Regime shifts driven by dynamic correlations in gene expression noise

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Gene expression is a noisy process that leads to regime shift between alternative steady states among individual living cells, inducing phenotypic variability. The effects of white noise on the regime shift in bistable systems have been well characterized, however little is known about such effects of colored noise (noise with non-zero correlation time). Here, we show that noise correlation time, by considering a generic circuit of autoactivation, can have significant effect on the regime shift in gene expression. We demonstrate this theoretically, using stochastic potential, stationary probability density function and first-passage time based on the Fokker-Planck description, where the Ornstein-Uhlenbeck process is used to model colored noise. We find that increase in noise correlation time in degradation rate can induce a regime shift from low to high protein concentration state and enhance the bistable regime, while increase in noise correlation time in basal rate retain the bimodal distribution. We then show how cross-correlated colored noises in basal and degradation rates can induce regime shifts from low to high protein concentration state, but reduce the bistable regime. In addition, we show that early warning indicators can also be used to predict shifts between distinct phenotypic states in gene expression. Predictions that a cell is about to shift to a harmful phenotype could improve early therapeutic intervention in complex human diseases.

I. INTRODUCTION

Natural systems can undergo sudden, large and irreversible changes under the influence of small stochastic perturbations [1, 2]. Such qualitative sudden changes are known as “regime shifts” have been found in a variety of ecological systems [3, 4], climate systems [5], biological systems [6, 7], financial markets [8], physical systems [9, 10, 11, 12], etc. It has been identified that regime shifts generally occur at tipping points (namely bifurcation points) [12, 13], where the system abruptly shifts from one stable state to another stable state. There are also examples of purely noise induced regime shifts (known as stochastic switching) [14, 15]. Regime shifts have the potential to invoke serious and harmful consequences for environment as well as human well-being [16, 17, 18, 19].

Understanding the mechanisms of regime shifts and predicting them using early warning signals (EWS) have been recently emerged as a challenging area of research due to the potential application in management and prevention of sudden catastrophes in complex systems. Numerous studies have been carried out to develop EWS for successfully predicting regime shifts [2, 14, 18, 20]. Extensive research on EWS suggests that statistical signatures, such as concurrent increase in “variance”, “autocorrelation”, “skewness” can predict regime shifts in a wide variety of complex systems [2, 13, 21]. These EWS are mainly derived from the phenomenon of critical slowing down, which is associated with a tipping point at which the stability of an equilibrium state changes as the dominant real eigenvalue becomes zero [1, 2, 14]. As a result, rate of recovery from small stochastic perturbations becomes slow as the system approaches a tipping point, resulting concurrent increase in variance, autocorrelation and skewness prior to a regime shift. However, sometimes these EWS are not present before a regime shift due to statistical limitations and confer false alarms [21]. In such a situation, apart from the aforementioned indicators, other indicators, e.g., “conditional heteroskedasticity” [22, 23] can be very useful to detect regime shifts. Conditional heteroskedasticity is used to investigate the possible links between time series data and their volatilities [24]. This indicator generally avoids the chance of false alarms as it is associated with significant test and their probabilities. Majority of the earlier studies on predicting regime shifts using EWS have focused on the ecological and climate systems [1, 17, 21]. However, few recent studies have reported the huge potential of EWS as risk markers from molecular biology to chronic human diseases [4, 10, 17, 24, 25].

Regime shifts those arise in medical conditions can increase the risk of diseases and even result in sudden death [10, 26]. Recently, EWS for detecting regime shifts in ecology have got special attention in medical sciences [4, 10, 27]. The ability to predict such regime shifts could prove fruitful in early detection of diseases [25–31]. An important example of regime shift in molecular biology is genetic regulatory system, which includes sudden transition in protein production level in individual cells resulting disease onset [32]. In genetically identical cells fluctuations in transcription and translation give rise to regime shifts between alternative states (i.e., phenotypic variability) in intracellular protein concentrations [33]. Indeed, in positive-feedback regulation individual cells can exist in different steady states, some live in the “on” expression state and others live in the “off” expression state [34]. These “on” and “off” states are mainly related with protein production. Also, the cells perform a range of specialized functions for protein production that depend upon gene expression states. For instance, β cells in the pancreas produce the protein...
hormone insulin that depends upon HLA-encoding gene states, α cells produce the hormone glucagon, lymphocytes of the immune system produce antibodies-proteins (gamma globulin’s), while developing red blood cells produce the oxygen-transport protein hemoglobin. Finding the causes of regime shift and predicting that a cell is about to shift to a harmful gene expression state can improve critical care management for complex human diseases.

In previous studies, the stochastic fluctuations associated with gene expression are considered as Gaussian white noise (noise with zero correlation time) [34–38]. In contrast, few recent studies have shown that gene expression noise can also be colored in nature (noise with non-zero correlation time) [39–43]. These studies have measured the variability of protein levels in human cellular system and showed that cell to cell variability of protein levels can be correlated over generations [40]. It has also been measured experimentally that gene expression noise has a finite correlation time [41]. Moreover, colored noise can break bistability in different ways than that of white noise [42]. In order to address these issues, it is important to study the effects of noise correlation on regime shifts in gene expression.

One of the key questions addressed in this paper is: How the dynamic correlation in gene expression noise affects the characteristics of sudden regime shifts between alternative steady states (i.e., low and high protein concentration states)? For this, we begin with a stochastic version of gene regulatory system: a genetic autoactivating switch. The colored noise is modeled using Ornstein-Uhlenbeck process. We compute the stochastic potential and the stationary probability density function to quantify the effects of noise intensity and correlation time on the relative stability of alternative steady states using Fokker-Planck description. We then obtain the mean first-passage time (MFPT) for escape over the potential barrier. We show that increase in the noise correlation time in degradation rate can induce a regime shift from low to high protein concentration state and enhance the bistable regime, while noise in basal rate retain the bimodal distribution of the system steady states. We also show that cross-correlated colored noises in basal and degradation rates can induce regime shifts from low to high protein concentration state, however reduce the bistable regime. Further, we examine EWS prior to a regime shift in gene expression dynamics, which can prove to be very useful to predict that a cell is about to shift to a harmful phenotype.

The paper is organized as follows: Section II presents the description of a stochastic model of gene expression. In Sec. III A, steady state analysis of the stochastic model is presented. Impacts of noise correlation time, noise intensity and cross-correlation strength on the effective potential landscape and the stationary probability density function are calculated in Sec. III B. We then examine the MFPT of the system driven by the correlated noise in Sec. III C and precursors of regime shift in Sec. III D.

Finally, in Sec. IV, we conclude the study by discussing the key findings reported in this paper.

### II. A STOCHASTIC MODEL OF GENE EXPRESSION

To understand the effects of noise correlation, we consider a well studied stochastic model of gene expression: the autoactivating switch, which consists multiple stable states [37, 38, 40–46]. A schematic picture of the genetic circuit is shown in Fig. 1 which involves a single gene that transcribes a single protein called activator TF-A. On dimerization the protein TF-A dimer stimulates transcription when binds to the responsive element TF-RE in the DNA sequence. The mRNA produced in transcription and protein monomer produced in translation then follow post-transcriptional degradation which is an important regulatory step (see Fig. 1). Letting $x(t)$ and $y(t)$ as concentrations of the activator protein TF-A and the mRNA respectively, we can write the rate equations describing the evolution of $x(t)$ and $y(t)$:

\[
\frac{dx}{dt} = Ky - k_{\text{deg}}x, \tag{1a}
\]

\[
\frac{dy}{dt} = F(x) - k_{\text{degm}}y, \tag{1b}
\]

where the parameter $K$ is the translation rate, $F(x)$ is the mRNA transcription rate, $k_{\text{deg}}$ and $k_{\text{degm}}$ are the degradation rates of the protein monomers and the mRNA. The function $F(x)$ is given by a Hill-type function [48]:

\[
F(x) = \frac{k_{\text{max}} x^H}{k_d + x^H} + k_f,
\]

where $k_{\text{max}}$ is the maximum transcription rate, $k_d$ is the Hill constant, $k_f$ is the basal transcription rate and $H$ is the Hill coefficient which we consider $H = 2$ [49]. The degradation rate of mRNA molecules is usually much faster than that of proteins [48], i.e., $k_{\text{degm}} >> k_{\text{deg}}$.
Since the fast reactions equilibrate quickly, to reduce the dimension of the system it is useful to apply the quasi-
steady state approximation (QSSA) which replaces state
variables involved in the fast reactions with their equi-
librium values. This dimension reduction greatly simpli-
fies the complexity of the system [50]. Now employing
the QSSA in Eq. (1) by replacing the equilibrium value
\( y = F(x)/k_{deg_m} \) from the “fast” Eq. (1) into the “slow”
Eq. (4) and taking \( H = 2 \), we obtain the following re-
duced system:

\[
\frac{dx}{dt} = \frac{K}{k_{deg_m}} \left( k_{max} x^2 \right) \left( k_{d} + x^2 + k_f \right) - k_{deg_r} x. \tag{2}
\]

The above Eq. (2) can also be written as [51]:

\[
\frac{dx}{dt} = R + a \frac{x^2}{k_d + x^2} - k_{deg_r} x, \tag{3}
\]

where \( R = \frac{k_i K}{k_{deg_m}} \) is the basal expression rate and \( a = \frac{k_{max}}{k_{deg_m}} \) is the maximum transcription rate. Now the di-

dimensionless version of equation Eq. (4) is:

\[
\frac{d\tilde{x}}{dt} = \tilde{r} + \tilde{a} \frac{\tilde{x}^2}{1 + \tilde{x}^2} - \tilde{x}, \tag{4}
\]

where \( \tilde{x} = \frac{x}{\sqrt{a}} \), \( \tilde{t} = k_{deg_r} t \), \( \tilde{a} = \frac{a}{k_{deg_r} \sqrt{k_d}} \), and \( \tilde{r} = R \frac{k_{deg_r}}{\sqrt{k_d}} \). Finally, we use \( x, t, r \) and \( a \) in place of \( \tilde{x}, \tilde{t}, \tilde{r} \) and \( \tilde{a} \), and Eq. (4) reads:

\[
\frac{dx}{dt} = r + a \frac{x^2}{1 + x^2} - x. \tag{5}
\]

For a range of \( a \), if \( 0 < r < 1/3 \sqrt{3} \approx 0.19245 \) then Eq. (5) exhibits two types of asymptotic behaviors: monostabi-

lity and bistability (i.e., it leads to phenotypic variability) [51]. In the case of bistability the system has three equi-
librium points, the middle one (say \( x_u \)) is unstable and the other two are stable. In the bistable regime, the ini-
tial condition (say \( x_i \)) plays a key role in determining the final equilibrium state of the system. All the initial values \( x_i > x_u \) will evolve to the upper equilibrium point and others \( x_i < x_u \) will evolve to the lower equilibrium point in the stationary state. Figure 2 depicts the phase diagram of the model [5] in the \( (a, r) \)-plane for different values of the control parameters \( a \) and \( r \). The region of bistability is bounded by a saddle-node bifurcation curve at which transition occurs from monostable to bistable regime or vice versa. A thorough analysis of the determin-

istic model [5] is given in [32].

As already discussed in the introduction, here we are mainly interested in understanding the effects of cor-
related gene expression noise on the regime switching between two alternative steady states. Therefore, in the model [34] we incorporate correlated stochastic process in the form of two fluctuating rates. We assume that variability in the basal and the degradation rates causes the production rate of protein to fluctuate [33].

That is, in Eq. (5) the basal rate varies stochastically as \( r \rightarrow r + \eta(t) \) and also the degradation rate varies stochas-
tically as \( 1 \rightarrow 1 + \xi(t) \). We consider \( \xi(t) \) and \( \eta(t) \) to be Ornstein-Uhlenbeck (OU) processes [32]: positively corre-
lated Gaussian noise (i.e., colored Gaussian noise) with a zero mean and correlation time \( \tau_1 \) and \( \tau_2 \), respectively. The Langevin equation corresponding to Eq. (5) which contains both the Gaussian colored noises \( \eta(t) \) and \( \xi(t) \) can be written as [31, 35]:

\[
\frac{dx}{dt} = (r + \eta(t)) + a \frac{x^2}{1 + x^2} - (1 + \xi(t)) x,
\]

\[
= f(x) + g_1(x) \xi(t) + g_2(x) \eta(t), \tag{6}
\]

where \( f(x) = r + \frac{ax^2}{1 + x^2} - x \), \( g_1(x) = -x \) and \( g_2(x) = 1 \). Thus, here the noise \( \xi(t) \) can be considered as multiplica-
tive colored noise in comparison to \( \eta(t) \), which works as additive colored noise [34]. The OU processes \( \xi(t) \) and \( \eta(t) \) satisfy the following equations:

\[
\xi(t) = -\frac{\xi(t)}{\tau_1} + \sqrt{2 \sigma_1 \tau_1} \xi_1(t),
\]

\[
\eta(t) = -\frac{\eta(t)}{\tau_2} + \sqrt{2 \sigma_2 \tau_2} \eta_1(t),
\]

where \( \xi_1(t) \) and \( \eta_1(t) \) are white Gaussian noises with zero mean and unit variance [52]. The parameters \( \sigma_i \) and \( \tau_i (\neq 0) \), for \( i = 1,2 \) are noise strength and self correlation time of \( \xi(t) \) and \( \eta(t) \), respectively. The colored Gaussian noises \( \xi(t) \) and \( \eta(t) \) satisfy the following statistical properties:

\[
\langle \xi(t) \rangle = \langle \eta(t) \rangle = 0,
\]

\[
\langle \xi(t) \xi(t') \rangle = (\sigma_1 / \tau_1) \exp(-|t - t'| / \tau_1),
\]

\[
\langle \eta(t) \eta(t') \rangle = (\sigma_2 / \tau_2) \exp(-|t - t'| / \tau_2),
\]

\[
\langle \xi(t) \eta(t') \rangle = (\lambda \sqrt{\sigma_1 \sigma_2 / \tau_1 \tau_2}) \exp(-|t - t'| / \tau_3),
\]

where \( \lambda \) measures the coupling strength between \( \xi(t) \) and \( \eta(t) \), \( \tau_3 \) is the correlation time between the noises, while \( t \) and \( t' \) denote two different moments.

FIG. 2. (Color online) Phase diagram of the gene expression model [5] in \((a, r)\)-plane. The curve separating the monos-
table region from the bistable region is a saddle-node bifurca-
tion curve.
In order to understand the influence of colored noises on the rapid switching between two alternative stable states, we employ theoretical calculations of probability densities, potential functions, and MFPTs of Eq. (6).

III. RESULTS

A. Steady state analysis of the stochastic system

To solve the stochastic Eq. (6), we begin with the probability density $P(x, t)$, which is the probability that the protein concentration will attain the value $x$ at time $t$. The approximate Fokker-Planck equation (AFPE) for $P(x, t)$ corresponding to Eq. (6) is [53, 54]:

$$\frac{\partial P(x, t)}{\partial t} = -\frac{\partial}{\partial x} [A(x) P(x, t)] + \frac{\partial^2}{\partial^2 x} [B(x) P(x, t)], \tag{8}$$

where,

$$A(x) = f(x) + \frac{\sigma_1 x}{1 - \tau_1 f'(x_s)} - \frac{\lambda \sqrt{\sigma_1 \sigma_2}}{1 - \tau_2 f'(x_s)}, \tag{9a}$$

$$B(x) = \frac{\sigma_1 x^2}{1 - \tau_1 f'(x_s)} - \frac{2 \lambda \sqrt{\sigma_1 \sigma_2} x}{1 - \tau_3 f'(x_s)} + \frac{\sigma_2}{1 - \tau_2 f'(x_s)}, \tag{9b}$$

and $f'(x_s)$ is the derivative of $f(x)$ at the equilibrium point $x_s$. The derivative $f'(x_s)$ is given by:

$$f'(x_s) = \frac{2ax_s}{(1 + x_s^2)^2} - 1,$$

where the equilibrium point $x_s$ is:

$$x_s = \frac{m}{2} + \sqrt{\frac{m}{2}^2 + \left(\frac{l}{3}\right)^3} + \sqrt{-\frac{m}{2} - \sqrt{\frac{m}{2}^2 + \left(\frac{l}{3}\right)^3 - \frac{n}{3}}}, \tag{10}$$

with $l$, $m$ and $n$ as: $l = 1 - \frac{(r+a)^2}{3}$, $m = \frac{1}{2}r(r + a)^3 + \frac{1}{3}(r + a)$, and $n = -(r + a)$. The point $x_s$ is the only real solution of $f(x) = 0$. Relation between the two functions $A(x)$ and $B(x)$ are given by:

$$A(x) = f(x) + \frac{d}{2 dx} B(x).$$

Moreover, the AFPE [8] is valid for $1 - \tau_i f'(x_s) > 0$ ($i = 1, 2, 3$) [54].

The stationary probability density function (SPDF) $P_s(x)$ of $x$, which is the stationary solution of the AFPE [8], is given by:

$$P_s(x) = \frac{N_c}{B(x)} \exp \left[ \int_x^\infty \frac{A(u)}{B(u)} du \right],$$

$$= \frac{\sigma_1 x^2}{1 - \tau_1 f'(x_s)} - \frac{2 \lambda \sqrt{\sigma_1 \sigma_2} x}{1 - \tau_3 f'(x_s)} + \frac{\sigma_2}{1 - \tau_2 f'(x_s)} \times$$

$$\exp \left[ \int_x^\infty \frac{f(u) + \frac{\sigma_1 u}{1 - \tau_1 f'(x_s)} - \frac{\lambda \sqrt{\sigma_1 \sigma_2} u}{1 - \tau_3 f'(x_s)} + \frac{\sigma_2}{1 - \tau_2 f'(x_s)} \right] du, \tag{11}$$

where $N_c$ is normalization constant obtained from:

$$\int_0^\infty P_s(x) dx = 1.$$ 

In analogy with the physical situation of a particle moving in a potential, the SPDF peaks correspond to the valleys of the potential (i.e., attractors) and troughs correspond to the tops of the potential (i.e., repellers). We can also introduce a stochastic potential by writing the SPDF [11] in the form:

$$P_s(x) = N_c e^{-\phi(x)}, \tag{12}$$

where

$$\phi(x) = \frac{1}{2} \ln \left[ \frac{\sigma_1 x^2}{1 - \tau_1 f'(x_s)} - \frac{2 \lambda \sqrt{\sigma_1 \sigma_2} x}{1 - \tau_3 f'(x_s)} + \frac{\sigma_2}{1 - \tau_2 f'(x_s)} \right]$$

$$- \int_x^\infty \frac{f(u)}{\frac{\sigma_1 u^2}{1 - \tau_1 f'(x_s)} - \frac{2 \lambda \sqrt{\sigma_1 \sigma_2} u}{1 - \tau_3 f'(x_s)} + \frac{\sigma_2}{1 - \tau_2 f'(x_s)}} du, \tag{13}$$

is the stochastic potential of the system. The stochastic potential provides information about the relative stability of the steady states, likewise the deterministic potential of a system.

It is also important to know the stationary state of the system for arbitrary noise intensities. More specifically, we are interested in understanding the transition phenomena between stationary states that occur due to the presence of correlated noise. For the deterministic model [10], this can be best visualized by the corresponding bifurcation diagram representing the equilibrium protein concentration $x$, for a range of control parameter. In the stochastic model [8], a qualitative change in the stationary state is accurately reflected by the behavior of the extrema of the SPDF $P_s(x)$ [55]. The extrema of $P_s(x)$ can easily be found form the equation given below [32]:

$$f(x) - \frac{\sigma_2}{1 - \tau_2 f'(x_s)} = 0. \tag{14}$$

Using the above steady state calculations of the stochastic model [8], in next subsection we mainly focus on the dynamical consequences due to the presence of dynamic correlations in noise.
B. Effective potential landscape and stationary probability density function

In order to study the effects of variations in the stochastic parameters (i.e., $\sigma_i$, $\tau_i$ and $\lambda$), we use the evolution equation for SPDF (11). The SPDF, potential function and extrema of SPDF are examined for three different cases: (i) When noise is present only in the degradation rate. (ii) When noise is present only in the basal rate. (iii) When noise is present in both the rates, respectively. In Table I, we summarize the values of stochastic parameters corresponding to the above three cases.

| Parameters: $\sigma_1$ $\sigma_2$ $\lambda$ $\tau_1$ $\tau_2$ $\tau_3$ |
|---------------------------------------------------------------|
| Case (i): $\neq 0$ $= 0$ $= 0$ $\neq 0$ $= 0$ $= 0$ |
| Case (ii): $= 0$ $\neq 0$ $= 0$ $= 0$ $\neq 0$ $= 0$ |
| Case (iii): $\neq 0$ $\neq 0$ $\neq 0$ $\neq 0$ $\neq 0$ $\neq 0$ |

1. Correlated noise in the degradation rate

We now consider the presence of correlated Gaussian noise which alters the degradation rate in Eq. (11). The corresponding Langevin Eq. (6) can be rewritten in the form:

$$\frac{dx}{dt} = r + a \frac{x^2}{1 + x^2} - (1 + \xi(t))x.$$  (15)

Here the noise $\xi(t)$ is modulated due to the multiplication with the state variable $x$. Therefore, a small random fluctuation in the degradation rate can lead to a sudden regime shift in the protein concentration. The role of noise intensity $\sigma_1$ and correlation time $\tau_1$ of the noise $\xi(t)$ are very important factors, because they can act as system parameters. For fixed values of the control parameters $r$ and $a$, changes in the noise intensity $\sigma_1$ and the correlation time $\tau_1$ can trigger sudden regime shifts in the level of protein concentration.

From Eq. (11), the SPDF corresponding to Eq. (15) can be rewritten as:

$$P_s(x) = \frac{N_0}{B(x)} \exp \left[ \int^x \frac{A(u)}{B(u)} du \right] = \frac{N_0}{\sigma_1^2 x^2} \times \exp \left[ \int^x \frac{f(u)}{\sigma_1 \sigma_2} - \frac{\sigma_2}{\sigma_1} \frac{u}{1 - \tau_1 \int^u f(x) dx} \right] du.$$  (16)

The potential function is derived from Eq. (15) and is given by:

$$\phi(x) = \frac{1}{2} \ln \left( \frac{\sigma_1 x^2}{1 - \tau_1 f(x)} \right) - \int^x \frac{f(u)}{\sigma_1 u^2} \frac{\sigma_1 x^2}{1 - \tau_1 f(x)} du.$$  (17)

The role of correlated noise on the relative stability between two alternative steady states can be well understood by illustrating the SPDF (15) and the potential (17) for an exemplary set of parameters. Figures 3(a)-(b) show the influence of the colored noise intensity $\sigma_1$ on the shape of the potential $\phi(x)$ and the SPDF $P_s(x)$. It can be seen that for a fixed value of $\tau_1$, increasing values of $\sigma_1$ entail an increase in the likelihood of undesired regime shifts from one stable state to another stable state (Fig. 3(a)). With increasing values of $\sigma_1$, the SPDF peak at the low protein concentration $x$ is increasing and that of the high protein concentration $x$ is decreasing. Hence, an increase in the noise intensity $\sigma_1$ can induce a sudden regime shift from high to low protein concentration state. However, the dynamic correlation time $\tau_1$ has inverted effect on the stability of the system (Figs. 3(c)-(d)). Figure 3(d) depicts the changes in the SPDF $P_s(x)$ peaks with changes in $\tau_1$ for a fixed value of $\sigma_1$. It is evident from the $P_s(x)$ peaks that at low values of $\tau_1$ the lower state is more stable and at high values of $\tau_1$ the upper state becomes more stable. In fact, $\tau_1$ has nontrivial effect on the stationary state and an increase in $\tau_1$ can cause a regime shift form low to high protein concentration state. The above results indicate that probability of shifting to the lower stable state is more in the case of increasing noise intensity $\sigma_1$, whereas probability of finding upper stable state is more in the case of increasing correlation time $\tau_1$. Figure 4 shows the continuous evolution of the SPDF $P_s(x)$ with increasing values $\tau_1$. From Eq. (17), now the extrema of $P_s(x)$ can be writ-
as a function of the maximum transcription rate $\tau_1$. The other parameters are $\sigma_1 = 0.5$, $r = 0.1$ and $a = 3.5$. As the $P_s(x)$ corresponding the right potential well has increased with increase in the $\tau_1$, the system experiences a regime shift from low to high protein concentration state.

$$f(x) - \frac{\sigma_1 x}{1 - \tau_1 f'(x_s)} = 0. \quad (18)$$

Using the above Eq. (18), the extrema of $P_s(x)$ is plotted in Fig. 5 as a function of the maximum transcription rate $a$. With the help of the extrema, we investigate the occurrence of critical transition (i.e., any qualitative changes in the stationary state) in the stochastic system by changing the noise intensity $\sigma_1$ and the correlation time $\tau_1$. Changes in $\sigma_1$ and $\tau_1$ have opposite effects on the steady state behavior of the system. For a fixed $\tau_1$, increasing values of $\sigma_1$ decreases the bistability regime (Fig. 5(a)) and for a fixed $\sigma_1$, increasing values $\tau_1$ increases the bistability regime (Fig. 5(b)).

2. Correlated noise in the basal rate

We now focus only on the effect of correlated noise source $\eta(t)$ in the basal rate in Eq. (6) with stochastic parameters $\sigma_2 \neq 0$ and $\tau_2 \neq 0$ (see Table I). In this case, Eq. (11) can be written as:

$$P_s(x) = \frac{N_c}{B(x)} \exp \left[ \int_x^\infty \frac{A(u)}{B(u)} du \right]$$

$$= \frac{N_c}{\sigma_2^2} \exp \left[ \int_x^\infty \frac{f(u)}{1 - \tau_2 f'(x_s)} du \right], \quad (19)$$

and the potential function is derived from Eq. (13) is given by:

$$\phi(x) = \frac{1}{2} \ln \left[ \frac{\sigma_2}{1 - \tau_2 f'(x_s)} \right] - \int_x^\infty \frac{f(u)}{\sigma_2^2} \frac{du}{1 - \tau_2 f'(x_s)}. \quad (20)$$

Figure 5 depicts the stochastic potential $\phi(x)$ and SPDF $P_s(x)$ for different values of the noise intensity $\sigma_2$, and the noise correlation time $\tau_2$. We set the parameters in such a way that the system is in the bistability regime, i.e., both the high and low protein concentration states. Our results show that for a fixed $\tau_2$ increasing values of $\sigma_2$ have equal effect on the relative stability of both the steady states (Figs. 6(a)–(b)). The same result follows for fixed $\sigma_2$ and increasing values of $\tau_2$ (Figs. 6(c)–(d)). What we find is that the bimodal distribution of $\phi(x)$ and $P_s(x)$ is retained, and the positions of the steady states also remains almost the same, however the valleys and the tops of $P_s(x)$ decay in height with increase in both $\sigma_2$ and $\tau_2$.

3. Correlated noise in both the basal and degradation rate with cross-correlation strength $\lambda$

In this section, we consider the Langevin Eq. (6) in the presence of both the colored noises $\xi(t)$ and $\eta(t)$. Furthermore, $\xi(t)$ and $\eta(t)$ are statistically cross correlated with the cross-correlation strength $\lambda$. The cross correlation between $\xi(t)$ and $\eta(t)$ is chosen due to the regulation of feedback mechanism, i.e., in the presence of noise.
the protein concentration $x$ is chemically coupled to the degradation rate $[56]$. Here, our goal is to understand the impact of the cross-correlation strength $\lambda$ and correlation time $\tau_3$ between two noises $\xi(t)$ and $\eta(t)$, on the steady states of the system and the transition between them.

Using Eqs. (11) and (13) we compute the SPDF $P_s(x)$ and the potential function $\phi(x)$ for the system (9). Figures 7(a)-(b) show the radical effect of the cross-correlation strength $\lambda$ on the shape of $\phi(x)$ and $P_s(x)$. For a fixed value of $\tau_3$, with increasing values of $\lambda$, the SPDF peak at low protein concentration state is reducing and that of high protein concentration state is increasing (see Fig. 7(b) for $\lambda = 0.9$). Hence, an increase in $\lambda$ can induce a sudden regime shift from low protein concentration state to high protein concentration state.

Moreover, the correlation time $\tau_3$ has similar effect on the shape of $\phi(x)$ and $P_s(x)$ likewise the effect of cross-correlation strength $\lambda$ (Figs. 7(c)-(d)). It is evident from the $P_s(x)$ peak that at low value of $\tau_3$, the lower steady state is more stable in comparison with the higher steady state, whereas at high value of $\tau_3$, the scenario is just opposite (Fig. 7(d)). The above results indicate that probability of shifting to the upper steady state is more for both the cases: Increasing the cross-correlation strength $\lambda$ and the correlation time $\tau_3$ [57]. Figures 8(a)-(b) show the continuous evolution of the SPDF $P_s(x)$ with increas-
coupled with the correlation parameters of the noise. The relative stability of the bistable states is dynamically even if it can reduce it to monostable state. Moreover, the regulation can significantly affect the bistable states and indicate that correlated stochastic fluctuations in gene regulation model (6) driven by cross-correlated noise $s$.

For stochastic bistable systems, it is important to estimate the amount of time between shifts from one steady state to another steady state. As it helps to quantify the effects of noise on the regime switching between alternative steady states. This time is often referred as first-passage time. When the first-passage time is averaged over many realizations, the resulting time is called mean first-passage time (MFPT) \[^{52}\]. To examine the robustness of steady states, MFPT provides a very useful characterization. A longer MFPT implies the state is more stable. Now, we study the influence of cross-correlation strength $\lambda$ and correlation time $\tau_3$ on the MFPT.

Using Eq. \[^{14}\], the extrema of SPDF $P_s(x)$ is depicted in Figs. \[^{9}\]a)-(b) as a function of the maximum transcription rate $a$. Notice that, with increasing values of $\lambda$ and $\tau_3$ both extrema curves exhibit similar behavior. As an example, Fig. \[^{9}\]a) shows that increase in $\lambda$ between two noises reduce the bistability region and for higher values of $\lambda$, bistability completely disappears. These results indicate that correlated stochastic fluctuations in gene regulation can significantly affect the bistable states and even it can reduce it to monostable state. Moreover, the relative stability of the bistable states are dynamically coupled with the correlation parameters of the noise.

C. Mean first-passage time of the system driven by cross-correlated noises

For stochastic bistable systems, it is important to estimate the amount of time between shifts from one steady state to another steady state. As it helps to quantify the effects of noise on the regime switching between alternative steady states. This time is often referred as first-passage time. When the first-passage time is averaged over many realizations, the resulting time is called mean first-passage time (MFPT) \[^{52}\]. To examine the robustness of steady states, MFPT provides a very useful characterization. A longer MFPT implies the state is more stable. Now, we study the influence of cross-correlation strength $\lambda$ and correlation time $\tau_3$ on the MFPT.

![Figure 9](image-url) FIG. 9. (Color online) Extrema of the SPDF $P_s(x)$ of the gene regulation model driven by cross-correlated noises, as a function of $a$: (a) For increasing values of the cross-correlation strength $\lambda$ with other parameter values are $r = 0.1, \sigma_1 = 0.2, \sigma_2 = 0.5$, $\tau_1 = 0.01, \tau_2 = 0.01$ and $\tau_3 = 0.1$, and (b) for increasing values of the correlation time $\tau_3$ with other parameter values are $r = 0.1, \sigma_1 = 0.2, \sigma_2 = 0.5$, $\tau_1 = 0.5$, $\tau_2 = 0.5$ and $\lambda = 0.1$. The bistability regime reduces with increase in both $\lambda$ and $\tau_3$.

![Figure 10](image-url) FIG. 10. (Color online) The effect of $\lambda$ and $\tau_3$ on the MFPT. (a) The MFPT $\langle T_{x^l_t \rightarrow x^u_t} \rangle$ decreases and $\langle T_{x^u_t \rightarrow x^l_t} \rangle$ increases with the increase of $\lambda$ for $\tau_3 = 0.03$. (b) Similar situation arises with the increase of $\tau_3$ for $\lambda = 0.3$. The other parameters are same as in Fig. \[^{8}\].

To start with, let $x^l_t$ be the low and $x^u_t$ be the high protein concentration states, separated by a potential barrier $x^b_t$ (working as a basin boundary between the two steady states $x^l_t$ and $x^u_t$) of the system \[^{10}\]. The basin of attraction of the state $x^u_t$ extends from $x^b_t$ to $+\infty$, as it is in the right of $x^l_t$. The MFPT $\langle T(x) \rangle$, can be obtained by solving the following ordinary differential equation \[^{52}\]:

$$A(x) \frac{\partial\langle T \rangle}{\partial x} + \frac{1}{2} B(x) \frac{\partial^2 \langle T \rangle}{\partial x^2} = -1,$$  \(21\)

with boundary conditions $\langle T(x^b_t) \rangle = 0$ and $\frac{\partial \langle T(x) \rangle}{\partial x} = 0$, where $A(x)$ and $B(x)$ are respectively given by Eqs. \[^{9}\) and \[^{9}\).}

By solving the Eq. \[^{21}\], we obtain the expressions of MFPT for $x^l_t$ and $x^u_t$. The expressions for MFPT
FIG. 11. (Color online) Early warning signals for simulated time series data of the stochastic model in the case of: (a) CSD and (b) SS. The variance and autocorrelation are calculated using moving window of half the length of the time series segments (segments are indicated by the shaded regions): (a) For CSD: parameter values are \( r = 0.1, \sigma_1 = 0.002, \sigma_2 = 0.09, \lambda = 0.8, \tau_1 = 5, \tau_2 = 5 \) and \( \tau_3 = 1 \); (b) For SS: parameter values are \( r = 0.1, \alpha = 1.9, \sigma_1 = 0.005 \) and \( \sigma_2 = 0.007, \lambda = 0.01, \tau_1 = 0.09, \tau_2 = 0.09 \) and \( \tau_3 = 1 \). The increase in variance act as a robust indicator for CSD, whereas variance fails in the case of SS. The autocorrelation gives weak trend in both CSD and SS.

\[
\langle T_{x_{l}^{st} \rightarrow x_{u}^{st}} \rangle \text{ and } \langle T_{x_{u}^{st} \rightarrow x_{l}^{st}} \rangle \text{ are given by [52]:}
\]
\[
\langle T_{x_{l}^{st} \rightarrow x_{u}^{st}} \rangle = 2 \int_{x_{l}^{st}}^{x_{u}^{st}} dy \int_{0}^{\omega(z)/B(z)} \omega(z) dz, \quad (22)
\]
\[
\langle T_{x_{u}^{st} \rightarrow x_{l}^{st}} \rangle = 2 \int_{x_{u}^{st}}^{x_{l}^{st}} dy \int_{\omega(z)/B(z)}^{\infty} \omega(z) dz, \quad (23)
\]

where
\[
w(x) = \exp \left( \int_{x_0}^{x} \frac{2A(u)}{B(u)} du \right),
\]
with \( x_0 = 0 \) for the \( x_{l}^{st} \rightarrow x_{u}^{st} \) transition and \( x_0 = x_{u}^{st} \) for the \( x_{u}^{st} \rightarrow x_{l}^{st} \) transition.

Effects of changing \( \lambda \) and \( \tau_3 \) on the MFPT are shown in Fig. 10. We found that the MFPT \( \langle T_{x_{l}^{st} \rightarrow x_{u}^{st}} \rangle \) decreases and \( \langle T_{x_{u}^{st} \rightarrow x_{l}^{st}} \rangle \) increases, with increase in the cross-correlation strength \( \lambda \) (Fig. 10a)). Hence, an increase in \( \lambda \) results in a regime shift from the left potential well (low concentration state of \( x \)) to the right potential well (high concentration state of \( x \)). We observe similar dynamics with variations in \( \tau_3 \) (Fig. 10b)). The conclusions drawn from the analysis of MFPT are also consistent with the SPDF \( P_s(x) \) shown in Fig. 8. This result highlights the significance of correlated noise in gene expression dynamics.

D. Precursors of regime shift

Here, the main emphasis is to explore the robustness of EWS (e.g., lag-1 autocorrelation, variance and conditional heteroskedasticity) as indicators of regime shifts in protein concentration levels. In clinical medicine, EWS can be considered as bio-markers because these are indicators of regime shifts in biological state for living organism [27]. However, earlier techniques or bio-markers are mainly used to investigate the current disease state of an organ based on metabolites or individual protein level [57, 58].

For our analysis, we consider stochastic time series of the model [5] for both the cases, critical slowing down (CSD) and stochastic switching (SS) [2, 14, 18, 21]. The presence of cross-correlated noise in the degradation and basal rates are considered. Numerical simulations have been performed using the Euler-Maruyama method [59].
with an integration step-size of 0.001. In the time series, we first visually identify shifts between low to high protein concentration. Then we took time series segments (the shaded regions in Fig. 11) prior to a regime shift and analyze them for the presence of EWS. For stationarity in residuals, we used Gaussian detrending with bandwidth 40, before performing any statistical analysis of the data. Then we used a moving window size of half the length of the considered time series segment. The time series analysis have been performed using the “Early Warning Signals Toolbox” (http://www.early-warning-signals.org). First, we calculate the variance and lag-1 autocorrelation, as these two indicators are known to be most appropriate to anticipate regime shifts. The autocorrelation at lag-1 is given by the autocorrelation function (ACF):

\[ \rho_1 = \frac{E[(x(t) - \mu)(x(t+1) - \mu)]}{\sigma^2} \]

where \( E \) is the expected value operator, \( x(t) \) is the value of the state variable at time \( t \), and \( \mu \) and \( \sigma^2 \) are the mean and variance of \( x(t) \), respectively. Variance is the second moment around the mean \( \mu \) and measured as: \( \sigma^2 = \frac{1}{N} \sum_{t=1}^{N} (x(t) - \mu)^2 \), where \( N \) is the number of observations within the considered moving window. A concurrent rise in these indicators forewarn an upcoming regime shift [1, 2].

Figure 11(a) shows increase in \( \sigma^2 \) and decrease in \( \rho_1 \) before a regime shift for the case of CSD. Hence, in this case \( \sigma^2 \) is able to successfully detect a regime shift in protein concentration, whereas \( \rho_1 \) fails. However, in the case of SS (Fig. 11(b)), both of these indicators fails. For SS, the failure of \( \sigma^2 \) and \( \rho_1 \) as EWS is in agreement with the previous studies [16, 17, 60, 61]. The result of EWS analysis also depends on the choice of factors like filtering bandwidth and moving window size, used to calculate the standard deviation and autocorrelation [18]. Hence, it is important to investigate the robustness of our results with respect to the choice of these factors. In particular, we perform sensitivity analysis which is necessary for the selection of bandwidth and moving window size to maximize the estimated trend of EWS. For CSD, we estimate variance and autocorrelation in window size ranging from 25% to 71% (i.e., 96 to 271 data points) of the time series length, and for filtering bandwidth ranging from 5% to 100% (see Figs. 12(a) and 12(b)). For SS, we use window size ranging from 25% to 68% (i.e., 1430 to 1496 data points) and bandwidth ranging from 2% to 100% (see Figs. 12(c) and 12(d)). Figures 12(a) and 12(c) represent contour plots of rolling window size verses bandwidth for the autocorrelation, similarly Figs. 12(b) and 12(d) for the variance. The empty ovals in Fig. 12 indicate the choices of the window size and filtering bandwidth used in the calculations in Fig. 11. It is clear that the autocorrelation in both cases
the cases CSD (Fig. 12(a)) and SS (Fig. 12(c)) do not give proper result due to the low value of Kendall’s coefficient [18]. However, increasing trend in variance is found in the case of CSD due to the proper selection of window size and bandwidth corresponding to the high value of Kendall’s coefficient, which is also evident from the Fig. 12(b).

We compute CH using moving window Lagrange multiplier test (window width 10% of the data) [22]. First we extract the residuals of a fitted model to the time series, then we fit an auto-regressive model of selected order:

\[ x_t = a_0 + \sum_{i=1}^{q} a_i x_{t-i} + \epsilon_t, \]

where the order \( q \) is selected according to the Akaike information criterion [22] which is a measure of the relative goodness of the fit. Then we squared the residuals \( \epsilon_t \), and finally the residuals are regressed on themselves lagged by one time step:

\[ \epsilon_t^2 = \alpha_0 + \sum_{i=1}^{q} \alpha_i \epsilon_{t-i}^2, \]

where \( \alpha_0 \) and \( \alpha_i \) denotes the regression coefficients. The relationship between squared residuals \( \epsilon_t^2 \) at lag-1 gives the properties of CH. We also perform chi square test to compare the values of squared residuals to a \( \chi^2 \) distribution to identify the number of significant tests where the CH is observed. The cumulative number of significant tests (C) for CH applied to time series, is expected to increase as the regime shift is approached. Here Fig. 13(a) (Fig. 11(a)) represents the CH estimated on the CSD (SS) dataset prior to a regime shift which shows the positive relationship of error variance and represents the significant CH (i.e., squared residuals) above the significance level. In Figs. 13(a) and Fig. 14(a), the significance level is represented by the red line. The residuals above this red line indicates that there is presence of CH. Figure 13(b) (Fig. 14(b)) shows the result of cumulative number of significant tests (C) for CH applied to time series for the case of CSD (SS) and which is increasing prior to a regime shift and gives positive EWS. It is important to observe that in the case of SS the indicator CH is successful in comparison with autocorrelation and variance and this is evident from Figs. 12 and 14.

Although autocorrelation and variance are known to be the most preferred indicators to predict regime shifts, the fact is that they are not always successful as shown in the previous examples. This arises because not all the regime shifts are associated with CSD [15]. Moreover, improper data length, statistical limitations and other types of transitions, such as purely noise-induced transitions increase the risk of false predictions. We cannot avoid the possibility of false alarms completely [13] [21]. Hence, we further tested another indicator conditional heteroskedasticity (CH) (see Figs. 13 and 14) [22]. CH is denoted by the persistence in the conditional variance of the error terms. In time series, it looks like a cluster of high variability near a critical transition and cluster of low variability far from the transition. This type of clustering is known to be a leading indicator of regime shifts. CH provides threshold value for detecting regime shift and gives an indication of upcoming regime shift [22].

IV. DISCUSSION

Noise correlation can play a pivotal role in controlling the regulatory functions of gene expression [34] [41] [42]. In this paper, we have presented theoretical analysis and numerical simulation of a gene expression model to study the role of Gaussian colored noise in inducing sudden regime shifts at the levels of protein concentration. We have used the Ornstein-Uhlenbeck process with the Langevin and Fokker-Plank descriptions to study the effects of Gaussian colored noise. Though one of our main goals is to investigate the effects of noise correlation, for the sake of completeness we also simultaneously studied the effects of colored noise intensity. The theoretical tools used to serve our purpose are the stochastic potential, the stationary probability density function and
the mean first-passage time [52]. For the presence of colored noise in the protein degradation rate, we have shown that for a fixed correlation time increase in the noise intensity induces regime shift from high (“on” state) to low (“off” state) protein concentration state. Surprisingly, for a fixed noise intensity an increase in the correlation time produces opposite result, it induces regime shift from low (“off” state) to high (“on” state) protein concentration state. Moreover, with the help of the extrema of SPDF we show that for a fixed correlation time, increasing values of noise intensity reduces the bistability regime and for a fixed noise intensity, increasing values of noise correlation increases the bistability regime. Our results also show that colored noise in the basal rate retain the bimodal distribution of the steady states. In the case of cross-correlated colored noises in basal and degradation rates, we have shown that both the cross correlation strength and cross correlation time can induce regime shifts from low to high protein concentration state, but reduce the bistable regime. The results of MFPT for cross-correlated colored noises also matches with the outcome of stochastic potential and SPDF. Thus, unlike earlier studies on gene expression noise [17, 23, 24, 27, 28], our findings suggest that Gaussian colored noise can also induce sudden phenotypic variability (i.e., regime shifts between “on” and “off” expression state) in cells and the noise correlation time can act as a control parameter for that.

Anticipation of regime shifts in gene expression could improve early therapeutic intervention in complex human diseases [4, 10, 25]. Furthermore, EWS for predicting state shifts in complex biological systems can be very useful as a bio-marker for incurable and chronic human diseases where the stage of the disease is an important factor of therapy and prognosis; for example in liver cancer and lymphoma [27]. Keeping in mind the complexity of cancer, if the stage of cancer can be identified by using EWS, it would be remarkable. Nonetheless, the success of EWS in anticipating catastrophic shifts in ecosystem experiments [5] suggests that it could be possible to develop and employ EWS in cancer biology based on clinical trials [4, 26]. Considering, both CSD and SS time series data of the gene expression model we show that variance and autocorrelation sometimes can work as indicators of regime shifts in the levels of protein concentration. However, these indicators can also produce false alarms due to statistical limitations. We also performed sensitivity analysis for the best choice of statistical parameters to be used in time series analysis as to avoid false alarms. When the variance and autocorrelation fails to predict regime shifts, we have shown that other indicator like conditional heteroskedasticity can be successful. The implication of EWS as bio-markers for complex diseases demands experimental verification and is a future challenge for experimental biologists. For predicting regime shifts in gene expression in experiments, one can use single cell flow cytometry measurements which gives rapid analysis of multiple characteristics of single cell [17, 63]. Flow cytometry monitors the distribution of number of proteins in a cell culture.

Further work on extending the kind of analysis presented here to more complex gene networks is needed. Earlier studies in the direction of understanding and predicting regime shifts in gene expression advanced our perception, however there is still lack of quantitative understanding of regime shifts in genetic networks due to its inherent complexity. The main advantage of the mathematical formalism adopted in this paper is that it is simple and easy to understand. We hope that, this reductionist approach could form the basis for more rigorous studies on regime shifts of complex gene networks. Moreover, in this study like many other studies on gene expression we have employed the Langevin and Fokker-Planck description due to their simplicity and analytic tractability [24, 38, 52], but one can also use the master equation and its Monte-Carlo simulation [52]. Finally, acquiring in depth knowledge about the factors those drive shifts in gene expression states could have significant impact in clinical biology.

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