Dose Response Analysis for Combination Products

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Scope

- Two drugs in a fixed dose combination
- At least one of the drugs is effective alone
- One (continuous) clinical endpoint
- Assume there is no PK interaction
- Literature review

Example Combination Drug Product

Vytorin

Ezetimibe – inhibits cholesterol absorption

Simvastatin – inhibits cholesterol production

Indication: Hypercholestrolemia

Doses: 10/10, 10/20, 10/40, 10/80

Vytorin (eze/simva) *	10/10	10/20	10/40	10/80
Lowering of LDL(%)	-45	-52	-55	-60
Ezetimibe *	10 mg			
Lowering of LDL(%)	-39			
Simvastatin *	10 mg	20 mg	40 mg	80 mg
Lowering of LDL(%)	-33	-34	-41	-49

[* Vytorin label (PDR)]

Outline

- Central Questions
- Multiple comparison procedures (MCP)
  - Minimum efficacious dose combination (MED)
  - Therapeutic synergy and contribution
- Modeling methods
  - Polynomial response surface
  - Mechanistic modeling
  - Empirical synergy
- Conclusions

What do Regulators Want?

- 21 CFR 300.50 and ICH E4 (1994) require that ‘each component make a **contribution** to the claimed effects’
- at the fixed doses, the combination must be superior to each of its two components alone at the same dose.
- Eff(d1, d2) > Eff(d1, 0) and Eff(d1, d2) > Eff(0, d2)

Central Questions (part 1)

Multiple Comparisons

1. Is there evidence that each drug contributes at some dose combination? (comparators are each drug alone)
2. What dose combinations give better results than each drug alone (at the same dose)?
3. Is there a dose combination that is *therapeutically synergistic*?

   Therapeutic synergy: effect of combo is greater than max effect achievable by either component
   [Laska et al 1997 Stat in Med 16:2211-2228]

[Adapted from Ruhberg 1995 & Pinheiro et al 2005]

Central Questions (part 2)

Modeling

4. What response models give good predictions?
5. What is the optimal dose combination?
6. What do the results contribute to the understanding of the mechanism of action of the drugs alone or in combination?

[Adapted from Ruhberg 1995 & Pinheiro et al 2005]

MCP methods

- Provide assessment of contribution and therapeutic synergy
- Treat dose as categorical
- Less sensitive to assumptions
- Requires less prior knowledge
- Allow for strong control of FWER

Minimum Efficacious Dose (MED) combo

MED = “lowest” dose combination where both drugs contribute

K x N combo drug trial with
Drug A at doses i = 0, …, K
Drug B at doses j = 0, …, N
parallel groups of n subjects

mean response μ_{ij} (monotone)

	0	1	…	N
0		μ_{01}	μ_{0s}	
1	μ_{10}	μ_{11}		
	μ_{r0}		μ_{rs}	
K				μ_{KN}

expected gain $\theta_{ij} = \min(\mu_{ij} - \mu_{i0}\ ,\ \mu_{ij} - \mu_{0j}\ )$

dose (r,s) = MED if $\theta_{rs} > 0$ and

$\theta_{ij} = \theta_{rj} = \theta_{is} = 0$ for all i < r, j < s

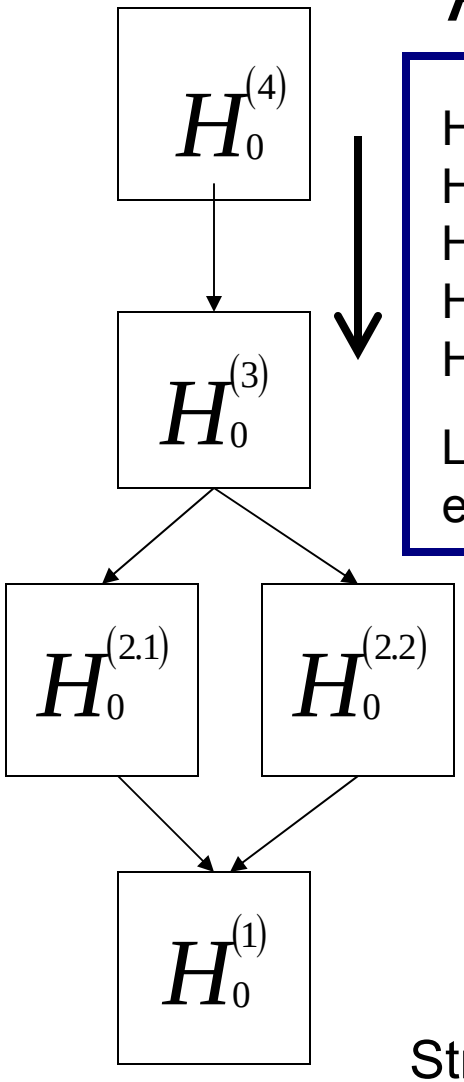
Then these are the lowest doses where both drugs contribute

$\mu_{rs} > \mu_{r0}$, $\mu_{rs} > \mu_{0s}$

	1	…	N
1	θ_{11}		θ_{1N}
K	θ_{K1}		θ_{KN}

[Soulakova and Sampson (2007) *Stat in Biopharm Res*]

AVE Test for MED Dose Combos



Decision Tree for 2x2

$H_0^{(4)}$: $\theta 11 = \theta 12 = \theta 21 = \theta 22 = 0$
$H_0^{(3)}$: $\theta 11 = \theta 12 = \theta 21 = 0$
$H_0^{(2.1)}$: $\theta 11 = \theta 12 = 0$
$H_0^{(2.2)}$: $\theta 11 = \theta 21 = 0$
$H_0^{(1)}$: $\theta 11 = 0$

Last rejected Ho gives estimated MED dose combo

	0	1	2
0		μ_{01}	μ_{02}
1	μ_{10}	μ_{11}	μ_{12}
2	μ_{20}	μ_{21}	μ_{22}

$$T_A = \sum\sum \hat{\theta}_{ij} / (C_I \hat{\sigma})$$

Average over the C_I values in the set of estimated θ for the hypothesis

$$\hat{\theta}_{ij} = \min((\bar{y}_{ij} - \bar{y}_{i0}), (\bar{y}_{ij} - \bar{y}_{0j}))$$

Strongly controls FWER (assuming monotonicity: $\theta_{ij} \geq 0$)

[Soulakova and Sampson (2007) *Stat in Biopharm Res*]

Example: AVE Test for MED Dose Combo

Mean reduction in DBP
Drug A

Drug B	0	1	2
0	0	4	5
1	5	7	9
2	5	8	10

Gain
Drug A

$$\hat{\theta}_{ij} = \min((\bar{y}_{ij} - \bar{y}_{i0}), (\bar{y}_{ij} - \bar{y}_{0j}))$$

Drug B	1	2
1	2	4
2	3	5

	1	2
1	θ_{11}	θ_{12}
2	θ_{21}	θ_{22}

$H_0^{(4)}$: $\theta 11 = \theta 12 = \theta 21 = \theta 22 = 0$
$H_0^{(3)}$: $\theta 11 = \theta 12 = \theta 21 = 0$
$H_0^{(2.1)}$: $\theta 11 = \theta 12 = 0$
$H_0^{(2.2)}$: $\theta 11 = \theta 21 = 0$
$H_0^{(1)}$: $\theta 11 = 0$

Ho	Ave($\hat{\theta}$)		Crit value (0.05-level)	
4	3.5	>	1.85	Reject
3	3	>	2.02	Reject
2.1	3	>	2.61	Reject
2.2	2.5	<	2.61	Accept
1	2		3.03	

Last rejected Ho gives estimated MED dose combo

[Adapted from Soulakova and Sampson (2007) *Stat in Biopharm Res*]

Pairwise Test for Contribution or for Therapeutic Synergy

Therapeutic Synergy: Effect of combo is greater than max effect achievable by either component (μ_{A0} , μ_{0B})

$H_0 = H_{01}: \mu_{rs} \leq \mu_{A0} \cup H_{02}: \mu_{rs} \leq \mu_{0B}$

$H_1: \mu_{rs} > \mu_{A0}$ and $\mu_{rs} > \mu_{0B}$

Test H_{01} and H_{02} at α-level to get an α-level of H_0
Under normality assumptions these can be two t-tests

A similar procedure provides test of contribution for a specific combination

[MIN test: Laska et al 1997 Stat in Med 16:2211-2228]

Example Test for Therapeutic Synergy

Treatment	Lowering LDL (%) (N=146-150)	Compare to combo
		p-value
Eze (10 mg)	-18.9	<0.001
Simva (80 mg)	-48.5	<0.001
Eze/Simva (10/80)	-60.2	

> Assume 10 mg Eze and 80 mg Simva as providing maximal effect when given alone
> the combo is better than each of these alone
> conclude **Therapeutic Synergy at p < 0.001**

[Adapted from Bays et al 2004 Clin Ther 20:1758-1773]

Summary of MCP

- Useful even if few dose combinations are studied
- Provide assessments of contribution and of therapeutic synergy
- Closed series of tests can control FWER

Modeling

- Dose as continuous
- Assume parametric form for relationships
- Requires better understanding/description of dose-response relationship
- May be more useful for simulations and for planning future studies
- May provide a way to investigate the mechanism of action

Types of modeling efforts

- Polynomial response surface modeling
- Mechanistic modeling
- Empirical synergy

Response Surface Methods (RSM)

- Polynomial is fit to the 3 dimensional surface (“French curve”)
- May provide a description of surface when number of doses is too few for fitting more mechanistic models
- No convergence issues
- No clear interpretation of parameter values
- Dangerous for extrapolation

Polynomial Response Surface

$$E_k = \beta_0 + \beta_1 \text{dose}_{1k} + \beta_2 \text{dose}_{2k} + \beta_3 \text{dose}_{1k}\,\text{dose}_{2k} + \beta_4 \text{dose}_{1k}^2 + \beta_5 \text{dose}_{2k}^2 + \varepsilon_k$$

, for k-th subject

Fitting by OLS or linear mixed effects

May be useful to scale doses to -1 to +1

- avoids numerical problems
- allows each drug to be evaluated in an equivalent manner .

$$X_{ik} = (\text{dose}_{ik} - \text{mean}(\text{dose}_{ik}))/(\max(\text{dose}_{ik}) - \text{mean}(\text{dose}_{ik}))$$

drugs i=1,2

Example Combo Drug Study

Two drugs dosed in factorial combinations
e.g. 16 parallel groups of subjects,
2 drugs: atorvastatin (AD), gemcabene (GD)
15 subjects per group

AD	GD	AD	GD	AD	GD	AD	GD
0	0	0	300	0	600	0	900
10	0	10	300	10	600	10	900
40	0	40	300	40	600	40	900
80	0	80	300	80	600	80	900

[Herman et al 2005, PAGE Meeting, Pamploma, Spain]

Polynomial Response Surface Fit

Parameter	Estimate	SE	p-value
Intercept	-3.03	6.78	0.656
Atorva (AD)	-1.18	0.124	**<0.0001**
Gemca (GD)	-0.0295	0.00984	**0.003**
AD*AD	0.00935	0.00140	**<0.0001**
AD*GD	0.000203	8.80E-05	**0.0222**
GD*GD	1.18E-05	1.02E-05	**0.245**
Baseline LDL	-0.0791	0.0353	**0.0259**

Response variable is percent change in LDL

Parameters significant except quadratic term on GD (this term could be dropped)

Predicted Maximum Effective Combo

Stationary point: AD = 54.8 mg, GD = 776 mg;
Predicted value: -60.8 (% change in LDL)

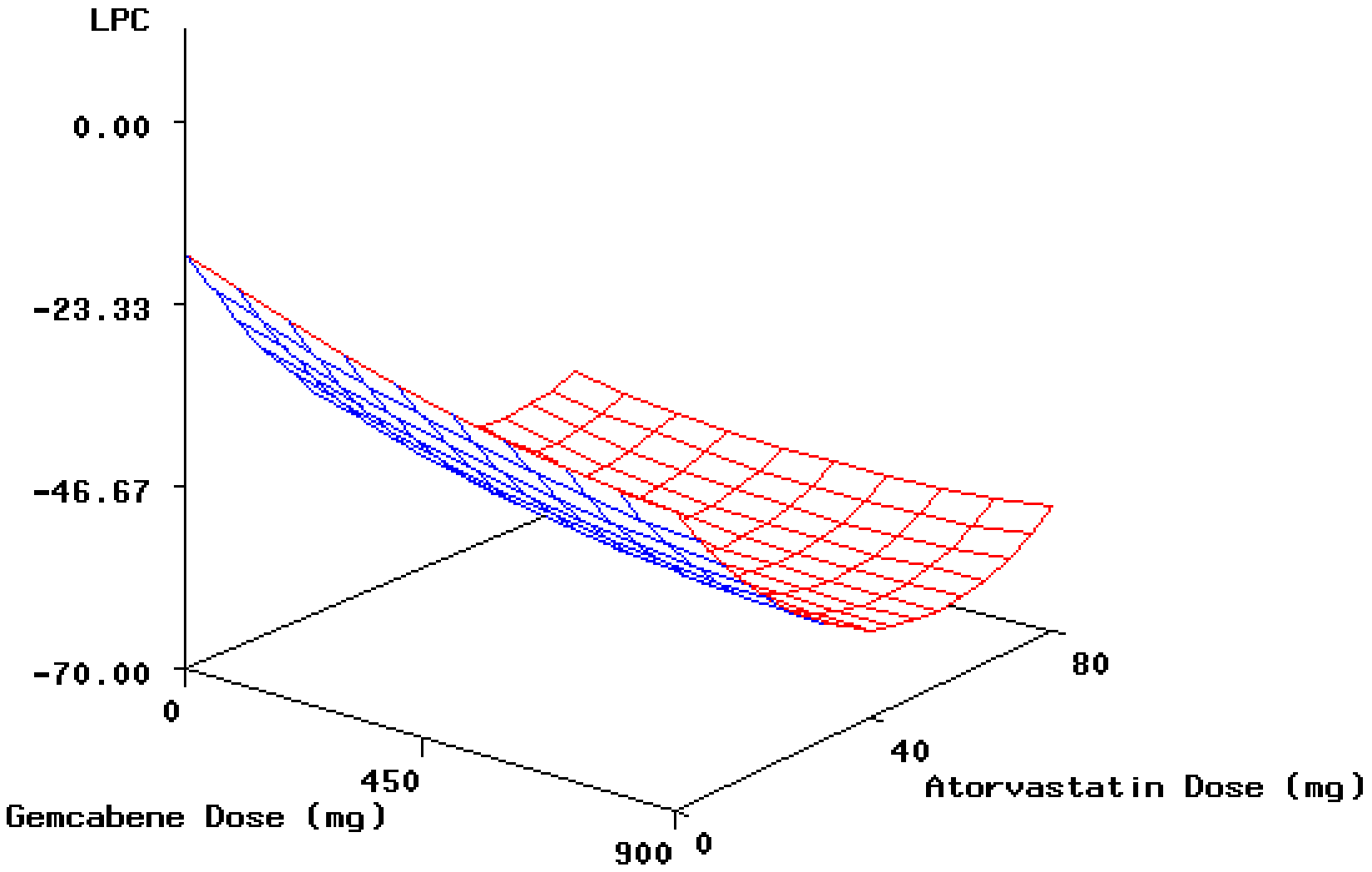
For confidence region on dose levels for maximum combo see:
Peterson et al 2002 Biometrics 58:422-431

By comparison

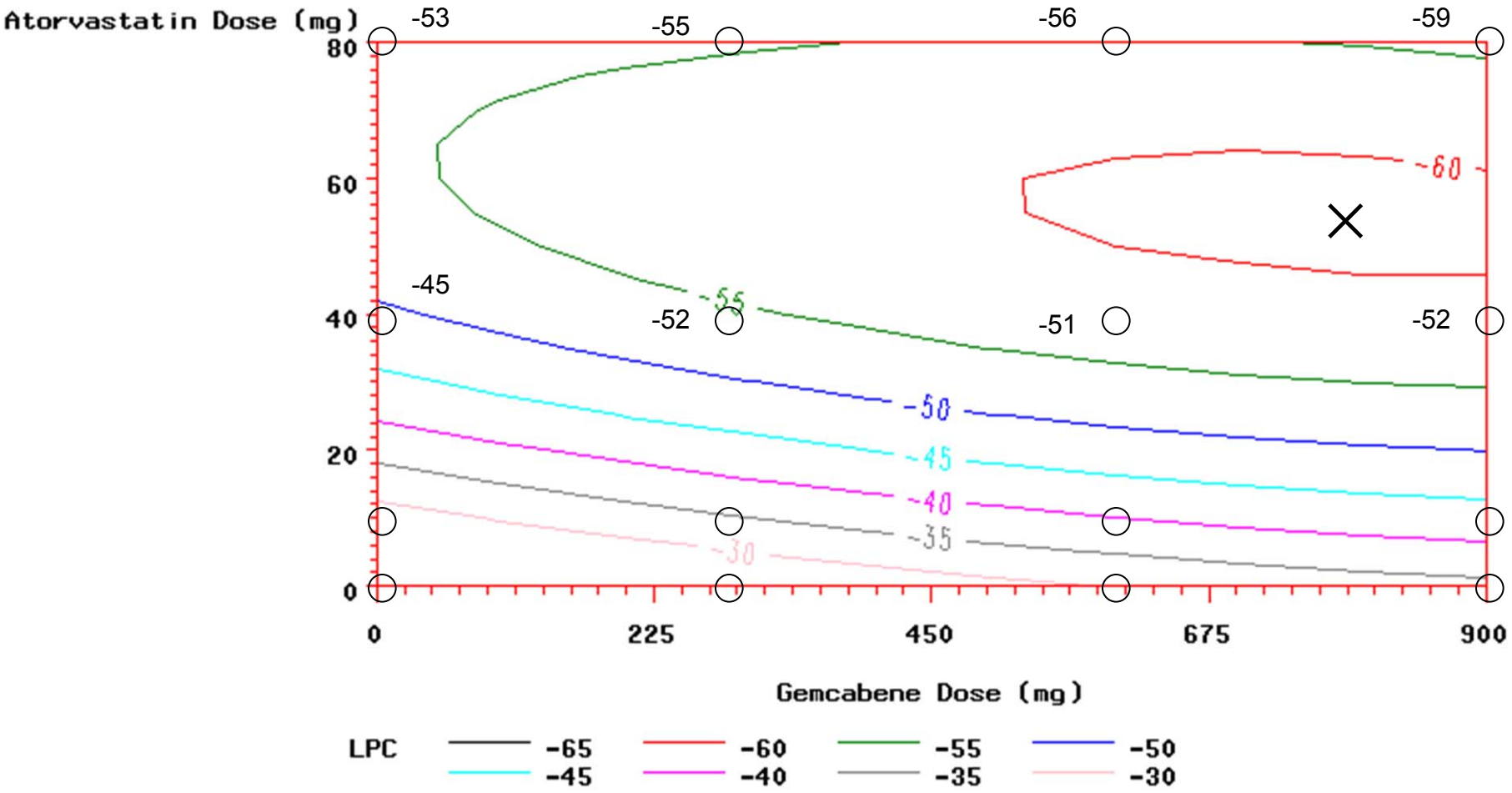
Vytorin (eze/simva) *	10/10	10/20	10/40	**10/80**
Lowering of LDL(%)	-45	-52	-55	**-60**
Atorvastatin *	10 mg	20 mg	40 mg	**80 mg**
Lowering of LDL(%)	-39	-43	-50	**-60**
Gemcabene	300 mg	600 mg	900 mg	
Lowering of LDL(%)	-18	-25	-31	

[* Product labels (PDR)]

3-D Surface Plot



Contour Plot



Summary of Polynomial RSM

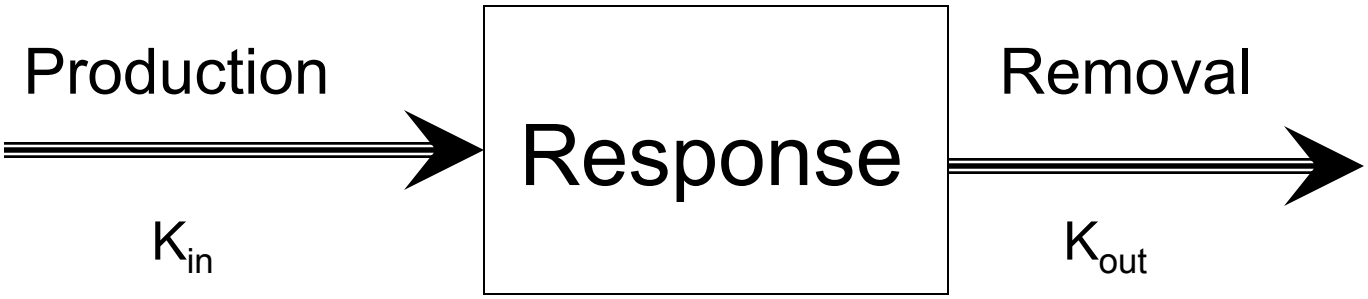
- Provide a description of 3-D effect surface
- Allow for interpolation and prediction of optimal dose combination
- Parameter values have little meaning
- Need to check for lack of fit and consider relevance to physiology

Mechanistic Modeling

- Drug1 + Drug2 + System = Combined Response
- Quite elaborate system models have been devised to describe and predict biology and the actions of drug.
- For illustrative purposes we will discuss only a few very simple models.

Indirect Response Models

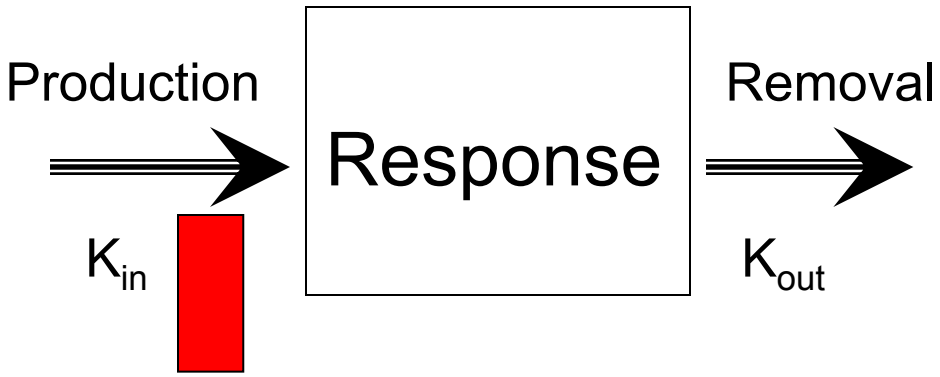
Homeostatic System

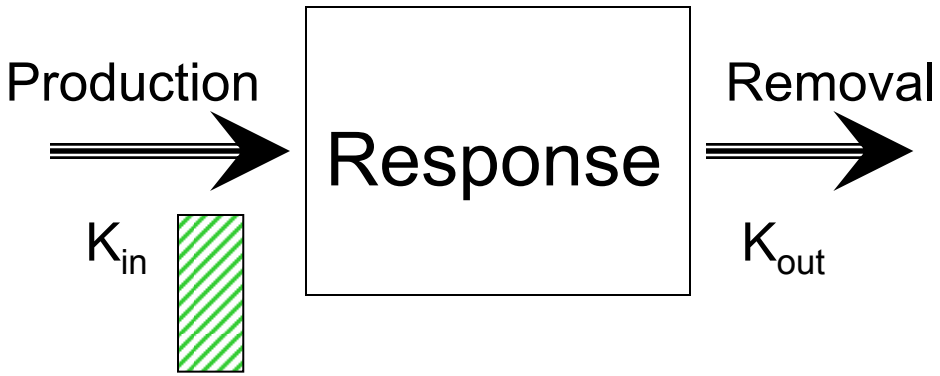


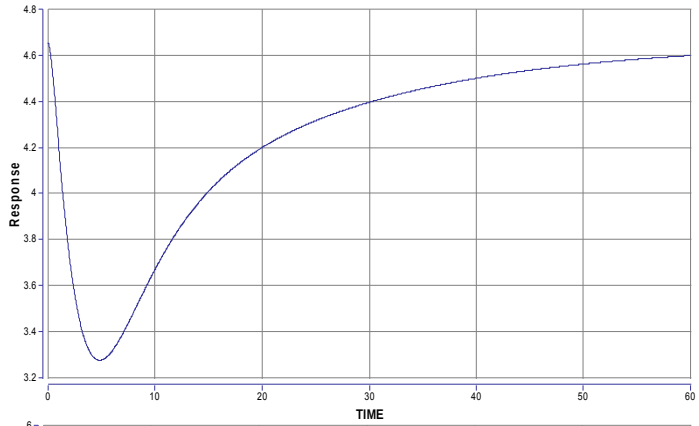
System is in equilibrium until addition of drug perturbs the system.

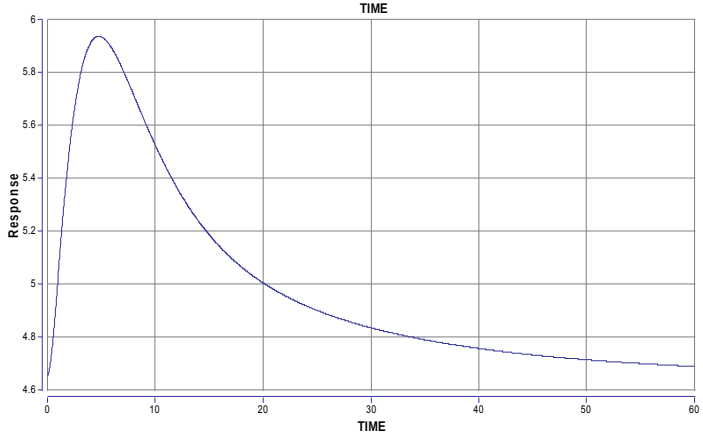
Indirect Response Models

System and Action of Drug 1



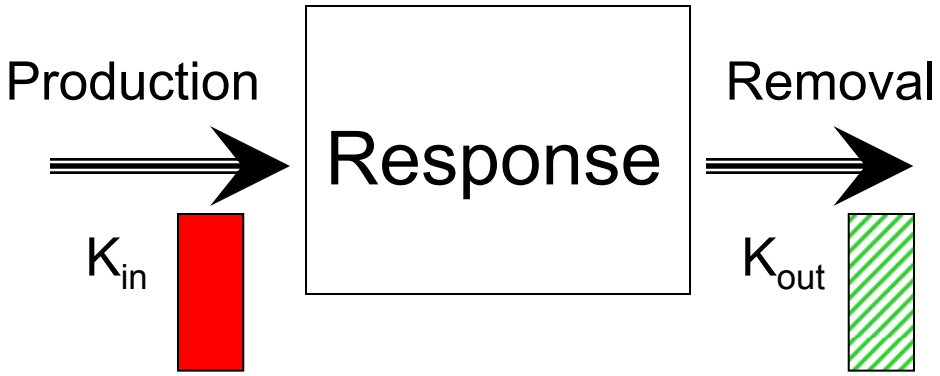


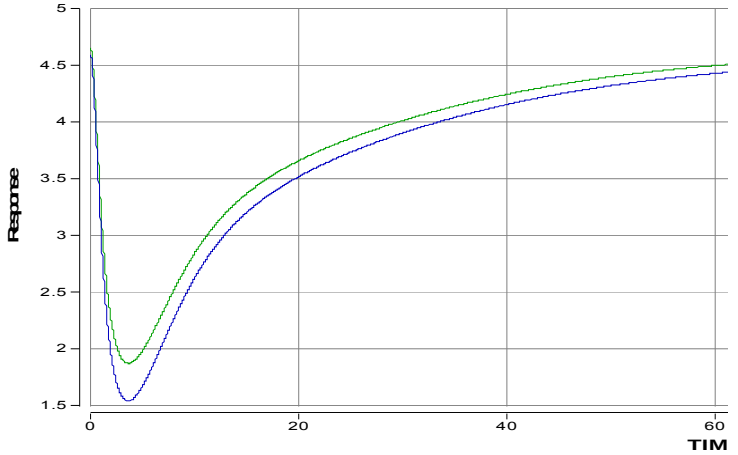


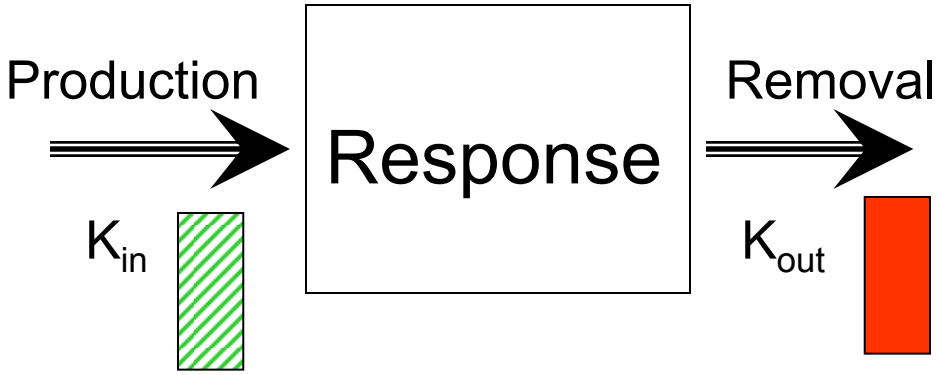


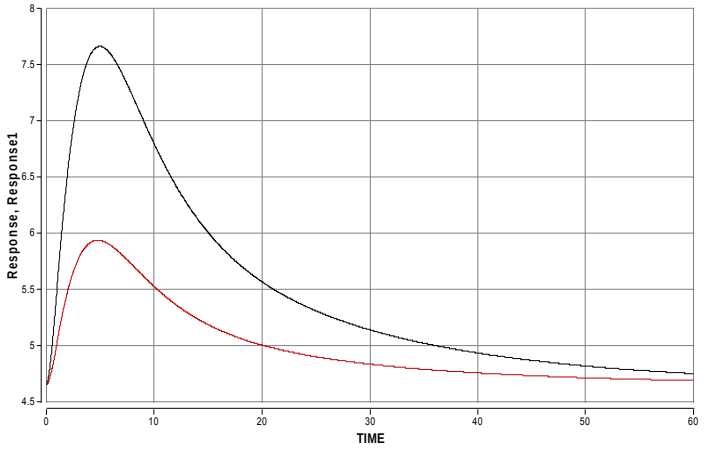
[Dayneka et al 1993 JPB 21:611-635]

Joint action involving different processes



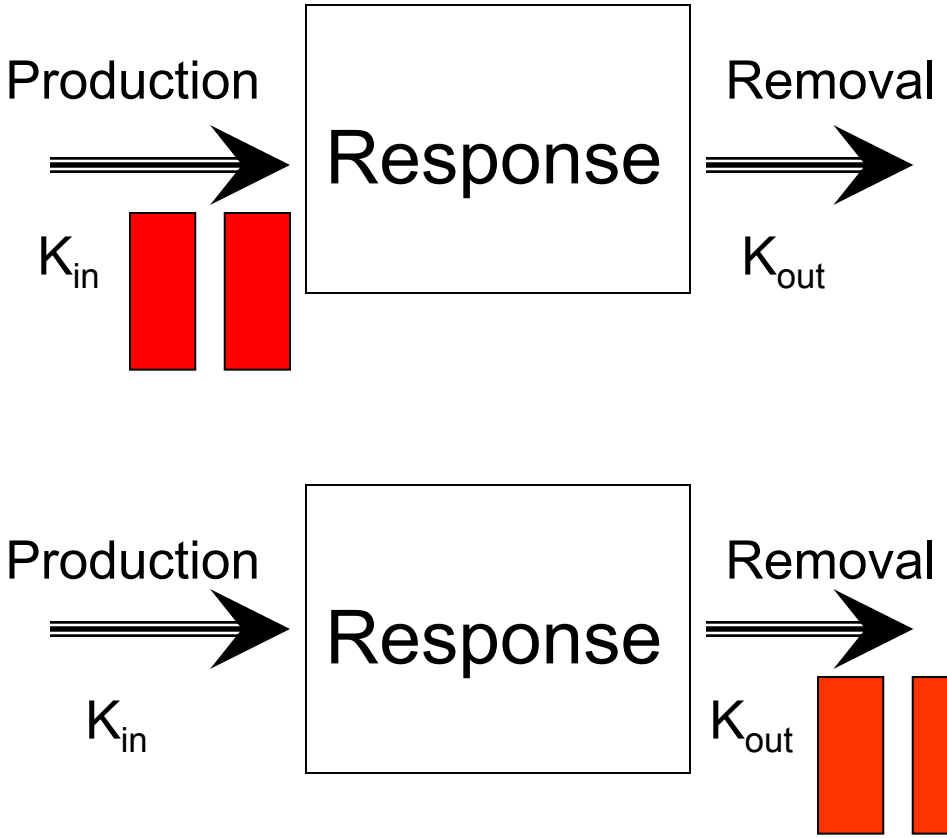


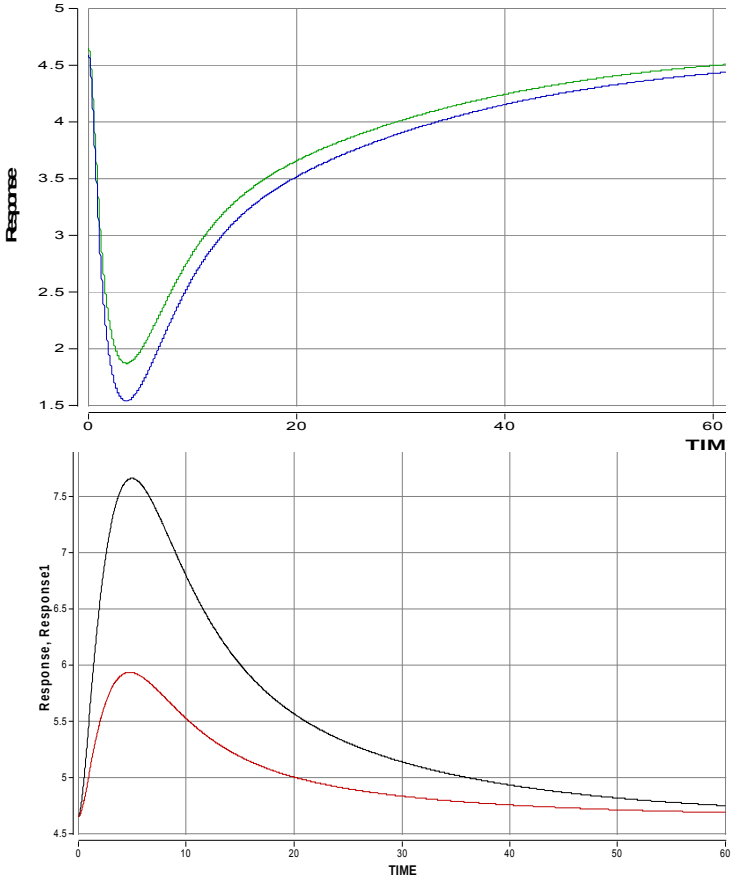




[Earp et al 2004 JPP 31:345-380]

Joint action involving the same process (non-competitive)





[Earp et al 2004 JPP 31:345-380]

Steady-state Dose-Response

Css = Dose*F/(CL*τ) = (Dose/τ)/(CL/F)

$$\frac{dR}{dt} = k_{in}\{1+H_1(C_1)\} - K_{out}\{1+H_2(C_2)\}R$$

where $H_n(C_i) = -\ Imax_i\ C_i\ /\ (IC50_i + C_i)$

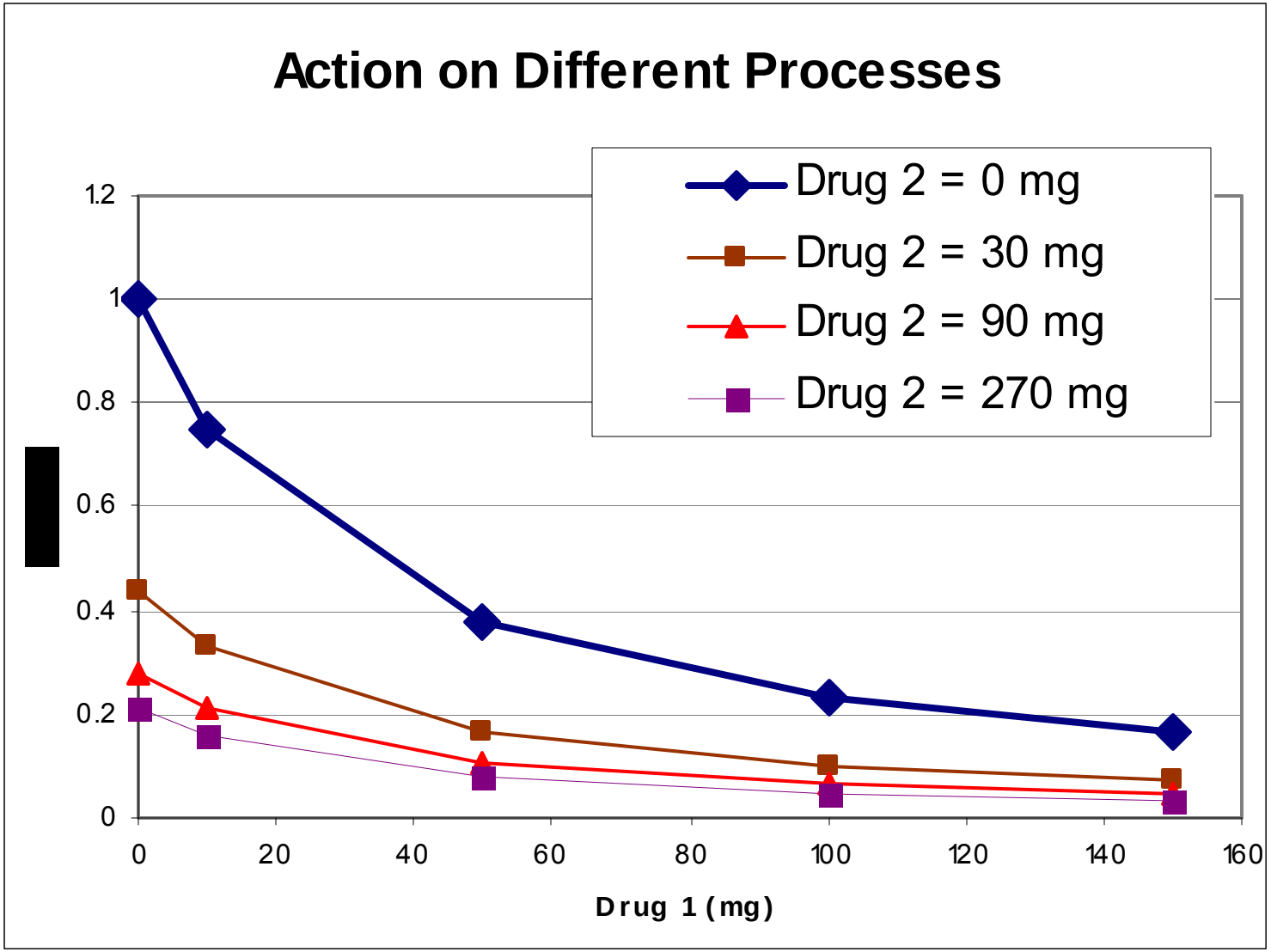
or $= Smax_i\ C_i\ /\ (SC50_i + C_i)$

then $$\frac{R_{ss,\max}}{R_o} = \frac{1+H_1(C_1)}{1+H_2(C_2)}$$ for different processes

or $$\frac{R_{ss,\max}}{R_o} = \{1+H_1(C_1)\}\{1+H_2(C_2)\}$$ if both on K_{in}

and $$\frac{R_{ss,\max}}{R_o} = \frac{1}{\{1+H_1(C_1)\}\{1+H_2(C_2)\}}$$ both on K_{out}

[Earp ibid]



Simulated data shows that amount of interaction varies with dose levels

Summary of Mechanistic Modeling

- Parameter values have biological meaning
- Best done with time course data and data from several dose levels
- Can lead to a better understanding of the mechanism of action

Empirical Assessment of Synergy

"The Search for Synergy"

something more than expected

Starts with choice of "what is expected"

- Loewe Additivity
- Bliss Independence

[Greco et al 1995]

Loewe Additivity

Implies that each drug contributes to joint action independently in accord with its individual potency.

$d_1 + d_2\,\rho$ = dose of drug 1 equiv to (d_1, d_2) , where ρ = rel. potency

D_1 and D_2 are equi-effective doses of two individual drugs

(d_1, d_2) dose pairs that in combination give the same effect as dose D_1 alone or dose D_2 alone

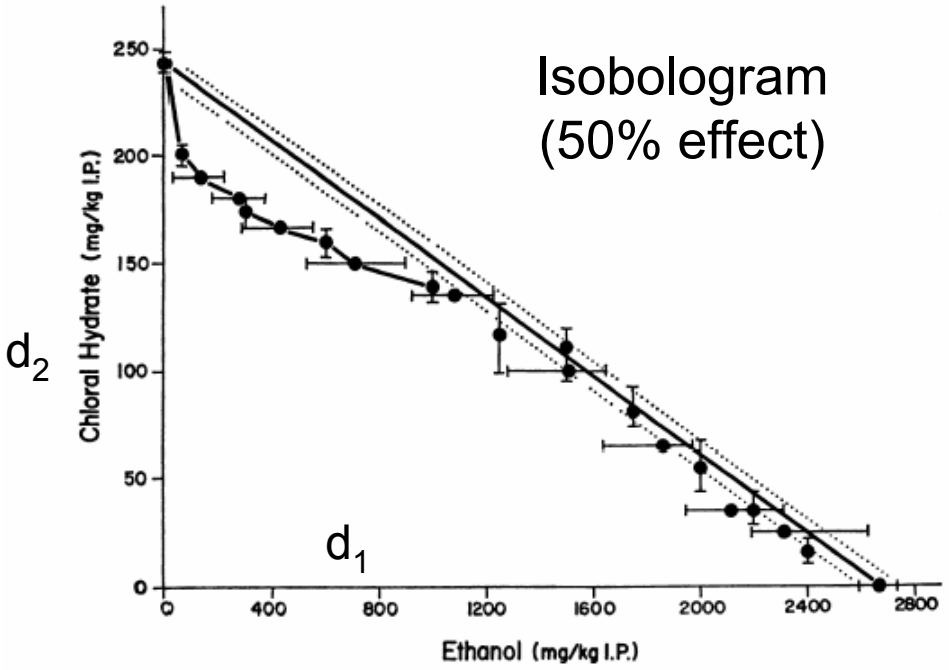
$$\frac{d_1}{D_1} + \frac{d_2}{D_2} = I$$

I = 1, implies additivity

I < 1, synergism

I > 1, antagonism

Can roll in dose response functions for each drug alone and estimate them in pooled dataset simultaneously with I (using a root finder). URSA method: Greco et al 1990



[Gessner and Cabana. 1970. J Pharm Exp Ther. 174: 247-259]

Bliss Independence (one of many forms)

Combined response *C* for two single compounds (Drugs 1 and 2) with effects *A* and *B* is

$$C = A + B + \alpha A*B*0.01$$

α = 1 for independence
α < 1 for synergy
α > 1 for antagonism

where each effect is expressed as a percentage decrease (-100,0)

Example:

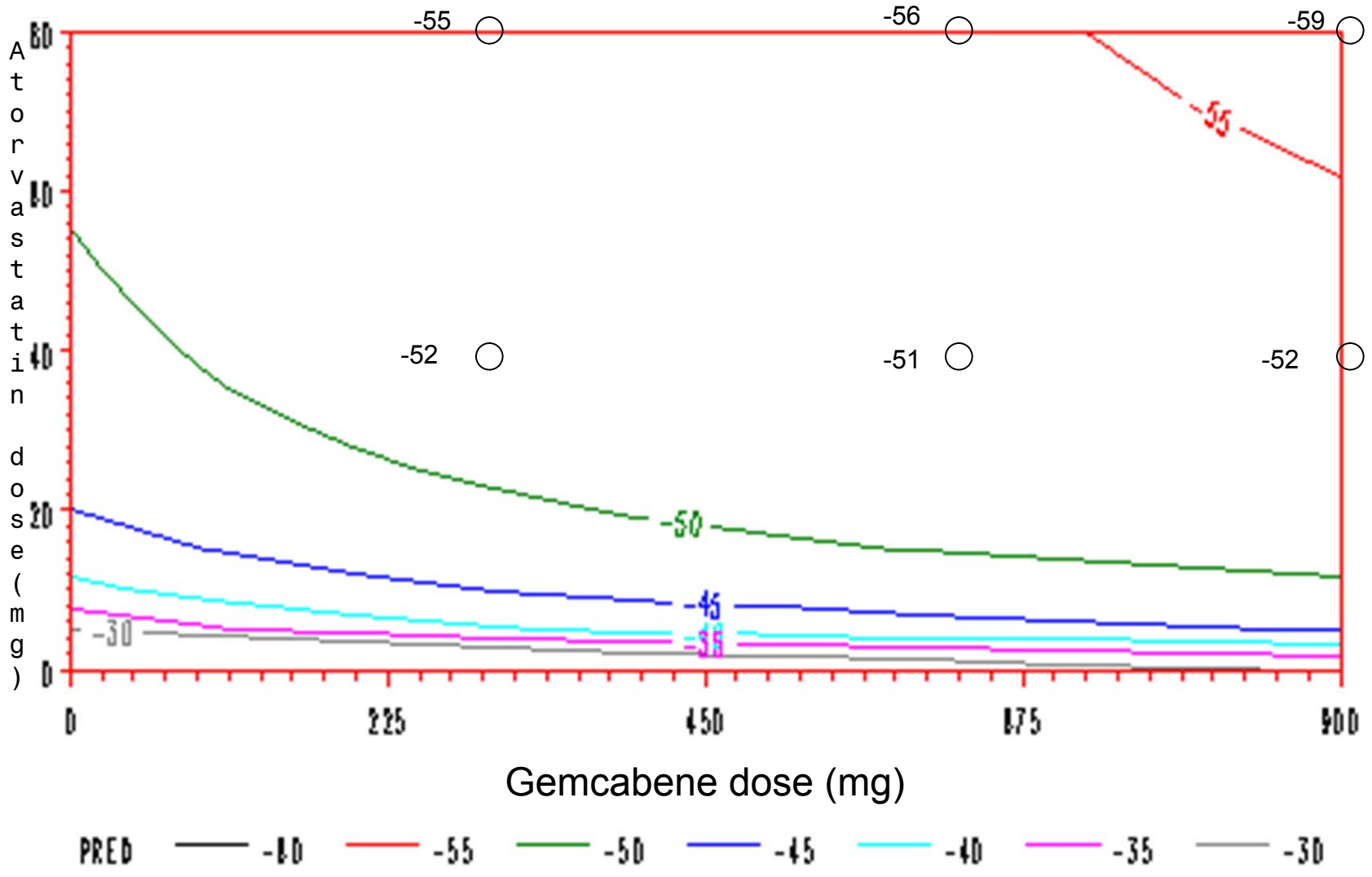
Drug 1 causes a 50% decr in LDL
Drug 2 causes a 30% decr in LDL

If acting independently
100mg/dL => 50mg/dL => 35mg/dL
(a 65% decr)
(-50) + (-30) + (1)(1500)(0.01) = -65

Can roll in dose response functions for each drug alone, e.g. Effect = Emax*Dose/(ED50 + Dose)

[Peterson and Novick 2007]

Atorvastatin-Gemcabene Bliss Independence Model



Assumptions of Empirical Synergy Methods

Both Loewe additivity and Bliss independence:

- interaction relationship is the same quality and magnitude at all dose levels of both components

Loewe additivity:

- the individual dose-response curves have "parallelism", e.g. Emax1 = Emax2 and shapes of effect curves are similar

Extensions overcome the these issues by
increasing number of parameters
White et al (2003): adds up to ~30 parameters
Kong and Lee (2006): adds up to 9 parameters

Empirical Synergy versus Therapeutic Synergy

	Bliss independence factor (α) *	Loewe additivity factor (I)	Empirical Synergy (Bliss/Loewe)	Therapeutic Synergy
Atorva-Gemca	1.69 (1.49, 1.88) antagonism	0.696 (0.448, 0.944) synergy	antagonism / synergy	No
Simva-Eze	1 independence	Not available	independence / not assessed	Yes

[* Mandema et al 2005]

versus Contribution

Atorva-Gemca	Dose	10/600	40/900	80/900	N = ~15
	p-value	0.02	0.05	0.19	
Simva-Eze **	Dose	10/10	40/10	80/10	N= ~150
	p-value	<0.001	<0.001	<0.001	

[**Adapted from Bays et al 2004]

Summary of Empirical Synergy Methods

- Provides a way to combine the dose response curves of each drug alone and predict the response surface of the combination
- Gives one number to represent synergy level
- Applicable where relationships between dose and effect appear simple and direct
- Extensions are available to broaden the assumptions
- Lack of empirical synergy does not imply that the two drugs do not contribute
- Empirical synergy is unrelated to therapeutic synergy.

Conclusions

- Assessment of dose response for combo is best done with good prior understanding of component drugs
- MCPs exist for analysis of studies with few dose combinations
- RSM and mechanistic modeling methods allow for more complete description and understanding of dose response
- Empirical synergy may not predict therapeutic synergy or contribution