# Synergy scores

## Drug response matrix:

There is the row drug (A) and the column drug (B). Each coefficient $(i, j)$ in the matrix corresponds to the relative inhibition ($y(i, j) =$ pourcentage of cells that have died) when drug A has been applied with concentration conc(ith row) and drug B has been applied with concentration conc(jth col).

Different scores with different assumptions have been developed. A model is built from the single drug responses (first row and first column of the drug response matrix), and an expected response $y_e$ is computed from this model for drug combinations at any dosage (conc(drug A), conc(drug B)).

The score is then computed as the difference between the expected response $y_e$ and the measured response $y_m$. If $y_e > y_m$, the drugs are called antagonist, and if $y_e < y_m$, the drugs are called synergistic.

## HSA:

The expected response is $y_e(i, j) = max(y_m(i, 0), y_m(0, j))$. The final score is averaged over all elements of the matrix, but the first row and first column

$$S = \frac{1}{(i_{max}-1)(j_{max}-1)} \sum_{i \neq 0, j \neq 0} (y_m(i, j) - y_e(i, j))$$

In this model, what is expected is that adding a second drug does not help at all (does not change the response) until the effect of the second drug alone would be stronger

## BLISS:

We assume that the cells treated with a given drug D at a given concentration $c_D$ have a given probability to die $y_D^{c_D}$.

If the effect of drug A and B or independent, some cells will die because of drug A (with proba $y_A^{c_A}$) and then the rest of the cells (expected to be $1 - y_A^{c_A}$ of the initial amount of

cells) will die because of drug B (with proba $y_B^{c_B}$). Here we assume that the effect of one drug is independent from the other drug. The expected response is for the combination is:

$$y_e^{c_A,c_B} = y_m^{c_A,0} + (1 - y_m^{c_A,0}) y_m^{0,c_B}$$

$$= y_m^{0,c_B} + (1 - y_m^{0,c_B}) y_m^{c_A,0}$$

$$= y_m^{0,c_B} + y_m^{c_A,0} - y_m^{0,c_B} y_m^{c_A,0}$$

In terms of the elements of the matrix, the effect is computed as:

$$y_e(i,j) = y_m(i,0) + y_m(0,j) - y_m(i,0) y_m(0,j)$$

The final score is averaged over all the elements (but first row and first column) as before.

## ZIP

a regression is performed on each the single drug responses (i.e. the first row and the first column) with $x$ the concentration of the drug.

$$\hat{y}_D^x = \frac{y_{min} + y_{max} (x/m_d)^\lambda}{1 + (x/m^D)^\lambda}.$$

The four parameters to be fitted are ($y_{min}$, $y_{max}$, $\lambda$, $m_d$).

- $y_{min}^D$ corresponds to the minimum effect of the drug D (when applied alone). $y_{min}$ will often be $0$ as a drug shouldnt have any effect when applied at very small concentration.
- $y_{max}^D$ corresponds to the maximum effect of the drug D (when applied alone), at high concentration.
- $m^D$ is the concentration of the drug at which the effect is the midpoint between $y_{min}$ and $y_{max}$.
- $\lambda^D$ is the slope of the curve

We use this model to predict the effect of a drug at a given concentration and then we make the same independence assumption as in the BLISS model.

The expected response is:

$$y_e^{c_A,c_B} = \hat{y}_A^{c_A} + \hat{y}_B^{c_B} - \hat{y}_A^{c_A} \hat{y}_B^{c_B}$$

$$= \frac{y_{min}^A + y_{max}^A (c_A/m^A)^{\lambda^A}}{1 + (c_A/m^A)^{\lambda^A}} + \frac{y_{min}^B + y_{max}^B (c_B/m^B)^{\lambda^B}}{1 + (c_B/m^B)^{\lambda^B}} - \frac{y_{min}^A + y_{max}^A (c_A/m^A)^{\lambda^A}}{1 + (c_A/m^A)^{\lambda^A}} \frac{y_{min}^B + y_{max}^B (c_B/m^B)^{\lambda^B}}{1 + (c_B/m^B)^{\lambda^B}}$$

The final score is still an average over the elements of the matrix

## Loewe

A regression model is fitted jointly on both single drug responses. Compared to the previous model, we enforce $\lambda^A = \lambda^B$, $y^A_{min} = y^B_{min}$, $y^A_{max} = y^B_{max}$

The expected response is:

$$y_e^{c_A,c_B} = \frac{y_{min}+y_{max}(c_A/m^A+c_B/m^B)^\lambda}{1+((c_A/m^A+c_B/m^B)^\lambda}$$

## Reference


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