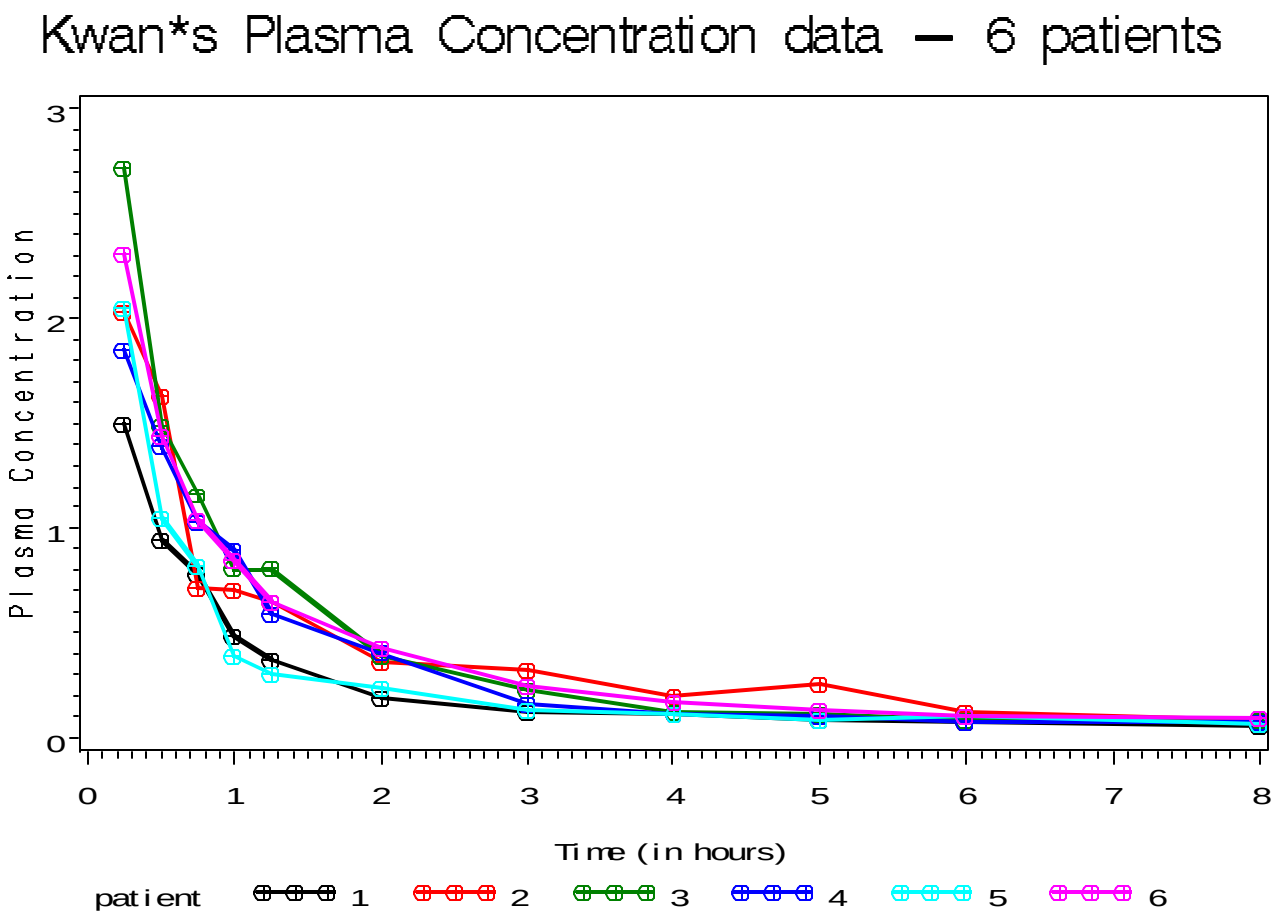
```
data one;
  do patient=1 to 6;
  do time=.25 to 1.25 by .25,2,3,4,5,6,8;
    input y @@; plasma=y/100; drop y; output;
  end; end; cards;
150  94  78 48 37 19 12 11  8  7 5 203 163  71 70 64 36 32 20 25 12 8
272 149 116 80 80 39 22 12 11  8 8 185 139 102 89 59 40 16 11 10  7 7
205 104  81 39 30 23 13 11  8 10 6 231 144 103 84 64 42 24 17 13 10 9
;
axis1 label=(a=90 h=1.2 'Plasma Concentration');
axis2 label=(h=1.2 'Time (in hours)');
symbol1 v=+ i=join;   symbol2 v=x i=join;      symbol3 v=* i=join;
symbol4 v=dot i=join; symbol5 v=circle i=join; symbol6 v=$ i=join;
proc gplot;
  title 'Kwan*s Plasma Concentration data - 6 patients';
  plot plasma*time=patient / vaxis=axis1 haxis=axis2;
run;
```




```
proc nlmixed;
  title2 'First NLMixed';
  parms b1=3.5 b2=3.6 b3=.5 b4=.5 s2e=.1;
  rhs=b1*exp(-b2*time)+b3*exp(-b4*time);
  model plasma~normal(rhs,s2e);
run;
```

```
                    Kwan*s Plasma Concentration data - 6 patients
                                        First NLMixed
                                    The NLMIXED Procedure
                                        Specifications
```

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

Dimensions

Observations Used	66
Observations Not Used	0
Total Observations	66
Parameters	5

Parameters

b1	b2	b3	b4	s2e	NegLogLike
3.5	3.6	0.5	0.5	0.1	8.33289851

Iteration History

Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	3	3.4384567	4.894442	172.9536	-764.206
2	5	-1.4232288	4.861686	1526.778	-1213.32
3	7	-13.439342	12.01611	1579.88	-88.4512
4	9	-16.90499	3.465648	568.3236	-131.798
5	10	-21.677908	4.772918	50.53786	-34.011
6	12	-22.708064	1.030156	5.55457	-1.09749
7	14	-22.892297	0.184233	18.02782	-0.17107
8	15	-23.075592	0.183295	18.49232	-0.11108
9	16	-23.282576	0.206984	13.65229	-0.15439
10	17	-23.550416	0.26784	21.69526	-0.20755
11	20	-23.580217	0.029801	23.73035	-0.18221
12	21	-23.62484	0.044623	23.34184	-0.20664
13	23	-23.637642	0.012802	15.43954	-0.03557
14	25	-23.641186	0.003545	7.172706	-0.00568
15	27	-23.642182	0.000996	0.442527	-0.00125
16	29	-23.642223	0.000041	0.025877	-0.00007
17	31	-23.642223	5.454E-7	0.000438	-9.49E-7
18	33	-23.642223	3.28E-10	0.000056	-666E-12

NOTE: GCONV convergence criterion satisfied.

Fit Statistics

-2 Log Likelihood	-47.3
AIC (smaller is better)	-37.3
AICC (smaller is better)	-36.3
BIC (smaller is better)	-26.3

Parameter Estimates

Parameter	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper	Gradient
b1	2.7734	0.2485	66	11.16	<.0001	0.05	2.2773	3.2695	7.173E-7
b2	2.4263	0.5997	66	4.05	0.0001	0.05	1.2289	3.6236	-1.49E-6
b3	0.6067	0.3010	66	2.02	0.0479	0.05	0.005707	1.2078	0.000012
b4	0.3356	0.1542	66	2.18	0.0331	0.05	0.02778	0.6434	-0.00002
s2e	0.02860	0.004979	66	5.74	<.0001	0.05	0.01866	0.03854	0.000056

```
proc nlmixed;
  title2 'Second NLMixed';
  parms b1=3.5 b2=3.6 b3=.5 b4=.5 s2e=.1 s2b1=.1 s2b3=.1 cb13=0;
  rhs=(b1+u1)*exp(-b2*time)+(b3+u3)*exp(-b4*time);
  model plasma~normal(rhs,s2e);
  random u1 u3~normal([0,0],[s2b1,cb13,s2b3]) subject=patient;
run;
```

Second NLMixed

The NLMIXED Procedure

Specifications

Data Set	WORK.ONE
Dependent Variable	plasma
Distribution for Dependent Variable	Normal
Random Effects	u1 u3
Distribution for Random Effects	Normal
Subject Variable	patient
Optimization Technique	Dual Quasi-Newton
Integration Method	Adaptive Gaussian Quadrature

Dimensions

Observations Used	66
Observations Not Used	0
Total Observations	66
Subjects	6
Max Obs Per Subject	11
Parameters	8
Quadrature Points	1

Parameters

b1	b2	b3	b4	s2e	s2b1	s2b3	cb13	NegLogLike
3.5	3.6	0.5	0.5	0.1	0.1	0.1	0	-1.942018

Iteration History

Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	10	-41.535395	39.59338	48.5876	-1281.81
2	14	-41.686047	0.150652	208.4506	-170.857
3	15	-44.794611	3.108564	84.39916	-46.9492
4	16	-47.909464	3.114853	2080.284	-26.1192
5	17	-51.962225	4.052762	603.0112	-16.3397
6	20	-53.321539	1.359314	52.06539	-17.7323
7	22	-53.775943	0.454404	191.1314	-16.7221
8	23	-54.485174	0.709231	128.0621	-0.93387
9	24	-55.308265	0.823092	290.7366	-1.02753
10	26	-55.70427	0.396005	42.56328	-0.5114
11	28	-55.906494	0.202224	50.30985	-0.12817
12	30	-56.027434	0.12094	9.20841	-0.14874
13	32	-56.055505	0.028071	16.67781	-0.04986
14	34	-56.069362	0.013856	32.30925	-0.02316
15	35	-56.0867	0.017338	5.046259	-0.01623
16	37	-56.097675	0.010976	18.6281	-0.01358
17	38	-56.113863	0.016187	16.19018	-0.00855
18	40	-56.115196	0.001333	2.53357	-0.00286
19	42	-56.115234	0.000038	0.599244	-0.00008
20	44	-56.115236	1.322E-6	0.209606	-2.62E-6
21	46	-56.115236	7.308E-8	0.022325	-1.41E-7

NOTE: GCONV convergence criterion satisfied.

Fit Statistics

-2 Log Likelihood	-112.2
AIC (smaller is better)	-96.2
AICC (smaller is better)	-93.7
BIC (smaller is better)	-97.9

Parameter Estimates

Parameter	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper	Gradient
b1	2.7733	0.2761	4	10.04	0.0006	0.05	2.0066	3.5400	0.000025
b2	2.8139	0.3600	4	7.82	0.0014	0.05	1.8144	3.8135	0.000017
b3	0.7870	0.1731	4	4.55	0.0104	0.05	0.3064	1.2676	-0.00001
b4	0.4195	0.07116	4	5.90	0.0041	0.05	0.2220	0.6171	-0.0002

s2e	0.006739	0.001298	4	5.19	0.0066	0.05	0.003134	0.01034	-0.02232
s2b1	0.3346	0.2338	4	1.43	0.2256	0.05	-0.3145	0.9837	-0.00017
s2b3	0.04391	0.03076	4	1.43	0.2266	0.05	-0.04148	0.1293	0.000288
cb13	-0.00179	0.05782	4	-0.03	0.9767	0.05	-0.1623	0.1587	-0.00042

```
proc nlmixed;
  title2 'Third NLMixed';
  parms b1=3.5 b2=3.6 b3=.5 b4=.5 s2e=.1 s2b1=.1;
  rhs=(b1+u1)*exp(-b2*time)+b3*exp(-b4*time);
  model plasma~normal(rhs,s2e);
  random u1~normal(0,s2b1) subject=patient;
run;
```

Kwan*s Plasma Concentration data - 6 patients

Third NLMixed

The NLMIXED Procedure

Specifications

Data Set	WORK.ONE
Dependent Variable	plasma
Distribution for Dependent Variable	Normal
Random Effects	u1
Distribution for Random Effects	Normal
Subject Variable	patient
Optimization Technique	Dual Quasi-Newton
Integration Method	Adaptive Gaussian Quadrature

Dimensions

Observations Used	66
Observations Not Used	0
Total Observations	66
Subjects	6
Max Obs Per Subject	11
Parameters	6
Quadrature Points	1

Parameters

b1	b2	b3	b4	s2e	s2b1	NegLogLike
3.5	3.6	0.5	0.5	0.1	0.1	7.1483049

Iteration History

Iter	Calls	NegLogLike	Diff	MaxGrad	Slope
1	3	0.40820442	6.7401	106.1361	-804.029
2	8	-4.5376213	4.945826	361.1744	-1208.14
3	9	-9.038175	4.500554	2035.475	-85.9738
4	12	-10.999074	1.960899	2916.67	-110.687
5	13	-21.583587	10.58451	1343.589	-248.255
6	15	-29.879058	8.295471	681.4587	-88.3487
7	16	-34.615977	4.736919	224.2697	-20.5765
8	17	-42.831873	8.215896	307.4321	-9.59248
9	19	-43.76015	0.928277	95.63255	-2.6342
10	20	-45.081124	1.320973	319.5574	-1.20542
11	22	-45.884223	0.803099	243.0233	-0.91535
12	24	-46.234406	0.350184	96.69242	-0.86076
13	26	-46.361499	0.127092	31.45469	-0.34933
14	28	-46.394611	0.033112	28.54144	-0.10425
15	30	-46.414208	0.019597	1.002017	-0.03083
16	32	-46.41526	0.001052	4.707557	-0.0016
17	34	-46.418217	0.002956	1.513829	-0.00064
18	35	-46.423252	0.005036	12.07684	-0.00351
19	37	-46.425376	0.002124	2.116958	-0.00347
20	39	-46.425404	0.000028	0.126848	-0.00005

```
                  21        41    -46.425404    1.156E-7    0.000293    -2.13E-7
                          NOTE: GCONV convergence criterion satisfied.

                                        Fit Statistics
                                  -2 Log Likelihood                 -92.9
                                  AIC (smaller is better)           -80.9
                                  AICC (smaller is better)          -79.4
                                  BIC (smaller is better)           -82.1

                                      Parameter Estimates
                          Standard
  Parameter  Estimate     Error    DF  t Value  Pr > |t|   Alpha     Lower     Upper  Gradient
  b1           2.7617    0.2816     5     9.81    0.0002    0.05    2.0377    3.4856  -0.00004
  b2           2.1108    0.2473     5     8.53    0.0004    0.05    1.4750    2.7467  0.000039
  b3           0.4522    0.1426     5     3.17    0.0248    0.05   0.08557    0.8189  -0.00009
  b4           0.2617   0.08520     5     3.07    0.0277    0.05   0.04271    0.4807  -0.00003
  s2e         0.01098  0.002005     5     5.48    0.0028    0.05  0.005828   0.01614  0.000293
  s2b1         0.3680    0.2330     5     1.58    0.1750    0.05   -0.2309    0.9669  0.000038
```

```
proc nlmixed;
  title2 'Fourth NLMixed';
  parms b1=3.5 b2=3.6 b3=.5 b4=.5 s2e=.1 s2b1=.1 s2b3=.1;
  rhs=(b1+u1)*exp(-b2*time)+(b3+u3)*exp(-b4*time);
  model plasma~normal(rhs,s2e);
  random u1 u3~normal([0,0],[s2b1,0,s2b3]) subject=patient;
run;
```

```
                    Kwan*s Plasma Concentration data - 6 patients
                                    Fourth NLMixed
                                The NLMIXED Procedure
                                   Specifications
                Data Set                                    WORK.ONE
                Dependent Variable                          plasma
                Distribution for Dependent Variable         Normal
                Random Effects                              u1 u3
                Distribution for Random Effects             Normal
                Subject Variable                            patient
                Optimization Technique                      Dual Quasi-Newton
                Integration Method                          Adaptive Gaussian
                                                            Quadrature

                                        Dimensions
                              Observations Used                   66
                              Observations Not Used                0
                              Total Observations                  66
                              Subjects                             6
                              Max Obs Per Subject                 11
                              Parameters                           7
                              Quadrature Points                    1

                                        Parameters
      b1          b2          b3          b4         s2e        s2b1        s2b3    NegLogLike
     3.5         3.6         0.5         0.5         0.1         0.1         0.1     -1.942018

                                   Iteration History
                Iter     Calls    NegLogLike        Diff     MaxGrad       Slope
                   1        10    -41.557828    39.61581    48.39523    -1281.77
                   2        14    -41.738208     0.18038    242.9403    -130.359
                   3        15    -44.949003    3.210795    93.09032    -50.4509
                   4        16    -48.330041    3.381038    1978.091    -24.9754
                   5        17     -53.04157    4.711529    69.62924    -13.6693
                   6        19    -53.685856    0.644285    21.55489    -11.7101
```

7	20	-54.550165	0.864309	123.0247	-0.92651
8	21	-55.459691	0.909526	55.00583	-1.36354
9	24	-55.526122	0.06643	90.90399	-0.29614
10	26	-55.74738	0.221259	55.72594	-0.53086
11	28	-55.891494	0.144114	62.27574	-0.17673
12	29	-56.016127	0.124633	71.5607	-0.15762
13	31	-56.054607	0.038479	7.158757	-0.06715
14	33	-56.07082	0.016214	10.50715	-0.01337
15	34	-56.097487	0.026667	23.73402	-0.01913
16	36	-56.112433	0.014946	15.97742	-0.02672
17	38	-56.114722	0.002289	3.74832	-0.0042
18	40	-56.114749	0.000027	1.228792	-0.00005
19	42	-56.114751	2.328E-6	0.104417	-3.78E-6
20	44	-56.114751	4.264E-8	0.000218	-8.74E-8

NOTE: GCONV convergence criterion satisfied.

Fit Statistics

-2 Log Likelihood	-112.2
AIC (smaller is better)	-98.2
AICC (smaller is better)	-96.3
BIC (smaller is better)	-99.7

Parameter Estimates

Parameter	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper	Gradient
b1	2.7736	0.2756	4	10.06	0.0005	0.05	2.0085	3.5388	-0.00002
b2	2.8132	0.3594	4	7.83	0.0014	0.05	1.8155	3.8110	-0.00001
b3	0.7865	0.1724	4	4.56	0.0103	0.05	0.3080	1.2651	0.000052
b4	0.4192	0.07058	4	5.94	0.0040	0.05	0.2233	0.6152	-0.00022
s2e	0.006741	0.001297	4	5.20	0.0065	0.05	0.003139	0.01034	0.000139
s2b1	0.3334	0.2302	4	1.45	0.2211	0.05	-0.3058	0.9726	0.000111
s2b3	0.04374	0.03016	4	1.45	0.2206	0.05	-0.04000	0.1275	0.00003