PERSPECTIVE

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Elements of biological oscillations in time and space

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Oscillations in time and space are ubiquitous in nature and play critical roles in dynamic cellular processes. Although the molecular mechanisms underlying the generation of the dynamics are diverse, several distinct regulatory elements have been recognized as being critical in producing and modulating oscillatory dynamics. These include negative and positive feedback, time delay, nonlinearity in regulation, and random fluctuations ('noise'). Here we discuss the specific roles of these five elements in promoting or attenuating oscillatory dynamics, by drawing on insights from quantitative analyses of natural or synthetic biological networks.

Oscillatory dynamics is prevalent in all facets of life and plays critical roles in fundamental processes such as controlling gene expression[1], providing temporal cues in dynamic environments (for example, the circadian clock)[2] and determining cell-fate decisions[3,4]. Spatial oscillatory behavior can give rise to periodic patterns, such as skin patterns and vertebrate segmentation[5,6].

Extensive studies have been conducted to elucidate the molecular mechanisms underlying the generation of oscillatory dynamics (reviewed in refs. 7–9). Depending on the context, these mechanisms are extremely diverse in network complexity, temporal and spatial scales, and biological functions. For example, metabolic oscillations can operate on a time scale of minutes[10], whereas ecological oscillations operate with a period of multiple years[11]. Likewise, periodic patterns can emerge from oscillatory dynamics in single cells, with a length scale of <1 μm (ref. 12), or in groups of cells or multicellular organisms, with scales reaching up to meters in length[13].

Despite this diversity, five elements are recognized as critical for generating or modulating temporal or spatial oscillatory dynamics: negative feedback, time delay, positive feedback, nonlinearity in regulation, and noise (**Fig. 1**). These elements contribute to one or multiple aspects of oscillatory dynamics. Moreover, depending on the overall network architecture, each element can either enhance or attenuate the generation of oscillations. Here we discuss these contributions by examining recent computational and experimental studies of natural and synthetic systems. Our analysis aims at deducing general insights into the roles of various design elements within biological oscillations for both basic understanding and practical applications.

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Temporal oscillations: from simple to complex systems

The fundamental requirement to generate autonomous oscillations is negative feedback[7,14] (**Fig. 1a**). However, negative feedback alone cannot generate oscillations unless it is coupled with other elements. A common way to generate oscillations is to couple negative feedback with a sufficiently long time delay. In fact, negative feedback with minimal time delay has been used as a strategy to stabilize gene expression[15], a result exactly the opposite of generating oscillations.

Time delay emerges spontaneously in many biological processes. During transcription, a finite time is required to generate a transcript, thus leading to a gene-expression time delay[16] that can act as a source of oscillations. Indeed, Swinburne *et al.* have used an autoregulated tet repressor fused to introns of varying lengths to investigate the effects of transcriptional delay on oscillations in negative feedback, and have demonstrated that longer introns increase the transcriptional time delay, thereby generating oscillations with increasing periods[17]. Time delay can also emerge from translation and contribute to the generation of oscillations[18].

Time delay can be extended when an action (for example, transcriptional activation or repression) involves a cascade of multiple intermediate regulators[19]. Many natural biological oscillators adopt such an architecture (**Fig. 1b**). For example, the p53 tumor suppressor is negatively regulated by its transcriptional target *mdm2*. *mdm2* acts in an intermediary step, creating a time delay in the negative feedback loop that facilitates the generation of oscillations under certain conditions[20,21]. A similar strategy has been adopted in engineering the *Escherichia coli* repressilator, which consists of three transcriptional repressors sequentially repressing one another[22].

A potential limitation of an oscillator consisting solely of delayed negative feedback is that it can be prone to noise; this phenomenon becomes important when regulatory components are present in low amounts[23]. However, the robustness in a delayed negative feedback oscillator can be enhanced by proper tuning of network parameters[24,25].

Coupling negative and positive feedback can result in various dynamical responses, including bistability and excitable pulses[26]. This network architecture has also been shown to enhance oscillations and to confer noise resistance[27,28]. Positive feedback can create a time delay in activator accumulation before the activator level sharply rises and triggers repression in a switch-like manner. The activator is then slowly turned off (i.e., it 'relaxes' to the low state) before the cycle repeats itself. Such oscillations are known as relaxation-type oscillations[9]. Integrated positive–negative feedback enhances robustness to noise and increases the tunability of key oscillation

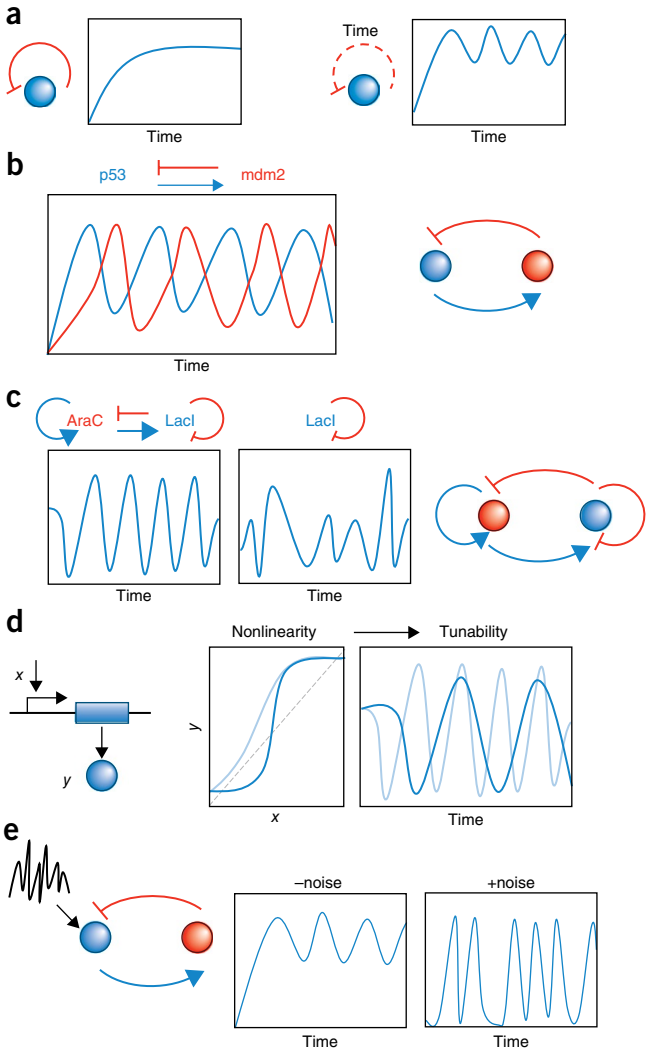

Figure 1 Generation of temporal oscillations. (**a**) Negative feedback can generate oscillation when it is coupled with a sufficiently long time delay. (**b**) A negative feedback motif consisting of two proteins: p53 activates mdm2, which in turn represses p53. With appropriate parameters, the motif can generate oscillations. (**c**) Coupling positive feedback with negative feedback can enhance the robustness of oscillations with respect to noise, in comparison with negative feedback alone. (**d**) Nonlinearity in regulation enables greater tunability of oscillatory dynamics. (**e**) Noise can enhance the generation of oscillations under certain conditions. Levels are indicated on *y* axes.

parameters[29]. Indeed, interlinked negative–positive feedback has been shown to increase robustness by enabling amplitude-invariant oscillations over a wide range of frequencies, in comparison with circuits consisting of only negative feedback[30]. This benefit can be enhanced by using multiple positive feedback loops in a coherent manner[31], thereby broadening the range of bistability and enhancing the sharpness of the transition of the activator from the low state to the high state.

Oscillations consisting of interlinked positive and negative feedback have been implemented in both cell-free systems[32] and living cells[33–35]. One of the best examples is the circuit described by Stricker *et al.*[36], which, after activation, can generate oscillations in >99% of all cell lineages. These oscillations are robust to environmental perturbations, and the period is tunable over a wide range by modulation of feedback strength. In this circuit, positive feedback is critical for enhancing the robustness of oscillations (**Fig. 1c**) but not for their generation: cells carrying only the negative feedback loop still oscillate, but with decreased regularity[36]. A unique property of the Stricker oscillator is the saturation of the degradation machinery by circuit regulators, thus promoting zero-order degradation of these regulators. This 'degrade-and-fire' mechanism can generate oscillations with a period decoupled from, and well beyond, the time delay in protein synthesis, even with solely negative feedback[25,36]. Such nonlinear degradation may enhance the generation of oscillations in natural biological oscillators[37,38].

Beyond nonlinear degradation, nonlinear regulation can also play a critical role in generating oscillations or in ensuring their robustness. Consider output activation by an input signal following a Hill equation,

$$y = \frac{x^n}{1 + x^n}$$

where y is the output normalized to its maximum, and x is the input normalized to its activation threshold (**Fig. 1d**). This regulation is considered to be nonlinear when $n > 1$. The same convention applies to the repression of an output by an input. In the classical Goodwin oscillator model, which consists of a single negative feedback, a sufficiently large Hill coefficient in repression is required to generate oscillations[39]. The high nonlinearity facilitates the generation of oscillations by creating a time delay in the action of the repressor: repression is negligible until the repressor reaches a threshold level. Nonlinear regulation can function in conjunction with other strategies, such as use of positive feedback[31], to enhance generation of oscillations.

Another strategy to counteract the effects of noise is chemical-mediated communication among cells. This communication can be achieved in two ways. First, cell-cell communication can be used to couple the oscillators in different cells to achieve synchronized oscillations. A common molecular mechanism to implement this coupling is bacterial quorum sensing (QS)[40]. Using this strategy, Danino *et al.* have demonstrated the synchronization of relaxation oscillators in a population of bacterial cells[41]. Such synchronized oscillations resemble those generated by some natural oscillators. For example, after starvation, *Dictyostelium discoideum* cells produce intracellular cyclic AMP (cAMP) in stochastic pulses, which then diffuses extracellularly. Transient extracellular cAMP stimulates its own production in neighboring cells, thereby propagating cAMP induction throughout the population. Individual cell oscillators synchronize after cAMP reaches a critical threshold[42], and oscillations observable at the population level are achieved. Depending on the length scale of the transport of the coupling molecule, synchronization of oscillations can be extended to longer distances. Prindle *et al.* have demonstrated intercolony synchronization of oscillations through gas-phase signaling, in which the oscillation in each colony is controlled by QS-mediated synchronization[43]. Such long-distance synchronization may also underlie the synchronization of natural biological clocks.

Second, cell–cell communication can be used to couple intracellular gene expression and population growth dynamics. In these cases, the growth and death of one or multiple populations are critical components of the overall oscillator. This strategy has been adopted to generate oscillations in single[44,45] or multiple populations[46], entirely on the basis of delayed negative feedback.

Although the presence of noise is typically detrimental, it can sometimes be the source of oscillations, as can occur, for example, when feedback alone is insufficient. Indeed, one study has examined the effect of temperature noise on a generic nonisothermal chemical system described by a single negative feedback loop. A study

using parameters incapable of driving deterministic limit cycles has found that fluctuations in temperature can be sufficient to generate oscillations[47] (**Fig. 1e**). Noise can also cause oscillations even in the absence of active feedback regulation. For example, Tanouchi *et al.* have recently found that bacterial cell-size control can be described by a linear map which reveals that, on average, a larger cell will grow for a shorter time before division[48]. Only when the linear map is coupled with noise can it generate transient oscillations in either initial cell size or gene expression in a fraction of the cell lineages, thus accounting for the experimental observations[48]. These transient oscillations differ from the typical limit-cycle oscillations in that they result from the modulation of random fluctuations by the linear map.

Oscillatory dynamics in space: periodic patterns

In space, oscillatory dynamics can result in well-defined periodic patterns[7]. Similarly to the generation of temporal oscillations, one or more of the five elements are required to generate oscillations in space. Again, negative feedback is the most fundamental requirement, and incorporating time delay with negative feedback can enhance robustness. Spatial oscillations have been extensively studied in animal embryonic development[5,49]. For example, the formation of somites in vertebrate embryos is controlled by a molecular oscillator, the segmentation clock[50]. The segmentation clock generates a temporal periodicity that can be translated spatially into the periodic boundaries of the somites[51,52]. Here, negative feedback is realized through Notch signaling[53,54]. In zebrafish, multiple layers of negative feedback are involved in the periodic activation of Notch. Notch then drives expression of *her1* and *her7*, which establish negative feedback regulation by suppressing their own expression[53]. The delayed negative feedback due to this intracellular inhibitory loop is thought to be the fundamental generator of the oscillations of the segmentation clock[55,56]. In turn, the secreted growth factor FGF 8 has been suggested to convert temporal oscillations into periodic somite boundaries. In particular, FGF 8 is expressed in the posterior of the presomitic mesoderm (PSM). During PSM growth, the gradient of FGF 8 generates a moving wavefront near the anterior, thereby determining the position of the segment boundary as well as the axial identity[57,58].

Similarly, Liu *et al.* have found that metabolic limitation during *Bacillus subtilis* biofilm formation creates a delayed negative feedback loop between peripheral and internal cells, thereby generating oscillations during colony expansion[59]. The authors have shown that consumption of glutamate from the cells in the periphery of the colony inhibits ammonium production from the interior cells. Because ammonium production promotes glutamate consumption, this interplay creates a delayed negative feedback in glutamate consumption in the peripheral cells and therefore causes oscillatory dynamics in colony growth[60] (**Fig. 2a**).

Positive feedback coupled with negative feedback is another common way to increase robustness in spatial oscillations. During *E. coli* cell division, the spatial oscillations of MinC, MinD and MinE are critical in determining the correct location for forming the ring-like structure of FtsZ (Z ring). ATP-bound MinD preferentially attaches to the cell membrane where other MinD–ATP complexes are bound, thereby forming positive feedback. MinE binds to MinD–ATP and triggers ATP hydrolysis and release of MinD–ADP from the membrane, thereby forming negative feedback (**Fig. 2b**). The pole-to-pole oscillations in MinD and MinE lead to localization of MinD at the poles. MinD binds and activates MinC, thereby also localizing the activity of MinC to the poles. As a result, the Z ring, which is inhibited by MinC, forms around the cell center, where MinC activity is lowest[61–63]. MinD-mediated positive feedback has been shown to increase the robustness of these spatial oscillations[64,65] and in turn the precision of cell division near the center.

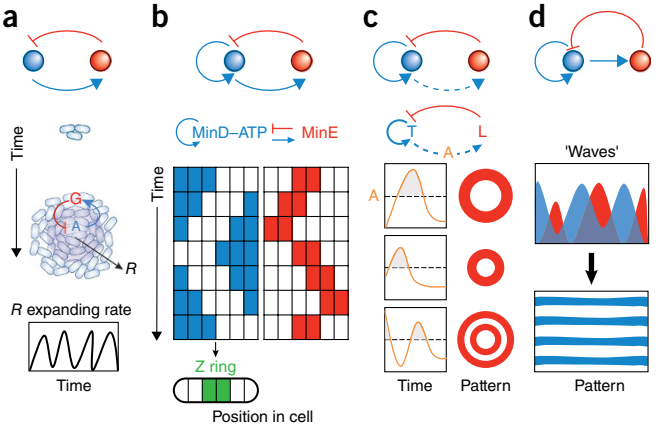

Figure 2 Generation of spatial oscillations by negative feedback or negative feedback coupled with positive feedback. (**a**) Delayed negative feedback emerges from the interplay between two subpopulations in a colony[60]. During cell growth, consumption of glutamate (G) from cells at the periphery of the colony is triggered by ammonium (A). Simultaneously, glutamate limits ammonium production from the interior cells; this process leads to oscillations in the expansion rate of the colony radius (*R*). (**b**) Generation of spatial oscillations inside the cell. During cell division, MinD and MinE oscillate from one pole to the other, thus leading to preferential localization of MinD at the poles. MinD then binds and activates MinC (not shown), thereby confining MinC activity to the poles. In turn, the Z ring (green), which is inhibited by MinC, forms around the cell center, where MinC activity is lowest[65]. (**c**) Generation of spatial patterns in a growing colony. An activator, T7 RNAP (T), activates itself and a diffusible signal, AHL (A). AHL leads to repression of the activator by inducing T7 lysozyme (L). Depending on the temporal dynamics of AHL, different sizes and numbers of ring patterns can emerge[66]. (**d**) Generation of Turing patterns by local activation and long-range inhibition. With proper parameters, the activator and inhibitor form periodic patterns in space.

At the population level, Payne *et al.* have demonstrated that gene expression of genetically programmed *E. coli* can self-organize into robust ring patterns[66,67]. Synthesis of the diffusible molecule acyl-homoserine lactone (AHL) is controlled by a positive feedback loop. When the concentration of AHL is sufficiently high, downstream negative feedback is activated. AHL dynamics is responsible for triggering the formation and maintenance of ring patterns. The timing to activate the negative feedback arm can be modulated by addition of exogenous AHL, thus leading to formation of a double-ring pattern[66] (**Fig. 2c**).

Liu *et al.* have adopted a similar network architecture in a synthetic gene circuit engineered to generate periodic stripes in a growing bacterial colony[68]. The circuit contains a density-sensing module through synthesis and release (by diffusion) of AHL. At a sufficiently high concentration, AHL triggers downstream gene expression that suppresses cell motility. Cells carrying this circuit sequentially form alternating stripes of high and low density. The circuit embeds positive feedback consisting of mutual inhibition: high cell density decreases cell motility, and high cell motility decreases the local cell density. Additionally, the delayed negative feedback arm is formed between nutrient and cell density. The strength of positive feedback can be modulated by adjusting the inhibition of cell motility by cell density, which in turn controls the number of stripes formed[68].

One of the most studied pattern-formation mechanisms is the reaction–diffusion model proposed by Alan Turing[69]. With appropriate

kinetic parameters, the model can generate diverse patterns (for example, stripes or spots) from a homogeneous initial state[70]. This model has been invoked to describe the generation of periodic patterns in several experimental systems[6,71]. For example, Nakamasu *et al.* have demonstrated that nonlinearities in local activation and long-range inhibition in zebrafish are the necessary conditions for periodic pattern formation[72], as predicted by mathematical studies[73] (**Fig. 2d**).

As with temporal oscillations, noise is often detrimental because it introduces variability and disrupts pattern formation[74,75]. However, under certain conditions, instability driven by noise can enhance the robustness and sustainability of spatial oscillations. A system driven by a deterministic reaction–diffusion mechanism is able to generate periodic Turing patterns. Maini *et al.* have shown that a stochastically excited system can form patterns more rapidly than its deterministic counterpart. Additionally, noise inherent in stochastic systems is able to produce more sustained patterns[76]. To date, however, noise-induced pattern formation has yet to be demonstrated experimentally.

Perspectives

The generation of temporal oscillations can be considered a means of encoding the information conveyed by a scalar input (for example, pH, temperature or chemical concentration)[77]. The oscillations can then drive distinct cellular processes[78]. For example, the dynamics of the p53 tumor suppressor (e.g., sustained or oscillatory) can drastically alter the cell-fate decision[79]. The ability to deconstruct oscillatory signals to determine upstream inputs would substantially contribute to interpreting the role of such oscillations in complex systems.

Periodic pattern formation in biology is critical for defining the body plan during development. Understanding the basic elements driving the generation of spatial oscillations may provide insights into how self-organized system-level integrated oscillations are achieved during embryonic development. However, a periodic pattern by a biological circuit can also be considered to be a spatial manifestation or encoding of environmental signals. For example, in bacteria, the formation of the division ring as determined by the oscillatory Min system is nutrient dependent[80,81].

Given the vast diversity and complexity of oscillating biological systems, it is advantageous that most, if not all, of them can be reduced to a combination of a few basic elements. This simplicity can facilitate analysis and interpretation of biological oscillations in defining the roles of specific molecular components. In the study of natural biological oscillators, the role of feedback control is well appreciated. In contrast, the consequences of time delay, noise and nonlinearity are less explored and are more challenging to address. This prospect is made even more difficult by the role of each element being context dependent. Noise can either promote or suppress oscillations, depending on the system. The same regulatory motif can generate oscillations in one system but not in another, as a result of differences in environmental parameters. For a particular system, a small perturbation in a critical parameter can fundamentally change the overall system dynamics, such as the transition from transient pulsatile dynamics to sustained oscillations[82]. Moreover, apparently similar dynamics can be driven by very different mechanisms[26]. In future studies, understanding how these dynamic elements emerge from molecular components may be critical for understanding the biological roles of the latter.

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