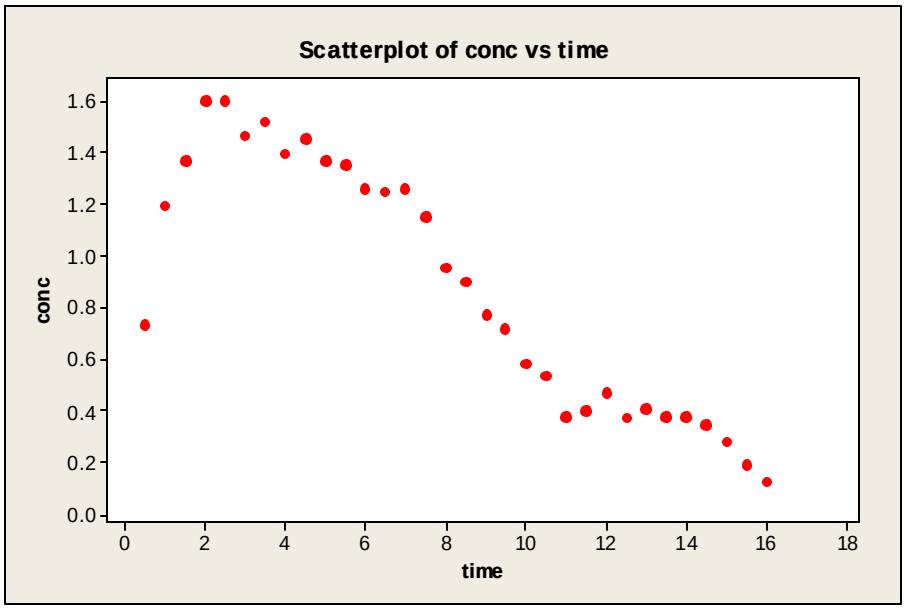
```
data one;
  do time=0.5 to 16 by 0.5;
    input conc @@; output;
  end; datalines;
0.73491 1.19450 1.36887 1.59890 1.59994 1.46580 1.51797 1.39002 1.45207 1.37051
1.35264 1.26148 1.24561 1.25900 1.15097 0.95105 0.89895 0.76953 0.71271 0.57851 0.53198
0.37821 0.40231 0.46940 0.36961 0.40307 0.37491 0.37525 0.34422 0.28192 0.18845 0.12393
;
title 'Pharmacokinetic Modelling';
proc plot;
  plot conc*time;
run;
```




```
proc nlin;
  parms th1=0.4 th2=0.1 auc=16;
  ex1=exp(-th1*time); ex2=exp(-th2*time); diff=ex2-ex1;
  model conc=auc*(th1*th2/(th1-th2))*diff;
  output out=two r=r p=p;
run;
proc plot; plot r*p; run;
```

```
                          Pharmacokinetic Modelling
                                The NLIN Procedure
                            Dependent Variable conc
                              Method: Gauss-Newton
                                Iterative Phase

                                                                  Sum of
      Iter         th1         th2         auc                  Squares
         0      0.4000      0.1000     16.0000                   4.4844
         1      0.8200      0.1401     14.1413                   0.9326
         2      0.5542      0.1716     15.3025                   0.2793
         3      0.5663      0.1823     15.2172                   0.2312
         4      0.5701      0.1812     15.2587                   0.2311
         5      0.5707      0.1811     15.2605                   0.2311
         6      0.5709      0.1811     15.2609                   0.2311
         7      0.5709      0.1811     15.2610                   0.2311
         8      0.5709      0.1811     15.2610                   0.2311
NOTE: Convergence criterion met.

                          Estimation Summary
                Method                     Gauss-Newton
                Iterations                            8
```

R	2.387E-6
PPC(th1)	1.45E-6
RPC(th1)	7.64E-6
Object	1.88E-10
Objective	0.231075
Observations Read	32
Observations Used	32
Observations Missing	0

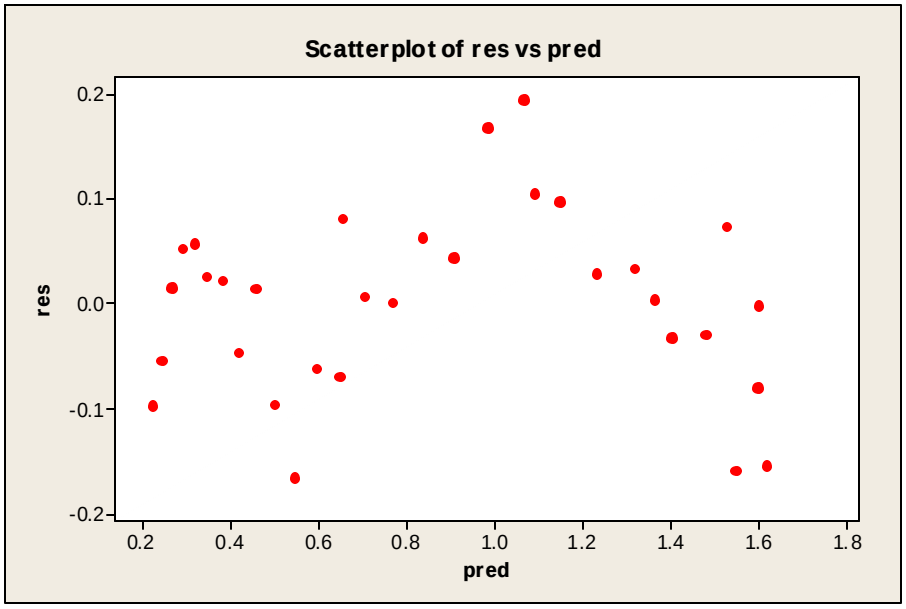
NOTE: An intercept was not specified for this model.

Source	DF	Sum of Squares	Mean Square	F Value	Approx Pr > F
Model	3	31.7650	10.5883	1328.84	<.0001
Error	29	0.2311	0.00797		
Uncorrected Total	32	31.9960			

Parameter	Estimate	Approx Std Error	Approximate 95% Confidence Limits	
th1	0.5709	0.0653	0.4373	0.7045
th2	0.1811	0.0153	0.1498	0.2123
auc	15.2610	0.4088	14.4249	16.0971

Approximate Correlation Matrix

	th1	th2	auc
th1	1.0000000	-0.9031835	0.6001821
th2	-0.9031835	1.0000000	-0.7733192
auc	0.6001821	-0.7733192	1.0000000




```
proc nlmixed ecov data=one;
  parms th1=0.8 th2=0.05 phi=16 sig=0.06;
  ex1=exp(-th1*time); ex2=exp(-th2*time); diff=ex2-ex1; rec=1/(th1-th2);
  tmax=rec*log(th1/th2); cmax=th1*phi*exp(-th1*tmax);
  mean=th1*th2*phi*rec*diff; var=sig*sig;
  model conc~normal(mean,var);
  estimate 't-max' tmax;
  estimate 'c-max' cmax;
run;
```

The NLMIXED Procedure
Specifications

Data Set	WORK.ONE
Dependent Variable	conc
Distribution for Dependent Variable	Normal
Optimization Technique	Dual Quasi-Newton
Integration Method	None

Dimensions

Observations Used	32
Observations Not Used	0
Total Observations	32
Parameters	4

Parameters

th1	th2	phi	sig	NegLogLike
0.8	0.05	16	0.06	1200.84259

Iteration History

Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	11	-18.688724	1219.531	494.0727	-2.804E7
2	16	-25.473298	6.784574	149.0044	-1864.3
3	17	-27.701625	2.228327	132.3305	-3.49502
4	19	-28.548707	0.847082	108.0631	-0.78174
5	21	-28.701081	0.152374	141.8646	-0.82231
6	23	-31.832572	3.131492	57.91089	-0.47181
7	27	-32.477194	0.644621	39.84025	-2.99329
8	30	-32.54727	0.070077	80.06569	-0.32558
9	32	-32.593764	0.046494	51.17942	-0.07954
10	34	-33.058036	0.464272	110.0283	-0.01562
11	35	-33.261665	0.203629	78.71216	-0.47367
12	36	-33.419698	0.158033	70.63451	-0.45374
13	38	-33.481136	0.061438	9.758704	-0.20175
14	40	-33.485573	0.004437	0.318453	-0.01058
15	42	-33.485963	0.000391	0.52318	-0.00063
16	44	-33.485979	0.000016	0.016506	-0.00003
17	46	-33.485979	1.169E-8	0.008721	-4.82E-8

NOTE: GCONV convergence criterion satisfied.

Fit Statistics

-2 Log Likelihood	-67.0
AIC (smaller is better)	-59.0
AICC (smaller is better)	-57.5
BIC (smaller is better)	-53.1

Parameter Estimates

Parameter	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper	Gradient
th1	0.5709	0.06888	32	8.29	<.0001	0.05	0.4306	0.7112	0.000483
th2	0.1811	0.01561	32	11.60	<.0001	0.05	0.1493	0.2129	0.002628
phi	15.2610	0.3989	32	38.26	<.0001	0.05	14.4485	16.0735	3.247E-6
sig	0.08498	0.01062	32	8.00	<.0001	0.05	0.06334	0.1066	0.008721

Additional Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
t-max	2.9457	0.1233	32	23.89	<.0001	0.05	2.6945	3.1968
c-max	1.6211	0.02913	32	55.65	<.0001	0.05	1.5617	1.6804

Covariance Matrix of Additional Estimates

Row	Label	Cov1	Cov2
1	t-max	0.01520	-0.00076
2	c-max	-0.00076	0.000848

```
proc iml;
  start neg2lla(th) global(xx,yy,nn);
    th1=th[1]; th2=th[2]; phi=th[3]; sig=th[4]; sig2=sig*sig;
    ex1=exp(-th1*xx); ex2=exp(-th2*xx); diff=ex2-ex1; rec=1/(th1-th2);
    eta=th1*th2*phi*rec*diff; res=yy-eta;
    thingy=nn*log(sig2)+(1/sig2)*t(res)*res;
    return(thingy);
  finish neg2lla;

  start neg2llb(th) global(xx,yy,nn); nn2=nn-1; on2=j(nn2,1);
    th1=th[1]; th2=th[2]; phi=th[3]; sig2=th[4]; rho=th[5];
    ex1=exp(-th1*xx); ex2=exp(-th2*xx); diff=ex2-ex1; rec=1/(th1-th2);
    eta=th1*th2*phi*rec*diff; res=yy-eta; rest=res[2:nn,]; ress=res[1:(nn-1),];
    xxt=xx[2:nn,]; xxs=xx[1:(nn-1),]; xxp=xxt-xxs; rhop=rho##(xxp); respp=rest-rhop#ress;
    rhop2=rho##(2*xxp); logrp=log(1-rhop2); wt=sqrt(1/(1-rhop2)); resp=wt#respp;
    thingy=nn*log(sig2)+t(logrp)*on2+(1/sig2)*( res[1]*res[1]+t(resp)*resp );
    return(thingy);
  finish neg2llb;

  xx={0.5,1,1.5,2,2.5,3,3.5,4,4.5,5,5.5,6,6.5,7,7.5,8,8.5,9,9.5,
      10,10.5,11,11.5,12,12.5,13,13.5,14,14.5,15,15.5,16};
  yy={0.73491,1.19450,1.36887,1.59890,1.59994,1.46580,1.51797,1.39002,1.45207,1.37051,
     1.35264,1.26148,1.24561,1.25900,1.15097,0.95105,0.89895,0.76953,0.71271,0.57851,0.53198
     0.37821,0.40231,0.46940,0.36961,0.40307,0.37491,0.37525,0.34422,0.28192,0.18845,0.12393
  nn=nrow(xx); opt={.,0};
  th0a={0.7 0.1 10 1};
  cona={0.001 0.000001 1 0.0001,
          .       .    .    .  };
  th0b={0.7 0.1 10 1 0.7};
  conb={0.001 0.000001 1 0.0001 0.0001,
          .       .    .    .   0.9999};
  call nlptr(rc,thetaa,"neg2lla",th0a,opt,cona); minn2lla=neg2lla(thetaa); print thetaa minn2
  call nlptr(rc,thetab,"neg2llb",th0b,opt,conb); minn2llb=neg2llb(thetab); print thetab minn2
  neg2llmin=neg2llb(thetab); ans=j(50,5);
  do jj=1 to 50;
    ans[jj,3]=neg2llmin+2.71;
    ans[jj,4]=neg2llmin+3.84;
    ans[jj,5]=neg2llmin+6.63;
    star=0.05; fini=0.97; rho=star+(fini-star)*(jj-1)/49; ans[jj,1]=rho;
    th0b=thetab; opt={.,0};
    th0b[5]=rho; conb[1,5]=rho; conb[2,5]=rho;
    call nlptr(rc,thtil,"neg2llb",th0b,opt,conb);
    ans[jj,2]=neg2llb(thtil);
  end;
  create dset from ans[colname={rho negll cut90 cut95 cut99}];
  append from ans;
quit;
data final; set dset;
  y=negll;  zz=1; output;
  y=cut90;  zz=2; output;
  y=cut95;  zz=3; output;
  y=cut99;  zz=4; output;
axis1 w=2 minor=none label=(a=90 font=swiss 'Profile Likelihood');
axis2 w=2 minor=none label=(font=swiss 'RHO - AR1 Parameter');
symbol1 i=join v=point w=5 l=1 c=blue;
symbol2 i=join v=point w=3 l=2 c=blue;
symbol3 i=join v=point w=3 l=3 c=blue;
symbol4 i=join v=point w=3 l=4 c=blue;
proc gplot data=final;
  plot y*rho=zz / fr vaxis=axis1 nolegend haxis=axis2;
run;
```

THETAA				MINN2LLA
0.1810802	0.5708944	15.260993	0.0849769	-125.784

THETAB					MINN2LLB
0.6247655	0.1728786	15.344363	0.0073746	0.4185682	-141.9209