Topological Generalization of network Motifs

- Three node Sub graphs - 13
- Four Node Sub graphs - 199
- Five Node Sub graphs – Over 9000
- Seven Node Subgraphs – Million
- Fortunately, Most Biological Network shows families of dominant motifs
  - Eg: Transcription Networks Show
    - Feed Forward Loops (FFL)
    - Dense Overlapping Regulons (DOR)
    - Single Input Modules (SIM)
Generalizing motifs – Role replication
First-In First-Out (FIFO) Program

\[ K_{xz1} > K_{xz2} > K_{xz3} \quad K'_{xz1} < K'_{xz2} < K'_{xz3} \]
FIFO program

- The FFL works as an FIFO program here because of the OR functions at $Z_i$
- Notice that threshold levels have to be reversed for Y and Z
Aside: E Coli Flagella – Technological wonder

Single cell, 1 micron length

Contains only ~1000 protein types at any given moment

still : Amazing technology
FIFO program is governed by a FFL

- **Feedforward loop triad (FFL)**

- **4-node generalization of the feedforward loop triad**
  - Double input
  - Double Y
  - Double output

- **Multi-node simple generalization of the feedforward loop triad**
  - Multi input
  - Multi Y
  - Multi output
Multi-input FFL in Neuronal Networks

- **Nose Touch**
- **Noxious Chemicals Nose Touch**

**FLP**

**ASH**

**AVD**

**AVA**

**Backward movement**
Dense Overlapping Regulon (DOR)
DORs

- The Genes in each DOR have a shared Global function
  - Such as stress response
  - Nutrient metabolism
  - Biosynthesis of key classes of cellular components
- The DOR forms the back bone of networks global structure
- So Can we use motifs to simplify networks?
How do Network Motifs Integrate?

A Master Regulators Layer (lots of Auto-Reg.)

A single DOR Layer

Where are the X→Y→Z?

FFLs and SIMs are integrated within DORs

The E.coli Transcription Network (partial)
Compare with…

$\text{gene } x \quad \text{gene } y$

X → Y
DORs in transcription networks

- Form single layers - do not form cascades
- No ‘Single line’ cascades
  - Rate limited networks tend not to employ such cascades
  - Cascades are found in networks with interactions that are rapid compared to the timescale in which the network needs to function.
Network Motifs in developmental transcription networks

- These are not rate limited
Developmental Transcription Networks

The TF expression profile in a developing Drosophila embryo
Developmental Transcription Networks

Two-node Feedback Loops - Locking

- Both X **AND** Y are ON at the same time.
- Genes regulated by X and Y belong to the same tissue (or strip).

- X **OR** Y is ON at a given time.
- Genes regulated by X and Y belong to different tissues (strips).
Developmental Transcription Networks

Regulating Feedback Loops

Double Positive Loops

Double Negative Loops

Regulated Feedback Loops
Developmental Transcription Networks

Regulated Feedback Loops as a Memory Element
Developmental Transcription Networks

Cascades

\[ X \rightarrow Y \rightarrow Z \]

\[ X \rightarrow Y \rightarrow Z \]

[X]

[Y]

[Z]

Time
Feed Back Loops in developmental transcription networks

- $X$ transcriptionally activates $X$.
- $Y$ inhibits $X$.

- $Z$ transcriptionally activates $X$ and $Y$.
- $X$ forms a complex with $Y$.
- $X$ phosphorylates $Y$.

Power $\rightarrow$ Heater $\rightarrow$ Temperature

-Thermostat

(Fast) Protein-Protein Interactions
(Slow) Transcriptional Interactions
Feed Back Loops Produce Oscillation (remember from Control theory?)

Cdc20 oscillator controls Cell Cycle

Mutation of the Drosophila CWO gene
The critically damped response of the oscillator is described by the equation:

\[ x = e^{-\gamma t} \left[ x_0 + (v_0 + \gamma x_0) t \right] \]

which is a combination of an exponential and a linear term.

Oscillator with resonant frequency 10 rad/s started from rest.
After Barger & Olsson
Cell Signaling networks

- What are cell signaling networks?
Signal Transduction Cascades
Popular Motifs in Signal Transduction Cascades

BiFan

Diamond

Generalization of DOR

Multi-layer Perceptrons (multi-DORs)
Multi Layer Perceptorns in Signal Transduction Cascades
Dynamics of Signal Transduction Cascades

\[ \frac{dY}{dt} = v_1 X_1 Y_o + v_2 X_2 Y_o - \alpha Y_p \]

\[ \frac{dY}{dt} = 0 \quad \text{At Steady State} \]

\[ \frac{Y_p}{Y} = f (w_1 X_1 + w_2 X_2) \]

\[ w_2 = \frac{v_2}{\alpha}, \quad w_1 = \frac{v_1}{\alpha} \]

\[ w_1 X_1 + w_2 X_2 > 1 \quad \text{Activation Threshold} \]
Dynamics of Signal Transduction Cascades

**“AND” gate**

\[ w_2 = 0.7 \]

\[ w_1 = 0.7 \]

**“OR” gate**

\[ w_2 = 2 \]

\[ w_1 = 2 \]
Dynamics of Signal Transduction Cascades

\[ \frac{Z_p}{Z} = f(w_{z1}Y_1 + w_zY_2) \]

“OR” gate

“AND” gate
Dynamics of Signal Transduction Cascades
Summary

- Network motifs can function in:
  - several biological processes (sensory systems, development).
  - different time scales (milliseconds, cell generations).

- Network motifs can produce temporal programs (LIFO, FIFO, oscillation).

- Motifs within a network may be arranged in organized structures (perceptrons, interlocking FFL).

- It is possible to understand network topology better by reducing the network to motif - topology.