Using R For Flexible Modelling Of Pre-Clinical Combination Studies

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Discovery Statistics

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life inspiring ideas

Modelling Drug Combinations

- Why?
- The theory
- An example
- The practicalities in R

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Why Drug Combinations?

- Making better use of our assets
- Some marketed compounds are combinations e.g. Symbicort
- In some disease areas, e.g oncology, HIV, polypharmacy is the norm
- Compounds licensed only for use in combination with a specific other agent
  - Lapatinib (GSK – Breast cancer) is approved for use in combination with capecitabine
- Increased molecular & pathway level understanding
  - Hypothesise and understanding synergistic actions
  - Link with systems biology

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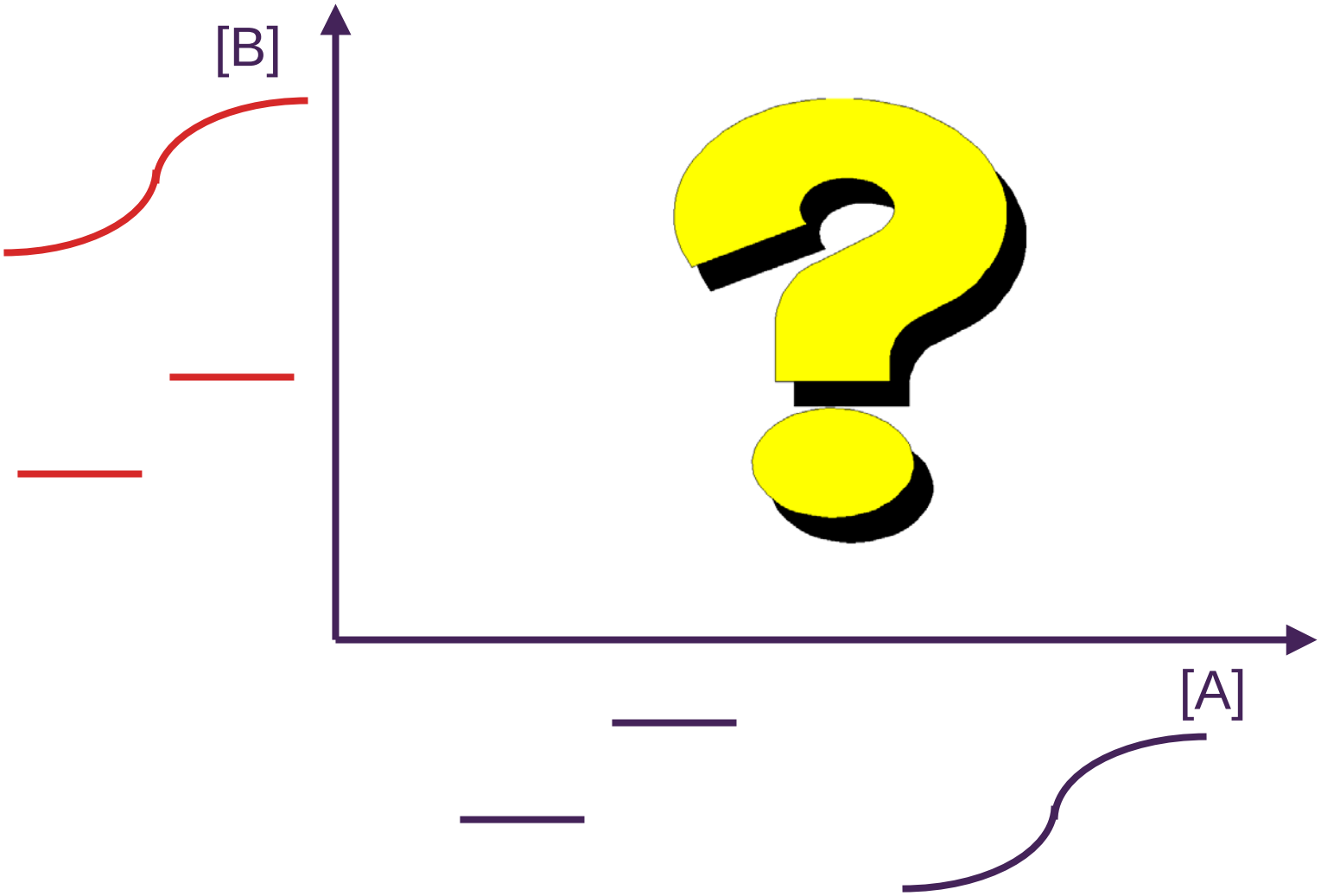
Combination Studies



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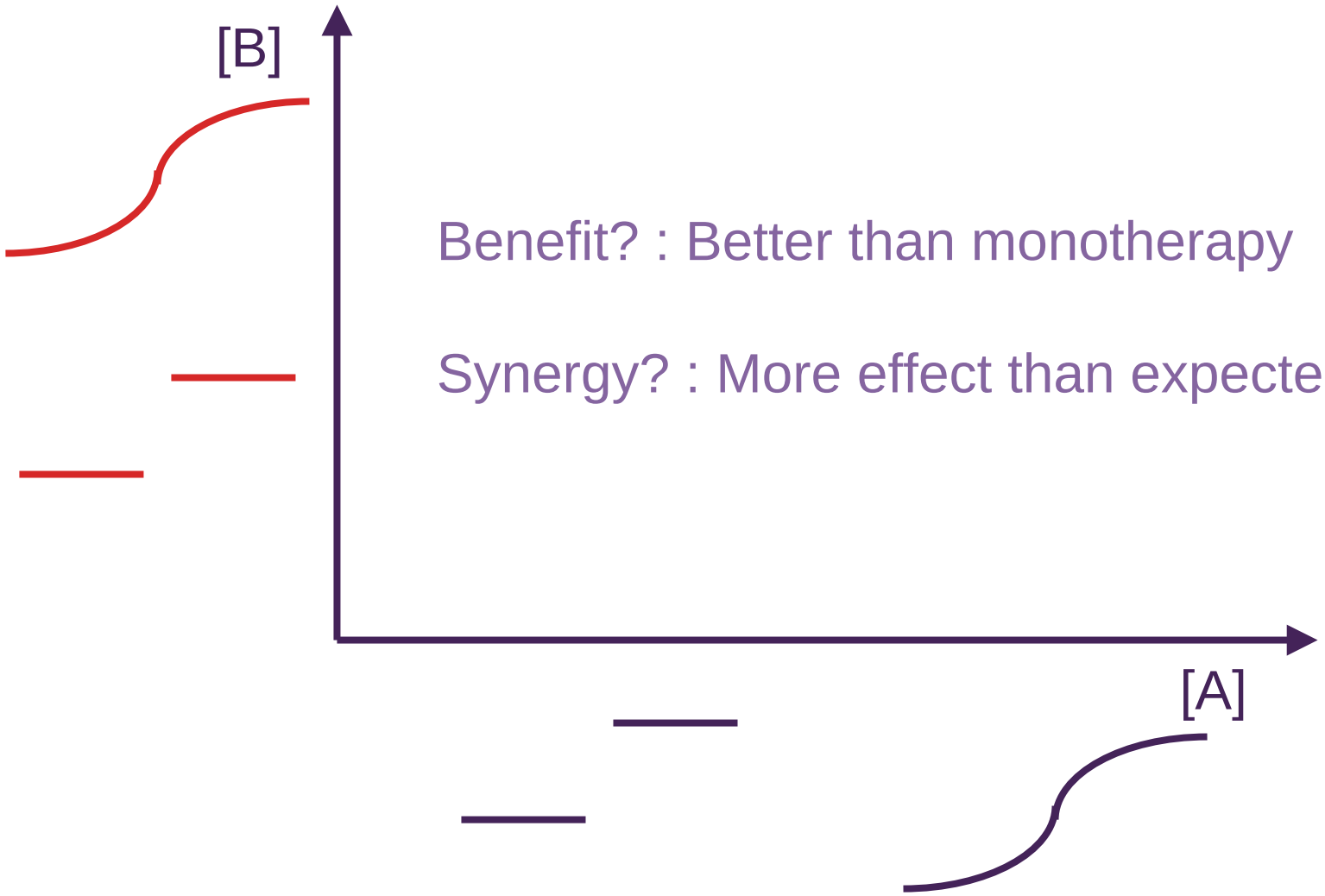
Combination Studies



Benefit? : Better than monotherapy

Synergy? : More effect than expected

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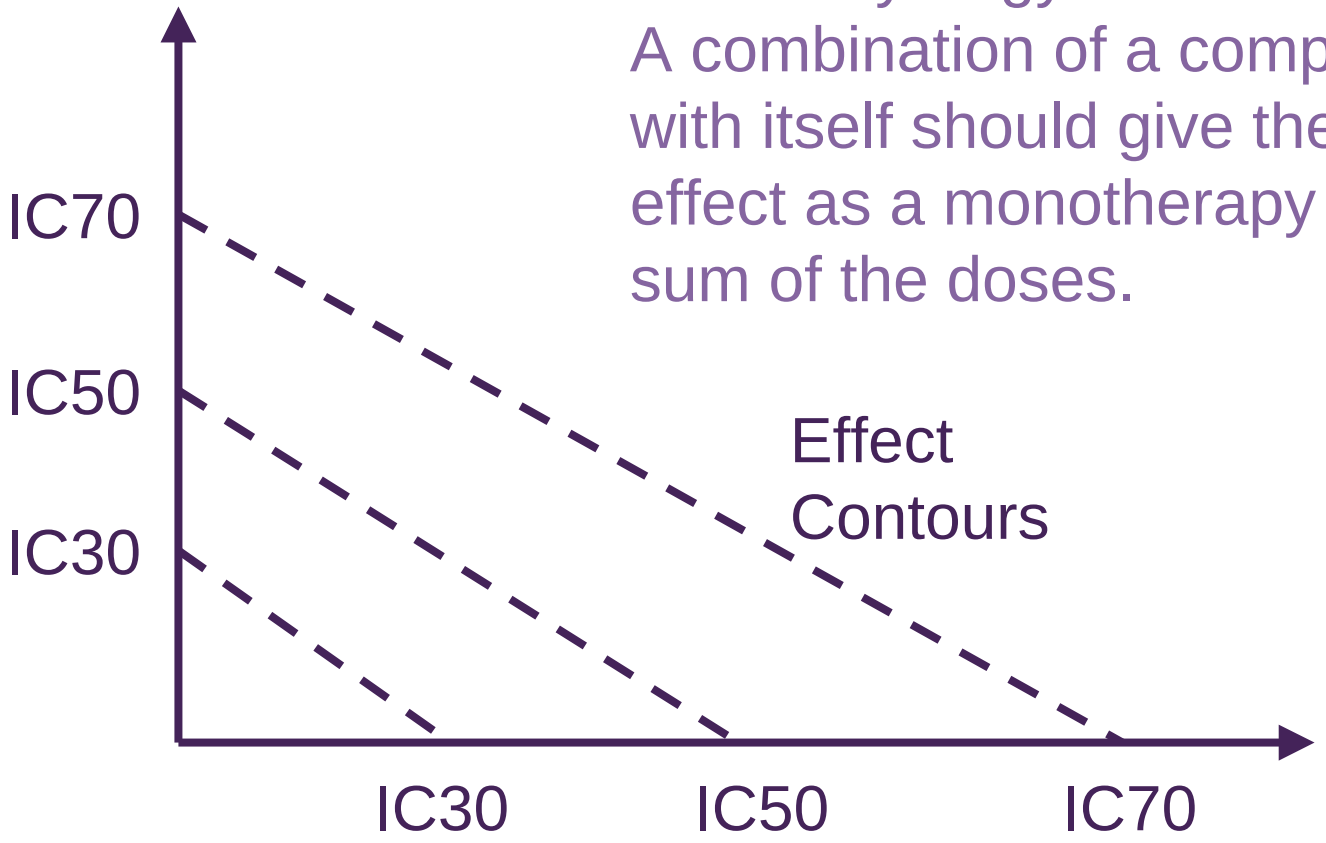
Assessing Synergy
Loewe Additivity

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.



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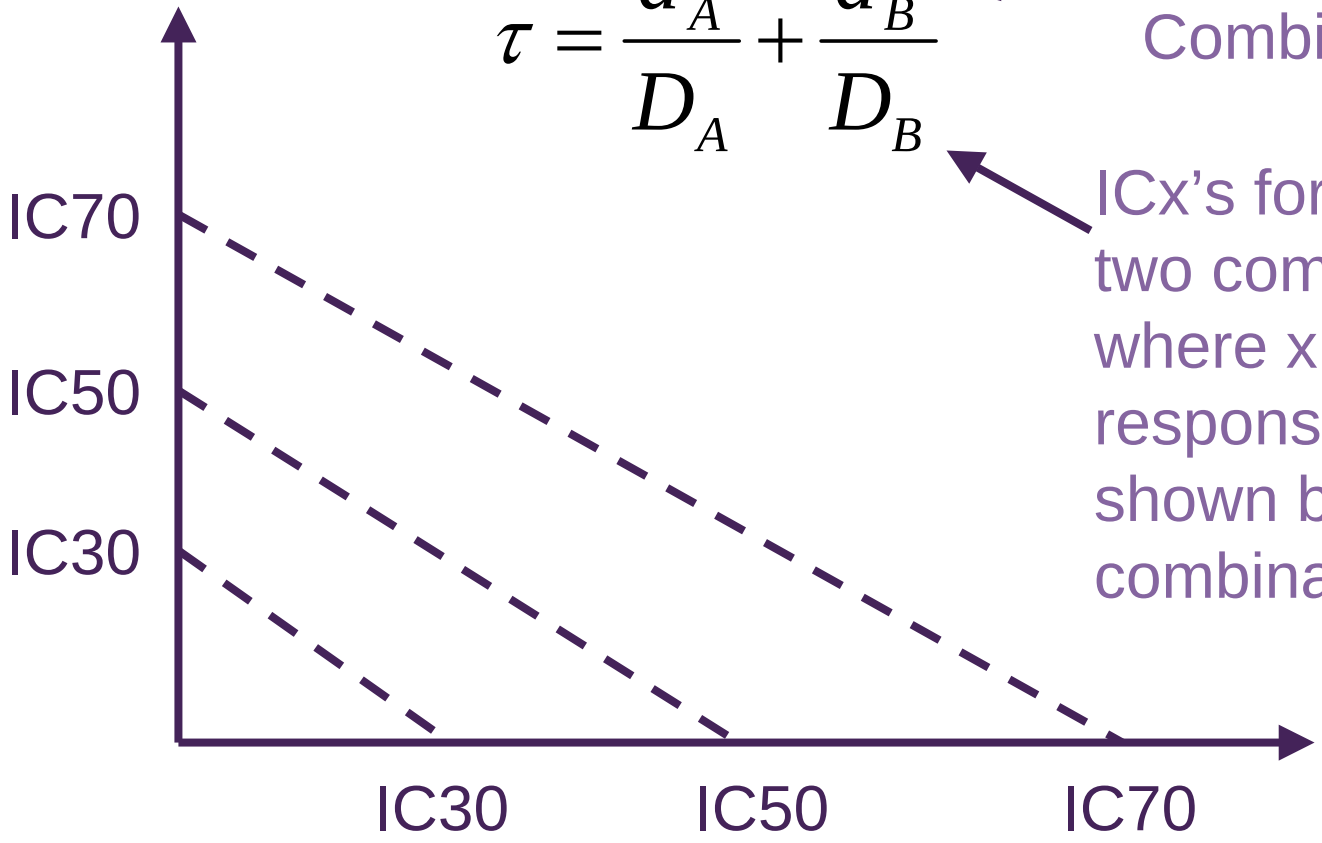
Interaction Index – Berenbaum Combination Index – Chou & Talalay

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

Doses in Combination

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



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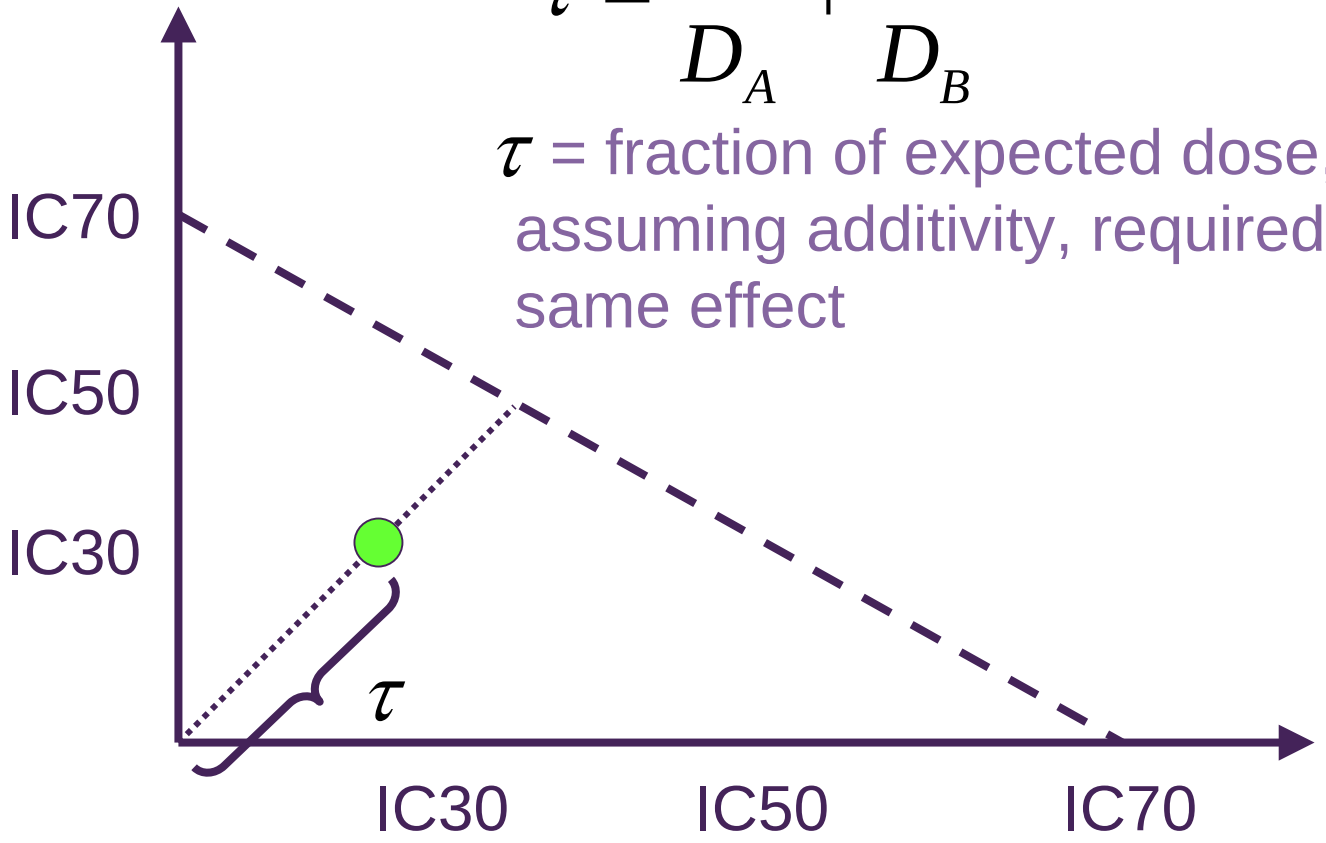
Interaction Index – Berenbaum
Combination Index – Chou & Talalay

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

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



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Interaction Index – Berenbaum
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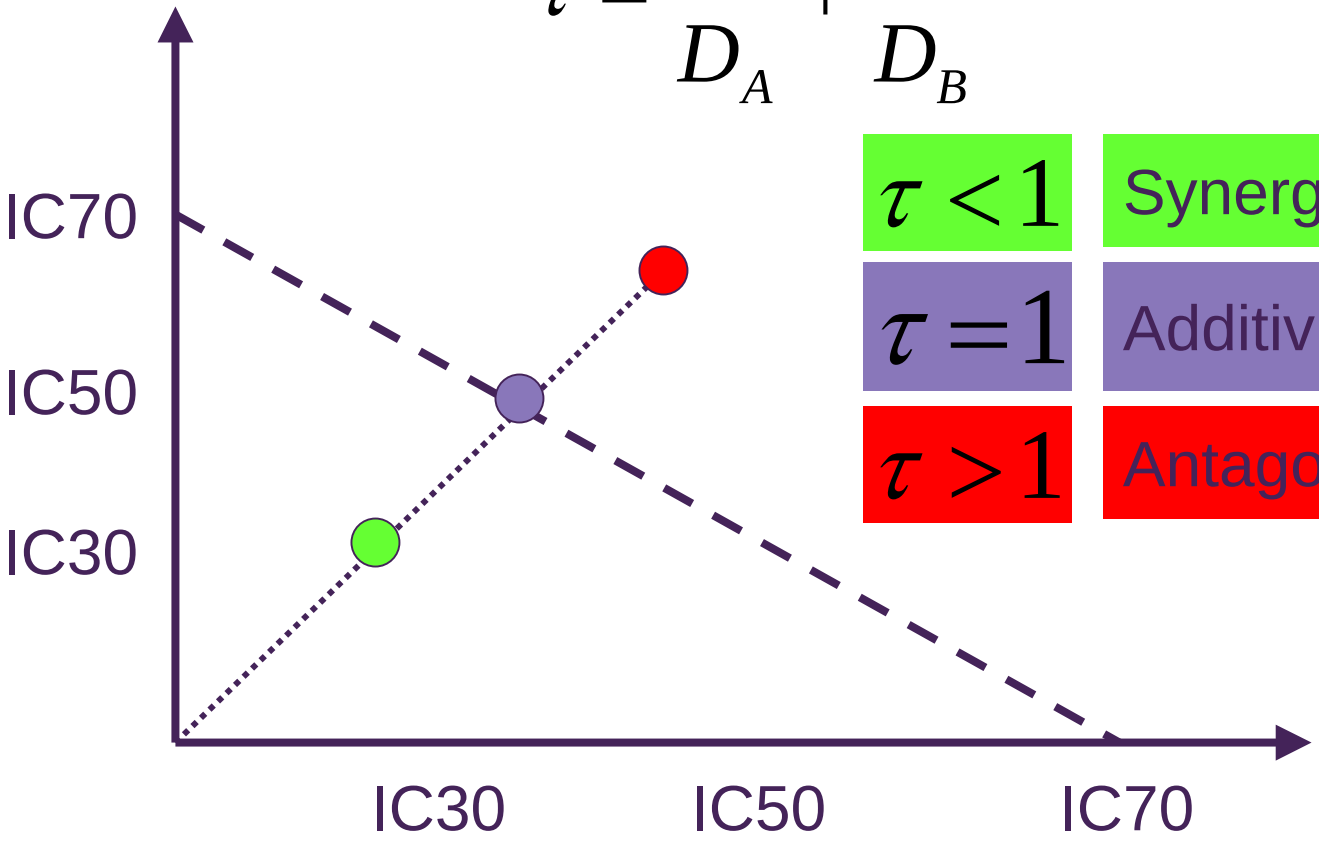

$\tau < 1$	Synergy
$\tau = 1$	Additivity
$\tau > 1$	Antagonism

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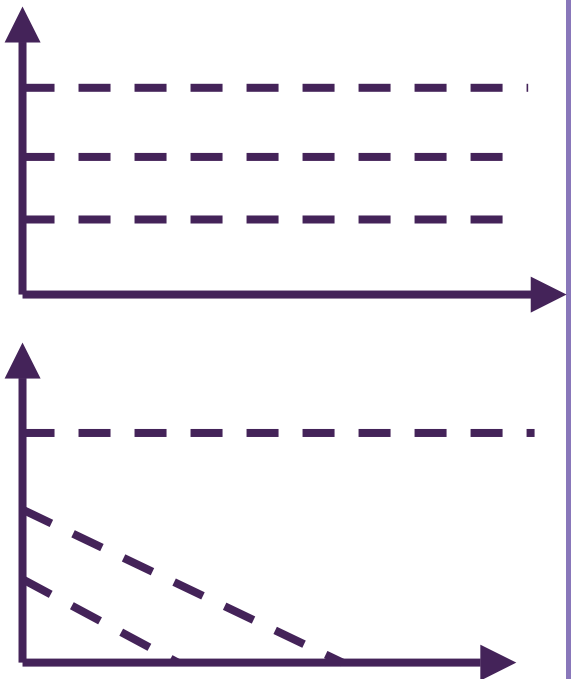
Interaction Indices

- Wish to calculate these:
  - With standard errors / confidence intervals
    - Statements of confidence – significance tests
- Use more flexibly and powerfully
  - Combining combination doses together
  - Overall assessments of synergy
- Covering a wide variety of situations
  - Inactive agent
  - Partial Response Agent
  - Multiple Plates / Experiments



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Unified Tau

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

- 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
  - could fit tau as a continuous function of dose or ray

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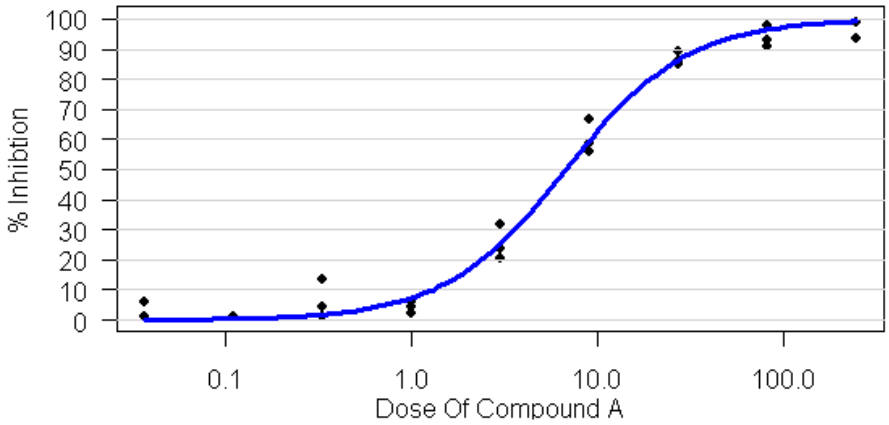
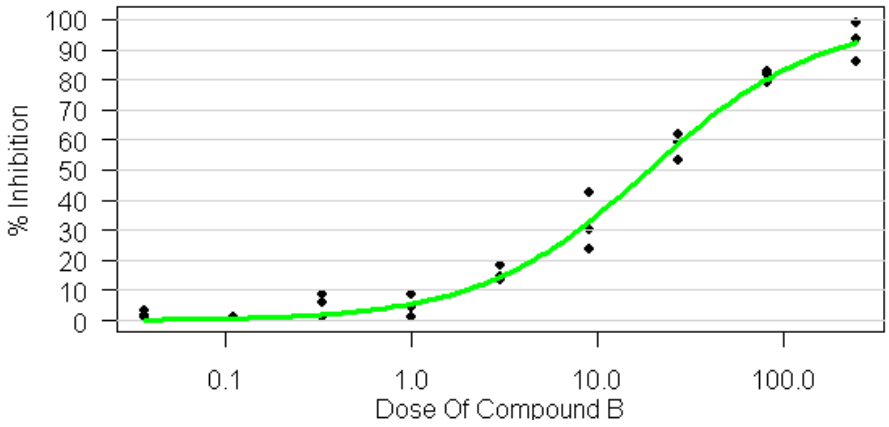
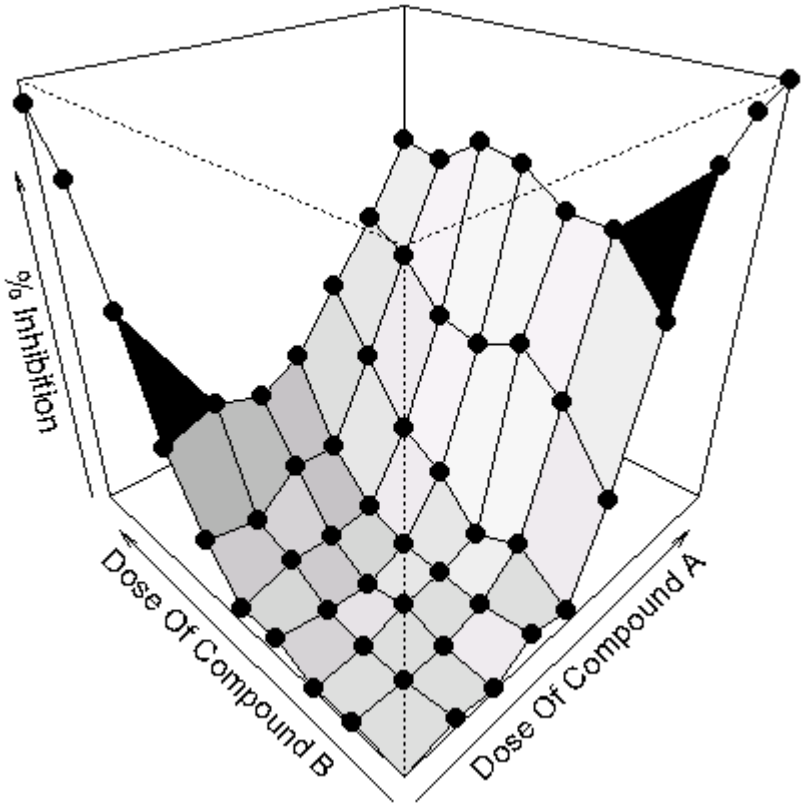
An Example

Monotherapies





Combinations



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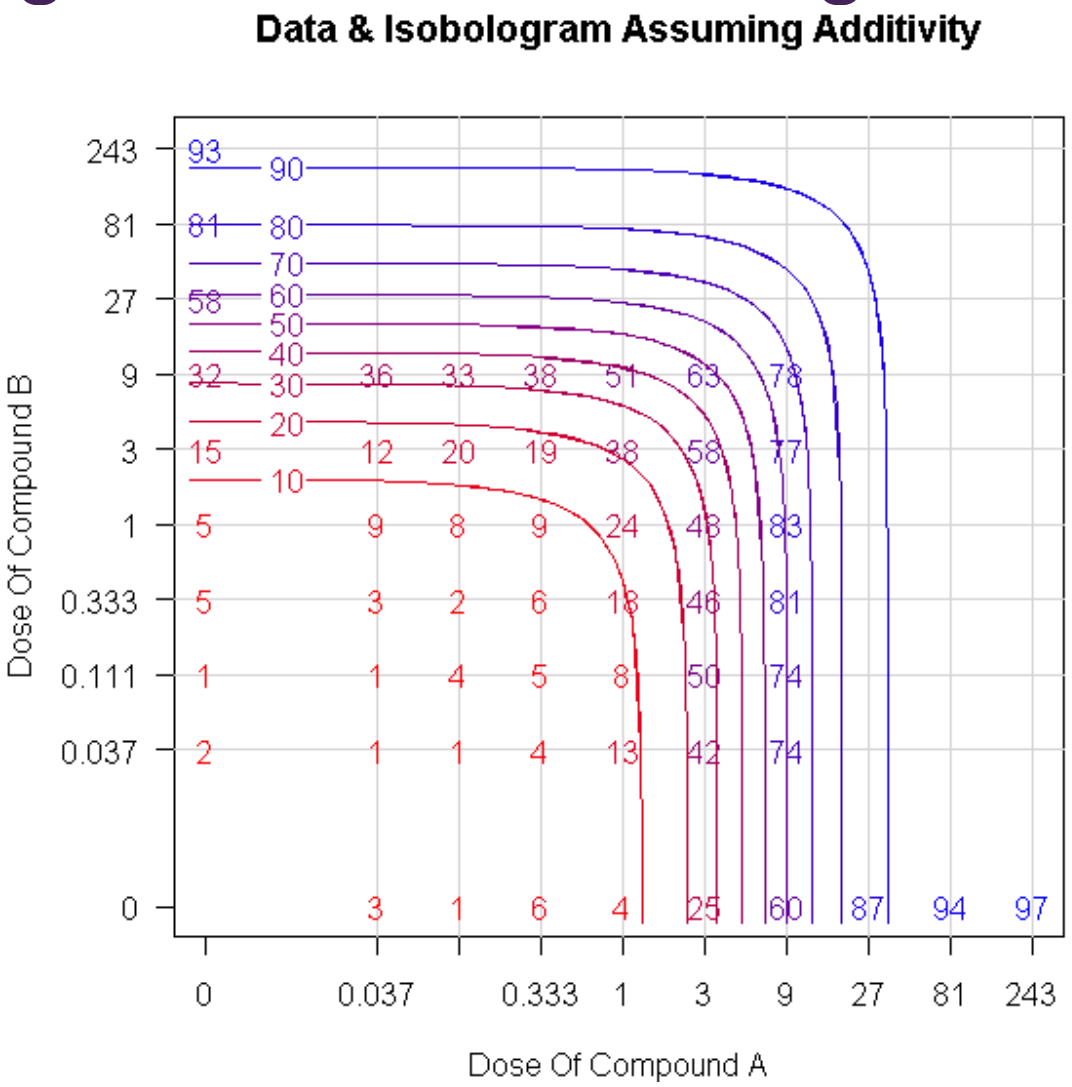
EDA Suggests Synergy At Higher Doses Of Drug A



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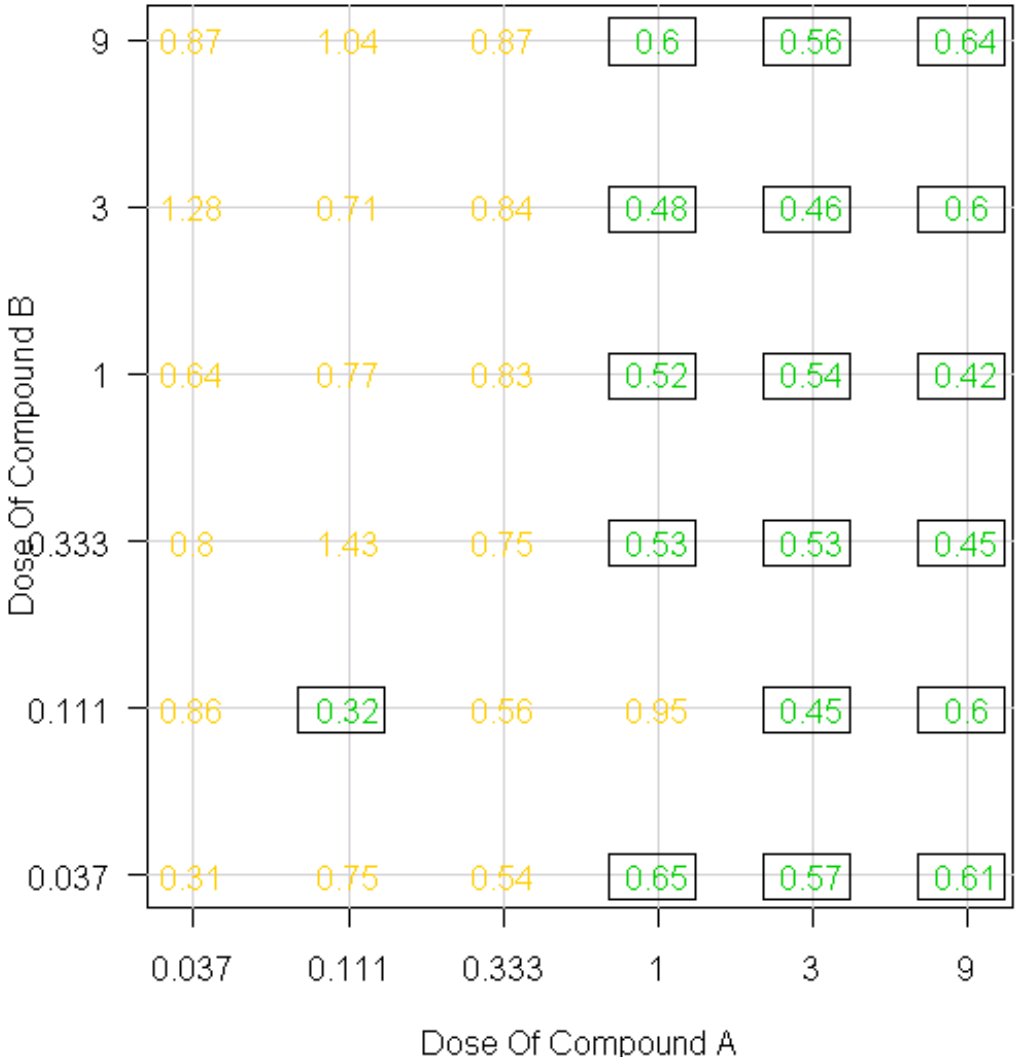
Identify Individual Combinations Significantly Demonstrating Synergy



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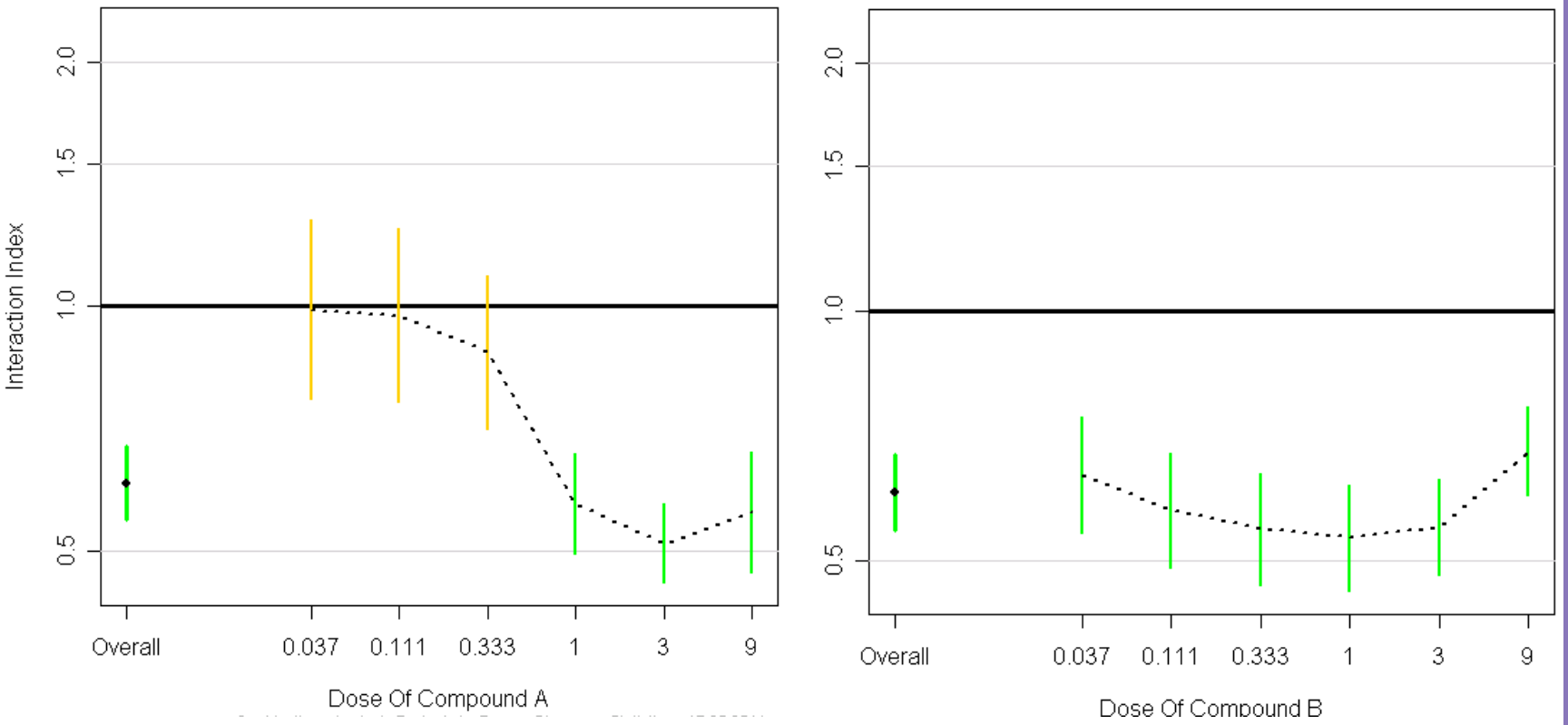
Estimates Of Synergy With 95% CIs Overall & For Different Dose Levels



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Fitting in R

fit <- mynls(formula , start=inits)

Robust version of nls()

Selection of starting parameters

response ~ tau.model(…..)

Flexibly building formula

Formula expressed as
1 ~ f(Y , parameters)
Not
Y ~ f(parameters)

as.formula(paste(…))

Iterative fitting

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Flexibly Building Formula

Varying number of combination parameters to be fit:

```
as.formula(paste("resp ~ tau.model(parameters,
paste("logtau" , 1:ntaus , sep="" , collapse=","),
"gp= c(",paste(groupindex,collapse=",") ,
"))"     ))
```

- Build as a text string, then convert to a formula
- Varying numbers of tau parameters
- Convert group index vector into a text string in the right format

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Iterative Fitting of Formula

Iterative Non-linear curve-fitting performed by nls() :
monotherapy and tau parameters

tau.model(d_1,d_2,m_1,m_2,lower$_1$,lower$_2$,ldm$_1$,ldm$_2$,taus)

For each observation :

Make initial estimate of Y

Calculate D_1 & D_2 –
monotherapies required to achieve Y using Hill equation

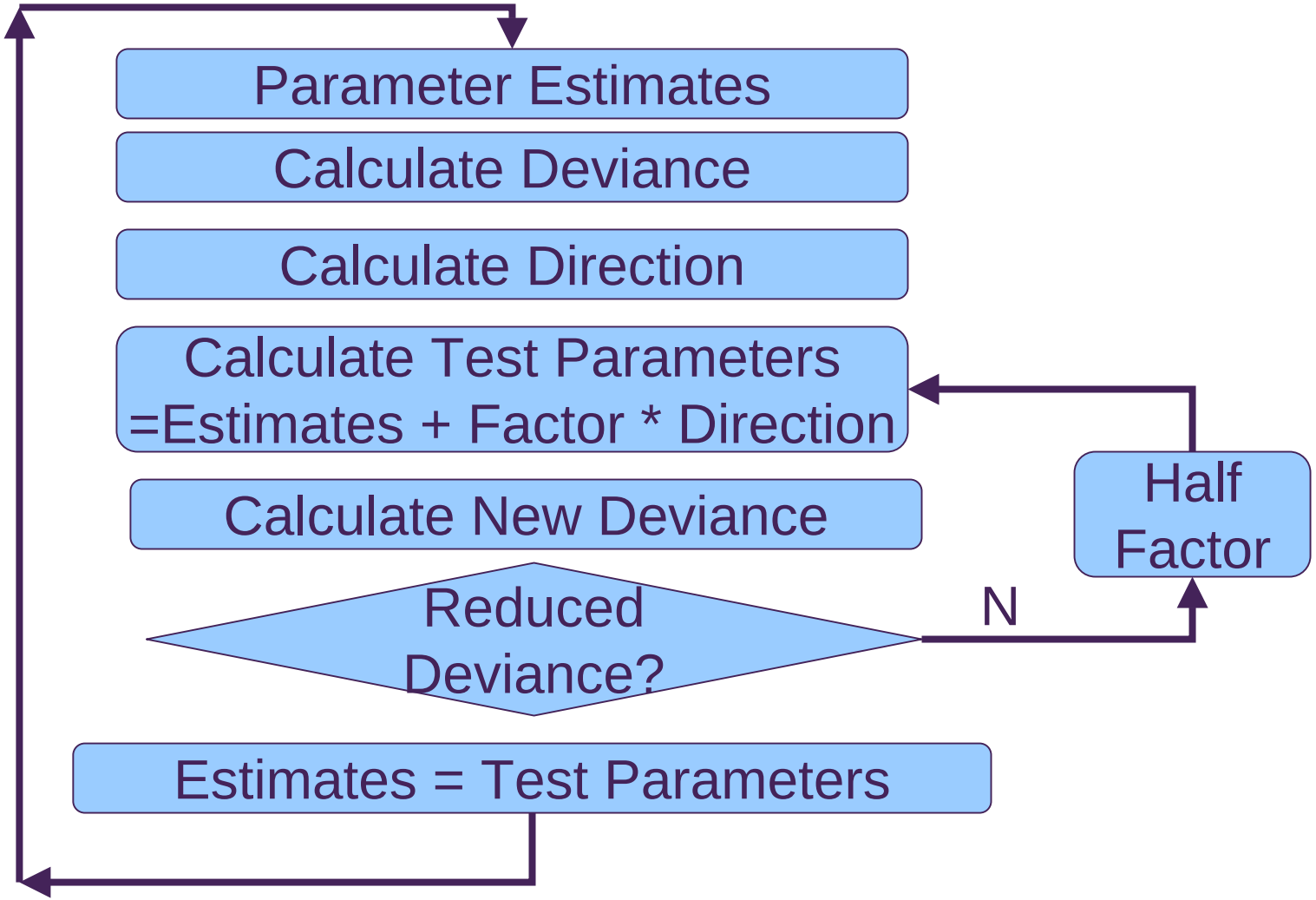
Adjust Y up or down depending on whether

$$\frac{d_1 / \tau_{(i)}}{D_1} + \frac{d_2 / \tau_{(i)}}{D_2}$$ is >1 or < 1

Iterate until Y is accurately estimated

Based on code developed by Lee *et al*

mynls() : A less temperamental nls()



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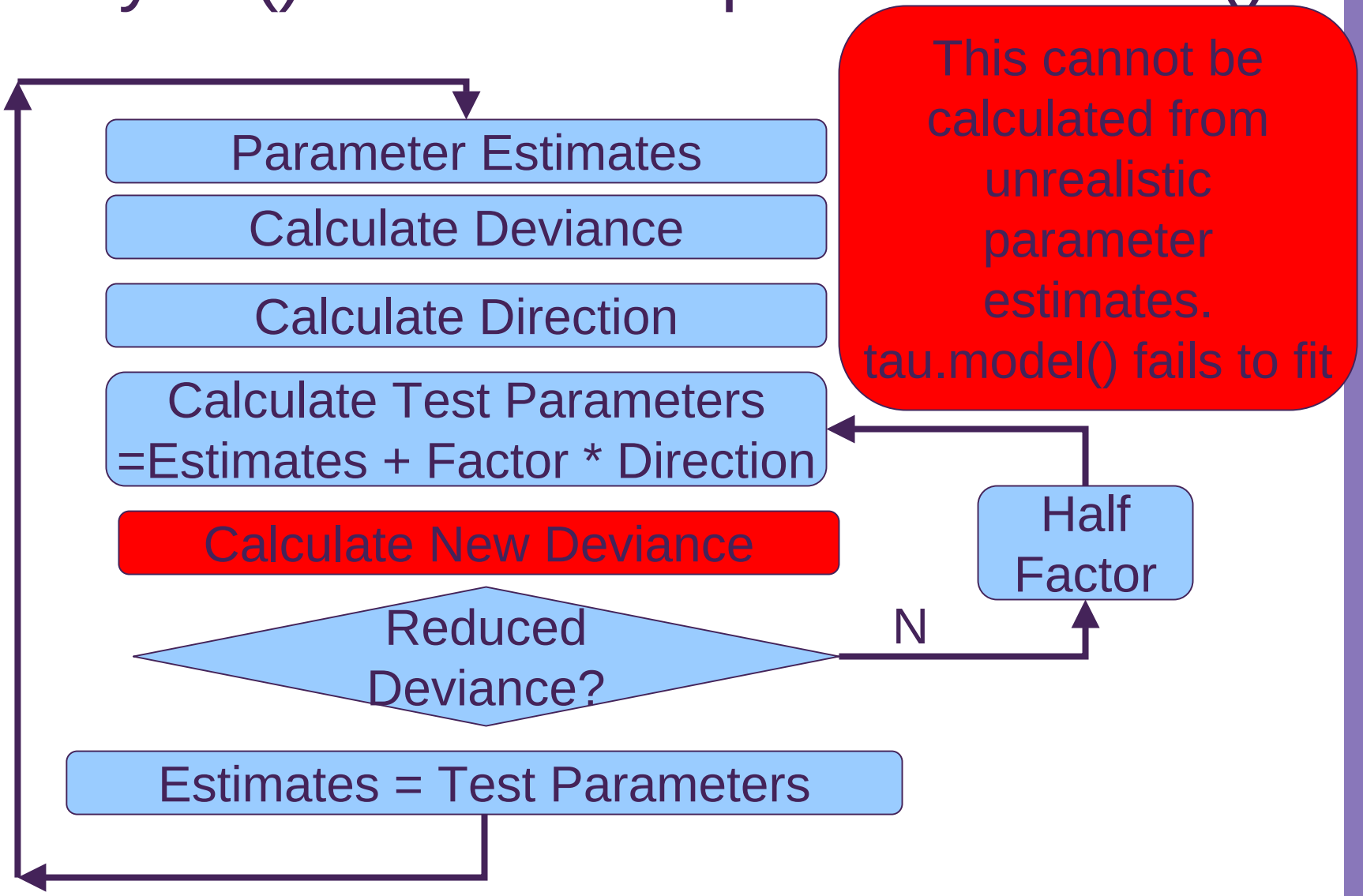

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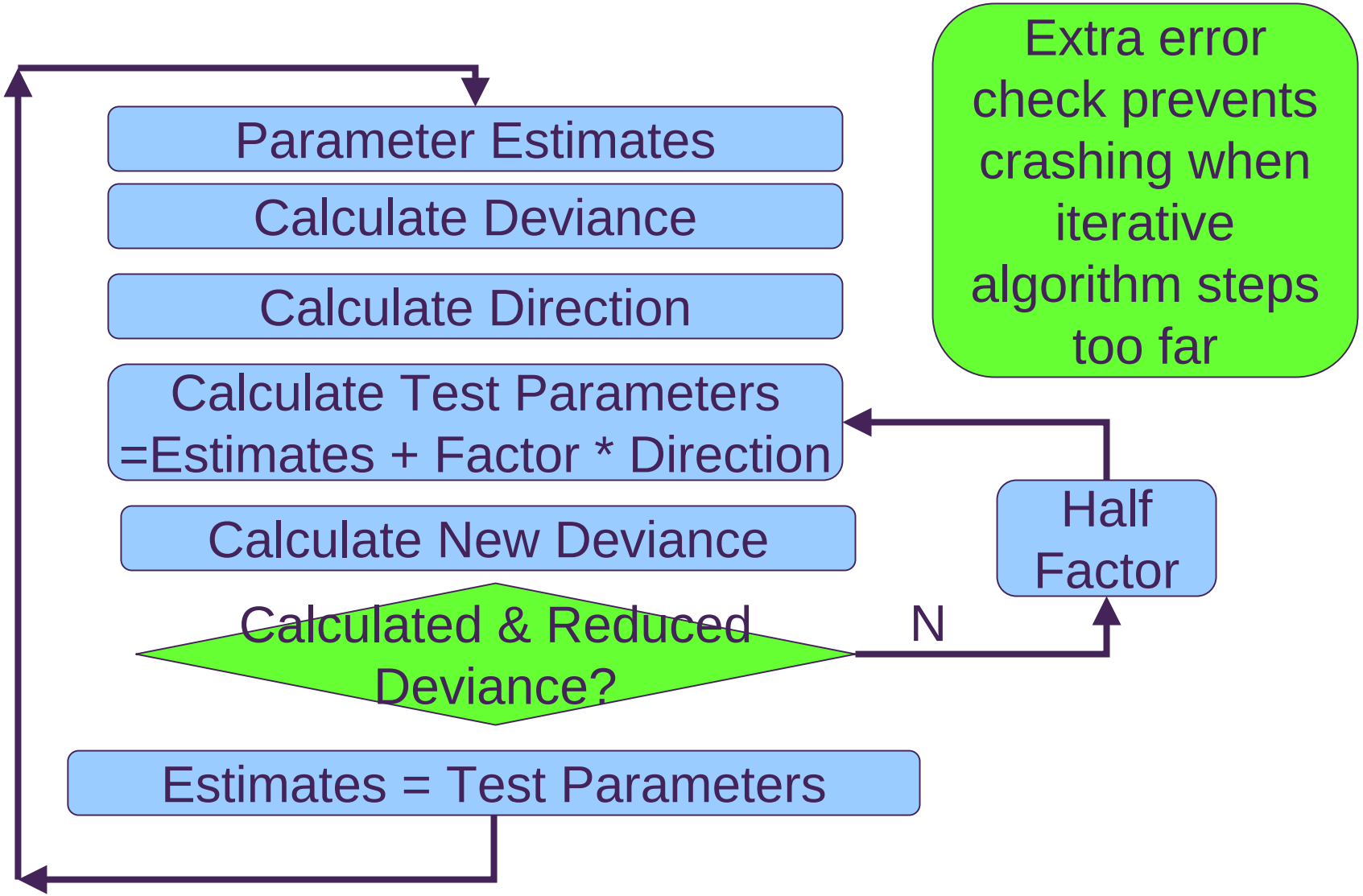

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Starting Parameters

- Good starting parameters from fitting marginal distributions (e.g. monotherapies) and direct calculations
  - In some situations, this can be done exactly, so nls() converges immediately to the starting parameters, but with standard errors added
- Starting from multiple starting points decrease risks of local minima
- Identify and fix parameters likely to shoot off to infinity beforehand

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Summary

- Early identification of synergistic drug combinations of strategic importance within the pharmaceutical industry
- Powerful and flexible methodology for identifying and characterising synergy
- R provides a powerful environment for fitting and visualising these models
- Careful programming increases the of robustness and success rate of R in fitting these models

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