RELATIONS BETWEEN STRUCTURE AND DYNAMICS OF TRANSCRIPTION REGULATORY NETWORKS

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Introduction

- Gene regulatory networks are enormous in size
- To understand the dynamics of a regulatory network we need to represent its structural properties in the simplest possible way
- Our analysis suggests that the major parts of gene regulatory networks are hierarchical with few small feedback loops present in them
- The hierarchic part regulates the dynamics of the cyclic parts and not the vice versa
- The hierarchic parts exhibit simple monostable behaviour and act as signal transporter or amplifier
- The cyclic parts are very rich in dynamics and act as decision makers
Structural Complexity of Gene Regulatory Network

- A collection of protein-DNA and protein-protein interactions
- The structures of regulatory networks are dynamic
- At any instant of time only a small subset of all protein interactions takes place
- At any instant of time only a subnetwork of the whole network can be observed
- The whole network consists of all p-p and p-d interactions throughout the life cycle of an organism
- Instantaneous subnetworks are much simpler than the whole network
- It’s not possible to figure out an exact subnetwork at any particular cellular state

E. Coli Transcription regulatory network: Data Collected from Ecocyc database: visualized by Cytoscape v.2.5.1
GENE REGULATORY NETWORKS: STRUCTURAL CHAOS

A full regulatory network is structurally chaotic.

The structural chaos arises from the presence of large numbers of long cycles.

Such a network is dynamically chaotic too.

It’s meaningless to study the full regulatory network because it is not observable.

Current technology is insufficient to construct the instantaneous subnetworks.

A level of abstraction is required to study the dynamics of these networks.

Network constructed from all the p-p and p-d interactions that takes place throughout the life cycle of Yeast: Data collected from BIND database. The graph shows how many feedback loops are found in the network and how long are they.
ABSTRACTION

- We use all the protein-DNA and only those protein-protein interactions which takes place during TF-TF dimer formation to construct our network.
- Current databases consist of very noisy interaction data.
- Reducing huge amount of interaction data reduces the noise to substantial amount.
- Eliminating most of the p-p interactions eliminate inter cellular state network edges.
- The reduced networks are not accurate representations of gene regulatory networks.
- The reduced networks are less erroneous, simpler, analyzable and represents an overview of the original networks.
GENE REGULATORY NETWORK OF S. CEREVISIAE
The regulatory network of *S. cerevisiae*

Visualisation tool used: Cytoscape V2.5.1.
Structural properties of Yeast regulatory network: Network motif analysis

Most Significant Network Motifs

- Significance levels indicate relative frequency of occurrence compared to random networks
- Most significant networks have directed acyclic structures
- Hierarchic motifs are more significant than continuous paths
- This indicates the absence of long continuous paths in gene regulatory networks
- The results indicate towards hierarchical network configurations
- A hierarchic network is a directed acyclic graph
Structural properties of Yeast regulatory network: Network motif analysis

Least Significant Network Motifs

All of the least significant motifs have cyclic structures
A non-zero significance level of cyclic motifs suggests the presence of small number of small cycles. 

Network motif analysis is not sufficient to confirm the presence of large cyclic structures. 

Depth first search algorithm is carried out to find all cycles. 

No cycle found in E.coli network. 

Five small cycles found in the Yeast network data set. 

Eleven auto regulatory circuit found in Yeast network. 

The Yeast data set is incomplete. 

Feedback loops found in yeast are embedded within each other in two different modules.
The hierarchical structure of yeast regulatory network

Yeast Gene Regulatory Network: A visual representation of a partial ordering imposed on its vertices

Total Nodes: 685, Total Weakly Connected Subgraphs: 11, All subgraphs DAG.
The hierarchical structure of regulatory network has non monotonic outdegree distribution

The middle layers of the hierarchy has greater out degrees than the terminal layers

The middle layer nodes handle the managerial bottlenecks in the network

Middle layer nodes has significant contribution towards ‘decision making’ in genetic dynamics

Top level genes receive signals from protein-protein interaction

Mid-level genes ‘makes the decision’ depending on the received signal

Bottom level genes transport the decision to p-p pathways

Bottom level genes are less influential but more essential for survival

DYNAMICS
DYNAMICS OF NETWORK MOTIFS

- Single input Motif: found in all regulatory networks
- Bifan Motif: found in all regulatory networks
- Dense Overlapping Regulons: found in all regulatory networks
- Autoregulatory motif: found in all regulatory networks
- Regulator Chain Motif: found in all regulatory networks
- Feed-Forward loop Motif: found in all regulatory networks
- Multi-Component loop Motif: six of these motifs are found in yeast gene regulatory network, yet to be found in bacterial gene regulatory networks

- These are the most frequently occurring modules in regulatory networks of E. coli and Yeast.
- The overall dynamics of a regulatory network is too difficult to analyze.
- We shall rather start with the dynamics of individual motifs.
Dynamics Of FFL Motif

Structurally FFL motifs are directed acyclic graphs.

FFL motifs mono-stable dynamics (one stable steady state)

The linearization matrix of the dynamic equations always yield negative real eigenvalues.

The eigenvalues of the linearization matrix do not depend on any kinetic parameter.

The eigenvalues of the linearization matrix do not depend on the equilibrium point.

The stability of FFL motifs is absolutely immune to its parameter value.

\[
\begin{align*}
\frac{dx}{dt} &= B_x + \gamma_x f_x(t) - \alpha_x x \\
\frac{dy}{dt} &= B_y + \gamma_y f_y(t) + \beta_y \left( \frac{x^2}{K^2_{xy} + x^2} \right) - \alpha_y y \\
\frac{dz}{dt} &= B_z + \beta_z \left( \frac{x^2}{K^2_{xz} + x^2} \right) \left( \frac{1}{1 + y^2/K^2_{yz}} \right) - \alpha_z z \\
\end{align*}
\]

where \( M = (x_{ep}^2 + K_{xz}^2) (y_{ep}^2 + K_{yz}^2) \)

Visualization of three dimensional phase portrait of the FFL motif. Two sample trajectories and their corresponding stability tubes are also shown.
FFL motifs show monostable dynamics which is immune to any perturbation to their reaction rate constants.

FFL Motifs are structurally directed acyclic graphs.

Similar analysis on all acyclic motifs yields similar results.

Making a larger network by connecting a set of acyclic motifs in an arbitrary way yields a directed acyclic graph.

All network which have directed acyclic structure exhibits robust monostable dynamics.

All directed acyclic structure are hierarchical.
The bistability of autoregulatory circuit arises only for positive autoregulation.

Negative autoregulatory circuits are always monostable.

The dynamics of multicomponent loop motif depends on its parameter values and the types of regulations.

The cyclic structures may exhibit monostable, multistable or oscillatory behaviour.

The dynamics of the feedback loops depends on their parameter values, and the regulating part of the network.

Only cyclic structures may exhibit complex dynamics and may serve as decision makers.
Location of The Cyclic Structures in The Hierarchy

- Bifurcation analysis of the composite loops without inner loops reveals the presence of Hopf Bifurcation depending on the parameter values.
- Including the inner repressive loops makes the system less bifurcative due to parameter perturbation.
- The bifurcation of the system remains equally prone to the effect of the regulating network with or without inner repressive loops.
- The nitrogen catabolite feedback system is robust against parameter perturbation.
- It changes dynamic modes depending on the regulating genes (e.g., GLN3).

Because of the capability of the conjugate loop structure to exhibit diverse dynamics, they are placed in the midlevel to act as ‘decision makers’.
There are evidence of other feedback loops in yeast regulatory network.

**SWI-5, SBF, FKH1** conjugate loop is a part of cell cycle of yeast, so is **CKI, Cln and cdc-28 loop** (Sriram et. Al. IET Syst. Biol, vol1, no.6, 2007)

All these loops lie in the mid-level of the hierarchy.
Effect of adding small feedback loops in a large hierarchical structure

Linearization matrix of an n node hierarchical network

\[
\begin{bmatrix}
-a_1 & 0 & 0 & 0 & 0 \\
- & -a_2 & 0 & 0 & 0 \\
- & - & -a_3 & 0 & 0 \\
- & - & - & ... & 0 \\
- & - & - & - & -a_n
\end{bmatrix}
\]

Adding feedback from node 3 to node 2

Linearization matrix of an n node hierarchical network with an added feedback from node 3 to node 2

\[
\begin{bmatrix}
-a_1 & 0 & 0 & 0 & 0 \\
- & -a_2 & m & 0 & 0 \\
- & n & -a_3 & 0 & 0 \\
- & - & - & ... & 0 \\
- & - & - & - & -a_n
\end{bmatrix}
\]

Eigenvalues of triangular linearization matrix of the hierarchical network

\[\lambda_i = -a_i\]

Eigenvalues of block triangular linearization matrix of the hierarchical network with added feedback

\[\lambda_{2,3} = \frac{(a_2 + a_3) \pm \sqrt{(a_2 + a_3)^2 - 4(a_2a_3 + mn)}}{2}\]

\[\lambda_i = -a_i, i \not\in \{2,3\}\]

- Without feedback the linearization matrix is triangular with –ve real eigenvalues
- Small feedback makes the linearization matrix block triangular
- The eigenvalues of the block triangular matrix remains mostly same apart from those related to the loop
- The stability of the rest of the network is not affected due to addition of small feedback loops
Gene regulatory networks are mostly stable and robust

Only the loop structures may go unstable

The stability of cyclic modules does not affect the rest of the network

The cyclic structures process the received signals, make a decision, deliver the decision to the bottom level genes

The rest of the network act as signal transporter and amplifier
Conclusion

- The study is based on reasonable abstraction of real regulatory networks.
- The analysis of dynamics is based on differential equation model of gene transcription.
- This study explains the reason of stability, and relates the structure and behaviour of regulatory networks.
THANK YOU