

### Combinatory Options

**Additivism / additive = addition, no interaction**

$$\text{Effect}_{(dA, dB)} = \text{Effect}_{(dA)} + \text{Effect}_{(dB)}$$

**Synergism / synergistic = over-additive effect**

$$\text{Effect}_{(dA, dB)} > \text{Effect}_{(dA)} + \text{Effect}_{(dB)}$$

**Antagonism / antagonistic = no or negative effect**

$$\text{Effect}_{(dA, dB)} < \text{Effect}_{(dA)} + \text{Effect}_{(dB)}$$

5

### Definition of Synergy by Berenbaum (1977, 1989)

$$E(d_a, d_b) = E(d_a) + E(d_b) \quad \text{Summation}$$

$$E(d_a, d_b) < E(d_a) + E(d_b) \quad \text{Antagonism}$$

$$E(d_a, d_b) > E(d_a) + E(d_b) \quad \text{Synergy}$$

**Interaction Index**

$$I = \sum i(x_i/X_i) = 1 \quad \text{0 interaction}$$

$$< 1 \quad \text{synergism}$$

$$> 1 \quad \text{antagonism}$$

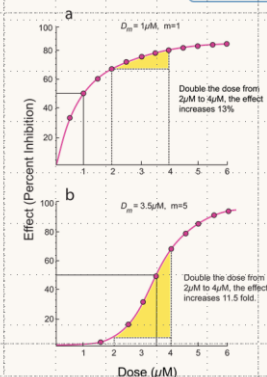
- I: interaction index
- X<sub>i</sub>: dose of the individual component in the combination,
- X<sub>i</sub>: dose which generates the same effect as the combination
- i: the i<sup>th</sup> individual component in the combination

Berenbaum introduced a mathematical method in form of the interaction index and applied the isobol method as an „elegant geometric counterpart“.

Berenbaum 1989

8

### Determination of Synergism



Why determination of Synergism is more complicated than expected:

We need both **Potency (D<sub>m</sub>)** and **Shape (m)**

Chou, T.C.

13

# Coming soon: Methods to assess Synergy

## An Introduction to Synergy Research

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### The Median Effect Equation (T.C. Chou, J Theor. Biol. 69:235-276, 1976)

Hyperbolic (first order or Michaelis-Menten),  $m = 1$ ,  
Sigmoidal (higher order),  $m > 1$

$$\text{For both cases: } \frac{fa}{fu} = \left( \frac{D}{Dm} \right)^m$$

- fa = fraction of system affected, e.g. fractional inhibition
- fu = (1-fa) = fraction unaffected
- D = dose required to produce fa
- Dm = dose required to produce median effect. i.e. ED<sub>50</sub>, IC<sub>50</sub>
- m = sigmoidicity (shape)

The Chou Plot & Equation:

$$\text{Log}(fa/fu) = m \text{ Log } D - m \text{ Log } Dm; (y=ax + b)$$

15

### Towards a Unified Theory

Derivation of Major Biochemical and Biophysical Equations from the Median-Effect Equation

Henderson-Hasselbalch equation

$$\log[H^+] = \log K_a + \log \frac{[A^-]}{[A]}$$

$$\text{pH} = \text{p}K_a + \log \frac{[A^-]}{[A]}$$

Michaelis-Menten equation

$$v/V_{max} = [1 + (K_m/S)]^{-1}$$

$$\frac{fa}{fu} = \left( \frac{D}{Dm} \right)^m$$

The Median-Effect Equation

Chou, J. Theor. Biol. 69: 253-276, 1976

$$f_a / (1 - f_a) = (D / D_m)^m$$

$$f_a = [1 + (D_m / D)^m]^{-1}$$

$$\log [f_a / (1 - f_a)] = m [\log(D) - \log(D_m)]$$

$$\log [(f_a)^{-1} - 1]^{-1} = m \log(D) - m \log(D_m)$$

$$F_a / f_{a0} = D / D_m$$

Hill equation

$$\log [v / (V_{max} - v)] = n \log(S) - \log(K)$$

Scatchard equation

$$\frac{[L]_b}{[L]_f} = \frac{n[M]_f}{K_d} - \frac{[L]_b}{K_d}$$

Chou, T.C., Synergy 2014

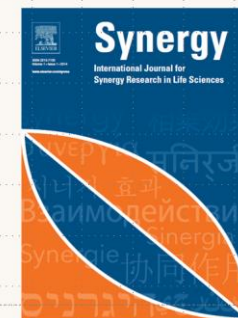
17

### Synergy - International Journal for Synergy Research

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31