

Scenario 1: one combination of interest

Step 1

Remove RMSE > 0.3 measurements for both libraries
Filter for lib1_RMSE ≤ 0.3 & lib2_RMSE ≤ 0.3

Step 2

Do you find combination activity?
Filter for combo_MaxE ≥ 0.5 (or similar)

yes

no

1

In how many cell line-combination pairs?

one

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

2

several

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?

Count # of models passing certain thresholds and/or
Rank models by effect size for synergy metric and/or ΔMaxE

6

Chosen data might not contain relevant combination responses

no

Are less pronounced combination activity effects of interest?
e.g. combo_MaxE < 0.5

yes

Rank models by combination activity
Sort models by combo_MaxE

3

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?

- Step 1** **Quality control**
Filter for RMSE ≤ 0.3 for both libraries
(at the moment: on libraries only)

Step 2 **Determine whether there is any combination activity**
Use combination MaxE

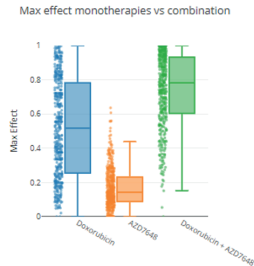
Step 3 **Compare combination with single agent response**
a) Use synergy scores
b) Use ΔMaxE for both libraries

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

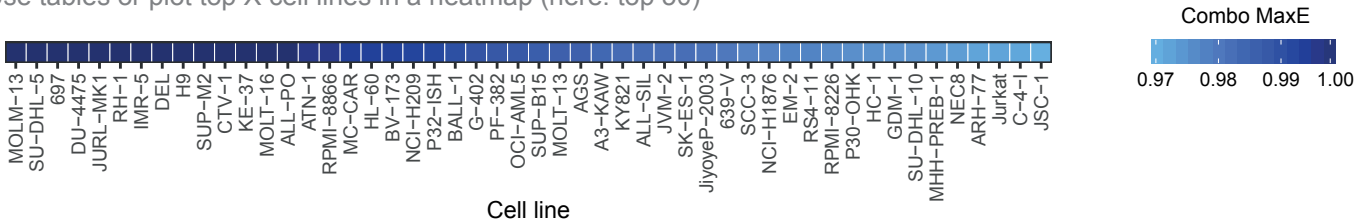
Scenario 1: one combination of interest

Example: Doxorubicin (Anthracyclin) + AZD7648 (DNAPK)

- 1
- Combination activity: plot Combo_MaxE
Use available plots in MatrixExplorer (Combination level)
To colour by Day1: plot individually
- 2
- Visualise cell line-combination pair
Use available plots in MatrixExplorer (Cell line-Combination level)



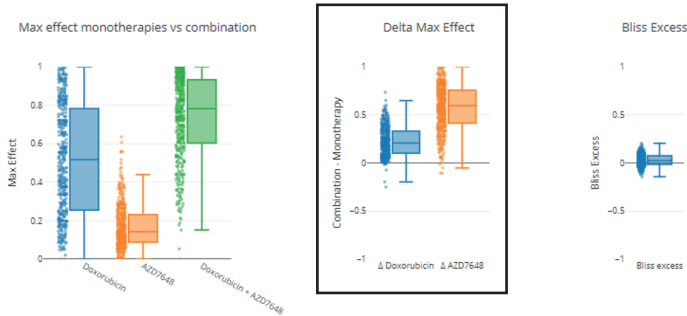
- 3
- Rank models by combination activity
Use tables or plot top X cell lines in a heatmap (here: top 50)



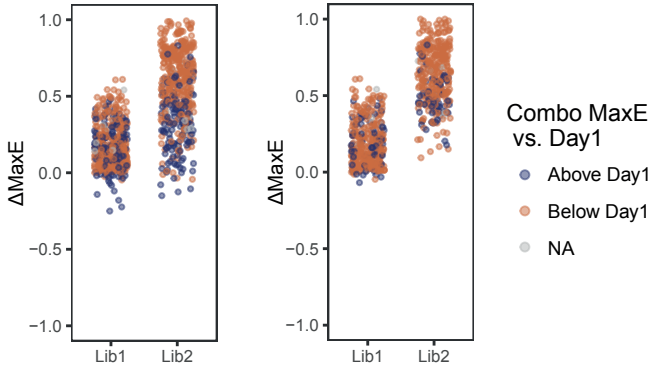
- 4
- Compare combination with single agent response: ΔMaxE
Use available ΔMaxE plots in MatrixExplorer (Combination level)
To implement filters or colour by Day1: plot individually

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

Max Effect - Monotherapies vs Combination

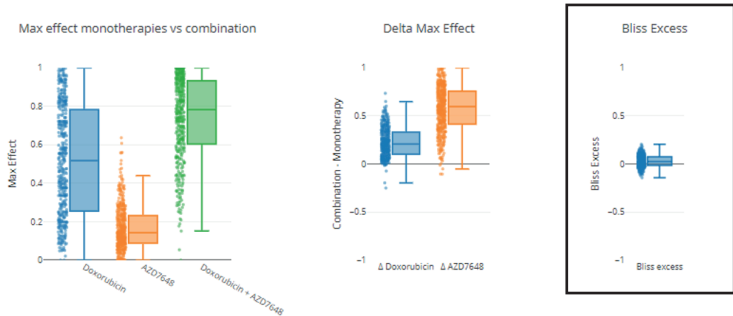


Coloured by Day1
All cell lines Filter Combo_MaxE ≥ 0.5

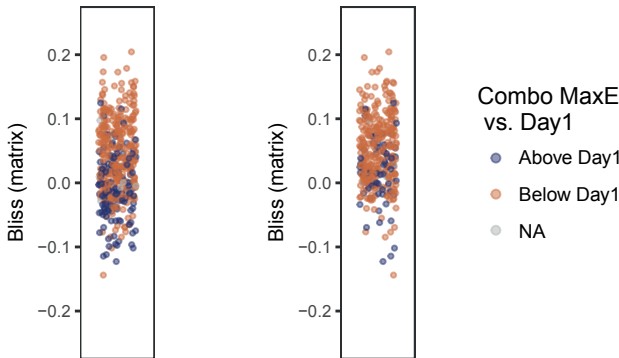


- 5
- Investigate synergy
Use available synergy plots in MatrixExplorer (Combination level)
To implement filters or colour by Day1: plot individually

Max Effect - Monotherapies vs Combination



Coloured by Day1
All cell lines 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 (matrix)

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))

