

Network Synergy Project Intro

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Synergy via Potency

Just a simple visualization of Bliss Synergy.

Promises of Synergistic Combinations

- Overcoming chemoresistance
- Repurposing existing drugs
- Increasing efficacy
- Reducing toxicity

And then I do the bit where I say that potency synergy only actually enables consideration of the first 3.

XKCD comic about killing cancer cells with a handgun.
Other avenues are needed to more accurately predict clinical benefits of drug combinations in early in vitro experiments.

Synergy via Biological Networks

Consider the effects of drugs on a biological network, such as a GRN.
Image of a network.
Enables qualitative assessment of drug interaction.

Module Approach



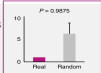
Antihypertensive
Combinations
(FDA-approved, ClinicalTrials.gov,
& pre-clinical literature)

Adverse drug
interactions
(high-blood pressure)

a Overlapping exposure



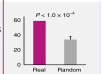
Number of drug pairs



b Complementary exposure



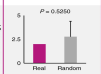
Number of drug pairs



c Indirect exposure



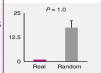
Number of drug pairs



d Single exposure



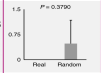
Number of drug pairs



e Non-exposure



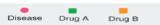
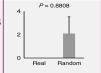
Number of drug pairs



f Independent action



Number of drug pairs



CANCER
DRUG COMBINATIONS

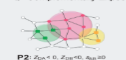
a Overlapping Exposure



Number of drug pairs



b Complementary Exposure



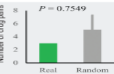
Number of drug pairs



c Indirect Exposure



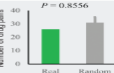
Number of drug pairs



d Single Exposure



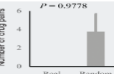
Number of drug pairs



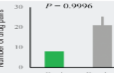
e Non-exposure



Number of drug pairs



Number of drug pairs



Module Approach - Further Directions

The Barabasi paper only really discusses efficacy of the principles via approved drug combinations — biased.

Try to expand on this method by:

- Performing network analysis of drug combinations (0, A, B, AB) in various principles.
- Considering Tumor Microenvironments (TMEs).
- Similarity scores were reduced to binary ≥ 0 or < 0 — do smaller/larger similarity scores make a difference?

Quantitative Approach

Apply the concepts of Potency Synergy onto biological networks.

- Which genes/proteins/metabolites are over/under-active in the combination, relative to what we would expect from the monotherapies?
- GSEA \Rightarrow Which cell functions are over/under-active?

Does this method provide any benefit over the Module Approach? What is the drug module of AB — is it greater than $A \cup B$?

Network Synergy in TMEs

Cancer cells are not the only part of the tissue that contribute to cancer activity.

Reinclude fig from "Module Approach"

TMEs may expand and specialize the disease module into modules $D_1, \dots D_K$. What network principles do we see with these TME modules?

Multiplex Implantable Microdevice Assay

(This is the Joe Gray paper)

Utilizes spatial analysis of the TME to predict efficacious combinations of targeted/chemotherapeutic drugs with immunotherapy.

"multiplex immunostaining and imaging process that measures the expression levels of > 30 different protein markers in each cell. Computational analysis of the resulting multiplex images provided information about drug-induced changes in the compositions, functional states and organizations of the tumor and TME cells. These measurements provided mechanistic insights that were used to select drug combinations that were predicted to be effective when administered systemically. These combinations included targeting treatment-resistant cancer stem cells."

Never mentions networks. What principles are exhibited in these data?

Predicting in vivo efficacy

More generally, the goal of this project is to develop a metric that is:

- Inexpensive to obtain
- Simple to calculate
- Predictive of *in vivo* outcomes

As a result, would likely need either to conduct *in vivo* (e.g. murine) studies, or try to utilize existing data.