A data driven approach to predict pairwise drug synergy within cancer

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Combination therapies for various cancers have been shown to increase efficacy, lower toxicity and escape resistance. However, systematically interrogating all possible synergistic therapies is experimentally unfeasible due to the sheer volume of possible combinations. Here, we apply a novel big data approach in the evaluation and ultimately the prediction of drug synergy by using the recently released NCI-ALMANAC, the largest publically available synergic drug efficacy dataset to date. The NCI-ALMANAC has pairwise tested over a 100 diverse drugs within 60 cancer cell lines. Using this data we aim to answer numerous different questions:

1. What characteristics attribute to drug synergy between two drug partners and can we begin to understand the mechanism of drug synergy?
2. Is drug synergy context specific or widespread throughout diverse cancer types?
3. Can drug similarity be leveraged to predict synergy or antagonism between drugs?

Synergistic and antagonistic drug pairs varied in many drug similarity features, demonstrating a difference in their underlying biology and mechanism.

Conclusions

• Pairwise drug synergy is context specific - with little overlap between cell lines from differing primary sites. Therefore, strengthening the need for a predictive computational method.
• Drug pair synergy was also related to the class of drugs, which leads to structure similarity between drugs being predictive of combination results.
• Numerous drug similarity metrics are predictive of drug synergy. Drug structure and target similarity were among the top predictive features.
• A multi-task machine learning model best predicts drug synergy and antagonism by taking into account cellular context.
• Without prior experimental data this model can predict context specific synergistic drug combinations.