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Specificity and Evolvability in Eukaryotic Protein Interaction Networks

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General goal

- Maybe not all of the known interactions are conserved. To what extent are protein-interactions conserved during evolution?
- How can we study the evolution of protein interaction networks ?

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Meme on the rise:
Comparative Interactomics

The availability of more information on protein interaction networks in many species has lead to an increase in comparative studies.

- **Directly comparing interaction networks using ortholog assignments**
  - Cesareni G, Ceol A, Gavrila C, Palazzi LM, Persico M, et al. (2005) Comparative interactomics. FEBS Lett 579: 1828-1833
  - Gandhi TK, Zhong J, Mathivanan S, Karthick L, Chandrika KN, et al. (2006) Analysis of the human protein interactome and comparison with yeast, worm and fly interaction datasets. Nat Genet 38: 285-293
- **Directly comparing networks by homology**
  - Kelley, B. P., Sharan, R., Karp, R., Sittler, E. T., Root, D. E., Stockwell, B. R., and Ideker, T. Conserved pathways within bacteria and yeast as revealed by global protein network alignment. Proc Natl Acad Sci U S A 100, 11394-9 (2003).
- **Indirect measures of network evolution (…)**

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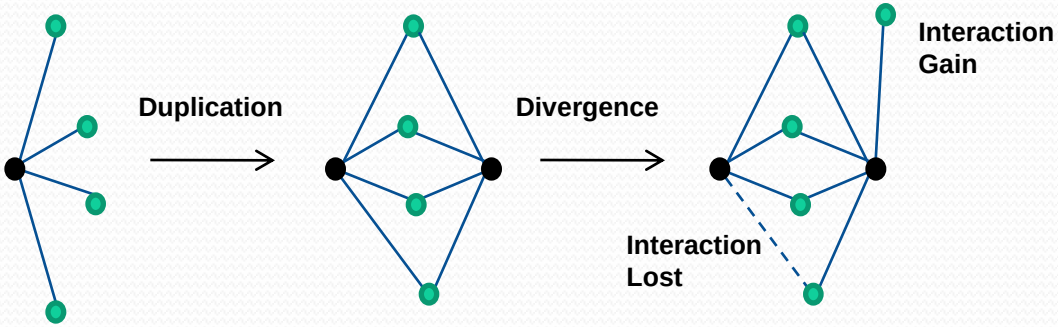
Indirect measure of network evolution

Even without comparing interaction networks of different species it should be possible to gain insights into protein network evolution by studying gene duplications.



Based on 13 interactions found within pairs of duplicated proteins, Wagner calculated a rate of 2.88 10^{-6} new interactions per protein pair per My. Approximately **50 newly evolved interactions per million years**.

According to Wagner (2001), after 50My less than 20% of duplicates share interactions

Wagner A (2001) The yeast protein interaction network evolves rapidly and contains few redundant duplicate genes. Mol Biol Evol 18: 1283-1292.

Evolution of PINs

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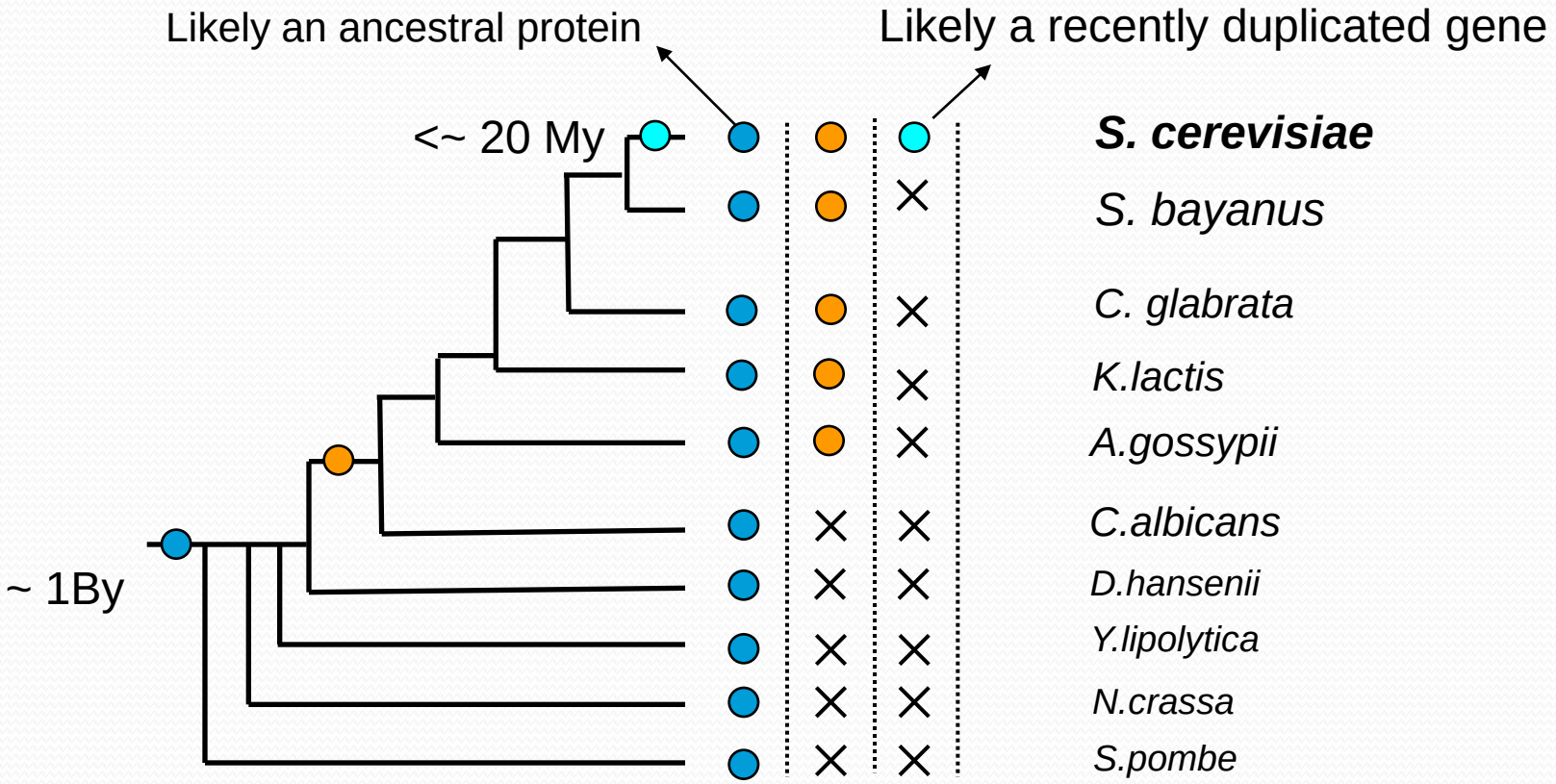
Assign protein "age" by looking at the phylogenetic distribution of orthologs



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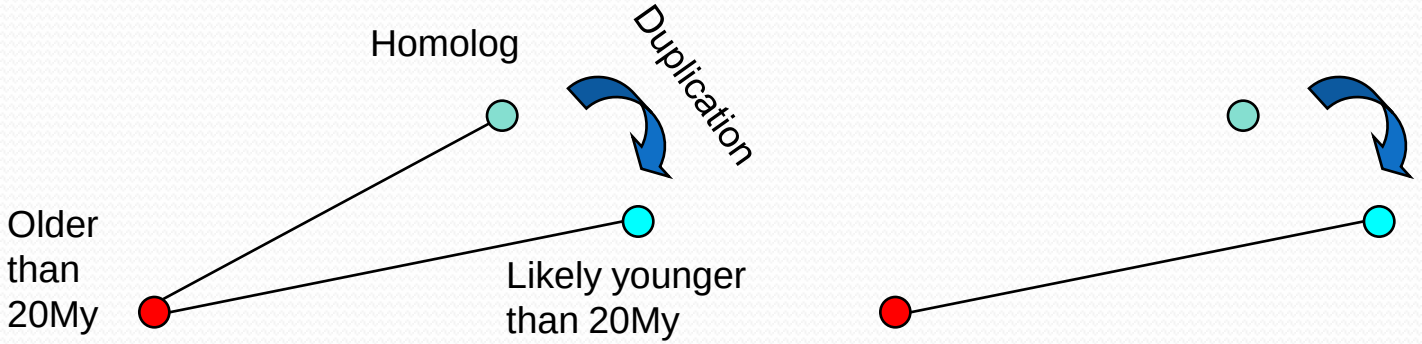
Evolution of PINs



The interaction was inherited with the duplication

The interaction was created or lost in one of the proteins after duplication

OR poor coverage

Rate = <u>interactions between old and new + interactions between new proteins</u>

possible proteins pairs * divergence time

Eukaryotic network evolution

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Species studied	*D. melanogaster*	*C. elegans*	*S. cerevisiae*	*H. sapiens*
Approximate divergence from reference species (My)	40	100	20	70
Older proteins with interactions	5761	1774	4190	6111
Recently duplicated proteins with interactions	788	412	514	266
Interactions to a new protein	3721	892	1207	729
Interactions gained or lost	3615	854	1120	623
Percentage of interactions conserved after duplication (%)	3	4	7	15
Rate for change of interactions (per protein pair per My)	$1.86\ 10^{-5}$	$1.05\ 10^{-5}$	$2.45\ 10^{-5}$	$5.36\ 10^{-6}$

Eukaryotic interactomes have added new interaction in the recent evolutionary past at a rate on the order of **$1\ 10^{-5}$ new interactions per protein pair per My.**

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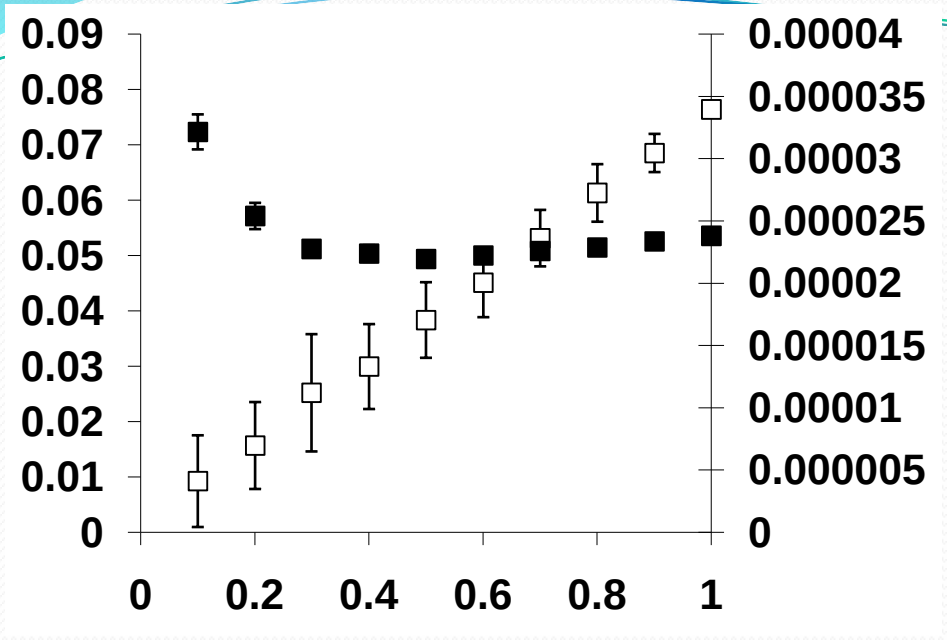
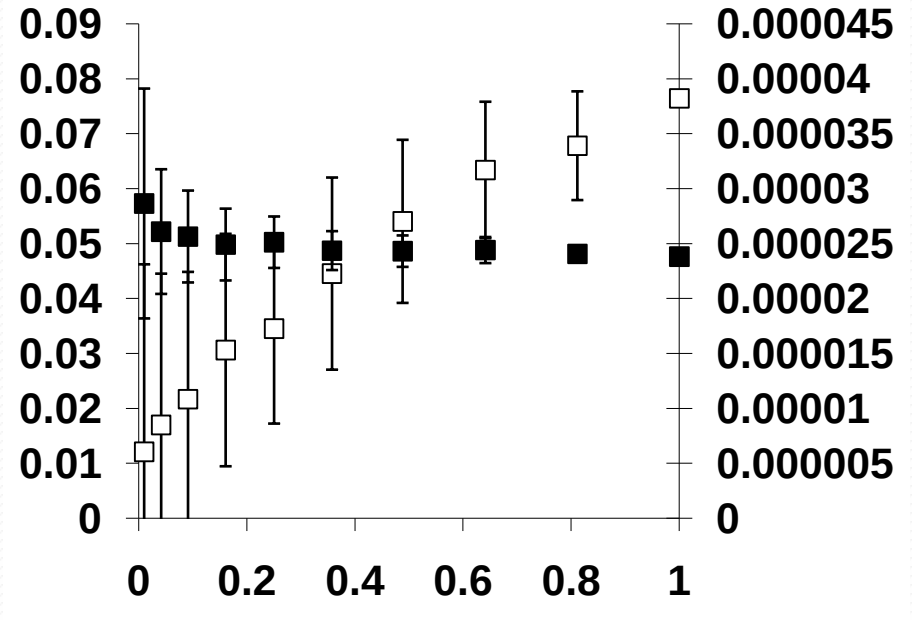
Random interaction removal



Random node removal



Percentage of inherited interactions depends on network coverage

The rate of change of interactions is mostly independent on network size.

Impact of estimated rate

- 100 to 1000 new interactions might be change every My
- Estimated **link turnover** would likely change **0.5% to 3% of the interactions every My**
- Link dynamics can have a very significant impact on the protein interaction networks in a relative short amount of (evolutionary) time.
- Does not mean functions are not conserved

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Preferential turnover

- Bin “old” proteins according to the number of interactions they have among themselves
- For each group calculate the rate of change of interactions

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Preferential turnover

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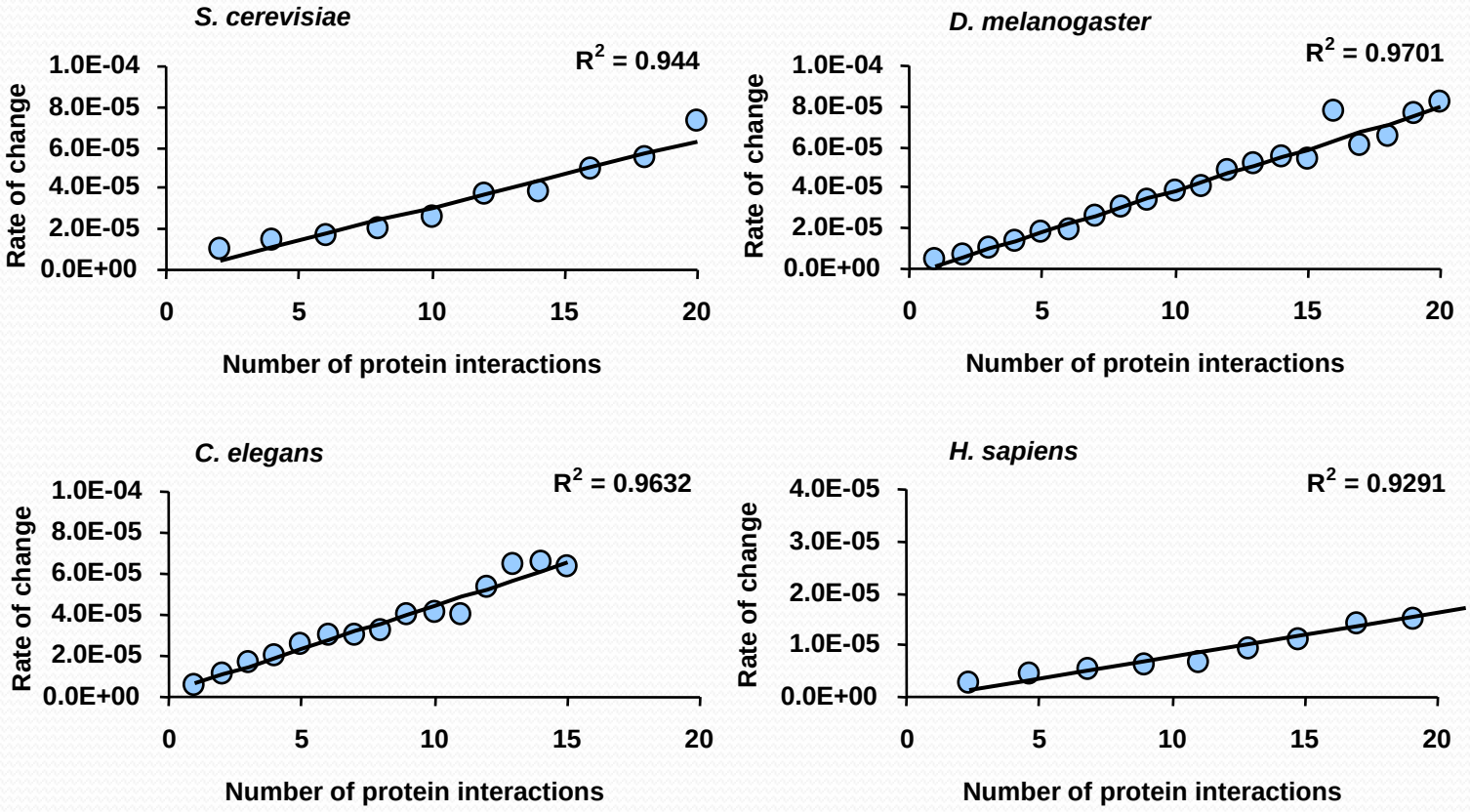

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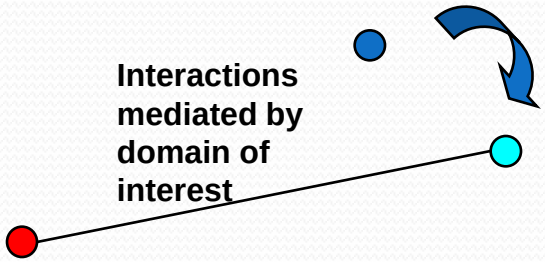
Specificity and evolvability

What protein domains associate with fast evolution of protein interactions?

Domain rate of change > average rate in 3 of 4 species



Domain Name
BTB/POZ
Band 4.1
UBA
Protein kinase
SH2
PDZ
SH3
SH3 variant

Except the UBA and BTB/POZ domain, all other are known to bind peptides.

- Bind linear peptides
- Low specificity interactions

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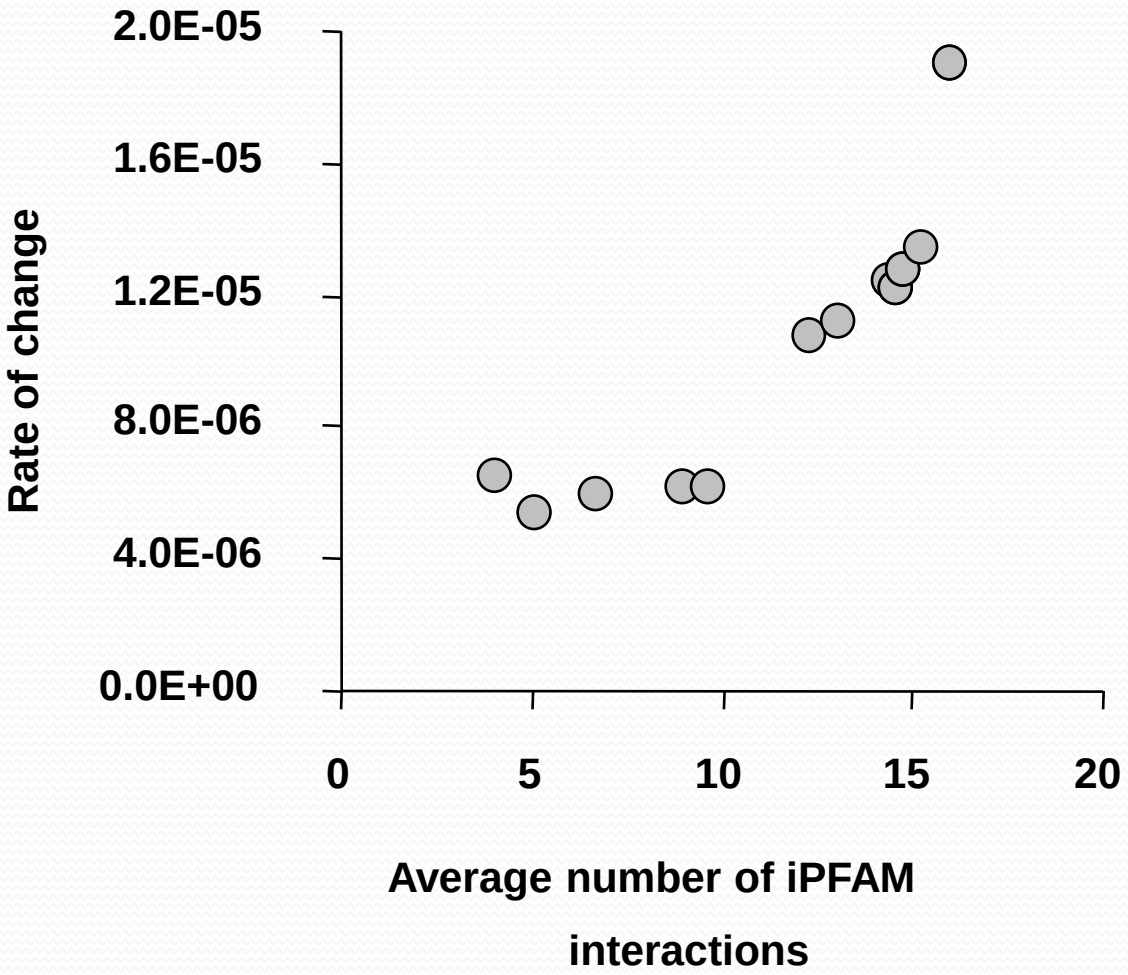
Specificity and evolvability



Protein specificity might be a factor determining likelihood of change of new interactions.

Using iPfam , a database of structures with interacting protein domains (including crystal contacts), we binned protein binding domains with increasing number of interactions.

We used the number of iPfam interactions as a proxy for binding specificity.

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Specificity and evolvability

Using only the Human interactions network and excluding the high-throughput interactions.

Selected "old" proteins that have promiscuous domains, selective domains or peptide binding domains.

	Average for proteome	Selective domains	Peptide binding domains	Promiscuous domains
Number of Interactions	5.17	5.92	11.26	11.48
Rate	6.21×10^{-06}	6.35×10^{-06}	1.23×10^{-05}	1.81×10^{-05}
Ratio to average rate		1.02	1.98	2.92
p-value Mann U test		0.866	0.015	5.767×10^{-08}

Less specific interaction types evolve faster

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Protein function and evolvability

- Natural selection will likely bias the interactions that are retained in a population
- Different functions will have proteins with different likelihoods of adding (and maintaining trough selection) new interactions.
- To test this we grouped proteins according to GO function

Selection for interaction turnover

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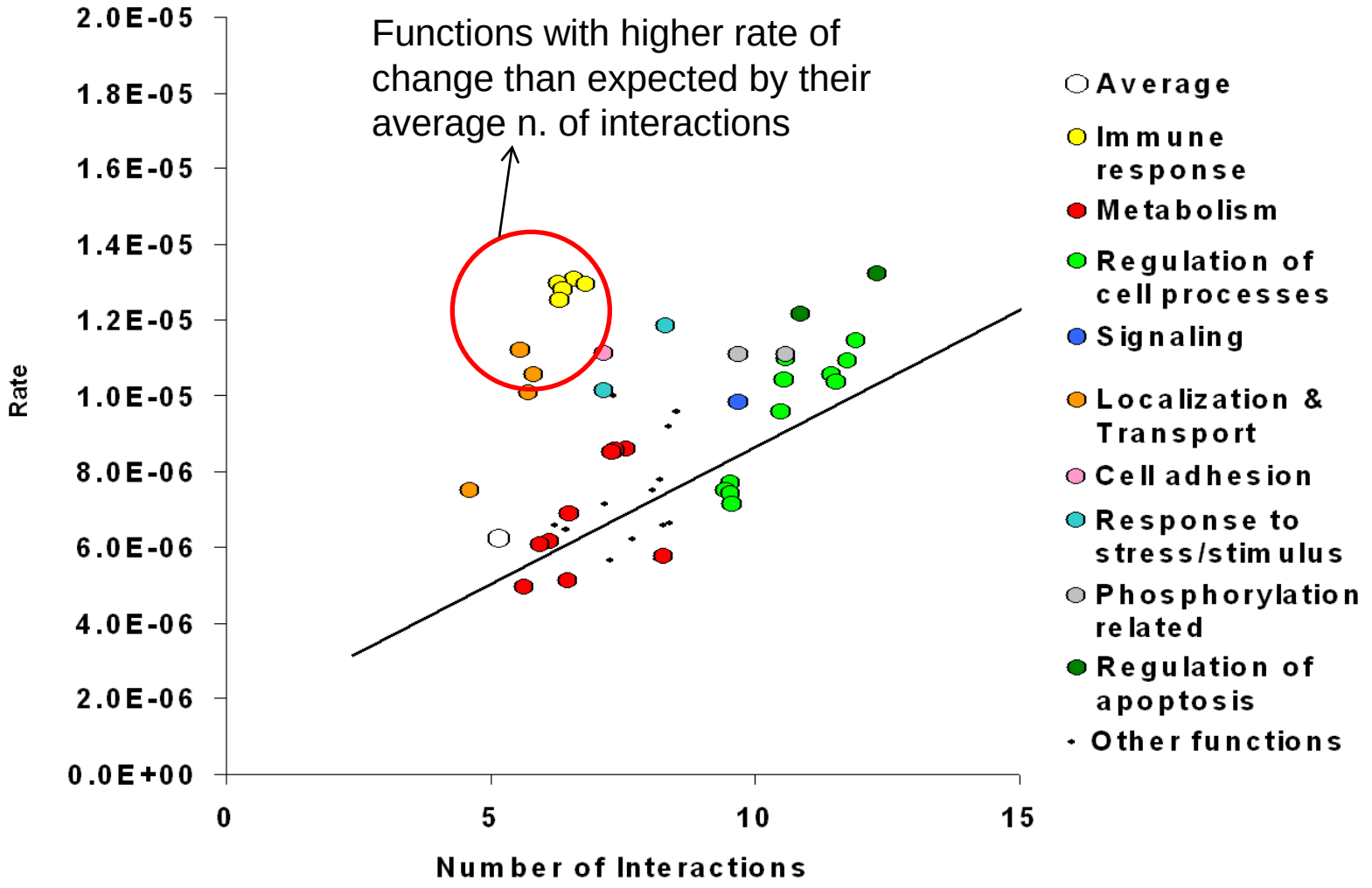

Summary

- Interaction networks have changed interactions at a fast rate.
  - Link dynamics plays an import role in the evolution of protein interaction networks
- Specificity of binding is a factor determining the likelihood of change of interactions.
  - Hypothesis – Cells require binding domains with different specificities and this in turn determines the power law distribution.
- Even at this stage (of low coverage) it is possible to look for functions under positive selection for fast link dynamics
  - Human proteins involved in immune response, transport and establishment of localization

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Searching for solutions

- Mutations at the protein level
  - Improving proteins (enzyme's rate, protein stability)
- Link dynamics
  - Looking for network solutions (bistability, noise suppression)

Fast link dynamics allows for the search of optimal network solutions to biological problems.

If so, we should observe convergent evolution of network motifs in protein interactions networks

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