

A background network diagram consisting of numerous white nodes (small circles) connected by thin white lines, forming a complex web of connections. The nodes are distributed across the entire frame, with some clusters and some isolated nodes.

# Conservation of properties of genetic interactions

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# Outline

- What are genetic interactions?
- Properties of genetic interactions
- Conservation of genetic interactions
- Conservation of genetic interaction properties

# Genetic interactions

Definition: the combination of multiple mutations leads to an phenotype that is unexpected given the phenotype of the single mutants

- In **positive genetic interactions**, the phenotype is *less* severe than expected given the single mutant phenotypes
- In **negative genetic interactions**, the phenotype is *more* severe than expected given the single mutant phenotypes

# Positive genetic interaction



**Healthy**

wild-type



**Sick**

disease allele



**Healthy**

disease allele  
+  
suppressor mutation

# Negative genetic interaction



**Healthy**  
wild-type



**Mild disease**  
disease allele

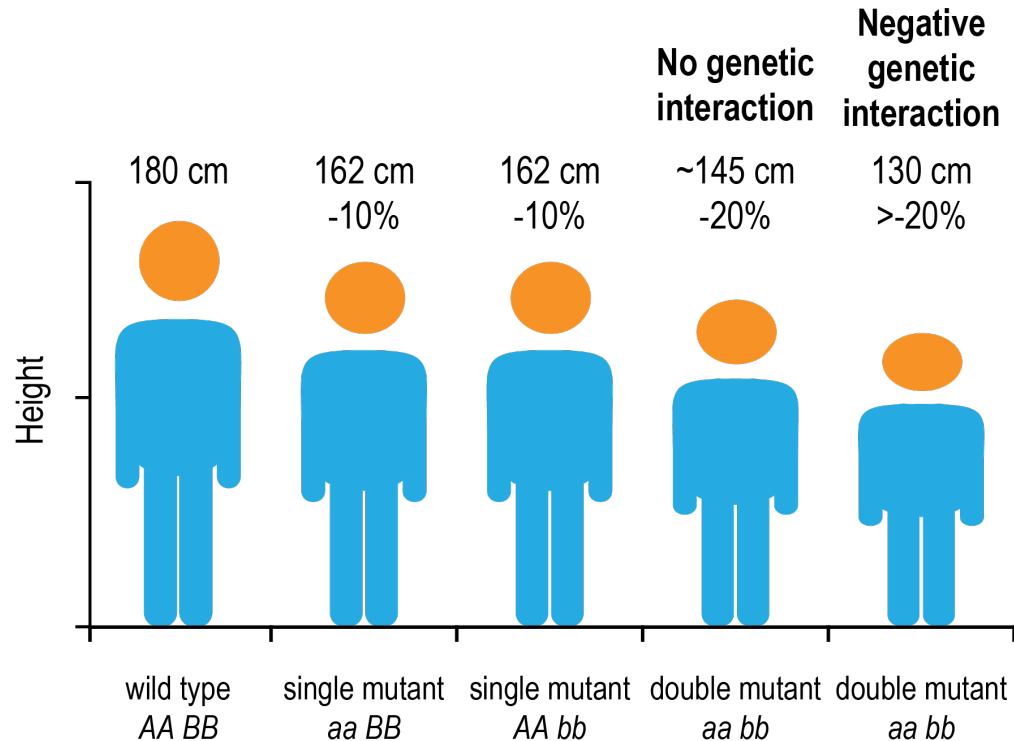


**Sick**  
disease allele  
+  
enhancer mutation

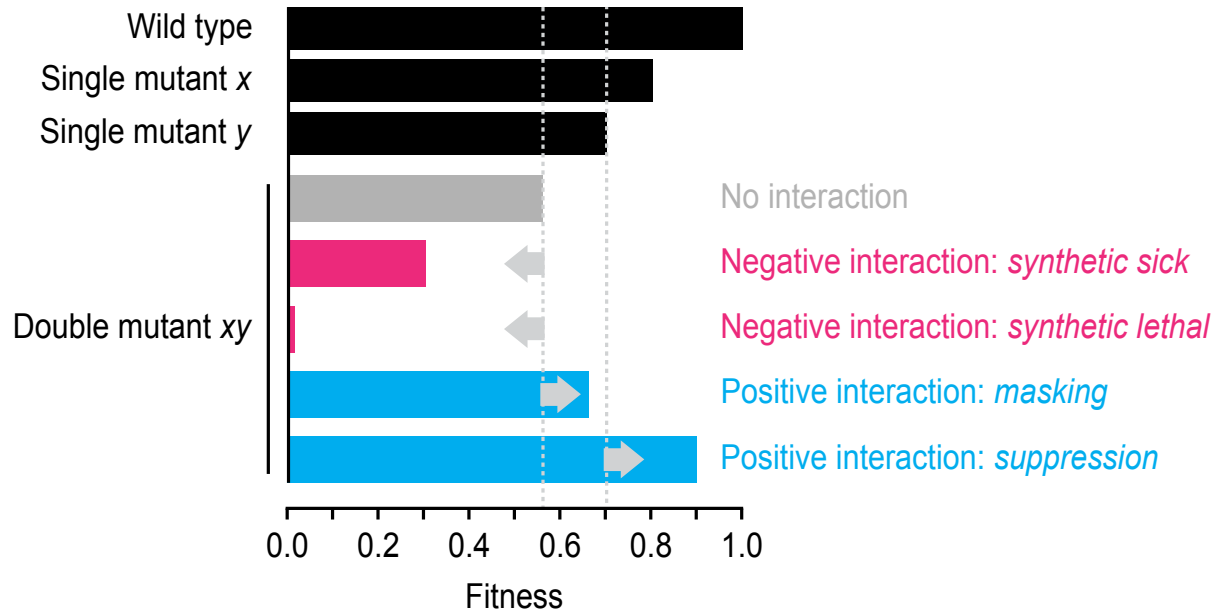
# Genetic interactions

- Genetic interactions are also called **gene-gene interactions** or **epistasis**, but be careful, some people use the word epistasis to describe positive genetic interactions specifically or use the term gene-gene interactions to describe oligogenicity
- Note the differences between:
  - “simple” oligogenic traits, where the alleles of multiple genes affect a phenotype, but these are not thought to interact. In other words, the phenotypic effect of a mutation does not depend on the presence of another mutation.
  - and genetic interactions, in which the effect of a mutant allele differs depending on the presence of other mutations.

# “simple” oligogenic traits versus genetic interactions



# Quantifying genetic interactions



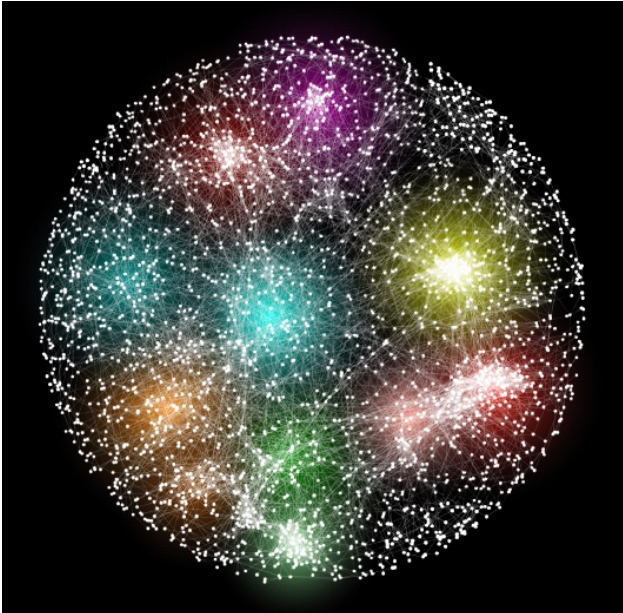
Multiplicative model:  $\epsilon = W_{xy} - W_x \times W_y$



# Outline

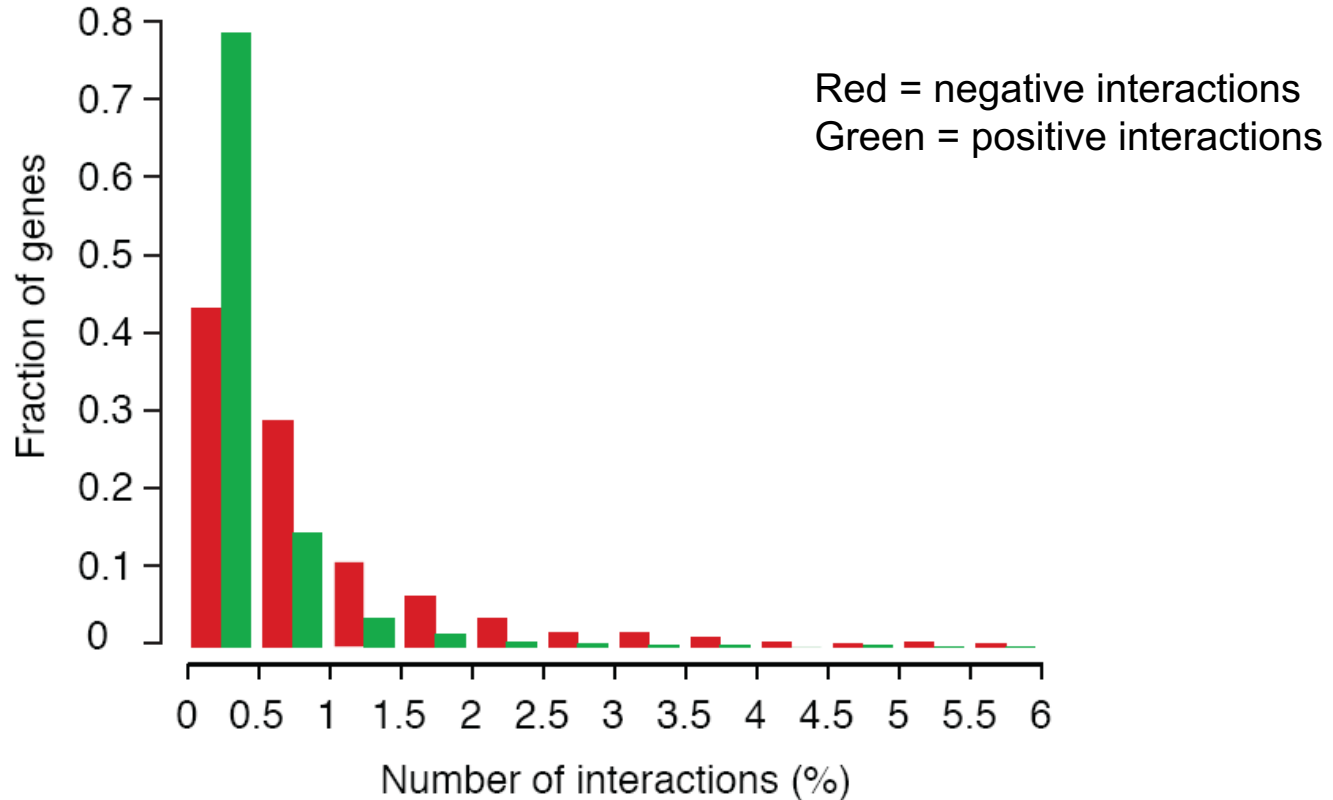
- What are genetic interactions?
- **Properties of genetic interactions**
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# The genetic landscape of a cell

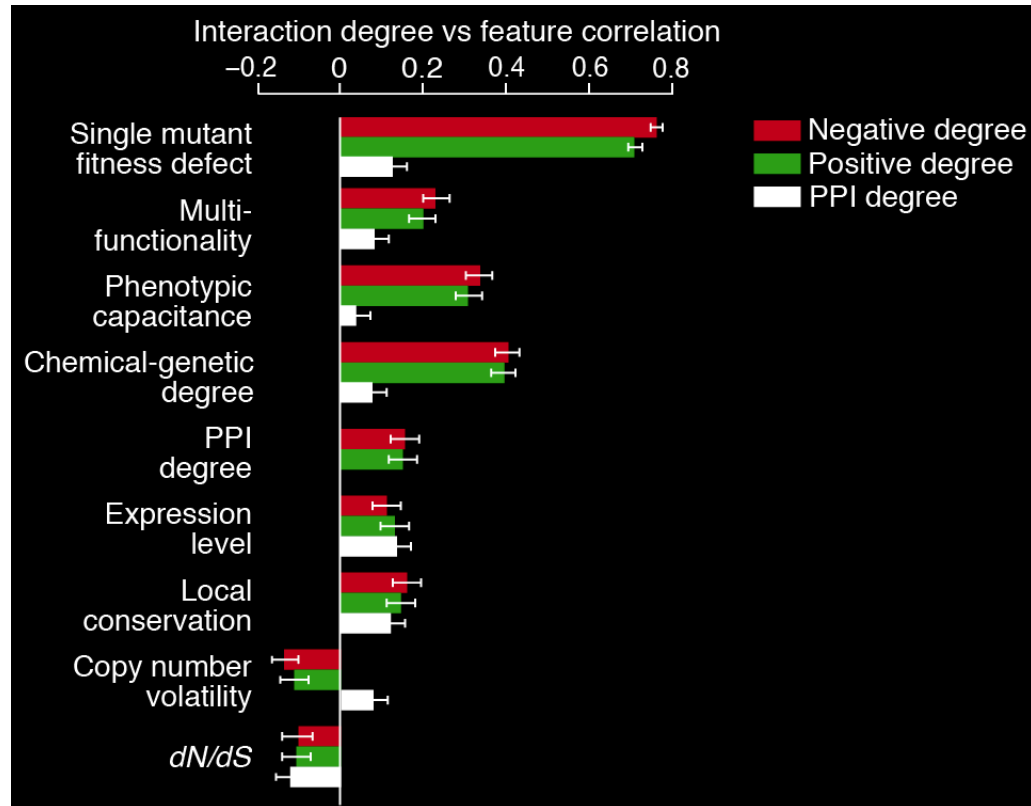


- Budding yeast genetic interaction network
- 1712 x ~3900 genes
- ~5.4 million gene pairs  
(~30% of all possible gene-gene combinations)

# Genetic interaction distribution per gene



# Biological features predictive of genetic interaction degree



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# Genetic interaction maps across species

Species	# of pairs screened	
<i>S. cerevisiae</i>	~18 million	Costanzo et al., Science, 2016
<i>S. pombe</i>	~200k	Dixon et al., PNAS, 2008 Roguev et al., Science, 2008
<i>E. coli</i>	~700k	Butland et al., Nat Methods, 2008 Babu et al., Plos Genet, 2014
<i>C. elegans</i>	~75k	Lehner et al., Nat Genet, 2006 Byrne et al., J Biol, 2007
<i>D. melanogaster</i>	~100k	Fischer et al., eLife, 2015
<i>H. sapiens</i>	~200k	Horlbeck et al., Cell, 2018

## Evidence for interaction conservation between 1:1 orthologs

*S. cerevisiae* - *S. pombe*

23% conservation

Dixon et al., PNAS, 2008

17% conservation

Roguev et al., Science, 2008

*S. cerevisiae* - *C. elegans*

5% conservation

Tischler et al., Nat Genet, 2008

82% conservation

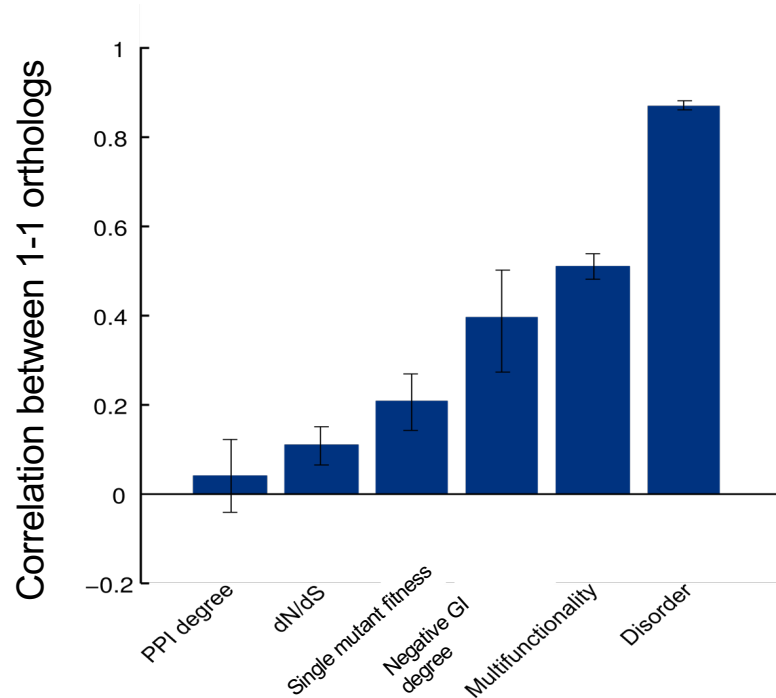
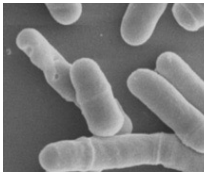
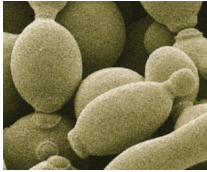
McClellan et al., Plos Genet, 2012

*S. cerevisiae* - *H. sapiens*

??

McManus et al., PNAS, 2009

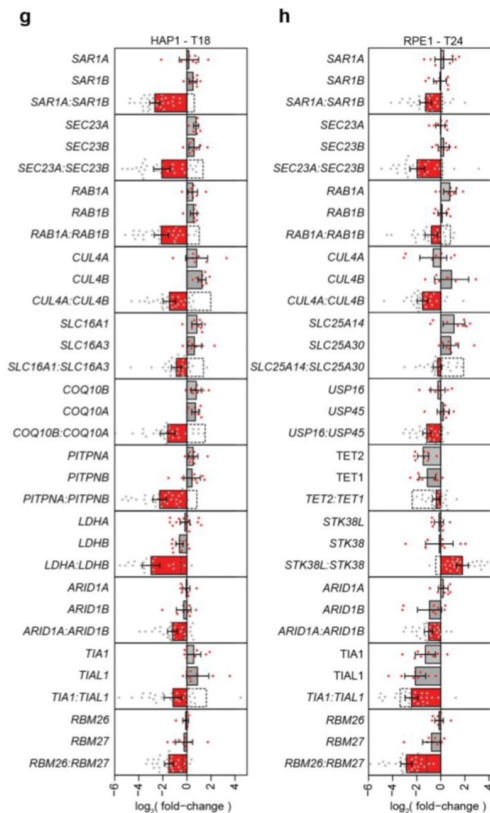
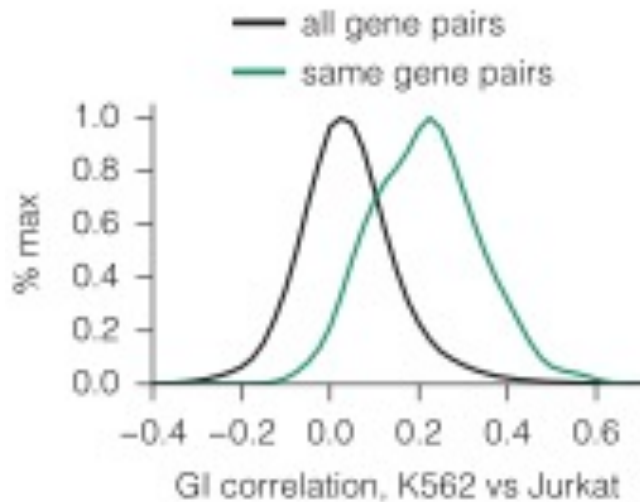
# Individual gene characteristics are not well conserved



*S. pombe* vs. *S. cerevisiae*



# Conservation of genetic interactions between cell lines

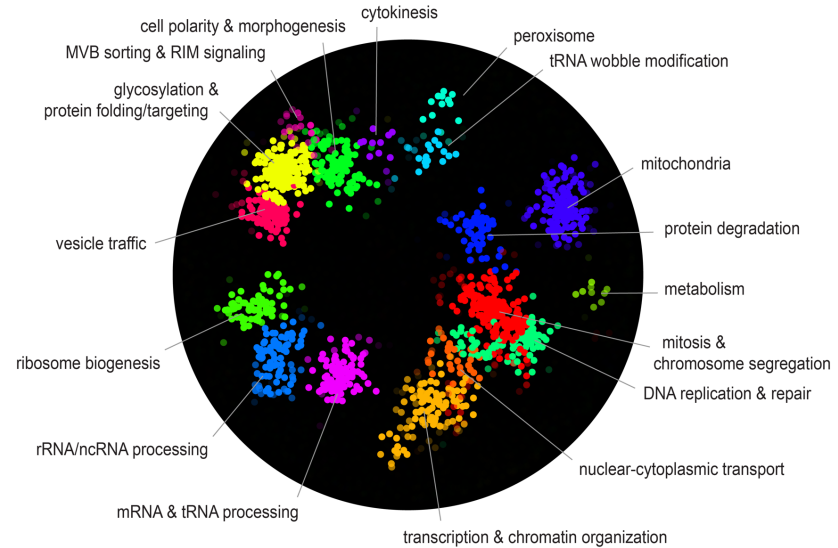
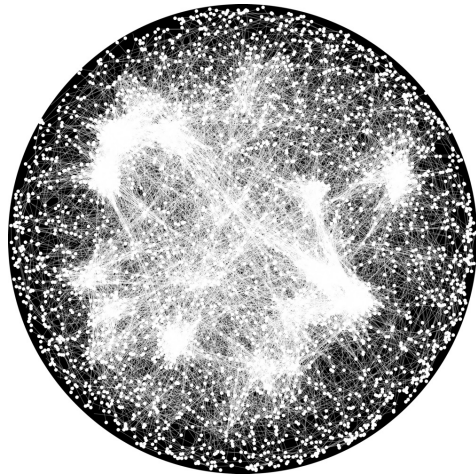


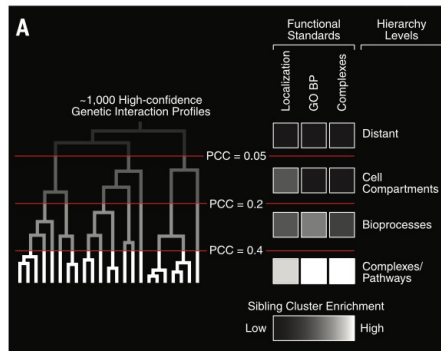
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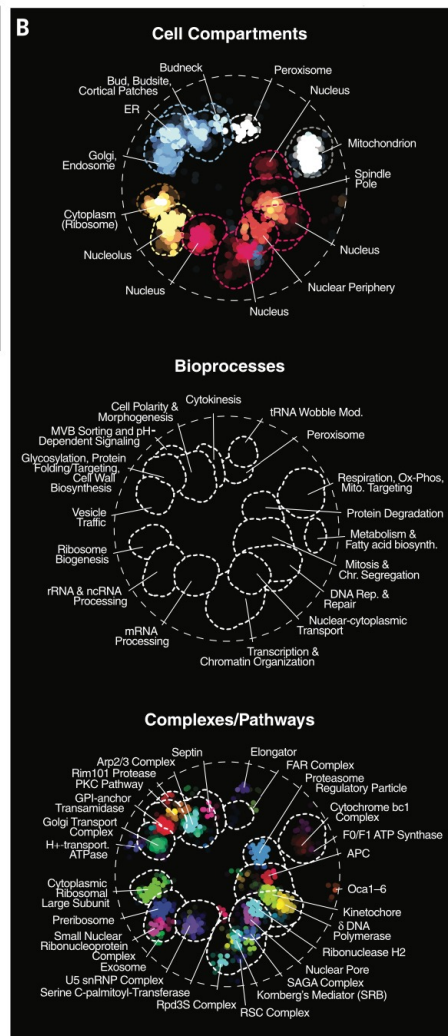
# Patterns vs individual interactions

Genome-wide genetic interaction patterns tell you more about the function of a gene than the individual interactions themselves

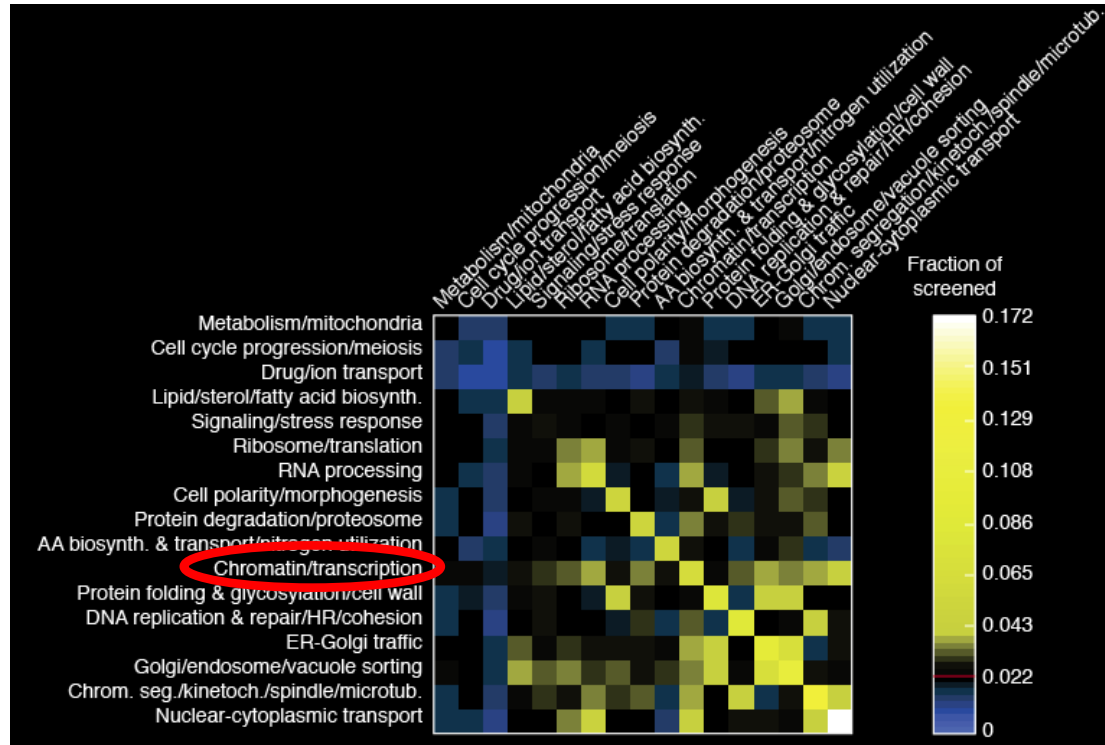




**Fig. 2. The global genetic interaction profile similarity network reveals a hierarchy of cellular function.** (A) A schematic representation of a genetic interaction profile–derived hierarchy. Genes with highly correlated genetic interaction profiles ( $PCC > 0.4$ ) form small, densely connected clusters representing specific pathways or protein complexes. At an intermediate range of profile similarity ( $0.2 < PCC < 0.4$ ), sibling clusters representing distinct pathway or complexes combine together into larger biological process–enriched clusters. At a lower range of profile similarity ( $0.05 < PCC < 0.2$ ), bioprocess–enriched clusters, in turn, combine together to form larger clusters corresponding to different cell compartments. The gray–white scale bar illustrates enrichment of sibling clusters for the same set of terms from the indicated functional standard. See also fig. S7. (B) The genetic network hierarchy visualized using SAFE analysis, which identified regions in the global similarity network enriched for specific cellular compartments, biological processes, or protein complexes.

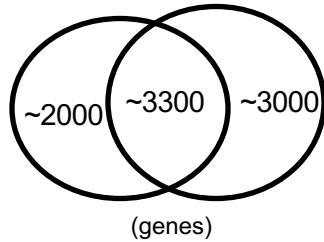
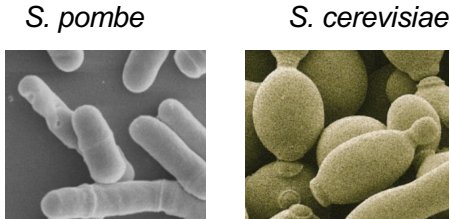


# Frequency of genetic interactions between biological processes



Chromatin Regulators are hubs on Yeast and Worm networks  
 General network properties (e.g. hub genes) may be conserved!

# Example 1: comparing genetic interaction networks across yeasts

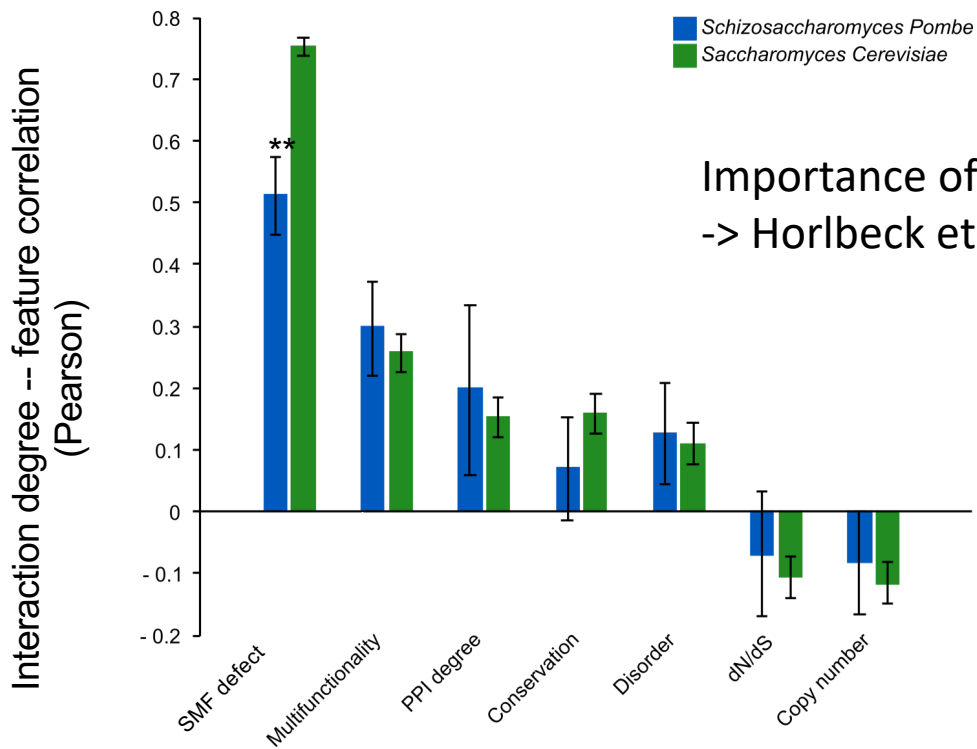


common ancestor ~400  
million years ago

- Roguev et al. 2008
  - ~500 x 500 pairs
  - conservation of modular structures, but significant rewiring of interactions between modules
- Dixon et al. 2008
  - ~200 x 200 pairs
  - ~30% conservation at the negative interaction level for one-to-one orthologs

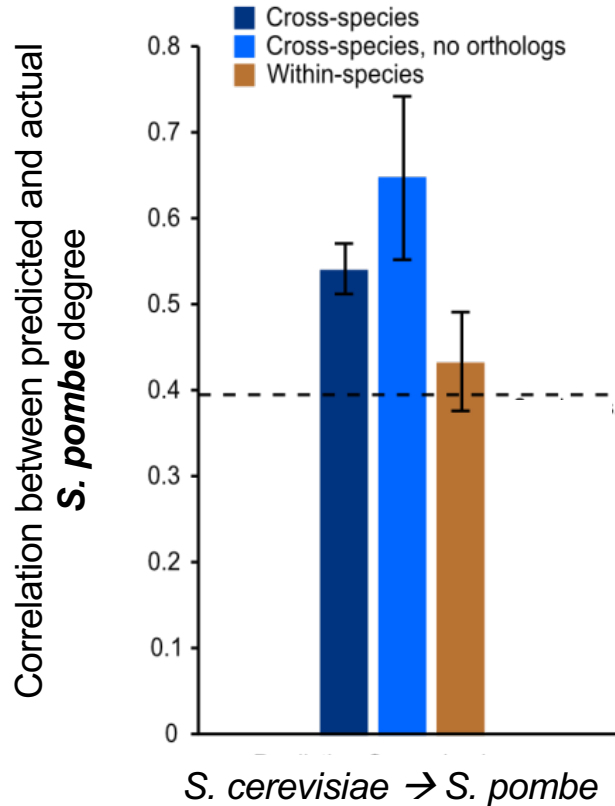
**Question:** Can a *S. cerevisiae*-based model predict *S. pombe* hub genes from the Roguev and Dixon datasets?

# Relation between gene characteristics and interaction degree is conserved



Importance of SMF conserved in human  
-> Horlbeck et al., Cell, 2018

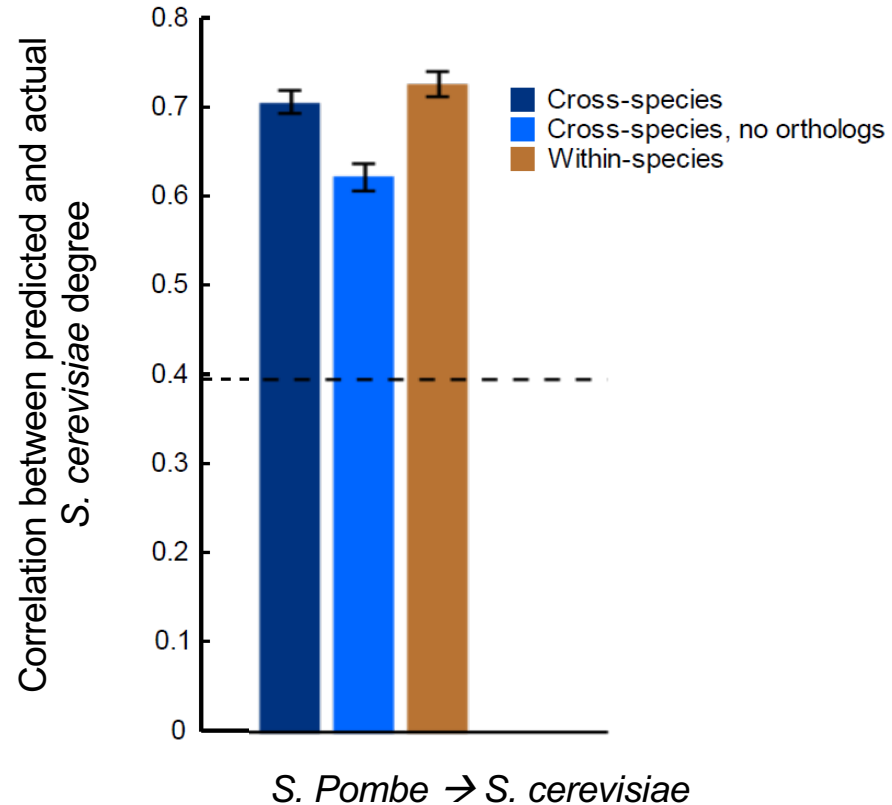
# *S. cerevisiae*-derived model predicts GI degree in *S. pombe*



- cross-species predictions are at least as good as model trained within species
- cross-species predictions are better than ortholog degree correlation
- model applies equally well to non-orthologs

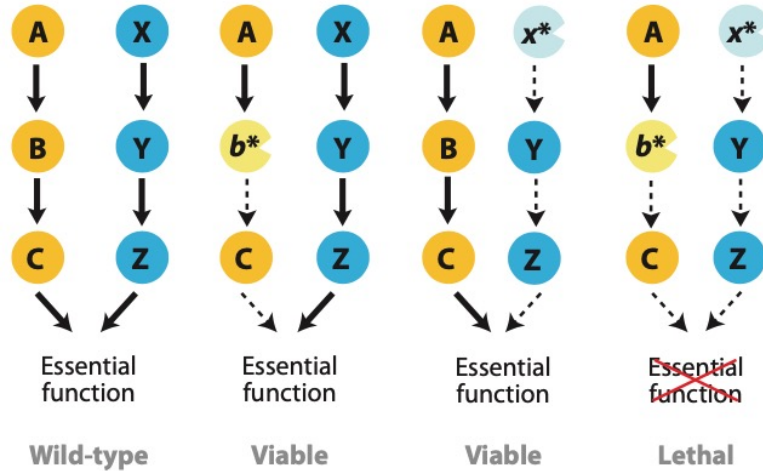


# *S. pombe*-derived model predicts GI degree in *S. cerevisiae*

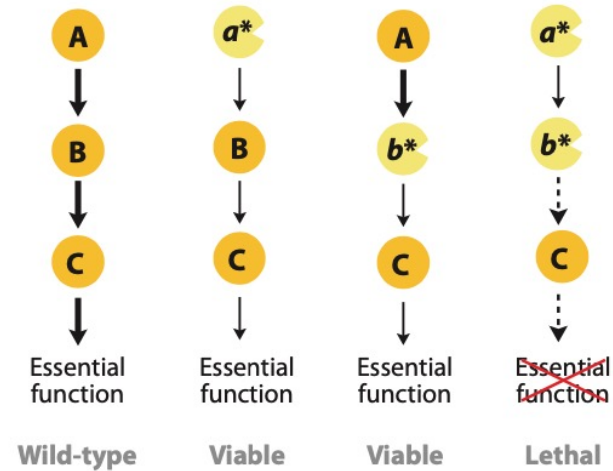


## Example 2: from patterns in yeast to human disease

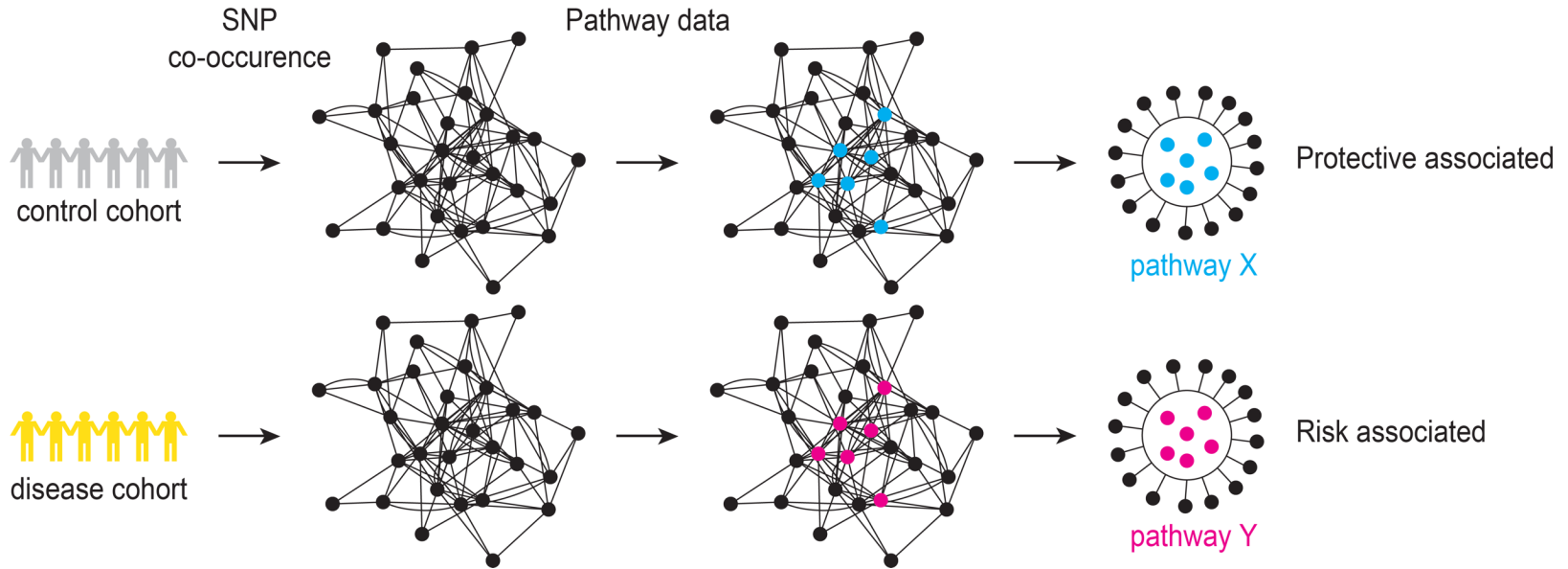
Between pathway genetic interactions (nonessential pathways)



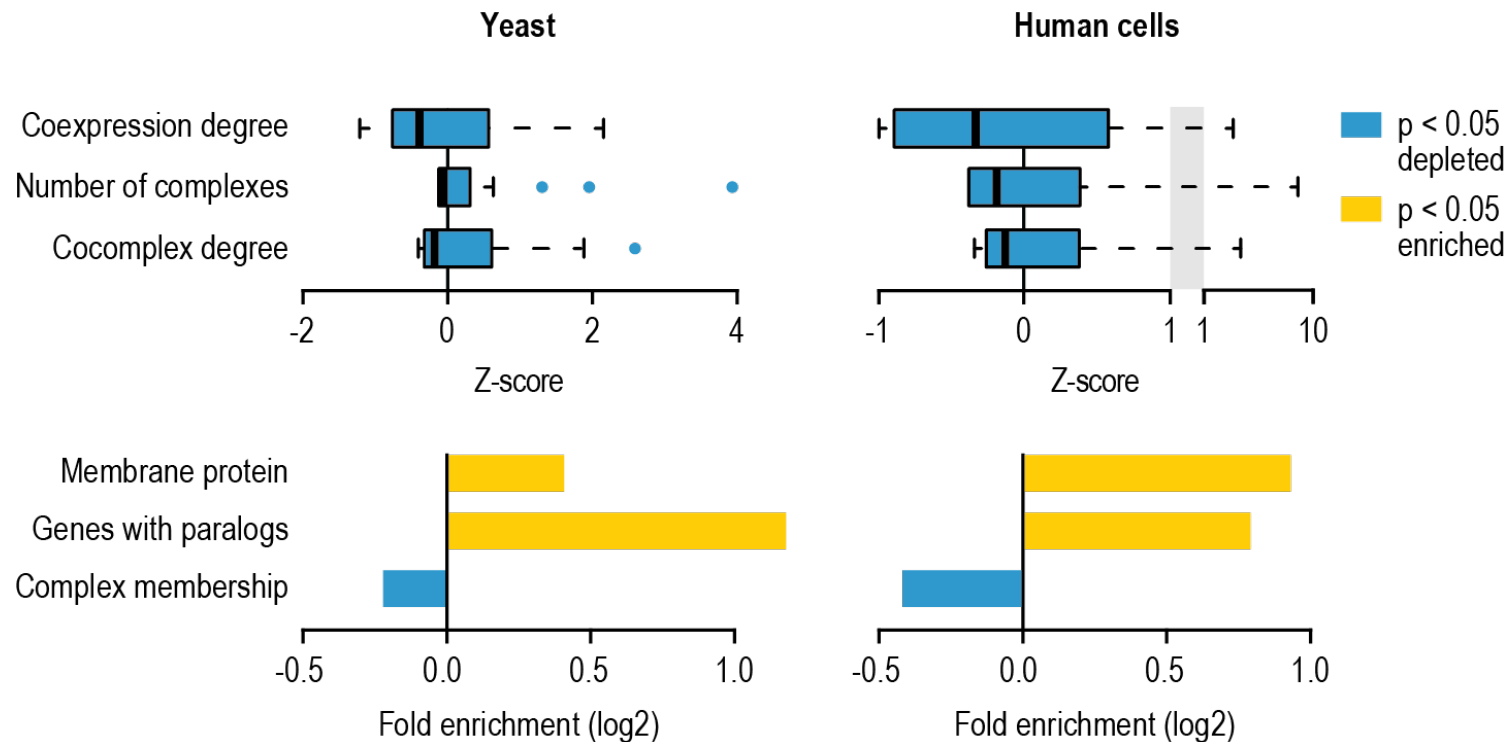
Within pathway genetic interactions (essential pathways)



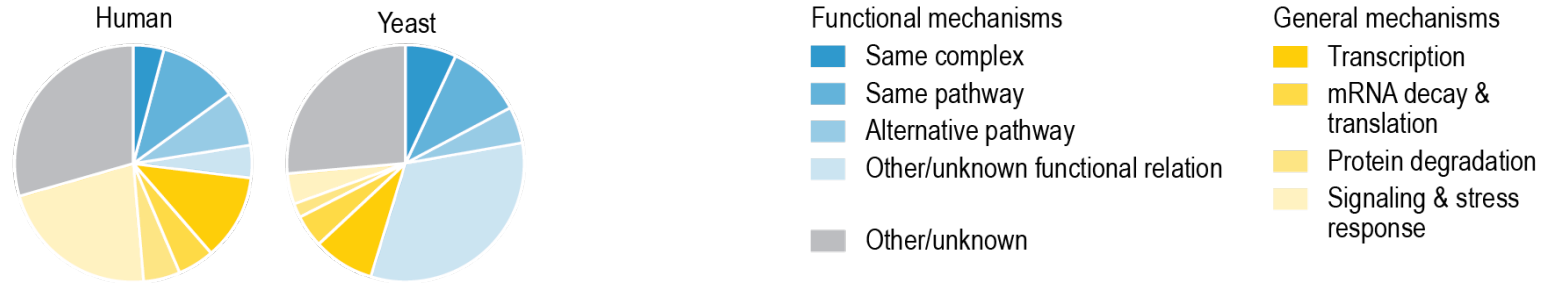
# BridGE (Bridging Genes with Epistasis)



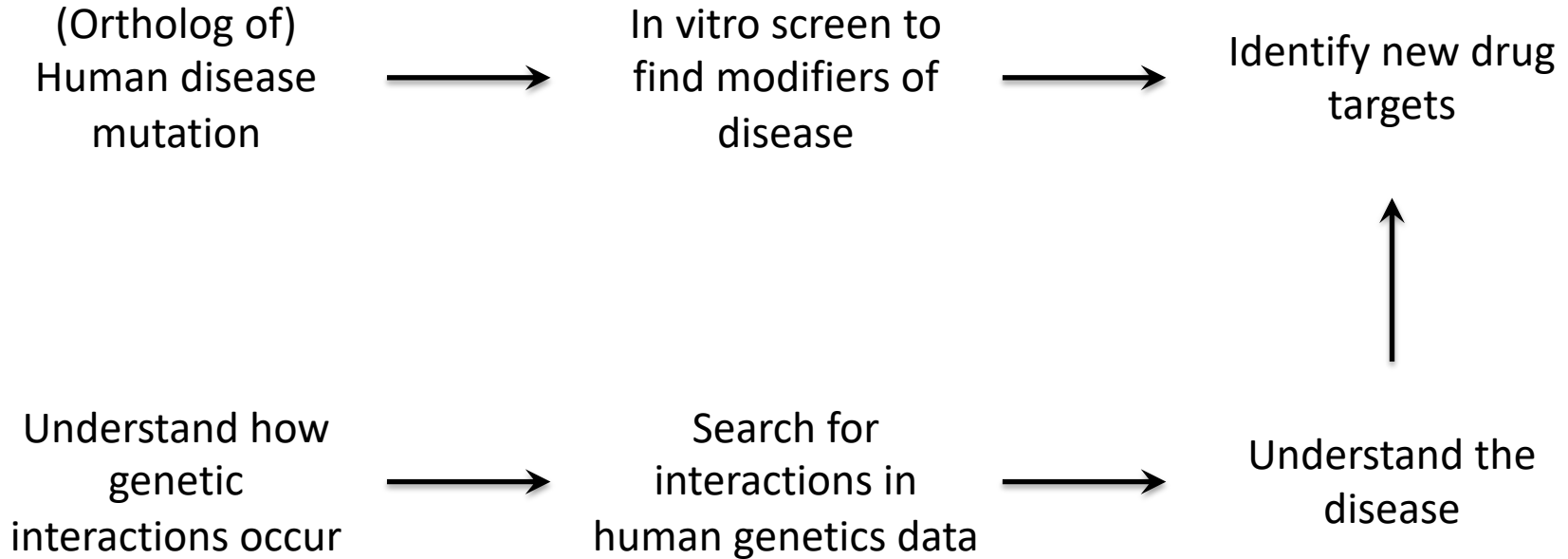
# Example 3: conservation of properties of dispensable essentiality



# Example 4: conservation of mechanisms of suppression



# Systems genetics



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