM program for this example using data file pop3PD.dat and parameter file pop3PD.prm. The PK model parameters ($CL_t, V_C, CL_d, V_P, IC(1), IC(2)$) are not estimated, but they are fixed to their subject specific estimates as read from the file pop3PDFIX.csv. In the program run, the Lognormal distribution option was selected for the model parameters and the Diagonal population covariance matrix was selected. Figure 10.12 shows several of the plots stored in the pop3PD.eps file.

```
ADAPT 5  MLEM -- MAXIMUM LIKELIHOOD EM POP. EST.  Mon Jan 19 09:29:30 2009

Enter file name for storing session run (*.run): pop3PD.run

      ----- MODEL INPUT/OUTPUT INFORMATION -----

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop3PD.dat

    - Successfully read all   50 subjects in the data file.

     ----- INITIALIZE PARAMETERS -----

 Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop3PD.prm

 Indicate which parameters are to be estimated:

               Value     Estimate? (Y/N)
 CLt          6.000           n
 Vc           30.00           n
 CLd          12.00           n
 Vp           60.00           n
 Kin          20.00           y
 IC50        0.5000           y
```

Figure 10.12 MLEM run for example pop3 – PD portion.

Figure 10.12 (continued)

```
IC(   1)    0.000           n
IC(   2)    0.000           n
IC(   3)    100.0           y
SDinterPD   5.000           y
SDslopePD   0.000           n

Fix non estimated parameters to subject specific values (Y/N)?  y

Enter file name with individual subject values (*FIX.csv): pop3PKFIX.csv

Select parameter distribution model (1 - Normal, 2 - Lognormal):  2

Select full or diagonal covariance matrix (1 - Full, 2 - Diagonal):  2

Enter number of samples/EM iteration (1000 - 3000):      1000

Enter number of EM iterations:        15
```

```
     ----- MLEM FINAL POPULATION PARAMETER ESTIMATES -----

Mon Jan 19 09:34:05 2009

Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop3PD.dat

Model:  POP3PD.for - IRM, PD part of PK/PD pop modeling

Number of data sets analyzed successfully:    50

Importance Sampler with number samples/iteration:    1000

Total number of EM iterations:   15

Lognormal distribution option

-2logLikelihood:    4697.25

Model Selection Criteria
 AIC:        4711.25
 BIC:        4743.11

       --- A. Population Mean & Population Standard Deviation ---

Parameter     Mean        %RSE         Std.Dev.    SD as CV%     %RSE
 Kin          19.1        5.78          6.41         33.6         13.4
 IC50        0.481        6.54         0.184         38.3         16.3
 IC(   3)     96.8        3.96          25.9         26.8         15.6
 CLt          5.86      Not estimated
 Vc           31.6      Not estimated
 CLd          12.3      Not estimated
 Vp           59.7      Not estimated
```

Figure 10.12 (continued)

```
 IC(   1)     0.00      Not estimated
 IC(   2)     0.00      Not estimated

       --- B. Full Population Covariance of Estimated Parameters ---

 As Covariance Matrix:

          Kin       IC50      IC(   3)
Kin        41.1
IC50       0.00     0.340E-01
IC(   3)   0.00      0.00      670.

 As Covariance Matrix for ln(parameters):

          Kin       IC50      IC(   3)
Kin       0.113
IC50       0.00     0.147
IC(   3)   0.00      0.00     0.716E-01

 Standard Errors of Estimated Covariance Matrix for ln(parameters):

          Kin       IC50      IC(   3)
Kin       0.294E-01
IC50      -1.00     0.379E-01
IC(   3)  -1.00     -1.00     0.215E-01

       --- D. Error Variance Model Parameters ---

Parameter     Estimate    %RSE
 SDinterPD     4.99       3.93
 SDslopePD     0.00      Not estimated

       --- F. Population Mean and Covariance (ADAPT Format) ---  {Not Shown}
```

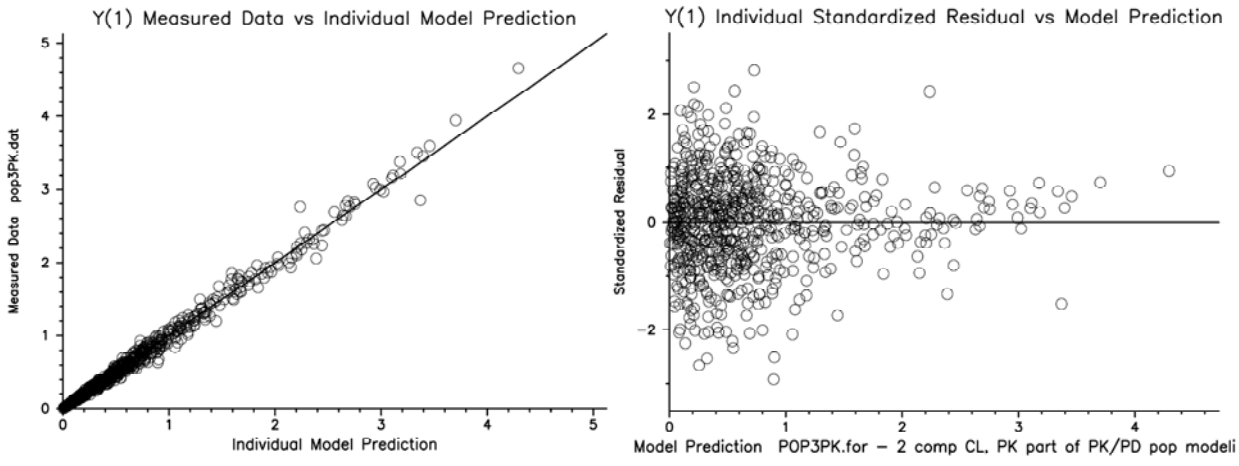


Figure 10.13 Example pop3 – PD portion. Selected plots from the file pop3PD.eps.

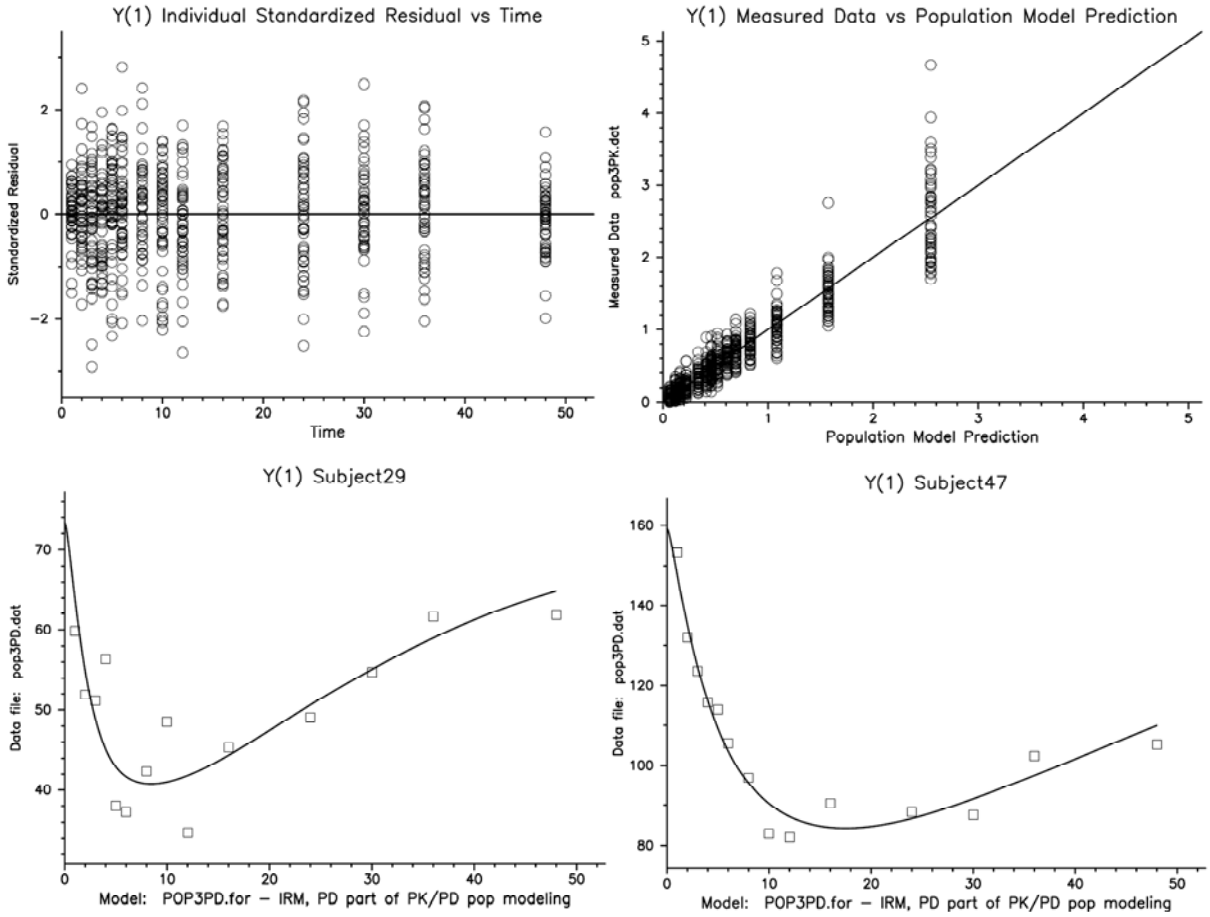


Figure 10.13 (cont.) Example pop3 – PD portion. Selected plots from the file pop3PD.eps.

10.4 Example pop4: STS – ML Estimation

In this example the STS program applied to the model and data used in example pop1 above. The exact model, data and parameters files used for the pop1 example are used here but have been renamed to pop4.for, pop4.dat and pop4.prm. Figure 10.14 shows a run of the STS program using the ML estimation option (initial section and estimation summary sections), while Figure 10.15 shows selected plots from the file pop4.eps. These results can be compared to the corresponding results obtain using the MLEM program. As described on Chapter 6.3, the file created containing each individual's parameter estimates, pop4IND.csv, can be used in the place of a *.prm file if the STS program is rerun. The values in the pop4IND.csv file will then serve as the individual specific initial guesses for the estimated parameters.

```
ADAPT 5  STS -- STANDARD TWO STAGE POP. EST.  Mon Jan 19 10:24:18 2009

Enter file name for storing session run (*.run): pop4.run

      ----- MODEL INPUT/OUTPUT INFORMATION -----

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop4.dat

    - Successfully read all   50 subjects in the data file.

 Enter the compartment number for each bolus input (e.g. 1,3,...):    2

      ----- ESTIMATOR SELECTION -----

 The following estimation procedures are available:
      1. Weighted least squares (WLS)
      2. Maximum likelihood (ML)
      3. Maximum a posteriori probability (MAP)

 Enter option number:  2

     ----- INITIALIZE ESTIMATION PROCEDURE -----

 Parameter file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop4.prm

 Enter initial values for parameters & specify those to be estimated:

            Old Value    New Value      Estimate?
                       (skip if same)    (Y/N)
 CL         8.000            y
 V          30.00            y
 Ka         1.000            y
 IC(   1)   0.000            n
 IC(   2)   0.000            n
 SDinter    .1000            y
 SDslope    .1000            y

 Fix non estimated parameters to subject specific values (Y/N)?  n

 Enter maximum number of iterations per subject:       999

      ----- SUMMARY OF PARAMETER ESTIMATES -----

 Mon Jan 19 10:24:56 2009

 Data file name: C:\Program Files\BMSR\ADAPT 5\Examples\pop4.dat

 Model:  POP4.FOR: - 1 comp. pop. example base model

 Number of data sets analyzed successfully:    50
```

Figure 10.14 STS run for example pop4.

Figure 10.14 (continued)

```
            --- A. System Parameters ---

Parameter     Mean      Median     Std.Dev.    Min        Max
 CL           8.347      7.734      2.159      4.930      13.56
 V            31.65      31.02      8.888      10.04      53.18
 Ka           1.064      1.023     0.3468     0.3007      2.126
 IC(   1)     0.000     Not estimated
 IC(   2)     0.000     Not estimated


            --- B. Variance Model Parameters ---

Parameter     Mean      Median     Std.Dev.    Min        Max
 SDinter     0.8893E-02 0.2141E-07 0.2106E-01 0.1695E-11 0.8708E-01
 SDslope     0.5620E-01 0.8062E-01 0.4014E-01 0.7076E-08 0.1628


            --- C. Full Covariance of Estimated System Parameters ---

 As Parameter Covariance Matrix:

          CL        V         Ka
CL         4.66
V         -3.38      79.0
Ka        -.210E-01  1.32     0.120

 As Parameter Correlation Matrix:

          CL        V         Ka
CL          1.00
V          -0.18      1.00
Ka         -0.03      0.43      1.00


            --- D. Parameter Mean and Covariance (ADAPT Format) ---

      Pmean(  1) =   8.347059         ! CL
      Pmean(  2) =   31.65449         ! V
      Pmean(  3) =   1.064148         ! Ka

      Pcov(  1,  1) =   4.661885      ! CL         & CL
      Pcov(  2,  1) =  -3.379068      ! V          & CL
      Pcov(  2,  2) =   78.99181      ! V          & V

      Pcov(  3,  1) = -0.2097815E-01  ! Ka         & CL
      Pcov(  3,  2) =   1.316012      ! Ka         & V
      Pcov(  3,  3) =  0.1202989      ! Ka         & Ka
```

Figure 10.14 (continued)

```
            --- E. Secondary Parameters ---

Parameter      Mean       Median     Std.Dev.     Min         Max
 Kel          0.2919     0.3747     0.1326      0.1076      0.6675
 LAM1         0.2919     0.3747     0.1326      0.1076      0.6675
 t1/2-LAM1     2.829      4.138      1.148       1.038       6.440
```

```
List of Files Created    {Not Shown}
```

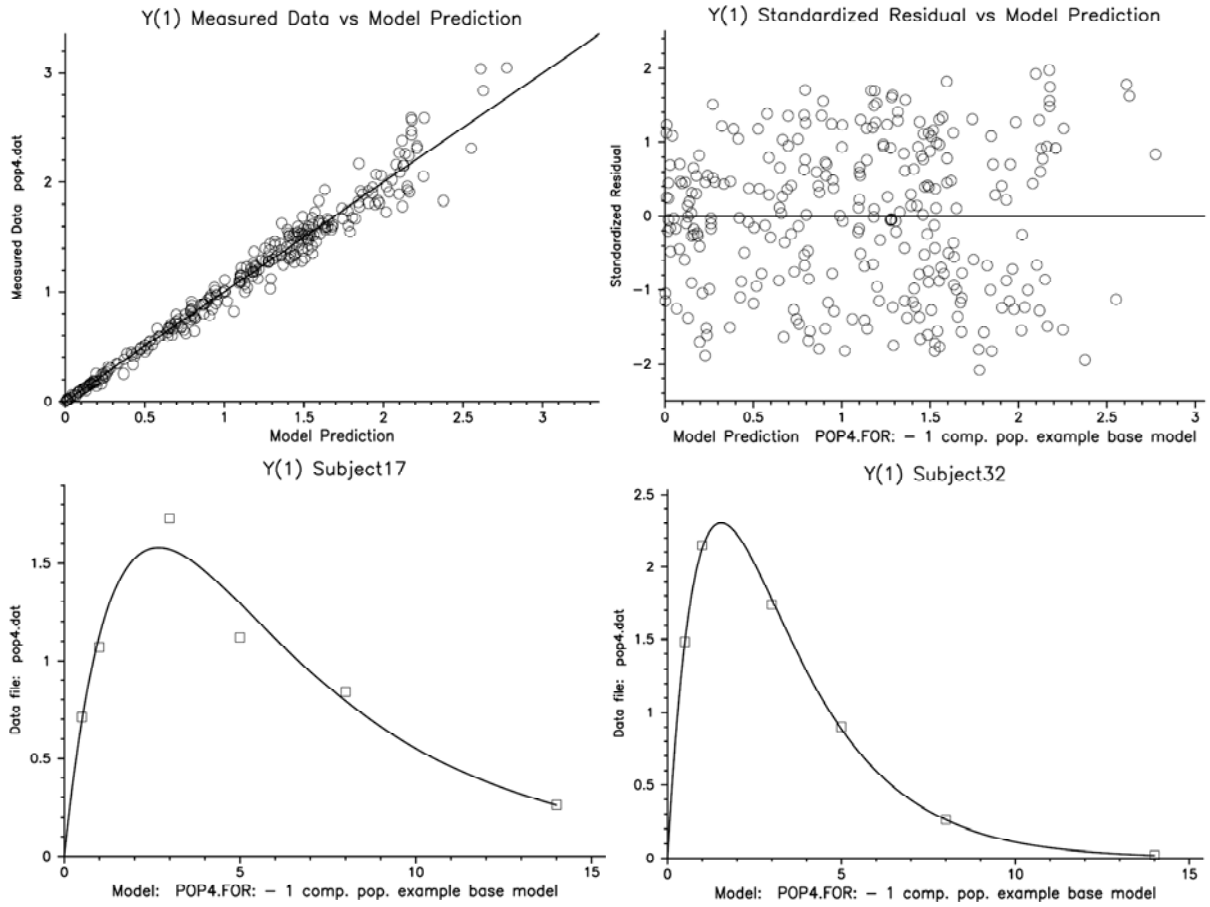


Figure 10.15 Example pop4. Selected plots from the file pop1.eps. Concentrations in $\mu g / ml$.

CHAPTER 11

ADAPT Model Library

11.1 Introduction

This Chapter details the pharmacokinetic/pharmacodynamic models that are included in the ADAPT Model Library and provided with the ADAPT distribution. Many of the Model Files contained in the Library implement pharmacokinetic/ pharmacodynamic models commonly used in basic and clinical pharmacological research and drug development. Others, illustrate some of the varied modeling capabilities of ADAPT. All Model Files in the Library can accommodate single or nonuniform multiple dose regimens for model inputs, unless indicated. All the Model Files, moreover, can be readily modified, extended or otherwise customized for specific user applications. The Model Files contained in the ADAPT Library are summarized in Table 11.1 (pharmacokinetic models), Table 11.2 (pharmacokinetic/pharmacodynamic models), and Table 11.3 (some user requested and contributed models).

All of these library models are also available as standalone, executable programs bundled with each of the ADAPT high-level programs. Interested users can download any of these executable programs, together with a sample run, from the BMSR web site.

The Library of Model Files presented in this Chapter represent only some of the models that can be implemented in ADAPT. The generality of ADAPT is such that any model that can be written as a set of first order, linear or nonlinear differential and/or algebraic equations can be handled by ADAPT.

The format used for each of the Library Models presented in the pages to follow is outlined below.

1. A brief description of the model.
2. The name of the Fortran file containing the model.
3. A block diagram representing the model.

4. The differential, output and variance equations for the model, as well as any secondary model parameters. The Fortran code is also given.

5. Comments on the model and notes on modifying and generalizing the Model File.

In describing the Library Models, the following conventions are employed: $r(t)$ - piece-wise constant input (e.g., IV input); b - bolus input; x - differential equation variables (e.g., drug amounts, concentrations, physiological variables, etc.); y - model outputs (e.g., drug concentrations, urine amounts, drug effects, etc.); K_{ij} - inter-compartmental rate constant; CL - inter-compartmental clearance; V - compartment volumes; F - fraction of dose absorbed; τ - absorption delay.

Table 11.1 Pharmacokinetic Library Models

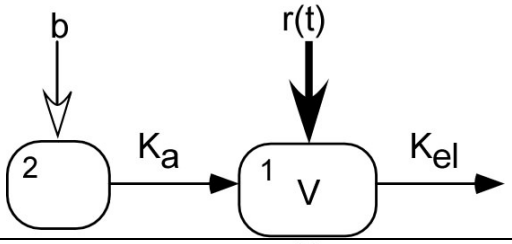
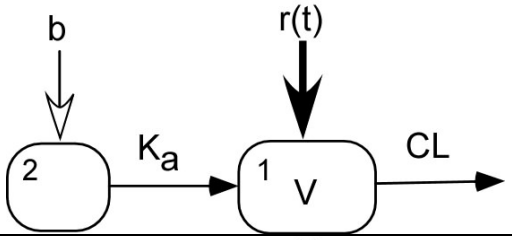
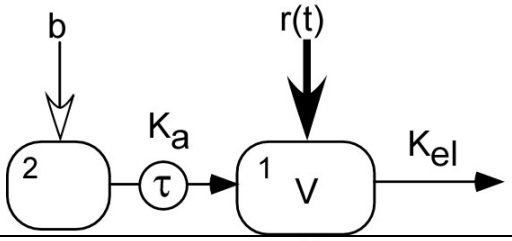
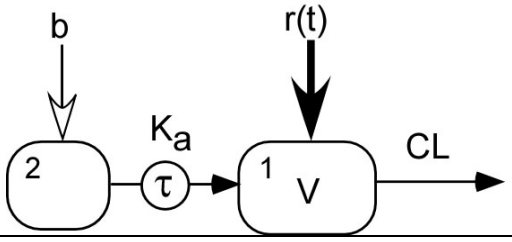
1COMPK		Linear 1-compartment IV and/or 1st order absorption. Rate constant parameterization.
1COMPCL		Linear 1-compartment IV and/or 1st order absorption. Clearance parameterization.
1LAGK		Linear 1-compartment 1st order absorption with lag, w/o IV. Rate constant parameterization.
1LAGCL		Linear 1-compartment 1st order absorption with lag, w/o IV. Clearance parameterization.

Table 11.1 (cont.) Pharmacokinetic Library Models

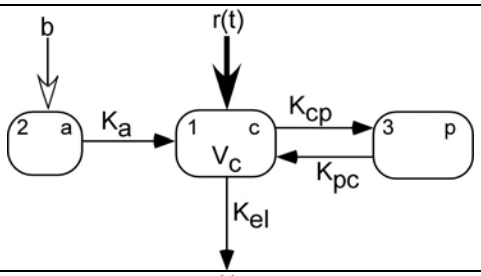
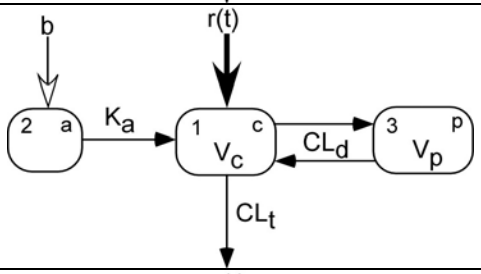
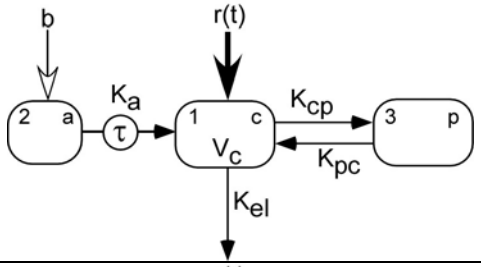
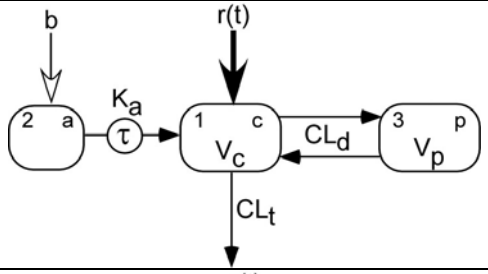
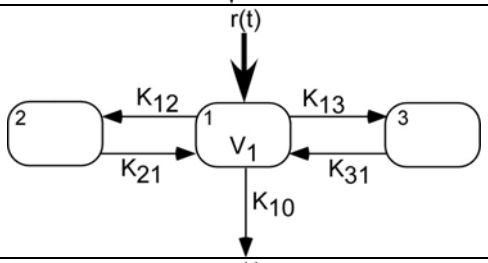
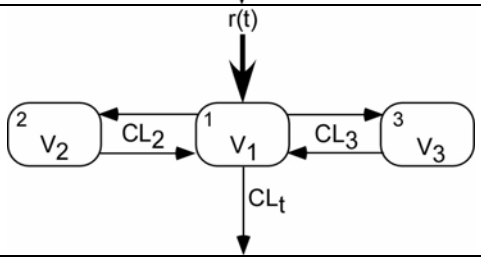
2COMPK		Linear 2-compartment IV and/or 1st order absorption. Rate constant parameterization.
2COMPCL		Linear 2-compartment IV and/or 1st order absorption. Clearance parameterization.
2LAGK		Linear 2-compartment 1st order absorption with lag, w/o IV. Rate constant parameterization.
2LAGCL		Linear 2-compartment 1st order absorption with lag, w/o IV. Clearance parameterization.
3COMPK		Linear 3-compartment IV. Rate constant parameterization.
3COMPCL		Linear 3-compartment IV. Clearance parameterization.

Table 11.1 (cont.) Pharmacokinetic Library Models

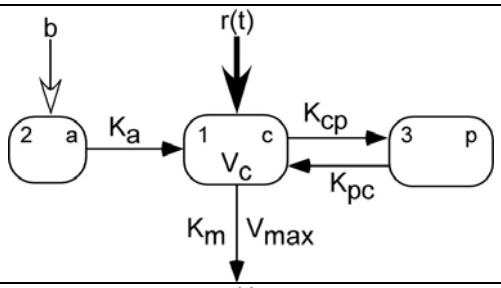
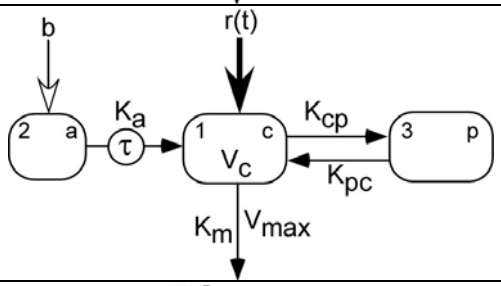
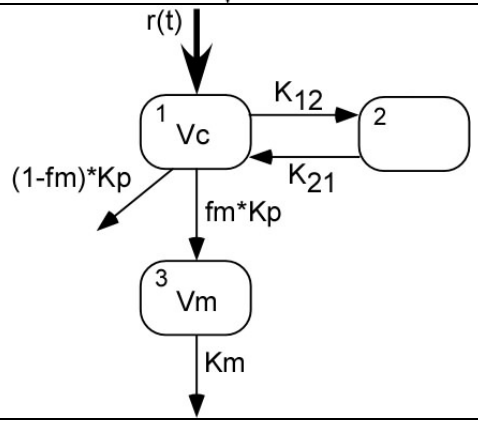
2COMPMM		2-compartment IV and/or 1st order absorption. Michaelis-Menton elimination.
2LAGMM		2-compartment 1st order absorption with lag, w/o IV. Michaelis-Menton elimination.
PMETAB		Parent (linear 2-compartment disposition with IV)-metabolite (linear 1-compartment disposition). Rate constant parameterization.

Table 11.2 Pharmacokinetic/Pharmacodynamic Library Models

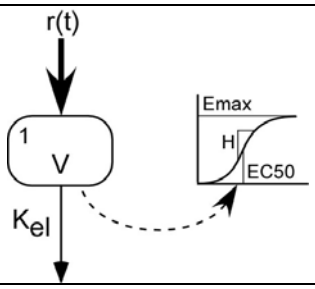
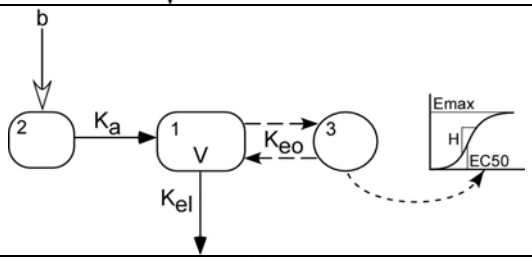
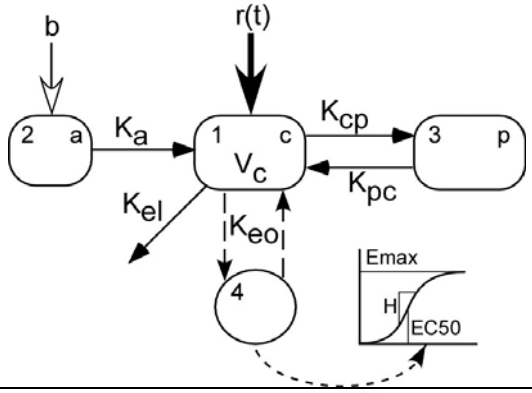
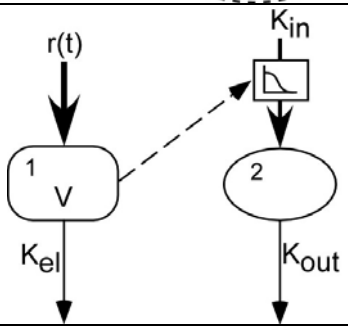
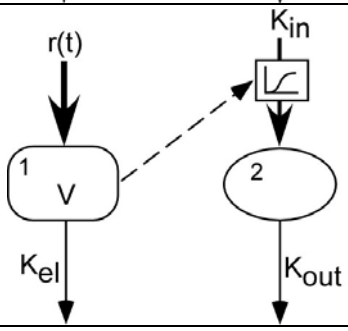
DIRECT		PK model: 1 compartment disposition with IV. PD model: Hill (sigmoid-Emax) response equation linked to plasma concentration.
LINK1		PK model: 1 compartment 1st order absorption. PD model: effect compartment with hill response equation. Single dose. Following Sheiner *et al.*
LINK2		PK model: 2-compartment IV and/or 1st order absorption. PD model: effect compartment with Hill response equation. Following Sheiner *et al.*
IRMPROD1		PK model: 1 compartment disposition with IV. PD model: Indirect Response Model with production linked to plasma concentration (inhibition). Following Jusko *et al.*
IRMPROD2		PK model: 1 compartment disposition with IV. PD model: Indirect Response Model with production linked to plasma concentration (stimulation). Following Jusko *et al.*

Table 11.2 (cont.) Pharmacokinetic/Pharmacodynamic Library Models

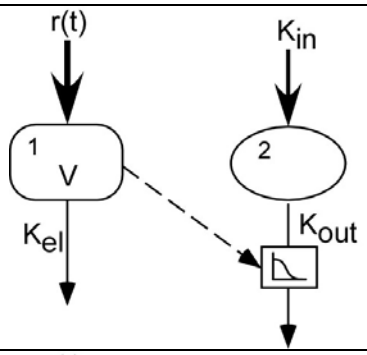
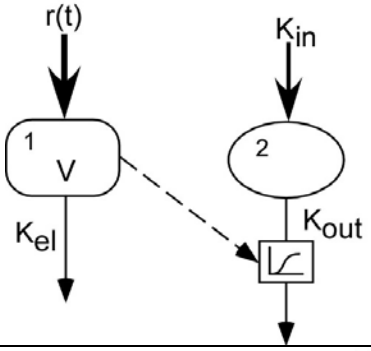
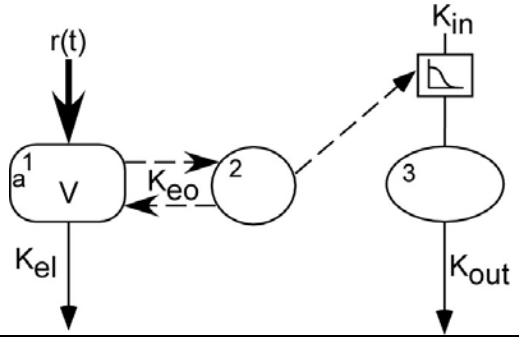
IRMREM1		PK model: 1 compartment disposition with IV. PD model: Indirect Response Model with removal linked to plasma concentration (inhibition). Following Jusko *et al.*
IRMREM2		PK model: 1 compartment disposition with IV. PD model: Indirect Response Model with removal linked to plasma concentration (stimulation). Following Jusko *et al.*
IRMLINK		PK model: 1 compartment disposition with IV. PD model: Indirect Response Model with production linked to effect compartment concentration. Following Jusko *et al.*

Table 11.3 User Requested and Contributed Models

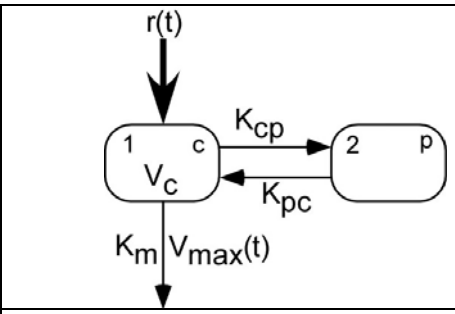
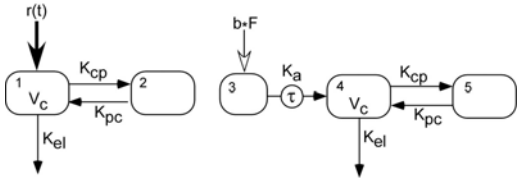
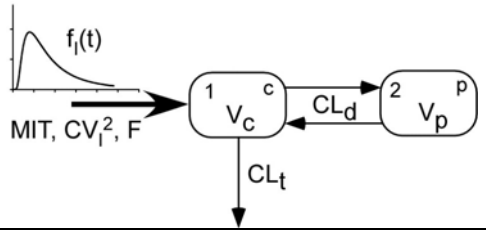
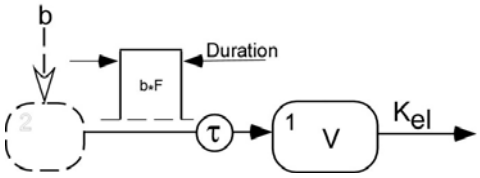
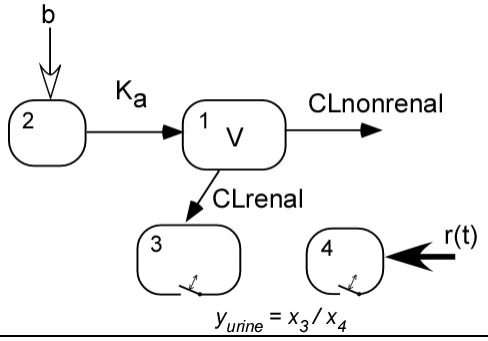
INDUCT		2-compartment IV with Michaelis-Menten elimination. Enzyme induction modeled as increase in Vmax with time after start of dose. Contributed by John Rodman.
MULTMOD		Simultaneous modeling of oral (first order absorption with lag) and IV kinetics. Disposition model, linear 2-compartment. Contributed by Alan Forrest.
IGABS		2-compartment disposition with inverse Gaussian function input. Contributed by Jian Wang and Michael Weiss.
ZEROIN		1-compartment disposition with zero-order input and lag. Fraction absorbed, duration of input and lag time included as parameters. Requested by Lloyd Whitfield.
PLASMA URINE		Plasma and urine concentration data (allows for missing urine measurements). Linear 1-compartment IV and/or 1st order absorption. Requested by Alan Forrest and Paul Berringer.

Table 11.3 (cont.) User Requested and Contributed Models

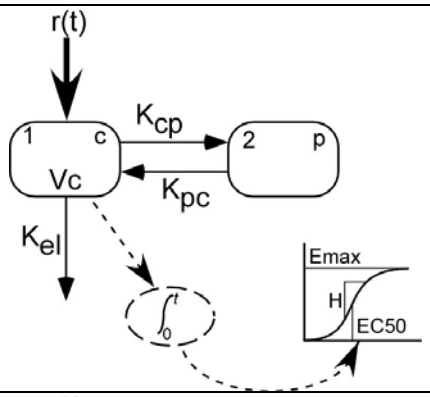
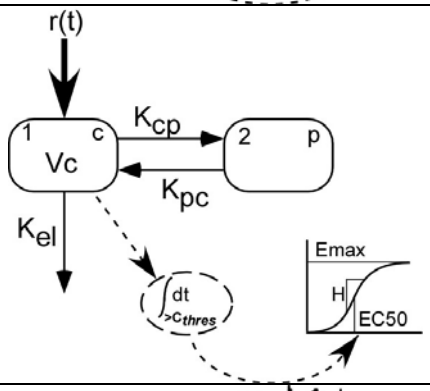
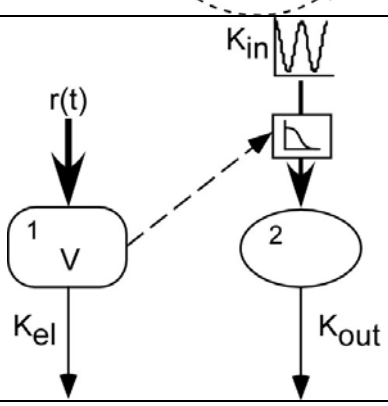
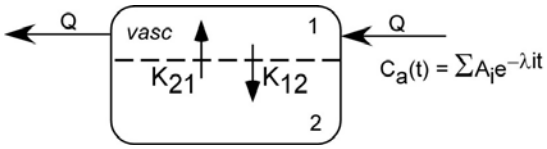
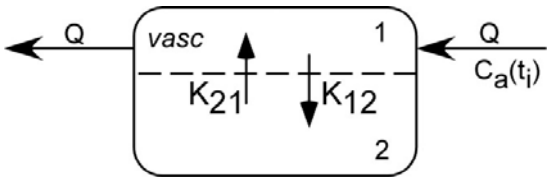
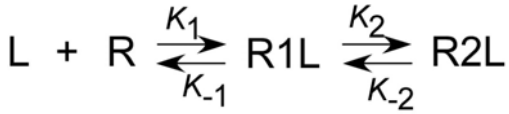
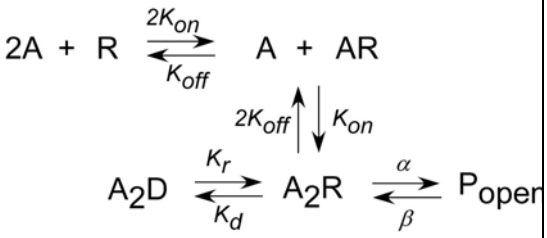
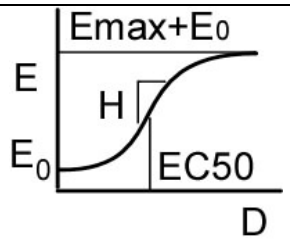
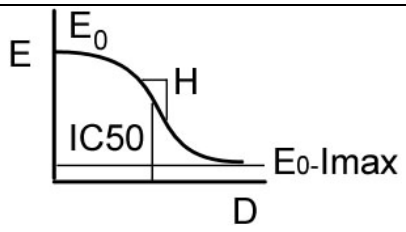
AUCRESP		PK model: 2 compartment disposition with IV. PD model: Hill response equation, with response at time t linked to area under the plasma concentration from 0 to t. Contributed by Alan Forrest.
DURATION		PK model: 2 compartment disposition with IV. PD model: Hill response equation, with response at t linked to the cumulative time plasma conc. Is above a threshold value. Requested by Merrill Egorin.
CIRCAD		PK model: 1 compartment disposition with IV. PD model: Indirect Response Model with endogenous production governed by a circadian rhythm and inhibited by plasma concentration. Contributed by Wojciech Krzyzanski.
ORGAN1		Isolated organ disposition model with arterial drug concentration input represented as sum of exponentials. Contributed by Bill Ebling.
ORGAN2		Isolated organ disposition model with measured arterial concentration data represented as piece-wise linear input. Requested by Bill Ebling

Table 11.3 (cont.) User Requested and Contributed Models

RECEPTOR		Receptor-ligand binding kinetics. One binding site, two conformational states. Contributed by Deanna Najman.
NMDA		Kinetic model of Glutamate NMDA receptor with desensitization. Contributed by Deanna Najman, Jim-Shih Liaw and Theodore Berger.
ESIGMAX		Excitatory sigmoid Emax model. Requested by Edward Acosta.
ISIGMAX		Inhibitory sigmoid Emax model. Requested by Edward Acosta

11.2 Pharmacokinetic Models

1COMPK

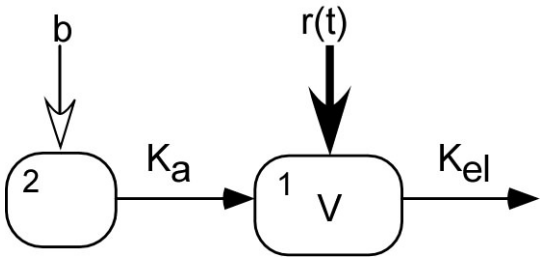
Description

One compartment linear model with first-order elimination parameterized as a rate constant. The model input is via IV infusion or first-order absorption, or both. Also both inputs can accommodate multiple dose regimens. The model differential equations are solved via analytic solution with the differential equations listed in subroutine DIFFEQ for reference only.

Model File Name

1COMPK.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -K_{el}x_1(t) + K_a x_2(t) + r(t)$$
$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

```
XP(1) = -P(1)*X(1) + P(3)*X(2) + R(1)
XP(2) = -P(3)*X(2)
```

Output Equations:

$$y(t) = x_1(t)/V$$

```
Y(1) = X(1)/P(2)
```

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$$

```
V(1) = (PV(1) + PV(2)*Y(1))**2
```

Secondary Parameters:

$$CL = K_{el} * V$$
$$\lambda_1 = K_{el}$$
$$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1$$

```
PS(1) = P(1)*P(2)
PS(2) = P(1)
PS(3) = DLOG(2.0)/PS(2)
```

Symbol Table:

system		variance		secondary	
K_{el}	-P(1)	σ_{inter}	-PV(1)	CL	-PS(1)
V	-P(2)	σ_{slope}	-PV(2)	λ_1	-PS(2)
K_a	-P(3)			$t_{1/2} - \lambda_1$	-PS(3)

Notes

This Model File is a special case of the linear two compartment model given in the Model File 2COMPK, with $K_{cp} = K_{pc} = 0$. The variables $x_1(t)$ and $x_2(t)$ represent amounts of drug in compartments 1 and 2, respectively, with $y(t)$ representing drug concentration in compartment 1. The variable $r(t)$ represents the rate of infusion of drug into compartment 1, if any, with b denoting any bolus doses absorbed through the first-order route.

1COMPCL

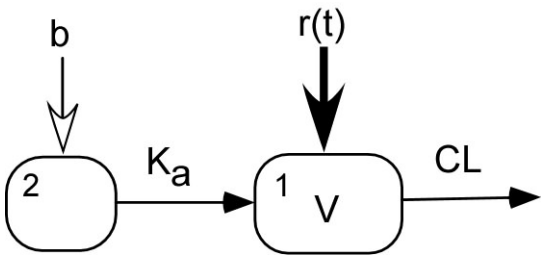
Description

One compartment linear model with first-order elimination parameterized as clearance. The model input is via IV infusion or first-order absorption, or both. Also both inputs can accommodate multiple dose regimens. The model differential equations are solved via analytic solution with the differential equations listed in subroutine DIFFEQ for reference only.

Model File Name

1COMPCL.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\frac{CL}{V}x_1(t) + K_a x_2(t) + r(t)$$
$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

```
XP(1) = -(P(1)/P(2))*X(1) + P(3)*X(2) + R(1)
XP(2) = -P(3)*X(2)
```

Output Equations:

$$y(t) = x_1(t)/V$$

```
Y(1) = X(1)/P(2)
```

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$$

```
V(1) = (PV(1) + PV(2)*Y(1))**2
```

Secondary Parameters:

$$K_{el} = CL/V$$
$$\lambda_1 = K_{el}$$
$$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1$$

```
PS(1) = P(1)/P(2)
PS(2) = PS(1)
PS(3) = DLOG(2.0)/PS(2)
```

Symbol Table:

system		variance		secondary	
CL	- P(1)	σ_{inter}	- PV(1)	K_{el}	- PS(1)
V	- P(2)	σ_{slope}	- PV(2)	λ_1	- PS(2)
K_a	- P(3)			$t_{1/2} - \lambda_1$	- PS(3)

Notes

This Model File is a special case of the linear two compartment model given in the Model File 2COMPCL, with $CL_d = 0$. The variables $x_1(t)$ and $x_2(t)$ represent amounts of drug in compartments 1 and 2, respectively, with $y(t)$ representing drug concentration in compartment 1. The variable $r(t)$ represents the rate of infusion of drug into compartment 1, if any, with b denoting any bolus doses absorbed through the first-order route.

1LAGK

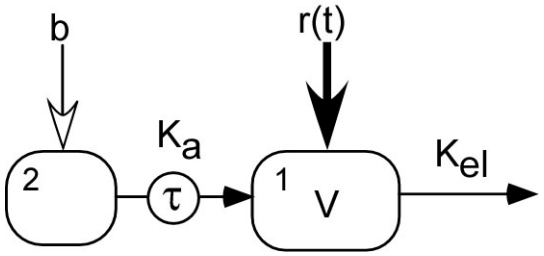
Description

One compartment linear model with first-order elimination parameterized as a rate constant. The model input is via first-order absorption that is subject to an absorption delay. The first-order absorption input can accommodate multiple doses, but the same delay is assumed for all doses. A simultaneous IV infusion input can also be specified. The model differential equations are solved via analytic solution with the differential equations listed in subroutine DIFFEQ for reference only.

Model File Name

1LAGK.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -K_{el}x_1(t) + K_a x_2(t)$$
$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

```
XP(1) = -(P(1)/P(2))*X(1) + P(3)*X(2) +R(1)
XP(2) = -P(3)*X(2)
```

Output Equations:

$$y(t) = x_1(t)/V$$

```
Y(1) = X(1)/P(2)
```

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$$

```
V(1) = (PV(1) + PV(2)*Y(1))**2
```

Secondary Parameters:

$$CL = K_{el} * V$$
$$\lambda_1 = K_{el}$$
$$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1$$

```
PS(1) = P(1)*P(2)
PS(2) = P(1)
PS(3) = DLOG(2.0)/PS(2)
```

System Table:

system		variance		secondary	
K_{el}	- P(1)	σ_{inter}	- PV(1)	CL	- PS(1)
V	- P(2)	σ_{slope}	- PV(2)	λ_1	- PS(2)
Ka	- P(3)			$t_{1/2} - \lambda_1$	- PS(3)
τ	- P(4)				

Notes

This Model File is a special case of the linear two compartment model given in the Model File 2LAGK, with $K_{cp} = K_{pc} = 0$. The variables $x_1(t)$ and $x_2(t)$ represent amounts of drug in compartments 1 and 2, respectively, with $y(t)$ representing drug concentration in compartment 1. The variable $r(t)$ represents the rate of infusion of drug into compartment 1, if any, with b denoting any bolus doses absorbed through the first-order route..

The absorption delay is accomplished by shifting all doses by the amount of the delay; this is, however, transparent to the user. The code needed to perform the dose shifting is accessed through subroutine OUTPUT in the Model File. This implementation can handle single or multiple doses, but for the latter it assumes the same delay exists for all doses. **N.B.** To use this Model File, it is necessary to include an observation time = 0.0 in the data. If one does not exist in the original problem, it can be added using the missing data number (default -1) in place of the observation.

1LAGCL

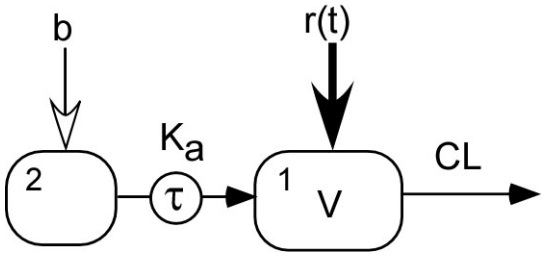
Description

One compartment linear model with first-order elimination parameterized as clearance. The model input is via first-order absorption that is subject to an absorption delay. The first-order absorption input can accommodate multiple doses, but the same delay is assumed for all doses. A simultaneous IV infusion input can also be specified. The model differential equations are solved via analytic solution with the differential equations listed in subroutine DIFFEQ for reference only.

Model File Name

1LAGCL.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\frac{CL}{V}x_1(t) + K_a x_2(t)$$
$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

```
XP(1) = -(P(1)/P(2))*X(1) + P(3)*X(2) +R(1)
XP(2) = -P(3)*X(2)
```

Output Equations:

$$y(t) = x_1(t)/V$$

```
Y(1) = X(1)/P(2)
```

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$$

```
V(1) = (PV(1) + PV(2)*Y(1))**2
```

Secondary Parameters:

$$K_{el} = CL / V$$
$$\lambda_1 = K_{el}$$
$$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1$$

```
PS(1) = P(1)/P(2)
PS(2) = P(1)
PS(3) = DLOG(2.0)/PS(2)
```

System Table:

system		variance		secondary	
CL	-P(1)	σ_{inter}	-PV(1)	K_{el}	-PS(1)
V	-P(2)	σ_{slope}	-PV(2)	λ_1	-PS(2)
Ka	-P(3)			$t_{1/2} - \lambda_1$	-PS(3)
τ	-P(4)				

Notes

This Model File is a special case of the linear two compartment model given in the Model File 2LAGCL, with $CL_d = 0$. The variables $x_1(t)$ and $x_2(t)$ represent amounts of drug in compartments 1 and 2, respectively, with $y(t)$ representing drug concentration in compartment 1. The variable $r(t)$ represents the rate of infusion of drug into compartment 1, if any, with b denoting any bolus doses absorbed through the first-order route.

The absorption delay is accomplished by shifting all doses by the amount of the delay; this is, however, transparent to the user. The code needed to perform the dose shifting is accessed through subroutine OUTPUT in the Model File. This implementation can handle single or multiple doses, but for the latter it assumes the same delay exists for all doses. **N.B.** To use this Model File, it is necessary to include an observation time = 0.0 in the data. If one does not exist in the original problem, it can be added using the missing data number (default -1) in place of the observation.

2COMPK

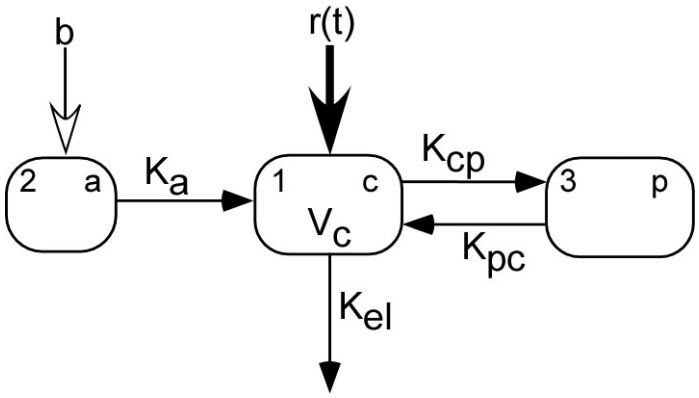
Description

Two compartment linear model parameterized using rate constants. The model input is via IV infusion or first-order absorption, or both. Also both inputs can accommodate multiple dose regimens. The model differential equations are solved via analytic solution with the differential equations listed in subroutine DIFFEQ for reference only.

Model File Name

2COMPK.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(K_{el} + K_{cp}\right)x_1(t) + K_a x_2(t) + K_{pc} x_3(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

$$\frac{dx_3(t)}{dt} = K_{cp} x_1(t) - K_{pc} x_3(t)$$

```
XP(1) = -(P(1)+P(4))*X(1)+P(3)*X(2)+P(5)*X(3)+R(1)
XP(2) = -P(3)*X(2)
XP(3) = P(4)*X(1)-P(5)*X(3)
```

Output Equations:

$y(t) = x_1(t)/V_C$ `Y(1) = X(1)/P(2)`

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$

Secondary Parameters:

$$CL_t = K_{el} * V_C \qquad V_C = V_C$$
$$CL_d = K_{cp} * V_C \qquad V_P = V_C * K_{cp} / K_{pc}$$
$$\lambda_1 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) + \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$
$$\lambda_2 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) - \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$
$$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1 \qquad t_{1/2} - \lambda_2 = \ln 2 / \lambda_2$$

```
PS(1)=P(1)*P(2)          PS(2)=P(2)
PS(3)=P(4)*P(2)          PS(4)=P(2)*P(4)/P(5)
PS(5)=((P(1)+P(4)+P(5))+DSQRT((P(1)+P(4)+P(5))**2-
                              4*P(1)*P(5)))/2.
PS(6)=((P(1)+P(4)+P(5))-DSQRT((P(1)+P(4)+P(5))**2-
                              4*P(1)*P(5)))/2.
PS(7)=DLOG(2.0)/PS(5)
PS(8)=DLOG(2.0)/PS(6)
```

Symbol Table:

system		variance		secondary	
K_{el}	P(1)	σ_{inter}	PV(1)	CL_t	PS(1)
V_C	P(2)	σ_{slope}	PV(2)	V_C	PS(2)
K_a	P(3)			CL_d	PS(3)
K_{cp}	P(4)			V_P	PS(4)
K_{pc}	P(5)			λ_1	PS(5)
				λ_2	PS(6)
				$t_{1/2} - \lambda_1$	PS(7)
				$t_{1/2} - \lambda_2$	PS(8)

Notes

The variables $x_1(t)$, $x_2(t)$ and $x_3(t)$ represent amounts of drug in compartments 1, 2 and 3, respectively, with $y(t)$ representing drug concentration in compartment 1. The variable $r(t)$ represents the rate of infusion with b denoting any bolus doses absorbed through the first-order route.

2COMPCL

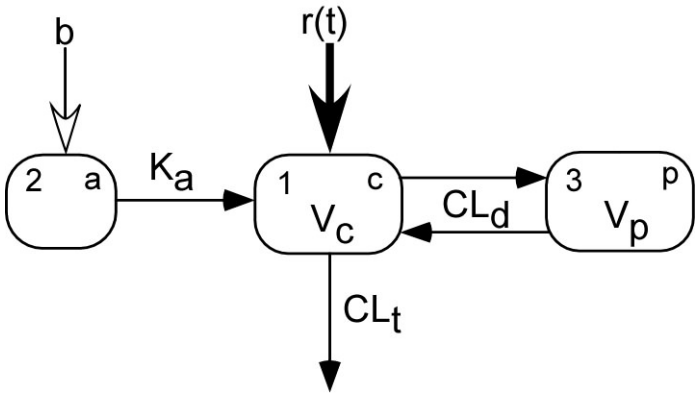
Description

Two compartment linear model parameterized using clearances. The model input is via IV infusion or first-order absorption, or both. Also both inputs can accommodate multiple dose regimens. The model differential equations are solved via analytic solution with the differential equations listed in subroutine DIFFEQ for reference only.

Model File Name

2COMPCL.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(\frac{CL_t}{V_C} + \frac{CL_d}{V_C}\right)x_1(t) + K_a x_2(t) + \frac{CL_d}{V_P}x_3(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

$$\frac{dx_3(t)}{dt} = \frac{CL_d}{V_C}x_1(t) - \frac{CL_d}{V_P}x_3(t)$$

```
XP(1) = -(P(1)+P(4))/P(2)*X(1)+P(3)*X(2)+P(4)/P(5)*X(3)+R(1)
XP(2) = -P(3)*X(2)
XP(3) = P(4)/P(2)*X(1) - P(4)/P(5)*X(3)
```

Output Equations:

$y(t) = x_1(t)/V_C$ `Y(1) = X(1)/P(2)`

Variance Model:

$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$ `V(1)=(PV(1)+PV(2)*Y(1))**2`

Secondary Parameters:

$K_{el} = CL_t * V_C$ $V_C = V_C$

$K_{cp} = CL_d * V_C$ $K_{pc} = Cl_d / V_P$

$$\lambda_1 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) + \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$

$$\lambda_2 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) - \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$

$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1$ $t_{1/2} - \lambda_2 = \ln 2 / \lambda_2$

```
IF(P(2).ne.0.0) PS(1) = P(1)/P(2)
PS(2) = P(2)
IF(P(2).ne.0.0) PS(3) = P(4)/P(2)
IF(P(5).ne.0.0) PS(4) = P(4)/P(5)
PS(5) = ((PS(1)+PS(3)+PS(4))+DSQRT((PS(1)+PS(3)+PS(4))**2-
            4.0*PS(1)*PS(4)))/2.0
PS(6) = ((PS(1)+PS(3)+PS(4))-DSQRT((PS(1)+PS(3)+PS(4))**2-
            4.0*PS(1)*PS(4)))/2.0
IF(PS(5).ne.0.0) PS(7) = DLOG(2.0D0)/PS(5)
IF(PS(6).ne.0.0) PS(8) = DLOG(2.0D0)/PS(6)
```

Symbol Table:

system		variance		secondary	
CL_t	P(1)	σ_{inter}	PV(1)	K_{el}	PS(1)
V_C	P(2)	σ_{slope}	PV(2)	V	PS(2)
K_a	P(3)			K_{cp}	PS(3)
CL_d	P(4)			K_{pc}	PS(4)
V_P	P(5)			λ_1	PS(5)
				λ_2	PS(6)
				$t_{1/2} - \lambda_1$	PS(7)
				$t_{1/2} - \lambda_2$	PS(8)

Notes

The variables are defined as given above in model 2COMPK.

2LAGK

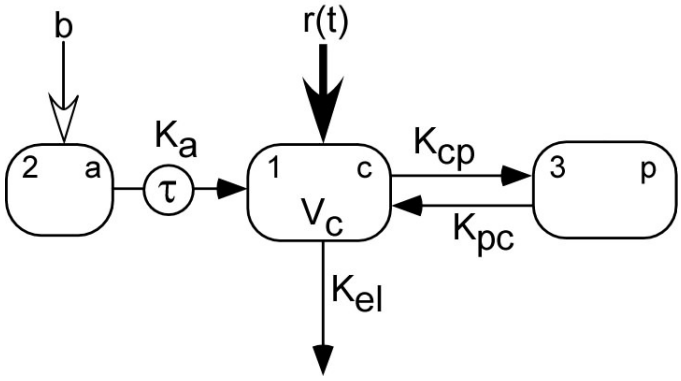
Description

Two compartment linear model parameterized using rate constants. The model input is via first-order absorption that is subject to an absorption delay. The first-order absorption input can accommodate multiple doses, but the same delay is assumed for all doses. A simultaneous IV infusion input can also be specified. The model differential equations are solved via analytic solution with the differential equations listed in subroutine DIFFEQ for reference only.

Model File Name

2LAGK.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(K_{el} + K_{cp}\right)x_1(t) + K_a x_2(t) + K_{pc} x_3(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

$$\frac{dx_3(t)}{dt} = K_{cp} x_1(t) - K_{pc} x_3(t)$$

```
XP(1) = -(P(1)+P(4))*X(1)+P(3)*X(2)+P(5)*X(3)+R(1)
XP(2) = -P(3)*X(2)
XP(3) = P(4)*X(1)-P(5)*X(3)
```

Output Equations:

$$y(t) = x_1(t)/V_C$$

```
Y(1) = X(1)/P(2)
```

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$

Secondary Parameters:

$$CL_t = K_{el} * V_C \qquad V_C = V_C$$
$$CL_d = K_{cp} * V_C \qquad V_P = V_C * K_{cp} / K_{pc}$$
$$\lambda_1 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) + \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$
$$\lambda_2 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) - \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$
$$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1 \qquad t_{1/2} - \lambda_2 = \ln 2 / \lambda_2$$

```
PS(1)=P(1)*P(2)                    PS(2)=P(2)
PS(3)=P(4)*P(2)                    PS(4)=P(2)*P(4)/P(5)
PS(5)=((P(1)+P(4)+P(5))+DSQRT((P(1)+P(4)+P(5))**2-
                        4*P(1)*P(5)))/2.
PS(6)=((P(1)+P(4)+P(5))-DSQRT((P(1)+P(4)+P(5))**2-
                        4*P(1)*P(5)))/2.
PS(7)=DLOG(2.0)/PS(5)
PS(8)=DLOG(2.0)/PS(6)
```

Symbol Table:

system		variance		secondary	
K_{el}	P(1)	σ_{inter}	PV(1)	CL_t	PS(1)
V_C	P(2)	σ_{slope}	PV(2)	V_C	PS(2)
K_a	P(3)			CL_d	PS(3)
K_{cp}	P(4)			V_P	PS(4)
K_{pc}	P(5)			λ_1	PS(5)
τ	P(6)			λ_2	PS(6)
				$t_{1/2} - \lambda_1$	PS(7)
				$t_{1/2} - \lambda_2$	PS(8)

Notes

The variables $x_1(t)$, $x_2(t)$ and $x_3(t)$ represent amounts of drug in compartments, 2 and 3, respectively, with $y(t)$ representing drug concentration in compartment 1. (See **Notes** under 1LAGK.)

2LAGCL

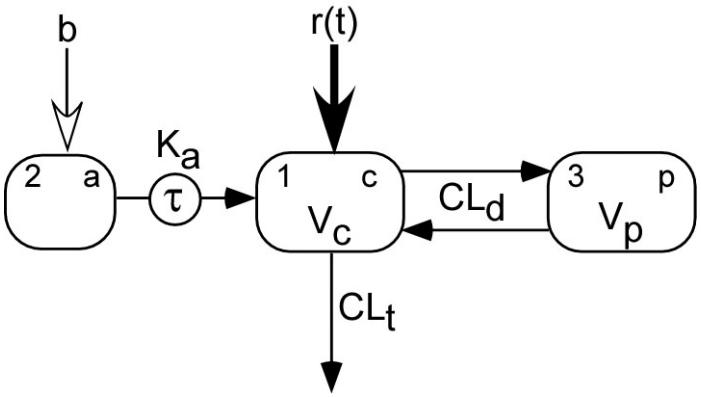
Description

Two compartment linear model parameterized using clearances. The model input is via first-order absorption that is subject to an absorption delay. The first-order absorption input can accommodate multiple doses, but the same delay is assumed for all doses. A simultaneous IV infusion input can also be specified. The model differential equations are solved via analytic solution with the differential equations listed in subroutine DIFFEQ for reference only.

Model File Name

2LAGCL.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(\frac{CL_t}{V_C} + \frac{CL_d}{V_C}\right)x_1(t) + K_a x_2(t) + \frac{CL_d}{V_P}x_3(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

$$\frac{dx_3(t)}{dt} = \frac{CL_d}{V_C}x_1(t) - \frac{CL_d}{V_P}x_3(t)$$

```
XP(1) = -(P(1)+P(4))/P(2)*X(1)+P(3)*X(2)+P(4)/P(5)*X(3)+R(1)
XP(2) = -P(3)*X(2)
XP(3) = P(4)/P(2)*X(1)-P(4)/P(5)*X(3)
```

Output Equations:

$y(t) = x_1(t)/Vc$ `Y(1) = X(1)/P(2)`

Variance Model:

$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$ `V(1)=(PV(1)+PV(2)*Y(1))**2`

Secondary Parameters:

$K_{el} = CL_t * V_C$ $V_C = V_C$

$K_{cp} = CL_d * V_C$ $K_{pc} = Cl_d / V_P$

$$\lambda_1 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) + \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$

$$\lambda_2 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) - \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$

$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1$ $t_{1/2} - \lambda_2 = \ln 2 / \lambda_2$

```
PS(1)=P(1)*P(2)          PS(2)=P(2)
PS(3)=P(4)*P(2)          PS(4)=P(2)*P(4)/P(5)
PS(5)=((P(1)+P(3)+P(4))+DSQRT((P(1)+P(3)+P(4))**2-
                          4*P(1)*P(5)))/2.
PS(6)=((P(1)+P(3)+P(4))-DSQRT((P(1)+P(3)+P(4))**2-
                          4*P(1)*P(5)))/2.
PS(7)=DLOG(2.0)/PS(5)    PS(8)=DLOG(2.0)/PS(6)
```

Symbol Table:

system		variance		secondary	
CL_t	P(1)	σ_{inter}	PV(1)	K_{el}	PS(1)
V_C	P(2)	σ_{slope}	PV(2)	V	PS(2)
K_a	P(3)			K_{cp}	PS(3)
CL_d	P(4)			K_{pc}	PS(4)
V_P	P(5)			λ_1	PS(5)
τ	P(6)			λ_2	PS(6)
				$t_{1/2} - \lambda_1$	PS(7)
				$t_{1/2} - \lambda_2$	PS(8)

Notes

The variables $x_1(t)$, $x_2(t)$ and $x_3(t)$ represent amounts of drug in compartments 1, 2 and 3, respectively, with $y(t)$ representing drug concentration in compartment 1. (See **Notes** under 1LAGCL.)

3COMPK

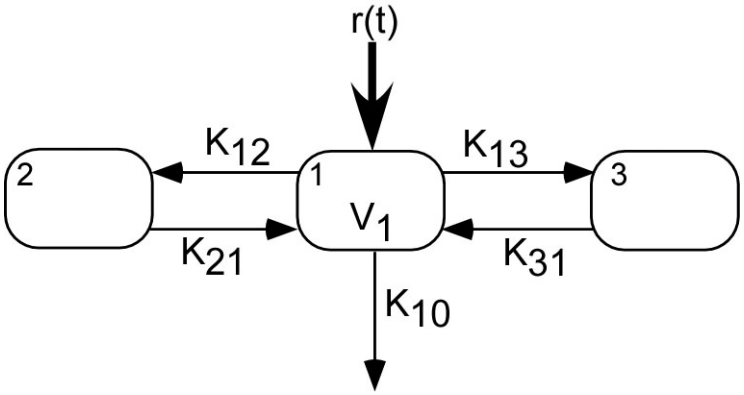
Description

Three compartment linear model parameterized using rate constants. The model input is via IV infusion or first-order absorption, or both. Also both inputs can accommodate multiple dose regimens. The model differential equations are solved via analytic solution with the differential equations listed in subroutine DIFFEQ for reference only.

Model File Name

3COMPK.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -(K_{10} + K_{12} + K_{13})x_1(t) + K_{21}x_2(t) + K_{31}x_3(t) + r_1(t)$$

$$\frac{dx_2(t)}{dt} = K_{12}x_1(t) - K_{21}x_2(t)$$

$$\frac{dx_3(t)}{dt} = K_{13}x_1(t) - K_{31}x_3(t)$$

```
XP(1) = -(P(1)+P(2)+P(4))*X(1)+P(3)*X(2)+P(5)*X(3)+R(1)
XP(2) = P(2)*X(1)-P(3)*X(2)
XP(3) = P(4)*X(1)-P(5)*X(3)
```

Output Equations:

$y(t) = x_1(t)/V_1$ `Y(1) = X(1)/P(6)`

Variance Model:

$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$ `V(1)=(PV(1)+PV(2)*Y(1))**2`

Secondary Parameters:

$CL_t = K_{10} * V_1$ $V_1 = V_1$
$CL_2 = K_{12} * V_1$ $V_2 = V_1 * K_{12} / K_{21}$
$CL_3 = K_{13} * V_1$ $V_3 = V_1 * K_{13} / K_{31}$
$\lambda_1, \lambda_2, \lambda_3$ – (solution to cubic equation)
$\tau_{1/2} - \lambda_1 = \ln 2 / \lambda_1$, $\tau_{1/2} - \lambda_2 = \ln 2 / \lambda_2$, $\tau_{1/2} - \lambda_3 = \ln 2 / \lambda_3$

```
PS(1)=P(1)*P(6)              PS(2)=P(6)
PS(3)=P(2)*P(6)              PS(4)=P(6)*P(2)/P(3)
PS(5)=P(4)*P(6)              PS(6)=P(6)*P(4)/P(5)
PS(7), PS(8), PS(9) (from Subroutine CUBIC**)
PS(10)=DLOG(2.0)/PS(7)       PS(11)=DLOG(2.0)/PS(8)
PS(12)=DLOG(2.0)/PS(9)
```

Symbol Table:

system		variance		secondary			
K_{10}	P(1)	σ_{inter}	PV(1)	CL_t	PS(1)	λ_1	PS(7)
K_{12}	P(2)	σ_{slope}	PV(2)	V_1	PS(2)	λ_2	PS(8)
K_{21}	P(3)			CL_2	PS(3)	λ_3	PS(9)
K_{13}	P(4)			V_2	PS(4)	$t_{1/2} - \lambda_1$	PS(10)
K_{31}	P(5)			CL_3	PS(5)	$t_{1/2} - \lambda_2$	PS(11)
V_1	P(6)			V_3	PS(6)	$t_{1/2} - \lambda_3$	PS(12)

Notes

The variables $x_1(t)$, $x_2(t)$ and $x_3(t)$ represent amounts of drug in compartments 1, 2 and 3, respectively, with $y(t)$ representing drug concentration in compartment 1.

** The characteristic values, λ_1, λ_2 and λ_3, are calculated by the built-in 3 compartment solution routine `CUBIC` and passed into the Model File (see code).

3COMPCL

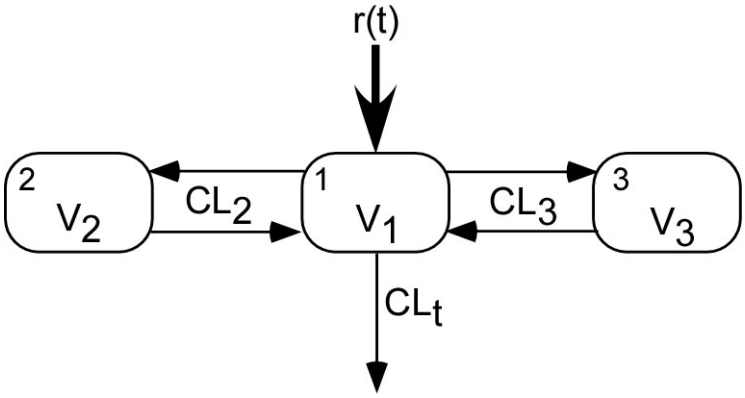
Description

Three compartment linear model parameterized using clearances. The model input is via IV infusion or first-order absorption, or both. Also both inputs can accommodate multiple dose regimens. The model differential equations are solved via analytic solution with the differential equations listed in subroutine DIFFEQ for reference only.

Model File Name

3COMPCL.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(\frac{CL_t}{V_1} + \frac{CL_2}{V_1} + \frac{CL_3}{V_1}\right)x_1(t) \frac{CL_2}{V_2}x_2(t) + \frac{CL_3}{V_3}x_3(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = \frac{CL_1}{V_1}x_1(t) - \frac{CL_2}{V_2}x_2(t)$$

$$\frac{dx_3(t)}{dt} = \frac{CL_1}{V_1}x_1(t) - \frac{CL_3}{V_3}x_3(t)$$

```
XP(1)=-(P(1)+P(3)+P(4))/P(2)*X(1)+P(3)/P(4)*X(2)+
                  P(4)/P(5)*X(3)+R(1)
XP(2)=P(3)/P(2)*X(1)-P(3)/P(4)*X(2)
XP(3)=P(5)/P(2)*X(1)-P(5)/P(6)*X(3)
```

Output Equations:

$y(t) = x_1(t)/V_1$ Y(1) = X(1)/P(2)

Variance Model:

$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$ V(1)=(PV(1)+PV(2)*Y(1))**2

Secondary Parameters:

$K_{10} = CL_t / V_1$ $K_{12} = CL_2 / V_1$
$K_{21} = CL_2 / V_2$ $K_{13} = CL_3 / V_1$
$K_{31} = CL_3 / V_3$ $V_1 = V_1$
$\lambda_1, \lambda_2, \lambda_3$ – (solution to cubic equation)
$\tau_{1/2} - \lambda_1 = \ln 2 / \lambda_1$, $\tau_{1/2} - \lambda_2 = \ln 2 / \lambda_2$, $\tau_{1/2} - \lambda_3 = \ln 2 / \lambda_3$

```
PS(1)=P(1)/P(2)              PS(2)=P(3)/P(2)
PS(3)=P(3)/P(4)              PS(4)=P(5)/P(2)
PS(5)=P(5)/P(6)              PS(6)=P(2)
PS(7), PS(8), PS(9) (from Subroutine CUBIC**)
PS(10)=DLOG(2.0)/PS(7)       PS(11)=DLOG(2.0)/PS(8)
PS(12)=DLOG(2.0)/PS(9)
```

Symbol Table:

system		variance		secondary			
CL_t	-P(1)	σ_{inter}	-PV(1)	K_{10}	-PS(1)	λ_1	-PS(7)
V_1	-P(2)	σ_{slope}	-PV(2)	K_{12}	-PS(2)	λ_2	-PS(8)
CL_2	-P(3)			K_{21}	-PS(3)	λ_3	-PS(9)
V_2	-P(4)			K_{13}	-PS(4)	$t_{1/2} - \lambda_1$	-PS(10)
CL_3	-P(5)			K_{31}	-PS(5)	$t_{1/2} - \lambda_2$	-PS(11)
V_3	-P(6)			V_1	-PS(6)	$t_{1/2} - \lambda_3$	-PS(12)

Notes

The variables $x_1(t)$, $x_2(t)$ and $x_3(t)$ represent amounts of drug in compartments 1, 2 and 3, respectively, with $y(t)$ representing drug concentration in compartment 1.

** The characteristic values, λ_1, λ_2 and λ_3, are calculated by the built-in 3 compartment solution routine `CUBIC` and passed into the Model File (see code).

2COMPMM

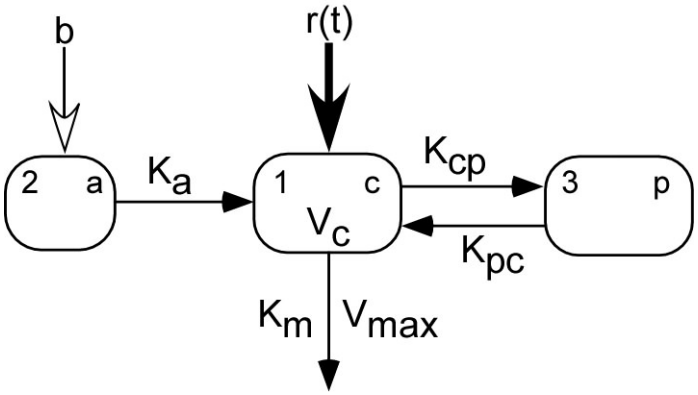
Description

Two compartment linear disposition with Michaelis-Menten elimination, parameterized using rate constants. The model input is via IV infusion or first-order absorption, or both. Also both inputs can accommodate multiple dose regimens. The model differential equations are solved via the differential equation solver.

Model File Name

2COMPMM.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(\frac{Vmax}{Km + x_1(t)/V_C}\right)\left(\frac{x_1(t)}{V_C}\right) - K_{cp}x_1(t) + K_a x_2(t) + K_{pc}x_3(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

$$\frac{dx_3(t)}{dt} = K_{cp}x_1(t) - K_{pc}x_3(t)$$

```
XP(1) = -(P(2)/(P(1)+X(1)/P(3))*(X(1)/P(3))-P(5)*X(1)+
                        P(4)*X(2)+P(6)*X(3)+R(1)
XP(2) = -P(4)*X(2)
XP(3) = P(5)*X(1)-P(6)*X(3)
```

Output Equations:

$$y(t) = x_1(t)/V_C \qquad \texttt{Y(1)=X(1)/P(3)}$$

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$

Secondary Parameters:

$$CL_d = K_{cp} * V_C$$
$$V_P = V_C * K_{cp} / K_{pc}$$

```
PS(1)=P(5)*P(3)
PS(2)=P(5)*P(3)/P(6)
```

Symbol Table:

system		variance		secondary	
Km	- P(1)	σ_{inter}	- PV(1)	CL_d	- PS(1)
Vmax	- P(2)	σ_{slope}	- PV(2)	V_P	- PS(2)
V_C	- P(3)				
K_a	- P(4)				
K_{cp}	- P(5)				
K_{pc}	- P(6)				

Notes

The variables $x_1(t)$, $x_2(t)$ and $x_3(t)$ represent amounts of drug in compartments 1, 2 and 3, respectively, with $y(t)$ representing drug concentration in compartment 1.

NB: This model file assumes the units for *Vmax* are amount/time. In previous version of this user's guide the units used for *Vmax* were assumed to be concentration/time.

2LAGMM

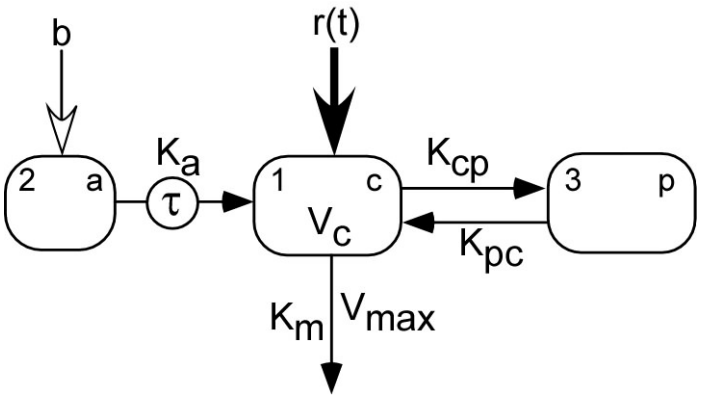
Description

Two compartment linear disposition with Michaelis-Menten elimination, parameterized using rate constants. The model input is via first-order absorption that is subject to an absorption delay. The first-order absorption input can accommodate multiple doses, but the same delay is assumed for all doses. A simultaneous IV infusion input can also be specified. Also both inputs can accommodate multiple dose regimens. The model differential equations are solved via the differential equation solver.

Model File Name

2LAGMM.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(\frac{V_{\max}}{K_m + x_1(t)/V_C}\right)\left(\frac{x_1(t)}{V_C}\right) + K_{cp}x_1(t) + K_a x_2(t) + K_{pc}x_3(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

$$\frac{dx_3(t)}{dt} = K_{cp}x_1(t) - K_{pc}x_3(t)$$

```
XP(1) = -(P(2)/(P(1)+X(1)/P(3))*(X(1)/P(3))-P(5)*X(1)+
                        P(4)*X(2)+P(6)*X(3)+R(1)
XP(2)=-P(4)*X(2)
XP(3)=P(5)*X(1)-P(6)*X(3)
```

Output Equations:

$$y(t) = x_1(t)/V_C \qquad \texttt{Y(1)=X(1)/P(3)}$$

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$

Secondary Parameters:

$$CL_d = K_{cp} * V_C$$
$$V_P = V_C * K_{cp} / K_{pc}$$

```
PS(1)=P(5)*P(3)
PS(2)=P(5)*P(3)/P(6)
```

Symbol Table:

system		variance		secondary	
K_m	- P(1)	σ_{inter}	- PV(1)	CL_d	- PS(1)
V_{max}	- P(2)	σ_{slope}	- PV(2)	V_P	- PS(2)
V_C	- P(3)				
K_a	- P(4)				
K_{cp}	- P(5)				
K_{pc}	- P(6)				
τ	- P(7)				

Notes

The variables $x_1(t)$, $x_2(t)$ and $x_3(t)$ represent amounts of drug in compartments 1, 2 and 3, respectively, with $y(t)$ representing drug concentration in compartment 1. The variable b denotes the bolus doses absorbed through the first-order route. (See **Notes** under **1LAGK**.)

NB: This model file assumes the units for V_{max} are amount/time. In previous version of this user's guide the units used for *Vmax* were assumed to be concentration/time.

PMETAB

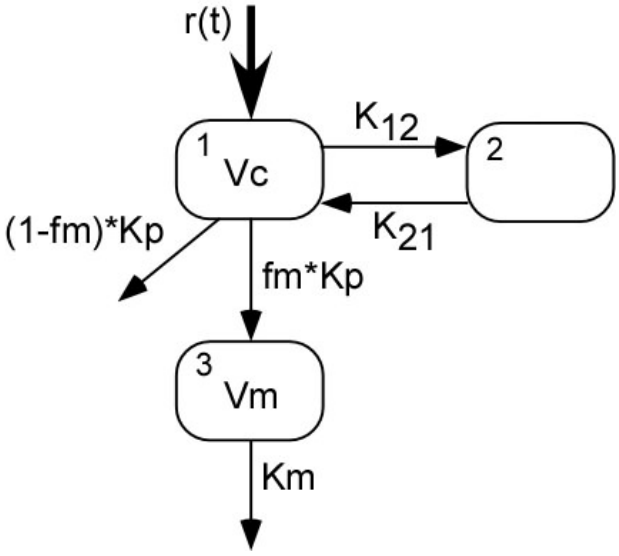
Description

Parent/metabolite kinetic model. The parent is a two compartment linear model and the metabolite is a one compartment linear model. The total rate constant for disappearance of the parent compound (elimination plus metabolism) is denoted K_p, while the metabolite elimination rate constant is K_m. The distribution volume for the metabolite is denoted V_m, the fraction of parent metabolized is f_m and their ratio (V_m / f_m) is estimated.

Model File Name

PMETAB.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(K_p + K_{12}\right)x_1(t) + K_{21}x_2(t) + r_1(t) \qquad (K_p \text{ is parent elimination rate.})$$

$$\frac{dx_2(t)}{dt} = K_{12}x_1(t) - K_{21}x_2(t)$$

$$\frac{dx_3(t)}{dt} = K_p x_1(t) - K_m x_3(t) \qquad (x_3(t) \text{ is metabolite amount divided by } f_m.)$$

```
XP(1) = -(P(1)+P(3))*X(1) + P(4)*X(2) + R(1)
XP(2) = P(3)*X(1) - P(4)*X(2)
XP(3) = P(1)*X(1) - P(5)*X(3)
                ! Note X(3) is (amount metab)/fm
```

Output Equations:

$y_1(t) = x_1(t)/V_1$ `Y(1)=X(1)/P(2)`

$y_2(t) = x_3(t)/(V_m / f_m)$ `Y(2)=X(3)/P(6)`

Variance Model:

$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2$ `V(1)=(PV(1)+PV(2)*Y(1))**2`

$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2$ `V(2)=(PV(3)+PV(4)*Y(2))**2`

Secondary Parameters:

$CL_p = K_p * V_p$ $CL_p - dist = K_{12} * V_p$

$CL_m / f_m = K_m * (V_m / f_m)$

```
PS(1) = P(1)*P(2)          PS(2) = P(3)*P(2)
PS(3) = P(5)*P(6)
```

Symbol Table:

system		variance		secondary	
K_p	- P(1)	σ_{inter1}	- PV(1)	CL_p	- PS(1)
V_p	- P(2)	σ_{slope1}	- PV(2)	$CL_p - dist$	- PS(2)
K_{12}	- P(3)	σ_{inter2}	- PV(3)	CL_m / f_m	- PS(3)
K_{21}	- P(4)	σ_{slope2}	- PV(4)		
K_m	- P(5)				
V_m / f_m	- P(6)				

Notes

The variables $x_1(t)$ and $x_2(t)$ represent amounts of parent compound in the central and peripheral compartments, while $x_3(t)$ is the amount of the metabolite divided by the fraction of parent metabolized.

11.3 Pharmacokinetic/Pharmacodynamic Models

DIRECT

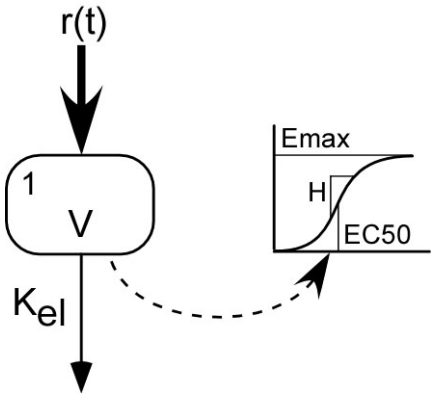
Description

PK Model: One compartment linear model with .rst-order elimination parameterized as a rate constant. The model input is via multiple dose IV infusion. PD Model: Drug response is related via the Hill equation (sigmoid-Emax model) to plasma concentration.

Model File Name

DIRECT.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -K_{el}x_1(t) + r(t)$$

```
XP(1) = -P(1)*X(1)+R(1)
```

Output Equations:

$$y_1(t) = x_1(t)/V$$
$$y_2(t) = \frac{Emax}{\left(EC50^H + y_1^H\right)} y_1^H$$

```
Y(1) = X(1)/P(2)
Y(2) = P(3)*Y(1)**P(5)/(P(4)**P(5)+Y(1)**P(5))
```

Variance Model:

$$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$
$$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2 \qquad \texttt{V(2)=(PV(3)+PV(4)*Y(2))**2}$$

Secondary Parameters:

$$CL = K_{el} * V$$
$$\lambda_1 = K_{el}$$
$$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1$$

```
PS(1) = P(1)*P(2)
PS(2) = P(1)
PS(3) = DLOG(2.0)/PS(2)
```

Symbol Table:

system		variance		secondary	
K_{el}	P(1)	σ_{inter1}	PV(1)	CL	PS(1)
V	P(2)	σ_{slope1}	PV(2)	λ_1	PS(2)
$Emax$	P(3)	σ_{inter2}	PV(3)	$t_{1/2} - \lambda_1$	PS(3)
$EC50$	P(4)	σ_{slope2}	PV(4)		
H	P(5)				

Notes

The variable $x_1(t)$ represents the amount of drug in plasma, with $y_1(t)$ representing drug concentration in plasma and $y_2(t)$ representing drug effect. The variable $r(t)$ represents the rate of infusion of drug into compartment 1. The model can be easily modified to accept other PK models.

LINK1

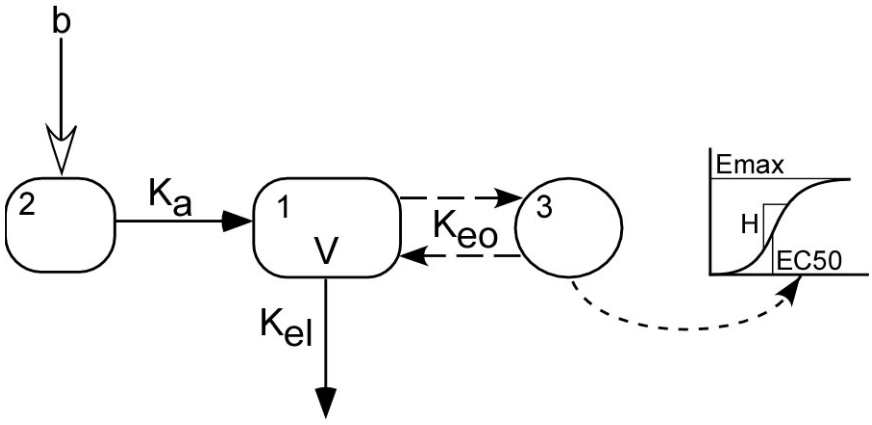
Description

PK Model: One compartment linear model with first-order absorption and elimination parameterized as a rate constant. PD Model: Drug response is related via the Hill equation (sigmoid-Emax model) to drug concentration in a hypothetical effect site. Analytic solutions are used for both the PK and PD portions of the model, and only a single bolus dose is allowed. Following Sheiner *et al*.

Model File Name

LINK1.FOR

Model Diagram



Model Equations

Differential Equations:

None

Output Equations:

$$y_1(t) = \frac{bK_a}{V(K_a - K_{el})}\left(e^{-K_e t} - e^{-K_a t}\right)$$

$$y_2(t) = \frac{E\max}{\left(EC50^H + C_e^H\right)}C_e^H$$

where

$$Ce = \frac{bK_aK_{eo}}{V}\left(\frac{e^{-K_{el}t}}{(K_a-K_{el})(K_{eo}-K_{el})}+\frac{e^{-K_at}}{(K_{el}-K_a)(K_{eo}-K_a)}+\frac{e^{-K_{eo}t}}{(K_{el}-K_{eo})(K_a-K_{eo})}\right)$$

```
Y(1)=B(1)*P(3)/(P(2)*(P(3)-P(1)))*(DEXP(-P(1)*T)-DEXP(-P(3)*T))
Ce=(B(1)*P(3)*P(4)/P(2))*(DEXP(-P(1)*T)/((P(3)-P(1))*(P(4)-
                    P(1)))+DEXP(-P(3)*T)/((P(1)-P(3))*(P(4)-
                    P(3)))+DEXP(-P(4)*T)/((P(1)-P(4))*(P(3)-
                    P(4))))
Y(2)=P(5)*Ce**P(7)/(P(6)**P(7)+Ce**P(7))
```

Variance Model:

$$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1}y_1(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$

$$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2}y_2(t)\right)^2 \qquad \texttt{V(2)=(PV(3)+PV(4)*Y(2))**2}$$

Secondary Parameters:

$$CL = Kel*V \qquad \texttt{PS(1) = P(1)*P(2)}$$

Symbol Table:

system		variance		secondary	
K_{el}	P(1)	σ_{inter1}	PV(1)	CL	PS(1)
V	P(2)	σ_{slope1}	PV(2)		
K_a	P(3)	σ_{inter2}	PV(3)		
K_{eo}	P(4)	σ_{slope2}	PV(4)		
$Emax$	P(5)				
$EC50$	P(6)				
H	P(7)				

Notes

The variable $y_1(t)$ represents drug concentration in plasma and $y_2(t)$ represents drug effect. The model allows only a single dose at time zero.

LINK2

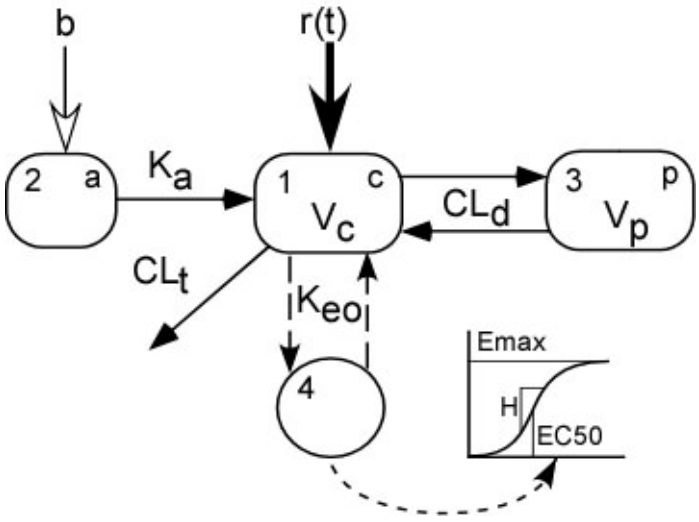
Description

PK Model: Two compartment linear model parameterized using rate constants. The model input is via IV infusion or first-order absorption, or both. PD Model: Drug response is related via the Hill equation (sigmoid-Emax model) to drug concentration in an effect compartment. Following Sheiner *et al*. See the attachment to this library model description providing a general derivation for the differential equation describing the concentration of drug in an effect compartment, which can be used with any pharmacokinetic model.

Model File Name

LINK2.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(\frac{CL_t}{V_C} + \frac{CL_d}{V_C}\right)x_1(t) + K_a x_2(t) + \frac{CL_d}{V_P}x_3(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

$$\frac{dx_3(t)}{dt} = \frac{CL_d}{V_C}x_1(t) - \frac{CL_d}{V_P}x_3(t)$$

$$\frac{dx_4}{dt} = K_{eo}(x_1 / V_c - x_4)$$

```
XP(1) = -(P(1)+P(4))/P(2)*X(1)+P(3)*X(2)+P(4)/P(5)*X(3)+R(1)
XP(2) = -P(3)*X(2)
XP(3) = P(4)/P(2)*X(1) - P(4)/P(5)*X(3)
XP(4) = P(6)*(X(1)/P(2) – X(4))
```

Output Equations:

$$y_1(t) = x_1(t)/V$$

$$y_2(t) = \frac{E\max}{\left(EC50^H + C_e^H\right)} C_e^H$$

```
Y(1)= X(1)/P(2)
Y(2)= P(7)*x(4)**P(9)/(P(8)**P(9)+x(4)**P(9))
```

Variance Model:

$$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2$$

```
V(1)=(PV(1)+PV(2)*Y(1))**2
```

$$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2$$

```
V(2)=(PV(3)+PV(4)*Y(2))**2
```

Secondary Parameters:

$K_{el} = CL_t * V_C$ $\qquad$ $V_C = V_C$

$K_{cp} = CL_d * V_C$ $\qquad$ $K_{pc} = Cl_d / V_P$

$$\lambda_1 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) + \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$

$$\lambda_2 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) - \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$

$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1$ $\qquad$ $t_{1/2} - \lambda_2 = \ln 2 / \lambda_2$

```
IF(P(2).ne.0.0) PS(1) = P(1)/P(2)
PS(2) = P(2)
IF(P(2).ne.0.0) PS(3) = P(4)/P(2)
IF(P(5).ne.0.0) PS(4) = P(4)/P(5)
PS(5) = ((PS(1)+PS(3)+PS(4))+DSQRT((PS(1)+PS(3)+PS(4))**2-
           4.0*PS(1)*PS(4)))/2.0
PS(6) = ((PS(1)+PS(3)+PS(4))-DSQRT((PS(1)+PS(3)+PS(4))**2-
           4.0*PS(1)*PS(4)))/2.0
IF(PS(5).ne.0.0) PS(7) = DLOG(2.0D0)/PS(5)
IF(PS(6).ne.0.0) PS(8) = DLOG(2.0D0)/PS(6)
```

Symbol Table:

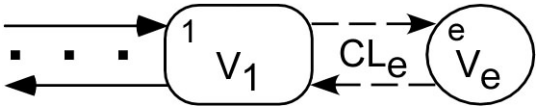
system		variance		secondary	
CL_t	-P(1)	σ_{inter1}	-PV(1)	K_{el}	-PS(1)
V_C	-P(2)	σ_{slope1}	-PV(2)	V	-PS(2)
K_a	-P(3)	σ_{inter2}	-PV(3)	K_{cp}	-PS(3)
CL_d	-P(4)	σ_{slope2}	-PV(4)	K_{pc}	-PS(4)
V_P	-P(5)			λ_1	-PS(5)
K_{eo}	-P(6)			λ_2	-PS(6)
$Emax$	-P(7)			$t_{1/2}-\lambda_1$	-PS(7)
$EC50$	-P(8)			$t_{1/2}-\lambda_2$	-PS(8)
H	-P(9)				

Notes

The variables $x_1(t)$, $x_2(t)$ and $x_3(t)$ represent amounts of drug in compartments 1, 2 and 3, respectively, with $x_4(t)$ representing the drug concentration in the effect site. $y_1(t)$ represents drug concentration in the plasma and $y_2(t)$ represents drug response. The variable $r(t)$ represents the rate of infusion of drug into compartment 1, if any, with b denoting any bolus doses absorbed through the first-order route.

Attachment to LINK2 Model
Effect Compartment Differential Equation

Diagram



Effect Compartment Differential Equation Derivation

The following symbols are used:

Ae	amount of drug in effect site
A_1	amount of drug in pharmacokinetic compartment
CL_e	clearance of drug between kinetic and effect sites
V_e	volume of effect site
V_1	volume of pharmacokinetic compartment
C_e	concentration of drug in effect site $\left(A_e / V_e\right)$
C_1	concentration of drug in pharmacokinetic compartment $\left(A_1 / V_1\right)$
Keo	effect site elimination rate constant $\left(Cl_e / V_e\right)$

$$\frac{dA_e(t)}{dt} = \frac{CLe}{V_1} A_1 - \frac{CLe}{V_e} A_e$$

substituting for A_1 / V_1 and A_e / V_e

$$\frac{dA_e(t)}{dt} = CLe \cdot C_1 - CLe \cdot C_e$$

dividing by *Ve*

$$\frac{d(A_e / V_e)}{dt} = \frac{CLe}{V_e} C_1 - \frac{CLe}{V_e} C_e = \frac{CLe}{V_e}\left(C_1 - C_e\right)$$

substituting for *Ae/Ve* and *CLe/Ve*

$$\frac{dCe}{dt} = K_{eo}\left(C_1 - C_e\right)$$

IMPROD1

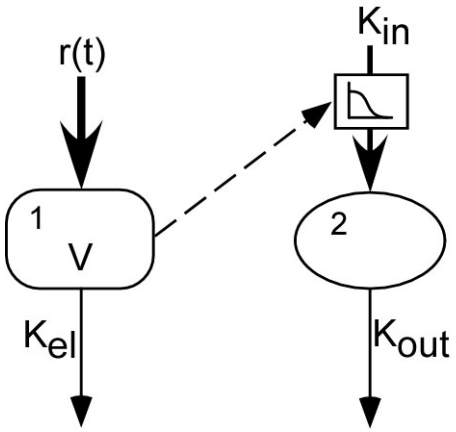
Description

PK Model: One compartment linear model with first-order elimination parameterized as a rate constant. The model input is via multiple dose IV infusion. PD Model: Indirect response model with production of the response variable inhibited by the concentration of the drug in the plasma. Following Jusko *et al*.

Model File Name

IRMPROD1.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -K_{el}x_1(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{in}\left(1 - \frac{Imax\left(x_1(t)/V\right)}{\left(IC50 + x_1(t)/V\right)}\right) - \frac{K_{in}}{IC(2)}x_2(t)$$

(**NB:** $K_{out} = \frac{K_{in}}{IC(2)}$)

```
XP(1) = -P(1)*X(1)+R(1)
XP(2) = P(3)*(1-P(5)*X(1)/P(2)/(P(4)+X(1)/P(2)))-
                              P(3)/IC(2)*X(2)
```

Output Equations:

$$y_1(t) = x_1(t)/V$$
$$y_2(t) = x_2(t)$$

```
Y(1)= X(1)/P(2)
Y(2)= X(2)
```

Variance Model:

$$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$
$$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2 \qquad \texttt{V(2)=(PV(3)+PV(4)*Y(2))**2}$$

Secondary Parameters:

$$CL = K_{el} * V$$
$$K_{out} = K_{in} / IC(2)$$

```
PS(1)= P(1)*P(2)
PS(2)= P(1)
```

Symbol Table:

system		variance		secondary	
K_{el}	- P(1)	σ_{inter1}	- PV(1)	CL_t	- PS(1)
V	- P(2)	σ_{slope1}	- PV(2)	K_{out}	- PS(2)
K_{in}	- P(3)	σ_{inter2}	- PV(3)		
$IC50$	- P(4)	σ_{inter2}	- PV(4)		
$Imax$	- P(5)				

Notes

The variable $x_1(t)$, represents the amount of drug in compartment 1 and $y_1(t)$ represents drug concentration in the plasma. The variable $r(t)$ represents the rate of infusion of drug into compartment 1. The variables $x_2(t)$ and $y_2(t)$ represent the pharmacodynamic response, and IC(2) is the control (pre-drug) value of the response.

IRMPROD2

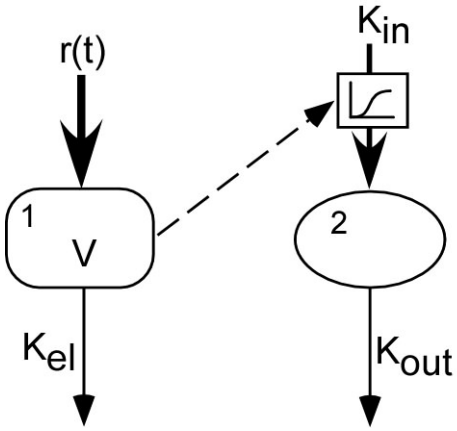
Description

PK Model: One compartment linear model with .rst-order elimination parameterized as a rate constant. The model input is via multiple dose IV infusion. PD Model: Indirect response model with production of the response variable stimulated by the concentration of the drug in the plasma. Following Jusko *et al*.

Model File Name

IRMPROD2.FOR

Model Diagram



Model Equations

Differential Equations

$$\frac{dx_1(t)}{dt} = -K_{el}x_1(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{in}\left(1 + \frac{Emax\left(x_1(t)/V\right)}{\left(EC50 + x_1(t)/V\right)}\right) - \frac{K_{in}}{IC(2)}x_2(t)$$

(**NB:** $K_{out} = \frac{K_{in}}{IC(2)}$)

```
XP(1) = -P(1)*X(1)+R(1)
XP(2) = P(3)*(1-P(5)*X(1)/P(2)/(P(4)+X(1)/P(2)))-
                                P(3)/IC(2)*X(2)
```

Output Equations:

$$y_1(t) = x_1(t)/V$$
$$y_2(t) = x_2(t)$$

```
Y(1)= X(1)/P(2)
Y(2)= X(2)
```

Variance Model:

$$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$
$$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2 \qquad \texttt{V(2)=(PV(3)+PV(4)*Y(2))**2}$$

Secondary Parameters:

$$CL = K_{el} * V$$
$$K_{out} = K_{in} / IC(2)$$

```
PS(1)= P(1)*P(2)
PS(2)= P(3)/IC(2)
```

Symbol Table:

system		variance		secondary	
K_{el}	- P(1)	σ_{inter1}	- PV(1)	CL_t	- PS(1)
V	- P(2)	σ_{slope1}	- PV(2)	K_{out}	- PS(2)
K_{in}	- P(3)	σ_{inter2}	- PV(3)		
$IC50$	- P(4)	σ_{inter2}	- PV(4)		
$Emax$	- P(5)				

Notes

The variable $x_1(t)$, represents the amount of drug in compartment 1 and $y_1(t)$ represents drug concentration in the plasma. The variable $r(t)$ represents the rate of infusion of drug into compartment 1. The variables $x_2(t)$ and $y_2(t)$ represent the pharmacodynamic response, and IC(2) is the control (pre-drug) value of the response.

IRMREM1

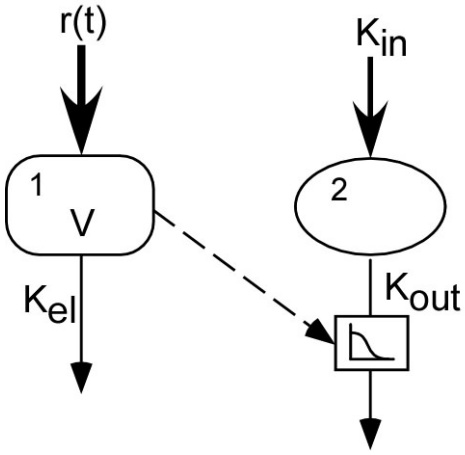
Description

PK Model: One compartment linear model with first-order elimination parameterized as a rate constant. The model input is via multiple dose IV infusion. PD Model: Indirect response model with removal of the response variable inhibited by the concentration of the drug in the plasma. Following Jusko *et al*.

Model File Name

IRMREM1.FOR

Model Diagram



Model Equations

Differential Equations

$$\frac{dx_1(t)}{dt} = -K_{el}x_1(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{in} - \frac{K_{in}}{IC(2)}\left(1 - \frac{Imax\left(x_1(t)/V\right)}{\left(IC50 + x_1(t)/V\right)}\right)x_2(t)$$

(**N.B.** $K_{out} = \frac{K_{in}}{IC(2)}$)

```
XP(1)=-P(1)*X(1)+R(1)
XP(2)=P(3)-(P(3)/IC(2))*(1-P(5)*X(1)/P(2)/(P(4)+X(1)/P(2)))
                        *X(2)
```

Output Equations:

$$y_1(t) = x_1(t)/V$$
$$y_2(t) = x_2(t)$$

```
Y(1)= X(1)/P(2)
Y(2)= X(2)
```

Variance Model:

$$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$
$$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2 \qquad \texttt{V(2)=(PV(3)+PV(4)*Y(2))**2}$$

Secondary Parameters:

$$CL = K_{el} * V$$
$$K_{out} = K_{in} / IC(2)$$

```
PS(1)= P(1)*P(2)
PS(2)= P(3)/IC(2)
```

Symbol Table:

system		variance		secondary	
K_{el}	- P(1)	σ_{inter1}	- PV(1)	CL_t	- PS(1)
V	- P(2)	σ_{slope1}	- PV(2)	K_{out}	- PS(2)
K_{in}	- P(3)	σ_{inter2}	- PV(3)		
$IC50$	- P(4)	σ_{inter2}	- PV(4)		
$Imax$	- P(5)				

Notes

The variable $x_1(t)$, represents the amount of drug in compartment 1 and $y_1(t)$ represents drug concentration in the plasma. The variable $r(t)$ represents the rate of infusion of drug into compartment 1. The variables $x_2(t)$ and $y_2(t)$ represent the pharmacodynamic response, and IC(2) is the control (pre-drug) value of the response.

IRMREM2

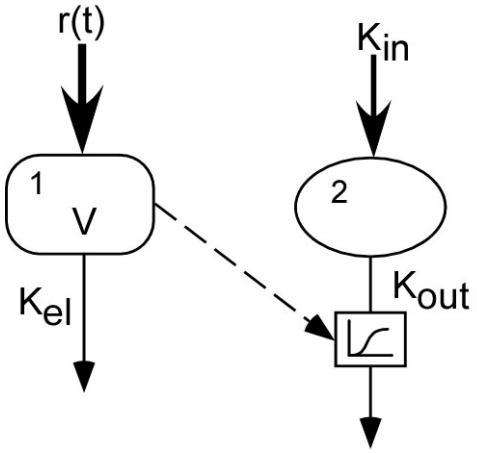
Description

PK Model: One compartment linear model with .rst-order elimination parameterized as a rate constant. The model input is via multiple dose IV infusion. PD Model: Indirect response model with removal of the response variable stimulated by the concentration of the drug in the plasma. Following Jusko *et al*.

Model File Name

IRMREM2.FOR

Model Diagram



Model Equations

Differential Equations

$$\frac{dx_1(t)}{dt} = -K_{el}x_1(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{in} - \frac{K_{in}}{IC(2)}\left(1 + \frac{Emax\left(x_1(t)/V\right)}{\left(EC50 + x_1(t)/V\right)}\right)x_2(t)$$

(**NB:** $K_{out} = \frac{K_{in}}{IC(2)}$)

```
XP(1) = -P(1)*X(1)+R(1)
XP(2) = P(3)-(P(3)/IC(2))*(1+P(5)*X(1)/P(2)/(P(4)
                          +X(1)/P(2)))*X(2)
```

Output Equations:

$$y_1(t) = x_1(t)/V$$
$$y_2(t) = x_2(t)$$

```
Y(1)= X(1)/P(2)
Y(2)= X(2)
```

Variance Model:

$$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$
$$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2 \qquad \texttt{V(2)=(PV(3)+PV(4)*Y(2))**2}$$

Secondary Parameters:

$$CL = K_{el} * V$$
$$K_{out} = K_{in} / IC(2)$$

```
PS(1)= P(1)*P(2)
PS(2)= P(3)/IC(2)
```

Symbol Table:

system		variance		secondary	
K_{el}	- P(1)	σ_{inter1}	- PV(1)	CL_t	- PS(1)
V	- P(2)	σ_{slope1}	- PV(2)	K_{out}	- PS(2)
K_{in}	- P(3)	σ_{inter2}	- PV(3)		
$EC50$	- P(4)	σ_{inter2}	- PV(4)		
$Emax$	- P(5)				

Notes

The variable $x_1(t)$, represents the amount of drug in compartment 1 and $y_1(t)$ represents drug concentration in the plasma. The variable $r(t)$ represents the rate of infusion of drug into compartment 1. The variables $x_2(t)$ and $y_2(t)$ represent the pharmacodynamic response, and IC(2) is the control (pre-drug) value of the response.

IRMLINK

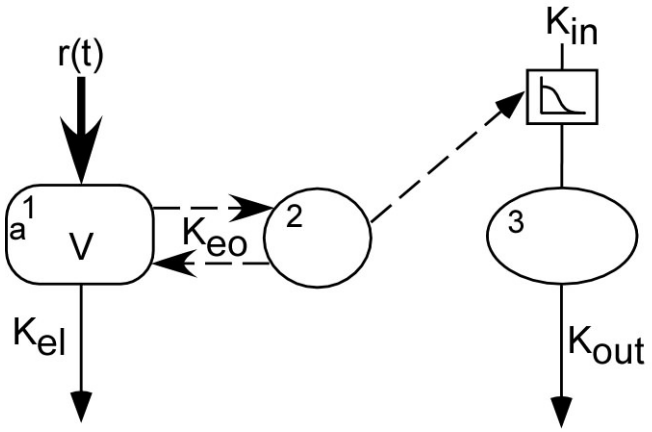
Description

PK Model: One compartment linear model with first-order elimination parameterized as a rate constant. The model input is via multiple dose IV infusion. PD Model: Indirect response model with production of the response variable inhibited by the concentration of the drug in an effect site. Following Jusko *et al*.

Model File Name

IRMLINK.FOR

Model Diagram



Model Equations

Differential Equations

$$\frac{dx_1(t)}{dt} = -K_{el}x_1(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{eo}\left(\frac{x_1(t)}{V} - x_2(t)\right)$$

$$\frac{dx_3(t)}{dt} = K_{in}\left(1 - \frac{Imax(x_2(t))}{(IC50 + x_2(t))}\right) - \frac{K_{in}}{IC(3)}x_3(t)$$

(**NB:** $K_{out} = \frac{K_{in-zero}}{IC(3)}$)

```
XP(1) = -P(1)*X(1)+R(1)
XP(2) = P(3)*(X(1)/P(2)-X(2))
XP(3) = P(4)*(1-P(6)*X(2)/(P(5)+X(2)))-P(4)/IC(3)*X(3)
```

Output Equations:

$$y_1(t) = x_1(t)/V$$
$$y_2(t) = x_3(t)$$

```
Y(1)= X(1)/P(2)
Y(2)= X(3)
```

Variance Model:

$$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$
$$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2 \qquad \texttt{V(2)=(PV(3)+PV(4)*Y(2))**2}$$

Secondary Parameters:

$$CL = K_{el} * V$$
$$K_{out} = K_{in} / IC(2)$$

```
PS(1)= P(1)*P(2)
PS(2)= P(3)/IC(2)
```

Symbol Table:

system		variance		secondary	
K_{el}	- P(1)	σ_{inter1}	- PV(1)	CL_t	- PS(1)
V	- P(2)	σ_{slope1}	- PV(2)	K_{out}	- PS(2)
K_{eo}	- P(3)	σ_{inter2}	- PV(3)		
K_{in}	- P(4)	σ_{slope2}	- PV(4)		
$IC50$	- P(5)				

Notes

The variable $x_1(t)$, represents the amount of drug in compartment 1, $y_1(t)$ represents drug concentration in the plasma, and $r(t)$ represents the rate of infusion of drug into compartment 1. The variable. $x_2(t)$ represents drug concentration in the effect site. The variables $x_2(t)$ and $y_2(t)$ represent the pharmacodynamic response, and IC(3) is the control (pre-drug) value of the response.

11.4 User Contributed and Requested Models

INDUCT

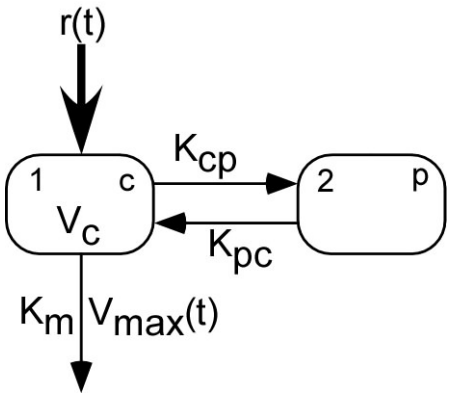
Description

The model simulates enzyme induction by incorporating an exponential increase in the effective *Vmax* from a pre-drug baseline value of *VmBase* to a steady-state value of *VmBase* + *VmAdd*. An exponential rate constant for induction is also included as a model parameter. Contributed by **John Rodman.**

Model File Name

INDUCT.FOR

Model Diagram



Model Equations

Differential Equations:

$$Vmax = VmBase + VmAdd\left(1 - e^{-Kinduct \cdot t}\right)$$

$$\frac{dx_1(t)}{dt} = -\left(\frac{V_{\max}}{K_m + x_1(t)/V_C}\right)\frac{x_1(t)}{V_C} - K_{cp}x_1(t) + K_{pc}x_2(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{cp}x_1(t) - K_{pc}x_2(t)$$

```
Vmax = P(3)+P(4)*(1.0D0-DEXP(-P(5)*T))
XP(1) = -(Vmax/(P(2)+X(1)/P(1))*(X(1)/P(1))-P(6)*X(1)+
```

```
                                  P(7)*X(2)+R(1)
XP(2) = P(6)*X(1) - P(7)*X(2)
```

Output Equations:

$y(t) = x_1(t)/Vc$ `Y(1) = X(1)/P(1)`

Variance Model:

$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$ `V(1)=(PV(1)+PV(2)*Y(1))**2`

Secondary Parameters:

$CL_d = K_{cp} * V_c$

$V_p = V * K_{cp} / K_{pc}$

```
PS(1)= P(6)*P(1)
PS(2)= P(6)*P(1)/P(7)
```

Symbol Table:

system		variance		secondary	
Vc	- P(1)	σ_{inter}	- PV(1)	*CLd*	- PS(1)
Km	- P(2)	σ_{slope}	- PV(2)	*Vp*	- PS(2)
VmBase	- P(3)				
VmAdd	- P(4)				
Kinduct	- P(5)				
Kcp	- P(6)				
Kpc	- P(7)				

Notes

The variables $x_1(t)$, and $x_2(t)$ represent the amount of drug in compartments 1, and 2, respectively, with $y(t)$ representing drug concentration in compartment 1.

NB: This model file assumes the units for *Vmax* (*VmBase* and *VmAdd*)are amount/time. In previous version of ADAPT the units used for these paramteres were assumed to be concentration/time.

MULTMOD

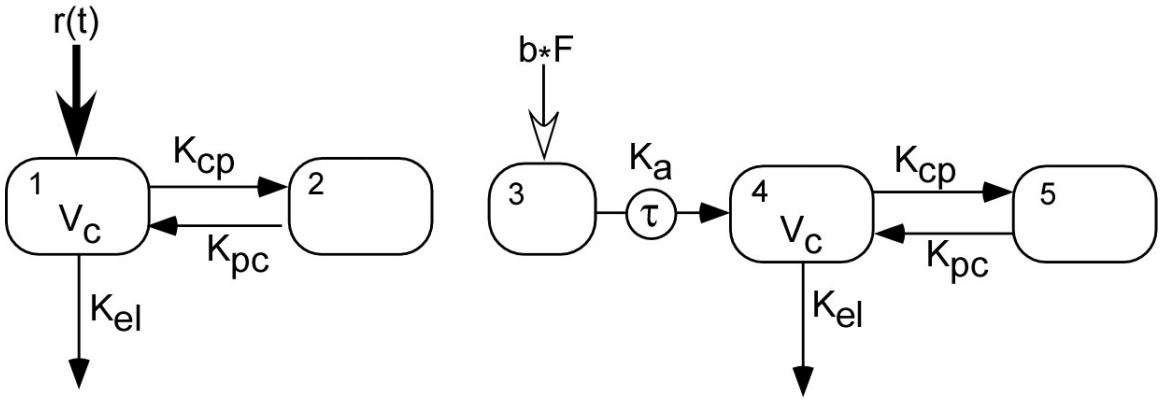
Description

Model file for simultaneous analysis of data from separate intravenous and oral studies on the same subject. Disposition is described by a two compartment linear model parameterized using rate constants. Oral administration is described by first-order absorption subject to a delay. Contributed by **Alan Forrest**.

Model File Name

MULMOD.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(K_{el} + K_{cp}\right)x_1(t) + K_{pc}x_2(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{cp}x_1(t) - K_{pc}x_2(t)$$

$$\frac{dx_3(t)}{dt} = -K_a x_3(t)$$

$$\frac{dx_4(t)}{dt} = -\left(K_{el} + K_{cp}\right)x_4(t) + K_a x_3(t) + K_{pc}x_5(t)$$

$$\frac{dx_5(t)}{dt} = K_{cp}x_4(t) - K_{pc}x_5(t)$$

```
XP(1) = -(P(1)+P(4))*(1)+P(5)*X(2)+R(1)
XP(2) = P(4)*X(1)-P(5)*X(2)
XP(3) = -P(3)*X(3)
XP(4) = -(P(1)+P(4))*X(4)+P(5)*X(5)+P(3)*X(3)
XP(5) = P(4)*X(4)-P(5)*X(5)
```

Output Equations:

$y_1(t) = x_1(t)/Vc$ `Y(1) = X(1)/P(2)`

$y_2(t) = x_4(t) \cdot F/Vc$ `Y(2) = X(4)*P(7)/P(2)`

Variance Model:

$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y_1(t)\right)^2$ `V(1)=(PV(1)+PV(2)*Y(1))**2`

$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y_2(t)\right)^2$ `V(2)=(PV(1)+PV(2)*Y(1))**2`

Secondary Parameters:

$CLt = Kel * Vc$ $Vc = Vc$

$CLd = Kcp * Vc$ $Vp = Vc * Kcp / Kpc$

$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1$ $t_{1/2} - \lambda_2 = \ln 2 / \lambda_2$ where

$$\lambda_1 = \left((Kel + Kcp + Kpc) + \sqrt{(Kel + Kcp + Kpc)^2 - 4KelKpc} \right) \Big/ 2$$

$$\lambda_2 = \left((Kel + Kcp + Kpc) - \sqrt{(Kel + Kcp + Kpc)^2 - 4KelKpc} \right) \Big/ 2$$

```
PS(1)=P(1)*P(2)                 PS(2)=P(2)
PS(3)=P(4)*P(2)                 PS(4)=P(2)*P(4)/P(5)
PS(5)=((P(1)+P(4)+P(5))+DSQRT((P(1)+P(4)+P(5))**2-
                        4*P(1)*P(5)))/2.
PS(6)=((P(1)+P(4)+P(5))-DSQRT((P(1)+P(4)+P(5))**2-
                        4*P(1)*P(5)))/2.
PS(7)=DLOG(2.0)/PS(5)
PS(8)=DLOG(2.0)/PS(6)
```

Symbol Table:

system		variance		secondary	
Kel	- P(1)	σ_{inter}	- PV(1)	*CLt*	- PS(1)
V_c	- P(2)	σ_{slope}	- PV(2)	*Vc*	- PS(2)
Ka	- P(3)			*CLd*	- PS(3)
Kcp	- P(4)			*Vp*	- PS(4)
Kpc	- P(5)			λ_1	- PS(5)
τ	- P(6)			λ_2	- PS(6)
Emax	- P(7)			$t_{1/2} - \lambda_1$	- PS(7)
				$t_{1/2} - \lambda_2$	- PS(8)

Notes

While this particular analysis could have been performed using the NPD program as illustrated in Chapter 8.1, this model file illustrates the general concept of state augmentation that allows several sub models with common parameters to be written as a single (larger) composite model.

The variables $x_1(t)$, ... $x_5(t)$ represent amounts of drug in compartments 1, through 5, with $y_1(t)$ representing drug concentration following intravenous administration (in compartment 1) and $y_2(2)$ representing drug concentration following oral administration (in compartment 3). The variable b denotes bolus doses absorbed through the first-order route.

The absorption delay is accomplished by shifting all oral doses by the amount of the delay; this is, however, transparent to the user. The code needed to perform the dose shifting is accessed through subroutine OUTPUT in the Model File. This implementation can handle single or multiple doses, but for the latter it assumes the same delay exists for all doses. **N.B.** To use this Model File, it is necessary to include an observation time = 0.0 in the data. If one does not exist in the original problem, it can be added using the missing data number (default -1) in place of the observation.

IGABS

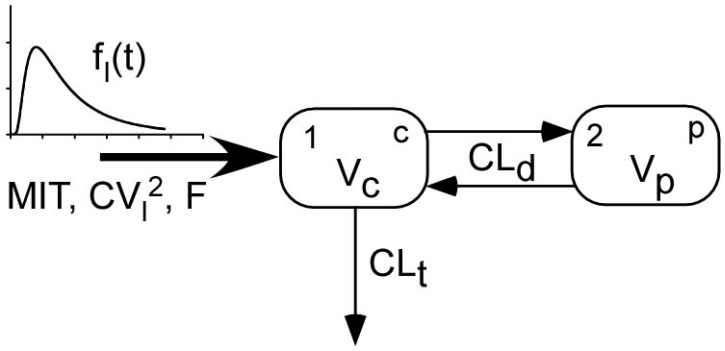
Description

This model illustrates the use of the inverse Gaussian function to describe the oral absorption process of a delayed release compound. It is assumed that the plasma drug concentration following oral administration of the drug can be decomposed into an independent input process (representing dissolution, transit and absorption processes) followed by the disposition process, which in this example is modeled as a two compartment system. Contributed by **Jian Wang** and **Michael Weiss**.

Model File Name

IGABS.FOR

Model Diagram



Model Equations

Differential Equations:

$$f_I(t) = D \cdot F \sqrt{\frac{MIT}{2\pi CV_I^2 t^3}} \exp\left[-\frac{(t-MIT)^2}{2CV_I^2 MIT t} \right]$$

$$\frac{dx_1(t)}{dt} = -\left(\frac{CL_t}{V_C} + \frac{CL_d}{V_C} \right) x_1(t) + K_a x_2(t) + f_I(t)$$

$$\frac{dx_2(t)}{dt} = \frac{CL_d}{V_C} x_1(t) - \frac{CL_d}{V_P} x_2(t)$$

```
fI = F*B(1)*dsqrt(MIT/(2.0*pi*CVI2*t**3))*
           dexp(-(t-MIT)**2/(2.0*CVI2*MIT*t))
XP(1) = -(P(1)+P(3))/P(2)*X(1) + P(3)/P(4)*X(2) + fI
XP(2) = P(3)/P(2)*X(1) - P(3)/P(4)*X(2)
```

Output Equations:

$$y(t) = x_1(t)/V_C \qquad \texttt{Y(1) = X(1)/P(2)}$$

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2 \qquad \texttt{V(1)=(PV(1)+PV(2)*Y(1))**2}$$

Secondary Parameters:

$$t_{I,\max} = MIT\left(\sqrt{1+\frac{9}{4}CV_I^4} - \frac{3}{2}CV_I^2\right)$$

```
PS(1) = P(5)*(dsqrt(1.0+9.0*P(6)**2/4.0) –
                3.0*P(6)/2.0 )
```

Symbol Table:

system		variance		secondary	
CL_t	P(1)	σ_{inter}	PV(1)	*tImax*	PS(1)
V_C	P(2)	σ_{slope}	PV(2)		
CL_d	P(3)				
V_P	P(4)				
MIT	P(5)				
CV_I^2	P(6)				
F	P(7)				

Notes

The input process can itself be decomposed into an independent dissolution (or gastrointestinal transit time) component followed by an absorption component. Such a dissolution-absorption process can be modeled using an inverse Gaussian function to describe the drug's dissolution/transit (using the parameters *MDT* and CV_D) followed by a first-order absorption model (with rate constant $k_a = 1/MAT$). In this case, the mean input time is the sum, $MIT = MDT + MAT$. See Wang *et al.* [43].

ZEROIN

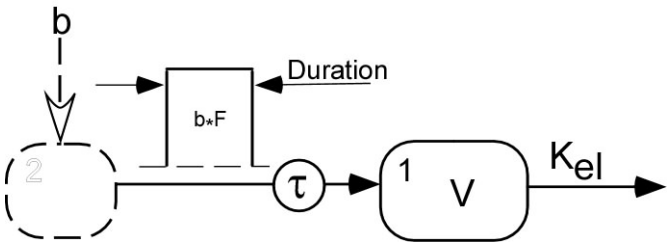
Description

One compartment linear model with first-order elimination parameterized as a rate constant. The model input is via a zero-order absorption process with delay. Both the duration of the absorption process and the fraction of dose absorbed are model parameters. The model can accommodate multiple doses, but the same duration, delay and fraction absorbed are assumed for all doses. Requested by **Lloyd Whitfield**.

Model File Name

ZEROIN.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -K_{el}x_1(t) + Rate$$

```
XP(1) =  -P(1)*X(1) + RATE
```
(see code in model file)

Output Equations:

$$y(t) = x_1(t)/V$$
```
Y(1) = X(1)/P(2)
```

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope}y(t)\right)^2$$
```
V(1)=(PV(1)+PV(2)*Y(1))**2
```

Secondary Parameters:

$CL = K_{el} * V$

$\lambda_1 = K_{el}$

$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1$

```
PS(1) = P(1)*P(2)
PS(2) = P(1)
PS(3) = DLOG(2.0)/PS(2)
```

Symbol Table:

system		variance		secondary	
Kel	-P(1)	σ_{inter}	-PV(1)	*CL*	-PS(1)
V	-P(2)	σ_{slope}	-PV(2)	λ_1	-PS(2)
τ	-P(3)			$t_{1/2} - \lambda_1$	-PS(3)
Duration	-P(4)				
F	-P(5)				

Notes

The variables $x_1(t)$ represents the amount of drug in compartment 1, with $y(t)$ representing drug concentration in compartment 1. Additional code provides the correct input to the differential equation given values for absorption delay, its duration, and the amount and fraction of the dose absorbed. The amount of drug administered at each dose is specified using the model input (not bolus input) mechanism.

The absorption delay is accomplished by shifting all doses by the amount of the delay, however, this is transparent to the user. The code needed to perform the dose shifting is contained in the Model File in subroutine OUTPUT. This implementation can handle single or multiple doses, but for the latter it assumes the same delay exists for all doses. To use this Model File, it is necessary to include an observation time = 0.0 in the data. If one does not exist in the original problem, it can be added using the missing data number (default -1) in place of the observation.

PLASMAURINE

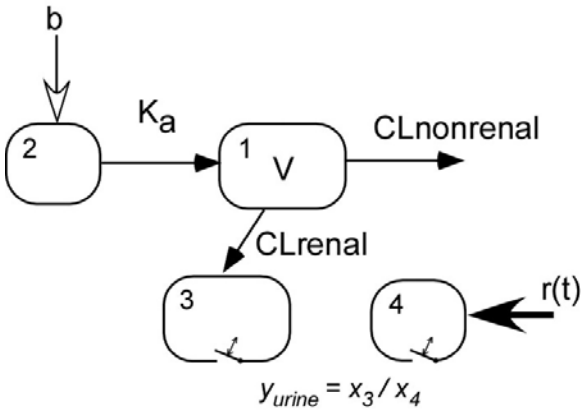
Description

Model for plasma and urine drug concentration data. The one compartment first order absorption model includes a compartment representing amount of drug collected in the urine (x_3) and another representing urine volume (x_4). In the model file the urine compartment is used to define the amount of drug in the urine during each collection interval while the volume compartment defines the volume of urine formed during each collection interval. At the end of each collection interval, the states x_3 and x_4 are set to 0.0 by the code in the Subroutine OUTPUT of the model file. Requested by **Alan Forrest** and **Paul Berringer**.

Model File Name

PLASMAURINE.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(\frac{CLnonrenal}{V} + \frac{CLrenal}{V}\right)x_1(t) + K_a x_2(t)$$

$$\frac{dx_2(t)}{dt} = -K_a x_2(t)$$

$$\frac{dx_3(t)}{dt} = \frac{CLrenal}{V} x_1(t)$$

$$\frac{dx_4(t)}{dt} = r(t)$$

```
XP(1) = -(P(1)/P(3)+P(2)/P(3))*X(1) + P(4)*X(2)
XP(2) = - P(4)*X(2)
XP(3) = (P(2)/P(3))*X(1) ! X(3)-Drug amount in urine
XP(4) = R(1)        ! X(4)-Volume of urine collected
```

Output Equations:

$y_1(t) = x_1(t)/V$	`Y(1)=X(1)/P(3)`
$y_2(t) = x_3(t)/x_4(t)$	`Y(2)=X(3)/X(4)`

Variance Model:

$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2$	`V(1)=(PV(1)+PV(2)*Y(1))**2`
$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2$	`V(2)=(PV(3)+PV(4)*Y(2))**2`

Secondary Parameters:

$Knonrenal = CLnonrenal/V$	`PS(1) = P(1)/P(3)`
$Krenal = CLrenal/V$	`PS(2) = P(2)/P(3)`
$\lambda_1 = Knonrenal + Krenal$	`PS(3) = PS(1)+PS(2)`
$t_{1/2} - \lambda_1 = \ln 2/\lambda_1$	`PS(4) = DLOG(2.0D0)/PS(3)`

Symbol Table:

system		variance		secondary	
$CLnonrenal$	`-P(1)`	σ_{inter1}	`-PV(1)`	$Knon-ur$	`-PS(1)`
$CLrenal$	`-P(2)`	σ_{slope1}	`-PV(2)`	$Kurine$	`-PS(2)`
V_c	`-P(3)`	σ_{inter2}	`-PV(1)`	λ_1	`-PS(3)`
K_a	`-P(4)`	σ_{slope2}	`-PV(2)`	$t_{1/2} - \lambda_1$	`-PS(4)`

Notes

A new model input must be added to the data file that indicates the amount of volume collected at each collection time. When an input time is not a collection time enter 0. for the amount volume collected. If the volume is lost enter the misdat number as the volume (e.g., -1). An obervation at t=0 needs to occur. Use misdat # if needed. At each collection time a corresponding observation time must be specified. If no measurement is made use misdat #.

AUCRESP

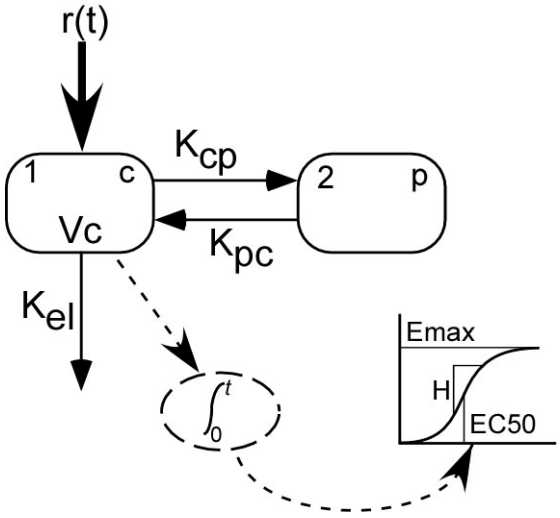
Description

PK Model: Two compartment linear model parameterized using rate constants. The model input is via IV infusion. PD Model: Drug response at time t is related to the area under the plasma concentration-time curve from time 0 to time t, through a sigmoid-Emax model. Contributed by **Alan Forrest**.

Model File Name

AUCRESP.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(K_{el} + K_{cp}\right)x_1(t) + K_{pc}x_2(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{cp}x_1(t) - K_{pc}x_2(t)$$

$$\frac{dx_3(t)}{dt} = x_1(t)/V_c$$

```
XP(1)=-(P(1)+P(3))*X(1)+P(4)*X(2)+R(1)
XP(2)=P(3)*X(1)- P(4)*X(2)
XP(3)=X(1)/P(2)
```

Output Equations:

$$y(t) = x_1(t)/V_c$$

$$y_2(t) = \frac{Emax}{\left(EC50^H + x_3^H(t)\right)} x_3(t)^H$$

```
Y(1)=X(1)/P(2)
Y(2)=P(5)*X(3)**P(7)/(P(6)**P(7)+X(3)**P(7))
```

Variance Model:

$$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2$$

```
V(1)=(PV(1)+PV(2)*Y(1))**2
```

$$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2$$

```
V(2)=(PV(3)+PV(4)*Y(2))**2
```

Secondary Parameters:

$$CL_t = K_{el} * V_C \qquad V_C = V_C$$

$$CL_d = K_{cp} * V_C \qquad V_P = V_C * K_{cp} / K_{pc}$$

$$\lambda_1 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) + \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$

$$\lambda_2 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) - \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$

$$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1 \qquad t_{1/2} - \lambda_2 = \ln 2 / \lambda_2$$

```
PS(1)=P(1)*P(2)          PS(2)=P(2)
PS(3)=P(3)*P(2)          PS(4)=P(2)*P(3)/P(4)
PS(5)=((P(1)+P(3)+P(4))+DSQRT((P(1)+P(3)+P(4))**2-
                              4*P(1)*P(4)))/2.
PS(6)=((P(1)+P(3)+P(4))-DSQRT((P(1)+P(3)+P(4))**2-
                              4*P(1)*P(4)))/2.
PS(7)=DLOG(2.0)/PS(5)
PS(8)=DLOG(2.0)/PS(6)
```

Symbol Table:

system		variance		secondary	
K_{el}	- P(1)	σ_{inter1}	- PV(1)	CL_t	- PS(1)
V_c	- P(2)	σ_{slope1}	- PV(2)	V_c	- PS(2)
K_{cp}	- P(3)	σ_{inter2}	- PV(3)	CL_d	- PS(3)
K_{pc}	- P(4)	σ_{slope2}	- PV(4)	V_p	- PS(4)
$Emax$	- P(5)			λ_1	- PS(5)
$EC50$	- P(6)			λ_2	- PS(6)
H	- P(7)			$t_{1/2}-\lambda_1$	- PS(7)
				$t_{1/2}-\lambda_1$	- PS(8)

Notes

The variables $x_1(t)$, and $x_2(t)$ represent the amount of drug in compartments 1 and 2, respectively, with $y_1(t)$ representing drug concentration in compartment 1. The variable $x_3(t)$ is the area under the plasma concentration-time curve (AUC) from time 0.0 to time t, and $y_2(t)$ is the drug response related to AUC through the sigmoid-Emax model. The variable $r(t)$ represents the rate of infusion of drug into compartment 1.

DURATION

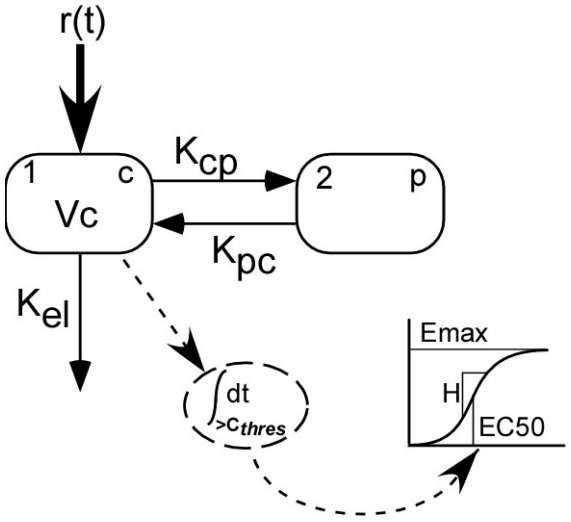
Description

PK Model: Two compartment linear model parameterized using rate constants. PD Model: Drug response at time t is related to the total duration of time that plasma concentration exceeds a threshold value up to time t, through a sigmoid-Emax model. Requested by **Merril Egorin**.

Model File Name

DURATION.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(K_{el} + K_{cp}\right)x_1(t) + K_{pc}x_2(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{cp}x_1(t) - K_{pc}x_2(t)$$

$$\frac{dx_3(t)}{dt} = 1.0 \qquad \text{when } x_1(t)/Vc \geq Cthres$$

$$\frac{dx_3(t)}{dt} = 0.0 \qquad \text{when } x_1(t)/Vc < Cthres \quad \text{(see code in model file)}$$

```
XP(1) = -(P(1) + P(3))*X(1) + P(4)*X(2) + R(1)
XP(2) = P(3)*X(1) - P(4)*X(2)
IF(X(1)/P(2).GE.P(5)) THEN
     XP(3) = 1.0
ELSE
     XP(3)= 0.0
END IF
```

Output Equations:

$$y(t) = x_1(t)/V_c$$

$$y_2(t) = \frac{Emax}{EC50^H + x_3(t)^H} x_3(t)^H$$

```
Y(1)=X(1)/P(2)
Y(2)=P(6)*X(3)**P(8)/(P(7)**P(8)+X(3)**P(8))
```

Variance Model:

$$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2$$

```
V(1)=(PV(1)+PV(2)*Y(1))**2
```

$$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2$$

```
V(2)=(PV(3)+PV(4)*Y(2))**2
```

Secondary Parameters:

$$CL_t = K_{el} * V_C \qquad V_C = V_C$$

$$CL_d = K_{cp} * V_C \qquad V_P = V_C * K_{cp} / K_{pc}$$

$$\lambda_1 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) + \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$

$$\lambda_2 = \left(\left(K_{el} + K_{cp} + K_{pc}\right) - \sqrt{\left(K_{el} + K_{cp} + K_{pc}\right)^2 - 4K_{el}K_{pc}} \right) \Big/ 2$$

$$t_{1/2} - \lambda_1 = \ln 2 / \lambda_1 \qquad t_{1/2} - \lambda_2 = \ln 2 / \lambda_2$$

```
PS(1)=P(1)*P(2)          PS(2)=P(2)
PS(3)=P(3)*P(2)          PS(4)=P(2)*P(3)/P(4)
PS(5)=((P(1)+P(3)+P(4))+DSQRT((P(1)+P(3)+P(4))**2-
                              4*P(1)*P(4)))/2.
PS(6)=((P(1)+P(3)+P(4))-DSQRT((P(1)+P(3)+P(4))**2-
                              4*P(1)*P(4)))/2.
PS(7)=DLOG(2.0)/PS(5)
PS(8)=DLOG(2.0)/PS(6)
```

Symbol Table:

system		variance		secondary	
K_{el}	-P(1)	σ_{inter1}	-PV(1)	CL_t	-PS(1)
V_c	-P(2)	σ_{slope1}	-PV(2)	V_c	-PS(2)
K_{cp}	-P(3)	σ_{inter2}	-PV(3)	CL_d	-PS(3)
K_{pc}	-P(4)	σ_{slope2}	-PV(4)	V_p	-PS(4)
Cthres	-P(5)			λ_1	-PS(5)
Emax	-P(6)			λ_2	-PS(6)
*EC*50	-P(7)			$t_{1/2} - \lambda_1$	-PS(7)
H	-P(8)			$t_{1/2} - \lambda_2$	-PS(8)

Notes

The variables $x_1(t)$, and $x_2(t)$ represent the amount of drug in compartments 1 and 2, respectively, with $y_1(t)$ representing drug concentration in compartment 1. The variable $x_3(t)$ is the total duration of time that plasma concentration exceeds the threshold value, and $y_2(t)$ is the drug response related to time duration above threshold through the sigmoid-Emax model. The variable $r(t)$ represents the rate of infusion of drug into compartment 1.

CIRCAD

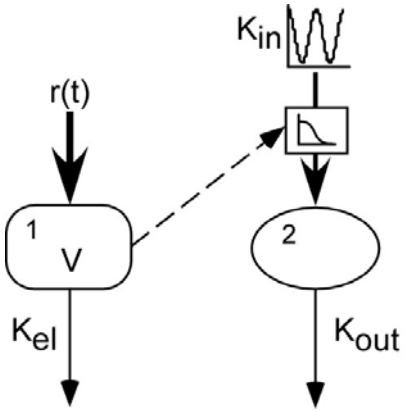
Description

PK Model: One compartment linear model with first-order elimination parameterized as a rate constant. The model input is via multiple dose IV infusion. PD Model: Indirect response model with production of the response variable inhibited by the concentration of the drug in the plasma. Endogenous production rate governed by a circadian rhythm. Contributed by **Wojciech Krzyzanski**.

Model File Name

CIRCAD.FOR

Model Diagram



Model Equations

Differential Equations

$$K_{mean} = K_{out} \cdot IC(2) - \frac{K_{amp} \cdot K_{out}^2}{K_{out}^2 + (2\pi/24)^2} \cdot \left[\cos(\frac{2\pi}{24} \cdot t_{peak}) - \frac{2\pi}{24K_{out}} \sin(\frac{2\pi}{24} \cdot t_{peak}) \right]$$

$$K_{in} = K_{mean} + K_{amp} \cos\left(\frac{t - t_{peak}}{24} \cdot 2\pi \right)$$

$$\frac{dx_1(t)}{dt} = -K_{el} x_1(t) + r(t)$$

$$\frac{dx_2(t)}{dt} = K_{in} \left(\frac{1 - x_1(t)/V}{\left(IC50 + x_1(t)/V \right)} \right) - K_{out} x_2(t)$$

```
Kmean=IC(2)*P(4)-((P(5)*P(4)**2/(P(4)**2+(2.0*pi/24.0)**2))
                *(DCOS((2.0*pi/24.0)*P(6))-(2.0*pi/(P(4)*24)
                *DSIN((2.0*pi/24.0)*P(6)))
Kin=Kmean+P(5)*DCOS((t - P(6))*2.0*pi/24.0)

XP(1)=-P(1)*X(1)+R(1)
XP(2)=Kin*(1-X(1)/P(2)/(P(3)+X(1)/P(2)))-P(4)*X(2)
```

Output Equations:

$y_1(t) = x_1(t)/V$ — `Y(1)=X(1)/P(2)`

$y_2(t) = x_2(t)$ — `Y(2)=X(2)`

Variance Model:

$\sigma_1^2 = \left(\sigma_{inter1} + \sigma_{slope1} y_1(t)\right)^2$ — `V(1)=(PV(1)+PV(2)*Y(1))**2`

$\sigma_2^2 = \left(\sigma_{inter2} + \sigma_{slope2} y_2(t)\right)^2$ — `V(2)=(PV(3)+PV(4)*Y(2))**2`

Secondary Parameters:

$CL = Kel * V$ — `PS(1) = P(1)*P(2)`

Symbol Table:

system		variance		Secondary	
K_{el}	-P(1)	σ_{inter}	-PV(1)	CL	-PS(1)
V	-P(2)	σ_{slope}	-PV(2)		
$IC50$	-P(3)	σ_{inter2}	-PV(3)		
K_{out}	-P(4)	σ_{slope2}	-PV(4)		
K_{amp}	-P(5)				
T_{peak}	-P(6)				

Notes

The variable $x_1(t)$, represents the amount of drug in compartment 1 and $y_1(t)$ represents drug concentration in the plasma. The variable $r(t)$ represents the rate of infusion of drug into compartment 1. The variable $x_2(t)$ (and $y_2(t)$) represents the pharmacodynamic response, and IC(2) is the control (pre-drug) value of the response. **NB:** The trigonometric equation used to model the circadian variation in production rate assumes time is measured in hours.

ORGAN1

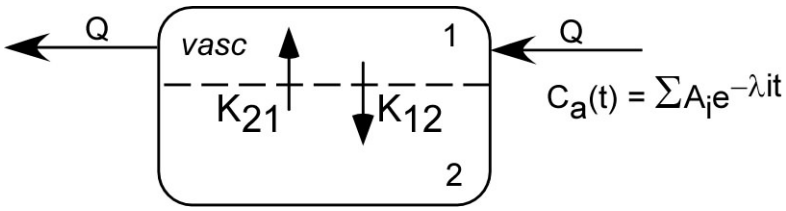
Description

The model presented describes an isolated organ experiment in which arterial drug concentration, represented as a known sum of exponentials, serves as the input to the model. The organ model includes a vascular and tissue space with first-order processes describing the exchange between the two regions. The model output is measured concentration of the drug in the venous effluent. Contributed by **William Ebling**.

Model File Name

ORGAN1.FOR

Model Diagram



Model Equations

Differential Equations:

$$Ca = Ae^{-\lambda_1 t} + Be^{-\lambda_2 t}$$

$$\frac{dx_1(t)}{dt} = -\left(\frac{Q}{Vvasc} + K_{12}\right)x_1(t) + K_{12}x_2(t) + Q \cdot Ca$$

$$\frac{dx_2(t)}{dt} = K_{12}x_1(t) - K_{21}x_2(t)$$

```
   CA = (P(5)*DEXP(-P(6)*T)+P(7)*DEXP(-P(8)*T))
XP(1) = -(P(1)/P(2)+P(3))*X(1)+P(4)*X(2)+P(1)*CA
XP(2) = P(3)*X(1)-P(4)*X(2)
```

Output Equations:

$y_1(t) = x_1(t)/V$ Y(1)= X(1)/P(2)

Variance Model:

$\sigma^2 = \left(\sigma_{\text{inter}} + \sigma_{\text{slope}} y(t)\right)^2$ V(1)=(PV(1)+PV(2)*Y(1))**2

Secondary Parameters:

none

Symbol Table:

system		variance		Secondary
Q	- P(1)	σ_{inter}	- PV(1)	*none*
$Vvasc$	- P(2)	σ_{slope}	- PV(2)	
K_{12}	- P(3)			
K_{21}	- P(4)			
$Ca-A$	- P(5)			
$Ca-Lam1$	- P(6)			
$Ca-B$	- P(7)			
$Ca-LAM2$	- P(8)			

Notes

The variables $x_1(t)$, and $x_2(t)$ represent amounts of drug in the vascular and tissue spaces of the organ, with $y(t)$ representing drug concentration in the venous effluent which is assumed to be in equilibration with the blood in the tissue.

ORGAN2

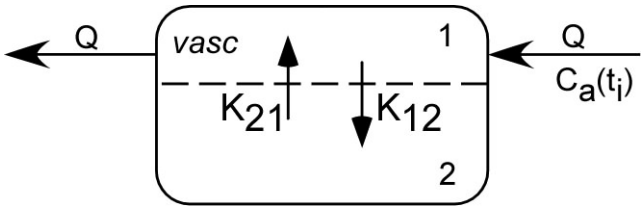
Description

The model presented describes an isolated organ experiment in which measured arterial drug concentration serves as the input to the model. It is assumed that the arterial drug concentration varies linearly between each measured arterial drug concentration value. The function LINE (added at the end of the model file for this example) performs the needed linear interpolation. The measured values of arterial concentration and the corresponding measurement times are entered using the model input entry when the program is run. The organ model includes a vascular and tissue space with first-order processes describing the exchange between the two regions. The model output is measured concentration of the drug in the venous effluent. Requested by **William Ebling**.

Model File Name

ORGAN2.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dx_1(t)}{dt} = -\left(\frac{Q}{Vvasc} + K_{12}\right)x_1(t) + K_{12}x_2(t) + Q \cdot Ca$$

$$\frac{dx_2(t)}{dt} = K_{12}x_1(t) - K_{21}x_2(t)$$

```
Call LINE(t, u)
XP(1)=-(P(1)/P(2)+P(3))*X(1)+P(4)*X(2)+P(1)*u
XP(2)=P(3)*X(1)-P(4)*X(2)
```

Output Equations:

$y_1(t) = x_1(t)/V$ `Y(1)= X(1)/P(2)`

Variance Model:

$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$ `V(1)=(PV(1)+PV(2)*Y(1))**2`

Secondary Parameters:

none

Symbol Table:

	system		variance	Secondary
Q	-P(1)	σ_{inter}	-PV(1)	*none*
Vvasc	-P(2)	σ_{slope}	-PV(2)	
K_{12}	-P(3)			
K_{21}	-P(4)			

Notes

The variables $x_1(t)$, and $x_2(t)$ represent amounts of drug in the vascular and tissue spaces of the organ, with $y(t)$ representing drug concentration in the venous effluent which is assumed to be in equilibration with the blood in the tissue.

RECEPTOR

Description

Receptor-ligand model describing the association of the ligand L and receptor R to form the complex R1L, which in turn under goes a change of state to R2L. The model represents the kinetics of a receptor with one binding site and two conformational states. Contributed by **D. Najman**

Model File Name

RECEPTOR.FOR

Model Diagram

Model Equations

Differential Equations:

$$\frac{dL}{dt} = -k_1 \cdot L \cdot R + k_{-1} \cdot R1L$$

$$\frac{dR}{dt} = -k_1 \cdot L \cdot R + k_{-1} \cdot R1L$$

$$\frac{dR1L}{dt} = k_1 \cdot L \cdot R - k_{-1} \cdot R1L - k_2 \cdot R1L + k_{-2} \cdot R2L$$

$$\frac{dR2L}{dt} = k_2 \cdot R1L - k_{-2} \cdot R2L$$

```
XP(1) = -P(1)*X(1)*X(2) + P(2)*X(3)
XP(2) = -P(1)*X(1)*X(2) + P(2)*X(3)
XP(3) = P(1)*X(1)*X(2) - P(2)*X(3) - P(3)*X(3) + P(4)*X(4)
XP(4) = P(4)*X(3) - P(5)*X(4)
```

Output Equations:

$y_1(t) = L$	Y(1)= X(1)
$y_2(t) = R$	Y(2)= X(2)
$y_3(t) = R1L$	Y(3)= X(3)
$y_4(t) = R2L$	Y(4)= X(4)

Variance Model:

none

Secondary Parameters:

none

Symbol Table:

	system	variance	Secondary
K_1	-P(1)	*none*	*none*
K_{-1}	-P(2)		
K_2	-P(3)		
K_{-2}	-P(4)		

Notes

The variables $x_1(t)$ and $x_2(t)$ ($y_1(t)$ and $y_2(t)$) represent the concentration of free ligand and receptor, while $x_3(t)$ and $x_4(t)$ ($y_3(t)$ and $y_4(t)$) represent the concentration of receptor ligand in conformation states R1L and R2L, respectively.

NMDA

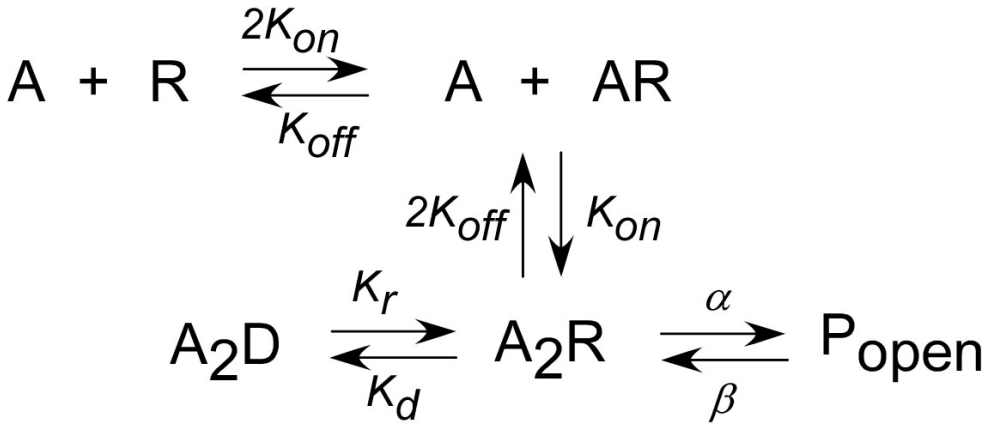
Description

Model for NMDA receptor-ligand kinetics. Model assumes two binding sites and incorporates a receptor-ligand desensitized state. Contributed by **D. Najman, J-S Liaw and T. Berger**.

Model File Name

NMDA.FOR

Model Diagram



Model Equations

Differential Equations:

$$\frac{dA}{dt} = -2K_{on}A\cdot R + K_{off}A\cdot AR - K_{on}A\cdot AR + 2K_{off}A2R$$

$$\frac{dR}{dt} = -2K_{on}A\cdot R + K_{off}A\cdot AR$$

$$\frac{dAR}{dt} = 2K_{on}A\cdot R - K_{off}A\cdot AR - K_{on}A\cdot AR + 2K_{off}A2R$$

$$\frac{dA2R}{dt} = K_{on}A\cdot AR - 2K_{off}A2R + \beta\cdot P_{open} - \alpha\cdot A2R + K_{r}A2D - K_{d}A2R$$

$$\frac{dP_{open}}{dt} = \alpha\cdot A2R - \beta\cdot P_{open}$$

$$\frac{dA2D}{dt} = K_{d}A2R - K_{r}A2D$$

```
XP(1) = -2.0*P(1)*X(1)*X(2)+P(2)*X(1)*X(3)-P(1)*X(1)*X(3)
          +2.0*P(2)*X(4)
XP(2) = -2.0*P(1)*X(1)*X(2)+P(2)*X(1)*X(3)
XP(3) = 2.0*P(1)*X(1)*X(2)-P(2)*X(1)*X(3)-P(1)*X(1)*X(3)
          +2.0*P(2)*X(4)
XP(4) = P(1)*X(1)*X(3)-2.0*P(2)*X(4)+P(3)*X(5)-P(4)*X(4)
          +P(5)*X(6)-P(6)*X(4)
XP(5) = P(4)*X(4)-P(3)*X(5)
XP(6) = P(6)*X(4)-P(5)*X(6)
```

Output Equations:

$y_1(t) = A$	`Y(1)= X(1)`
$y_2(t) = R$	`Y(2)= X(2)`
$y_3(t) = AR$	`Y(3)= X(3)`
$y_4(t) = A2R$	`Y(4)= X(4)`
$y_5(t) = P_{open}$	`Y(5)= X(5)`
$y_6(t) = A2D$	`Y(6)= X(6)`

Variance Model:

none

Secondary Parameters:

none

Symbol Table:

system		variance	Secondary
K_{on}	`-P(1)`	*none*	*none*
K_{off}	`-P(2)`		
β	`-P(3)`		
α	`-P(4)`		
K_r	`-P(5)`		
K_d	`-P(6)`		

ESIGMAX

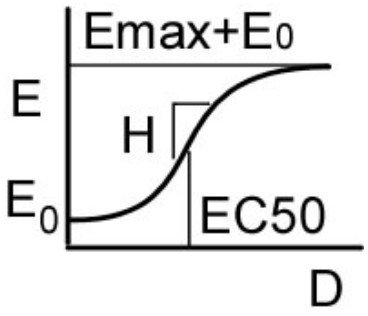
Description

Excitatory sigmoid *Emax* model. Requested by **Edward Acosta and Burgess B. Freeman.**

Model File Name

ESIGMAX.FOR

Model Diagram



Model Equations

Differential Equations:

None

Output Equations:

$$y_1(t) = E_0 + \frac{Emax}{\left(EC50^H + t^H\right)} t^H$$

Note: The independent variable *t* is used to represent *D*.

```
Y(1) =P(1) + P(2)*t**P(4)/(P(3)**P(4)+t**P(4))
```

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$$

```
V(1)=(PV(1)+PV(2)*Y(1))**2
```

Secondary Parameters:

none

Symbol Table:

system		variance		Secondary
E_0	-P(1)	σ_{inter}	-PV(1)	*none*
Emax	-P(2)	σ_{slope}	-PV(2)	
*EC*50	-P(3)			
H	-P(4)			

Notes

ISIGMAX

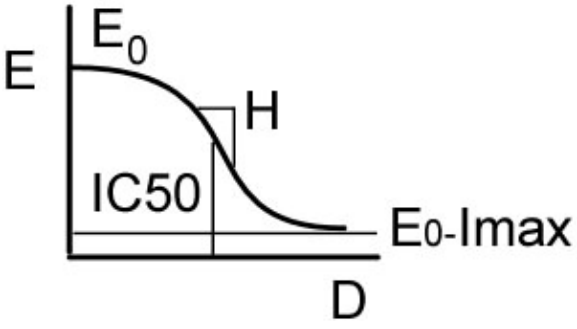
Description

Inhibitory sigmoid *Emax* model. Requested by **Edward Acosta and Burgess B. Freeman.**

Model File Name

ESIGMAX.FOR

Model Diagram



Model Equations

Differential Equations:

None

Output Equations:

$$y_1(t) = E_0 - \frac{Imax}{\left(IC50^H + t^H\right)} t^H$$

Note: The independent variable *t* is used to represent *D*.

```
Y(1) =P(1) - P(2)*t**P(4)/(P(3)**P(4)+t**P(4))
```

Variance Model:

$$\sigma^2 = \left(\sigma_{inter} + \sigma_{slope} y(t)\right)^2$$

```
V(1)=(PV(1)+PV(2)*Y(1))**2
```

Secondary Parameters:

none

Symbol Table:

system		variance		Secondary
E_0	-P(1)	σ_{inter}	-PV(1)	*none*
Imax	-P(2)	σ_{slope}	-PV(2)	
*IC*50	-P(3)			
H	-P(4)			

Notes

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APPENDIX

A. Setting Variables in the Globals.inc File

On installation of ADAPT, certain constants defining maximum values for model variables and values for numerical tolerances are incorporated into the compiled program libraries. These and other constants are specified in the file `globals.inc` located in the installation folder (default: `C:\Program File\BMSR\ADAPT 5`). As distributed, the `globals.inc` file contains certain default values for these constants (see section from file in Figure A.1). The numerical tolerances and other constants defined in `globals.inc` are discussed in Chapters 5. If desired, the default values included in `globals.inc` can be changed by editing this file. If any of the constants in `globals.inc` are changed after the initial installation, ADAPT must be reinstalled by running the RecompileADAPT program in the ADAPT Program Group. If ADAPT is uninstalled, the file `globals.inc` is not deleted from the ADAPT installation folder; whether it has been modified by the user or not. If ADAPT is then reinstalled, the existing `globals.inc` file is used by the program.

Maximum values should not be increased arbitrarily above what is expected to be needed for the user's application, as degradation in computing performance can result. In particular the constants indicating the maximum number of parameters estimated (`MaxNPest`) and the maximum number of total observations (`MaxOBE`) critically influence program memory requirements and thus speed of computation. In ADAPT 5, the constant `MaxNPest` can be set independently of the `MaxNSP` and `MaxNSP` to allow large models.

Table A.1 Excerpt from file Globals.inc

```
C  Define maximum value constants.
      Integer MaxNDE,MaxNSP,MaxNRI,MaxNBI,MaxND
      Integer MaxNOE,MaxNOB,MaxOBE
      Integer MaxNVP,MaxSIM,MaxPLT,MaxNSECP,MaxNSO
      Integer MaxNSubs, MaxNITS, MaxNSAMP
      Integer MaxNPest, MaxNTest
      Integer MaxNCP
      Parameter (MaxNDE=25)    ! Max Number of Differential Equations
      Parameter (MaxNSP=35)    ! Max Number of System Parameters
      Parameter (MaxNRI=10)    ! Max Number of Rate Inputs
      Parameter (MaxNBI=10)    ! Max Number of Bolus Inputs
      Parameter (MaxND=200)    ! Max Number of Dose Events
      Parameter (MaxNOE=15)    ! Max Number of Output Equations
      Parameter (MaxNOB=100)   ! Max Number of Observations per Output
      Parameter (MaxOBE=300)   ! Max Number of Total Observations
      Parameter (MaxNVP=20)    ! Max Number of Variance Parameters
      Parameter (MaxSIM=5000)  ! Max Number of Simulations
      Parameter (MaxNSECP=15)  ! Max Number of Secondary Parameters
      Parameter (MaxNSO=10)    ! Max Number of Secondary Outputs
      Parameter (MaxPLT=1000)  ! Number of Points used for Smooth Plots
                               !   MaxPLT>=MaxOBE
      Parameter (MaxNSubs=500) ! Max Number of Subjects
      Parameter (MaxNITS=1000) ! Max Number of ITS and EM Iterations
      Parameter (MaxNSAMP=3000)! Max Number of Samples per EM Iteration
                               !   for Importance Sampler
      Parameter (MaxNPest=25)  ! Max Number of Parameters Estimated
                               !   ( <= MaxNSP+MaxNDE )
      Parameter (MaxNTest=20)  ! Max Number of Sample Times Optimized
                               !   ( <= MaxNOB )
      Parameter (MaxNCP = 35)  ! Max Number Covariate Model Parameters

C  Stopping tolerance for Nelder-Mead algorithm.
      Real*8 Reqmin
      Parameter (Reqmin = 1.0d-06)

C  Missing data number.
      Real*8 Misdat
      Parameter (Misdat=-1.0D0)

C  Define constants for LSODA (see documentation in LSODA code).
C   Note that DimRW must be set MANUALLY based on the value of MaxNDE.
      Integer ITOL,ITASK,IOPT,DimRW,LIW,JT
      Real*8 RTOL,ATOL
      Parameter (ITOL=1)
      Parameter (ITASK=1)
      Parameter (IOPT=0)
      Parameter (LIW=MaxNDE+20)
      Parameter (JT=2)
      Parameter (DimRW=872)     ! DimRW = 22 + MaxNDE*Max(16,MaxNDE+9)
      Parameter (RTOL=1.0D-06)  ! Rel. error tolerance for LSODA
      Parameter (ATOL=1.0D-06)  ! Abs. error tolerance for LSODA
```