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Coupling switches and oscillators as a means to shape cellular signals in biomolecular systems

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ABSTRACT

To understand how a complex biomolecular network functions, a decomposition or a reconstruction process of the network is often needed so as to provide new insights into the regulatory mechanisms underlying various dynamical behaviors and also to gain qualitative knowledge of the network. Unfortunately, it seems that there are still no general rules on how to decompose a complex network into simple modules. An alternative resolution is to decompose a complex network into small modules or subsystems with specified functions such as switches and oscillators and then integrate them by analyzing the interactions between them. The main idea of this approach can be illustrated by considering a bidirectionally coupled network in this paper, i.e., coupled Toggle switch and Repressilator, and analyzing the occurrence of various dynamics, although the theoretical principle may hold for a general class of networks. We show that various biomolecular signals can be shaped by regulating the coupling between the subsystems. The approach presented here can be expected to simplify and analyze even more complex biological networks.

1. Introduction

Living cells can react to external and internal stimuli such as the depletion of nutrients, the variations in hormone levels, and the reception of sensory signals by mediating specific responses that are governed by the underlying regulatory networks [1]. An essential attribute of living cells is their capacity to switch between distinct states in response to external stimuli or as a result of internal development. Such switching phenomena have been found across a wide range of cellular processes including metabolic responses [2], signal transductions [3], cell-cycle transitions [4], and cell fate decisions [5]. Bistability, i.e., two stable steady states coexisting under the same cellular conditions, is the most prevalent switching mechanism in living cells [5–10]. Cells can toggle between two alternative internal states to accommodate environmental and intercellular conditions and convert a transient trigger stimulus into a decisive or an irreversible transition under some circumstances [11].

The possibility of bistability in simple genetic and metabolic networks has been realized for quite a long time [12]. One of the first experimental observations of bistability dates back over 50 years to Novick and Weiner, who characterized induction of the lactose (*lac*) operon with a gratuitous inducer [2]. It was shown that there existed a range of inducer concentration under which cells can be in one of two stable steady states: not expressed or fully induced *lac* operon. The composition of the cell population would depend on its history: initially fully induced cells would remain the 'on' state for many generations, whereas initially uninduced cells will remain mostly 'off' and would have a small probability of switching to the 'on' state [1]. Later, Jacob and Monod proposed that a direct positive feedback or a double-negative feedback could create

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alternative stable states and realized that these or similar circuits might explain cell differentiation [13]. Since then, many biological switches have been identified, including the lysis-lysogeny decision in bacteriophage λ [6,14], the *lac* operon in bacteria [7], the induction of maturation in *Xenopus laevis* oocytes [5,8], the switch in the JNK cascade [15,16], the cell cycle progression [17–20], the antibiotic production in *Streptomyces coelicolor* [21], and cell fate determination in sea urchin [22,23] and hematopoietic stem cells [24]. In addition, synthetic bistable switches have also been constructed in both bacteria and mammals [25–30]. One well known example is the Toggle switch which consists of two repressors: LacI and cI encoded by genes *lacI* and *cI*, respectively [25]. The synthesis of the two repressors is regulated in a mutually exclusive way. It is easy to verify further that only two of those steady states, with lower LacI (inactive LacI) and higher LacI (active LacI), are stable whereas the middle one is unstable (hence the term bistability).

It has been suggested that a simple way of encoding the presence of a stress or stimulus for living cells is to shift the concentration of a group of molecules from one steady-state level to another. However, this scheme has potential disadvantages including the cost of continuous production of molecules at a high level and unwanted cross-talk between pathways. Therefore, cells also encode changing environmental conditions in a time-varying way and oscillations are such a commonly adopted way [31]. Oscillations play important roles in physiological response to changing external and internal conditions and have been observed in many biological processes such as circadian rhythm, cell cycle, apoptosis, immune response, development, metabolism, and intracellular calcium and other signaling pathways [32–35,37–40].

Earlier examples of biological oscillations in metabolic control were recognized in the glycolysis [41–44], cyclic AMP production [45], and peroxidase–oxidase reaction [46,47]. Goodwin presented a minimal model of periodic oscillations based on a negative feedback regulation of a translated protein which inhibits its own transcription in 1965 [48] and Higgins published a ground-breaking paper on the theory of biochemical oscillations in enzyme-catalysed reaction networks in 1967 [49]. Prigogine and Lefever proposed the Brusselator model, a famous model of chemical reactions with oscillations in 1968 [50], and Sel'kov introduced a well known reaction–diffusion system, the Sel'kov model, as a model for glycolysis [51]. Later, more oscillations in biomolecular networks were discovered, such as the cyclin proteins in eukaryotic cell-cycle control [52,53], the period (PER) proteins in circadian rhythms [54], NF-κB signaling [33,34], and p53-Mdm2 signaling [36]. In addition, synthetic oscillators have also been constructed both *in vivo* and *in vitro* [55], including the Repressilator [56], amplified negative feedback oscillators [27,57–59], Fussenegger oscillators [60,61], Smolen oscillator [62–64], variable link oscillators [65], gene-metabolic oscillators [66], and transcriptional oscillators [67].

Biomolecular networks are composed of complicated interactions among components. In addition, some significantly recurring small subnetworks termed network motifs have been uncovered [68–70]. These motifs exhibit different dynamical functions and have been found to predominate in various networks such as gene regulatory networks and even larger-scale networks [71]. Among the network motifs, various feedback and feed-forward loops play important dynamical roles and may be useful for understanding how intracellular networks elicit specific cell behaviors [72].

The major functional characteristics of feedback loops in simple networks have been elucidated by experimental and theoretical studies [68,72–84]. For instance, positive feedback loops can convert graded signals into binary ones [26], act as a buffer for propagating noise while increasing sensitivity at the same time [75], exhibit ultrasensitivity [5,16], be involved in the amplification of signals [76] and memory generation [8,77], and induce phenotypic diversity [78] and genetic competence [79]. In contrast, negative feedback loops can behave as noise suppressors [80], oscillators [81], linearizers [82], output limiter [83], and transient generator [84].

Biomolecular networks contain various feedback loops, and interestingly, such feedback loops often exist in a coupled rather than isolated form in almost all cases [72,85–94]. It was shown that interlinking fast and slow positive feedback loops could result in a switch with rapid activation and slow deactivation times and a marked resistance to noise in the upstream signaling pathway [86], create an optimal bistable switch in cell signaling [87], and enhance robustness to stochasticity and persistence of memory [88]. In contrast, coupling of two negative feedback loops could independently stabilize basal signaling and limit maximal signal output [72] and enhance sustained oscillations and homeostasis [89]. In addition, combination of positive and negative feedback loops can tune frequency of oscillations without changing their amplitudes and possesses a greater robustness and reliability [92], effectively modulate signal responses while suppressing noise [89], create a flexible motif that can modulate itself among various functions such as bistable switches, oscillators, and excitable devices [93], and confer exquisite flexibility to biochemical switches [94]. Moreover, crosstalk between different pathways may help cells to process wide range of inputs and trigger appropriate response using limited and shared components [95].

This paper aims to unravel the compositional rules that govern the dynamics of systems containing simple modules with specific functions. Systems of coupled oscillators have been intensively studied [96]. However, biomolecular systems of coupled switches and oscillators need to be further investigated. Dynamical properties resulting from unidirectional coupling between the Repressilator and the Toggle switch were studied [97]. Such unidirectional couplings may be presented at multiple stages of genetic regulatory networks which were shown to be hierarchical [97]. However, bidirectional (mutual) coupling between biological switches and oscillators also exist in many biological networks, e.g., bidirectional coupling between the ATM switch and the p53-Mdm2 oscillator in the p53 signaling network [98]. The ATM switch transmits a switching signal to the p53-Mdm2 oscillator. The 'off' state of the switch leads to a low p53 level, whereas the 'on' state drives a series of p53 pulses. Meanwhile, the p53