Comparative Analysis of Molecular Interaction Networks

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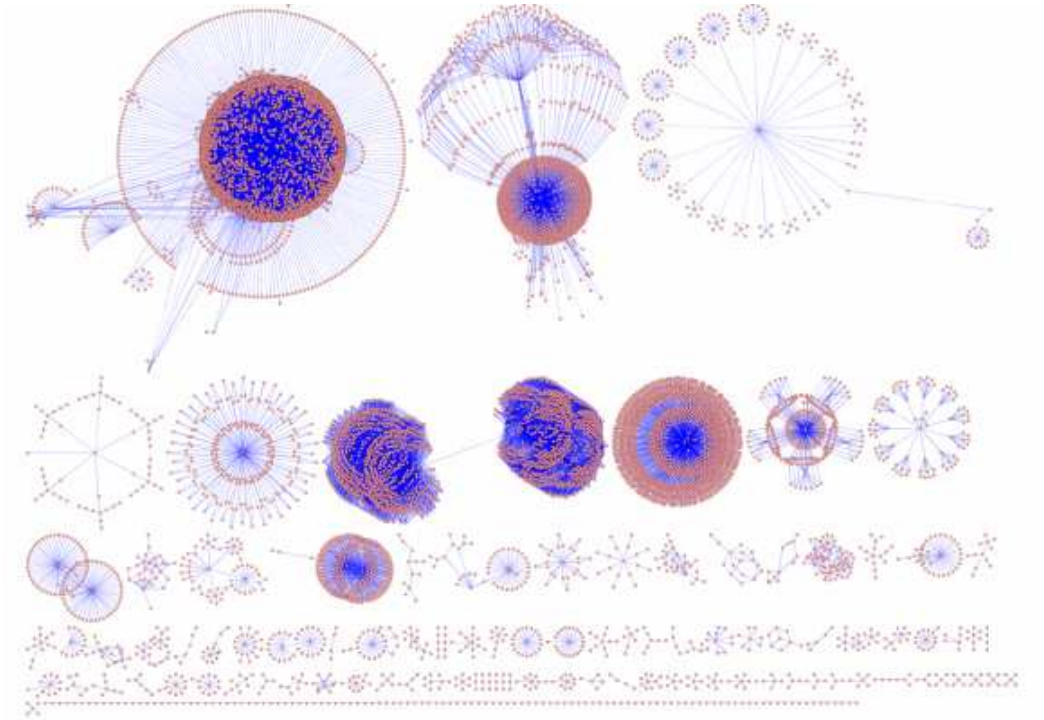
Outline

- Molecular Interaction Networks
  - Modeling, evolution, problems, practical implications
- Algorithms for Analyzing Molecular Interaction Networks
  - Conservation, Inference, Projection, Up- and Down-scaling
- Networks, Annotations, and Phenotypic Characterization
  - Correlations across genotype, SNPs, transcriptional relationships, etc.

The AfCS Molecule Pages



The complete state network of Molecule Pages, which currently consists of 13883 states and 20556 transitions among these states (`http://www.signaling-gateway.org/molecule/`).

Evolution of Molecular Interactions

- "Evolution thinks modular" (Vespignani, *Nature Gen.*, 2003)
- Cooperative tasks require all participating units
  - Selective pressure on preserving interactions & interacting proteins
  - Interacting proteins follow similar evolutionary trajectories (Pellegrini et al., *PNAS*, 1999)
- Orthologs of interacting proteins are likely to interact (Wagner, *Mol. Bio. Evol.*, 2001)
  - Conservation of interactions may provide clues relating to conservation of function
- Modular conservation and alignment hold the key to critical structural, functional, and evolutionary concepts in systems biology

Conserved Interaction Patterns

- Given a collection of interaction networks (belonging to different species), find sub-networks that are common to an interesting subset of these networks (Koyutürk, Grama, & Szpankowski, *ISMB*, 2004)
  - A sub-network is a group of interactions that are tied to each other (connected)
  - Frequency: The number of networks that contain a sub-network, is a coarse measure of statistical significance
  - Subgraph Isomorphism!

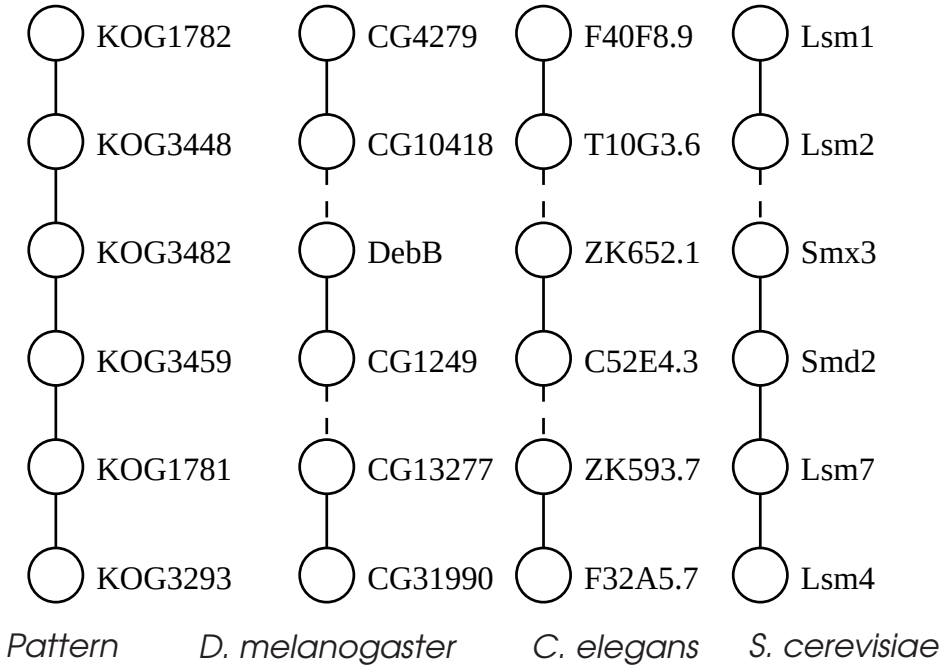
Algorithmic Insight: Ortholog Contraction

- Contract orthologous nodes into a single node
- No subgraph isomorphism
  - Graphs are uniquely identified by their edge sets
- Key observation: Frequent sub-networks are preserved $\Rightarrow$ No information loss
  - Sub-networks that are frequent in general graphs are also frequent in their ortholog-contracted representation
  - Ortholog contraction is a powerful pruning heuristic
- Discovered frequent sub-networks are still biologically interpretable!
  - Interaction between proteins becomes interaction between ortholog groups

Results: Analyzing PPI Networks

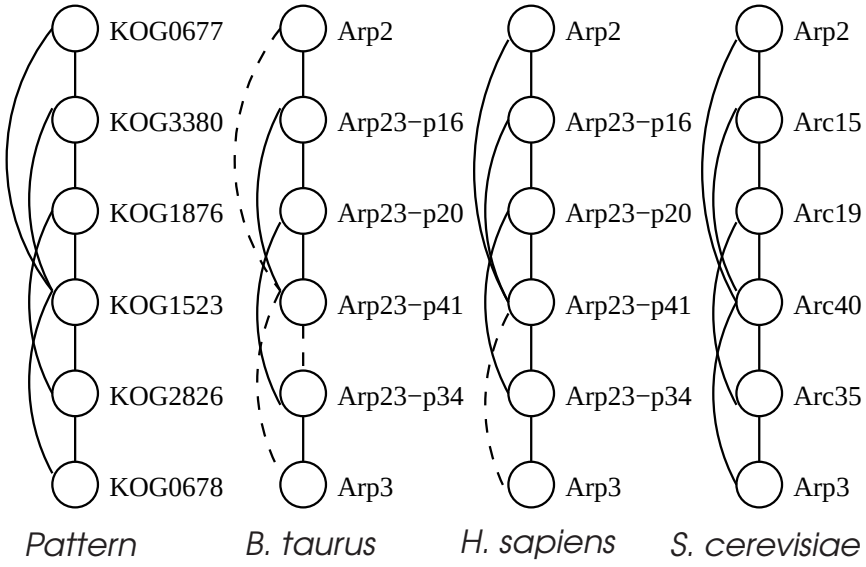
- PPI networks for 9 eukaryotic organisms derived from BIND and DIP
  - *A. thaliania, O. sativa, S. cerevisiae, C. elegans, D. melanogaster, H. sapiens, B. taurus, M. musculus, R. norvegicus*
  - # of proteins ranges from 288 (*Arabidopsis*) to 8577 (*fruit fly*)
  - # of interactions ranges from 340 (*rice*) to 28829 (*fruit fly*)
- Ortholog contraction
  - Group proteins according to existing COG ortholog clusters
  - Merge Homologene groups into COG clusters
  - Cluster remaining proteins via BLASTCLUST
  - Ortholog-contracted *fruit fly* network contains 11088 interactions between 2849 ortholog groups
- MULE is available at `http://www.cs.purdue.edu/pdsl/`

Conserved Protein Interaction Patterns



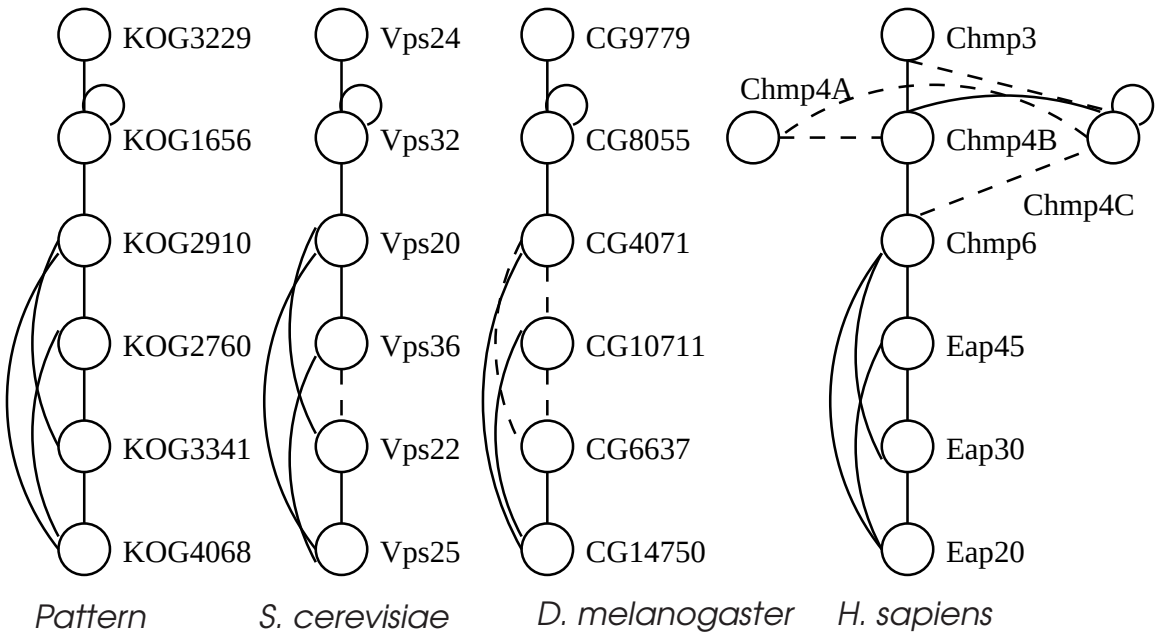
Small nuclear ribonucleoprotein complex ($p < 2e - 43$)

Conserved Protein Interaction Patterns



Actin-related protein Arp2/3 complex ($p < 9e - 11$)

Conserved Protein Interaction Patterns



Endosomal sorting ($p < 1e - 78$)

State of the Art

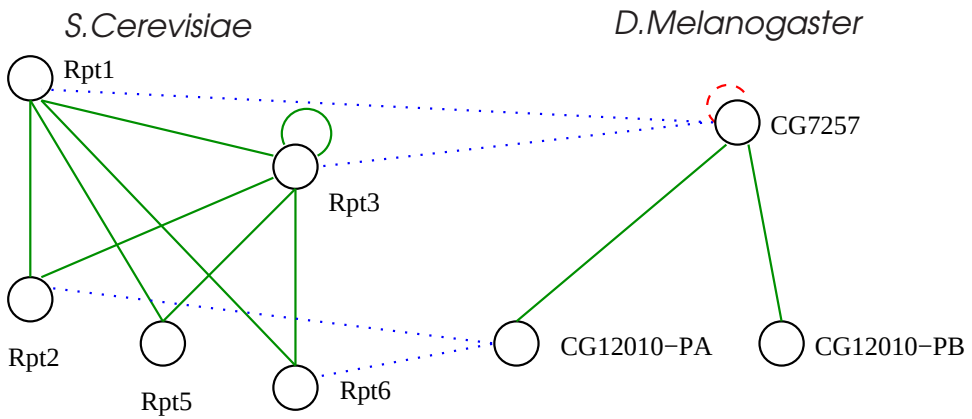
- Data is the bottleneck (in-silico construction of the network?).
- Reliable data on no more than ten organisms. Networks with thousands of nodes and tens of thousands of interactions.
- The exponential complexity of these algorithms makes them ideal candidates for large-scale platforms.
- Current implementations scale to thousands of processors and take days of runtime.

Alignment of Networks

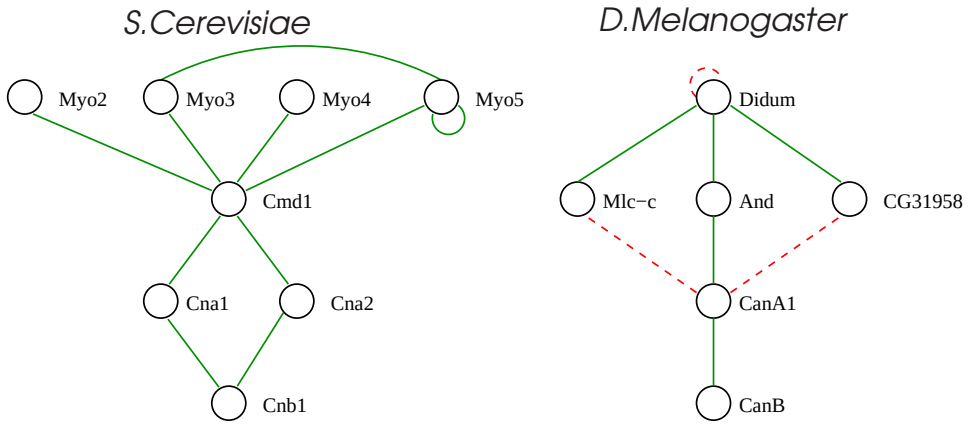
- Given two PPI networks that belong to two different organisms, identify sub-networks that are similar to each other
  - Biological implications
  - Mathematical modeling
- Existing algorithms
  - PathBLAST aligns pathways (linear chains) to simplify the problem while maintaining biological meaning (Kelley et al., *PNAS*, 2004)
  - NetworkBLAST compares conserved complex model with null model to identify significantly conserved subnets (Sharan et al., *J. Comp. Biol.*, 2005)
- Our approach (Koyutürk et al., *RECOMB*, 2005) (Koyutürk et al., *J. Comp. Biol.*, 2006)
  - Guided by models of evolution
  - Scores evolutionary events
  - Identifies sets of proteins that induce high-scoring sub-network pairs

Subnets Conserved in Yeast and Fruit Fly Using our Technique

Proteosome regulatory particle subnet



Calcium-dependent stress-activated signaling pathway



State of the Art

- Local methods are suited to identification of modularity.
- Global methods (IsoRank, Berger et al.) support functional orthology.
- Can we improve the search efficiency and coverage of greedy (local) methods?
- Speed up the eigenvalue computations of spectral methods.
- Current algorithms scale to thousands of processors.
- Data quality is a key concern.

Continuing Developments

- Building comprehensive maps that model crosstalk and weak signals (inference, modularity).
- Constructing accurate flux models (data?)
- Full scale flux analysis for molecular processes.

Continuing Developments

- Scaling molecular networks in space and time.
- Spatial scales must integrate atomistic models, scaling to cellular scale, tissue scale, individual, populations, ecosystems.
- Temporal scales must reconstruct evolution and project trajectories.

Functional and Phenotypic Characterization

- Integrate large-scale SNP data, genomic data into functional characterization of networks.
- Comprehensively characterize causality in disease specific networks.
- Supporting full-scale in-silico design of molecules.

References

- J. Pandey, M. Koyuturk, S. Subramaniam, and A. Grama. Functional coherence in domain interaction networks, Bioinformatics Suppl. on ECCB'08.
- M. Koyuturk, W. Szpankowski, and A. Grama, Assessing significance of connectivity and conservation in protein interaction networks, Journal of Computational Biology, 14(6), 747-764, 2007.
- M. Koyuturk, Y. Kim, S. Subramaniam, W. Szpankowski, and A. Grama, "Detecting conserved interaction patterns in biological networks", *Journal of Computational Biology*, 13(7), 1299-1322, 2006.
- M. Koyuturk, Y. Kim, U. Topkara, S. Subramaniam, W. Szpankowski, and A. Grama, Pairwise Alignment of Protein Interaction Networks, *Journal of Computational Biology*, 13(2), 182-199, 2006.
- Y. Kim, M. Koyuturk, U. Topkara, A. Grama, and S. Subramaniam, Inferring Functional Information from Domain Co-evolution, *Bioinformatics*, 22(1), pp. 40-49, 2006.

References

- M. Koyutürk, A. Grama, and W. Szpankowski, An Efficient Algorithm for Detecting Frequent Subgraphs in Biological Networks, *Bioinformatics*, Vol. 20, Suppl. 1, pp i200-i207, 2004.
- M. Koyuturk, A. Grama, and W. Szpankowski, Assessing Significance of Connectivity and Conservation in Protein Interaction Networks, *10th International Conference on Research in Computational Molecular Biology (RECOMB)*, LNBI 3909, pp. 45-59, 2006.
- M. Koyutürk, A. Grama and W. Szpankowski, Pairwise Local Alignment of Protein Interaction Networks Guided by Models of Evolution, RECOMB 2005.

Available from `http://www.cs.purdue.edu/pdsl`