Network Motifs

PRESENTED BY: DANIT GOLDBERG AND SHAI GAZIT
BASED ON: “AN INTRODUCTION TO SYSTEMS BIOLOGY” BY URI ALON
Network Motifs

Motifs – what are they?

Motif Detection

Motif Families and Functions in Sensory Transcription Networks

- Negative Auto-Regulation (NAR)
- Forward-Feeding Loops (FFLs)
- Single-Input Modules (SIMs)
- Dense Overlapping Regulons (DORs)

Motifs Functions in Different Networks

- Developmental Transcription Networks
- Signal Transduction Networks
- Neuronal Networks
Motifs

**Definition:** Patterns that occur in the real network significantly more often than in a randomized networks are called network motif.

So what is a randomized network?
- Has the same basic features of the real network – the same number of edges and vertices – but the distribution of the edges is random.
E. Coli Transcription Network

#Nodes = 424, #Edges = 519

#Expected Self-Edges (in randomized network) = 1

#Self-Edges = 40
Chapter 3

'Real' network

- $N = 10$ nodes
- $E = 14$ edges
- $N_{self} = 4$ self-edges

Randomized network (Erdos – Renyi)

- $N = 10$ nodes
- $E = 14$ edges
- $N_{self} = 1$ self-edge
Why is Negative Autoregulation a Network Motif?

**Negative autoregulation** occurs when a transcription factor $X$ represses its own transcription.

Negative autoregulation can therefore use a strong promoter to give an initial fast production, and then use auto-repression to stop production at the desired steady state.
Feed-Forward Loops (FFLs)

After comparison of the subgraphs between the real networks and the randomized, we are left with one motif and one anti-motif.
Why are FFLs selected against randomizing forces

Of the 8 options, 90% of the FFLs are C1 (Coherent type 1) and I1 (Incoherent type 1).
C1 FFL

The C1 FFL is a sign-sensitive delay element.

It operates in a manner similar to an AND function.

Sign-sensitive delay can protect against brief input fluctuations.
Single-Input Modules

One regulator control a group of genes (usually also regulates itself)

Common Themes:
- X regulates a group of targets
- Each target gene is regulated by X only
- The regulation sign is similar for all targets
- X is autoregulatory

Can generate temporal programs of expression, meaning genes are turned on one by one in a specific order.

Target genes share a common function –
- for example, all part of the same metabolic pathway
- Another example – response to stress or damage
Temporal order

In E. Coli, the temporal programs match the functional order of the gene products – a protein isn’t created before it is needed.

Temporal order creates an assembly line

The temporal order is created by different thresholds for each target

De-activation is also temporal, in the opposite order (LIFO)

Other examples:
- Circadian clocks (with coregulators)
- Meaning SIMs can have more than one regulator, as long as there is one main regulator
SIM evolution

There are examples of SIMs that regulate the same target genes in different organisms, but the master regulator is different.

Shows that SIM functions have been rediscovered throughout mutations in each organism separately.
Dense Overlapping Regulons (DORs)

Dense arrays of regulators that combinatorically control a dense array of output genes.

Can carry out “decision-making” based on many different input functions.

Contains 2 groups we will talk about:
- Multi-FFLs
- Bi-fans (We’ll acknowledge them later on)
Multi-FFLs

We can “enlarge” FFLs to create larger subgraphs

For example – duplicate a node and its edges

The most significant in appearance – Multi-Output FFLs
Flagella Motors in E. Coli

Let’s look at a specific example – the creation of a flagella motor in E. Coli.

Flagella = a “propeller” E. Coli grows to move to a better environment.

Created by a Multi-Output FFL made of 2 regulator and 6 operons (output genes).

Between X and Y there is an OR function
FIFO Temporal Order

There is a temporal order. When a new flagella is needed, concentration of X rises, and slowly turns on the Z genes one by one.

Here there is FIFO order of shutdown using reversed thresholds on Y

This avoids deactivation of Z due to short loss of X activity
Motif Families

before far we mentioned motifs with defined number of nodes.

SIMs and DORs are larger motifs with common themes within the family

They have free parameters

- N for target genes in SIMs
- N for regulators and M for target genes in DORs
Motifs in other Networks

Until now – talked about motifs in sensory transcription networks. (rapid response, easily reversed)

Now we can talk about other networks:
  ◦ Developmental transcription networks – (slow response, irreversible)
  ◦ Signal transduction networks – (quick read and quick response)
  ◦ Neuronal networks – (complex decision making)
Developmental Transcription Networks

Include earlier motifs, plus:

- Two-Node Positive Feedback Loops
  - Two positive interactions - X and Y activate each other
  - Two negative interactions - X is active and Y isn’t, or the opposite, but never both active or neither active

Cause irreversible decisions
Developmental Transcription Networks

- Regulated and Regulation Feedbacks
  - Regulated feedbacks – two-node with third node regulating both (creates a “memory” of the third node)
  - Regulating feedback – two-node with third node being regulated by both

- Long Transcription Cascades – possible due to larger timescale (cell generations)
Signal Transduction Networks

The nodes are signaling proteins and the edges are directed interactions.

The input for the network is detected by receptors in the membrane of the cell.

Outer end detects molecules (ligands), inner end change messenger proteins.

Causes chain reaction in messenger protein changes.

Motif found in these networks – Multi-Layer Perceptrons
  ◦ Cascading DORs
  ◦ Due to many layers, can perform detailed computations.
  ◦ As such, are studied in the context of AI, and have similar properties
    ◦ Discrimination - the ability to accurately recognize certain stimuli patterns
    ◦ Generalization – the ability to “fill in gaps” in partial stimuli patterns
    ◦ Graceful degradation – damage to elements doesn’t “crash” the network
Neuronal Network in C. Elegans

C. Elegans – small work with 300 neurons in its head

Networks are made up of neurons as nodes and synaptic connections as edges.

Share motifs with transcription and signal transduction networks

° Due to shared goals - information processing

° Different – in transcription networks we have multi-output FFLs, here we have multi-input FFLs
° Multi-input FFLs activate only when there is enough “weight” from the input
° Or many short insignificant inputs in a short amount of time that together are meaningful

° Most common motif – multi-layer perceptrons – due to detailed computation abilities
References

- “An Introduction to Systems Biology”
  - Uri Alon
  - Chapters 3-6
Questions?