Network Motifs – Recurring Circuitry Components in Biological Systems

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Goals of Lecture

- Consider reasons for focusing on motifs and circuits
- Look at ideas of motifs, networks, circuits in cells and tissues
- Examine some motifs and their ‘behavior’ for idealized conditions
- Consider several biological examples and the motifs that control specific responses
- Discuss level of detail that can be introduced in computational models of complex circuits
Abstract | Transcription regulation networks control the expression of genes. The transcription networks of well studied microorganisms appear to be made up of a small set of recurring regulation patterns, called network motifs. The same network motifs have recently been found in diverse organisms from bacteria to humans, suggesting that they serve as basic building blocks of transcription networks. Here I review network motifs and their functions, with an emphasis on experimental studies. Network motifs in other biological networks are also mentioned, including signalling and neuronal networks.

Logic circuits are made up of organized arrays of network motifs


I. Positive/double-negative Feedback Loop Motif

(1) Irreversible bistable switch (w/ strong feedback strength)

Dynamical response

Steady-state response
I. Positive/double-negative Feedback Loop Motif

(2) Reversible bistable switch (w/ weak feedback strength)

Dynamical response

Steady-state response

Different off/on thresholds - hysteresis

Ultrasensitive motif

II. Negative Feedback Loop Motif

(1) Accelerate response time

Gene Expression of Y
II. Negative Feedback Loop Motif

(2) Negative gene autoregulation reduces noise in gene expression

\[ X \rightarrow Y \]

Gene Expression of Y

Time (h)

(3) Cellular adaptation and homeostasis

\[ \text{Stressor} \]

\[ \text{Transcription factor} \rightarrow \text{Anti-stress genes} \rightarrow \text{Controlled variable} \]

\[ \text{Sensor} \]

Adaptation (dynamical response)

Steady-state response

Controlled variable

Time

Proportional feedback – imperfect adaptation and monotonic response
Integral feedback – perfect adaptation and threshold response
II. Negative Feedback Loop Motif

(4) Generate oscillations

III. Feedforward Loop Motif

Another family of network motifs is the feedforward loop (FFL). This motif consists of three regulators: X, which regulates Y, and Z, which is regulated by both X and Y. Because each of the three regulatory interactions in the FFL can be either activation or repression, there are eight possible structural types of FFL.
Type I Coherent Feedforward Loop

(1) Detect persistent signal and introduce time delay

(2) Filtering out small transient noise

Type I ICFFL

Type I Incoherent Feedforward Loop

(1) Generate pulses or transient responses

(2) Accelerate response time

Type I ICFFL
**Type I Incoherent Feedforward Loop**

(3) Cellular adaptation, homeostasis and nonlinear response

- Imperfect adaptation – monotonic response
- Perfect adaptation – threshold response
- Over adaptation – nonmonotonic (hormetic response)

Depending on the strength of feedforward control (degree of ultrasensitivity)

- Sensor → Stressor
- Transcription factor → Anti-stress genes → Controlled variable

Adaptation (dynamical response) vs. Steady-state response

**Type I Incoherent Feedforward Loop**

(4) Detect fold-change rather than absolute-change

X Y Z Type I ICFFL

X Y Z Time
Transcriptional regulatory networks:

This network is made of three incoherent feed forward loops (iFFLs), which generate pulses of Z1, Z2, and Z3; and one coherent feed forward loops (FFLs) that produces Y2.

How would these transcriptional nodes be expected to behave over time of treatment and concentration (dose)?
Ecdysone signal is transient, leading through a series of gene expression changes to induce larval development in the fly.

Thummel, Insect Biochemistry and Molecular Biology 2002

Cascade discussed by Landers and Spelsberg, 1992. Reversible developmental network associated with cyclic uterine growth
Such changes can be reversible as in uterus following estradiol treatment of immature female rats.

We can begin to appreciate the breadth of gene changing, but there are challenges in extracting information regarding the network, i.e., circuit structure.

How might that be accomplished?
Cannabinoid receptor 1 (CB1R) regulates neuronal differentiation. Results of transcription factor activation experiments that used pharmacological inhibitors of kinases revealed a network organization of partial OR gates regulating kinases stacked above AND gates that control transcription factors, which together allow for distributed decision-making in CB1R-induced neurite outgrowth.

Science 2008
Bioinformatic tools and data processing to extract the pathway from the transcription factor results.

Simple schematic of signal flow through Src, MAPK, and PI3K during neurite outgrowth. CB1R stimulation by HU-210 (HU) activates the alpha subunits of Gi and Go (αi/o) and leads to activation of Stat3 through the kinase Src. BRCA1 is depicted in blue. The putative interaction between BRCA1 and Akt is shaded gray.
Integration of activated transcription factors with the upstream signaling network during CB1R-induced neurite outgrowth. Cells were treated with inhibitors of MAPK, PI3K or Src and transcriptional analyses conducted to assess alterations in the presence of the inhibitors.

Proposed decision logic for cell-state change during CB1R-stimulated neurite outgrowth. Stacked below are three AND gates that connect the kinases to the transcription factors. The components and connections are in black. The gray arrows and gate symbols are in gray to denote information flow and the abstract nature of the pOR and AND gates.
Levels of Model Detail

- Alon and the ‘conceptual’ approach to evaluating circuit behaviors
- Giving detail to key pieces of the biology – our examples
- Having a sense of the system you need to examine - experience
- Isolating the perturbation and modules associated with dose-response – knowing the problem
- Learning about needed technologies to conduct meaningful biological studies – bridging disciplines

Detail in Models

- How much is needed?
- What is important?
- How does the cell coordinate all these inputs?
- Parsimony versus full reality

Summary - Circuits and Motifs

- Circuits and Networks are made up of simpler motifs connected in various manners

- Much as in electronics, we have to appreciate the behavior of the individual motifs in isolation first to see how they perform in a larger ‘integrated circuit’

- The task of informed dose-response modeling is likely to involve determining the circuit structure of the system under study and a focus on key (not all) parts of the circuit affected by chemicals