



MAPK Signaling Pathway Analysis

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Presentation by:

Gergana Bounova, Michael Hanowsky and Nandan Sudarsanam

Faculty: Chris Magee



Agenda

- Biological Network Analysis in the Literature
- Motifs and Coarse Graining
- Results
- Where to next



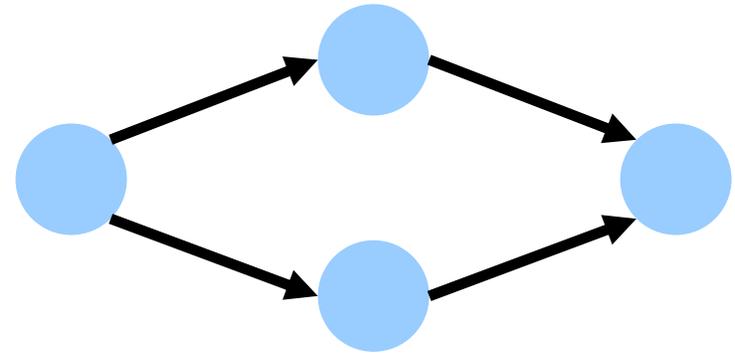
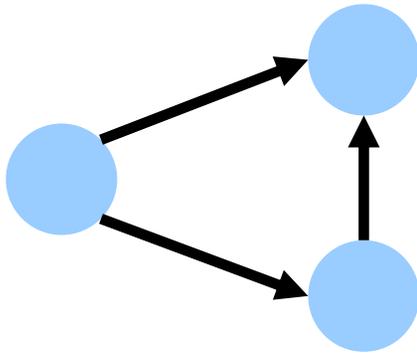
Literature Review

- Biological networks are full of patterns
 - Functional Structures (Maslov and Kneppen [3], Barabasi and Oltvar [6])
 - Motifs (Milo et al. [8])
 - Coarse-Graining (Iztkovitz et al. [7])
- Network graph behavior
 - Degree distribution follows a power law (Jeong et al. [2], [6])
 - Robustness ([3])



Motifs and Coarse-Graining (Milo et al.)

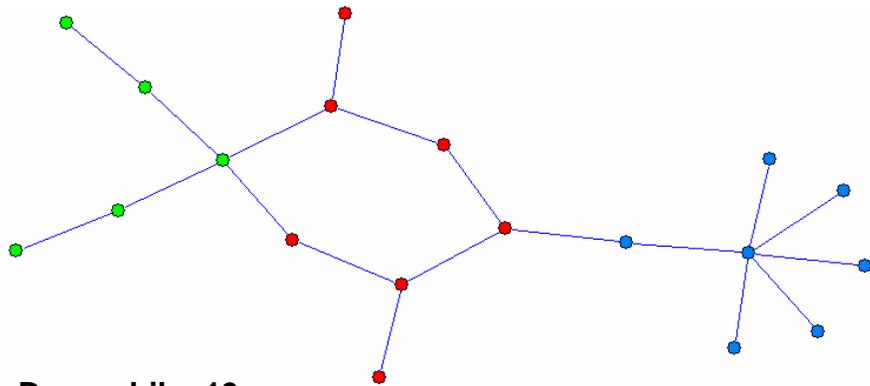
- Some motifs occur much more often in biological networks than they would randomly



- ...but many of the Milo motifs do not occur in our network!
 - Do not occur
 - Look for other patterns
 - Our data has already been coarse-grained

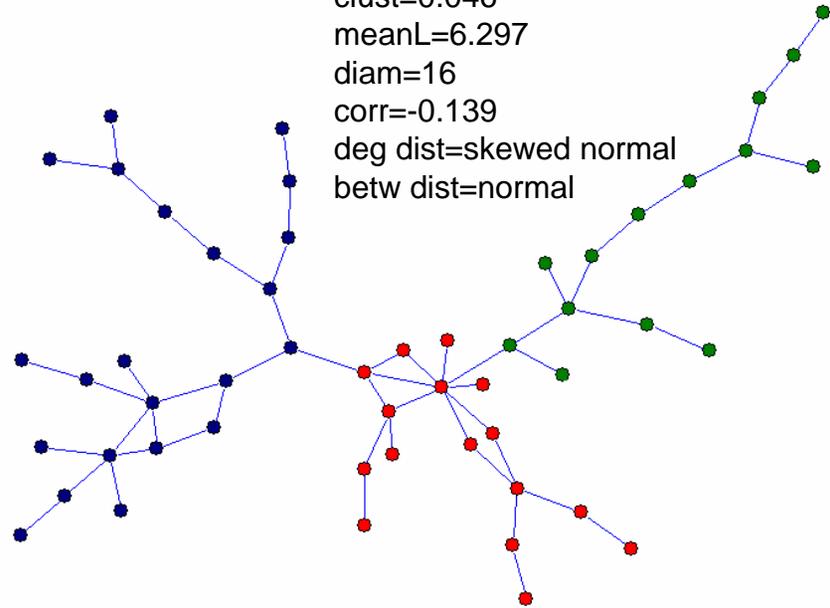


Results I: Undirected



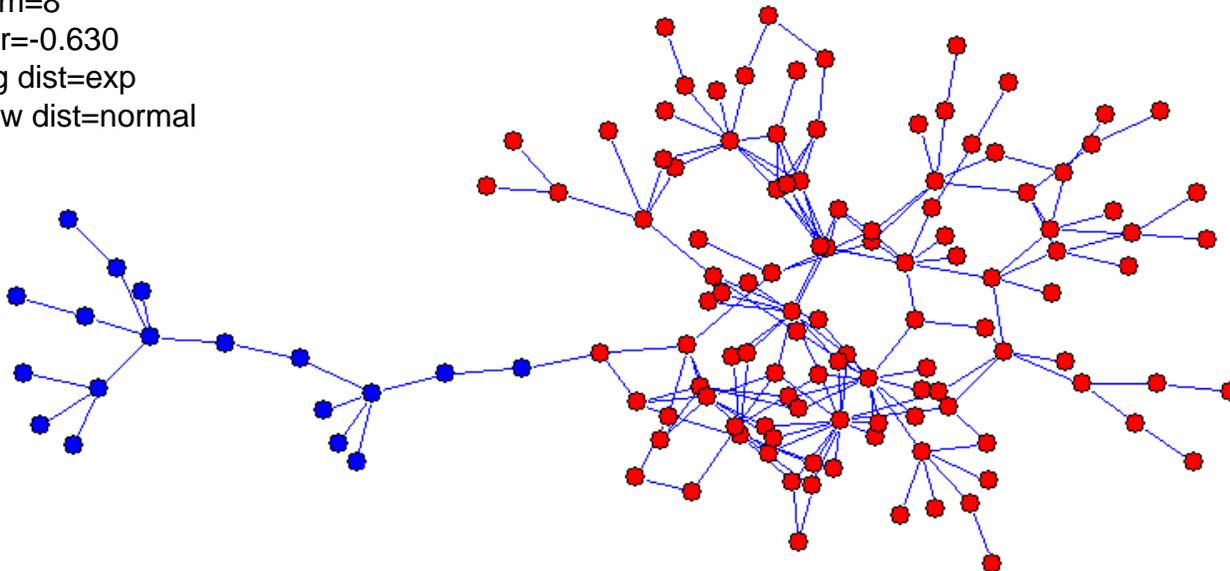
Drosophila: 19

$m/n=1$
clust=0
meanL=3.836
diam=8
corr=-0.630
deg dist=exp
betw dist=normal



Yeast: 56

$m/n=1.069$
clust=0.046
meanL=6.297
diam=16
corr=-0.139
deg dist=skewed normal
betw dist=normal



Human: 148

$m/n=1.264$
clust=0.005
meanL=6.454
diam=17
corr=-0.306
deg dist=skewed normal
betw dist=not quite normal



Results II: Directed

- All directed graphs are mostly disconnected
- Distributions different in most cases: skewed normal and double peaked distributions
- Central nodes are different from directed graph analysis
- Performed flow experiment: find essential nodes on source (stimuli) to sink (products) shortest paths
 - D. Melanogaster: Tor, Drk, Ph1, Dsor1, Rolled
 - S. cerevisiae: Ste11, Ste20
 - Human: ASK1



Results III

	Drosophila	Yeast	Human
Number of nodes	19	56	148
Number of edges	19	62	187
Edge to node ratio	1.0	1.069	1.264
Connected?	Yes	No	No
Number of conn components	1	5	16 { }
Deg {min, mean, min }	{6,2,1 }	{8,2.296,1 }	{15, 2.831, 1 }
Max degree node	9 (Rolled)	Kks2	98: p38
Degree correlation	-0.630	-0.139	-0.306
Average clustering coefficient	0.0	0.046	0.005
Highest clustering coeff node	n/a	3	106
Number of triangle loops	0	4	3
Number of rectangle loops	0		
Mean path-length	3.836	6.297	6.454
Network diameter	8	16	17
Node-betw {max, mean, min }	{27, 23.737, 20 }	{198, 90.481, 63 }	{4639, 1035.538, 384 }
Most in-between node	Drk, Egfr, Grk, Boss, Sev	Dig1,2	cAMP
Degree distribution	Exponential	skewed normal	skewed normal
Betweenness distribution	normal	normal	Normal-like with other peaks
Clustering coeff distribution	all zero	~ uniformly zero	~ uniformly zero
Pathlength distribution	Normal		
Source to sink shortest paths highest in-betweenness nodes	Tor, Drk, Ph1, Dsor1, Rolled	44,48: Ste11, Ste20	ASK1



Moving Forward...

- Much of the literature focuses on applying topological analyses to biological networks
 - Does not seek to explain the cause of observed behavior
 - Generalizes important network properties
- ...But we can also look at what the biology tells us about networks
 - Focus on the communicative aspects of the network
 - Consider the directionality of the network
 - Treat activators and inhibitors differently



MAPK Pathway (Directed)

Image removed for copyright reasons.

See: http://www.genome.jp/dbget-bin/get_pathway?org_name=ko_hsa&mapno=04010



Literature

- [1] Ito et al., *A Comprehensive Two-Hybrid Analysis to Explore the Yeast Protein Interactome*, PNAS, vol. 98 no. 8 pp 45-69, 2001
- [2] Jeong, Mason, Barabasi, and Oltvai, *Lethality and Centrality in Protein Networks*, Nature vol. 411 pp 41-42, 2001
- [3] Maslov and Kneppen, *Specificity and Stability in Topology of Protein Networks*, Science vol. 296 pp 910-913, 2002
- [4] Mansfield, Judson, Knight, Lockshon, Narayan, Srinivasan, Pochart, et al., *A Comprehensive Analysis of Protein-Protein Interactions in Saccharomyces cerevisiae*, Nature vol. 403 p 623, 2000
- [5] Sole, Pastor-Santorras, Smith, and Kepler, *A Model of Large-Scale Proteome Evolution*, Advances in Complex Systems vol. 5 pp 43-54, 2002
- [6] Barabasi and Oltvar, *Network Biology: Understanding the Cell's Functional Organization*, Nature Reviews vol. 5 pp 101-114, Feb 2004
- [7] Itzkovitz, Levitt, Kashtan, Milo, Itzkovitz, and Alon, *Coarse-Graining and Self-Dissimilarity of Complex Networks*, Physical Review vol. 71, 2005
- [8] Milo, Shen-Orr, Itzkovitz, Kashtan, Chklovskii, and Alon, *Network Motifs: Simple Building Blocks of Complex Networks*, Science vol. 298 pp 824-827, 2002
- [9] Buonova, Hanowsky, and Nandan, *MAPK Signaling Pathway Analysis*, ESD.342, Spring 2006



Additional Slides....



Drosophila Data Table

Network Metrics	Drosophila Undirected	Drosophila Directed
Number of nodes	19	19
Number of edges	19	19
Edge to node ratio	1.0	1
Connected?	yes	No
Number of conn components	1	n/a
Deg {min, mean, min}	{6,2,1}	in: {3,2,1}, out: {5,2,1}
Max degree node	9 (Rolled)	in: Drk, out: Rolled
Degree correlation	-0.630	n/a
Average clustering coefficient	0.0	0.0
Highest clustering coeff node		n/a
Number of triangle loops	0	0
Number of rectangle loops	0	0
Mean path-length	3.836	4.0752 (among non-inf paths)
Network diameter	8	n/a
Node-betw {max, mean, min}	{27, 23.737, 20}	{14, 8, 1}
Most in-between node	Drk, Egfr, Grk, Boss, Sev	Tll, Hkb, Dorsal Patterns, Boss, Sev
Degree distribution	Exponential	Exponential
Betweenness distribution	normal	2-peak distribution
Clustering coeff distribution	n/a	n/a
Pathlength distribution	Normal	Uniform-like
Source to sink shortest paths highest in-betweenness nodes	Tor, Drk, Ph1, Dsor1, Rolled	Ph1, Dsor1, Rolled



Yeast Data Table

Network Metrics	Yeast Undirected	Yeast Directed
Number of nodes	56	56
Number of edges	62	56
Edge to node ratio	1.069	1
Connected?	No	No
Number of conn components	5	
Deg {min, mean, min}	{8,2.296,1}	{8, 2, 0}, in: {5,1,0}, out: {4,1,0}
Max degree node	Kks2	6, in: 6, out: 45
Degree correlation	-0.139	
Average clustering coefficient	0.046	0.0119
Highest clustering coeff node	3	38
Number of triangle loops	4	0.5?
Number of rectangle loops		
Mean path-length	6.297	
Network diameter	16	inf
Node-betw {max, mean, min}	{198, 90.481, 63}	{28, 12.125, 1}
Most in-between node		8, 19
Degree distribution	skewed normal	skewed normal, in-degree: skewed normal, out-degree: poisson
Betweenness distribution	normal	2-peak distribution
Clustering coeff distribution		n/a
Pathlength distribution		
Source to sink shortest paths highest in-betweenness nodes	44,48: Ste11, Ste20	MATalpha



Mammal Data Table

Network Metrics	Mammals Undirected	Mammals Directed
Number of nodes	148	148
Number of edges	187	187
Edge to node ratio	1.264	1.264
Connected?	No	No
Number of conn components	16 { }	
Deg { min, mean, min }	{ 15, 2.831, 1 }	{ 15, 2.527, 0 }, in-deg: { 6, 1.264, 0 }, out-deg: { 13, 1.264, 0 }
Max degree node	98: p38	98: p38, in: 23: CREB, out: 98: p38
Degree correlation	-0.306	
Average clustering coefficient	0.005	0
Highest clustering coeff node	106	0
Number of triangle loops	3	0
Number of rectangle loops		
Mean path-length	6.454	
Network diameter	17	
Node-betw { max, mean, min }	{ 4639, 1035.538, 384 }	{ 383, 37.6689, 1 }
Most in-between node	12	145: DNA2
Degree distribution	skewed normal	skewed normal, in-degree: poisson, out-degree: normal
Betweenness distribution		exponential
Clustering coeff distribution		
Pathlength distribution		
Source to sink shortest paths highest in-betweenness nodes	ASK1	AKT

