Short Course on
Modeling and Data Analysis in Pharmacokinetics and Pharmacodynamics using ADAPT 5

Dresden, Germany
July 15-16, 2008

Lecturers

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Los Angeles

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Martin Luther University Halle-Wittenberg
Halle (Saale)

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Max Planck Institute for Physics of Complex Systems

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Course Instructors

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With Support From

The Biomedical Simulations Resource, University of Southern California
Section of Pharmacokinetics, Martin Luther University

Preface

The Short Course is intended for basic and clinical research scientists who are actively involved in the application of modeling, computational and data analysis methods to problems involving drug kinetics and drug response. Background lectures and case studies will cover the following topics: population modeling – theory and applications; PK/PD models (indirect & target mediated response models); modeling with covariates; modeling using inverse Laplace transformation (absorption, metabolite PK); least squares, maximum likelihood and Bayesian estimation; estimation with multiple response models.

It is hoped that this Short Course will give the participants a thorough exposure to the broad class of pharmacokinetic/ pharmacodynamic modeling and data analysis problems that can be solved using ADAPT 5.

David Z. D'Argenio
Los Angeles

Michael Weiss
Halle/Salle

ADAPT Short Course Schedule
Tuesday, 15 July 2008

8:30 Background: **Modeling with ADAPT 5**

9:45 Case Study: **Doses and Covariates**

10:30 **Break**

10:45 Background: **Parameter Estimation**

11:45 Case Study: **WLS/ML Estimation**

12:30 **Lunch Break**

ADAPT Short Course Schedule
Tuesday, 15 July 2008

13:30 Case Study : **Multiresponse Estimation**

14:15 Case Study: **Recirculatory Modeling of Disposition**

15:00 **Break**

15:15 Case Study: **Models for Drug-Receptor Interaction**

16:00 Case Study: **Direct Response PK/PD Models**

16:45 **Dinner Excursion**

ADAPT Short Course Schedule
Wednesday, 16 July 2008

9:00 Case Study: **Indirect Response PK/PD Models**

9:45 Background: **Population PK/PD Modeling**

10:45 **Break**

11:00 Case Study: **The ADAPT Population Programs**

11:45 Case Study: **The MLEM Program**

12:30 **Lunch Break**

ADAPT Short Course Schedule
Wednesday, 16 July 2008

13:30 Case Study: **Absorption/Disposition Modeling**

14:15 Background: **Population Modeling with Covariates**

15:00 **Break**

15:15 Case Study: **Modeling Building with Covariates**

15:45 Case Study: **PK/PD Population Modeling Example**

16:30 **Summary Comments**

16:45 **Adjourn**

MODELING with ADAPT

Model Formulation

- Model Equations
- Inputs
- Measurement Model
- Parameter Model
- Secondary Parameters

Implementing the Model in ADAPT

- Model Equations – Model File
- Inputs/Measurements – Data File
- Parameter Values – Parameter File

MODELING with ADAPT

Comments on Computational Methods

- Solving Differential Equations (LSODA)
- Function Minimization (Nelder Mead Simplex)

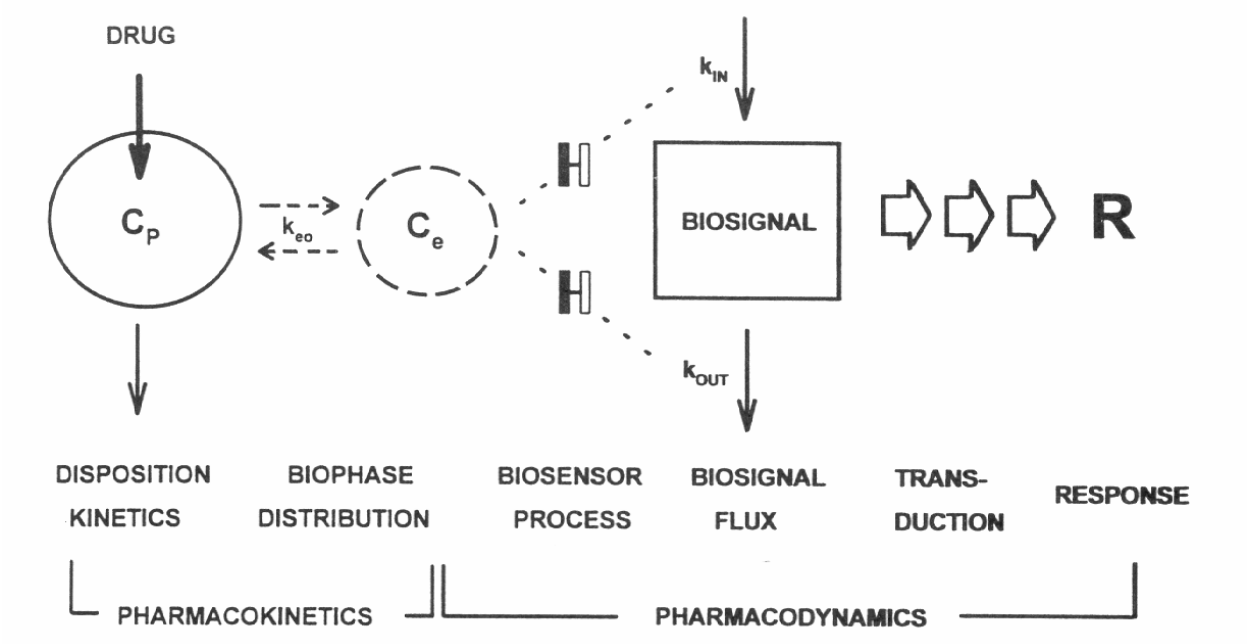
The Programs

- SIM, ID, SAMPLE
- NPD, STS, ITS, MLEM

Library Models

Dissemination and Support

PK/PD Paradigm



(From Jusko J. Pharmacokin. Biopharm.)

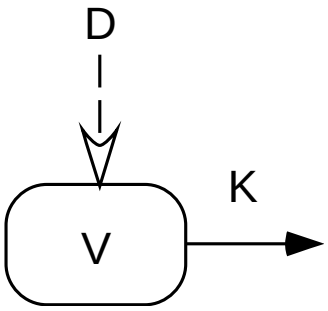
Model Formulation

- Model Equations (state space formulation)

$$\frac{dx(t)}{dt} = f(x(t), \alpha, r(t), t), \qquad x(0) = c$$
$$y(t) = h(x(t), \alpha, r(t), t)$$

$x(t)$	amount of drug in compartment; concentration of drug in tissue; effect site concentration; receptor activity; signaling protein; physiological variable; disease state
α	rate constant; clearance; distribution volume; binding constant; partition coefficient; diffusivity; EC50; Emax; effect site elimination rate; physiological production/elimination rate; etc.
$r(t)$	drug infusion regimen; covariate (e.g., body weight, creatinine clearance, liver enzyme, cardiac output)
c	initial values of x: compartment amounts; biological variables
$y(t)$	plasma concentration; drug exposure; drug effect (biomarker; surrogate endpoint; clinical response); etc.

- Model Equations - Examples



1: *x* - amount of drug, *y* - concentration of drug:

$$\frac{dx(t)}{dt} = -Kx(t), \qquad x(0) = D$$
$$y(t) = x(t)/V$$

- Model Equations - Examples

2: *x* - concentration of drug, *y* - concentration of drug:

$$\frac{dx(t)}{dt} = -Kx(t), \qquad x(0) = D/V$$
$$y(t) = x(t)$$

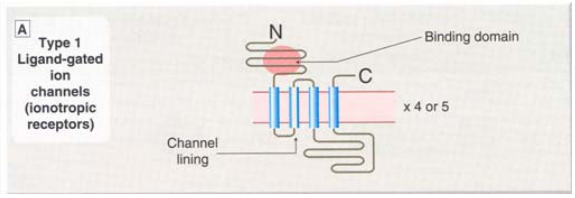
3: analytic solution, *y* - concentration of drug:

$$y(t) = \frac{D}{V} e^{-Kt}$$

- Model Equations - Examples

Receptor – Ligand Interaction Model

One Binding Site – Two Conformational States



$$L + R \underset{K_2}{\overset{K_1}{\rightleftarrows}} RL1 \underset{K_4}{\overset{K_3}{\rightleftarrows}} RL2$$

$$\frac{dL(t)}{dt} = -K_1 \cdot L(t) \cdot R(t) + K_2 \cdot RL1(t), \qquad L(0)$$

$$\frac{dR(t)}{dt} = -K_1 \cdot L(t) \cdot R(t) + K_2 \cdot RL1(t), \qquad R(0)$$

$$\frac{dRL1(t)}{dt} = K_1 \cdot L(t) \cdot R(t) - K_2 \cdot RL1(t) - K_3 \cdot RL1(t) + K_4 \cdot RL2(t), \qquad RL1(0)$$

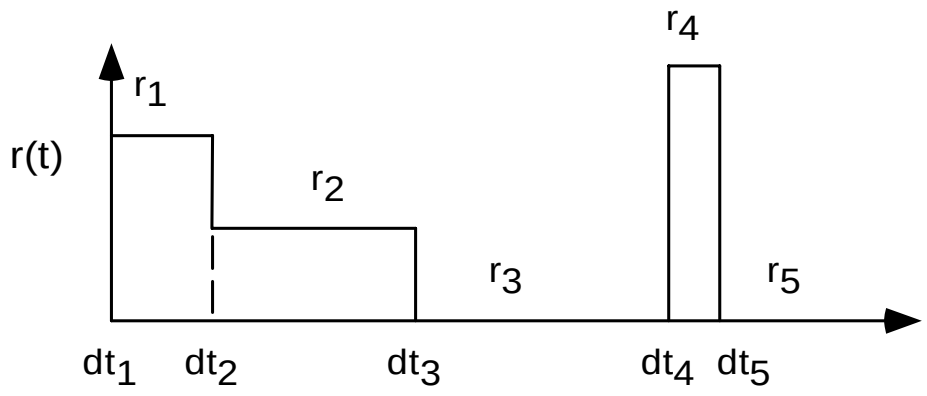
$$\frac{dRL2(t)}{dt} = K_3 \cdot RL1(t) - K_4 \cdot RL2(t), \qquad RL2(0)$$

- Inputs

1. Model Inputs → appear explicitly in equations; piecewise constant

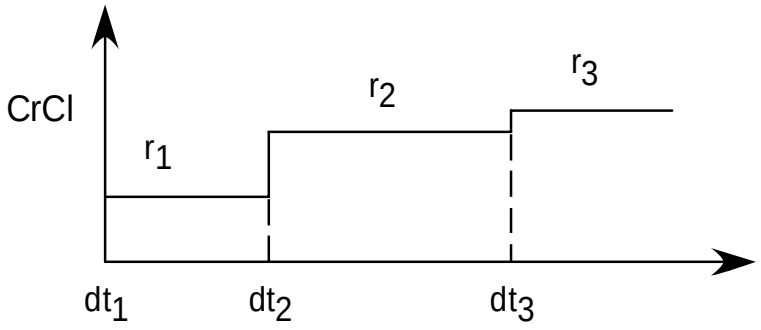
$$r(t) = r_{i-1}, \qquad dt_{i-1} < t \le dt_i \qquad i = 2, \ldots, nd+1$$

e.g., r(t) - IV Infusion Regimen

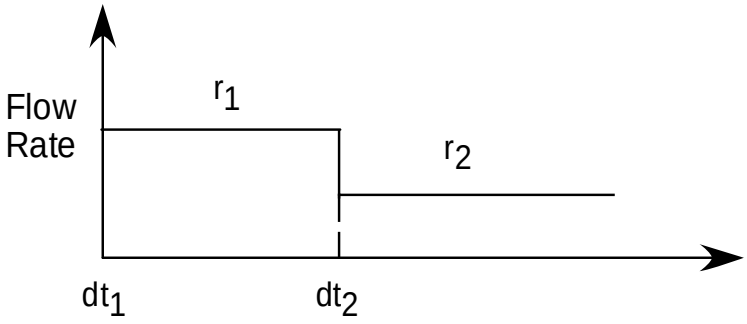


1. Model Inputs → appear explicitly in equations; piecewise constant

e.g., r(t) – Covariate (e.g., CrCl ; BW)

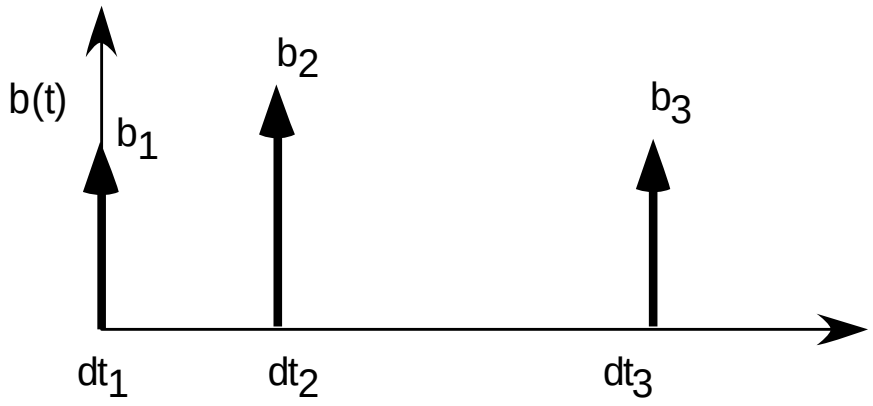


e.g., r(t) - Organ Blood Flow



2. Bolus Inputs $\rightarrow$ not in equations; change states instantaneously; specified at program run

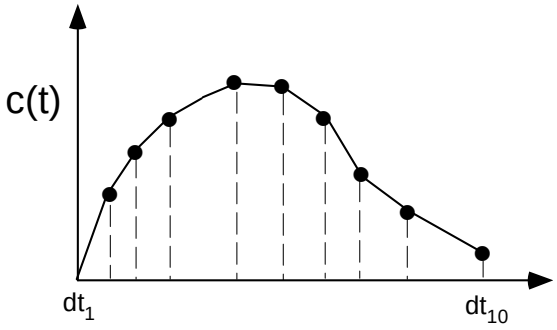
$$x(dt_i^+) = x(dt_i^-) + b(dt_i), \qquad i = 1, \ldots, nd$$



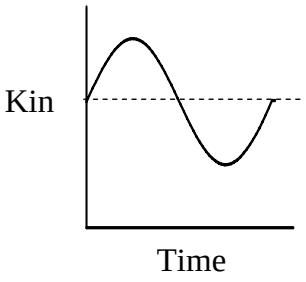
Delayed model inputs/bolus inputs OK: $r(t-\tau)$, $b(t-\tau)$

3. Other Inputs

e.g., Piecewise linear



e.g., Algebraic equation (sum of exponentials, sin)



circadian variation of physiological property

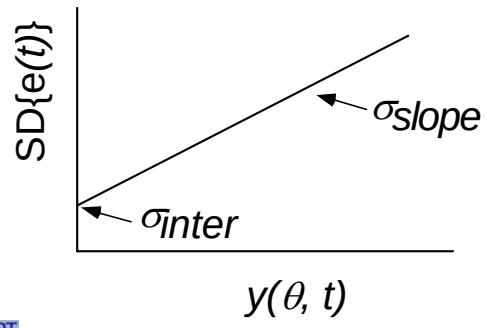
- Measurement Model
  - Measurement Equation $\left(\text{let } \theta = [\alpha | c],\ y(t_j) \rightarrow y(\theta, t_j)\right)$

$$z(t_j) = y(\theta, t_j) + e(t_j), \qquad j = 1, \ldots, m$$

  - Variance Model

$$Var\{e_i(t_j)\} = g_i(y_i(\theta, t_j), \beta) \quad j = 1, \ldots, m, \ i = 1, \ldots, l$$

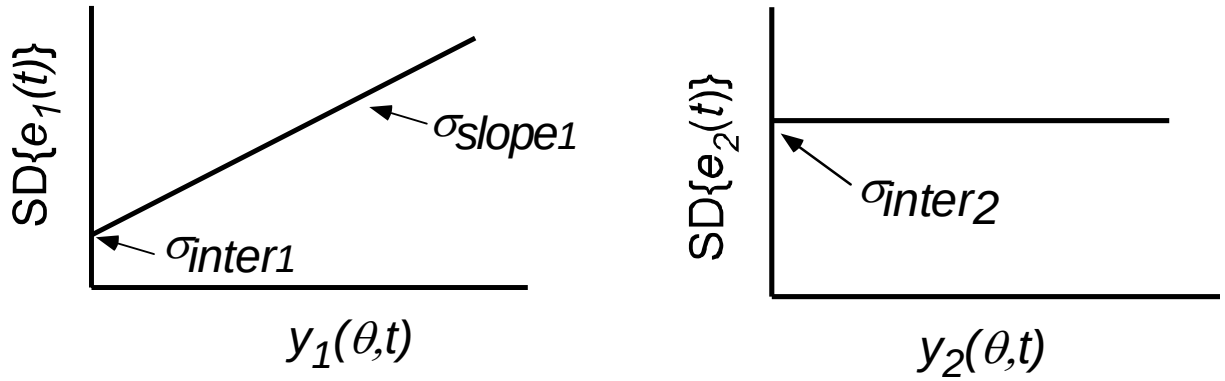
e.g., One output - $l = 1$



$$Var\{e(t)\} = (\sigma_{inter} + \sigma_{slope}\, y(\theta, t))^2$$

$$\beta = [\sigma_{inter} \quad \sigma_{slope}]$$

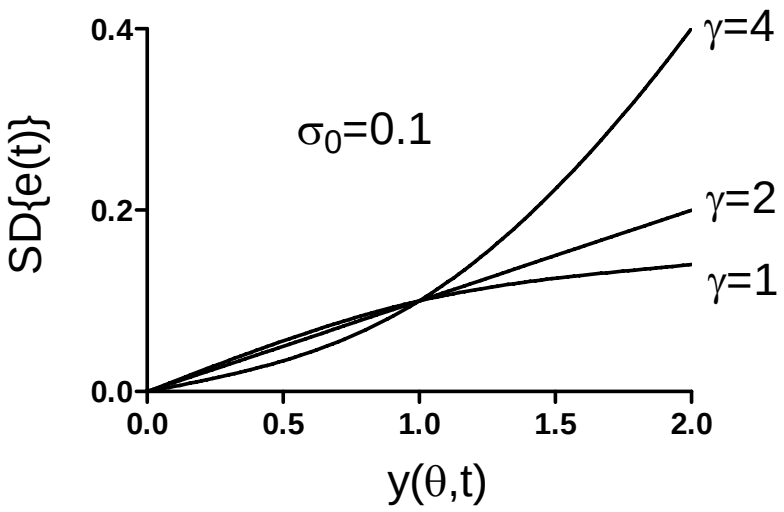
e.g., Two outputs - $l = 2$



$$Var\{e_1(t)\} = (\sigma_{inter1} + \sigma_{slope1}\, y_1(\theta,t))^2 \qquad Var\{e_2(t)\} = \sigma^2_{inter2}$$

$$\beta = [\sigma_{inter1} \quad \sigma_{slope1} \quad \sigma_{inter2}]$$

e.g., One outputs - $l = 1$



$$Var\{e(t)\} = \sigma_0^2 y(\theta,t)^{\gamma}$$

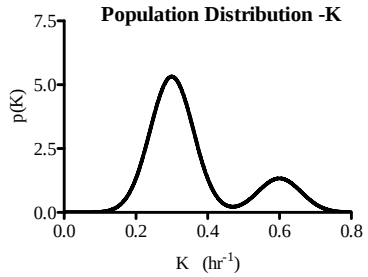
$$\beta = [\sigma_0 \quad \gamma]$$

- Distribution of the Output Error $e(t)$

1. Continuous (interval) data: Normal, Log Normal Distribution
   e.g., drug concentration, physiological variables
2. Count data: Poisson Distribution
   e.g., radioactivity
3. Categorical data (nominal/ordinal):
   a. Dichotomous (Binary) Data: Binomial Distribution
      e.g., relief of pain
   b. Multiple categories: Multinomial Distribution
      e.g., pain severity, cancer stage
4. Time to event data
   e.g., time to onset of pain relief

- Parameter Model
  - $\theta \rightarrow$ constant (known or unknown)
  - $\theta \rightarrow$ random vector with distribution $p(\theta)$ - $\theta \sim p(\theta)$

$p(\theta) = N(\mu,\Sigma)$	multivariate Normal
$p(\theta) = LN(\mu,\Sigma)$	multivariate lognormal
$p(\theta) = U(0, \alpha_{max})$	independent uniform
$p(\theta) = NI,\ \theta>0$	noninformative
$p(\theta) = \sum w_k N(\mu_k, \Sigma_k)$	mixture model



  - Recall, $\theta = [\alpha | c]$

IC's (initial conditions) modeled as constant or random

Secondary Parameters:

$$\gamma = w(\theta) \qquad \gamma = \left[\gamma_1 \cdots \gamma_s\right]$$

Example - two compartment model:

System parameters:

$$\theta = \left[K_{el}\ V\ K_{cp}\ K_{pc} \right]$$

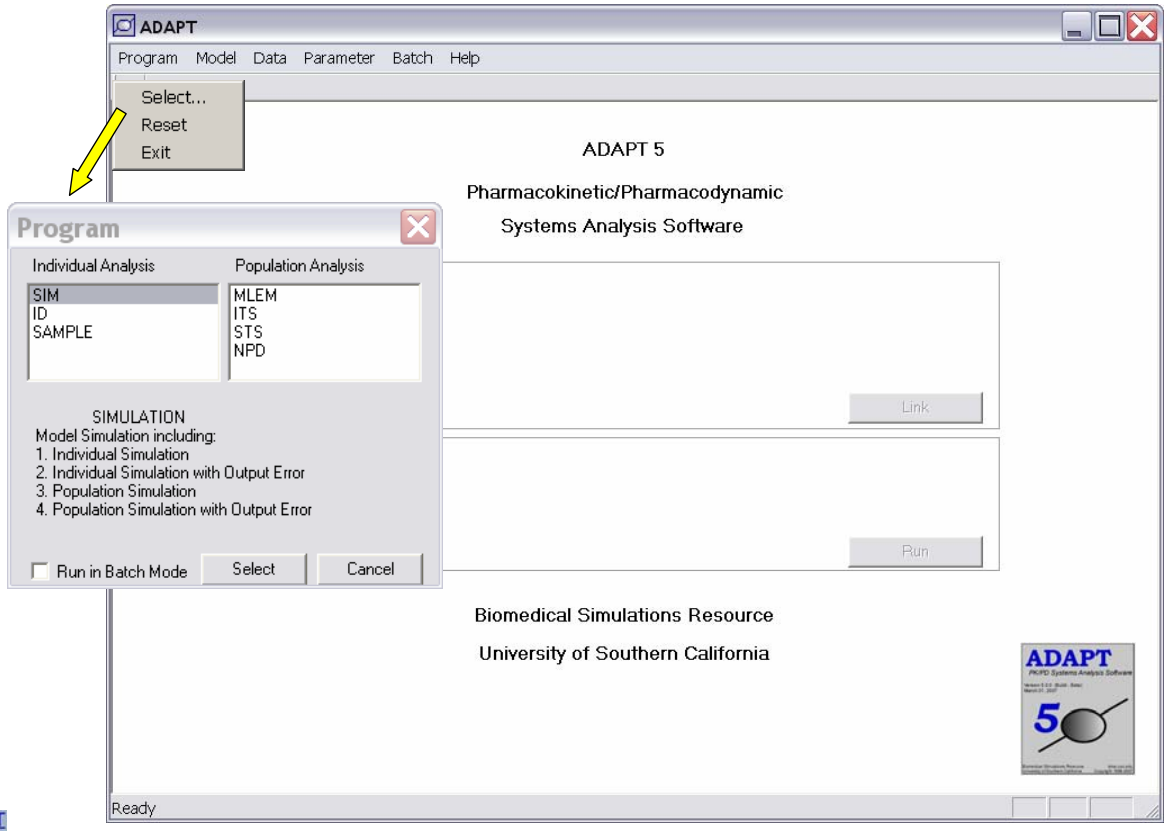
Secondary parameters:

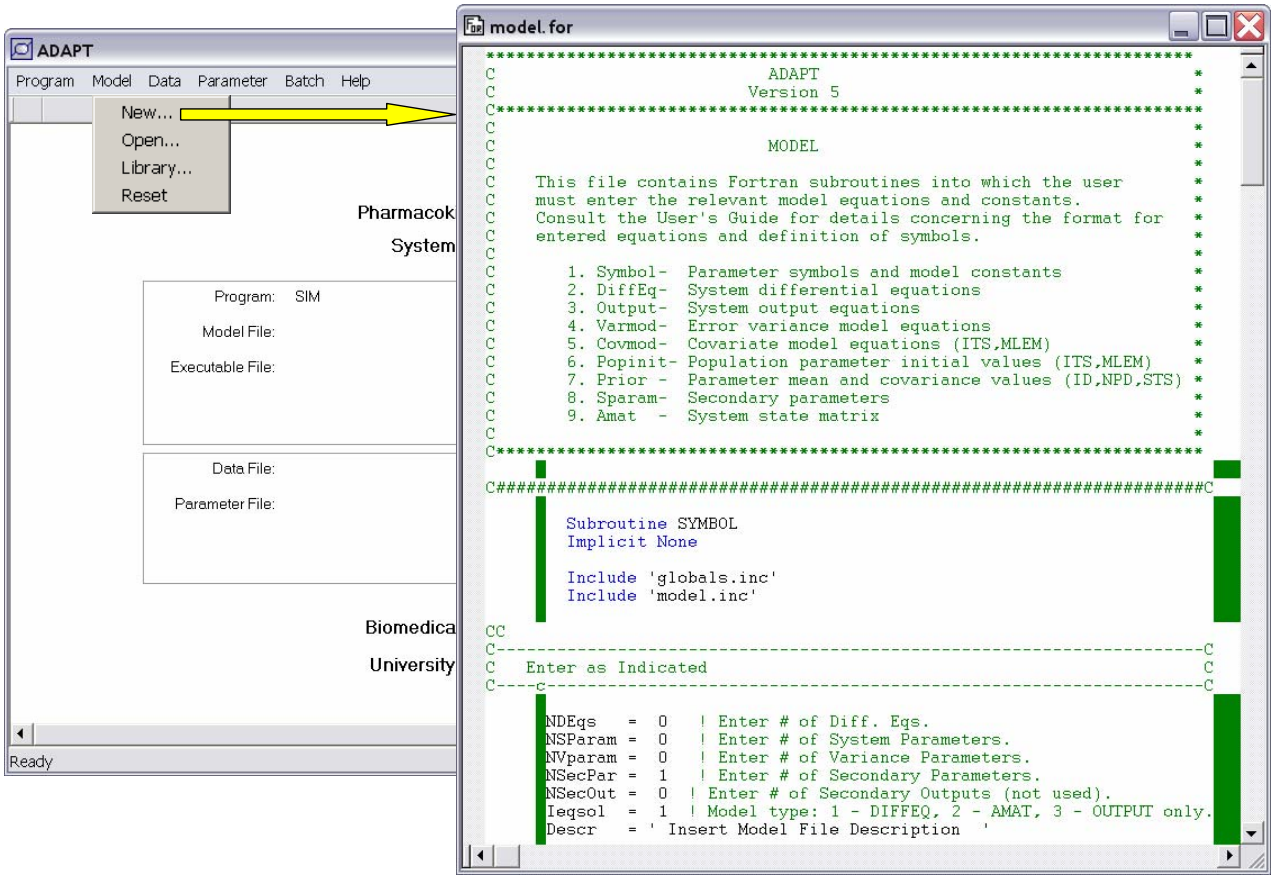
$$\gamma = \left[CL_t\ V_C\ CL_d\ V_p\right]$$

$$CL_t = VK_{el} \quad V_c = V$$

$$CL_d = VK_{cp} \quad V_p = VK_{cp} / K_{pc}$$

Implementing the Model in ADAPT 5




ADAPT
Program Model Data Parameter Batch Help
New...
Open...
Library...
Reset
Pharmacok
System
Program: SIM
Model File:
Executable File:
Data File:
Parameter File:
Biomedica
University
Ready
model.for
C ADAPT
C Version 5
C MODEL
C This file contains Fortran subroutines into which the user
C must enter the relevant model equations and constants.
C Consult the User's Guide for details concerning the format for
C entered equations and definition of symbols.
C 1. Symbol- Parameter symbols and model constants
C 2. DiffEq- System differential equations
C 3. Output- System output equations
C 4. Varmod- Error variance model equations
C 5. Covmod- Covariate model equations (ITS,MLEM)
C 6. Popinit- Population parameter initial values (ITS,MLEM)
C 7. Prior - Parameter mean and covariance values (ID,NPD,STS)
C 8. Sparam- Secondary parameters
C 9. Amat - System state matrix
Subroutine SYMBOL
Implicit None
Include 'globals.inc'
Include 'model.inc'
C Enter as Indicated
NDEqs = 0 ! Enter # of Diff. Eqs.
NSParam = 0 ! Enter # of System Parameters.
NVparam = 0 ! Enter # of Variance Parameters.
NSecPar = 1 ! Enter # of Secondary Parameters.
NSecOut = 0 ! Enter # of Secondary Outputs (not used).
Ieqsol = 1 ! Model type: 1 - DIFFEQ, 2 - AMAT, 3 - OUTPUT only.
Descr = ' Insert Model File Description '

Implementing the Model in ADAPT 5

- The ADAPT Model File

```
C*********************************************************************
C                            ADAPT                                    *
C                          Version 5                                  *
C*********************************************************************
C                                                                     *
C                            MODEL                                    *
C                                                                     *
C    This file contains Fortran subroutines into which the user       *
C    must enter the relevant model equations and constants.           *
C    Consult the User's Guide for details concerning the format for   *
C    entered equations and definition of symbols.                     *
C                                                                     *
C       1. Symbol-  Parameter symbols and model constants             *
C       2. DiffEq-  System differential equations                     *
C       3. Output-  System output equations                           *
C       4. Varmod-  Error variance model equations                    *
C       5. Covmod-  Covariate model equations (ITS,MLEM)              *
C       6. Popinit- Population parameter initial values (ITS,MLEM)    *
C       7. Prior -  Parameter mean and covariance values (ID,NPD,STS) *
C       7. Sparam-  Secondary parameters                               *
C       8. Amat  -  System state matrix                               *
C*********************************************************************
```

```
C######################################################################C
        Subroutine SYMBOL
        Implicit None
        Include 'globals.inc'
        Include 'model.inc'
CC
C-----------------------------------------------------------------------C
C   Enter as Indicated                                                  C
C----c------------------------------------------------------------------C
      NDEqs   = ?  ! Enter # of Diff. Eqs.
      NSParam = ?  ! Enter # of System Parameters.
      NVparam = ?  ! Enter # of Variance Parameters.
      NSecPar = ?  ! Enter # of Secondary Parameters.
      Ieqsol  = ?  ! Model type: 1 - DIFFEQ, 2 - AMAT, 3 - OUTPUT only.
      Descr   =     'Enter Model File Description Here'
C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C   Enter Symbol for Each System Parameter (eg. Psym(1)='Kel')          C
C----c------------------------------------------------------------------C
       Enter System Parameter Symbols Here
       Psym(1)= 'Kel'
       Psym(2)= 'Vc'
        …
C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
```

```
C-------------------------------------------------------------------------C
C   Enter Symbol for Each Variance Parameter {eg: PVsym(1)='Sigma'}   C
C----c--------------------------------------------------------------------C
```

Enter Variance Parameter Symbols Here

```
      PVsym(1)='Sigma'

CC
C-------------------------------------------------------------------------C
C   Enter Symbol for Each Secondary Parameter {eg: PSsym(1)='CLt'}    C
C----c--------------------------------------------------------------------C
```

Enter Secondary Parameter Symbols Here

```
      PSsym(1)='CLt'

C-------------------------------------------------------------------------C
C-------------------------------------------------------------------------C
C
```

```
C#########################################################################C
        Subroutine DIFFEQ(T,X,XP)
        Implicit None
        Include 'globals.inc'
        Include 'model.inc'
        Real*8 T,X(MaxNDE),XP(MaxNDE)
CC
C-------------------------------------------------------------------------C
C   Enter Differential Equations Below  {e.g.  XP(1) = -P(1)*X(1) }    C
C----c--------------------------------------------------------------------C
       Enter Differential Equations Here
       XP(1) = -P(1)*X(1)
       ------------------------------
       XP(1) = -P(1)*X(1) + R(1)
C-------------------------------------------------------------------------C
C-------------------------------------------------------------------------C
C
        Return
        End
```

```
C#######################################################################C
        Subroutine OUTPUT(Y,T,X)
        Implicit None
        Include 'globals.inc'
        Include 'model.inc'
        Real*8 Y(MaxNOE),T,X(MaxNDE)
CC
C-----------------------------------------------------------------------C
C   Enter Output Equations Below   {e.g.  Y(1) = X(1)/P(2) }          C
C----c------------------------------------------------------------------C
```

Enter Output Equations Here

```
        Y(1) = X(1)/P(2)
      ------------------------------
        Y(1) = X(1)/(P(2)*R(2))
C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C
        Return
        End
```

```
C#########################################################################C
        Subroutine VARMOD(V,T,X,Y)
        Implicit None
        Include 'globals.inc'
        Include 'model.inc'
        Real*8 V(MaxNOE),T,X(MaxNDE),Y(MaxNOE)
CC
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
```

Enter Variance Model Equations Here

```
        V(1) = (PV(1) + PV(2)*Y(1))**2
C-------------------------------------------------------------------------C
C-------------------------------------------------------------------------C
C
        Return
        End
```

```
C#######################################################################C
       Subroutine COVMOD(PC, P, IC)
       Implicit None
       Include 'globals.inc'
       Include 'model.inc'
CC
C-----------------------------------------------------------------------C
C     Enter # of Covariate Parameters                                   C
C----c------------------------------------------------------------------C

       NCparam = ? ! Enter # of Covariate Parameters.

CC
C-----------------------------------------------------------------------C
C   Enter Symbol for Covariate Params. {eg: PCsym(1)='CLRenal'}         C
C----c------------------------------------------------------------------C
```

Enter Covariate Parameter Symbols Here

```
       PCsym(1)='CLnonRen'
       PCsym(2)='CLRenal'
```

```
CC
C-------------------------------------------------------------------------C
C   For the Model Params. that Depend on Covariates Enter the Equation C
C         {e.g. Pmean(1) =  PC(1)*R(2) }                                  C
C----c--------------------------------------------------------------------C
```

Enter Covariate Model Equations Here

```
      Pmean(1) = PC(1) + PC(2)*R(2)

C-------------------------------------------------------------------------C
C-------------------------------------------------------------------------C
C
      Return
      End
```

```
C######################################################################C
        Subroutine POPINIT(PmeanI,ICmeanI,PcovI,ICcovI, PCI)
C  Initial parameter values for population program parameters (ITS, MLEM)
        ...
CC
C-----------------------------------------------------------------------C
C  Enter Initial Values for Population Means                            C
C          {  e.g. PmeanI(1) = 10.0    }                               C
C----c------------------------------------------------------------------C
```

Enter Initial Values for Population Means Here

```
CC
C-----------------------------------------------------------------------C
C   Enter Initial Values for Pop. Covariance Matrix (Lower Triang.)     C
C         {  e.g. PcovI(2,1) = 0.25    }                              C
C----c------------------------------------------------------------------C
```

Enter Initial Values for Pop. Covariance Matrix Elements Here

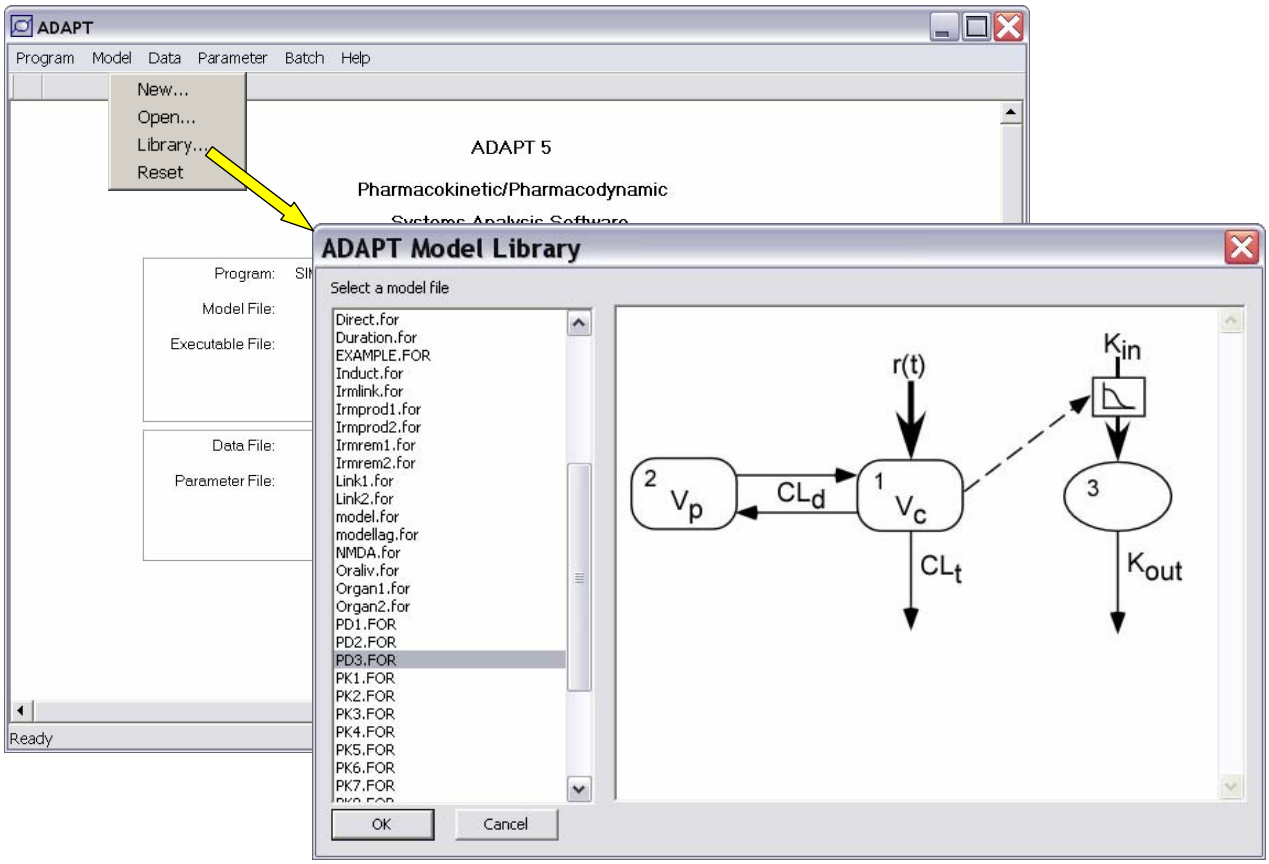
```
CC
C-----------------------------------------------------------------------C
C   Enter Values for Covariate Model Parameters                         C
C         {  e.g. PCI(1) = 2.0    }                                     C
C----c------------------------------------------------------------------C
```

Enter Initial Values for Covariate Model Parameters Here

```
CC
C-----------------------------------------------------------------------C
```

```
C######################################################################C
        Subroutine PRIOR(Pmean,Pcov,ICmean,ICcov)
        Implicit None
        Include 'globals.inc'
        Include 'model.inc'
        Integer I,J
        Real*8 Pmean(MaxNSP+MaxNDE), ICmean(MaxNDE)
        Real*8 Pcov(MaxNSP+MaxNDE,MaxNSP+MaxNDE), ICcov(MaxNDE,MaxNDE)
CC
C----------------------------------------------------------------------C
C   Enter Nonzero Elements of Prior Mean Vector                        C
C          {  e.g. Pmean(1) = 10.0    }                               C
C----c-----------------------------------------------------------------C
       Enter Population Mean Values Here
       Pmean(1) = 0.25

C----------------------------------------------------------------------C
CC
C----------------------------------------------------------------------C
C   Enter Nonzero Elements of Covariance Matrix (Lower Triang.)       C
C         {  e.g. Pcov(2,1) = 0.25    }                              C
C----c-----------------------------------------------------------------C
       Enter Population Covariance Values Here
       Pcov(1,1) = 0.1
```

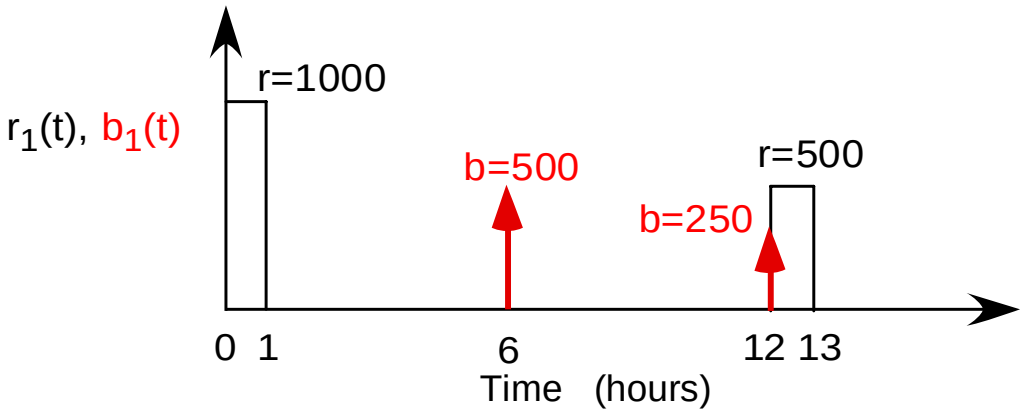
```
        Subroutine SPARAM(PS,P,IC)
        Implicit None
        Include 'globals.inc'
        Real*8 PS(MaxNSECP), P(MaxNSP+MaxNDE), IC(MaxNDE)
CC
C-------------------------------------------------------------------C
C   Enter Equations Defining Secondary Paramters                    C
C           {  e.g.  PS(1) = P(1)*P(2)   }                          C
C----c--------------------------------------------------------------C
        Enter Secondary Parameter Equations Here
        PS(3) = P(2)*P(3)/P(4)
C-------------------------------------------------------------------C
C-------------------------------------------------------------------C
C
        Return
        End
```


ADAPT
Program Model Data Parameter Batch Help
New...
Open...
Library...
Reset
ADAPT 5
Pharmacokinetic/Pharmacodynamic
Program:
Model File:
Executable File:
Data File:
Parameter File:
Ready
ADAPT Model Library
Select a model file
Direct.for
Duration.for
EXAMPLE.FOR
Induct.for
Irmlink.for
Irmprod1.for
Irmprod2.for
Irmrem1.for
Irmrem2.for
Link1.for
Link2.for
model.for
modellag.for
NMDA.for
Oraliv.for
Organ1.for
Organ2.for
PD1.FOR
PD2.FOR
PD3.FOR
PK1.FOR
PK2.FOR
PK3.FOR
PK4.FOR
PK5.FOR
PK6.FOR
PK7.FOR
OK
Cancel
r(t)
Kin
2
Vp
CLd
1
Vc
3
CLt
Kout

- Supplying Inputs

  Spread Sheet Format
  - model inputs (e.g., drug infusions, covariates)
  - bolus inputs
  - input event times

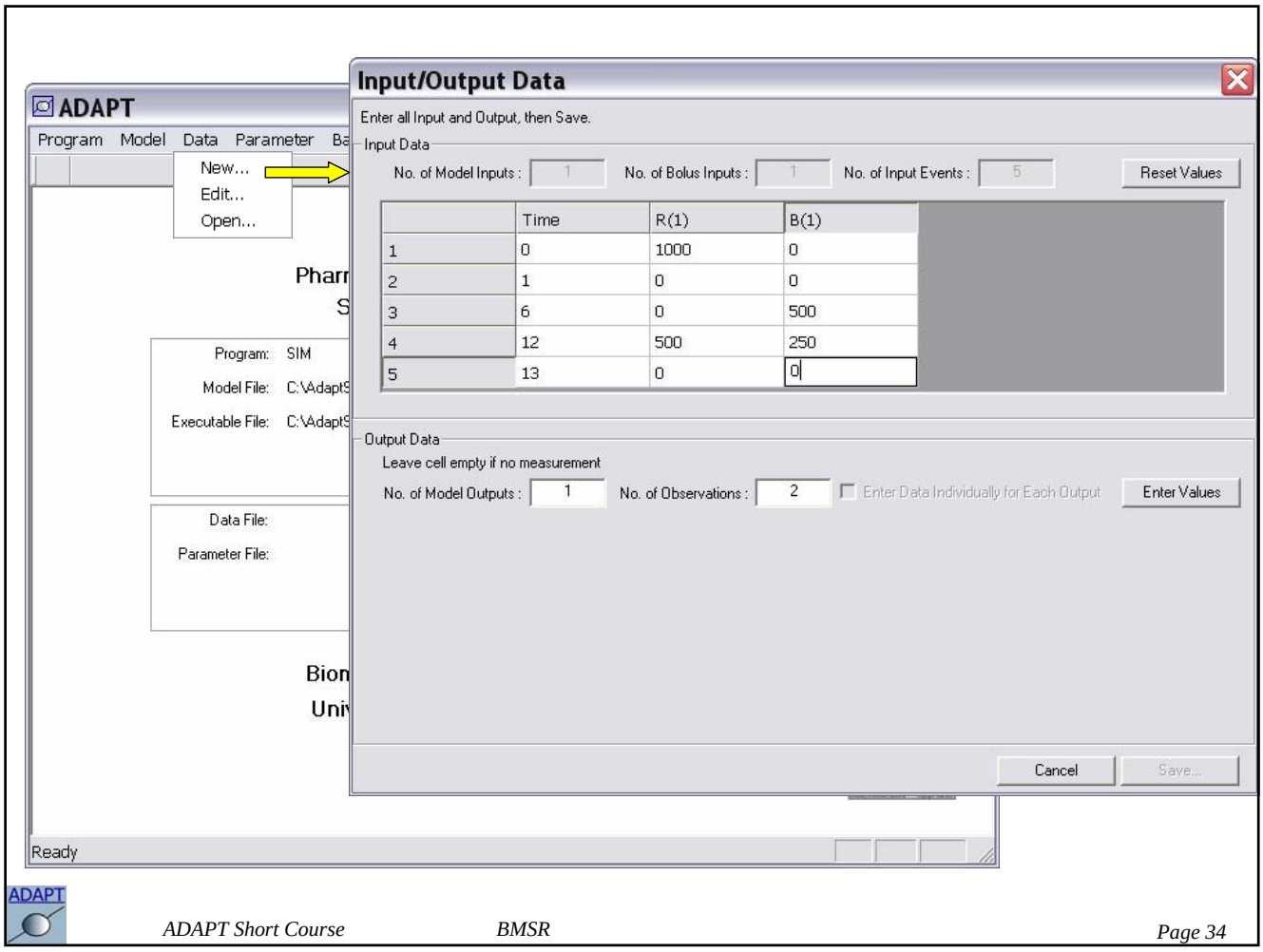
  Example #1: IV and Bolus administration



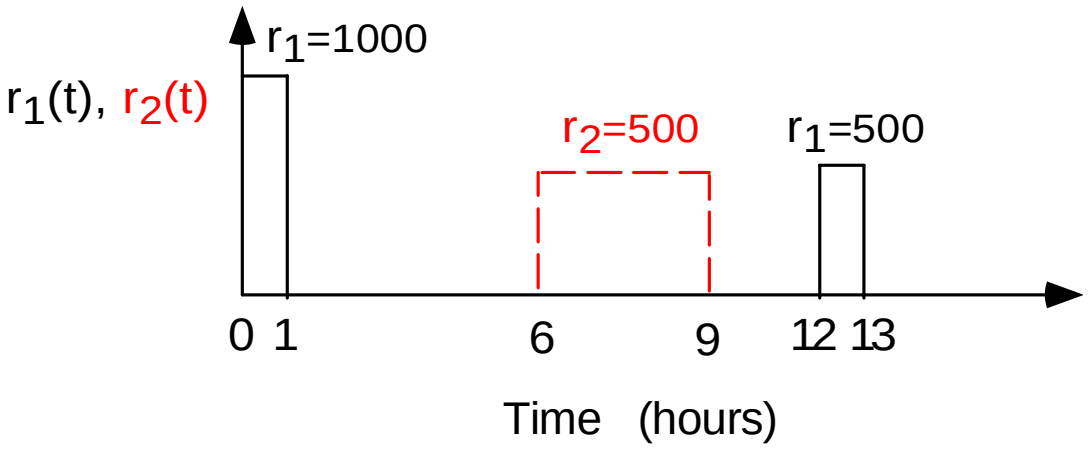
1 model input; 1 bolus input; 5 input event times, 0, 1, 6, 12, 13 hrs.

Spread Sheet for Example #1

Input Event Time (hr)	Infusion Rate r (mg/hr)	Bolus Amount b (mg)
0	1000	0
1	0	0
6	0	500
12	500	250
13	0	0


ADAPT
Program Model Data Parameter Ba
New...
Edit...
Open...
Program: SIM
Model File: C:\Adapt
Executable File: C:\Adapt
Data File:
Parameter File:
Ready
Input/Output Data
Enter all Input and Output, then Save.
Input Data
No. of Model Inputs : 1
No. of Bolus Inputs : 1
No. of Input Events : 5
Reset Values
Time R(1) B(1)
1 0 1000 0
2 1 0 0
3 6 0 500
4 12 500 250
5 13 0 0
Output Data
Leave cell empty if no measurement
No. of Model Outputs : 1
No. of Observations : 2
Enter Data Individually for Each Output
Enter Values
Cancel
Save...

Example #2: IV administration of two drugs



2 model inputs: $r_1(t)$, $r_2(t)$ (mg/hr)
6 input event times: 0, 1, 6, 9, 12, 13 hrs

Spread Sheet for Example #2

Input Event Time (hr)	Infusion Rate r1 (mg/hr)	Infusion Rate r2 (mg/hr)
0	1000	0
1	0	0
6	0	500
9	0	0
12	500	0
13	0	0

- Supplying Measurements

  Simultaneous Entry of Observations for all Outputs

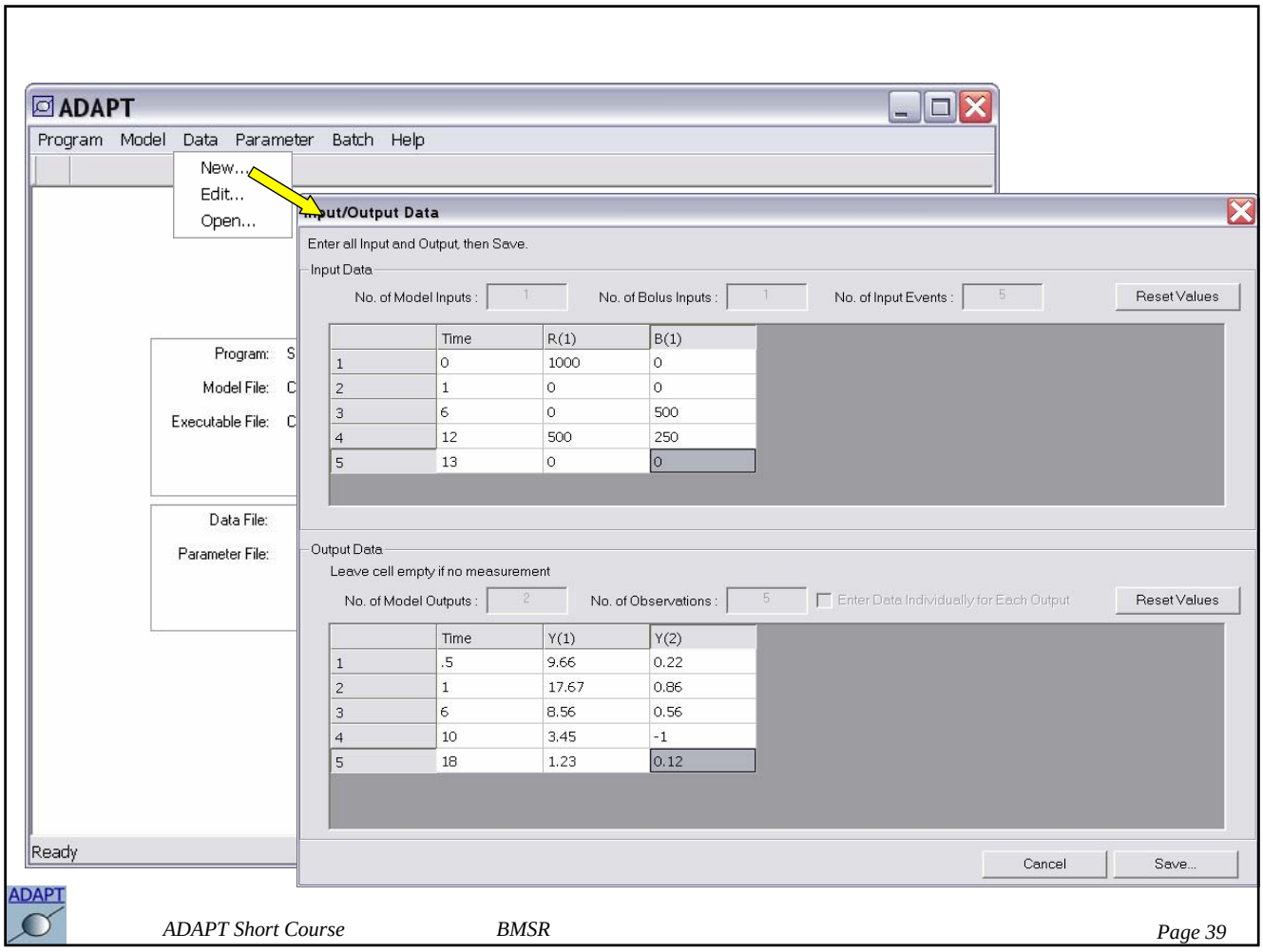
  - Use when outputs measured at same times
  - Occasional missed measurements indicated by using the missing data number (-1 default)
  - e.g., PK model of parent & metabolite

Observation	Time Units,	Measured Value for Each Output Y(1), … , Y(2)	
1.	0.500	9.66	0.22
2.	1.000	17.67	0.86
3.	6.000	8.56	0.56
4.	10.00	3.45	-1
5.	18.00	1.23	0.12

Individual Entry of Observations for Each Output

- Used when different outputs measured at different times
- e.g., PK/PD models with kinetic & dynamic data

```
Enter the number of observations for Y(1): 5
                Time      Measured Value For
Observation     Units ,       Y(1)
      1.        1,            10.2
      2.        2,            8.13
      3.        4,            5.54
      4.        8,            2.32
      5.        12,           1.41

Enter the number of observations for Y(2): 4
                Time      Measured Value For
Observation     Units ,       Y(2)
      1.        3,            3.23
      2.        6,            7.67
      3.        9,            5.32
      4.        18,           1.33
```


ADAPT
Program Model Data Parameter Batch Help
New...
Edit...
Open...
Program: S
Model File: C
Executable File: C
Data File:
Parameter File:
Ready
Input/Output Data
Enter all Input and Output, then Save.
Input Data
No. of Model Inputs : 1
No. of Bolus Inputs : 1
No. of Input Events : 5
Reset Values
Time R(1) B(1)
1 0 1000 0
2 1 0 0
3 6 0 500
4 12 500 250
5 13 0 0
Output Data
Leave cell empty if no measurement
No. of Model Outputs : 2
No. of Observations : 5
Enter Data Individually for Each Output
Reset Values
Time Y(1) Y(2)
1 .5 9.66 0.22
2 1 17.67 0.86
3 6 8.56 0.56
4 10 3.45 -1
5 18 1.23 0.12
Cancel
Save...

Comments on Numerical Methods

- Solving Differential Equations (LSODA)

  Livermore **S**olver for **O**rdinary **D**ifferential equations with **A**utomatic method switching for stiff and nonstiff problems

  - Variable Step Methods
  - Variable Order Methods (Adam's)
  - Overshooting and Interpolation
  - Stiff Equations (Gear's Method)

  Error Control (local error)

  e - LSODA estimate of error at time t_j

  step size, method and method order selected so that:

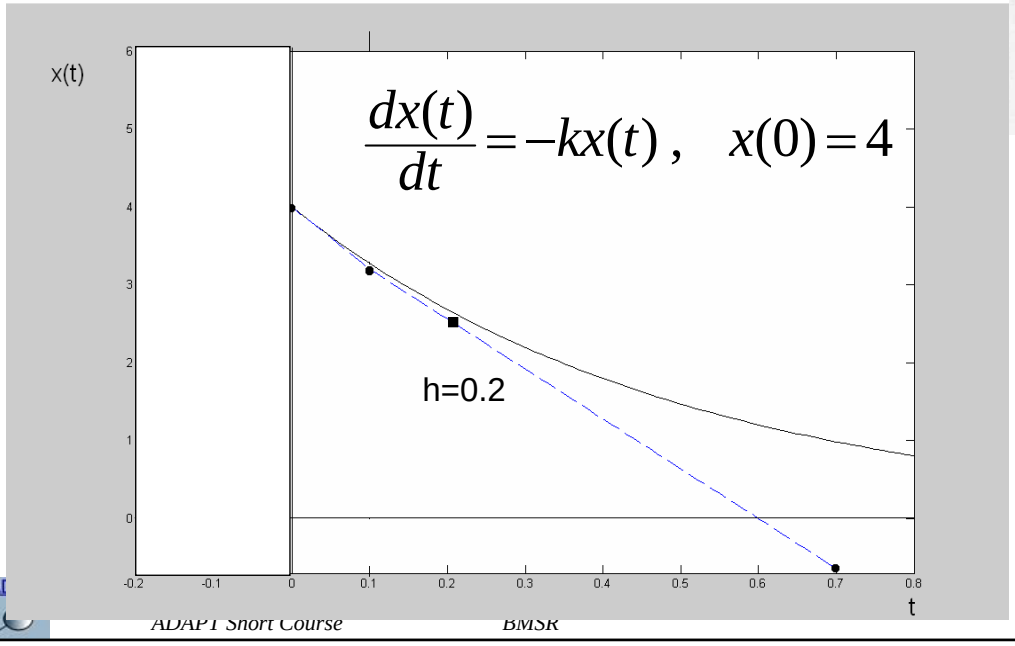
  $e < \text{RTOL}\,|x(t_j)| + \text{ATOL}$

  RTOL & ATOL = 10^{-6} in globals.inc

Euler's Method

$$\frac{dx(t)}{dt} = f(x(t), t), \quad x(0) = c$$

- Graphical Interpretation



Euler's Method

$$\frac{dx(t)}{dt} = f(x(t), t), \quad x(0) = c$$

- Definition of Derivative

$$\frac{dx(t)}{dt} \approx \frac{x(t+h) - x(t)}{h}$$

$$\frac{x(t+h) - x(t)}{h} \approx f(x(t), t)$$

$$x(t+h) = x(t) + h \cdot f(x(t), t)$$

- Function Minimization

  Nelder Mead Simplex Method

  Direct search method (Does not use derivatives)

  Convergence Control - min $O(\theta)$

  $|O(\theta_i)/O(\theta_{i+1}) - 1| < REQMIN$

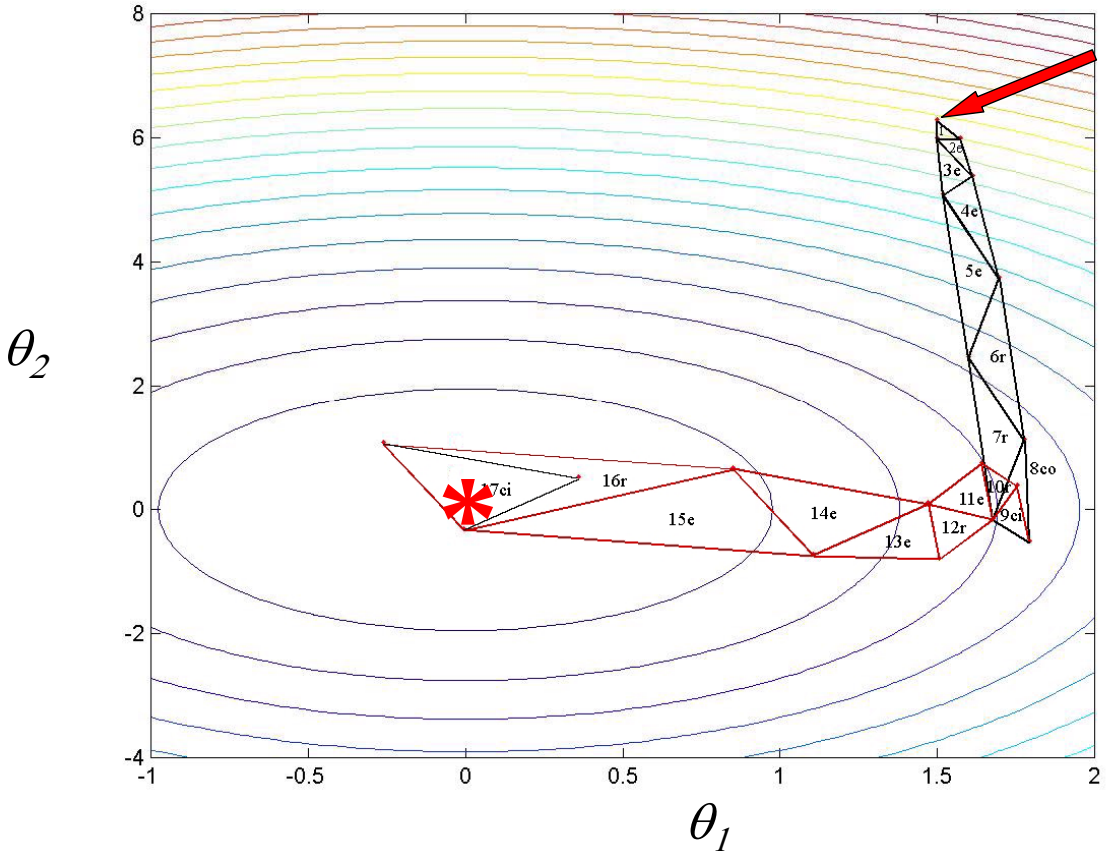
  REQMIN = 10^{-6} in globals.inc

  Function Evaluation, Iteration

- Sampling Based Methods (Population Analysis)

  Importance Sampling

Two Parameter Illustration of Nelder-Mead Simplex Method



The Programs

- **SIM**
  Individual simulation
  Individual simulation with output error
  Population simulation
  Population simulation with output error

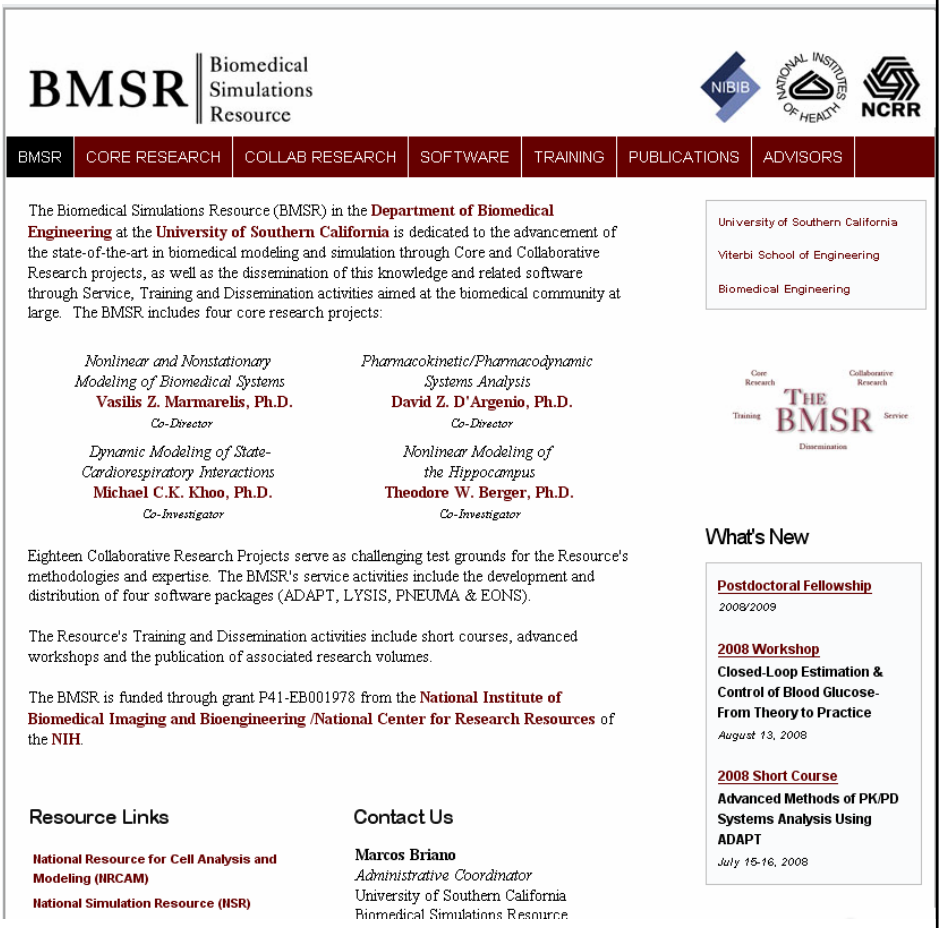
- **ID**
  Weighted least squares (WLS)
  Maximum likelihood (ML)
  Generalized least squares (GLS)
  Maximum a posteriori probability (MAP)

- **SAMPLE**
  D optimality
  C optimality

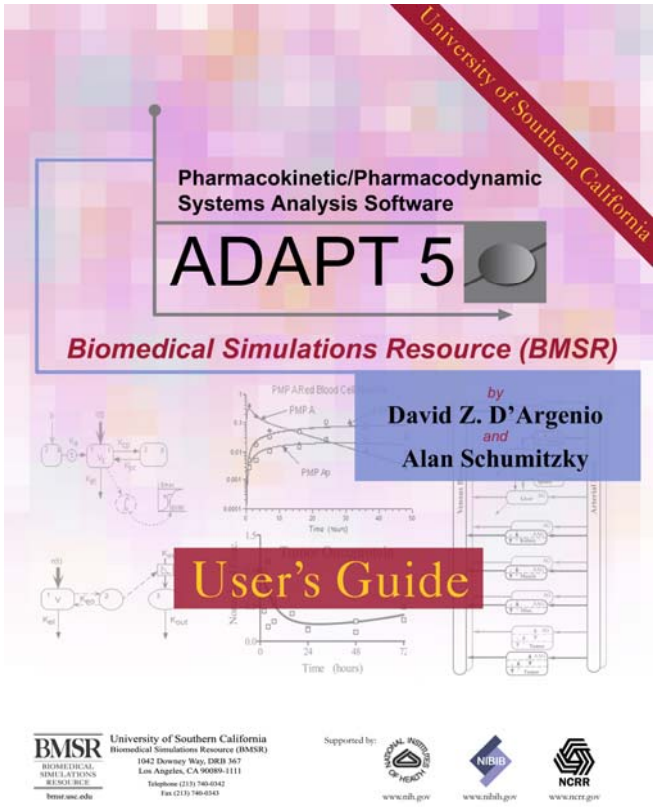
The Programs

- **MLEM**
  Parametric maximum likelihood (EM/Sampling)
- **ITS**
  Iterative two stage
- **STS**
  Weighted least squares (WLS)
  Maximum likelihood (ML)
  Maximum a posteriori probability (MAP)
- **NPD**
  Weighted least squares (WLS)
  Maximum likelihood (ML)
  Maximum a posteriori probability (MAP)

- **BMSR Web Site (bmsr.usc.edu)**



- **Citing ADAPT in Publications**



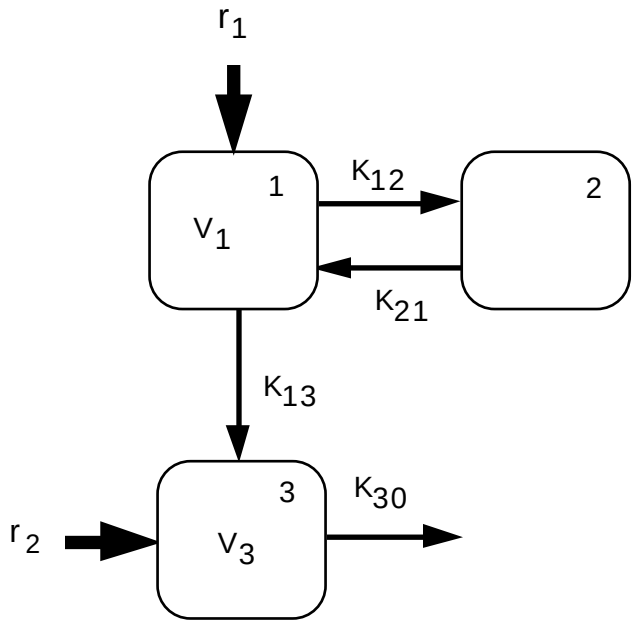
D'Argenio, D.Z. and A. Schumitzky.
ADAPT 5 User's Guide: Pharmacokinetic/
Pharmacodynamic Systems Analysis Software.
Biomedical Simulations Resource,
Los Angeles, 2008.

- **Searching the ADAPT Citation Library**

Case Study - Doses and Covariates

This case study is designed to illustrate how to specify model inputs. The first example involves simulating the simultaneous infusion of a parent drug and its metabolite. The second example in this case study incorporates a measured covariate that changes with time during the simulation.

Consider the following 3 compartment model with the infusion inputs shown ($r_1(t)$ represents the parent and $r_2(t)$ the metabolite). Assume that we are interested in simulating the concentrations in compartments 1 and 3



1. The three differential equations and two output equations describing this model have been coded and entered in a Model File named **dc1.for**, along with all other code necessary to define the model. The following correspondence between the kinetic parameters and Fortran symbols has been used:

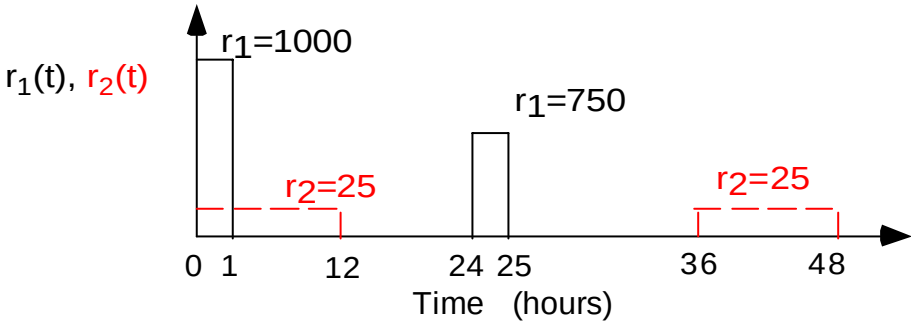
V_1 - P(1)	K_{13} - P(4)
K_{12} - P(2)	K_{30} - P(5)
K_{21} - P(3)	V_3 - P(6)

Examine the file **dc1.for** using the Fortran Editor (double click on the file) to verify that the model has been correctly coded.

2. Consider the following dosing regimen for the parent and metabolite:

parent: 1000mg/hr - 0.0-1.0 hrs; 750mg/hr - 24.-25. hrs;
metabolite: 25mg/hr - 0.0-12.hrs; 25mg/hr - 36.-48. hrs.

The figure below illustrates the dose regimen for parent (solid) and metabolite (dashed).



The table below shows the entries required to specify the above dose regimen in ADAPT.

Number of model inputs: **2**

Number of bolus inputs: **0**

Number of input event times: **7**

Input Event	Time Units	Value for all Inputs R(1)	R(2)
1	**0.0**	**1000**	**25**
2	**1.0**	**0**	**25**
3	**12**	**0**	**0**
4	**24**	**750**	**0**
5	**25**	**0**	**0**
6	**36**	**0**	**25**
7	**48**	**0**	**0**

The model input information for this example is stored in the Adapt Data File, **dc1.dat**, along with output information. Inspect this file in the Adapt Data Editor. First select the Program **SIM** and then from the Model menu Open **dc1.for**. Next, from the Data menu select Edit and browse for the file **dc1.dat**. After inspecting the file in the Adapt Data Editor, select Cancel.

3. The following values for the model parameters are stored in the parameter file **dc1.prm**.

V_1 = 50 L,	K_{13} = 0.05 hr^{-1}
K_{12} = 0.2 hr^{-1}	K_{30} = 0.3 hr^{-1}
K_{21} = 0.1 hr^{-1}	V_3 =25. L.

Also, all three initial conditions (IC(1), IC(2), IC(3)) are 0.0. Inspect this file in the Adapt Parameter Editor

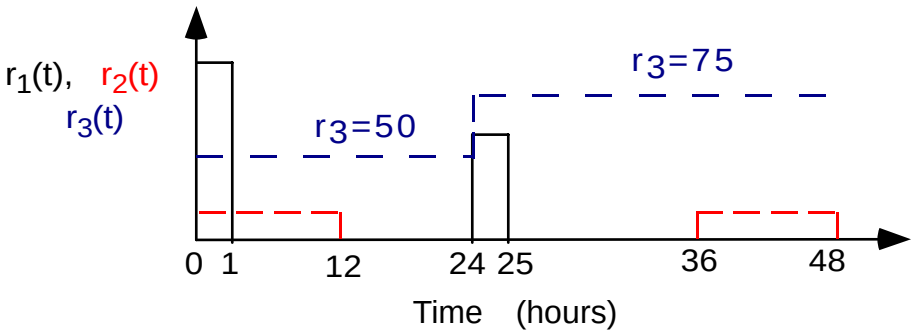
Simulate the model and examine the results.

4. The model equations used above have been modified to allow both V_1 and V_3 to depend linearly on measured body weight as a covariate. A third model input, R(3), is used to represent body weight. This can be done by replacing the variables V_1 and V_3 in the original output equations, with V1slope*R(3) and V3slope*R(3), respectively. A Model File named **dc2.for** contains these modified equations. Examine this Model File in the Fortran Editor.

5. We want to simulate this new model using the same infusion regimen given above as well as the same observation times and parameter values. To do this we need to define the body weight during the dose regimen. Assume body weight is given as follows:

BW(t): 50 Kg - 0.0 to 24.0 hrs 75 Kg - after 24 hrs

The following figure shows the dose regimen described previously with the body weight covariate information added.



The data file **dc2.dat** includes this information. Examine this data file in the Adapt Data Editor.

Now simulate the model **dc2.for** with the data file **dc2.dat**, letting the new parameters, V1slope and V3slope, equal 1.0 and 0.5, respectively. The parameter file **dc2.prm** contains all the parameter values for this example. Examine the parameter summary and view the plots using the default option.

6. How would you modify the model equations used in part 5, to allow K_{30} to depend on measured serum creatinine as a second covariate in the model. A fourth input, R(4), can be used to represent serum creatinine. The model file **dc3.for** contains the needed equations to implement this two drug infusion, two covariate example. Examine this Model File in the Fortran Editor.

PARAMETER ESTIMATION – INDIVIDUAL

Review of Notation

- Model Equations
- Measurements
- Parameters

The Estimation Problem and Methods

- The Problem
- The Methods

Least Squares Estimation

- Gauss's Solution
- Weighting

PARAMETER ESTIMATION

Likelihood Estimation

- The Problem
- Maximum Likelihood Estimation
- ELS, GLS, & Iteratively Re-Weighted Least Squares

Bayesian Estimation

- The Problem
- MAP Estimation

Model Selection Criteria

- AIC and BIC for WLS & ML Estimation
- GEN-IC for MAP Estimation

Review of Notation

- Model Equations

$$\frac{dx(t)}{dt} = f(x(t), \alpha, r(t), t), \qquad x(0) = c$$
$$y(t) = h(x(t), \alpha, r(t), t)$$

$\theta \rightarrow$ Collection of all model parameters

- Measurements

$$z(t_j) = y(\theta, t_j) + e(t_j), \qquad j = 1, \ldots, m$$

$$e(t) \sim N\left(0,\ g(y(\theta,t),\ \beta)\right)$$

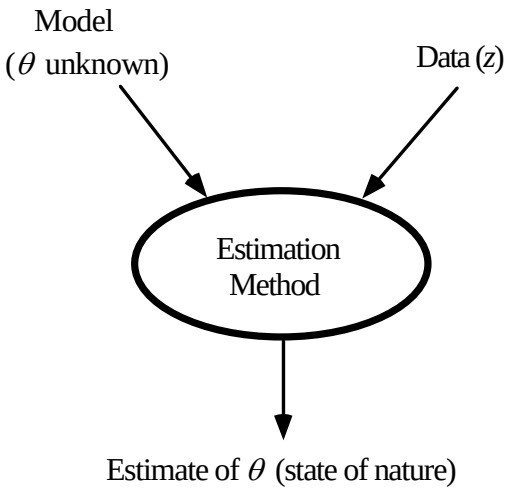
$\beta \rightarrow$ All variance model parameters

- Parameters

$\theta -$ constant or $\theta \sim \mathrm{N}(\mu, \Sigma)$ or $\mathrm{LN}(\mu, \Sigma)$

The Estimation Problem and Methods

- The Problem



- Methods
  - Least Squares
    - Ordinary nonlinear least squares (OLS)
    - Weighted nonlinear least squares (WLS)
  - Likelihood Estimation
    - Maximum Likelihood (ML)
    - Extended Least Squares (ELS)
    - Iteratively Re-Weighted Least Squares
    - Generalized Least Squares (GLS)
  - Bayesian Estimation
    - The Problem
    - Maximum A Posterior Estimation (MAP)

Least Squares Estimation

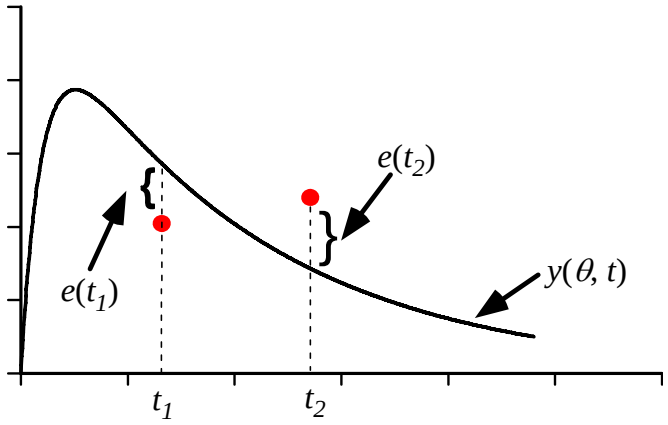
- Gauss's Solution


The Schwarz portrait of Gauss (1803)

Gauss suggested:

"…the most probable value of the unknown quantities will be that in which the sum of squares of the differences between the actually observed and computed values multiplied by numbers that measure the degree of precision is a minimum."

Single Output Case:



$$\hat{\theta}_{WLS} \rightarrow \min \sum_{j=1}^{m} w_j e(t_j)^2 = \min \underbrace{\sum_{j=1}^{m} w_j (z(t_j) - y(\theta, t_j))^2}$$

Objective or Criterion Function $\longrightarrow O_{WLS}$

Some Comments:

- Weighting
- Multiple Output Case (ADAPT User's Guide)
- Standard errors of the parameter estimates - *SE* of $\hat{\theta}_{WLS}$ and standard errors for model predictions - *SE* of $y\left(\hat{\theta}_{WLS}, t\right)$ (ADAPT User's Guide)

- Weighting
  - If all weights are equal → OLS

    Weighting Option 1 in ADAPT

  Generally would like $w_j \propto 1/\sigma_j^2$ → WLS

  - Weighting Option 3 in ADAPT: σ_j^2 known

    Enter the value of σ_j at each time

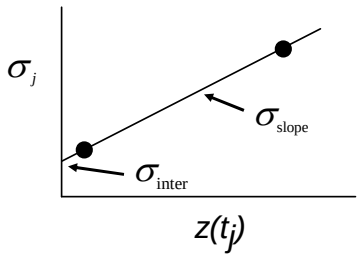
  - Weighting Option 2 in ADAPT: linear variance

    $\sigma_j = \sigma_{\text{inter}} + \sigma_{\text{slope}} y(\theta, t_j)$ and σ_{inter}, σ_{slope} known

    replace $y(\theta, t_j)$ with $z(t_j)$ to approximate σ_j

  - Weighting Option 2 in ADAPT enter 2 points on line

$\sigma_j = \sigma_{\text{inter}} + \sigma_{\text{slope}} z(t_j)$



then ADAPT sets

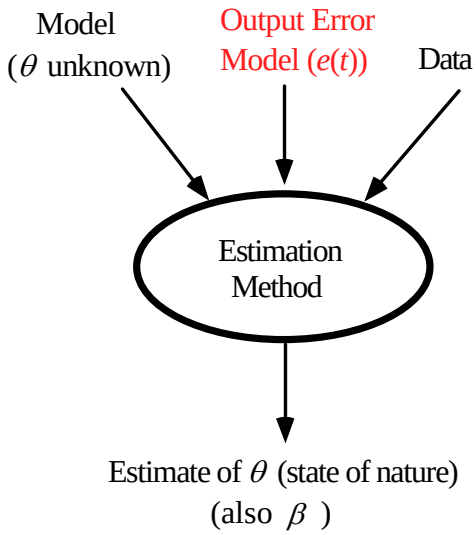
$w_j \propto 1/\sigma_j^2$

Example:

$\sigma_{\text{inter}} = 0.0,\ \sigma_{\text{slope}} = 0.1 \Rightarrow CV\% = 10.$

therefore $\sigma_j = 0.1 z(t_j)$ and $w_j \propto 1/0.01 z(t_j)^2$

Maximum Likelihood Estimation



Error Model

$$e(t_j) \sim N\left(0,\ \sigma_j^2\right)$$

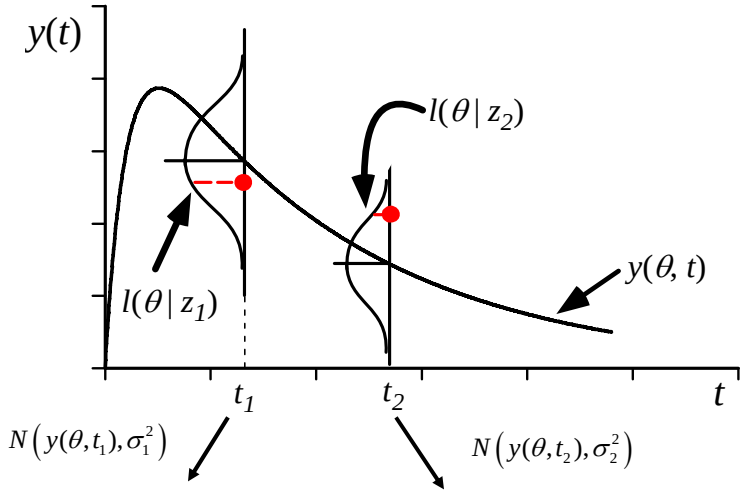
e.g.

$$\sigma_j^2 = \left(\sigma_{inter} + \sigma_{slope} y(\theta, t_j)\right)^2$$

$$\beta = [\sigma_{inter}\ \ \sigma_{slope}]$$

$e(t_j)\quad j = 1, \ldots, m$ are independent

Single Output Case:



$$l(\theta \mid z_1) = \frac{1}{\sigma_1\sqrt{2\pi}} \exp\left(\frac{-\left(z_1 - y(\theta, t_1)\right)^2}{2\sigma_1^2}\right) \qquad l(\theta \mid z_2) = \frac{1}{\sigma_2\sqrt{2\pi}} \exp\left(\frac{-\left(z_2 - y(\theta, t_2)\right)^2}{2\sigma_2^2}\right)$$

Joint likelihood function (independent errors):

$$l(\theta|z) = l(\theta|z_1)l(\theta|z_2)\cdots l(\theta|z_m)$$

$$l(\theta|z) = \left(\frac{1}{\sigma_1\sqrt{2\pi}}\right)\cdots\left(\frac{1}{\sigma_m\sqrt{2\pi}}\right)\exp\left(\sum_{j=1}^{m}\left(\frac{-\left(z_1 - y(\theta,t_j)\right)^2}{2\sigma_j^2}\right)\right)$$

The maximum likelihood estimate:

$$\hat{\theta}_{ML} \rightarrow \max l(\theta|z) \quad \text{or} \quad \min(\underbrace{-\ln l(\theta|z)}_{O_{NLL}})$$

$$O_{NLL} \equiv m\ln(2\pi)/2 + \frac{1}{2}\sum_{j=1}^{m}\left(\frac{\left(z(t_j) - y(\theta,t_j)\right)^2}{\sigma_j^2} + \ln\sigma_j^2\right)$$

Recall: $Var\{e(t_j)\} = \sigma_j^2 = g(y(\theta, t_j), \beta)$; e.g. $\sigma_j^2 = \left(\sigma_{inter} + \sigma_{slope}\, y(\theta, t_j)\right)^2$

Some Comments:

- Relation to WLS estimation
- Estimate all or subsets of θ, β
- Multiple Output Case (ADAPT User's Guide)
- Standard errors of the parameter estimates - SE of $\hat{\theta}_{ML}$
  and standard errors for model predictions - SE of $y\left(\hat{\theta}_{ML}, t\right)$
  (ADAPT User's Guide)
- Other distributions for the output error
  e.g., categorical data (dichotomous)

- ELS, GLS and Iteratively Reweighted Least Squares
  - ELS the same as ML; Interpretation depends on distributional assumptions
  - GLS – Generalized Least Squares

    An alternative to ML

    More robust than ML to deviations from Normal assumption

    Has some computational advantages, i.e., two smaller optimization problems

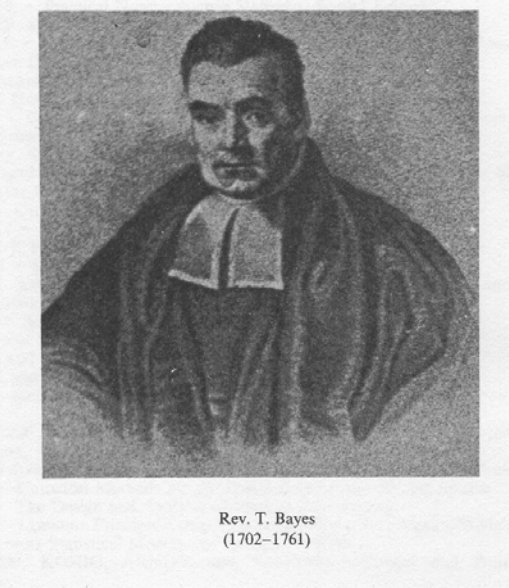
    Basic approach implemented in ADAPT, see User's Guide

    ML and GLS often yield similar estimates
  - Iteratively reweighted least squares; use ML or GLS

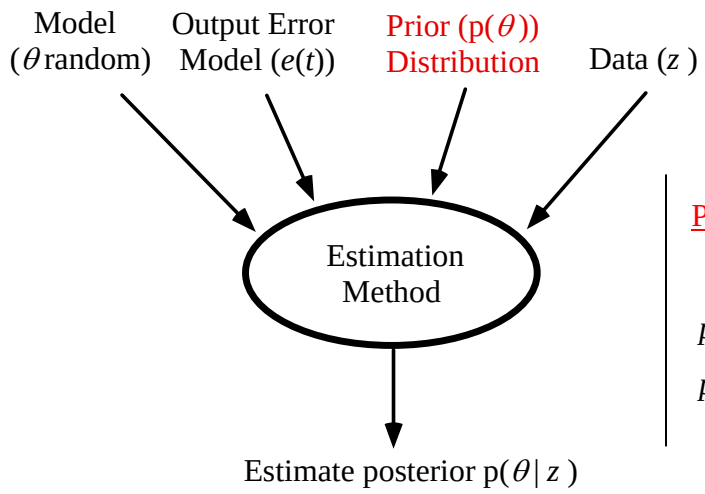
Ronald Fisher
1890-1962

Fisher at his desk calculator at Whittingehame Lodge, 1952.

Bayesian Estimation



Rev. T. Bayes
(1702–1761)



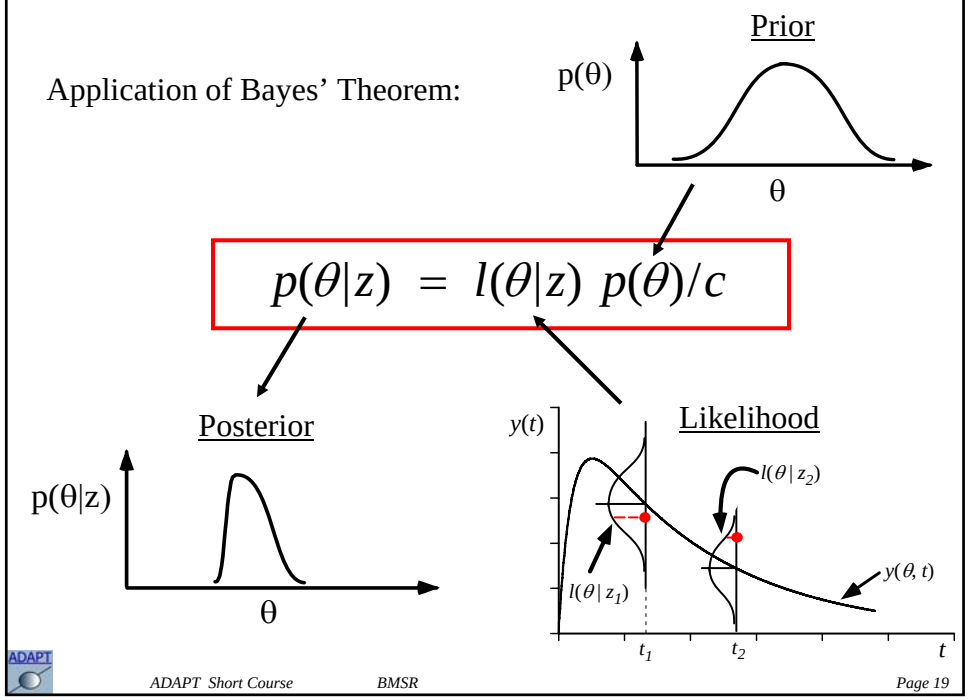
Prior Distribution

e.g.

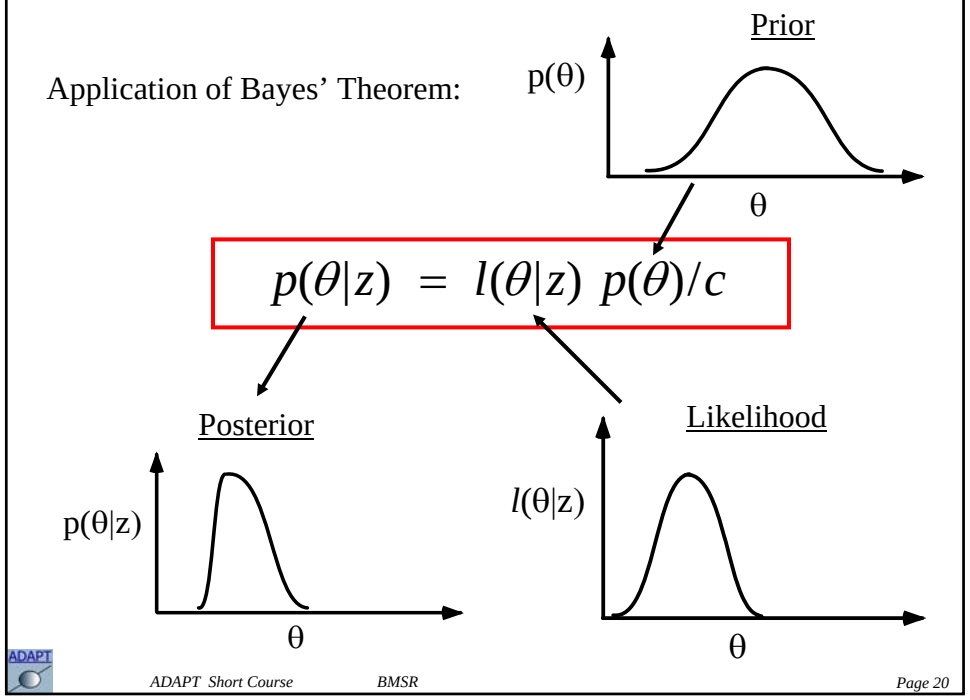
$$p(\theta) = N\left(\mu, \Sigma\right)$$

$$p(\theta) = LN\left(\mu, \Sigma\right)$$

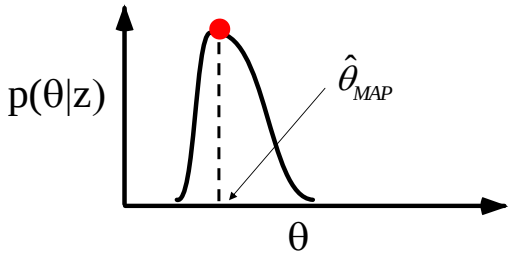
Application of Bayes' Theorem:



Application of Bayes' Theorem:



- Maximum *a Posteriori* Estimate (MAP)



  - One unknown parameter case: $\theta \sim N(\mu, \sigma_\theta^2)$

$$p(\theta|z) \propto l(\theta|z)\ p(\theta)$$

$$p(\theta\,|\,z) \propto \left(\frac{1}{\sigma_1\sqrt{2\pi}}\right)\cdots\left(\frac{1}{\sigma_m\sqrt{2\pi}}\right)\exp\left(\sum_{j=1}^{m}\left(\frac{-\left(z_1 - y(\theta,t_j)\right)^2}{2\sigma_j^2}\right)\right)\text{x}$$

$$\left(\frac{1}{\sigma_\theta\sqrt{2\pi}}\right)\exp\left(\frac{-(\theta-\mu)^2}{2\sigma_\theta^2}\right)$$

$$\hat{\theta}_{MAP} \rightarrow \max p(\theta|z) \quad \text{or} \quad \min(\underbrace{-\ln p(\theta|z)}_{O_{MAP}})$$

$$O_{MAP} \equiv \sum_{j=1}^{m}\left(\frac{\left(z(t_j) - y(\theta,t_j)\right)^2}{\sigma_j^2} + \ln\sigma_j^2\right) + \frac{(\theta-\mu)^2}{\sigma_\theta^2}$$

  - Multi parameter case: $\theta \sim N(\mu, \Sigma)$

$$O_{MAP} \equiv \sum_{j=1}^{m}\left(\frac{\left(z(t_j) - y(\theta,t_j)\right)^2}{\sigma_j^2} + \ln\sigma_j^2\right) + (\theta-\mu)^T\,\Sigma^{-1}(\theta-\mu)^T$$

With informative data on an individual, the data will dominate the prior: $\hat{\theta}_{MAP} \rightarrow \hat{\theta}_{ML}$

With poorly informative data on an individual, the prior will matter: $\hat{\theta}_{MAP} \rightarrow \mu$

Some Comments:

- Noninformative prior for some parameters
- Estimate all or subsets of θ, β
- Multiple Output Case (ADAPT User's Guide)
- Standard errors of the parameter estimates - *SE* of $\hat{\theta}_{MAP}$ and standard errors for model predictions - *SE* of $y\left(\hat{\theta}_{MAP}, t\right)$ (ADAPT User's Guide)
- How are μ and Σ determined?

  From a Population Analysis.

Model Selection Criteria

Method for comparing fit of different models with same data

- Akiake (AIC) and Bayesian (BIC) Information Criteria

  For WLS (*m* observations, *l* outputs & *p* parameters):

$$AIC = l \cdot m \cdot \ln \mathrm{O}_{\mathrm{WLS}} + 2 \cdot p$$

$$BIC = l \cdot m \cdot \ln \mathrm{O}_{\mathrm{WLS}} + \ln\left(l \cdot m\right) p$$

  For ML (q variance model parameters)

$$AIC = \ln \mathrm{O}_{\mathrm{NLL}} + 2(p+q)$$

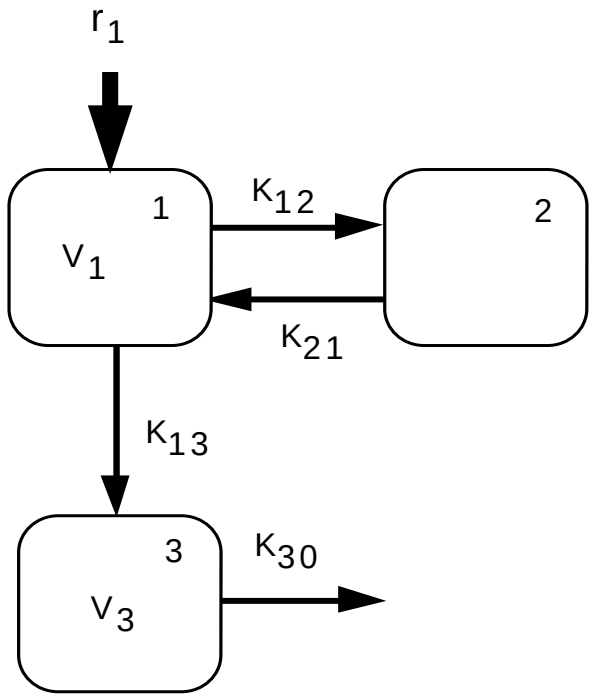
$$BIC = \ln \mathrm{O}_{\mathrm{NLL}} + \ln\left(l \cdot m\right)(p+q)$$

- General Information Criterion for MAP Estimation

$$GEN - IC = \mathrm{O}_{\mathrm{MAP}} + \frac{2 \cdot (p+q)}{m}$$

Case Study - WLS/ML Estimation

The linear compartment model shown below has been used to simulate measured concentration values from compartments 1 and 3, following an infusion into compartment 1 (1000 mg/hr over 1 hour). A total of 12 observations for each output have been simulated between 0.0 and 72 hours. We will use this model and the simulated data with measurement error, to illustrate some of the estimation methods discussed previously. The model to be used is contained in the file **mout.for** and the data are in the file **mout.dat**. The model file has two measured outputs, representing the concentration of drug in compartments 1 and 3 shown below.



1. Using the model file **mout.for**, the data file **mout.dat** and the intitial guesses for the parameters in the file **mout.prm**, find the maximum likelihood estimates for the system parameters V_1, K_{12}, K_{21}, K_{13}, V_3, and K_{30}, and the two variance parameters indicated in the table below. Linear models for the standard deviation of the output errors will be assumed as specified in subroutine VARMOD of the model file **mout.for.** The table below shows the initial guesses for the parameters that are stored in the file **mout.prm** as well as which parameters are to be estimated. View all the results stored in the **run** file as well as the plots.

Parameter	Initial Value	Estimate ?	ML Estimate
V_1	50.0	Y	62.10
K_{12}	0.2	Y	0.1713
K_{21}	0.1	Y	0.1084
K_{13}	0.05	Y	0.03925
K_{30}	0.3	Y	0.3522
V_3	25.0	Y	19.83
$IC(1)$	0.0	N	-
$IC(2)$	0.0	N	-
$IC(3)$	0.0	N	-
SD_{inter1}	0.0	N	-
SD_{slope1}	0.25	Y	0.2221
SD_{inter2}	0.0	N	-
SD_{slope2}	0.1	Y	0.08431
$R^2 - Y(1)$	-	-	
$SS - Y(1)$	-	-	
$R^2 - Y(2)$	-	-	
$SS - Y(2)$	-	-	

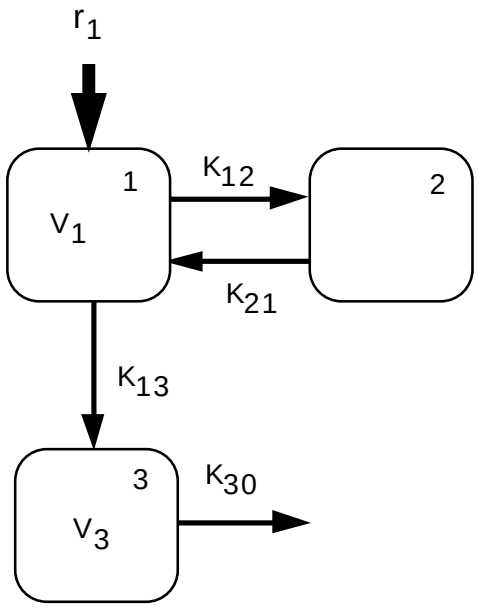
2. Using the model file **mout.for**, the data file **mout.dat** and the intitial guesses for the parameters in the file **mout.prm**,, find the weighted least squares estimates of V_1, K_{12}, K_{21}, K_{13}, V_3, & K_{30}. Assign a weight of 1 to each response (output). For y_1 , use the linear inverse variance option (weighting option 2): low concentration and associated standard deviation of 1.0 and 0.25; high concentration and associated standard deviation of 10 and 2.5. For y_2 , also use the linear inverse variance option (weighting option 2): low concentration and associated standard deviation of 1.0 and 0.1; high concentration and associated standard deviation of 10 and 1.0. The table below shows the initial guesses for the parameters that are stored in the file **mout.prm** as well as which parameters are to be estimated. View all the results stored in the **run** file as well as the plots.

Parameter	Initial Value	Estimate ?	WLS Estimate
V_1	50.0	Y	69.96
K_{12}	0.2	Y	0.1555
K_{21}	0.1	Y	0.09546
K_{13}	0.05	Y	0.03641
K_{30}	0.3	Y	0.3597
V_3	25.0	Y	18.82
$IC(1)$	0.0	N	-
$IC(2)$	0.0	N	-
$IC(3)$	0.0	N	-
$R^2 - Y(1)$	-	-	
$SS - Y(1)$	-	-	
$R^2 - Y(2)$	-	-	
$SS - Y(2)$	-	-	

3. Compare the estimates obtained for this model and data set from the two estimators, WLS and ML.

Case Study - Multiresponse Estimation

The linear compartment model shown below has been used to simulate noisy concentration values from compartments 1 and 3, following an infusion into compartment 1 (1000 mg/hr over 1 hour). A total of 12 observations for each output have been simulated between 0.0 and 72 hours. We will use this model and the simulated data to illustrate the idea of estimating model parameters by simultaneously fitting both sets of concentration measurements, versus estimating subsets of the model parameters using the measured outputs individually.



The following three data files have been constructed.

mout.dat	contains both outputs
mout1.dat	contains only compartment 1 values
mout2.dat	contains only compartment 3 values

The following three model files have also been created:

mout.for	model shown above (two outputs)
mout1.for	model w/o comp. 3 and one output from compartment 1
mout2.for	model shown above with one output from compartment 3

The remaining units are as follows: V's in L, K's in hrs^{-1}, concentrations in μg/ml. Corresponding parameter files (***.prm**) have also been created.

1. Using the model file **mout1.for,** the data file **mout1.dat** and the initial guesses for the parameters in the file **mout1.prm**, find the Maximum Likelihood estimates for the parameters V_1, K_{12}, K_{21}, and K_{13}. The table below shows the initial guesses for the parameters that are stored in the file **mout1.prm** as well as which parameters are to be estimated. View all the results stored in the **log** file as well as the plots and record the estimates.

Parameter	Initial Value	Estimate ?	ML Estimate
V_1	50.0	Y	64.9
K_{12}	0.2	Y	0.108
K_{21}	0.1	Y	0.0253
K_{13}	0.05	Y	0.0175
$IC(1)$	0.0	N	-
$IC(2)$	0.0	N	-
SD_{inter1}	0.0	N	-
SD_{slope1}	0.25	N	-

2. Using the model file **mout2.for** and the data file **mout2.dat** and the initial guesses for the parameters in the file **mout2.prm**, find the Maximum Likelihood estimates for the parameters V_3, and K_{30}. Fix the parameters V_1, K_{12}, K_{21}, and K_{13} at their ML estimates obtained in part 1. As initial parameter values for the parameters V_3, and K_{30} use the numbers given in the table below. (All these parameter values are stored in the file **mout2.prm**.) View all the results stored in the **run** file as well as the plots and record the estimates

Parameter	Initial Value	Estimate ?	ML Estimate
K_{30}	0.3	Y	0.279
V_3	25.0	Y	9.9
$IC(1)$	0.0	N	-
$IC(2)$	0.0	N	-
$IC(3)$	0.0	N	-
SD_{inter2}	0.0	N	-
SD_{slope2}	0.1	N	-

3. Using the model file **mout.for**, the data file **mout.dat**, and the initial guesses for the parameters in the file **mout.prm**, find the Maximum Likelihood estimates for all six of the parameters V_1, K_{12}, K_{21}, K_{13}, V_3, and K_{30}. Do not estimate the variance model parameters. The table below shows the initial guesses for the parameters that are stored in the file **mout.prm** as well as which parameters are to be estimated. View all the results stored in the **run** file as well as the plots and record the estimates.

Parameter	Initial Value	Estimate ?	ML Estimate
V_1	50.0	Y	62.9
K_{12}	0.2	Y	0.169
K_{21}	0.1	Y	0.106
K_{13}	0.05	Y	0.0392
K_{30}	0.3	Y	0.352
V_3	25.0	Y	19.91
IC(1)	0.0	N	-
IC(2)	0.0	N	-
IC(3)	0.0	N	-
SD_{inter1}	0.0	N	-
SD_{slope1}	0.25	N	-
SD_{inter2}	0.0	N	-
SD_{slope2}	0.1	N	-

4. Compare the estimates obtained from parts 1 and 2 to those that were obtained in part 3 using both measured outputs simultaneously. The actual parameter values used to generate the observations are the Initial Values given in the table of part 3.

5. **NB:** In other multiresponse examples, performing a simultaneous estimation is inferior to performing a sequential estimation. This can occur, for example, when the data of the first response is very informative while the data from the second response variable is minimal (because of few observations or noisy data).

Recirculatory Modeling of Drug Disposition

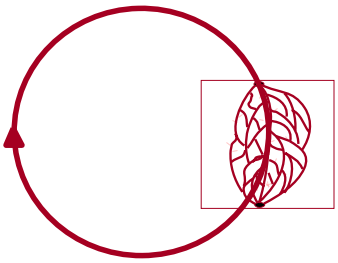
- Why? Modeling of distribution kinetics

  Important for initial distribution (vascular mixing),e.g., thiopental

- No well-mixed compartments: Laplace transformation
- Case study: Sorbitol disposition in humans

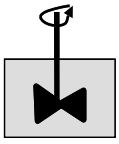
Mixing/Distribution

Body



Circulation through fractal network

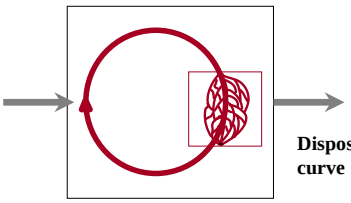
Reactor



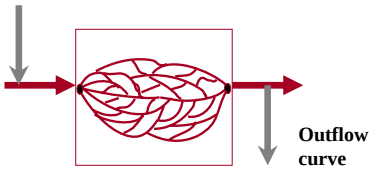
Turbulent mixing

Blood volume ~ 5 *L* , *Cardiac output* ~ 5 *L/min* → *Mixing time* ~ 1 *min*

Residence time Sytem



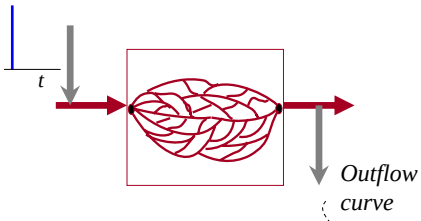
Transit time Sytem



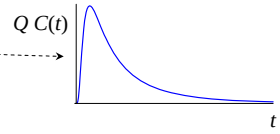
Mean transit time ⇨ **Extent of distribution**

Transit time dispersion ⇨ **Rate of distribution**

Transit Time Distribution



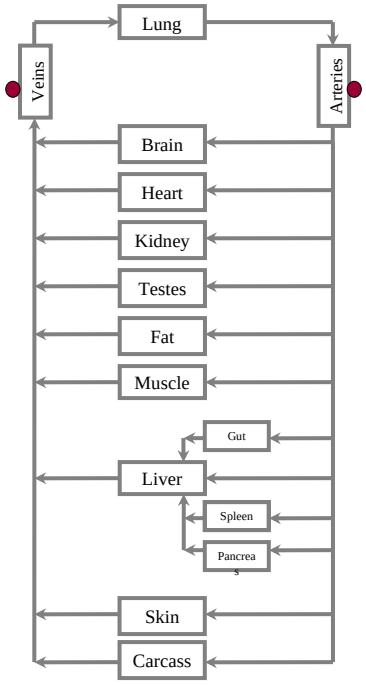
$$f_{IG}(t) = \sqrt{\frac{MTT}{2\pi RD^2 t^3}} \exp\left[-\frac{(t - MTT)^2}{2RD^2\, MTT\, t}\right]$$



Density function of Inverse Gaussian Distribution

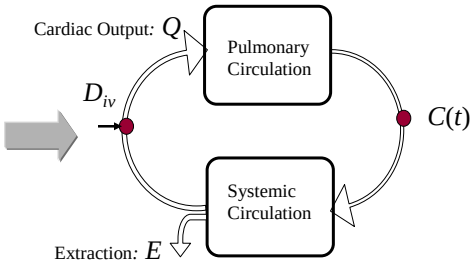
$MTT \rightarrow$ **Extent of distribution,** Distribution volume: $V = MTT\, Q$

$$RD^2 = \frac{VTT}{MTT^2} \rightarrow \textbf{Rate of distribution}$$



Minimal Circulatory Model

Heterogeneous subsystems



Weiss et al., Br J Clin Pharm, 1996

Model Formulation in the Laplace Domain

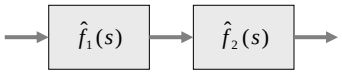
Model Structure:

- Compartments → Differential Equations
- Subsystems → Transit Time Density Functions, $f_i(t)$ (Impulse Response)

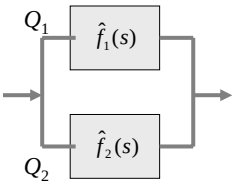
Limitation of using compartments as subsystems → *exponential distributed transit times*

Advantage of model building in Laplace domain → *simple rules for connecting subsystems*

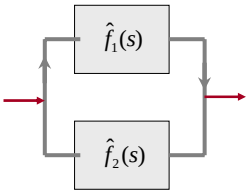
Model building: Laplace Transformation



$$\hat{f}(s) = \hat{f}_1(s)\,\hat{f}_2(s)$$

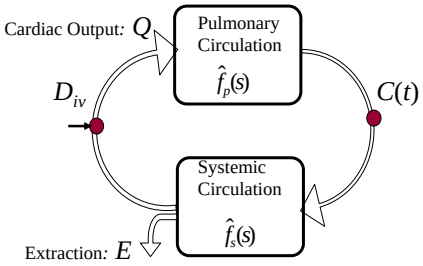


$$\hat{f}(s) = q\hat{f}_1(s) + (1-q)\,\hat{f}_2(s)$$
$$q = Q_1/Q$$



$$\hat{f}(s) = \frac{\hat{f}_1(s)}{1-\hat{f}_1(s)\hat{f}_2(s)}$$

Recirculatory PK Model



$$\hat{C}(s) = \frac{D_{iv}}{Q}\,\frac{\hat{f}_p(s)}{1-(1-E)\,\hat{f}_s(s)\,\hat{f}_p(s)}$$

$$f_i(t) = \sqrt{\frac{V_i/Q}{2\pi RD_i^2 t^3}}\exp\left[-\frac{(t-V_i/Q)^2}{2RD_i^2(V_i/Q)t}\right]$$

$$E = \frac{CL}{Q}$$

Numerical inverse Laplace Transformation

$$C(t) = L^{-1}\left\{\frac{D}{Q}\,\hat{f}_{circ}(s)\right\}$$

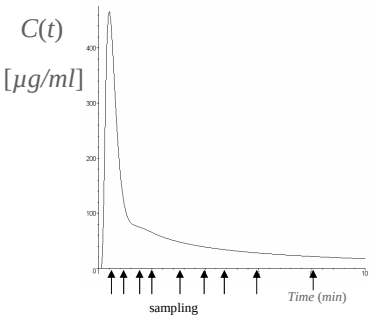
ADAPT II + Talbot's Method

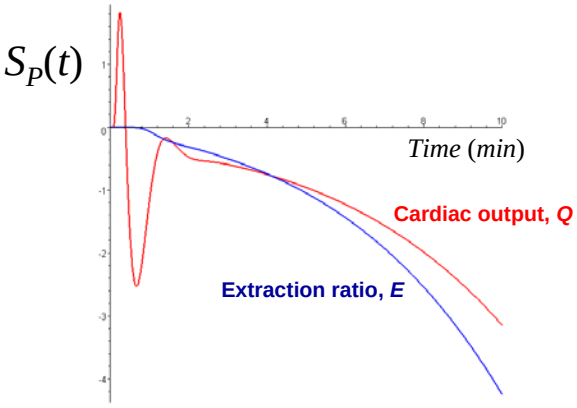
Schalla & Weiss, Eur J Pharm Sci, 1999

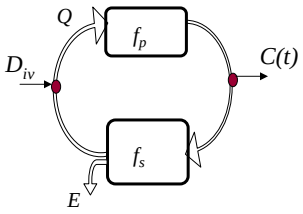
Sensitivity

Sorbitol in humans

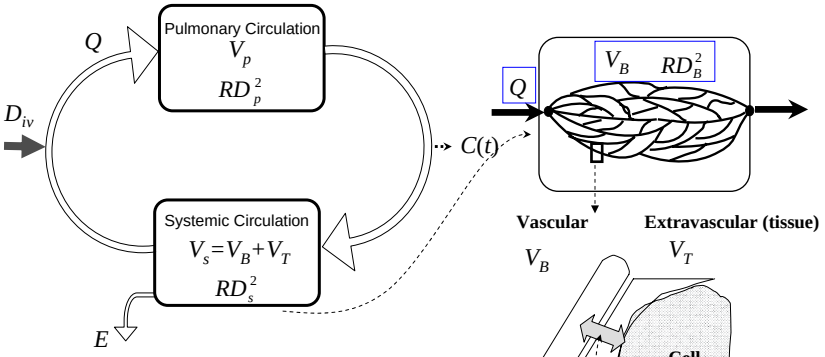
Bolus dose, 0.8 g







Physiological Interpretation of RD^2

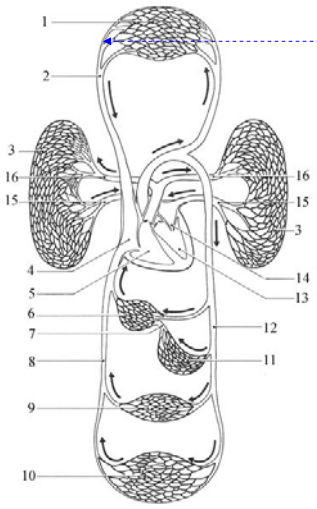


$$RD_s^2 = RD_B^2 + \frac{Q}{PS}\frac{2(V_T/V_B)^2}{(1+V_T/V_B)^2}$$

Weiss, Pharm Res, 2007

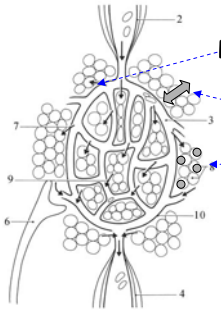
W1

First-principles modeling of distribution kinetics



Advective transport

Advective dispersion → Vascular mixing



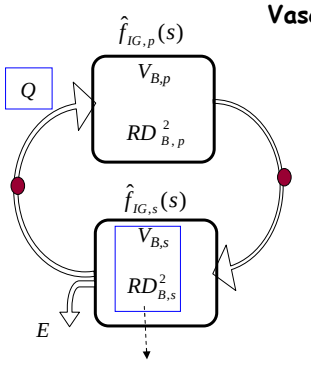
Permeation (Capillary uptake)

Diffusion (Extravascular)

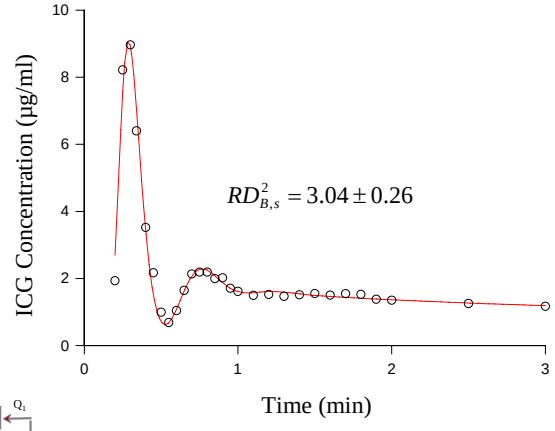
Tissue Binding

Vascular Mixing Kinetics

Vascular Marker (ICG) in Dog

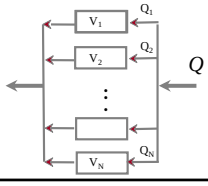


Relative dispersion
-> Intravascular mixing



Predicted from V_i and Q_i data of Benowitz et al. in monkeys

$RD^2_{B,s} = 2$



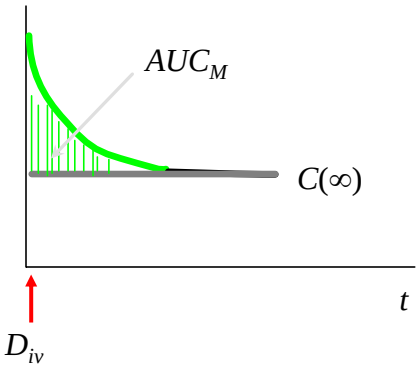
$MTT_i = V_i / Q_i$

Weiss, Krejcie & Avram, Am J Physiol Heart Circ, 2006

Slide 11

W1 Weiss, 6/10/2005

Distribution Kinetics: Area Under the Mixing Curve

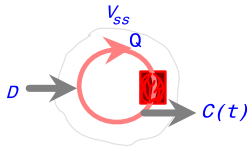


$$AUC_M = \frac{D_{iv}}{Q}\frac{1}{2}(RD_c^2 - 1)$$

$$RD_c^2 = \frac{VCT}{MCT^2}$$

Relative Dispersion of Transit Time ⇒ Rate of Distribution

$AUC_M = 0$
well-mixed system



Closed (noneliminating) system ($CL = 0$)

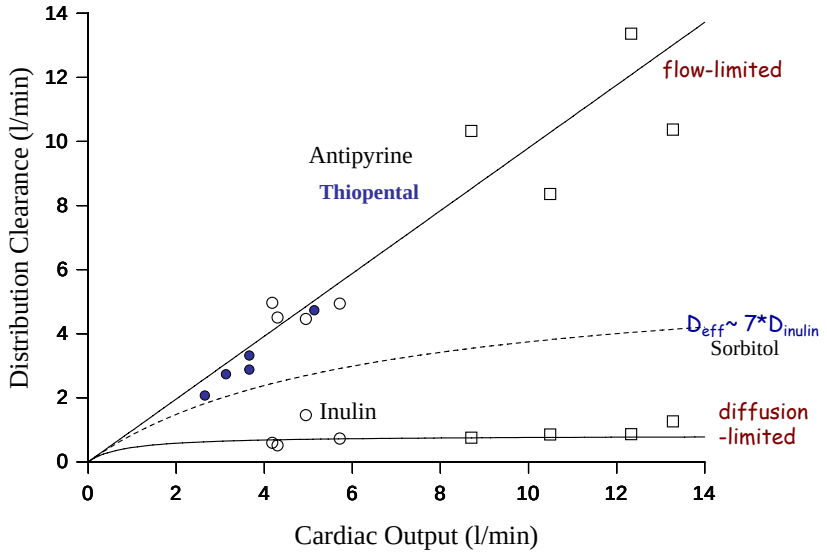
Distribution Clearance

$$CL_M = \frac{D_{iv}}{AUC_M}$$

Weiss & Pang, J Pharmacokin Biopharm, 1992

From Flow-to Diffusion-Limited Distribution Kinetics

A Continuous Transition



Weiss, Krejcie & Avram, Pharm Sci, 2007

Model Parameters

$$Q, V_{pul}, RD^2_{pul} \qquad V_s, RD^2_s, E_s$$

Distribution

Kinetics

$$CL_M = \frac{2Q}{RD_s^2 - 1}$$

Steady-state

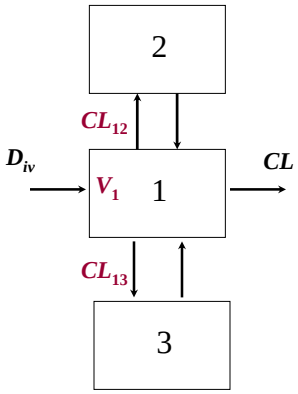
$$V_{ss} = (MTT_p + MTT_s) * Q = V_p + V_s$$

Elimination

$$CL = E_s Q$$

3-Compartment Model

Fit excellent for t > about 2 min



- V_1 : no meaning in terms of initial distribution
- CL_{12}, CL_{21} : no meaning in terms of underlying distribution processes
- Estimation and interpretation of steady-state parameters (CL, V_{ss}) is straightforward:
  V_{ss}, CL model independent

References:

Weiss M, Hübner GH, Hübner GI, Teichmann W. Effects of cardiac output on disposition kinetics of sorbitol: recirculatory modelling. *Br J Clin Pharmacol* 41: 261-268 (1996)

Weiss M, Krejcie TC, Avram MJ. Transit time dispersion in the pulmonary and systemic circulation: effects of cardiac output and solute diffusivity. *Am J Physiol: Heart Circ Physiol* 291: H861-870 (2006)

Weiss M. Residence time dispersion as a general measure of drug distribution kinetics: estimation and physiological interpretation. *Pharm Res* 24: 2025-2030 (2007)

Weiss M, Krejcie TC, Avram MJ. Circulatory transport and capillary-tissue exchange as determinants of the distribution kinetics of inulin and antipyrine in dog. *J Pharm Sci* 96: 913-926 (2007)

Schalla M, Weiss M. Pharmacokinetic curve fitting using numerical inverse Laplace transformation. *Eur J Pharm Sci* 7: 305-309 (1999)

The latter paper describes the implementation of FORTRAN subroutine of Talbot's algorithm by Murli and Rizzardi (Algorithm 682 – Talbot's Method for the Laplace inversion problem. ACM Trans. Math. Softw. 16, 158–168, 1990) into ADAPT (used in recirc.for).

Availability of this FORTRAN subroutine:

Case Study – Recirculatory Modeling of Drug Disposition

The method is applied to disposition data of sorbitol measured after rapid intravenous injection and arterial sampling in patients who had undergone cardiac catheterization whereby the cardiac output was measured (Weiss et al., 1996).

Model equations coded in Model File **recirc.for**.

Y(1): Concentration-time curve, *C*(*t*)

Parameters:

D iv Bolus Dose
Q Cardiac Output (Plasma Flow: $Q_{plasma} = Q_{blood}(1\text{-}Hct)$; Hct : Hematocrit)
RDp Relative Dispersion of Transit Time across the Pulmonary Circulation, RD_p^2
V_p Distribution Volume of Pulmonary Circulation
RDs Relative Dispersion of Transit Time across the Systemic Circulation, RD_s^2
Vs Distribution Volume of Systemic Circulation
Es Systemic Extraction Ratio

```
Complex Function FLAP(S)
……..

Complex s,D,Q,RDp,Vp,RDs,Vs,Fs
      D=CMPLX(P(1),0)
      Q=CMPLX(P(2),0)
      RDp=CMPLX(P(3),0)
      Vp=CMPLX(P(4),0)
      RDs=CMPLX(P(5),0)
      Vs=CMPLX(P(6),0)
      Es=CMPLX(P(7),0)
```

$$\hat{C}(s) = \frac{D_{iv}}{Q} \frac{\hat{f}_p(s)}{1-(1-E)\,\hat{f}_s(s)\,\hat{f}_p(s)}$$

$$f_i(t) = \sqrt{\frac{V_i/Q}{2\pi RD_i^2 t^3}} \exp\left[-\frac{(t-V_i/Q)^2}{2RD_i^2 (V_i/Q)t} \right]$$

```
    FLAP=(D/Q)*CEXP(1/RDp-sqrt(2*(Vp/Q)/RDp*(s+1/(2*(Vp/Q)*RDp))))/
    1 (1-(1-Es)*CEXP(1/RDp-sqrt(2*(Vp/Q)/RDp*(s+1/(2*(Vp/Q)*RDp))))*
    2 CEXP(1/RDs-sqrt(2*(Vs/Q)/RDs*(s+1/(2*(Vs/Q)*RDs)))))
     Return
     End
……

CALL TSUM(FLAP,CONLAM,CONSIG,CONNU,NOPTS,TVALUE,INVF,IER)
    Y(1) = INVF
```

Secondary Parameters:

1. Clearance

$CL = E_s Q$

2. Volume of Distribution at Steady-State

$V_{ss} = V_p + V_s$

3. Distribution Clearance

$$CL_M = \frac{2Q}{RD_s^2 - 1}$$

Analysis:

1. Data file, **recircd.dat** contains the bolus input information and drug concentration values.
   - ML Estimation, **recircp.prm** contains initial values (Q measured by thermodilution).
   - *D* and *Q* fixed
   - view plots (PostScript file)
   - results (run file), enter estimates in Table, below (first column)

RE-ESTIMATION: change initial values
- estimate Q: initial value 2000 (measured 3600), only D fixed
- view plots (PostScript file)
- enter the results in Table , below (second column)

Table

	Q = 3600	Q estimated
	measured	Ini: 2000
AIC		
Q	fixed	
RD_p		
V_p		
RD_s		
V_s		
E_s		
CL		
V_{ss}		
CL_M		

Discussion

1. The data (design of experiment) do not allow a reliable estimation of cardiac output and pulmonary distribution kinetics (RD_p)

2. The systemic extraction ratio E_s of ≈ 10 % may reflect fractional liver blood flow. $CL = E_s Q = CL_{liv} = E_{liv} Q_{liv} \approx Q_{liv}$, since the hepatic extraction of sorbitol is nearly 100%, $E_{liv} \approx 1$. This patient (congestive cardiomyopathy) has a relatively low Q and Q_{liv}.

3. The steady-state distribution volume of ≈16 l matches that of the extracellular volume (*ECV*).

4. The distribution clearance exceeds elimination clearance (in this patient).

Modeling Drug-Receptor Interaction

- Why? "Slow" receptor binding in PK/PD modeling

  Discrimination between receptor binding and signal transduction

- Link model assumes instantaneous binding

- Case study: Digoxin PK/PD in humans

  What causes the delayed inotropic response?

The 1989 Harry Gold Award Lecture

A Pharmacokinetic Odyssey

Arthur J. Atkinson, Jr., MD
Director of Clinical Pharmacology and
Professor of Medicine and Pharmacology,
Northwestern University Medical School

„I suspect, but have no proof, that the process of digoxin distribution from plasma to ist myocardial site of action is responsible for this clinically important delay. „

There is no honor that could have the same impact on me as the Harry Gold Award. Not only is it conferred by a distinguished society in the memory of one of the illustrious pioneers of clinical pharmacology, but Harry Gold was one of my teachers when I was a medical student at Cornell. It is perhaps intrinsic to human nature that, no matter how much we learn during our professional careers, we instinctively continue to attribute infinitely more knowledge and wisdom to our teachers. However, even when subjected to the most critical scrutiny, nothing could have been more auspicious for a future clinical pharmacologist than to have been a medical student at Cornell in the late 1950s and early 60s.

It was an unparalleled privilege to have learned biochemistry, physiology, and pharmacology in departments chaired respectively by Vincent du Vigneaud, Robert Pitts, and Walter Riker (Table 1). I also owe a special debt of gratitude to the mentors who guided me at certain critical periods after I completed my formal education: Mones Berman and Marge Weiss, who taught me kinetic modeling when I was a Clinical Associate at the National Institutes of Health; Les Webster, who fostered my early development as a junior member of the

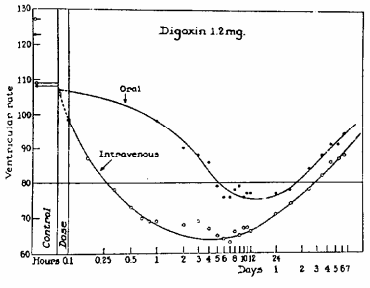
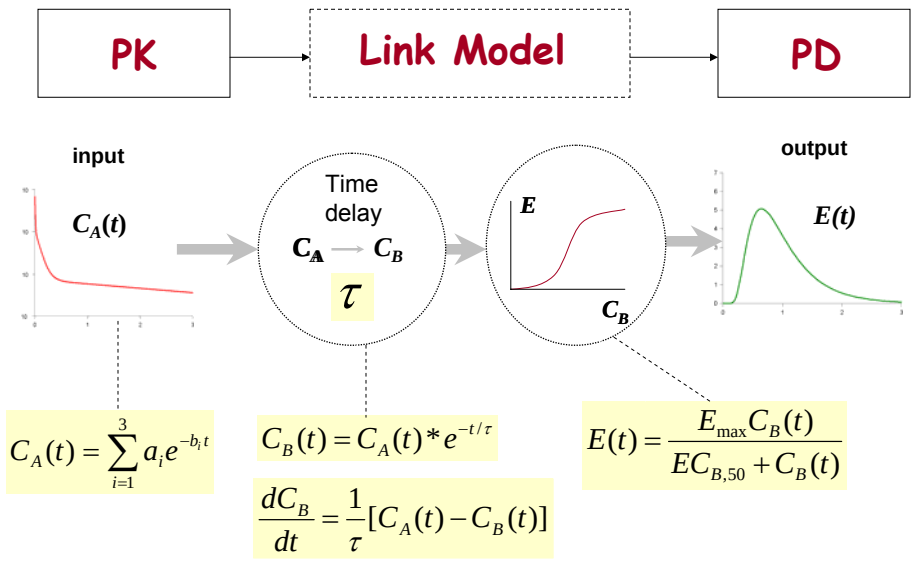


Fig. 1. Curve of onset and disappearance of digoxin action in patients with atrial fibrillation (Reprinted from Gold et al., 1953, with permission).

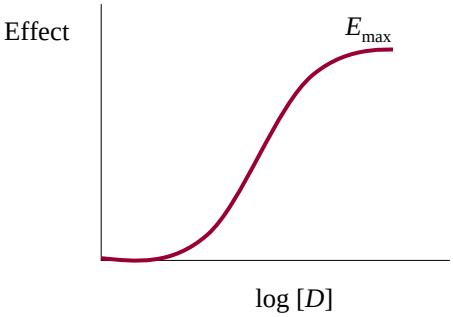
PK/PD



Traditional Method to Analyse Drug-Receptor Interaction

Steady-state experiments → no integration of kinetic information

Dose (or Concentration) -Response Curves



Occupation Theory

$$[D] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} [DR]$$

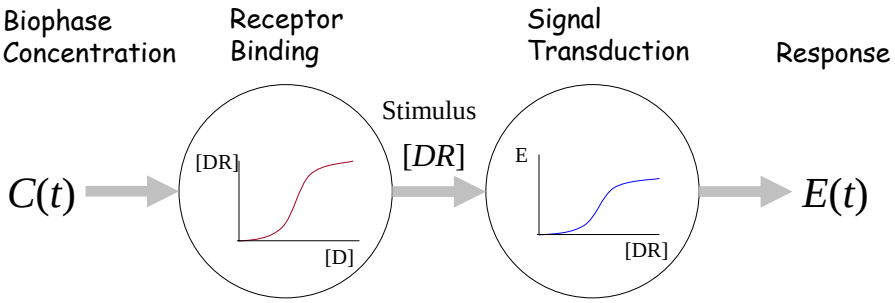
$$\frac{E}{E_{max}} = \frac{e[DR]}{[R_{tot}]} = \frac{e[D]}{[D] + K_A}$$

K_D : D producing 50% of E_{max}

Dissociation constant

more general: $[DR]$ → Stimulus → Response

Operational Model



Steady state: $[DR] \sim \frac{[D]}{[D]+K_D}$ $E \sim \frac{[DR]}{[DR]+K_E}$

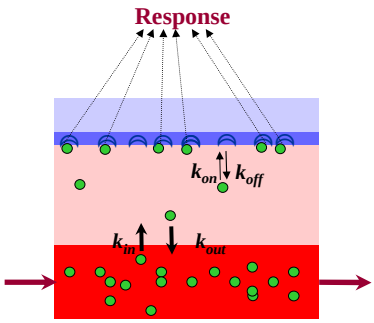
Transient state: $[DR](t)$

Transient State

$$\frac{dDR(t)}{dt} = k_{on}(R_{tot} - DR(t))D_{biophase}(t) - k_{off}DR(t)$$

$\Rightarrow$ $E(t) = eDR(t)$

$$D + R \underset{k_{on}}{\overset{k_{off}}{\leftrightarrows}} DR$$



Average inotropic response data in human volunteers obtained after 1mg digoxin

(A) as bolus dose

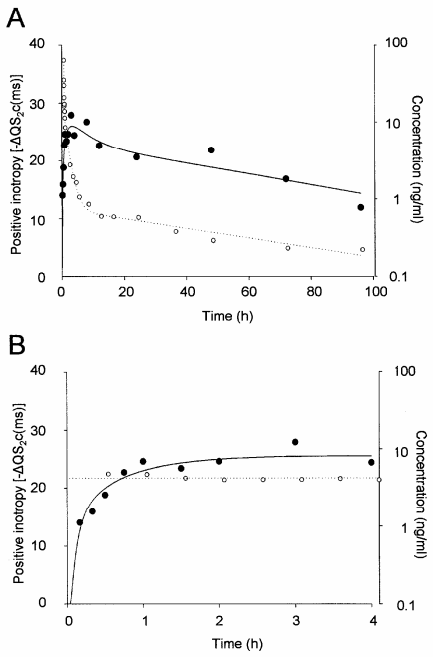
$C(t) = 57.3e^{-0.164\,t} + 9.99e^{-0.011\,t} + 0.74e^{-0.00024\,t}$

Kramer et al., JPB, 1979

(B) infused in concentration-clamp experiments

C = 4.2 ng/ml, 0 < t < 4 hr

Weiss et al., Eur J Clin Pharmacol, 1983



Empirical Link Model for Digoxin in Humans

$$C_B(t) = C(t) * e^{-t/\tau} \qquad E(t) = \frac{E_{\max} C_B(t)}{EC_{B,50} + C_B(t)}$$

- Fits bolus dose PD data (τ = 19 h)
- Fails to fit step response PD data.

model

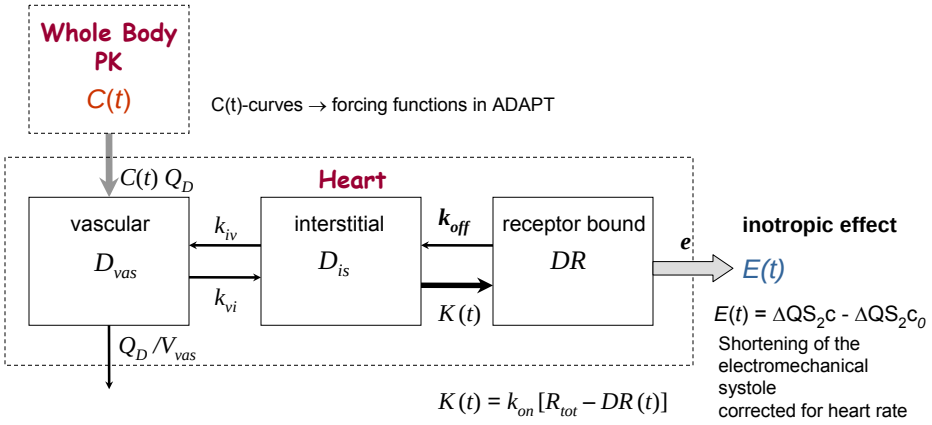
$$E_{step}(t) = \frac{E_{\max} C_0 (1 - e^{-t/\tau})}{EC_{B,50} + C_0 (1 - e^{-t/\tau})}$$

experiment

$$\sim (1 - e^{-t/\tau_{step}})$$

τ_{step} = 1.3 h

Mechanistic PK/PD Model for Digoxin in Humans



Preassigned physiological/anatomical parameters : $\boldsymbol{Q_D}$, $\boldsymbol{V_{vas}}$, $\boldsymbol{k_{vi}}$, $\boldsymbol{k_{iv}}$

Adjustable parameters: $\boldsymbol{k_{on}}$, $\boldsymbol{k_{off}}$, $\boldsymbol{R_{tot}}$, $\boldsymbol{e}$

Weiss & Kang, Pharm Res, 2004

Differential Equations

$$D_{vas}(t)/dt = -(Q_D / V_{vas} + k_{vi})\, D_{vas}(t) + k_{iv}\, D_{is}(t) + Q_D\, C(t) \quad (1)$$

$$D_{is}(t)/dt = k_{vi}\, D_{vas}(t) - [k_{iv} + k_{on}(R_{tot} - DR(t))]\, D_{is}(t) + k_{off}\, DR(t) \quad (2)$$

$$DR(t)/dt = k_{on}[R_{tot} - DR(t)]\, D_{is}(t) - k_{off}\, DR(t) \quad (3)$$

$$E(t) = e\, DR(t) \quad (4)$$

Mechanistic PK/PD Model for Digoxin in Humans

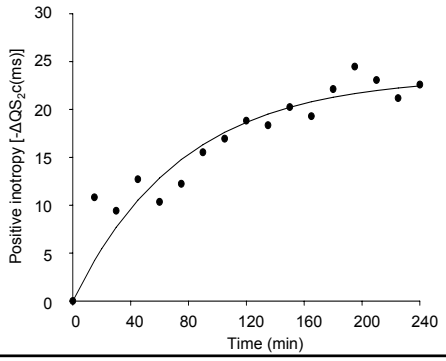
Step response (Concentration clamp experiment)

$$E_{step} = E_{ss}(1 - e^{-t/\tau_{step}}) \qquad \tau_{step} = \frac{1}{k_{on} D_{is} + k_{off}}$$

When transcapillary exchange is not rate-limiting ($\tau_{step} >> 1/k_{vi}$).

Estimated: τ_{step} = 1.3 h

Prediction from k_{on} and k_{off} ?



References:

Weiss M, Kang W. Inotropic effect of digoxin in humans: mechanistic pharmacokinetic/pharmacodynamic model based on slow receptor binding. *Pharm Res* 21: 231-236 (2004)

Kramer WG, Kolibash AJ. Lewis RP, Bathala MS, Visconti JA, Reuning RH. Pharmacokinetics of digoxin: relationship between response intensity and predicted compartmental drug levels in man. *J. Pharmacokinet. Biopharm.* **7:**47-61 (1979).

Weiss M, Sziegoleit W, Fahr A, Förster W. Rapid achievement of a serum concentration plateau of digoxin through controlled infusion. *Eur J Clin Pharmacol* 25: 455-457 (1983)

Kang W, Weiss M. Digoxin uptake, receptor heterogeneity and inotropic response in the isolated rat heart: A comprehensive kinetic model. *J Pharmacol Exp Ther* 302: 577-583 (2002)

Case Study – Digoxin PK/PD in Humans

Fit of digoxin plasma concentration and inotropic response after a 1 mg iv dose in human volunteers, see (Weiss and Kang, Pharm Res, 2004), mean data from (Kramer et al., J Pharmacokin Biopharm, 1979).

Model equations are coded in Model File **dig.for**.

Y(1): Inotropic response, E(t)

```
Real*8  Ca, PMX3
     Ca=P(9)*dexp(-P(10)*t)+P(11)*dexp(-P(12)*t)+P(13)*dexp(-P(14)*t)

     If (P(5) .GT. X(3)) Then
      PMX3 = P(5) - X(3)

     XP(1)= -(P(1)/P(2)+P(3))*X(1)+P(4)*X(2) + P(1)*Ca
     XP(2)= P(7)*X(3)-PMX3*P(6)*X(2)
    x       +P(3)*X(1)-P(4)*X(2)
     XP(3)= PMX3*P(6)*X(2)-P(7)*X(3)

      End If
```

```
Psym(1) = 'Q'
Psym(2) = 'V1'
Psym(3) = 'Kvi'
Psym(4) = 'Kiv'
Psym(5) = 'Rtot'
Psym(6) = 'kon‘
Psym(7) = 'koff'
Psym(8) = 'e'
Psym(9) =  'A1'
Psym(10) = 'b1'
Psym(11) = 'A2'
Psym(12) = 'b2'
Psym(13) = 'A3'
Psym(14) = 'b3'
```

A priori knowledge (literature, experiments)

Disposition curve (forcing function)

$$C_{iv}(t) = A_1 e^{-b_1 t} + A_2 e^{-b_2 t} + A_3 e^{-b_3 t}$$

Parameter estimated by fitting $C_{iv}(t)$ data

Parameters:

Psym(5) = 'Rtot' Total functional receptor amount
Psym(6) = 'kon'
Psym(7) = 'koff'
Psym(8) = 'e' efficacy (effect per occupied receptor, E/AR)

Parameter estimation:

Fix Psym(1) - Psym(4) and Psym(9) - Psym(14)

Secondary Parameter:

1. $K_d = k_{off}/k_{on}$: Apparent dissociation constant (digoxin binding to myocardial Na/K-ATPase)

2. Time constant τ_{step} of the increase of E(t) in a concentration clamp experiment

$$E_{step} = E_{ss}(1-e^{-t/\tau_{step}}) \qquad \tau_{step} = \frac{1}{k_{on}D_{is} + k_{off}}$$

3. k_{vi}/k_{on} Ratio of time constants of transport(vascular to interstitial) and receptor binding

Analysis:

Fit data of inotropic response after a 1 mg iv dose of digoxin (Model File **dig.for**).
Data file, **digd.dat**
- ML estimation, **digp.prm** contains initial values (including fixed parameter values)
- view plots (PostScript file)
- results (run file)

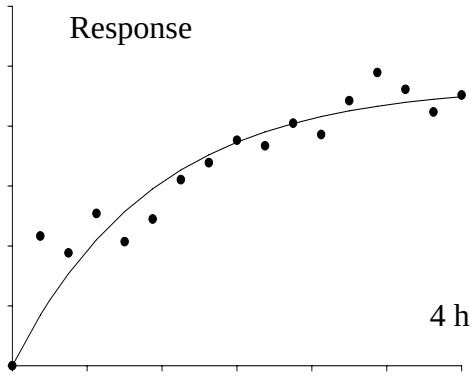
Discussion:

The mechanistic approach - but not the link model - allowed a modeling of digoxin PD which is consistent with available inotropic response data.

Uncertainty in estimation of R_{tot} (dose too low to reach saturation).

Estimates of K_d and R_{tot} similar to that obtained in human myocardial tissue in vitro.

Estimate of τ_{step} is in agreement with the value of 1.3 h estimated by fitting the step response data (concentration clamp experiment).

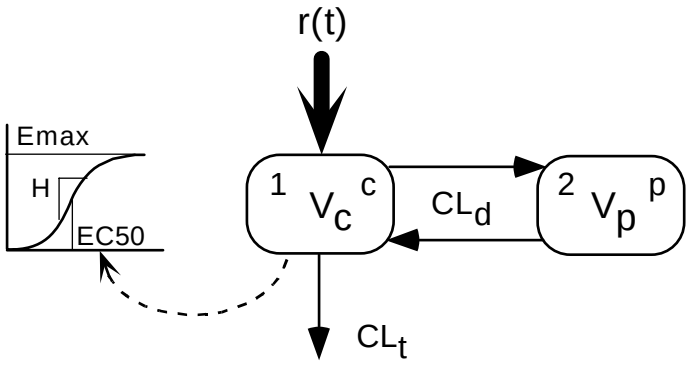


Case Study - Direct Response PD Models

This case study involves parameter estimation using direct response models. In Part 1, a PK/PD model incorporating a direct connection between the measured drug response and plasma concentration will be fitted to data consisting of both measured plasma concentration and measured drug response. In Part 2, the pharmacodynamic portion of the model will be changed to include an effect compartment.

Part 1

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). In the pharmacodynamic portion of the model, the drug's effect is related to plasma concentration using a Hill-type model (Emax model – H=1).



The following equations define the drug's plasma concentration and response, where x_1 and x_2 are compartment amounts (mg), y_1 is plasma concentration (μg/ml) and y_2 is drug response (% of maximum).

$$\frac{dx_1}{dt} = -(\frac{CLt}{Vc} + \frac{CLd}{Vc})x_1 + \frac{CLd}{Vp}x_2 + r(t)$$

$$\frac{dx_2}{dt} = \frac{CLd}{Vc}x_1 - \frac{CLd}{Vp}x_2$$

$$y_1 = x_1 / Vc$$

$$y_2 = \frac{E_{max} y_1}{EC50 + y_1}$$

1. These equations have been coded and entered in the Model File **drm1.for**, along with linear variance models for the two outputs. Several secondary parameters have been defined as well. Inspect the model file **drm1.for** in the Fortran editor. The following system, variance and secondary parameters have been defined:

system		**variance**		**secondary**	
CLt	- P(1)	SD_{inter1}	- PV(1)	*Kel*	- PS(1)
Vc	- P(2)	SD_{slope1}	- PV(2)	*V*	- PS(2)
CLd	- P(3)	SD_{inter2}	- PV(3)	*Kcp*	- PS(3)
Vp	- P(4)	SD_{slope2}	- PV(4)	*Kpc*	- PS(4)
Emax	- P(5)			λ_1	- PS(5)
EC50	- P(6)			λ_2	- PS(6)
				$t_{1/2} - \lambda_1$	- PS(7)
				$t_{1/2} - \lambda_2$	- PS(8)

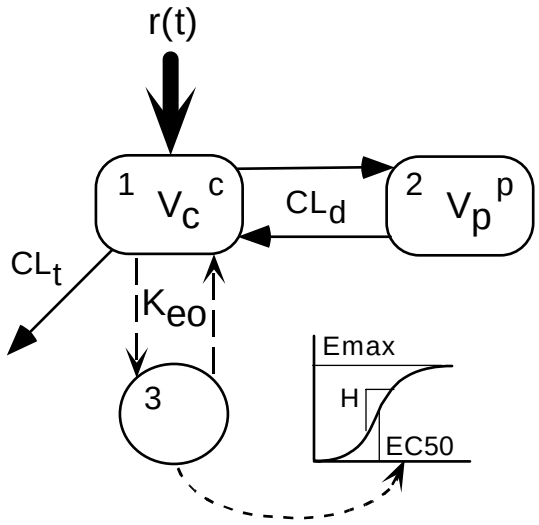
The parameters have the following units: *CL's* (L/hr^{-1}); *V's* (L); *Emax* (% max response); *EC50* (μg/ml).

2. The data file **drm.dat** contains the dose regimen information along with measured values for plasma concentration and drug response. Fit the model to the data stored in this file using the ML estimation option of ID, with initial values for model parameters as listed below (parameter file **drm1.prm**). Compare the ML estimates to those in the table below, along with AIC. View the graphs of the fitted model response.

Parameter	Initial Value	Estimate?	ML Estimate
CLt	6.0	Y	6.326
Vc	30.0	Y	29.56
CLd	12.0	Y	10.35
Vp	60.0	Y	51.19
Emax	100.0	Y	68.75
EC50	1.0	Y	0.3413
IC(1)	0.0	N	-
IC(2)	0.0	N	-
SD_{inter1}	0.05	N	-
SD_{slope1}	0.1	N	-
SD_{inter2}	2.5	N	-
SD_{slope2}	0.1	N	-
AIC	-	-	91.1

Part 2

Consider the same linear two compartment PK model and Hill-type PD model used above. In this case, however, it will be assumed that the response is mediated through a hypothetical effect compartment as illustrated in the following figure.



The additional differential equation given below (x_3) describes the concentration in the effect site; it has been coded and added to the differential equations. The second output equation has also been modified as indicated below. The model file **drm2.for** contains the modified equations needed to describe this effect site model.

$$\frac{dx_3}{dt} = K_{eo}(x_1 / V_c - x_3)$$

$$y_2 = \frac{E_{\max} x_3}{EC50 + x_3}$$

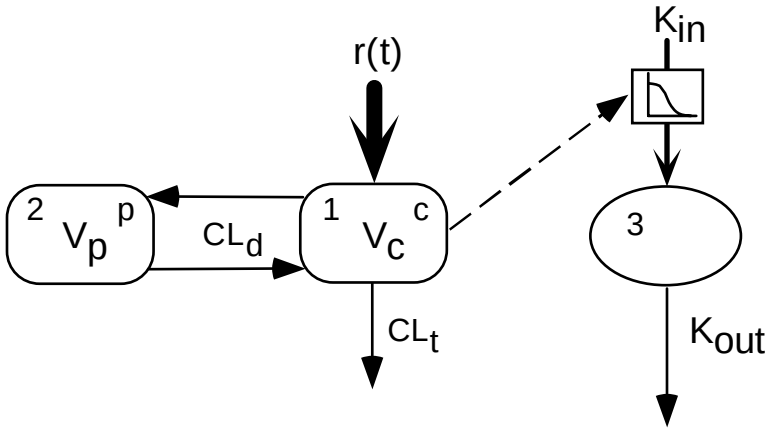
1. These equations have been coded and entered in the Model File **drm2.for**. Inspect this file in the Fortran editor.

2. Fit the model to the data stored in the file **drm.dat** (the same data used in Part 1 of this Case Study) using the maximum likelihood estimation option of ID, with initial values for model parameters as listed below; these values are also stored in the parameter file **drm2.prm**. Compare the ML estimates to those in the table below, along with AIC. Examine the model prediction summary table. View the graphs of the fitted model response.

Parameter	Initial Value	Estimate?	ML Estimate
CLt	6.0	Y	5.812
Vc	30.0	Y	27.91
CLd	12.0	Y	12.45
Vp	60.0	Y	60.93
Emax	100.0	Y	101.5
EC50	1.0	Y	0.9022
Keo	0.5	Y	0.4775
IC(1)	0.0	N	-
IC(2)	0.0	N	-
IC(3)	0.0	N	-
SD_{inter1}	0.05	N	-
SD_{slope1}	0.1	N	-
SD_{inter2}	2.5	N	-
SD_{slope2}	0.1	N	-
AIC	-	-	82.3

Case Study - Indirect Response PD Models

This case study involves parameter estimation using an indirect response model. Indirect response models (IRM), as introduced by Jusko, are used to model a drug's effect when the physiological, biochemical, immunological, etc. variable that the drug alters is itself under dynamic process control. The pharmacokinetic/pharmacodynamic IRM used in this case study is shown below. 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).



1. The following equations define the plasma concentration and response.

$$\frac{dx_1}{dt} = -(\frac{CLt}{Vc} + \frac{CLd}{Vc})x_1 + \frac{CLd}{Vp}x_2 + r(t)$$

$$\frac{dx_2}{dt} = \frac{CLd}{Vc}x_1 - \frac{CLd}{Vp}x_2$$

$$\frac{dx_3}{dt} = Kin(1 - \frac{x_1(t)/Vc}{IC50 + x_1(t)/Vc}) - \frac{Kin}{IC(3)}x_3(t)$$

$$y_1 = x_1/Vc$$

$$y_2 = x_3$$

To insure a return to the pre-drug control value of the drug response after the drug is cleared completely, *Kout* has been replaced by *Kin/IC(3*) in the above equations. View these equations in the Model File **irm.for**. in the Adapt editor.

The following system, variance and secondary parameters have been defined:

system		**variance**		**secondary**	
CLt	- P(1)	SD_{inter1}	- PV(1)	*Kel*	- PS(1)
Vc	- P(2)	SD_{slope1}	- PV(2)	*V*	- PS(2)
CLd	- P(3)	SD_{inter2}	- PV(3)	*Kcp*	- PS(3)
Vp	- P(4)	SD_{slope2}	- PV(4)	*Kpc*	- PS(4)
Kin	- P(5)			λ_1	- PS(5)
IC50	- P(6)			λ_2	- PS(6)
				$t_{1/2} - \lambda_1$	- PS(7)
				$t_{1/2} - \lambda_2$	- PS(8)
				Kout	- PS(9)

The parameters have the following units: *CL's* (L/hr^{-1}); *V's* (L); *Kin* (units/hr); *IC50* (μg/ml).

2. The data file **irm.dat** contains the dose regimen information along with measured values for plasma concentration and drug response, and the initial guesses for the parameters in the file **irm.prm**. Fit the model to the data stored in this file using the maximum likelihood estimation option of ID. Note that the initial value of the response variable (IC(3)) is also estimated. The table below shows the initial guesses for the parameters that are stored in the file **irm.prm** as well as which parameters are to be estimated. View all the results stored in the **run** file as well as the plots and confirm the results shown in the table below.

Parameter	Initial Value	Estimate?	ML Estimate
CLt	6.0	Y	6.040
Vc	30.0	Y	28.35
CLd	12.0	Y	12.10
Vp	60.0	Y	56.75
Kin	20.0	Y	22.34
IC50	0.5	Y	0.5036
IC(1)	0.0	N	-
IC(2)	0.0	N	-
IC(3)	100.0	Y	100.6
SD_{inter1}	0.0	N	-
SD_{slope1}	0.1	N	-
SD_{inter2}	10.	N	-
SD_{slope2}	0.0	N	-

POPULATION PK/PD MODELING

The Population Problem

- The Concept
- Notation
- Hierarchical Framework

Solution via Maximum Likelihood

- The Concept
- Simple Example
- The General Problem

POPULATION PK/PD MODELING

Some Basic Probability

- Random Variables
- Distribution of a Random Variable
- Expected Value
- Distribution of two Random Variables

The MLEM Algorithm

- Iterative Equations
- Conditional Mean/Covariance for Subject
- Sampling Methods
- Programs using the EM Algorithm

POPULATION PK/PD MODELING

ADAPT 5 Population Programs

- Population Model Definition
- Population Data File
- Model File for Population Analysis
- NPD Analysis
- STS Analysis
- ITS Analysis

The Population Problem

• Notation

- Model Equations (state space formulation)

$$\frac{dx_i(t)}{dt} = f_i(x_i(t), \alpha_i, r_i(t), t), \quad x_i(0) = c_i$$

$$y_i(t_{ji}) = h_i(x_i(t_{ji}), \alpha_i, r_i(t_{ji}), t_{ji}) + e_i(t_{ji}), \quad j = 1, \ldots m_i$$

$$i = 1, \ldots, N \quad \text{(subjects)}$$

- or <u>More Compactly</u>

$$\theta_i = [\alpha_i \quad c_i] \qquad \text{ith subject's parameters}$$

$$Y_i = h_i(\theta_i) + e_i \quad , \quad i = 1, \ldots, N$$

Measurements for the ith subject

Model for the ith subject

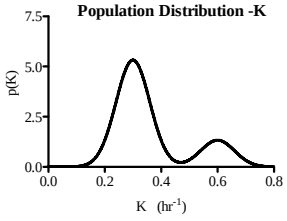
- The Parametric Population Problem

$\theta \rightarrow$ random vector with distribution $p(\theta)$

$p(\theta) = N(\mu, \Sigma)$ multivariate Normal

$p(\theta) = LN(\mu, \Sigma)$ multivariate lognormal

$p(\theta) = \sum w_k N(\mu_k, \Sigma_k)$ mixture of Normals



• Hierarchical Framework

Stage 1: *Individual Subject Variation (Intra-Individual)*

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

or $Y_i \mid \theta_i, \beta \sim N\left(h_i(\theta_i), G_i\left(h_i(\theta_i), \beta\right)\right), \quad i = 1, \ldots, N$

Stage 2: *Inter-Individual Variation*

$$\theta_i \sim N(\mu, \Sigma) \text{ or } LN(\mu, \Sigma) \equiv p(\theta \mid \mu, \Sigma)$$

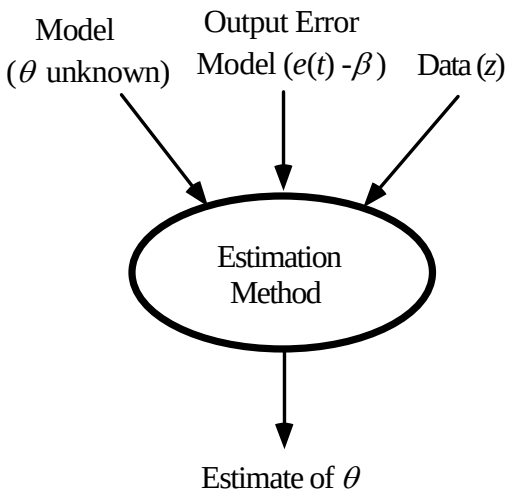
Want to Estimate:

$$\mu \quad \Sigma \quad \beta \quad \theta_i, i = 1, \ldots, N$$

Solution via Maximum Likelihood

• The Concept

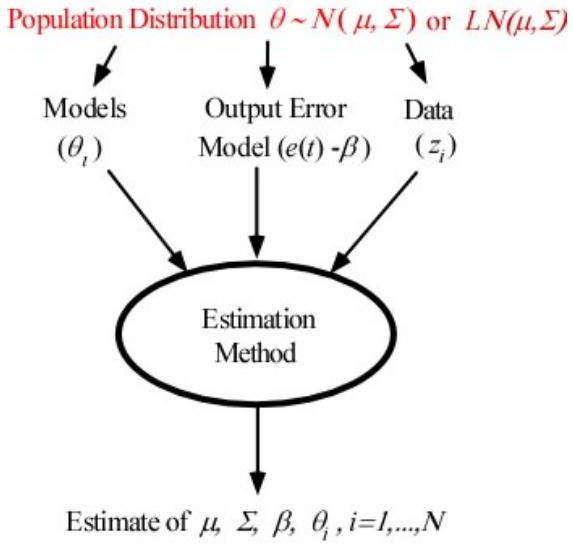
For the Individual



Solution via Maximum Likelihood

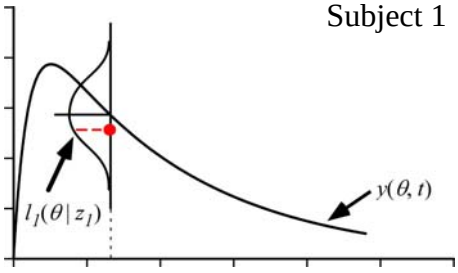
- The Concept

For the Population



- A Simple Example (one parameter, two subjects)

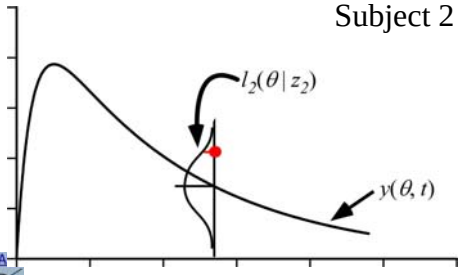
Subject 1



Likelihood Subject 1

$l_1(\theta|Y_1)$

Subject 2



Likelihood Subject 2

$l_2(\theta|Y_2)$

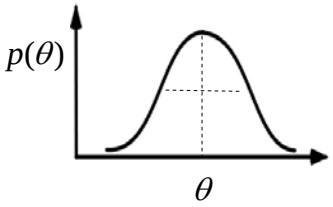
- The Overall Likelihood for both Subjects

$l_1(\theta|Y_1)l_2(\theta|Y_2)$ since errors are independent

- But θ is a Random Variable Defined by the Distribution

$$p(\theta) = N(\mu, \sigma^2)$$

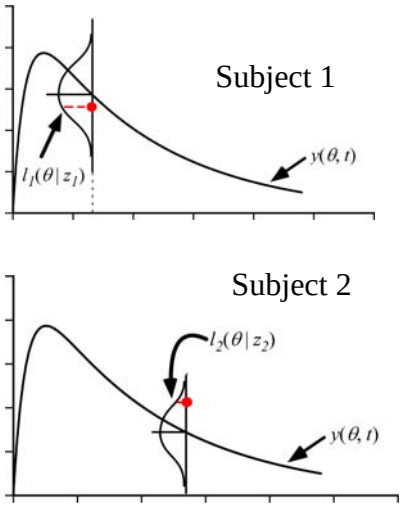
$$p(\theta|\mu,\sigma^2) \equiv p(\theta)$$



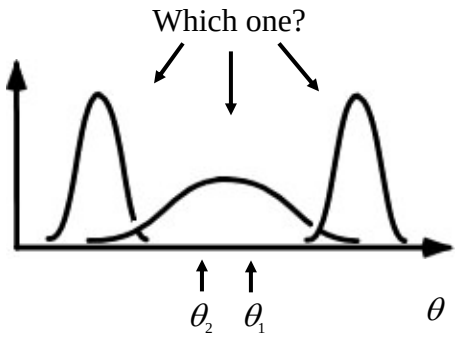
- The Estimation Problem is to find

μ and σ

- Relation Between μ, σ and $l_1(\theta|Y_1)l_2(\theta|Y_2)$



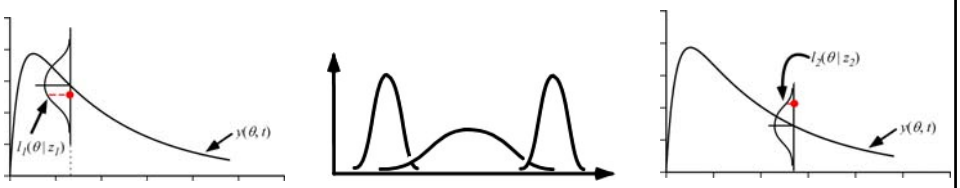
$$p(\theta|\mu,\sigma^2) = N(\mu,\sigma^2)$$



True

- The Average (Expected) Value of $l_1(\theta|Y_1)l_2(\theta|Y_2)$

$$\int l_1(\theta|Y_1)l_2(\theta|Y_2)p\left(\theta|\mu,\sigma^2\right)d\theta$$



pick $\mu^{(0)},\sigma^{(0)}$ sample $\theta_i = N\left(\mu^{(0)},\sigma^{(0)^2}\right)$ $\frac{1}{M}\sum_{i=1}^{M} l_1(\theta_i|Y_1)l_2(\theta_i|Y_2)$

pick $\mu^{(1)},\sigma^{(1)}$ sample $\theta_i = N\left(\mu^{(1)},\sigma^{(1)^2}\right)$ $\frac{1}{M}\sum_{i=1}^{M} l_1(\theta_i|Y_1)l_2(\theta_i|Y_2)$

want $\mu^{(k)},\sigma^{(k)}$ maximizes $\frac{1}{M}\sum_{i=1}^{M} l_1(\theta_i|Y_1)l_2(\theta_i|Y_2)$

- The General Problem

Overall Data Likelihood

$$L(\mu, \Sigma, \beta) = \prod_{i=1}^{N} \int l_i(Y_i \mid \theta, \beta)\, p(\theta \mid \mu, \Sigma) d\theta$$

Problem: Find μ, Σ, β to maximize $L(\mu, \Sigma, \beta)$

How?

1. Directly maximize: big nonlinear optimization, integration
2. Approximate likelihood (linearization - NONMEM)
3. EM algorithm: iterative solution to 2 simpler problems, plus sampling-based methods

Produces the Exact Maximum Likelihood Estimate

Some Basic Probability

Random Process: Any process whose possible results are known but whose *actual* results cannot be predicted with certainty in advance.

Random Variable (RV): Outcome of a random process.

Experiment: A procedure used to generate outcomes (or make measurements) from a random process.

- Random Variable - Discrete

Definition: RV that can take on only one of a finite set of values

Example 1: Outcome of a coin toss – H or T

Represent the RV by X and its value by x

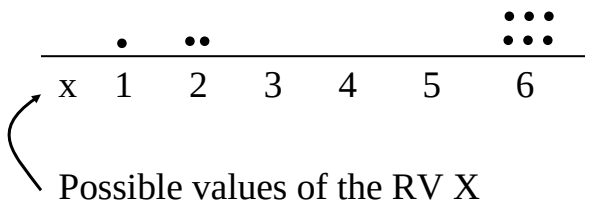
	H	T
x	1	2

Prob (X=x) ?

Prob (X=1)=1/2

Prob (X=2)=1/2

Example 2: Outcome of a rolling a die – RV # dots showing



Prob (X=x) ?

Prob (X=1)=1/6
Prob (X=2)=1/6
…
Prob (X=6)=1/6

- Random Variable - Continuous

Definition: RV that can take on any value in a range

Example 1: Body temperature of humans:

X in ^{0}C: min → 37^0 → max

Example 2: Detectable HIV1 virus in children born to infected mothers:

X in viral RNA copies/ml blood: 0 → max

Example 3: Forced expiratory volume in 1 sec (FEV1):

X in L: min → 2.5L → max

Degree of Randomness - Probability X is within a range

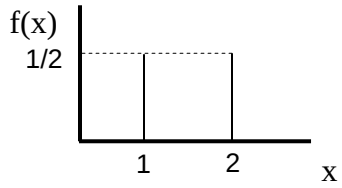
- Probability Density Function

Let X denote a discrete RV with values: $x_1, x_2, \ldots, x_k$

The Probability Density Function of X is denoted f(x), where

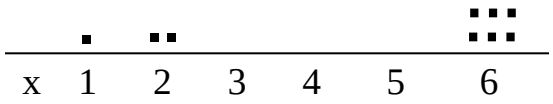
$$f(x) = \text{Prob}(X=x)$$

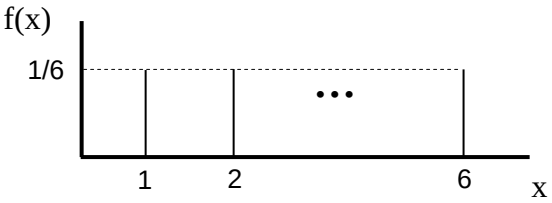
Example 1: Outcome of a coin toss – H ($x=x_1=1$) or T ($x=x_2=2$)



$$f(x) = 1/2, \quad x = 1,\ x = 2$$
$$0, \quad \text{elsewhere}$$

Example 2: Outcome of a rolling a die – # dots showing





$$f(x) = 1/6, \quad x = 1, 2, \ldots, 6$$
$$0, \quad \text{elsewhere}$$

- Probability Density Function - Continuous RV

How to describe the "degree of randomness" of a continuous RV X?

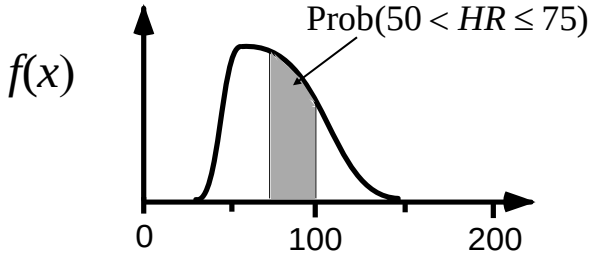
$f(x) \geq 0$ such that

$$\text{Prob}(a < X \leq b) = \int_a^b f(x)dx$$

Properties

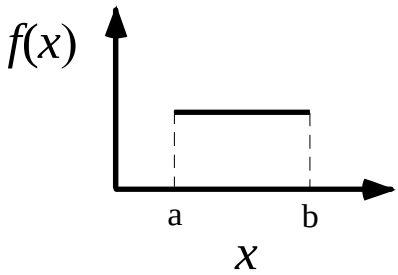
$f(x) \geq 0$

$\int_{-\infty}^{\infty} f(x)dx = 1$



1. Uniform Density

$$f(x) = \frac{1}{b-a}, \quad a < x \leq b, \quad 0 \text{ elsewhere}$$

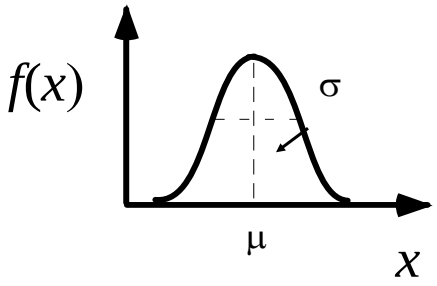


$X \sim U(a, b)$

Special case $X \sim U(0, 1)$ uniform 0, 1

2. Normal or Gaussian Density

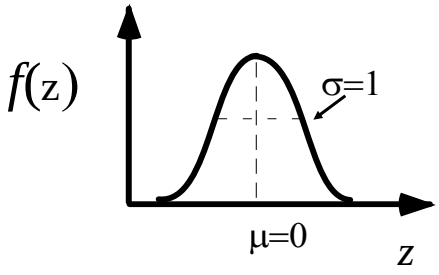
$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left(\frac{-(x-\mu)^2}{2\sigma^2} \right)$$



$$X \sim N(\mu, \sigma^2)$$

3. Standard Normal Density (special case)

$$f(z) = \frac{1}{\sqrt{2\pi}} \exp\left(\frac{-(z)^2}{2} \right) \qquad \mu = 0 \quad \sigma^2 = 1$$



$$Z \sim N(0, 1)$$

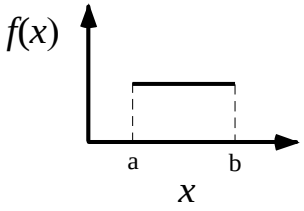
- Expected Value

Definition:

$$X \sim f(x) \qquad E[X] = \int_{-\infty}^{\infty} x f(x) dx \equiv \mu$$

Example:

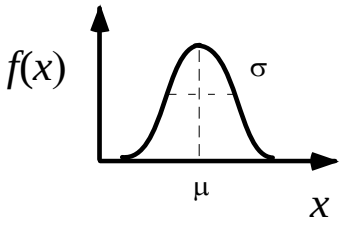
$$f(x) = \frac{1}{b-a}, \quad a < x \le b, \quad 0 \text{ elsewhere}$$



$$E[X] = \int_a^b x\left(\frac{1}{b-a}\right)dx = \left(\frac{1}{b-a}\right)\frac{x^2}{2}\Big|_a^b = \frac{a+b}{2}$$

Example:

$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left(\frac{-(x-\mu)^2}{2\sigma^2}\right)$$



$$E[X] = \mu$$

In general:

$$E[g(x)] = \int_{-\infty}^{\infty} g(x) f(x) dx$$

Example:

$$y = g(x) = a + bx$$

$$E[y] = \int_{-\infty}^{\infty} g(x) f(x) dx = \int_{-\infty}^{\infty} (a + bx) f(x) dx$$

$$= a \int_{-\infty}^{\infty} f(x) dx + b \int_{-\infty}^{\infty} x f(x) dx$$

$$= a + bE[X]$$

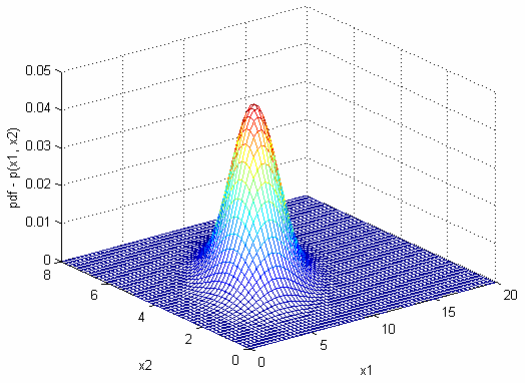
$$\mu_y = a + b\mu_x$$

Also: $\sigma_y = b\sigma_x$

- Distribution of Two Random Variables

RV: X_1 and X_2 – p.d.f. $f(x_1, x_2)$

1. Bivariate Normal $f(x_1, x_2) = N(\mu, \Sigma)$



$$\mu = \begin{bmatrix} \mu_1 \\ \mu_2 \end{bmatrix}, \quad \Sigma = \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{bmatrix}$$

$$\rho = \frac{\sigma_{12}}{\sigma_1 \sigma_2}$$

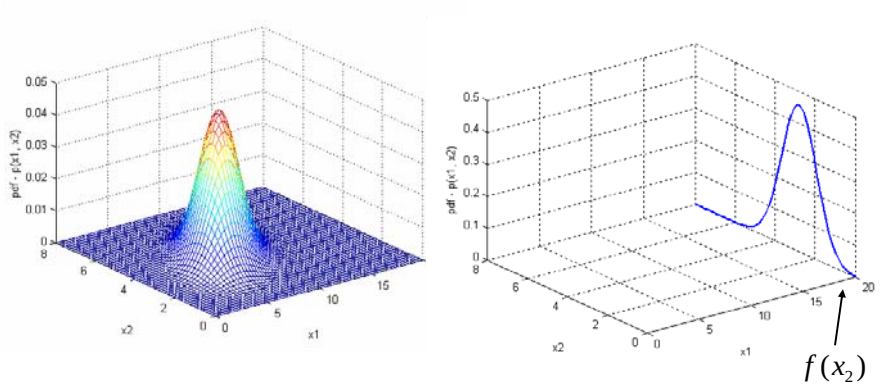
If $\rho = 0$ then

X_1 and X_2 are independent

$f(x_1, x_2) = f(x_1) f(x_2)$

$$f(x_1, x_2) = \frac{1}{\sqrt{2\pi}\,|\Sigma|^{1/2}} \exp\left(-(x-\mu)^T \Sigma^{-1} (x-\mu)/2\right)$$

2. Marginal Density (Distribution)



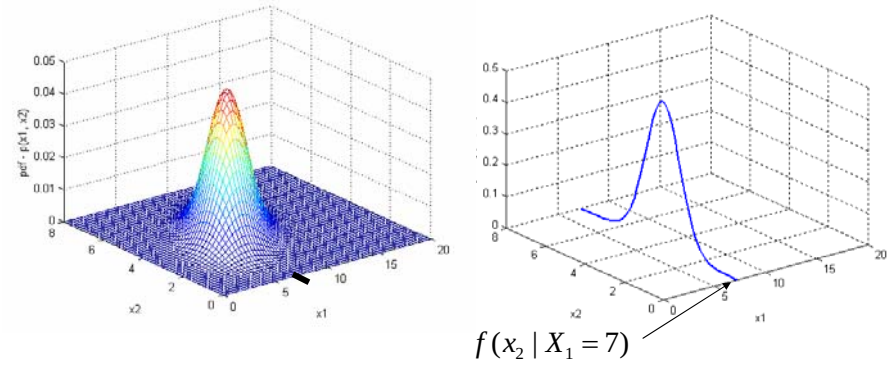
$f(x_2)$

if $f(x_1, x_2) = N(\mu, \Sigma)$, then $f(x_1) = N(\mu_1, \sigma_1^2)$

and $f(x_2) = N(\mu_2, \sigma_2^2)$

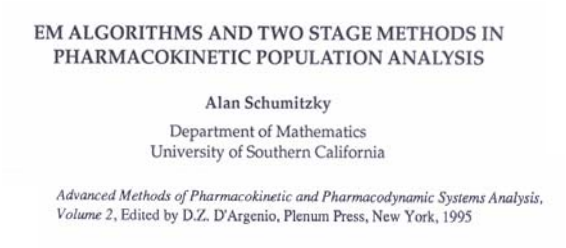
3. Conditional Density (Distribution)

$f(x_1 \mid X_2 = x_2)$ and $f(x_2 \mid X_1 = x_1)$



$f(x_2 \mid X_1 = 7)$

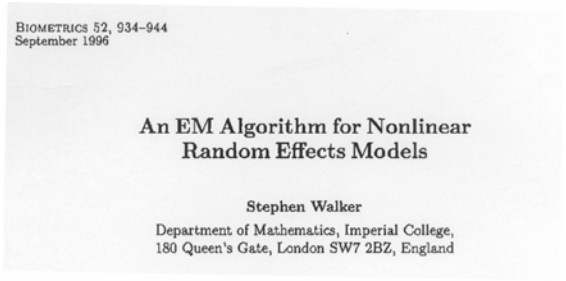
The MLEM Algorithm



EM ALGORITHMS AND TWO STAGE METHODS IN PHARMACOKINETIC POPULATION ANALYSIS

Alan Schumitzky
Department of Mathematics
University of Southern California

Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis, Volume 2, Edited by D.Z. D'Argenio, Plenum Press, New York, 1995



BIOMETRICS 52, 934–944
September 1996

An EM Algorithm for Nonlinear Random Effects Models

Stephen Walker
Department of Mathematics, Imperial College,
180 Queen's Gate, London SW7 2BZ, England

- The Iterative Equations

  - Initialization

    initial guesses: $\mu^{(0)}$ $\Sigma^{(0)}$ $\beta^{(0)}$ $\theta_i^{(0)}$ $k = 0$

  - Stage 1 – Estimation (E Step)

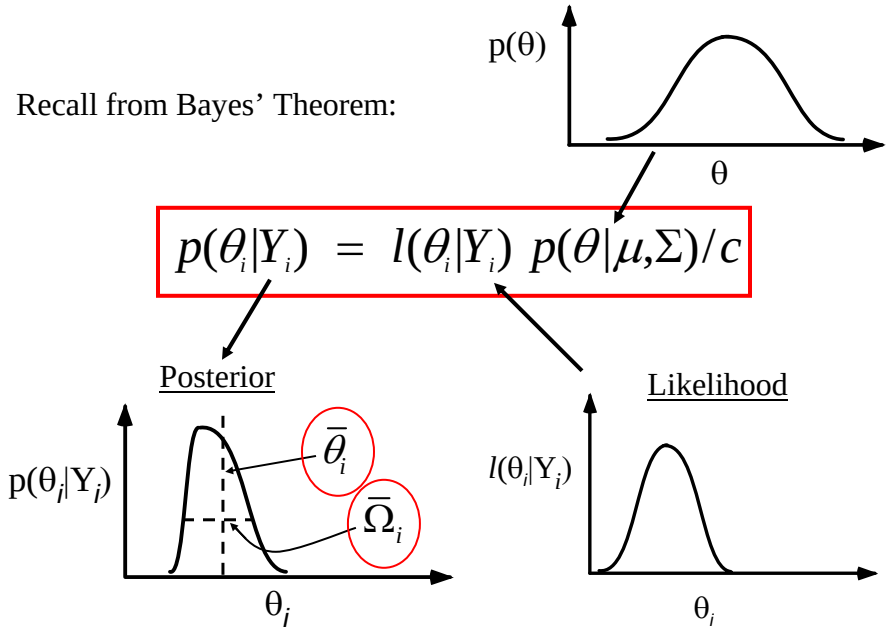
Conditional Mean for each subject

$$\bar{\theta}_i^{(k)} = E\left[\theta \mid Y_i, \mu^{(k)}, \Sigma^{(k)}, \beta^{(k)}\right]$$

Conditional Covariance for each subject

$$\bar{\Omega}_i^{(k)} = E\left[\left(\theta - \bar{\theta}_i^{(k)}\right)\left(\theta - \bar{\theta}_i^{(k)}\right)^T \mid Y_i, \mu^{(k)}, \Sigma^{(k)}, \beta^{(k)}\right]$$

Recall from Bayes' Theorem:



- Stage 2 – Maximization (M Step)

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

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

$$\beta^{(k+1)} = \beta^{(k)} - H^{-1}\frac{\partial \log L\left(\mu^{(k)}, \Sigma^{(k)}, \beta^{(k)}\right)}{\partial \beta}$$

Repeat Steps 1 and 2

• EM Algorithm Guarantees

$$\mu^{(k)} \quad \Sigma^{(k)} \quad \beta^{(k)},\ k = 0,\ldots$$

maximizes

$$L(\mu,\ \Sigma, \beta) = \prod_{i=1}^{N} \int l_i(Y_i \mid \theta, \beta)\, p(\theta \mid \mu, \Sigma) d\theta$$

(at least local solution)

• Conditional Mean and Covariance for Each Subject (<u>hard to calculate</u>)

The conditional mean $\bar{\theta}_i^{(k)}$ and conditional covariance $\bar{\Omega}_i^{(k)}$ for the ith subject at the kth iteration are given by:

$$\bar{\theta}_i^{(k)} = E\left[\theta \mid Y_i, \mu^{(k)}, \Sigma^{(k)}, \beta^{(k)}\right]$$

$$\bar{\Omega}_i^{(k)} = E\left[\left(\theta - \bar{\theta}_i^{(k)}\right)\left(\theta - \bar{\theta}_i^{(k)}\right)^T \mid Y_i, \mu^{(k)}, \Sigma^{(k)}, \beta^{(k)}\right]$$

The conditional density of θ is:

$$p(\theta \mid Y_i, \mu, \Sigma, \beta) = \frac{p_i(Y_i \mid \theta, \beta)\, p(\theta \mid \mu, \Sigma)}{\int p_i(Y_i \mid \theta, \beta)\, p(\theta \mid \mu, \Sigma) d\theta}$$

- Sampling Based Methods used to Calculate Conditional Means and Variances

  - Densities and Samples

$$p(\theta), \quad \theta_i, \; i = 1, \ldots$$

Densities ⟷ Samples from Densities

- Given a sample can approx. recreate a density (e.g., histogram, moments (e.g. mean), etc.)

- Update a sample from $p(\theta)$ to a sample from $p(\theta \mid Y)$ through the likelihood function $l(\theta \mid Y)$

- Monte Carlo Sampling

$$p(\theta \mid Y) = \frac{l(\theta \mid Y)\, p(\theta)}{\int l(\theta \mid Y)\, p(\theta) d\theta}$$

1. **Sample** $\theta_i, \; i = 1, \ldots, n,$ **from** $p(\theta)$
2. **Calculate** $l(\theta_i \mid Y), \; i = 1, \ldots, n$
3. **Calculate** $q_i = \dfrac{l(\theta_i \mid Y)}{\sum_{i=1}^{n} l(\theta_i \mid Y)}, \; i = 1, \ldots, n$
4. **Select** θ **from the discrete distribtion** $\{\theta_1, \ldots, \theta_n\}$ **placing mass** q_i **on** θ_i

$$\theta \text{ approx.} \sim p(\theta \mid Y) \; (n \to \infty)$$

- Standard Errors also Calculated for the Following:

$$\mu \quad \Sigma \quad \beta$$

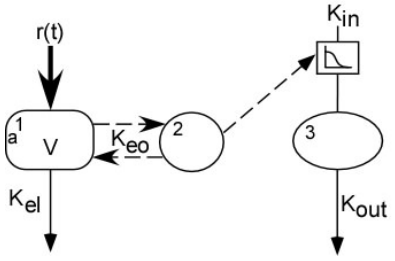
$$\theta_i \quad h_i(\theta_i), \quad i = 1, \ldots, N$$

- Programs Using the EM Algorithm for Pop PK/PD
  - ADAPT 5
  - S-ADAPT (Bob Bauer - distributed via BMSR)
  - MONOLIX (Marc Lavielle, Univ. Paris) – Stochastic EM
  - PDx-MCPEM (Globomax/Icon)

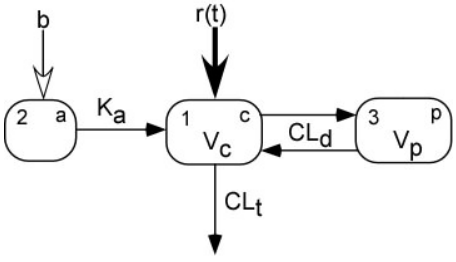
ADAPT 5 Population Programs

- Population Model Definition
  - Define a composite model for all subjects.
  - Allows different model and bolus inputs, as well as different measured outputs for each subject.

Plasma or response measurements



Oral or IV dosing



- Population Data File
  - collection of individual subject data files

```
Subject1
   0
   1
   1
    0.000     100.000000
              1
              3
    0.100       7.807446
    0.250       7.370744
    0.500       7.320860
Subject2
   0
   1
   1
    0.000      40.000000
              1
              4
    1.000      16.049698
    2.000      13.047071
    4.000       7.723986
    6.000       4.983869

 ...
```


- Population Data File - Example
  - Subject 1 – plasma only
  - Subject 2 – response only

```
Subject1
   0
   1
   1
    0.000     100.000000
              2
              3
    0.100    7.807446  -1
    0.250    7.370744  -1
    0.500    7.320860  -1
Subject2
   0
   1
   1
    0.000      40.000000
              2
              4
    1.000  -1  16.049698
    2.000  -1  13.047071
    4.000  -1   7.723986
    6.000  -1   4.983869

 ...
```

- Population Data File - Example
  - Subject 1 – IV infusion
  - Subject 2 – Oral dose as bolus

```
Subject1
   1
   0
   2
    0.000      100.000000
    1.000        0.0
           1
           3
    0.100        7.807446
    0.250        7.370744
    0.500        7.320860
Subject2
   0
   1
   1
    0.000       40.000000
           1
           4
    1.000       16.049698
    2.000       13.047071
    4.000        7.723986
    6.000        4.983869

 ...
```



```
C#########################################################################C
        Subroutine POPINIT(PmeanI,ICmeanI,PcovI,ICcovI, PCI)
C  Initial parameter values for population program parameters (ITS,MLEM)
         ...
CC
C-------------------------------------------------------------------------C
C  Enter Initial Values for Population Means                              C
C          {  e.g. PmeanI(1) = 10.0    }                                  C
C----c--------------------------------------------------------------------C
```

Enter Initial Values for Population Means Here

```
CC
C-------------------------------------------------------------------------C
C   Enter Initial Values for Pop. Covariance Matrix (Lower Triang.)       C
C         {  e.g. PcovI(2,1) = 0.25    }                                 C
C----c--------------------------------------------------------------------C
```

Enter Initial Values for Pop. Covariance Matrix Elements Here

```
CC
C-------------------------------------------------------------------------C
C   Enter Values for Covariate Model Parameters                           C
C         {  e.g. PCI(1) = 2.0    }                                       C
C----c--------------------------------------------------------------------C
```

Enter Initial Values for Covariate Model Parameters Here

```
CC
C-------------------------------------------------------------------------C
```

• NPD Analysis

$$Y_i = h_i(\theta_i) + e_i \quad , \quad i = 1, \ldots, N$$ (N - # subj. or exp.)

$\theta_i = \theta$ Same for each subject/experiment

and no model for θ

- Can use WLS, ML or MAP as in Individual Analysis

- Different Designs/Repeated Experiments

• STS Analysis

$$Y_i = h_i(\theta_i) + e_i \quad , \quad i = 1, \ldots, N$$ (N - # subj. or exp.)

θ_i Different for each subject/experiment

and no model for θ

- Can use WLS, ML or MAP for each subject as in Individual Analysis

$$\bar{\theta} = \frac{1}{N}\sum_{i=1}^{N}\theta_i \qquad \text{cov}_\theta = \frac{1}{N}\sum_{i=1}^{N}\left\{\left(\theta_i - \bar{\theta}\right)\left(\theta_i - \bar{\theta}\right)^T\right\}$$

- Calculating μ and Σ in a Standard Two Stage Analysis

Example 1: One parameter case – K

$$K_1,\ K_2,\ K_3,\ldots$$

$$\mu = \bar{K} = E(K) = \frac{1}{N}\sum_i K_i$$

$$\Sigma = \sigma_K^2 = \mathrm{var}(K) = \frac{1}{N-1}\sum_i (K_i - \bar{K})^2$$

Example 2: Two parameter case – K and V

$$(K_1,V_1),\ (K_2,V_2),\ (K_3,V_3),\ldots$$

$$\bar{K} = \frac{1}{N}\sum_i K_i \qquad \bar{V} = \frac{1}{N}\sum_i V_i$$

$$\sigma_K^2 = \frac{1}{N}\sum_i (K_i - \bar{K})^2 \quad \sigma_V^2 = \frac{1}{N}\sum_i (V_i - \bar{V})^2 \quad \sigma_{KV} = \frac{1}{N}\sum_i (K_i - \bar{K})(V_i - \bar{V})$$

$$\mu = \begin{bmatrix} \bar{K} \\ \bar{V} \end{bmatrix} \qquad \Sigma = \begin{bmatrix} \sigma_K^2 & \sigma_{KV} \\ \sigma_{KV} & \sigma_V^2 \end{bmatrix} \qquad \text{(Also } \rho = \frac{\sigma_{KV}}{\sigma_K^2 \sigma_V^2}\text{)}$$

Calculations via Excel, for example.

• ITS Analysis

Stage 1: *Individual Subject Variation (Intra-Individual)*

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

Stage 2: *Inter-Individual Variation*

$$\theta_i \sim N(\mu, \Sigma)$$

Want to Estimate:

$$\mu \quad \Sigma \quad \beta \quad \theta_i, i = 1, \ldots, N$$

ITS Algorithm

- Initialization

initial guesses: $\mu^{(0)} \quad \Sigma^{(0)} \quad \beta^{(0)} \quad \theta_i = \theta^{(0)}, i = 1, \ldots, N$

$k = 0$

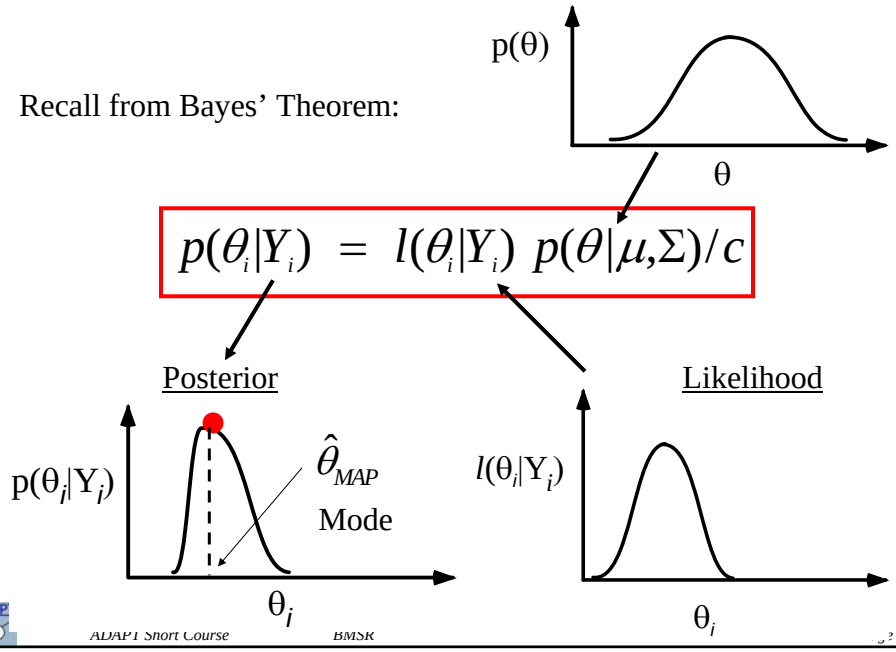
- Stage 1 – Estimation (Individual MAP Estimates)

MAP estimate for each subject $\hat{\theta}_i^{(k)}, i = 1, \ldots, N$

Approx. SE for each subject $\hat{\Omega}_i^{(k)}, i = 1, \ldots, N$

MAP Estimate and Approximate Standard Error of Estimate

Recall from Bayes' Theorem:



- Stage 2 – Updating

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

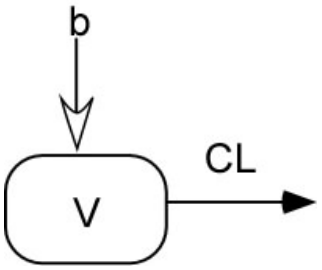
$$\Sigma^{(k+1)} = \frac{1}{N}\sum_{i=1}^{N}\left\{\left(\hat{\theta}_i^{(k)} - \mu^{(k+1)}\right)\left(\hat{\theta}_i^{(k)} - \mu^{(k+1)}\right)^T + \hat{\Omega}_i^{(k)}\right\}$$

$$\beta^{(k+1)} = \arg\max_{\beta}\prod_{i=1}^{N} p_i(Y_i \mid \hat{\theta}_i^k, \beta)$$

Repeat Steps 1 and 2

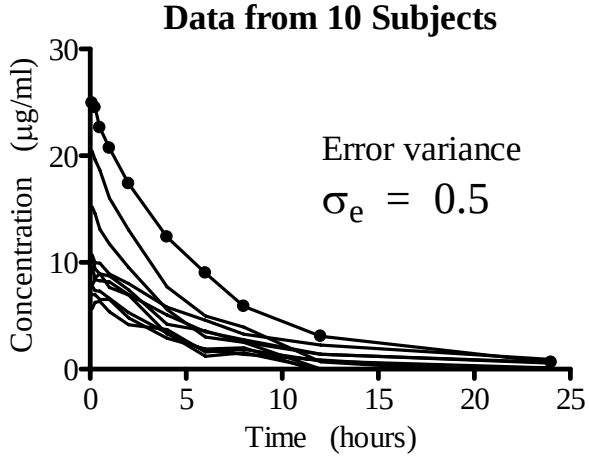
Case Study – The ADAPT Population Programs

This case study is intended to familiarize you with the ADAPT population programs MLEM, ITS, STS and NPD. A simple two parameter, one compartment, IV bolus PK model is used in this example, along with a Normal distribution model for the population parameters.



$$(Cl, V) \sim N(\mu, \Sigma)$$

	μ	σ	$\sigma_{CL,V}$
$CL\ (L/hr)$	2.0	0.6 (30%)	$1.44\,(r = 0.8)$
$V\ (L)$	10.0	3.0 (30%)	



Part 1 – The NPD Program

While naïve pooled data (NPD) analysis is not a population modeling approach (all the data are assumed to arise from one set of model parameters – no inter subject variability), it is useful to apply it to the data set in this example. The model, data and parameters are contained in the files **x.for**, **x.dat** and **x.prm**.

The analytic solution of the PK model is coded in the file **x.for** (subroutine OUTPUT). Also inspect the data file **x.dat** to see the format of a population data file.

Perform a naïve pooled data (NPD) analysis using the maximum likelihood estimation option (enter **xnpd.run** as the name of the run file when prompted). The table below shows the initial guesses for the parameters that are stored in the file **x.prm** as well as which parameters are to be estimated. View all the results stored in the **run** file as well as the plots and confirm the results shown in the table below.

Parameter	Initial Value	Estimate?	ML Estimate
CL	2.0	Y	1.620
V	10.0	Y	8.178
Sigma	0.5	Y	3.847

As expected all of the between subject variability in the data is attributed to output error variance, resulting in an estimate of 3.8 while the true value was 0.5.

Part 2 – The STS Program

Next, perform a standard two stage analysis (STS) analysis using the maximum likelihood estimation option for individual subject estimation (enter **xits.run** as the name of the run file when prompted). Again use the model, data and parameters contained in the files **x.for**, **x.dat** and **x.prm**. View the results stored in the **run** file and confirm the results shown in the table below taken from the SUMMARY OF PARAMETER ESTIMATES found at the end of the run file.

```
      ----- SUMMARY OF PARAMETER ESTIMATES -----
                 ....
            --- A. System Parameters ---

Parameter     Mean      Median     Std.Dev.    Min        Max
 CL           1.926      1.719     0.7888     0.7064     2.948
 V            9.784      10.03      3.773      3.977     15.73

             --- B. Variance Model Parameters ---

Parameter     Mean      Median     Std.Dev.    Min        Max
 Sigma       0.3684     0.5489     0.6467E-01 0.2547     0.4718
```

The standard two stage approach will generally overestimate intersubject variability. In this example the overestimation is small, can you explain why this is the case? Inspect the results present in the **xits.ind** and **xits.rsd** files.

Part 3 – The MLEM Program

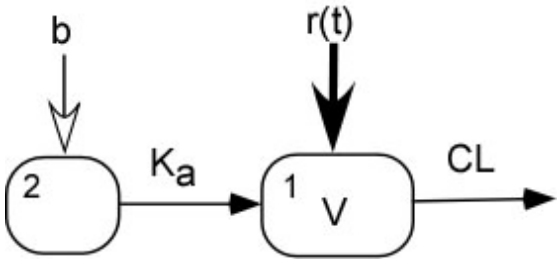
Initial values (guesses) for all population mean, population covariance and error variance parameters are entered in the POPINIT subroutine in the model file **x.for** (view this section of the model file).

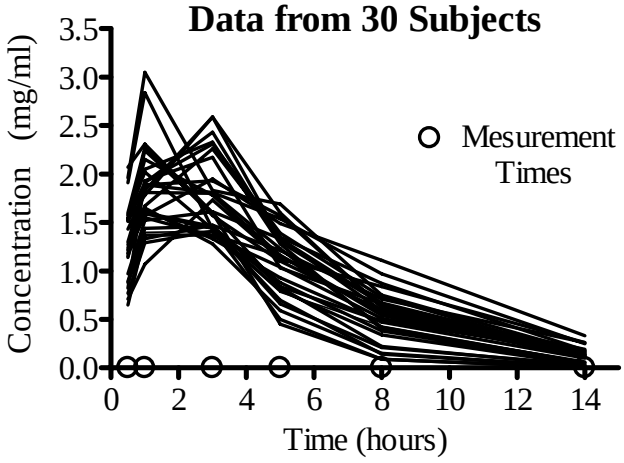
Perform a population maximum likelihood (MLEM) analysis using the model, data and parameters contained in the files **x.for**, **x.dat** and **x.prm** (enter **x.run** as the name of the run file when prompted). Select a Normal parameter distribution model with a Full covariance. Use 1000 samples/EM iteration and perform 15 EM iterations. View the results stored in the **x.run** file and confirm the results shown in the table below taken from the MLEM FINAL POPULATION PARAMETER ESTIMATES found at the end of the run file.

```
     ----- MLEM FINAL POPULATION PARAMETER ESTIMATES -----
                          ...

       --- A. Population Mean & Population Standard Deviation ---

Parameter     Mean        %RSE         Std.Dev.   SD as CV%     %RSE
 CL           1.92        16.0         0.738        38.4        55.9
 V            9.79        13.6          3.57        36.5        45.1

       --- B. Full Population Covariance of Estimated Parameters ---

 As Covariance Matrix:

          CL        V
CL        0.544
V          2.29      12.8

 As Correlation Matrix:

          CL        V
CL          1.00
V           0.87      1.00

 Standard Errors of Estimated Covariance Matrix:

          CL        V
CL        0.609
V          2.27      11.5

       --- D. Error Variance Model Parameters ---
```

Case Study – The MLEM Program

This case study uses the MLEM program to perform a population analysis of data from 30 subjects using a one compartment, first order absorption model (1COMPCL library model file is used).





The 1COMPCL library model file has been copied and renamed **mlem.for** for use in this example. Initial values (guesses) for all population mean, population covariance and error variance parameters are entered in the POPINIT subroutine in the model file **mlem.for** (view this section of the model file using the Fortran editor).

Perform a population maximum likelihood (MLEM) analysis using the model, data and parameters contained in the files **mlem.for**, **mlem.dat** and **mlem.prm** (enter **mlem.run** as the name of the run file when prompted).

The bolus input is into compartment 2. Estimate those parameters indicated in the following table.

Parameter	Initial Value	Estimate?
CLt (L/hr)	8.0	Y
Vc (L)	30.0	Y
Ka (hr^{-1})	1.0	Y
IC(1)	0.0	N
IC(2)	0.0	N
SDinter	0.0	N
SDslope	0.1	Y

Do Not Fix non estimated parameters, and select a Lognormal parameter distribution model with a Full covariance. Use 1000 samples/EM iteration and perform 30 EM iterations. View the results stored in the **mlem.run** file and confirm the results shown in the table below taken from the MLEM FINAL POPULATION PARAMETER ESTIMATES found at the end of the run file.

```
     ----- MLEM FINAL POPULATION PARAMETER ESTIMATES -----

Sun Jun 29 12:41:24 2008

Data file name: D:\test\mlem.dat

Model:  MLEM.FOR: - 1 comp. pop. example

Number of data sets analyzed successfully:    30

Importance Sampler with number samples/iteration:    1000

Total number of EM iterations:   30

Lognormal distribution option

Negative Log Likelihood:   -32.8502

Model Selection Criteria
 AIC:       -45.7003
 BIC:       -13.7707
```

```
       --- A. Population Mean & Population Standard Deviation ---

 Parameter     Mean        %RSE         Std.Dev.   SD as CV%     %RSE
  CLt          8.39        5.27          2.04        24.3         29.2
  Vc           30.1        7.17          5.98        19.9         48.9
  Ka           1.02        6.77         0.146        14.3         100
  IC(   1)     0.00      Not estimated
  IC(   2)     0.00      Not estimated

       --- B. Full Population Covariance of Estimated Parameters ---

  As Covariance Matrix:

           CLt       Vc        Ka
 CLt        4.17
 Vc        -1.51      35.7
 Ka        -.130E-02 -.321     0.212E-01

  As Covariance Matrix for ln(parameters):

           CLt       Vc        Ka
 CLt       0.592E-01
 Vc        -.598E-02 0.395E-01
 Ka        -.151E-03 -.104E-01 0.203E-01

  As Correlation Matrix:

           CLt       Vc        Ka
 CLt         1.00
 Vc         -0.12      1.00
 Ka          0.00     -0.37      1.00

  Standard Errors of Estimated Covariance Matrix:

           CLt       Vc        Ka
 CLt        2.43
 Vc         5.04      34.9
 Ka        0.227     0.645     0.424E-01

       --- D. Error Variance Model Parameters ---

Parameter     Estimate    %RSE
  SDslope     0.181       6.08
  SDinter      0.00      Not estimated

       --- E. Secondary Parameters: Pop. Mean & Pop. Std. Dev. ---

 Parameter     Mean       Std.Dev.
  Kel         0.279      0.928E-01
  LAM1        0.279      0.928E-01
  t1/2-LAM1    2.49      0.827
```

Absorption/Disposition Modeling

Rate and Extent of Bioavailability

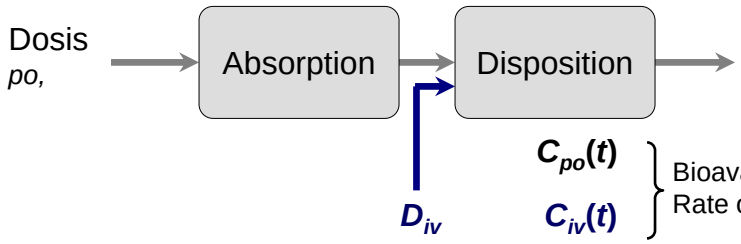
- Why? To avoid biased estimates due to model misspecification

  Determination of the absorption kinetics

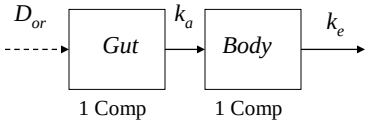
- Maximum absorption rate is not achieved instantaneously

- Case study: Extended release product

Identifiability



Simplification:



reality

$$C_{iv}(t) = \sum_{i=1}^{3} B_i e^{-\lambda_i t}$$

$$Input(t) = I_0 e^{-k_a t} \qquad C_{iv}(t) = C_0 e^{-\lambda t}$$

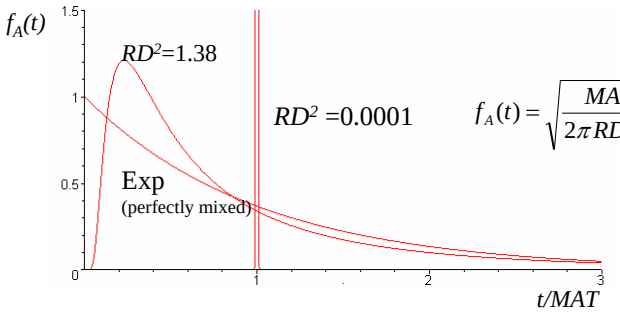
unrealistic

$$C_{or}(t) = B(e^{-\lambda t} - e^{-k_a t})$$

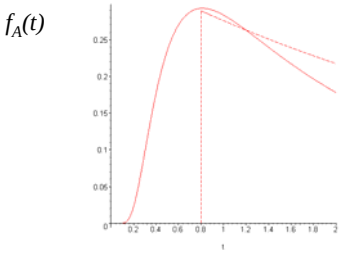
$k_a \neq$ real absorption rate constant!

$\lambda \neq k_e$!

Absorption Rate: Inverse Gaussian Density



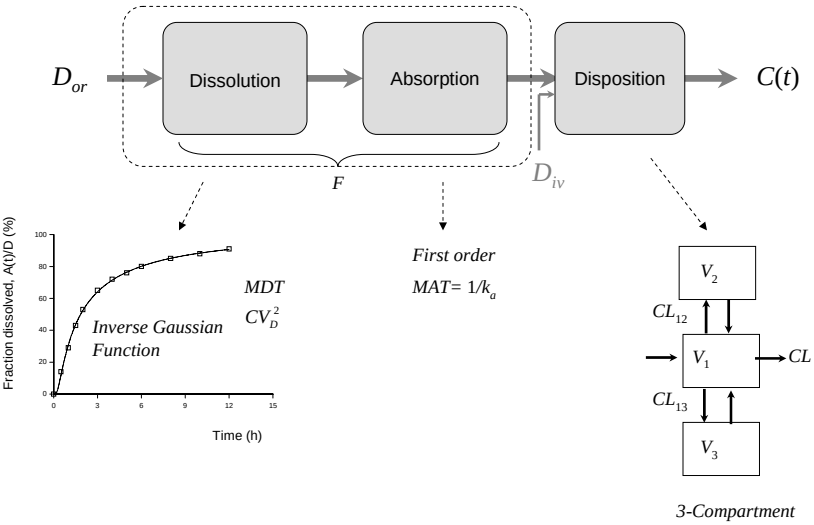
$$f_A(t) = \sqrt{\frac{MAT}{2\pi RD^2 t^3}} \exp\left[-\frac{(t-MAT)^2}{2RD^2 MATt}\right]$$

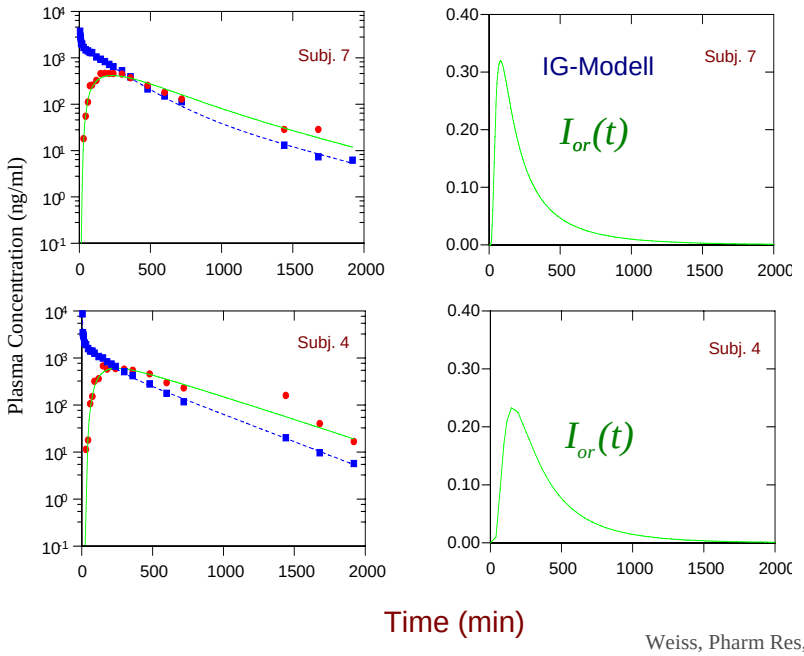


$MAT=5$

$RD^2 = 2$

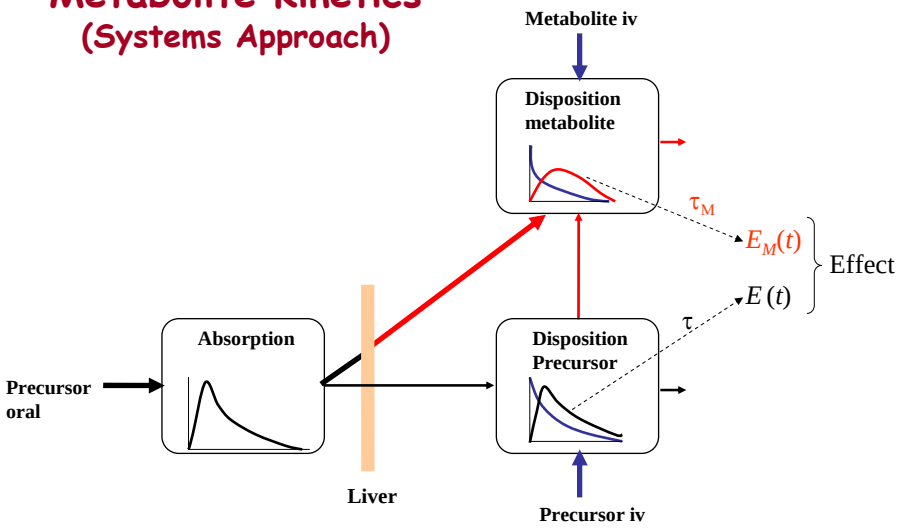
Subsystems





Weiss, Pharm Res, 1996

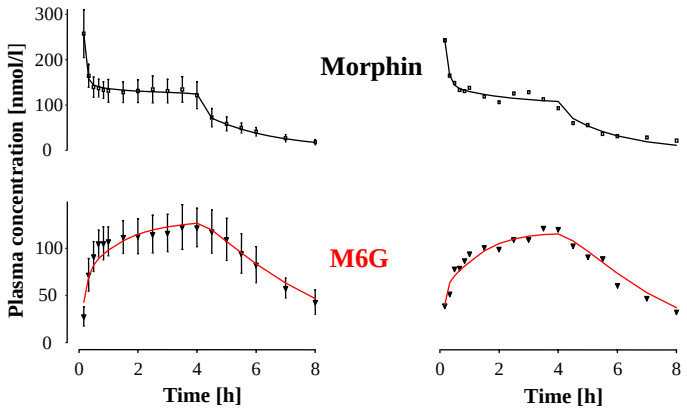
Metabolite Kinetics
(Systems Approach)



Weiss, Drug Metab Dispos, 1998

Modelling Metabolite Kinetics, D_{iv}

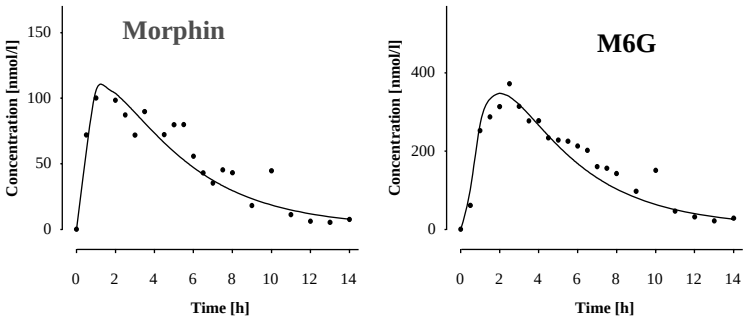
Formation of morphine-6-glucuronide (M6G) from morphin



Lötsch et al, Anesthesiology, 1999

Modelling Metabolite Kinetics, D_{po}

Morphin 90 mg sustained release tablet (MST$^{®}$)



Lötsch et al, Anesthesiology, 1999

References:

Weiss M. A novel extravascular input function for the assessment of drug absorption in bioavailability studies. *Pharm Res* 13: 1547-1553 (1996)

Wang J, Weiss M, D'Argenio DZ. A note on population analysis of dissolution-absorption models using the inverse Gaussian function. *J Clin Pharmacol* 48: 719-725 (2008)

Lötsch J, Weiss M, Ahne G, Kobal G, Geisslinger G. Pharmacokinetic modeling of M6G formation after oral administration of morphine in healthy volunteers. *Anesthesiology* 90: 1026-1038 (1999)

Weiss M. Analysis of metabolite formation pharmacokinetics after intravenous and oral administration of the parent drug using inverse Laplace transformation. *Drug Metab Disp* 26: 562-565 (1998)

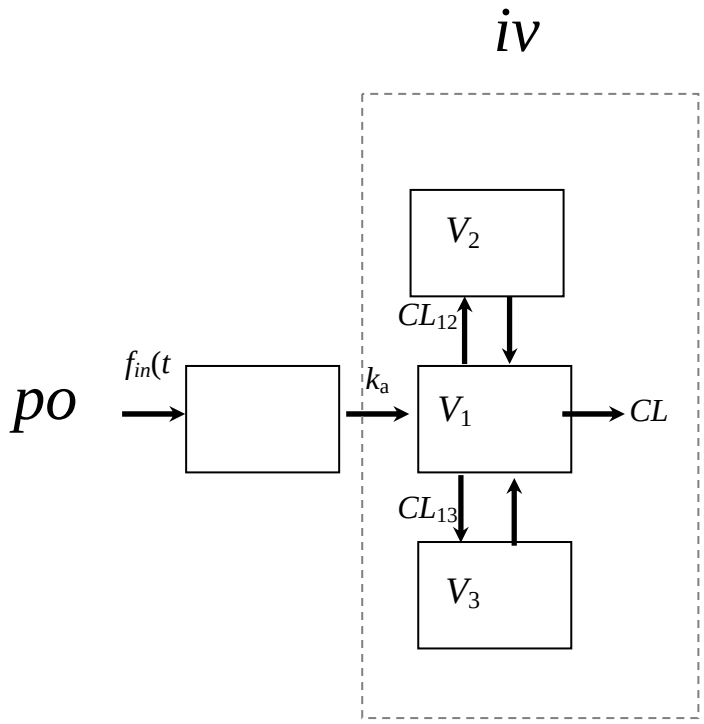
Case Study – Population Analysis of Dissolution-Absorption Models

The method is applied to data of an oral extended-release product investigated together with an intravenous reference in a bioavailability study (Wang, Weiss & D'Argenio, 2008).

Model equations are coded in Model File **absdis.for**.

Y(1): = X(1) Oral concentration-time curve

X(1) Concentration in central compartment (3-compartment disposition model + 1 absorption compartment) with input function (dissolution rate), $f_{in}(t)$ to the absorption compartment:



4-Compartment model (differential equations) in Library
+ dissolution rate function $f_{in}(t)$ as input in absorption compartment

```
if(t .eq. 0.0) then
      fAofT = 0.0
     else
     fAofT = F*10000000.0*dsqrt(MIT/(2*pi*CVA2*t**3))*
    x         dexp(-(t-MIT)**2/(2.0D0*CVA2*MIT*t))
     endif
…….

XP(4) = - X(4)/P(10) + fAofT
```

Parameters:

PSym(1) = 'CLt'	CL	Total clearance
PSym(2) = 'V1'	V_1	Volume of sampling compartment
PSym(3) = 'CL2'	CL_{12}	
PSym(4) = 'V2'	V_2	
PSym(5) = 'CL3'	CL_{13}	
PSym(6) = 'V3'	V_3	
PSym(7) = 'MIT'	MIT	Mean input time (mean dissolution time)
PSym(8) = 'CVA2'	RD^2	Relative dispersion of input time
PSym(9) = 'F'	F	Bioavailability
PSym(10) = 'MAT'	MAT	Mean absorption time ($1/k_a$)

Parameter estimation:

1. Fit of iv data to estimate Psym(1) - Psym(6)
2. Fix Psym(1) - Psym(6) and fit po data to estimate Psym(7) - Psym(8)

Secondary Parameter:

1. The time at which the input (dissolution) rate attains its maximum value (mode of the inverse Gaussian)

$$t_{I,\max} = MIT\left[\sqrt{1+\frac{9}{4}RD^4} - \frac{3}{2}RD^2\right]$$

Analysis:

Data for 10 subjects with 19 (oral) and 24 (iv) plasma concentrations collected between 5 minutes and 32 hours will be analyzed.

1. We start with a separate fit of the intravenous data (Model File **dis.for**).
   Data file, **disd.dat** contains the bolus input information and iv drug concentration values.
   - MLEM estimation, **disp.prm** contains initial values
   - view plots (PostScript file)
   - results (run file), conditional estimates for all subjects are entered in fixed parameter file **iv.fix**

2. The parameter estimates of the dis-subsystem obtained by the separate fit of the intravenous data are used as fixed values in the simultaneous abs-dis-fit.
   Data file, **absdisd.dat** contains the input information and oral drug concentrations.
   - MLEM estimation, **absdisp.prm** contains initial values
   - CL, V_1, CL_{12}, V_2, CL_{13}, V_3 to be fixed: **iv.fix**
   - view plots (PostScript file)
   - results (run file), enter estimates (means) of F, MIT, RD^2 , MAT and t_{Imax} in Table, below (first column)

3. RE-ESTIMATION: assuming rapid distribution (1-compartment behavior)
   keeping $k_e = CL/V_1$ constant
   - repeat 2. using **ivre.fix** where all CL2 = 1000 CL_{12} (est.) and CL3 = 1000 CL_{13}(est.)
   - view plots (PostScript file))
   - results (run file), enter estimates of *F*, *MIT*, RD^2 and *MAT* in Table, below (first column)

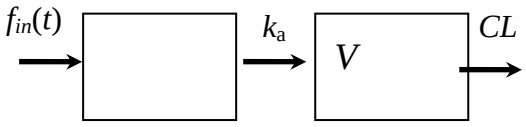
   Table

	real CL_{1i}	high CL_{1i}
AIC		
F		
MIT		
RD^2		
MAT		
t_{Imax}		

Discussion:

Correct modeling of drug disposition (independent iv study) is essential for estimation of unbiased absorption parameters.

Note that in this case the assumption of 1-compartment-like distribution kinetics (1000-fold increase in CL_{12} and CL_{13} with unchanged $V_{ss} \approx V_1$ or $k_e \approx MRT = V_{ss}/CL$) affected mainly *MAT* and $t_{I,max}$ (RD^2).



Misspecification of the disposition model

Model Building with Covariates

The Population Problem with Covariates

- Base Model Notation
- Notation with Covariate Model
- The Concept

Solution via the MLEM Algorithm

- Iterative Equations with Covariates
- Specifying the Covariate Model in ADAPT

Covariate Model Building

The Population Problem

• Base Model Notation

Stage 1: *Individual Subject Variation (Intra-Individual)*

$$Y_i = h_i(\theta_i) + e_i \quad , \quad i = 1, \ldots, N$$

$$e_i \sim N(0, G_i(h_i(\theta_i), \beta))$$

Stage 2: *Inter-Individual Variation*

$$\theta_i \sim N(\mu, \Sigma) \text{ or } LN(\mu, \Sigma) \equiv p(\theta \mid \mu, \Sigma)$$

Want to Estimate: μ Σ β $\theta_i, i = 1, \ldots, N$

• Notation with Covariate Model

Stage 1: Same

Stage 2: *Inter-Individual Variation*

$$\theta_i \sim N(\mu_i, \Sigma) \text{ or } LN(\mu_i, \Sigma) \equiv p(\theta \mid \mu_i, \Sigma)$$

Covariate Model

$$\mu_i = v(c, r_i)$$

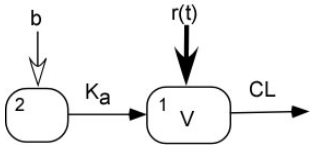
r_i - vector of covariate values for ith subject

c - vector of covariate model parameters
assumed to be the same for all subjects

Want to Estimate: c Σ β $\theta_i, i = 1, \ldots, N$

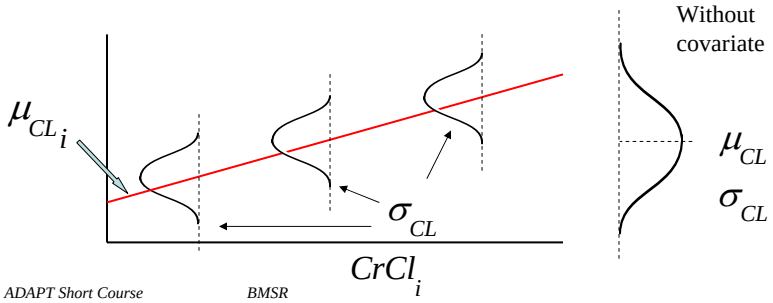
• The Concept

- Example

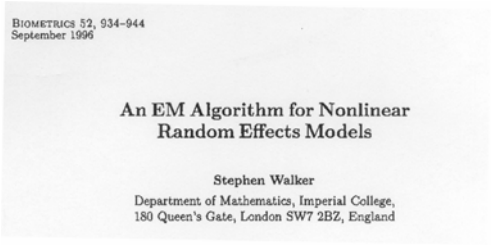


$$(CL_i, V_i, Ka_i) \sim N\left(\left(\mu_{CL_i}, \mu_V, \mu_{Ka}\right), \Sigma\right)$$

$$\mu_{CL_i} = CL_{non\ renal} + CL_{renal\ slope} \cdot CrCl_i \equiv v(c, r_i)$$



Solution via The MLEM Algorithm



BIOMETRICS 52, 934–944
September 1996

An EM Algorithm for Nonlinear Random Effects Models

Stephen Walker
Department of Mathematics, Imperial College, 180 Queen's Gate, London SW7 2BZ, England

Special Case (Linear Model)

$$\mu_i = C\, r_i$$

MONTE CARLO PARAMETRIC EXPECTATION MAXIMIZATION (MC-PEM) METHOD FOR ANALYZING POPULATION PHARMACOKINETIC/ PHARMACODYNAMIC DATA

Robert J. Bauer and Serge Guzy
XOMA (US) LLC
Berkeley, California

Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis, Volume 3, Edited by D.Z. D'Argenio, Kluwer Academic Publishers, Boston, 2004

General Case

$$\mu_i = v(c,\ r_i)$$

- Iterative Equations with Covariates

  - Initialization

    initial guesses: $c^{(0)}$ $\Sigma^{(0)}$ $\beta^{(0)}$ $\theta_i^{(0)}$ $k = 0$

  - Stage 1 – Estimation (E Step)

Conditional Mean for each subject

$$\bar{\theta}_i^{(k)} = E\left[\theta \mid Y_i, c^{(k)}, \Sigma^{(k)}, \beta^{(k)}\right]$$

Conditional Covariance for each subject

$$\bar{\Omega}_i^{(k)} = E\left[\left(\theta - \bar{\theta}_i^{(k)}\right)\left(\theta - \bar{\theta}_i^{(k)}\right)^T \mid Y_i, c^{(k)}, \Sigma^{(k)}, \beta^{(k)}\right]$$

Note: $\mu_i^{(k)} = v(c^{(k)},\ r_i)$

- Stage 2 – Maximization (M Step)

- Update covariate model parameters:

$$c^{(k+1)} = \arg\min \frac{1}{N}\sum_{i=1}^{N}\left(\left(\bar{\theta}_i^{(k)} - v(c, r_i)\right)^T \Sigma^{(k)} \left(\bar{\theta}_i^{(k)} - v(c, r_i)\right)\right)$$

which updates the population mean for each subject:

$$\mu_i^{(k+1)} = v(c, r_i)$$

- Update intersubject covariance:

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

• Specifying the Covariate Model in ADAPT

Example: $\mu_{CL_i} = CL_{non\ renal} + CL_{renal\ slope} \cdot CrCl_i$

```
C######################################################################C
       Subroutine COVMOD(PC, P, IC)
       Implicit None
       Include 'globals.inc'
       Include 'model.inc'
CC
C-----------------------------------------------------------------------C
C     Enter # of Covariate Parameters                                   C
C----c------------------------------------------------------------------C

       NCparam = 2 ! Enter # of Covariate Parameters.
CC
C-----------------------------------------------------------------------C
C   Enter Symbol for Covariate Params. {eg: PCsym(1)='CLRenal'}         C
C----c------------------------------------------------------------------C

       PCsym(1)='CLnonrenal'
       PCsym(2)='CLrenalslope'
```

```
CC
C-----------------------------------------------------------------------C
C   For the Model Params. that Depend on Covariates Enter the Equation C
C         {e.g. Pmean(1) =  PC(1)*R(2) }                                C
C----c------------------------------------------------------------------C

       Pmean(1) = PC(1) + PC(2)*R(2)

C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C
       Return
       End
```

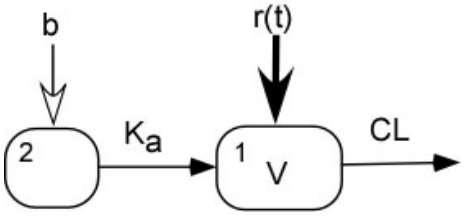
```
C#######################################################################C
       Subroutine POPINIT(PmeanI,ICmeanI,PcovI,ICcovI, PCI)
C  Initial parameter values for population program parameters (ITS, MLEM)
       ...
C-----------------------------------------------------------------------C
C   Enter Values for Covariate Model Parameters                         C
C         {  e.g. PCI(1) = 2.0    }                                     C
C----c------------------------------------------------------------------C

      PC(1)=2.0     ! CLnonrenal
      PC(2)=0.01    ! CLrenalslope
C-----------------------------------------------------------------------C
```

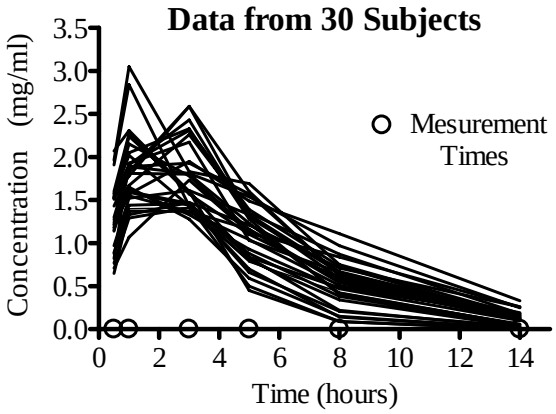


```
C#######################################################################C
       Subroutine POPINIT(PmeanI,ICmeanI,PcovI,ICcovI, PCI)
C  Initial parameter values for population program parameters (ITS, MLEM)
       ...
C-----------------------------------------------------------------------C
C   Enter Values for Covariate Model Parameters                         C
C         {  e.g. PCI(1) = 2.0    }                                     C
C----c------------------------------------------------------------------C

      PC(1)=2.0     ! CLnonrenal
      PC(2)=0.01    ! CLrenalslope
CC
C-----------------------------------------------------------------------C
```

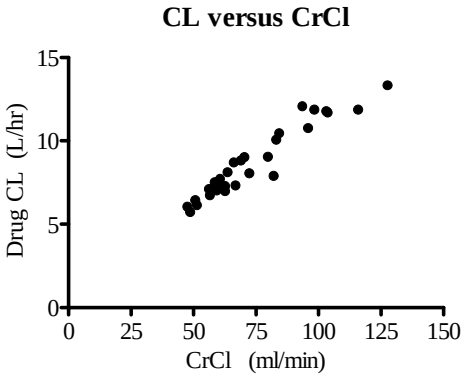
Case Study – Model Building with Covariates

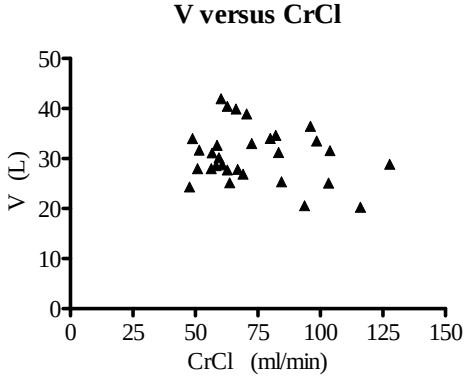
This case study uses the MLEM program to perform a population analysis with covariates. The example presented previously involving a one compartment, first order absorption model to analysis the data from 30 subjects following single dose oral administration is also used.





Creatine clearance (CrCl) was also determined in each of these 30 subjects. We would like to explore if CrCl can explain any of the intersubject variability in drug CL estimate in the previous analysis. In the following graphs the estimated values for CL and V for each of the 30 subjects (from the population analysis using the base model above) are plotted versus the subject's CrCl.





These plots suggest that CrCl may be an explanatory covariate for CL but not for V.

To test this hypothesis, the population analysis of the data is performed using CrCl as a covariate for drug CL. The relation between the mean value of CL in the population and CrCl is modeled as follows:

Model Equation	ADAPT Code
$\mu_{CL} = c_1 \cdot CrCl$	`Pmean(1) = PC(1)*(R(2)/70)`

The model file **mlemcov.for** incorporates this covariate model in subroutine COVMOD (inspect this file in the Fortran editor). Initial values (guesses) for all population mean (when not modeled with covariates), population covariance, error variance and now covariate parameters are entered in the POPINIT subroutine in the model file **mlemcov.for** (also view this section of the model file using the Fortran editor).

Perform a population maximum likelihood (MLEM) analysis using the model, data and parameters contained in the files **mlemcov.for**, **mlem.dat** and **mlem.prm** (enter **mlemcov.run** as the name of the run file when prompted). The bolus input is into compartment 2. Estimate those parameters indicated in the following table.

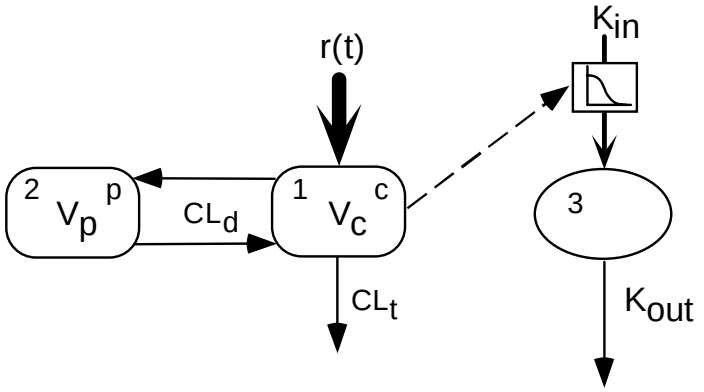
Parameter	Initial Value	Estimate?
CLt	8.0	Y
Vc	30.0	Y
Ka	1.0	Y
IC(1)	0.0	N
IC(2)	0.0	N
SDinter	0.0	N
SDslope	0.1	Y
CLslope	1.0	Y

Do Not Fix non estimated parameters, and select a Lognormal parameter distribution model with a Full covariance. Use 1000 samples/EM iteration and perform 30 EM iterations. View the results stored in the **mlem.run** file and confirm the results shown in the table below taken from the MLEM FINAL POPULATION PARAMETER ESTIMATES found at the end of the run file.

```
      ----- MLEM FINAL POPULATION PARAMETER ESTIMATES -----
                              ...

 Model:  MLEMcov.FOR: - 1 comp. pop. example w/ covariates

 Number of data sets analyzed successfully:    30

 Importance Sampler with number samples/iteration:    1000

 Total number of EM iterations:   30

 Lognormal distribution option

 Negative Log Likelihood:   -69.5241

 Model Selection Criteria
  AIC:       -119.048
  BIC:       -87.1186

        --- A. Population Mean & Population Standard Deviation ---

 Parameter     Mean        %RSE         Std.Dev.    SD as CV%     %RSE
  CLt           --          --             --         3.98         68.9
  Vc          30.1        7.13           6.12         20.3         46.8
  Ka          1.02        7.46          0.143         14.1         85.5
  IC(   1)    0.00      Not estimated
  IC(   2)    0.00      Not estimated

        --- B. Full Population Covariance of Estimated Parameters ---

  As Covariance Matrix for ln(parameters):

           CLt       Vc        Ka
 CLt       0.158E-02
 Vc        0.950E-04 0.412E-01
 Ka        0.894E-03 -.872E-02 0.198E-01

  As Correlation Matrix:

           CLt       Vc        Ka
 CLt         1.00
 Vc          0.01      1.00
 Ka          0.16     -0.31      1.00

  Standard Errors of Estimated Covariance Matrix for ln(parameters):

           CLt       Vc        Ka
 CLt       0.218E-02
 Vc        0.614E-02 0.353E-01
 Ka        0.104E-01 0.206E-01 0.329E-01

             --- C. Covariate Model Parameters ---

Parameter     Estimate    %RSE
  CLslope      8.26       2.43
```

Case Study – Population PK/PD Analysis

This case study involves population parameter estimation using an indirect response model (IRM). The pharmacokinetic/pharmacodynamic IRM used in this case study is shown below. 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 in a previous Case Study.



Both PK (plasma concentration) and PD (response variable) are available from 50 simulated subjects, which will be used to perform a population analysis. In this case study a sequential analysis will be performed. In **part 1** of this example a population PK analysis will be performed using the plasma concentration data alone, which will yield a population model for the PK as well as estimates for the PK parameters for each of the 50 subjects. In **part 2**, each individual subject's estimated PK parameters 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.

Part 1 – Population PK Analysis

The two equations for the PK model have been coded and entered into the model file **irmPK.for**. Initial values (guesses) for all population mean, population covariance and error variance parameters are entered in the POPINIT subroutine in the model file **irmPK.for** (view this section of the model file using the Fortran editor).

Perform a population maximum likelihood (MLEM) analysis using the model, data and parameters contained in the files **irmPK.for**, **irmPK.dat** and **irmPK.prm** (enter **irmPK.run** as the name of the run file when prompted). Estimate those parameters indicated in the following table.

Parameter	Initial Value	Estimate?
CLt (L/hr)	6.0	Y
Vc (L)	30.0	Y
Cld (L/hr)	12.0	Y
Vp (L)	60.0	Y
IC(1)	0.0	N
IC(2)	0.0	N
SDinterPK	0.0	N
SDslopePK	0.1	Y

Do Not Fix non estimated parameters, and select a Lognormal parameter distribution model with a Diagonal covariance. Use 1000 samples/EM iteration and perform 15 EM iterations. View the results stored in the **irmPK.run** file and confirm the results shown in the table below taken from the MLEM FINAL POPULATION PARAMETER ESTIMATES found at the end of the run file.

```
    ----- MLEM FINAL POPULATION PARAMETER ESTIMATES -----

 Mon Jun 30 17:27:52 2008

 Data file name: D:\test\irmPK.dat

 Model:  irmpopPK.for - ADAPT Short Course Example

 Number of data sets analyzed successfully:    50

 Importance Sampler with number samples/iteration:    1000

 Total number of EM iterations:   15

 Lognormal distribution option

 Negative Log Likelihood:   -931.254

 Model Selection Criteria
  AIC:       -1844.51
  BIC:       -1803.55

        --- A. Population Mean & Population Standard Deviation ---

 Parameter     Mean        %RSE         Std.Dev.   SD as CV%     %RSE
  CLt          5.58        4.72          1.74        31.3         12.1
  Vc           30.3        5.66          9.25        30.6         12.1
  CLd          11.7        4.88          3.39        28.9         13.8
  Vp           57.4        4.32          15.5        27.0         14.4
  IC(   1)     0.00      Not estimated
  IC(   2)     0.00      Not estimated

        --- B. Full Population Covariance of Estimated Parameters ---

                    ...

  As Covariance Matrix for ln(parameters):

           CLt       Vc        CLd       Vp
 CLt       0.977E-01
 Vc         0.00     0.934E-01
 CLd        0.00      0.00     0.834E-01
 Vp         0.00      0.00      0.00     0.731E-01

  Standard Errors of Estimated Covariance Matrix:

           CLt       Vc        CLd       Vp
 CLt       0.736
 Vc         0.00      20.6
 CLd        0.00      0.00      3.17
 Vp         0.00      0.00      0.00      69.3

        --- D. Error Variance Model Parameters ---

Parameter     Estimate    %RSE
  SDslopePK   0.979E-01   3.29
```

Part 2 – Population PD Analysis

The complete equations for the PK/PD model have been coded and entered into the model file **irmPD.for**. Initial values (guesses) for the only those population mean and population covariance parameters to be estimated, as well as error variance parameters are entered in the POPINIT subroutine in the model file **irmPD.for** (view this section of the model file using the Fortran editor).

Using the irmPK.ind file create from the PK analysis, a file name **irmPK.fix** containing the estimated PK parameters from each of the 50 subjects has been created. View this file in an editor.

Perform a population maximum likelihood (MLEM) analysis using the model, data and parameters contained in the files **irmPD.for**, **irmPD.dat** and **irmPD.prm** (enter **irmPD.run** as the name of the run file when prompted). Estimate those parameters indicated in the following table.

Parameter	Initial Value	Estimate?
CLt (L/hr)	6.0	N
Vc (L)	30.0	N
Cld (L/hr)	12.0	N
Vp (L)	60.0	N
Kin (units/hr)	0.0	Y
IC50 (μg/ml)	0.0	Y
IC(1)	0.0	N
IC(2)	0.0	N
IC(3)	100.0	Y
SDinterPD	5.0	Y
SDslopePD	0.0	N

Fix non estimated parameters (file **irmPK.fix**), and select a Lognormal parameter distribution model with a Diagonal covariance. Use 1000 samples/EM iteration and perform 15 EM iterations. View the results stored in the **irmPD.run** file and confirm the results shown in the table below taken from the MLEM FINAL POPULATION PARAMETER ESTIMATES found at the end of the run file.

```
     ----- MLEM FINAL POPULATION PARAMETER ESTIMATES -----

Mon Jun 30 17:59:14 2008

Data file name: D:\test\irmPD.dat

Model:  irmpopPD.for - ADAPT Short Course Example

Number of data sets analyzed successfully:    50

Importance Sampler with number samples/iteration:    1000

Total number of EM iterations:   15

Lognormal distribution option

Negative Log Likelihood:    2348.62

Model Selection Criteria
 AIC:        4711.24
 BIC:        4743.10

       --- A. Population Mean & Population Standard Deviation ---

Parameter     Mean        %RSE         Std.Dev.   SD as CV%     %RSE
 Kin           19.0        5.81          6.43        33.8        15.2
 IC50         0.482        6.58         0.185        38.4        12.3
 IC(   3)      96.7        3.96          25.8        26.7        15.4
 CLt           5.85      Not estimated
 Vc            31.6      Not estimated
 CLd           12.2      Not estimated
 Vp            59.6      Not estimated
 IC(   1)      0.00      Not estimated
 IC(   2)      0.00      Not estimated

       --- B. Full Population Covariance of Estimated Parameters ---

 As Covariance Matrix:

                 ....

 As Covariance Matrix for ln(parameters):

          Kin       IC50      IC(   3)
Kin       0.114
IC50       0.00     0.148
IC(   3)   0.00      0.00     0.713E-01

 Standard Errors of Estimated Covariance Matrix:

          Kin       IC50      IC(   3)
Kin        12.6
IC50       0.00     0.843E-02
IC(   3)   0.00      0.00      206.

       --- D. Error Variance Model Parameters ---
```