

Scenario 1: one combination of interest

Step 1

Remove RMSE > 0.3 measurements for both libraries
Filter for $\text{lib1_RMSE} \leq 0.3$ & $\text{lib2_RMSE} \leq 0.3$

Step 2

yes

Do you find combination activity?
Filter for $\text{combo_MaxE} \geq 0.5$ (or similar)

no

In how many cell line-combination pairs?

Visualise cell line-combination pair in MatrixExplorer (combo-CL level)

one

Chosen data might not contain relevant combination responses

Are less pronounced combination activity effects of interest?
e.g. $\text{combo_MaxE} < 0.5$

1

no

yes

Step 3

Investigate synergy
Recommended metric¹: Bliss_matrix

5

Q: which models have the biggest effect?

Compare combination with single agent response
Use ΔMaxE to investigate differential combination response

4

Q: in which models is the combination better than the single agents

Rank models by combination activity
Sort models by combo_MaxE

Q: which models have the biggest effect?

3

Compare combination with single agent response
Use ΔMaxE to investigate differential combination response

4

Q: in which models is the combination better than the single agents

Count # of models passing certain thresholds and/or
Rank models by effect size for one or both of the above

6

Step 1 Quality control

Filter for $\text{RMSE} \leq 0.3$ for both libraries
(at the moment: on libraries only)

Step 2 Determine whether there is any combination activity

Use combination MaxE

Step 3 Compare combination with single agent response

- a) Use synergy scores
- b) Use ΔMaxE for both libraries

¹ Other synergy metrics are available and could be explored including metrics based on 3x3 windows.

Scenario 1 one combination of interest

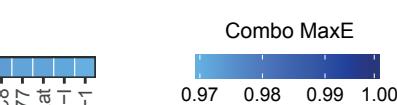
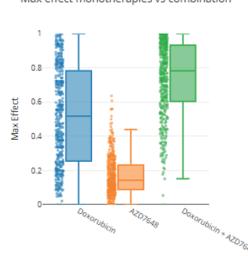
Example: Doxorubicin (Anthracycline) + AZD7648 (DNAPK)

1 Combination activity: plot Combo_MaxE

Use available plots in MatrixExplorer (Combination level)

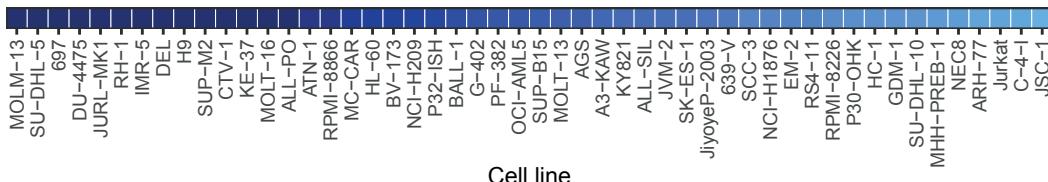
To colour by Day1: plot individually (for example see No. 4, right side)

Max effect monotherapies vs combination



2 Visualise cell line-combination pair

Use available plots in MatrixExplorer (Cell line-Combination level)



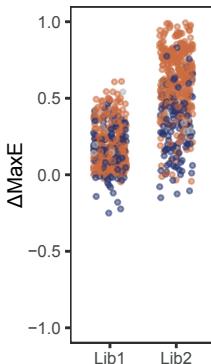
Cell line

3 Rank models by combination activity

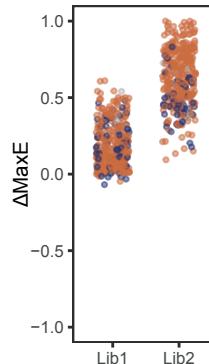
Use tables or plot top X cell lines in a heatmap (here: top 50)

Note: "below Day1" refers to viability scale =
Combo more potent than Day1 reference

Coloured by Day1 All cell lines



Coloured by Day1 Filter Combo_MaxE ≥ 0.5

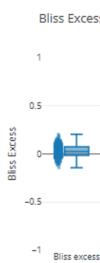
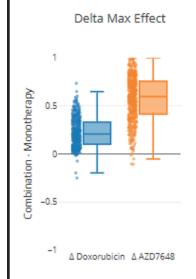
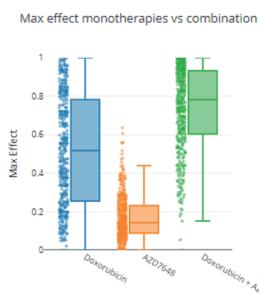


4 Compare combination with single agent response: ΔMaxE

Use available ΔMaxE plots in MatrixExplorer (Combination level)

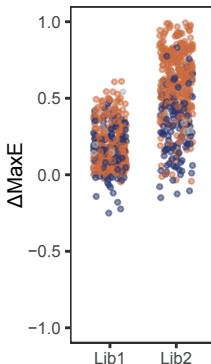
To implement filters or colour by Day1: plot individually

Max Effect - Monotherapies vs Combination

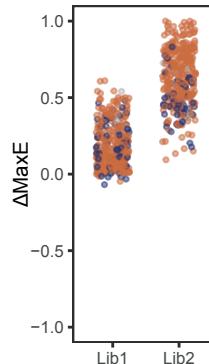


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Coloured by Day1 All cell lines



Coloured by Day1 Filter Combo_MaxE ≥ 0.5

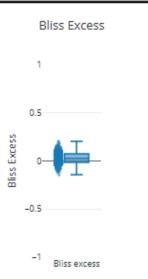
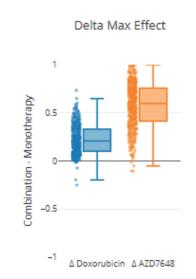
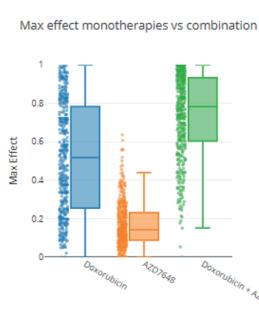


5 Investigate synergy

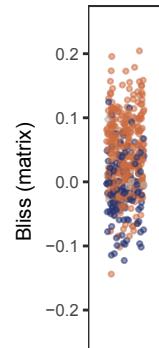
Use available synergy plots in MatrixExplorer (Combination level)

To implement filters or colour by Day1: plot individually

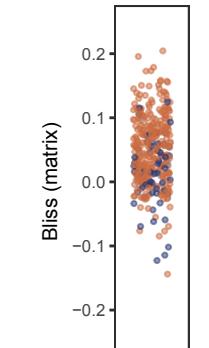
Max Effect - Monotherapies vs Combination



Coloured by Day1 All cell lines



Coloured by Day1 Filter Combo_MaxE ≥ 0.5



6 Count # of models passing certain thresholds

Thresholds used here:

- 1) Combo_MaxE ≥ 0.5, 2) Positive ΔMaxE lib1, 3) Positive ΔMaxE lib2,
- 4) Positive Bliss (window, synergy only)

TISSUE	Cell lines	Combo MaxE ≥ 0.5	Pos ΔMaxE Lib1	Pos ΔMaxE Lib2	Pos Bliss	Pass.all Both ΔMaxE	Pass.all One ΔMaxE
Haematopoietic and Lymphoid	67	65	63	67	65	63	65
Lung	68	48	66	66	43	36	37
Breast	24	19	23	23	17	17	17
Large Intestine	23	17	21	21	12	12	12
Central Nervous System	17	12	17	17	12	11	11

24 Tissues available, 42 cancer types

Example of top 5 combinations (sorted by # of cell lines passing all filters (green))

Pos_dMaxE_Lib1

Pos_dMaxE_Lib2

