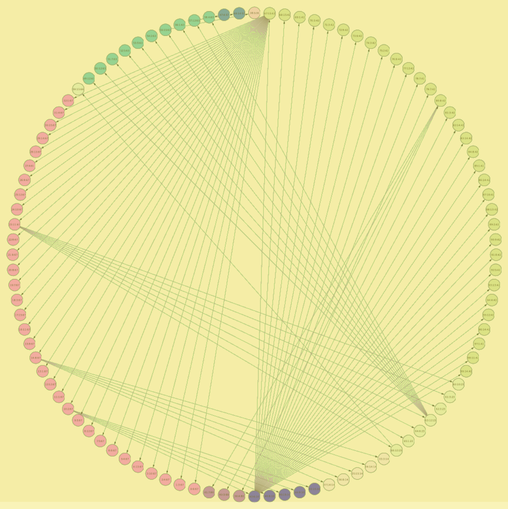

Hierarchical Boolean Networks

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Introduction

Gene networks are sets of genes whose products, proteins or non-coding DNA, determine the activity of the other genes in the network. Thus, networks are dynamic systems whose steady states and cycles,i.e. attractors, correspond to patterns of gene expression.

Boolean networks, see e.g.[1], are classic mathematical models of gene networks that have yielded fundamental insights into the dynamics of gene networks.

Classic Boolean networks ignore epigenetic control of gene activity [2]. Epigenetic regulators put genomic loci of multiple genes, i.e. domains, into a state that permits or blocks transcription. Hierarchical Boolean networks extend Boolean networks with simple epigenetic regulation.

Research Questions

- How does the epigenetic regulation change the behavior of Boolean networks?
- What are the characteristic differences between classic and hierarchical networks?
- In a hierarchical network, how are the number and length of attractors related to the number of hierarchical regulated domains.
- What is nature and distribution of basins of attraction in random network?

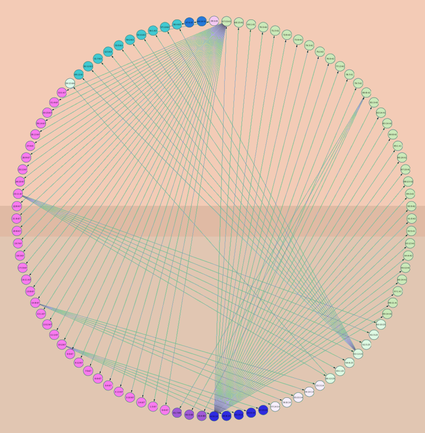
Boolean Network Model

Classic Boolean networks are represented by directed graphs (digraphs) where vertices represent genes and edges represent transcription factors. The logical interaction of transcription factors is represented by a Boolean function.

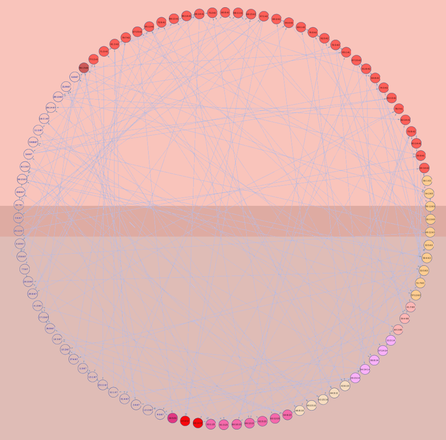
Epigenetic, i.e. hierarchical Boolean networks add an additional level of regulatory control by partitioning the graph into domains where each domain contains multiple genes. Members of each domain are regulated by a gene outside their domain.

Programmatically, a network is represented by an array of vertices where each vertex, i.e. gene, contains:

- a list of indexes to other genes in the network that supply the gene's. transcription factors.
- a Boolean function that controls the transcription factors' effect on the gene's activity.
- an index to the gene's regulator whose value either permits or prevents transcription.



domain regulation



transcription factors

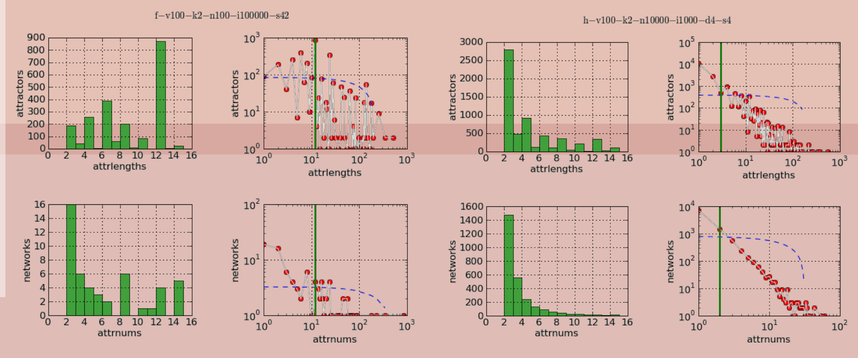
A simulation begins by assigning random values to a network's vertices. Starting with a random initial state, the network is evaluated and the resulting states sorted, compared and stored in the search of an attractor. Data including attractor lengths, counts and predecessors are accumulated and written to disk for post processing and analysis.

References

[1] S. A. Kauffman, Journal of Theoretical Biology **22**, 437 (1969).
[2] R. van Driel, P. F. Fransz, and P. J. Verschure, Journal of Cell Science **116**, 4067 (2003).
[3] M. S. Marshall, Ph.D. thesis, University of Bordeaux, (2001).

Results (preliminary)

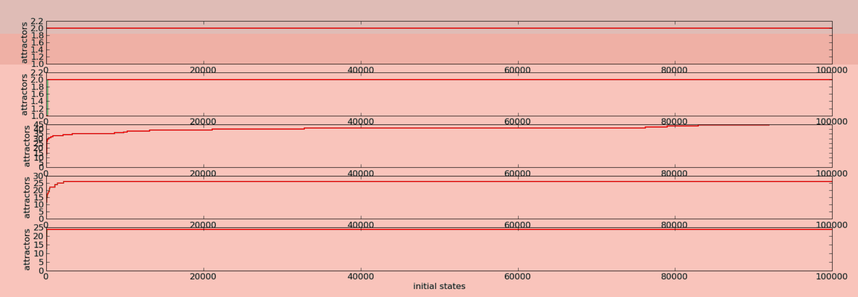
- Attractors from hierarchical networks were fewer and shorter than those found in comparable classic networks.
- The propensity for few and short attractors does not seem to depend on how a network is partitioned.



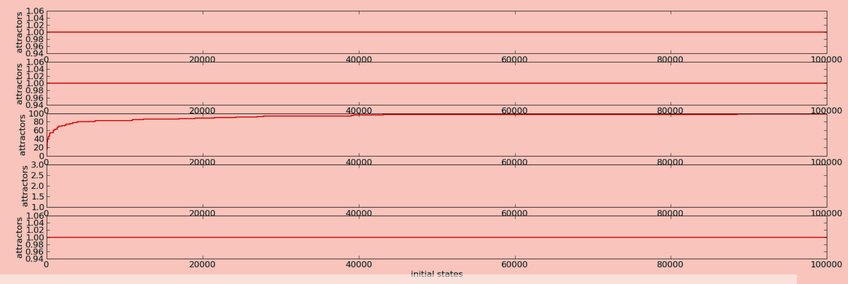
classic networks hierarchical networks

Basins of Attraction

Our simulations appeared to find most of the networks' attractors. However, we occasionally saw simulations where we found additional attractors only after many thousands more iterations. This implies that these networks have several dominating basins of attraction; and a number of smaller basins of attractions that are rarely found.



selected classic networks



selected hierarchical networks

Conclusions and future work

- We propose an extension to the classic Boolean gene network model that includes simple epigenetic regulation.
- We observed a distinct difference in the length and number of attractors in classic and hierarchical networks.

Future work:

- Investigate why hierarchical networks show a propensity for few and short attractors.
- Investigate whether graph structure metrics such as tree depth spreading activation and recursive citation[3] can shed light on network dynamics.
- Investigate whether a hierarchical network can be approximated by a classic network containing only epigenetic regulators.