Enhanced Logical Stochastic Resonance in Synthetic Genetic Networks

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***Abstract*— In this brief, the concept of logical stochastic resonance is applied to implement the Set–Reset latch in a synthetic gene network derived from a bacteriophage λ. Clear Set–Reset latch operation is obtained when the network is only subjected to periodic forcing. The correct probability of obtaining the desired logic operation first increases to unity and then decreases as the amplitude of the periodic forcing increases. In addition, the output logic operation can be easily morphed by tuning the frequency and the amplitude of the periodic forcing. At the same time, we indicate that adding moderate periodic forcing to the background Gaussian noise may increase the length of the optimal plateau of getting the desired logic operation in genetic regulatory network. We also point out that robust Set–Reset latch operation can be obtained using the interplay of periodic forcing and background noise when the noise strength is lower than what is required.**

***Index Terms*— Genetic network, memory gates, stochastic resonance.**

I. Introduction

Recently, the phenomenon of logical stochastic resonance (LSR) has been demonstrated in [1]. This phenomenon is a nonlinear system driven by weak signals can obtain logic outputs under noisy background. Furthermore, the logic operation can be switched by simply morphing the nonlinear characteristics. The LSR affords a path to the practical implementation of a new generation of computing systems.

The genetic regulatory network (GRN) can be visualized as composed of subsets of simple biological components, interconnected through the input and output signals [2]. GRN plays an important role in the emerging field of synthetic biology. One defining goal of synthetic biology is the development of engineering-based approaches that enable the construction of GRN according to design specifications generated from computational modeling [3]. Engineers have yielded an ever-growing number of synthetic biological devices with different functional capabilities, such as switches [4], oscillators [5], and amplifiers [6]. Gene regulation is an intrinsically noisy process, where stability and synchronization of the genetic networks have been studied by the Lyapunov method and the Lur'e system approach [7], [8]. Intriguingly, several researchers have applied the idea of the LSR to the synthetic gene network and obtained interesting results. AND/OR gate is obtained by an auto-regulatory gene network in the bacteriophage λ [9]. Hellen *et al.* [10] verified the noise-enhanced logic behavior in an electronic analog of a synthetic genetic network. Xu *et al.* [11] investigated the LSR phenomenon in synthetic genetic networks induced by non-Gaussian noise. Sharma *et al.* [12] realized logic gates with time-delayed synthetic genetic networks and showed this delay could either enhance or diminish logic behavior.

Two prerequisites, namely, nonlinearity and noise, are needed to implement LSR in GRN. Noise can be classified as external noise and internal noise. External noise refers to any disturbance, random or deterministic forcing. However, all the aforementioned studies are about the random fluctuated noise. To the best of our knowledge, studies have not been conducted on whether the GRN system can obtain the LSR phenomenon when it is subjected to deterministic forcing and on obtaining consistent memory operation in GRN. Gupta *et al.* [13] proposed that the LSR could be obtained in noise-free bistable system, where the role of noise is taken by periodic forcing. Kohar *et al.* [14] demonstrated that the LSR phenomenon could be strengthened when the system was subjected to noise in conjunction with periodic forcing in a bistable potential model. Inspired by the above two studies, we focus on the realization of memory device, especially the Set–Reset latch (the truth table is shown in Table I), which is a single-bit stored, fundamental, and omnipresent building block of computing systems. The conventional Set–Reset latch is constructed from a pair of cross-coupled NOR logic gates, and the response speed of Set–Reset latch restricts the speed of the whole system. Here, we use single GRN to implement the latch truth table, and the operation of the system can be easily morphed to realize the other logic functions by tuning the parameters. Then, we propose a method to enhance the LSR when the background noise strength is lower than needed in the GRN system.

TABLE I
Relationship Between the Two Inputs and the Output of Set–Reset Latch

Set(I_1)	Reset(I_2)	Q_{next}	Action
0	0	Q	Hold state
0	1	0	Reset
1	0	1	Set
1	1	X	Not allowed

Q means this output will follow the former logic, and X means this output is invalid.

In this brief, we demonstrate the Set–Reset latch operation can be obtained in a GRN system subjected to periodic forcing and the conjunction of periodic forcing and Gaussian noise can enhance the LSR phenomenon in the GRN system. This brief is organized as follows. Section II describes the bistable GRN system. Section III discusses the effect of sinusoidal forcing on the probability of obtaining the LSR by numerical stimulation. Section IV presents the adaptive approach to enhance the LSR phenomenon. The conclusion is given in Section V.

II. Bistable Genetic Regulatory Network Model

We only need two possible states to indicate logical 0 and 1, so we choose a single-gene network, which is bistable. In this brief, we use the quantitative model of the regulation of the promoter PRM of λ phage [15]. This promoter consists of three tandem operational sites, OR1, OR2 (activated transcription), and OR3 (repressed transcription). The chemical reaction of the model under ambient noise is given by suitable rescaling [15], [16]

$$\dot{x} = \dot{U}(x) + I(t) + \xi(t) \tag{1}$$

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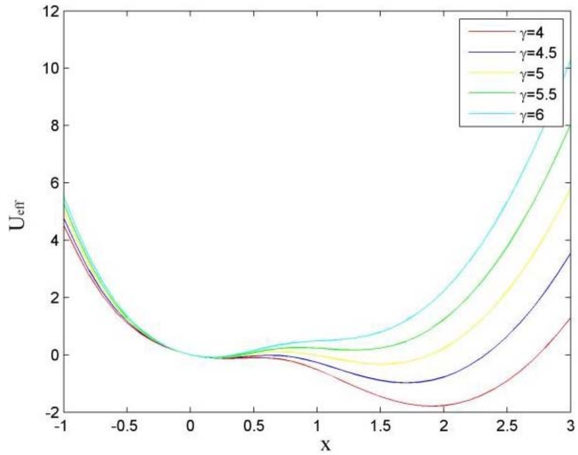

Fig. 1. Effective potential obtained by integrating the function $\dot{U}(x)$.

where

$$\dot{U}(x) = \frac{m(1 + x^2 + \alpha\sigma_1 x^4)}{1 + x^2 + \sigma_1 x^4 + \sigma_1\sigma_2 x^6} - \gamma x \quad (2)$$

represents the production of the repressor due to transcription, and x is the repressor concentration. The even polynomials in x occur because of dimerization and subsequent binding to the promoter region. m represents the number of plasmids per cell. We set $m = 1$ in this brief. Parameter γ, which is directly proportional to protein degradation rate, denotes the steady-state concentration of the repressor. This parameter can be tunable in the construction of artificial network.

The genetic network of (2) has two stable states, the low and high protein repressor concentrations. We denote the outcome to be logical 1 when it is in one stable state and logical 0 when it is in another stable state. Fig. 1 shows the effective potential of (2). Since the parameter γ can affect the depth of the potential well, we can get different logic operations by changing γ. We set $\gamma = 4.5$ to obtain Set–Reset latch operation, while the other value of γ will modulate the GRN system to behave as OR/AND operation, and so on. $\sigma_1 = 1.95$, $\sigma_2 = 0.08$, and $\alpha = 10.9$ are valued for the operator region of the λ phage

$$\xi(t) = A\sin(2\pi f t) + D\eta(t) \quad (3)$$

is the ambient noise added to the system. $\eta(t)$ is Gaussian white noise with D being the intensity. A and f are the amplitude and frequency of the sinusoidal forcing.

$I(t)$ consists of two low amplitude input signals I_1 and I_2, with I_1 and I_2 being the two trains of square pulses encoding the two logic inputs. To obtain the Set–Reset latch operation, we inverse I_2 before importing to the system, so $I(t) = I_1(t) - I_2(t)$.

III. Effect of Periodic Forcing on GRN Response

First, we investigate how the GRN system behaves when it is only fluctuated by periodic forcing, specifically sinusoidal forcing. Fig. 2 shows the response of the system when subjected to sinusoidal forcing. It proves that this GRN can yield clear Set–Reset latch operation when it is driven by sinusoidal forcing alone. On the other hand, numerical stimulation shows that when the system is only subjected to Gaussian noise, which has the same density as the periodic forcing ($D = 0.12$), the outcome of the system is not in accordance with the Set–Reset truth table. This indicates that periodic forcing is able to drive the system obtaining clearer logic function than random forcing.

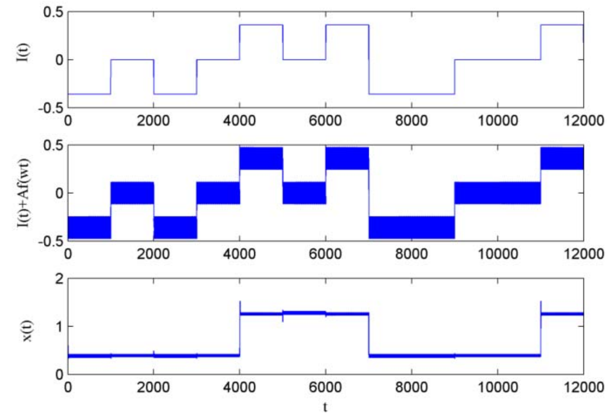

Fig. 2. From top to bottom, panel 1 shows $I(t) = I_1 - I_2$, panel 2 shows $I(t) + Af(\omega t)$, and panel 3 shows the response of the system. Here, the value of the two inputs I_1 and I_2 takes the value of 0.18 when the logic input is 1, and -0.18 when the logic input is 0, and $A = 0.12$, $f = 0.01$, and $\omega = 2\pi f$.

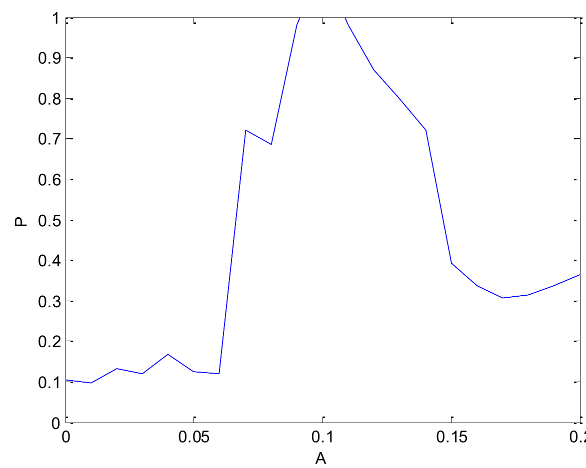

Fig. 3. In the Set–Reset latch, the success probability P versus the amplitude of the periodic forcing, here $f = 0.01$.

To study the effect of the sinusoidal forcing characteristics on the outcomes of the system, we calculate the correct probability P of obtaining the right logic function. The method of calculating P can refer to [17].

We first investigate how the sinusoidal forcing amplitude affects the system with its frequency fixed. The correct probability P as a function of amplitude is plotted in Fig. 3. It indicates that at a fixed frequency the correct probability of getting the right logical output first increases and then decreases as the amplitude increases. Typical LSR behavior is observed. At the optimal window of amplitude, the logic outputs of the system can be almost 100% accurate when the system is driven by periodic forcing only.

Furthermore, we also calculate the probability of obtaining different logic operations (OR and AND) by the single-genetic network with different driving frequencies (Fig. 4). It is clear from Fig. 4 that the system can get different logic operations by easily morphing the parameter γ. When the desired logic is OR operation (green area), the system needs stronger driving force, and the driving frequency has little influence on the $P \sim 1$ map. When Set–Reset latch and AND logic are the desired logic, the optimal range of the driving amplitude shifts with the change of driving frequency.

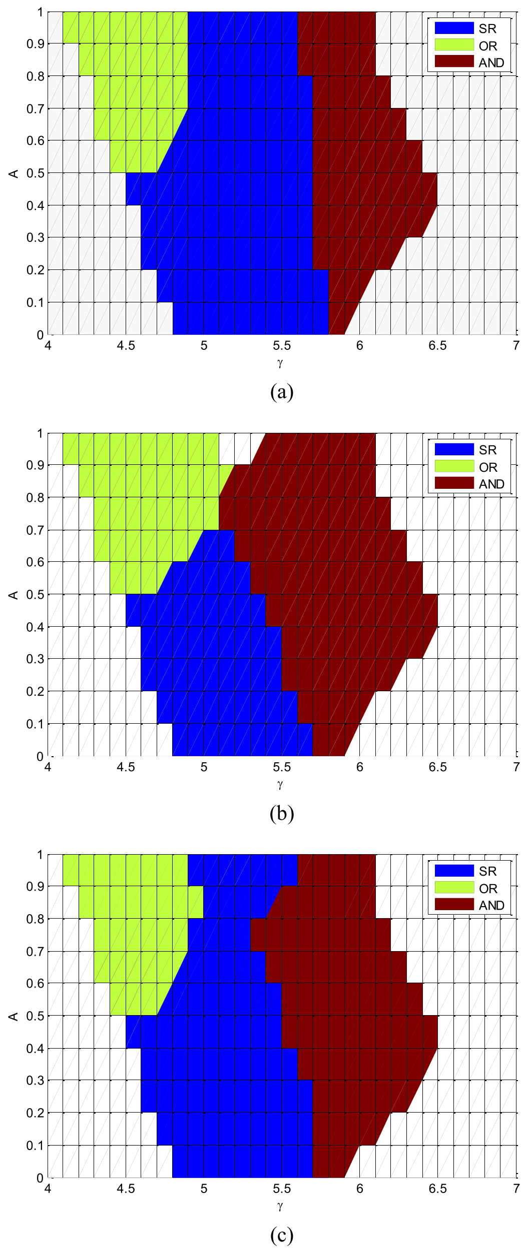

Fig. 4. Success probability $P \sim 1$ versus parameter γ (x-axis) and the amplitude A (y-axis). From top to bottom, the driving frequency is 0.005, 0.01, and 0.1, respectively. Green: SR latch. Blue: OR logic. Red: AND logic. (a) $f = 0.005$. (b) $f = 0.01$. (c) $f = 0.1$.

Furthermore, tuning the driving frequency or the amplitude can transform different logic operations when parameter γ is within the range of 4.7–5.7. When the logic operation is decided by γ, f, and A, we call it the fuzzy area. For example, we can get AND logic operation by setting $\gamma = 5.3$ when $A = 0.7$ and $f = 0.01$. However, the output logic becomes Set–Reset latch operation when $f = 0.1$ with the other parameters maintains unchanged. This scenario is only observed when the driving force is periodic forcing, which is an advantage aspect in designing changeable logic gates. For another example, leaving the other parameters unchanged ($f = 0.1$, $\gamma = 5.7$), the logic operation can exchange between AND logic and Set–Reset latch by tuning the amplitude.

To fully investigate the effect of driving frequency on the response of the system, we implement numerical stimulation with different driving frequencies, ranging from 0.001 to 100. It shows that the system can get 100% correct logic operation at a very wide range of driving frequency for $f > 0.003$. When the driving frequency is lower than 0.003, the response speed of the whole system is slowed down, and the relaxation time is too long. Therefore, the correct probability is below the required value (Fig. 5). Notably, we need to tune the sample frequency to adapt to different driving frequencies. The sample frequency is ∼10 times of the driven frequency: $f_{\text{sample}} \sim 10f$. When the sample frequency is lower than $10f$, the dither error will destroy the LSR phenomenon. A very high sample frequency is unnecessary and will reduce the computation speed.

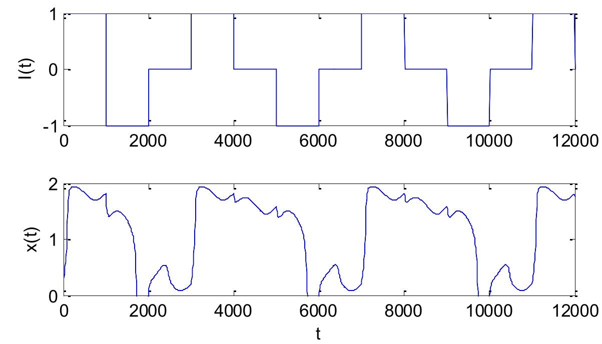

Fig. 5. Output and the response of the system when the driving frequency is $f = 0.001$.

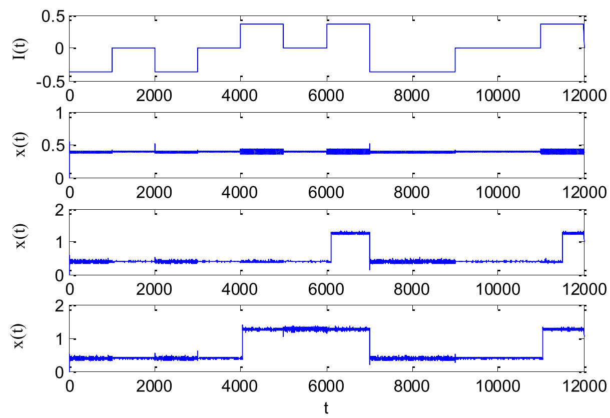

Fig. 6. Panels from top to bottom, the input signal, the responses of the system to periodic forcing, Gaussian noise, and periodic forcing together with Gaussian noise. Here, $A = 0.05$, $D = 0.03$, and $f = 0.01$.

IV. ADAPTIVE LSR

In the conventional LSR, moderate noise is necessary to drive the nonlinear system to obtain the desired logic operation. Since the intensity of the background noise is not under control, the system can hardly get highly robust logical output without special modulation. Tuning parameters of the nonlinear system to adapt to different noise intensities are used to obtain LSR behavior in the electronic circuits [18]. However, the characteristic of the system is changed in this method. Another way to obtain adaptive LSR is via the modulation of the intensity and property of the background noise [19], which is difficult to implement.

In the above sections, we have studied the effect of periodic forcing on the responses of the GRN system. Further, to ensure robust operation in the random noisy background, we can add periodic forcing at the low noise strength and switch OFF the periodic forcing when the noise density is sufficient to get LSR. Fig. 6 shows the responses of the system to Gaussian noise, periodic forcing, and both

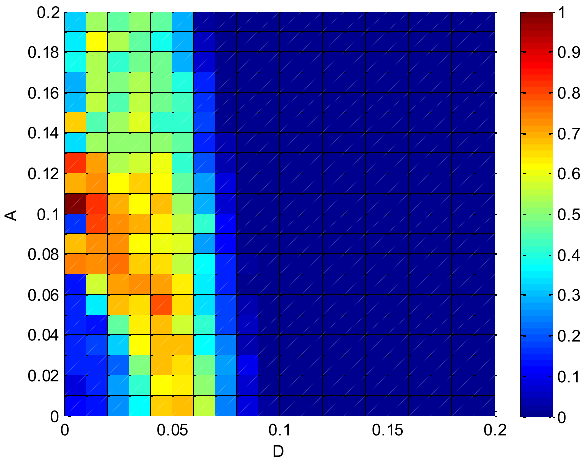

Fig. 7. In the Set–Reset latch, the correct probability when the system is both subjected to sinusoidal forcing and Gaussian noise. Here, the frequency of the sinusoidal forcing is 0.1.

Gaussian noise and periodic forcing. When driven by Gaussian noise and periodic forcing separately, the system does not obtain correct responses. However, when we add periodic forcing to the Gaussian noise, the system yields clear Set–Reset latch operation.

Fig. 7 shows the correct probability of getting Set–Reset latch operation when the GRN system in (2) is subjected to periodic forcing and Gaussian noise. When the parameters of the GRN system are set as the given value, periodic forcing is a better choice than Gaussian noise to induce the system jumping into the right stable state. The correct probability of getting the desired logic function evolves nonmonotonically with increasing noise intensity when the system is only subjected to Gaussian noise. Therefore, the LSR phenomenon occurs. However, the peak of correct probability is only about 60%, which is far lower than what is required for robust logic operation. At the same time, the system yields logic operation with near center probability, i.e., $P \sim 1$, when driven by optimal periodic forcing. Adding periodic forcing with moderate amplitude and frequency to Gaussian noise will enhance the reliability of getting the desired logical response in the low noise background. However, if the noise level crosses some threshold (>0.05), we cannot obtain consistent logical output only by adding periodic forcing. Moreover, the width of the optimal window of the Gaussian noise band increases by utilizing the constructive interplay of noise and periodic forcing.

V. Conclusion

Synthetic biology offers an opportunity to build single module, which can be easily used to create futuristic biological circuits. LSR is an intriguing paradigm, which can help the design of integrated circuits, wherein the background noise floor cannot be suppressed by constructing interplay of noise and nonlinearity. In this brief, we apply the idea of LSR to implement a memory device in GRN derived from the bacteriophage λ. Robust Set–Reset latch operation is obtained when the system is subjected to periodic forcing. Numerical experiments are conducted to study the effects of periodic forcing on the outcome of the nonlinear system. The reliability of obtaining the appropriate operation evolves nonmonotonically as the amplitude of the periodic forcing increases. The output logic operation can also be easily morphed by tuning the frequency and the amplitude of the periodic forcing. Furthermore, we show that adding moderate periodic forcing to low strength noise will increase the probability of getting desired logic operation. The results presented in this brief may help with the design of the new GRN systems paradigm.

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