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

(brief overview)

There are several medical conditions such as HIV, malaria, and cancer where the response in patients is better when drugs are used together in treatment. This better outcome is called a synergistic effect of the drug combination- the combined effect of the drugs is better than what it would be compared to the drugs’ individual effects. Traditionally, screening for drug combinations has been a slow process. Better understanding which drug combinations show synergistic effects is important for more effective treatments in patients. It is known that similar compounds show similar activities or have similar properties, an important concept in cheminformatics called the Similarity Property Principle. However, it is unclear if this is also true for combinations of drugs.

Since NCATS uses high throughput screening (HTS), data for thousands of drug combinations can be generated quickly. Screening a drug combination at incrementing levels of each drug results in a response surface. Having thousands of response surface presents the opportunity to do large scale analysis. I had the opportunity this summer to intern for NCATS where I worked on the analysis aspect to see if similar drug combinations have similar properties.

(more detailed steps if necessary)

In order to show that the similarity property principle holds for drug combinations, two correlations should exist. Comparing chemical structures will show how dissimilar drug combinations are. Comparing single agent dose responses will show how dissimilar their activities are. If both of these correlate to the how dissimilar the two response surfaces are, then it may suggest the similarity property principle holds true for drug combinations.

The process to answer this question requires several steps. The concept of synergy has been introduced, but there are different models of synergy that were important to investigate including: highest single agent, bliss independence model and Loewe additivity model. In the context of high throughput screening, bliss independence model is the most robust and appropriate. The rest of the analysis was done based using it as the model for synergy. Then, there is the question of characterizing how different, or dissimilar, the responses of two different drug combinations are. There are several methods to characterize how dissimilar two matrices are that we explored including: Root Mean Standard Error, Euclidean Distance, and two- sample Kolmogorov-Simonov test. However, the three of these are insensitive to the spatial distribution across the matrix. In the context of comparing the shapes within the numbers of the two matrices, how the numbers exist in relation to each other, or the spatial distribution is critical. In response to this issue, the Syrjala Test was used to compare matrices.

The next step was to see if there was a correlation between dissimilarity of the chemical structures of the drug combinations and the dissimilarities of the combinations responses. To calculate dissimilarity of chemical structures, corresponding x agents and corresponding y agents were compared based on their fingerprints using the circular method. Then, the average was taken of the two values. This was repeated for all pairs of drug combinations. There was not a correlation found between dissimilarity of chemical structure in drug combinations and their corresponding response matrix dissimilarities (R2 = 0.0198) or synergy matrix dissimilarities (R2 = 0.0056 ).

This process was repeated to find out if there was a correlation between the dissimilarity of the dose responses and the dissimilarities of the combinations responses. Comparing dose responses was done using Lin’s Concordance Correlation Coefficient. There was a correlation found between dissimilarity of dose responses in drug combinations and their corresponding response matrix dissimilarities (R2 = 0.4365), but not synergy matrix dissimilarities (R2 = 0.0521).

For the Similarity Property Principle to hold, both of these would have to correlate, but that was not the case. This means that the SPP does not appear to hold for drug combinations and suggests that combinations responses are not a simple function of the individual agent responses. Understanding and comparing drug combinations is more complex than individual compounds.

To further the analysis, we went back and looked at the data for the individual compounds within the assays we were working with for this analysis. We might expect structural dissimilarity to correlate with dose response dissimilarity, but that was not the case (R2 = 0.0141). This suggests that using dose response as the compound property does not appear to be supported by the SPP. This presents a limitation. For future work it would be important to use a compound property that does illustrate the SPP well in individual compounds in order to draw better conclusions about drug combinations.

Another way to look at the data is to group together similar response surfaces and see if the compounds are targeting some type of similar underlying biological pathways. The underlying biological target of a drug can be characterized by the Gene Ontology (GO) terms. There are different ways to determine the number of clusters that is appropriate for the dataset. One mathematical method is to optimize the average silhouette width of different numbers of clusters. Another more biological method is to optimize the similarity of the Gene Ontology (GO) terms for different numbers of clusters. We were able to do some preliminary analysis of comparing the biology of one cluster compared to the other clusters and would like to do more in the future. For future analysis, it is important to note that for this method only works for targets that have GO terms associated with them.

Additionally for future work, we want to analyze larger, more diverse volumes of data to strengthen any conclusions.