Pharmacokinetic-Pharmacodynamic Data Analysis: a Hands-on Course using ADAPT 5

18-19 March 2013

BY

FACULTY OF PHARMACEUTICAL SCIENCES, NARESUAN UNIVERSITY, PHITSANULOK, THAILAND



Lectures

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BMSR Biomedical Simulations Resource
bmsr.usc.edu

Population Modeling in Pharmacokinetics and Pharmacodynamics using ADAPT 5

Phitsanulok, Thailand
18-19 March, 2013

Course Instructors

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With Support From

The Biomedical Simulations Resource, University of Southern California
Naresuan 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. In this hands-on short course, background lectures and case studies will cover the following topics: population modeling; PK/PD models (indirect & target mediated response models); absorption modeling; physiologically-based models; modeling with covariates; population model validation.

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
Phitsanulok

ADAPT Short Course Schedule
Monday, 18 March 2013

7:45 Opening Ceremony

8:00 Background: **Modeling with ADAPT**

9:15 Case Study: **Model Building Example (SIM)**

10:00 **Break**

10:15 Background: **Individual Estimation: Fundamentals**

11:15 Case Study: **WLS/ML/MAP Estimation (ID)**

12:00 **Lunch Break**

ADAPT Short Course Schedule
Monday, 18 March 2013

13:00 Background: **Population Modeling: Fundamentals**

14:00 Case Study: **PK Compartment Model (MLEM)**

14:45 **Break**

15:00 Case Study: **Dissolution/Absorption Profiles: *in vitro* and *in vivo* (MLEM)**

15:45 Case Study: **Attendee suggestions**

16:30 **Adjourn**

ADAPT Short Course Schedule
Tuesday, 19 March 2013

8:00 Background: **Population Modeling with Covariates**

8:45 Case Study: **Modeling Building with Covariates (MLEM)**

9:30 Case Study: **Recirculatory Models of Drug Disposition (MLEM)**

10:15 **Break**

10:30 Case Study: **Pharmacodynamic Models (ID)**

11:15 Case Study: **Modeling of Biologics (SIM)**

12:00 **Lunch Break**

ADAPT Short Course Schedule
Tuesday, 19 March 2013

13:00 Case Study: **Attendee suggestions**

14:00 Case Study: **PK/PD Modeling Based on Receptor Binding Kinetics (MLEM)**

14:45 **Break**

15:00 Case Study: **Attendee suggestions**

16:00 **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

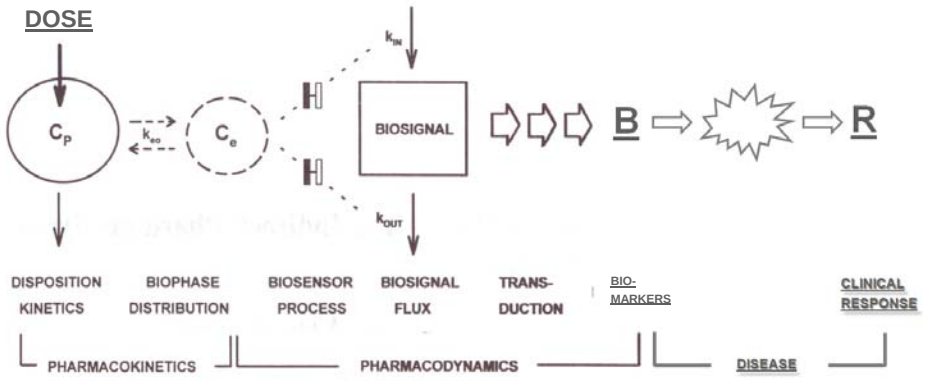
- SIM, ID, SAMPLE
- MLEM, NPD, STS, ITS

Installation/Validation

Library Models

Dissemination and Support

PK/PD/Disease Response Paradigm



Modified from Jusko et al., *J. Pharmacokinet. Pharmacodyn.*, **23**:1995.

Model Formulation

- Model Equations (state space formulation)

$$\frac{dx(t)}{dt} = f(x(t), \theta, r(t), t), \quad x(0) = g(\theta)$$
$$y(t) = h(x(t), \theta, r(t), t)$$

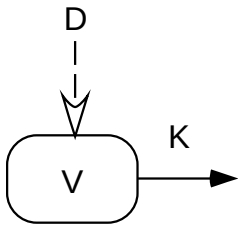
$x(t)$ amount of drug in compartment; concentration of drug in tissue; effect site concentration; receptor activity; signaling protein; physiological variable; disease state; …

θ rate constant; clearance; distribution volume; binding constant; partition coefficient; diffusivity; EC50; Emax; effect site elimination rate; physiological production/elimination rate; initial conditions, … etc.

$r(t)$ drug infusion regimen; covariate (e.g., body weight, creatinine clearance, liver enzyme, cardiac output

$y(t)$ 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:

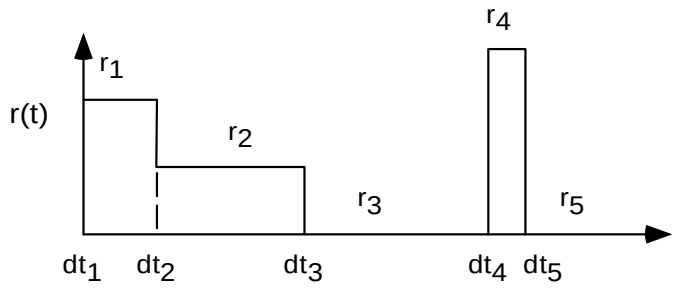
$$y(t) = \frac{D}{V}e^{-Kt}$$

• Inputs

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

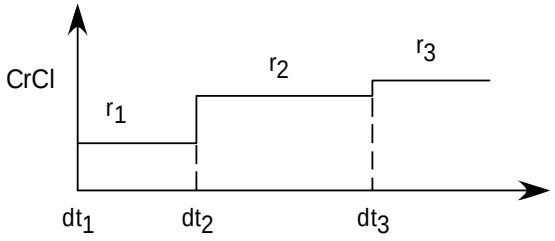
$$r(t) = r_{i-1}, \qquad dt_{i-1} < t \le dt_i \qquad i = 2,\ldots,nd+1$$

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

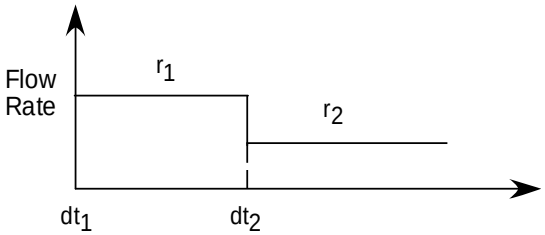


1. Model Inputs → appear explicitly in equations; piecewise constant

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

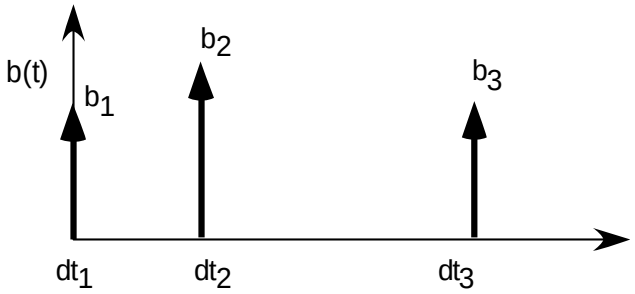


e.g., r(t) - Organ Blood Flow



2. Bolus Inputs → not in equations; change states instantaneously; specified at program run

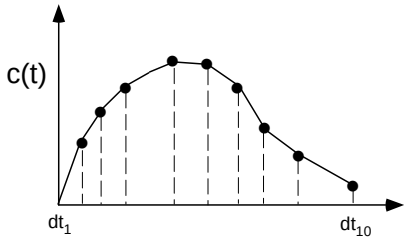
$$x(dt_i^+) = x(dt_i^-) + b(dt_i), \qquad i = 1,\ldots,nd$$



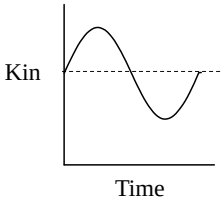
Delayed model inputs/bolus inputs OK: $r(t-\tau)$, $b(t-\tau)$

3. Other Inputs

e.g., Piecewise linear



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



circadian variation of physiological property

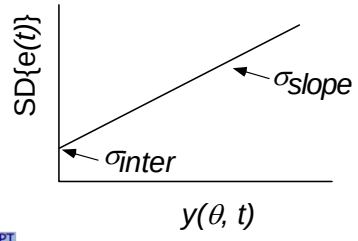
- Measurement Model
  - Measurement Equation $\left(\text{let } y(t_j) \rightarrow y(\theta, t_j)\right)$

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

  - Variance Model for Output Error

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

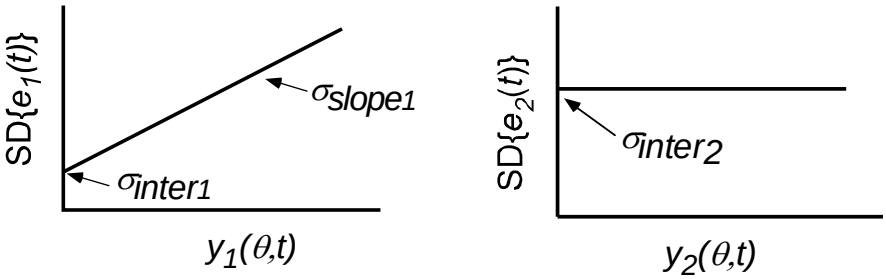
e.g., One output - $l = 1$



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

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

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



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

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

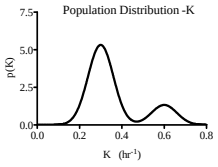
- Distribution of the Output Error $e(t)$

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 (a. nominal/ b. ordinal):
   a. Dichotomous (Binary) and Polychotomous Data
      e.g., symptom present
   b. Ordered Categories
      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	(SIM/ID/MLEM/NPD/ITS)
$p(\theta) = LN(\mu,\Sigma)$	multivariate lognormal	(SIM/ID/MLEM/NPD/ITS)
$p(\theta) = U(0, \alpha_{max})$	independent uniform	(SIM/ID/NPD)
$p(\theta) = NI, \theta>0$	noninformative	(ID/NPD)
$p(\theta) = \sum w_k N(\mu_k, \Sigma_k)$	mixture model	(SIM)



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

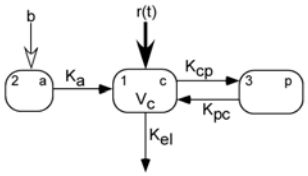
Secondary Parameters:

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

Example - two compartment model

System parameters:

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

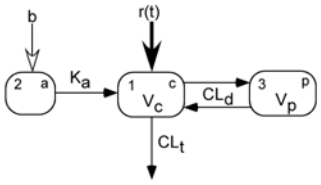


Secondary parameters:

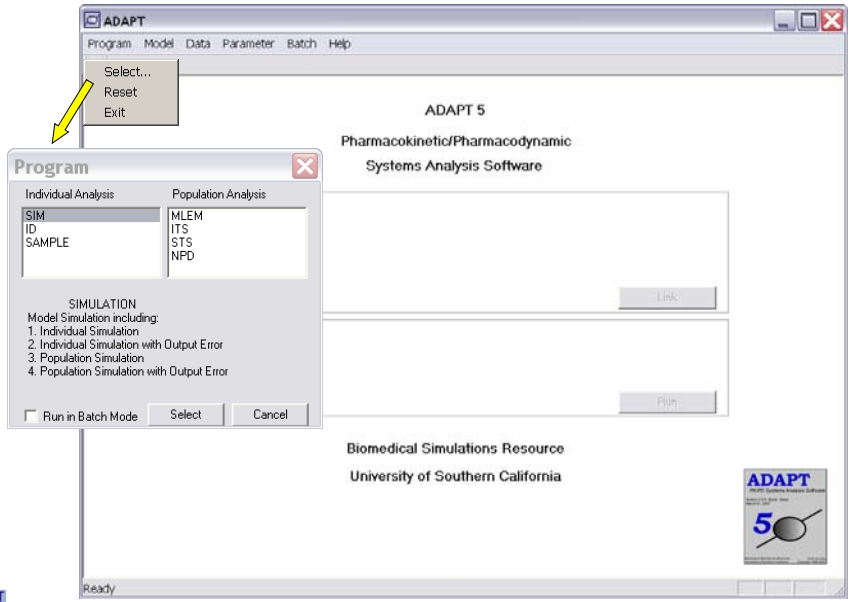
$$\gamma = \left[CL_t\ V_C\ CL_d\ V_p \right]$$

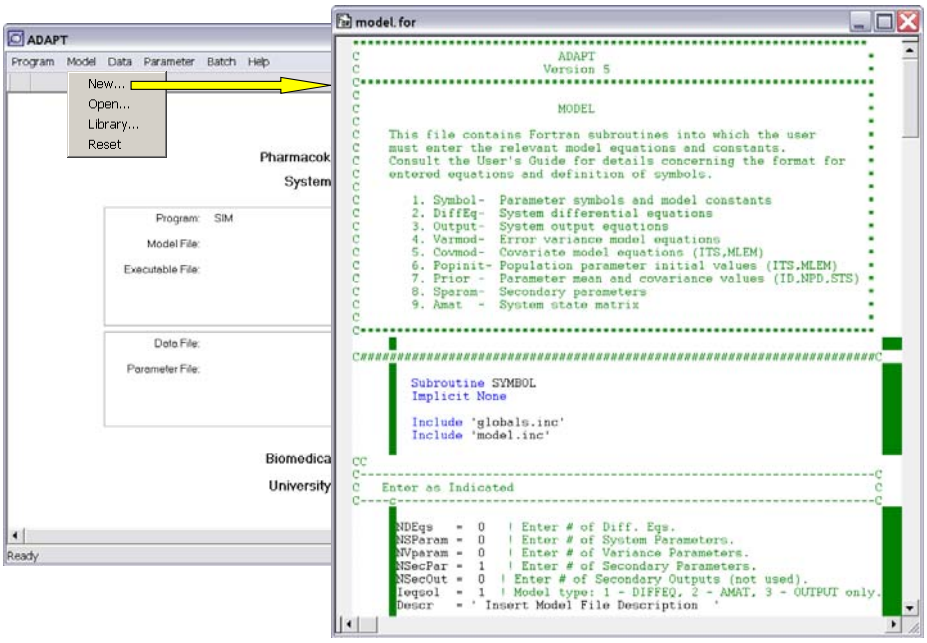
$$CL_t = VK_{el} \qquad V_c = V$$

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



Implementing the Model in ADAPT 5





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       8. Sparam-  Secondary parameters                             *
C       9. Amat   -  System state matrix                             *
C                                                                    *
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
```

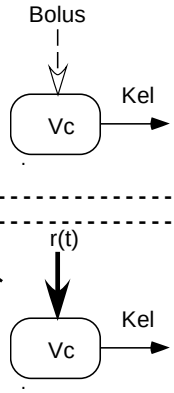


```
C-------------------------------------------------------------------------C
C   Enter Symbol for Each Variance Parameter {eg: PVsym(1)='Sigma'}   C
C----c--------------------------------------------------------------------C
       Enter Variance Parameter Symbols Here
       PVsym(1)='Sigma'

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

```
        Real*8 Kel
        Kel=P(1)

        XP(1) = -Kel*X(1)
        -------------------------------
        XP(1) = -Kel*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

```
        Real*8 Vc
        Vc=P(2)
        Y(1) = X(1)/Vc
       -------------------------------
        Y(1) = X(1)/(Vc*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 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   !  Kel

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    !  Kel/Kel
```

```
        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

```
        Real*8 V, Kcp, Kpc
        V=P(4)
        Kcp=P(3)
        Kpc=P(4)

        PS(3) = V*Kcp/Kpc   ! Vp

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



```
C#####################################################################C
       Subroutine COVMOD(PC, P, IC)
       Implicit None
       Include 'globals.inc'
       Include 'model.inc'

       Real*8  CLnonRen, CLRenSlope
       CLnonRen =  PC(1)
       CLRenSlope =PC(2)

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

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

```
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) = CLnonRen + CLRenSlope*R(2)   ! Kel

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

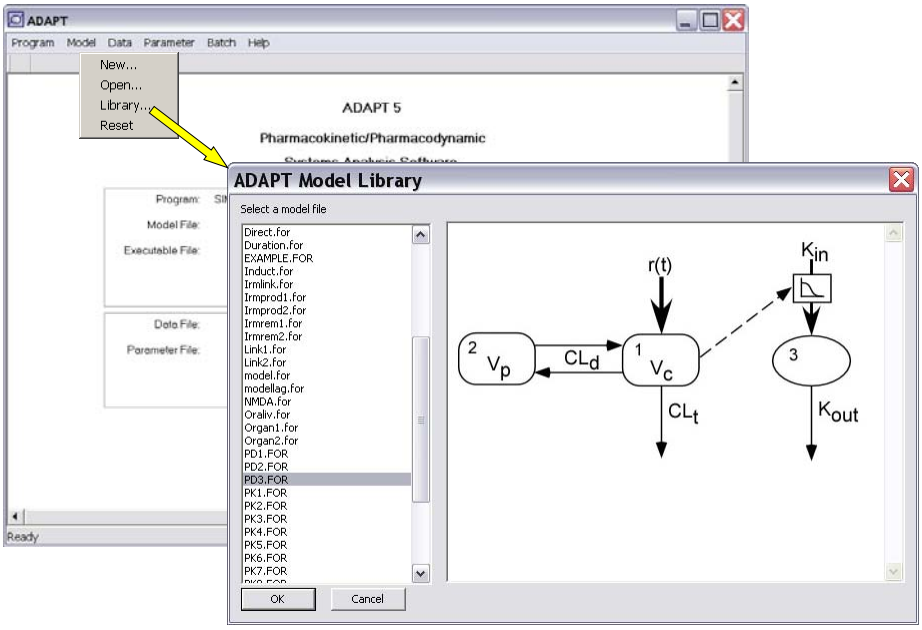
```
CC
C-------------------------------------------------------------------C
C   Enter Initial Values for Pop. Covariance Matrix (Lower Triang.)  C
C         {  e.g. PcovI(2,1) = 0.25    }                          C
C----c--------------------------------------------------------------C
```

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

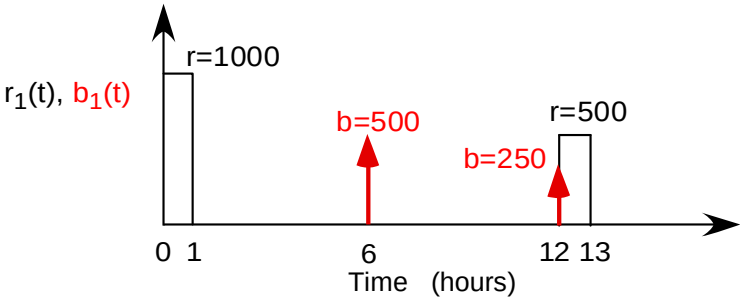
```
CC
C-------------------------------------------------------------------C
```



- Supplying Inputs

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

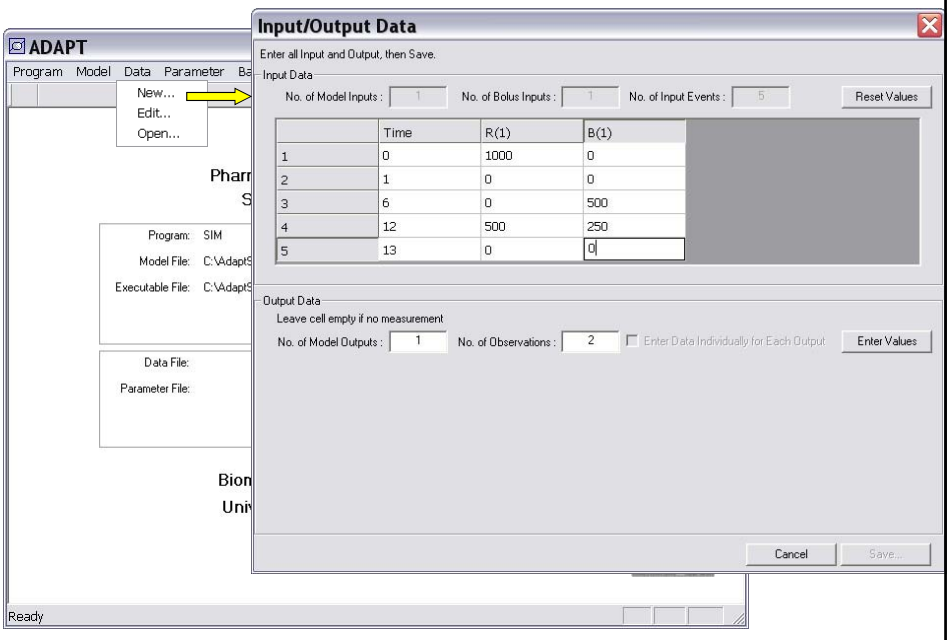
  Example #1: IV and Bolus administration



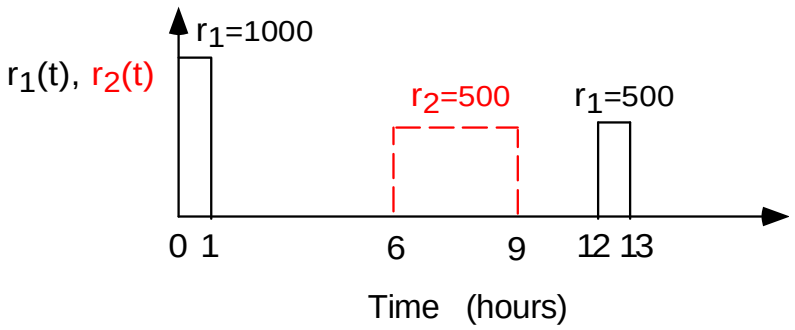
1 model input; 1 bolus input; 5 input event times, 0, 1, 6, 12, 13 hrs.

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



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

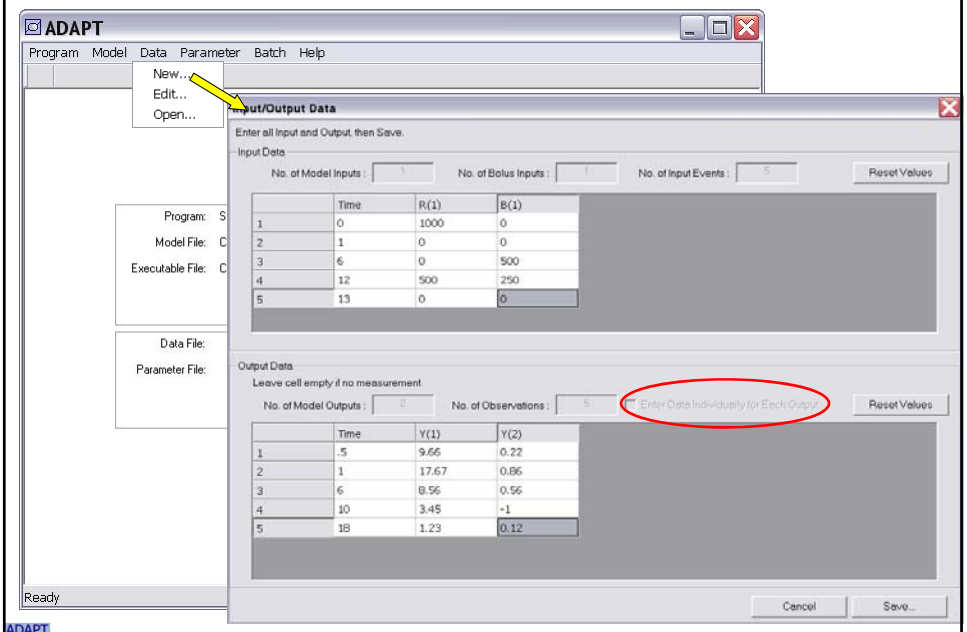
- Use when outputs measured at same times
- Occasional missed measurements indicated by using the missing data number (-1 default)
- e.g., PK model of parent & metabolite

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
```



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

- 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

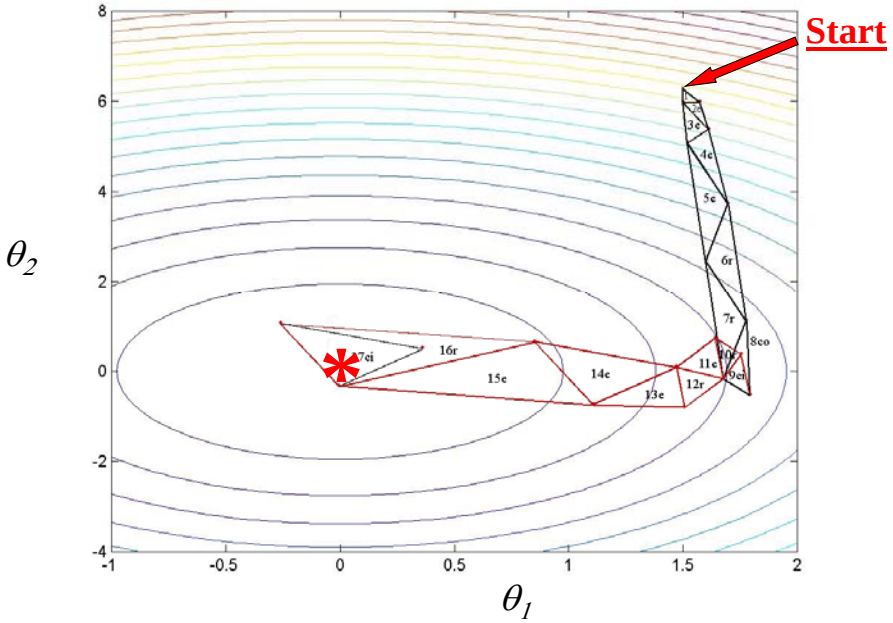
- Partial Derivatives

  Central Difference using machine/solution percision

- 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

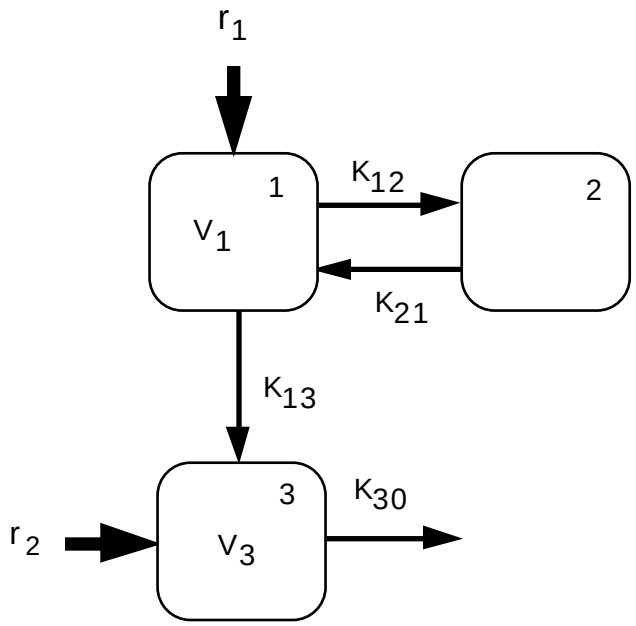
The Programs

- **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)

Case Study – Model Building and Inputs

This case study is designed to illustrate how to build models and 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:

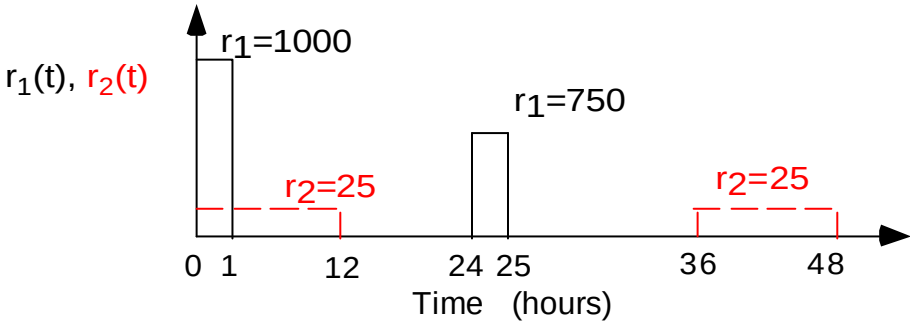
V_1 - P(1)	K_{13} - P(4)
K_{12} - P(2)	K_{30} - P(5)
K_{21} - P(3)	V_3 - P(6)

Examine the file **dc1.for** using the Fortran Editor (or open it in WordPad) 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

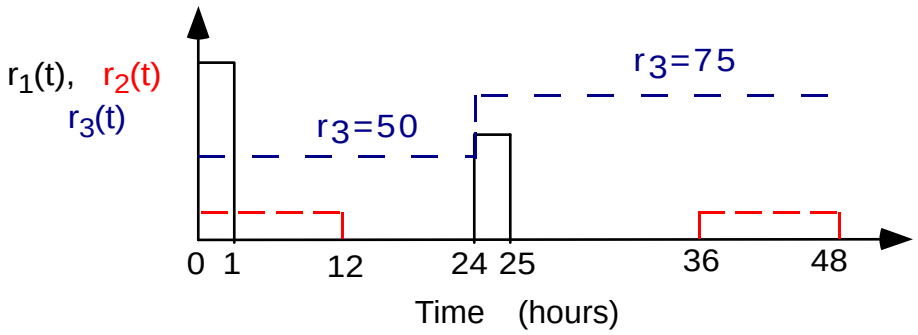
Simulate the model and examine the results.

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 (or open it in WordPad).

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.

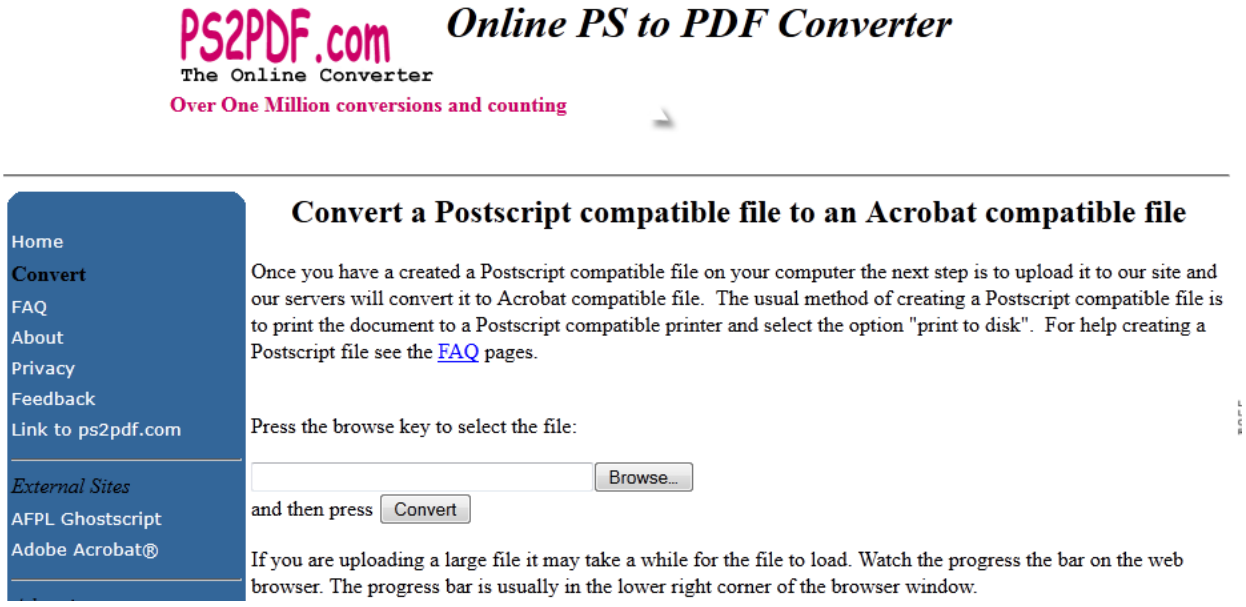


The data file **dc2.dat** includes this information. Examine this data file in the Adapt Data Editor.

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 (or open it in WordPad).

Display ADAPT Created *.eps (postscript) files



INDIVIDUAL ESTIMATION: FUNDAMENTAL PRINCIPLES

Notation

- Model Equations
- Measurements
- Parameters

The Estimation Problem and Methods

- The Problem
- The Methods

Least Squares Estimation

- Gauss's Solution
- Weighting

INDIVIDUAL ESTIMATION: FUNDAMENTAL PRINCIPLES

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

Notation

• Model Equations (state space formulation)

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

$$y(t) = h(x(t), \theta, r(t), t)$$

θ Collection of all model parameters

• Measurements

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

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

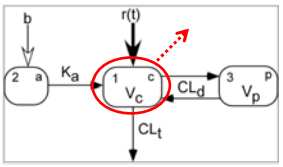
β All variance model parameters

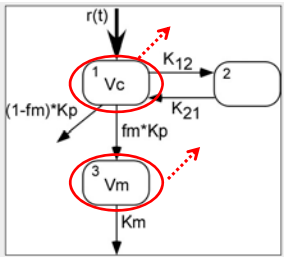
• Parameters

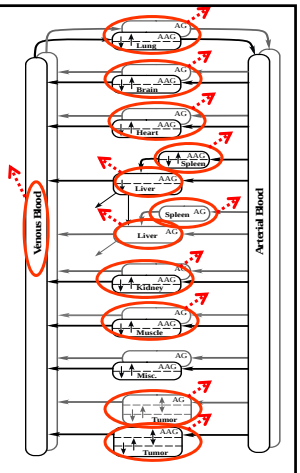
θ – constant or $\theta \sim N(\mu, \Sigma)$ or $LN(\mu, \Sigma)$

Examples

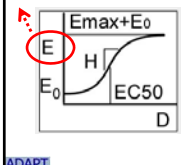
• PK:

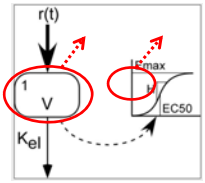


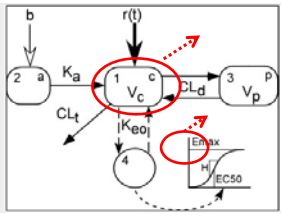


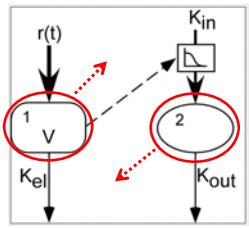


• PD and PK/PD:



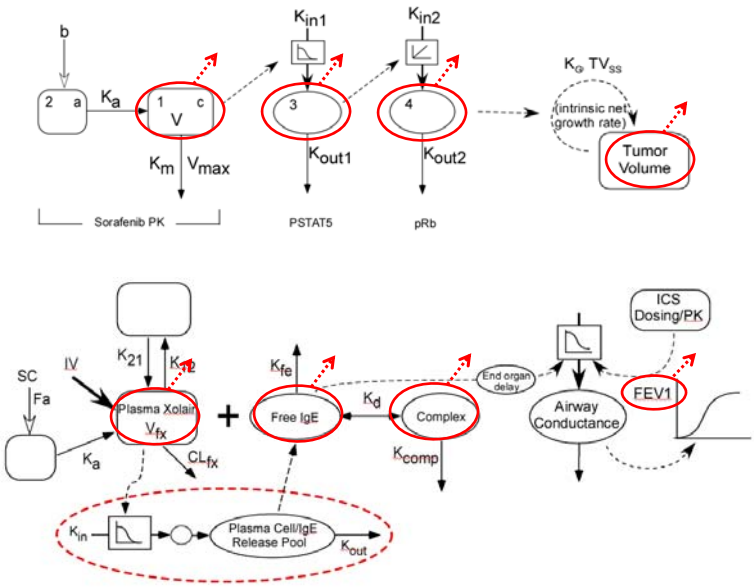






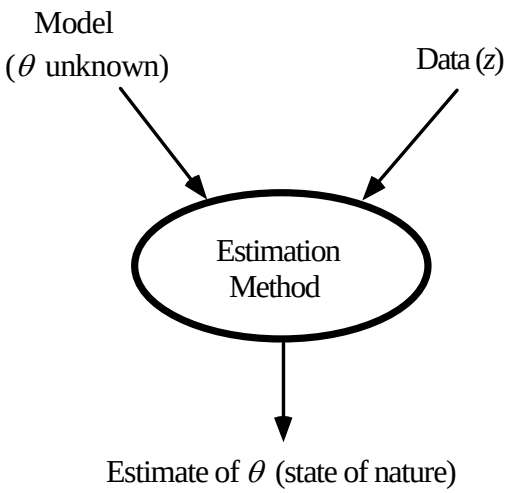
Examples

• PK/PD/Efficacy:



The Estimation Problem and Methods

• The Problem



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

Least Squares Estimation

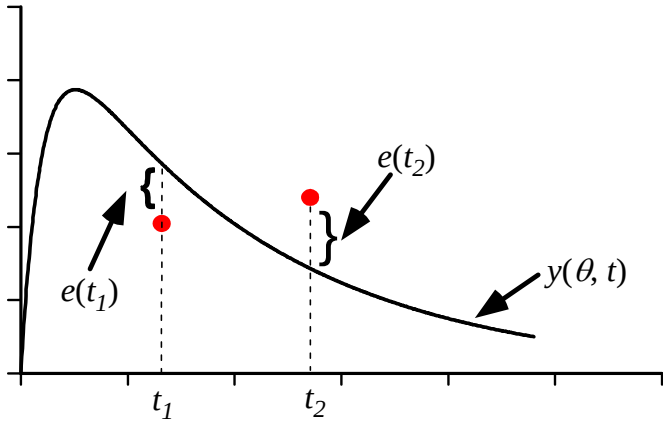
- Gauss's Solution


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:



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

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

Some Comments:

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

- Weighting
- Multiple Output Case (ADAPT User's Guide)
- Standard errors of the parameter estimates -

$Cov(\theta_{WLS})$ SE of θ_{WLS}

- Model predictions with standard errors -

$y(\theta_{WLS}, t)$ $Cov(y(\theta_{WLS}, t))$ SE of $y(\theta_{WLS}, t)$

- 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

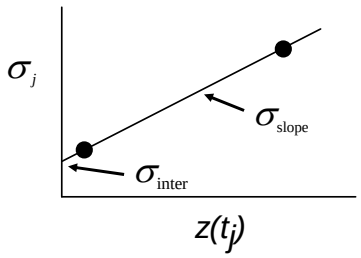
  - Weighting Option 2 in ADAPT: linear variance

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

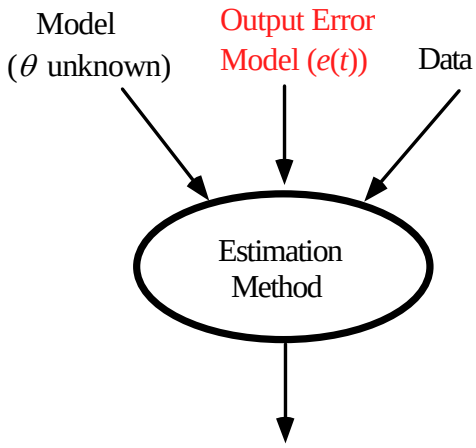
$w_j \propto 1/\sigma_j^2$

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

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

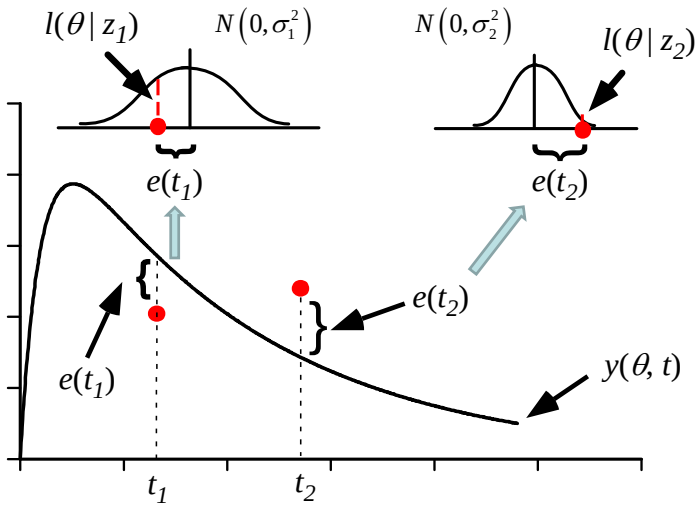
e.g.

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

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

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

Single Output Case: $z(t_j) = y(\theta, t_j) + e(t_j)$



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

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:

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

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

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 θ_{ML}
  and standard errors for model predictions - SE of $y(\theta_{ML}, t)$
  (ADAPT User's Guide)
- Other distributions for the output error
  e.g., categorical data (dichotomous)

Why use Maximum Likelihood

- Consistency

$$\theta_{ML} \rightarrow \theta_{True} \quad \text{as} \quad m \rightarrow \infty$$

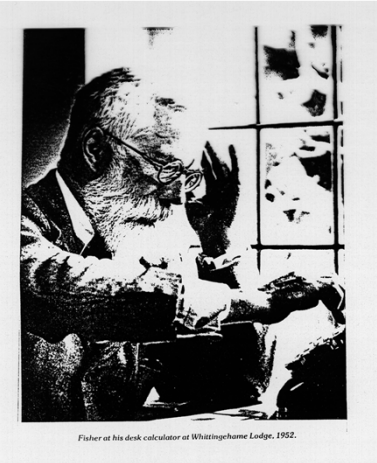
- Asymptotic Efficiency

$$\frac{\text{var}\,\theta_{ML}}{\text{var}\,\theta_{OTHER}} \leq 1 \quad \text{as} \quad m \rightarrow \infty$$

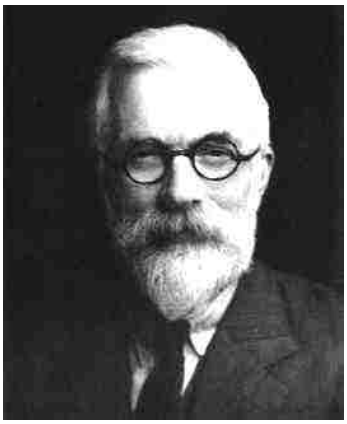
- Well-developed asymptotic theory allows hypothesis testing

- ELS, GLS and Iteratively Reweighted Least Squares
  - 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
  - ELS the same as ML; Interpretation depends on distributional assumptions
  - Iteratively reweighted least squares; use ML or GLS

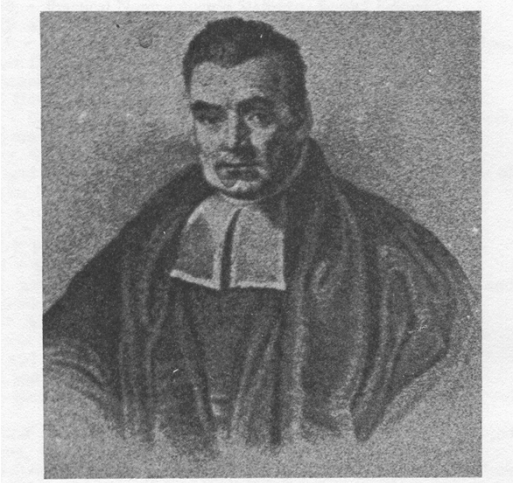
Ronald Fisher
1890-1962



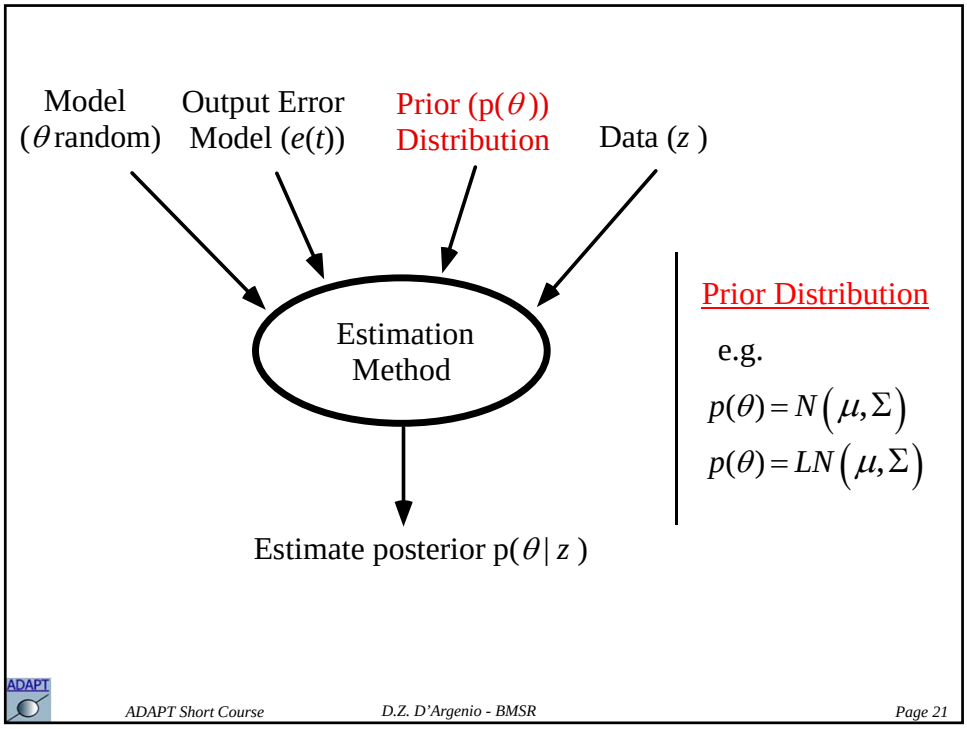
Fisher at his desk calculator at Whittingehame Lodge, 1952.

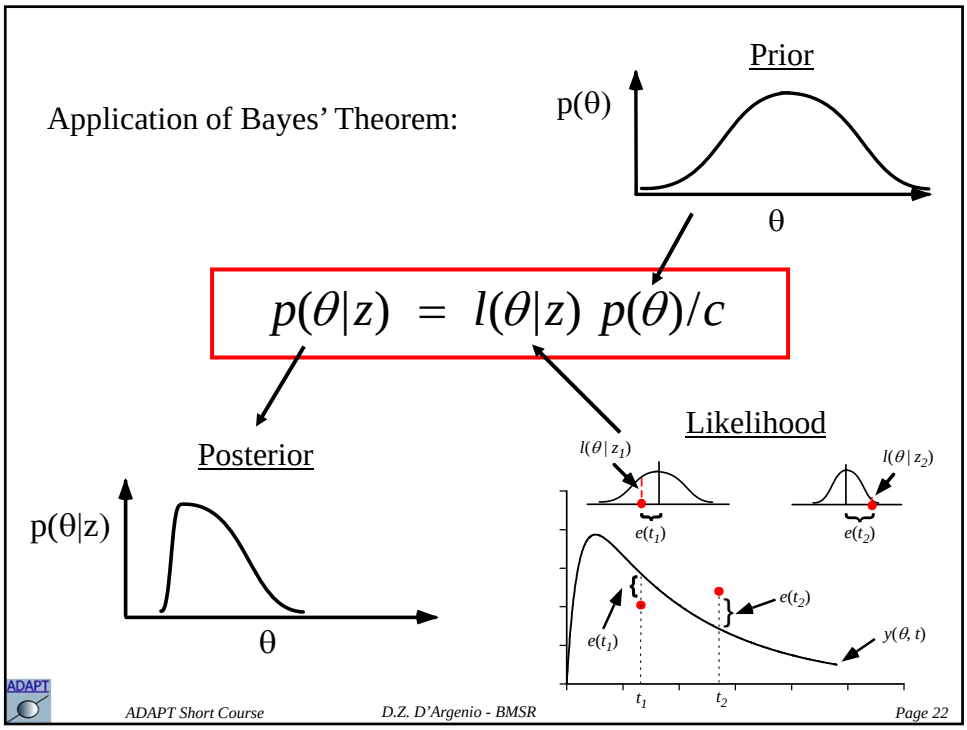


Bayesian Estimation

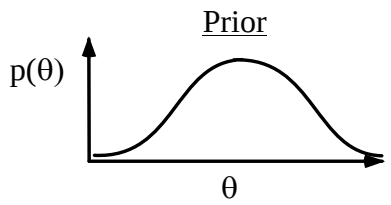


Rev. T. Bayes
(1702–1761)

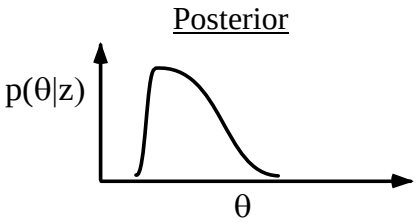

Model
(θ random)
Output Error
Model ($e(t)$)
Prior (p(θ))
Distribution
Data (z)
Estimation
Method
Estimate posterior p($\theta | z$)
Prior Distribution
e.g.
$p(\theta) = N(\mu, \Sigma)$
$p(\theta) = LN(\mu, \Sigma)$

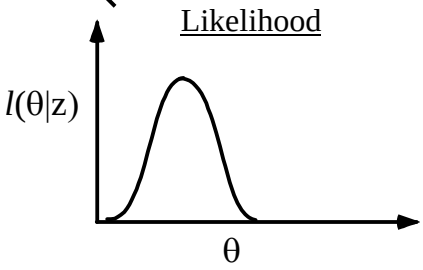

Application of Bayes' Theorem:
Prior
p(θ)
θ
$p(\theta|z) = l(\theta|z)\ p(\theta)/c$
Likelihood
Posterior
p(θ|z)
θ
$l(\theta | z_1)$
$l(\theta | z_2)$
$e(t_1)$
$e(t_2)$
$y(\theta, t)$
t_1
t_2

Application of Bayes' Theorem:

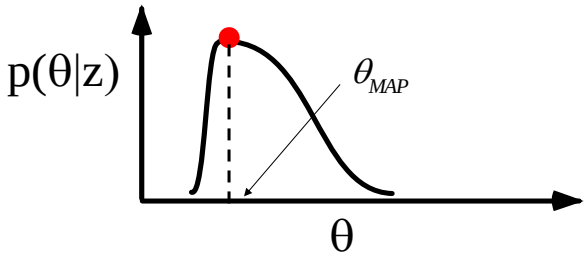


$$p(\theta|z) = l(\theta|z)\ p(\theta)/c$$





- Maximum *a Posteriori* Estimate (MAP)



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

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

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

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

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

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

- 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: $\theta_{MAP} \rightarrow \theta_{ML}$

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

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 θ_{MAP} and standard errors for model predictions - SE of $y(\theta_{MAP},t)$ (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):

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

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

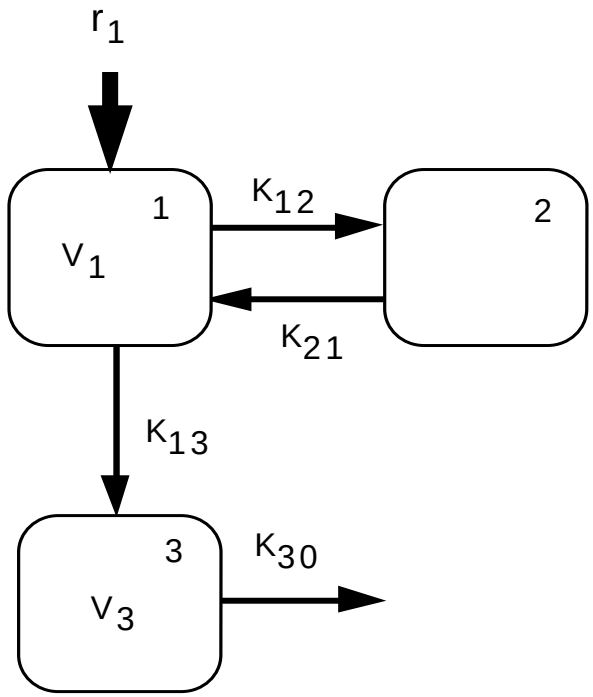
  For ML (q variance model parameters)

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

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

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
$R^2 - Y(1)$	-	-	0.823
$SS - Y(1)$	-	-	29.5
$R^2 - Y(2)$	-	-	0.968
$SS - Y(2)$	-	-	0.248

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.

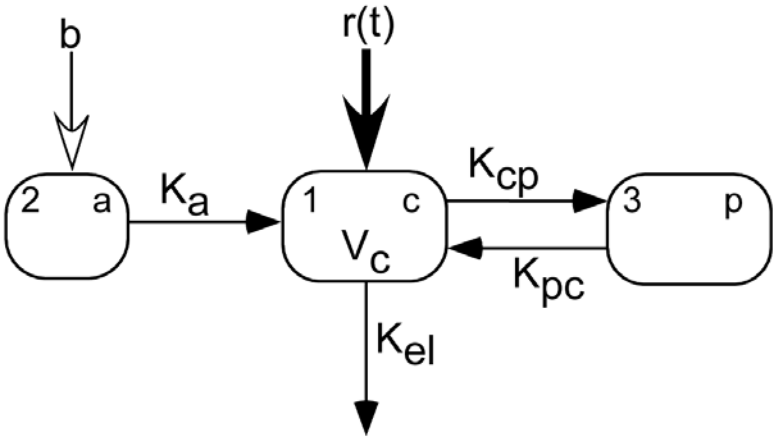
Parameter	Initial Value	Estimate ?	WLS Estimate
V_1	50.0	Y	69.96
K_{12}	0.2	Y	0.1555
K_{21}	0.1	Y	0.09546
K_{13}	0.05	Y	0.03641
K_{30}	0.3	Y	0.3597
V_3	25.0	Y	18.82
$IC(1)$	0.0	N	-
$IC(2)$	0.0	N	-
$IC(3)$	0.0	N	-
$R^2 - Y(1)$	-	-	0.832
$SS - Y(1)$	-	-	30.46
$R^2 - Y(2)$	-	-	0.969
$SS - Y(2)$	-	-	0.232

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

Parameter	ML Estimate	WLS Estimate
V_1	62.10	69.96
K_{12}	0.1713	0.1555
K_{21}	0.1084	0.09546
K_{13}	0.03925	0.03641
K_{30}	0.3522	0.3597
V_3	19.83	18.82
IC(1)	-	-
IC(2)	-	-
IC(3)	-	-
R^2 *– Y(1)*	-	
SS – Y(1)	0.2221	
R^2 *– Y(2)*	-	
SS – Y(2)	0.08431	

Case Study - MAP Bayesian Estimation

The two compartment, first-order absorption Library Model (**2compk.for**) will be used to describe the plasma concentration of lidocaine following an intravenous infusion of the drug. The compartment model coded in this Model File is shown below:



Assume the following lidocaine concentration measurements are obtained from a patient that received lidocaine as an intravenous infusion at a rate of 75 mg/min for 1.0 min and at a rate of 1.45 mg/min thereafter:

time (min)	concentration (µg/ml)
20	2.04
40	3.00
80	3.80
120	4.40
180	5.20

Further assume a **lognormal** prior parameter distribution with:

parameter (units)	mean	std. dev.
Kel (min^{-1})	0.0242	0.0121
V (L)	30.0	15.0
Ka (min^{-1})	0	-
Kcp (min^{-1})	0.066	0.033
Kpc (min^{-1})	0.038	0.0190

The parameter covariances are zero. The measurement error has a constant standard deviation of 0.5 µg/ml: **SDinter = 0.5** and **SDslope = 0.0**.

1. The file **2compk.for** has been copied to a file named **bayes.for** and the parameter mean and covariances have been entered in the subroutine PRIOR. Examine this file in the Fortran editor to verify that the statistics of the prior distribution have been entered correctly.

2. Use the observations given above to estimate the individual's parameter values using MAP estimation in ID for each of the following three cases:

    a. With only the first observation (use file **bayes1.dat**).
    b. With the first three observations (use file **bayes3.dat**).
    c. With all five observation (use file **bayes5.dat**).

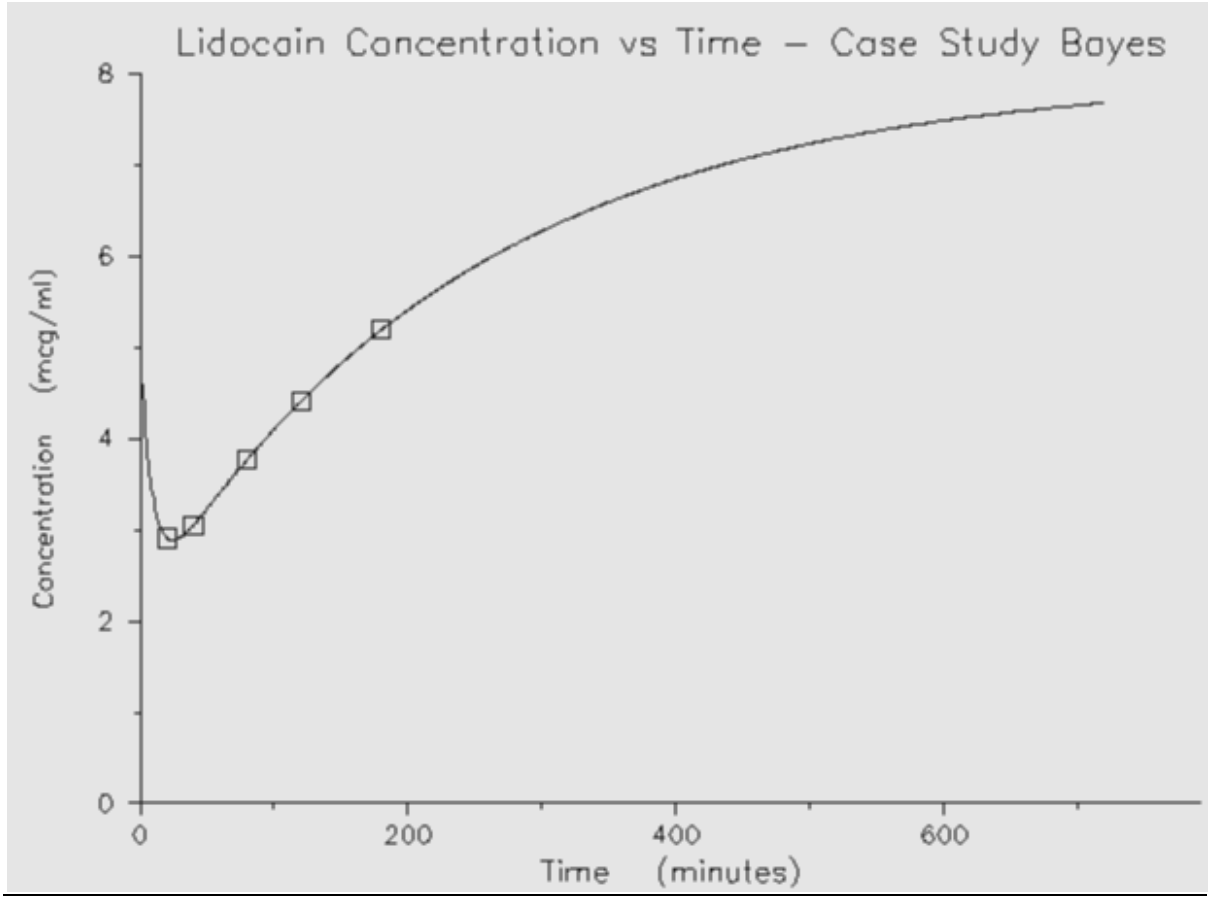
    As initial parameter guesses use the numbers given in the file **bayes.prm**.

    For each case, confirm the MAP estimates and corresponding standard errors (as CV %) recorded in the table below. Do these results make sense to you, when you consider the true values used to generate the data as well as the population mean parameter values? Examine the model prediction summaries and view the plots for each of the three data sets.

3. Obtain the least squares estimates (unity weighting) using all five observations (bayes5.dat file) and confirm (or not) the values in the table below. Compare these results to the MAP estimates for the same data set.

Bayesian Case Study Results

Param	MAP-1	MAP-3	MAP-5	LS-5	True	Mean
K_{el}	0.0174	0.0129	0.0106	0.1737	0.0121	0.0242
V	21.9	18.2	17.6	0.1347	15	30
K_a	-	-	-	-	-	-
K_{cp}	0.0477	0.0494	0.0544	170.2	0.066	0.066
K_{pc}	0.0271	0.0366	0.0381	0.556	0.038	0.038



POPULATION MODELING: FUNDAMENTALS

The Population Problem

- The Concept
- Notation
- Hierarchical Framework

Solution via Maximum Likelihood

- The Concept
- Simple Example
- The General Problem

POPULATION ESTIMATION

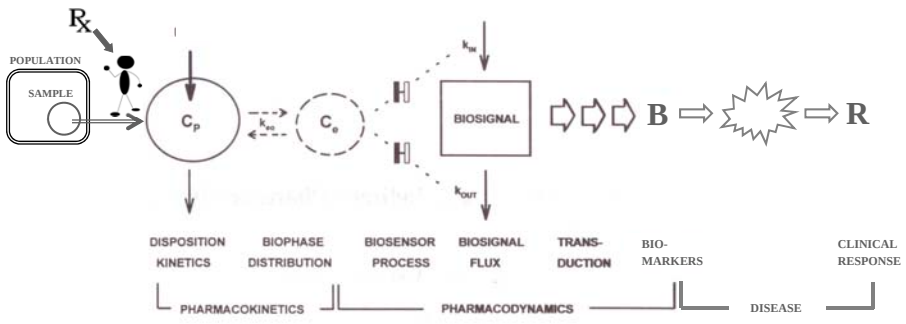
The MLEM Algorithm

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

ADAPT 5 Population Programs

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

Population PK/PD Framework in Drug Development



Modified from Jusko et al., *J. Pharmacokinet. Pharmacodyn.*, **23**:1995.

The Population Problem

- Expanded Notation to Incorporate Multiple Subjects
  - Model Equations (state space formulation)

Single Subject

$$\frac{dx(t)}{dt} = f(x(t), \theta, r(t), t), \quad x(0) = g(\theta)$$
$$y(t_j) = h(x(t_j), \theta, r(t_j), t_j), \qquad j = 1, \ldots, m$$

All Subjects

$$\frac{dx_i(t)}{dt} = f_i(x_i(t), \theta_i, r_i(t), t), \quad x_i(0) = g(\theta_i)$$
$$y_i(t_{ji}) = h_i(x_i(t_{ji}), \theta_i, r_i(t_{ji}), t_{ji}) + e_i(t_{ji}), \quad j = 1, \ldots m_i$$
$$i = 1, \ldots, N \quad \text{(subjects)}$$

- or <u>More Compactly</u>

θ_i 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

Error for the ith subject

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

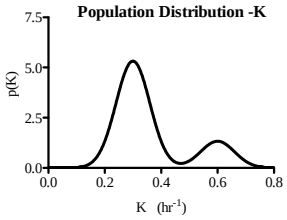
- The <u>Parametric</u> Population Problem

$\theta \rightarrow$ 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*

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

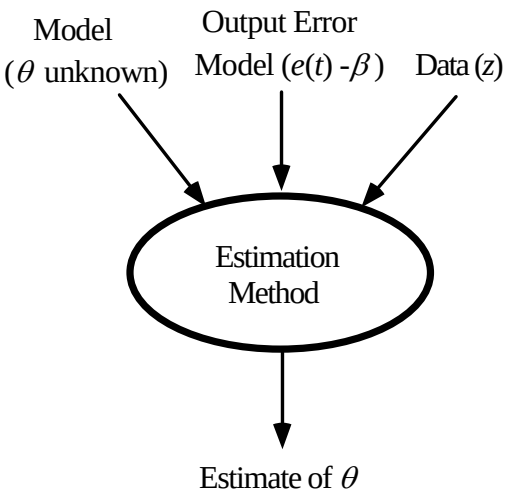
Want to Estimate:

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

Solution via Maximum Likelihood

• The Concept

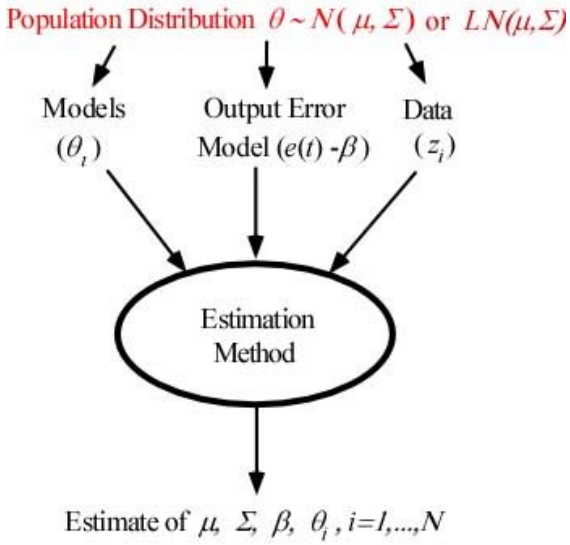
For the Individual



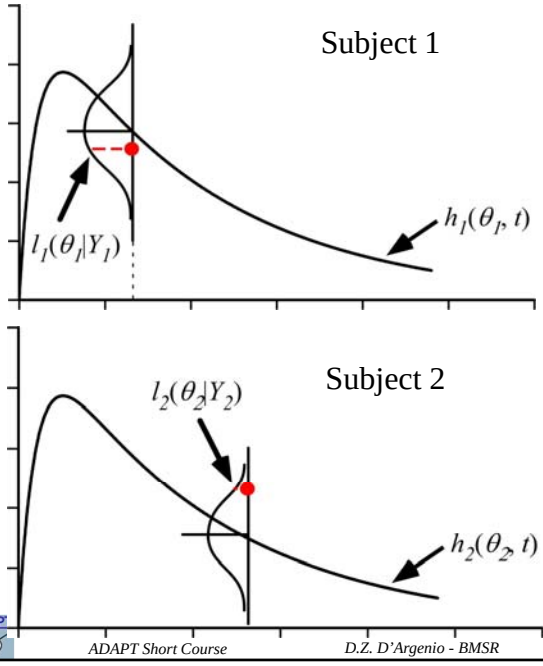
Solution via Maximum Likelihood

• The Concept

For the Population



• A Simple Example (one parameter, two subjects, one sample)



Likelihood Subject 1

$l_1(\theta_1 | Y_1)$

Likelihood Subject 2

$l_2(\theta_2 | Y_2)$

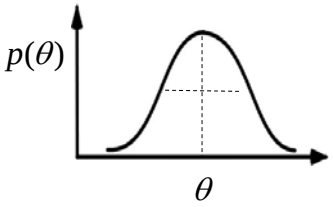
- The Overall Likelihood for both Subjects

$l_1(\theta_1 | Y_1) l_2(\theta_2 | Y_2)$ since errors are independent

- **But** θ is a Random Variable Defined by the Distribution

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

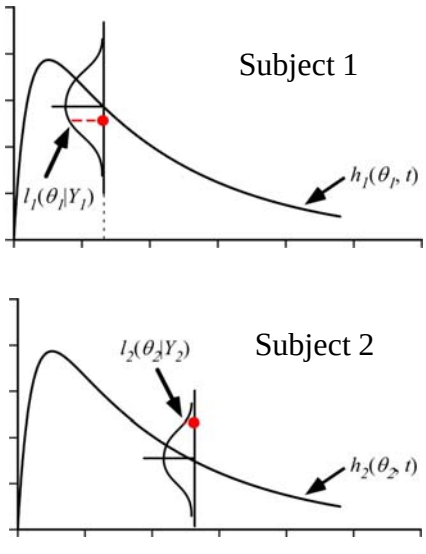
$$p(\theta | \mu, \sigma^2) \equiv p(\theta)$$



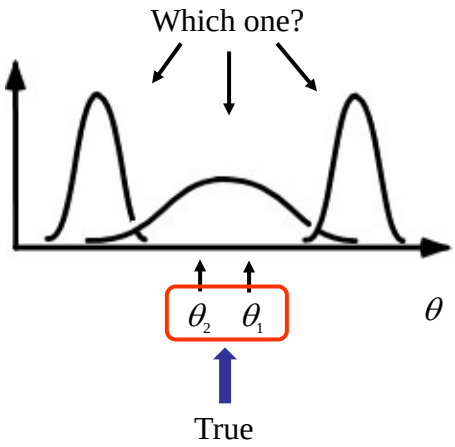
- The Estimation Problem is to find

μ and σ

- Relation Between μ, σ and $l_1(\theta_1 | Y_1) l_2(\theta_2 | Y_2)$

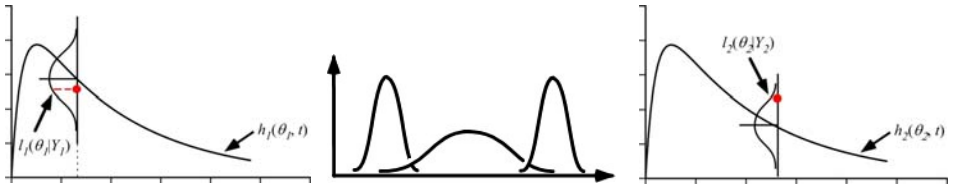


$$p(\theta | \mu, \sigma^2) = N(\mu, \sigma^2)$$



- The Average (Expected) Value of $l_1(\theta_1 | Y_1) l_2(\theta_2 | Y_2)$

$$\int l_1(\theta_1 | Y_1) l_2(\theta_2 | Y_2) p\left(\theta | \mu, \sigma^2\right) d\theta$$



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

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

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

Why use Maximum Likelihood

- Consistency

$$\theta_{ML} \rightarrow \theta_{True} \quad \text{as} \quad m \rightarrow \infty$$

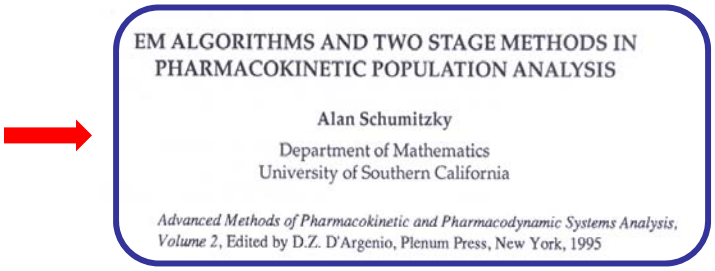
- Asymptotic Efficiency

$$\frac{\text{var}\,\theta_{ML}}{\text{var}\,\theta_{OTHER}} \leq 1 \quad \text{as} \quad m \rightarrow \infty$$

- Well-developed asymptotic theory allows hypothesis testing

NOT True for Approximate ML Approaches!

Solution of the ML problem via the EM Algorithm

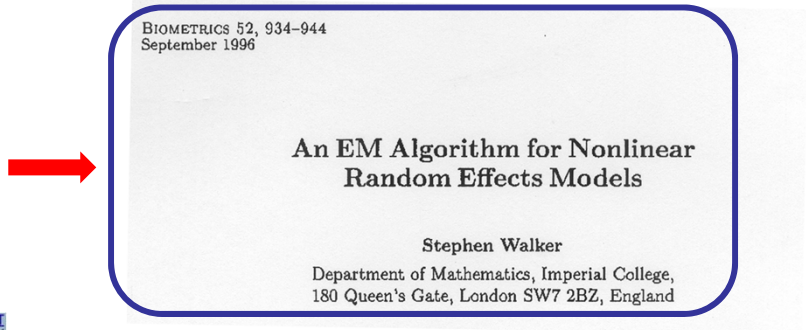


EM ALGORITHMS AND TWO STAGE METHODS IN PHARMACOKINETIC POPULATION ANALYSIS

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

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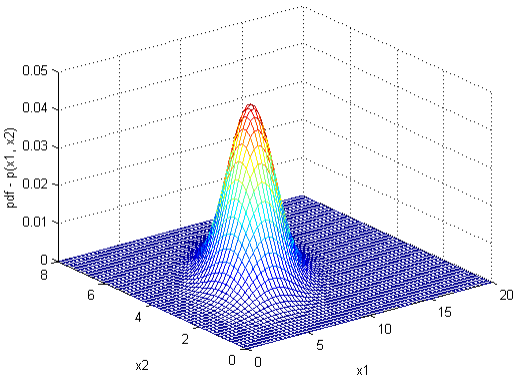
- Distribution of Two Random Variables

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

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



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

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

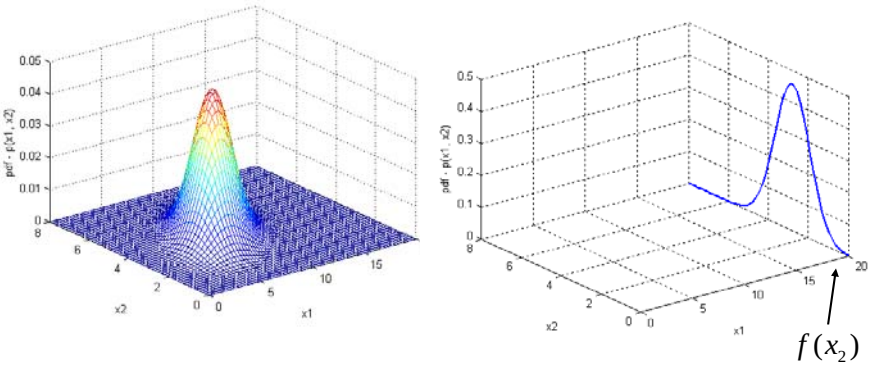
If $\rho = 0$ then

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)

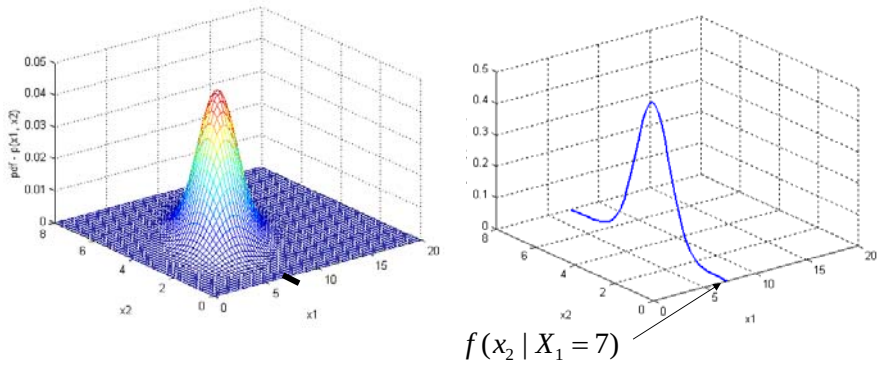


if $f(x_1, x_2) = N(\mu, \Sigma)$, then $f(x_1) = N(\mu_1, \sigma_1^2)$

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 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

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

- 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 (hard! to calculate)

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:

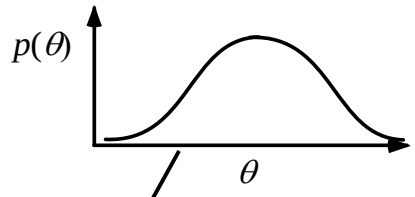
$$\bar{\theta}_i^{(k)} = E\left[\theta \mid Y_i, \mu^{(k)}, \Sigma^{(k)}, \beta^{(k)}\right]$$

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

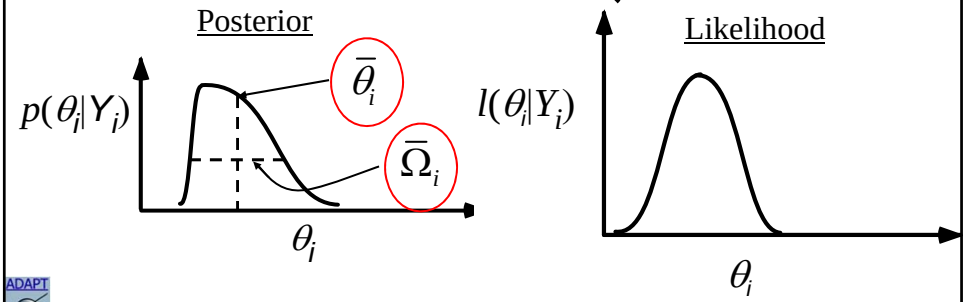
The conditional density of θ is:

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

Recall from Bayes' Theorem:



$$p(\theta_i|Y_i) = l(\theta_i|Y_i)\, p(\theta|\mu,\Sigma)/c$$



- Sampling Based Methods used to Calculate Conditional Means and Variances

- Concept: Densities and Samples

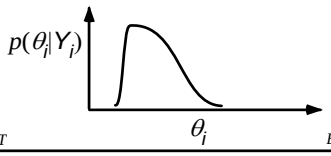
$$p(\alpha), \qquad \alpha_i,\ i = 1, \ldots$$

Densities ⟷ Samples from Densities

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

$$\mu_\alpha \approx \bar{\alpha} = \frac{1}{n}\sum \alpha_i \qquad \sigma_\alpha^2 \approx s_\alpha^2 = \frac{1}{n-1}\sum \left(\alpha_i - \bar{\alpha}\right)^2$$

- OK, we need samples from $p(\theta \mid Y_i, \mu, \Sigma, \beta)$



via Importance Sampling
(see p 64 ADAPT User's Guide)

- Standard Errors also Calculated for the Following:

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

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

- Extensions
  - ✓ General error variance model
  - ✓ Covariates (constant and time varying)
  - ✓ Non-Normal additive error (nominal - dichotomous)
  - ✗ Inter occasion variability
  - ✗ Mixture Models

Programs Using the EM Algorithm to Solve the Parametric ML Likelihood Problem in Population PK/PD

- ADAPT 5
- S-ADAPT (Bob Bauer - distributed via BMSR)
- MONOLIX (Marc Lavielle, Univ. Paris) – Stochastic EM
- NONMEM 7 (Icon)
- PDx-MCPEM (Icon)

Comparison of EM Approaches to Traditional Approximate Methods

Lyon 2004-2005 Comparison of NLME Methods

Presented at PAGE 2005

Stochastic EM algorithms in population PKPD analyses

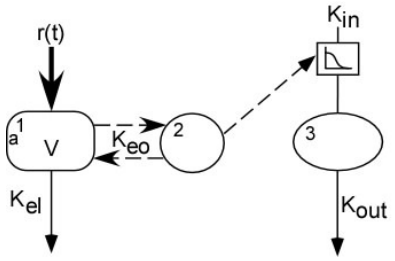
Pr France Mentré, INSERM U738, University Paris Diderot
Pr Marc Lavielle, INRIA, Universities Paris 5 & 11
Paris, France

France Mentré, ACOP, March 2008

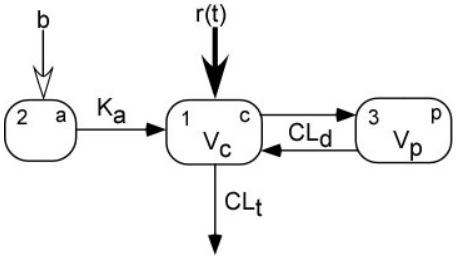
ADAPT 5 Population Programs

- 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 data files

```
Subject1
   0                # No. Model Inputs
   1                # No. Bolus Inputs
   1                # No. Input Events
    0.000     100.0  # Input Time, Bolus Value
   1                # No. Output Equations
   3                # No. Observations
    0.100       7.8  # Obs. time, Measurement
    0.250       7.4  # Obs. time, Measurement
    0.500       7.1  # Obs. time, Measurement
Subject2
   0                # No. Model Inputs
   1                # No. Bolus Inputs
   1                # No. Input Events
    0.000      40.0  # Input Time, Bolus Value
    1                # No. Output Equations
    4                # No. Observations
    1.000      16.0  # Obs. time, Measurement
    2.000      13.0  # Obs. time, Measurement
    4.000       7.7  # Obs. time, Measurement
    6.000       4.9  # Obs. time, Measurement

 ...
```

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

```
Subject1
   0                  # No. Model Inputs
   1                  # No. Bolus Inputs
   1                  # No. Input Events
    0.000     100.0   # Input Time, Bolus Value
   2                  # No. Output Equations
   3                  # No. Observations
    0.100    7.8  -1  # Obs. time, Meas. 1, Meas. 2
    0.250    7.4  -1  # Obs. time, Meas. 1, Meas. 2
    0.500    7.1  -1  # Obs. time, Meas. 1, Meas. 2
Subject2
   0                  # No. Model Inputs
   1                  # No. Bolus Inputs
   1                  # No. Input Events
    0.000      40.0   # Input Time, Bolus Value
   2                  # No. Output Equations
   4                  # No. Observations
    1.000  -1  16.0   # Obs. time, Meas. 1, Meas. 2
    2.000  -1  13.0   # Obs. time, Meas. 1, Meas. 2
    4.000  -1   7.7   # Obs. time, Meas. 1, Meas. 2
    6.000  -1   4.9   # Obs. time, Meas. 1, Meas. 2

 ...
```


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

```
Subject1
   1                    # No. Model Inputs
   1                    # No. Bolus Inputs
   2                    # No. Input Events
 0.000     100.0  0.0   # Input Time, IV Rate, Bolus Value
 0.000       0.0  0.0   # Input Time, IV Rate, Bolus Value
   1                    # No. Output Equations
   3                    # No. Observations
    0.100       7.8     # Obs. time, Measurement
    0.250       7.4     # Obs. time, Measurement
    0.500       7.1     # Obs. time, Measurement
Subject2
   1                    # No. Model Inputs
   1                    # No. Bolus Inputs
   1                    # No. Input Events
    0.000      0.0  40.0 # Input Time, IV Rate, Bolus Value
    1                    # No. Output Equations
    4                    # No. Observations
    1.000      16.0      # Obs. time, Measurement
    2.000      13.0      # Obs. time, Measurement
    4.000       7.7      # Obs. time, Measurement
    6.000       4.9      # Obs. time, Measurement

 ...
```

```
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

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

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

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

Example 2: Two parameter case – K and V

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

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

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

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

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

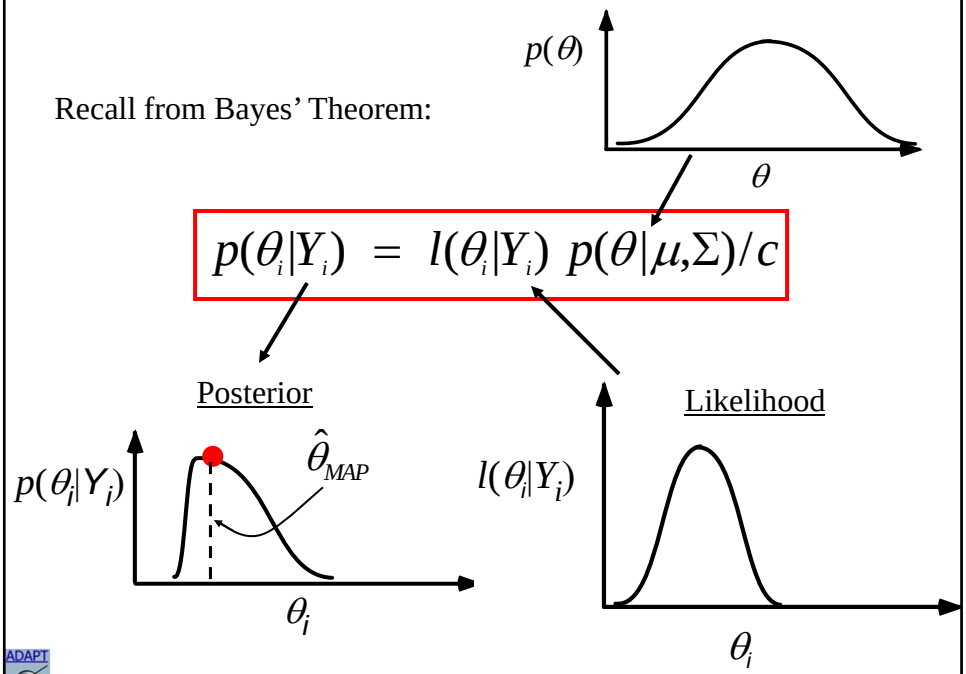
$k = 0$

- Stage 1 – Estimation (Individual MAP Estimates)

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

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

Recall from Bayes' Theorem:



- Stage 2 – Updating

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

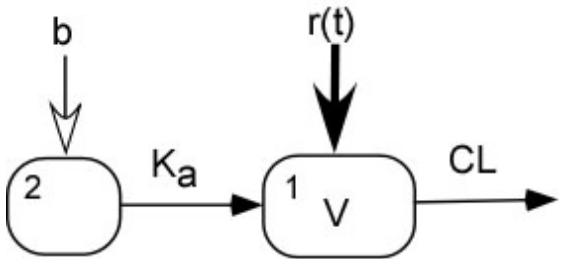
$$\Sigma^{(k+1)} = \frac{1}{N}\sum_{i=1}^{N}\left\{\left(\hat{\theta}_i^{(k)} - \mu^{(k+1)}\right)\left(\hat{\theta}_i^{(k)} - \mu^{(k+1)}\right)^T + \hat{\Omega}_i^{(k)}\right\}$$

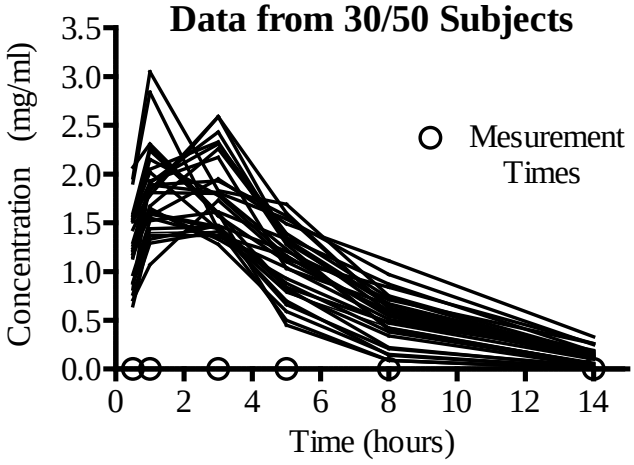
$$\beta^{(k+1)} = \arg\max_{\beta}\prod_{i=1}^{N} p_i(Y_i \mid \hat{\theta}_i^k, \beta)$$

Repeat Steps 1 and 2

Case Study – One Compartment Model - MLEM

This case study uses the MLEM program to perform a population analysis of data from 50 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 **pop1.for** for use in this example. Initial guesses for all population mean ands population covariance are entered in the POPINIT subroutine in the model file **pop1.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 **pop1.for**, **pop1.dat** and **pop1.prm** (enter **pop1.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?
CL (L/hr)	8.0	Y
V (L)	30.0	Y
Ka (hr^{-1})	1.0	Y
IC(1)	0.0	N
IC(2)	0.0	N
SDinter	0.1	Y
SDslope	0.1	Y

Use the following option values:

Fix non estimated system parameters? **n**
Parameter distribution model: **Lognormal**
Covariance matrix: **Full**
Number of samples/EM iteration: **1000**
Number of EM iterations: **40**

View the results stored in the **pop1.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 -----

Sat Aug 20 13:27:13 2011

Data file name: D:\AdaptV5\usersguide\Examples\pop1.dat

Model:  POP1.FOR: - 1 comp. pop. example base model

Number of data sets analyzed successfully:    50

Importance Sampler with number samples/iteration:    1000

Total number of EM iterations:   40

Lognormal distribution option

-2logLikelihood:   -259.295

Model Selection Criteria
 AIC:       -237.295
 BIC:       -196.554
```

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

 Parameter     Mean        %RSE         Std.Dev.   SD as CV%     %RSE
  CL           8.10        3.81          1.99        24.6        16.2
  V            30.8        4.11          7.45        24.2        19.6
  Ka           1.02        4.19         0.207        20.4        18.8
  IC(   1)     0.00      Not estimated
  IC(   2)     0.00      Not estimated

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

  As Covariance Matrix:

           CL        V         Ka
 CL         3.97
 V         -3.32      55.5
 Ka        -.234E-01 0.167     0.430E-01

  As Covariance Matrix for ln(parameters):

           CL        V         Ka
 CL        0.605E-01
 V         -.133E-01 0.585E-01
 Ka        -.285E-02 0.535E-02 0.416E-01

  As Correlation Matrix:

           CL        V         Ka
 CL          1.00
 V          -0.22      1.00
 Ka         -0.06      0.11      1.00

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

           CL        V         Ka
 CL        0.198E-01
 V         0.123E-01 0.229E-01
 Ka        0.120E-01 0.130E-01 0.162E-01

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

Parameter     Estimate    %RSE
  SDinter     0.164E-02   155.
  SDslope     0.105       6.80

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

  Parameter     Mean       Std.Dev.
  Kel          0.263      0.100
  LAM1         0.263      0.100
  t1/2-LAM1     2.64       1.01
```

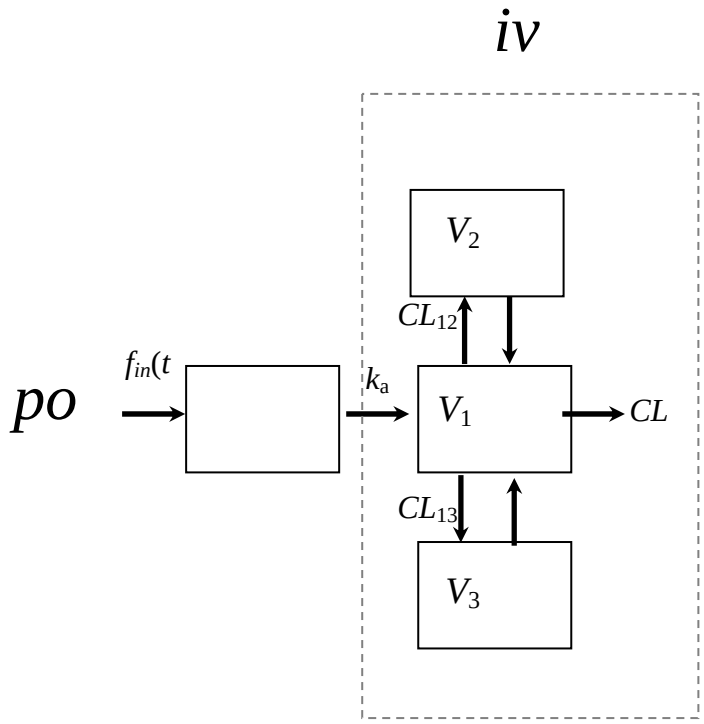
Case Study – Population Analysis of Dissolution-Absorption Models

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)

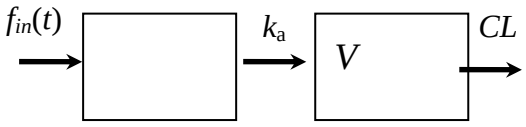
   Table

	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

Absorption/Disposition Modeling

Rate and Extent of Bioavailability

- Why?

  To avoid biased estimates due to model misspecification

  Determination of the absorption kinetics (extent and rate)

- First-order model is an oversimplification

  Maximum absorption rate is not achieved instantaneously
  Dissolution is often rate limiting

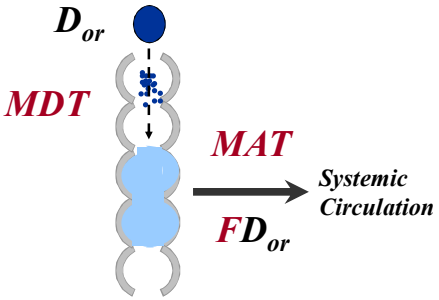
- Case study: Extended release product

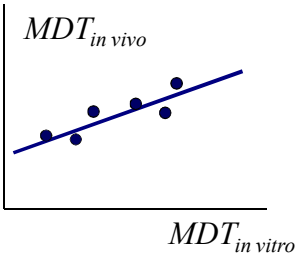
Oral Administration

Mean Input Time $MIT = MDT + MAT$

Dissolution MDT

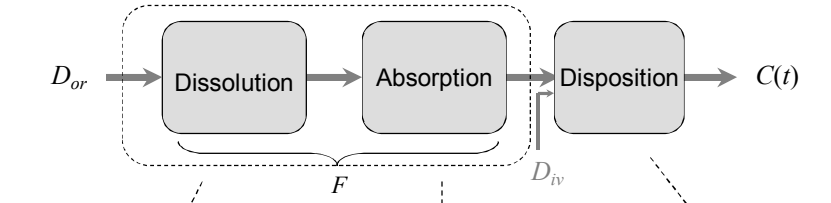
Absorption MAT

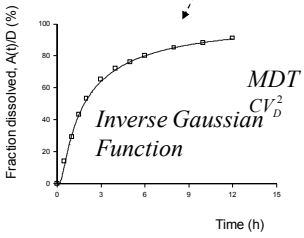




Dissolution as Determinant of Bioavailability

"Extended Release" dosage form

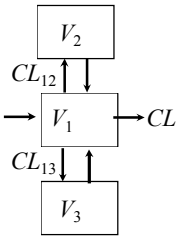




First order
MAT=
$1/k_a$

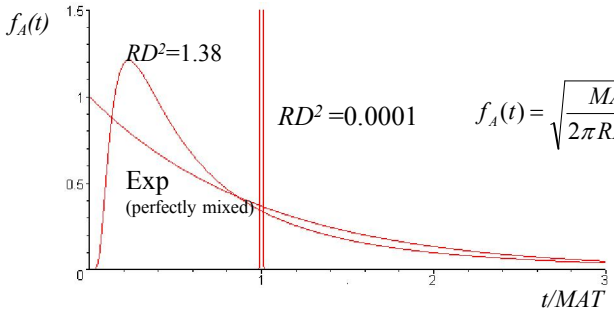
1. Fit of iv data

2. Fit of oral data with 3-comp. Parameters fixed

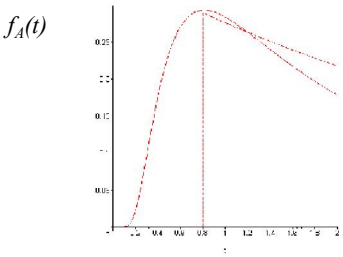


3-Compartment

Input Rate: Inverse Gaussian Density

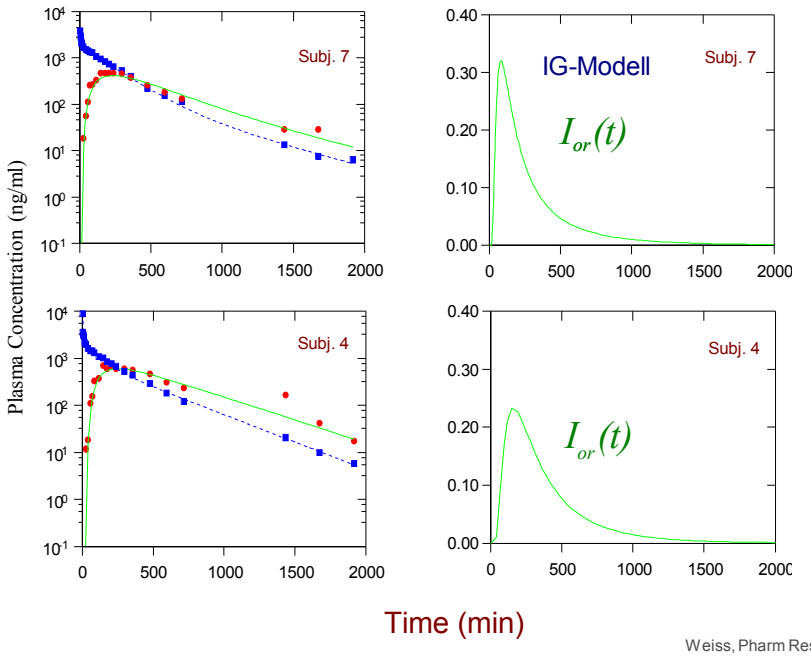


$$f_A(t) = \sqrt{\frac{MAT}{2\pi RD^2 t^3}} \exp\left[-\frac{(t-MAT)^2}{2RD^2\, MAT t}\right]$$



MAT=5

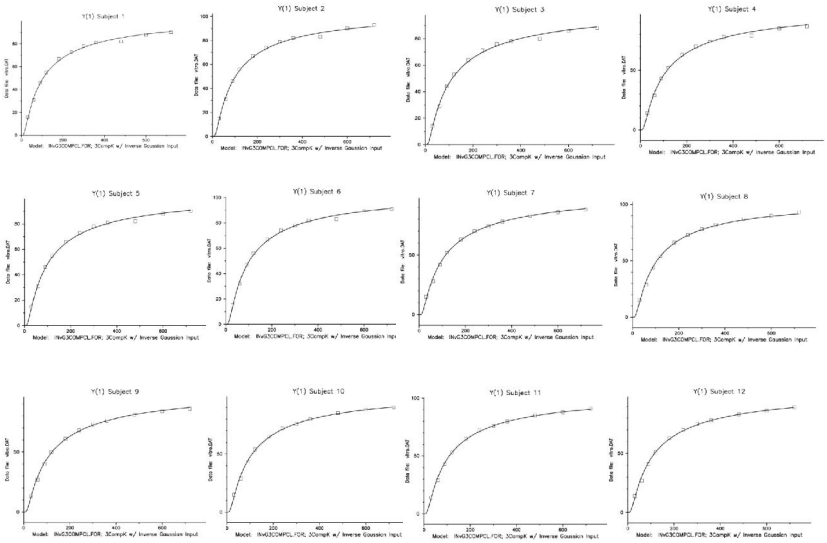
$RD^2 = 2$



Weiss, Pharm Res, 1996

IG- Fit of Dissolution Data (ADAPT Population Analysis)

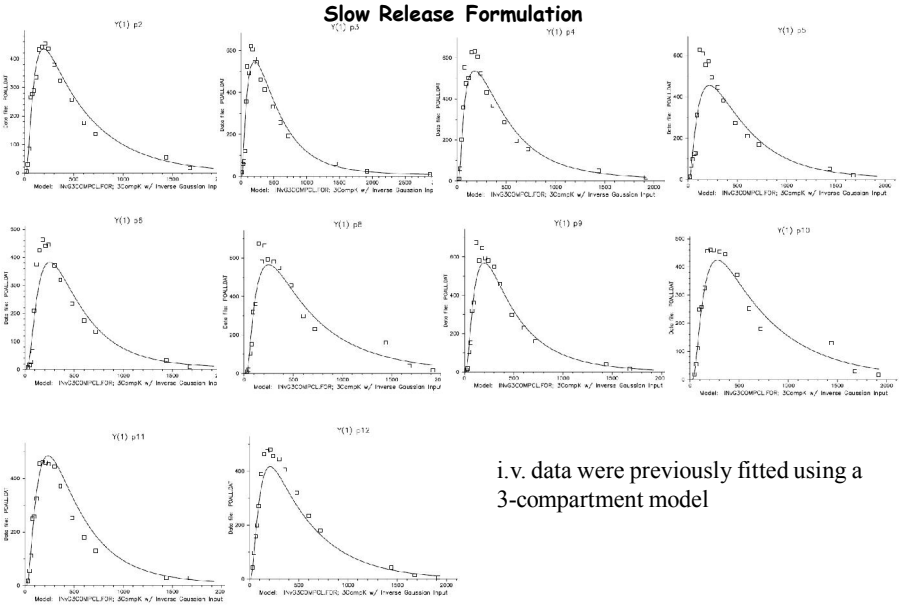
Slow Release Formulation



Wang, Weiss, D'Argenio J Clin Pharmacol, 2008

IG-Input Model Fit of Oral Data (ADAPT Population Analysis)

Slow Release Formulation



i.v. data were previously fitted using a 3-compartment model

Wang, Weiss D'Argenio J Clin Pharmacol ,2008

Comparison of the Population Analysis of Oral Data for the Extended-Release Dosage Form Using the 2 Different Input Models

	IG/MAT Model			IG Model	
	Population Mean	Population SD		Population Mean	Population SD
F, %	69.9	9.22	F, %	69.8	9.10
MDT, min	318	115	MIT,min	332	77.7
MAT, min	33.9	14.4			
CV^2_D	1.93	0.369	CV^2_I	1.22	0.178
$t_{D,max}$	53.4	19.8	$t_{I,max}$	84.8	19.7
$MDT_{invitro}$, min	302	39			
AIC	1954			1970	

IG, inverse Gaussian; AIC, Akaike information criterion.

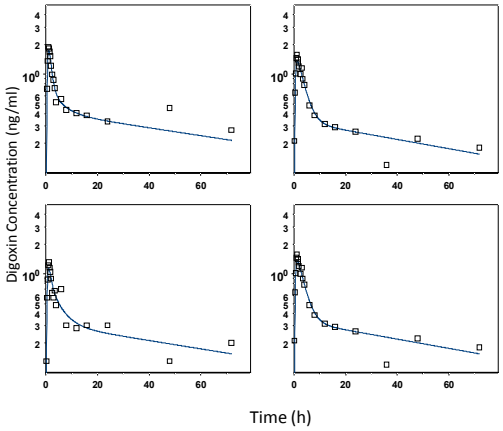
Wang, Weiss D'Argenio J Clin Pharmacol ,2008

Digoxin Tablets
(0.5 mg Lanicor®)

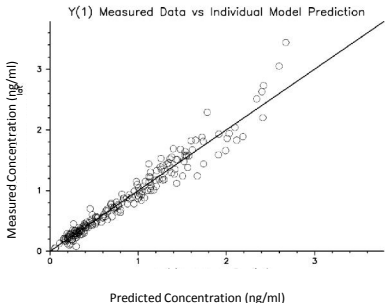
Crossover study: digoxin alone and concomitantly with oral talinolol (100 mg).

No iv data.

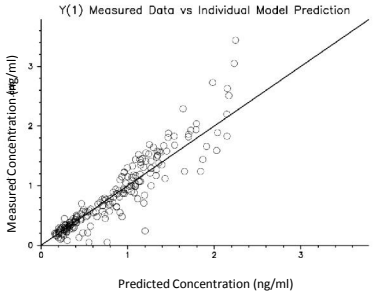
Population analysis using iv data from the literature



inverse Gaussian absorption model

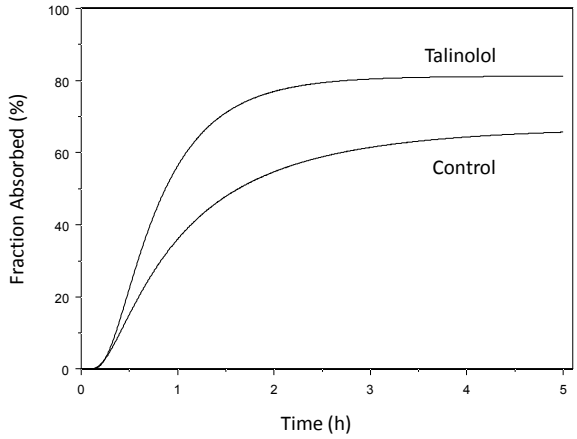


first-order absorption model



Weiss et al, J Clin Pharmacol.,2011

Effect of P-Glycoprotein Inhibition: Bioavailability

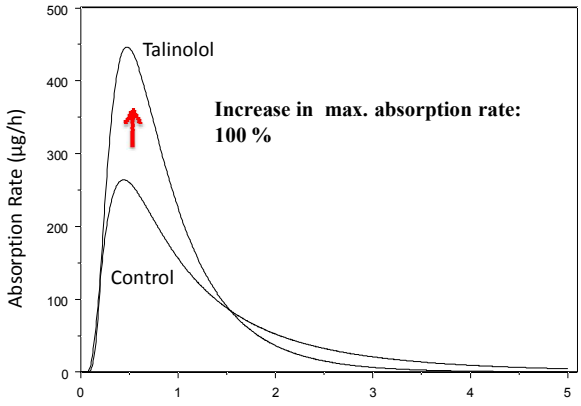


Increase in *F*: 21 %

67.1%

Weiss et al, J Clin Pharmacol,2011

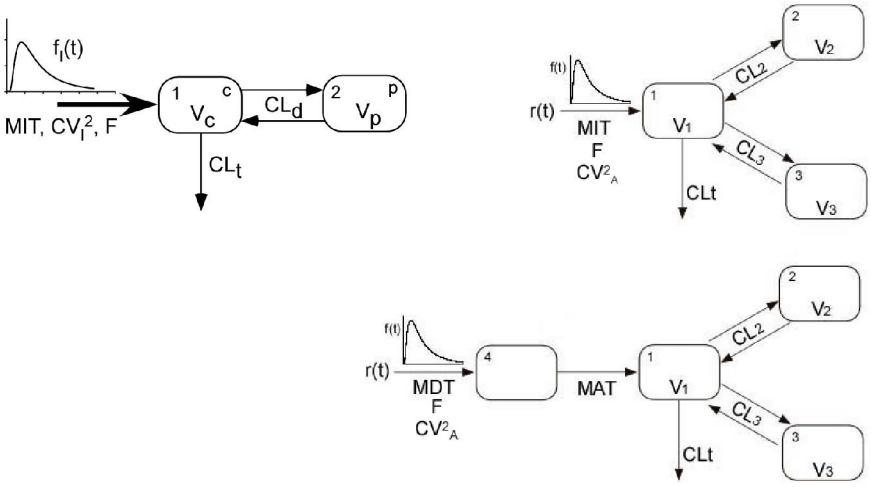
Effect of P-Glycoprotein Inhibition Absorption Rate



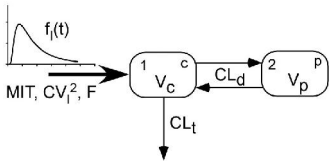
Weiss et al, J Clin Pharmacol,2011

Modeling in ADAPT

ADAPT Library: IGABS



IGABS



igabs.for *

```
      Subroutine DIFFEQ(T,X,XP)
      Implicit None

      Real*8 fI, MIT, CVI2, F
      MIT=P(5)
      CVI2=P(6)
      F=P(7)

C  Define the Inverse Gaussian Input Funtion fI
      if(t .eq. 0.0) then
       fI = 0.0
      else
       fI = F*B(1)*dsqrt(MIT/(2.0*pi*CVI2*t**3))*
     x           dexp(-(t-MIT)**2/(2.0*CVI2*MIT*t))
      endif

C PK Model with Inv. Gaussian Representing Systemic Drug Delivery
      XP(1) = -(P(1)+P(3))/P(2)*X(1) + P(3)/P(4)*X(2)  + fI
      XP(2) = P(3)/P(2)*X(1) - P(3)/P(4)*X(2)
```

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)

Weiss M, Sermsappasuk P, Siegmund W. Modeling the Kinetics of Digoxin Absorption: Enhancement by P-Glycoprotein Inhibition. *J Clin Pharmacol* 2011 Feb 22. [Epub ahead of print].

Population Modeling with Covariates

The Population Problem with Covariates

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

Solution in MLEM

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

Coding the Covariate Model

The Population Problem with Covariates

• 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*

$$\theta_i \sim N(\mu, \Sigma) \text{ or } LN(\mu, \Sigma)$$

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

• Notation with Covariate Model

Stage 1: Same

Stage 2: *Inter-Individual Variation*

$$\theta_i \sim N(\mu_i, \Sigma) \quad \text{or} \quad LN(\mu_i, \Sigma)$$

Covariate Model

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

r_i - vector of covariate values for ith subject

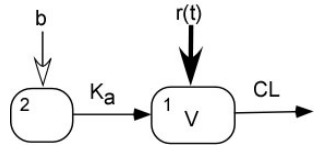
c - vector of covariate model parameters

assumed to be the same for all subjects

Want to Estimate: $c \quad \Sigma \quad \beta \quad \theta_i, i = 1, \ldots, N$

• The Concept

- Example



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

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

Without covariate

μ_{CL}

σ_{CL}

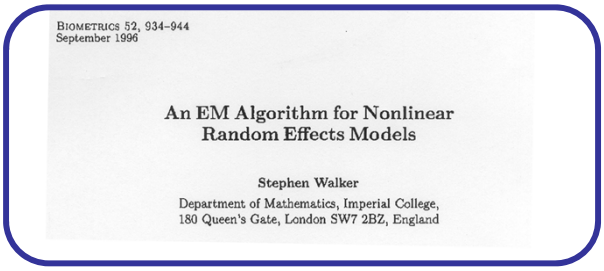
With covariate

μ_{CL_i}

$\sigma_{CL} \mid \mu_{CL_i}$

$CrCl_i$

Solution in MLEM



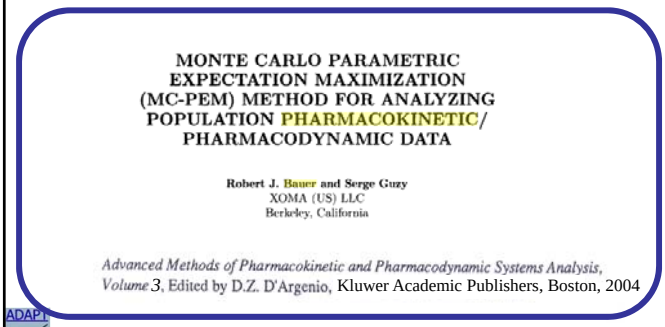
BIOMETRICS 52, 934–944
September 1996

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:

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

Solved via Nelder-Mead in MLEM

which updates the population mean for each subject:

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

- Update intersubject covariance:

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

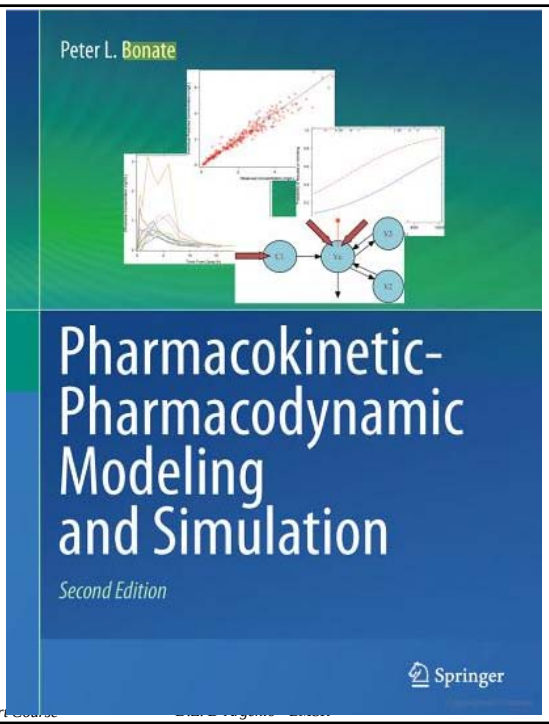
Coding the Covariate Model

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

```
C######################################################################C
       Subroutine COVMOD(PC, P, IC)
       Implicit None

       Real*8  CLnonRen, CLRenSlope
       CLnonRen =  PC(1)
       CLRenSlope =PC(2)
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)='CLRenSlope'
```

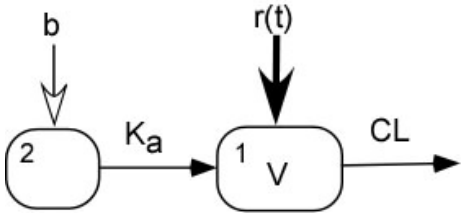
```
CC
C-----------------------------------------------------------------------C
C   For the Model Params. that Depend on Covariates Enter the Equation C
C         {e.g. Pmean(1) =  PC(1)*R(2) }                                C
C----c------------------------------------------------------------------C

       Pmean(1) = CLnonRen + CLRenSlope*R(2)   ! Kel
C-----------------------------------------------------------------------C
C-----------------------------------------------------------------------C
C
       Return
       End
```

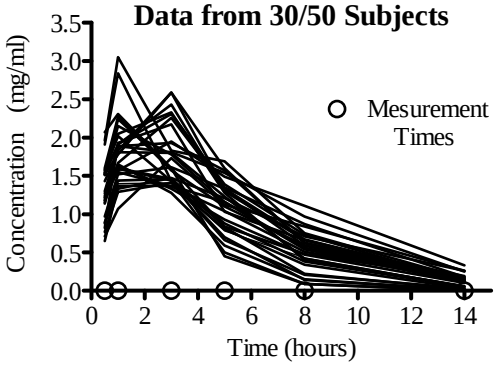
```
C#######################################################################C
       Subroutine POPINIT(PmeanI,ICmeanI,PcovI,ICcovI, PCI)
C  Initial parameter values for population program parameters (ITS, MLEM)
       ...
C-----------------------------------------------------------------------C
C  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

      PC(1)=2.0     ! CLnonRen
      PC(2)=0.01    ! CLRenSlope
C-----------------------------------------------------------------------C
```

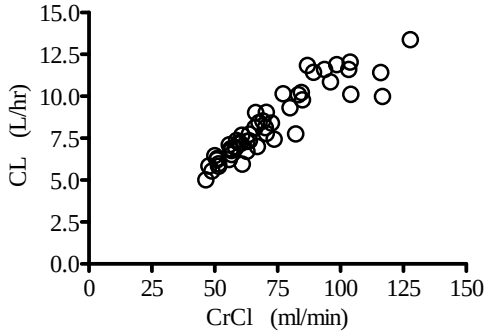
Case Study – Drug Absorption w/ Covariates - MLEM

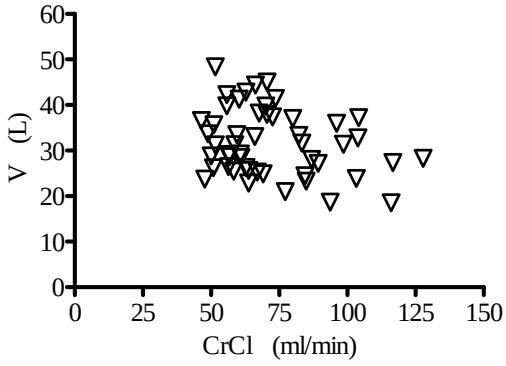
This case study uses the MLEM program to perform a population analysis with covariates. The example presented previously involving a one compartment, first order absorption model to analysis the data from 50 subjects following single dose oral administration is also used.





Creatine clearance (CrCl) was also determined in each of these 50 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 50 subjects (from the analysis using the base model) 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 **pop2.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 **pop2.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 **pop2.for**, **pop2.dat** and **pop2.prm** (enter **pop2.run** as the name of the run file when prompted). The bolus input is into compartment 2. Estimate those parameters indicated.

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	0.1	y
SDslope	0.1	Y

Also, estimate the covariate model parameter

Parameter	Initial Value	Estimate?
CLslope	1.0	Y

Use the following option values:

Fix non estimated system parameters? **n**
Parameter distribution model: **Lognormal**
Covariance matrix: **Full**
Number of samples/EM iteration: **1000**
Number of EM iterations: **30**

View the results stored in the **pop2.run** file (end of file).

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

 Sat Aug 20 15:12:05 2011

 Data file name: D:\AdaptV5\usersguide\Examples\pop2.dat

 Model:  POP2.FOR: - 1 comp. pop. example w/ covariate

 Number of data sets analyzed successfully:    50

 Importance Sampler with number samples/iteration:    1000

 Total number of EM iterations:   30

 Lognormal distribution option

 -2logLikelihood:   -355.330

 Model Selection Criteria
  AIC:       -333.330
  BIC:       -292.589

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

 Parameter     Mean        %RSE         Std.Dev.   SD as CV%     %RSE
  CL            --          --            --        8.34         14.9
  V            30.8        4.13          7.44       24.1         18.5
  Ka           1.02        4.24         0.209       20.5         18.2
  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):

           CL        V         Ka
 CL        0.695E-02
 V         -.565E-03 0.583E-01
 Ka        -.105E-02 0.571E-02 0.422E-01

  As Correlation Matrix:

……..

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

……..

             --- C. Covariate Model Parameters ---

Parameter     Estimate    %RSE
  CLslope      8.15       1.71

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

Parameter     Estimate    %RSE
  SDinter     0.172E-02   140.
  SDslope     0.104       6.37
```

Recirculatory Modeling of Drug Disposition

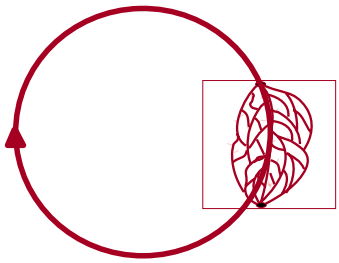
- Why? Modeling of distribution kinetics

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

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

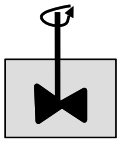
Mixing/Distribution

Body



Circulation through fractal network

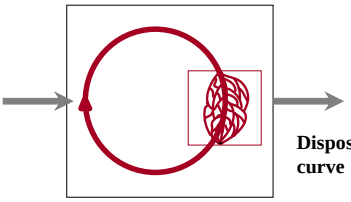
Reactor



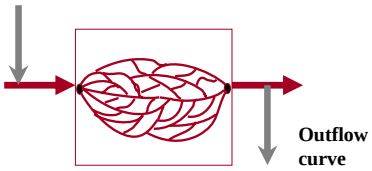
Turbulent mixing

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

Residence time Sytem



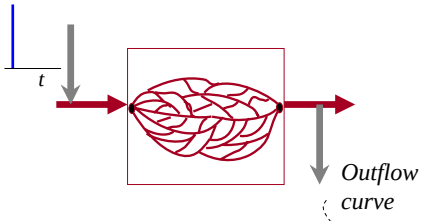
Transit time Sytem



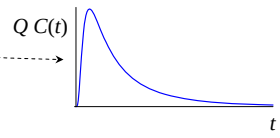
Mean transit time ⇨ **Extent of distribution**

Transit time dispersion ⇨ **Rate of distribution**

Transit Time Distribution



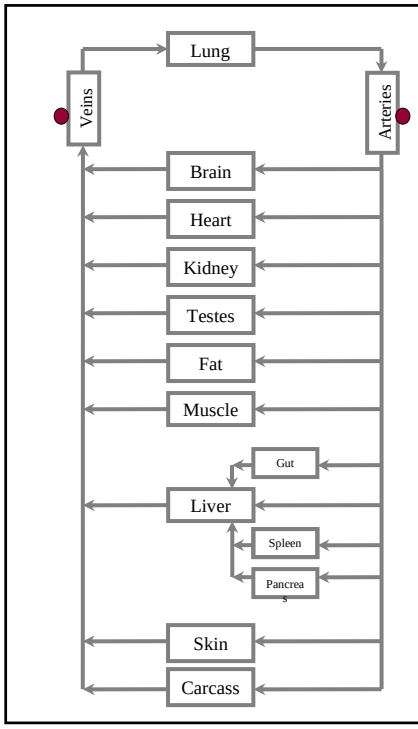
$$f_{IG}(t) = \sqrt{\frac{MTT}{2\pi RD^2 t^3}} \exp\left[-\frac{(t - MTT)^2}{2RD^2 MTT\, t}\right]$$



Density function of Inverse Gaussian Distribution

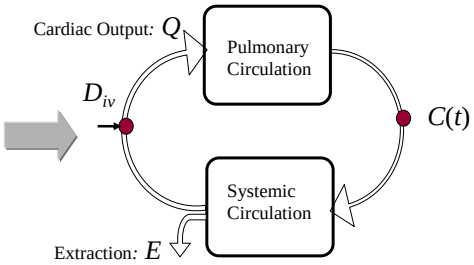
$MTT \rightarrow$ **Extent of distribution,** Distribution volume: $V = MTT\ Q$

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



Minimal Circulatory Model

Heterogeneous subsystems



Weiss et al., Br J Clin Pharm, 1996

Model Formulation in the Laplace Domain

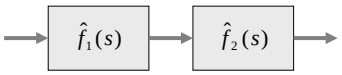
Model Structure:

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

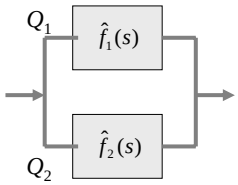
Limitation of using compartments as subsystems → *exponential distributed transit times*

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

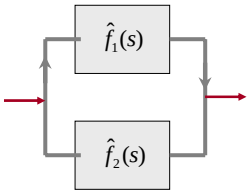
Model building: Laplace Transformation



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

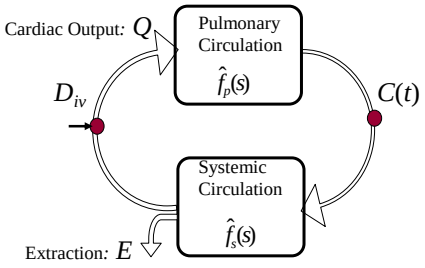


$$\hat{f}(s) = q\hat{f}_1(s) + (1-q)\,\hat{f}_2(s)$$
$$q = Q_1/Q$$



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

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

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

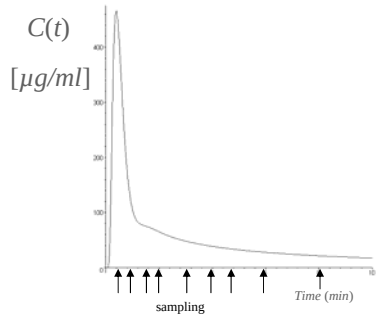
ADAPT II + Talbot's Method

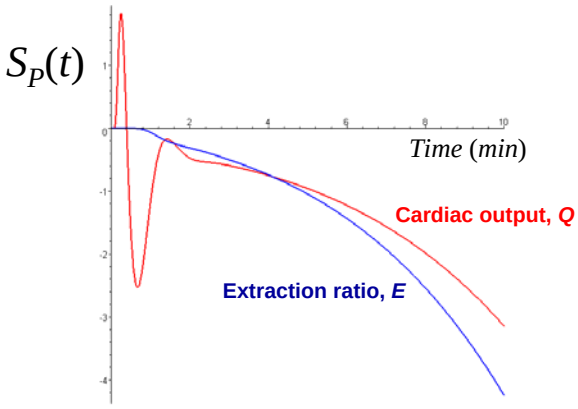
Schalla & Weiss, Eur J Pharm Sci, 1999

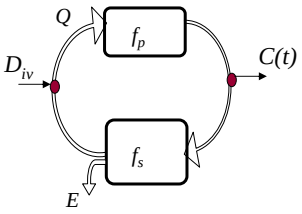
Sensitivity

Sorbitol in humans

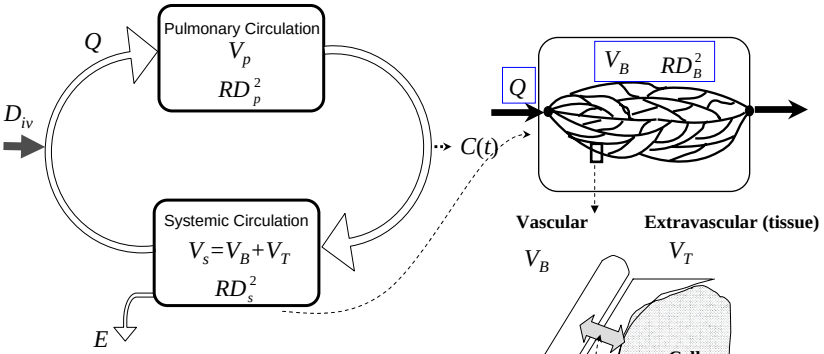
Bolus dose, 0.8 g







Physiological Interpretation of RD²

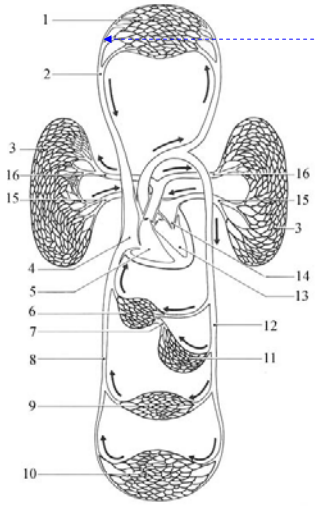


$$RD_s^2 = RD_B^2 + \frac{Q}{PS}\frac{2(V_T/V_B)^2}{(1+V_T/V_B)^2}$$

Weiss, Pharm Res, 2007

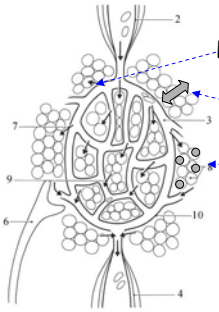
W1

First-principles modeling of distribution kinetics



Advective transport

Advective dispersion → Vascular mixing



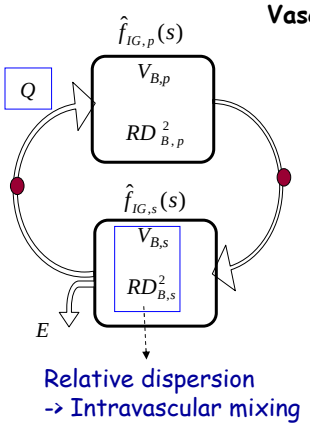
Permeation (Capillary uptake)

Diffusion (Extravascular)

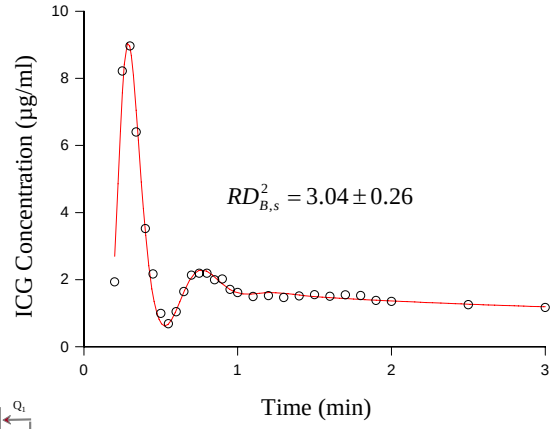
Tissue Binding

Vascular Mixing Kinetics

Vascular Marker (ICG) in Dog

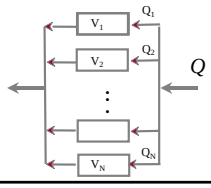


Relative dispersion
-> Intravascular mixing



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

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

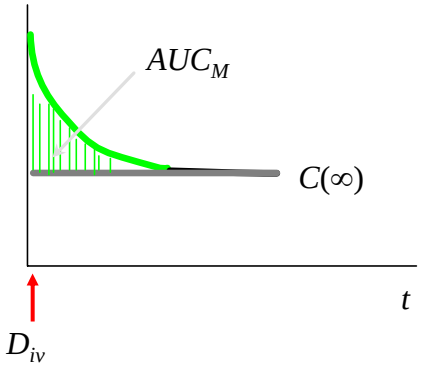


$MTT_i = V_i / Q_i$

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

W1 Weiss, 6/10/2005

Distribution Kinetics: Area Under the Mixing Curve

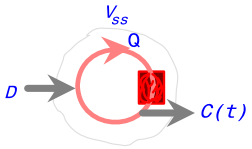


$$AUC_M = \frac{D_{iv}}{Q}\frac{1}{2}(RD_c^2 - 1)$$

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

Relative Dispersion of Transit Time ⇒ Rate of Distribution

$AUC_M = 0$
well-mixed system



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

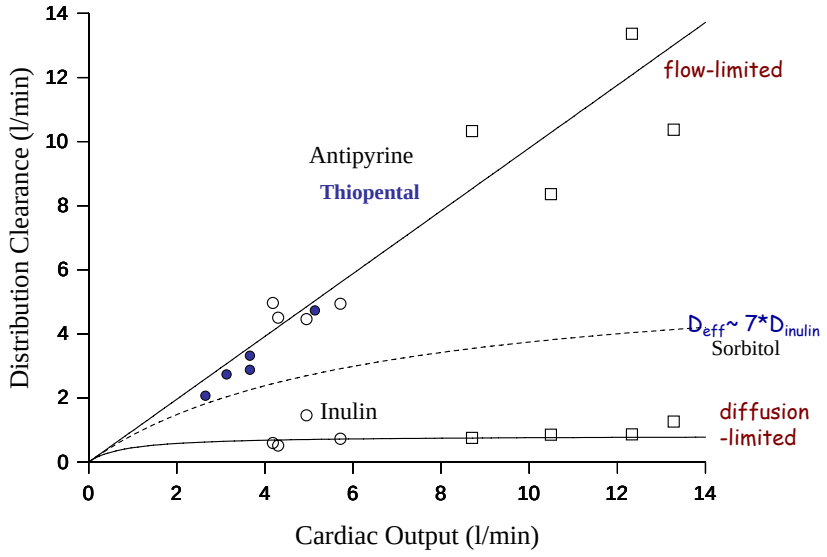
Distribution Clearance

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

Weiss & Pang, J Pharmacokin Biopharm, 1992

From Flow-to Diffusion-Limited Distribution Kinetics

A Continuous Transition



Weiss, Krejcie & Avram, Pharm Sci, 2007

Model Parameters

$$Q, V_{pul}, RD_{pul}^2 \qquad V_s, RD_s^2, E_s$$

Distribution

Kinetics

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

Steady-state

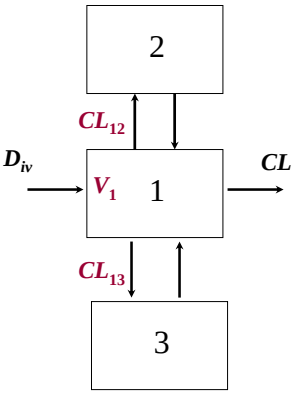
$$V_{ss} = (MTT_p + MTT_s) * Q = V_p + V_s$$

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*).

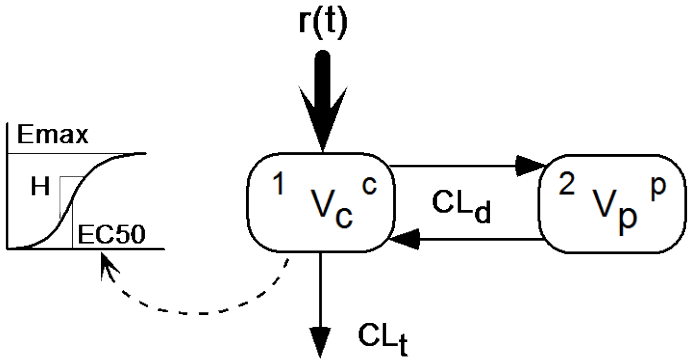
4. The distribution clearance exceeds elimination clearance (in this patient).

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)

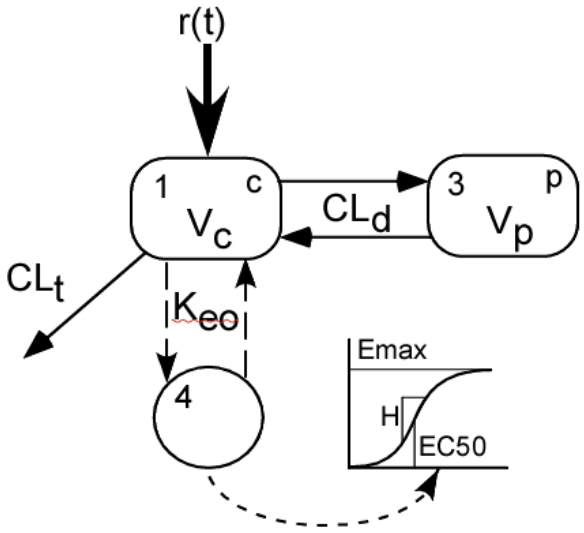
The parameters have the following units: *CL's* (L/hr^{-1}); *V's* (L); *Emax* (% max response); *EC50* (μg/ml).

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

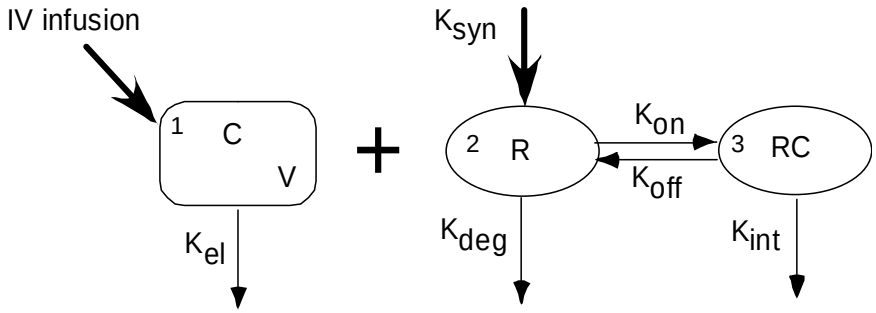
Case Study - Target Mediated Drug Disposition

Contributed by Tong Lu, Ph.D. BMSR Amgen Postdoctoral Fellow.

This case study illustrates a model for target mediated drug disposition as introduced by Mager and Jusko (JPKPD **28**:2001) and motivated by the insights of G. Levy (CPT **56**:1994).

This case study illustrates two models: the full TMDD model proposed by Mager and Jusko and the model assuming equilibrium between target and drug-target complex reported by Mager and Krzyzanski, (Pharm. Res. 22:1589–1596, 2005). Originally referred to as "the quasi-equilibrium model", this second model is now called the "rapid binding model".

Full model



$$\frac{dC}{dt} = \frac{IVrate}{V} - K_{el}C - K_{on}C \cdot R + K_{off}RC, \quad C(0)$$

$$\frac{dR}{dt} = K_{syn} - K_{deg} \cdot R - K_{on}C \cdot R + K_{off}RC, \quad R(0) \quad \left(K_{syn} = K_{deg} \cdot R(0)\right)$$

$$\frac{dRC}{dt} = -K_{int}RC + K_{on}C \cdot R - K_{off}RC, \quad RC(0)$$

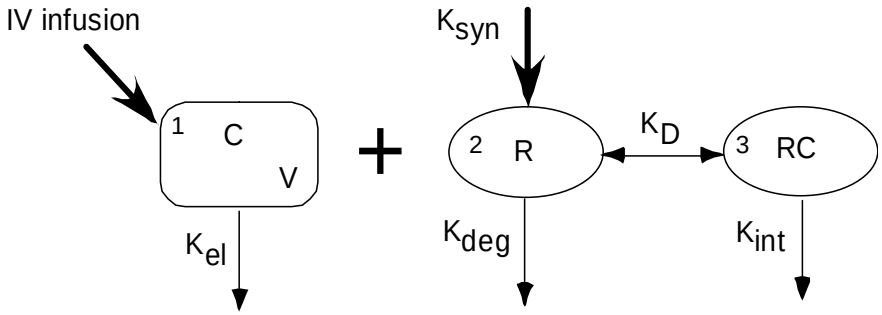
$$y_1 = C + RC$$

$$y_2 = R$$

$$y_3 = R + RC$$

The model file **TMDD.for**, data file **TMDD.dat** and parameter file **TMDD.prm** correspond to the full model.

Rapid binding model



$$C = \frac{1}{2}\left(C_{total} - R_{total} - K_D\right) + \frac{1}{2}\sqrt{\left(C_{total} - R_{total} - K_D\right)^2 - 4K_D C_{total}}$$

$$\frac{dC_{total}}{dt} = \frac{IVrate}{V} - K_{el}C - K_{int}\left(C_{total} - C\right), \quad C_{total}(0)$$

$$\frac{dR_{total}}{dt} = K_{syn} - K_{deg}\left(R_{total} - \left(C_{total} - C\right)\right) - K_{int}\left(C_{total} - C\right), \quad R_{total}(0) \quad \left(K_{syn} = K_{deg}R_{total}(0)\right)$$

$$y_1 = C_{total}$$

$$y_2 = R_{total} - \left(C_{total} - C\right)$$

$$y_3 = R_{total}$$

The model file **TMDDrb.for**, data file **TMDDrb.dat** and parameter file **TMDDrb.prm** correspond to the QE model.

Examine each of these two model files (**TMDD.for** and **TMDDrb.for**), to see how these models are implemented in ADAPT.

Using the program SIM, perform simulations for each of the two models (use run files names **TMDD.run** and **TMDDrb.run**) and compare there results.

How can you change the parameter values used with the full model simulation, so that the model outputs approach those from the quasi-equilibrium model? Show this via simulation.

The units for parameters and variables are given as follows:

Concentrations: ng/mL
Time: day

Parameter	Kel	Kdeg	Kint	V
Unit	1/day	1/day	1/day	L

Parameter	KD	Ksyn	kon	Koff
Unit	nmol/L	nmol/L/day	1/nmol/L/day	1/day

Dosage: 600mg/subject

Infusion rate	Infusion time
5184000 mg/day	0.000116 day (10 second)

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

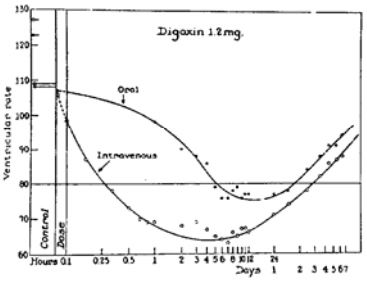
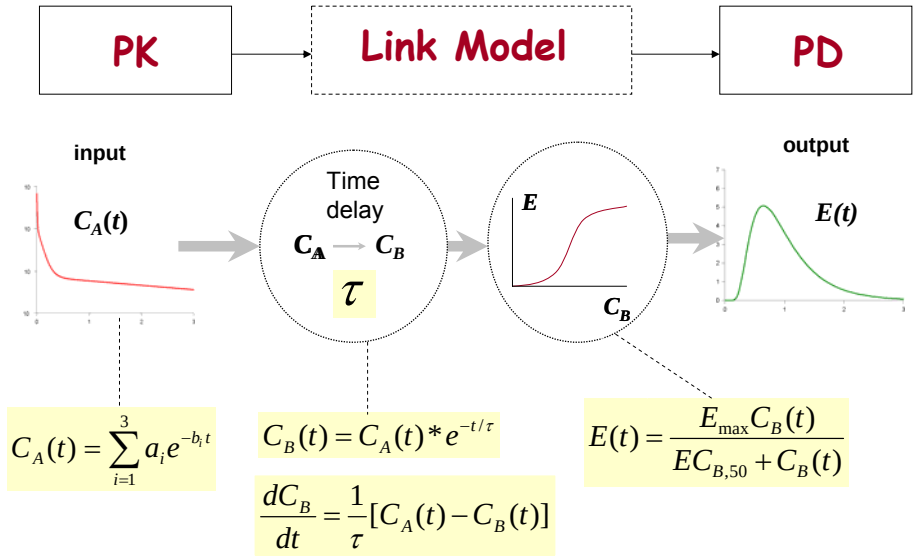


Fig. 1. Curve of onset and disappearance of digoxin action in patients with atrial fibrillation (Reprinted from Gold et al., 1953, with permission).

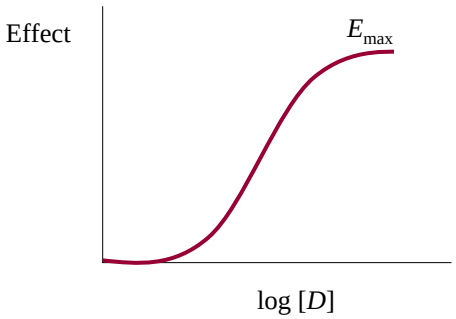
PK/PD



Traditional Method to Analyse Drug-Receptor Interaction

Steady-state experiments → no integration of kinetic information

Dose (or Concentration) -Response Curves



Occupation Theory

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

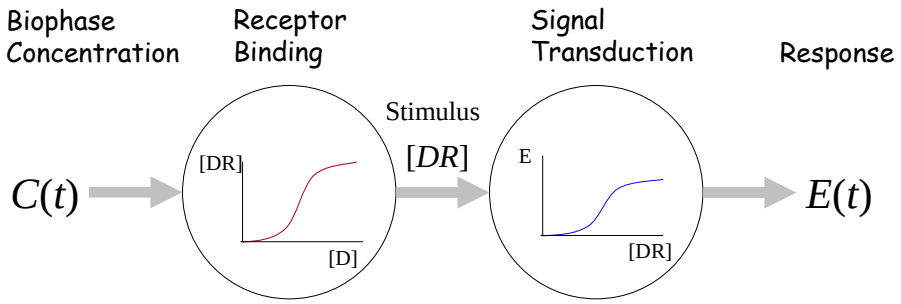
$$\frac{E}{E_{max}} = \frac{e[DR]}{[R_{tot}]} = \frac{e[D]}{[D] + K_A}$$

K_D : D producing 50% of E_{max}

Dissociation constant

more general: [DR] → Stimulus → Response

Operational Model



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

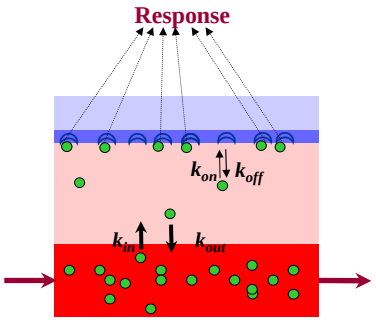
Transient state: $[DR](t)$

Transient State

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

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

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



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

(A) as bolus dose

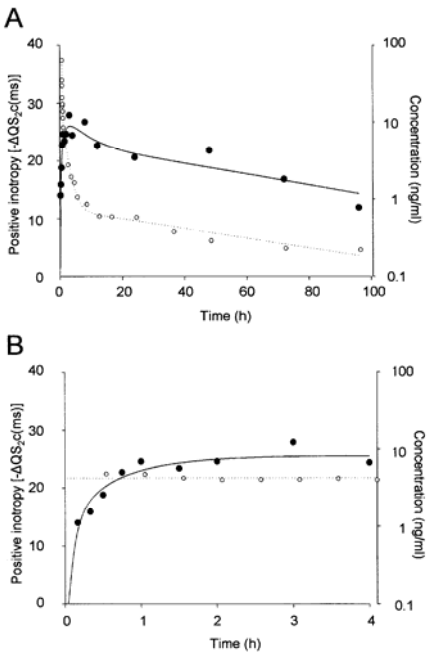
$C(t) = 57.3e^{-0.164\,t} + 9.99e^{-0.011\,t} + 0.74e^{-0.00024\,t}$

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

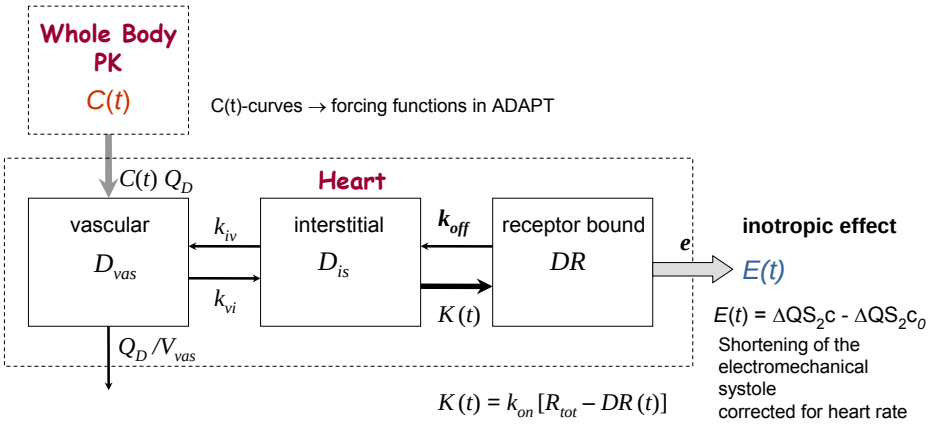
$$E_{step}(t) = \frac{E_{\max} C_0 (1 - e^{-t/\tau})}{EC_{B,50} + C_0 (1 - e^{-t/\tau})}$$

experiment

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

$\tau_{step} = 1.3$ 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

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

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

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

$$\boldsymbol{E(t)} = e\, DR(t) \qquad (4)$$

Mechanistic PK/PD Model for Digoxin in Humans

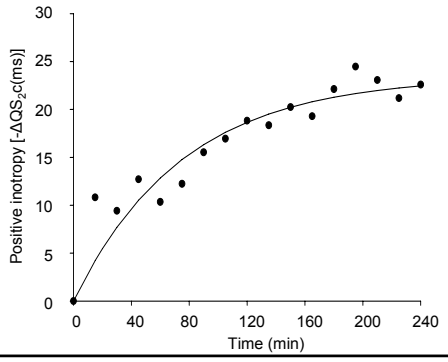
Step response (Concentration clamp experiment)

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

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'

A priori knowledge (literature, experiments)

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'

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).