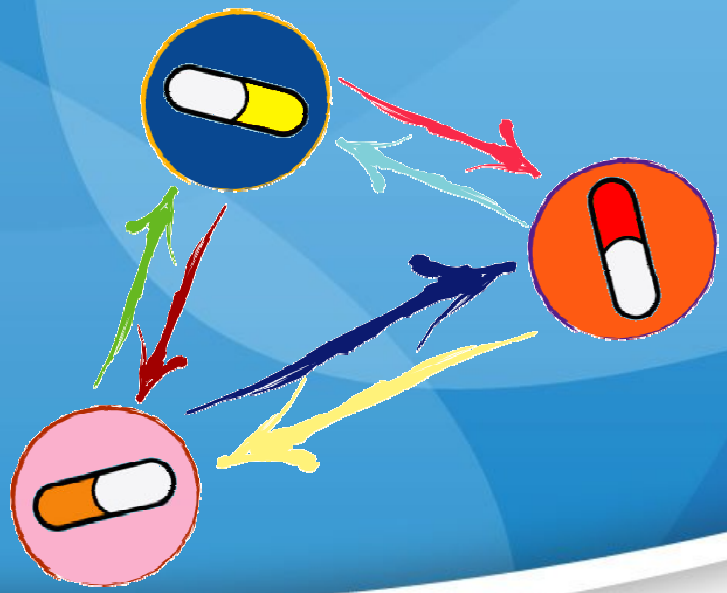
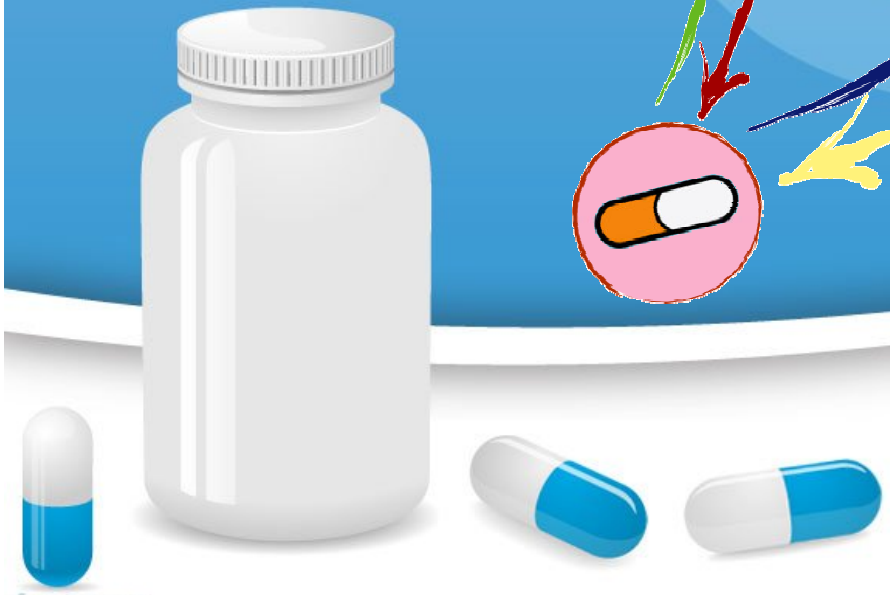
Functional classification of drugs by properties of their pairwise interactions

Pamela Yeh, Ariane I. Tschumi and Roy Kishony, *Nature Genetics*, 2006

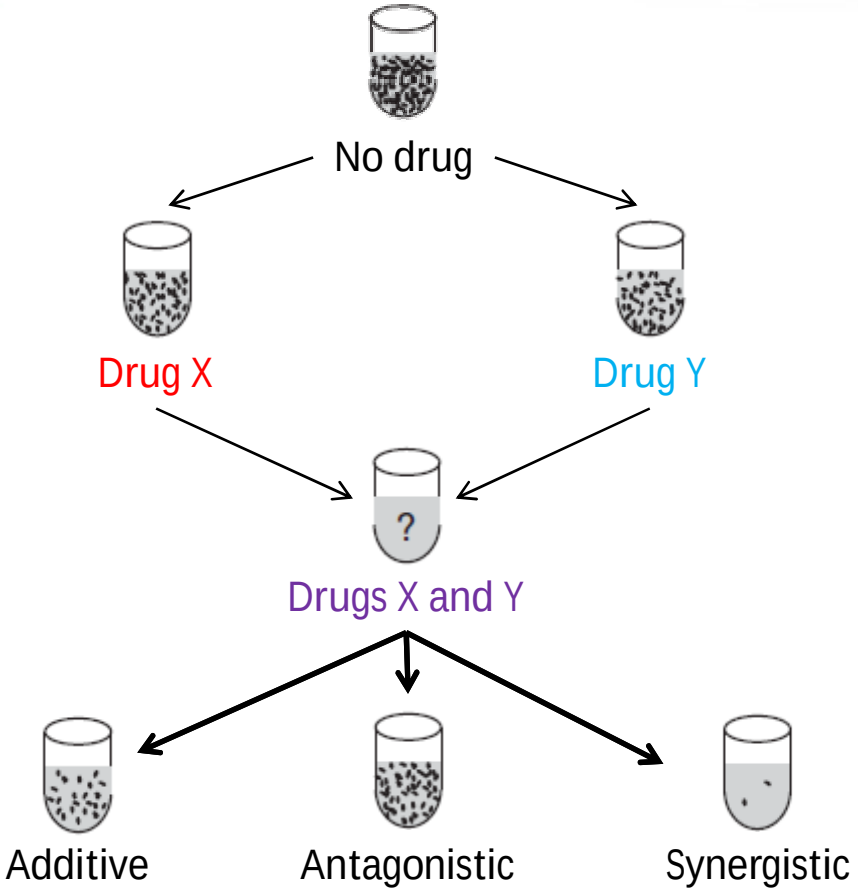


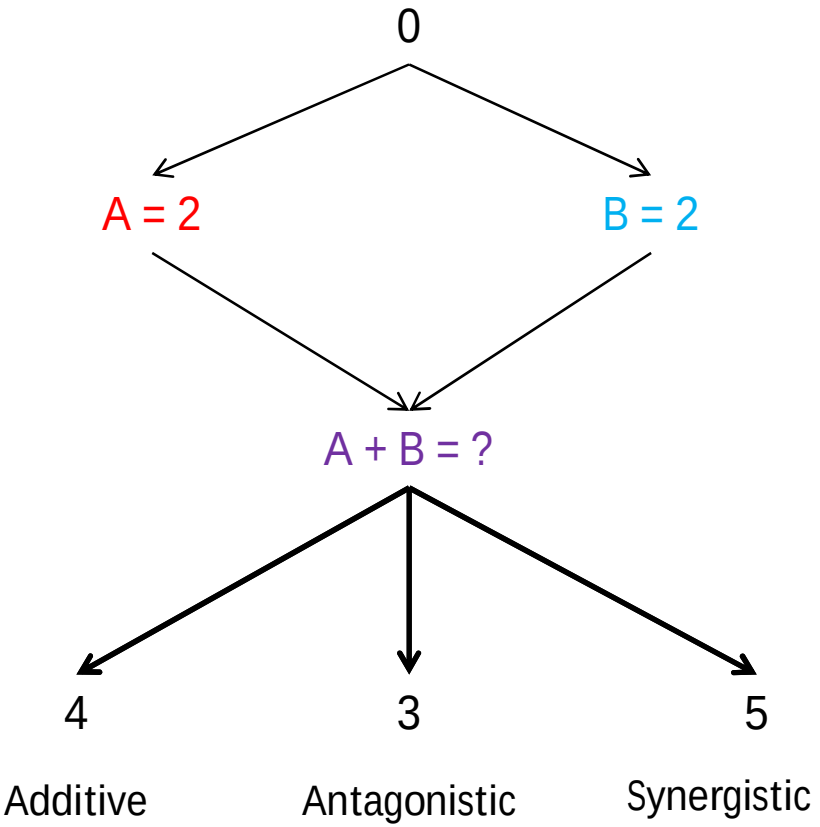


Iryna Nikolayeva
David Fuente Herraiz
Cyprien Verseux

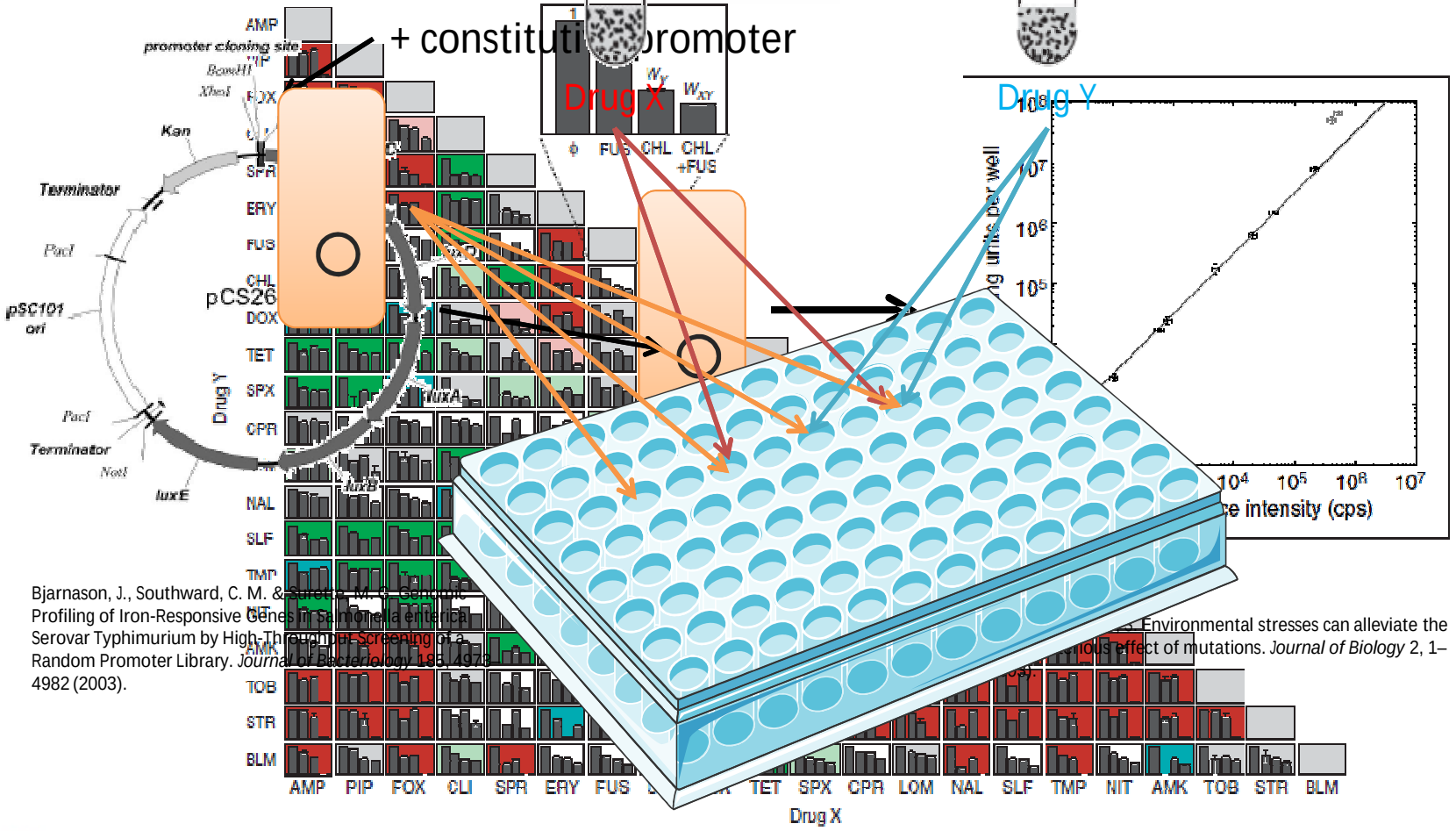
mSSB, December 2012

Interaction-based classification





Pairwise interaction experiments

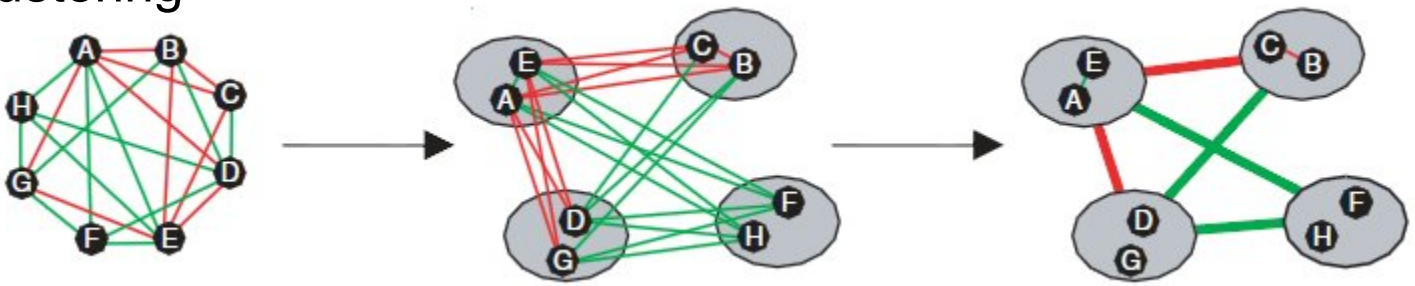


Bjarnason, J., Southward, C. M. & Surette, M. G. Genomic Profiling of Iron-Responsive Genes in Salmonella enterica Serovar Typhimurium by High-Throughput Screening of a Random Promoter Library. *Journal of Bacteriology* 185, 4973–4982 (2003).

Environmental stresses can alleviate the ...ious effect of mutations. *Journal of Biology* 2, 1–...

Network creation

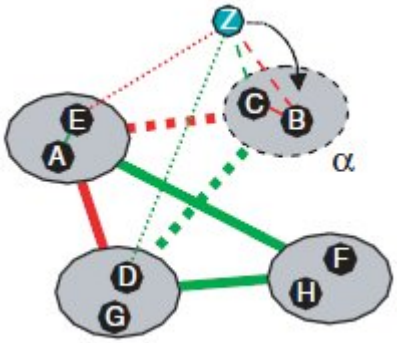
- Clustering



Ungrouped

Clustered

- Adding a new drug

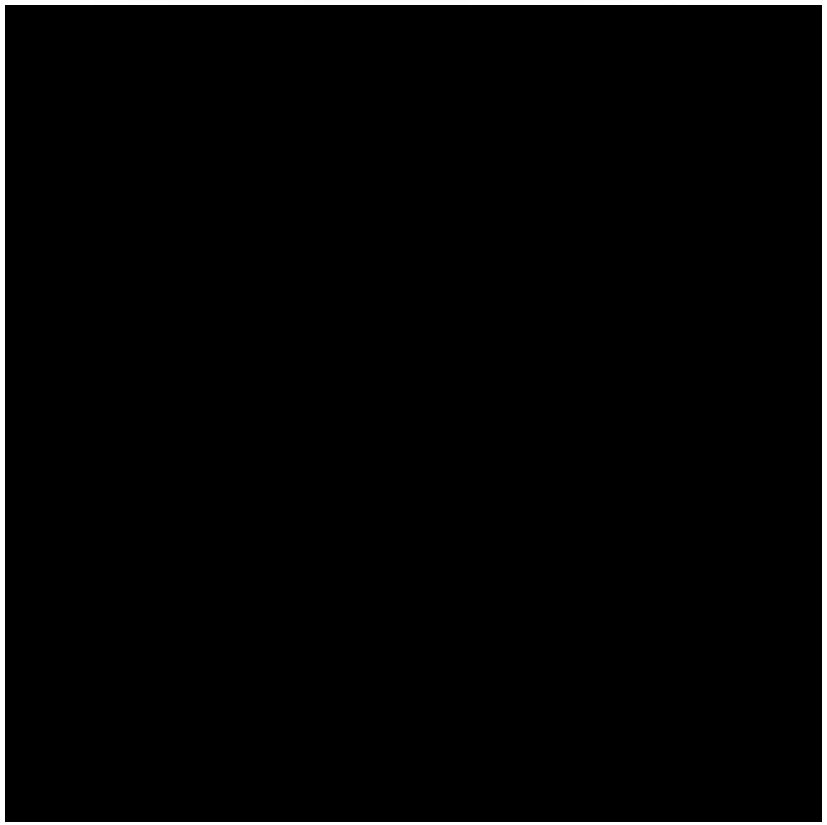


Main clustering rules

1. Mixed intraclass interactions
2. Non conflictive interclass interactions

Prism Algorithm

Video

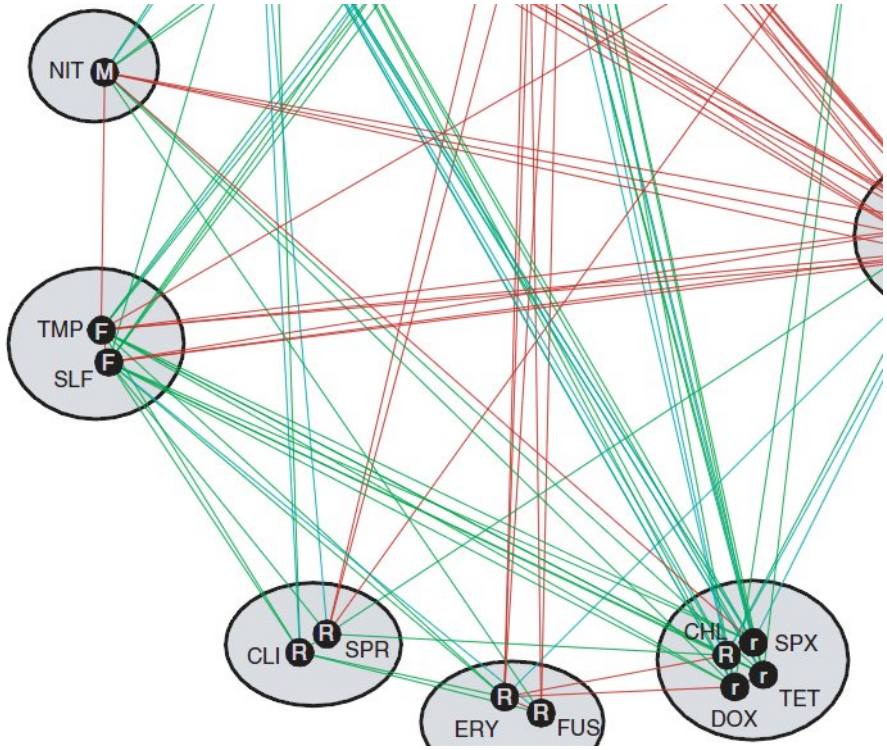


http://www.nature.com/ng/journal/v37/n1/extref/ng1489-S11.avi

Prism Algorithm

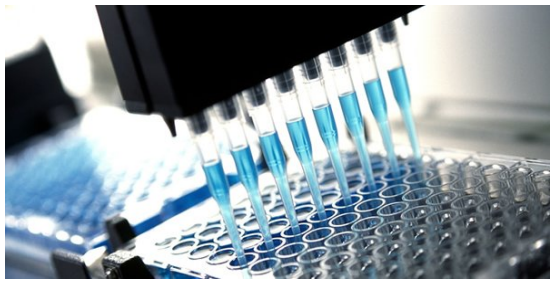
Prism II:

- Monochromaticity is not strictly enforced



Methods

- Bioluminescence technique



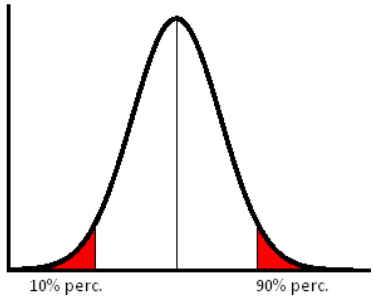
- Dosage fine-tuning

- Well replicates

  - 100 no drugs
  - 16 single drugs
  - at least 2 for each double-drug combination

- Normalized Growth rate: WiC = giC / gΦ (Exp. growth)

  - 10%, 90% percentiles as WminC and WmaxC, with n > 10
  - Direct values for WminC and WmaxC, with n < 10

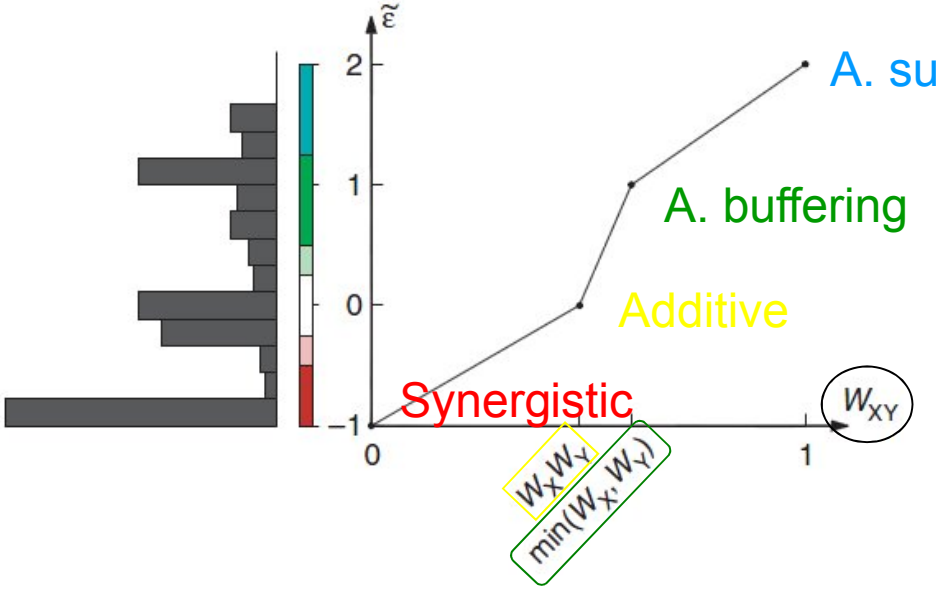


Interaction classification

$$0 < W_{XY} < W_X W_Y \qquad \tilde{\varepsilon} = (W_{XY} - W_X W_Y) / W_X W_Y$$

$$W_X W_Y < W_{XY} < \min[W_X, W_Y] \qquad \tilde{\varepsilon} = (W_{XY} - W_X W_Y) / |\min[W_X, W_Y] - W_X W_Y|$$

$$\min[W_X, W_Y] < W_{XY} \qquad \tilde{\varepsilon} = (W_{XY} - \min[W_X, W_Y]) / (1 - \min[W_X, W_Y]) + 1$$



Interaction classification rule

$\tilde{e}_{max} < -0.5$ ⇨ Synergistic

$\tilde{e}_{min} > 0.5$ ⇨ Antagonistic

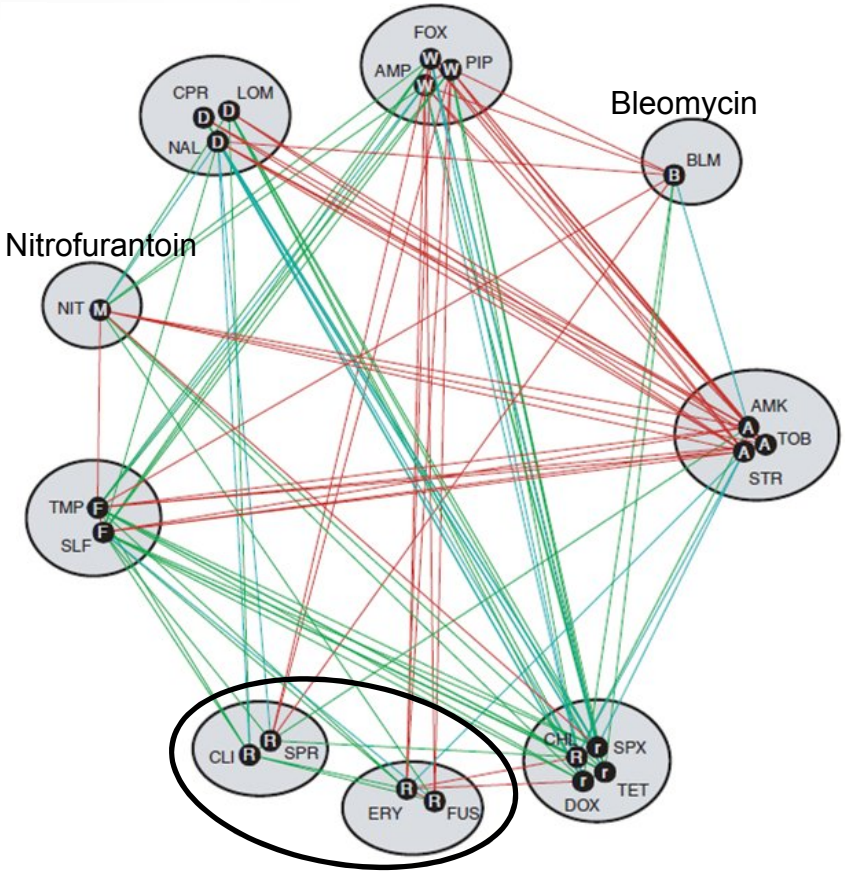
Results

✓ Drugs clustered in classes that interact monochromatically.

✓ Classification correponds almost perfectly to the function they target.

✓ Higher level classifications are also enabled.

Results depend on concentrations of drugs and chosen ε values



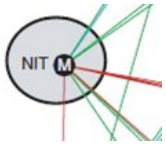
Inhibition of protein synthesis via 50S ribosomal subunit

Putative uses

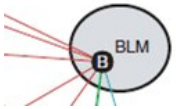
- Classification of drugs:

From drug-drug level to functional classes' level

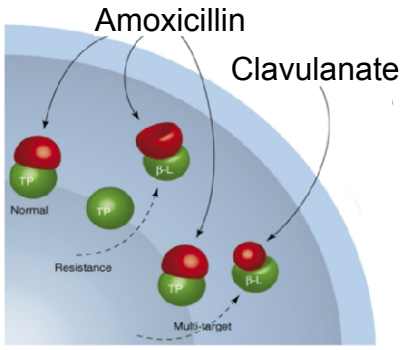
- Detect multi-functionnal drugs?
- Identify drugs with novel mechanisms of action
- Suggest drug combinations
- Study gene-environment interactions



Nitrofurantoin



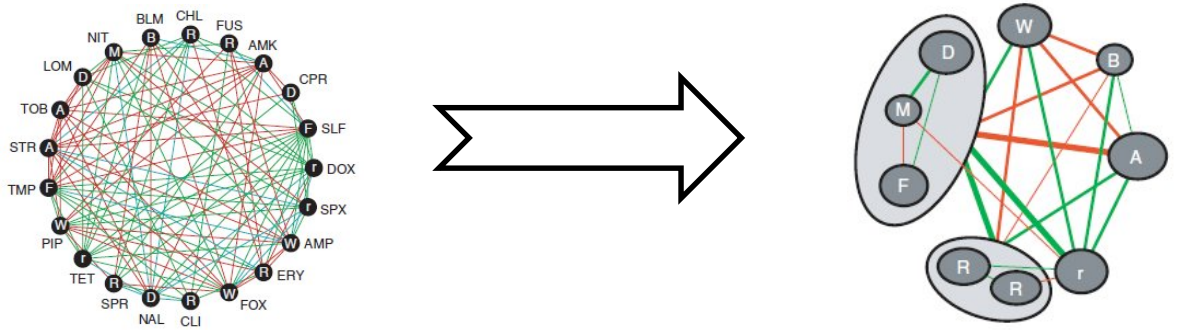
Bleomycin



Multi-target therapeutics: When the whole is greater than the sum of the Parts, Zimmerman & al, *2007, Drug Discovery Today*

Conclusion

- Result of the systematic analysis:



- A tool to help identify new drugs? New drug combinations?

- One day: adaptation of this systematic method for *in-vivo* studies?