Drug combinations: quantifying synergistic or antagonistic interactions

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Introduction
Interaction of two or more agents is important

Drug treatment
  combinational therapies
  inadvertent combinations
Environment
Toxicology

Yet missing in most pharmacology textbooks
Terminology of the interaction can be a source of confusion in itself

**Zero interaction**, additivity, noninteraction, inertism, independence

**Synergy**, superadditivity, supra-additivity, potentiation, augmentation, coalism

**Antagonism**, subadditivity, depotentiation, negative interaction, negative synergy, infra-additivity
In one very specific case, the “expected” is easy to agree on.
**Most common approaches**

<table>
<thead>
<tr>
<th>No method</th>
<th>Empirical</th>
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<tr>
<td></td>
<td>“By far the most often used... in which explicit criteria are conspicuous by their absence”</td>
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<td>Berenbaum 1989 Pharm Reviews</td>
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<thead>
<tr>
<th>Effect based</th>
<th>Dose based</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Subthresholding</td>
<td>- Isoboles (Loewe)</td>
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<td>- HSA</td>
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<td>- Sum</td>
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<tr>
<td><strong>- Product (Bliss)</strong></td>
<td><strong>Saariselkä (Finland) agreement 1992</strong></td>
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Effect based approaches
Subthresholding, if applicable, takes purely statistical approach
HSA postulates that two drugs are expected to be only as good as the better one.
Response summation assumes that drugs act independently on the same target (site) and dose-response is linear.
Bliss independence assumes that the drugs act independently on different sites.

- **Subthresholding**: Drug A (NS), Drug B (NS), Drug A+B (marked with an asterisk).
- **Highest Single Agent**: Drug A, Drug B, Drug A+B.
- **Effect Summation**: Drug A, Drug B, Drug A+B.
- **Bliss independence**: Effect formula: $E_a + E_b - E_a \times E_b$. 

Graphs showing the effect of drug combinations under different conditions.
Most common criticism of effect based approaches: (1) impose a mechanism; (2) fail in sham combination test
Dose based approach
Loewe isoboles
What is isobole and how can I get one?
What is isobole and how can I get one?

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Tallarida RJ 2012 J Pharmacol Exp Ther
There is an isobole for every effect, not just 50%

Tallarida RJ 2007 Pharmacol Ther
The synergy is not only about the dose and effect, it is also about the ratio of compounds.
What is the equation of the isobole line we just saw?
Meet the notation

\( a \) – concentration of drug A

\( b \) – concentration of drug B

\( E_{ab} \) – effect of the combination

\( A \) – concentration of drug A alone that gives effect \( E_{ab} \)

\( B \) – concentration of drug B alone that gives effect \( E_{ab} \)
What is the equation of the isobole line we just saw? Derive the equation

So, dose additivity

\[ b + a \]

The key concept, the trick, is to find isoeffective, equivalent dose

\[ b + b' \]
\[ b + a \times \frac{B}{A} = B \]
\[ a \frac{A}{B} + B = 1 \]

We actually wanted to have an equation for the isobole:

\[ b = B - a \times \frac{B}{A} \]
What did we just do when we were adding the doses?
What is isobole and how can I get one?

\[ b = B - a \times \frac{B}{A} \]
What about when the potency ratio is not fixed?

\[ b' = \frac{EC_{50}^b}{\left[ \frac{E_{max}^b}{E_{max}^a} \left( 1 + \frac{EC_{50}^{a^q}}{a^q} \right) - 1 \right]^{\frac{1}{p}}} \]

\( p \) – hill coefficient for B
\( q \) – hill coefficient for A
Criticism of Loewe additivity

Linear isoboles are rarity

Often, no clear prediction can be generated

(1) if hill coefficients are different, $b+b'$ (P) and $a+a'$ (Q) give different isoboles

(2) Boundary conditions need some additional solutions if (i) one effect is very low, or (ii) if drug B has higher $E_{\text{max}}$ ($b'$ is not readily available)

*Tallarida RJ 2007 Pharmacol Ther*
Few additional, perhaps even most important take home thoughts
Therapeutic synergy and in vitro synergy are different things

Increased selectivity

Other, more important reasons for combinational therapy

“It may be useful to study the changes observed in a well-characterized, empiric combined action caused by changes in other variables (other drugs, cell lines, temperature, pH etc)”

_Greco WR et al. 1996 J Natl cancer Inst_