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Memorizing environmental signals through feedback and feedforward loops

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Abstract

Cells in diverse organisms can store the information of previous environmental conditions for long periods of time. This form of cellular memory adjusts the cell's responses to future challenges, providing fitness advantages in fluctuating environments. Many biological functions, including cellular memory, are mediated by specific recurring patterns of interactions among proteins and genes, known as "network motifs." In this review, we focus on three well-characterized network motifs - negative feedback loops, positive feedback loops, and feedforward loops, which underlie different types of cellular memories. We describe the latest studies identifying these motifs in various molecular processes and discuss how the topologies and dynamics of these motifs can enable memory encoding and storage.

Living organisms can remember previous experience and adjust their behaviors to future challenges. The most well-known examples are neuronal memory and adaptive immunity in metazoans, both of which require interactions and cooperation among many different cells. Similarly, individual cells can also memorize prior environmental signals and modulate their responses to subsequent cues. This type of "cellular memory" is mediated by interactions and cooperation of different genes and molecules inside the cell [1]. How these biochemical interactions enable the storage of prior environmental information remains a challenging question. Several recurring patterns of regulatory interactions, defined as "network motifs" [2], have been found to confer memory behaviors. In this review, we focus on the latest progress in characterizing these network motifs in diverse cellular systems, as well as in understanding how their structures and dynamics contribute to the encoding and maintenance of cellular memories.

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Conflict of interest

The authors declare no conflict of interest.

Negative feedback loops – desensitization

Odors and light become less noticeable after prolonged exposure. Similarly, continuous use of drugs and alcohol can cause refractoriness to their further administration. These familiar experiences that we have encountered in daily life stem from a general phenomenon - "desensitization," in which a stimulus triggers a response inside the cell and, at the same time, it also induces a process that inhibits the response to a future exposure to the same stimulus [3]. From the network perspective, desensitization, in many cases, is mediated by a negative feedback loop after a delay (Fig. 1).

A classic example is the desensitization of G protein-coupled receptor (GPCR) signaling, which mediates the effects of many hormones and neurotransmitters [4]. Agonist binding to GPCRs increases the intracellular level of the second messenger cAMP, which in turn activates protein kinase A (PKA). PKA then phosphorylates downstream cellular substrates and regulates many aspects of cellular physiology. Once the external signal is transduced into the cell and elicits cellular responses, the desensitization process is initiated. In addition to the well-established feedback inhibition of GPCRs by β-arrestin [5,6], a recent study found a delayed negative feedback loop through chaperone-assisted ubiquitination and degradation of the activated PKA catalytic subunit, resulting in a refractory phase that uncouples further agonist stimulation from continuous signal propagation [7].

Similarly, the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling that mediates innate immunity is also subject to desensitization. In mammals, type I interferon (IFN-I) is secreted upon pathogen infection and binds to the IFN-I receptor on the cell membrane, leading to activation of JAK and tyrosine kinase 2 (TYK2) that in turn phosphorylate transcription factors STAT1 and STAT2 and trigger the formation of IFN-stimulated gene factor 3 (ISGF3) complex. ISGF3 translocates to the nucleus and induces the expression of over 300 IFN-stimulated genes (ISGs), exerting anti-proliferative and anti-pathogenic effects [8,9]. Previous studies showed that one of the ISGs encodes the ubiquitin-specific peptidase 18 (USP18), which is a major inhibitor of JAK-STAT signaling that acts at the receptor level [10,11]. IFN pretreatment induces a delayed upregulation of *USP18*, resulting in long-lasting refractoriness to further stimulations [12,13] (Fig. 1b).

In both examples, desensitization is mediated by negative feedback loops with a delay (Fig. 1c). This delay is functionally relevant as it allows efficient signal propagation and response activation upon the initial stimulus and, importantly, it can enable signal processing of the initial stimulus for memory encoding. For instance, the delay enables a "persistence detector" that can filter out transient inputs: a brief pulse of stimulus that is shorter than the delay time does not induce pathway inhibition, whereas only persistent signals can lead to strong desensitization. This function is particularly crucial for cells in a fluctuating environment to avoid inappropriately entering a refractory phase triggered by spurious signals. Many mechanisms can give rise to a delay in feedback inhibition, including extensive nucleosome occupancy at the promoter regions [14–16], multi-layer activation cascades [17,18], or specific gene network topologies (e.g. feedforward loops) [19,20]. We recently found that cell cycle regulation and DNA methylation can also contribute to the

delay in feedback inhibition (e.g. in the case of *USP18* upregulation), which leads to stimulus duration-dependent refractoriness [12].

Positive feedback loops – hysteresis and priming

As opposed to desensitization, in many biological systems, previous exposure to a stimulus can accelerate or boost the responses to subsequent stimulations. This process is often mediated by positive feedback loops, which are well-known to give rise to bistability that enables long-lasting or permanent memories of past environmental conditions [21–23]. Increasing evidence has shown that, in the contexts of metabolic shifts or animal development, an identical environmental signal can lead to distinct outcomes in genetically identical cells. For example, a stimulus that causes some cells to differentiate can induce proliferation in other cells. The outcome upon a stimulus is generally determined by the metabolic or developmental state of the cell, which depends on the environmental history of the cell. This type of history-dependent behavior, defined as “hysteresis,” often arises from the bistability mediated by positive feedback loops, in which a previous environmental condition can permanently switch the cell to an induced state, resulting in different response dynamics and steady state, from those of uninduced cells, upon future stimuli [24,25] (Fig. 2).

Metabolic regulatory networks underlying the adaptation of microorganisms to carbon source changes, e.g. the *lac* operon in *E. coli*, are classic examples of such systems [26,27]. A recent study in yeast [28] showed that previous exposure to maltose can switch the cell to a stable respiratory state through positive feedback loops, such as those mediated by the heme-activated protein complex [29], which can shorten the lag time needed for adapting to a recurring carbon source switch from glucose to maltose, even in daughter cells that have not experienced the first change (Fig. 2b, left). Along the same line, researchers built a semi-synthetic regulon in yeast that controls the utilization of xylose, a nutrient that is non-native for yeast, and showed that positive feedback loops are sufficient to generate bistability and hysteresis, enabling history-dependent behaviors [30].

Epigenetic modification, a major mechanism underlying persistent cellular memory and cell differentiation, is also driven by positive feedback loops that enable stable and heritable states of DNA regions [31,32]. Such positive feedback loops involve the recruitment of specific enzymes to a modified histone, which catalyze the same modifications on neighboring histones [33]. For instance, a recent study showed that this type of modification-based positive feedback of histone H3 lysine 9 methylation (H3K9me), coupled with the autoregulation of the H3K9 methylthansferase Clr4, can reinforce the maintenance of gene silencing across many cell cycles [34] (Fig. 2b, right). Inspired by the self-propagating mode of regulation observed in nature, researchers also developed a synthetic epigenetic system in mammalian cells that can read and write N6-methyladenine (m6A), a DNA modification not commonly found in metazoans [35]. The incorporation of a positive feedback loop in the system enables a persistent epigenetic memory of transcriptional states.

We note that the irreversible state transition (Fig. 2c) is not required for memory generation by positive feedback. In reversible systems, positive feedback loops can still function to

prolong the duration of priming effects from prior treatments (Fig. 2d). For example, in the JAK-STAT pathway, an IFN-I pretreatment induces the accumulation of STAT1, STAT2, and IRF9, the components of ISGF3 mediating IFN-driven gene expression [12,13,36], which primes the cell for accelerated responses to future stimulations. In this case, the positive feedback loop produces a time delay in the decay of cellular memory, extending the period that priming effects can last after the removal of pretreatment (Fig. 2d).

Feedforward loops – phase separation and information storage

A growing number of recent studies have revealed that, in addition to feedback loops, feedforward loops also play important roles in encoding memories of environmental signals (Fig. 3a). Intriguingly, many of these feedforward loops involve signal-induced formation of phase-separated assemblies or granules, resulting in a period of desensitization or priming phase depending on the nature of the aggregates formed. For example, Caudron et al showed that, whereas pheromone stimulation leads to cell cycle arrest in yeast, prior signal exposures from an unsuccessful mating partner encounter can trigger aggregation and thereby inactivation of Whi3, an RNA-binding protein required for the G1/S arrest, thereby causing a stable pheromone-refractory state that lasts for many cell cycles [37].

It is generally believed that protein aggregates are detrimental to the cell. However, emerging evidence reveals that they can also function as beneficial storage devices for cellular memories (Fig. 3, b and c). For instance, in bacteria, proteotoxic stresses induce protein aggregates that can be asymmetrically inherited for many generations, conferring a significantly increased resistance to future stress [38]. Similarly, the cytoskeleton-associated protein Lsb2 forms a metastable prion in yeast under heat shock, which further promotes the conversion of other proteins into prions. These prions can be passed across several generations after the initial stress and can help enhance cell survival against future challenges [39]. Another study showed that stress can induce phase separation and sequestering of the yeast translation termination factor Sup35 through its prion-like domain, providing a heritable fitness advantage after the stress [40]. The [$SMAUG^{+}$] prion has been identified in yeast to encode memories of recurring environmental fluctuations from the ancestors and to regulate gene expression, growth and stress resistance, enabling an anticipation of future environmental changes [41,42].

Processing bodies (PBs) and stress granules (SGs) are stress-induced cytoplasmic messenger ribonucleoprotein (mRNP) granules, conserved from yeast to mammals. In response to stress, the mRNAs of some stress-responsive genes can be localized in PBs and SGs, which regulate the translation, degradation and storage of these mRNAs [43,44]. In our recent work [45], we found that the storage of newly synthesized mRNAs in PBs and SGs upon an initial stress, constituting a variant of feedforward loops, enables a long-lasting plateau of acquired stress resistance that accelerates the adaptation to future stresses (Fig. 3, d and e). The initiation of the storage process is elicited by protein kinase A (PKA) signals, whereas the duration of the memory depends on the amount of mRNA being stored in PBs/SGs and hence depends on both the amplitude and duration of the initial stress. This regulatory scheme allows the cell to determine how long the memory can last, based on the severity and period of the initial stress.

In the examples described above, cellular memories arise from feedforward loops through signal-induced phase-separation, featuring a reversible process with slow kinetics. In particular, after stimulus removal, the slow release of functional monomers from aggregates is crucial for the persistence of memories. This slow releasing kinetics allows the spreading of signal effects in time, maintaining sustained acquired functions after the initial stimulus is gone (Fig. 3, c and e). A recent study, combining mathematical modeling and optogenetic stimulus experiments, showed that the inherent physics of protein droplets (e.g. Ostwald ripening) can also enable the cell to memorize the spatial patterns of clustered regulatory factors induced by transient localized stimuli [46].

Feedforward loops that are unrelated to phase separation can also generate memory. For example, in *Drosophila*, odor or electric shock signals activate PKA to phosphorylate the transcription factor CREBB to enable long-term neuronal memory. PKA also activates a conserved kinase, *Meng-Po*, which inhibits the degradation of CREBB, contributing to maintenance of the CREBB level in the mushroom bodies of the brain without the continuous presence of the initial signal [47].

Conclusions and perspectives

Recent progress in quantitative cell biology has dramatically pushed forward our understanding of the mechanisms underlying cellular memory. These studies integrate new measurement technologies, such as microfluidics and advanced time-lapse imaging, with computational modeling, which provides a powerful suite of new tools to elucidate how genes and molecules interact dynamically to generate sustained cellular responses to transient stimuli, enabling long-lasting memories. As described above, multiple network motifs have been identified, each with different dynamic behaviors and contributing to different types of memory effects. Emerging questions along this direction include the combined effects of multiple network motifs operating in a single pathway and the role of heterogeneity in network dynamics and memory encoding.

In many biological systems, a single regulatory pathway often contains several network motifs that are coupled to one another. For example, the JAK-STAT pathway is comprised of multiple positive and negative feedback loops, which act collectively to modulate the cellular responses to varying interferon signals [12,13]. Future studies will be needed to investigate how the functions of these network motifs are dynamically coordinated and what are the functional benefits of the coupling and cooperation among these motifs, e.g. plasticity [48], robustness [49], multistability [50–52], synergy [53,54], or redundancy over different time scales [55,56]. Unravelling such complexity will require systematic genetic perturbation analyses in combination with dynamic measurements and computational modeling.

Recent single-cell analyses demonstrated the existence of substantial clonal heterogeneity in cellular responses to signals [57]. Interesting questions that deserve further investigation are whether individual cells differ in their abilities to memorize the same environmental signals and, if that is the case, what the mechanisms are which underlie the cell-to-cell variabilities, how different network motifs influence the stochasticity in responses, and how these

variabilities contribute to biological functions in the physiological contexts. Advances in single-cell technologies will enable us to track the dynamic responses of individual cells and analyze the source, the control and the consequence of the cell-to-cell heterogeneity in memorizing environmental signals.

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through STAT2 and IRF9, whereas a high dose of prestimulation desensitizes the pathway through negative feedback loops by USP18 and SOCS1. Further use of the model revealed that the basal levels of USP18 and STAT2 in primary hepatocytes from patients can predict the responsiveness to IFN treatments, suggesting potential diagnostic markers for personalized medicine. This study, together with Mudla et al [12], provides a comprehensive picutre about how interconnected feedback loops govern the dynamics of JAK-STAT responses to repetitive IFN simulations.

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synthetically implemented from the native galacotose-responsive pathway, are sufficient to generate bistability and hysteresis, supporting high growth rate and cell density, independent of galactose metabolism. This study highlights the functional relevance of network motifs in regulating cell physiology and provides a paradigm for engineering nutrient sensing netowrks in microorganisms.

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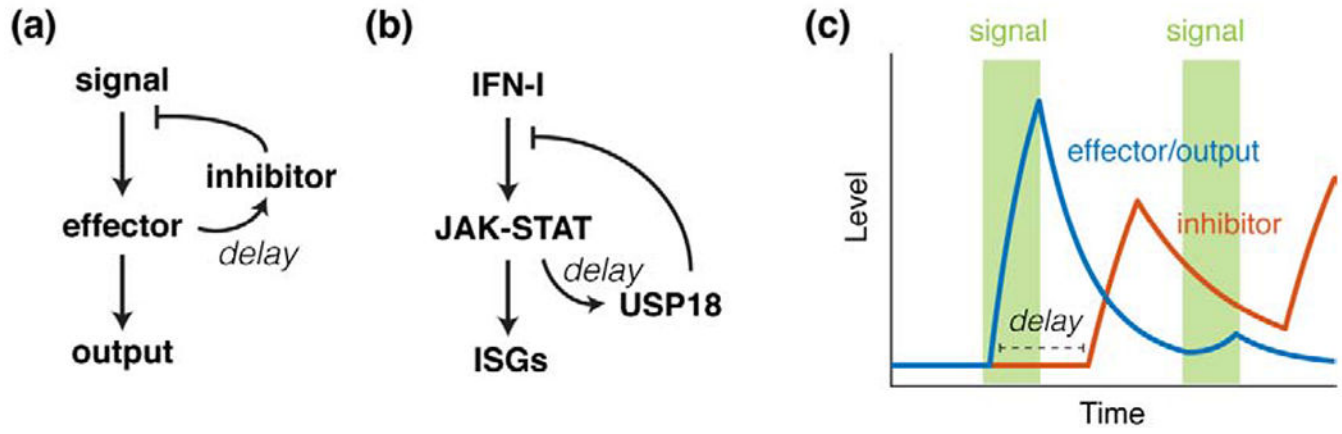

Figure 1. Negative feedback loops lead to desensitization.

(a) Topology of a general negative feedback loop. (b) An example of negative feedback system that causes desensitization - the USP18-mediated negative feedback loop in the JAK-STAT pathway. (c) Time traces of a delayed negative feedback system in response to repetitive stimulations. Green – signal; blue – effector/output; red – inhibitor.

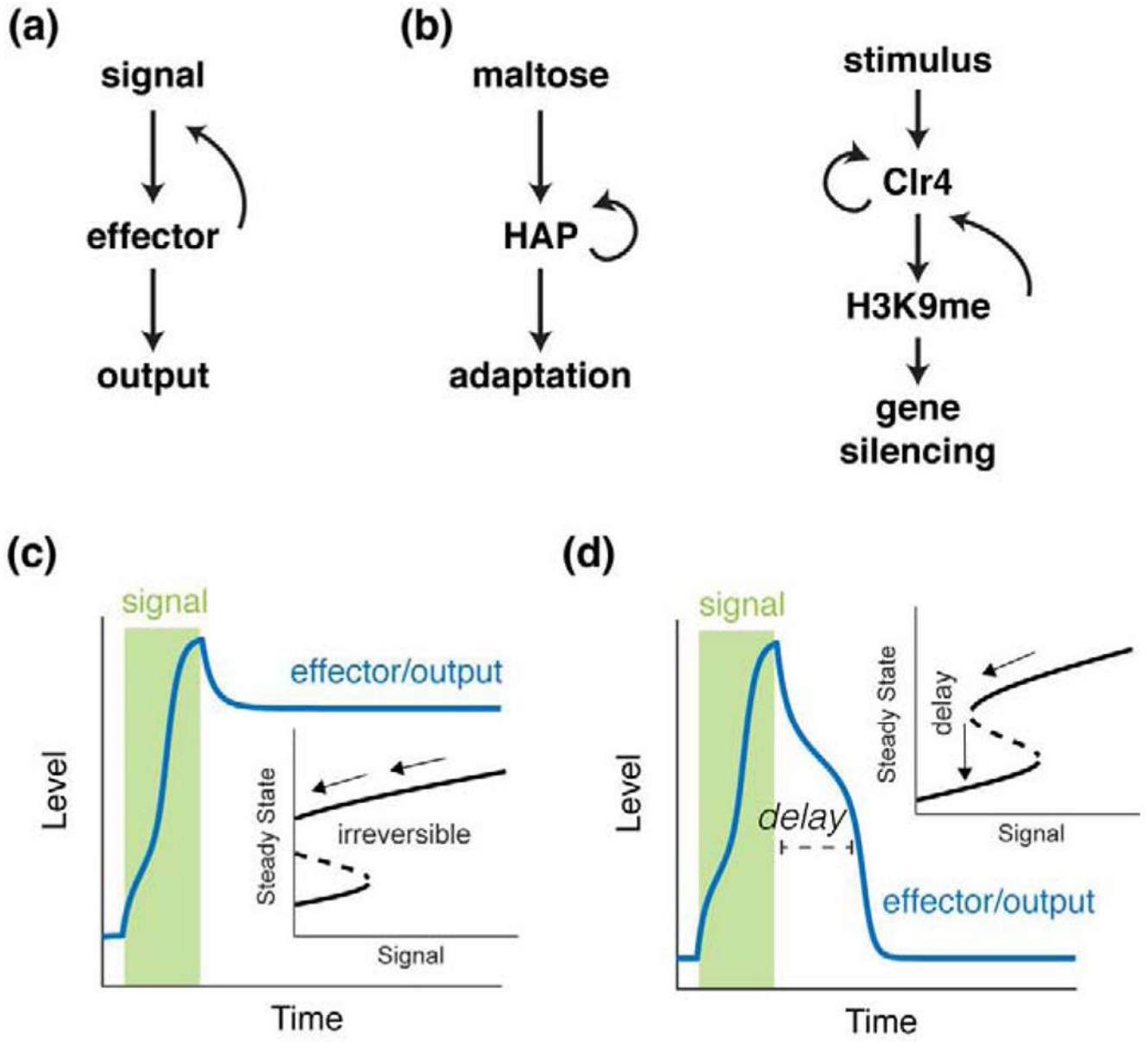

Figure 2. Positive feedback loops enable hysteresis and priming effects.

(a) Topology of a general positive feedback loop. (b) Examples of positive feedback loops that generate cellular memories. Left: a diagram of the regulatory network underlying the adaptation to carbon source switch from glucose to maltose. Right: a diagram of the epigenetic regulatory network underlying H3K9me3-mediated gene silencing. (c) The time trace of a positive feedback system that induces an irreversible state transition in response to a transient stimulus. Inset: a bifurcation diagram that shows the steady state values as a function of the signal level, illustrating the origin of irreversibility. (d) The time trace of a positive feedback system that induces a reversible response upon a transient stimulus. Inset: a bifurcation diagram that shows the steady state values as a function of the signal level, illustrating the origin of the delay in recovery time.

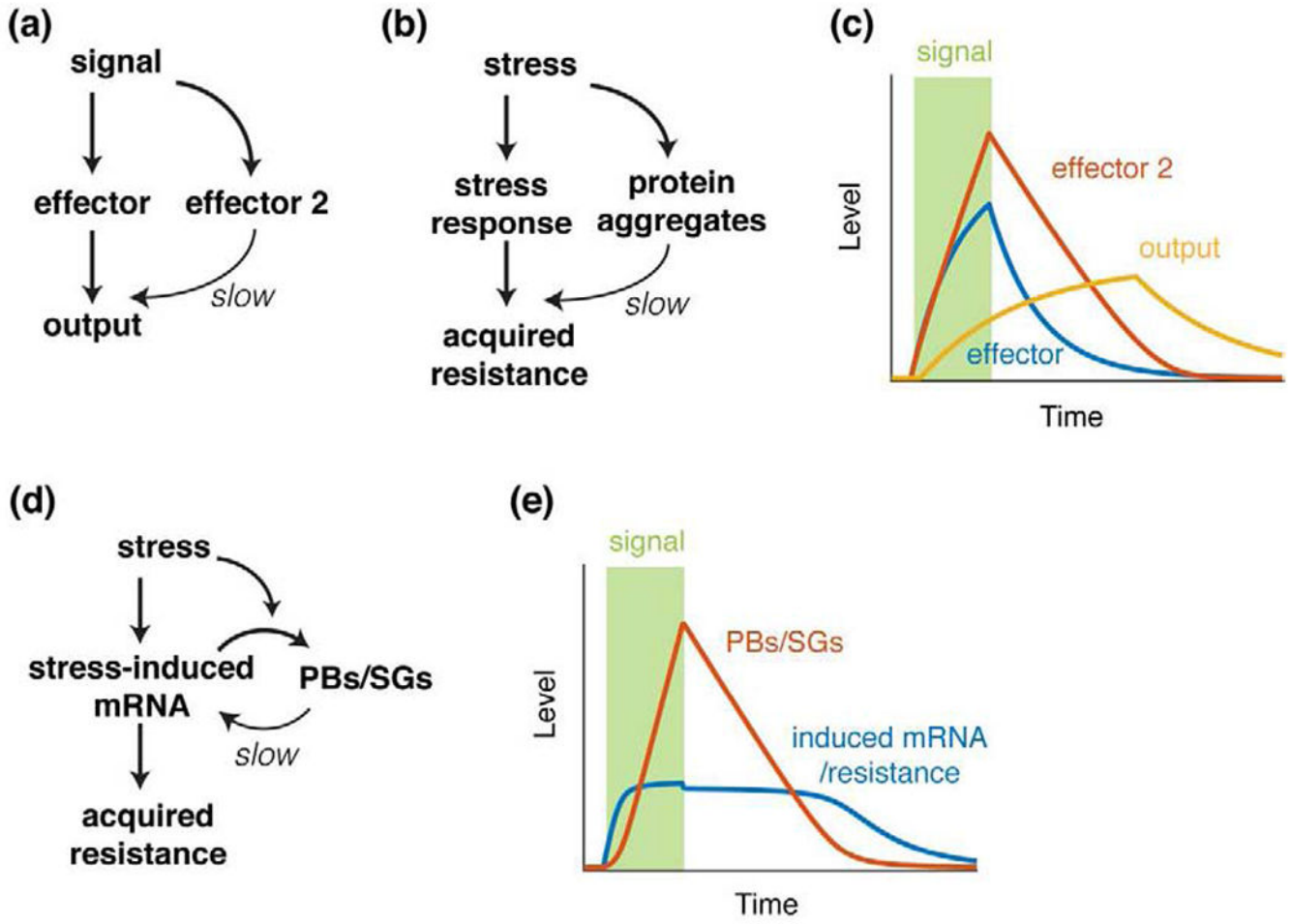

Figure 3. Feedforward loops allow the spreading of signal effects in time.

(a) Topology of a general feedforward loop. (b) An example of a feedforward loop that generates cellular memory through signal-induced protein aggregation. (c) The time trace of a feedforward system that enables a long-lasting response to a transient signal. Green – signal; blue – effector; red – effector 2 (slow); yellow - output. (d) An example of a variant of feedforward loops that generates cellular memory through signal-induced mRNA storage in PBs/SGs. (e) The time trace of the feedback forward system in (d) that enables long-lasting plateau of gene expression response and acquired stress resistance upon a transient stimulus. Green – signal; red – mRNAs stored in PBs/SGs; blue – stress-induced functional mRNAs/acquired stress resistance.