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No tradeoff between versatility and robustness in gene circuit motifs

Joshua L. Payne [*]

University of Zurich, Institute of Evolutionary Biology and Environmental Studies, Zurich, Switzerland
Swiss Institute of Bioinformatics, Lausanne, Switzerland

HIGHLIGHTS

- I exhaustively analyze a space of nearly 17 million model gene circuits.
- These are mapped to circuit motifs, in order to study versatility and robustness.
- Individual gene circuits exhibit a tradeoff between versatility and robustness.
- In contrast, circuit motifs exhibit no such tradeoff.

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ABSTRACT

Circuit motifs are small directed subgraphs that appear in real-world networks significantly more often than in randomized networks. In the Boolean model of gene circuits, most motifs are realized by multiple circuit genotypes. Each of a motif's constituent circuit genotypes may have one or more functions, which are embodied in the expression patterns the circuit forms in response to specific initial conditions. Recent enumeration of a space of nearly 17 million three-gene circuit genotypes revealed that all circuit motifs have more than one function, with the number of functions per motif ranging from 12 to nearly 30,000. This indicates that some motifs are more functionally versatile than others. However, the individual circuit genotypes that constitute each motif are less robust to mutation if they have many functions, hinting that functionally versatile motifs may be less robust to mutation than motifs with few functions. Here, I explore the relationship between versatility and robustness in circuit motifs, demonstrating that functionally versatile motifs are robust to mutation despite the inherent tradeoff between versatility and robustness at the level of an individual circuit genotype.

1. Introduction

Gene regulatory networks are highly stylized, diagrammatic representations of the transcriptional and post-transcriptional mechanisms that cells use to control gene expression. In such networks, nodes represent genes and directed edges represent regulatory interactions between genes. One structural property that is common to the gene regulatory networks of organisms as different as yeast and human is the statistical enrichment of particular directed subgraphs known as circuit motifs [1–3]. Examples include three-gene motifs such as the feedforward loop and four-gene motifs such as the bi-fan [4] (Fig. 1). Experimental and theoretical analyses of these and other motifs have revealed their capacity to accelerate

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[*] Correspondence to: University of Zurich, Institute of Evolutionary Biology and Environmental Studies, Zurich, Switzerland.
E-mail address: joshua.payne@ieu.uzh.ch.

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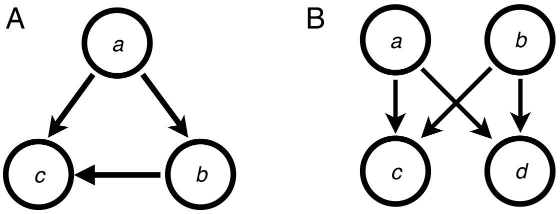

Fig. 1. *Two examples of circuit motifs.* A gene regulatory circuit is a small subgraph of a larger gene regulatory network. Such circuits vary in their architecture (*i.e.*, the wiring diagram of "who" regulates "whom"). Each distinct architecture is referred to as a motif. For example, in the (A) feedforward motif, gene *a* regulates gene *b* and both genes *a* and *b* regulate gene *c*, whereas in the (B) bi-fan motif, genes *a* and *b* both regulate genes *c* and *d*.

response times to intracellular signals [5] and to buffer against transient fluctuations in gene expression levels [6], suggesting that the architecture of a circuit (*i.e.*, its motif) partly determines its function [7,8].

The function of a circuit is embodied in the expression pattern of its constituent genes—their level, timing, and location of expression. For example, a function of the gap gene circuit of *Drosophila melanogaster* is to form discrete bands of gene expression orthogonal to the anterior–posterior axis of the developing embryo, a function that is essential for the proper development of the fly's segmented body plan [9]. Other examples of circuit function include chemotaxis [10] and competence control [11] in bacteria, mating behavior in yeast [12], lateral root development in plants [13], endoderm specification in the sea urchin [14], and digit formation in the vertebrate limb [15].

Gene circuits are often multifunctional, meaning that they form distinct expression patterns in different tissues or developmental stages, or in response to different combinations or levels of signaling molecules [16]. Said differently, multifunctional circuits drive multiple metastable expression states that are different from one another, and that are triggered by distinct sets of input signals. This phenomenon is exemplified by the *Hedgehog* gene circuit in butterflies, which both patterns the wing blade and helps to form the wing's eyespots [17]. Other examples include the segment polarity network in *D. melanogaster*, which is involved in denticle patterning and the specification of neuroblasts [18], and the circuit controlling mating behavior and the specification of cell type in yeast [19]. Multifunctional circuits are also of interest to synthetic biologists, who engineer circuits to perform complex information processing tasks. For example, using transcription factors with engineered DNA binding domains, a circuit has been constructed that switches among the logical functions `AND` and `OR` in response to specific input signals [20].

An important property of both natural and synthetic circuits is the robustness of their functions to genetic perturbation. Several theoretical and experimental studies have investigated the robustness of various gene circuits and networks [21–28], yet we still know very little about the relationship between the architecture of a circuit and the robustness of its functions. This is mainly because earlier studies have focused on just one or a few circuit architectures, and only under a small subset of all possible initial conditions [29–31,8]. Further, they did not consider multifunctional circuits, and they were limited to studying only a small fraction of the many regulatory programs that a given motif may implement. Such programs – referred to as signal-integration logic – are encoded in the regulatory regions of the circuit's genes, namely by the number, location, spacing, and orientation of transcription factor binding sites [32,33], promoter strength [34], and other local sequence features [35–37]. Mutations that alter a circuit's signal-integration logic may result in a new circuit function [38].

The *sin* operon in *Bacillus subtilis* provides an illustrative example of a circuit motif that can realize several distinct functions via changes in signal-integration logic [24]. The circuit's native function is a bistable switch that controls sporulation behavior, and the threshold of this switch can be fine-tuned via mutations in one of the circuit's two promoters. Mutations in the other promoter can lead to more drastic changes, transforming the circuit's function from a switch to a graded response, an oscillator, or a pulse generator. Importantly, these changes do not alter the circuit's architecture. This motif is therefore highly versatile: small changes in signal-integration logic generate a diversity of circuit functions.[1]

It is not yet possible to experimentally characterize the functions of circuit motifs exhaustively [39], so any comprehensive analysis of the relationship between circuit architecture and the robustness of circuit functions will necessitate the use of models. Kauffman's Boolean model [40] provides a useful framework for such an analysis. This is largely due to the model's explicit representation of a circuit's signal-integration logic, which determines the circuit's motif [41] and its functions [16]. Moreover, for small circuits, it is possible to exhaustively enumerate all possible forms of signal-integration logic and under all possible initial conditions, facilitating the comprehensive exploration of the interplay between circuit architecture, circuit function, and the robustness of these functions to perturbation.

Previous work with the Boolean model has demonstrated a tradeoff between the number of functions (gene expression patterns) that an individual circuit may realize and the robustness of these functions to mutation [16]. Said differently, the more functions a circuit has, the less robust these functions are to genetic perturbation. Yet it remains to be seen whether this tradeoff also applies to circuit motifs, which are typically represented by many distinct circuits, each with their own signal-integration logic and functions [41].

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[1] It is important to stress the difference between a circuit motif realizing multiple functions and an individual circuit being multifunctional. The former arises because motifs typically comprise many individual circuits, each with their own signal-integration logic, whereas the latter arises because individual circuits may yield different gene expression patterns in response to different initial conditions.