Protein Complexes are Essential in the Monochromatic Genetic Landscape of the Yeast Cell

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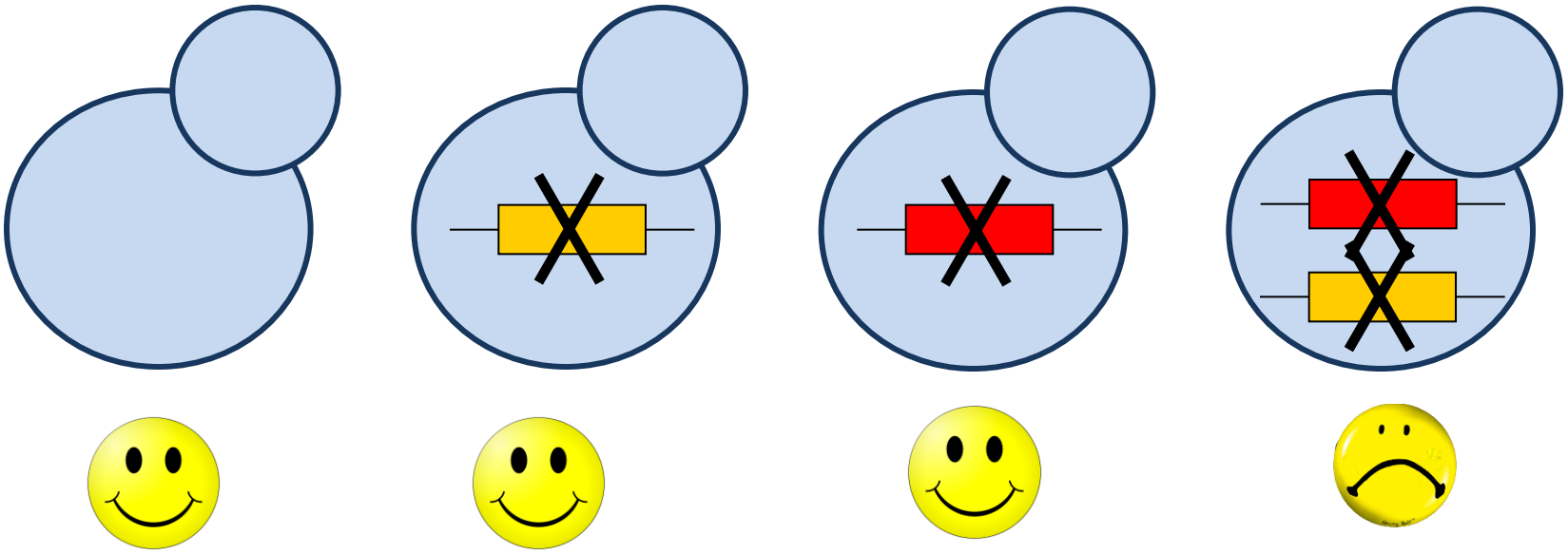
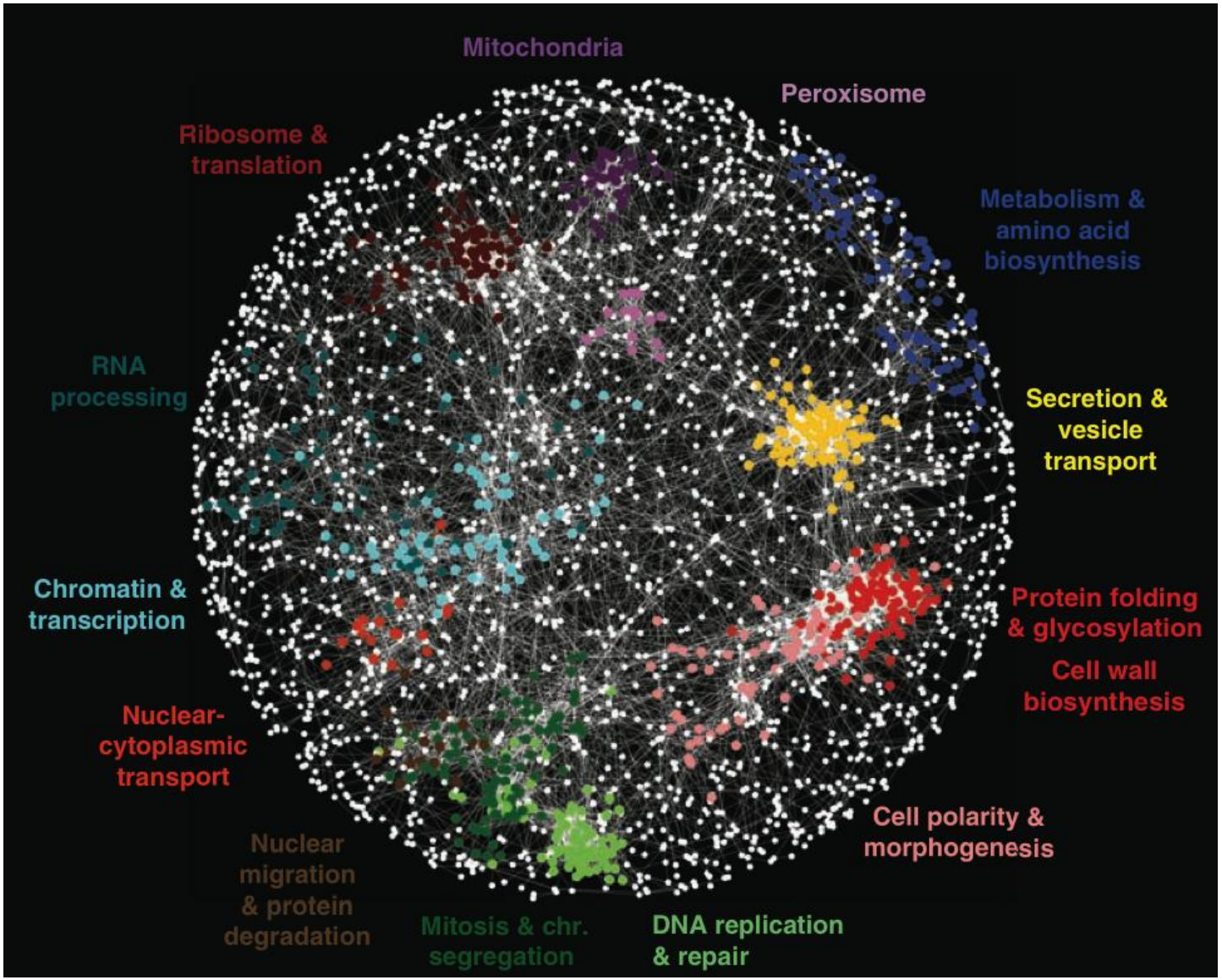
A genetic interaction is a functional relationship between 2 genes

Genes A and B genetically interact when:

simultaneous perturbation
≠
combination of individual effects.



Genetic interactions help map gene function



Costanzo *et al.*, **The genetic landscape of a cell**, *Science* 2010, 327(5964):425-431

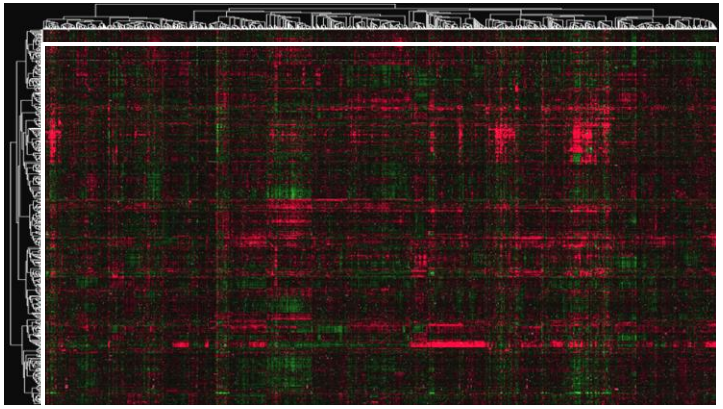
Large scale quantitative mapping has become possible

Synthetic Genetic Array (SGA) technique [Costanzo 2010]

- 5.4 millions gene-gene pairs tested (~30% of all pairs)
- genetic interaction profiles for ~75% of the yeast genes

~3800 genes

~1700 genes



SGA genetic interaction matrix

Negative interaction

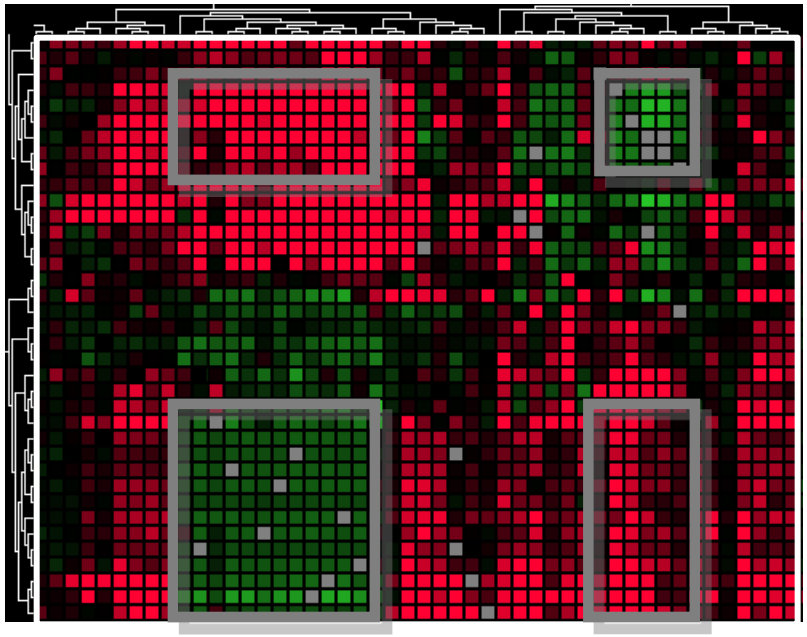
Positive interaction

Other techniques: dSLAM [Pan 2006], GIM [Decourty 2008], E-MAP [Schuldiner 2005]
Other species: S. pombe, E. coli, C. elegans, mammalian cell culture

Clustering this data shows monochromatic patterns

Monochromatic red connection

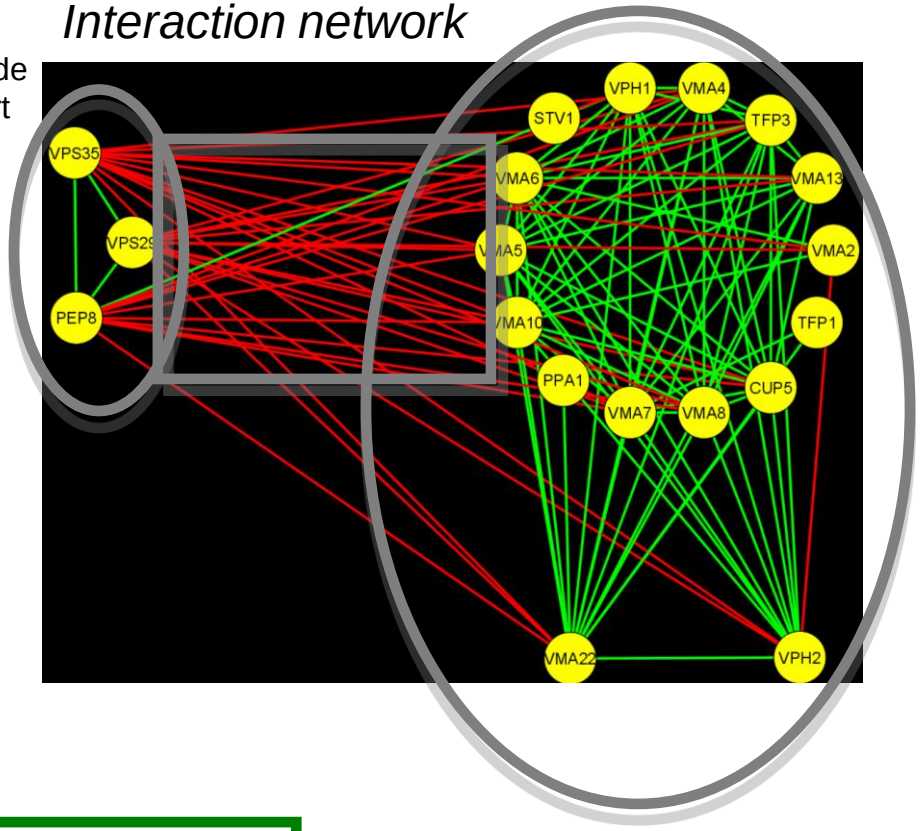
Interaction matrix



Vacuolar ATPase

Retrograde transport

Interaction network



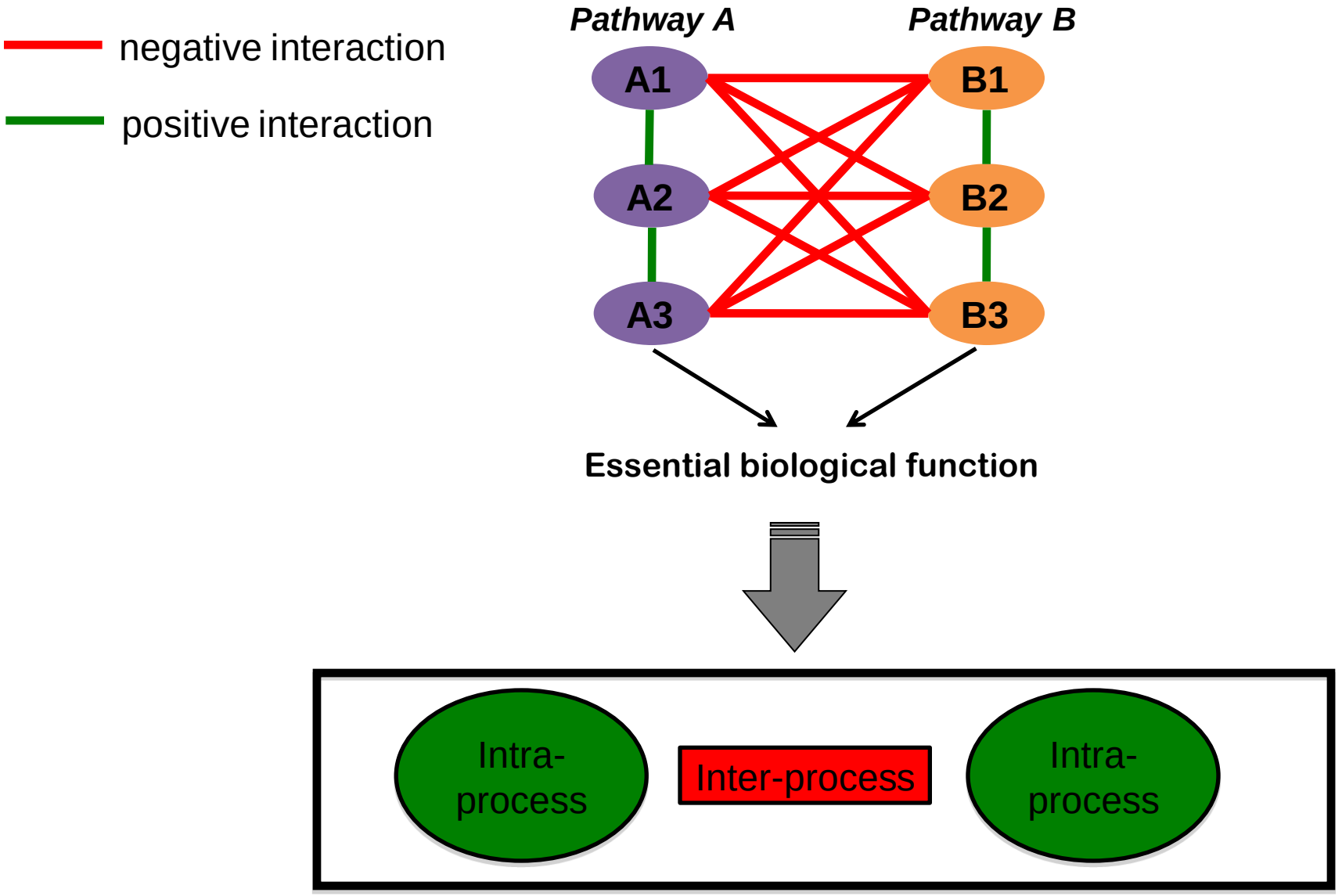
Monochromatic green processes

Vacuolar ATPase

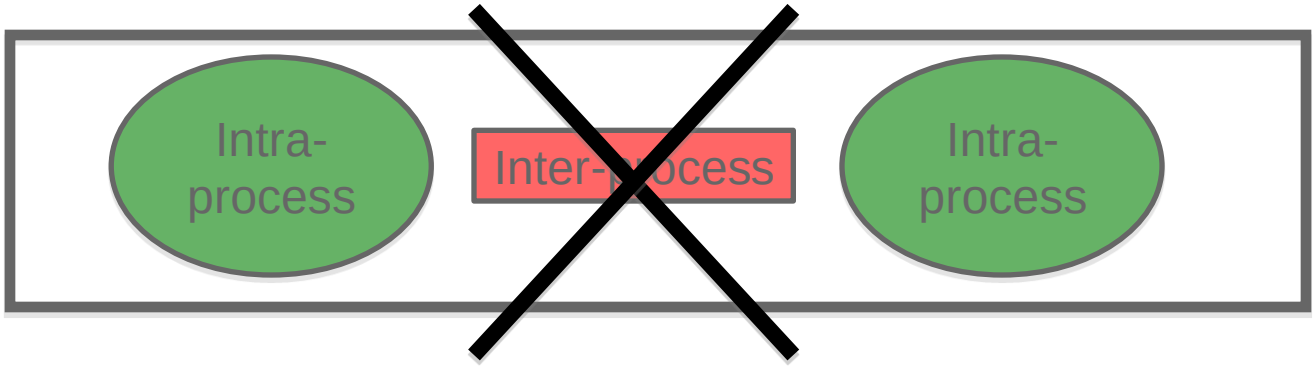
negative

positive

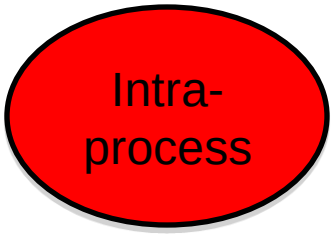
Current model states that these monochromatic patterns identify pathways and complexes



But recent results suggest the model has to be revisited

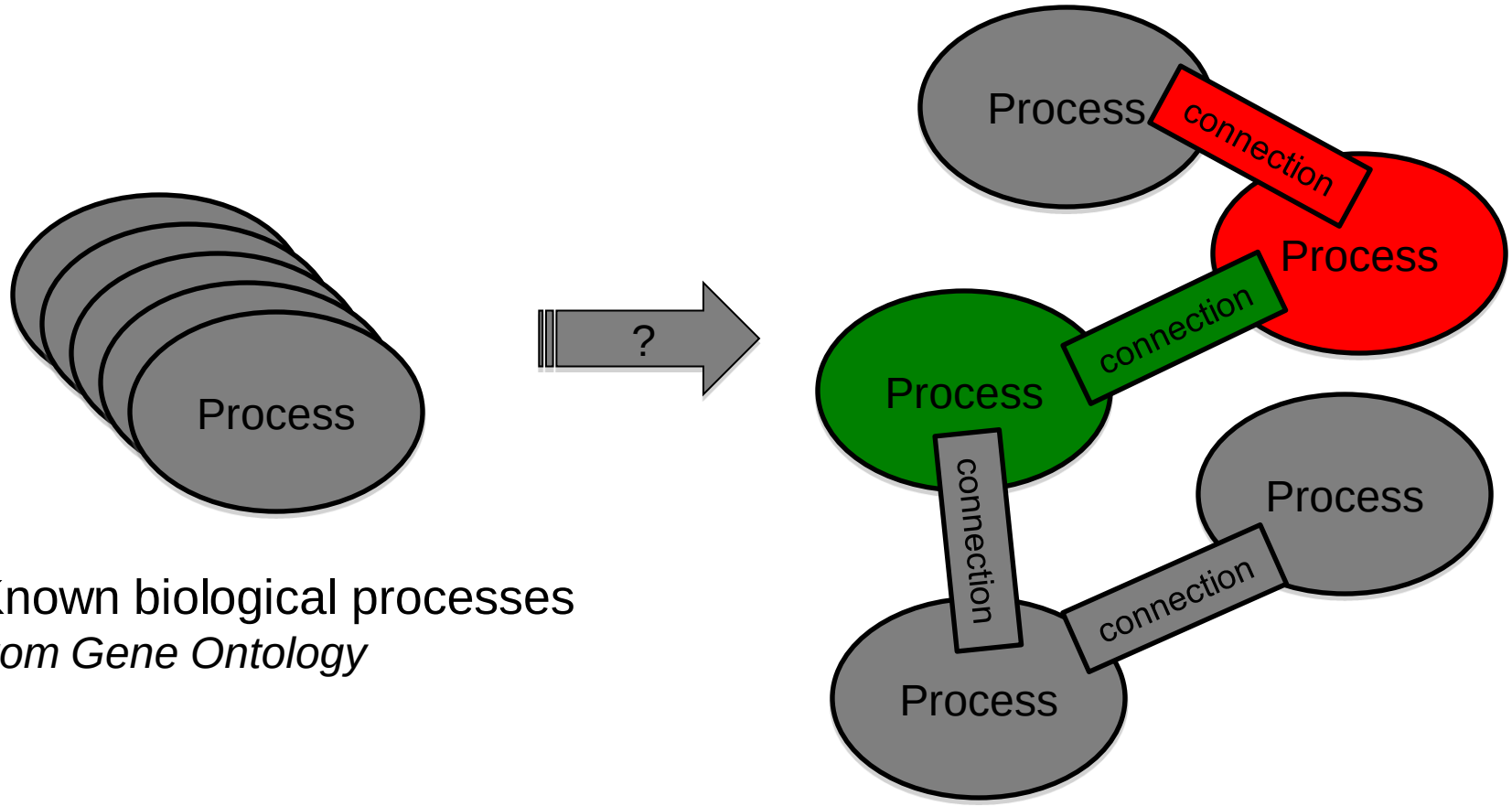


- Protein **complexes** with essential genes tend to be monochromatic **red** [Bandyopadhyay *et al.*, 2008]



- Many **connections** between biological processes tend to be monochromatic **green** [Costanzo *et al.*, 2010]

Does it hold for all biological processes and their connections?



Known biological processes
from Gene Ontology

We systematically evaluated the monochromatic patterns for known biological processes

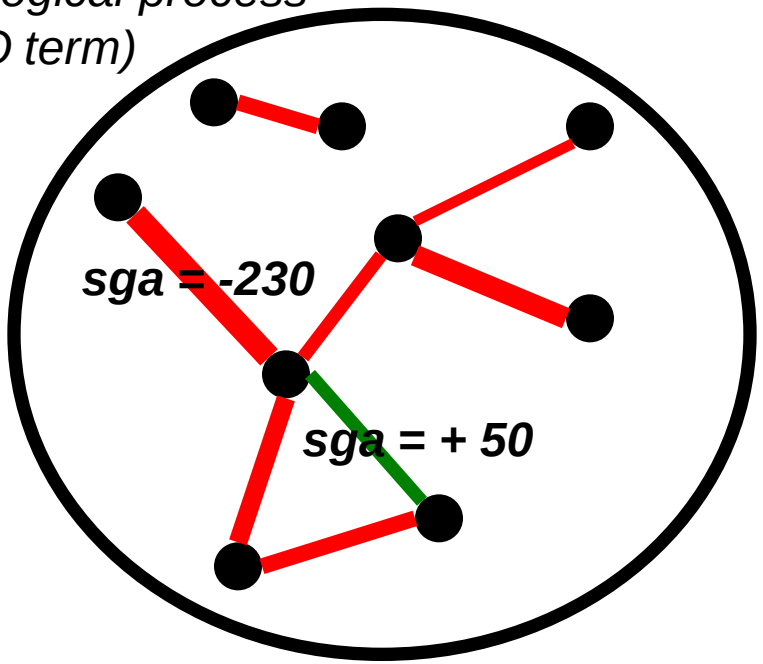
17,595
processes in GO

2,917
for yeast

1,377
with
SGA interactions

566
with good
SGA coverage

Biological process
(GO term)



$$Score = \frac{\sum sga}{\sum |sga|}$$

Random networks
shuffle labels

$$Z - score = \frac{Score - \mu}{\sigma}$$

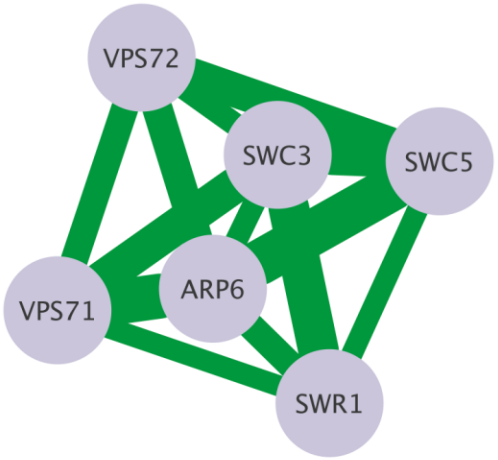
All red -> Score = -1
All green -> Score = +1

10% of yeast biological processes are monochromatic

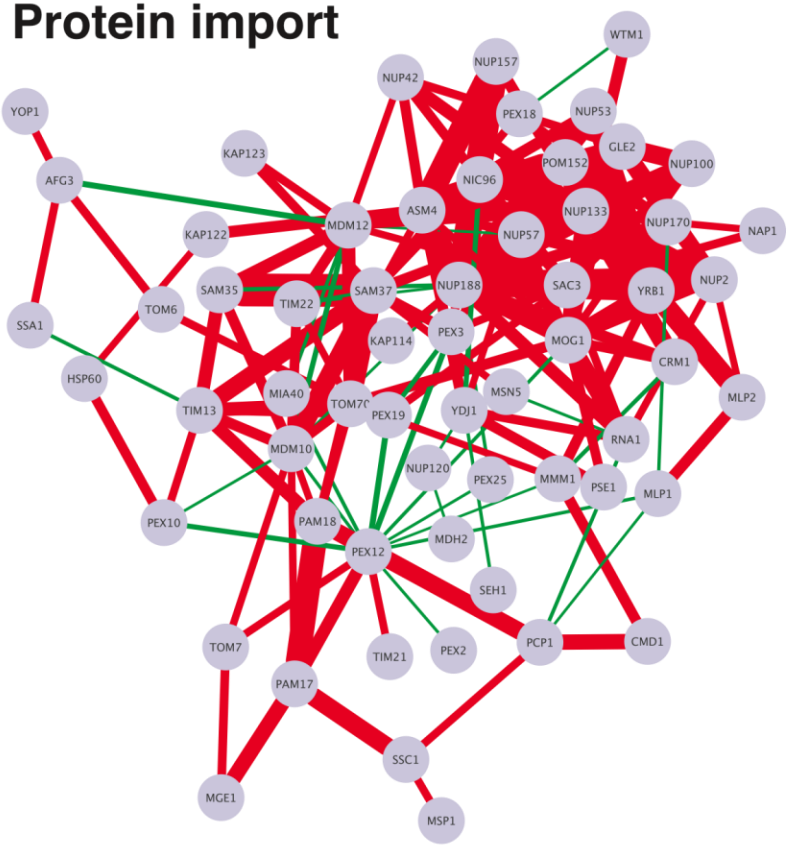
566 processes covered by SGA data

50 monochromatic processes
- 45 negative
- 5 positive

Histone exchange

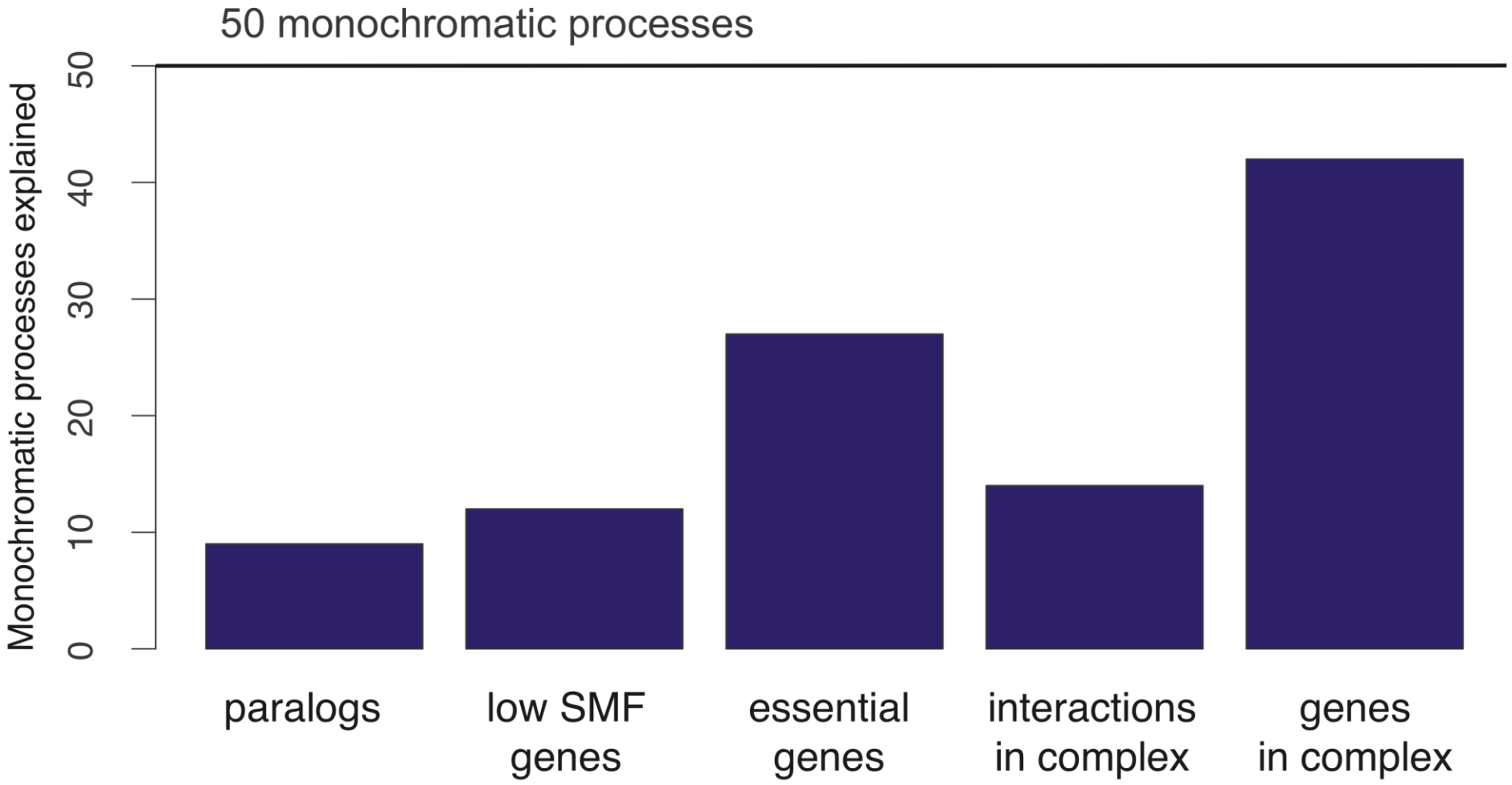


Protein import



Protein complexes play a major role in these patterns

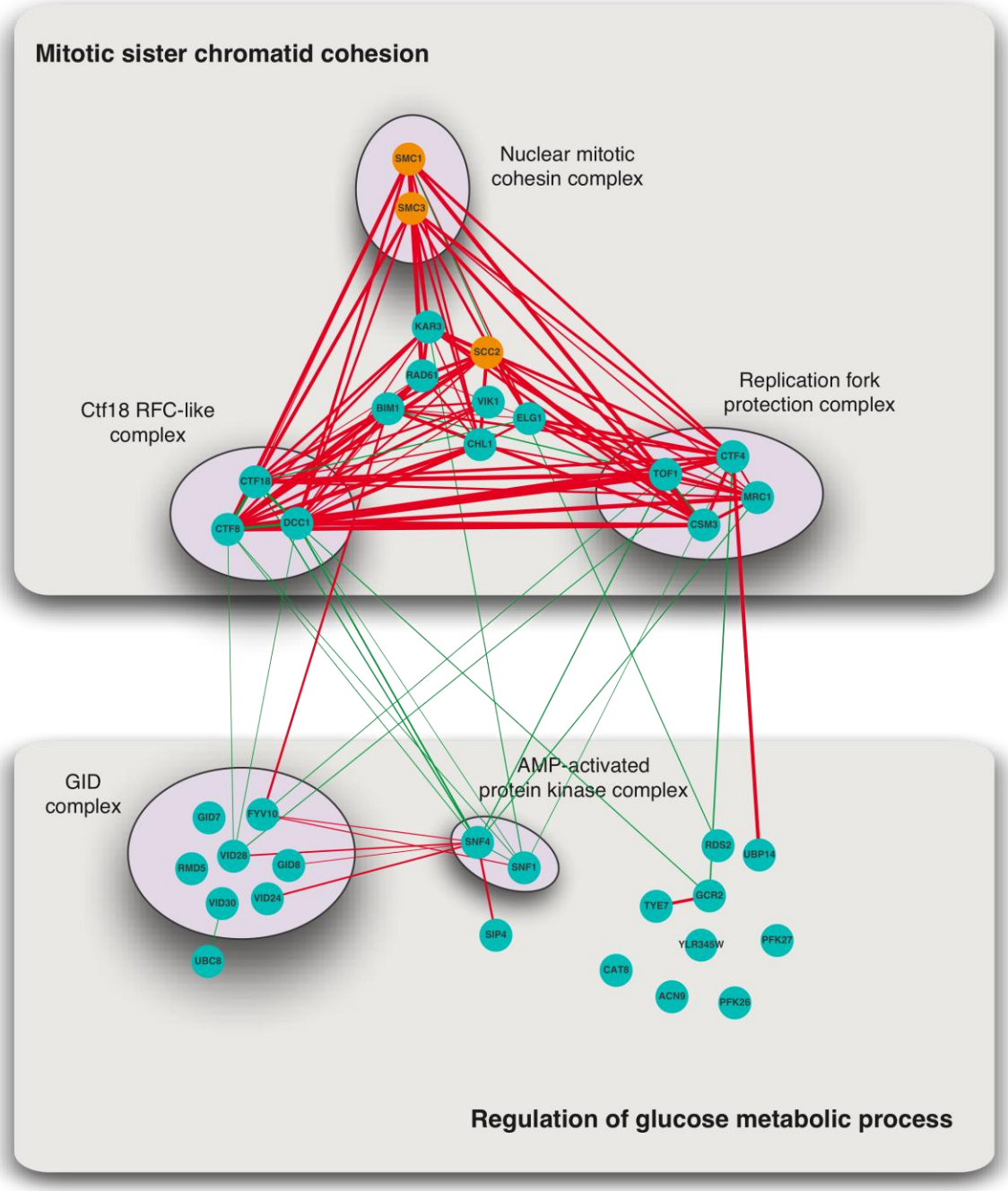
- We remove protein complexes and assess monochromatic patterns again



Monochromatic green connection

614 positive
773 negative

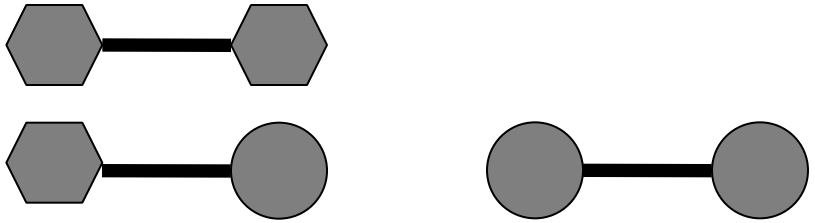
mainly due to complexes



Interactions are biased towards protein complexes

Gene in a **complex**

Gene **not** in any **complex**

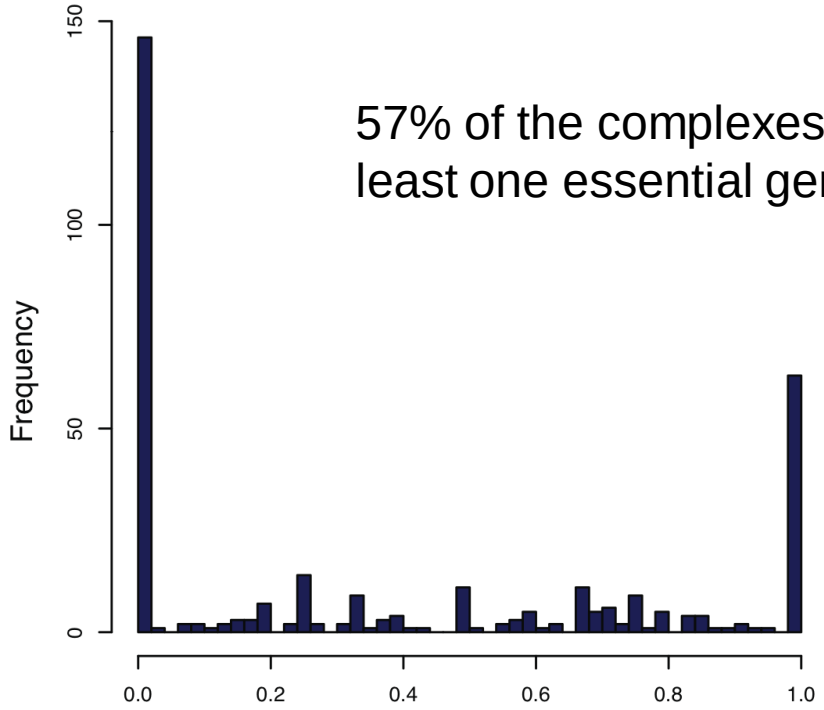


	Complex	No complex
Tested interactions	2,801,630 (49%)	2,898,509 (51%)
Observed interactions	119,871 (63%)	70,125 (37%)

Fisher test p-value $< 10^{-5}$

Genes encoding proteins in complexes are more likely to genetically interact than genes encoding proteins not in any complex.

Most complexes are essential for yeast growth



57% of the complexes have at least one essential gene.

	In complex	Not in complex
Essential gene	684 (61%)	438 (39%)
Non essential gene	1,111 (20%)	4,378 (80%)

Fisher test p-value ~ 0

Essential genes tend to be in protein complexes.

Concluding remarks

- Systematic study of the monochromatic nature of biological processes and their connections
  - ~10% of processes are monochromatic in SGA
  - Monochromatic connections are rare (~1%)
- Revisited model of the genetic landscape in yeast
  - Both monochromatic negative and positive processes
  - Both monochromatic negative and positive connections between processes
  - Protein complexes explain most of the patterns
  - Genetic interactions are biased towards protein complexes
  - Complexes are essential for yeast growth
- Mapped monochromatic processes and their connections in cell growth in yeast

This hierarchical and modular monochromatic map of sensitive and redundant biological systems...

- ... can an help
  - Understand the organization of sensitive and redundant biological systems
  - Unravel anti-cancer therapy
  - Predict drug synergy
- ... has to be explored
  - For other species
  - For other conditions

Acknowledgments

- Bader lab (Toronto)
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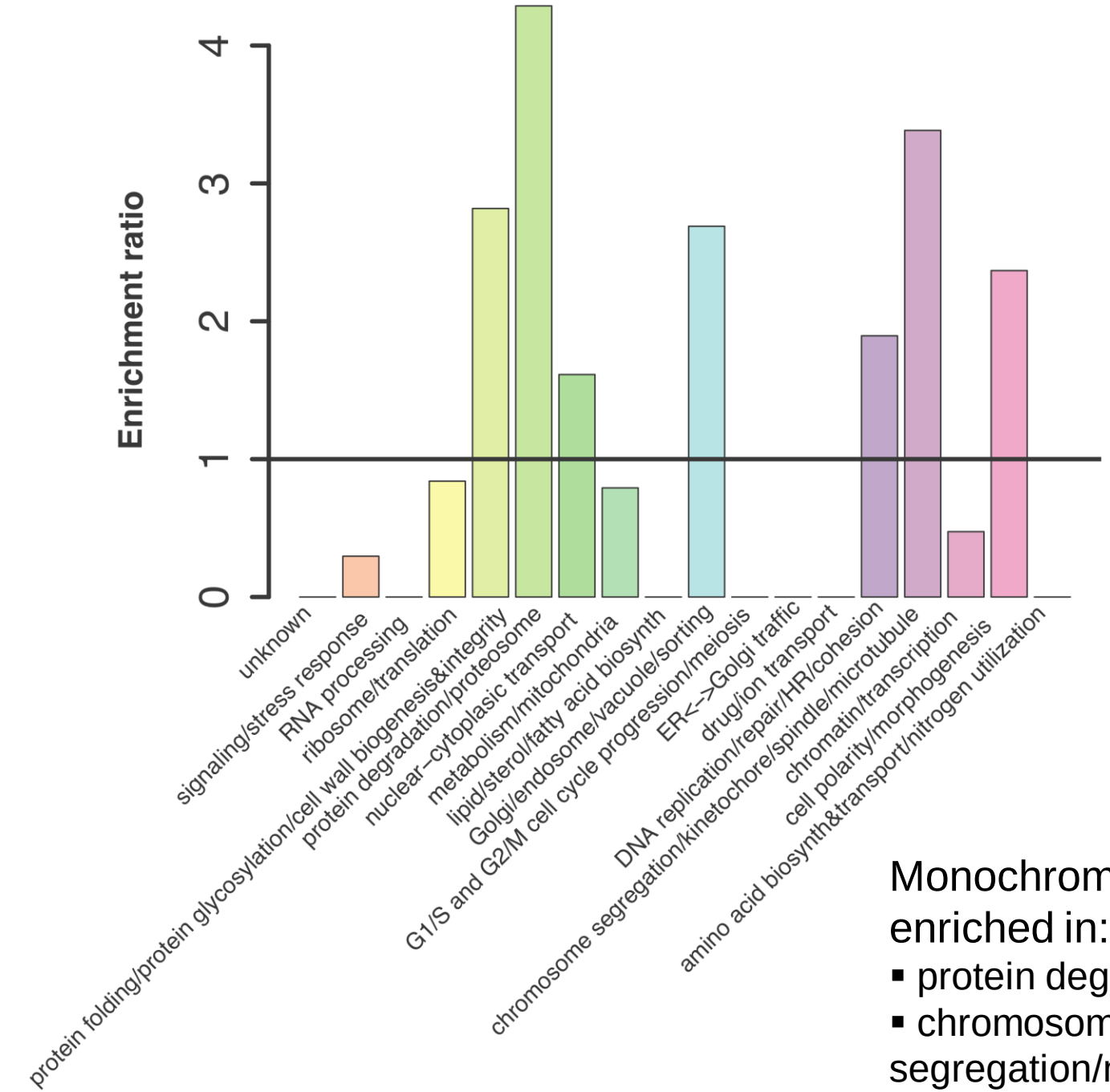


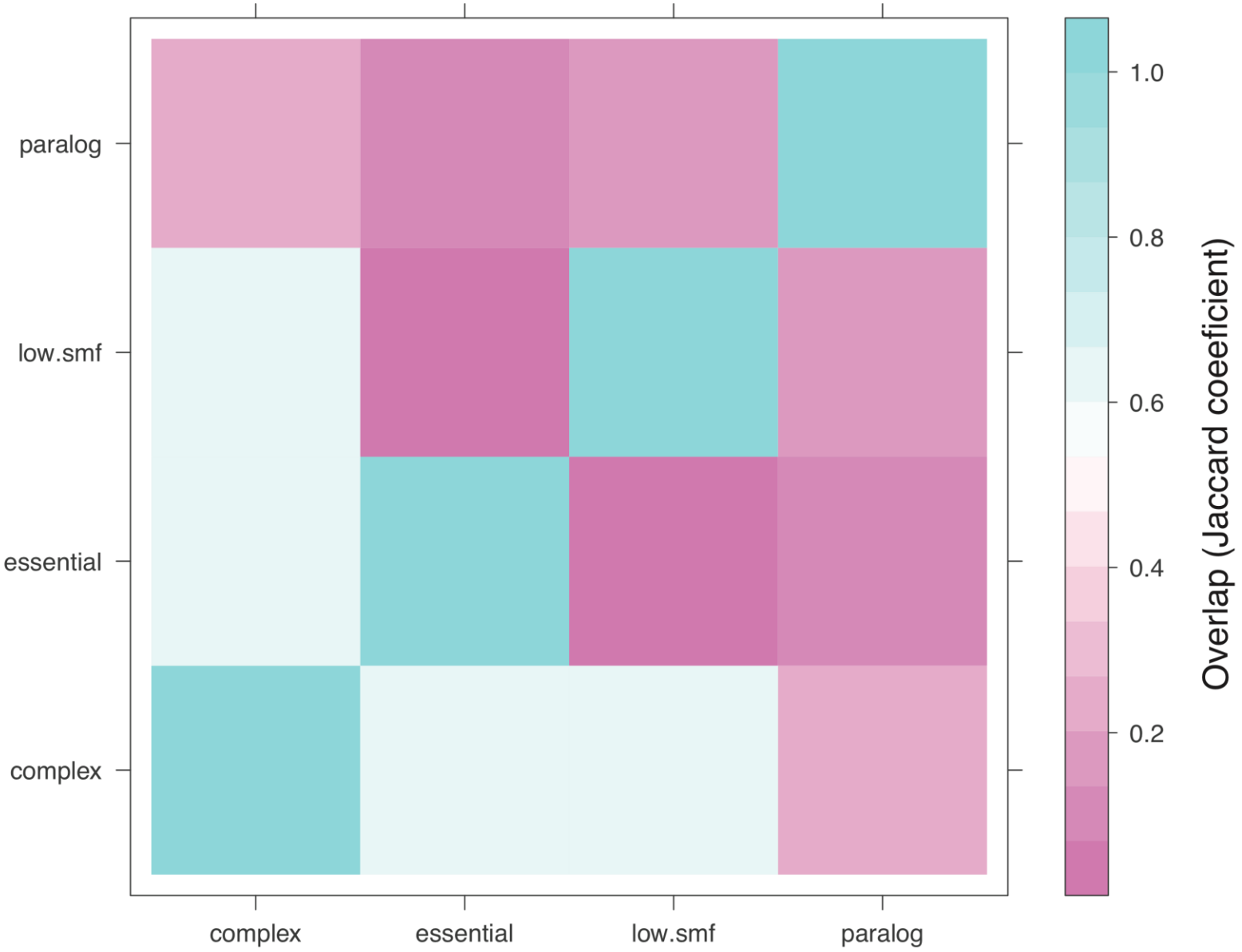
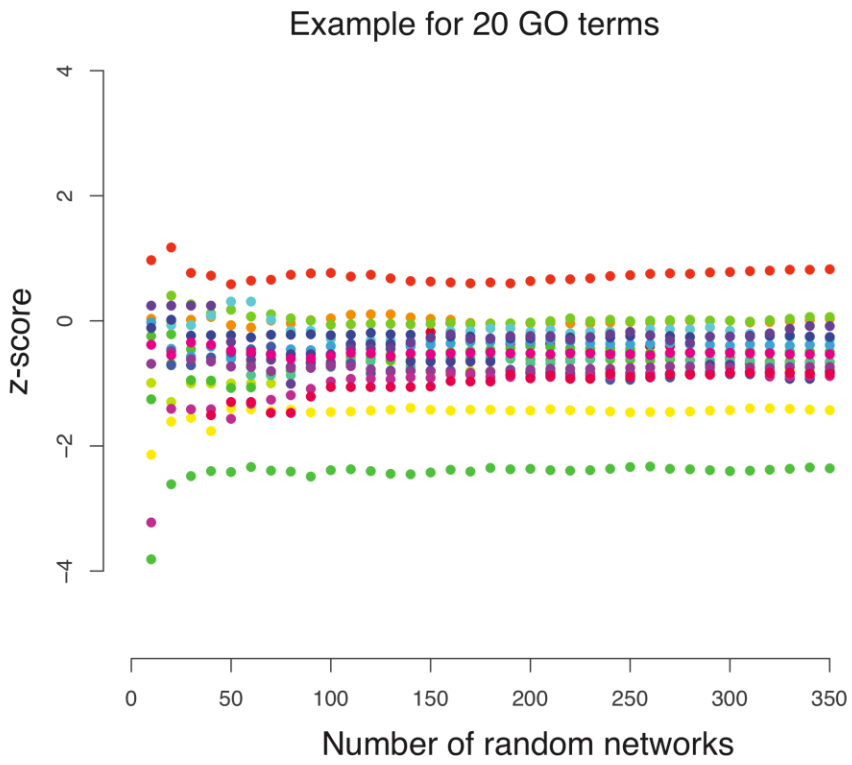
Monochromatic processes are enriched in:

- protein degradation/proteasome
- chromosome segregation/microtubule

The result holds for different coverage cutoffs

Coverage cutoff	Covered processes	Monochromatic processes	Ratio (%)
0	1031	68	6.6
0.2	1019	68	6.7
0.4	833	66	7.9
0.6	566	50	8.8
0.8	99	9	9.0
1	25	2	8.0

The various features are overlapping



Saturation tests indicate that 350 iterations is enough