



## 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

  Response Matrix
- Better effect: synergism
- Same effect: additive
- Worse effect: antagonism

## **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 <sup>1</sup>
- Three Models:
- 1. Highest Single Agent (HSA)
- 2. Bliss Independence Model
- 3. Loewe Additivity Model
- Used Bliss Independence Modelconvenient and more robust in a high throughput screening setting
- Synergistic- more blue; Antagonistic more red

### Similarity Property Principle (SPP)

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

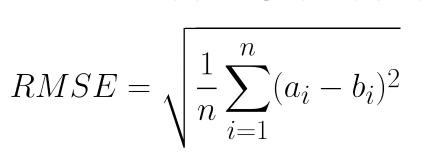
## Questions

- 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

Root Mean Standard Error



2. Euclidean Distance

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

3. Two- Sample Kolmogorov-Smirnov Test

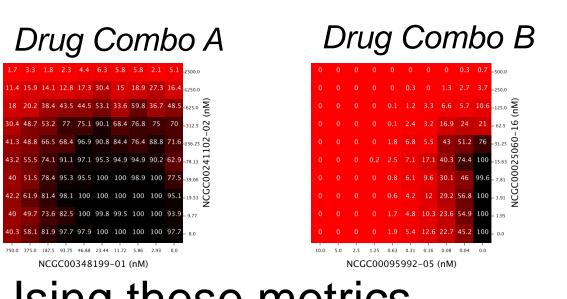
## Methods Sensitive to Spatial Distribution

Drug X

Synergy Matrix-

△ Bliss

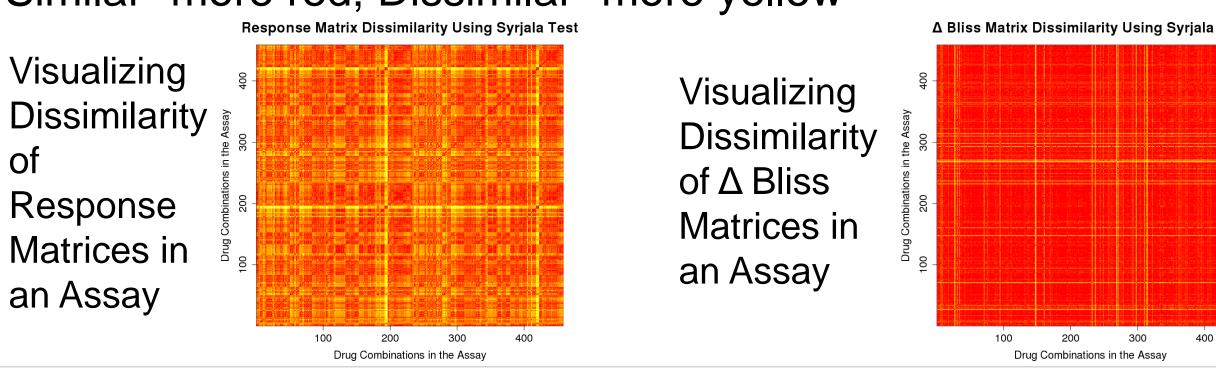
4. Syrjala Test <sup>4</sup>



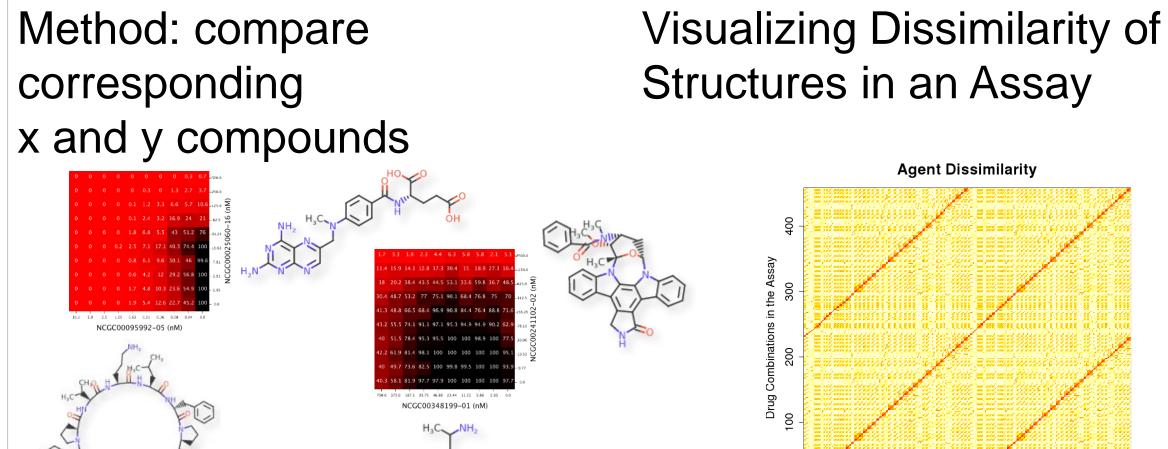
Using these metrics, dissimilarity was computed for all pairs of drug combinations

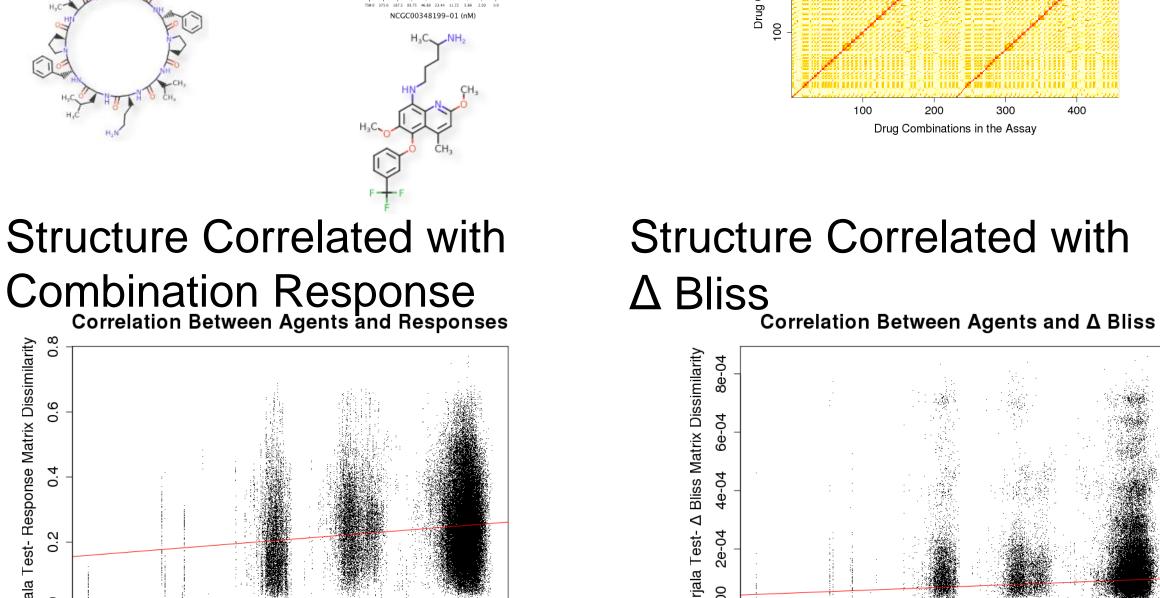
## Q1: Visualizing Dissimilarity in an Assay

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

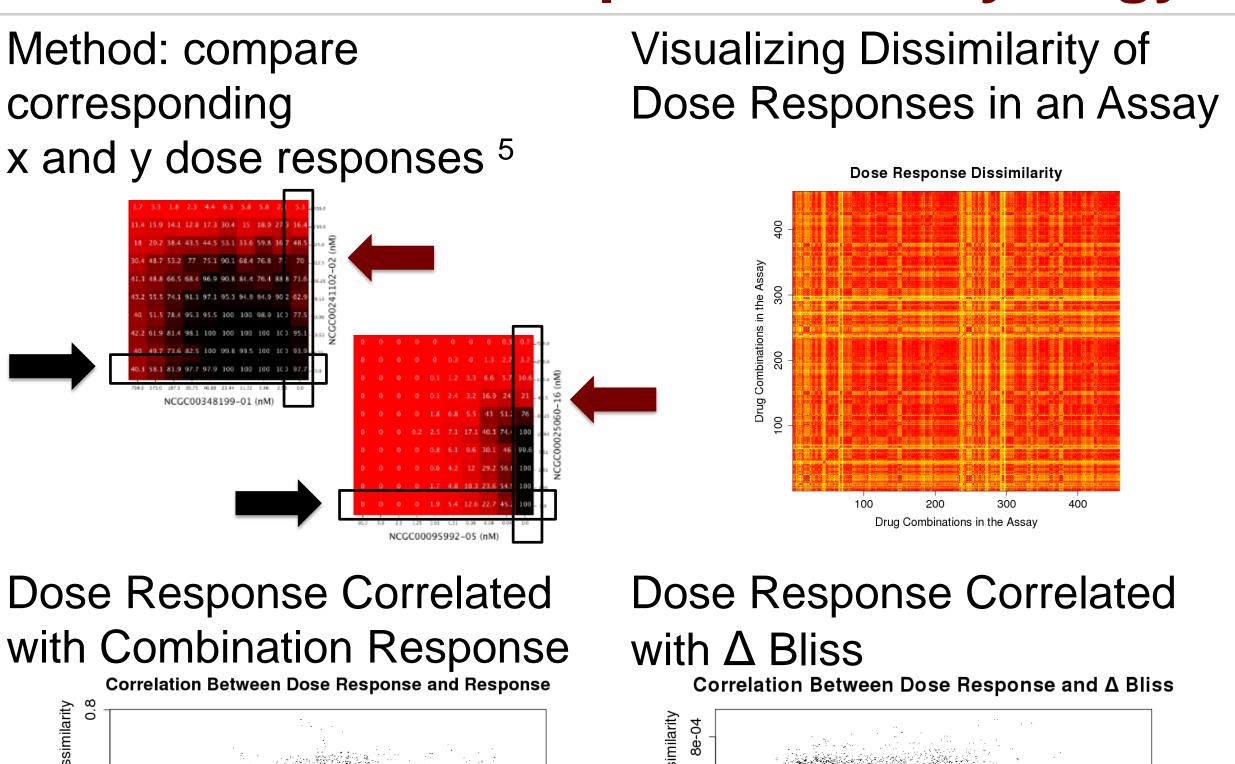


## Q2: Chemical Structure Correlated with Combination Response and Synergy





# Q3: Dose Response Correlated with Combination Response and Synergy



Dose Response Dissimilarity

Dose Response Dissimilarit

## Conclusion

### **Individual Compounds:**

- We might expect structural similarity to correlate with dose response similarity
- However, these do not correlate (R<sup>2</sup> = 0.014; no correlation)
- Suggests that using dose

   Suggests that using dose
   response as the compound property does not appear to be supported by the SPP

## **Drug Combinations:**

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

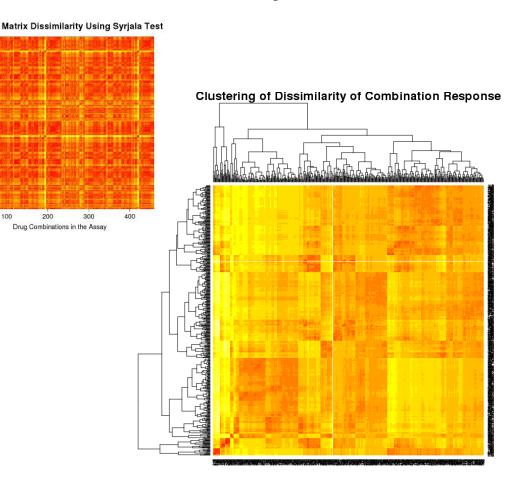
## Discussion

#### 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

- <sup>1</sup> Nikolaus J. Sucher (2014). Searching for synergy in silico, in vitro and in vivo. *Synergy*, 1(1), 30-43.
- <sup>2</sup> 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.
- <sup>3</sup> 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.
- <sup>4</sup> Stephen E. Syrjala, (1996). A Statistical Test for a Difference between the Spatial Distributions of Two Populations. *Ecology, 77*(1), 75-80.
- Populations. Ecology, 77(1), 75-80.
   Lawrence I-Kuei Lin. (1989). A Concordance Correlation Coefficient to Evaluate Reproducibility. Biometrics, 45(1), 255-268.