Modelling drug combinations for cancer

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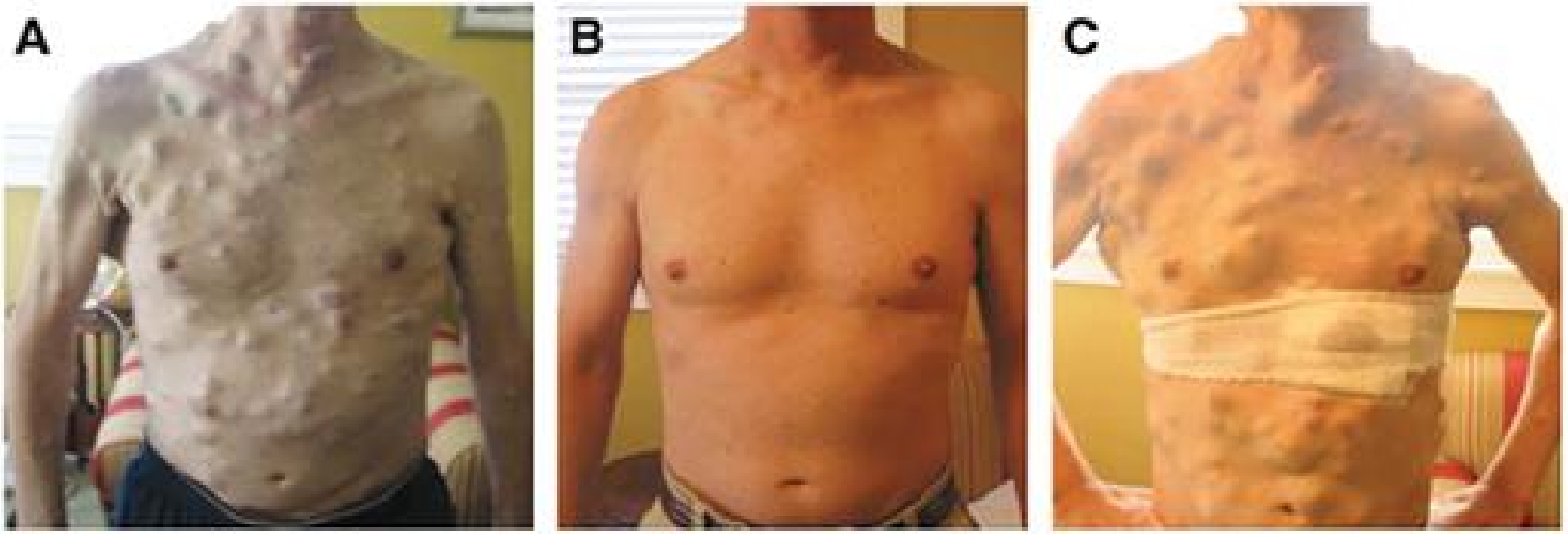
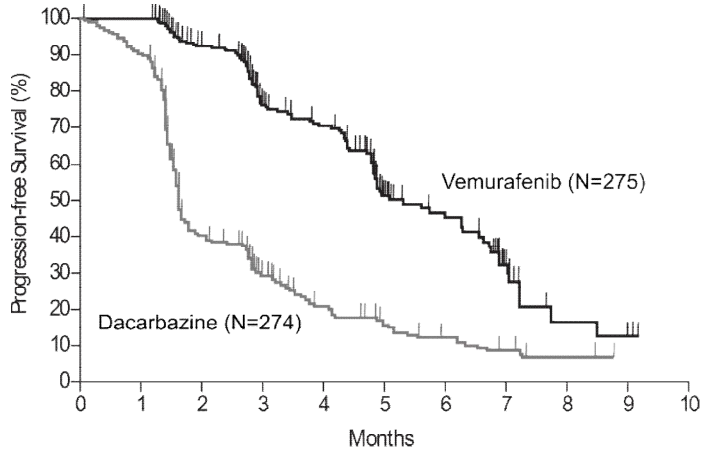
Fighting cancer





Chapman *et al.,* 2011. N. Engl. J. Med., 364, 2507-2516

EDITORS' CHOICE | CANCER

Two Drugs Are Better than One—Modeling Drug Combinations in Cancer Therapy

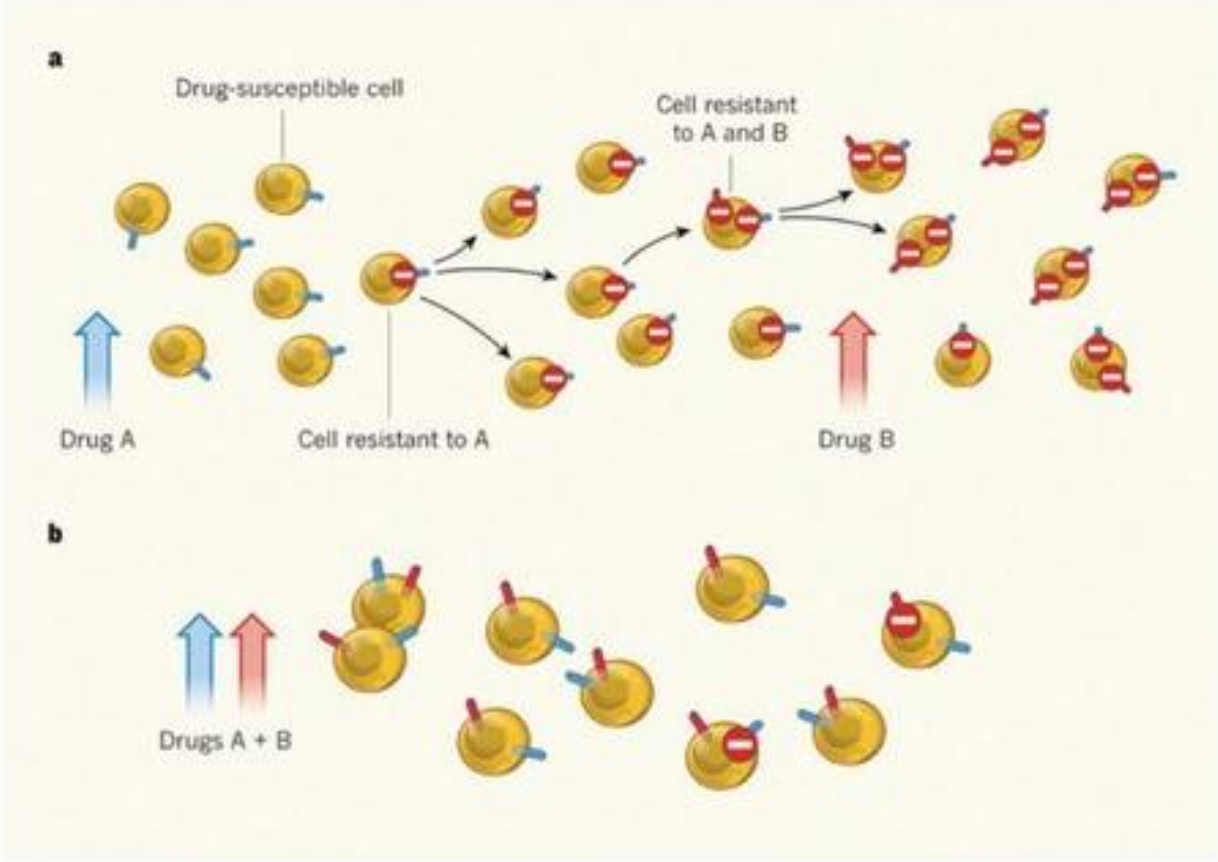
Margaret K. Callahan

+ Author Affiliations

Science Translational Medicine 17 Jul 2013:
Vol. 5, Issue 194, pp. 194ec116
DOI: 10.1126/scitranslmed.3006923

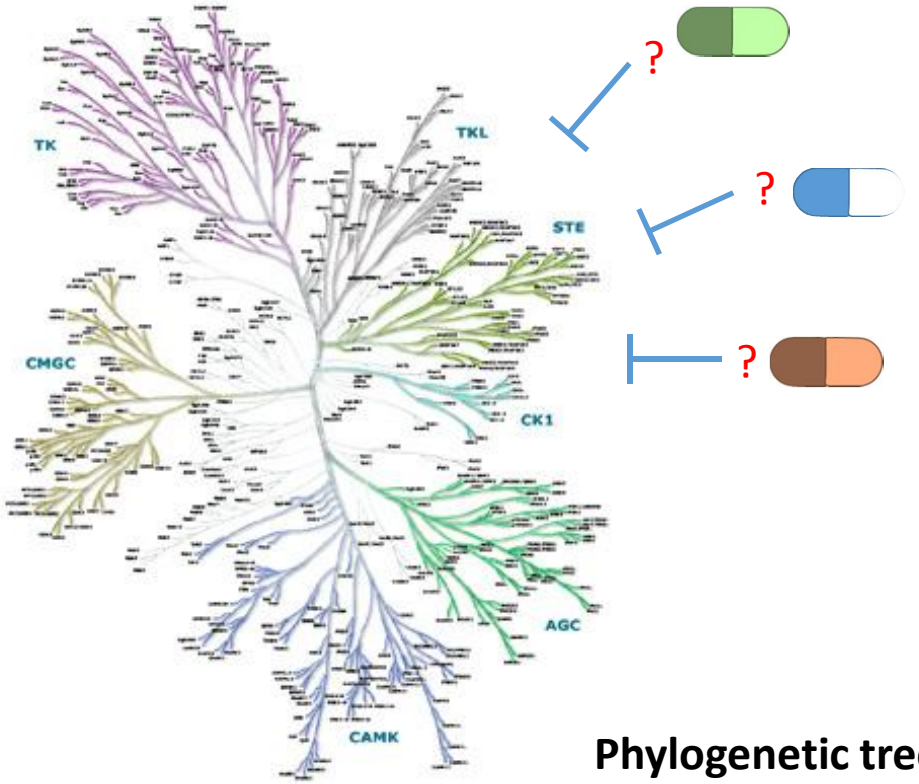
+ Maximize cancer selectivity

- Minimize drug resistance



Needs for predictive and testable models

- **If it is necessary to inhibit multiple targets, how do we choose/predict which ones?**



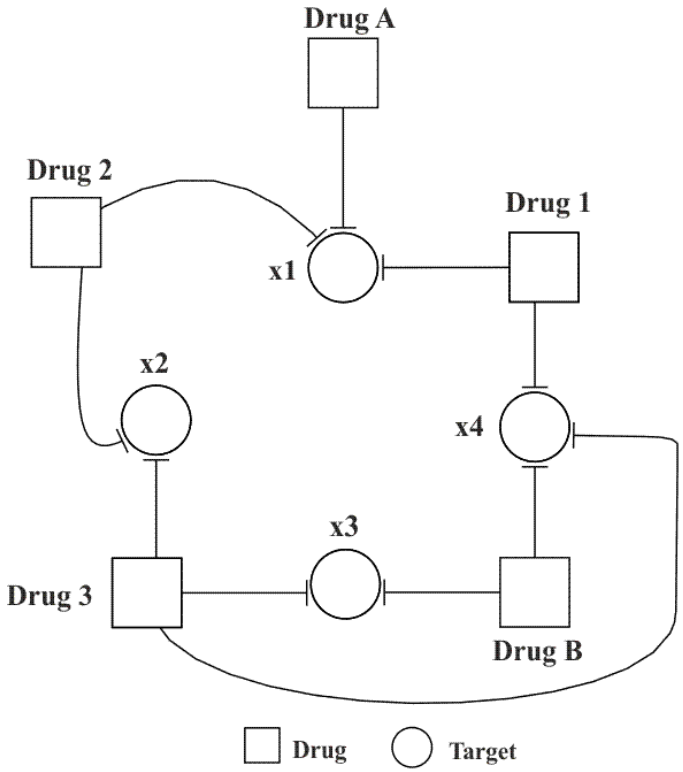
Phylogenetic tree of the human kinome

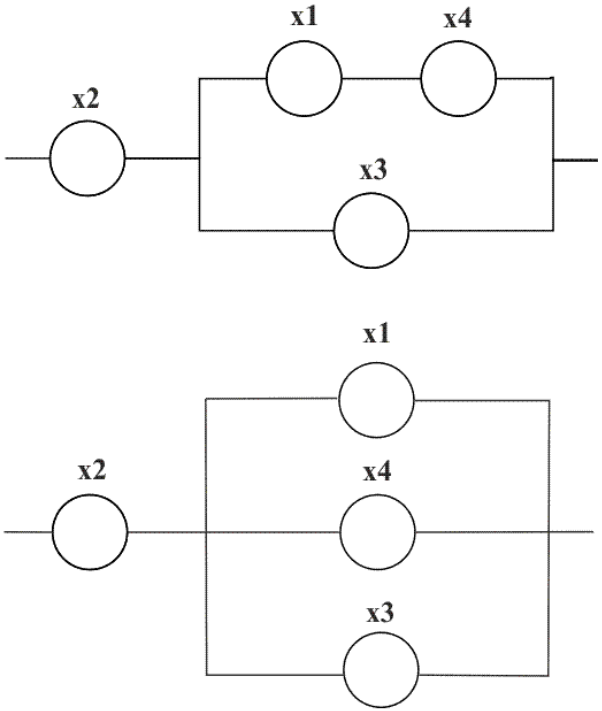
http://www.cellsignal.com

The research questions

- If drug A kills 30% of the cancer cells and drug B kills 20%, can we answer the following questions:
  1) What is the effect if drug A and B are combined?
  2) Whether such a combinatorial effect is beneficial compared to monotherapies?
  3) How to evaluate the statistical and therapeutic significances?

Target inhibition network approach





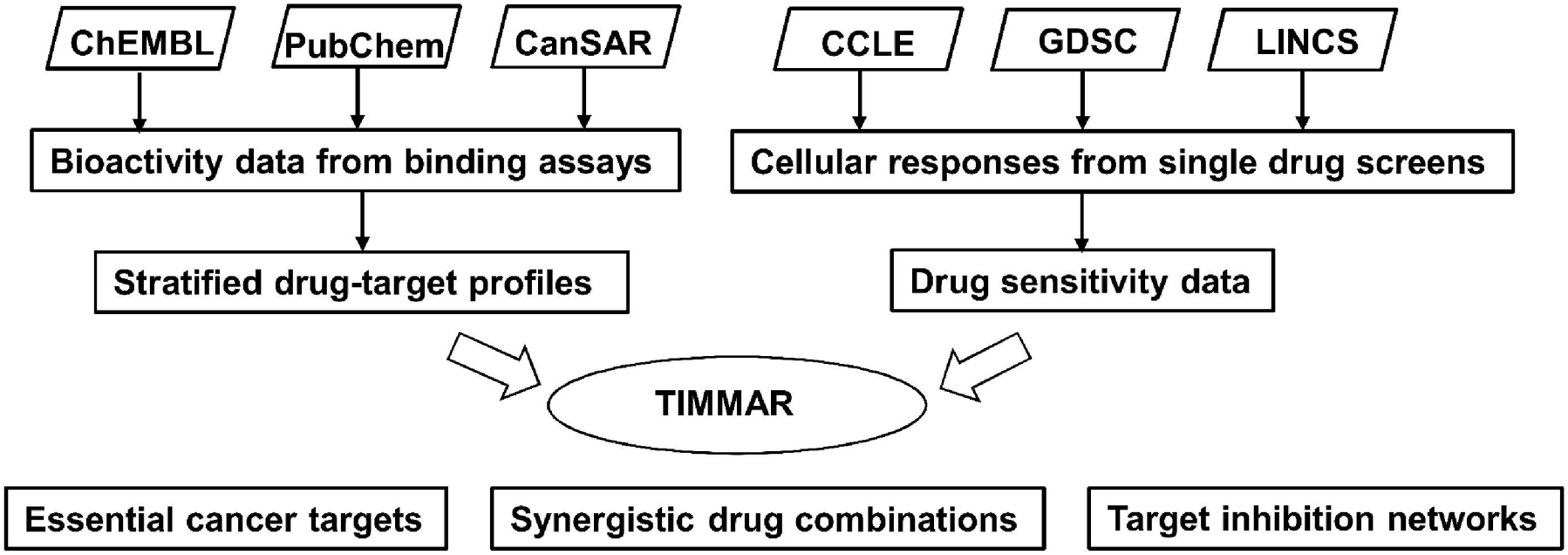
Drug target network + Drug sensitivity data = Target inhibition network

Assumption: A drug combination can be inferred from their target combinations

Pal and Berlow, 2012, Pacific Symposium on biocomputing, 351-362

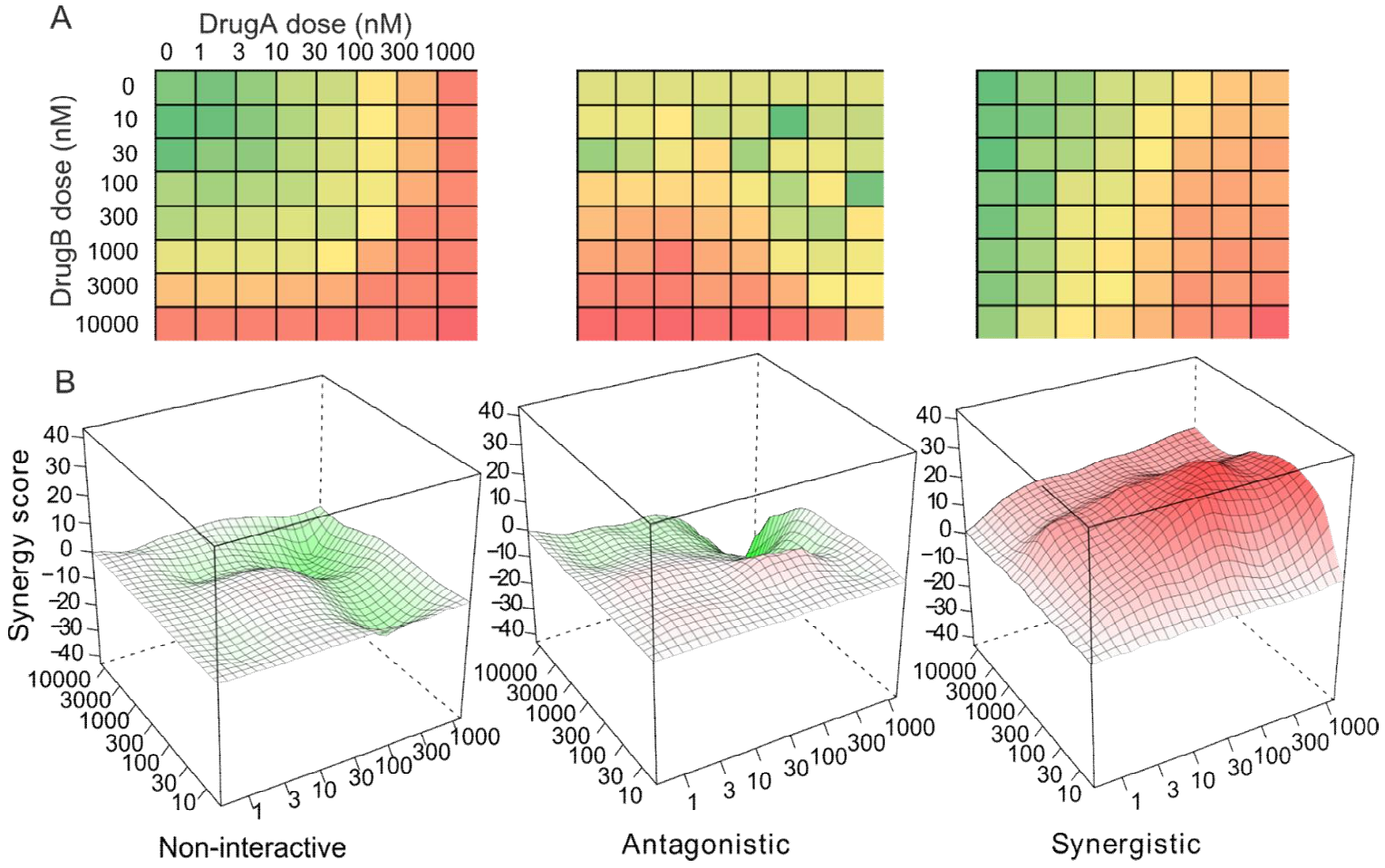
Tang et al. PLoS Comput Biol 2013; 9(9): e1003226.

TIMMA @R



He et al. Bioinformatics 2015; 31, 1866-1868.

Test of drug combinations



$y_c = y_{EXP}$ $y_c < y_{EXP}$ $y_c > y_{EXP}$

Tang, et al., 2017; Methods Mol. Biol. 1636:485-506.

Test of drug combinations

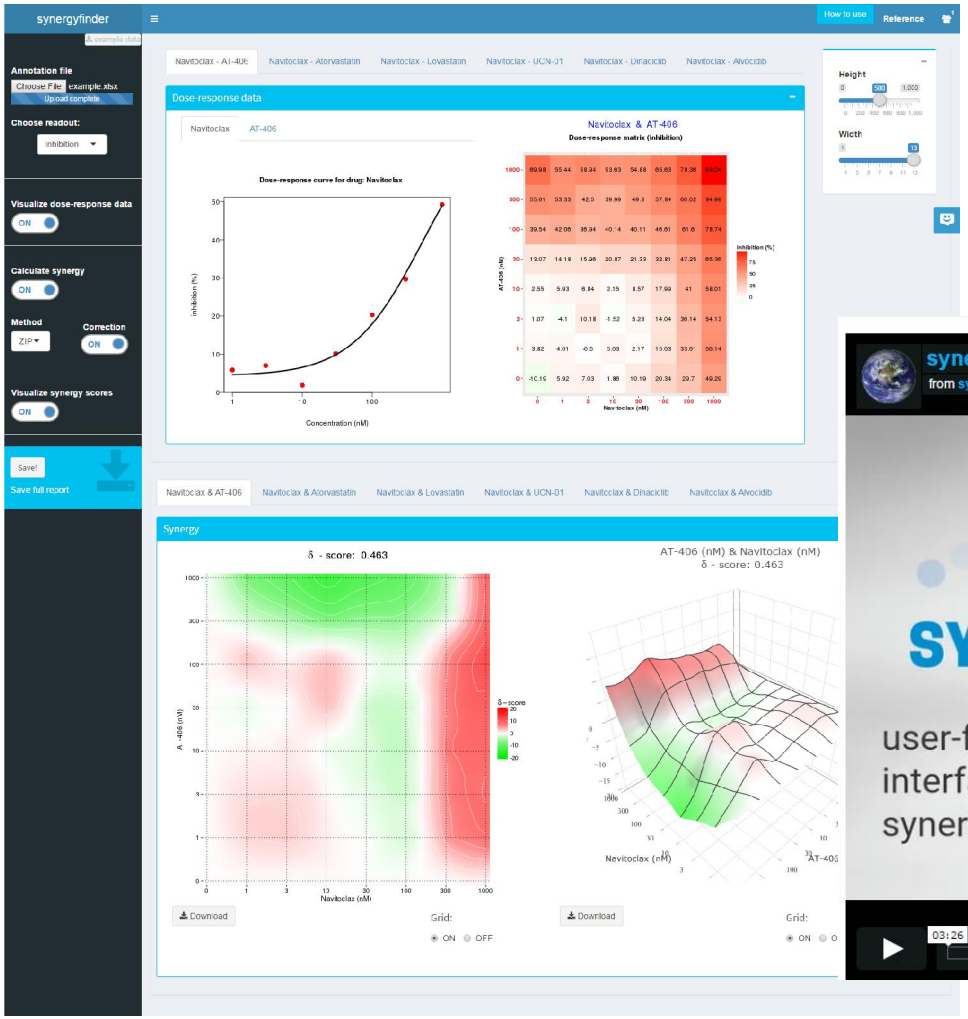
Reference models

- Highest single agency $y_{\mathrm{HSA}} = \max(y_1, y_2)$
- Bliss independence $y_{\mathrm{BLISS}} = y_1 + y_2 - y_1 y_2.$
- Loewe additivity $\frac{x_1}{X^1_{\mathrm{LOEWE}}} + \frac{x_2}{X^2_{\mathrm{LOEWE}}} = 1,$
- Zero interaction potency

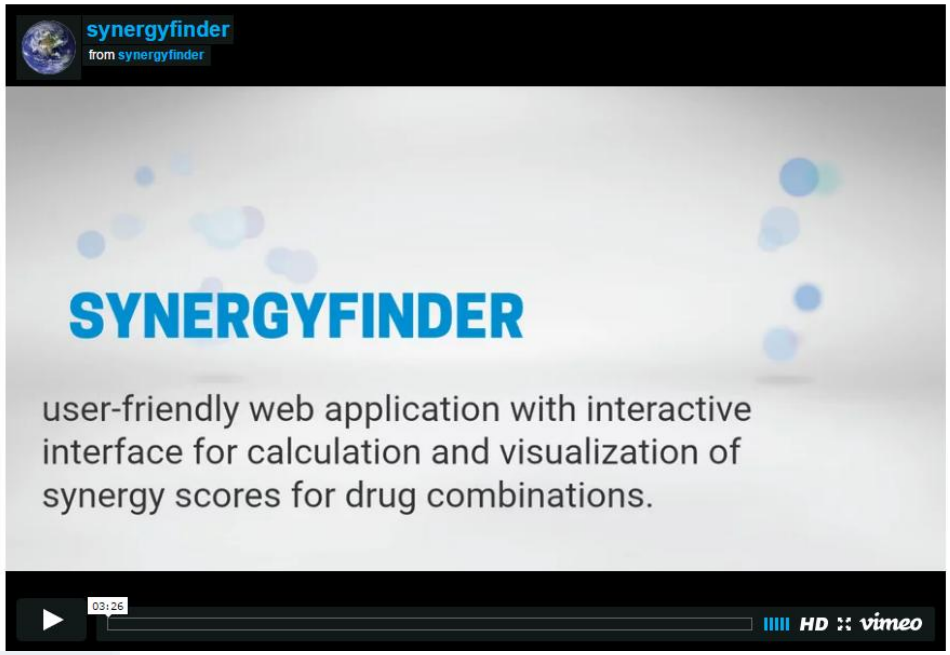
$$\delta(\theta) = \frac{1}{2}\left(\frac{\frac{1}{1+(\frac{m_2}{x_2})^{\lambda_2}} + (\frac{x_1}{m_{2\to1}})^{\lambda_{2\to1}}}{1+(\frac{x_1}{m_{2\to1}})^{\lambda_{2\to1}}} + \frac{\frac{1}{1+(\frac{m_1}{x_1})^{\lambda_1}} + (\frac{x_2}{m_{1\to2}})^{\lambda_{1\to2}}}{1+(\frac{x_2}{m_{1\to2}})^{\lambda_{1\to2}}} \right) - \left(\frac{(\frac{x_1}{m_1})^{\lambda_1}}{1+(\frac{x_1}{m_1})^{\lambda_1}} + \frac{(\frac{x_2}{m_2})^{\lambda_2}}{1+(\frac{x_2}{m_2})^{\lambda_2}} - \frac{(\frac{x_1}{m_1})^{\lambda_1}}{1+(\frac{x_1}{m_1})^{\lambda_1}} \frac{(\frac{x_2}{m_2})^{\lambda_2}}{1+(\frac{x_2}{m_2})^{\lambda_2}} \right),$$

He et al. Methods Mol. Biol. In press
Ianevski et al. Bioinformatics, 2017, 33, 2413-2415

SynergyFinder @Bioconductor @web



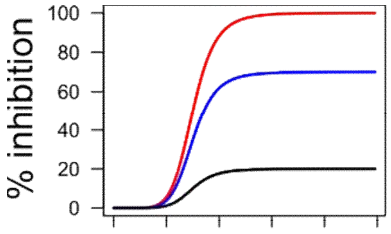
https://synergyfinder.fimm.fi



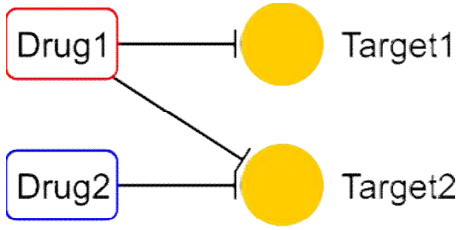
Ianevski et al. Bioinformatics, 2017, 33, 2413-2415

The drug combination prediction pipeline

Input

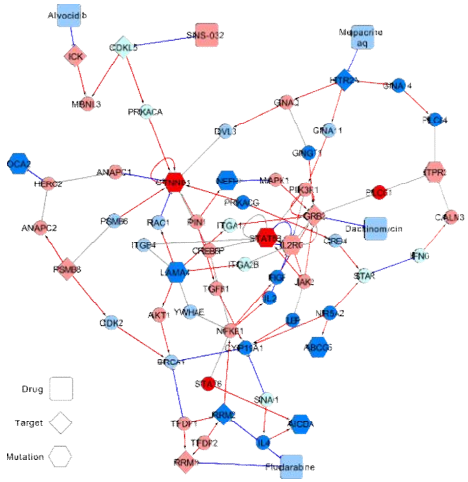


Single drug responses

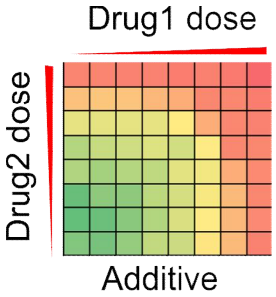


Drug-target interactions

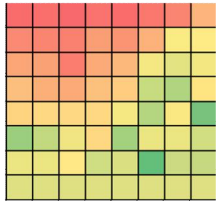
Modeling/ Prediction



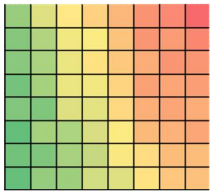
Validation



Additive



Antagonistic



Synergistic

Data curation → TIMMA → SynergyFinder

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