

WinNonlin Compartmental Modeling Analysis

Version 4.0.1 Build 200210171634

User-defined ASCII model:

```
MODEL
remark *****
remark Developer: Pravin Jadhav
remark Model Date: 08-07-2006
remark Model Version: 1.0
remark *****
remark
remark - define model-specific commands
COMMANDS
  NCONSTANTS 6
  NFUNCTIONS 4
  NPARAMETERS 3
  P NAMES 'Ke0', 'Emax', 'EC50'
END
remark - define temporary variables
TEMPORARY
  CL=CON(1)
  V=CON(2)
  DOSE1=CON(3)
  DOSE2=CON(4)
  DOSE3=CON(5)
  DOSE4=CON(6)
  K=CL/V
  Ke0=P(1)
  Emax=P(2)
  EC50=P(3)
  TIME=X
END
remark - define algebraic functions
FUNCTION 1
  CONCEFF=( (DOSE1/V)*Ke0/(Ke0-K))*(EXP(-K*TIME)-EXP(-KE0*TIME))
  F= Emax*CONCEFF/(EC50+CONCEFF)
END
FUNCTION 2
  CONCEFF=( (DOSE2/V)*Ke0/(Ke0-K))*(EXP(-K*TIME)-EXP(-KE0*TIME))
  F= Emax*CONCEFF/(EC50+CONCEFF)
END
FUNCTION 3
  CONCEFF=( (DOSE3/V)*Ke0/(Ke0-K))*(EXP(-K*TIME)-EXP(-KE0*TIME))
  F= Emax*CONCEFF/(EC50+CONCEFF)
END
FUNCTION 4
  CONCEFF=( (DOSE4/V)*Ke0/(Ke0-K))*(EXP(-K*TIME)-EXP(-KE0*TIME))
  F= Emax*CONCEFF/(EC50+CONCEFF)
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

Input data:

<u>TIME (hr)</u>	<u>EFF ({units})</u>	<u>DOSE (mg)</u>
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	E _{max}	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	Ke0	Ke0	Ke0	Ke0	Ke0	E _{max}	E _{max}	E _{max}	E _{max}	E _{max}	E _{max}	E _{max}	EC50	EC50	EC50	EC50	EC50	EC50	EC50
0	0	0	0	0	0	0	m	m	m	m	m	m	m	50	50	50	50	50	50	50
St	CV	Un	Un	PI	PI	ax	ax	ax	ax	ax	ax	ax	ax	_S	_C	_U	_U	_P	_P	
dE	%	iva	iva	an	an		_S	_C	_U	_U	_P	_P		td	V	ni	ni	la	la	
rro		rCl	rCl	ar	ar		td	V	ni	ni	la	la		Er	%	va	va	na	na	
r		_L	_U	Cl	Cl		Er	%	va	va	na	na		ror		rCl	rCl	rCl	rCl	
		ow	pp	_L	_U		ror		rCl	rCl	rCl	rCl				_L	_U	_L	_U	
		er	er	ow	pp				_L	_U	_L	_U				ow	pp	ow	pp	
				er	er				ow	pp	ow	pp				er	er	er	er	
									er	er	er	er								
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 32 455 136 06	64 308 14 259

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	-0.176775	0.930736	1

Eigenvalues

Number	Value
1	8729
2	13.98
3	0.2851

Condition Numbers

Iteration	Rank	Condition
0	3	7.867688
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_Yh at	Standard_Res
5	1	0.36	1.0000	0.3600	0.3594	0.0006	1.0000	0.0001	0.2139
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	-0.7155
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	-0.8628
5	19	0.18	19.0000	0.1800	0.1835	-0.0035	1.0000	0.0001	-1.2902
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	1.6303
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	-0.5242
50	7	3.68	7.0000	3.6800	3.6827	-0.0027	1.0000	0.0005	-1.0256
50	8	3.5	8.0000	3.5000	3.5012	-0.0012	1.0000	0.0005	-0.4562
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	-0.0809
50	11	2.91	11.0000	2.9100	2.9127	-0.0027	1.0000	0.0004	-1.0373
50	12	2.72	12.0000	2.7200	2.7188	0.0012	1.0000	0.0004	0.4443
50	13	2.53	13.0000	2.5300	2.5306	-0.0006	1.0000	0.0004	-0.2353
50	14	2.35	14.0000	2.3500	2.3496	0.0004	1.0000	0.0004	0.1429
50	15	2.18	15.0000	2.1800	2.1768	0.0032	1.0000	0.0004	1.2210
50	16	2.01	16.0000	2.0100	2.0126	-0.0026	1.0000	0.0004	-0.9878
50	17	1.86	17.0000	1.8600	1.8575	0.0025	1.0000	0.0004	0.9386
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	-0.6008
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	1.3008
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	-1.7922
100	11	4.51	11.0000	4.5100	4.5115	-0.0015	1.0000	0.0004	-0.5525
100	12	4.28	12.0000	4.2800	4.2753	0.0047	1.0000	0.0004	1.7707
100	13	4.04	13.0000	4.0400	4.0391	0.0009	1.0000	0.0004	0.3280
100	14	3.81	14.0000	3.8100	3.8052	0.0048	1.0000	0.0005	1.8173
100	15	3.58	15.0000	3.5800	3.5753	0.0047	1.0000	0.0005	1.7847
100	16	3.35	16.0000	3.3500	3.3509	-0.0009	1.0000	0.0005	-0.3279
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	-1.0819
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	0.5057
250	2	7.38	2.0000	7.3800	7.3806	-0.0006	1.0000	0.0008	-0.2391
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	-1.1038
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	0.0250
250	11	6.73	11.0000	6.7300	6.7267	0.0033	1.0000	0.0006	1.2518
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	0.7012
250	14	6.06	14.0000	6.0600	6.0563	0.0037	1.0000	0.0006	1.4085
250	15	5.82	15.0000	5.8200	5.8181	0.0019	1.0000	0.0006	0.7179
250	16	5.57	16.0000	5.5700	5.5751	-0.0051	1.0000	0.0006	-1.9359
250	17	5.33	17.0000	5.3300	5.3286	0.0014	1.0000	0.0007	0.5563
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	-0.2717
250	20	4.58	20.0000	4.5800	4.5821	-0.0021	1.0000	0.0008	-0.8073

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	-593.6434
All	SBC	-586.49732

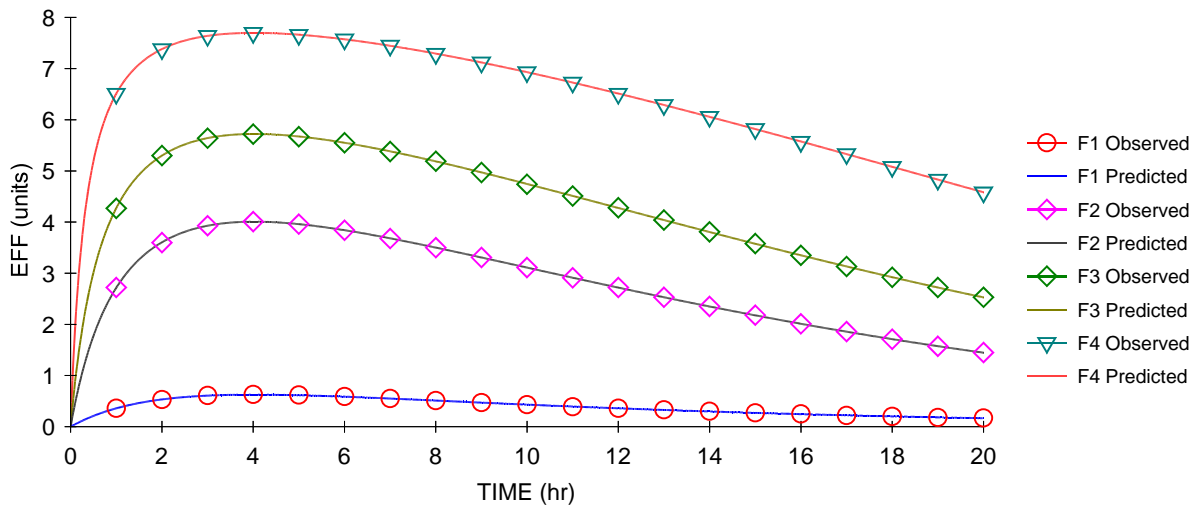
Partial Derivatives

Function	Time (hr)	Ke0	Emax	EC50
1	1	3.28065420	0.03594138	-0.03461694

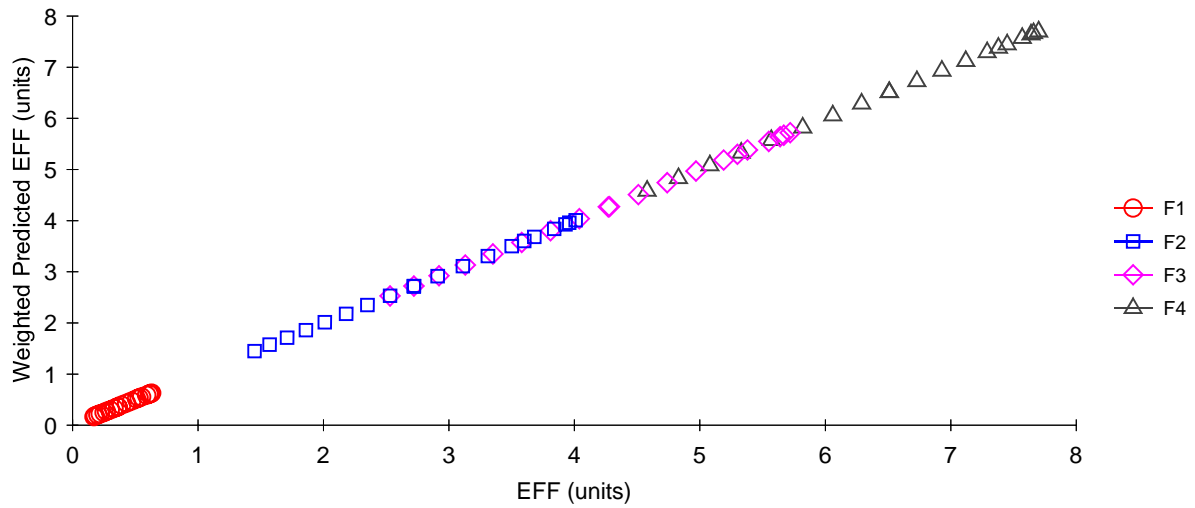
1	2	4.47832467	0.05334086	-0.05044890
1	3	4.68424734	0.06076858	-0.05702338
1	4	4.39862871	0.06267248	-0.05869084
1	5	3.87748563	0.06151461	-0.05767763
1	6	3.26048458	0.05870874	-0.05521120
1	7	2.62580158	0.05508144	-0.05199942
1	8	2.01679579	0.05111798	-0.04845995
1	9	1.45631356	0.04710080	-0.04484052
1	10	0.95491338	0.04319052	-0.04128645
1	11	0.51580889	0.03947420	-0.03788038
1	12	0.13791192	0.03599466	-0.03466634
1	13	-0.18227594	0.03276830	-0.03166457
1	14	-0.44948814	0.02979603	-0.02888080
1	15	-0.66897009	0.02706989	-0.02631206
1	16	-0.84604221	0.02457717	-0.02395027
1	17	-0.98584456	0.02230283	-0.02178457
1	18	-1.09319552	0.02023101	-0.01980272
1	19	-1.17252217	0.01834585	-0.01799199
1	20	-1.22783459	0.01663204	-0.01633969
2	1	18.72551639	0.27156879	-0.19767928
2	2	20.43780163	0.36039471	-0.23036779
2	3	19.56984377	0.39283666	-0.23837622
2	4	17.97648917	0.40070577	-0.24000180
2	5	16.06041088	0.39594080	-0.23903225
2	6	13.95522586	0.38412431	-0.23643211
2	7	11.73505582	0.36825720	-0.23250177
2	8	9.45944100	0.35010832	-0.22738942
2	9	7.18210142	0.33078562	-0.22122303
2	10	4.95120679	0.31101074	-0.21413996
2	11	2.80817222	0.29126492	-0.20628774
2	12	0.78677999	0.27187283	-0.19781806
2	13	-1.08705749	0.25305374	-0.18888038
2	14	-2.79499531	0.23495401	-0.17961693
2	15	-4.32559673	0.21766853	-0.17015935
2	16	-5.67347833	0.20125517	-0.16062655
2	17	-6.83837718	0.18574466	-0.15112366
2	18	-7.82421765	0.17114768	-0.14174160
2	19	-8.63822583	0.15745989	-0.13255733
2	20	-9.29011955	0.14466567	-0.12363433
3	1	23.15901802	0.42713976	-0.24455636
3	2	22.08355971	0.52983845	-0.24899776
3	3	20.17232580	0.56408145	-0.24579151
3	4	18.32252483	0.57214838	-0.24469499
3	5	16.48172614	0.56727449	-0.24537305
3	6	14.56709324	0.55504308	-0.24686553
3	7	12.53552235	0.53828651	-0.24842459
3	8	10.37833827	0.51863738	-0.24953770
3	9	8.11039298	0.49712834	-0.24987128
3	10	5.76118952	0.47445949	-0.24922187
3	11	3.36832188	0.45113116	-0.24748113
3	12	0.97273207	0.42751575	-0.24461107
3	13	-1.38467191	0.40389926	-0.24062620
3	14	-3.66538281	0.38050649	-0.23558024
3	15	-5.83489816	0.35751689	-0.22955583
3	16	-7.86374399	0.33507480	-0.22265624
3	17	-9.72804872	0.31329621	-0.21499851
3	18	-11.40976252	0.29227343	-0.20670766
3	19	-12.89659491	0.27207835	-0.19791176
3	20	-14.18173042	0.25276493	-0.18873770
4	1	21.50328296	0.65084605	-0.22717086
4	2	17.13631045	0.73803619	-0.19329214
4	3	14.79462444	0.76387340	-0.18033198
4	4	13.26372938	0.76975222	-0.17719661

4	5	12.02578111	0.76620954	-0.17909432
4	6	10.84282747	0.75719441	-0.18381021
4	7	9.59211583	0.74454693	-0.19015216
4	8	8.20706297	0.72926067	-0.19739019
4	9	6.65297903	0.71193571	-0.20502844
4	10	4.91564388	0.69296967	-0.21270181
4	11	2.99523893	0.67264871	-0.22012492
4	12	0.90274980	0.65119512	-0.22706554
4	13	-1.34240374	0.62879400	-0.23333032
4	14	-3.71411224	0.60560900	-0.23875752
4	15	-6.18101659	0.58179169	-0.24321344
4	16	-8.70782397	0.55748715	-0.24659122
4	17	-11.25659604	0.53283687	-0.24881066
4	18	-13.78804846	0.50798000	-0.24981858
4	19	-16.26285983	0.48305334	-0.24958896
4	20	-18.64295912	0.45819056	-0.24812268

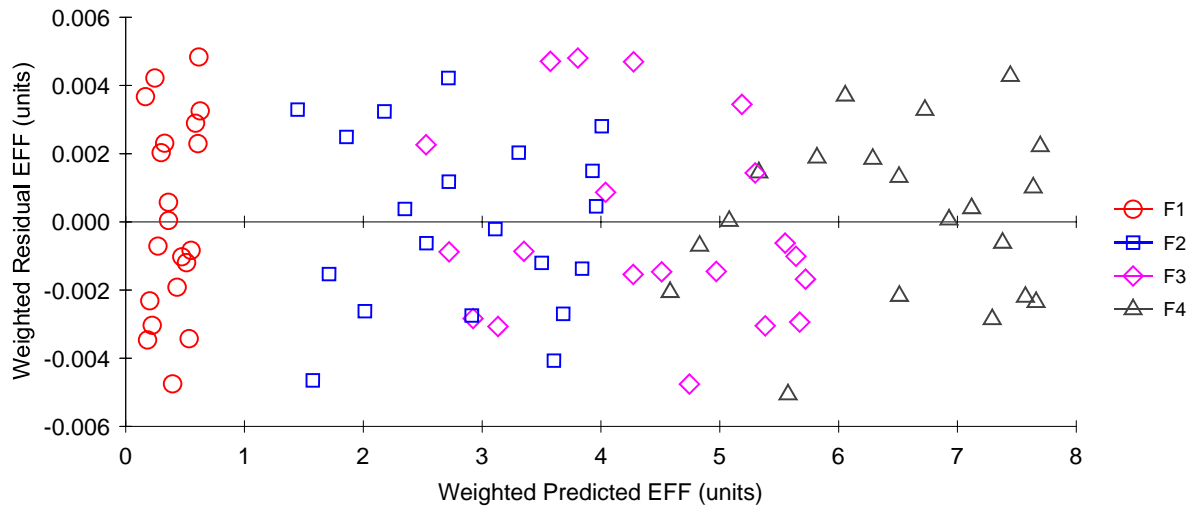
X vs. Observed Y and Predicted Y



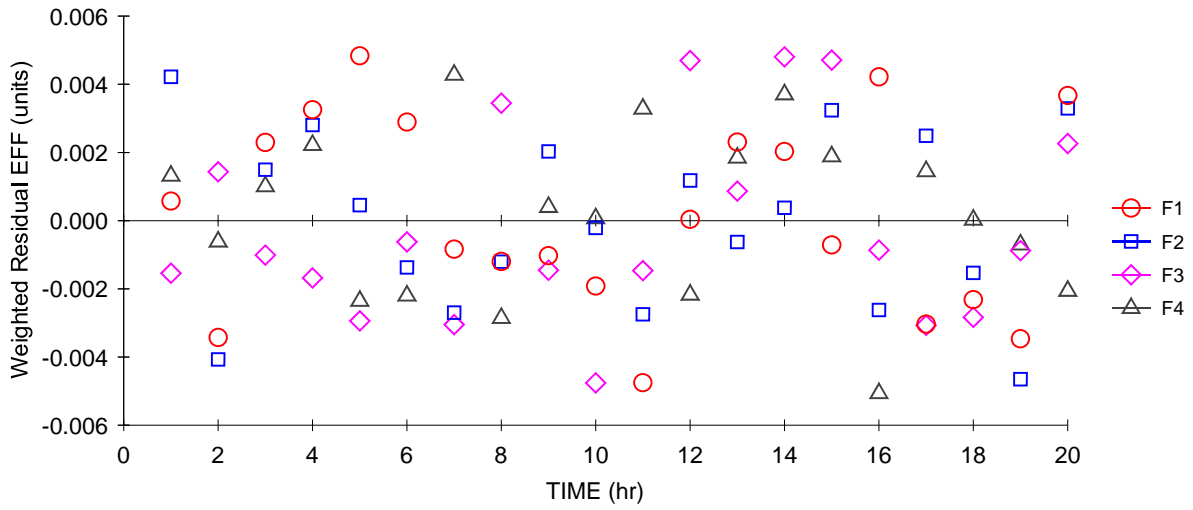
Observed Y vs. Weighted Predicted Y



Weighted Predicted Y vs. Weighted Residual Y



X vs. Weighted Residual Y



Partial Derivatives

