Similar Compounds Show Similar Activities- Is This True for Compound Combinations?

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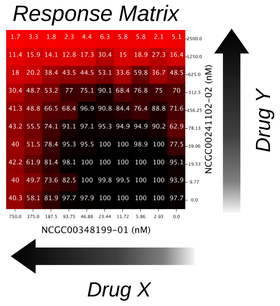
Introduction

Drug Combination and Synergy

- Drug combinations are used to treat many medical conditions such as: HIV, malaria, and cancer
- Sometimes the combined effect of drugs is different than their individual effects
  - Better effect: synergism
  - Same effect: additive
  - Worse effect: antagonism

Response Matrix



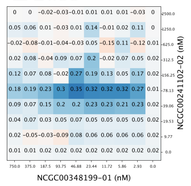
Combination Screening

- Traditionally, screening for drug combinations is slow process
- Since NCATS has high throughput screening, data for thousands of drug combinations can be generated quickly
- Presents opportunity to do large-scale analysis

Metrics to Measure Synergy

- Synergy is quantified with respect to a model of additivity [1]
- Three Models:
  1. Highest Single Agent (HSA)
  2. Bliss Independence Model
  3. Loewe Additivity Model
- Used Bliss Independence Model- convenient and more robust in a high throughput screening setting
- Synergistic- more blue; Antagonistic - more red

Synergy Matrix- Δ Bliss



Similarity Property Principle (SPP)

- "Similar compounds have similar properties" [2,3]
- Want to know if this is true for drug combinations

Questions

1. What are metrics for dissimilarity between combination responses?
2. Does chemical structure correlate to combination response? Synergy?
3. Does dose response correlate to combination response? Synergy?

Q1: Metrics to Compute Matrix Dissimilarity

Methods Insensitive to Spatial Distribution

1. Root Mean Standard Error

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(a_i - b_i)^2}$$

2. Euclidean Distance

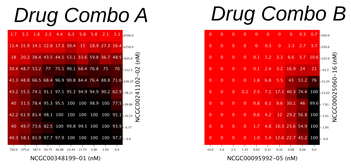
$$ED = \sqrt{\sum_{i=1}^{n}(a_i - b_i)^2}$$

3. Two- Sample Kolmogorov-Smirnov Test

Methods Sensitive to Spatial Distribution

4. Syrjala Test [4]

Drug Combo A *Drug Combo B*

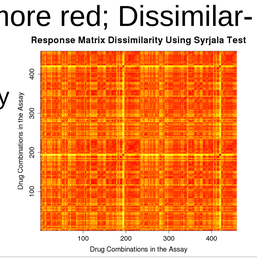


Using these metrics, dissimilarity was computed for all pairs of drug combinations

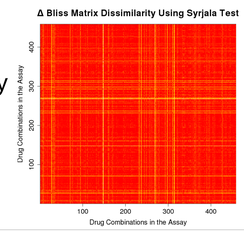
Q1: Visualizing Dissimilarity in an Assay

Malaria Assay ID 1764: screening 480 drug combinations
Similar- more red; Dissimilar- more yellow

Visualizing Dissimilarity of Response Matrices in an Assay

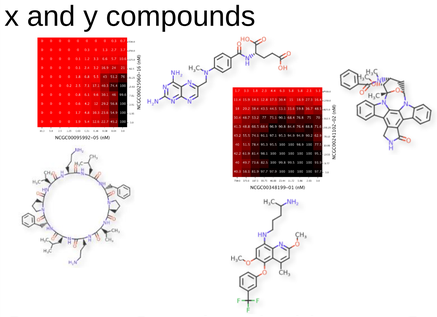


Visualizing Dissimilarity of Δ Bliss Matrices in an Assay

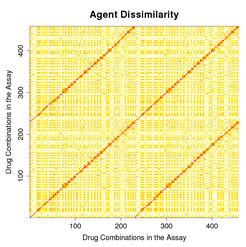


Q2: Chemical Structure Correlated with Combination Response and Synergy

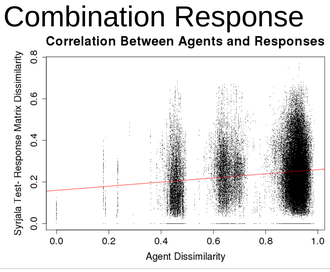
Method: compare corresponding x and y compounds



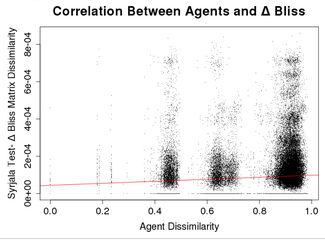
Visualizing Dissimilarity of Structures in an Assay



Structure Correlated with Combination Response

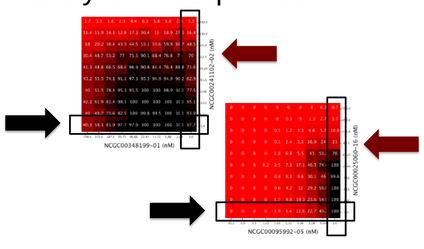


Structure Correlated with Δ Bliss

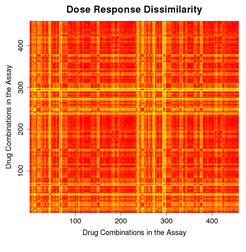


Q3: Dose Response Correlated with Combination Response and Synergy

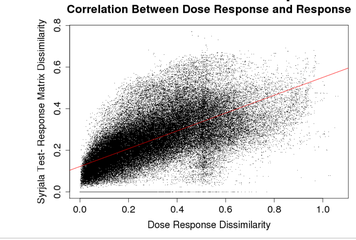
Method: compare corresponding x and y dose responses [5]



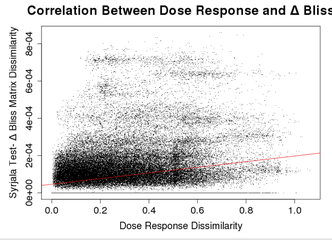
Visualizing Dissimilarity of Dose Responses in an Assay



Dose Response Correlated with Combination Response

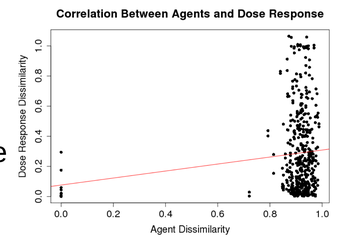


Dose Response Correlated with Δ Bliss



Conclusion

Individual Compounds:



- We might expect structural similarity to correlate with dose response similarity
- However, these do not correlate (R^2 = 0.014; no correlation)
- Suggests that using dose response as the compound property does not appear to be supported by the SPP

Drug Combinations:

	Structural Dissimilarity	Dose Response Dissimilarity
Combination Response Dissimilarity	R^2 = 0.020 no correlation	R^2 = 0.437 correlation
Δ Bliss Dissimilarity	R^2 = 0.006 no correlation	R^2 = 0.052 no correlation

- For SPP to hold, both have to correlate- this is not the case
- Correlations with Δ Bliss even weaker than response
- SPP does not appear to hold
- Suggests that combination responses are not a simple function of the individual agent responses

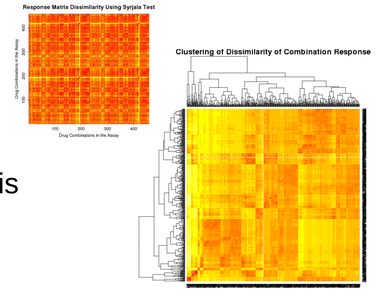
Discussion

Limitations

- Dose response was not a compound property that illustrated the SPP well
- Will be able to draw better conclusions about the SPP for drug combinations using a different compound property that is supported by the SPP

Future Work

- Clustering of response matrices- group together the drug combinations based on which have similar response matrices
- Work on SPP within specific clusters
- Perform more analysis:
  - Data for other medical conditions in addition to this work on Malaria,
  - Larger overall volume of data



References

[1] Nikolaus J. Sucher (2014). Searching for synergy in silico, in vitro and in vivo. *Synergy*, 1(1), 30-43.

[2] Yvonne C. Martin, James L. Kofron, Linda M. Traphagen (2002). Do Structurally Similar Molecules Have Similar Biological Activity? *Journal of Medicinal Chemistry*, *45* (19), 4350-4358.

[3] Rajarshi Guha, John H. Van Drie (2008). Structure-Activity Landscape Index: Identifying and Quantifying Activity Cliffs. *Journal of Chemical Informatics and Modeling*, 48(3), 646-658.

[4] Stephen E. Syrjala, (1996). A Statistical Test for a Difference between the Spatial Distributions of Two Populations. *Ecology, 77*(1), 75-80.

[5] Lawrence I-Kuei Lin. (1989). A Concordance Correlation Coefficient to Evaluate Reproducibility. *Biometrics, 45*(1), 255-268.