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Stochastic analysis of feedback control by molecular sequestration

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Abstract— **Sequestration of a protein by another decoy molecule, such that the protein is no longer available to perform its biological function, forms a fundamental layer of regulation in biomolecular systems. To quantify how fluctuations in protein level is controlled by decoys, we formulate a model where both proteins and decoys are stochastically expressed, with fast binding/unbinding of the protein to the decoy. Our analysis reveals that when the noise in the decoy copy number is small, the noise in the free protein numbers (as quantified by the Fano factor) monotonically decreases to the Poisson limit with the increasing average number of decoys. In contrast, for a high noise in decoys production, the response becomes nonmonotonic — the noise level in protein counts is amplified at first with the increasing decoy numbers, before attenuating back to the Poisson limit. Motivated by recent biological examples, we next implement feedback control in the sequestration process by having the free proteins upregulate the decoy synthesis. Thus any random increase in the abundance of free proteins also results in higher decoy numbers, and hence more sequestered proteins. Intriguingly, our results show that as before, noise in free protein levels can get amplified with increasing decoys, albeit with a lesser magnitude as compared to the no feedback case. In summary, molecular decoys can play a key role in either amplifying or dampening the stochastic fluctuation of protein levels, and this study systematically quantifies this behavior across parameter regimes.**

I. INTRODUCTION

Genetically identical cells in the same external environment express proteins exhibiting remarkable cell-to-cell variability [1], [2], [3], [4]. This variation in protein expression level of a gene commonly known as gene expression noise. A major source of the noise arises from the inherent stochasticity of biochemical reactions (such as binding/unbinding, production and degradation) occurring at low molecular copy number. The noise in gene expression has several important roles in establishing phenotypic diversity in a population of organism [5], [6], [7], [8], [9], deciding the fate of cells during lysis-lysogenic bifurcation in phage lambda [2] and other circumstances [10], and determining cellular fitness [11], [12]. However, in many cases, the stability against the noise is essential [13], e.g. the cell differentiation in developing embryos [14], [15], [16].

Generally, the regulation of a protein synthesis happens by binding of proteins (known as transcription factor proteins) to the specific region of a target gene (promoter) and thereby activating or inhibiting the transcription process. A protein for a target gene not only binds to the promoter but also can bind to other nonfunctional sites of a genome [17], [18], [19], [20], [21], [22], [23]. These nonspecific binding sites for proteins are known as *decoy binding sites*. The binding of proteins is not limited to specific and nonspecific binding sites of a genome. A protein can also bind to other partner proteins and indirectly regulates expression of a gene [24]. For example, in the case of heat shock response, such protein-protein interaction exists [25], [26]. There are some RNAs such as long non-coding RNAs can also serve as binding sites of proteins [27], [28]. We refer these molecules with protein binding sites as decoy molecules. While the total genomic decoy binding sites are fixed in a cell, the total number of decoy molecules fluctuates as their productions and decays are stochastic. In past, several theoretical studies [29], [30], [31], [32], [33] have addressed the role of decoys by considering the number of the total decoy sites constant and have found that the protein binding to decoy sites suppresses noise in gene expression. However, the role of decoy binding of a protein is not well studied when the number of total decoy site fluctuates.

To quantify how the random fluctuations in protein levels are controlled by decoys, we formulate a model where both proteins and decoys are stochastically expressed in the presence and absence of any feedback mechanisms (Fig. 1). The binding of proteins to the decoys can enhance "cooperative stability" of proteins [34], [30]. In our model, we assume proteins bound decoy do not degrade like several previous studies [30], [35], [32], [33]. First, we write down the chemical master equation and then solve its moment statistics using the Linear Noise Approximation (LNA) method [36]. We quantify noise for protein counts in terms of the Fano factor which is the ratio of the variance to the mean and derive analytical expressions of the mean and noise at the steady state. We find that a sufficiently noisy decoy synthesis can enhance noise in the protein count even in the presence of negative feedback.

II. MODEL FORMULATION

We study how the protein-decoy interaction affects the gene expression noise using a simple model as schematically shown in Fig. 1. The synthesis of protein and decoy species are assumed to occur from consecutive genes in bursts. In the case of a protein synthesis, in this bursty limit, the dynamics of mRNA is neglected assuming the lifetime of mRNA is very short compared to that of the protein [37], [38], [39]. The decoy species binds to proteins reversibly to form bound complex. We again note that this protein-decoy binding are different from the binding of proteins to the nonspecific genomic sites as the productions of decoy molecules are

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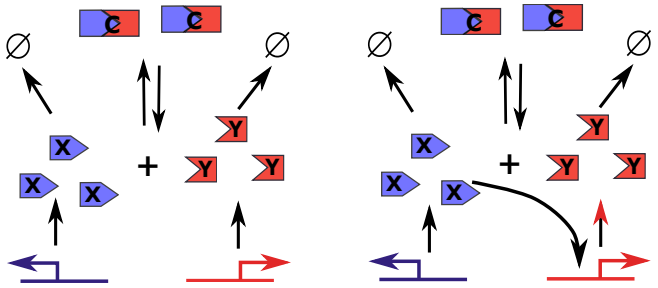

Fig. 1. A schematic representation of the models with protein-decoy interaction. The protein X and decoy species Y are synthesized in bursts. A protein X molecule reversibly binds to a decoy Y and form complex C. We assume the binding/unbinding reactions are very fast compared to the production and degradation reactions. (I) In the absence of feedback, Y syntheis is independent of X. (II) In the presence of negative feedback, X activates Y synthesis.

fluctuating whereas the total number of nonspecific binding sites is constant. The free protein not only binds to free decoy molecules, but it also can act as transcription factors for the gene producing decoy molecules and directly enhances its production. Consequently, it increases the sequestration of proteins and creates a negative feedback loop for the decoy production. We investigate both the cases: (I) no feedback case i.e. protein does not influence decoy production, and (II) negative feedback case, i.e, protein enhances decoy production (see Fig. 1).

Let us denote the protein species by X and decoy species by Y and their copy numbers by x and y, respectively. During X synthesis which occurs at rate k_x, B_x copies of X are released. Similarly, B_y copies of Y are produced during Y synthesis. The rate for this event $k_y(x)$ may depend on the copy number of x. We choose a linear dependence, $k_y(x) = k_y^0 + k_y^1 x/\overline{\langle x \rangle}$. The scaling with the steady state mean level of X, $\overline{\langle x \rangle}$, makes the dimension of k_y^0 and k_y^1 the same, and it does not affect the results presented in this paper. For the no-feedback case $k_y^1 = 0$, meaning X does not influence Y production (case (I)). For $k_y^1 > 0$ i.e., when X activates Y imply a negative feedback. In the latter case, we consider $k_y(x) = k_y^1 x/\overline{\langle x \rangle}$ by choosing $k_y^0 = 0$ for simplicity (case (II)). The random variables B_x and B_y are drawn from the probability distributions $\alpha_x(B_x)$ and $\alpha_x(B_x)$. The protein reversibly binds to a decoy molecule with rate k_b to form a complex C and unbinds with rate k_u. The species X and Y degrade with rates γ_x and γ_y, respectively. As the binding/unbinding of molecules happens very fast, we assume the binding and unbinding rates are very large compared to other reactions.

The distributions of protein bursts follow geometric distributions [40], [41]. We choose the following geometric distributions for species X and Y [35],

$$\alpha_x(i) = (1 - 1/\langle B_x \rangle)^{i-1}/\langle B_x \rangle, \text{ and} \tag{1a}$$
$$\alpha_y(i) = (1 - 1/\langle B_y \rangle)^{i-1}/\langle B_y \rangle, \tag{1b}$$

for $i \in [1, 2, ...)$, where $\langle B_x \rangle$ and $\langle B_y \rangle$ is the average burst sizes for X and Y, respectively. For these shifted geometric distributions, the second order moments are related to their first order moments as, $\langle B_x^2 \rangle = 2\langle B_x \rangle^2 - \langle B_x \rangle$ and $\langle B_y^2 \rangle = 2\langle B_y \rangle^2 - \langle B_y \rangle$. These relations will be useful to write down the final expressions of the noise in terms of the average burst sizes.

The mathematical description of the all the reactions and their probabilities of occurrences at time t during an infinitesimal time dt are summarized below:

Synthesis of X :
$$\text{Prob}\{x(t) \to x(t) + B_x\} = k_x\, \alpha_x(B_x)\, dt, \tag{2a}$$
Synthesis of Y :
$$\text{Prob}\{y(t) \to y(t) + B_y\} = k_y(x)\, \alpha_y(B_y)\, dt, \tag{2b}$$
Binding :
$$\text{Prob}\{x(t) \to x(t) - 1, y(t) \to y(t) - 1, c(t) \to c(t) + 1\} = k_b\, x(t)\, y(t)\, dt, \tag{2c}$$
Unbinding :
$$\text{Prob}\{x(t) \to x(t) + 1, y(t) \to y(t) + 1, c(t) \to c(t) - 1\} = k_u c(t) dt, \tag{2d}$$
Degradation of X :
$$\text{Prob}\{x(t) \to x(t) - 1\} = \gamma_x\, x(t)\, dt, \tag{2e}$$
Degradation of Y :
$$\text{Prob}\{y(t) \to y(t) - 1\} = \gamma_y\, y(t)\, dt, \tag{2f}$$

where, $c(t)$ is the number of the bound complex C at time t.

The time evolution of the probability density $p_t(x, y, c)$, for having x copies of X, y copies of Y and c copies of C at time t, is given by the chemical master equation (CME),

$$\begin{aligned}
\frac{\partial p_t(x,y,c)}{\partial t} &= k_x \sum_{i=1}^{x} \alpha_x(i) p_t(x-i,y,c) \\
&+ \sum_{i=1}^{y} \alpha_y(i) k_y(x) p_t(x,y-i,c) \\
&+ k_b(x+1)(y+1) p_t(x+1,y+1,c-1) \\
&+ k_u(c+1) p_t(x-1,y-1,c+1) + \gamma_x(x+1) p_t(x+1,y,c) \\
&+ \gamma_y(y+1) p_t(x,y+1,c) \\
&- [k_x + k_y(x) + k_b x\, y + k_u c + \gamma_x x + \gamma_y y]\, p_t(x,y,c).
\end{aligned} \tag{3}$$

The analytical solution for the $p_t(x, y, c)$ is a hard problem. As our goal is to quantify noise, we solve the moment dynamics of the above equation rather than solving for the full probability density function. In particular, we are interested in the first order and second order statistical moments. To obtain a moment equation of an arbitrary order $\langle x^{m_1} y^{m_2} c^{m_3} \rangle$, we multiply $x^{m_1} y^{m_2} c^{m_3}$ (for $m_1, m_2, m_3 \in 0, 1, 2, ..$) both side of the Eq. (3) and sum over all possible

values of x, y, and c. The general form of moments equations for a set of reactions is given by Dynkin's formula [42]. For our system, the Dynkin's formula is presented in the appendix.

As the terms associated with binding events in the above equation are nonlinear, the moments dynamics are not closed in a sense that the time derivative of moments of a given order depend on their higher-order moments [43], [44]. For example, in this model, the mean dynamics of species X depends on the second order moment $\langle x\, y\rangle$. In such cases, an approximation solution can be obtained using various moment closure approximation schemes [45], [46], [47], [44], [48], [49], [50], [43]. We use the method of linear noise approximation (LNA) [36], [43], [51] to obtain close moment dynamics. Under this approximation, we linearise the nonlinear term $x\, y$ around steady state mean by, $x\,\overline{\langle y\rangle} + \overline{\langle x\rangle}\, y - \overline{\langle x\rangle}\,\overline{\langle y\rangle}$, where $\overline{\langle x\rangle}$ and $\overline{\langle y\rangle}$ are the mean copy numbers of species X and Y in the steady-state. Under this approximation, from the Dynkin's formula, we get the first order moment dynamics,

$$\begin{aligned}
\frac{d\langle x\rangle}{dt} &= \langle B_x\rangle k_x + k_u c - k_b(\langle x\rangle\overline{\langle y\rangle} + \overline{\langle x\rangle}\langle y\rangle \qquad (4a)\\
&\quad - \overline{\langle x\rangle}\,\overline{\langle y\rangle}) - \langle x\rangle\gamma_x,\\
\frac{d\langle y\rangle}{dt} &= \langle B_y\rangle(k_y^0 + k_y^1\langle x\rangle/\overline{\langle x\rangle}) + k_u c - k_b(\langle x\rangle\overline{\langle y\rangle} \qquad (4b)\\
&\quad + \overline{\langle x\rangle}\langle y\rangle - \overline{\langle x\rangle}\,\overline{\langle y\rangle}) - \langle y\rangle\,\gamma_y,\\
\frac{d\langle c\rangle}{dt} &= -k_u c + k_b(\langle x\rangle\overline{\langle y\rangle} + \overline{\langle x\rangle}\langle y\rangle - \overline{\langle x\rangle}\,\overline{\langle y\rangle}), \qquad (4c)
\end{aligned}$$

where, $\langle\cdot\rangle$ and $\overline{\langle\cdot\rangle}$ denote the ensemble averages at the transient and steady state, respectively.

III. RESULTS

By solving Eqs. (4) at the steady state, we obtain the mean count of X, Y, and C at the steady state and these are given by, $\overline{\langle x\rangle} = k_x\langle B_x\rangle/\gamma_x$, $\overline{\langle y\rangle} = (k_y^0 + k_y^1)\langle B_y\rangle/\gamma_y$, and $\overline{\langle c\rangle} = \overline{\langle x\rangle}\,\overline{\langle y\rangle}/k$, where $k = k_u/k_b$ is the dissociation constant. Note that $\overline{\langle x\rangle}$ is independent Y. However, we will observe that the noise in X copy number depends on Y in an interesting way.

To calculate noise, we need to solve the dynamical equations of the second order moments using the LNA in the steady state. Similar to calculations of the first moments, we use the following steps for the second moments: (1) We write down the dynamical equations for all the second moments ($\langle x^2\rangle$, $\langle y^2\rangle$, $\langle c^2\rangle$, $\langle x\, y\rangle$, $\langle x\, c\rangle$, and $\langle y\, c\rangle$) using the Dynkin's formula presented in the appendix. (2) We use the LNA to linearize the binding term. (3) We solve the dynamical equations at the steady state by setting time derivatives to zero. (4) Finally, we simplify the Fano factor expression in the fast binding/unbinding limit, $k_u/k_b = k =$ finite, with $k_b \to \infty$.

In the case of a simple bursty production, the problem becomes linear, and the exact expression of the Fano factor can be obtained. For this case, the Fano factor for species X is given by, $(\langle B_x^2\rangle + \langle B_x\rangle)/(2\langle B_x\rangle)$ [52] which becomes $\langle B_x\rangle$ for the shifted geometric distribution (Eq. (1b)). If the value of the Fano factor for X copy numbers in the presence of decoy binding is higher than $\langle B_x\rangle$, then the decoy acts as a noise enhancer, and if it reduces the noise level from $\langle B_x\rangle$, then the decoy behaves as a noise buffer. Below, we present the expression of the Fano factors for X counts in the presence of decoy molecules.

Case I: No feedback

First, we focus on the no-feedback case. Here, $k_y = k_y^0$ and $k_y^1 = 0$. When $\gamma_x = \gamma_y$, the expression of the Fano factor is given by,

$$\begin{aligned}
Fano_I = \frac{\overline{\langle x^2\rangle} - \overline{\langle x\rangle}^2}{\overline{\langle x\rangle}} = \frac{k\langle B_x\rangle + \overline{\langle y\rangle}}{k + \overline{\langle x\rangle} + \overline{\langle y\rangle}} + \\
\frac{(\langle B_x\rangle\overline{\langle x\rangle} + \langle B_y\rangle\overline{\langle y\rangle} + 2k\langle B_x\rangle)\overline{\langle x\rangle}}{(k + \overline{\langle x\rangle} + \overline{\langle y\rangle})(2k + \overline{\langle x\rangle} + \overline{\langle y\rangle})},
\end{aligned} \qquad (5)$$

where $k = k_u/k_b$ is the dissociation constant. Note that in the limit of the small Y count, i.e., $\overline{\langle y\rangle} \to 0$, the noise is purely coming from the bursty production of X, and $Fano_I = \langle B_x\rangle$, as expected. In the limit of large Y count, $\overline{\langle y\rangle} \to \infty$, the noise in X counts approaches to the Poisson limit, i.e., $Fano_I = 1$. For $\langle B_x\rangle > 1$, the approach to the Poisson limit as a function of $\overline{\langle y\rangle}$ can be *non-monotonic*, depending on the value of burst size $\langle B_y\rangle$. For example, in the limit of strong binding (i.e., dissociation constant $k \to 0$), neglecting all the terms associated with k, it can be shown that the peak in the Fano factor appears for $\langle B_y\rangle^{th}_{no-feedback} \geq 2\langle B_x\rangle - 1$. It implies that for a given $\langle B_x\rangle$, there exists a threshold burst size for Y, $\langle B_y\rangle_{th,no-feedback}$, below which no enhancement and nonmonotonicity in the noise are observed.

Case II: With negative feedback

We now focus on the negative feedback case. Here, $k_y = k_y^1 x/\overline{\langle x\rangle}$ and $k_y^0 = 0$.The analytical expression of the Fano factor for $\gamma_x = \gamma_y$ is given by,

$$\begin{aligned}
Fano_{II} = \frac{\overline{\langle x^2\rangle} - \overline{\langle x\rangle}^2}{\overline{\langle x\rangle}} = \frac{k\langle B_x\rangle + \overline{\langle y\rangle}}{k + \overline{\langle x\rangle} + \overline{\langle y\rangle}} + \\
\frac{\langle B_x\rangle(\overline{\langle x\rangle}^2 + 2k\overline{\langle x\rangle} - k\overline{\langle y\rangle}) + \langle B_y\rangle\overline{\langle x\rangle}\,\overline{\langle y\rangle}}{(k + \overline{\langle x\rangle} + \overline{\langle y\rangle})(2k + \overline{\langle x\rangle} + 2\overline{\langle y\rangle})}.
\end{aligned} \qquad (6)$$

As in the case of no feedback, in the limit $\overline{\langle y\rangle} \to 0$, $Fano_{II} = \langle B_x\rangle$, and in the limit $\overline{\langle y\rangle} \to \infty$, $Fano_{II} = 1$. For $\langle B_x\rangle > 1$, the approach to the Poisson limit as a function of $\overline{\langle y\rangle}$ can be non-monotonic, depending on the value $\langle B_y\rangle$. In the limit of strong binding ($k \to 0$), it can be shown that the peak in the Fano factor appears for $\langle B_y\rangle_{th,neg-feedback} \geq 3\langle B_x\rangle - 1$. It should be stressed that even in the presence of negative feedback noise enhancement is observed. However, the negative feedback increases the threshold in the burst size $\langle B_y\rangle$ to observe a noise enhancement.

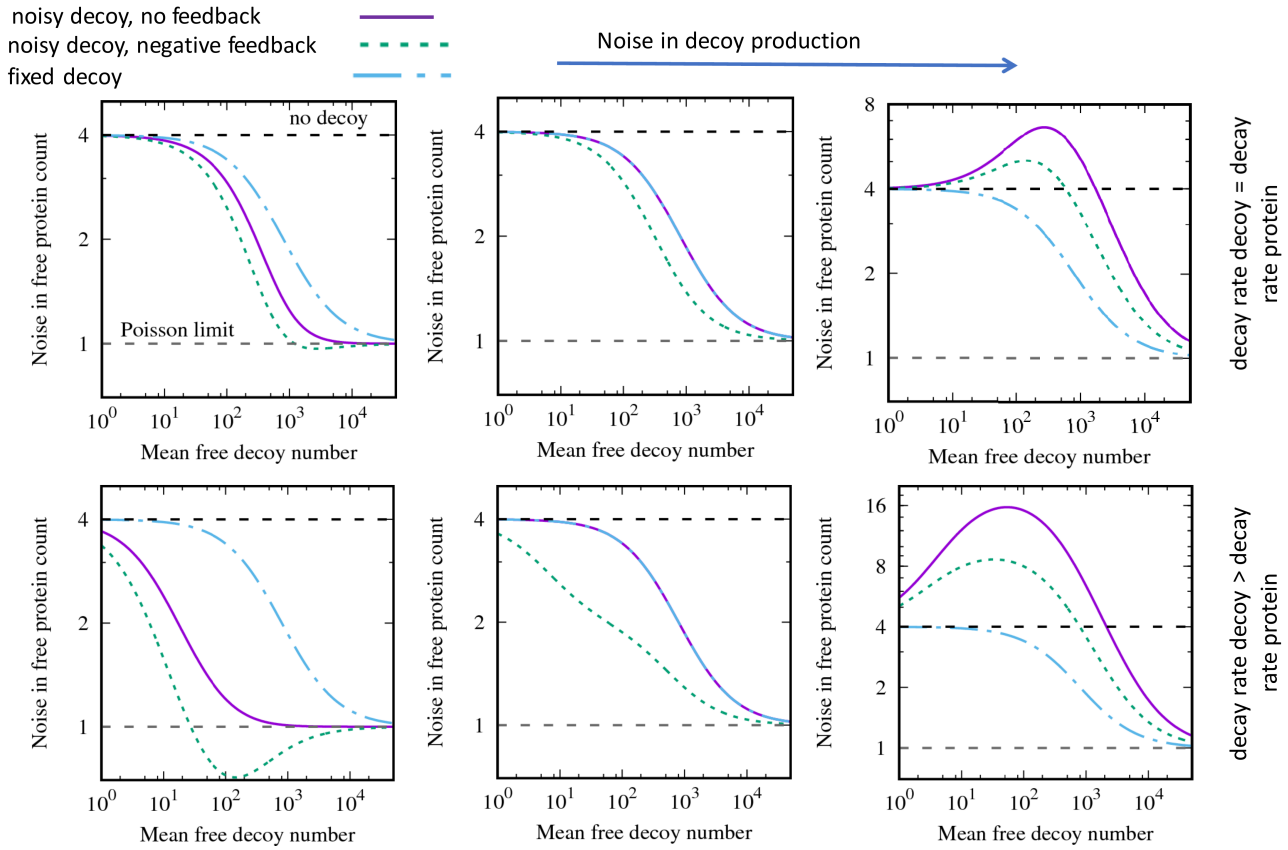

Fig. 2. Nonmonotonic behavior of noise in the protein copy number due to noisy production of decoys. The noise The Fano factor in free protein counts is plotted against the mean decoy abundance. We vary burst frequencies k_y^0 or k_y^1 to increase the mean decoy abundance at the steady state. **(Top panel):** The decay rates for both the protein and decoy molecules are the same. The noise in the decoy production ($\langle B_y \rangle$) increases as we move from the left to right plot. (Left) The decoy production is less noisy than that of protein production. (Middle) Both productions are equally noisy. (Right) The decoy production noise is very high compared to that of the protein. For the less noisy decoys, the noise decay monotonically to the Poisson limit as a function of the mean free decoy number ($\overline{\langle x \rangle}$). It is interesting to see that the noise in the protein count remains smaller than that of the fixed decoy case. When both the decoy and protein productions are equally noisy, the noise in the no-feedback case and fixed decoy site case the same. A nonmonotonic behaviour in the noise is seen for high decoy noise. **(Bottom panel):** The decay rate for the decoy is large than that of the protein. For high decoy production noise, the protein count noise becomes very large compared to the top panel. For a low decoy production noise, the noise becomes sub-Poissonian in the presence of negative feedback. **Parameter used:** Parameters for the proteins $\langle B_x \rangle = 4$, $k_x = 1$, and $\gamma_x = 0.01$. Parameters for the decoy: $\langle B_y \rangle = 1$ (left panel), $\langle B_y \rangle = 4$ (middle panel) and $B_y = 20$. Dissociation constant for the binding, $k = k_u/k_b = 1$ (right panel); $\gamma_y = \gamma_x$ (top panel) and $\gamma_y = 50\gamma_x$ (bottom panel).

Case III: Fixed decoy species

Here, we discuss another case where the decoys are not expressed stochastically, but the total number is fixed. This case was studied earlier, and results are known [35]. However, to understand the role of a stochastically expressed decoy, we should compare our results with fixed decoy case. In this case the noise in protein count is given by [35],

$$Fano_{III} = \frac{\langle B_x \rangle (k + \overline{\langle x \rangle}) + \overline{\langle y \rangle}}{k + \overline{\langle x \rangle} + \overline{\langle y \rangle}}, \tag{7}$$

where $\overline{\langle y \rangle}$ is the steady state mean of free decoy abundance. Here, the total number of decoy sites, $\overline{\langle y \rangle} + c$, is constant. It is important to note that the noise formula (Eq. (5)) in the no-feedback case of stochastically expressed decoys, surprisingly, reduces to the equation for the fixed decoy case (Eq. (7)) when the burst sizes for both the protein and decoy are the same, i.e., $\langle B_x \rangle = \langle B_y \rangle$.

In the top panel of Fig. 2, we plot the noise in the protein counts due to stochastically expressed decoy molecules as a function of the steady-state free decoy counts $\overline{\langle y \rangle}$, when both the decay rates are the same, $\gamma_x = \gamma_y$. We vary the decoy burst frequency to increase $\overline{\langle y \rangle}$. The Fano factor for all the three cases are plotted for different values of decoy burst sizes and decoy decay rates. As we discussed before, for a simple bursty process with the geometric burst size distribution given by Eq. (1b), the Fano factor in protein copy numbers is the average burst size. This implies the noise in the decoy production can be increased by increasing

the average burst size for the decoy. In the limit when the average number of decoy sites are very very large, the molecular sequestration by decoys makes the noise in protein counts *Poissonian*. The noise in the negative feedback case is always smaller compared to the no-feedback case. When the decoy sites are highly noisy (large decoy burst size), the noise curves show a nonmonotonic behavior for both with and without feedback cases and stays above the fixed decoy species case. It should be noted that the noisy decoys suppress the noise better than the fixed for $\langle B_y\rangle < \langle B_x\rangle$. For $\langle B_x\rangle = \langle B_y\rangle$, interestingly, the noise level for case-I and case-III are the same. In the bottom panel of Fig. 2, we plot the noise for $\lambda_y > \lambda_x$. We see a similar noise behavior as $\lambda_x = \lambda_y$. However, in this case, the noise gets further amplified. The noise enhancement becomes smaller for $\lambda_y < \lambda_x$ compared to that of when $\lambda_y = \lambda_x$ (not shown here).

The results presented above agree quite well with the exact stochastic simulations performed using the Gillespie algorithm [53]. If the binding affinity is very large (i.e. the effect of the nonlinear term is large), it shows a deviation. However, the qualitative behavior of the results does not depend on the approximation due to the LNA.

IV. DISCUSSION

The decoy species can play a vital role in gene expression sequestering proteins and building feedback loops in regulatory circuits [26]. While the most previous studies consider the total number of decoy species fixed, this number can fluctuate when partner proteins or RNAs act as a decoy. In this work, we have studied the role of decoy-protein interaction in the gene expression noise, considering fluctuation in decoy numbers. We formulate a model where both the protein and decoy are expressed stochastically. Using the linear noise approximation, we quantify the noise in the protein count by the Fano factor. We find that the noise in protein counts crucially depends on the noisy production of the decoy molecules. Our main findings on the noise in protein counts include: (i) the molecular sequestration of proteins by decoys can make the noise *Poissonian*, in the limit of large decoy abundance, (ii) if the synthesis of decoy species "sufficiently" noisy compared to that of the proteins, noise in protein copy number show an enhancement as we vary the decoy abundance, (iii) the enhancement in noise persists even in the presence of a negative feedback but in lesser magnitude compared to that of no feedback case, (iv) if the decoy species synthesis is less noisy, the negative feedback can reduce the noise to below the Poisson limit, and finally, (iv) the noise enhancement gets further amplified if decoy species are less stable than the protein.

The gene expression noise could be beneficial for the survival of organisms in a population under fluctuating external environments. It can cause diseases and induce defects in developing embryos where precision is important. Our results show that, depending on contexts, the decoy can be used to amplify or suppress gene expression noise.

APPENDIX

Dynamical equation for moments

Let $\phi(x,y,c) = x^{m_1}y^{m_2}c^{m_3}$ (for $m_1, m_2, m_3 \in 0, 1, 2, ..$) be any arbitrary moment. The time evolution of $\phi(x,y,c)$ obeying the chemical master equation Eq. (3) in the main text is given by,

$$\begin{aligned}\frac{d\langle\phi(x,y,c)\rangle}{dt} &= \langle k_x \textstyle\sum_{i=1}^{\infty} \alpha_x(i)\,[\phi(x+i,y,c) - \phi(x,y,c)]\rangle \\ &+\langle k_y(x) \textstyle\sum_{i=1}^{\infty} \alpha_y(i)\,[\phi(x,y+i,c) - \phi(x,y,c)]\rangle \\ &+\langle \gamma_x x\,[\phi(x-1,y,c) - \phi(x,y,c)] \\ &+\langle \gamma_y y\,[\phi(x,y-1,c) - \phi(x,y,c)]\rangle \\ &+\langle k_u c\,[\phi(x+1,y+1,c-1) - \phi(x,y,c)]\rangle \\ &+\langle k_b xy\,[\phi(x-1,y-1,c+1) - \phi(x,y,c)]\rangle.\end{aligned}$$

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