PK8 - Two-compartment distribution models

Objectives

- To analyze a dataset exhibiting multiphase decay
- To apply different parameterizations of this behavior
- To specify the model as an integrated solution and a set of differential equations

Problem specification

The data used in this exercise are taken from the literature (Colburn [1983]), and show how to discriminate between five different models that incorporate a bi-phasic decline.

A 100 μg intravenous bolus dose of compound *X* was given and plasma concentrations were measured at the time points shown by the concentration-time data presented in Figure 8.1 and in the program output. The distribution model is shown in Figure 8.2.

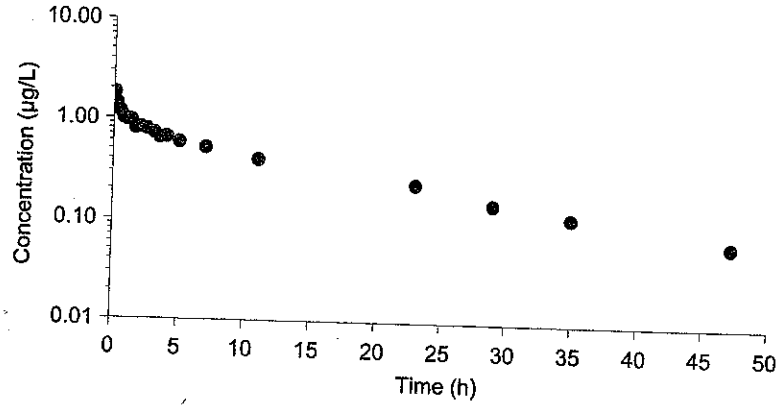

Figure 8.1 *Semi-logarithmic plot of observed concentration-time data following a 100 μg intravenous bolus dose of compound X.*

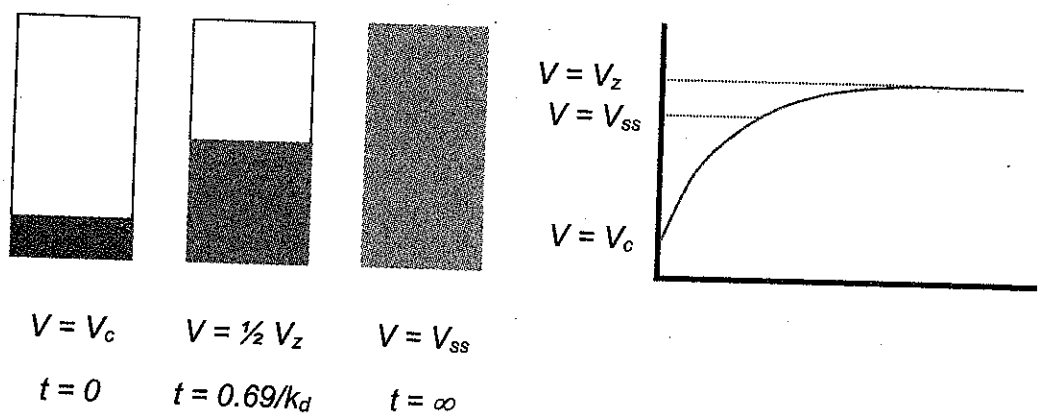

Figure 8.2 *Volume of distribution as a function of time. Assuming that the drug is administered as an intravenous bolus, it distributes initially in a volume corresponding to V_c and then gradually reaches pseudo-equilibrium at V_z. The boxes to the left represent how the measured apparent volume of distribution increases from time zero to infinity.*

Here, we demonstrate and use the simple relationship between distribution volume and time that was originally proposed by Takada and Asada [1981] and Colburn [1983].

Note that the volume increases as a function of time, starting at the central volume, and increasing to V_z. V_z is estimated as $D_{iv}/(AUC \cdot \lambda_z)$ and corresponds to V_β in a two-compartment system, which is calculated as $D_{iv}/(AUC \cdot \beta)$. The true volume of distribution at steady state V_{ss}, is somewhat lower than V_z, since the terminal slope also influences V_z.

One may consider the volume of distribution V as a function of time. Immediately after a bolus dose drug is assumed to distribute momentarily into the central volume. After one distribution half-life (i.e., $t_{1/2d} = 0.693/k_d$) drug has equilibrated into *50%* of the distribution volume. At infinite time ($t = \infty$) drug has distributed into the whole body space.

The five models we wish to discriminate between are as follows. The first approach is to specify the model as the traditional bi-exponential model

$$C = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} \tag{8:1}$$

The second method is to specify the volume of distribution as a function of time as in Takada's distribution model

$$C = \frac{D_{iv}}{V_c + V_t} \cdot e^{-\beta \cdot t} \tag{8:2}$$

V_c corresponds to the volume of the central compartment and V_t is defined as

$$V_t = \frac{V_{max} \cdot t}{K_d + t} \tag{8:3}$$

A third approach is to utilize the Colburn distribution model

$$C = \frac{D_{iv}}{V_c + V_t} \cdot e^{-\beta \cdot t} \tag{8:4}$$

where V_t is defined as

$$V_t = V_{max} \cdot \left[1 - e^{-K_v \cdot t}\right] \tag{8:5}$$

Fourthly, one may reparameterize the bi-exponential model with D_{iv} and Cl, and fit this model to the data. The model in Equation 8:6 derives from Equation 8:1

$$Cl = \frac{D_{iv}}{\frac{A}{\alpha} + \frac{B}{\beta}} \tag{8:6}$$

which when rearranged yields

$$A = \alpha \cdot \left[\frac{D_{iv}}{Cl} - \frac{B}{\beta}\right] \tag{8:7}$$

and re-inserted into Equation 8:1 yields

$$C = \alpha \cdot \left[\frac{D_{iv}}{Cl} - \frac{B}{\beta} \right] \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \qquad (8:8)$$

Finally, the model may be specified in terms of differential equations. A general diagram showing the two-compartment model is drawn in Figure 8.3.

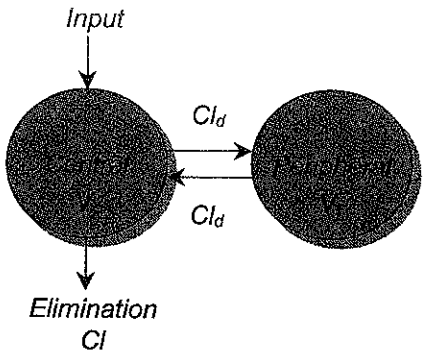

Figure 8.3 *Schematic diagram of the two-compartment (bi-exponential) model. The four parameters are V_c, Cl, Cl_d and V_t.*

The physiological model parameters are then Cl, V_c, Cl_d, and V_t, which correspond to plasma clearance, the volume of the central compartment, inter-compartmental diffusion, and the volume of the peripheral compartment, respectively. *In* is the input function, which corresponds to the bolus dose in this example. The equation for the central compartment is

$$V_c \frac{dC}{dt} = In - Cl \cdot C - Cl_d \cdot C + Cl_d \cdot C_t \qquad (8:9)$$

The equation for the peripheral compartment is

$$V_t \frac{dC_t}{dt} = Cl_d \cdot C - Cl_d \cdot C_t \qquad (8:10)$$

Initial parameter estimates

Bi-exponential model

A	= 2.0 (μg/L)
α	= 2.0 (h^{-1})
B	= 1.0 (μg/L)
β	= 0.1 (h^{-1})

Colburn's model

V_1	= 100 (L)
β	= 0.1 (h^{-1})
V_t	= 140 (L)
k_v	= 1.0 (h^{-1})

Takada's model

V_1	= 100 (L)
β	= 0.1 (h^{-1})
V_{max}	= 140 (L)
k_d	= 1.0 (h^{-1})

Reparameterized *Cl*-model

Cl	= 6.0 (L/h)
α	= 2.0 (h^{-1})
B	= 1.0 (μg/L)
β	= 0.1 (h^{-1})

Differential equation model

V_c	= 50 (L)
Cl	= 7 ($L \cdot h^{-1}$)
Cl_d	= 50 (L/h)
V_t	= 60 (L)

Interpretation of results and conclusions

Observed and predicted (Equation 8:1) data are shown in Figure 8.4.

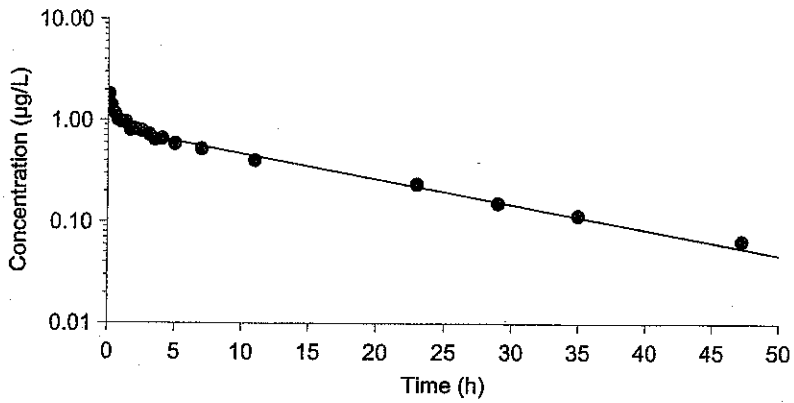

Figure 8.4 *Semi-logarithmic plot of observed (symbols) and predicted (soli line, bi-exponential model) concentration-time data following an intravenous bolus dose.*

Five different structural models have been fit to the data. The Poisson error model could either be specified as *WT = 1/F* in the model file or with the *REWEIGHT –1* command. Both weighting schemes are equivalent to an iterative reweighted least squares *IRLS* approach.

In this exercise there is a marginal difference between the quality of fits, and all models generated a low correlation between parameters, and high parameter precision. The difference was in the precision of some of the parameters. Observe that Takada's model gave the lowest *WRSS*, while the differential equation model showed the lowest condition number.

Table 8.1 Final parameter estimates

Model	WRSS	Cond. #
Bi-exponential model	0.0437	125.2
Takada's model	0.0169	3186
Colburn's model	0.0294	2243
Reparameterized model	0.0435	2306
Differential eqn. model	0.0436	29.69

Thus the Takada model would appear to provide the best fit amongst the five models. However, this should be confirmed by an analysis of the residuals. This indicates that the Takada and Colburn models show fewer runs in the residuals than the other models.

In conclusion, in this example we have elaborated a clear bi-exponential system that included enough information (number of observations) during each phase in order to accurately estimate all parameters. One often comes across datasets where the initial phase is hardly discernible, yet it cannot be excluded from analysis. In such a case we would propose the non-compartmental approach (*NCA*), as one does not need to make any assumptions about the number of compartments.

Data were generated with a Poisson error model. This implies that one should use a weighting function according to the formula below, where the exponent λ is equal to unity (1).

$$W_i = \frac{1}{\hat{C}_i}$$

Ideally, to compare the *WRSS*, a weighting scheme with constant weights should have been applied. When this is done, the Takada model is still the model of choice for this dataset.

You have

- analyzed a typical two-compartment (bi-exponential) system
- applied different parameterizations of the two-compartment system
- learned to derive the initial parameter estimates
- characterized the pharmacokinetics after a single bolus dose administration to one subject

The next step in the characterization of kinetics would be to give multiple doses via the intended route of administration.

Solution I - Bi-exponential model

```
TITLE 1
Ordinary bi-exponential model
MODEL
 COMM
  NPARM 4
  NSEC 6
  NCON 1
  PNAMES 'A', 'ALPHA', 'B','BETA'
  SNAMES 'CL','VC','AUC','AUMC','MRT','Vdss'
END
```

```
    1: TEMP
    2: DIV=CON(1)
    3: T=X
    4: END
    5: FUNC1
    6: F=A*DEXP(-ALPHA*T) + B*DEXP(-BETA*T)
    7: WT=1/(F)
    8: END
    9: SECO
   10: AUC=A/ALPHA + B/BETA
   11: S(1)=DIV/(AUC)
   12: S(2)=DIV/(A + B)
   13: S(3)=AUC
   14: S(4)=A/(ALPHA**2) + B/(BETA**2)
   15: S(5)=S(4)/S(3)
   16: S(6)=S(1)*S(5)
   17: END
   18: EOM
NVARIABLES 2
NPOINTS 100
XNUMBER 1
YNUMBER 2
CONSTANTS 100
METHOD 2  'Gauss-Newton (Levenberg and Hartley)
REWEIGHT -1
ITERATIONS 50
INITIAL 2,2,1,.1
LOWER BOUNDS .1,.1,.1,.01
UPPER BOUNDS 10,5,2,1
NOBSERVATIONS 19
DATA 'WINNLIN.DAT'
BEGIN
```

PARAMETER	ESTIMATE	STANDARD ERROR	CV%	UNIVARIATE C.I.	PLANAR C.I.
A	1.035902	.081171	7.84	.862890	1.208914
ALPHA	1.891659	.260222	13.76	1.337012	2.446307
B	.840451	.026039	3.10	.784950	.895952
BETA	.057496	.002808	4.88	.051510	.063481

*** CORRELATION MATRIX OF THE ESTIMATES ***

PARAMETER	A	ALPHA	B	BETA
A	1.00000			
ALPHA	.525278	1.00000		
B	-.728035E-01	.600041	1.00000	
BETA	-.774795E-01	.339257	.652658	1.00000

Condition_number= 125.2

X	OBSERVED Y	PREDICTED Y	RESIDUAL	WEIGHT	SE-PRED	STANDARDIZ RESIDU
.8000E-01	1.810	1.727	.8298E-01	.5790	.6067E-01	2.262
.2500	1.400	1.474	-.7401E-01	.6784	.3561E-01	-1.346
.5000	1.170	1.219	-.4893E-01	.8204	.3072E-01	-.9589
.7500	1.010	1.056	-.4569E-01	.9473	.2940E-01	-.9721
1.000	.9700	.9497	.2027E-01	1.053	.2528E-01	.4397
1.330	.9580	.8623	.9573E-01	1.160	.1946E-01	2.074

PK9 - Two-compartment model discrimination

Objectives

- To analyze a dataset following intravenous administration
- To use the goodness-of-fit criteria for model discrimination
- To analyze results with respect to accuracy, precision, and correlation
- To use the F-test

Problem specification

The aim of this exercise is to characterize the pharmacokinetics of compound B in a human volunteer. The following plasma concentration-time data are taken from a male volunteer during the 6 h period following an intravenous bolus dose of 100 mg of substance B. Observed data are shown in Figure 9.1 and the program output.

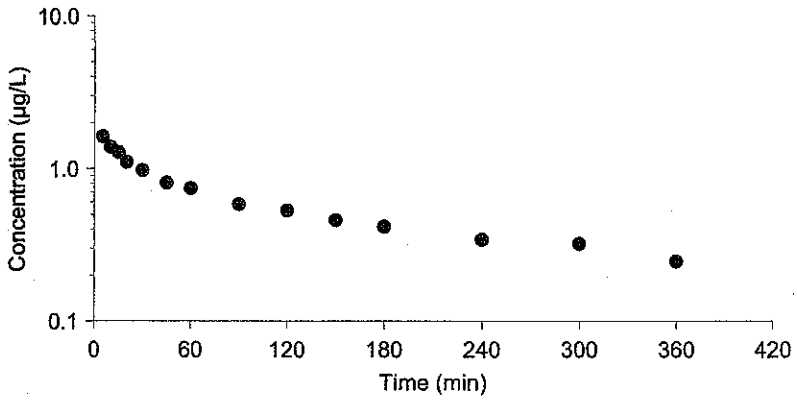

Figure 9.1 *Semi-logarithmic plot of observed concentration-time data following an intravenous bolus dose of 100 mg to a male volunteer.*

We will fit a bi-exponential and three-exponential model to this dataset and analyze the results of the two fits. First, we will therefore implement and fit Equations 9:1 and 9:2.

$$C_p = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} \qquad (9:1)$$

$$C_p = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} + C \cdot e^{-\lambda \cdot t} \qquad (9:2)$$

We will observe the weighted residual sum of squares (*WRSS*) and the correlation coefficient and search for trends in the residual plots. Then we will apply the *Akaike* [1978] and *F*-tests for the bi- and three-exponential models. The *Akaike Information Criterion* (*AIC*) attempts to represent the information content of a given set of parameter estimates by relating the *WRSS* to the number of parameters that were required to obtain the fit. When comparing two models with different numbers of parameters, this criterion places the burden on the model with more parameters to not only have a lower *WRSS*, but also to quantify how much better it must be for the model to be deemed the

more appropriate.

$$AIC = N_{obs} \cdot \ln(WRSS) + 2 \cdot N_{par} \qquad (9:3)$$

The *AIC*, as defined above, is dependent on the magnitude of residuals as well as on the number of observations. The most appropriate model is the one with the smallest value of *AIC*. The *Schwarz criterion* (*SC*) is used in very much the same manner as the *AIC*.

$$SC = N_{obs} \cdot \ln(WRSS) + N_{par} \cdot \ln(N_{obs}) \qquad (9:4)$$

Note: One must be careful when interpreting the result of a fit from only *AIC* and *SC*. Never judge the goodness-of-fit without a battery of statistical tools. We show you the application of these tests in more detail elsewhere in the book (see e.g., PD3).

Initial parameter estimates

$A = 1.1$ (μg/L)
$\alpha = 1.0$ (min^{-1})
$B = 0.2$ (μg/L)
$\beta = 0.01$ (min^{-1})

$A = 1.0$ (μg/L)
$\alpha = 1.0$ (min^{-1})
$B = 0.7$ (μg/L)
$\beta = 0.1$ (min^{-1})
$C = 0.2$ (μg/L)
$\gamma = 0.001$ (min^{-1})

Interpretation of results and conclusions

Let us first compare the fit of the bi- and three-exponential models. Figure 9.2 shows observed and predicted data from the two models. The difference is barely visible within the present concentration and time range. A larger dose and time range would be needed to separate these two models.

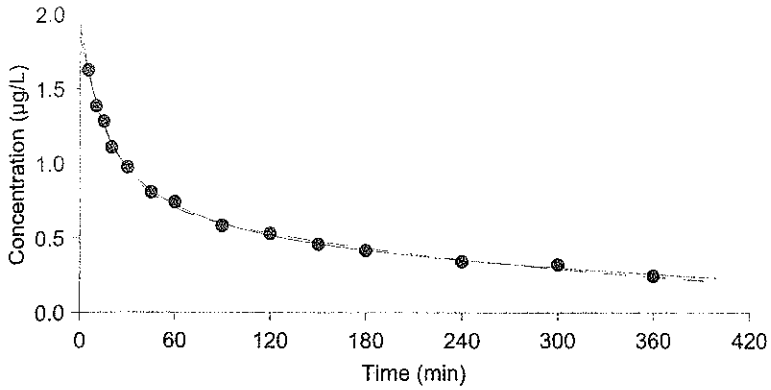

Figure 9.2 Semi-logarithmic plot of observed (symbols) and predicted (solid line is three-exponential model and dashed line the bi-exponential model) concentration-time data following an intravenous bolus dose of 100 mg to a male volunteer

For simplicity, we will only use the two runs with constant weight (weight equal to 1 or constant weight). In this case we may apply the *F-test*. $F(\alpha, \Delta df, df)$, where α, df, and Δdf are the level of significance, degrees of freedom ($N_{obs} - N_{par}$) for the three-exponential model and difference in degrees of freedom between the models, respectively. Δdf corresponds to the column numbers in Table 9.1 and $df_{3\text{-}exp}$ is the row number. F_{table} is indicated by the arrows.

Table 9.1 *F*-table

F distribution υ_1, υ_2 degrees of freedom P = 0.05

υ_1	Δdf->	1	2	3	4
υ_2	1	161.45	199.50	215.71	224.58
	2	18.513	19.000	19.164	19.247
	3	10.128	9.5521	9.2766	9.1172
	4	7.7086	6.9443	6.5914	6.3882
	5	6.6079	5.7861	5.4095	5.1922
	6	5.9874	5.1433	4.7571	4.5337
	7	5.5914	4.7374	4.3868	4.1203
	8	5.3177	**4.4590**	4.0662	3.8379
	9	5.1174	4.2565	3.8626	3.6331
	10	4.9646	4.1028	3.7083	3.4780

One approach to testing for the significance of the parameter in any model relates to the following question. *Does the model that includes the new parameter tell us significantly more about the outcome (or response) variable than a model that lacks that parameter?* If we apply an *F*-test as a measure of whether the three-exponential model is superior to the bi-exponential model we obtain

$$F^* = \frac{\frac{|WRSS_1 - WRSS_2|}{|df_1 - df_2|}}{\frac{WRSS_2}{df_2}} = 3.05 < F_{table} \qquad (9:5)$$

Note that F^* is smaller than F_{table} (= 4.459 from column number equal to $\Delta df = 2$ and row equal to $df_2 = 8$, $P = 0.05$). This suggests that the three-exponential model does

not provide a better fit to the data than the bi-exponential model. It does not, however, ensure that the two-compartment model provides an adequate fit.

It is usually a good rule of thumb to choose the simplest model that adequately describes the data. The bi-exponential fit shows a trend in the residuals. The three-exponential fit does not show the same trend in the residuals. However, a high correlation is found between several parameters and the standard errors are generally high for the three-exponential model.

Note: The *F*-test is not appropriate when using non-constant weights such as when weight (*WT*) is equal to *1/F* . Therefore, only the two unweighted runs were used in the example of the *F*-test above.

You have

- ☐ practised model discrimination
- ☐ learned to use the F-test
- ☐ learned to derive the initial estimates

The next step would be to practice this kind of analysis on your own data. See also PK4 for a discussion on model discrimination.

Solution I - Bi-exponential model

```
TITLE 1
Bi-exponential model
MODEL
 COMM
  NPARM 4
  PNAMES 'A', 'Alpha', 'B','Beta'
END
    1: TEMP
    2: T=X
    3: END
    4: FUNC1
    5: F= A*DEXP(-ALPHA*T) + B*DEXP(-BETA*T)
    6: END
    7: EOM
NVARIABLES 2
NPOINTS 100
XNUMBER 1
YNUMBER 2
METHOD 2  'Gauss-Newton (Levenberg and Hartley)
ITERATIONS 50
INITIAL 1.1,1,.2,.01
LOWER BOUNDS 0,0,0,0
UPPER BOUNDS 10,5,1.5,1
NOBSERVATIONS 14
DATA 'WINNLIN.DAT'
BEGIN
```

PARAMETER	ESTIMATE	STANDARD ERROR	CV%	UNIVARIATE C.I.	
A	1.056916	.044977	4.26	.956701	1.157131
ALPHA	.047973	.004700	9.80	.037500	.058447
B	.784751	.042500	5.42	.690054	.879448
BETA	.003308	.000306	9.24	.002626	.003989

```
*** CORRELATION MATRIX OF THE ESTIMATES ***
 PARAMETER              A            ALPHA              B             BETA
 A             1.00000
 ALPHA        -.520257E-01      1.00000
 B            -.553873           .813638         1.00000
 BETA         -.550489           .681080          .909699         1.00000

  Condition_number=        447.2

    FUNCTION   1

 X          OBSERVED    PREDICTED    RESIDUAL     WEIGHT     SE-PRED    STANDARDI
            Y           Y                                               RESIDUAL
  5.000       1.625       1.603       .2161E-01   1.000      .2179E-01    1.638
  10.00       1.384       1.413      -.2940E-01   1.000      .1323E-01   -1.351
  15.00       1.280       1.261       .1857E-01   1.000      .1252E-01    .8374
  20.00       1.105       1.139      -.3442E-01   1.000      .1364E-01   -1.600
  30.00       .9730       .9612       .1177E-01   1.000      .1382E-01    .5500
  45.00       .8060       .7983       .7739E-02   1.000      .1209E-01    .3453
  60.00       .7400       .7029       .3708E-01   1.000      .1231E-01    1.663
  90.00       .5820       .5968      -.1480E-01   1.000      .1352E-01   -.6856
  120.0       .5300       .5310      -.1007E-02   1.000      .1222E-01   -.0450
  150.0       .4580       .4786      -.2061E-01   1.000      .1056E-01   -.8894
  180.0       .4160       .4329      -.1687E-01   1.000      .9999E-02   -.7203
  240.0       .3420       .3548      -.1281E-01   1.000      .1169E-01   -.5662
  300.0       .3210       .2909       .3006E-01   1.000      .1396E-01    1.411
  360.0       .2460       .2386       .7432E-02   1.000      .1545E-01    .3670

  CORRECTED SUM OF SQUARED OBSERVATIONS =  2.49866
  WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS =  2.49866
  SUM OF SQUARED RESIDUALS =            .648679E-02
  SUM OF WEIGHTED SQUARED RESIDUALS =  .648679E-02
  S =  .254692E-01 WITH    10 DEGREES OF FREEDOM
  CORRELATION (OBSERVED,PREDICTED) =  .9987

 AIC criteria =        -62.53182
 SC  criteria =        -59.97559
```

Solution II - Three-exponential model

```
TITLE 1
Tri-exponential model
MODEL
 COMM
  NPARM 6
  PNAMES 'A', 'Alpha', 'B','Beta','C','Gam'
END
    1: TEMP
    2: T=X
    3: END
    4: FUNC1
    5: F = A*DEXP(-ALPHA*T) + B*DEXP(-BETA*T) + C*DEXP(-GAM*T)
    6: END
    7: EOM
NVARIABLES 2
NPOINTS 100
XNUMBER 1
YNUMBER 2
METHOD 2  'Gauss-Newton (Levenberg and Hartley)
INITIAL 1,1,.7,.1,.2,.001
LOWER BOUNDS 0,0,0,0,0,0
```