

Intrinsic direction in the human regulatory network

KKY

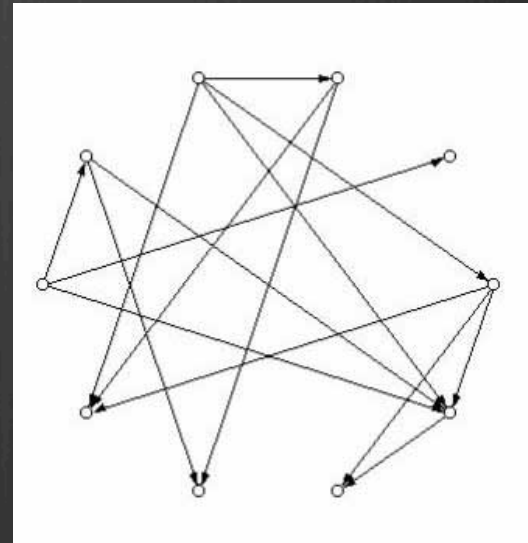
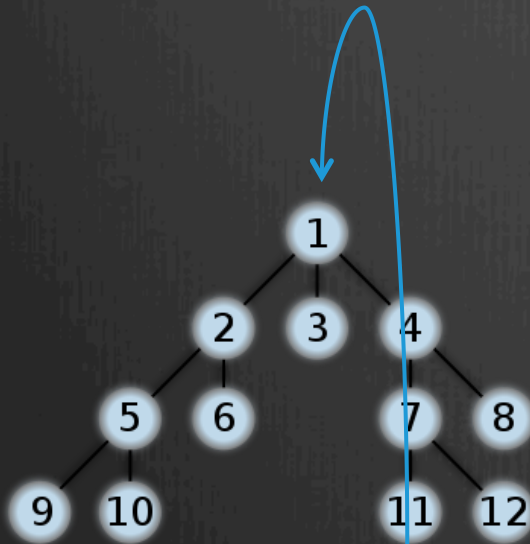
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Hierarchy and feedback: two faces of a coin

- ⊗ Hierarchical topology resembles a gradient of information flow
- ⊗ Feedback makes the gradient more fuzzy. Different amount of feedback offers different dynamics.
- ⊗ A hierarchical network in general has few feedback; the more feedback loops, the less hierarchical a network is.
- ⊗ No standard way to define hierarchy in the presence of feedback.

Looking for intrinsic direction: removal of feedback edges

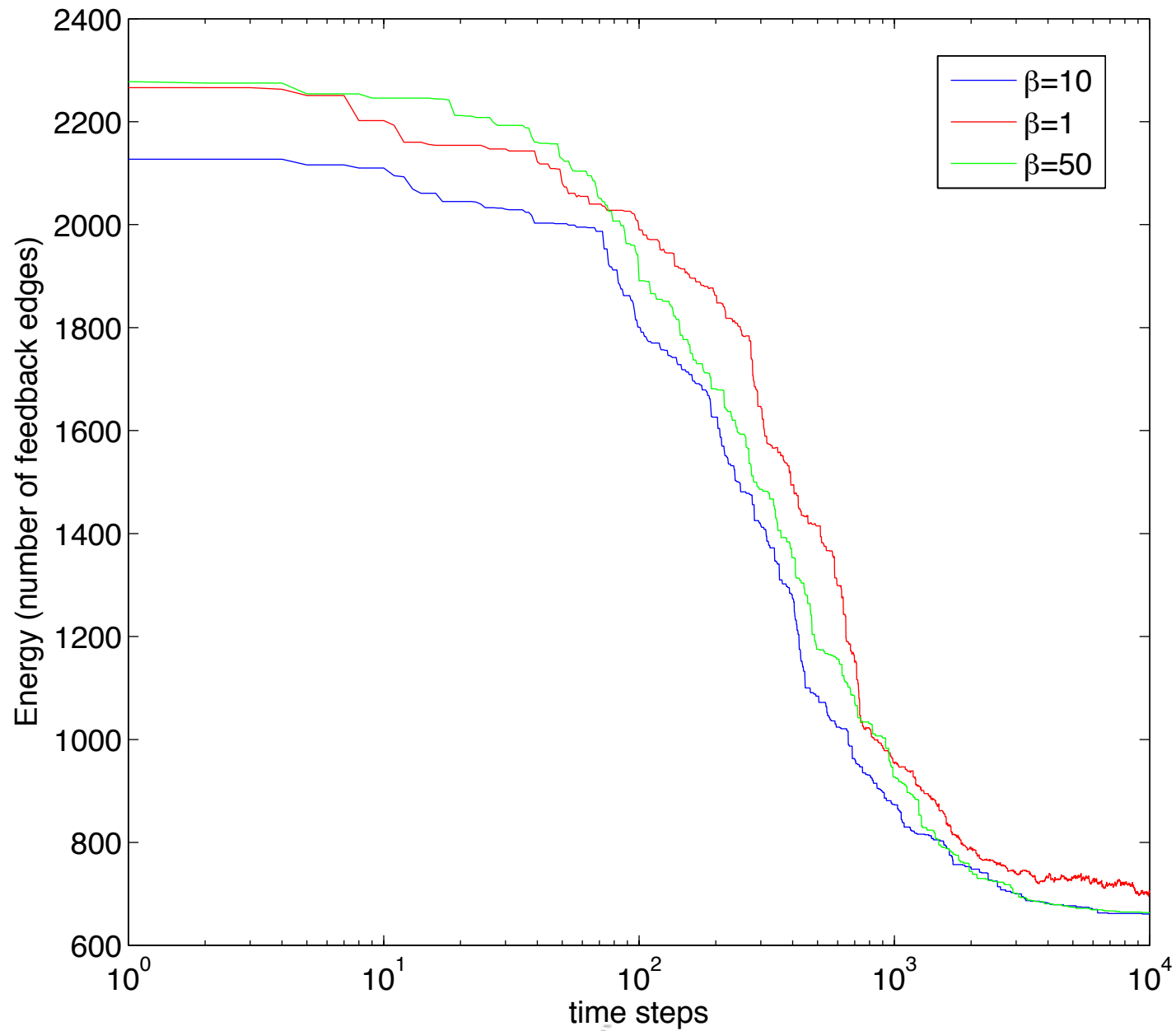
- ⊗ Many networks have built-in direction: transcription regulatory network, signaling network, management structure, call graphs
- ⊗ To extract the intrinsic direction by removing feedback loops



An optimization problem

- ⊗ Given a network of N nodes, and the number of hierarchical levels (L), how can we place the nodes at different levels such that the number of feedback edges is minimal
- ⊗ Metropolis algorithm
 - ⊗ Randomly assign nodes to the L levels, count the number of feedback edges (E)
 - ⊗ For each time step, update a new configuration by randomly relocate a node, and count the number of feedback
 - ⊗ If the number of feedback gets smaller, accept the new configuration,
 - ⊗ else, accept the configuration with probability $p = \exp(-\beta * (E_{\text{new}} - E_{\text{old}}))$
- ⊗ Test: A human transcriptional regulatory network by prediction: 213 TFs, 3660 edges (32 auto-regulation)

Ispolatov and Maslov, BMC Bioinformatics 2008

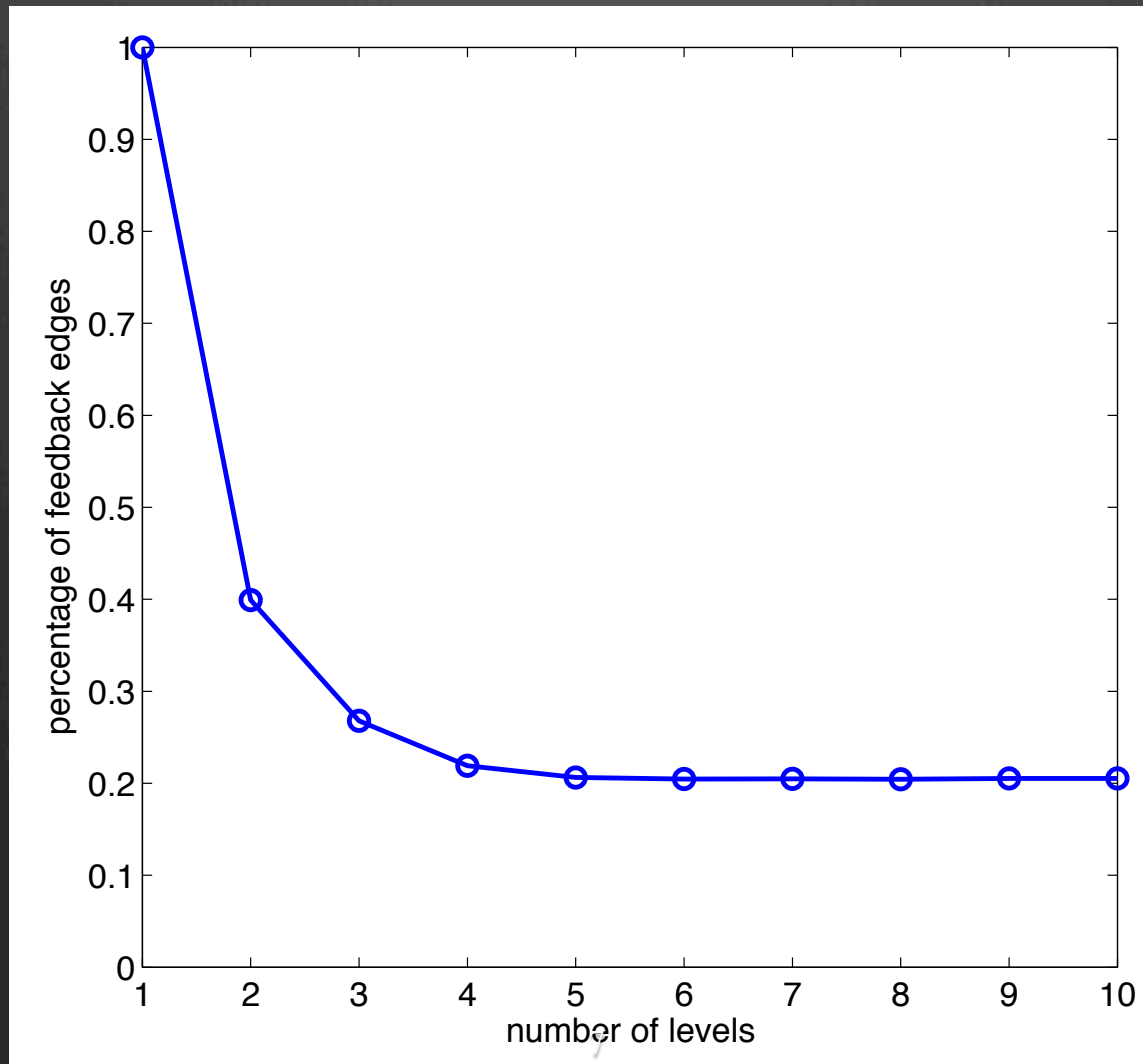


“Optimal” Solution

- 213 TFs in 6 levels: 3660 edges = 32 auto-regulation + 2967 forward edges + 330 feedback edges + 331 edges within the same level
- By removing 18% of edges, we guarantee the network loopless

level	Number of nodes	Average kout	Average kin
5	84	19.5	1.1
4	32	27.1	15.6
3	28	21.7	23.7
2	33	11.8	30.4
1	36	4.2	38.8

The number of levels



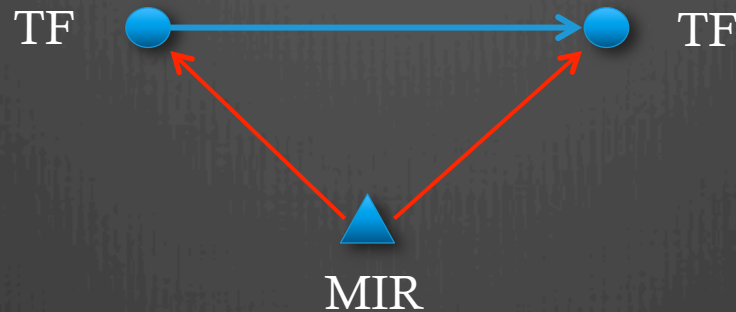
Generalizations

- ⊗ A prior information of master regulations or workhorses could be incorporated
- ⊗ Weight edges based on the number of levels they across. Feedback edges from the bottom back to the top could be punished.
- ⊗ Suppose we have the networks of a same set of TFs in different cell lines, or under different conditions etc, we could find the consensus intrinsic direction in the collection of network

What biology could we learn?

- ⊗ Given an intrinsic direction, what are the differences between forward edges and backward edges?
- ⊗ The discrimination of two types of edges is in complement with the current analysis of hierarchy, which
 - ⊗ Hide the information of feedback via the construction of hierarchy
 - ⊗ Focus on the discrimination of nodes at different levels

How miRNAs regulate the forward and backward edges?



	Number of edges	Number of motifs
forward edges	2967	1937
backward edges	330	275
Edges within the same level	363	886

those are my principles, if you
don't like them I have others

Groucho Marx