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.

Relevant XKCD

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

Include figs from Barabasi paper.
Discuss the different principles.

Module Approach - Further Directions

The Barabasi paper only really discusses efficacy 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).

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 $D_1, \ldots D_K$. 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?