WinNonlin Compartmental Modeling Analysis

Version 4.0.1 Build 200210171634

User-defined ASCII model:

```
MODEL
remark   ****************************************************
remark   Developer: Pravin Jadhav
remark   Model Date:       08-16-2006
remark   Model Version:    1.0
remark   ****************************************************
remark
remark - define model-specific commands
COMMANDS
NFUNCTIONS 4
NDERIVATIVES 8
NPARAMETERS 3
NCONSTANTS 6
PNAMES  'Ke0', 'Emax', 'EC50'
END
remark - define temporary variables
TEMPORARY
T=X
   CL=CON(1)
   V=CON(2)
   DOSE1=CON(3)
   DOSE2=CON(4)
   DOSE3=CON(5)
   DOSE4=CON(6)
K= CL/V

END
remark - define differential equations starting values
START
Z(1) = DOSE1/V
Z(2) = 0
Z(3) = DOSE2/V
Z(4) = 0
Z(5) = DOSE3/V
Z(6) = 0
Z(7) = DOSE4/V
Z(8) = 0

END
remark - define differential equations
DIFFERENTIAL
DZ(1) = -K*Z(1)
DZ(2) = Ke0*((Z(1)/V)-Z(2))
DZ(3) = -K*Z(3)
DZ(4) = Ke0*((Z(3)/V)-Z(4))
DZ(5) = -K*Z(5)
DZ(6) = Ke0*((Z(5)/V)-Z(6))
DZ(7) = -K*Z(7)
DZ(8) = Ke0*((Z(7)/V)-Z(8))
END

remark - define algebraic functions
FUNCTION 1
F= Emax*Z(2)/(EC50+Z(2))
END
```

```
FUNCTION 2
F=  Emax*Z(4)/(EC50+Z(4))
END
FUNCTION 3
F=  Emax*Z(6)/(EC50+Z(6))
END
FUNCTION 4
F=  Emax*Z(8)/(EC50+Z(8))
END
remark - define any secondary parameters
remark - end of model
EOM
```

Settings for analysis:

Input Workbook: C:\Data\misc\ACCP_2006\Data\WNLdata\EMAXEFF.pwo
Input Worksheet: Sheet1
Input Sort Keys: [none]
Gauss-Newton (Levenberg and Hartley) method used
Convergence criteria of 0.0001 used during minimization process
50 maximum iterations allowed during minimization process
0.001 value used in estimation of partial derivatives

Input data:

TIME (hr)	EFF ({units})	DOSE (mg)
1	0.36	5
2	0.53	5
3	0.61	5
4	0.63	5
5	0.62	5
6	0.59	5
7	0.55	5
8	0.51	5
9	0.47	5
10	0.43	5
11	0.39	5
12	0.36	5
13	0.33	5
14	0.3	5
15	0.27	5
16	0.25	5
17	0.22	5
18	0.2	5
19	0.18	5
20	0.17	5
1	2.72	50
2	3.6	50
3	3.93	50
4	4.01	50
5	3.96	50
6	3.84	50
7	3.68	50
8	3.5	50
9	3.31	50
10	3.11	50
11	2.91	50
12	2.72	50
13	2.53	50
14	2.35	50
15	2.18	50
16	2.01	50
17	1.86	50
18	1.71	50
19	1.57	50
20	1.45	50
1	4.27	100
2	5.3	100
3	5.64	100
4	5.72	100
5	5.67	100
6	5.55	100
7	5.38	100
8	5.19	100
9	4.97	100
10	4.74	100
11	4.51	100
12	4.28	100
13	4.04	100
14	3.81	100
15	3.58	100
16	3.35	100
17	3.13	100
18	2.92	100

19	2.72	100
20	2.53	100
1	6.51	250
2	7.38	250
3	7.64	250
4	7.7	250
5	7.66	250
6	7.57	250
7	7.45	250
8	7.29	250
9	7.12	250
10	6.93	250
11	6.73	250
12	6.51	250
13	6.29	250
14	6.06	250
15	5.82	250
16	5.57	250
17	5.33	250
18	5.08	250
19	4.83	250
20	4.58	250

Output data:

Initial Parameters

Parameter	Value	Lower	Upper
KE0	0.1	0	1
EMAX	10	0	100
EC50	10	0	100

Minimization Process

Iteration	Weighted_SS	Ke0	Emax	EC50
0	5.58E-04	0.1	10	10
1	5.56E-04	1.00E-01	10	10
1	5.56E-04	1.00E-01	10	10

Final Parameters

Ke0	Ke0_StdError	Ke0_CV%	Ke0_UnivarCl_Lower	Ke0_UnivarCl_Upper	Ke0_PlanarCl_Lower	Ke0_PlanarCl_Upper	Emax	Emax_StdError	Emax_CV%	Emax_UnivarCl_Lower	Emax_UnivarCl_Upper	Emax_PlanarCl_Lower	Emax_PlanarCl_Upper	EC50	EC50_StdError	EC50_CV%	EC50_UnivarCl_Lower	EC50_UnivarCl_Upper	EC50_PlanarCl_Lower	EC50_PlanarCl_Upper
0.0	0.0	0.0	0.0	0.1	0.0	0.1	10.	0.0	0.0	9.9	10.	9.9	10.	10.	0.0	0.0	9.9	10.	9.9	10.

999	000	3	999	000	998	000	000	021	2	960	004	942	006	000	046	5	909	009	870	013
82	32		17	46	89	74	343	45		71	615	32	455	137	06		65	310	15	260

Dosing

Constant	Value
CON(1)	0.5
CON(2)	1
CON(3)	5
CON(4)	50
CON(5)	100
CON(6)	250

Correlation Matrix

Parameter	Ke0	Emax	EC50
KE0	1		
EMAX	-0.321485	1	
EC50	-0.176774	0.930736	1

Eigenvalues

Number	Value
1	8729
2	13.98
3	0.2851

Condition Numbers

Iteration	Rank	Condition
0	3	7.867687
1	3	7.867691

Variance-Covariance Matrix

Parameter	Ke0	Emax	EC50
KE0	1.05E-09		
EMAX	-2.24E-08	4.60E-06	
EC50	-2.64E-08	9.20E-06	2.12E-05

Summary Table

DOSE (mg)	TIME_obs (hr)	EFF_obs ({units})	TIME (hr)	EFF ({units})	Predicted ({units})	Residual ({units})	Weight	SE_Yhat	Standard_Res
5	1	0.36	1.0000	0.3600	0.3594	0.0006	1.0000	0.0001	0.2140
5	2	0.53	2.0000	0.5300	0.5334	-0.0034	1.0000	0.0002	-1.2793

5	3	0.61	3.0000	0.6100	0.6077	0.0023	1.0000	0.0002	0.8566
5	4	0.63	4.0000	0.6300	0.6267	0.0033	1.0000	0.0002	1.2151
5	5	0.62	5.0000	0.6200	0.6152	0.0048	1.0000	0.0002	1.8042
5	6	0.59	6.0000	0.5900	0.5871	0.0029	1.0000	0.0002	1.0793
5	7	0.55	7.0000	0.5500	0.5508	-0.0008	1.0000	0.0002	-0.3108
5	8	0.51	8.0000	0.5100	0.5112	-0.0012	1.0000	0.0001	-0.4464
5	9	0.47	9.0000	0.4700	0.4710	-0.0010	1.0000	0.0001	-0.3817
5	10	0.43	10.0000	0.4300	0.4319	-0.0019	1.0000	0.0001	-0.7154
5	11	0.39	11.0000	0.3900	0.3948	-0.0048	1.0000	0.0001	-1.7717
5	12	0.36	12.0000	0.3600	0.3600	0.0000	1.0000	0.0001	0.0153
5	13	0.33	13.0000	0.3300	0.3277	0.0023	1.0000	0.0001	0.8588
5	14	0.3	14.0000	0.3000	0.2980	0.0020	1.0000	0.0001	0.7559
5	15	0.27	15.0000	0.2700	0.2707	-0.0007	1.0000	0.0001	-0.2638
5	16	0.25	16.0000	0.2500	0.2458	0.0042	1.0000	0.0001	1.5715
5	17	0.22	17.0000	0.2200	0.2230	-0.0030	1.0000	0.0001	-1.1306
5	18	0.2	18.0000	0.2000	0.2023	-0.0023	1.0000	0.0001	-0.8629
5	19	0.18	19.0000	0.1800	0.1835	-0.0035	1.0000	0.0001	-1.2903
5	20	0.17	20.0000	0.1700	0.1663	0.0037	1.0000	0.0001	1.3681
50	1	2.72	1.0000	2.7200	2.7158	0.0042	1.0000	0.0007	1.6305
50	2	3.6	2.0000	3.6000	3.6041	-0.0041	1.0000	0.0007	-1.5775
50	3	3.93	3.0000	3.9300	3.9285	0.0015	1.0000	0.0007	0.5783
50	4	4.01	4.0000	4.0100	4.0072	0.0028	1.0000	0.0007	1.0774
50	5	3.96	5.0000	3.9600	3.9595	0.0005	1.0000	0.0006	0.1745
50	6	3.84	6.0000	3.8400	3.8414	-0.0014	1.0000	0.0006	-0.5241
50	7	3.68	7.0000	3.6800	3.6827	-0.0027	1.0000	0.0005	-1.0255
50	8	3.5	8.0000	3.5000	3.5012	-0.0012	1.0000	0.0005	-0.4561
50	9	3.31	9.0000	3.3100	3.3080	0.0020	1.0000	0.0005	0.7681
50	10	3.11	10.0000	3.1100	3.1102	-0.0002	1.0000	0.0005	-0.0808
50	11	2.91	11.0000	2.9100	2.9127	-0.0027	1.0000	0.0004	-1.0372
50	12	2.72	12.0000	2.7200	2.7188	0.0012	1.0000	0.0004	0.4442
50	13	2.53	13.0000	2.5300	2.5306	-0.0006	1.0000	0.0004	-0.2354
50	14	2.35	14.0000	2.3500	2.3496	0.0004	1.0000	0.0004	0.1428
50	15	2.18	15.0000	2.1800	2.1768	0.0032	1.0000	0.0004	1.2209
50	16	2.01	16.0000	2.0100	2.0126	-0.0026	1.0000	0.0004	-0.9879
50	17	1.86	17.0000	1.8600	1.8575	0.0025	1.0000	0.0004	0.9385
50	18	1.71	18.0000	1.7100	1.7115	-0.0015	1.0000	0.0004	-0.5790
50	19	1.57	19.0000	1.5700	1.5747	-0.0047	1.0000	0.0004	-1.7545
50	20	1.45	20.0000	1.4500	1.4467	0.0033	1.0000	0.0004	1.2420
100	1	4.27	1.0000	4.2700	4.2715	-0.0015	1.0000	0.0008	-0.6007
100	2	5.3	2.0000	5.3000	5.2986	0.0014	1.0000	0.0007	0.5517
100	3	5.64	3.0000	5.6400	5.6410	-0.0010	1.0000	0.0006	-0.3855
100	4	5.72	4.0000	5.7200	5.7217	-0.0017	1.0000	0.0006	-0.6400
100	5	5.67	5.0000	5.6700	5.6729	-0.0029	1.0000	0.0005	-1.1162
100	6	5.55	6.0000	5.5500	5.5506	-0.0006	1.0000	0.0005	-0.2353
100	7	5.38	7.0000	5.3800	5.3830	-0.0030	1.0000	0.0005	-1.1524
100	8	5.19	8.0000	5.1900	5.1866	0.0034	1.0000	0.0004	1.3009
100	9	4.97	9.0000	4.9700	4.9715	-0.0015	1.0000	0.0004	-0.5479
100	10	4.74	10.0000	4.7400	4.7448	-0.0048	1.0000	0.0004	-1.7921
100	11	4.51	11.0000	4.5100	4.5115	-0.0015	1.0000	0.0004	-0.5524
100	12	4.28	12.0000	4.2800	4.2753	0.0047	1.0000	0.0004	1.7706
100	13	4.04	13.0000	4.0400	4.0391	0.0009	1.0000	0.0004	0.3279
100	14	3.81	14.0000	3.8100	3.8052	0.0048	1.0000	0.0005	1.8172
100	15	3.58	15.0000	3.5800	3.5753	0.0047	1.0000	0.0005	1.7846
100	16	3.35	16.0000	3.3500	3.3509	-0.0009	1.0000	0.0005	-0.3280
100	17	3.13	17.0000	3.1300	3.1331	-0.0031	1.0000	0.0006	-1.1690
100	18	2.92	18.0000	2.9200	2.9228	-0.0028	1.0000	0.0006	-1.0820
100	19	2.72	19.0000	2.7200	2.7209	-0.0009	1.0000	0.0006	-0.3354
100	20	2.53	20.0000	2.5300	2.5277	0.0023	1.0000	0.0006	0.8674
250	1	6.51	1.0000	6.5100	6.5087	0.0013	1.0000	0.0007	0.5059
250	2	7.38	2.0000	7.3800	7.3806	-0.0006	1.0000	0.0008	-0.2390
250	3	7.64	3.0000	7.6400	7.6390	0.0010	1.0000	0.0008	0.3935
250	4	7.7	4.0000	7.7000	7.6978	0.0022	1.0000	0.0009	0.8697
250	5	7.66	5.0000	7.6600	7.6624	-0.0024	1.0000	0.0008	-0.9248

250	6	7.57	6.0000	7.5700	7.5722	-0.0022	1.0000	0.0008	-0.8607
250	7	7.45	7.0000	7.4500	7.4457	0.0043	1.0000	0.0008	1.6607
250	8	7.29	8.0000	7.2900	7.2929	-0.0029	1.0000	0.0007	-1.1037
250	9	7.12	9.0000	7.1200	7.1196	0.0004	1.0000	0.0007	0.1532
250	10	6.93	10.0000	6.9300	6.9299	0.0001	1.0000	0.0006	0.0251
250	11	6.73	11.0000	6.7300	6.7267	0.0033	1.0000	0.0006	1.2519
250	12	6.51	12.0000	6.5100	6.5122	-0.0022	1.0000	0.0006	-0.8277
250	13	6.29	13.0000	6.2900	6.2882	0.0018	1.0000	0.0005	0.7011
250	14	6.06	14.0000	6.0600	6.0563	0.0037	1.0000	0.0006	1.4084
250	15	5.82	15.0000	5.8200	5.8181	0.0019	1.0000	0.0006	0.7178
250	16	5.57	16.0000	5.5700	5.5751	-0.0051	1.0000	0.0006	-1.9360
250	17	5.33	17.0000	5.3300	5.3286	0.0014	1.0000	0.0007	0.5562
250	18	5.08	18.0000	5.0800	5.0800	0.0000	1.0000	0.0007	0.0099
250	19	4.83	19.0000	4.8300	4.8307	-0.0007	1.0000	0.0008	-0.2718
250	20	4.58	20.0000	4.5800	4.5821	-0.0021	1.0000	0.0008	-0.8074

Diagnostics

Function	Item	Value
1	CSS	0.470055
1	WCSS	0.470055
1	SSR	1.57E-04
1	WSSR	1.57E-04
1	S	3.04E-03
1	DF	17
1	CORR_(OBS,PRED)	0.9998
2	CSS	14.0996
2	WCSS	14.0996
2	SSR	1.27E-04
2	WSSR	1.27E-04
2	S	2.74E-03
2	DF	17
2	CORR_(OBS,PRED)	1
3	CSS	21.4445
3	WCSS	21.4445
3	SSR	1.58E-04
3	WSSR	1.58E-04
3	S	3.04E-03
3	DF	17
3	CORR_(OBS,PRED)	1
4	CSS	19.579
4	WCSS	19.579
4	SSR	1.14E-04
4	WSSR	1.14E-04
4	S	2.59E-03
4	DF	17
4	CORR_(OBS,PRED)	1
All	TSSR	5.56E-04
All	TWSSR	5.56E-04
All	TOT_S	2.69E-03
All	TOT_DF	77
All	AIC	-593.64499
All	SBC	-586.49891

Differential Equations

Time	Z[1]	Z[2]	Z[3]	Z[4]	Z[5]	Z[6]	Z[7]	Z[8]
1	5.000000	0.000000	50.00000	0.000000	100.0000	0.000000	250.0000	0.000000

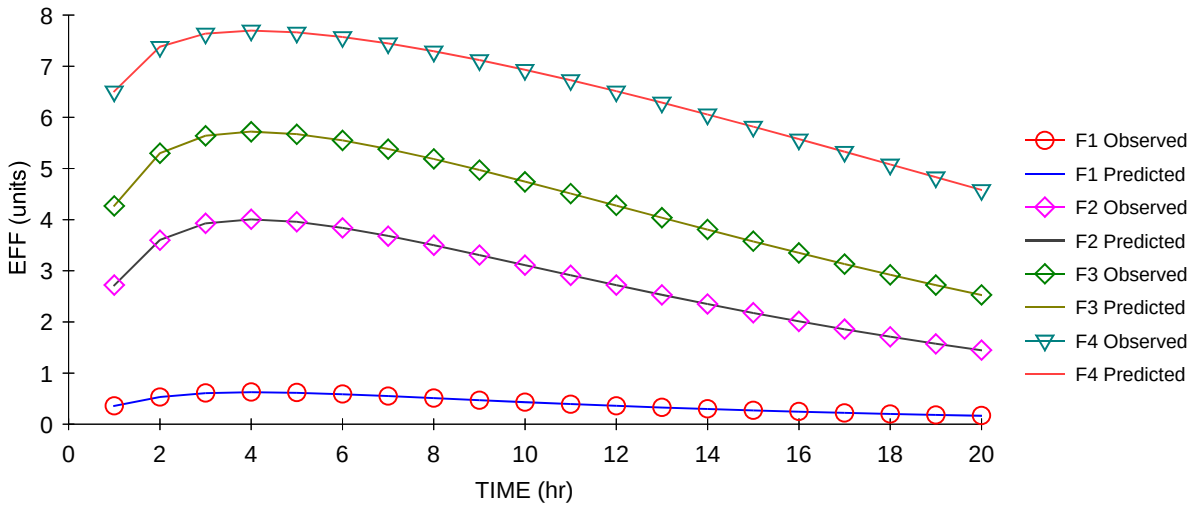
			0		00		00	
2	1.839397	0.563472	18.393965	5.634720	36.787930	11.269440	91.969826	28.173601
3	1.115650	0.647012	11.156501	6.470122	22.313003	12.940243	55.782507	32.350608
4	0.676676	0.668639	6.766756	6.686387	13.533513	13.372773	33.833782	33.431933
5	0.410424	0.655476	4.104243	6.554759	8.208486	13.109518	20.521215	32.773796
6	0.248935	0.623713	2.489348	6.237129	4.978696	12.474257	12.446740	31.185643
7	0.150987	0.582931	1.509865	5.829307	3.019730	11.658613	7.549325	29.146533
8	0.091578	0.538725	0.915779	5.387253	1.831558	10.774507	4.578895	26.936267
9	0.055545	0.494296	0.555448	4.942962	1.110895	9.885925	2.777238	24.714812
10	0.033690	0.451408	0.336896	4.514076	0.673792	9.028152	1.684479	22.570381
11	0.020434	0.410970	0.204338	4.109701	0.408675	8.219401	1.021688	20.548503
12	0.012393	0.373392	0.123934	3.733916	0.247869	7.467833	0.619672	18.669582
13	0.007517	0.338789	0.075168	3.387891	0.150337	6.775782	0.375842	16.939455
14	0.004559	0.307115	0.045591	3.071152	0.091182	6.142305	0.227955	15.355761
15	0.002765	0.278234	0.027652	2.782344	0.055304	5.564689	0.138259	13.911722
16	0.001677	0.251968	0.016771	2.519678	0.033543	5.039355	0.083856	12.598389
17	0.001017	0.228119	0.010172	2.281191	0.020344	4.562383	0.050860	11.405957
18	0.000617	0.206490	0.006170	2.064904	0.012339	4.129808	0.030848	10.324520
19	0.000374	0.186890	0.003742	1.868897	0.007484	3.737794	0.018710	9.344484
20	0.000227	0.169136	0.002270	1.691358	0.004539	3.382716	0.011348	8.456790

Partial Derivatives

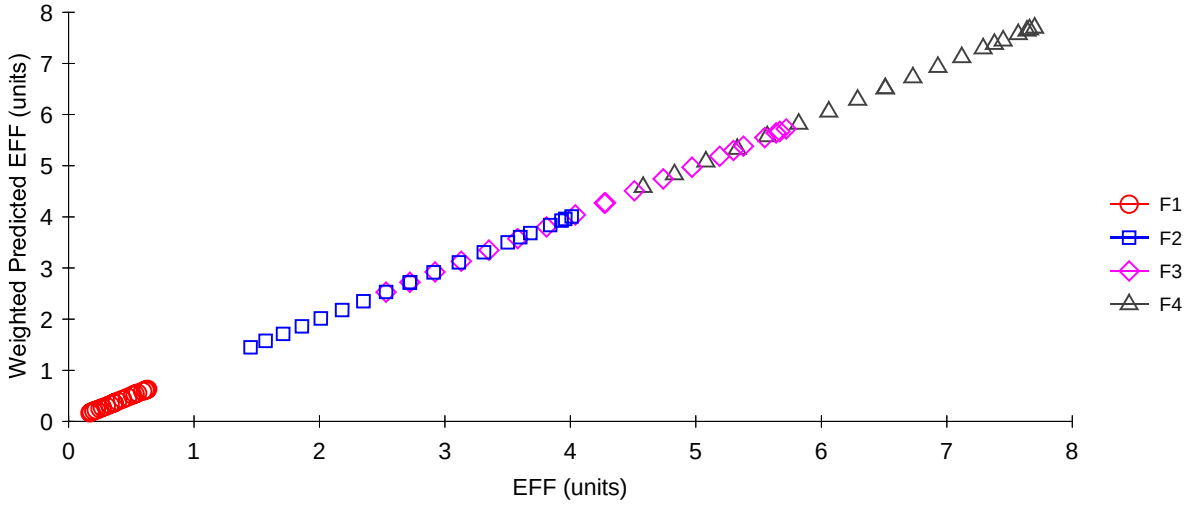
Function	Time (hr)	Ke0	Emax	EC50
1	1	3.28065445	0.03594138	-0.03461693
1	2	4.47832554	0.05334085	-0.05044889
1	3	4.68424849	0.06076858	-0.05702337
1	4	4.39863039	0.06267248	-0.05869084
1	5	3.87748734	0.06151461	-0.05767762
1	6	3.26048613	0.05870874	-0.05521119
1	7	2.62580293	0.05508144	-0.05199941
1	8	2.01679695	0.05111798	-0.04845994
1	9	1.45631455	0.04710080	-0.04484051
1	10	0.95491424	0.04319051	-0.04128644
1	11	0.51580965	0.03947419	-0.03788038
1	12	0.13791331	0.03599466	-0.03466634
1	13	-0.18227446	0.03276831	-0.03166457
1	14	-0.44948681	0.02979603	-0.02888080
1	15	-0.66896897	0.02706989	-0.02631206
1	16	-0.84604132	0.02457717	-0.02395027
1	17	-0.98584385	0.02230284	-0.02178457
1	18	-1.09319498	0.02023101	-0.01980272
1	19	-1.17252176	0.01834585	-0.01799199
1	20	-1.22783427	0.01663204	-0.01633969

2	1	18.72551898	0.27156877	-0.19767925
2	2	20.43780635	0.36039470	-0.23036776
2	3	19.56984917	0.39283665	-0.23837619
2	4	17.97649583	0.40070577	-0.24000177
2	5	16.06041779	0.39594080	-0.23903222
2	6	13.95523255	0.38412430	-0.23643208
2	7	11.73506207	0.36825719	-0.23250174
2	8	9.45944671	0.35010831	-0.22738938
2	9	7.18210660	0.33078561	-0.22122300
2	10	4.95121148	0.31101073	-0.21413992
2	11	2.80817648	0.29126490	-0.20628770
2	12	0.78678791	0.27187285	-0.19781804
2	13	-1.08704862	0.25305377	-0.18888036
2	14	-2.79498687	0.23495404	-0.17961692
2	15	-4.32558930	0.21766856	-0.17015934
2	16	-5.67347209	0.20125518	-0.16062654
2	17	-6.83837210	0.18574467	-0.15112365
2	18	-7.82421358	0.17114769	-0.14174159
2	19	-8.63822263	0.15745989	-0.13255732
2	20	-9.29011707	0.14466567	-0.12363431
3	1	23.15902218	0.42713972	-0.24455632
3	2	22.08356526	0.52983843	-0.24899772
3	3	20.17233168	0.56408144	-0.24579148
3	4	18.32253151	0.57214838	-0.24469495
3	5	16.48173314	0.56727449	-0.24537301
3	6	14.56710025	0.55504307	-0.24686550
3	7	12.53552914	0.53828650	-0.24842456
3	8	10.37834472	0.51863736	-0.24953767
3	9	8.11039901	0.49712832	-0.24987124
3	10	5.76119513	0.47445947	-0.24922184
3	11	3.36832708	0.45113114	-0.24748109
3	12	0.97274183	0.42751577	-0.24461104
3	13	-1.38466055	0.40389930	-0.24062617
3	14	-3.66537157	0.38050653	-0.23558022
3	15	-5.83488793	0.35751692	-0.22955581
3	16	-7.86373512	0.33507482	-0.22265622
3	17	-9.72804127	0.31329623	-0.21499849
3	18	-11.40975639	0.29227345	-0.20670764
3	19	-12.89658995	0.27207836	-0.19791174
3	20	-14.18172647	0.25276494	-0.18873768
4	1	21.50328810	0.65084602	-0.22717084
4	2	17.13631517	0.73803618	-0.19329212
4	3	14.79462902	0.76387339	-0.18033196
4	4	13.26373412	0.76975222	-0.17719659
4	5	12.02578614	0.76620954	-0.17909430
4	6	10.84283271	0.75719441	-0.18381019
4	7	9.59212115	0.74454692	-0.19015214
4	8	8.20706825	0.72926066	-0.19739017
4	9	6.65298418	0.71193570	-0.20502842
4	10	4.91564884	0.69296965	-0.21270179
4	11	2.99524367	0.67264869	-0.22012490
4	12	0.90275883	0.65119514	-0.22706550
4	13	-1.34239265	0.62879404	-0.23333029
4	14	-3.71410061	0.60560903	-0.23875748
4	15	-6.18100538	0.58179173	-0.24321341
4	16	-8.70781373	0.55748718	-0.24659118
4	17	-11.25658698	0.53283689	-0.24881063
4	18	-13.78804064	0.50798001	-0.24981855
4	19	-16.26285319	0.48305335	-0.24958893
4	20	-18.64295355	0.45819058	-0.24812264

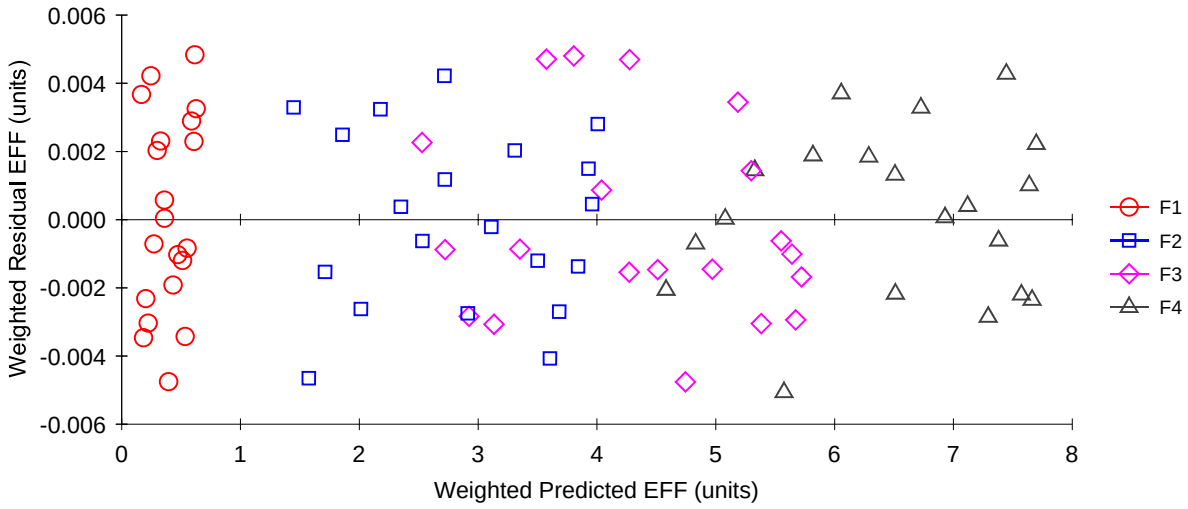
X vs. Observed Y and Predicted Y



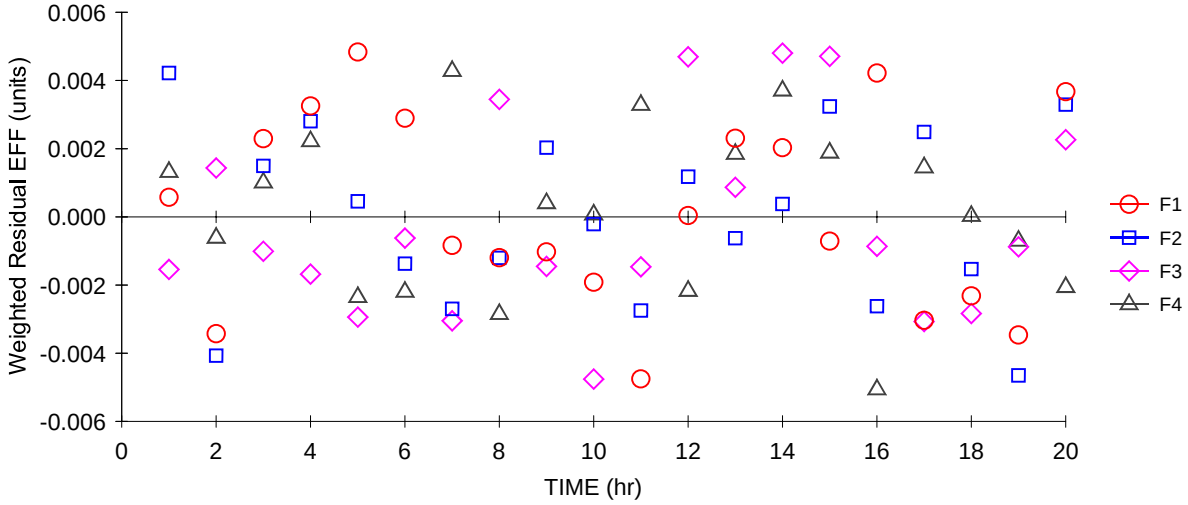
Observed Y vs. Weighted Predicted Y



Weighted Predicted Y vs. Weighted Residual Y



X vs. Weighted Residual Y



Partial Derivatives