

Bayesian Estimation and  
Population Analysis

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- Objective
- To Understand the Use of Population Parameters Values in Nomograms and Bayesian Estimations
  - To Understand Methods of Analysing Pharmacokinetic Population Data
    - Data Rich
    - Sparse Data

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- Population Data
- Use Population Data
    - Nomograms
    - Bayesian Analysis
  - Analysing Population Data
    - Data Rich Data by Two-step Method
    - Sparse Data by NONMEM Analysis

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### Using Population Data

- Nomogram
  - Used to Determine Initial Dose
  - Use Population Results previously determined
  - May be Based on Weight and Height
  - May Also include other Covariates such as Renal Function, Cardiac Function, Liver Status, Smoking Status

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### Using Population Data

Dose,  $V_m$

Css Km

From: Tozer, T.N. and M.E. Winter. "Phenytoin" in Applied Pharmacokinetics, ed. Evans W.E., Schentag, J.J., and Jusko, W.J. Applied Therapeutics, San Francisco, 1980

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### Population Based Parameters

- Information Available
  - Population Parameter Values
  - Population Parameter Standard Deviations
  - Effective/Toxic Concentrations

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### Bayesian Analysis

- Requires:
  - Population Values
  - Patient (Subject) Data
- Different Objective Function
- Non-linear Regression Analysis
- Possible Programs include Boomer or ADAPT II

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### Bayesian Analysis Example

- Population Values
  - Theophylline example
  - Cl  $0.86 \pm 0.35$  ml/min/kg
  - Half-life  $8.1 \pm 2.4$  hr

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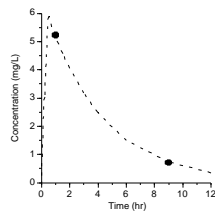
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### Bayesian Analysis Data

- Typical Data



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### Bayesian Analysis

- Objective Function

$$Obj = \sum_{i=1}^n \frac{(Calc_i - Obs_i)^2}{Variance_i} + \sum_{j=1}^m \frac{(Calc_j - Pop_j)^2}{PVariance_j}$$

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### Bayesian Analysis

- Data Weighting
  - Accurate (Not just Relative)

$$Wt = \frac{1}{a \cdot C_{obs}^b}$$

$$Wt = \frac{1}{a + b \cdot C_{obs}^c \cdot d^{(t_{last} - t)}}$$

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### Bayesian Analysis

- Results - Table (Boomer)

```

** FINAL PARAMETER VALUES **
# Name      Value      S.D.      C.V. %  Lower <-Limit-> Upper
      Population mean  S.D.      (Weight)  Weighted residual
1) kel      .19163     0.695E-01  36.     .00      1.0
      0.8560E-01  0.2500E-01  40.00   4.241
2) v        26.393     15.0      57.     1.0     0.10E+03
      42.20      15.00     0.6667E-01  -1.054
AIC = 11.17  SC = 33.44  Final MSS = 35.97
      R-squared = -2.400  Correlation Coeff = 1.000
    
```

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## Bayesian Analysis

- Results - Table (ADAPT II)

Parameter	Initial Value	Final Estimate	CV(%)	Confidence interval (95%)
V	(N) 35.00	41.37	9.525	[ 28.83 , 53.91 ]
Ke	(N) .8000E-01	.2628E-01	32.81	[ -0.1156E-02, 0.5371E-01 ]
Lam1	.8000E-01	.2628E-01	32.81	[ -0.1156E-02, 0.5371E-01 ]
TI/2 Lam1	8.664	26.38	.8621	[ 25.66 , 27.10 ]
CL	2.800	1.087	24.75	[ 0.2309 , 1.943 ]

Y( 1)

Obs.Num.	Time	Data	Model Est.	Residual	Variance
1	1.500	9.500	8.855	0.6451	1.000
2	10.00	11.00	12.24	-1.238	1.000
3	24.00	17.00	16.40	0.6006	1.000

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## Population Data Analysis

- Two Step Method
  - Data Rich Study
  - 'Traditional' PK Study
  - Combine Multi-Subject Results

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## Two Step Analysis

- Typical Data
  - Pharmacokinetic Study
  - Bioavailability Study
- Analyse Individual Data
- Combine Results
  - Simple Mean and Standard Deviation

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### Population Analysis

- NONMEM Analysis
  - Data-Sparse Study (1-3 samples per subject)
  - Combine Results from 'all' Subjects
  - Simultaneous Fit to the Data from ALL the subjects

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### NONMEM Analysis

- Typical Data - Some Examples
  - Clinical Data
    - Include Patient Covariates
      - Renal, Cardiac, Liver Function Assessment
      - Weight, Height, Sex
  - Bioavailability Data
    - Relative Bioavailability
  - Small Animal Study
    - Rats, Mice
    - Few samples per animal possible

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### NONMEM Analysis

- Three Examples
  - Clinical Study
  - Bioavailability Study
  - In Vitro Binding Study

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### NONMEM Approach

- Analysis includes Variability between Subjects and Variability within Subjects
- Analysis also includes Data Variability (Error or Variance)

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### NONMEM Analysis

$$C_p = \frac{Dose}{V} e^{-kel \cdot t} + \text{ErrorTerm}$$

$$y_{ij} = \frac{D}{V_j} \cdot e^{-kel_i \cdot t_{ij}} + ij$$

$$kel_i = [1 + 2 \cdot RF_i] \cdot (1 + i^{kel})$$

$$kel = (a + b \cdot Cl_{CR}) \times \text{ErrorTerm}$$

$$V_i = V \cdot (1 + i^V)$$

$$\text{var}(ij) = \sigma^2$$

$$\text{var}(i^{kel}) = \frac{2}{kel} \quad \text{var}(i^V) = \frac{2}{V}$$

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### NONMEM Procedure

- Prepare CONTROL and DATA Files
- Run NMTRAN to create NONMEM Files
- Run Make and Build to create executable
- Run NONMEM on File from NMTRAN

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### Example ONE

- Clinical Study
  - One Compartment Model
  - Drug Given by IV Infusion
  - Multiple Patient Data Simulated

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### Example Data - Clinical Study

- Data
- Model
- Estimation
- Output

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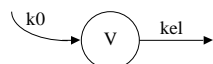
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### Example Data - Clinical Study



#### Model Specification

```

SPROBLEM Aminoglycoside example - Eta on Typical kel only
SINPUT ID AMT RATE TIME DV CRCL
SDATA TEST
SSUBROUTINES ADVAN1
SPK
TA = THETA(1)
TB = THETA(2)
TK = TA*CRCL + TB
K = TK*(1.+ETA(1))
V = THETA(3)*(1.+ETA(2))
S1 = V
ERROR
Y = F*(1. + ERR(1))
    
```

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## Example Data - Clinical Study

### Data Specification

```
$INPUT ID AMT RATE TIME DV CRCL
$DATA TEST
```

### Typical Data

```
1 70 70 0.0 0.0 72.34
1 0.0 0.0 1.50 3.4272 72.34
1 0.0 0.0 8.00 0.4081 72.34
2 80 80 0.0 0.0 83.53
2 0.0 0.0 2.50 1.80792 83.53
2 0.0 0.0 9.00 0.05992 83.53
3 70 70 0.0 0.0 63.51
3 0.0 0.0 1.25 3.78868 63.51
3 0.0 0.0 9.00 0.22855 63.51
4 140 140 0.0 0.0 20.91
4 0.0 0.0 1.25 8.9859 20.91
.....
```

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## Example Data - Clinical Study

### Estimation and Output Specification

```
$THETA (0.,.005,0.1) (0.,.01,1.0)
(1,15,100)
$OMEGA .2 .2
$SIGMA .2
$ESTIMATION PRINT=5 MAXEVALS=900
$COVARIANCE
$TABLE ID TIME AMT DV
$SCAT PRED VS DV UNIT
$SCAT WRES VS DV TIME CRCL
```

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## Example Data - Clinical Study

### Estimation Step

```
CUMULATIVE NO. OF FUNC. EVALS.: 179
PARAMETER: 0.9863E-01 0.1259E+00 0.9983E-01 -0.2210E-01 -0.9608E-02 -0.1539E-01
GRADIENT: -0.5304E+03 -0.3488E+02 0.2824E+03 0.6209E+01 0.2114E+03 0.1876E+03
ITERATION NO.: 25 OBJECTIVE VALUE: -0.1255E+04 NO. OF FUNC. EVALS.: 8

CUMULATIVE NO. OF FUNC. EVALS.: 219
PARAMETER: 0.9857E-01 0.1275E+00 0.9982E-01 -0.2210E-01 -0.9956E-02 -0.1528E-01
GRADIENT: -0.3205E+03 -0.1915E+02 0.9722E+02 -0.8242E+01 0.1142E+03 0.9623E+02
ITERATION NO.: 30 OBJECTIVE VALUE: -0.1255E+04 NO. OF FUNC. EVALS.: 0

CUMULATIVE NO. OF FUNC. EVALS.: 278
PARAMETER: 0.9887E-01 0.1216E+00 0.9986E-01 -0.2214E-01 -0.1024E-01 -0.1517E-01
GRADIENT: 0.1829E+02 0.3513E+00 -0.5171E+02 -0.1679E+02 -0.7762E+00 -0.1330E+00

MINIMIZATION SUCCESSFUL
NO. OF FUNCTION EVALUATIONS USED: 278
NO. OF SIG. DIGITS IN FINAL EST.: 3.4
```

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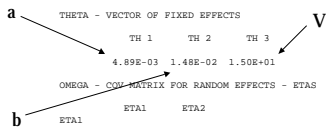
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### Example Data - Clinical Study

#### Estimation Output

```

MINIMUM VALUE OF OBJECTIVE FUNCTION  -1255.007
FINAL PARAMETER ESTIMATE
THETA - VECTOR OF FIXED EFFECTS
      TH 1      TH 2      TH 3
      4.89E-03  1.48E-02  1.50E+01
OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS
      ETA1      ETA2
      9.81E-03          <- 9.9 %
      0.00E+00  2.10E-03  <- 4.6 %
SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS
      EPS1
      4.60E-03          <- 6.8 %
    
```




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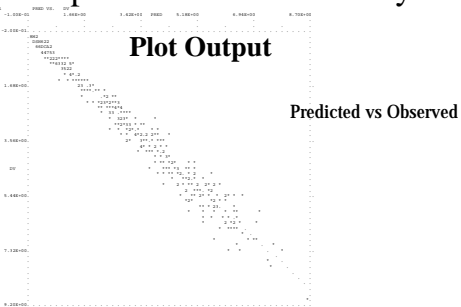
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### Example Data - Clinical Study

#### Plot Output




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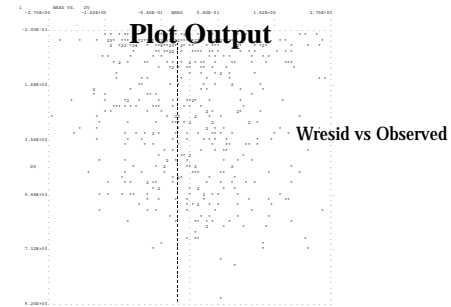
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### Example Data - Clinical Study

#### Plot Output




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### Example Data - Bioavailability

- Example Data
- Model
- Estimation
- Output

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### Example Data - Bioavailability

$$C = \frac{F \cdot \text{Dose} \cdot k_a}{V \cdot (k_a - k_{el})} \cdot \{ e^{-k_{el} \cdot t} - e^{-k_a \cdot t} \}$$

#### Model Specification

```

$PROB Simulated Data - Two Dose PO (REF V-55,75)
$INPUT ID AMT PROD TIME DV EVID
$DATA PO
$SUBROUTINE ADVAN2
$PK
KA1 = THETA(1)*(1.+ETA(1))
KA2 = THETA(5)*(1.+ETA(5))
F2 = THETA(4)*(1.+ETA(4))
KEL = THETA(2)*(1.+ETA(2))
VD = THETA(3)*(1.+ETA(3))
F1 = (2-PROD)*1.0 + (PROD-1)*F2
KA = (2-PROD)*KA1 + (PROD-1)*KA2
K = KEL
S2 = VD
$ERROR
Y = F*(1.+ERR(1))
    
```

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### Example Data - Bioavailability

#### Data Specification

```

$PROB Simulated Data - Two Dose PO (REF V-55,75)
$INPUT ID AMT PROD TIME DV EVID
$DATA PO
$SUBROUTINE ADVAN2
    
```

#### Typical Data

```

1 250 1 0.0 0.0 1
1 0.0 1 0.25 4.99 0
1 0.0 1 0.5 8.45 0
1 0.0 1 1 12.07 0
1 0.0 1 2 13.74 0
1 0.0 1 4 12.19 0
1 0.0 1 6 10.06 0
1 0.0 1 9 7.78 0
1 0.0 1 12 5.87 0
1 0.0 1 24 1.91 0
1 250 2 0.0 0.0 4
1 0.0 2 0.25 1.69 0
    
```

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## Example Data - Bioavailability

### Estimation and Output

### Specification

```

$THETA (0.5,1.5,5) (.001,0.1,1) (1,15,100)
          (0.5,0.75,1.25) (0.25,1,2.5)
$OMEGA .10 .10 .10 .10 .10
$SIGMA .10

$SEST PRINT=5 MAXEVAL=1500
$COVAR
$TABLE ID PROD DV
$SCAT DV PRED VS TIME
$SCAT PRED VS DV UNIT
$SCAT WRES VS TIME
    
```

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## Example Data - Bioavailability

### Estimation Step

```

ITERATION NO.: 75 OBJECTIVE VALUE: -0.1389E+04 NO. OF FUNC. EVALS.:24
CUMULATIVE NO. OF FUNC. EVALS.: 1065
PARAMETER: 0.8811E-01 0.9391E-01 0.1003E+00 0.1063E+00 0.8318E-01 0.3413E-01
0.1818E-01 -0.3041E-02 0.2953E-01 0.2234E-01
0.3287E-02
GRADIENT: 0.1332E+02 0.4338E+02 0.5042E+03 -0.8576E+01 0.6322E+01 0.7123E+01
-0.1558E+02 0.3528E+02 0.1821E+01 0.4132E+00
-0.5080E+03

ITERATION NO.: 76 OBJECTIVE VALUE: -0.1389E+04 NO. OF FUNC. EVALS.: 0
CUMULATIVE NO. OF FUNC. EVALS.: 1065
PARAMETER: 0.8811E-01 0.9391E-01 0.1003E+00 0.1063E+00 0.8318E-01 0.3413E-01
0.1818E-01 -0.3041E-02 0.2953E-01 0.2234E-01
0.3287E-02
GRADIENT: 0.1332E+02 0.4338E+02 0.5042E+03 -0.8576E+01 0.6322E+01 0.7123E+01
-0.1558E+02 0.3528E+02 0.1821E+01 0.4132E+00
-0.5080E+03

MINIMIZATION SUCCESSFUL
NO. OF FUNCTION EVALUATIONS USED: 1065
NO. OF SIG. DIGITS IN FINAL EST.: 3.3
    
```

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## Example Data - Bioavailability

### Estimation Output

```

MINIMUM VALUE OF OBJECTIVE FUNCTION -1388.533
FINAL PARAMETER ESTIMATE
THETA - VECTOR OF FIXED EFFECTS *****
      TH 1      TH 2      TH 3      TH 4      TH 5
1.29E+00 8.87E-02 1.51E+01 7.78E-01 7.90E-01
OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS *****
      ETA1      ETA2      ETA3      ETA4      ETA5
ETA1 1.17E-02
ETA2 0.00E+00 3.30E-03
ETA3 0.00E+00 0.00E+00 9.25E-05
ETA4 0.00E+00 0.00E+00 0.00E+00 8.72E-03
ETA5 0.00E+00 0.00E+00 0.00E+00 0.00E+00 4.99E-03
SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****
      EPS1
EPS1 1.08E-04
    
```

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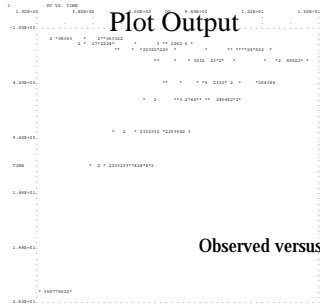
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### Example Data - Bioavailability



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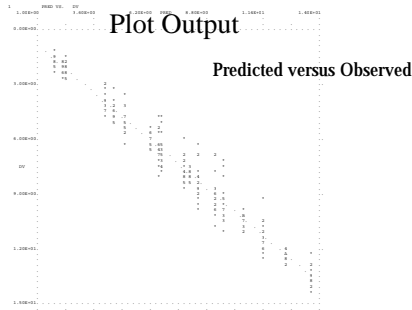
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### Example Data - Bioavailability



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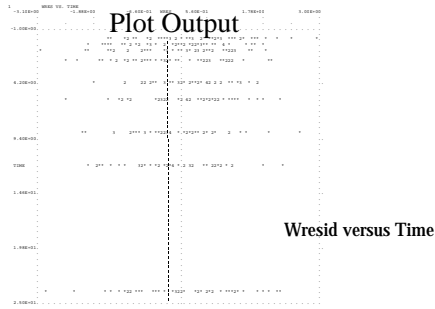
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### Example Data - Bioavailability



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### Example Data

- Binding Study
  - Data
  - Model
  - Estimation
  - Output

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### Example Data - Binding Study

$$C_f = \frac{(Ka \cdot Ct - 1 - Ka \cdot Pt) + \sqrt{(Ka \cdot Ct - 1 - Ka \cdot Pt)^2 + 4 \cdot Ka \cdot Ct}}{2 \cdot Ka}$$

#### Model Specification

```

$PROB   OSU BINDING DATA
$INPUT  ID TOTL DV
$DATA   BIND

$PRED

CT = TOTL
KA = THETA(1)*(1 + ETA(1))
PT = THETA(2)*(1 + ETA(2))

T1 = KA*CT - 1.0 - KA*PT
T2 = T1*T1 + 4*KA*CT
T3 = T1 + SQRT(T2)
CF = T3/(2*KA)

Y = CF*(1 + EPS(1))
    
```

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### Example Data - Binding Study

#### Plot Output

```

$INPUT  ID TOTL DV
$DATA   BIND
    
```

#### Typical Data

```

1 .00000504 .00000177
1 .0000501 .0000181
1 .0000191 .0000820
1 .0000336 .0000209
1 .0000494 .0000324
1 .0000609 .0000481
1 .0000772 .0000590
2 .00000499 .00000182
2 .0000477 .0000205
2 .00001751 .0000974
2 .0000337 .0000208
2 .000048 .0000338
    
```

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## Example Data - Binding Study

### Estimation and Output

#### Specification

```

$THETA (100,10000,500000) (.00001,.00004,.001)
$OMEGA .05 .05
$$SIGMA .10

$EST PRINT=5
$COVAR
$TABLE ID TOTL DV
$SCAT PRED VS DV UNIT
$SCAT WRES VS TOTL
    
```

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## Example Data - Binding Study

### Estimation Step

```

CUMULATIVE NO. OF FUNC. EVALS.: 83
PARAMETER: 0.2613E+00 0.6894E-01 0.1131E+00 0.7717E-01 -0.1677E-01
GRADIENT: -0.5063E+02 -0.2090E+03 0.4602E+02 0.6172E+02 0.1390E+03

ITERATION NO.: 15 OBJECTIVE VALUE: -0.1159E+04 NO. OF FUNC.
EVALS.: 7
CUMULATIVE NO. OF FUNC. EVALS.: 118
PARAMETER: 0.2668E+00 0.7066E-01 0.4218E-01 0.2805E-01 -0.1837E-01
GRADIENT: -0.8741E+01 -0.6836E+02 -0.7686E+01 -0.4136E+01 0.1264E+03

ITERATION NO.: 18 OBJECTIVE VALUE: -0.1159E+04 NO. OF FUNC.
EVALS.: 0
CUMULATIVE NO. OF FUNC. EVALS.: 138
PARAMETER: 0.2667E+00 0.7095E-01 0.4397E-01 0.2799E-01 -0.1870E-01
GRADIENT: 0.1155E+01 0.1722E+01 0.4752E-01 0.3432E+00 -0.2226E+02

MINIMIZATION SUCCESSFUL
NO. OF FUNCTION EVALUATIONS USED: 138
NO. OF SIG. DIGITS IN FINAL EST.: 3.1
    
```

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## Example Data - Binding Study

### Estimation Output

```

MINIMUM VALUE OF OBJECTIVE FUNCTION -1158.662
FINAL PARAMETER ESTIMATE
THETA - VECTOR OF FIXED EFFECTS

      TH 1      TH 2
6.77E+04 2.52E-05

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS
      ETA1      ETA2
ETA1 9.67E-03 <- 9.8 %
ETA2 0.00E+00 3.92E-03 <- 6.3 %

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS
      EPS1
EPS1 3.50E-03 <- 5.9 %
    
```

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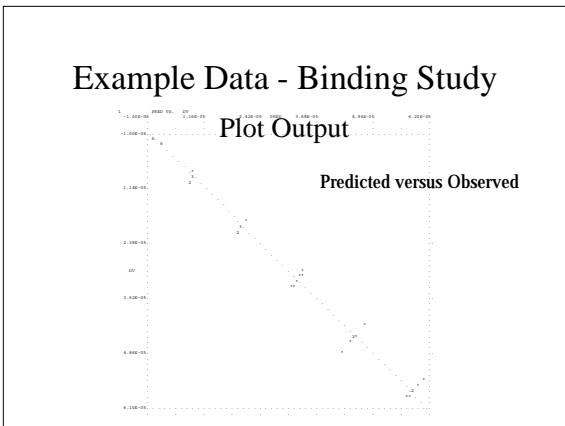
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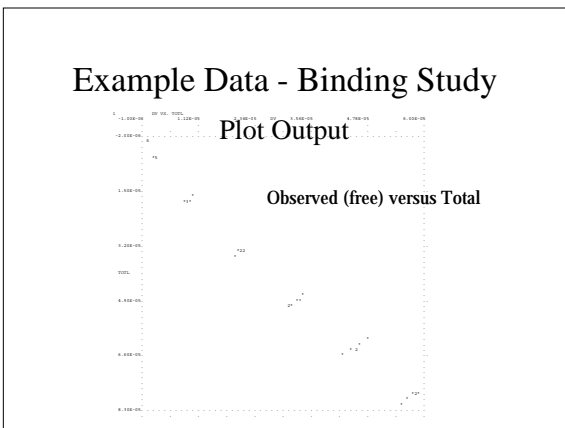
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- Objectives
- To Understand the Use of Population Parameters Values in Nomograms and Bayesian Estimations
  - To Understand Methods of Analysing Pharmacokinetic Population Data
    - Data Rich
    - Sparse Data

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