MatrixExplorer Documentation

Screen design

Information on screen design, cell lines, compounds and quality control can be downloaded in a separate file, please see MatrixExplorer Documentation site.

Single agent & combination response

Single agent responses are normalised to controls and fitted. Single agent maximum effect (MaxE) is derived from the fit of the single agent response at the highest screened concentration (fitted for individual replicates if available).
Measured inhibition of the combination wells is also normalised to controls. The combination maximum effect (combo_MaxE) corresponds to the second highest measured data point. There is currently no combination surface fit available in MatrixExplorer v1.

Synergy reference models

Highest Single Agent (HSA)

According to the HSA model, a combination of Drug 1 and Drug 2 is classified as synergistic if the effect of the combination ($E_{1,2}$) is larger than the effect of either Drug 1 (E_1) or Drug 2 (E_2) alone (whichever is larger).

Synergy: $$E_{1,2} > max(E_1, E_2)$$

Whilst the HSA model can simply and effectively identify combinations with a better effect than either of the single agents, it fails to distinguish between responses that are less than or greater than the additive response expected by combining the two drugs. Hence, the HSA model does not distinguish between additive and synergistic effects.

HSA excess is calculated by subtracting the highest effect of either single agent from the combination response ($E_{1,2}$), whereby a positive HSA excess indicates synergy.

HSA excess: $$E_{1,2} - max(E_1, E_2)$$

Bliss independence

Bliss independence is one of the most widely used synergy metrics. The null model assumes that the drug effects of two drugs are mechanistically, and therefore also probabilistically, independent. Additionally, Bliss scores assume the single agents have exponential dose effect curves.

To calculate a Bliss excess, the single agent activities of Drug 1 (E_1) and Drug 2 (E_2), as well as the observed effect of the combination ($E_{1,2}$), must be expressed as a probability between 0 and 1 ($0 \leq E_1 \leq 1$, $0 \leq E_2 \leq 1$, and $0 \leq E_{1,2} \leq 1$, respectively).

Additive Bliss effect: $$E_1 + E_2(1 - E_1) = E_1 + E_2 - E_1E_2$$

Bliss excess is currently calculated as the difference between the measured inhibition of the combination and the Bliss additivity of the monotherapies at the same concentrations.

Bliss excess: $$E_{1,2} - (E_1 + E_2 - E_1E_2)$$

Loewe additivity

Loewe additivity focusses on the concentrations necessary to produce a given effect, rather than the effects at given concentrations. To fulfil Loewe additivity, the combination effect $E_{1,2}$ at doses X_1 and X_2 has to produce the same inhibitory effect than the single agent doses at x_1 and x_2.

Loewe index: $(x_1/X_1) + (x_2/X_2)$

with an index = 1 indicating Loewe additivity, an index > 1 an effect greater than Loewe additivity and an index < 1 an effect smaller than Loewe additivity.

Loewe additivity assumes a constant potency ratio between the two drugs and that there is dose equivalence. This leads to the sham combination principle that an equivalent dose of drug 1 (x_1) can be substituted for drug 2 (x_2) to produce the same combined effect of $E_{1,2}$.

A fitted model of the combination interaction surface is currently not available. Hence, no reliable Loewe index can be calculated.

References

Foucquier and Guedj, "Analysis of drug combinations: current methodological landscape", Pharmacology Research and Perspectives, 2015.

Lehar et al., “Chemical combination effects predict connectivity in biological systems”, Molecular Systems Biology, 2007.

Bliss, “The toxicity of poisons applied jointly”, Annals of Applied Biology, 1939.

Full matrix vs. 3x3 window

Synergy metrics can be calculated across the entire combination dose matrix (i.e. across all the 49 wells), or across a smaller 3x3 sub-matrix (a “window”). The window is used to uncover dose ranges where highest synergy is seen and thereby describes localised synergy effects.

Reported are the windows with highest mean synergy across all 3x3 wells or across all synergistic wells within a 3x3 window. For this, mean synergy is calculated for all possible 3x3 windows in a matrix and the highest window is reported.

3x3 window: $sum\ of\ 9\ wells/9\ wells$

3x3 window, synergy only: $sum\ of\ synergistic\ wells\ in\ window/\#\ of\ synergistic\ wells\ in\ window$

To locate the window in a matrix two locators are available describing the upper right corner of the window, whereby dose1 describes the dose of drug 1 (horizontal) and dose2 describes the dose of drug 2 (vertical). Doses are reported on a scale from D1 to D7, with D1 being the highest screened concentration.