Bayesian Estimation and Population Analysis

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

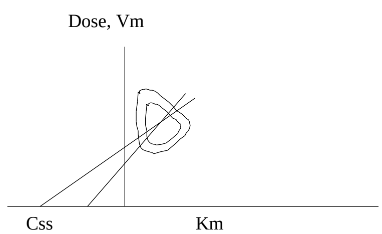
Population Data

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

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

Using Population Data



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

Population Based Parameters

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

Bayesian Analysis

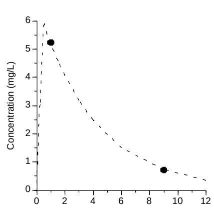
- Requires:
  - Population Values
  - Patient (Subject) Data
- Different Objective Function
- Non-linear Regression Analysis
- Possible Programs include Boomer or ADAPT II

Bayesian Analysis Example

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

Bayesian Analysis Data

- Typical Data



Bayesian Analysis

- Objective Function

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

Bayesian Analysis

- Data Weighting
  - Accurate (Not just Relative)

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

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

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 WSS =    35.97
              R-squared =   -2.400     Correlation Coeff =    1.000
```

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]
T1/2 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

Population Data Analysis

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

Two Step Analysis

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

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

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

NONMEM Analysis

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

NONMEM Approach

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

NONMEM Analysis

$$Cp = \frac{Dose}{V} e^{-kel \bullet t} + \text{ErrorTerm } \varepsilon$$

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

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

$$kel_i = [\theta_1 + \theta_2 \bullet RF_i] \bullet \left(1 + \eta_i^{kel}\right)$$

$$V_i = V \bullet \left(1 + \eta_i^{V}\right)$$

$$var\left(\varepsilon_{ij}\right) = \sigma^2$$

$$var\left(\eta_i^{kel}\right) = \omega_{kel}^2 \qquad var(\eta_i V) = \omega_V^2$$

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

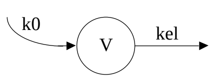
Example ONE

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

Example Data - Clinical Study

- Data
- Model
- Estimation
- Output

Example Data - Clinical Study



Model Specification

```
$PROBLEM  Aminoglycoside example - Eta on Typical kel only
$INPUT  ID AMT RATE TIME DV CRCL
$DATA  TEST
$SUBROUTINES  ADVAN1
$PK

  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))
```

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
...........
```

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
```

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
```

Example Data - Clinical Study

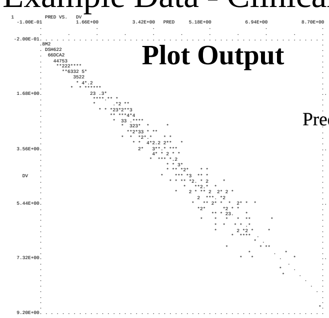
Estimation Output

```
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
ETA1
        9.81E-03               <- 9.9 %
ETA2
        0.00E+00  2.10E-03     <- 4.6 %

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS

            EPS1
EPS1
        4.60E-03               <- 6.8 %
```

a → 4.89E-03; b → 1.48E-02; V → 1.50E+01

Example Data - Clinical Study

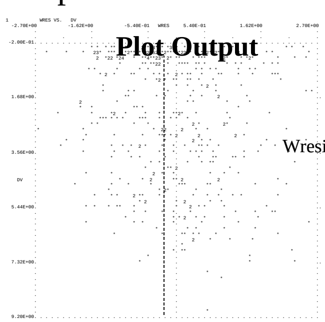
Plot Output



Predicted vs Observed

Example Data - Clinical Study

Plot Output



Wresid vs Observed

Example Data - Bioavailability

- Example Data
- Model
- Estimation
- Output

Example Data - Bioavailability

$$C = \frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet \left\{ e^{-kel \bullet t} - e^{-ka \bullet t} \right\}$$

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))
```

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
```

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

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

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
```

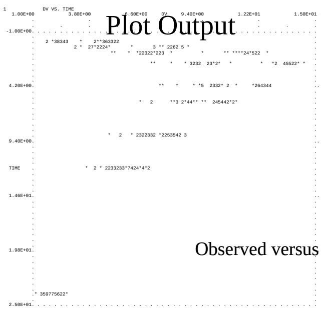
Example Data - Bioavailability

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                                              <- 10.8 %

 ETA2    0.00E+00  3.30E-03                                   <- 5.7 %

 ETA3    0.00E+00  0.00E+00  9.25E-05                         <- 1.0 %

 ETA4    0.00E+00  0.00E+00  0.00E+00  8.72E-03               <- 9.3 %

 ETA5    0.00E+00  0.00E+00  0.00E+00  0.00E+00  4.99E-03    <- 7.1 %

 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS  ****

            EPS1

 EPS1    1.08E-04                                             <- 1.0 %
```

Example Data - Bioavailability

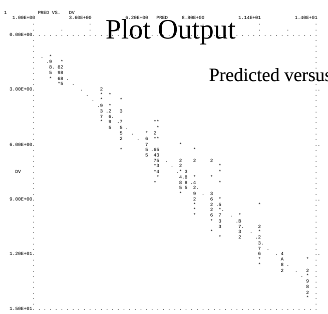
Plot Output



Observed versus Time

Example Data - Bioavailability

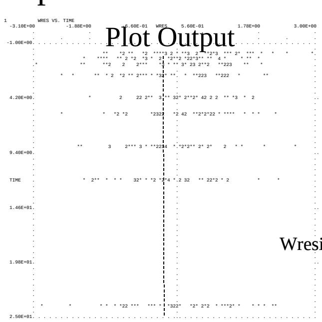
Plot Output



Predicted versus Observed

Example Data - Bioavailability

Plot Output



Wresid versus Time

Example Data

- Binding Study
  - Data
  - Model
  - Estimation
  - Output

Example Data - Binding Study

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

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))
```

Example Data - Binding Study

Plot Output

```
$INPUT   ID TOTL DV
$DATA    BIND
```

Typical Data

```
1 .000000504 .000000177
1 .00000501 .00000181
1 .0000191 .00000820
1 .0000336 .0000209
1 .0000494 .0000324
1 .0000609 .0000481
1 .0000772 .0000590
2 .000000499 .000000182
2 .00000477 .00000205
2 .00001751 .00000974
2 .0000337 .0000208
2 .000048 .0000338
```

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
```

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
```

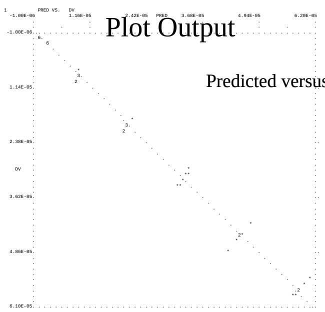
Example Data - Binding Study

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 %
```

Example Data - Binding Study

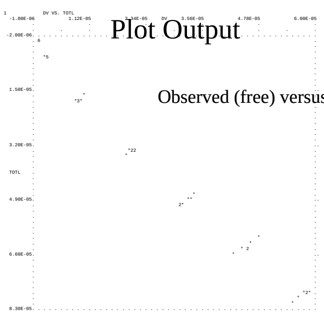
Plot Output



Predicted versus Observed

Example Data - Binding Study

Plot Output



Observed (free) versus Total

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