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

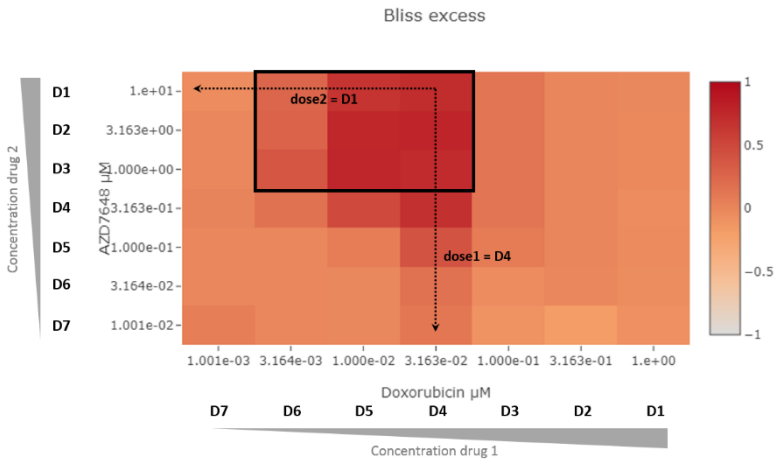
Synergy metrics can be calculated across the entire combination dose matrix (i.e. across all the 49 wells), or across a smaller 3x3 sub-matrix (a “window”). The window is used to uncover dose ranges where highest synergy is seen and thereby describes localised synergy effects.

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.



Glossary of terminology

The full glossary can be downloaded as a separate document on the MatrixExplorer Documentation site.

Screen-related metrics

Metric name	Explanation
BARCODE	Barcode of the assay plate
DRUGSET_ID	ID of the drug set used for the assay plate (Drug set describes the individual plate layout & drug composition)
cmatrix	Identifier for a combination matrix within a drug set
well_treatments	Combination of drug set library tags

Cell line-related metrics

Metric name	Explanation
CL	Cell line identifier used in the curve fit
CELL_LINE_NAME	Name of the cell line
MASTER_CELL_ID	Sanger database master ID
COSMIC_ID	COSMIC database identifier
SIDM	Sanger ID Model (Cell Model Passports identifier)
TISSUE	Sanger tissue classification
CANCER_TYPE	Sanger cancer type classification

Library drug-related metrics

The two drugs used in the matrices are called “lib1” and “lib2”, with lib1 being the first drug listed in the combination. All metrics below are available for both drugs.

Metric name	Explanation
lib1	Drug set library tag identifier
lib1_ID	Sanger database identifier of drug
lib1_name	Drug name
lib1_conc	Highest screened concentration (in µM)
lib1_RMSE	RMSE: root mean square error Describes how far the data points are from the single agent curve fit
lib1_MaxE	Fitted inhibition value at the highest used concentration
lib1_IC50_ln	Natural log of IC50
lib1_IC50_uM	IC50 in µM
lib1_target	Protein target(s)
lib1_pathway	Pathway of protein target(s)
lib1_owner	Sanger database drug owner

Combination response-related metrics

Metric name	Explanation
matrix_size	Number of wells treated with the combination e.g. 49 for a 7x7 matrix
combo_MaxE	Maximum inhibitory effect of the combination within the matrix Based on the 2nd highest data point in the matrix
Delta_MaxE_lib1	*combo_MaxE - lib1_MaxE*
Delta_MaxE_lib2	*combo_MaxE - lib2_MaxE*
Delta_combo_MaxE_day1	*combo_MaxE - day1_inhibition_scale*

Synergy-related metrics

All metrics below have been derived for two synergy reference models: Bliss excess and HSA excess. The used placeholder "X" thereby stands either for "Bliss" or for "HSA".

Metric name	**Explanation**
X_synergistic_wells	Number of wells with a response in excess of that expected by the synergy reference model
X_matrix	Mean excess effect over X across the matrix Calculated by *sum all wells* / *number of wells*
X_matrix_SO	Mean excess effect over X across the matrix (synergistic wells only) Calculated by *sum synergistic wells* / *number of synergistic wells*
X_window_size	Local sub-matrix size in one dimension e.g. "3" = 3x3 matrix
X_window	Mean excess effect over X across the window Calculated by *sum all wells* / *number of wells*
X_window_dose1	Locator of upper right corner of window (library 1) D1-D7 with D1 being the highest screened concentration
X_window_dose2	Locator of upper right corner of window (library 2) D1-D7 with D1 being the highest screened concentration
X_window_SO_size	Local synergy only sub-matrix size in one dimension e.g. "3" = 3x3 matrix
X_window_SO	Mean excess effect over X across the window (synergistic wells only) Calculated by *sum synergistic wells* / *number of synergistic wells*
X_window_SO_dose1	Locator of upper right corner of synergy only window (library 1) D1-D7 with D1 being the highest screened concentration
X_window_SO_dose2	Locator of upper right corner of synergy only window (library 2) D1-D7 with D1 being the highest screened concentration

Day1-related metrics

Metric name	**Explanation**
day1_intensity_mean	Mean observed luminescent intensity of Day1 plate
day1_intensity_sd	Standard deviation of observed luminescent intensities across Day1 plate
day1_viability_mean	Mean viability of Day1 plate, scale: 0-1 with 1 = full viability Calculated with respect to Day4 controls
day1_viability_sd	Standard deviation of Day1 plate viabilities
day1_inhibition_scale	Mean viability of Day1 plate converted to inhibition scale, scale: 0-1 with 1 = full inhibition *1 - day1_viability_mean*
growth_rate	$log_2((NC) / day1\_intensity\_mean)$ Where NC is the mean intensity of negative controls for the Day4 plate
doubling_time	Doubling time in hours $72 * log_2(2) / (log_2(NC) - log_2(day1\_intensity\_mean))$