

Complexity in the Role of Noise in Stochastic Systems

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Abstract

The role of noise in stochastic system could be constructive or destructive depending on the topology of the biochemical network, interaction mechanism and strength of the noise. The noise in genetic and chemical oscillators is studied using chemical Langevin equation and numerically using stochastic simulation algorithm to study the role of noise. The temporal behaviors of the variables in genetic oscillator are found to maintain their oscillatory nature at small system size limit ($V \leq 13 \pm 3$), but above this the oscillatory behaviors get start destroying by getting transition from fluctuated limit cycle to no oscillation limit as $V \rightarrow \infty$. However, in chemical oscillator case, in the limit $V \rightarrow \infty$ the oscillatory behaviors of the variables get transition from fluctuated limit cycle (tending destroy oscillatory behavior) to normal limit cycle (maintain sustain oscillations). The noise parameter calculated as a function of V for genetic oscillator first slowly decrease and increases as V increases. However the noise parameter in chemical oscillator decreases first ($V \leq 50 \pm 5$) and then remains constant as V increases. The calculated noise parameter via stochastic simulation algorithm is always found to be larger than that is obtained via chemical Langevin equation.

Keywords: Noise parameter; Genetic oscillator; Chemical oscillator; Master equation; Chemical Langevin equation

Introduction

The noise in stochastic system is due to random particle/molecular interaction of the participating particles/molecules in the system (intrinsic noise) [1,2], and exchange of external fluctuations of the surrounding environment with the system such as thermal, environmental fluctuations (external noise) [3,4]. This noise, in general, is known to be a parameter that induces hindrance to the signal associated with dynamical variables of the system [5]. However, there are important constructive roles of noise in stochastic systems, for example, detection and amplification of weak noise, the phenomenon known as stochastic resonance [6,7], lifting of cellular expression at different distinct expression state [8], noise in gene expression can drive stochastic switching among such states [9,10], noise induced stochastic phenotypic switching to different new level in living cells [11], noise induce generation of coherent motion [12], noise induced synchronization of stochastic systems [13] that can be found in inter-circadian networks via environmental fluctuations [14-16] etc. This noise parameter is also being used as a means of synchronizing or correlating behaviors of a group of biological systems such as group of biological cells in multi-cellular organism or group of unicellular organisms, i.e. quorum sensing in a group of bacteria via external environmental fluctuation [17]. The study of the role of noise in realistic systems is of main interest especially in biological areas.

The complex processes in stochastic system can be well described by Master equation formalism (ME) which is based on every individual particle/molecular interaction involve that leads to decay or/and creation of particles/molecules in the system [1,18,19]. Since solving ME for complex system is difficult, there have been other simplified techniques to deal with processes in the system, for example, chemical Langevin equation (CLE) [20], noise induce deterministic equation (Langevin equation) [19,21] and Linear noise approximation [19,22]. Noise in the system described by ME can be well estimated using generating function technique [18,19,23]. The strength of the noise in the system depends on various parameters such as systems size V , population of molecules accommodated in the systems (N) and dynamical variables in the system [1,20]. For instance, the noise

strength associated with single cell gene expression scales as N^{-1} of relative fluctuation amplitude [8] and in CLE it scales as $N^{-1/2}$.

Noise, on the other hand, is a parameter similar to thermodynamics limit which can distinguish stochastic and deterministic systems, where stochastic system becomes deterministic when noise becomes negligible [20,24]. This parameter is an inherent property of most of the biological systems, and can be technically controlled by controlling the noise term introduced in the system or controlling the parameters such as system size, dynamical variables in the system etc. But in real practice, it is hard to control the internal noise which is already associated with molecular events taking place in real biological systems. However the role of noise could be of different varieties, different for different noise strengths and system properties. We study certain roles of noise in this work which could happen in natural system, and may unfold many interesting roles of noise in various natural systems. Our work is organized as follows. We first briefly describe stochastic model of biochemical network followed by the analysis of Chemical Langevin formalisms in materials and methods. We then pick up two examples namely genetic and chemical oscillator, and study the role of noise numerically as well as analytically which are presented in results and discussions. Finally some conclusions are drawn based on the results we obtained in this work.

Materials and Methods

The random interaction of molecules in a well stirred stochastic system leads the dynamics of the variables in the system to noise-driven stochastic process [1,19,20]. Out of two types of interaction, namely

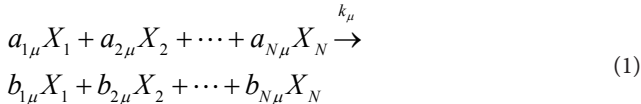
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reacting and non-reacting collisions [25], reacting interaction, which involves decay and creation of molecular species, plays major roles in the stochastic system is responsible for various stochastic functions. The complex reactions in the system in real situation can be reduced to elementary reactions where few reactants are involved [1,25]. If we consider the state of the system at any instant of time t is defined by a configurational state vector, $\vec{X}(t) = [X_1(t), X_2(t), \dots, X_N(t)]^T$, where N distinct molecular species are interacting via M elementary reaction channels in the system of the following type,



where, μ is the reaction number index: $\mu=1, \dots, N$, $a_{i\mu}$ and $b_{i\mu}$ are coefficient to define stoichiometric matrix $v_{i\mu} = (a_{i\mu} - b_{i\mu})$, and k_μ is the μ th macroscopic rate of reaction. The system evolves with various random reaction fired at random interval of time with decay or/and creation of particle/molecular species at any reaction event [1,18,19,25] which leads to the change in configurational state of the system. This allows to define a configurational probability $P(\vec{X};t)$ as the probability to get this state change in an interval of time $[t, t+\Delta t]$. Then the time evolution of configurational probability $P(\vec{X};t)$ obeys Chemical Master equation (ME) [1,18,19] given by,

$$\frac{\partial P(\vec{X};t)}{\partial t} = -\sum_{\vec{X}'} P(\vec{X};t) W_{\vec{X} \rightarrow \vec{X}'} + \sum_{\vec{X}'} P(\vec{X}';t) W_{\vec{X}' \rightarrow \vec{X}} \quad (2)$$

Where, $\{W\}$ are transition probabilities to jump from one state, \vec{X} of the molecular system to another state, \vec{X}' during the time interval $[t, t+\Delta t]$. The ME in general provides detail stochastic description of chemical kinetics, but it is very difficult to solve for complex systems [19].

The chemical Langevin equation (CLE) formalism is one method to approximate ME to simpler continuous Markov type equations by keeping conditions which are applicable in natural systems [20], and the accuracy of this CLE is found to be more than those of other formalisms such as linear noise approximation [26]. The approximation can be done by allowing to define a function $Q(\vec{X}, \Delta t)$ as the number of a particular reaction fired during an interval of time $[t, t+\Delta t]$ with $\Delta t > 0$. This is followed by excellent approximations by imposing two conditions, firstly, imposing small Δt limit such that the values of propensity functions $\omega[\vec{X}(t)]$ of the reactions remain constant during $[t, t+\Delta t]$, and secondly imposing large Δt limit which in turn leads to $\omega[\vec{X}(t)]\Delta t \gg 1$. These two conditions allow Q to approximate to statistically independent Poisson random variable and then the Poisson random variable is replaced by normal variable with the same mean and variance. Both the conditions are true in natural practice for large population limit. Then linearizing the normal variable, and defining macroscopic molecular concentration vector, $\left\{ \vec{x}(t) \right\} = \frac{1}{V} \vec{X}(t)$, where V is the systems size, we have general CLE,

$$\frac{d\vec{x}_i^s(t)}{dt} = F_i^s[\omega(\vec{x}^s), v] + G_i[\omega(\vec{x}^s), v, V] \xi \quad (3)$$

where, $F_i^s = \sum_{j=1}^M v_{ij} \omega_j \{ \vec{x}^s(t) \}$ $i=1, 2, \dots, N$ is the macroscopic contribution term and $G_i = \frac{1}{\sqrt{V}} \sum_{j=1}^M v_{ij} \left[\dot{u}_i \{ \vec{x}^s(t) \} \right]^{1/2}$ is the stochastic

contribution term to the dynamics. $\xi_i = \lim_{dt \rightarrow 0} N_i(0,1)/\sqrt{dt}$ is uncorrelated, statistically independent random noise parameters which satisfy $\xi_i(t) \xi_j(t') = \delta_{ij} \delta(t-t')$. The stochastic CLE (2) will become deterministic equation when $\xi \rightarrow 0$, and equation (2) becomes,

$$\frac{d\vec{x}_i^d(t)}{dt} = F_i^s[\omega(\vec{x}^d), v] \quad (4)$$

where, $F_i^s = \sum_{j=1}^M v_{ij} \omega_j \{ \vec{x}^d(t) \}$ is the deterministic function. If the stochastic and deterministic variables obtained from equations (3) and (4) are given by, $\vec{x}^s(t) = [\vec{x}_1^s(t), \vec{x}_2^s(t), \dots, \vec{x}_N^s(t)]^T$ and $\vec{x}^d(t) = [\vec{x}_1^d(t), \vec{x}_2^d(t), \dots, \vec{x}_N^d(t)]^T$ respectively then the noise parameter can be defined by $\vec{\eta}_i(t) = \vec{x}_i^s(t) - U_i \vec{x}_i^d(t)$, where $\vec{U} = [U_1(\vec{x}^d), U_2(\vec{x}^d), \dots, U_N(\vec{x}^d)]^T$. The reason could be the stochastic variables are noise-induced variables, whereas deterministic variables are approximately noise free variables and non-linearity of both the CLE and deterministic equations. The time evolution of $\vec{\eta}_i(t)$ can be expressed by,

$$\begin{aligned} \frac{d\vec{\eta}_i(t)}{dt} &= [F_i^s \{ \omega(\vec{x}^s), v \} - U_i F_i^d \{ \omega(\vec{x}^d), v \}] + \\ G_i[\omega(\vec{x}^s), v, V] \xi - \vec{x}_i^d \frac{dU_i}{dt} \end{aligned} \quad (5)$$

The dynamics of $\vec{\eta}_i(t)$ could be different for different stochastic systems and dependent on various parameters such as \vec{x}^s , V , ξ etc. The role of intrinsic noise in stochastic system could be different depending on the nature of interaction of the molecular species, network topology and system size. The steady state solution in $\vec{M}, \vec{S}, \vec{M}, \vec{Q}$ can be obtained from equation (5) as,

$$\begin{aligned} F_i^{*s}[\omega(\vec{x}^{*s}), v] &= U_i F_i^d[\omega(\vec{x}^{*d}), v] - \\ G_i[\omega(\vec{x}^{*s}), v, V] &+ \vec{x}_i^d \frac{dU_i}{dt} \end{aligned}$$

where, $F_i^{*s}, F_i^d, \vec{x}^{*s}$ and \vec{x}^{*d} are steady state solutions. If \vec{U} is found to be constant then \vec{x}^{*d} in stochastic CLE is proportional to the corresponding \vec{x}^{*d} in deterministic system.

We used standard stochastic simulation algorithm due to Gillespie [1] to simulate the biochemical reaction network model of stochastic system. The algorithm systematically takes into account each and every reaction events to allow transitions from one state to another along the trajectory of the variables by defining a joint probability density function $\Omega(\tau, \mu) = \Pi(\tau) \chi(\mu)$. The reaction time and reaction number fired at that time can be estimated computationally by generating two uniform independent random numbers r_1 and r_2 to identify τ by

$$\tau = \frac{1}{\sum_i \omega_i} \ln \left[\frac{1}{r_1} \right] \text{ and reaction number } \mu \text{ by } f_\mu = r_2 \sum_i \omega_i \text{ by imposing}$$

the relation $\sum_{i=1}^\mu \omega_i \leq f_\mu < \sum_{i=1}^{\mu+1} \omega_i$. Incorporating these two random numbers corresponding to the probabilities of finding reaction time and reaction number fired, the algorithm systematically calculate the state vector as a function of reaction time and one can find the temporal trajectory of the state vector.

The system size in the SSA can be associated by $V = \frac{\bar{V}}{N_A}$, where

N_A is Avogadro's number and \bar{V} is average system size. The factor V is incorporated in the SSA from the relation which connect microscopic transition rate or propensity function (c_{ij}) with macroscopic rate constant (k_{ij}), $c_{ij} = k_{ij} V^{1-\nu_{ij}}$ [1,27].

Results and Discussion

We study two stochastic models, namely genetic and chemical oscillators in which the roles of noise could be contrast. We concentrate mainly on the role of the noise in these oscillators by implementing the methods describe above and its dependence on various parameters. We then present numerical results using stochastic simulation algorithm.

Genetic oscillator

We use the minimal reaction model of Vilar et al. [28] based on the auto regulation of the two genes, an activator of A protein and a repressor of R protein: A acts as positive regulator binding to A promoter and R to increase their transcription rate, whereas R acts as negative regulator by sequestering A [28,29]. The regulatory mechanisms of A and R incorporate activator genes, D_a' and D_a and repressor genes, D_r' and D_r , which involves mRNA of A and R, M_a and M_r . C corresponds to the inactivated complex formed by A and R. The detail description of the biochemical reaction network is given in Table 1. This genetic oscillator model could able to generate 24 hour period of oscillation in A and R proteins and therefore can be taken as circadian clock.

The trajectory of the population variables involve in the genetic oscillator model as a function of time can be traced by identifying the state vector $\vec{X}(t) = [X_1, X_2, \dots, X_9]^T$ at any instant of time t. where, $X_1 = D_a'$, $X_2 = D_r'$, $X_3 = D_a$, $X_4 = D_r$, $X_5 = M_a$, $X_6 = M_r$, $X_7 = C$, $X_8 = A$, $X_9 = R$. The Master equation of the model based on the reaction network given in Table 1 is given by,

$$\begin{aligned} \frac{\partial P(D_a', D_a, \dots, R; t)}{\partial t} = & \theta_a (D_a' + 1) P(D_a - 1, D_a' + 1, \dots, t) + \gamma_a (D_a + 1) (A + 1) \\ & P(D_a + 1, D_a' - 1, A + 1, \dots, t) + \theta_r (D_r' + 1) P(D_r - 1, D_r' + 1, \dots, t) + \\ & \gamma_r (D_r + 1) (A + 1) P(D_r + 1, D_r' - 1, A + 1, \dots, t) + \\ & \alpha_r D_r' P(M_r - 1, \dots, t) + \alpha_r D_r P(M_r - 1, \dots, t) + \delta_{mr} (M_r + 1) \\ & P(M_r + 1, \dots, t) + \alpha_a' D_a' P(M_a - 1, \dots, t) + \alpha_a D_a P(M_a - 1, \dots, t) \\ & + \delta_{ma} (M_a + 1) P(M_a + 1, \dots, t) + \beta_r M_r P(R - 1, \dots, t) + \\ & \delta_r (R + 1) P(\dots, R + 1; t) + \delta_a (C + 1) P(\dots, C + 1, R - 1; t) \\ & + \beta_a M_a P(A - 1, \dots, t) + \theta_a D_a' P(A - 1, \dots, t) + \theta_r D_r' P(A - 1, \dots, t) \\ & + \delta_a (A + 1) P(A + 1, \dots, t) + \gamma_c (R + 1) (A + 1) P(\dots, R + 1, A + 1, C - 1; t) - \\ & (\theta_a D_a' + \gamma_a D_a A + \theta_r D_r' + \gamma_r D_r A + \alpha_r D_r' + \alpha_r D_r + \delta_{mr} M_r + \\ & \alpha_a' D_a' + \alpha_a D_a + \delta_{ma} M_a + \beta_r M_r + \delta_r R + \delta_a C \\ & + \beta_a M_a + \theta_a D_a' + \theta_r D_r' + \delta_a A + \gamma_c R A) P(D_a', D_a, \dots, R; t) \end{aligned} \quad (6)$$

The microscopic variables are connected to macroscopic variables via $\{\vec{x}(t)\} = \frac{1}{V} \vec{X}(t)$. This Master equation of the genetic oscillator model can be reduced to a set of CLE and can be obtained following

S. No.	Reactions	Description of the reactions	Transition rate	Rate constant values
1.	$D_a' \xrightarrow{\theta_a} D_a$	Conversion of activator genes with A to activator genes without A .	$\omega_1 = \theta_a D_a'$	$\alpha_a = 50$
2.	$A + D_a \xrightarrow{\gamma_a} D_a'$	Activation of activator gene without A to form activator gene with A .	$\omega_2 = \gamma_a \frac{AD_a}{V}$	$\alpha_a' = 500$
3.	$D_r' \xrightarrow{\theta_r} D_r$	Conversion of repressor promoter with R to repressor promoter without R .	$\omega_3 = \theta_r D_r'$	$\alpha_r = 0.01$
4.	$A + D_r \xrightarrow{\gamma_r} D_r'$	Activation of repressor promoter without R to form repressor promoter with R .	$\omega_4 = \gamma_r \frac{AD_r}{V}$	$\alpha_r' = 50$
5.	$\emptyset \xrightarrow{\alpha_a'} D_a' M_a$	Creation of mRNA of activator gene A activated by activator gene with A .	$\omega_5 = \alpha_a' D_a'$	$\beta_a = 50$
6.	$\emptyset \xrightarrow{\alpha_a} D_a M_a$	Creation of mRNA of activator gene A activated by activator gene without A .	$\omega_6 = \alpha_a D_a$	$\beta_r = 5$
7.	$M_a \xrightarrow{\delta_a} \emptyset$	Degradation of mRNA of activator gene A .	$\omega_7 = \delta_a M_a$	$\delta_{MA} = 10$
8.	$\emptyset \xrightarrow{\alpha_r'} D_r' M_r$	Creation of mRNA of repressor promoter R activated by repressor promoter with R .	$\omega_8 = \alpha_r' D_r'$	$\delta_{MR} = 0.5$
9.	$\emptyset \xrightarrow{\alpha_r} D_r M_r$	Creation of mRNA of repressor promoter R activated by repressor promoter without R .	$\omega_9 = \alpha_r D_r$	$\delta_a = 1$
10.	$M_r \xrightarrow{\delta_r} \emptyset$	Degradation of mRNA of repressor promoter R .	$\omega_{10} = \delta_r M_r$	$\delta_r = 0.2$
11.	$\emptyset \xrightarrow{\beta_r} M_r R$	Creation of repressor promoter R induced by mRNA of repressor promoter R .	$\omega_{11} = \beta_r M_r$	$\gamma_a = 1$
12.	$R \xrightarrow{\delta_r} \emptyset$	Degradation of repressor promoter R .	$\omega_{12} = \delta_r R$	$\gamma_r = 1$
13.	$C \xrightarrow{\delta_c} \emptyset$	Creation of repressor promoter R by R .	$\omega_{13} = \delta_c C$	$\gamma_c = 2$
14.	$\emptyset \xrightarrow{\beta_a} M_a A$	Creation of activator gene A induced by mRNA of activator gene A .	$\omega_{14} = \beta_a M_a$	$\theta_a = 50$
15.	$\emptyset \xrightarrow{\theta_a} D_a' A$	Creation of activator gene A induced by D_a' .	$\omega_{15} = \theta_a D_a'$	$\theta_r = 100$
16.	$\emptyset \xrightarrow{\theta_r} D_r' A$	Creation of activator gene A induced by D_r' .	$\omega_{16} = \theta_r D_r'$	
17.	$A \xrightarrow{\delta_a} \emptyset$	Degradation of activator gene A .	$\omega_{17} = \delta_a A$	
18.	$A + D_r \xrightarrow{\gamma_c} AR C$	Activation of activator gene A to form complex C with D_r .	$\omega_{18} = \gamma_c AR$	

Table 1: The biochemical reaction network of genetic oscillator, description of the reactions, transition rates and values of the rate constants used in the simulation [27].

Gillespie's approach [19] as given below,

$$\frac{dx_1(t)}{dt} = \theta_a x_2 - \gamma_a x_1 x_8 + \frac{1}{\sqrt{V}} \left[\sqrt{\theta_a x_2 \xi_1} - \sqrt{\gamma_a x_1 x_8 \xi_2} \right] \quad (7)$$

$$\frac{dx_2(t)}{dt} = \gamma_a x_1 x_8 - \theta_a x_1 + \frac{1}{\sqrt{V}} \left[\sqrt{\gamma_a x_1 x_8 \xi_3} - \sqrt{\theta_a x_2 \xi_4} \right] \quad (8)$$

$$\frac{dx_3(t)}{dt} = \theta_R x_4 - \gamma_R x_3 x_8 + \frac{1}{\sqrt{V}} \left[\sqrt{\theta_R x_4 \xi_5} - \sqrt{\gamma_R x_3 x_8 \xi_6} \right] z \quad (9)$$

$$\frac{dx_4(t)}{dt} = \gamma_R x_3 x_8 - \theta_R x_4 + \frac{1}{\sqrt{V}} \left[\sqrt{\gamma_R x_3 x_8 \xi_7} - \sqrt{\theta_R x_4 \xi_8} \right] \quad (10)$$

$$\frac{dx_5(t)}{dt} = \alpha'_A x_2 + \alpha_A x_1 - \delta_{MA} x_5 + \frac{1}{\sqrt{V}} \left[\sqrt{\alpha'_A x_2 \xi_9} + \sqrt{\alpha_A x_1 \xi_{10}} - \sqrt{\delta_{MA} x_5 \xi_{11}} \right] \quad (11)$$

$$\frac{dx_6(t)}{dt} = \alpha'_R x_4 + \alpha_R x_3 - \delta_{MR} x_6 + \frac{1}{\sqrt{V}} \left[\sqrt{\alpha'_R x_4 \xi_{12}} + \sqrt{\alpha_R x_3 \xi_{13}} - \sqrt{\delta_{MR} x_6 \xi_{14}} \right] \quad (12)$$

$$\frac{dx_7(t)}{dt} = \gamma_C x_8 x_9 - \delta_A x_7 + \frac{1}{\sqrt{V}} \left[\sqrt{\gamma_C x_8 x_9 \xi_{15}} - \sqrt{\delta_A x_7 \xi_{16}} \right] \quad (13)$$

$$\frac{dx_8(t)}{dt} = \beta_A x_5 + \theta_A x_2 + \theta_R x_4 - x_8 (\gamma_A x_1 + \gamma_R x_3 + \gamma_C x_9 + \gamma_C x_9) \quad (14)$$

$$+ \frac{1}{\sqrt{V}} \left[\sqrt{\beta_A x_5 \xi_{17}} + \sqrt{\theta_A x_2 \xi_{18}} + \sqrt{\theta_R x_4 \xi_{19}} - \sqrt{\gamma_A x_1 x_8 \xi_{20}} - \sqrt{\gamma_R x_3 x_8 \xi_{21}} - \sqrt{\gamma_C x_9 x_8 \xi_{22}} - \sqrt{\gamma_C x_9 x_8 \xi_{23}} \right]$$

$$\frac{dx_9(t)}{dt} = \beta_R x_6 - \gamma_C x_8 x_9 + \delta_A x_7 - \delta_R x_9 + \frac{1}{\sqrt{V}} \left[\sqrt{\beta_R x_6 \xi_{24}} - \sqrt{\gamma_C x_8 x_9 \xi_{25}} + \sqrt{\delta_A x_7 \xi_{26}} - \sqrt{\delta_R x_9 \xi_{27}} \right] \quad (15)$$

where, V is the systems size. The constraints to be satisfied by the activator and repressor genes are given by, $x_1 + x_2 = 1$ and $x_3 + x_4 = 1$. The CLEs reduce to deterministic equations when $V \rightarrow \infty, \xi_i \rightarrow 0$, and noise term in stochastic system described by CLEs is proportional to $V^{-1/2}$. The steady state solutions of the CLEs can be obtained by imposing the condition, $\left\{ \frac{dx_i(t)}{dt} \right\} = 0, i = 1, 2, \dots, 9$. For deterministic equations the steady state solutions for x_7^{*d}, x_8^{*d} and x_9^{*d} and are given by,

$$x_7^{*d} \sim \frac{\gamma_R \gamma_C \beta_R \alpha'_R v^2}{\delta_A \delta_R \delta_{MR} \varphi^2} \frac{\left(1 + \frac{\varphi u}{v^2}\right)^2}{\theta_R + \frac{\gamma_R v}{\varphi} \left(1 + \frac{\varphi u}{v^2}\right)} \quad (16)$$

$$x_9^{*d} \sim \frac{v}{\varphi} \left(1 + \frac{\varphi u}{v^2}\right) \quad (17)$$

$$x_9^{*d} \sim \frac{\beta_R}{\delta_R \delta_{MR}} \left[\frac{\frac{\gamma_R \alpha'_R v}{\varphi} \left(1 + \frac{\varphi u}{v^2}\right)}{\theta_R + \frac{\gamma_R v}{\varphi} \left(1 + \frac{\varphi u}{v^2}\right)} + \frac{\theta_R \alpha_R}{\theta_R + \frac{\gamma_R v}{\varphi} \left(1 + \frac{\varphi u}{v^2}\right)} \right] \quad (18)$$

$$\text{Where, } u = \frac{\beta_A \theta_A (\alpha_A - \alpha'_A)}{\gamma_A \delta_{MA}} - \frac{\gamma_C \beta_R \theta_R^2 (\alpha'_R - \alpha_R)}{\delta_R \delta_{MR} \gamma_R^2},$$

$$v = \frac{\beta_A \alpha'_A}{\delta_{MA}} + \frac{\gamma_C \beta_R \theta_R (\alpha'_R - \alpha_R)}{\delta_R \delta_{MR} \gamma_R}$$

and $\varphi = \delta_A + \frac{\gamma_C \beta_R \alpha'_R}{\delta_R \delta_{MR}}$ are constants. The above steady state

solutions are obtained by taking terms upto of the order of A^{-2} and keeping the condition, discriminant ≥ 0 which gives the condition:

$$\alpha'_A - \alpha_A \leq \frac{q^2}{g^2 p},$$

$$\text{where, } p = \varphi \frac{\beta_A \theta_A}{\gamma_A \delta_{MA}}, \quad q = \varphi \frac{\gamma_C \beta_R \theta_R^2}{\delta_R \delta_{MR} \gamma_R^2}$$

$$\text{and } g = \frac{\gamma_C \beta_R \theta_R}{\delta_R \delta_{MR} \gamma_R}.$$

Now the steady state solutions x_7^{*s}, x_8^{*s} and x_9^{*s} in stochastic system can be obtained by solving the CLEs in equations (7)-(15) and keeping terms upto of the order of $[x_7^{*s}]^{-2}$. The results are given by,

$$x_7^{*s}(x_7^{*d}, V, \xi_1) \sim U_1 x_7^{*d} \left[1 + \frac{\xi_1}{\sqrt{V}} \left(\frac{\Gamma + \Lambda}{x_8^{*d} x_9^{*d}} \right) \right] \quad (19)$$

$$x_8^{*s}(x_8^{*d}, V, \xi_2) \sim U_2 x_8^{*d} \left[1 - \frac{\xi_2}{\sqrt{V}} \Lambda \right] \quad (20)$$

$$x_9^{*s}(x_9^{*d}, V, \xi_3) \sim U_3 x_9^{*d} + \frac{3}{\sqrt{V}} \Gamma \quad (21)$$

Where, $\{\xi_i\}$ of the terms involved in deriving certain equation are taken to be the same to simplify the expression. The vector \vec{U} is found to be $\vec{U} = [U_1, U_2, U_3]^T = \left[6, \frac{8}{5}, \frac{7}{2} \right]^T$. The constant expressions Λ and Γ are given by,

$$\Lambda = \frac{I + \frac{vH}{\varphi} + \varphi J - uH - \frac{u\varphi I}{v}}{v^2 + \varphi u} \quad (22)$$

$$\Gamma = \frac{\beta_R}{\delta_R \delta_{MR}} \left[\alpha'_R + \sqrt{\frac{\alpha_R \theta_R}{\frac{v \gamma_R}{\varphi} \left(1 + \frac{\varphi u}{v^2}\right)}} + \frac{\alpha'_R \sqrt{\theta_R}}{\frac{v \gamma_R}{\varphi} \left(1 + \frac{\varphi u}{v^2}\right)} + \sqrt{V} \frac{\alpha'_R}{\delta_R} \sqrt{\frac{\beta_R}{\delta_{MR}}} \right] \quad (23)$$

And,

$$H = \frac{\gamma_C \beta_R}{\delta_R \delta_{MR}} \sqrt{\alpha'_R} + \sqrt{V} \frac{\delta_R \alpha'_R \sqrt{\beta_R}}{\delta_R \delta_{MR}} \quad (24)$$

S. No.	Reactions	Transition rate	Rate constant values
1.	$D_a \xrightarrow{\theta_a} D_a$	$\omega_1 = \theta_a D_a$	4×10^{-3}
2.	$X + Y \xrightarrow{k_2} B$	$\omega_2 = k_2 \frac{XY}{V}$	0.1
3.	$C + X \xrightarrow{k_3} 2X + Z$	$\omega_3 = k_3 CX$	1.04×10^{-2}
4.	$2X \xrightarrow{k_4} D$	$\omega_4 = k_4 \frac{1}{2V} X(X-1)$	1.6×10^{-2}
5.	$E + Z \xrightarrow{k_5} Y$	$\omega_5 = k_5 EZ$	1.3×10^{-2}

Table 2: The biochemical reaction channels involved in chemical oscillator (oregonator), microscopic transition rates and the values of the macroscopic rate constants used in our simulations in both deterministic and stochastic systems.

$$I = \sqrt{\alpha'_R} + \sqrt{\frac{\beta'_R \alpha'_R}{\delta_{MR}}} + \frac{\gamma_C \beta'_R \theta'_R \sqrt{\alpha'_R}}{2\delta_R \delta_{MR} \gamma_R} - \frac{\gamma_C \beta'_R \theta'_R (\alpha'_R - \alpha_R)}{\delta_R \delta_{MR} \gamma_R} + \frac{\gamma_C \theta'_R (\alpha'_R - \alpha_R)}{\delta_R \gamma_R} \sqrt{\frac{\beta'_R}{\delta_{MR}}} \quad (25)$$

$$J = \frac{\theta_A \sqrt{\alpha'_A}}{2\gamma_A} + \sqrt{\frac{\beta'_A \alpha'_A}{\delta_{MA}}} \frac{\theta_A (\alpha'_A - \alpha_A)}{2\gamma_A} - \frac{\theta_A (\alpha'_A - \alpha_A)}{\gamma_A} - \frac{\gamma_C \beta'_R \theta'^2_R (\alpha'_R - \alpha_R)}{2\delta_R \delta_{MR} \gamma'^2_R} \quad (26)$$

The noise terms in steady state solutions in equations (19), (20) and (21) are dependent on deterministic steady state solutions, V and ξ .

Chemical oscillator

The chemical oscillator model known as oregonator was devised by Field and Noyes [30] based on the criticism made by Tyson and Light [31] on the original Brusselator model which is two molecular species reaction model. The modified chemical oscillator model consists of three molecular species, X, Y and Z involved in the following five reaction channels which are given in the Table 2 with reaction rates.

The state vector at any instant of time t along the stochastic trajectories of the variables of the oregonator reaction model is given by, $\vec{S}(t) = [X(t), Y(t), Z(t)]^T$. Following the same procedure, the Master equation of this reaction model is given by,

$$\begin{aligned} \frac{\partial P(\vec{S}, t)}{\partial t} = & k_1 A(Y+1)P(X-1, Y+1, Z; t) + \\ & k_2 (X+1)(Y+1)P(X+1, Y+1, Z; t) \\ & + k_3 C(X-1)P(X-1, Y, Z-1; t) + \\ & \frac{1}{2} k_4 X(X+1)P(X+1, Y, Z; t) \\ & + k_5 E(Z+1)P(X, Y-1, Z+1; t) - \left[k_1 AY + k_2 XY + \right. \\ & \left. k_3 CX + \frac{1}{2} k_4 X^2 + k_5 EZ \right] P(X, Y, Z; t) \end{aligned} \quad (27)$$

where, $\{k_i\}$, $i = 1, 2, \dots, 5$ are reaction rate constants and A, B, C, D and E are constants in this model. The corresponding CLE of the oregonator model by approximating Master equation (27) and defining

macroscopic variable $\{\bar{x}(t)\} = \frac{1}{V} \bar{S}(t)$ are given by,

$$\frac{dx(t)}{dt} = k_1 Ay - k_2 xy + k_3 Cx - k_4 x^2 + \frac{1}{\sqrt{V}} \left[\sqrt{k_1 Ay} \xi_1 - \sqrt{k_2 xy} \xi_2 + \sqrt{k_3 Cx} \xi_3 - \sqrt{k_4 x^2} \xi_4 \right] \quad (28)$$

$$\frac{dy(t)}{dt} = -k_1 Ay - k_2 xy + k_5 Ez - \frac{1}{\sqrt{V}} \left[\sqrt{k_1 Ay} \xi_5 + \sqrt{k_2 xy} \xi_6 - \sqrt{k_5 Ez} \xi_7 \right] \quad (29)$$

$$\frac{dz(t)}{dt} = k_3 Cx - k_5 Ez + \frac{1}{\sqrt{V}} \left[\sqrt{k_3 Cx} \xi_8 - \sqrt{k_5 Ez} \xi_9 \right] \quad (30)$$

Proceeding in the same way as done in the genetic oscillator case, we calculated the deterministic steady state solutions ($\{\xi\} \rightarrow 0$) which are given by,

$$x_d^* = \frac{Ak_1}{2k_2} \left(\sqrt{1 + \frac{8Ck_2k_3}{Ak_1k_4}} - 1 \right) \quad (31)$$

$$y_d^* = \frac{Ak_1k_4}{4k_2^2} \left(\frac{4Ck_2k_3}{Ak_1k_4} - \sqrt{1 + \frac{8Ck_2k_3}{Ak_1k_4}} \right) \quad (32)$$

$$z_d^* = \frac{ACk_1k_3}{2Ek_2k_5} \left(\sqrt{1 + \frac{8Ck_2k_3}{Ak_1k_4}} - 1 \right) \quad (33)$$

Similarly the steady state solutions in stochastic system are obtained by solving the CLEs (28)-(30) in the same way and are given by,

$$x_s^*(x_d^*, \xi'_1, V) \sim U_1 x_d^* \left(1 + \frac{\xi'_1}{\sqrt{V}} L \right) \quad (34)$$

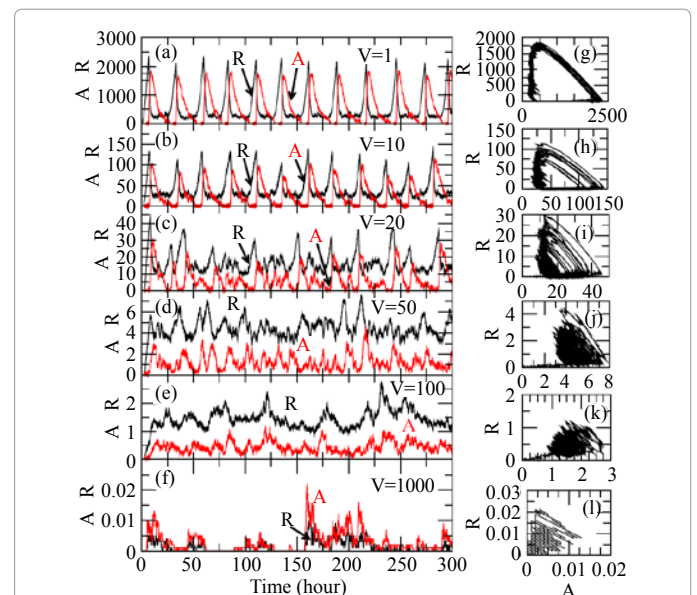


Figure 1: The plots of the dynamics of protein concentrations A and R for different values of system size, V=1, 20, 50, 100 and 1000 respectively. The parameter values are taken from Vilar et al. [3] for fixed point oscillation. Panels (a), (b), (c), (d), (e) and (f) show the variations of concentrations of A and R as a function of time in hours for various values of V. Panels (g), (h), (i), (j), (k) and (l) are two dimensional plots of A as a function of R for corresponding values of V.

$$y_s^*(y_d^*, \xi_2^*, V) \sim U_2 y_d^* \left[1 + \frac{\xi_2^*}{\sqrt{V}} \left(\frac{1}{2} L + \frac{1}{9 x_d^*} \sqrt{\frac{k_4}{V}} \right) \right] \quad (35)$$

$$z_s^*(z_d^*, \xi_3^*, V) \sim U_3 z_d^* \left[1 + \frac{\xi_3^*}{\sqrt{V}} \left(L + \frac{1}{\sqrt{3 C k_3 x_d^*}} \right) \right] \quad (36)$$

where, the vector of proportionality constants for this oregonator model is given by, $\vec{U} = (U_1, U_2, U_3)^T = \left(3, 18, \frac{3}{2} \right)^T$. The constant L is given by, $L = \frac{1 + e x_d^*}{f} - \frac{r}{1 + e x_d^*}$, where f , e and r are also constants given by, $f = 6\sqrt{k_4}$, $e = \frac{2k_2}{A k_1}$ and $r = \frac{8 C k_2 k_3}{9 A k_1 k_4} \left(\frac{\sqrt{k_4}}{2 C k_3} + \frac{2 k_2}{3 A k_1 \sqrt{k_4}} \right)$.

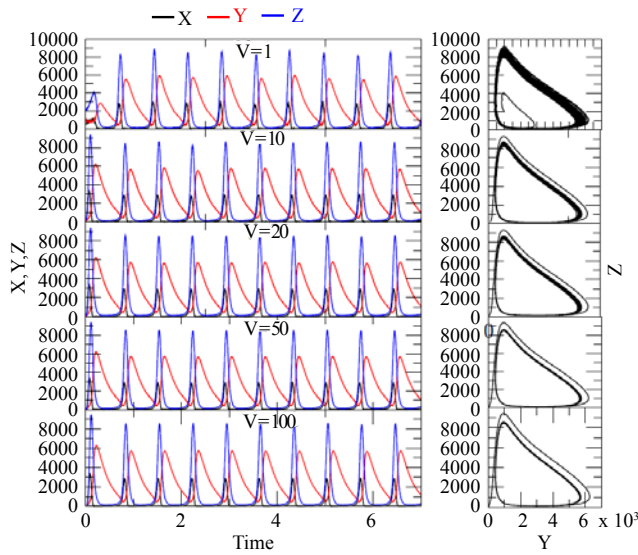


Figure 2: The plots of time evolution of the populations of X, Y and Z for various values of system sizes, $V=1, 10, 20, 50, 100$. The right panels are corresponding two dimensional plots of the dynamical behaviors.

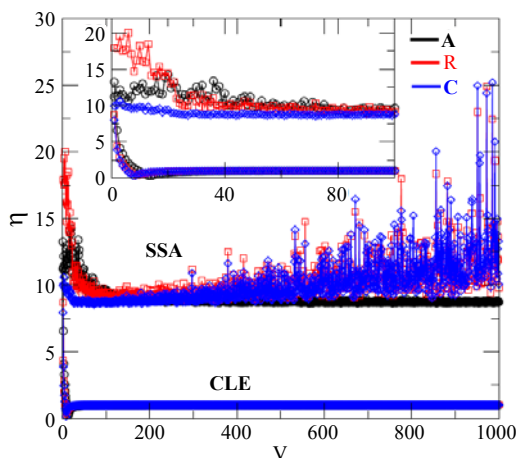


Figure 3: The variation of noise parameter η as a function of V in genetic oscillator model calculated by using stochastic simulation algorithm indicated by SSA and using chemical Langevin equations indicated by CLE for A, R and C respectively.

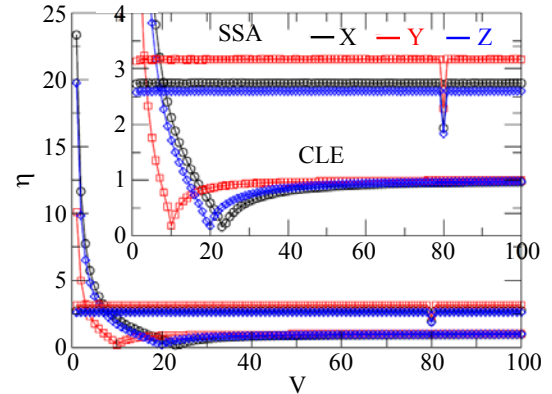


Figure 4: The plots of noise parameter η as a function of V for species X, Y and Z in chemical oscillator calculated by stochastic simulation algorithm and chemical Langevin equation indicated by SSA and CLE respectively.

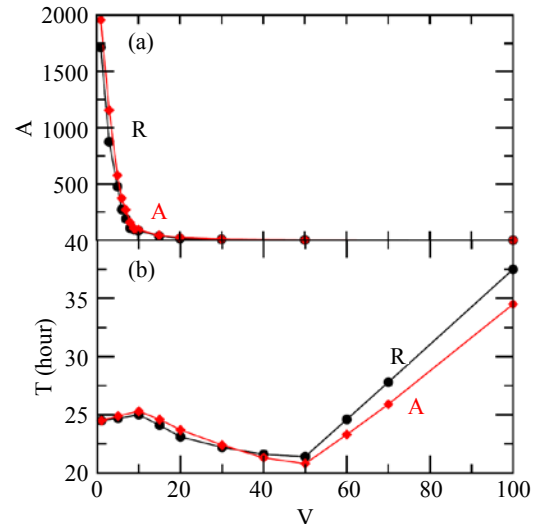


Figure 5: (a) The plot of amplitude A_c as a function of V for A and R. (b) Plot showing the variation of time period T of A and R with respect to V .

The two examples studied before indicate that $\vec{U} \sim \text{constant}$ for steady state solutions with approximations upto of the order of $O(\xi^2)$. This could lead the CLE in equation (3) and dynamics of noise in equation (5) to the following expression,

$$\frac{d\vec{x}_i^s(t)}{dt} \sim U_i F_i^d[\omega(\vec{x}^d), v] + G_i[\omega(\vec{x}^s), v, V] \xi \quad (37)$$

$$\frac{d\vec{\eta}_i(t)}{dt} \sim G_i[\omega(\vec{x}^s), v, V] \xi \quad (38)$$

We now present the stochastic simulation results of the biochemical reaction network of genetic oscillator for different values of system sizes, V by using SSA [1] and are shown in Figure 1. The results show that as V increases the fluctuation due to noise in the dynamics of A and R increases comparatively as shown in the figure. The populations of A and R reduce monotonically and the oscillatory behavior start vanishing as V increases as shown in panels Figure 1 (a)-(f). The panels Figure 1 (g)-(l) show the two dimensional plots of A and R indicate the loosing of oscillatory behavior as V increases as the system goes from stochastic

to deterministic regime, which is in agreement with earlier results [28]. We could see the drastic decrease in amplitude, destruction of 24 hour period and comparative increase in noise fluctuation as V increases. The dynamics of the variables tend to maintain least fluctuated sustain oscillation as V decreases ($V \leq 13 \pm 3$), above this the oscillatory behavior start getting destroyed and get transition from fluctuated to limit cycle oscillation to no oscillation regime as $V \rightarrow \infty$.

Similar results of temporal dynamics of X , Y and Z as a function of V for chemical oscillator which are shown in Figure 2. The left panels show the decrease in fluctuation in amplitude of oscillation of the variables and thickness in 2D plots in right panels of Figure 2 as V increases. The noise fluctuation becomes minimized around $V \sim 50 \pm 5$ and the oscillatory behavior goes to minimized limit cycle oscillation as shown in 2D plots in the right panels of Figure 2.

We next estimate the noise in the variable dynamics as a function of V by using the expression $\eta = \frac{\sigma}{m}$, where $m = \langle X_i \rangle$, $\{X_i\} = \{A, R, C, X, Y, Z\}$, is the mean with $\langle \dots \rangle$ as time average and $\sigma = \sqrt{\langle X_i^2 \rangle - \langle X_i \rangle^2}$, is the standard deviation. We calculated η for stochastic dynamics obtained by both SSA and CLE and time averaging between (50-300) hours which are shown in Figure 3 for genetic oscillator and Figure 4 for chemical oscillator respectively. In the genetic oscillator case, η for A , R and C in SSA are found to be decreased as V increases in the interval (1-145) hours, however η for R and C start increasing as a function of V for $V > 145$ hours, but η for A remains almost constant. This behavior of noise might help in maintaining oscillatory behavior in stochastic regime. However, in the case of CLE, η decreases as V increases till $V \sim 8, 10$ and 12 hours for C, R and A respectively; then η remains constant as V increases. The η s calculated using SSA for all variables are found to be larger than those calculated using CLE.

Similar calculation of η for chemical oscillator is done and the results are shown in Figure 4. The results of s of X, Y and Z due to SSA shows slow decrease in η as a function of V ($1 < V < 50$) then remain constant. The magnitude of η for Y is largest and that of Z is smallest. The η calculated using CLE for all variables are found to be smaller than those of the calculated using SSA.

The enormously decrease in amplitude of A and R are shown in Figure 5 (i). At the same time destruction of 24 hour period of oscillation of A and R as the function of V is shown in Figure 5 (ii). We also obtain that for large V ($V > 13 \pm 3$) the amplitudes become getting small and random in nature. However the time period becomes getting large and random in nature for large V ($V > 13 \pm 3$). This shows the destruction of rhythmic behavior for large V . The reason may be due to the noise which could able to maintain the rhythmic behavior in the dynamics of A and R in stochastic system.

The results of amplitudes and period of oscillations for X, Y and Z are different for chemical oscillator as shown in Figure 6. The amplitudes of these variables X, Y and Z found to slowly increasing till $V \leq 50 \pm 4$, then these amplitudes found to remain constant for $V > 50$. The time periods of these variables X (~ 0.51), Y (~ 0.48) and Z (~ 0.49) are found to be not much vary with V , but increase slowly till $V \leq 50 \pm 4$ and remain constant for $V > 50$.

The destructing or maintaining oscillatory behaviors of the variables as a function of system size could be mainly due to noise associated with the variables. The noise associated with the variables in genetic oscillator is found to be constructive in small system size limit (stochastic regime) which could maintain oscillatory behavior and destruct this oscillatory pattern at large system size limit (deterministic regime). The transition from fluctuated limit cycle limit to no oscillation limit as $V \rightarrow \infty$ supports this claim in genetic oscillator model.

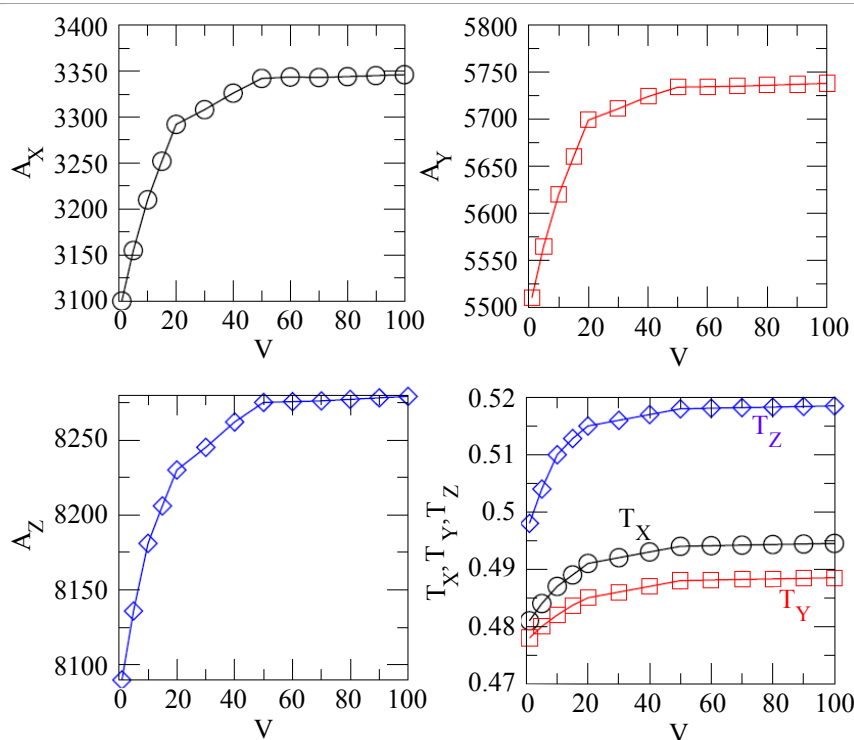


Figure 6: (a) The plot of amplitude A_c as a function of V for A and R . (b) Plot showing the variation of time period T of A and R with respect to V .

The opposite function of noise, as we found in genetic oscillator, is obtained in chemical oscillator case supported by the transition from fluctuated limit cycle to normal (minimized fluctuations) limit cycle (sustain oscillation) as $V \rightarrow \infty$. This shows that the role of noise depends on different factors, for example topology of the network, the way how the molecules interact in the network, system size, strength of the noise associated with the variables etc.

Conclusion

The calculation of steady state solutions of the noise free functions of all variables in CLE is found to be proportional to the deterministic steady state solutions. The function \bar{U} is found to be constant in the two oscillators but with different values. The noise term in CLE is comparatively small as compared to that in Master equation.

The behavior of noise is found to be different in different systems and depends on various parameters such as topology of the network, system size etc. The noise in genetic oscillator is found to be constructive to maintain oscillatory behavior in stochastic system but destructive in deterministic system by destructing oscillation. This role of noise in chemical oscillator is found to be contrast as compare to genetic oscillator i.e. noise in stochastic system fluctuates the dynamics of the variables tending to destruct the oscillatory behavior, whereas in deterministic regime the oscillatory behavior is maintained stable. There are different interesting issues to be studied in such systems such as phenomenon of stochastic resonance, switching behavior in biological systems, means of inter-oscillator communication etc. These studied could able to highlight different interesting roles of noise in different stochastic systems, especially in biological systems.

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