Reconstruction of Interaction Networks (With Applications to Transcriptional Regulation)

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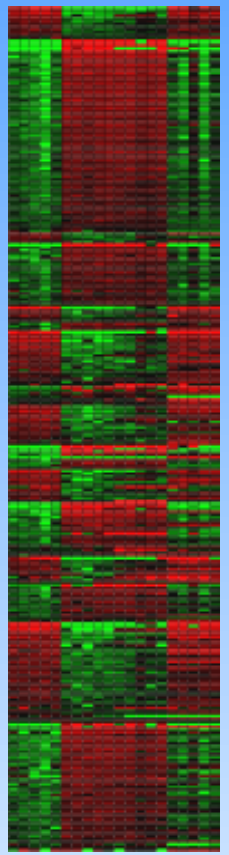
q-bio.MN/0411003, q-bio.MN/0410037

q-bio.MN/0410036, q-bio.QM/0406015

Gene expression analysis



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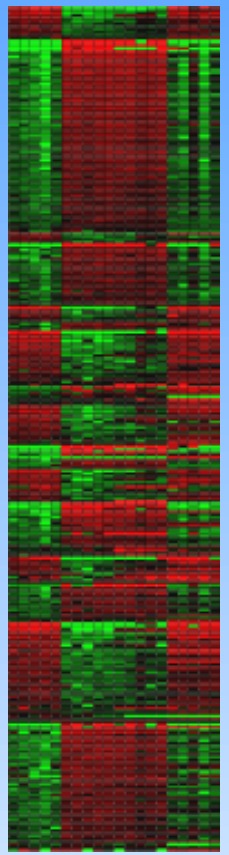

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- reconstructing networks – Holy Grail!

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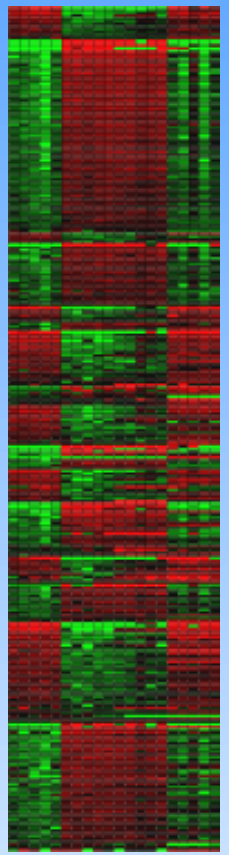

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- loops?
- what dependence (arrows) means?
- what approximations being made? controlling them?
- are approximations biologically sound?
- guarantees?

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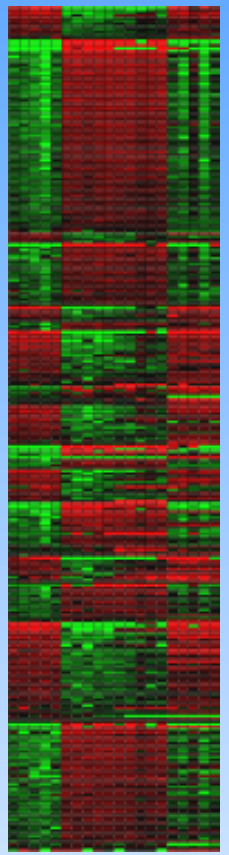

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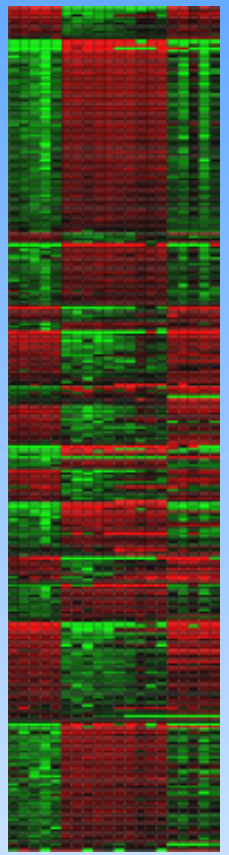

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Different conditions – different steady states.

Extremely many false positives (e. g. joint co-regulation).

Model of dependence

No time series $\longrightarrow$ steady state statistical dependencies only.

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$$-\log P(g_i) = \sum_i \phi_i(g_i) + \sum_{ij} \phi_{ij}(g_i, g_j) + \sum_{ijk} \phi_{ijk}(g_i, g_j, g_k) + \ldots$$

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- use MaxEnt to define ϕ
- connections with spin glasses, MNs, belief propagation
- enough data to evaluate 2-way marginals only;
- truncate at 2nd order potential (cannot reconstruct `XOR`), Bethe approximation (but inverse problem)
- Mutual information $I(g_i, g_j) = I_{ij}$ is enough to establish dependencies.

Notes

- changing $\phi(g_i)$ describes response to perturbations (but: directionality)

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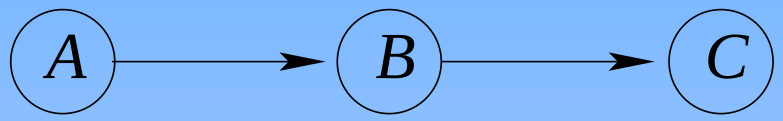
- biochemical dependencies persist as steady state statistical dependencies, but orders of interactions may change

Removing false positives – Data Processing inequality



$$I(A, C) \leq \min[I(A, B), I(B, C)]$$

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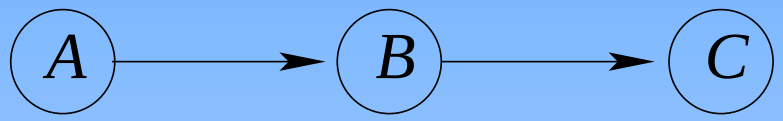

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<u>ARACNE:</u> Look at every triplet and remove the weakest link.

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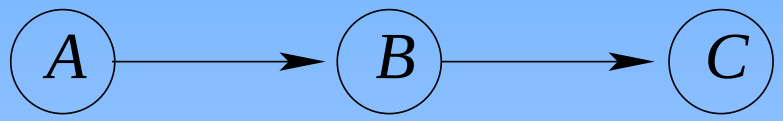

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ARACNE: Look at every triplet and remove the weakest link.

Every 3-gene loop is opened!

Guarantees

Theorem. If MIs can be estimated with no errors, then ARACNE reconstructs the underlying interaction network exactly, provided this network is a tree and has only pairwise interactions.

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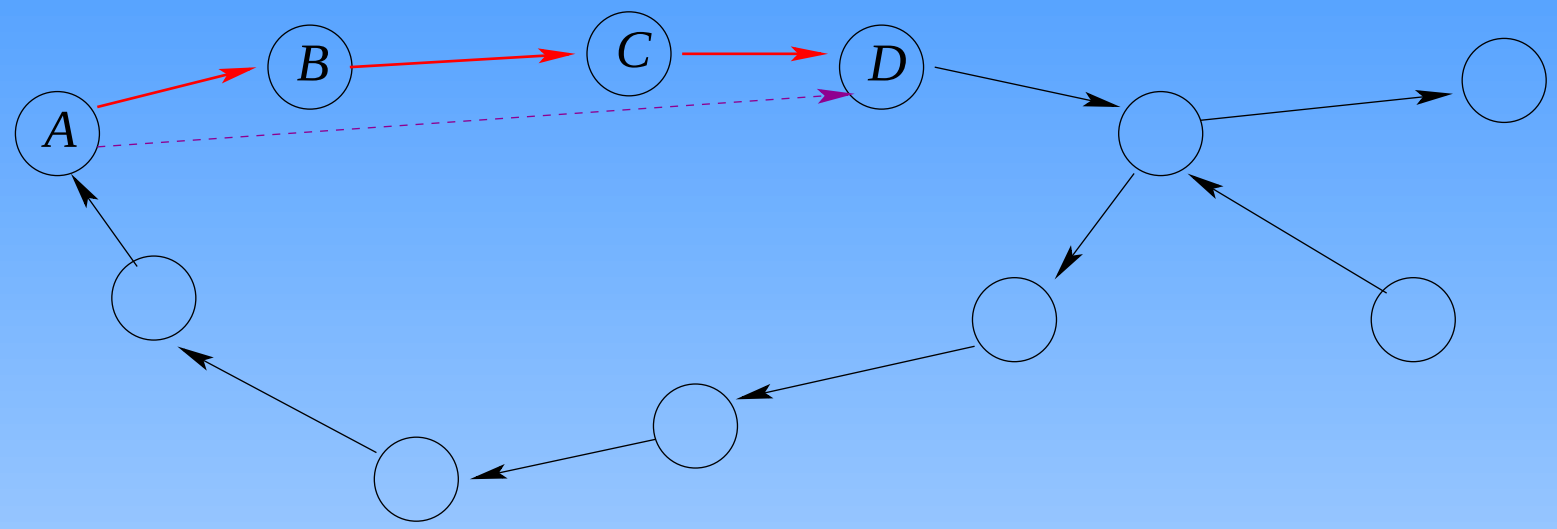
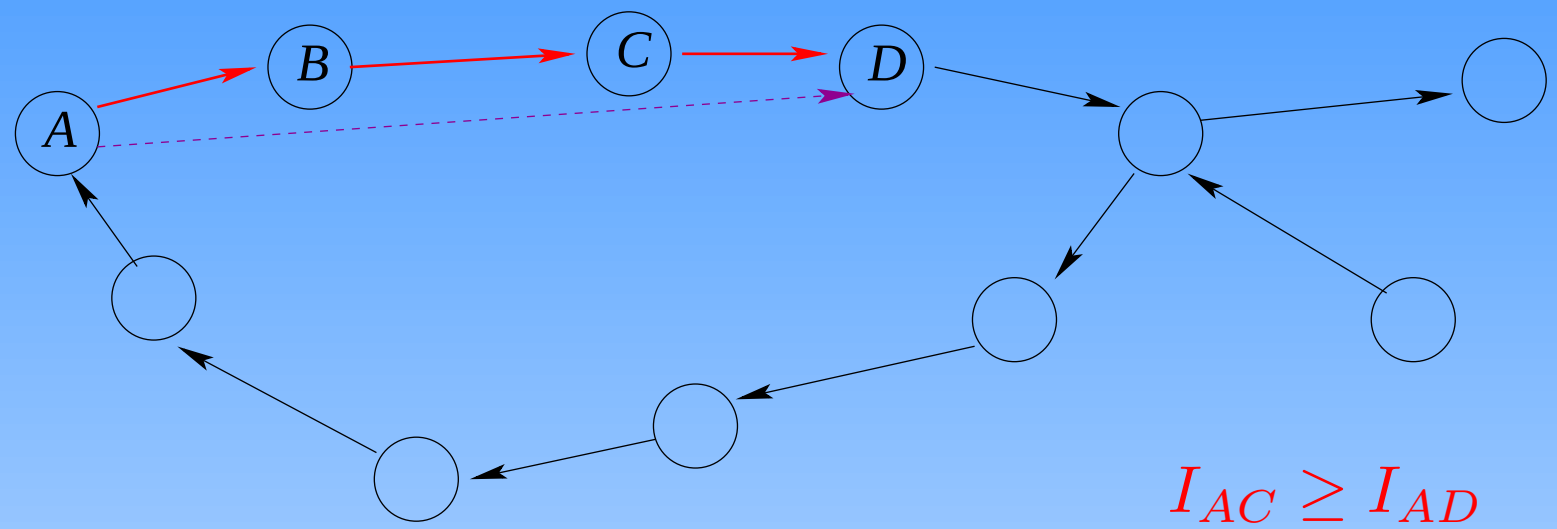
Theorem. The maximum Mutual Information spanning tree (Chow-Liu) is a subnetwork of the network reconstructed by ARACNE.



<u>Theorem</u>. Let π_{ik} be the shortest path between i and k. Then, if MIs are known, ARACNE reconstructs an interaction network without false positives edges, provided: (a) the network consists only of pairwise interactions, (b) for each $j \in \pi_{ik}$, $I_{ij} \geq I_{ik}$.



$$I_{AC} \geq I_{AD}$$
$$I_{AB} \geq I_{AD}$$

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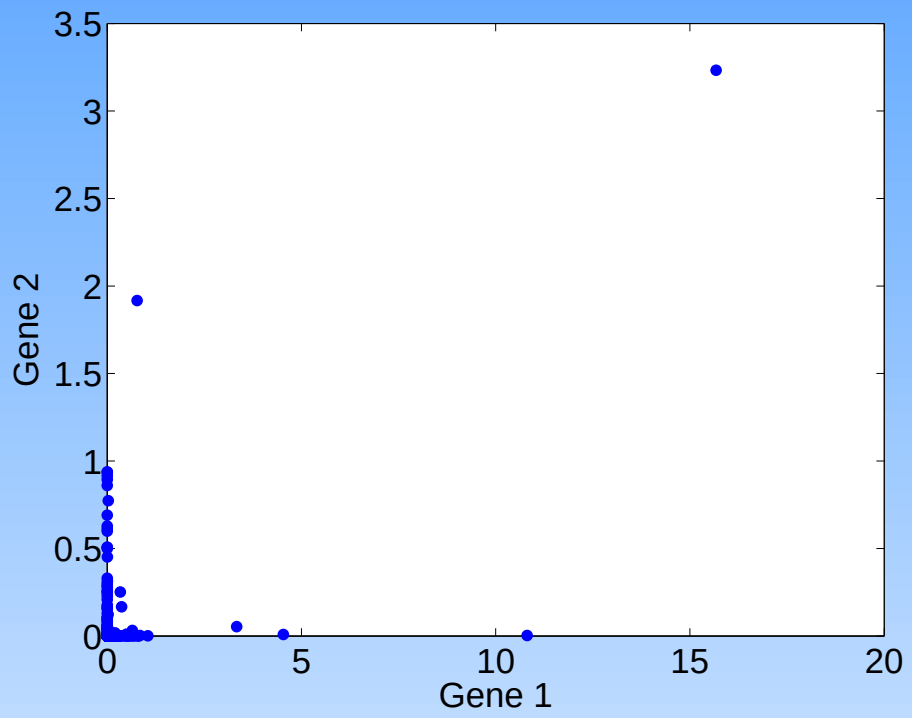
Why should it work?

- higher order interactions project into lower order ones
- large loops are locally trees (biological signals decorrelate very fast: $I(\mathrm{cMYK}, \mathrm{cMYK}) \approx 8$ bits, $I(\mathrm{cMYK},$ second best$) \approx 1$ bit.
- small loops (e. g., feed forward) are often transient

Kernel MI estimation: Copula transform



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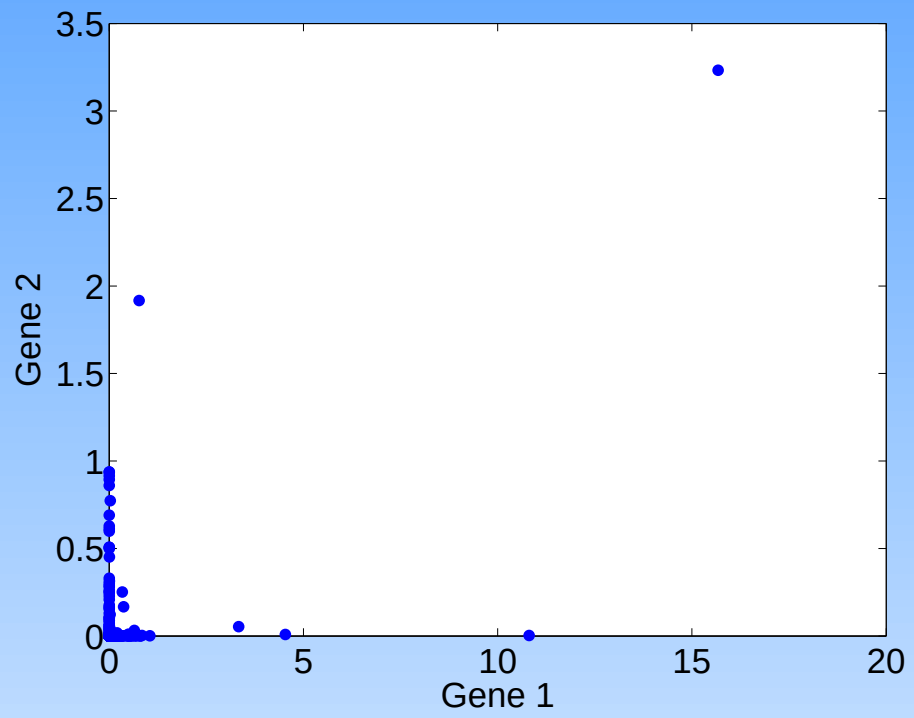

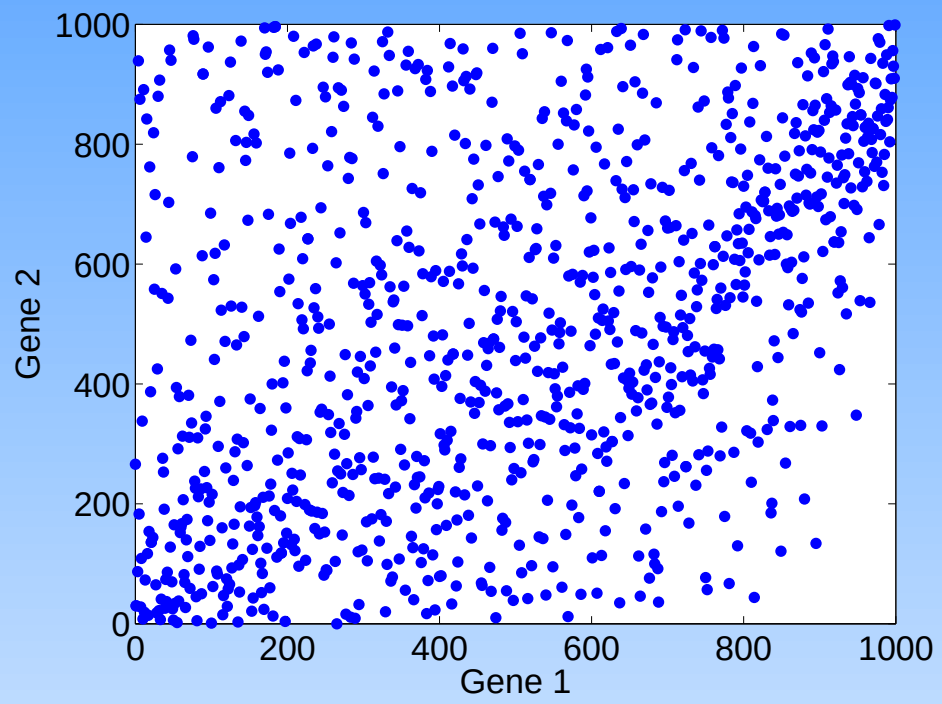

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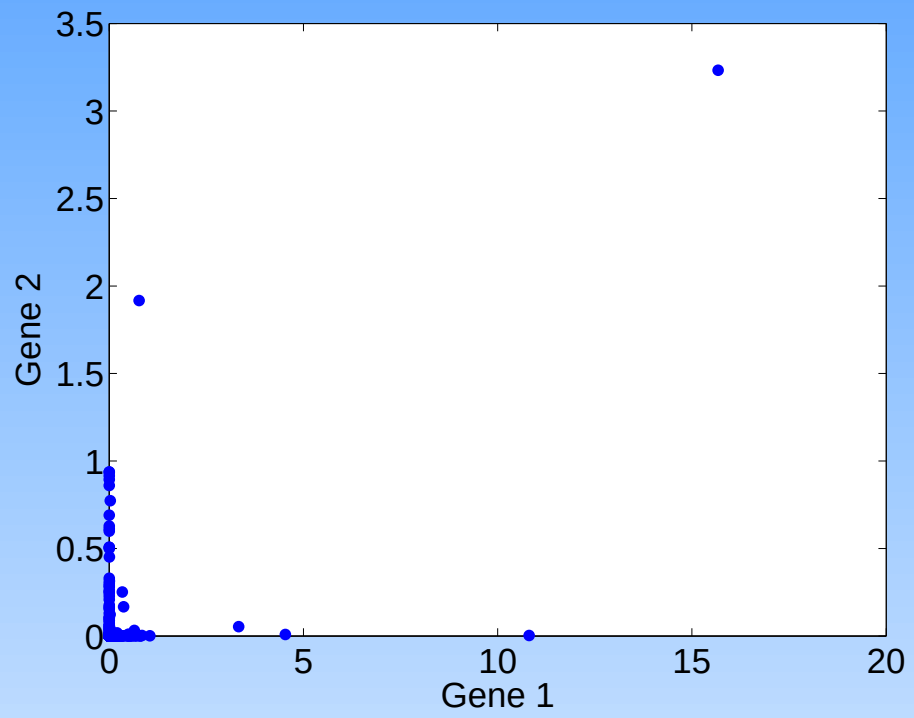
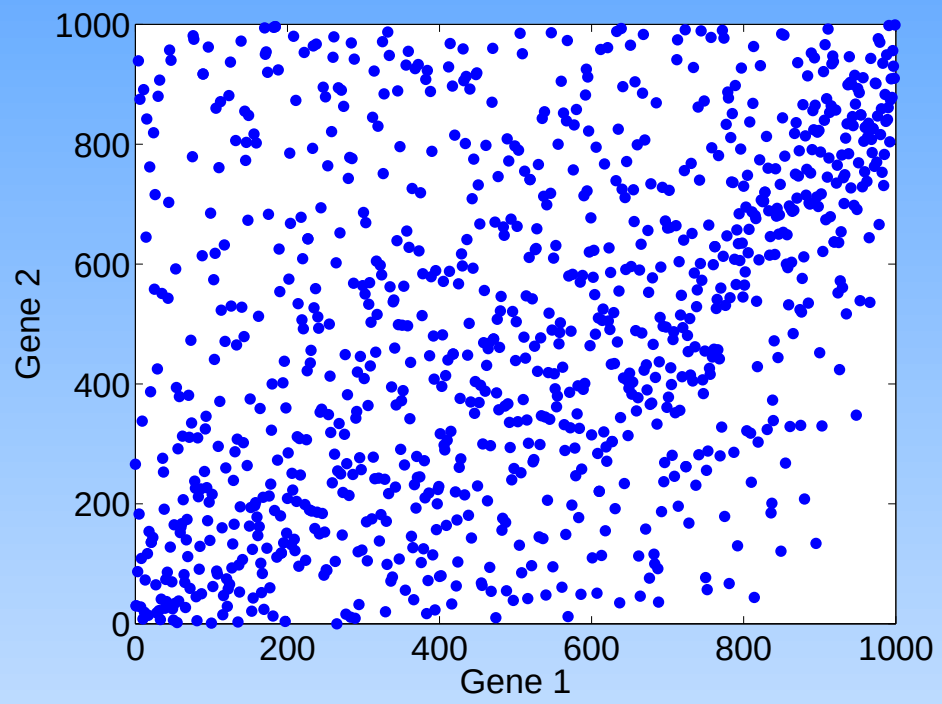
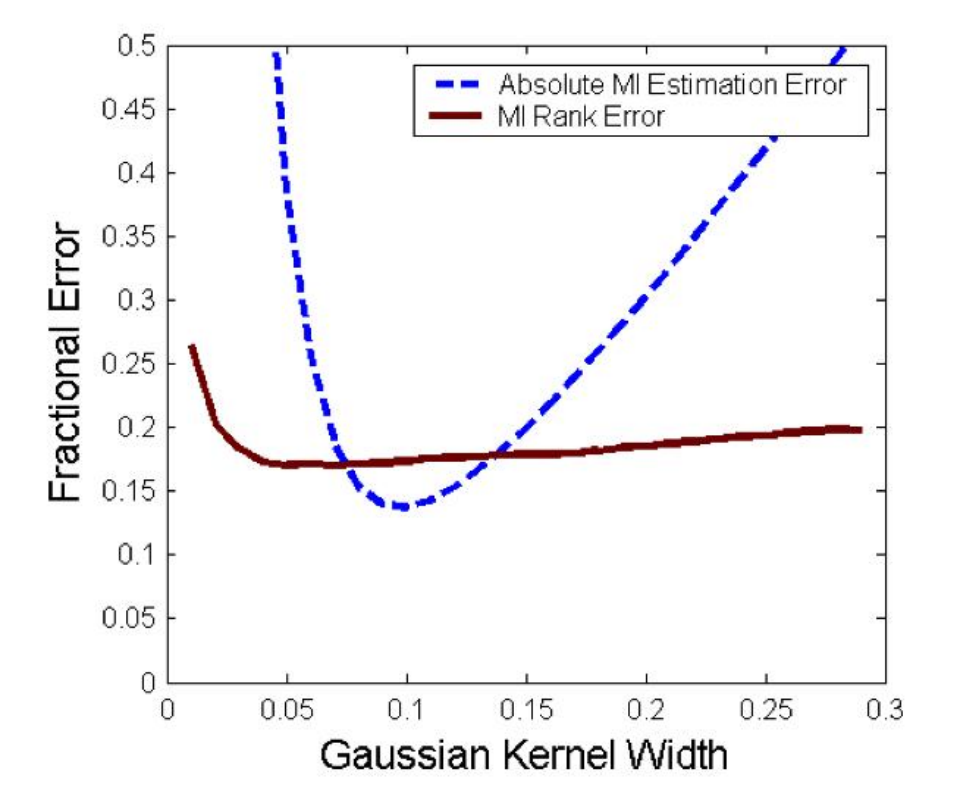




Do before estimating MI. No need for spatial inhomogeneity.

Mutual information error vs. ranking error



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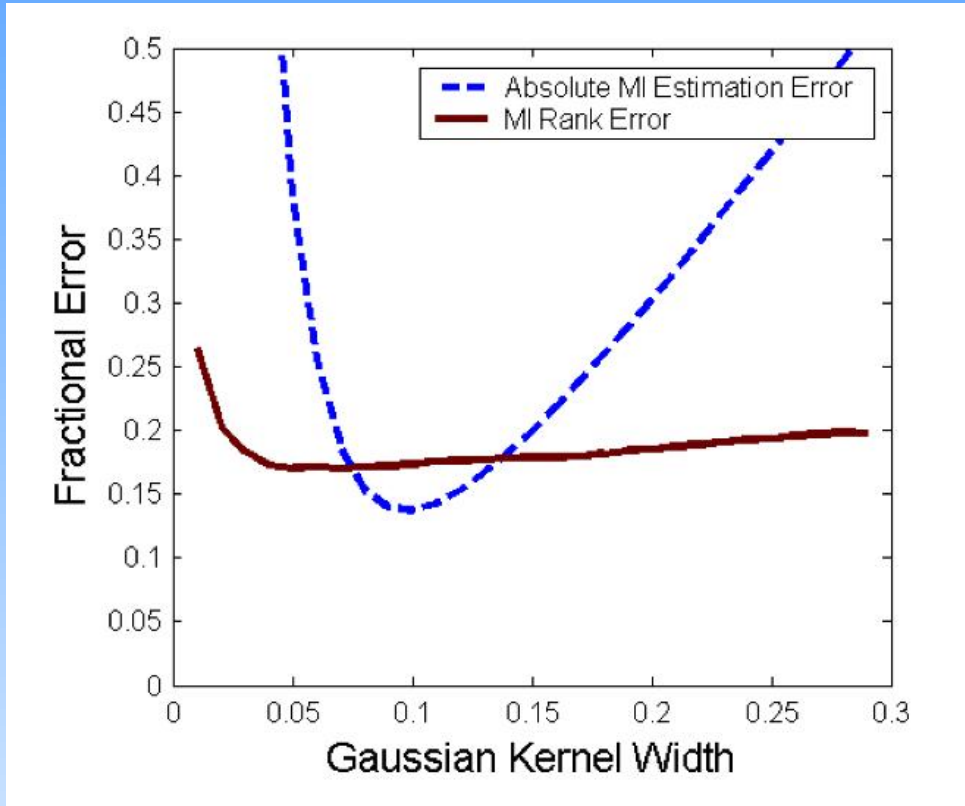
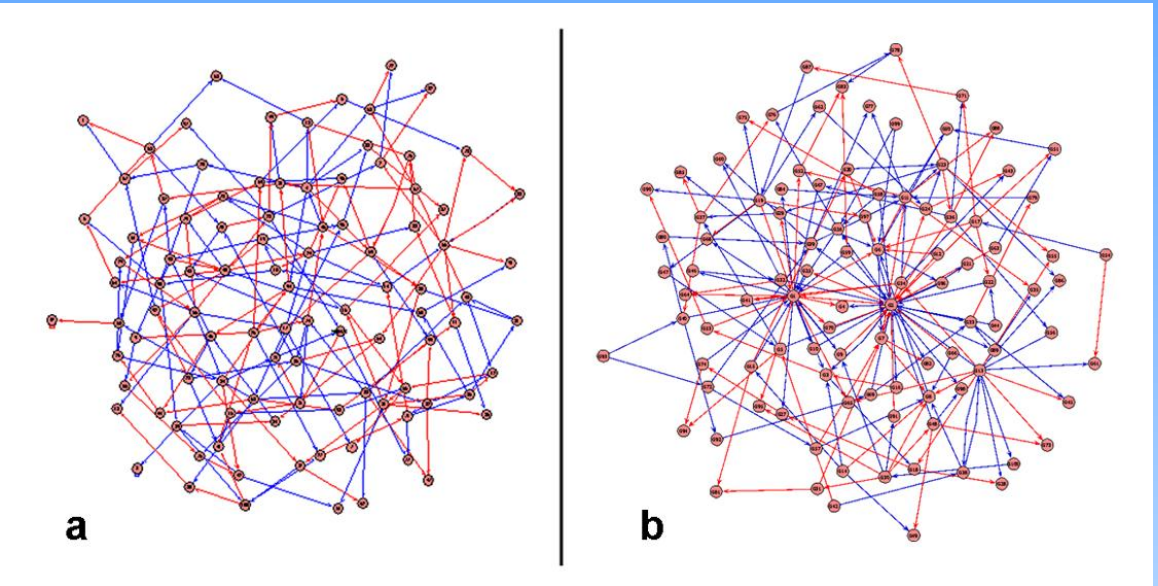


Can use universal best h.

Synthetic networks



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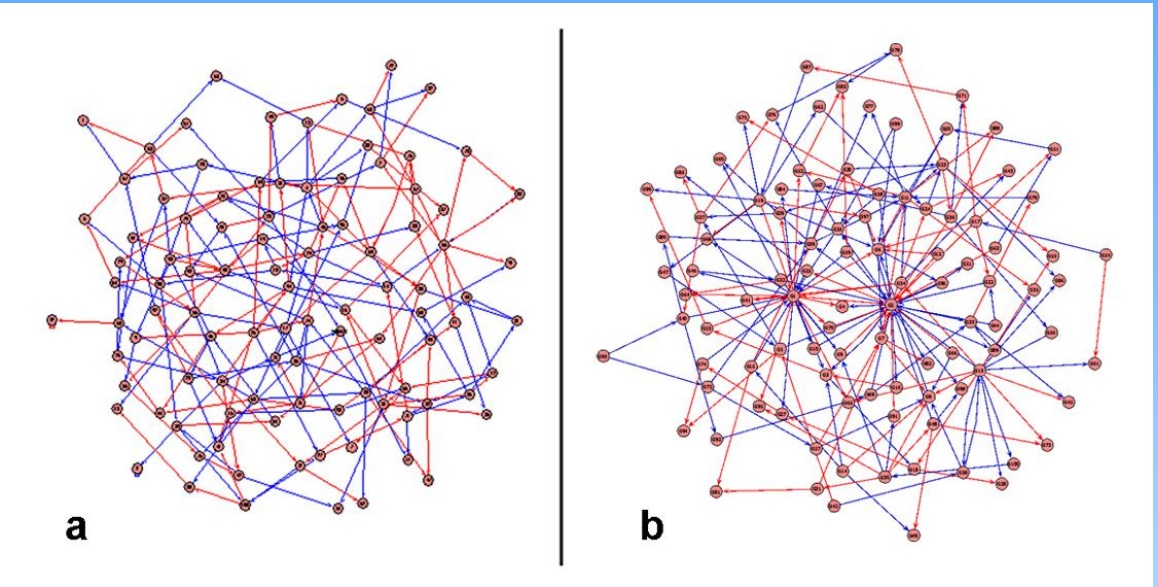
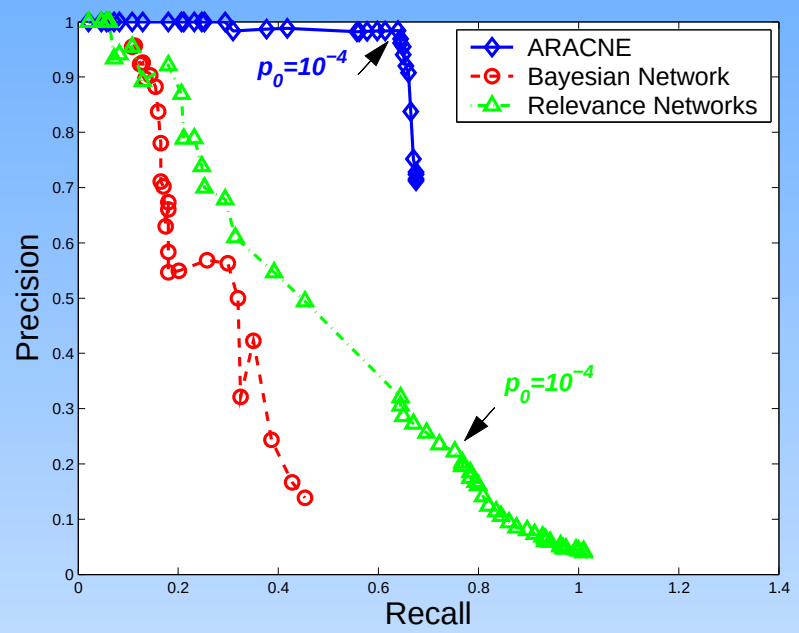
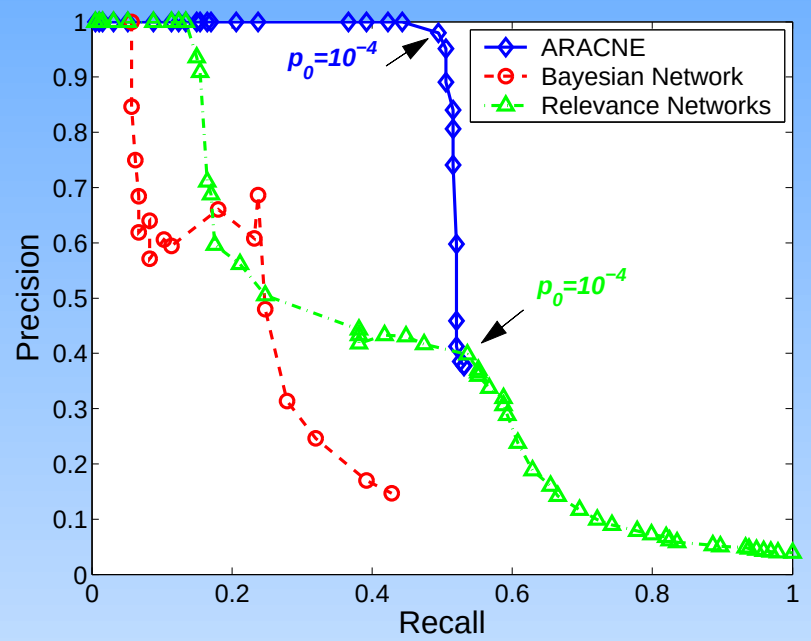


$$\frac{dx_i}{dt} = a_i \prod_j \frac{I_{0,j}^{\nu_j}}{I_j^{\nu_j} + I_{j,0}^{\nu_j}} \prod_j \left(1 + \frac{A_j^{\nu_j}}{A_j^{\nu_j} + A_{j,0}^{\nu_j}}\right) - b_i x_i$$

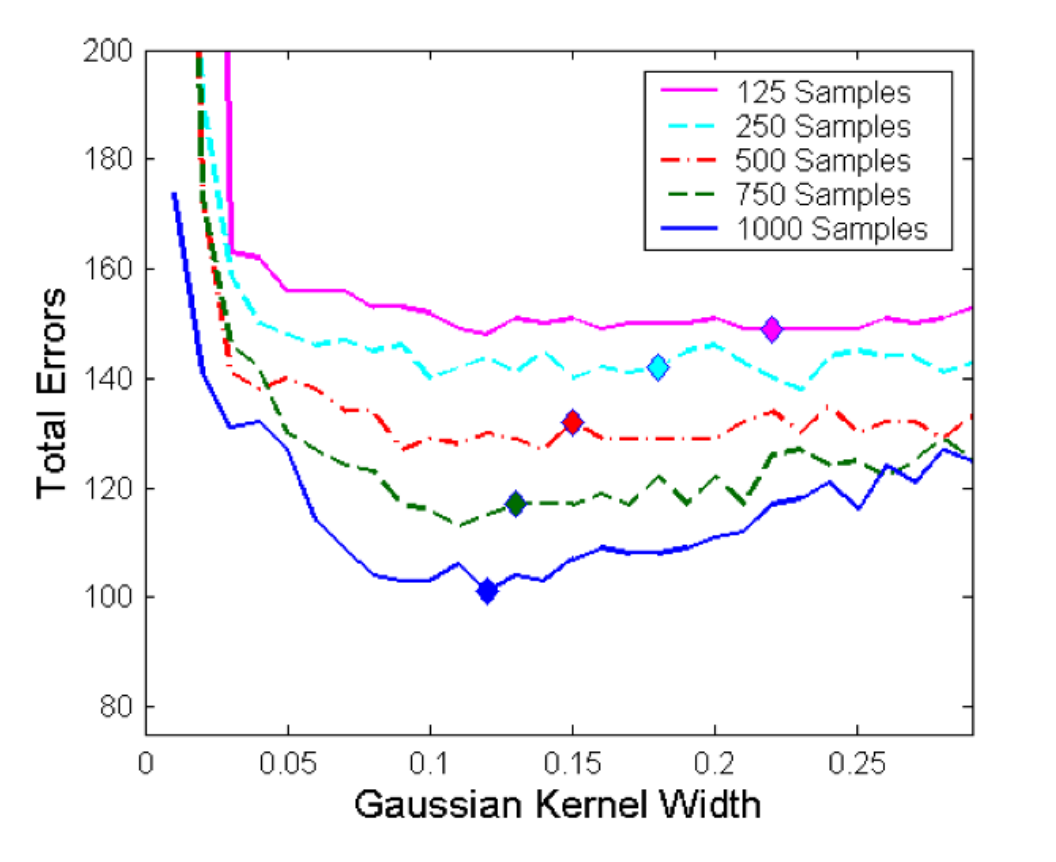
Benchmarks





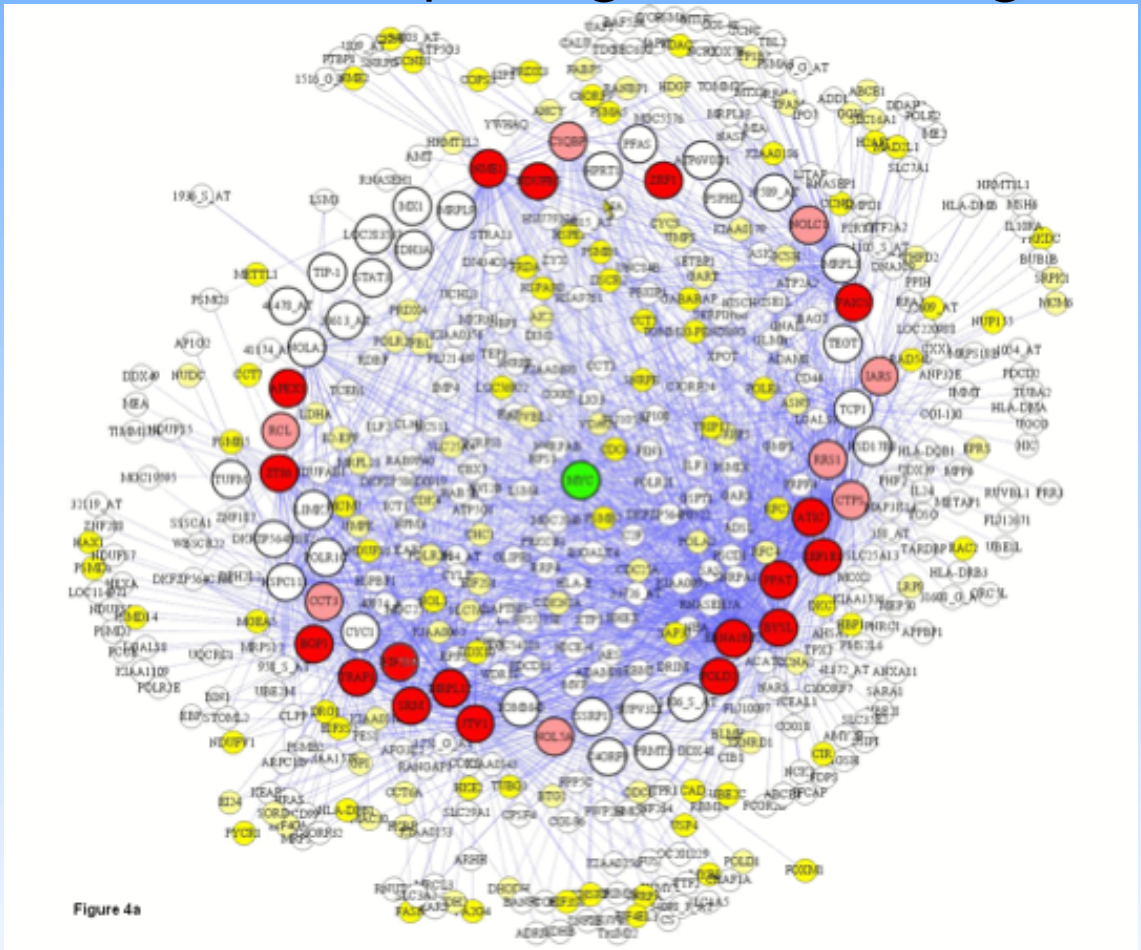
$$N_{TP} - N_{FP} = \max \text{ at } p = 10^{-4}.$$

No sampling catastrophe!



c-MYC TF centered network

Protooncogene, involved in many cellular processes, 12% background interactions, top 5% genetic hub, significant MI with ~ 2000 genes.



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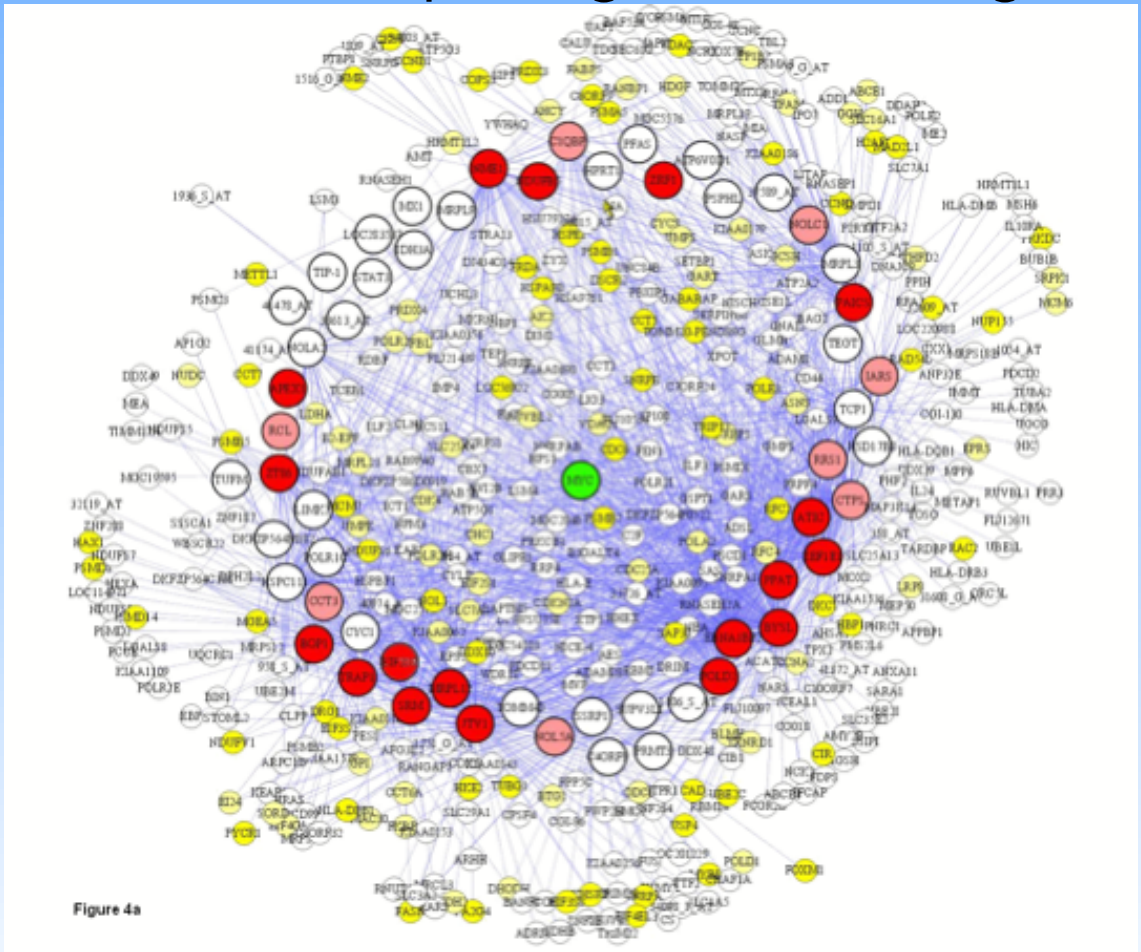


- 56 1st neighbors
- pre-known targets – 22
- ChIp-proven targets – 11/12
- 2nd neighbors – weaker enrichments
- Most 1st – major hubs

Hub 3-way interactions (conditional analysis)

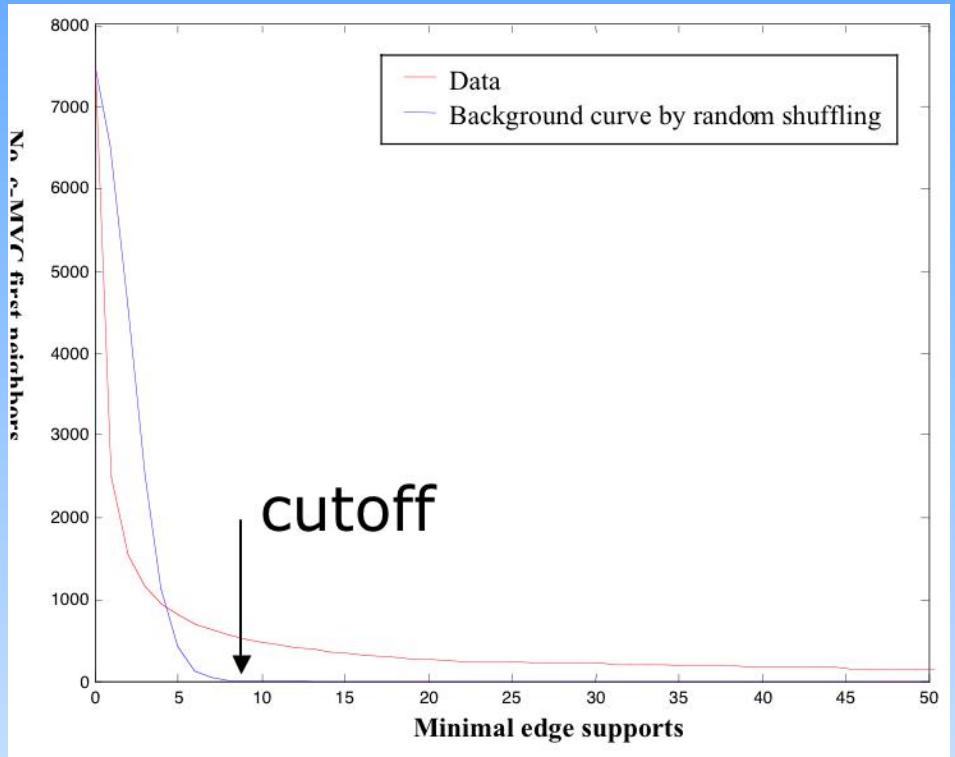
G^*_μ – coarse conditions (+/-) of correlated gene clusters

$$I(g_i, g_j | G^*_\mu)$$

- Independent of the hub (true 3-way interactions)
- Large dynamic range

	G_1^+	G_1^-	G_2^+	G_2^-	...	...	G_M^+	G_M^-
Edge 1	1	0	1	0	0	0	1	0
Edge 2	0	1	0	0	0	1	0	0
:	0	0	1	0	1	0	0	0
Edge N	1	0	0	1	0	0	0	1

Edge support conditions set size



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1	2422	437	0.18	6520.1	1
2	1458	278	0.19	4541.5	1
3	1066	224	0.21	2514.1	1
4	847	182	0.21	1131.6	1
5	710	157	0.22	423.13	0.60
6	591	132	0.22	136.04	0.23
7	511	119	0.23	37.03	0.072
8	459	110	0.24	9.18	0.02
9	406	104	0.26	1.9	< 0.01
10	367	96	0.26	0.37	< 0.01

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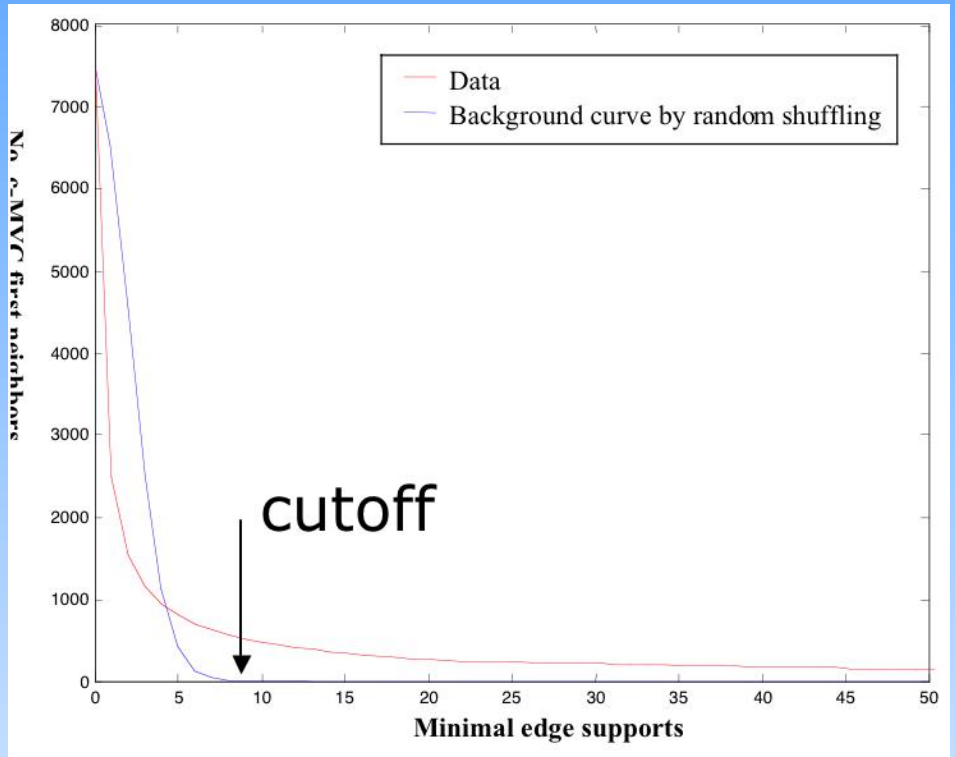

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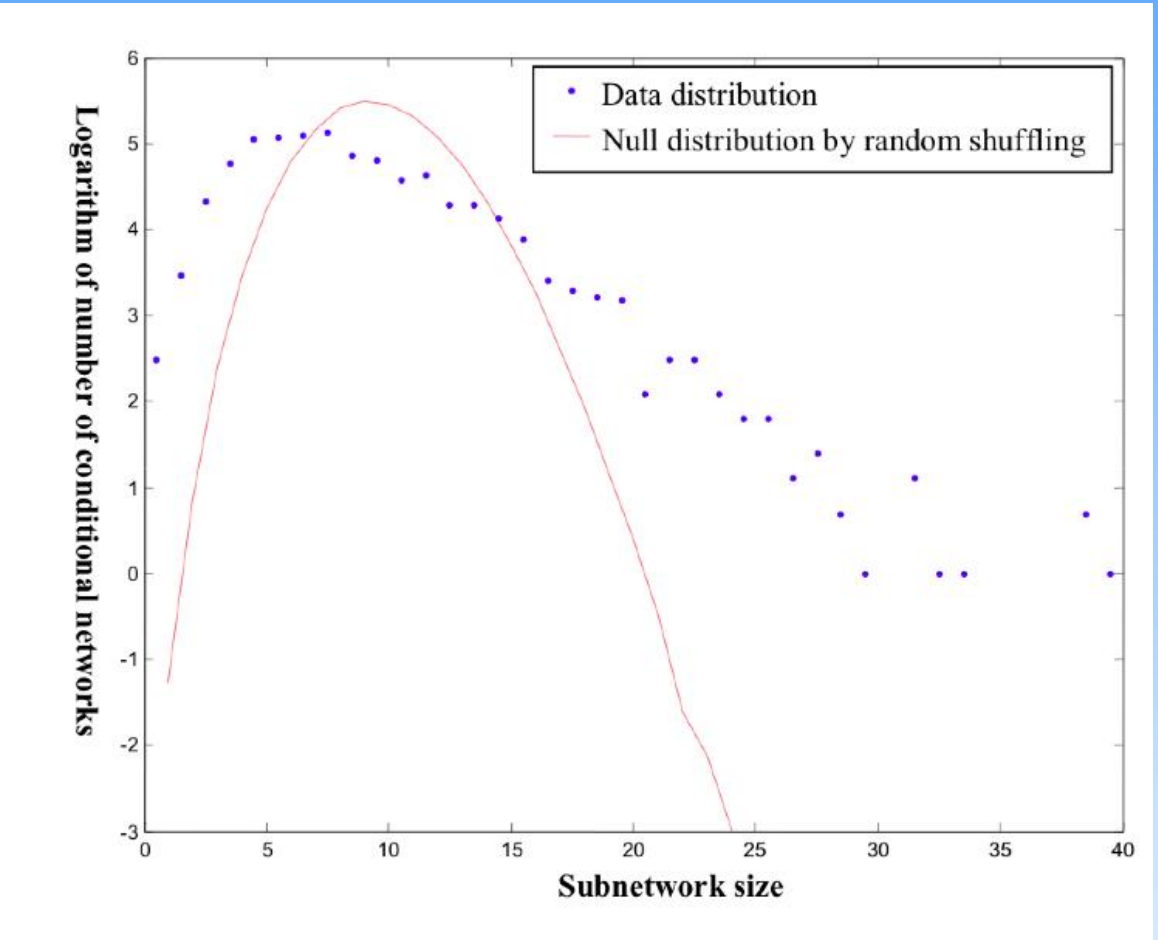
Probably better than original algorithm.

Conditional network sizes



Regulators, indeed

Of 168 c-MYC regulators:

GO Category	N_C	N_{Tot}	GO N_C	GO N_{Tot}	P
Transcription Regulator Activity (MF)	21	116	2089	21014	0.0049
Protein Kinase (MF)	13	116	1004	21014	0.003
IKBK/NFKB cascade (BP)	5	117	222	24373	0.004
Immune Response (BP)	19	117	1664	24373	0.0003
Humoral IR (BP)	9	117	378	24373	0.0001
Reg. of Transcription, DNA-dep. (BP)	26	117	1697	24373	1.2×10^{-7}