A Unified Approach to Flexible and Powerful Modeling Of Pre-Clinical Combination Studies

Chris Harbron

Discovery Statistics

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life inspiring ideas

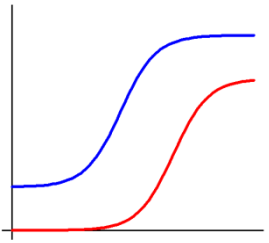
Why Drug Combinations?

- Making better use of our assets
- In many disease areas, e.g oncology, cardiovascular, HIV, polypharmacy is the norm
- Numerous examples of approvals for drug combinations
- Increasingly focussed and selective compounds
- Increased molecular & pathway level understanding
  - Hypothesise and understanding synergistic actions
  - Link with systems biology
- Recent FDA call for comments on combination drug treatments

Chris Harbron, A Unified Approach to Flexible and Powerful Modeling Of Pre-Clinical Combination Studies, NCSC 2010

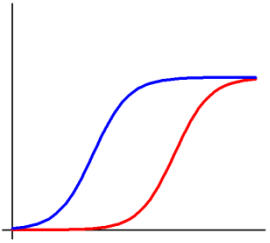
Classification Of Combinations

- **Efficacy Enhancing**



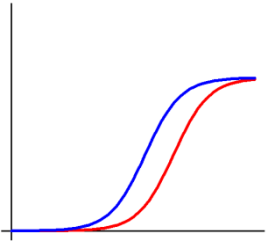
  - Increased efficacy in combination beyond what can be achieved by single agent
  - Synergy : greater response than expected under additivity
  - Indicative of a positive mechanistic interaction
  - Potential for Patentable Intellectual Property

- **Dose Sparing**



  - Efficacy in combination achieved at lower doses than by a single agent
  - Synergy : greater response than expected under additivity
  - Indicative of a positive mechanistic interaction
  - Potential for Patentable Intellectual Property

- **Beneficial**



  - Efficacy in combination achieved at lower doses than by a single agent
  - FDA guidelines on combinations refer to as contributing
  - May be compatible with compounds sharing pathways and mechanism of action

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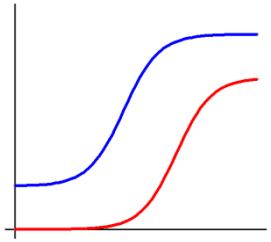
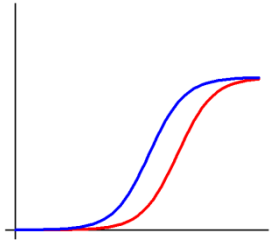
Analysis Of Combinations

Efficacy Enhancing



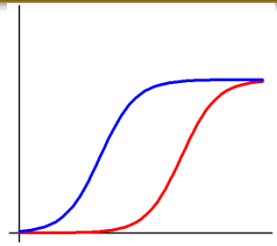
Beneficial



Relatively simple comparisons

ANOVA t-test or separate parameters in curve fit

Dose Sparing



Synergy : greater response than expected under additivity

Harder

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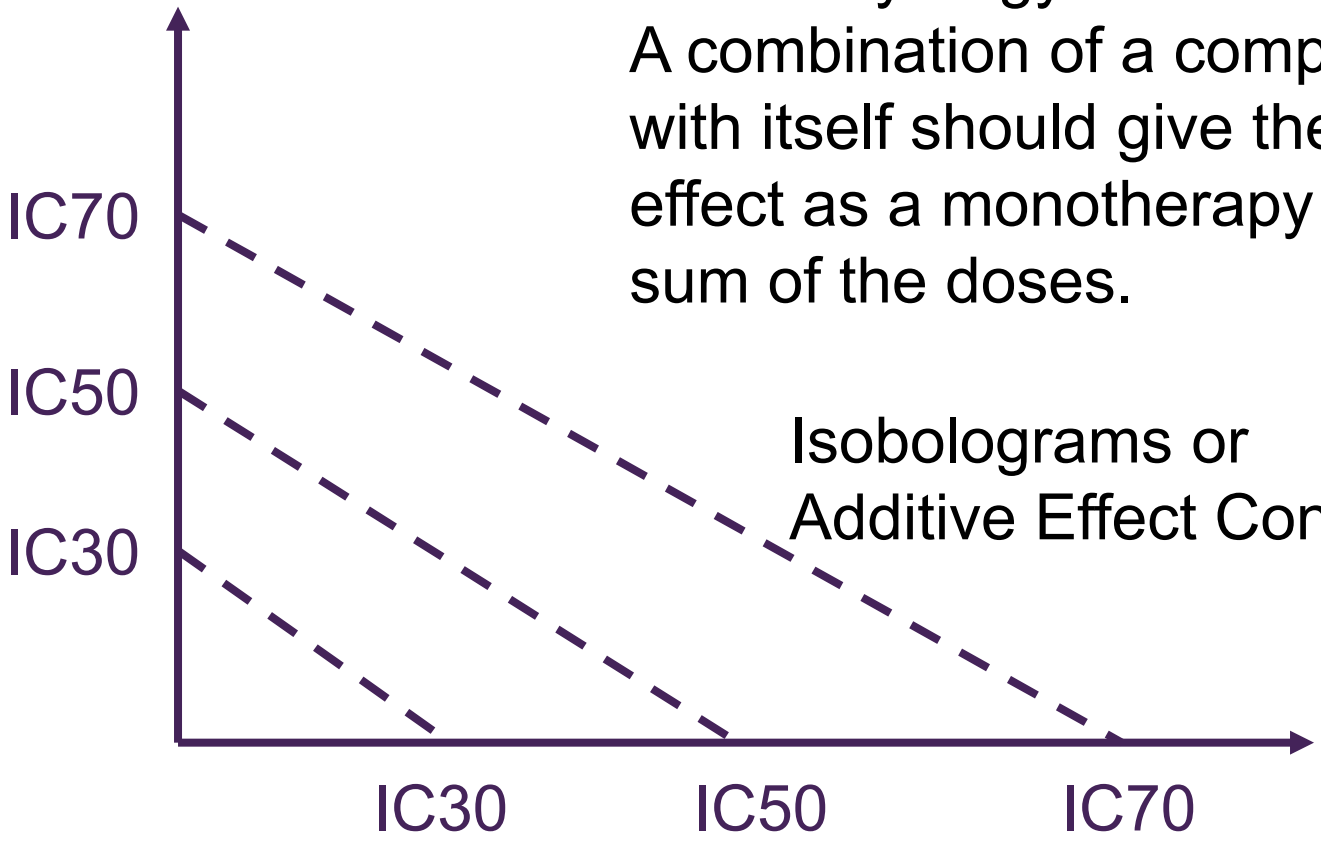
Assessing Synergy
Loewe Additivity

Based around “sham synergy” or “self synergy”
A combination of a compound with itself should give the same effect as a monotherapy at the sum of the doses.



Isobolograms or
Additive Effect Contours

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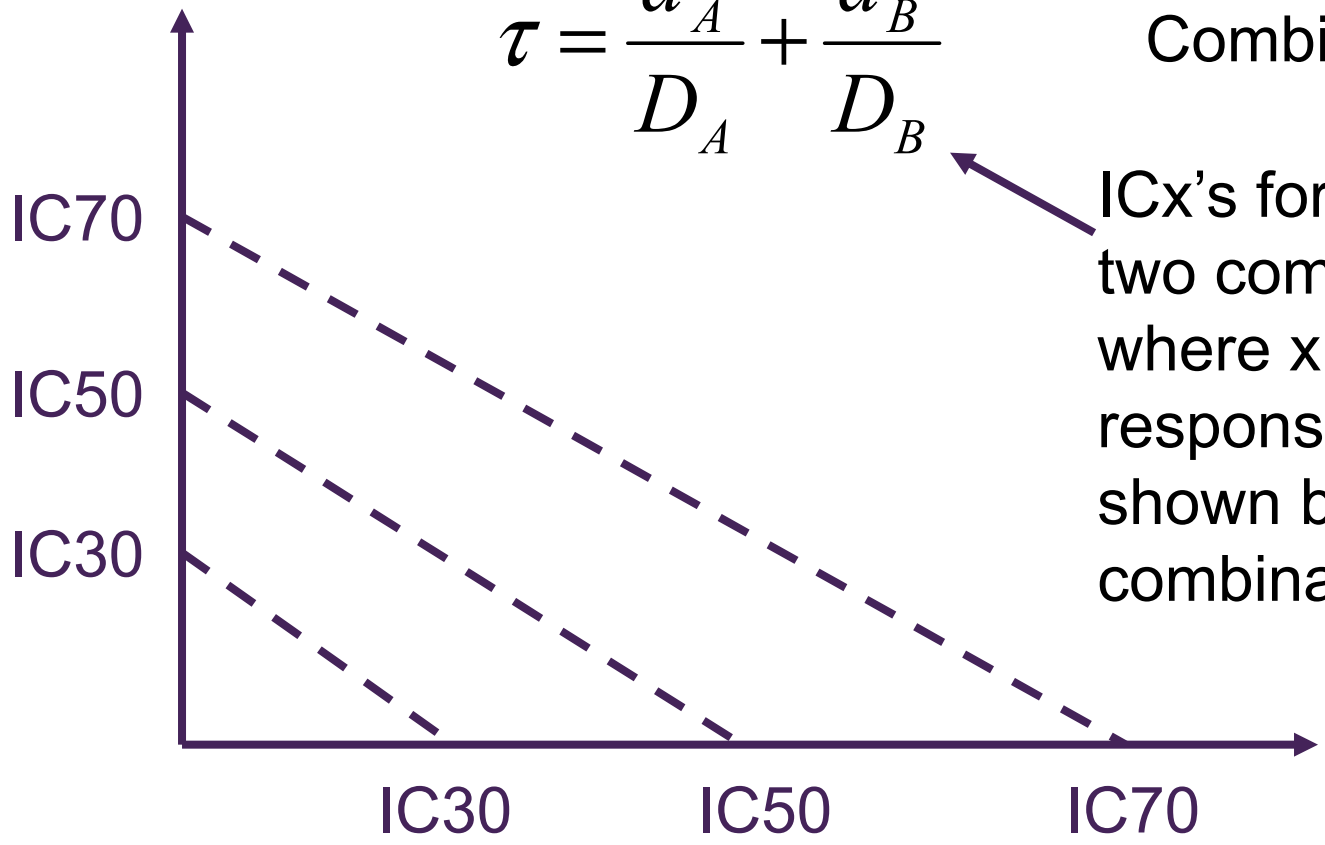
Interaction Index – Berenbaum
Combination Index – Chou & Talalay

$$\tau = \frac{d_A}{D_A} + \frac{d_B}{D_B}$$

Doses in Combination

ICx's for the two compounds where x is the response shown by the combination



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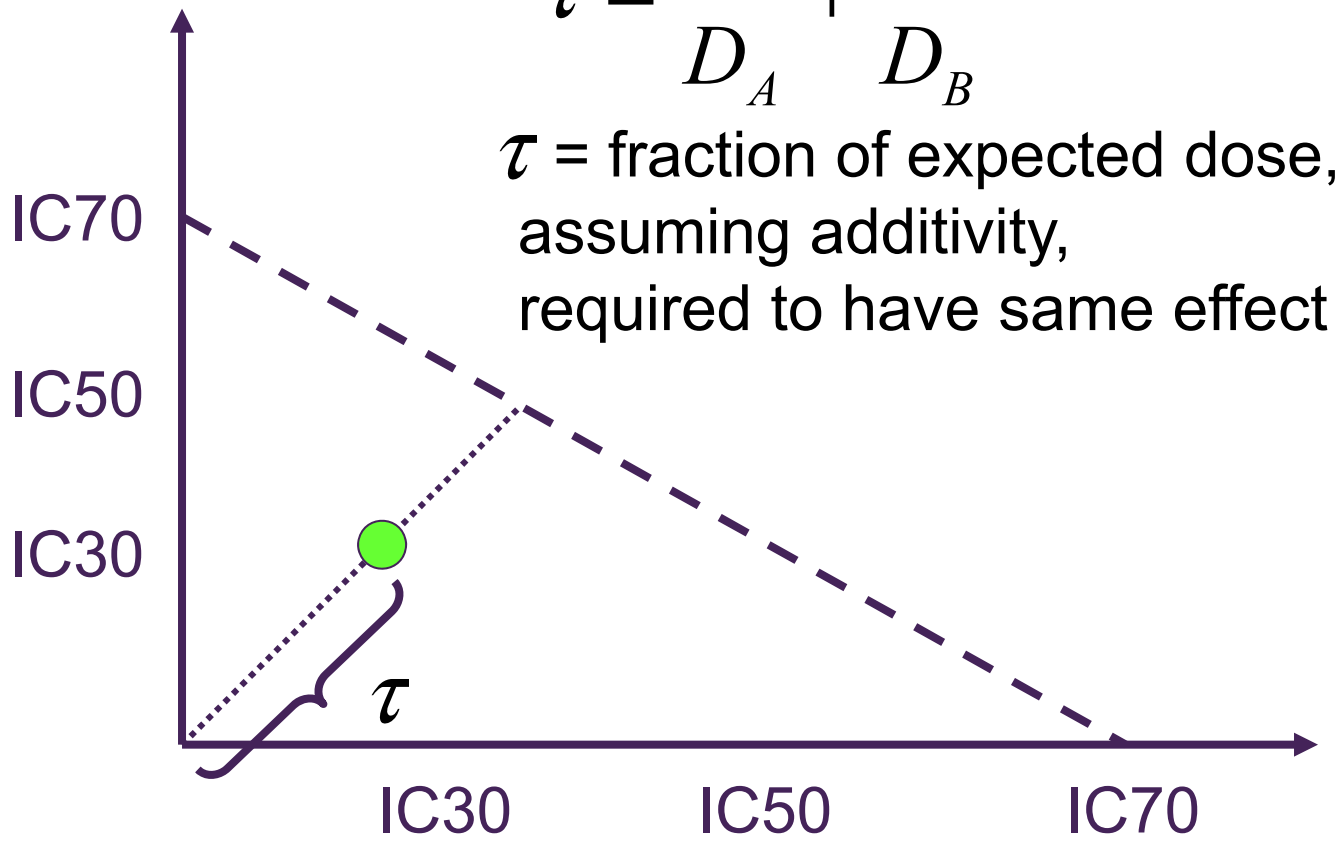
Interaction Index – Berenbaum
Combination Index – Chou & Talalay

$$\tau = \frac{d_A}{D_A} + \frac{d_B}{D_B}$$

τ = fraction of expected dose, assuming additivity, required to have same effect



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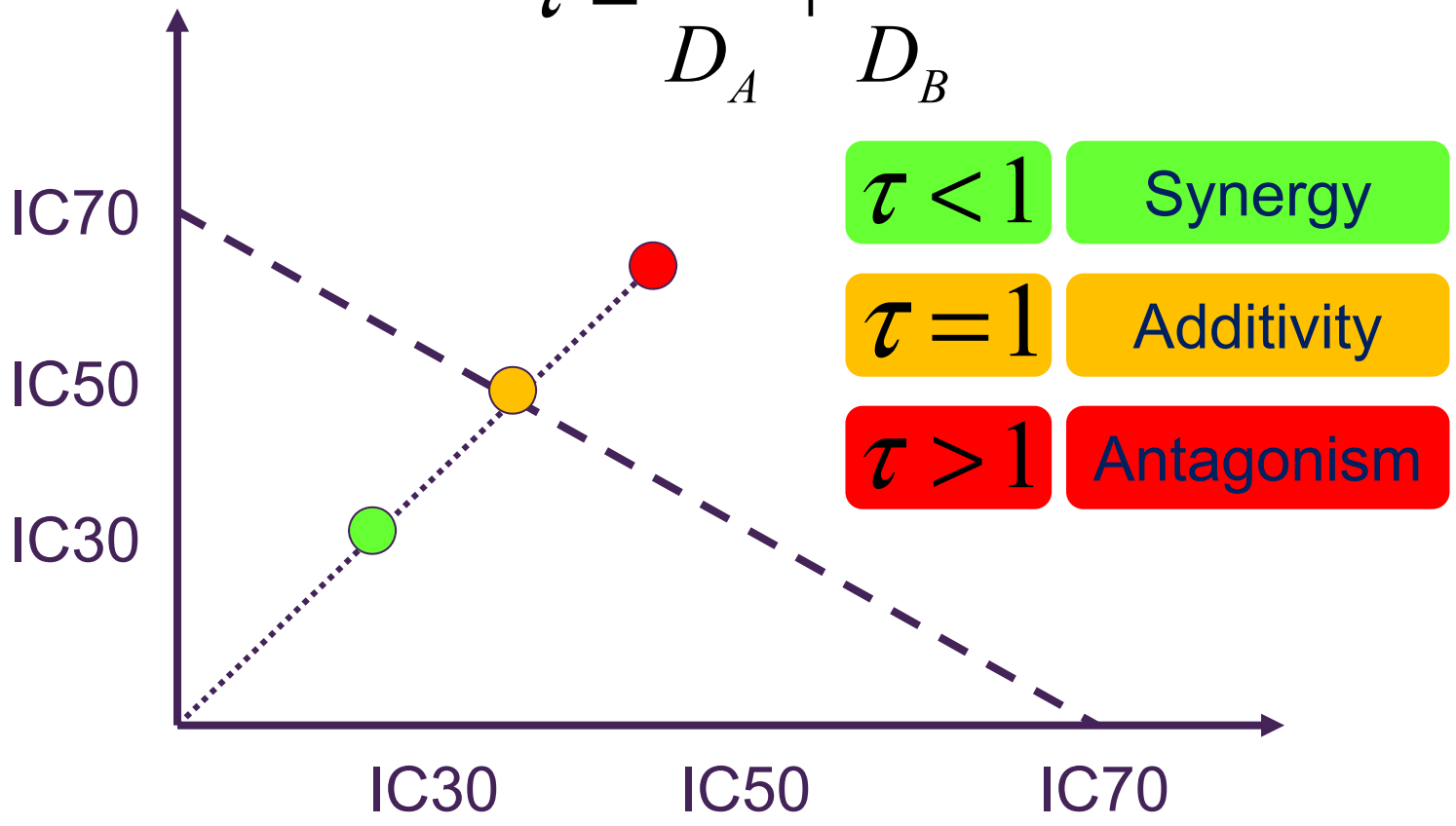

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Interaction Indices

- Wish to calculate these:
  - With standard errors / confidence intervals
  - Statements of confidence and significance tests
- Flexibly and powerfully
  - Utilise all data in a wide variety of designs
  - Combining combination doses together
  - Overall assessments of synergy
- Covering a wide variety of situations
  - Partial responses
  - Inactive compounds as monotherapies
  - Multiple subjects or plates

Unified Tau

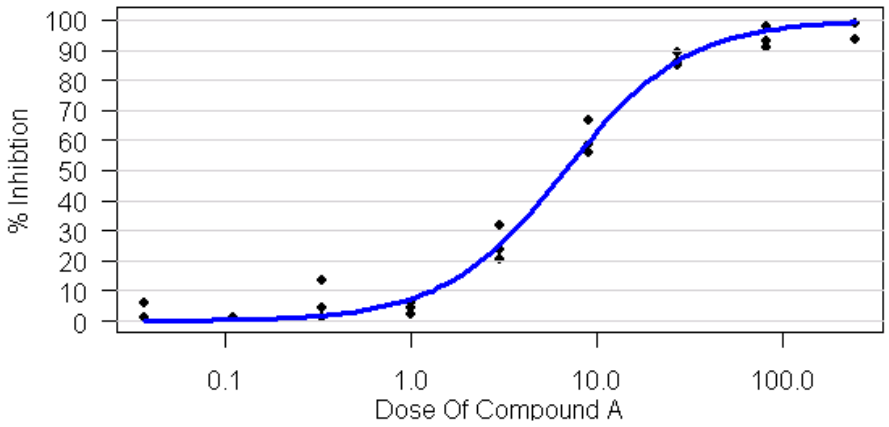
$$1 = \begin{cases} \dfrac{d_A}{D_A} + \dfrac{d_B}{D_B} & d_A \text{ or } d_B = 0 \quad \text{Monotherapies} \\ \dfrac{d_A / \tau_{(i)}}{D_A} + \dfrac{d_B / \tau_{(i)}}{D_B} & d_A \text{ and } d_B > 0 \quad \text{Combinations} \end{cases}$$

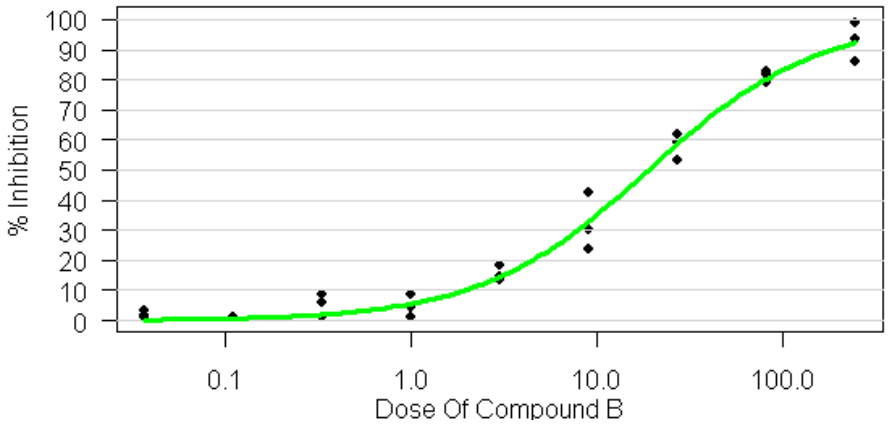
- Where $\tau_{(i)}$ is either:
  - a constant – response surface
    - (with discontinuities at the axes)
  - a separate value for each point
    - Berenbaum's interaction index
  - a separate value for each ray (segment)
  - a separate value for each dose level of a compound
  - a continuous function of dose or ray

An In-Vitro Example

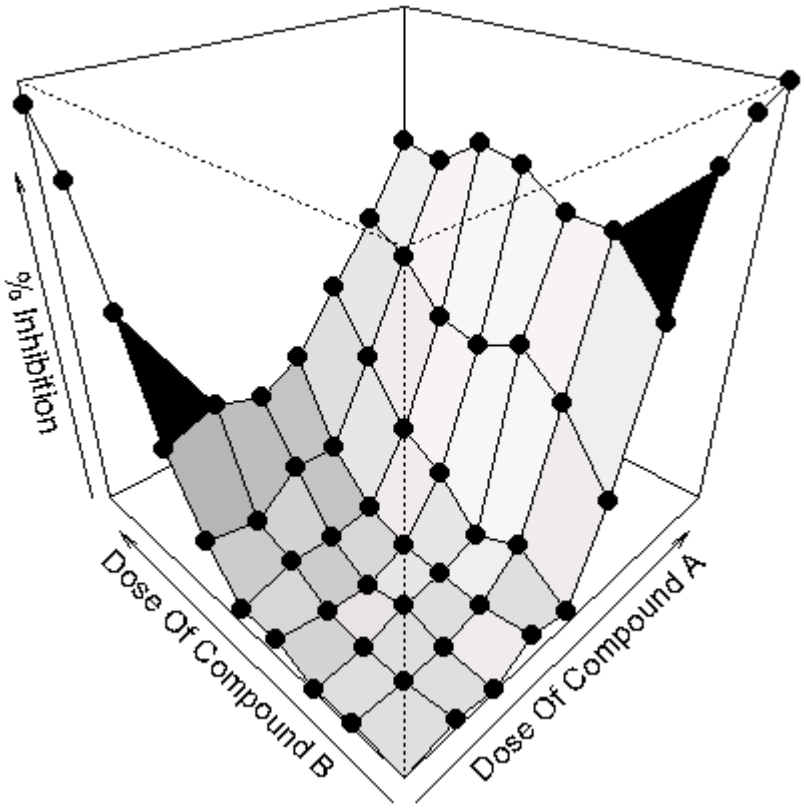
Inhibition of growth in cell lines

Monotherapies





Combinations



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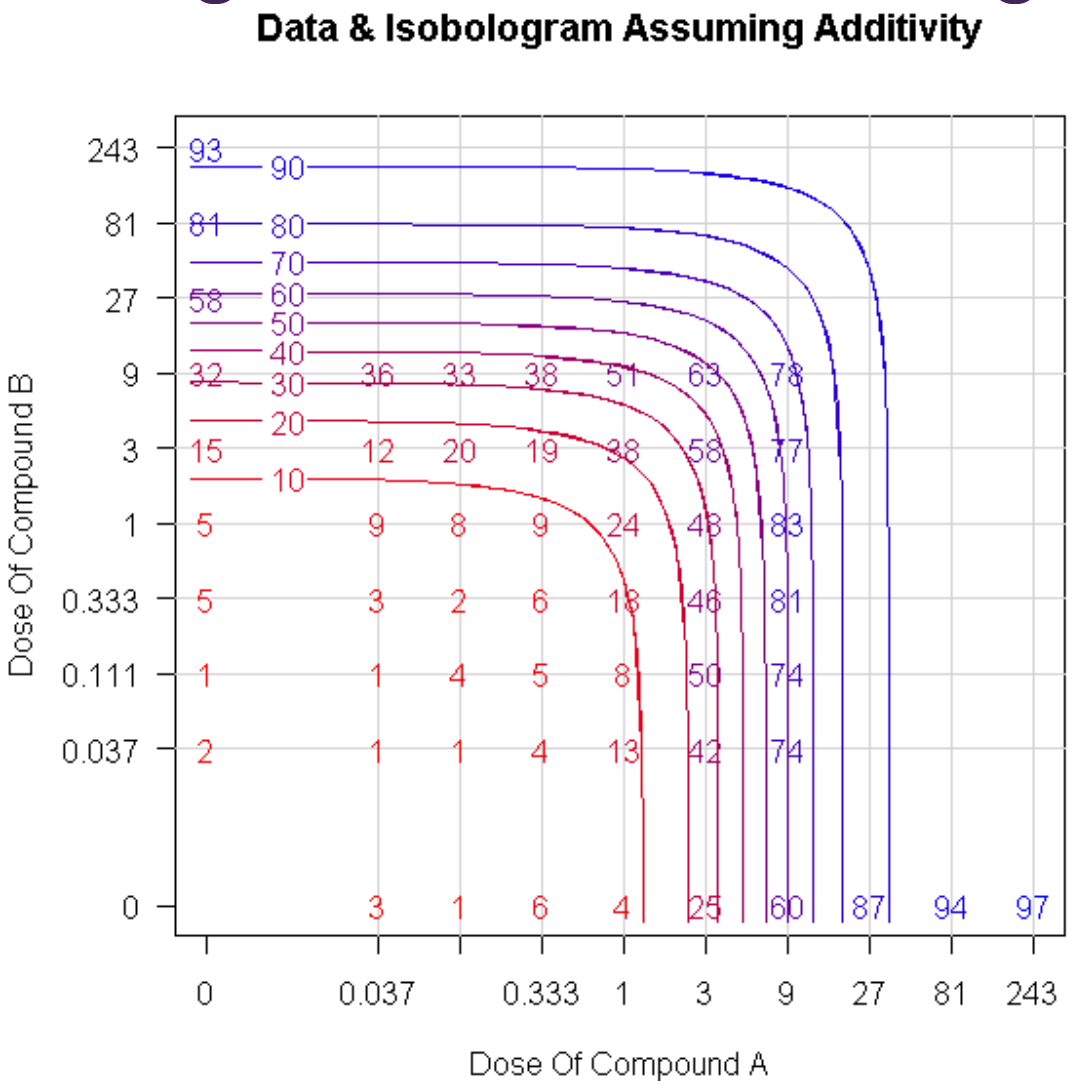
EDA Suggests Synergy At Higher Doses Of Drug A



Wish to quantify this considering uncertainty in observations & monotherapy fits

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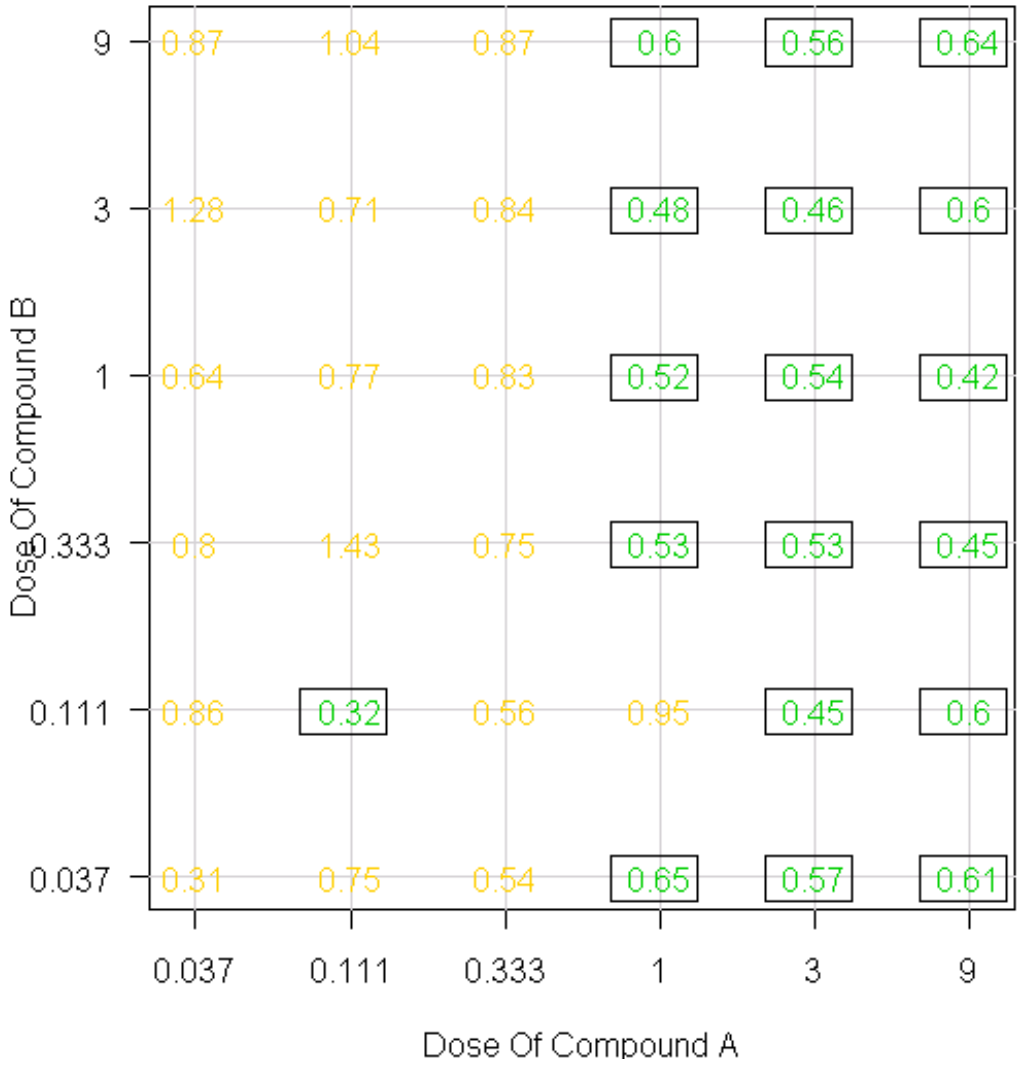
Identify Individual Combinations Significantly Demonstrating Synergy



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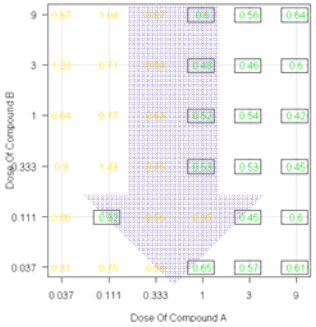
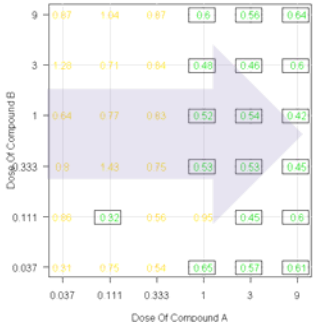
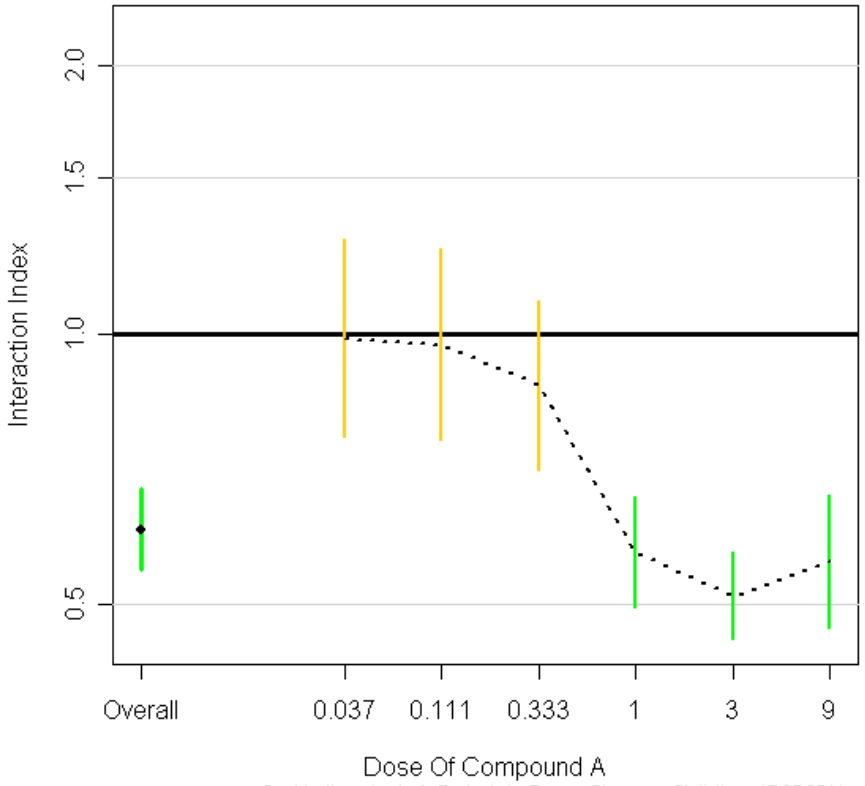
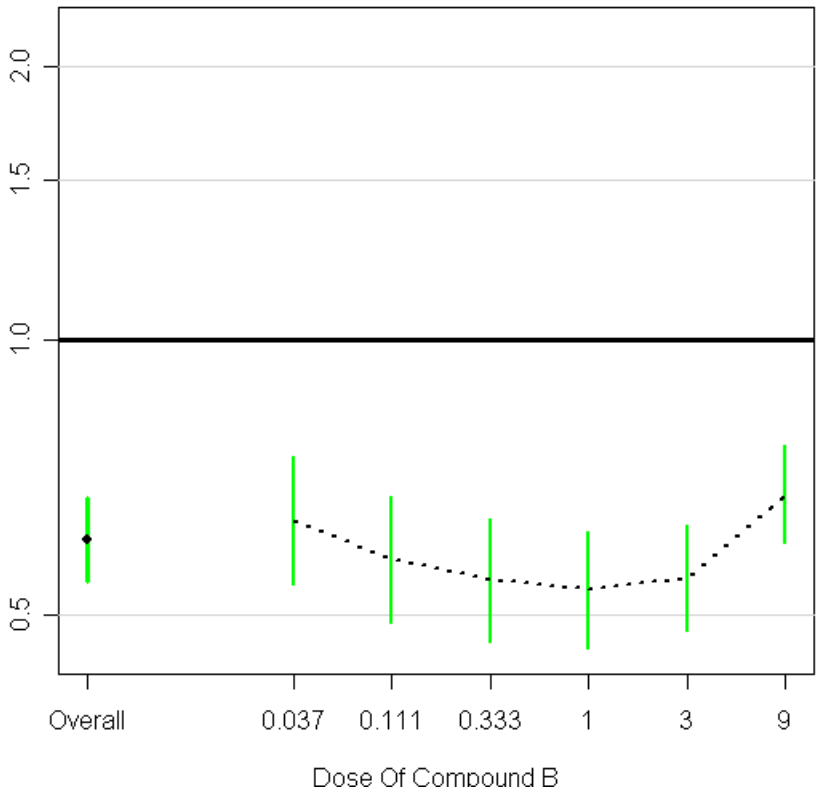
Estimates Of Synergy With 95% CIs Overall & For Different Dose Levels









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Testing Hierarchies of Models

Model	rdf	RSS	df	F	p-Value
Additive	158	5704			
Common τ	157	3672	1	86.86	$2x10^{-16}$
Linearly varying τ over doses of compound A	156	3130	1	27.00	$6x10^{-7}$
Separately varying τ over doses of compound A	152	2834	4	3.96	0.004
Separate τ for each combination	122	2079	30	1.47	0.072
Linearly varying τ over doses of compound B	156	3672	1	0.00	0.984
Separately varying τ over doses of compound B	152	3334	4	3.85	0.005
Separate τ for each combination	122	2079	30	2.45	0.0003

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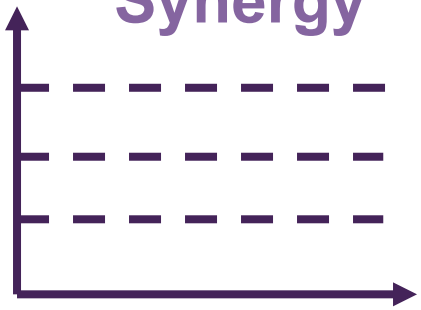
Naturally Extends To A Range of Situations

$$1 = \begin{cases} \dfrac{d_A}{D_A} + \dfrac{d_B}{D_B} & d_A \text{ or } d_B = 0 \\ \dfrac{d_A / \tau_{(i)}}{D_A} + \dfrac{d_B / \tau_{(i)}}{D_B} & d_A \text{ and } d_B > 0 \end{cases}$$

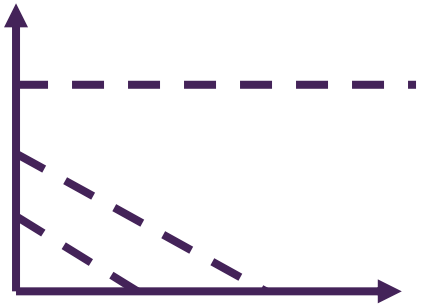
Monotherapies

Combinations

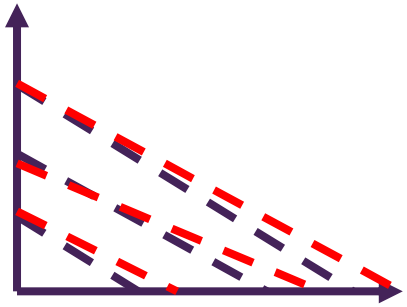
Inactive Agent / Therapeutic Synergy



Partial Response



Multiple Experiments



$D_B = \infty$

$D_B = \infty : R > U_B$

Separate Monotherapy Curves

Common $\tau_{(i)}$ parameters

Extendable to >2 agents

Summary

- Early identification of synergistic drug combinations of strategic importance within the pharmaceutical industry
- Powerful and flexible methodology for identifying, quantifying and characterising synergy
- Utilises all data to analyse any design with sufficient monotherapy data
- Consistent approach across different designs and response scenarios
- Found to be robust even to mis-specifications of response curves
- Implementation in R provides a powerful environment for fitting and visualising these models building upon standard functions e.g. nls() and anova()

A flexible unified approach to the analysis of pre-clinical combination studies, 2010,
Statistics in Medicine, 29 (16) 1746-1756

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