Nonspecific protein binding can enhance the oscillatory regime of a biomolecular clock

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Abstract—Rhythms in gene regulatory networks are ubiquitous, from the circadian clock to the segmentation clock of vertebrates. There are many nonspecific protein binding sites (decoys) in a genome where regulatory proteins bind, and such decoys critically control the expression of a gene. The role decoys play on oscillatory regulatory networks is not well understood. Here, in the presence of decoy binding sites, we investigate the stability and the precision of the well-known Goodwin oscillator, a minimal model for regulatory oscillators. We derive the stability criterion in the presence of decoys and find that increasing decoy abundance can expand the parameter space where oscillating solutions exist. If the Goodwin system does not show any oscillation without decoy binding sites, a sustained oscillation is possible in their presence. Finally, we study precision in oscillations using stochastic simulations and find that decoy sites can make the oscillation more precise in terms of reducing noise in both the time period and the amplitude. Whereas, in an open-loop circuit, the gene expression can become noisier in the presence of decoy sites.

I. INTRODUCTION

In living cells, the expression of a gene is inherently stochastic as biochemical reactions are occurring at very low copy numbers. For this reason, across a population of genetically identical cells under the same external environment, the mRNA and protein levels can show a great variability [1]–[5]. This variation is known as gene-expression noise. Depending on contexts, this noise in the gene-expression has many adverse or positive consequences [6]–[11]. For example, the gene expression noise can control cell fate [8], [12], can cause defects in developing embryos [13], [14]. The gene expression noise can enhance phenotypic diversity which is important for the survival of an organism in a population [9], [10].

Amid this randomness, many processes in life occur with great accuracies. A fascinating example is the existence of precise rhythms in biological process. The examples of biomolecular oscillators are ubiquitous, from the circadian clock to the segmentation clock of vertebrates [13]–[17]. Cells employ several regulatory mechanisms to create sustained oscillations [13], [18]. One of the simplest regulatory network that show sustained oscillations is the well-known Goodwin oscillator [19]. The essential ingredients that trigger oscillation in the Goodwin circuit are strong repression and “time delay” created by an intermediate protein. In this

article, we study effect of the nonspecific protein binding on the Goodwin oscillator.

There are many nonspecific (decoy) binding sites in a genome where regulatory proteins can bind with high affinities [20]. In specific binding, regulatory proteins bind to the specific site of a gene (known as promoter) and *directly* regulate its expression by activating or inhibiting the transcription process. The sequestration of these proteins to the decoy sites on the other hand modulates the activity of the regulatory protein and *indirectly*, controls the expression of the corresponding gene. The decoys has great therapeutic potential due to its ability to control the activity of the regulatory proteins [21]–[24]. Several recent studies investigate how the decoy binding affects the expression levels and the corresponding noises in various non-oscillatory circuits theoretically [25]–[30]. The decoys can affect the oscillatory dynamics as well. For an NF- κ B circuit it has been shown that decoy reduces the oscillation amplitude [31]. For activator-repressor motifs, the versatile role of decoys for tuning amplitude and frequency of the oscillation has been studied [32]. However a general understanding of decoys role on the mean and the noisy oscillatory dynamics is still missing.

Here, we investigate the role of decoys on the Goodwin oscillator by formulating a model where decoys bind to the inhibitory proteins and control its activity. In this study, we consider that both the free and bound proteins can decay and assume the decay rates to be the same. This decay could be due to active degradation process such as ubiquitin-mediated proteolysis or because of dilution due to cell growth/division [26], [33]. We note that previous studies often assume the decoy binding protects proteins from the degradations [27]–[30]. Before investigating the oscillatory circuit, we first discuss the role of the decoy on the activity of a protein in an open-loop circuit. We obtain the analytical expression for the free protein noise, using the linear noise approximation [34]. We find that the noise in free protein shows an enhancement for limited decoy abundances. Then, we derive the stability condition for the Goodwin system in the presence of decoy binding sites and find that decoy abundance increases the regime in the parameter space where oscillating solutions exist. Finally, we solve the stochastic dynamics using Monte Carlo simulations [35] to compute the noise in the time period and amplitude of the oscillations, as an analytical solution for the noise in the oscillatory system is hard. We find that decoys buffer the noise in the Goodwin oscillator, as opposed to the open-loop circuit.

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Fig. 1. Biochemical reactions for studying the noise properties in the presence of decoys in the open-loop circuit. The production of protein occurs in bursts with a frequency k_p and an average burst size $\langle B_p \rangle$. The proteins reversibly bind to decoy binding sites with fast rates and produce the bound complex. The protein can degrade with the same degradation rate, γ_p , irrespective of it is in the free or bound state.

II. AN OPEN-LOOP CIRCUIT IN THE PRESENCE OF DECOY BINDING SITES

Here, we study how decoy sites affect the noise in protein counts in the open loop circuit shown in Fig. 1. We consider a bursty production of the protein P from a constitutive gene. The frequency of the burst is k_p and the burst sizes are drawn from a geometrical distribution, $\alpha_p(i)$ [36]–[39]. We choose the following shifted geometric distribution [28],

$$\alpha_p(i) = (1 - 1/\langle B_p \rangle)^{i-1} / \langle B_p \rangle \quad \text{for } i \in \{1, 2, 3, \dots\}. \quad (1)$$

The free proteins bind to decoy binding sites reversibly and form bound proteins P_b . We assume the degradation rates for both free and bound proteins are the same, denoted as γ_p . The total number of decoy binding sites N is assumed to be fixed. The binding and unbinding rates, k_b and k_u , are very large compared to the production and degradation rates.

Symbols and notations used: The uppercase symbols represent the species name. The bold lowercase symbols denote the stochastic variables. The $\langle \cdot \rangle$, and $\overline{\langle \cdot \rangle}$ denote the transient and steady-state averages. For examples, $\mathbf{p}$ is the stochastic variables representing copy numbers of the protein P , and $\overline{\langle \mathbf{p} \rangle}$ is its steady-state mean. The normal (not bold) lowercase symbols such as p is the deterministic variables for P and $\tilde{p}$ is the corresponding fixed point value which can be obtained by setting time the derivatives terms of the dynamical equations to zero.

Given the copy numbers of the free and bound proteins at time t , $\mathbf{p}$ and $\mathbf{p}_b$, the probabilities of the production, binding, unbinding and degradations of proteins, occurring in the next

infinitesimal time $(t, t + dt)$ are given by

$$\mathbb{P}(\mathbf{p} + i, \mathbf{p}_b) = k_p \alpha_p(i) dt, \quad (2a)$$

$$\mathbb{P}(\mathbf{p} - 1, \mathbf{p}_b + 1) = k_b \mathbf{p} (N - \mathbf{p}_b), \quad (2b)$$

$$\mathbb{P}(\mathbf{p} + 1, \mathbf{p}_b - 1) = k_u \mathbf{p}_b, \quad (2c)$$

$$\mathbb{P}(\mathbf{p} - 1, \mathbf{p}_b) = \gamma_p \mathbf{p} dt, \quad (2d)$$

$$\mathbb{P}(\mathbf{p}, \mathbf{p}_b - 1) = \gamma_p \mathbf{p}_b dt. \quad (2e)$$

For the above system, we can write the Chemical Master Equation (CME) that provides the time evolution of the joint probability density function $q(\mathbf{p}, \mathbf{p}_b, t)$, for observing $\mathbf{p}$ free protein count, and $\mathbf{p}_b$ bound protein count within time t and $t + dt$ [40], [41]

$$\begin{aligned} \frac{dq(\mathbf{p}, \mathbf{p}_b, t)}{dt} = & k_p \sum_{i=1}^p \alpha_p(i) q(\mathbf{p} - i, \mathbf{p}_b, t) \\ & + \gamma_p (\mathbf{p} + 1) p(\mathbf{p} + 1, \mathbf{p}_b, t) + \gamma_p (\mathbf{p}_b + 1) q(\mathbf{p}, \mathbf{p}_b + 1, t) \\ & + k_b (\mathbf{p} + 1) (N - \mathbf{p}_b + 1) q(\mathbf{p} + 1, \mathbf{p}_b - 1, t) \\ & + k_u (\mathbf{p}_b + 1) q(\mathbf{p} - 1, \mathbf{p}_b + 1, t) - k_p q(\mathbf{p}, \mathbf{p}_b, t) \\ & - [\gamma_p (\mathbf{p} + \mathbf{p}_b) + k_u \mathbf{p}_b + k_b \mathbf{p} (N - \mathbf{p}_b)] q(\mathbf{p}, \mathbf{p}_b, t). \end{aligned} \quad (3)$$

As the terms involving bindings are nonlinear, the exact solution for the full probability density $q(\mathbf{p}, \mathbf{p}_b, t)$ is hard. In fact, we will see, the exact solution of moment dynamics for the above equation is also impossible. We use the well-known Linear Noise Approximation [34], [42]–[45] to obtain a closed-form formula the noise.

A. The deterministic dynamics

The deterministic dynamics free and bound protein level for the open-loop circuit are given by the chemical rate equations,

$$\frac{dp}{dt} = k_p \langle B_p \rangle - \gamma_p p - k_b (N - p_b) p + k_u p_b, \quad (4a)$$

$$\frac{dp_b}{dt} = -\gamma_p p + k_b (N - p_b) p - k_u p_b, \quad (4b)$$

where $\langle B_p \rangle$ is the average burst size for the protein. The equilibrium solution of free protein count can be obtained by setting time derivatives of Eq. (4) to zero. This system of second-order nonlinearity has a unique physical solution. The other solution is unphysical, as it yields negative concentrations for free and bound protein for positive rate constants. In the limit of fast binding/unbinding, the equilibrium value of free protein concentration is given by

$$\tilde{p} = \frac{1}{2} \left[\tilde{p}_0 - (k_d + N) + \sqrt{(\tilde{p}_0 - (k_d + N))^2 + 4k_d \tilde{p}_0} \right], \quad (5)$$

where $\tilde{p}_0 = k_p \langle B_p \rangle / \gamma_p$ is the fixed point solution without decoy binding sites, and $k_d = k_u / k_b$ is the dissociation constant. The fixed point value of bound proteins in terms of free protein level is given by,

$$\tilde{p}_b = N \tilde{p} / (k_d + \tilde{p}). \quad (6)$$

Note that the free protein counts $\tilde{p}$ decreases to zero as we increase the total number of decoy binding sites N [25]. Whereas, if bound proteins are protected from the

Fig. 2. The decoy binding sites can enhance the noise in the free protein counts. (A) The steady-state mean protein count decays monotonically as function of N . The decay becomes faster for a smaller dissociation constant k_d . (B) The steady-state Fano factors in free protein count show a nonmonotonic behavior with N . For intermediate values of N , there is an enhancement in the noise. For large values of N , the noise approaches to the Poissonian limit. The noise enhancement becomes stronger for a smaller k_d . Parameters used: $\langle B_p \rangle = 2$, $k_p = 1$, and $\gamma_p = 0.1$.

degradation $\tilde{p} = \tilde{p}_0$ independent of N [26], [28]. Fig. 2(A) shows how the mean free protein level decreases with N . The decay becomes stiffer for larger binding affinities (smaller dissociation constants).

B. Noise in free protein counts

To calculate the noise in free protein counts, we need to compute all the statistical moments up to the second order. From the CME for our model (Eq. 3), we obtain the dynamics of any arbitrary moment $\langle \mathbf{p}^{m_1} \mathbf{p}_b^{m_2} \rangle$ (for $m_1, m_2 \in 0, 1, 2, \dots$)

$$\begin{aligned} \frac{d\langle \mathbf{p}^{m_1} \mathbf{p}_b^{m_2} \rangle}{dt} = & \langle k_p \sum_{i=1}^{\infty} \alpha_p(i) [(\mathbf{p} + i)^{m_1} - \mathbf{p}^{m_1}] \mathbf{p}_b^{m_2} \rangle \\ & + \langle k_b \mathbf{p} (N - \mathbf{p}_b) [(\mathbf{p} - 1)^{m_1} (\mathbf{p}_b + 1)^{m_2} - \mathbf{p}^{m_1} \mathbf{p}_b^{m_2}] \rangle \\ & + \langle k_u \mathbf{p}_b [(\mathbf{p}_b + 1)^{m_1} (\mathbf{p}_b - 1)^{m_2} - \mathbf{p}^{m_1} \mathbf{p}_b^{m_2}] \rangle \\ & + \langle \gamma_p \mathbf{p} [(\mathbf{p} - 1)^{m_1} - \mathbf{p}^{m_1}] \mathbf{p}_b^{m_2} \rangle \\ & + \langle \gamma_p \mathbf{p}_b [(\mathbf{p}_b - 1)^{m_2} - \mathbf{p}_b^{m_2}] \mathbf{p}^{m_1} \rangle. \end{aligned} \quad (7)$$

The exact analytical solution for moments do not exist as the nonlinearity of binding reaction makes the moments dynamics unclosed [46]–[52], i.e., the dynamical equation of a lower order moment depends on the higher order moments. We do the linear noise approximation [34] by linearizing the nonlinear term $k_b \mathbf{p} \mathbf{p}_b$ around the mean for free and bound protein count $\langle \mathbf{p} \rangle$ and $\langle \mathbf{p}_b \rangle$ as $k_b \mathbf{p} \mathbf{p}_b = k_b (\mathbf{p} \langle \mathbf{p}_b \rangle + \langle \mathbf{p} \rangle \mathbf{p}_b - \langle \mathbf{p} \rangle \langle \mathbf{p}_b \rangle)$ [28]. In this approximation limit, the first order moment dynamics reduces to the deterministic dynamics (Eq. (4)) and $\langle \mathbf{p} \rangle = p$, and $\langle \mathbf{p}_b \rangle = p_b$. By solving the second order linearized dynamical equations at the steady state, we obtain the noise formula. We quantify the noise in free protein count by the Fano factor F_p , the ratio of the variance to the mean. In the limit of fast binding/unbinding,

the analytical expression is given by

$$\begin{aligned} F_p = & \frac{\langle \mathbf{p}^2 \rangle - \langle \mathbf{p} \rangle^2}{\langle \mathbf{p} \rangle} \\ = & 1 + \frac{[(\langle B_p \rangle - 1) \langle \mathbf{p} \rangle_0 + f^2 N] \langle \mathbf{p} \rangle}{(\langle \mathbf{p} \rangle_0 - f^2 N) (N f (1 - f) + \langle \mathbf{p} \rangle)}, \end{aligned} \quad (8)$$

where the steady-state averages are denoted using the notation $\langle \cdot \rangle$, $f = \langle \mathbf{p}_b \rangle / N$ is the fraction of the bound decoys, $\langle \mathbf{p} \rangle_0 = \tilde{p}_0 = k_p \langle B_p \rangle / \gamma_p$ is the steady-state value in the absence of decoy sites, and $\langle \mathbf{p} \rangle = \tilde{p}$ and $\langle \mathbf{p}_b \rangle = \tilde{p}_b$ are given by Eqs. 5 and 6. In the absence of any decoy sites, the exact analytical expression noise can be obtained [53]. In this limit, the noise becomes $F_p = F_{p,0} = \langle B_p \rangle$. In the limit of large decoy abundance, it can be shown that the noise approaches to the Poissonian limit, i.e. $F_p \rightarrow 1$ as $N \rightarrow \infty$.

In Fig. 2(B), we plot the Fano factor in the free protein counts. The noise in protein count shows a nonmonotonic behavior. As a function of N , the noise increases to a maximum value and then decays to the Poissonian limit ($F_p = 1$). We note this noise enhancement is absent in the case when proteins bound to decoys are protected from the degradation [26], [28]. In the latter case, the noise monotonically decays to the Poissonian limit [28].

III. THE GOODWIN OSCILLATOR IN PRESENCE OF DECOY BINDING SITES

How does the nonspecific protein binding affect the precision of biological clocks? To address this question, we study the effect of the decoy bindings on a simple oscillatory system, namely the Goodwin oscillator [19]. Therefore, we first introduce the oscillator and do basic stability analysis. Then, we perform stability in the presence of decoy binding sites. Finally, we investigate the precision in the oscillations using stochastic simulations.

A. The stability of the Goodwin oscillator

The Goodwin oscillator is one of the minimal regulatory circuits that generates sustained oscillations. The ingredients that trigger oscillation are strong repression and “time delay” created by an intermediate protein. The biochemical reactions in the stochastic model of Goodwin oscillator are shown in Fig. 3. The deterministic dynamics of Goodwin oscillator is given by the chemical rate equations

$$\frac{dm}{dt} = \frac{k_m}{1 + (p/p_{crit})^h} - \gamma_m m, \quad (9a)$$

$$\frac{de}{dt} = k_e m - \gamma_e e, \quad (9b)$$

$$\frac{dp}{dt} = k_p^0 \langle B_p \rangle e - \gamma_p p. \quad (9c)$$

The mRNA M translated into protein E and this protein activates the production of protein P . Finally, the protein P represses the mRNA production and the Hill function for the repression is $f(p) = 1 / [1 + (p/p_{crit})^h]$. Here, h is the Hill coefficient and p_{crit} is the repression coefficient, the level of p at which half-maximal repression is achieved. The productions rates are k_m , k_e , and k_p^0 , and the degradation

Biochemical reactions in Goodwin Oscillator

Fig. 3. Biochemical reactions in Goodwin oscillator in the presence of decoy binding sites. The regulatory protein P inhibits the transcription of mRNA M . The mRNA translated into the protein E . The protein E activates the bursty production of P . In the presence of D , the inhibitory protein reversibly binds to them with faster rates and produces bound complex P_b . The protein P can degrade, irrespective of it is in the free or bound state.

rates are γ_m , γ_e , and γ_p . We consider the bursty production for protein P with a burst size distribution given by Eq. (1). Note that a rescale of the production rate k_p^0 by its average burst size leads to the same deterministic dynamics as in the case of a simple birth process where the increment of protein counts happens by 1 at each time of production. However, it will be interesting to see how the precision in the oscillating pattern depends on $\langle B_p \rangle$.

Although the Goodwin system is highly nonlinear, it can be shown that there is a unique equilibrium point. This uniqueness comes from the negative regulation. Whereas a positive regulation can lead to multi-stability and this is absent in the Goodwin oscillator. Let $(\tilde{m}_0, \tilde{e}_0, \tilde{p}_0)$ be the fixed point. The Jacobian matrix at the equilibrium point is

$$\mathbf{A} = \begin{pmatrix} -\gamma_m & 0 & -g \\ k_e & -\gamma_e & 0 \\ 0 & k_p & -\gamma_p \end{pmatrix}, \quad (10)$$

where

$$g = \frac{h\gamma_m\gamma_e\gamma_p(1-f(\tilde{p}_0))}{k_e k_p^0}. \quad (11)$$

The characteristic polynomial of the Jacobian has the form $Q(x) = x^3 + ax^2 + bx + c$. The criteria for stable polynomial are: (i) $a, b, c > 0$, and (ii) $ab > c$ [54]. The first condition always holds true. The second condition implies that for an unstable (oscillatory) solution, the value of the Hill coefficient must be greater than a threshold value h_0^{thr} :

$$h > h_0^{thr} := \frac{(\gamma_m + \gamma_e)(\gamma_e + \gamma_p)(\gamma_p + \gamma_m)}{\gamma_m\gamma_e\gamma_p(1-f(\tilde{p}_0))}. \quad (12)$$

The functional form of the h_0^{thr} suggests that its minimum value is $8/(1-f(\tilde{p}_0)) > 8$. Therefore, to obtain an oscillatory

Fig. 4. The presence of decoys triggers oscillation in the mRNA counts: (A) For $h = 7$: In the absence of decoy, there is no oscillation, but the decoy's presence induces oscillation. (B): For $h = 12$: The oscillation is observed in the presence or absence of decoys. Interestingly, the decoy abundances increases the time period and the amplitude of the oscillation. Parameters used: $\langle B_p \rangle = 1$, $k_m = 20$, $k_e = 1$, $k_p(0) = 0.2$, $k_d = 1$, $\gamma_m = \gamma_e = \gamma_p = 0.1$, and $p_{crit} = 100$.

solution the value of the Hill coefficient must be greater than 8 [55].

B. The stability in the presence of decoy binding sites

Here, we consider binding of inhibitory proteins to the decoy sites (see Fig. 3). Like the study of the open-loop circuit, we assume the total decoy binding sites N is constant, and proteins decay with the same rate γ_p , regardless of binding to the decoys. The dynamics of protein and bound proteins are given by

$$\frac{dp}{dt} = k_p \langle B_p \rangle e - k_b(N - p_b)p + k_u p_b - \gamma_p p, \quad (13a)$$

$$\frac{dp_b}{dt} = k_b(N - p_b)p - k_u p_b - \gamma_p p_b. \quad (13b)$$

The presence of the decoy does not introduce any multistability, as we have seen in the case of the open-loop circuit. However, it alters the equilibrium values of m , p , and e from $\tilde{m}_0$, $\tilde{e}_0$, and $\tilde{p}_0$. In this study, we fix the equilibrium values to the corresponding values when there is no decoys, i.e. $\tilde{m} = \tilde{m}_0$, $\tilde{e} = \tilde{e}_0$, and $\tilde{p} = \tilde{p}_0$. In this way, we can compare the stability in the presence and absence of decoys around the “same” equilibrium point. To do that we increase the synthesis rate k_p with N in the following way,

$$k_p(N) := k_p = k_p^0 \left(1 + \frac{Nk_b}{\gamma_p + k_b(k_d + \tilde{p}_0)} \right). \quad (14)$$

The four dimensional Jacobian matrix at the equilibrium point is

$$\mathbf{A} = \begin{pmatrix} -\gamma_m & 0 & -g & 0 \\ k_e & -\gamma_e & 0 & 0 \\ 0 & k_p(N) & -\gamma_p - l & k_b(k_d + \tilde{p}_0) \\ 0 & 0 & l & -\gamma_p - k_b(k_d + \tilde{p}_0) \end{pmatrix}, \quad (15)$$

where

$$l = \frac{k_b N (\gamma_p + k_b k_d)}{\gamma_p + k_b(k_d + \tilde{p}_0)}.$$

The characteristic polynomial of the Jacobian has the form $Q(x) = x^4 + ax^3 + bx^2 + cx + d$. The criteria for stable

Fig. 5. The stochastic trajectories, the mean and the noise behavior in the presence of decoy sites for two different burst sizes: (A) The stochastic trajectories shows in the presence of decoy sites the amplitude and time period is larger than that of without decoys ($\langle B_p \rangle = 2$). (B) The average time period (squares) and its noise (circles) as a function of N : The average time period increases, while the noise decrease with N . (C) The average amplitude (squares) and its noise (circles) as a function of N : Similar to the time period, the average amplitude increases and the noise decrease with N . Parameters used: $k_m = 20$, $k_e = 1$, $k_d = 1$, $\gamma_m = \gamma_e = \gamma_p = 0.1$, $h = 12$, and $p_{crit} = 100$. $k_p^0 = 0.2$ for $\langle B_p \rangle = 1$ and $k_p^0 = 0.1$ for $\langle B_p \rangle = 2$.

polynomial are: (i) $a, b, c, d > 0$, (ii) $ab > c$, and (iii) $abc - c^2 > a^2d$ [54]. As the rate constants are positive, the first condition is always true. In the limit of fast/binding unbinding, considering the highest order term in k_b , one can show that the second condition will also hold true for any physical parameters. The third condition gives the condition for the stability in this system. Again considering the highest order term in k_b one can show unstable solution exist if

$$h > h_0^{thr} \left(1 - \frac{k_d N}{(k_d + \tilde{p}_0)(k_d + \tilde{p}_0 + N)} \right). \quad (16)$$

The above equation suggests that one can obtain oscillation even for $h < 8$ in the presence of decoys. Therefore, the decoy can enhance the region of instability. For $h > h_0^{thr}$, the Eq. 16 holds true for any N , and hence the decoy abundance cannot kill the oscillation that was present without decoys binding sites.

We solve the deterministic dynamics given by the ordinary differential equations (Eqns. 9 (a), (b), and 13), numerically. The time series data of mRNA level are presented in the Fig. 4 for $h = 7$ and $h = 12$. For $h = 7$, there is no sustained oscillation in the mRNA count when there is no decoys. Interestingly, in the presence of decoy, a sustained oscillation can be seen even for $h = 7$. For $h = 12$, sustained oscillations are observed both in the presence and absence of the decoy sites. However, the decoy abundance increases the time period and the amplitude of the oscillations. For an NF-kB circuit it has been shown that decoy reduces the oscillation amplitude [31]. For activator-repressor motifs, it is known that the decoy binding sites can tune the amplitude and the frequency, and can induce or kill the oscillations depending on whether decoys binds to the activators or repressors [32].

C. Noise properties using stochastic simulations

Here, we perform stochastic simulations to compute the precision in the time period and amplitude (the peak height). For exact stochastic simulations, we use kinetic Monte Carlo

method due to Gillespie [35]. The typical time trajectories for the mRNA are presented in Fig. 5. We quantify the noise in time period of the oscillation in mRNA count using the Fano factor,

$$F_\tau = \frac{\langle \tau_m^2 \rangle - \langle \tau_m \rangle^2}{\langle \tau_m \rangle}, \quad (17)$$

where, $\langle \tau_m \rangle$ is the mean time period, and the second moment $\langle \tau_m^2 \rangle$ at the oscillatory steady state. We also quantify the noise in the amplitude. For this, we compute the mRNA counts at peaks and define the following Fano factor

$$F_m = \frac{\langle m_{peak}^2 \rangle - \langle m_{peak} \rangle^2}{\langle m_{peak} \rangle}, \quad (18)$$

where $\langle m_{peak} \rangle$ and $\langle m_{peak}^2 \rangle$ is the first and second moment of the mRNA counts at the peaks at the oscillatory steady state.

In Fig. 5(B) and (C), we plot the mean and the noise behavior in the time period and amplitude of mRNA count for both the cases. The amplitude and time period increase with N as observed in the deterministic case. We observe that the noise in the amplitude is quite large compared to that of time period. The increase in the burst size can make the system more noisy, as expected. The both noises in the time period and amplitude decrease as a function of N . In contrast, decoy can enhance in the open-loop circuit (see Fig. 2).

IV. SUMMARY AND DISCUSSION

In summary, we have investigated the effect of nonspecific protein binding in the noise in gene expression for an open loop-circuit and an oscillatory regulatory circuit, in the limit of fast binding/unbinding. For the open-loop circuit, we have obtained an analytical expression for the noise in free protein counts considering proteins that are bound to the decoys are subjected to degrade, using the linear noise approximation. The case when bound proteins are stable were studied earlier in [26], [28]. We have found that, depending on the number

of binding sites and binding affinity to the proteins, decoys can act as noise amplifier, whereas, decoys always suppress noise when binding protects proteins from the degradation [26], [28].

For the oscillatory regulatory circuit, we have studied the stability and the precision in the well-known Goodwin oscillator [19] in the presence of decoy binding sites, by incorporating decoy binding with the inhibitory proteins. By keeping the equilibrium values the same with the no decoy case, we have derived the condition for oscillatory solutions. We have found that decoy binding increases the parameter regime for the existence of oscillatory solutions. If Goodwin system does not show any oscillation without decoy binding sites, a sustained oscillation is possible in their presence. The Goodwin system that oscillates without decoys remains oscillating in their presence. We also have observed that decoy presences can increase the amplitude and time period of the oscillation.

Finally, we have studied the precision the oscillation using stochastic simulations by quantifying the noise in time period and the amplitude. We have observed that the oscillation time period is more precise compared to the amplitudes. The presence of decoy can buffers the noise in the time period to a sub-Poissonian limit and the noise in the amplitude towards the Poissonian limit. Noise in gene expression has many advantageous and disadvantageous implications, from the phenotypic diversity, cell fate, to defects in developing embryos. Our results show the presence of decoys, depending on contexts, can enhance or buffer the noise as in an open-loop circuit. However, it always reduces the noise in the oscillation where precision is crucial.

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