Appendix I-B.   2- or 3-Drug Combinations in Vitro

Analysis of Combination Data in Table 11 for Taxol, Cisplatin and Topotecan

(Adopted from Table 11 and Appendix IV of Pharmacol Rev 58: 621-681, 2006)

Example I-B: Cancer Cell System: 2- or 3- Drugs

Computer Generated Report for Taxol, Cisplatin and Topotecan in 2-and 3-Drug Combinations (Analysis of Experimental Data Given in Table 11)

CompuSyn Report

APPENDIX IV. Example for 2- and 3- Drug Combinations: Paclitexel, Cisplatin and Topotecan

Experiment Name:	
Date:	04/02/2004
File Name:	A:\Sample.cse
Description	Paclitaxel + Cisplastin + Topotecan. 2-drug and 3-drug combinations at constant ratio (1:100:10) (For crude data and analysis, see Chou et al. J Natl Cancer Inst. 86:1517-1524, 1994)
Drug:	Paclitaxel (A) [μM]
Drug:	Cisplatin (B) [μM]
Drug:	Topotecan (C) [μM]
Drug Combo:	Paclitaxel + Cisplatin (A+B) (A+B [1:100])
Drug Combo:	Cisplatin + Topotecan (B + C) (B+C [10:1])
Drug Combo:	Paclitaxel +Topotecan (A + C) (A+C [1:10])
Drug Combo:	Pac + Cispt + Topot (A+B+C) (A+B+C [1:100:10])

Data for Drug: A [μM] — 5 data points entered.

Dose	Effect
0.0020	0.429
0.0040	0.708
0.0050	0.761
0.01	0.882
0.02	0.932

X-int: -2.6640
Y-int: 3.32420 +/- 0.22896
m: 1.24783 +/- 0.10195
Dm: 0.00217
r: 0.99013

Data for Drug: B [μM] — 6 data points entered.

Dose	Effect
0.05	0.055
0.1	0.233
0.2	0.301
0.5	0.559
1.0	0.821
2.0	0.953

X-int: -0.4946
Y-int: 0.72212 +/- 0.09243
m: 1.45990 +/- 0.12346
Dm: 0.32016
r: 0.98600

Data for Drug: C [μM] — 6 data points entered.

Dose	Effect
0.01	0.069
0.02	0.213
0.05	0.373
0.1	0.785
0.2	0.94
0.5	0.991

X-int: -1.3352
Y-int: 2.47666 +/- 0.16272
m: 1.85486 +/- 0.12506
Dm: 0.04621
r: 0.99103

Data for Drug Combo: A+B (A+B [1:100]) — 4 data points entered.

Dose A	Effect
0.0010+	0.45
0.0020+	0.701
0.0050+	0.91
0.01+	0.968

X-int: -0.9361
Y-int: 1.47111 +/- 0.00683
m: 1.57160 +/- 0.01093
Dm: 0.11586
r: 0.99995

Data for Drug Combo: B + C (B+C [10:1]) — 5 data points entered.

Dose A	Effect
0.05000+	0.304
0.10000+	0.413
0.20000+	0.675
0.5+	0.924
1.0+	0.977

X-int: -0.9360
Y-int: 1.48617 +/- 0.10394
m: 1.58782 +/- 0.13403
Dm: 0.11588
r: 0.98948

Data for Drug Combo: A + C (A+C [1:10]) — 4 data points entered.

Dose A	Effect
0.0010+	0.274
0.0020+	0.579
0.0050+	0.901
0.01+	0.965

X-int: -1.7382
Y-int: 3.28664 +/- 0.09192
m: 1.89081 +/- 0.06098
Dm: 0.01827
r: 0.99896

Data for Drug Combo: A+B+C (A+B+C [1:100:10]) — 4 data points entered.

Dose A	Effect
0.0010+	0.456
0.0020+	0.806
0.0030+	0.947
0.0050+	0.995

X-int: -0.8896
Y-int: 2.99211 +/- 0.27462
m: 3.36336 +/- 0.42992
Dm: 0.12894
r: 0.98405

Dose-Effect Curve for Drugs

Legend: A, B, C
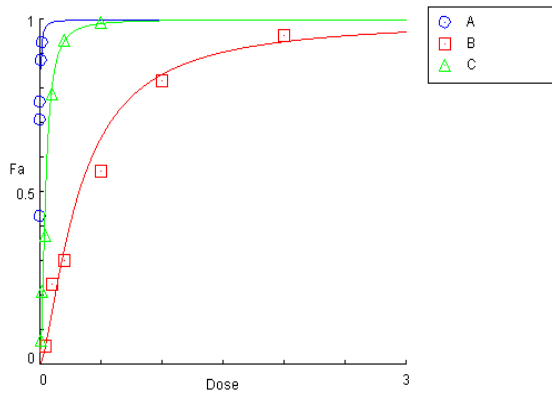
Dose-Effect Curve for Drug Combos

Legend: A+B, B + C, A + C, A+B+C
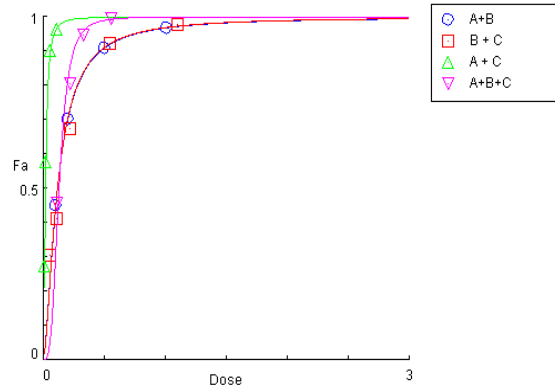
Median-Effect Plot for Drugs

Legend: A, B, C
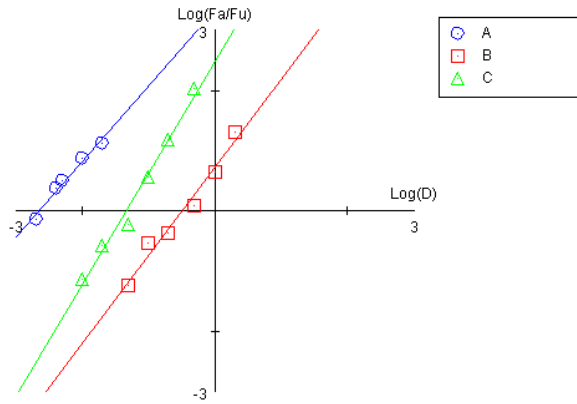
Median-Effect Plot for Drug Combos

Legend: A+B, B + C, A + C, A+B+C
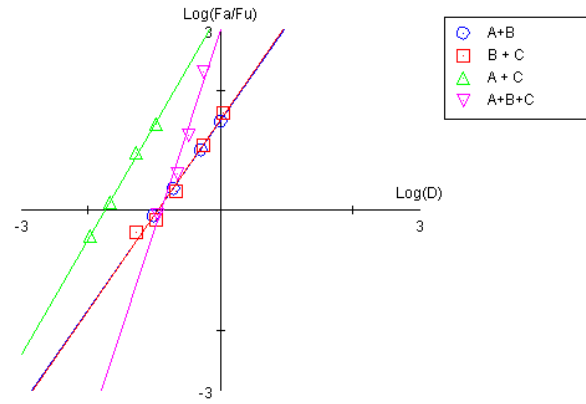
CI Data for Drug Combo: A+B (A+B [1:100])

Fa	CI Value	S.D.A. Analysis
0.05	1.27397	1.29720 +/- 0.35026
0.1	1.15934	1.17507 +/- 0.25163
0.15	1.09453	1.10667 +/- 0.20165
0.2	1.04860	1.05847 +/- 0.16885
0.25	1.01241	1.02067 +/- 0.14460
0.3	0.98203	0.98904 +/- 0.12540
0.35	0.95539	0.96140 +/- 0.10947
0.4	0.93127	0.93644 +/- 0.09585
0.45	0.90883	0.91327 +/- 0.08394
0.5	0.88749	0.89129 +/- 0.07338
0.55	0.86676	0.87000 +/- 0.06396
0.6	0.84622	0.84894 +/- 0.05561
0.65	0.82544	0.82768 +/- 0.04840
0.7	0.80393	0.80572 +/- 0.04261
0.75	0.78105	0.78243 +/- 0.03875
0.8	0.75585	0.75683 +/- 0.03760
0.85	0.72670	0.72731 +/- 0.03999
0.9	0.69014	0.69042 +/- 0.04671
0.95	0.63591	0.63595 +/- 0.05963
0.97	0.60063	0.60067 +/- 0.06821

CI values for actual experimental points:

Total Dose	Fa	CI Value
0.101	0.45	0.90016
0.202	0.701	0.81458
0.505	0.91	0.68132
1.01	0.968	0.60241

CI Data for Drug Combo: B + C (B+C [10:1])

Fa	CI Value	S.D.A. Analysis
0.05	0.56165	0.56841 +/- 0.13945
0.1	0.55825	0.56325 +/- 0.11529
0.15	0.55689	0.56095 +/- 0.10145
0.2	0.55625	0.55968 +/- 0.09161
0.25	0.55596	0.55892 +/- 0.08388
0.3	0.55591	0.55848 +/- 0.07744
0.35	0.55600	0.55825 +/- 0.07188
0.4	0.55623	0.55820 +/- 0.06694
0.45	0.55657	0.55829 +/- 0.06248
0.5	0.55701	0.55851 +/- 0.05841
0.55	0.55757	0.55886 +/- 0.05468
0.6	0.55827	0.55936 +/- 0.05128
0.65	0.55912	0.56003 +/- 0.04823
0.7	0.56018	0.56092 +/- 0.04563
0.75	0.56153	0.56210 +/- 0.04366
0.8	0.56331	0.56372 +/- 0.04270
0.85	0.56580	0.56605 +/- 0.04343
0.9	0.56969	0.56982 +/- 0.04738
0.95	0.57742	0.57752 +/- 0.05907
0.97	0.58404	0.58425 +/- 0.06994

CI values for actual experimental points:

Total Dose	Fa	CI Value
0.055	0.304	0.44454
0.11	0.413	0.65895
0.22	0.675	0.67049
0.55	0.924	0.56357
1.1	0.977	0.52625

CI Data for Drug Combo: A + C (A+C [1:10])

Fa	CI Value	S.D.A. Analysis
0.05	2.07991	2.12182 +/- 0.69406
0.1	1.76214	1.78786 +/- 0.45949
0.15	1.59522	1.61384 +/- 0.34990
0.2	1.48260	1.49700 +/- 0.28181
0.25	1.39722	1.40874 +/- 0.23357
0.3	1.32786	1.33725 +/- 0.19670
0.35	1.26880	1.27653 +/- 0.16705
0.4	1.21672	1.22311 +/- 0.14235
0.45	1.16951	1.17477 +/- 0.12125
0.5	1.12570	1.13000 +/- 0.10289
0.55	1.08418	1.08765 +/- 0.08675
0.6	1.04405	1.04678 +/- 0.07252
0.65	1.00447	1.00655 +/- 0.06016
0.7	0.96460	0.96608 +/- 0.04992
0.75	0.92342	0.92437 +/- 0.04249
0.8	0.87954	0.88000 +/- 0.03901
0.85	0.83072	0.83074 +/- 0.04048
0.9	0.77247	0.77212 +/- 0.04703
0.95	0.69222	0.69160 +/- 0.05855
0.97	0.64400	0.64335 +/- 0.06497

CI values for actual experimental points:

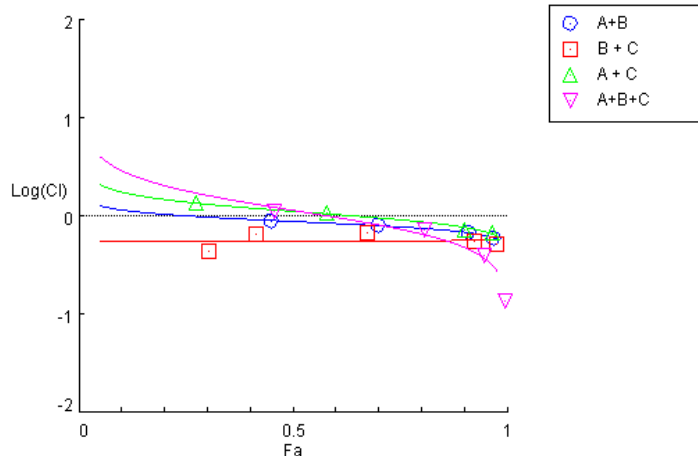| Total Dose	Fa	CI Value
0.011	0.274	1.37314
0.022	0.579	1.07913
0.055	0.901	0.72191
0.11	0.965	0.68525

CI Data for Drug Combo: A+B+C (A+B+C [1:100:10]) CI values for actual experimental points:

Fa	CI Value	S.D.A. Analysis
0.05	4.01225	4.09062 +/- 1.20573
0.1	2.89997	2.94428 +/- 0.71638
0.15	2.37773	2.40876 +/- 0.51488
0.2	2.05022	2.07393 +/- 0.39956
0.25	1.81559	1.83458 +/- 0.32289
0.3	1.63377	1.64942 +/- 0.26728
0.35	1.48526	1.49840 +/- 0.22456
0.4	1.35920	1.37037 +/- 0.19040
0.45	1.24892	1.25850 +/- 0.16224
0.5	1.15003	1.15829 +/- 0.13849
0.55	1.05942	1.06655 +/- 0.11810
0.6	0.97473	0.98089 +/- 0.10036
0.65	0.89405	0.89935 +/- 0.08481
0.7	0.81563	0.82018 +/- 0.07112
0.75	0.73771	0.74158 +/- 0.05915
0.8	0.65817	0.66143 +/- 0.04891
0.85	0.57398	0.57666 +/- 0.04065
0.9	0.47959	0.48174 +/- 0.03482
0.95	0.36068	0.36232 +/- 0.03174
0.97	0.29566	0.29710 +/- 0.03095

Total Dose	Fa	CI Value
0.111	0.456	1.12184
0.222	0.806	0.73098
0.333	0.947	0.40455
0.555	0.995	0.13710

Combination Index Plot

Legend:
- A+B
- B + C
- A + C
- A+B+C
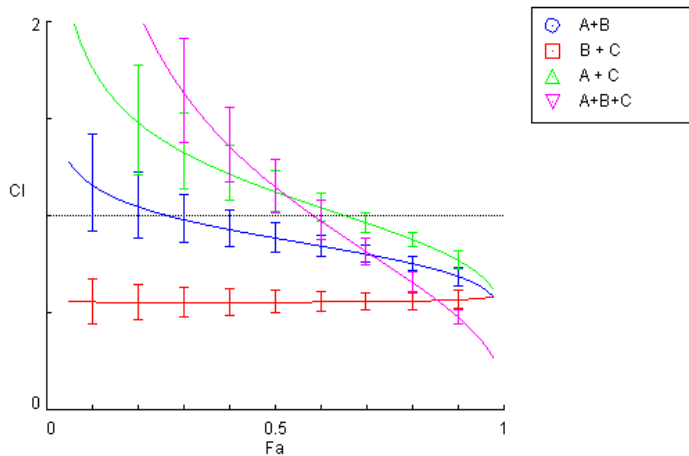
Logarithmic Combination Index Plot

Legend:
- A+B
- B + C
- A + C
- A+B+C

DRI Data for Drug Combo: A+B (A+B [1:100])

Fa	Dose A	Dose B	DRI A	DRI B
0.05	2.05E-4	0.04260	1.16220	2.41819
0.1	3.73E-4	0.07108	1.31479	2.50778
0.15	5.40E-4	0.09758	1.41914	2.56490
0.2	7.14E-4	0.12387	1.50314	2.60876
0.25	8.99E-4	0.15085	1.57625	2.64556
0.3	0.00110	0.17919	1.64303	2.67812
0.35	0.00132	0.20951	1.70613	2.70805
0.4	0.00157	0.24252	1.76736	2.73635
0.45	0.00185	0.27904	1.82814	2.76377
0.5	0.00217	0.32016	1.88972	2.79090
0.55	0.00255	0.36733	1.95337	2.81830
0.6	0.00300	0.42265	2.02055	2.84654
0.65	0.00356	0.48923	2.09306	2.87629
0.7	0.00427	0.57203	2.17344	2.90843
0.75	0.00523	0.67948	2.26552	2.94423
0.8	0.00658	0.82748	2.37572	2.98576
0.85	0.00870	1.05045	2.51634	3.03682
0.9	0.01261	1.44211	2.71606	3.10599
0.95	0.02295	2.40591	3.07266	3.22106
0.97	0.03514	3.46290	3.35455	3.30551

DRI values calculated at experimental points

Fa	Dose A	Dose B	DRI A	DRI B
0.45	0.00185	0.27904	1.84575	2.79039
0.701	0.00429	0.57390	2.14554	2.86949
0.91	0.01384	1.56181	2.76873	3.12361
0.968	0.03332	3.30846	3.33161	3.30846

DRI Data for Drug Combo: B + C (B+C [10:1])

Fa	Dose B	Dose C	DRI B	DRI C
0.05	0.04260	0.00945	2.58327	5.72911
0.1	0.07108	0.01414	2.69201	5.35382
0.15	0.09758	0.01814	2.76162	5.13389
0.2	0.12387	0.02189	2.81521	4.97429
0.25	0.15085	0.02556	2.86026	4.84622
0.3	0.17919	0.02927	2.90021	4.73704
0.35	0.20951	0.03310	2.93697	4.64000
0.4	0.24252	0.03714	2.97179	4.55102
0.45	0.27904	0.04147	3.00556	4.46729
0.5	0.32016	0.04621	3.03903	4.38674
0.55	0.36733	0.05149	3.07287	4.30765
0.6	0.42265	0.05750	3.10779	4.22840
0.65	0.48923	0.06452	3.14464	4.14730
0.7	0.57203	0.07297	3.18450	4.06235
0.75	0.67948	0.08356	3.22897	3.97083
0.8	0.82748	0.09758	3.28064	3.86859
0.85	1.05045	0.11774	3.34431	3.74833
0.9	1.44211	0.15109	3.43078	3.59435
0.95	2.40591	0.22604	3.57520	3.35890
0.97	3.46290	0.30106	3.68165	3.20082

DRI values calculated at experimental points

Fa	Dose B	Dose C	DRI B	DRI C
0.304	0.18153	0.02957	3.63061	5.91365
0.413	0.25164	0.03823	2.51636	3.82340
0.675	0.52819	0.06853	2.64093	3.42663
0.924	1.77201	0.17768	3.54402	3.55363
0.977	4.17466	0.34878	4.17466	3.48782

DRI Data for Drug Combo: A + C (A+C [1:10])

Fa	Dose A	Dose C	DRI A	DRI C
0.05	2.05E-4	0.00945	0.58498	2.69941
0.1	3.73E-4	0.01414	0.71709	2.72017
0.15	5.40E-4	0.01814	0.81345	2.73310
0.2	7.14E-4	0.02189	0.89444	2.74288
0.25	8.99E-4	0.02556	0.96739	2.75098
0.3	0.00110	0.02927	1.03596	2.75808
0.35	0.00132	0.03310	1.10245	2.76454
0.4	0.00157	0.03714	1.16852	2.77060
0.45	0.00185	0.04147	1.23559	2.77642
0.5	0.00217	0.04621	1.30504	2.78214
0.55	0.00255	0.05149	1.37840	2.78787
0.6	0.00300	0.05750	1.45751	2.79372
0.65	0.00356	0.06452	1.54486	2.79985
0.7	0.00427	0.07297	1.64401	2.80641
0.75	0.00523	0.08356	1.76055	2.81365
0.8	0.00658	0.09758	1.90413	2.82196
0.85	0.00870	0.11774	2.09372	2.83205
0.9	0.01261	0.15109	2.37505	2.84551
0.95	0.02295	0.22604	2.91143	2.86739
0.97	0.03514	0.30106	3.36535	2.88307

DRI values calculated at experimental points

Fa	Dose A	Dose C	DRI A	DRI C
0.274	9.93E-4	0.02733	0.99283	2.73286
0.579	0.00280	0.05488	1.39924	2.74379
0.901	0.01272	0.15200	2.54478	3.03996
0.965	0.03093	0.27628	3.09304	2.76284

DRI Data for Drug Combo: A+B+C (A+B+C [1:100:10])

Fa	Dose A	Dose B	Dose C	DRI A	DRI B	DRI C
0.05	2.05E-4	0.04260	0.00945	0.42303	0.88021	1.95210
0.1	3.73E-4	0.07108	0.01414	0.61652	1.17594	2.33868
0.15	5.40E-4	0.09758	0.01814	0.77844	1.40692	2.61549
0.2	7.14E-4	0.12387	0.02189	0.92784	1.61031	2.84531
0.25	8.99E-4	0.15085	0.02556	1.07264	1.80029	3.05028
0.3	0.00110	0.17919	0.02927	1.21750	1.98451	3.24139
0.35	0.00132	0.20951	0.03310	1.36596	2.16812	3.42533
0.4	0.00157	0.24252	0.03714	1.52122	2.35526	3.60687
0.45	0.00185	0.27904	0.04147	1.68665	2.54987	3.78998
0.5	0.00217	0.32016	0.04621	1.86619	2.75615	3.97841
0.55	0.00255	0.36733	0.05149	2.06483	2.97911	4.17621
0.6	0.00300	0.42265	0.05750	2.28938	3.22527	4.38823
0.65	0.00356	0.48923	0.06452	2.54960	3.50366	4.62080
0.7	0.00427	0.57203	0.07297	2.86049	3.82782	4.88301
0.75	0.00523	0.67948	0.08356	3.24681	4.21951	5.18895
0.8	0.00658	0.82748	0.09758	3.75349	4.71732	5.56275
0.85	0.00870	1.05045	0.11774	4.47388	5.39927	6.05155
0.9	0.01261	1.44211	0.15109	5.64885	6.45983	6.76782
0.95	0.02295	2.40591	0.22604	8.23258	8.63018	8.10805
0.97	0.03514	3.46290	0.30106	10.7628	10.6054	9.22037

DRI values calculated at experimental points

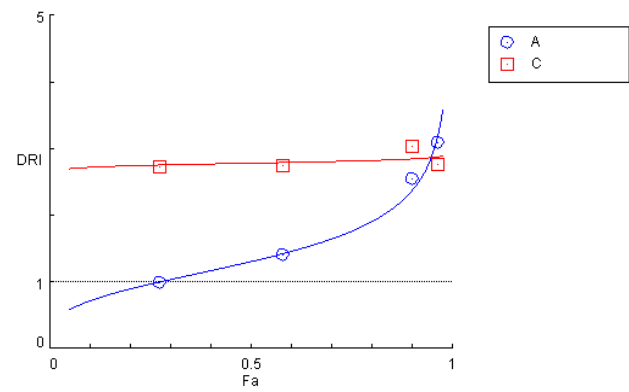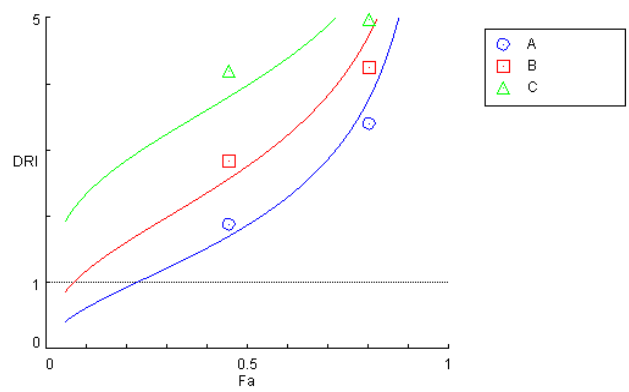| Fa	Dose A	Dose B	Dose C	DRI A	DRI B	DRI C
0.456	0.00188	0.28371	0.04202	1.88191	2.83706	4.20197
0.806	0.00679	0.84927	0.09959	3.39368	4.24633	4.97972
0.947	0.02185	2.30677	0.21867	7.28273	7.68925	7.28906
0.995	0.15076	12.0234	0.80193	30.1526	24.0468	16.0386

DRI Plot for Combo: B + C (B+C [10:1])
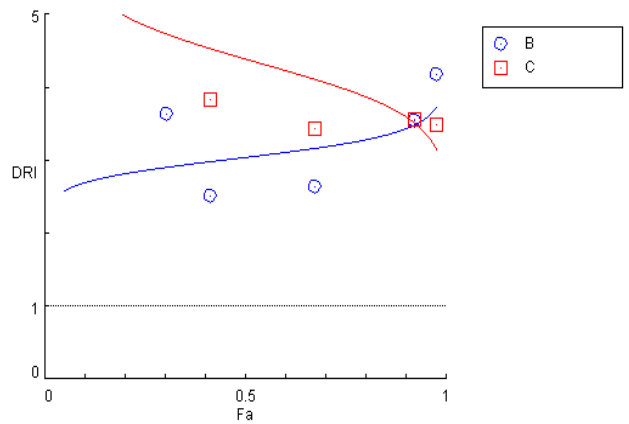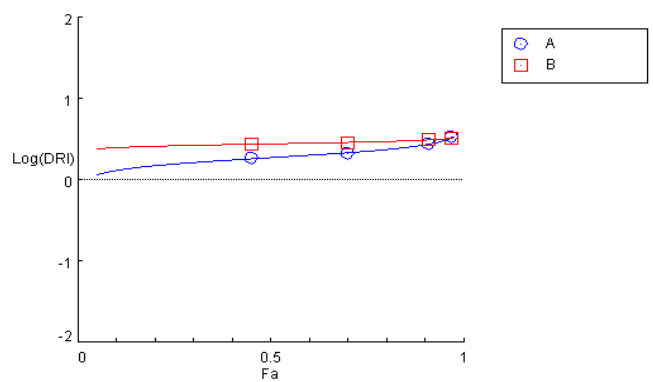
DRI Plot for Combo: A+B (A+B [1:100])
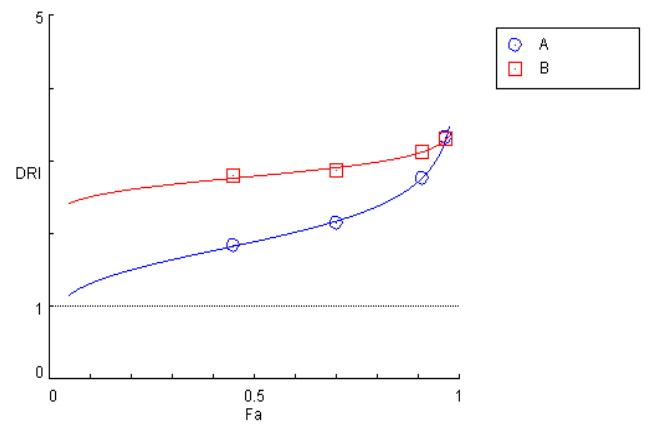
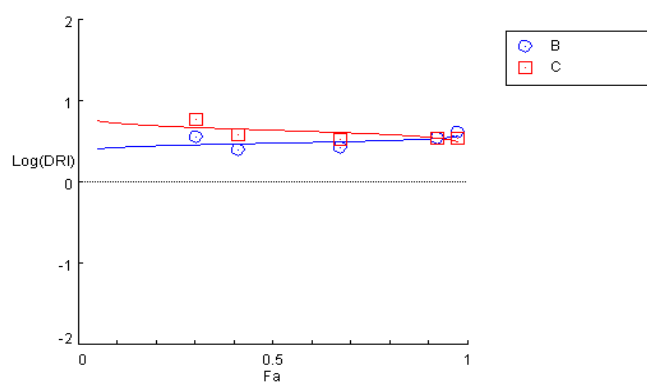DRI Plot for Combo: A + C (A+C [1:10])
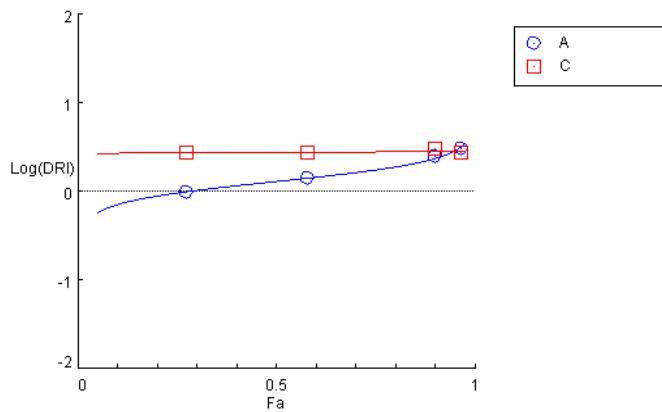
DRI Plot for Combo: A+B+C (A+B+C [1:100:10])

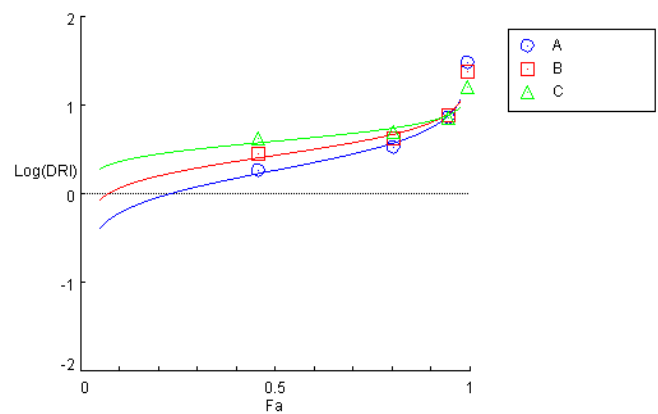Log(DRI) Plot for Combo: A+B (A+B [1:100])
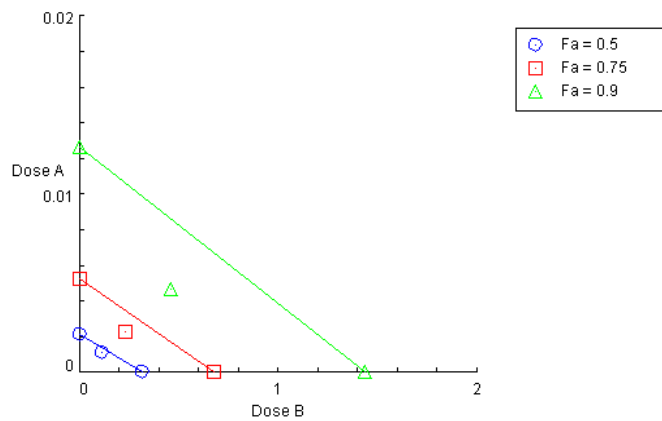
Log(DRI) Plot for Combo: B + C (B+C [10:1])

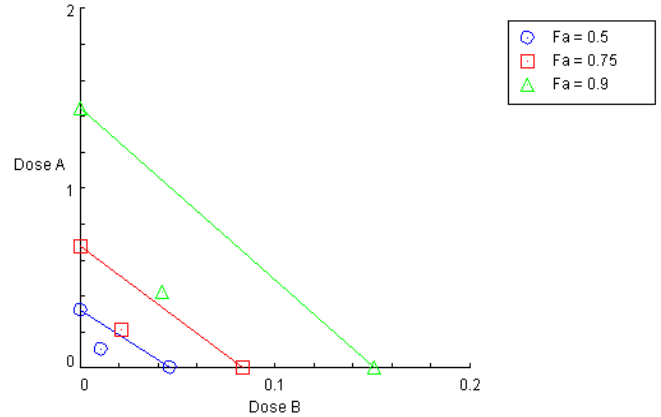## Log(DRI) Plot for Combo: A + C (A+C [1:10])

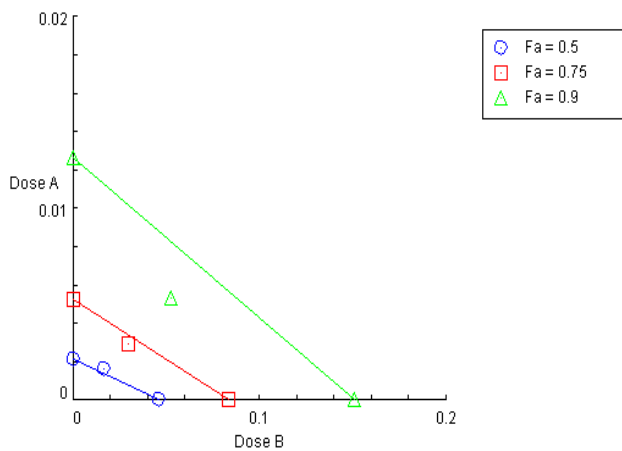## Log(DRI) Plot for Combo: A+B+C (A+B+C [1:100:10])
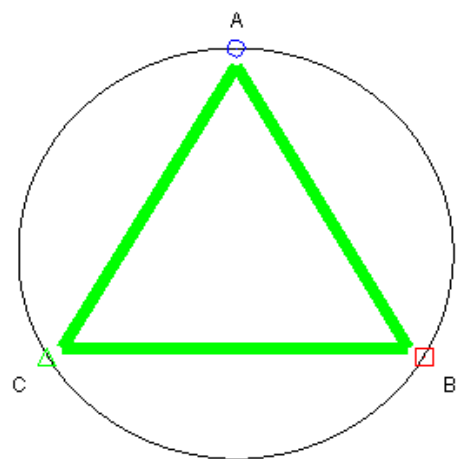

Isobologram for Combo: A+B (A+B [1:100])

Isobologram for Combo: B + C (B+C [10:1])

Isobologram for Combo: A + C (A+C [1:10])

Polygonogram at Fa = 0.95

Summary Table

Experiment Name:	APPENDIX IV. Example for 2- and 3- Drug Combinations: Paclitexel, Cisplatin and Topotecan
Date:	04/02/2004
File Name:	A:\Sample.cse
Description	Paclitaxel + Cisplastin + Topotecan. 2-drug and 3-drug combinations at constant ratio (1:100:10) (For crude data and analysis, see Chou et al. J Natl Cancer Inst. 86:1517-1524, 1994)
Drug:	Paclitaxel (A) [μM]
Drug:	Cisplatin (B) [μM]
Drug:	Topotecan (C) [μM]

Drug Combo: Paclitaxel + Cisplatin (A+B) (A+B [1:100])
Drug Combo: Cisplatin + Topotecan (B + C) (B+C [10:1])
Drug Combo: Paclitaxel +Topotecan (A + C) (A+C [1:10])
Drug Combo: Pac + Cispt + Topot (A+B+C) (A+B+C [1:100:10])

Drug/Combo	Dm	m	r
A	0.00217	1.24783	0.99013
B	0.32016	1.45990	0.98600
C	0.04621	1.85486	0.99103
A+B	0.11586	1.57160	0.99995
B + C	0.11588	1.58782	0.98948
A + C	0.01827	1.89081	0.99896
A+B+C	0.12894	3.36336	0.98405

CI values at:

Combo	ED50	ED75	ED90	ED95
A+B	0.88749	0.78105	0.69014	0.63591
B + C	0.55701	0.56153	0.56969	0.57742
A + C	1.12570	0.92342	0.77247	0.69222
A+B+C	1.15003	0.73771	0.47959	0.36068

Data for Fa = 0.95

Drug/Combo	CI value	Dose A	Dose B	Dose C
A		0.02295		
B			2.40591	
C				0.22604
A+B	0.63591	0.00747	0.74693	
B + C	0.57742		0.67294	0.06729
A + C	0.69222	0.00788		0.07883
A+B+C	0.36068	0.00279	0.27878	0.02788

Data for Fa = 0.97

Drug/Combo	CI value	Dose A	Dose B	Dose C
A		0.03514		
B			3.46290	
C				0.30106
A+B	0.60063	0.01048	1.04761	
B + C	0.58404		0.94058	0.09406
A + C	0.64400	0.01044		0.10442
A+B+C	0.29566	0.00327	0.32652	0.03265

Data for Fa = 0.5

Drug/Combo	CI value	Dose A	Dose B	Dose C
A		0.00217		
B			0.32016	
C				0.04621
A+B	0.88749	0.00115	0.11471	
B + C	0.55701		0.10535	0.01053
A + C	1.12570	0.00166		0.01661
A+B+C	1.15003	0.00116	0.11616	0.01162

Data for Fa = 0.75

Drug/Combo	CI value	Dose A	Dose B	Dose C
A		0.00523		
B			0.67948	
C				0.08356
A+B	0.78105	0.00231	0.23078	
B + C	0.56153		0.21043	0.02104
A + C	0.92342	0.00297		0.02970
A+B+C	0.73771	0.00161	0.16103	0.01610

Data for Fa = 0.9

Drug/Combo	CI value	Dose A	Dose B	Dose C
A		0.01261		
B			1.44211	
C				0.15109
A+B	0.69014	0.00464	0.46430	
B + C	0.56969		0.42034	0.04203
A + C	0.77247	0.00531		0.05310
A+B+C	0.47959	0.00223	0.22324	0.02232

In I-B, Examples for Other Options (Selected from Report Option)

F_a-CI plot without SDA:
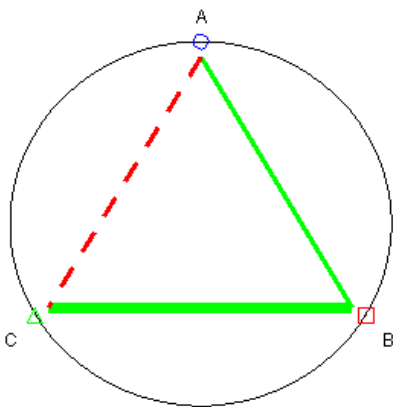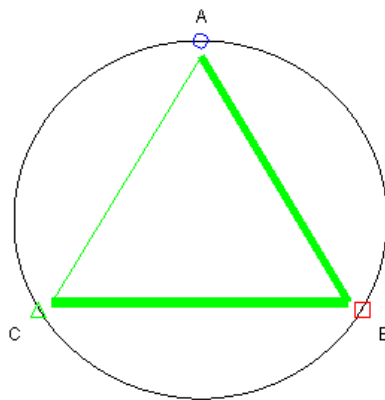(Generate Report, Check-off the graphs you don't need)

Combination Index Plot
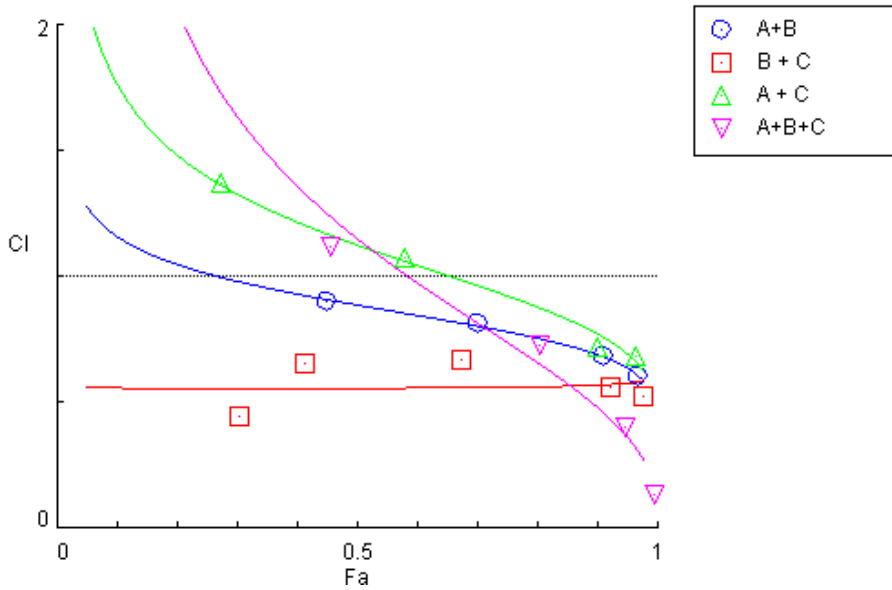
Polygonograms at Other F_a's:
(Generate Report, Check-off the graphs you don't need)

Polygonogram at Fa = 0.5

Polygonogram at Fa = 0.75

Polygonogram at Fa = 0.95