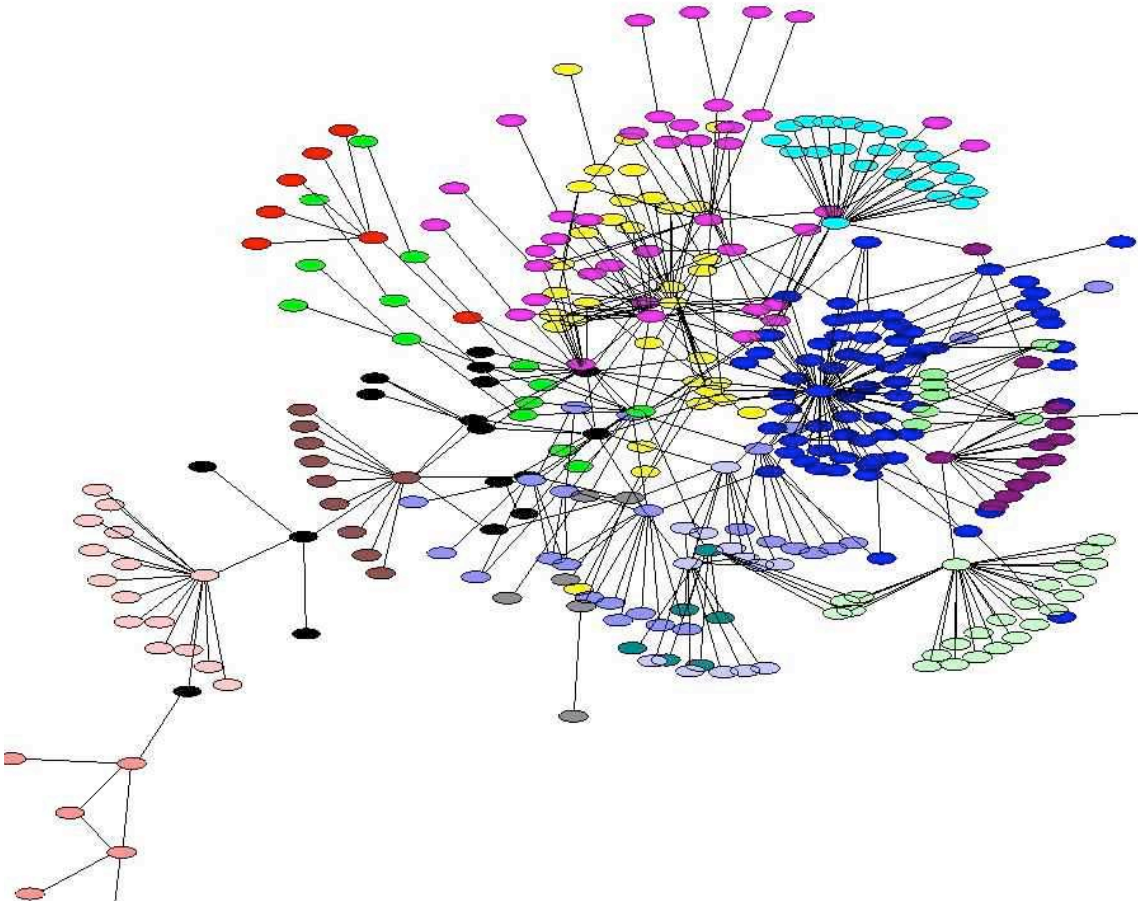
ECS 253 / MAE 253

April 26, 2016



“Intro to Biological Networks, Motifs, and Model selection/validation”

Announcement

- HW2, due May 3 (one week)
- HW2b, due May 5
- HW2a, due May 5. Will be posted on Smartsite.
  - A literature review for your project
  - Everyone doing the project must turn in an assignment
  - 1) Give an overview of the main ideas and goals of your project
  - 2) Give a brief literature review with 3-5 papers included in a bibliography.
  - 3) Each team member must do their own literature review. This will add breadth to your project.

Next time: How do we partition a network?

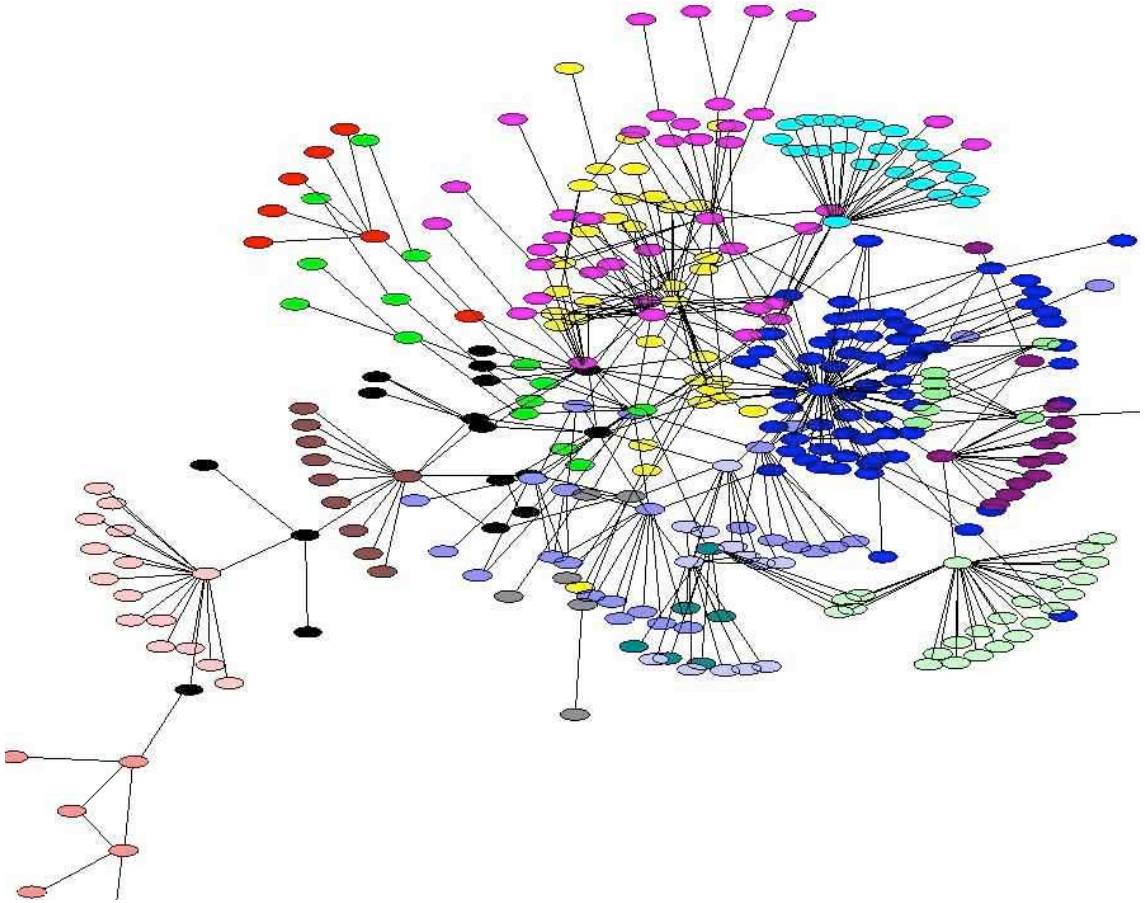
(Still an open question: tons of work on detecting communities, not so much work in interpreting what they mean.)

- Bottlenecks
- Social groups / collaboration networks
- US Congress:
  – Partisan / bi-partison voting patterns (both by party and region)
  – Central players
- Sometimes functional subgroups
  (some evidence in Gene Regulatory networks)

But does the partitioning have meaning?

- Different algorithms can give different results
- Even the same algorithm can give different results!
- In social systems, communities seem to be topically related.
- In biological systems, some evidence that communities relate to function, some evidence they do not relate.
- In mechanical systems proper function seems to span communities.
- Communities help us do good visualization layout (Porter et al AMS Notices 2009)

Today: Biological networks



Biological Networks / Systems Biology

** In Biology, often edges can be activating or inhibiting! **

- Luca Cardelli, http://lucacardelli.name/
- Eivind Almaas, http://www.ntnu.no/ansatte/eivind.almaas
- Sergey Nuzhdin, http://nlab.usc.edu/Site/Home.html

At UCD:

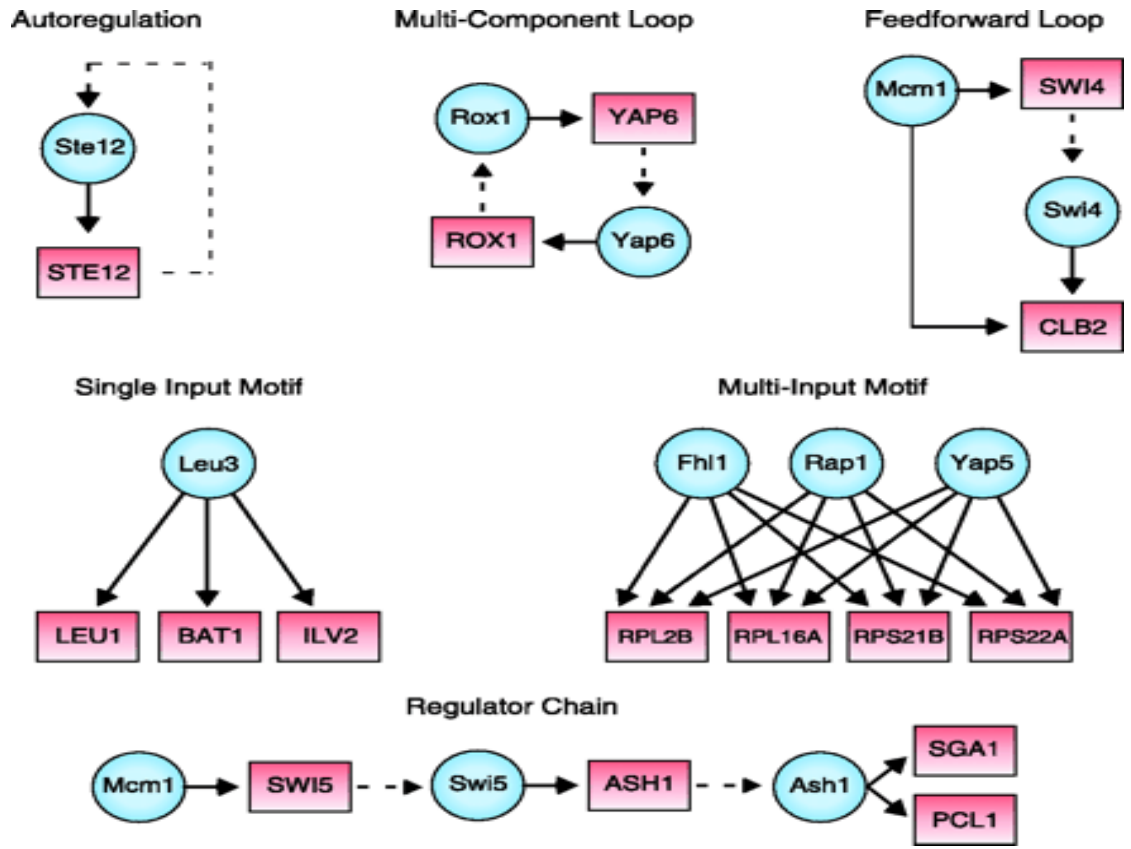
- CS: Vladimir Filkov, Ilias Tagkopoulos, Patrice Koehl, Dan Gusfield,
- Genome center / Biomed engineering: Savageau, Benham, Raychaudhuri, Saiz, Brady, Feihn ....
- Plant Biology: Dandekar, Maloof, ...

Intro to biological networks

See almaasBioNets.pdf

Network motifs

Network Analysis Detects Component Reuse (Network Motifs)



Sergey Nuzhdin slides:

Examples of Biological Networks?

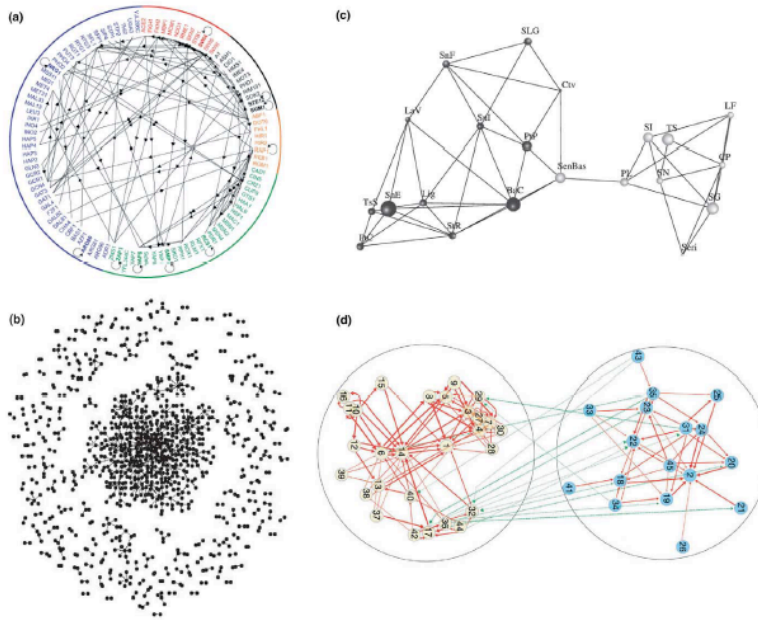
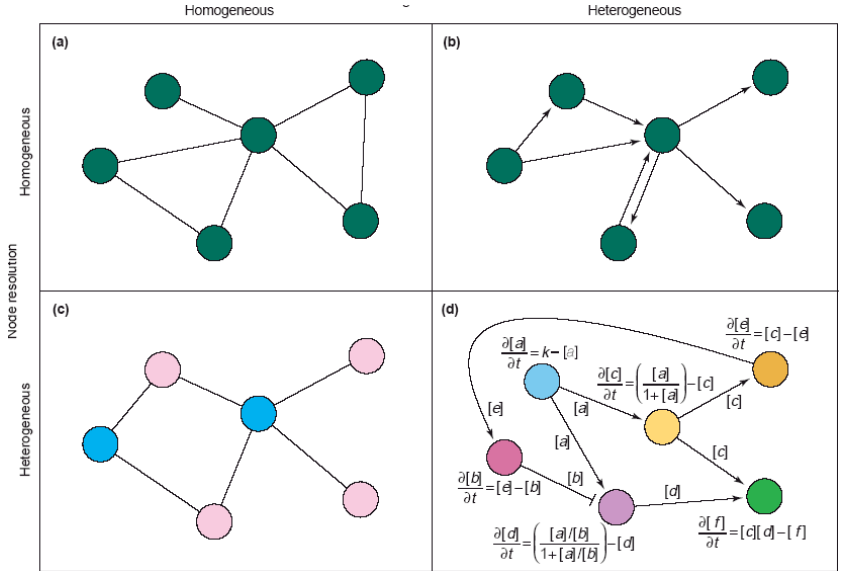
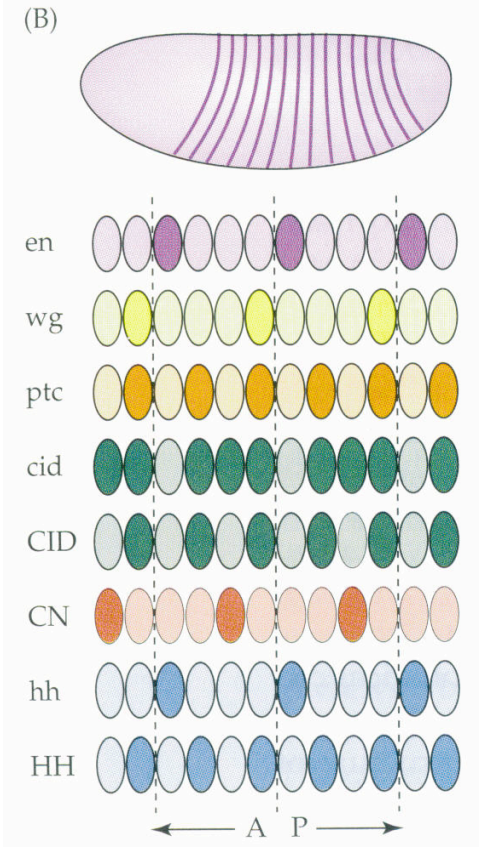
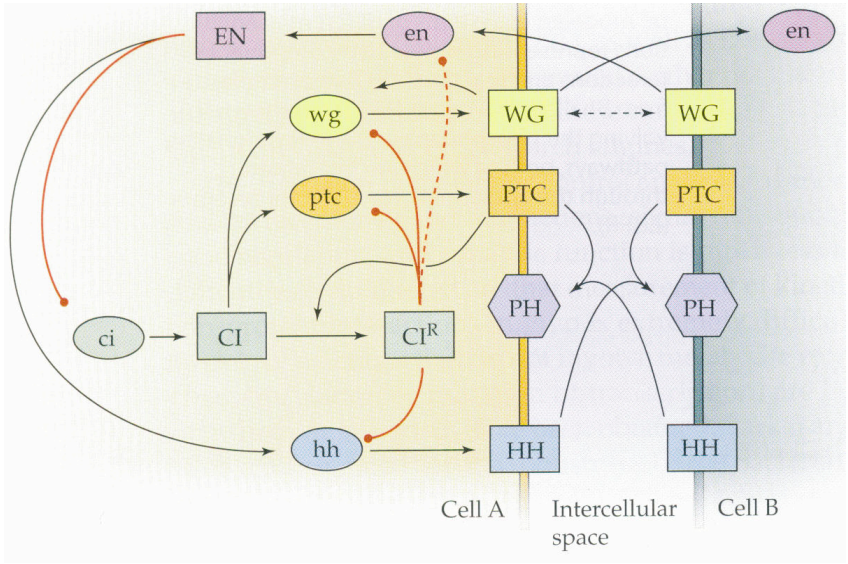


Figure 1. The use of network concepts to explore the structure and function of a variety of biological systems from genes **(a)** and proteins **(b)** to individuals within a population **(c)** and species within an ecosystem **(d)**. (a) The network of regulatory interactions in the yeast *Saccharomyces cerevisiae*, where genes encoding transcription factors interact by binding the regulatory regions of other regulatory genes [16]. (b) The protein interaction network in which proteins that physically interact are connected by edges [17]. (c) The genetic relationship of populations of the cactus *Lophocereus schottii* [18]. In this graph, edge length represents the fraction of the total genetic variation explained by the connected populations. (d) Predator–prey interactions in the Chesapeake Bay food web [19]. Reproduced, with permission from [16] (a), [17] (b), [18] (c) and [19] (d).

c. What are appropriate network descriptions?



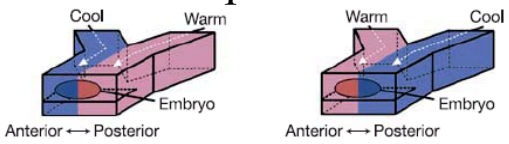


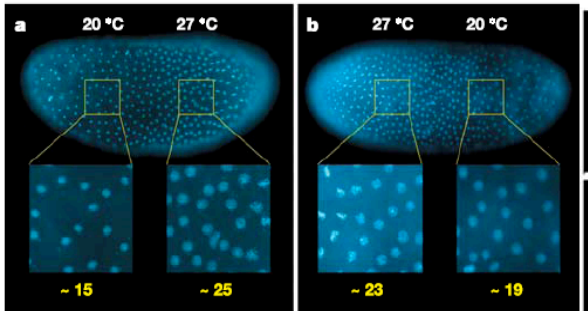


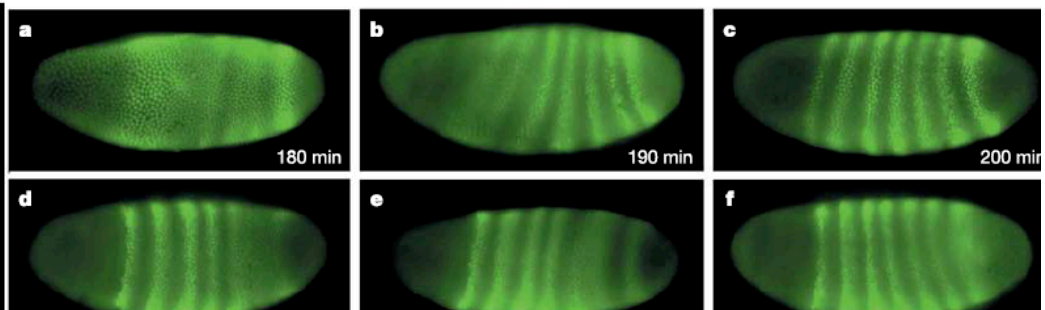
dynamic description
Garry O'Dell, Nature 2001:
19 equations, 54 parameters,

1/2000 random solutions → correct spatial structure.

Most parameters can vary 10,000 fold causing no changes,
Mutation-selection balance?







Literature on validation of network models

- is rather limited

Four useful papers:

- M. Middendorf, E. Ziv, and C. H. Wiggins, “Inferring network mechanisms: The Drosophila melanogaster protein interaction network”, *PNAS* **102** (9), 2005. (About 180 citations.)

- D. Alderson, L. Li, W. Willinger, and J. C. Doyle, “Understanding Internet Topology: Principles, Models, and Validation”, *IEEE/ACM Trans. on Networking*, **13** (6), 2005. (About 170 citations.)

- V. Filkov, Z.M. Saul, S. Roy, R.M. DSouza, P.T. Devanbu, “Modeling and verifying a broad array of network properties”, *Europhys. Lett.* **86**, 2009.

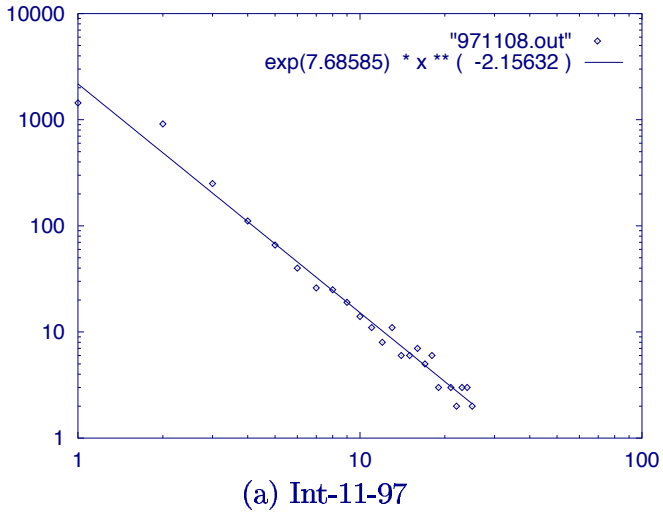
- J. Wang and G. Provan, “Generating Application-Specific Benchmark Models for Complex Systems”, *Proc. Twenty-Third AAAI Conf on Artificial Intelligence*, 2008.

Model validation: Overarching issues

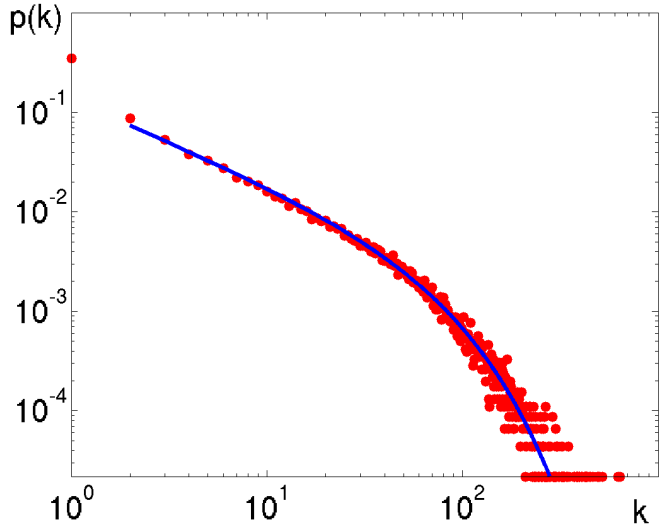
- Many models give rise to same large-scale statistics (e.g., degree distribution, diameter, clustering coefficient).
- Data sets have multiple attributes. Fitting one or two of them is not always sufficient.
- Data: Limited availability (expense or proprietary nature); small data sets

In the beginning – Power Laws

- 1999 - 2005, explosion of observations of “power laws” in networks also of “small-worlds”.



(a) Int-11-97



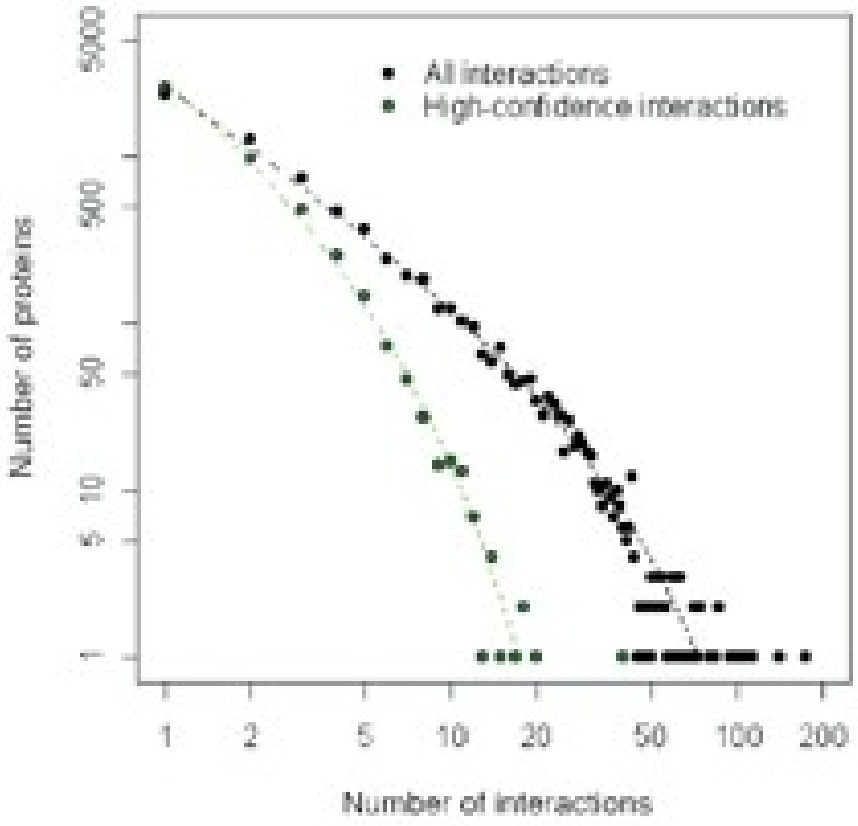
- M. Mitzenmacher, “The Future of Power Law Research” *Internet Mathematics*, **2** (4), 2006. (Editorial piece)
  - A call to move beyond observation and model building to validation and control.
  - Power laws ‘the signature of human activity’
- Clauset, Shalizi, Newman, “Power-law distributions in empirical data”, *SIAM Review* 51, 661-703 (2009).
  - Techniques to detect if actually have a power law, and if so, to extract exponents.

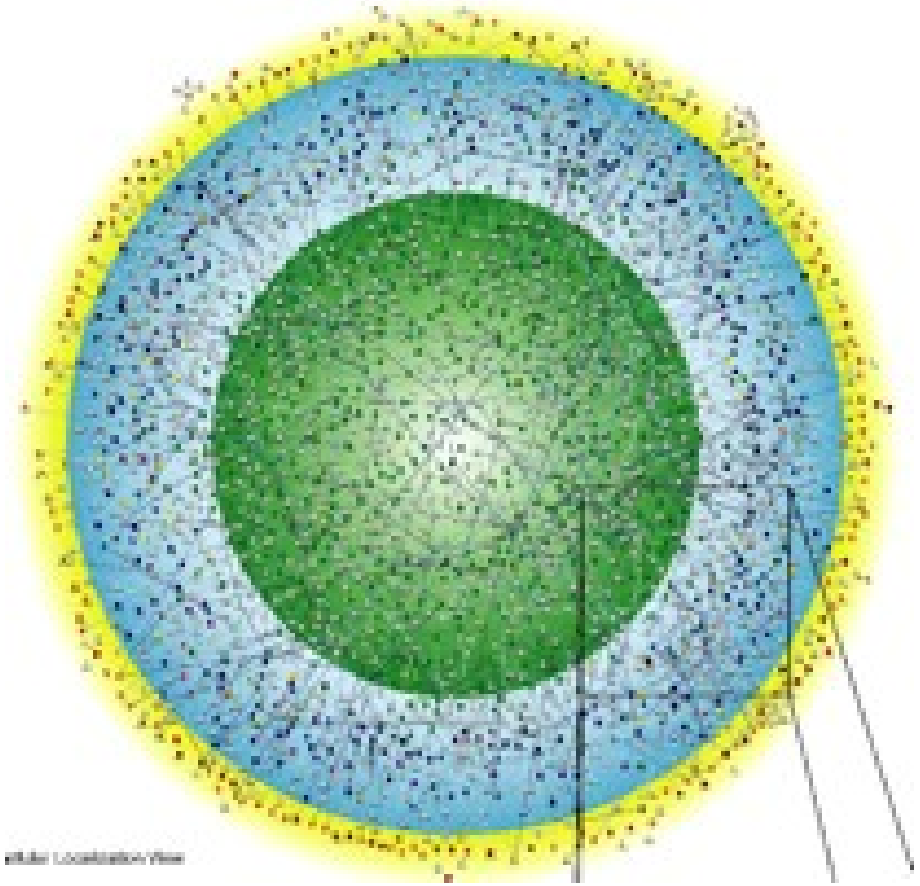
"Inferring network mechanisms: The Drosophila melanogaster protein interaction network"

Middendorf, Ziv, and Wiggins *PNAS* **102**, 2005

- Study the Drosophila protein interaction network
- Use machine learning techniques *(discriminative classification)* to compare with seven proposed models to determine which model best describes data.
- *Classification* rather than *statistical tests* on specific attributes.

Data:
Giot et al, Science 302, 1727 (2003)





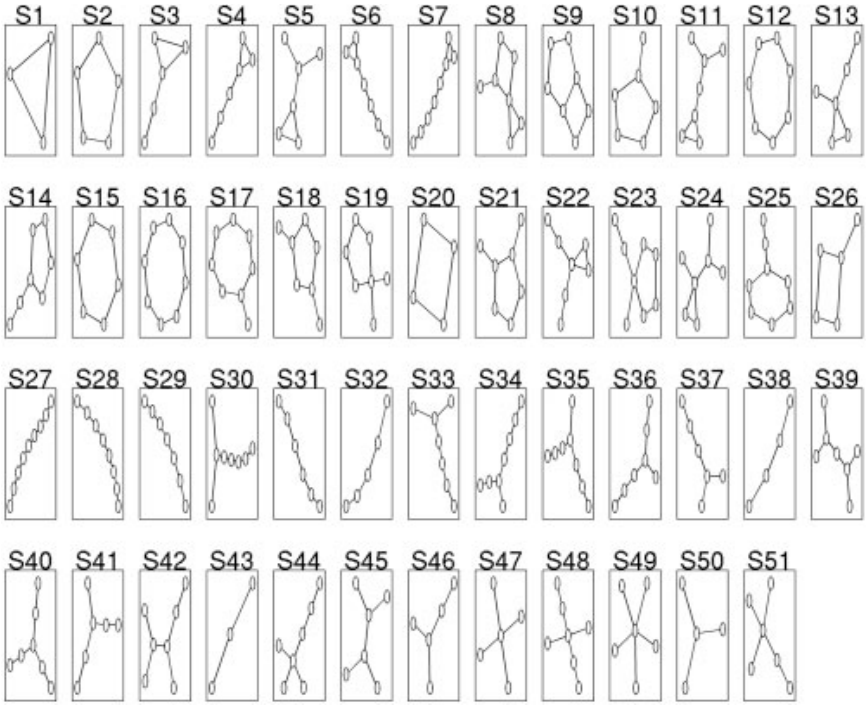
- Accept any edge with $p > 0.65$,
  3,359 vertices and 2,795 edges.

7 candidate models

- DMC – duplication-complementation-mutation (Vasquez et al)
- DMR – duplication-mutation with random mutations
- RDS – random static (Erdos-Renyi)
- RDG – random growing graph (Callaway et al.)
- LPA – Linear pref attachment (Barabasi-Albert)
- AGV – Aging vertices
- SMW – Small world (Watts-Strogatz)

The procedure

- Generate 1000 random instances of a network with N=3359 and E=2795 for each of the seven models (7000 random instances in total). (Training data)
- "Subgraph census" – classify each network by exhaustive search for all possible subgraphs up to a given size. ("Motifs")
- Classify each of the 7 mechanisms by raw subgraph counts.



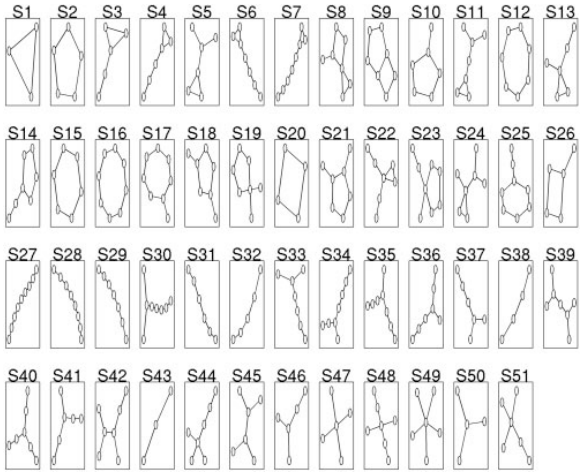
(Example subgraphs)

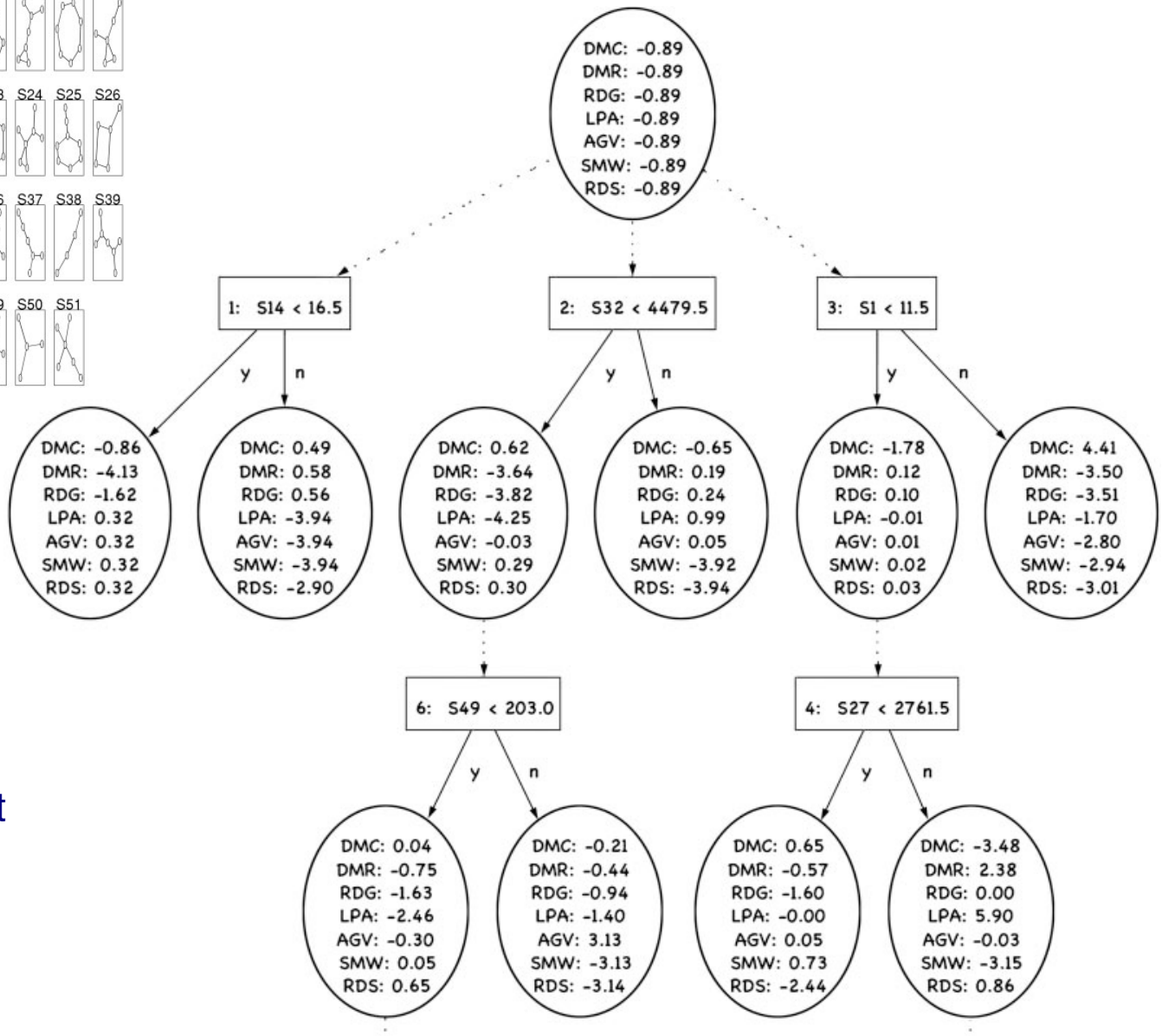
Notes on procedure

- Similar to techniques in social sciences (p*, exponential random graph models).
- Network "motifs", Milo et al *Science*, 2002. But motifs only up to $n = 3$ or $n = 4$ nodes.
- Note the term "clustering" here refers to machine learning technique to categorize data, not "clustering coefficient" (transitivity).

Build classifier from the training data (Learning Algorithm)

- Alternating Decision Tree (ADT), (Freund and Schapire, 1997).





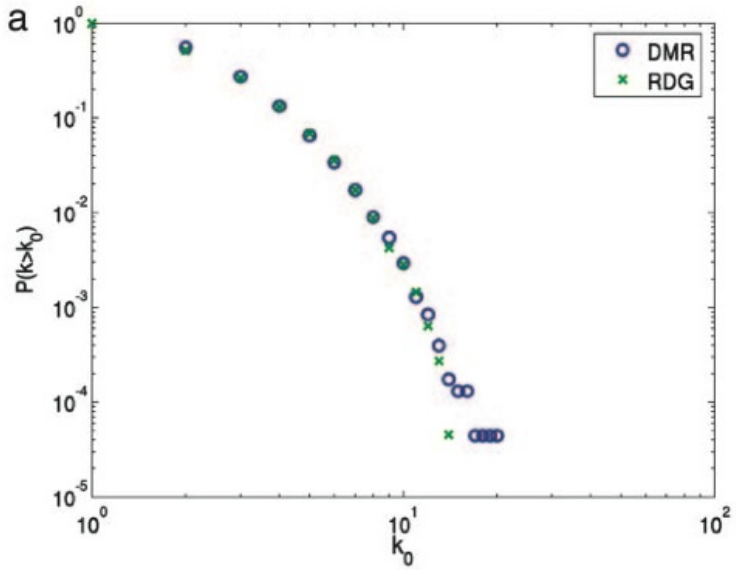
Which subgraphs best distinguish the models?

Validating classifier

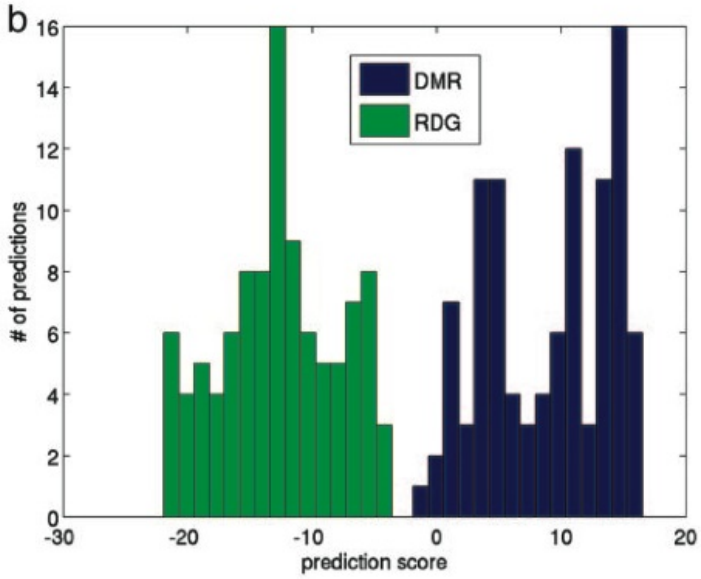
	Prediction						
Truth	DMR	DMC	AGV	LPA	SMW	RDS	RDG
DMR	99.3	0.0	0.0	0.0	0.0	0.1	0.6
DMC	0.0	99.7	0.0	0.0	0.3	0.0	0.0
AGV	0.0	0.1	84.7	13.5	1.2	0.5	0.0
LPA	0.0	0.0	10.3	89.6	0.0	0.0	0.1
SMW	0.0	0.0	0.6	0.0	99.0	0.4	0.0
RDS	0.0	0.0	0.2	0.0	0.8	99.0	0.0
RDG	0.9	0.0	0.0	0.1	0.0	0.0	99.0

- Slight overlap in models which are variations on one-another.

Validating classifier



	DMR	RDG
$\langle C \rangle$	$2.6\ 10^{-4} \pm 1.3\ 10^{-4}$	$5.4\ 10^{-4} \pm 3.7\ 10^{-4}$
$\langle \ell \rangle$	10.4 ± 0.1	9.6 ± 0.04



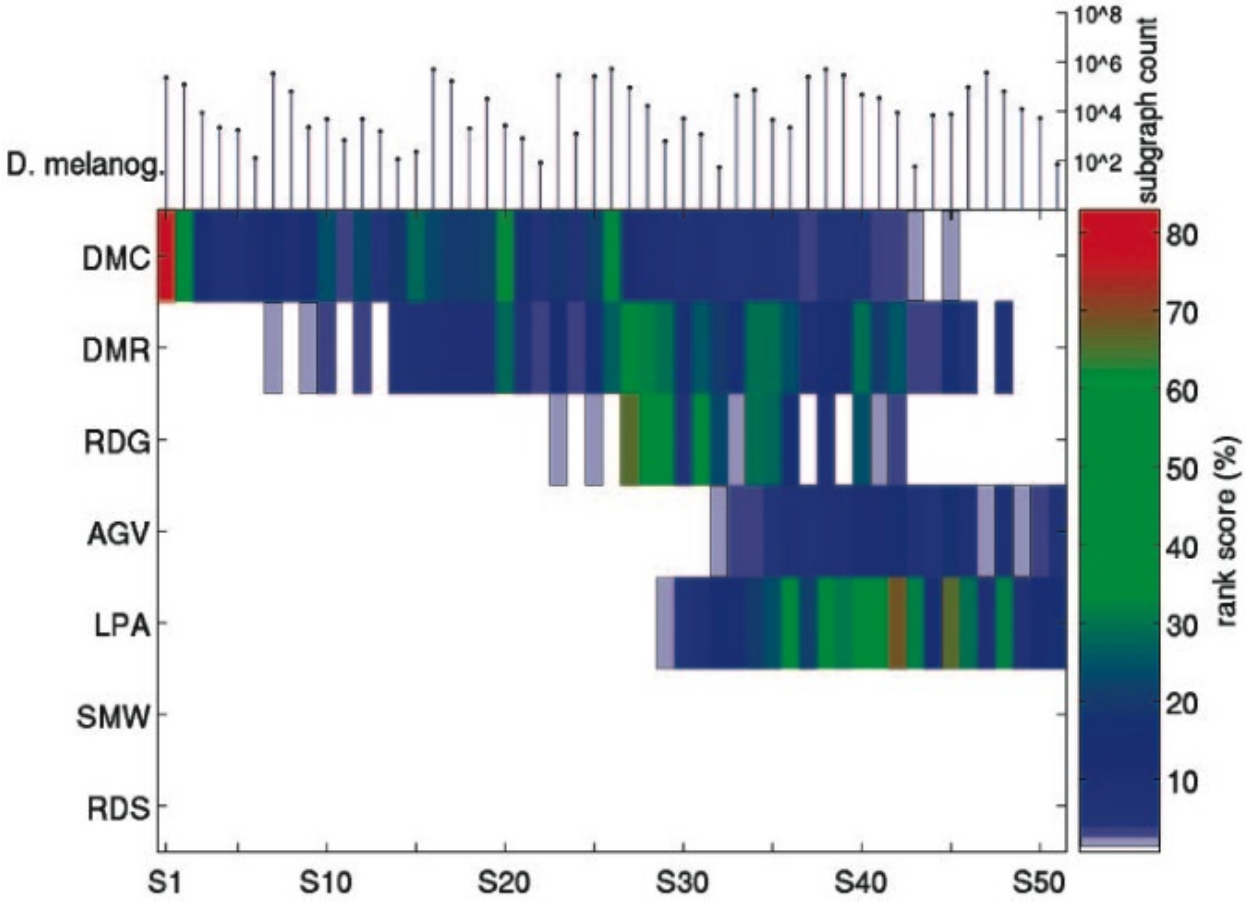
- (a) DMC and RDG produce similar statistical distributions.
- (b) Classifier can discriminate between the two models.

After classifier built, use it to characterize individual network realizations

(Walk the Drosophila data through the ADT)

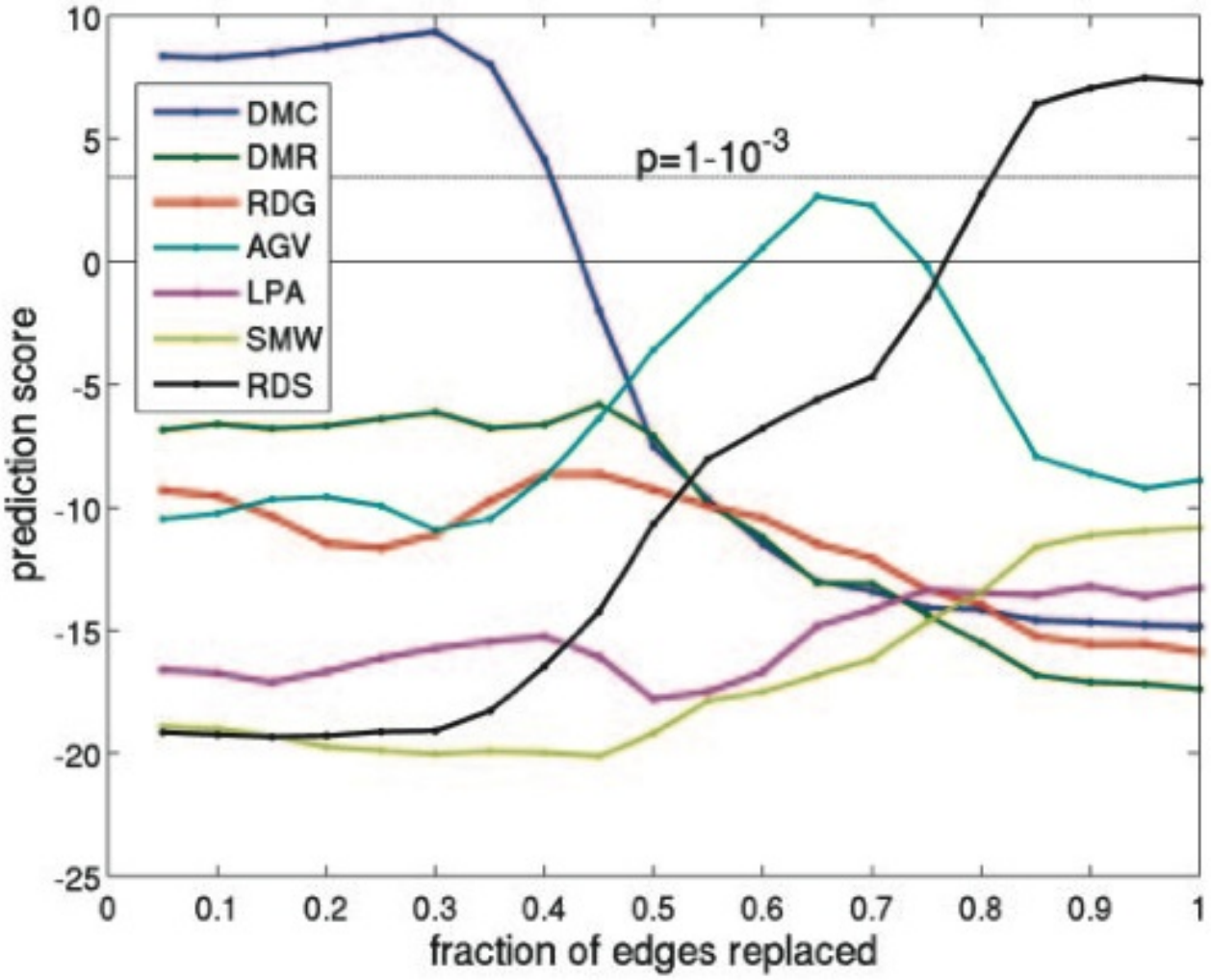
- A given network's subgraph counts determine paths in the ADT (decision nodes are rectangles)
- The ADT outputs a real-valued prediction score, which is the sum of all weights over all paths.
- The final weight for a model is related to probability that particular network realization was generated by that model.
- Model with the highest weight wins (best describes that particular network realization).
- DMC wins for Giot Drosophila data!

Comparison by subgraph counts



- Green is best (same median occurrence as in real Drosophila data).
- 0 means the subgraph is in data, but not in model.

Introducing noise – degree preserving edge rewiring



- Classifier robust.

Comments

- Model **selection** not validation. (Relative judgement)
  (i.e., which of these 7 models fits the data best?)

- Many of these 7 models considered produce similar macroscopic features (degree distribution, clustering, diameter, etc).

- Delve into microscopic details and let the data distinguish between the 7 models.

- Must start with models that are accurate statistical fits to data!
  (different type of model validation). (Acompanying commentary, Rice et al PNAS 2005, DMC does not reproduce giant component.)

Model Validation Lit Review: Conclusions

- New techniques being introduced (classifiers, PCA).
- Calls for necessity of validation (e.g., Mitzenmacher)
- Specifics may matter, constraint curves “first principles”.
- **Selection easier than validation!**