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# Noise Attenuation in the ON and OFF States of Biological Switches

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Ⓢ *Supporting Information*

ABSTRACT: Biological switches must sense changes in signal concentration and at the same time buffer against signal noise. While many studies have focused on the response of switching systems to noise in the ON state, how systems buffer noise at both ON and OFF states is poorly understood. Through analytical and computational approaches, we find that switching systems require different dynamics at the OFF state than at the ON state in order to have good noise buffering capability. Specifically, we introduce a quantity called the input-associated Signed Activation Time (iSAT) that concisely captures an intrinsic temporal property at either the ON or OFF state. We discover a trade-off between achieving good noise buffering in the ON versus the OFF states: a large iSAT corresponds to noise amplification in the OFF state in contrast to noise buffering in the ON state. To search for biological circuits that can buffer noise in both ON and OFF states, we systematically analyze all three-node circuits and identify mutual activation as a central motif. We also study connections among signal sensitivity, iSAT, and noise amplification. We find that a large iSAT at the ON state maintains signaling sensitivity while minimizing noise propagation. Taken together, the analysis of iSATs helps reveal the noise properties of biological networks and should aid in the design of robust switches that can both repress noise at the OFF state and maintain a reliable ON state.
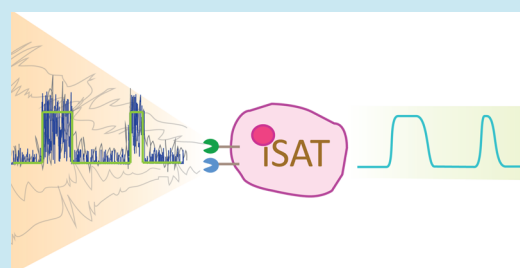
KEYWORDS: *noise, signaling switch, SAT, feedbacks, sensitivity, network motif*

Regulatory processes in biology often require switch-like behaviors that are resistant to noise. Although it has become clear that feedback loops are critical for mediating precise switching between mutually exclusive ON and OFF states in regulatory networks (e.g., calcium signaling,[1,2] p53 regulation,[3] galactose regulation,[4] cell cycle,[5−8] and budding yeast polarization[9−13]), their relationship to noise propagation is less clear. For example, some have demonstrated that positive feedback loops amplify noise and negative feedback loops attenuate noise,[14−16] while others have suggested that positive feedback loops can also attenuate noise and that there is no strong correlation between the sign of feedback loops and their noise propagation properties.[17−19] In a particularly insightful study of the latter, Brandman et al. proposed that two interlinked positive feedback loops with dual time scales (one slow and one fast) could effectively reduce noise in signal output and at the same time respond promptly to an activating signal.[20−25]

Since the sign of feedback does not by itself explain the noise propagation features of biological circuits, is there an intrinsic quantity that does? To address this question, we previously conducted a mathematical analysis and discovered that a critical quantity, termed the signed activation time (SAT), succinctly captures a system's ability to maintain a robust ON state under large disturbances.[26] The SAT is defined as the difference between a switch's deactivation and activation times multiplied by input noise frequency. We showed that systems with a small SAT are easily susceptible to noise in the ON state (intuitively,

this is because input fluctuations can turn the switch off more quickly than they can turn the switch back on), whereas systems with a large SAT buffer noise at the ON state (Figure 1). This means that noise attenuation can be achieved even in a single positive loop system, as long as the dynamics satisfy a high SAT.

While the focus of the previous study was on the ON state, many biological systems require a robust switch that not only prevents spurious deactivation at the ON state, but also spurious activation at the OFF state. Given that a high SAT buffers noise at the ON state, it stands to reason that a high SAT amplifies noise at the OFF state. A trade-off therefore emerges: how does a biological circuit prevent spurious activation at the OFF state and, at the same time, deactivation at the ON state? Here a common property of biological switches, bistability, sheds light. In the hysteresis region of a bistable switch, the ON and OFF states are both immune to changes in input concentration, thereby displaying superior noise buffering at both states.[27−31] If we ask what the SAT is in this hysteresis region, we quickly realize that there are in fact two SATs, since the ON state does not deactivate and the OFF state does not activate. That is, coming from a high input concentration, the SAT at the ON state is infinity, and coming from a low input concentration, the SAT at the OFF state is
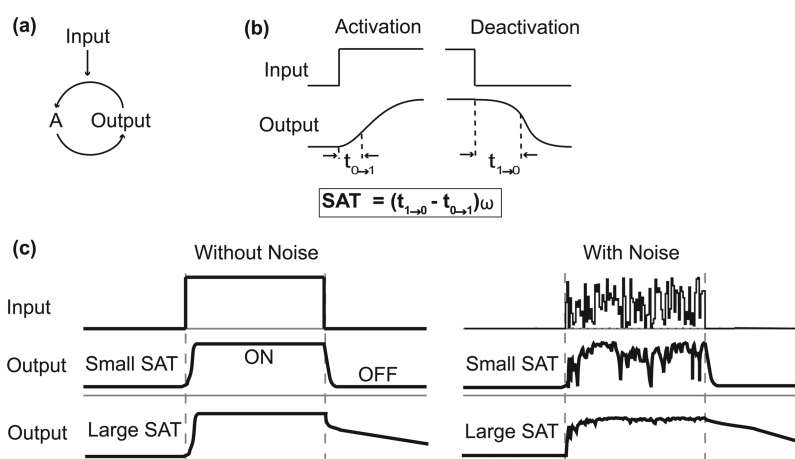
Figure 1. SAT and noise attenuation property at the ON state. (a) The single positive feedback module.[20] (b) The definition of SAT. ω is the noise frequency in the input. (c) Comparing outputs of systems with large SAT and small SAT when giving inputs without (left) and with noise (right).
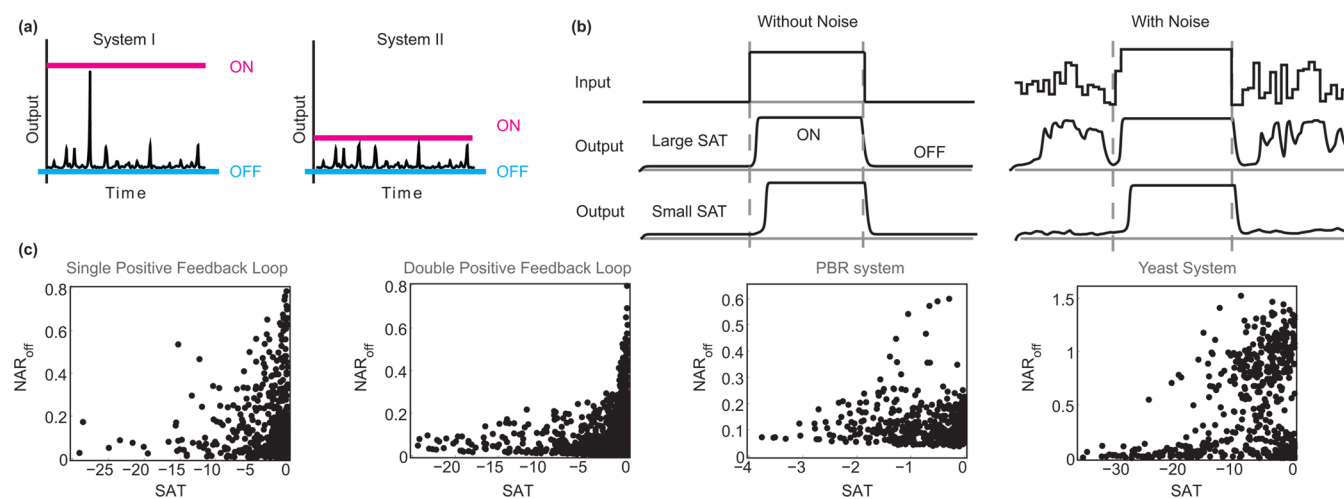

Figure 2. SAT and noise attenuation property at the OFF state. (a) Systems I and II have similar NAR, but system I stays closer to the OFF state than system II. (b) Comparison of outputs of systems with large SAT and small SAT when given inputs without (left) and with (right) noise. (c) NAR_{off} and SAT have a positive relationship in the single positive feedback module, the double positive feedback module, the polymyxin B resistance model in enteric bacteria, and the yeast cell polarization system.

negative infinity. The SAT, therefore, is not a single constant describing a circuit but is associated with the state of the circuit. Since we are interested in the noise tolerance of the OFF and ON states, we may introduce two SATs, which we call input-associated SATs (iSATs), each of which corresponds to the significantly different mean input concentration at the OFF and the ON states.

With these new quantities, we hypothesize that systems exhibiting superior resistance to input noise at both ON and OFF states are those exhibiting high iSATs at the ON state and low iSATs at the OFF state. In this paper, we first extend our mathematical analysis of SATs to noise propagation in the OFF state of switches, demonstrating that a low SAT indeed leads to a stable OFF state. We then explore 33 three-node circuits to find networks that can achieve high iSAT at the ON state and low iSAT at the OFF state. Though there is a general trade-off, we identify five networks that readily satisfy this condition. Interestingly, we find that all five networks share the mutual activation motif, suggesting the advantage of positive feedback in buffering noise. More generally, we believe that analyzing a network's iSAT values can provide a concise description of how a circuit may respond to input noise. To further understand

noise management, we also analyze the relation of sensitivity (or susceptibility), noise amplification rate, and iSATs.

■ RESULTS AND DISCUSSION

Low SAT Leads to a Stable OFF State. One commonly used quantity to measure noise is the standard noise amplification rate (NAR) defined as the ratio of the coefficient of variation between the output and the input:[32,33]

$$NAR = \frac{std(c)/\langle c \rangle}{std(u)/\langle u \rangle} \tag{1}$$

where c is the output, u is the input, $\langle \cdot \rangle$ represents the mean, and $std(\cdot)$ denotes the standard deviation. Direct application of NAR to the OFF state, however, leads to loss of one critical piece of information for switches: the relative size of the mean output to the distance between ON and OFF states. To illustrate this notion, in Figure 2a we present two systems with similar NAR. Yet system I is superior because the output stays closer to the OFF state, as the distance between the ON and the OFF in system I is larger. This example suggests the need for a measurement that not only takes into account variations in

the output but also considers its deviation from the OFF state. We therefore first introduce a more appropriate measurement of noise in this context, defined as the deviation from the OFF state, normalized by the distance between the steady state ON and OFF values:

$$\text{NAR}_{\text{off}} = \frac{\sqrt{\langle (c - \overline{c}_0)^2 \rangle} / (\overline{c}_1 - \overline{c}_0)}{\text{std}(u)/\langle u \rangle} \tag{2}$$

Here, $\overline{c}_1$ and $\overline{c}_0$ are the steady state values of output corresponding to static inputs at ON and OFF, respectively. Using this new measurement, system I in Figure 2a has a smaller NAR_{off} than system II, indicating a more desirable noise property at the OFF state. Consequently, systems with a low NAR_{off} are capable of attenuating local fluctuations at the OFF state as well as staying away from the ON state. The NAR defined in eq 1 will still be used to measure noise amplification at the ON state and will be denoted by NAR_{on} thereafter.

Naturally, we ask what the relation between SAT and NAR_{off} is and how SAT affects the noise property at the OFF state. Intuitively, a system that responds slowly to a pulse signal and falls back quickly after removal of the signal would tend to stay close to the OFF state. It is therefore natural to speculate that a strongly negative SAT ($t_{1\to0} < t_{0\to1}$) leads a low NAR_{off}.

This conjecture is immediately confirmed by numerical simulations in a single positive feedback module: smaller SAT corresponds to better noise attenuation at the OFF state (Figure 2b and the first panel in Figure 2c). To further explore the generality of this result, we simulated a double positive feedback module,[20] a polymyxin B resistance model in enteric bacteria,[34] and a yeast cell polarization system[35] (Supporting Information, Section A). In all simulations, selected parameters were randomly varied following a log uniform distribution in the 20-fold range of the base parameters in the original models (Tables S1−4, Supporting Information, Section A). All simulations consistently demonstrate a positive correlation between the NAR_{off} and SAT (Figure 2c). We also investigated the effect of using different frequencies and distributions in the input noise. The overall positive relation between SAT and NAR_{off} remains true (Supporting Information, Section B.7).

Attenuating Noise at Both ON and OFF. With the "design principles" for the OFF state in the previous section and those concluded in ref 26 for the ON state, a natural question arises: Can one find a system that attenuates noise at both ON and OFF states? At the first thought, it seems impossible. A system with large SAT *amplifies* noise at the OFF state but *attenuates* noise at the ON state; however, a system with small SAT *attenuates* noise at the OFF state but *amplifies* noise at the ON state (Figure 1c and Figure 2b). The dilemma resolves when a system can have different SATs at the ON and OFF states, which can be captured by the introduction of the input-associated SATs (iSATs):

$$\text{iSAT} = (t_{\text{high}\to\text{low}} - t_{\text{low}\to\text{high}}) \cdot \omega \tag{3}$$

Here, $t_{\text{low}\to\text{high}}$ is defined as the response time to a signal changing from u_{low} to u_{high}, and $t_{\text{high}\to\text{low}}$ is defined as the response time to a signal changing from u_{high} to u_{low} (Figure 3a green bars, and Supporting Information, Section A). As a result, the SAT in ref 26 is a special case of when $u_{\text{low}} = 0$ and $u_{\text{high}} = 1$.

Considering that the mean, variance, and frequency of the inputs at the ON and the OFF states are usually significantly different, the iSAT of a system should be allowed to vary between the ON and OFF states. Figure 3a shows a case where
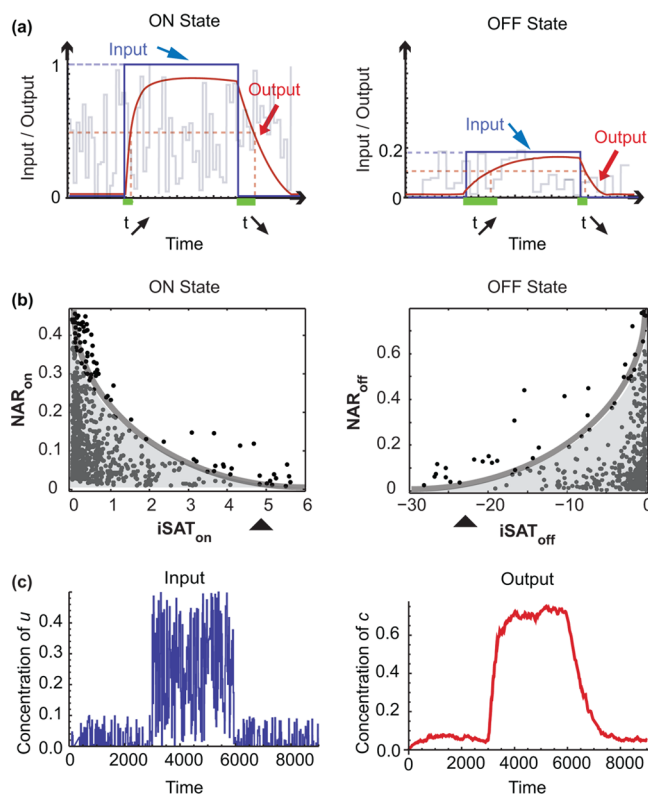

Figure 3. Relation of iSAT and NAR in the single positive feedback module. (a) Left: iSAT_{on} is positive ($t_{\text{low}\to\text{high}} < t_{\text{high}\to\text{low}}$) with respect to the stochastic input varying between 0 and 1 (the light gray curve in the background). Right: iSAT_{off} is negative ($t_{\text{low}\to\text{high}} > t_{\text{high}\to\text{low}}$) with respect to the stochastic input varying between 0 and 0.2 (the light gray curve). (b) In the single positive feedback module, iSAT_{on} has a negative relation with NAR_{on}, and iSAT_{off} has a positive relation with NAR_{off}. The triangles point to desirable parameter sets that give rise to high iSAT_{on} and low iSAT_{off}. (c) A single positive feedback module with small NAR_{off} and NAR_{on} at the same time. Left: a noisy input signal ranging uniformly from 0 to 0.1 at the OFF state and 0 to 0.5 at the ON state. Right: the output corresponding to the positive feedback system with $k_1 = 7$, $k_2 = 1$, $k_3 = 0.001$, $k_4 = 0.01$, and $\tau_b = 0.003$.

the input varies in $[0, 1]$ at the ON state (gray lines in Figure 3a left panel) and $[0, 0.2]$ at the OFF state (gray lines in Figure 3a right panel). At the ON state the new iSAT remains the same as SAT, whereas at the OFF state it is now defined to be associated with the response time to pulses ranging from 0 to 0.2 and 0.2 to 0. In this particular case, the iSAT is positive at the ON state and negative at the OFF state. For convenience, we hereafter denote the iSAT at the ON state as iSAT_{on} and the iSAT at the OFF state as iSAT_{off}. Compared with the original definition of SAT in ref 26, iSAT exhibits a stronger relationship with sensitivity of the system (introduced in the following section), given the same noise attenuation level (Figure S4b, Supporting Information).

Now if we examine the relation between iSAT and the noise amplification rate for the single positive feedback module, it is not hard to find a system with a good noise attenuation property at both ON and OFF states. One such case illustrated in Figure 3c has an $\text{iSAT}_{\text{on}} = 28.8$ and $\text{iSAT}_{\text{off}} = -10.1$.

To search for general systems that attenuate noises at both ON and OFF states, we systematically explore all three-node circuits, composed of an input node (I), an output node (O), and an intermediate node (A) (Figure 4a). The output and
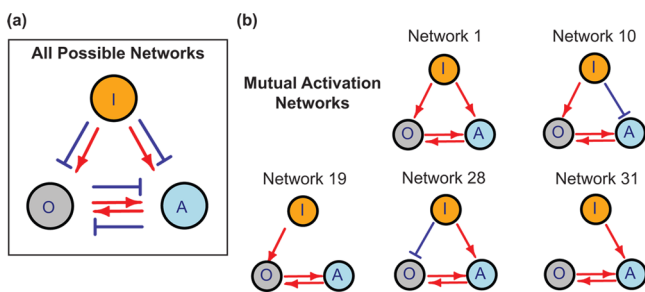
Figure 4. Three-node networks. (a) All possible three-node networks. Red arrows denote positive regulations, and blue ones represent inhibitions. I, the input; A the intermediate node; O, the output. (b) Five network structures that result in large $iSAT_{on}$ and small $iSAT_{off}$.

intermediate nodes can have incoming arrows, outgoing arrows, or no arrow, but the input node is not allowed to have incoming arrows, that is, the input is not subject to regulations from the output or the intermediate node. Each arrow can be either positive (activation) or negative (repression). Among all 81 possible configurations of the networks captured by this formulation, 33 of them are capable of producing the desired switching behaviors, that is, the output is high with a high input and low with a low input (Figure S2, Supporting Information, Section A.5).

Each network structure can give rise to a range of noise properties when varying the values of parameters. To identify networks that attenuate noise at both the ON and OFF states, around 6×10^4 random parameter sets were generated for each network, and the corresponding iSATs associated to the ON signal and the OFF signal were calculated, respectively. Here we define the "good iSAT region" as the top left corner in the $iSAT_{on}$–$iSAT_{off}$ plane (above the red dotted lines in Figure 5a as defined in the Supporting Information, Section A.5). Networks in this region can give rise to large (positive) $iSAT_{on}$ and small (negative) $iSAT_{off}$ and are expected to attenuate

noise at both states. We identify five systems (Figure 4b) that have parameter sets falling in this region (Figure 5a). Interestingly, all five networks contain the mutual activation motif. This is likely due to the fact that the positive feedback slows down the temporal dynamics to provide a longer averaging time beneficial to noise buffering.

Next, we confirm that these five mutual activation systems show an advantage in noise management. The NAR_{on} and NAR_{off} can be computed by giving a noisy signal to the networks defined by the 6×10^4 random parameters. The density plot is shown in Figure 5b. The same group of five networks is found to have better noise property at both states.

To quantitatively compare the noise properties among different networks, we define the "low noise region" as the bottom left corner in the NAR_{on}–NAR_{off} plane (under the green dotted lines in Figure 5b as defined in the Supporting Information, Section A.5). Points in this region have low noise level at both ON and the OFF states. In all 33 systems, on average 0.4% of the points fall in the "low noise region", while for systems corresponding to the "good iSAT region", this average percentage increases to 77%. Moreover, all points in the "low noise region" are contributed by the five mutual activation systems.

Compared to the simplest two-node linear network (network 27) that directly transmits an input signal to the output node, networks with extra regulation from the intermediate node (e.g., networks 19, 20, and 23) generally show a wider range of iSATs and hence have a better chance at noise attenuation. Among them, the ones with the mutual activation motif (e.g., network 19) are capable of reaching the "good iSAT region", which leads to the best noise attenuation at both ON and OFF states (Figure 6).

Still, a trade-off between the NAR_{on} and NAR_{off} exists for a majority of the networks: Data lie on the diagonal region of the NAR_{on}–NAR_{off} plane, showing a negative correlation of the noise amplification rates between the ON and OFF states
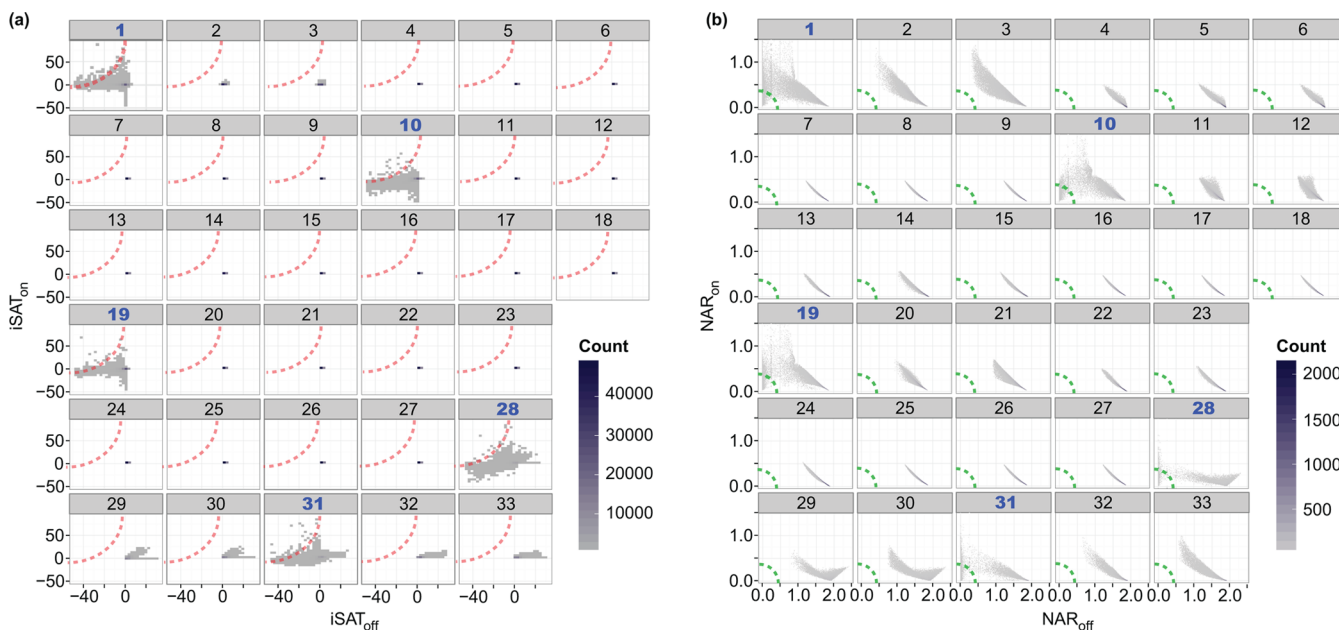

Figure 5. Temporal and noise properties for all 33 networks. (a) The density plot of $iSAT_{on}$ vs $iSAT_{off}$. The top left corner above the red dotted line is the "good iSAT region". Only networks 1, 10, 19, 28, and 31 have points in that region. (b) The density plot of NAR_{on} vs NAR_{off}. The bottom left corner under the green dotted line is the "low noise region". Only networks 1, 10, 19, 28, and 31 have points in that region.
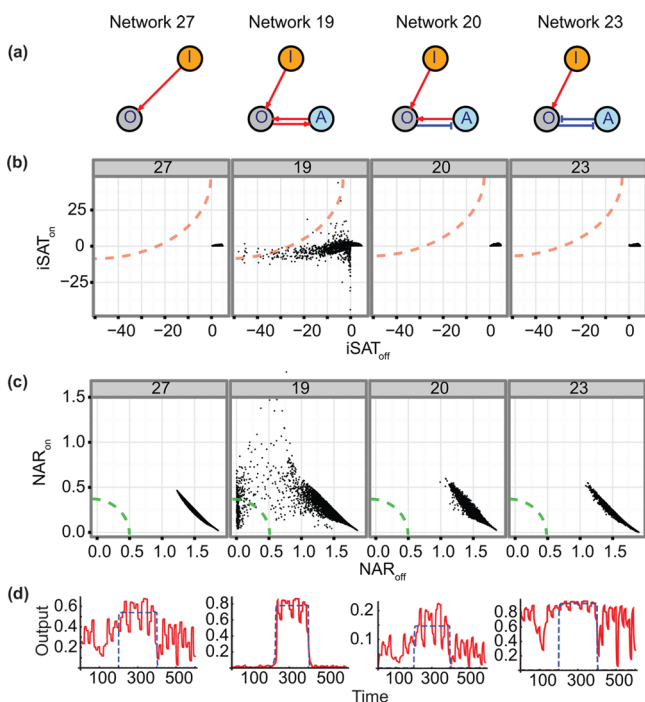
Figure 6. iSATs and noise properties for four sample networks. (a) From left to right: linear cascade, mutual activation, interlinked positive and negative feedback loop, and mutual inhibition. (b) iSAT$_{off}$ vs iSAT$_{on}$. (c) NAR$_{on}$ vs NAR$_{off}$. Panels b and c share the same 5000 randomly chosen data sets. (d) Typical output from each network. Dashed blue line: concentration of the output over time with a noise-free input. Solid red line: concentration of the output over time with a noisy input.

(Figure 5b). This implies that when a system is capable of attenuating noise at the ON state, it often comes at the cost of large noise amplification at the OFF state, and vice versa.

To further investigate the five mutual activation systems' noise properties, we sampled a set of random parameters six times larger than those in Figure 5. We evaluate a system's iSAT property by how close it is to the ideal case (the star symbol in Figure 7a). The "good iSAT region" is further divided into 4 groups (groups 2−5). Systems with a larger group number are closer to the ideal case and are defined to have better iSAT property (larger iSAT$_{on}$ and smaller iSAT$_{off}$).
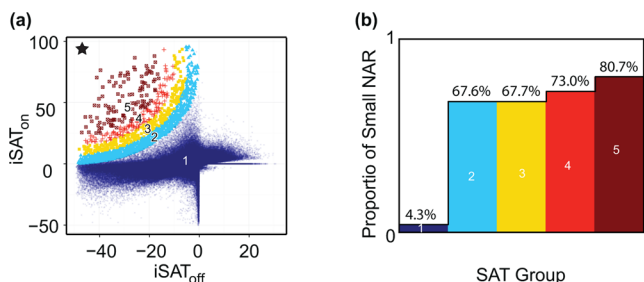

Figure 7. iSAT as an indicator of noise properties in the five mutual activation systems. (a) The randomly selected parameters used for the simulation are grouped into five groups (regardless of the choice of the five systems) according to their distance to the upper left corner (the spot indicated by the star). (b) The systems with parameters corresponding to better iSAT property (smaller iSAT$_{off}$ and larger iSAT$_{on}$) consistently show larger proportion falling in the "low noise region".

Group 1 consists of all other points falling outside the "good iSAT region". Figure 7 shows that for mutual activation systems, the better their iSAT property is, the better chance they have to achieve good noise attenuation (Figure 7b). In particular, independent of the specific mutual activation system chosen, the majority of the points lying in the second quadrant of the iSAT$_{off}$−iSAT$_{on}$ plane (Figure 7a) have values of NAR in the "low noise region" for both ON and OFF states.

Finally, we studied the single positive feedback system using different types of equations, specifically, mass-action kinetics versus Michaelis−Menten kinetics, to explore the relationship between SATs and NARs. We find consistent results among different representations of the same regulatory system (Supplementary Figure S8). In addition, we plot the relationship in the 33 three-node networks. It is interesting to observe that while the relationship between SATs and NARs shows a clear trend, there seems to be more outliers in the OFF state (Supplementary Figure S9). It is not surprising that NARs are likely to depend on other factors, as seen in our analytical studies of iSAT$_{off}$ and NAR$_{off}$ (e.g., eqs 19 and 22 in Supporting Information, Sections B.4 and B.5).

Sensitivity, iSAT, and Noise Amplification Rate at the ON State. Although it is important to control noise amplification at both ON and OFF states, a useful system must be able to respond to the input signal with sufficient sensitivity. One way to estimate how sensitively a system responds to an input at the ON state is by evaluating the sensitivity (or susceptibility) of the output in response to an infinitesimally small perturbation in the input: $s(u) = d(\ln c)/d(\ln u)$, in which u is evaluated at the ON state in the input and c is the output. Naturally, the noise amplification rate and the level of sensitivity of a system in the ON state exhibits a positive correlation.[36] But how do the noise amplification rate, iSAT, and the sensitivity relate to each other?

We study these relationships by first analyzing the single positive feedback module at the ON tate. The analytical estimate of the simple system suggests an interesting role of iSAT$_{on}$ in connecting NAR$_{on}$ and the sensitivity, denoted s_{on} (Supporting Information, Section B.3):

$$\mathrm{NAR_{on}} \approx \frac{s_{on}}{\sqrt{\mathrm{iSAT_{on}}}} \tag{4}$$

First, we notice a positive relationship between s_{on} and NAR$_{on}$ in eq 4. One challenge for noise management in a switching system is simultaneously attaining low NAR$_{on}$ and high s_{on}, as sensitivity to signal change seems inevitably linked to sensitivity to noises in the signal. Interestingly, our analysis reveals that by increasing iSAT$_{on}$, a low noise amplification rate and large sensitivity can be achieved simultaneously. Direct simulations of the single positive feedback module as well as the other three more complex systems, including the double positive feedback module, the polymyxin B resistance model in enteric bacteria, and the yeast cell polarization system, support and confirm this analytical relationship (Figure 8a).

Next, eq 4 indicates that the NAR$_{on}$ and iSAT$_{on}$ are negatively correlated with a fixed s_{on}, which is further confirmed through direct simulations of the four systems (Figure 8b). The result is consistent with the previous findings in ref 26 based on SATs (Figure S4a, Supporting Information). As expected, from eq 4, we observe a positive correlation between the noise amplification rate and sensitivity, as demonstrated in previous studies.[17,19]
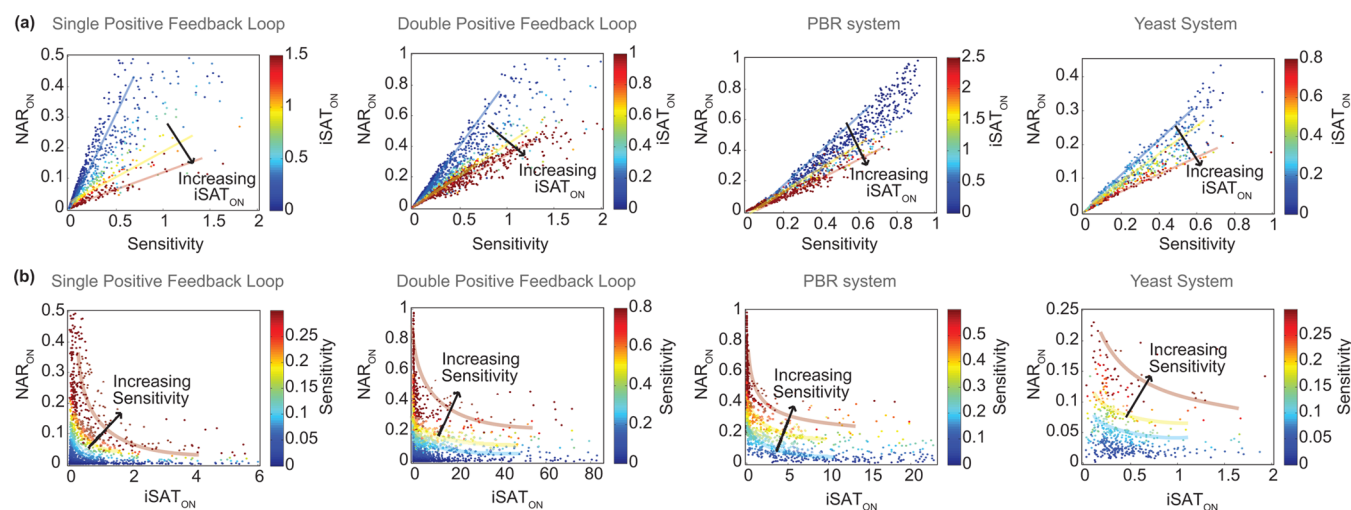
Figure 8. Direct simulations for iSAT, NAR$_{on}$ and sensitivity. (a) Noise amplification rate versus sensitivity. (b) Noise amplification rate versus signed activation time. In each panel, results from four systems are shown (from left to right): single positive feedback module, double positive feedback module, polymyxin B resistance model in enteric bacteria, and yeast cell polarization system.

Finally, these results are further validated by a two-sample t test between the high iSAT$_{on}$ group (highest quartile) and the low iSAT$_{on}$ group (lowest three quartiles). The mean ratio of NAR$_{on}$ and sensitivity in the high iSAT$_{on}$ group is significantly larger than that of the low iSAT$_{on}$ group, for all four models studied. This demonstrates that when iSAT$_{on}$ is small, the ratio of sensitivity and NAR$_{on}$ are small, and when iSAT$_{on}$ is large, the ratio of sensitivity and NAR$_{on}$ are large.

Interestingly, at the OFF state, only a weak positive relation between NAR$_{off}$ and sensitivity can be observed for the single positive feedback module according to our analysis (Supporting Information, Section B.6). However, the trend is not observed in more complex systems, and our numerical simulations do not show a consistent monotonic correlation of the two quantities. By scrutinizing the expression of NAR$_{off}$, one intuitive explanation is that increasing the sensitivity increases both the denominator and the numerator. Thus, a monotonic relation between s_{off} and NAR$_{off}$ should not be expected.

Finally, we would like to comment that the input noise used here is monochromatic. When varying the input noise frequency (Supplementary Figure S6) or replacing the uniformly distributed noise by the white noise (Supplementary Figure S7), the relations among NAR, iSAT, and sensitivity are conserved in the single positive feedback module. When the input noise is a superimposition of noises with different frequencies, one may use Fourier Transform to decompose the input into noises with frequency ω_i and amplitude a_i. It is likely that the one with the smallest frequency has more weight in the overall SAT, as also indicated by the two-time-scale asymptotic expansion of the solutions to the single positive feedback system, which has shown that fast varying noises are filtered out in such case.[26]

METHOD

All simulations were performed in Mathematica 8.0.[37] Data analysis and visualization were generated by Matlab 2010b[38] and R 2.15.2.[39] Please see Supporting Information for more details for the models, simulations, and mathematical analysis.

ASSOCIATED CONTENT

⑤ Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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