SnapShot: Network Motifs

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Cell

AUTOREGULATION

Negative

Speeds response time

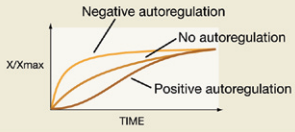
Reduces cell-cell variability of X concentration

Makes input function (response to signal) more graded

Positive

Slows response time

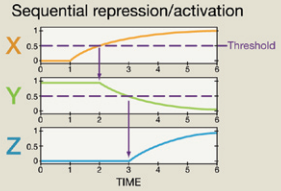
Possible bistability



CASCADES

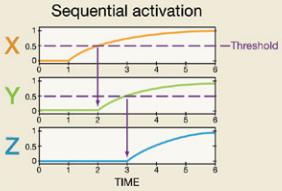
Negative

Sequential repression/activation



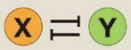
Positive

Sequential activation



POSITIVE-FEEDBACK LOOPS

Double-negative

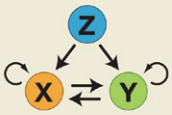


Exclusive bistability: X ON,Y OFF or vice versa

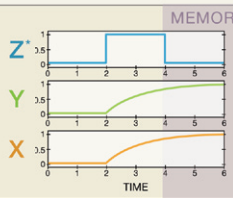
Double-positive

Joint bistability: X, Y either both ON or OFF

Regulated double-positive

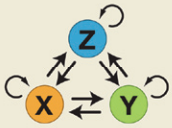


Lock-on



Memory: X, Y stay ON after input Z turns OFF

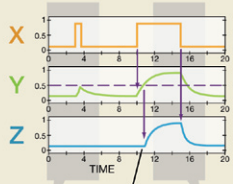
Fully connected triad



FEEDFORWARD LOOPS (FFLs)

Coherernt type I

AND gate

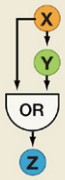


Filters transient ON input signals

Delayed ON response

Immediate OFF response

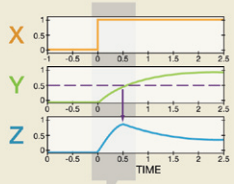
OR gate



- Filters transient OFF signals
- Immediate ON response
- Delayed OFF response

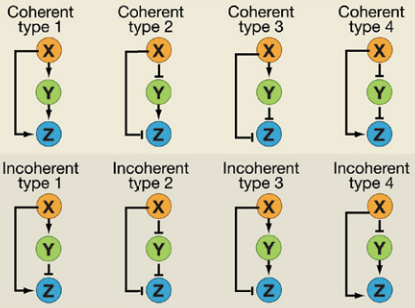
Incoherent type I

- Pulse generator
- Can detect relative (fold) changes in input
- Speeds response time



Pulse generator

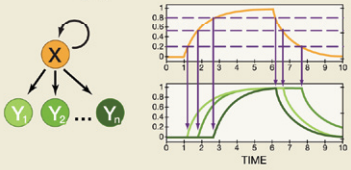
The 8 FFL types



Coherent type 1 and Incoherent type 1 are the most common in transcription networks

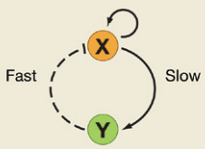
SINGLE-INPUT MODULE (SIM)

Can generate temporal program of expression (e.g., just-in-time transcription)

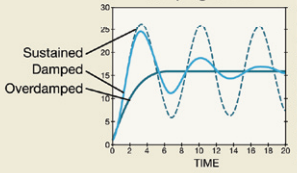


NEGATIVE-FEEDBACK LOOPS

Can generate oscillations

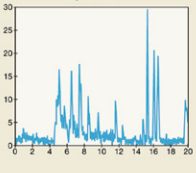


Oscillations at different damping levels

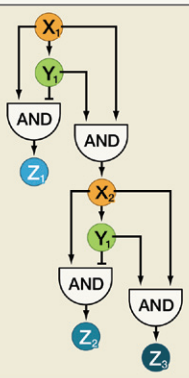


Can generate noise-driven excitable pulses

Noise driven excitable pulses



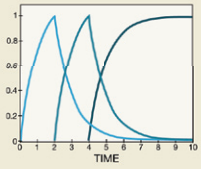
INTEGRATED FFLs



Example: *B. subtilis* sporulation

Acts as FFL for each output gene

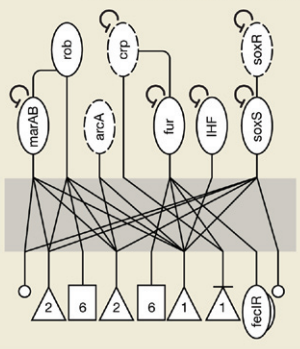
Can generate FIFO temporal order



Integrated coherent and incoherent FFLs generate series of expression pulses

INTEGRATED MOTIFS AND DENSE OVERLAPPING REGULONS

FFLs, SIMs are combined into dense overlapping regulons (DORs)



Example: Drug and superoxide DOR in *E. coli* transcription network

- Transcription factor (TF)
- Dense overlapping regulon (DOR)
- Single-input module (SIM)
- Coherent feedforward loop
- Incoherent feedforward loop
- Individual gene or operon

See online version for legend and references.

SnapShot: Network Motifs

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Cell

Transcription regulation and signaling networks are composed of recurring patterns called network motifs. Network motifs are much more prevalent in biological networks than would be expected by comparison to random networks and comprise almost the entire network structure. The same small set of network motifs has been found in diverse organisms ranging from bacteria to plants to humans. Experiments show that each network motif can carry out specific dynamic functions in the computation done by the cell. Here we review the main classes of network motifs and their biological functions.

Autoregulation

Negative autoregulation (NAR) occurs when a transcription factor represses the transcription of its own gene. (We use transcription to help make examples concrete; all circuits described here could operate also in other regulatory modes, e.g., a protein inhibiting its own activity by autophosphorylation.) This occurs in about half of the repressors in *E. coli* and can speed up the response time of gene circuits and reduce cell–cell variation in protein levels that are due to fluctuations in production rate. Positive autoregulation occurs when a transcription factor enhances its own rate of production. Response times are slowed and variation is usually enhanced. This motif, given sufficient cooperativity, can lead to bimodal (all-or-none) distributions, where the concentration of X is low in some cells but high in others.

Cascades

Cascades of gene expression create sequential activation of genes. The downstream gene is activated when its regulator reaches the relevant threshold. Using negative regulation, the genes can be sequentially activated and repressed.

Positive-Feedback Loops

Developmental transcription networks often use positive-feedback loops that are made of two transcription factors that regulate each other. The double-negative loop, in which two repressors repress each other, has two steady states: X is ON and Y is OFF, or the opposite. In the double-positive loop, either both X and Y are OFF, or both are ON. In either case, a transient signal can cause the loop to lock irreversibly into a steady state, providing memory of an input signal. Often, X and Y also positively regulate themselves. In a regulated feedback loop, an upstream regulator Z regulates X and Y, which locks the feedback loop into one of its steady states. Triads of mutually activating transcription factors are also common network motifs.

Feedforward Loops (FFLs)

The feedforward loop (FFL) appears in hundreds of gene systems in *E. coli* and yeast as well as in other organisms. This motif consists of a regulator, X, which regulates Y and Z, where Y also regulates Z. Because each of the three interactions in the FFL can be either activation or repression, there are eight possible structural types of FFLs. X and Y combine to regulate Z, often approximately as AND or OR gates. The two most common FFLs are the coherent type 1 FFL (C1-FFL) and the incoherent type 1 FFL (I1-FFL). The C1-FFL with an "AND" gate is a "sign-sensitive delay" element and a persistence detector. The I1-FFL is a pulse generator and response accelerator. For a range of parameters, the I1-FFL can also act as a fold-change detector, where the response dynamics depend only on the fold-change (rather than absolute change) of the input signal.

Single-Input Module (SIM)

In single-input modules, a regulator X regulates a group of target genes (typically X also regulates itself). This motif allows coordinated expression of genes with a shared function and can generate a temporal expression program, with a defined order of activation or repression of each of the target promoters. Stochastic pulses of X can provide proportional control according to the pulse frequency (as in CRZ1 in yeast).

Negative-Feedback Loops

Negative-feedback loops between two genes or proteins are often made up of interactions that take place on different timescales. For example, X can slowly activate Y, which in turn quickly inhibits X (for instance, slow transcriptional activation and rapid inhibition by degradation). This circuit can create oscillations. A symmetrically opposed motif, with fast activation and slow negative feedback, can generate noise-driven excitable pulses.

Integrated FFLs

FFLs may be combined into larger integrated structures and more complex transcription circuits. For example, integrated coherent and incoherent FFLs generate temporal waves of gene expression during the sporulation process of *B. subtilis*.

Integrated Motifs and Dense Overlapping Regulons (DORs)

Dense overlapping regulons are sets of regulators that combinatorially control a set of output genes. The DOR can be thought of as a gate-array, carrying out a computation by which multiple inputs are translated into multiple outputs.

Network motifs combine to form the global structure of the network. In the example shown, viewing an image of the network using symbols to denote the different motifs helps to portray the network in a compact way. Note that FFLs and SIMs are integrated into DORs. Usually the DORs occur in a single layer, thus most computations are carried out in a single "cortex." Developmental networks can have deeper layers of cascades.

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