Noisy signaling through promoter logic gates

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We study the influence of noisy transcription factor signals on cis-regulatory promoter elements. These elements process the probability of binary binding events analogous to computer logic gates. At equilibrium, this probability is given by the so-called input function. We show that transcription factor noise causes deviations from the equilibrium value due to the nonlinearity of the input function. For a single binding site, the correction is always negative resulting in an occupancy below the mean-field level. Yet for more complex promoters it depends on the correlation of the transcription factor signals and the geometry of the input function. We present explicit solutions for the basic types of AND and OR gates. The correction size varies among these different types of gates and signal types, mainly being larger in AND gates and for correlated fluctuations. In all cases we find excellent agreement between the analytical results and numerical simulations. We also study the *E. coli* Lac operon as an example of an AND NOR gate. We present a consistent mathematical method that allows one to separate different sources of noise and quantifies their effect on promoter occupation. A surprising result of our analysis is that Poissonian molecular fluctuations, in contrast to external fluctuations, do no contribute to the correction.

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INTRODUCTION

Life is a phenomenon emerging from the subtle interplay of physical processes on a molecular scale. Nowadays, these processes are directly observable in single molecule experiments. This opens the door for bottom-up approaches to understand cellular function such as genetic regulation. In this fundamental biological process transcription factors (TFs) bind in response to environmental or cellular signals to specific DNA regions, the promoter, thereby triggering or inhibiting the expression of genes. If multiple TFs bind to distinct sites, thus integrating multiple signals, the promoter comprises a *cis*-regulatory module controlling gene expression through the Boolean combination of bound TFs [1,2]. The input-output behavior attributed to the transcriptional logic gate has been measured for various genes [3–6] at constant inducer levels. Because many TFs are present in low copy numbers per cell, however, the regulatory processes are inevitably stochastic.

Although there has been intense theoretical [7–14] and experimental work [15–23] on fluctuations arising from gene expression to explain cell-to-cell variations, little focus has been on the effect of such fluctuations on TF binding [24,25]. A common framework for quantifying molecular fluctuations in biochemical reactions are master equations [26]. These have been successfully used for the analysis of gene expression noise by various authors [8–10,27]. The inherent nonlinearity arising from the bimolecular TF-promoter interaction, however, impedes the analysis of the binding reaction with master equations substantially because moment-closure schemes fail. Therefore previous investigations on TF-promoter binding either used rate equations [28] or thermodynamic equilibrium models [1,29,30]. When concerning noise in genetic networks, several authors have used mean-field approximations [8,10,19] which are equivalent to a linearization of the system. Although these works have provided groundbreaking insights into the propagation of noise in genetic cascades, a systematic analysis of this nonlinear stochastic system is missing so far. This paper presents a detailed analysis of a TF-promoter interaction finding and quantifying noise-induced corrections due to the nonlinearity of the reactions. For a single binding site we find a negative correction to the mean-field level, while for *cis*-regulatory modules the correction depends nontrivially on the geometry of the input function and the correlation of the TF signals.

SINGLE SITE

We start by studying a single site and then extend the model to *cis*-regulatory modules. The single-site model consists of two reaction steps: First, TFs are synthesized with constant rate Γ and degraded proportional to the total number of TFs, n, with first-order rate constant D. In principle, this could also be a reversible activation or dimerization reaction if the amount of inactive (or monomer) TFs can be considered as a reservoir. Second, active TFs reversibly bind to a single promoter site s at rate j^+n and, in turn, dissociate at rate j^-:

$$\emptyset \underset{Dn}{\overset{\Gamma}{\rightleftharpoons}} n \underset{j^-}{\overset{j^+n}{\rightleftharpoons}} sn. \tag{1}$$

This kinetic model has been proposed previously by Berg *et al.* [24]. The reaction scheme manifests in the corresponding master equation,

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$$\partial_t \boldsymbol{\rho}(n;t) = \left\{ [\Gamma(\mathcal{E}_n^- - 1) + D(\mathcal{E}_n^+ - 1)n]\mathbb{1} + \begin{pmatrix} -j^- & j^+\mathcal{E}_n^+ n \\ j^-\mathcal{E}_n^- & -j^+ \end{pmatrix} \right\} \boldsymbol{\rho}(n;t), \tag{2}$$

determining the time-evolution of the vector density $\boldsymbol{\rho}(n;t) = [\rho_1(n;t), \rho_0(n;t)]^\top$. The components describe the probability of finding n free TFs and the promoter either occupied, $\rho_1(n;t)$, or free, $\rho_0(n;t)$. The shift operators $\mathcal{E}_n^\pm$ change the argument of $\boldsymbol{\rho}(n;t)$ by ± 1, according to the associated change of molecules in the reaction [26]. The first term on the right-hand side (rhs). in Eq. (2) accounts for the production and degradation of TFs, the latter term governs the interaction. The stationary solution of Eq. (2) is given by a vector Poisson distribution:

$$\boldsymbol{\rho}(n) = \begin{pmatrix} h(a) \\ 1 - h(a) \end{pmatrix} P(n;a), \tag{3}$$

where the symbol $P(n;a) = e^{-a}(a)^n/n!$ defines the Poisson distribution with parameter $a = \Gamma/D = \langle n \rangle$, while the equilibrium input function h is given by

$$h(a) = a/(a + J) \tag{4}$$

with $J = j^-/j^+$. There are two things to note: First, the stationary distribution of the free TF is a Poisson distribution and unaffected by the binding reaction, $\rho(n) = \rho_0(n) + \rho_1(n) = P(n;\Gamma/D)$. Second, the degree of occupation $\rho_1 = \Sigma_n \rho_1(n) = h(\langle n \rangle)$ is completely determined by the mean TF abundance, although one might expect corrections due to molecular fluctuations. This is related to detailed balance, as discussed in [24]. We conclude that in this kinetic model, Poissonian molecular fluctuations do not cause corrections. Because there exists many other sources of noise in a realistic biological model in addition to Poissonian molecular fluctuations, we will present a systematic strategy for separating these two sources and quantifying their effect on the binding kinetics.

External noise

We include other sources of noise by letting the synthesis rate Γ be a stochastic process itself, i.e., $\Gamma \to \Gamma(\xi_t)$, where ξ_t is an external noise process. This arises, e.g., from mRNA fluctuations in gene expression noise [11] or signaling fluctuations in TF activation. In principle, ξ_t could also represent slowly varying factors commonly summarized as extrinsic noise.

Whereas the undisturbed system defined in Eq. (2) relaxes to the stationary vectorial Poissonian, Eq. (3), with a constant parameter $a = \Gamma/D$, external noise counteracts this process. Hence, instead of finding a single Poissonian distribution, one finds a superposition due to the noisy reaction rates. As shown in the Appendix, the resulting stationary distribution can be approximated for fast binding and slow fluctuations by

$$\boldsymbol{\rho}(n) \approx \int_0^\infty \begin{pmatrix} h(\alpha) \\ 1 - h(\alpha) \end{pmatrix} P(n;\alpha) f(\alpha) d\alpha. \tag{5}$$

This strategy is, in general, termed Poisson representation [31]. The function $f(\alpha)$ is the stationary probability density of a process defined by the stochastic differential equation (SDE):

$$\frac{d}{dt}\alpha_t = \Gamma(\xi_t) - D\alpha_t. \tag{6}$$

This process can be interpreted as the "center-of-mass" dynamics since it holds that $\langle n_t \rangle = \langle \alpha_t \rangle$. For the stationary variance one finds that $\sigma_n^2 = \langle n \rangle + \sigma_\alpha^2$. This addition rule of σ_n^2 results from lacking feedback [32]: $\langle n \rangle$ stems from internal molecular (Poissonian) fluctuations, while σ_α^2 is the variance caused by external noise. For mRNA fluctuations this accords with previous studies using moment-closure schemes [8,11].

The approximation in Eq. (5) is valid if the dynamics of the TF are slow compared to the binding reaction. Then the promoter is equilibrated with the fluctuations according to $h(\alpha)$. Studying the relevant rates shows that this condition is fulfilled *in vivo*: Being a random telegraph process, the interaction equilibrates at rate $j^+\langle n \rangle + j^-$. Previous theoretical and experimental investigations agree that TF search times are on the order of 10 s–1 min [33,34]. For TF abundances of 10–100 per cell, this yields $j^+\langle n \rangle \approx 1/\mathrm{s}$. In contrast, the characteristic rate of TF fluctuations is D, which can be assumed to be $D \approx 0.1\text{–}0.01/\mathrm{s}$. This is at least an order of magnitude slower than the binding dynamics, $D \ll j^+\langle n \rangle$; therefore the interaction is equilibrated on the time scale of TF fluctuations since the condition $D \ll j^+\langle n \rangle + j^-$ is fulfilled. In this case, the promoter occupation $h(\alpha)$ adiabatically follows external fluctuations. A quantitative discussion of this effect is given in the Appendix. There we also show that fluctuations faster than the binding kinetics are mediated rendering the mean-field value to be exact.

According to Eq. (5), the stationary promoter occupation is given by $\rho_1 = \int_0^\infty h(\alpha) f(\alpha) d\alpha$; it thus depends on the stationary distribution $f(\alpha)$. In most cases, however, only the first central moments $\mu_\alpha^{(i)}$ are known. We therefore expand this expression into a series,

$$\rho_1 = \sum_{i=0}^{\infty} \frac{h^{(i)}(\langle \alpha \rangle)}{i!} \mu_\alpha^{(i)} = \rho_1^{(0)} + \rho_1^{(2)} + \ldots, \tag{7}$$

where $h^{(i)}$ are the Taylor coefficients of h. If $|\mu_\alpha^{(i)} h^{(i)}(\langle \alpha \rangle)|$ vanishes sufficiently fast, one can truncate the sum after the second term giving rise to $\rho_1 \approx \rho_1^{(0)} + \rho_1^{(2)}$. Here $\rho_1^{(0)} = h(\langle n \rangle)$ is the mean-field result and $\rho_1^{(2)} = -J\sigma_\alpha^2/(J + \langle n \rangle)^3$ the first correction due to noise; the order $\rho_1^{(1)}$ vanishes since $\mu_\alpha^{(1)} = 0$. This type of approximation is sometimes referred to as small noise expansion [9]. To analyze if the second order causes a significant correction, we study its relative size

$$\frac{\rho_1^{(2)}}{\rho_1^{(0)}} = -\frac{x}{(1+x)^2}\eta_\alpha^2, \tag{8}$$

with the dimensionless parameters $x = \langle n \rangle / J$ and η_α^2

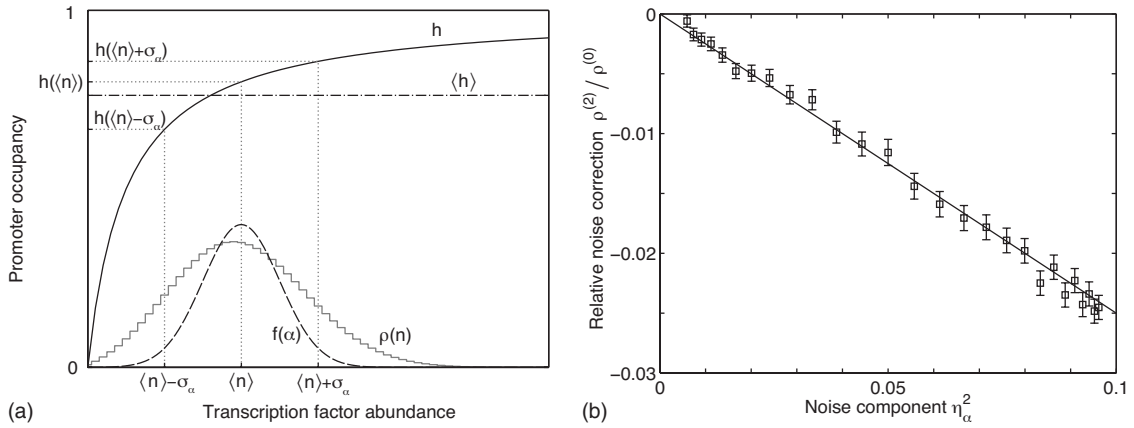

FIG. 1. (a) Schematic illustration of the noise correction. For slow TF fluctuations the promoter occupation is a saturating function h of the regulator abundance (black line). Under external noise, the distribution of the regulator, $\rho(n)$ (solid gray line), can be expressed as a superposition of Poisson distributions with a distribution $f(\alpha)$ (black dashed curve) with mean $\langle\alpha\rangle=\langle n\rangle$. According to Eq. (5) the distribution f determines the occupation level. Because of the curvature of h, positive deviations $\langle n\rangle+\sigma_\alpha$ have less influence on the occupation than negative ones, $\langle n\rangle-\sigma_\alpha$. Thus external fluctuations cause a negative correction to the mean-field level, $h(\langle n\rangle)$, leading to a smaller mean occupation $\langle h\rangle$ (black dash-dotted line). (b) The noise component $\eta_\alpha^2=\sigma_\alpha^2/\langle n\rangle^2$ causes a linear decrease of the mean promoter occupation. Shown are data for $x=\langle n\rangle/J=1$. The black line denotes the linear decrease with slope −0.25 as supposed by Eq. (8). The squares are the results of numerical simulations using the Gillespie algorithm [35] with increasing external noise levels. Error bars denote the standard deviation of the numerical estimator due to the finite simulation length.

$=\sigma_\alpha^2/\langle\alpha\rangle^2$. Independent of x, external noise η_α^2 causes a *negative* correction to the mean-field occupation, with a maximally possible value of $-\eta_\alpha^2/4$. This effect can be explained by the negative curvature of the input function h weighting negative deviations from the mean more strongly than positive ones as shown in Fig. 1(a). Yet this notion is somewhat oversimplified, since Poissonian molecular fluctuations do not contribute as discussed in the previous section. The predicted linear dependency on the noise component η_α^2 is fully supported by numerical simulations using the Gillespie algorithm [35] as depicted in Fig. 1(b). The noise correction is zero for $\eta_\alpha^2=0$; in this case the approximation exactly reproduces the mean-field value according to Eq. (3).

The noise component η_α^2 is defined by the stochastic differential equation Eq. (6). Thus different types of external noise processes ξ_t can lead to identical stationary moments of α, and hence to identical noise correction terms. We have tested this hypothesis and found that this is indeed the case (data not shown). Since the dampening $-D\alpha_t$ filters fast external noise components this ensures that the time-scale separation between binding kinetics and TF fluctuations remains valid.

The same expansion strategy holds for the unoccupied state ρ_0 yielding correction terms $\rho_0^{(i)}=-\rho_1^{(i)}$. Hence the noise correction for the unoccupied state is always positive. Furthermore, this result also ensures that the truncated series in Eq. (7) can be interpreted as a probability at every order since the correction terms for occupied and unoccupied states cancel pairwise.

PROMOTER LOGIC

Having found a strategy to quantify the effect of TF noise at a single site we are now able to study *cis*-regulatory elements. While the influence of noise at a single binding site could be represented as a function of the TF noise level, the effect at complex promoters depends on the combination of logic gate and the correlation structure of the multivariate input. We will first present a general approach and then derive explicit solutions for basic AND and OR gates.

For a promoter having M binding sites we define binary variables s_i denoting whether the ith binding site is free, $s_i=0$, or occupied, $s_i=1$, respectively. These will be summarized by a binary vector $\boldsymbol{s}=(s_1,\ldots,s_M)$. Reconsidering the single-site expression in Eq. (5) in an index notation, $\rho_s=\int h_s(\alpha)f(\alpha)d\alpha$ with $h_1(\alpha)=h(\alpha)$ and $h_0(\alpha)=1-h(\alpha)$, it is straight-forward to generalize this expression to the case of M binding sites and N different TFs. Then the probability for a given state $\boldsymbol{s}$ reads

$$\rho_s=\int h_s(\boldsymbol{\alpha})f(\boldsymbol{\alpha})d\boldsymbol{\alpha}. \tag{9}$$

The vector $\boldsymbol{\alpha}=(\alpha_1,\ldots,\alpha_N)$ contains the center-of-mass variables α_i of each TF n_i, which are distributed by a joint density $f(\boldsymbol{\alpha})$. The probability of occupying the state $\boldsymbol{s}$ at a given level of $\boldsymbol{\alpha}$ is given by the input function $h_s(\boldsymbol{\alpha})$ which can be determined by thermodynamical approaches [1,30]. The genetic induction will then be a product of the probability for the occupation state $\boldsymbol{s}$ and the corresponding induction rate accounting for the RNA polymerase affinity of that particular state. Logic gates arise from the idealization that successful transcription does only occur in one particular state, the gene is said to be *on*, and is fully suppressed—*off*—in the others.

Since we wish to link the mean occupation to the noise level we expand Eq. (9) similarly to the single-site case:

$$\rho_s = h_s(\langle \boldsymbol{\alpha} \rangle) + \frac{1}{2}\sum_{i,j=1}^{N} h_s^{(i,j)}(\langle \boldsymbol{\alpha} \rangle) C_{\boldsymbol{\alpha}}^{(i,j)} + \ldots =: \rho_s^{(0)} + \rho_s^{(2)} + \ldots . \tag{10}$$

The symbol $h_s^{(i,j)}(\langle \boldsymbol{\alpha} \rangle)$ denotes the partial derivative of h_s with respect to α_i and α_j; $C_{\boldsymbol{\alpha}}^{(i,j)}$ is the covariance matrix of $\boldsymbol{\alpha}$. The notion behind this approximation is similar to the single-site case: The correction due to noise $\rho_s^{(2)}$ is given by the curvature of the input function $h_s^{(i,j)}(\langle \boldsymbol{\alpha} \rangle)$ times the variability of the input signal in the $i-j$ direction, as given by $C_{\boldsymbol{\alpha}}^{(i,j)}$. The noise correction critically depends on the correlation structure of the input signal: For an uncorrelated input the sum consists only of N diagonal terms. For correlated input fluctuations, however, all N^2 terms contribute to the noise correction. We will explicitly illustrate this effect for the AND and OR gates.

So far, we have not specified the input function $h_s(\boldsymbol{\alpha})$ in Eq. (9). Assuming $M=N$ and independent binding kinetics for clarity, it is of product form, $h_s(\boldsymbol{\alpha}) = \Pi_{i=1}^{N} h_{s_i}(\alpha_i)$, with $h_{s_i}(\alpha_i) = h(\alpha_i)^{s_i}[1-h(\alpha_i)]^{1-s_i}$ being the single site input function of the state s_i in index notation. Since all TFs bind independently the mean-field order is a product of the corresponding single-site occupations:

$$\rho_s^{(0)} = h_s(\langle \boldsymbol{\alpha} \rangle) = \prod_{i=1}^{N} \rho_{s_i}^{(0)}. \tag{11}$$

It is also straightforward to calculate the Taylor coefficients by the derivatives of the single site input function $h(\alpha_i)$. For the relative size of the noise correction, it follows that

$$\frac{\rho_s^{(2)}}{\rho_s^{(0)}} = \frac{1}{2}\sum_{i,j=1}^{N} [\partial_i \partial_j \log h_{s_i}(\langle \alpha_i \rangle) \log h_{s_j}(\langle \alpha_j \rangle) + \delta_{ij}\partial_i^2 \log h_{s_i}(\langle \alpha_i \rangle)] C_{\boldsymbol{\alpha}}^{(i,j)}. \tag{12}$$

This expression can be readily evaluated for the different logic gates.

AND

In an AND gated promoter, all promoter sites s_i need to be occupied for the gene to be active. The corresponding probability thus is

$$\rho_{N,\mathrm{AND}} = \rho_{1,\ldots,1}. \tag{13}$$

For the independent input function it follows from Eq. (10) that the mean-field level is given by

$$\rho_{N,\mathrm{AND}}^{(0)} = \prod_{i=1}^{N} \frac{x_i}{1+x_i}, \tag{14}$$

with the dimensionless quantities $x_i = \langle n_i \rangle / J_i$. It is further convenient to assume that all kinetic rates are equal, $x_i = x$, thereby reducing parameter space. With increasing N the input function displays a sigmoid behavior corresponding to a genetic switch. The noise correction is, in principle, given by Eq. (12); yet it still depends on the input correlation $C^{(i,j)}{}_{\boldsymbol{\alpha}}$. Instead of presenting the general case it is thus elucidating to analyze two limits: Multiple independent transcription factors giving rise to an uncorrelated input signal, and a single type of regulator binding to multiple sites causing identical fluctuations at each binding site. In the first limit one has $C_{\boldsymbol{\alpha}}^{(i,j)} = \delta_{ij}\sigma_\alpha^2$. Since the covariance matrix is diagonal, Eq. (12) only sums the terms $h_{1,\ldots,1}^{(i,i)}(\langle \boldsymbol{\alpha} \rangle)$. This gives rise to a relative correction of

$$\frac{\rho_{N,\mathrm{AND}}^{(2)\perp}}{\rho_{N,\mathrm{AND}}^{(0)}} = N\frac{\rho_1^{(2)}}{\rho_1^{(0)}} = -N\frac{x}{(1+x)^2}\eta_\alpha^2. \tag{15}$$

Here, the superscript $\perp$ denotes the uncorrelated case. Comparing this result with Eq. (8), one finds that the relative correction for N independent regulators, each subject to a noise level η_α^2, is identical to the case of a single regulator with noise strength $N\eta_\alpha^2$. Hence its absolute value *increases* with the number of sites N as shown in Fig. 2(a) (black lines). As a result, the size of the correction could change easily by an order of magnitude if the gene is dependent on sufficiently many regulators.

For identical fluctuations it holds that $C_{\boldsymbol{\alpha}}^{(i,j)} = \sigma_\alpha^2$ for all i,j. Denoting this case with the symbol $\parallel$ one finds a correction, according to Eq. (12), of

$$\frac{\rho_{N,\mathrm{AND}}^{(2)\parallel}}{\rho_{N,\mathrm{AND}}^{(0)}} = \frac{N}{(1+x)^2}\left(\frac{N-1}{2} - x\right)\eta_\alpha^2. \tag{16}$$

Here, all of the $N(N-1)$ off-diagonal terms contribute to the noise correction in addition to the diagonal elements. For $x > \frac{N-1}{2}$ the correction is negative and, in the limit of large x, equals that of the uncorrelated case, whereas for $x < \frac{N-1}{2}$ the correction is *positive* and increases quadratically with N. Hence the noise correction changes sign as shown in Fig. 2(b) (black lines) because of the sigmoidal input function $h_{1,\ldots,1}(\langle \alpha \rangle) = h(\langle \alpha \rangle)^N$. Overall, both positive and negative corrections smear out the response of the genetic switch, thereby constraining ultrasensitivity [36]. This effect is illustrated in Fig. 3: While the mean-field result $\rho_{N,\mathrm{AND}}^{(0)}$ displays a distinct threshold, the noise-corrected response $\rho_{N,\mathrm{AND}}^{(0)} + \rho_{N,\mathrm{AND}}^{(2)}$ is less steep. An exception is the single-site case $N=1$ where noisy signals cause a steeper response. This counterintuitive effect, caused by the input function being hyperbolic, has been termed stochastic focusing [24,37].

OR

For an OR gated promoter it is already sufficient that one of N possible sites s_i is occupied in order to activate the transcription. The probability corresponding to this event is

$$\rho_{N,\mathrm{OR}} = 1 - \rho_{0,\ldots,0}. \tag{17}$$

The absolute noise correction for the state $\boldsymbol{s} = (1,\ldots,1)$ can be calculated from Eq. (12) for a given input correlation. We will again discuss the two opposite limits of multiple uncorrelated signals, and a single TF. The resulting second-order noise corrections to the mean-field OR state are presented in Table I. The correction terms are negative in both limits. As illustrated in Figs. 2(a) and 2(b) (gray lines) the maximal correction *decreases* with increasing N for uncorrelated fluc-

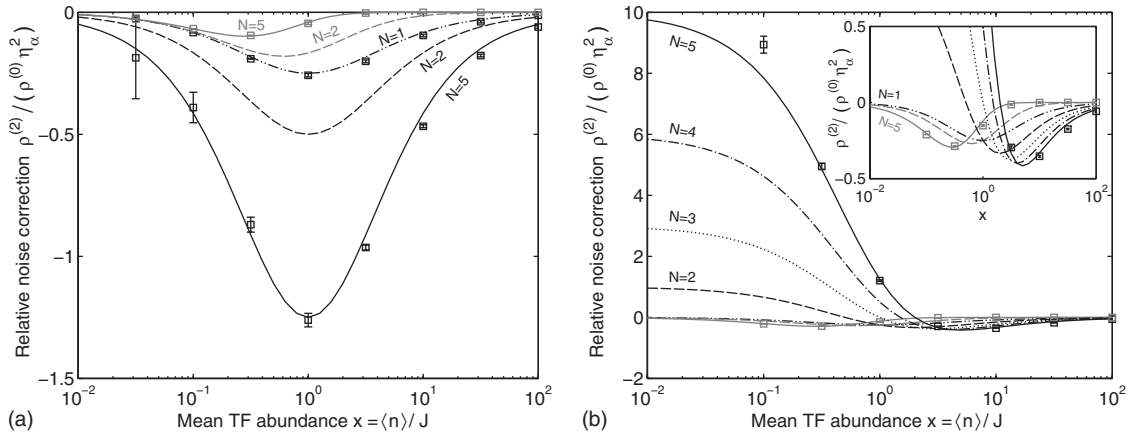

FIG. 2. Relative second order corrections to the mean-field result for different promoter logic. The gray lines denote results for the OR gate and the black lines for the AND gate, respectively. N indicates the number of binding sites. Square symbols represent results from numerical simulations; error bars were calculated from the variance of the numerical estimator for the occupancy. (a) Independent TFs/uncorrelated input signal. The relative size of the first correction increases with N for the AND gate, whereas it decreases for the OR gate. (b) A single TF binding to multiple sites/identical fluctuations. The noise correction changes sign for the AND gate for $N>1$. For the OR gate, the correction remains negative, however, the size does not increase significantly with N. The inset shows the relative correction on a smaller scale. The gray dashed line denotes the case $N=2$.

tuations but *increases* for identical external noise; in both cases it vanishes for large and small x.

The results for both types of gates and fluctuations are summarized in Table I. As required, all types of approximated gates reproduce the single site result for $N=1$. By construction, the results are linear in the noise component η_α^2. Hence for no external noise, i.e., vanishing η_α^2, all corrections are zero; it still holds that Poissonian fluctuations do not contribute to the noise correction in promoter logic gates.

We tested the validity of our analysis by numerical simulations using the Gillespie algorithm [35]. External noise was modeled as a Poisson process feeding into the production of regulators. As shown in Fig. 2 our analytical terms are in excellent agreement with the simulations.

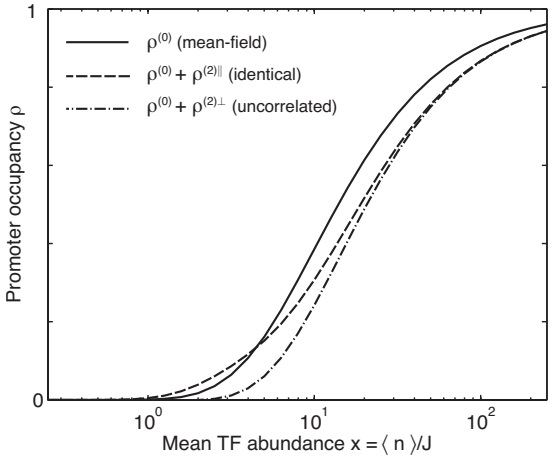

FIG. 3. Identical fluctuations counteract thresholding at AND gates. Shown are the mean-field value $\rho_{N,\mathrm{AND}}^{(0)}=[x/(1+x)]^N$ and the noise-corrected occupation according to $\rho_{N,\mathrm{AND}}^{(2)}$ for identical ($\|$) and uncorrelated ($\perp$) input fluctuations. While the pronounced threshold of the mean-field result is essentially shifted for uncorrelated TF signals, correlated fluctuations smear out the response. This situation arises, e.g., if there exists multiple binding sites for the same TF. Results shown are computed for $N=5$ binding sites and a noise level of $\eta_\alpha^2=0.4$.

Lac operon: AND NOR

From the definition Eq. (9) it is also possible to construct more complex logic gates. A prominent example that also nicely illustrates the notion of the noise correction is the *E. coli* Lac operon which resembles some properties of an AND NOT gate [3]. This operon regulates the expression of lactose digesting enzymes in the presence of this nutrient; otherwise the production is repressed. Successful transcription initiation only occurs if the activator, cAMP repressor protein (CRP), is bound and activated by cyclic adenosine monophosphate (cAMP), and the repressor LacR, which is induced by allolactose, is not. Thus cAMP and allolactose could be potential external noise sources. If the activator

TABLE I. Relative size of the first order corrections to the mean-field result, $\rho^{(2)}/\rho^{(0)}$, for different logic gates and input correlations. The number of binding sites is N, $x=\langle n\rangle/J$ denotes the rescaled mean TF abundance, and η_α^2 is the external noise component.

Gate	Uncorrelated ($\perp$)	Identical ($\|$)
AND	$\frac{-Nx}{(1+x)^2}\eta_\alpha^2$	$\frac{N}{(1+x)^2}\left(\frac{N-1}{2}-x\right)\eta_\alpha^2$
OR	$\frac{-1}{[(1+x)^N-1]}\frac{Nx^2}{(1+x)^2}\eta_\alpha^2$	$\frac{-1}{[(1+x)^N-1]}\frac{N(N+1)}{2}\frac{x^2}{(1+x)^2}\eta_\alpha^2$
NOR[a]	$\frac{Nx^2}{(1+x)^2}\eta_\alpha^2$	$\frac{N(N+1)}{2}\frac{x^2}{(1+x)^2}\eta_\alpha^2$

[a] $\rho_{N,\mathrm{NOR}}=\rho_{0,\ldots,0}$.

binds to site s_1 and the repressor to site s_2, the event of finding bound CRP and the LacR site unoccupied, i.e., "CRP AND NOT LacR," is given by $\boldsymbol{s}=(s_1,s_2)=(1,0)$. If activator and repressor are stochastically independent, the relative noise correction is, cf. Eq. (12), $\rho^{(2)}_{1,0}/\rho^{(0)}_{1,0}=\rho^{(2)}_1/\rho^{(0)}_1+\rho^{(2)}_0/\rho^{(0)}_0$.

In fact, however, the Lac operon contains three binding sites for the LacR repressor; it is thus an example of an AND NOR gate where neither of the repressor sites may be occupied. The event that the activator is bound but no repressor thus corresponds to the vector $\boldsymbol{s}=(1,0,0,0)$ where the last three digits denote the unoccupied LacR binding sites. If the activator is again stochastically independent from the repressor, the respective probability is $\rho_{1,0,0,0}=\rho_1\rho_{0,0,0}$. Since the LacR fluctuations are identical our theory predicts a correction according to Eq. (12) of

$$\frac{\rho^{(2)}_{1,0,0,0}}{\rho^{(0)}_{1,0,0,0}}=\frac{\rho^{(2)}_1}{\rho^{(0)}_1}+\frac{\rho^{(2)\|}_{0,0,0}}{\rho^{(0)}_{0,0,0}}, \tag{18}$$

where the first term on the rhs is the single-site correction to the CRP binding site as given by Eq. (8). The latter term is the NOR-gated correction of finding no LacR repressor, namely

$$\frac{\rho^{(2)\|}_{0,0,0}}{\rho^{(0)}_{0,0,0}}=\frac{1}{2}\left[\sum_{i\neq j}^{3}\frac{x_i x_j}{(1+x_i)(1+x_j)}+2\sum_{i=1}^{3}\frac{x_i^2}{(1+x_i)^2}\right]\eta^2_{\alpha_{\mathrm{LacR}}}. \tag{19}$$

Here we have dropped the assumption of identical binding kinetics and $x_i=\langle \mathrm{LacR}\rangle/J_i$ with J_i being the dissociation constant of each LacR binding site. The expression shows that even in the limit of strong interaction at all sites $x_i\gg 1$ the relative size of the noise correction does not vanish; instead it reaches a stationary value of $6\eta^2_\alpha$. Since the correction is always positive, we conclude that a mean-field approach systematically overestimates the strength of repression by LacR.

Including the effect of noisy CRP activation causes a more diverse correction landscape depending on the mean and external noise levels of CRP and LacR. The resulting total correction and the mean-field input function are shown in Fig. 4 assuming identical noise levels. Depending on the curvature of the input function, noise locally causes positive or negative corrections. Since the susceptibility to noise is strongest in regions with maximal curvature we conclude that, in most cases, a noisy TF input decreases the steepness of the transitions. In the Lac operon this is apparent by the sigmoidal shape of the LacR repression curve: Here the noise correction is strongest at its shoulder thereby flattening the average response.

Experiments indicate that the Lac repressor LacR is present at abundances of about 10 molecules/cell [34]. Low concentrations coincide, in general, with large noise levels. Because both correction terms in Eq. (18) are proportional to the corresponding noise levels, one or the other may dominate the correction depending on the relative noise strength. Since only the non-Poissonian noise component η^2_α contributes to the correction, this indicates two scenarios for LacR: If the activation is uniform the noise is purely Poissonian and the second term on the rhs of Eq. (18) vanishes. Then the correction depends solely on the first term, i.e., on the dynamics of CRP. Because CRP has only one binding site, the resulting correction is negative. Yet if the activation of LacR is bursty, the external noise component is large and may dominate the correction. In this limit, the overall correction is governed by the dynamics of LacR and changes sign depending on the local curvature.

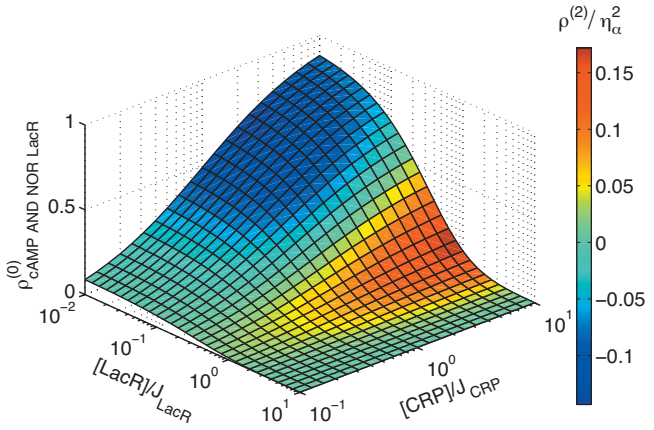

FIG. 4. (Color) The noise correction to the mean-field occupation depends on the geometry of the input function. Shown on the z axis is the mean-field occupation $\rho^{(0)}$ as a function of CRP and LacR concentrations in units of their corresponding promoter dissociation constants J. The color denotes the size of the noise correction $\rho^{(2)}$, Eq. (19). This plot illustrates the influence of the curvature: In regions with positive curvature, the correction is positive (red colors), whereas for negative curvature it is negative (blue colors). Positive corrections thus occur for intermediate repression but high induction by CRP, whereas negative corrections prevail for low repression but intermediate activation. For simplicity, it is assumed that all LacR binding sites have the same affinity and that noise levels of both CRP and LacR are equal.

We note that the presented kinetics are only an approximation of the complex interactions at the operon. DNA looping facilitates a stabilizing interaction between two LacR repressors bound at sites O_2 and O_3 [38,39]. Kinetically, this results in a slower dissociation rate of the LacR complex, which in turn alters the shape of the input function $h(\alpha)$. However, the time-scale separation between TF noise and binding kinetics is mainly based on the fast association rate. We therefore expect that the general approximation, Eq. (10), will still be valid for complex promoter dynamics. We conclude that, although the presented approach simplifies the complex regulation of the Lac operon, the resulting equilibrium input function displays the relevant features of experimentally observed induction curves [3,5]. Furthermore, the corresponding analytical expressions allowed us to explicitly calculate the predicted corrections for fluctuating inputs.

DISCUSSION

In summary, we presented a comprehensive analytical and numerical analysis of a stochastic transcription factor binding to promoters with one or multiple binding sites. We derived explicit expressions for the noise corrections arising

from slow TF fluctuations and fast binding. At a single site external noise reduces the average promoter occupation below the mean-field level due to saturation effects. In the discussed model Poissonian noise, surprisingly, does not contribute to the noise correction (Fig. 1). We note that although the non-Poissonian noise component cannot be measured directly, it could be inferred from the observable total noise level since $\eta^2 = 1/\langle n \rangle + \eta_\alpha^2$ where $\langle n \rangle$ is the average number of TFs. This relation also implies that the external noise component in most cases dominates the total noise level because the Poissonian contribution vanishes as $1/\langle n \rangle$.

The noise contribution η_α^2 is defined by the "center-of-mass" equation, Eq. (6). Interestingly, this is a Langevin equation which has also been used by other authors [14,19] and which is typically assumed to be a mesoscopic approximation to the discrete molecular description by master equations [26]. We modeled external noise entering additively through the process of TF synthesis $\Gamma(\xi_t)$. In a realistic biological model, also the degradation or deactivation reaction is regulated by other processes and hence subject to external fluctuations. Then noise enters the system multiplicatively through $-D(\xi_t)$. The presented method is also capable of handling this situation, however, calculating the resulting moments of α becomes slightly more complicated since the equations for the moments are not of closed form.

In vivo, most genes are combinatorially regulated by multiple TFs in both prokaryotes [40] and eukaryotes [2] enhancing the programmability of gene expression. Yet the strong nonlinearity in logic gates amplifies the effect of noise. We derived an exact analytical expression for an arbitrary occupational event accounting for the effect of external noise. A systematic expansion of this expression revealed that a combination of the geometry of the input function and the correlation structure of the TF signal determines the noise resistance of the gate. Having solved these expressions explicitly for the basic types of AND and OR gates we have shown that, in general, the noise correction increases with the number of binding sites in AND gates, whereas OR gates are only moderately affected. Combining these two types with a logical NOT allows one to construct the solutions for realistic promoters such as the *E. coli* Lac operon or even more complex ones. For the Lac operon we showed that noise causes nontrivial corrections depending on the mean levels of Lac repressor and CRP.

The analyzed models for the input function h simplify the binding dynamics at complex promoters, however, they qualitatively reproduce the characteristic nonlinearities and saturation effects which have been modeled by detailed thermodynamic approaches [1,30]. In prokaryotes the TF binding process is thought to require one-dimensional diffusion along DNA by nonspecific binding [33,34], cooperative interactions of the transcription factors [40], DNA looping [38,39], and many other phenomena. In eukaryotes an additional layer of complexity exists by chromatin remodeling [41]. Successful transcription initiation may also occur from more than one TF occupation state, most likely at different rates. The resulting genetic activation is then the sum of all active states weighted by their initiation rate.

Our analysis revealed that in nonequilibrium models, the nonlinearities are causing deviations from the mean-field levels since fluctuations do not compensate. Experimentally observed input functions also comprise effects downstream from the TF promoter interactions, basically generating "black box" models of gene response with the TFs, or their inducers, as inputs and the gene product (typically a fluorescent dye) as its output. Again, a common feature of all observed input functions are strong nonlinearities and saturation effects [3,6]. Extending the notion that noisy inputs cause deviations in the mean output for nonlinear gates, we expect that the same effect also holds for the experimentally assessed promoters.

We have assumed that external sources of noise arise from gene expression or TF activation by environmental stimuli. Recently it has been shown in yeast that regulation by the transcription factor Crz I occurs in a frequency-dependent manner through short bursts of nuclear localization [42]. This mechanisms is thought to coordinate the regulation of multiple target genes because of the identical peak amplitude. However, it also results in strong noise levels and thus in mean induction levels that might not accurately be accounted for by equilibrium approaches.

Experimentally observed noise levels in prokaryotes [15] and extrapolated values of eukaryotes [43] were on the order of $\eta^2 \sim 0.1$. For such noise levels our theory predicts the single-site corrections of $\sim 1\%$. This, in turn, states that modeling approaches with rate equations and thermodynamical equilibrium approaches have a high accuracy for simple binding kinetics. For AND gates with many inputs, however, we predict corrections on the order of 10%. In these cases, a macroscopic description might thus not be appropriate.

While most studies concerning noise in genetic networks have only focused on the propagation of noise while assuming that the mean dynamics are constant, our analysis reveals that fluctuations also quantitatively affect the mean dynamics of transcriptional regulation in a nontrivial way. As the mean dynamics are inherently linked to the noise levels, this, in turn, affects noise levels of the system. In summary, we conclude that this potentially also affects the qualitative behavior of complex genetic networks.

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APPENDIX: POISSON REPRESENTATION

The Poisson representation [31,44] was originally introduced to approximate nonlinear chemical master equations. However, it also allows one to quantify the influence of external fluctuations on a first-order chemical reaction such as TF synthesis or protein translation.

Introducing the time-evolution operators

$$\mathcal{L}_0 = [\Gamma(\mathcal{E}_n^- - 1) + D(\mathcal{E}_n^+ - 1)n]\mathbb{1}, \tag{A1}$$

$$\mathcal{L}_1 = \begin{pmatrix} -j^- & j^+\mathcal{E}_n^+ n \\ j^-\mathcal{E}_n^- & -j^+ \end{pmatrix}, \tag{A2}$$

the master equation, Eq. (2), has a compact representation $\partial_t \boldsymbol{\rho} = \{\mathcal{L}_0 + \mathcal{L}_1\}\boldsymbol{\rho}$. If all rates are constant, the corresponding stationary density is the vectorial Poissonian, Eq. (3) of the main text. If the production rate, however, depends on an external stochastic process $\Gamma = \Gamma(\xi_t)$, the solution $\boldsymbol{\rho}(n;t|[\xi_t])$ deviates from a Poisson distribution and depends functionally on the external process. The marginal distribution then reads $\boldsymbol{\rho}(n;t) = \int \boldsymbol{\rho}(n;t|[\xi_t])dP([\xi_t])$ where $P([\xi_t])$ is the probability measure of all trajectories $[\xi_t]$. To study the effect of the external noise, the main trick is to expand this density into real Poisson distributions,

$$\boldsymbol{\rho}(n;t|[\xi_t]) = \int_0^\infty P(n;\alpha)\boldsymbol{f}(\alpha;t|[\xi_t])d\alpha, \tag{A3}$$

with a bivariate function $\boldsymbol{f}(\alpha;t|[\xi_t]) = [f_1(\alpha;t|[\xi_t]), f_0(\alpha;t|[\xi_t])]^\top$. This is the vector case of the Poisson representation [44]. Partial integration of the master equation [Eq. (2)] yields, after summing over n,

$$\partial_t \boldsymbol{f}(\alpha;t|[\xi_t]) = \left\{ -\partial_\alpha[\Gamma(\xi_t) - D\alpha] + \begin{pmatrix} -j^- & j^+\alpha \\ j^- & -j^+\alpha \end{pmatrix} \right\} \boldsymbol{f}(\alpha;t|[\xi_t])$$

$$=: \{\hat{\mathcal{L}}_0(\xi_t) + \hat{\mathcal{L}}_1\}\boldsymbol{f}(\alpha;t|[\xi_t]), \tag{A4}$$

with the transformed operators $\hat{\mathcal{L}}_0(\xi_t)$ and $\hat{\mathcal{L}}_1$. The corresponding transformation of $\mathcal{L}_0(\xi_t)$ is based on the identities $(\mathcal{E}_n^- - 1)P(n;\alpha) = \partial_\alpha P(n;\alpha)$ and $(\mathcal{E}_n^+ - 1)P(n;\alpha) = \alpha\partial_\alpha P(n;\alpha)$; whereas $\mathcal{L}_1$ is transformed according to $\mathcal{E}_n^+ nP(n;\alpha) = \alpha P(n;\alpha)$, and $\mathcal{E}_n^- P(n;\alpha) = \alpha^{-1}P(n;\alpha)$. The dynamics of the density $\boldsymbol{\rho}(n;t|[\xi_t])$ acting on the discrete space is hereby mapped to the equivalent dynamics of $\boldsymbol{f}(\alpha;t|[\xi_t])$, which is defined on the positive real space. This has the advantage that the methods of stochastic calculus can be applied to quantify the effect of external noise. To illustrate the properties of the expansion (A3), however, we will first show how the moments of α are generally related to those of n. Let $f(\alpha) = \lim_{t\to\infty} \int \Sigma_{s=0,1} f_s(\alpha;t|[\xi_t])dP([\xi_t])$ be the marginalized stationary density. Then, by multiplying Eq. (A3) with n and summing over all states as well as integrating out $[\xi_t]$, one finds for the stationary mean

$$\langle n \rangle = \sum_{s=0,1} \sum_n n\rho_s(n) = \int_0^\infty \alpha f(\alpha)d\alpha = \langle \alpha \rangle. \tag{A5}$$

Thus the expectation of n and α coincide. Similarly, the variance is

$$\sigma_n^2 = \sum_{n=0}^\infty \int_0^\infty (n - \langle n \rangle)^2 P(n;\alpha)f(\alpha)d\alpha$$

$$= \sum_{n=0}^\infty \int_0^\infty (n-\alpha)^2 P(n;\alpha)f(\alpha)d\alpha + \int_0^\infty (\alpha - \langle\alpha\rangle)^2 f(\alpha)d\alpha$$

$$= \int_0^\infty \alpha f(\alpha)d\alpha + \sigma_\alpha^2 = \langle n \rangle + \sigma_\alpha^2, \tag{A6}$$

with $f(\alpha) = f_0(\alpha) + f_1(\alpha)$ being the stationary distribution of α. Here the variance contribution $\langle n \rangle$ corresponds to Poissonian fluctuations, whereas σ_α^2 stems from external noise. This is similar to previous results for the noise addition rule [32] and has been explicitly derived for mRNA fluctuations [11,27].

Moments of α

Having shown the relation between the moments of α and n, we will now derive an explicit expression for α in terms of the external noise process ξ_t. Marginalizing the operator state, i.e., summing over both components of f_s, $s = 0,1$, yields

$$\partial_t f(\alpha;t|[\xi_t]) = -\partial_\alpha[\Gamma(\xi_t) - D\alpha]f(\alpha;t|[\xi_t]), \tag{A7}$$

since $\hat{\mathcal{L}}_1$ vanishes under the sum. Equation (A7) is the "center-of-mass" dynamics of free transcription factors as $\Sigma_n n\rho(n;t|[\xi_t]) = \int \alpha f(\alpha;t|[\xi_t])$, i.e., $\alpha([\xi_t])$ can be identified with the (time-dependent) expectation value of free TF. One recognizes Eq. (A7) to be a Fokker-Planck equation with a stochastic drift $\Gamma(\xi_t) - D\alpha$ and vanishing diffusion, i.e., a Liouville equation. This is equivalent to an ensemble of realizations evolving according to the SDE

$$\frac{d}{dt}\alpha_t = \Gamma(\xi_t) - D\alpha_t, \tag{A8}$$

with a corresponding integral

$$\alpha_t - \alpha_{t_0} e^{-D(t-t_0)} = \int_{t_0}^t e^{-D(t-\tau)}\Gamma(\xi_\tau)d\tau. \tag{A9}$$

From this equation, the moments of $\alpha_t = \alpha([\xi_t])$ can be directly calculated as a function of the moments of ξ_t. For $\Gamma(\xi_t) = \Gamma\xi_t$, with ξ_t being a stationary process with mean $\langle\xi\rangle$, the resulting stationary expectation value reads

$$\langle\alpha\rangle = \Gamma \int_{-\infty}^0 e^{D\tau} \int \xi_\tau dP([\xi_\tau])d\tau = \frac{\Gamma}{D}\langle\xi\rangle \tag{A10}$$

because initial conditions vanish in the limit $t - t_0 \to \infty$. Similarly, the stationary variance and two-time-covariance can be shown to be

$$\sigma_\alpha^2 = \Gamma^2 \int_{-\infty}^0 \int_{-\infty}^0 e^{D(\tau+\tau')}\langle\xi_\tau, \xi_{\tau'}\rangle d\tau d\tau', \tag{A11}$$

$$\langle\alpha_t, \alpha_{t'}\rangle = \Gamma^2 \int_{-\infty}^t \int_{-\infty}^{t'} e^{D(\tau - t + t' - \tau')}\langle\xi_\tau, \xi_{\tau'}\rangle d\tau d\tau'. \tag{A12}$$

That is, the variance σ_α^2 depends on the *dynamical* properties of the external noise process. For the two-time-covariance of the external process decaying exponentially, as in the case of mRNA noise, $\langle \xi_t, \xi_{t'} \rangle = \sigma_\xi^2 e^{-k|t-t'|}$, the resulting variance is given by $\sigma_\alpha^2 = \Gamma^2/D^2 \cdot D/(k+D) \cdot \sigma_\xi^2$. One realizes that the variance vanishes if $k \gg D$, i.e., the external process being much faster than the TF decay.

Interaction

The quantity of interest is the stationary expectation of the operator s. It is given by multiplying both sides of Eq. (A4) with s and summing over the two possible values $s=0,1$ as well as integrating over α and averaging ξ_t

$$\begin{aligned}\partial_t \langle s_t \rangle &= \int_0^\infty \int \{ j^+ \alpha f(\alpha; t|[\xi_t]) \\ &\quad - (j^+\alpha + j^-) f_1(\alpha; t|[\xi_t]) \} dP([\xi_t]) d\alpha \\ &= j^+ \langle \alpha_t \rangle - \langle (j^+ \alpha_t + j^-) s_t \rangle. \end{aligned} \tag{A13}$$

Hence the dynamics of the operator site s are equivalent to the dynamics of a stochastic variable s_t governed by an SDE,

$$\frac{d}{dt} s_t = j^+ \alpha_t - (j^+ \alpha_t + j^-) s_t. \tag{A14}$$

Here, the process α_t acts both additively and multiplicatively.

Moment expansion. Introducing the mean-field value $s^{(0)} = J/(J+\langle \alpha \rangle)$ and the centered variable $\zeta_t = s_t - s^{(0)}$, the integral corresponding to Eq. (A14) reads

$$\zeta_t = \zeta_0 e^{-\int_{t_0}^t \lambda_\tau d\tau} + \frac{j^+ j^-}{\langle \lambda \rangle} \int_{t_0}^t e^{-\int_\tau^t \lambda_{\tau'} d\tau'} \Delta_\tau d\tau, \tag{A15}$$

with $\lambda_t = j^+ \alpha_t + j^-$ and $\Delta_t = \alpha_t - \langle \alpha \rangle$. The resulting expectation value reads in the stationary limit

$$\begin{aligned}\langle \zeta \rangle &= \frac{j^+ j^-}{\langle \lambda \rangle} \int_{-\infty}^0 e^{\langle \lambda \rangle t'} \langle e^{-j^+ \int_{t'}^0 \Delta_{t''} dt''} \Delta_{t'} \rangle dt' \\ &= -\frac{j^+ j^-}{\langle \lambda \rangle} \int_{-\infty}^0 e^{\langle \lambda \rangle t'} \sum_{i=0}^\infty \frac{(-j^+)^i}{i!} \left\langle \left(\int_{t'}^0 \Delta_{t''} dt'' \right)^i \Delta_{t'} \right\rangle dt' \\ &= -\frac{j^+ j^-}{\langle \lambda \rangle} \sum_{i=0}^\infty \frac{(-j^+)^i}{i!} \int_{-\infty}^0 \int_{t'}^0 \cdots \int_{t'}^0 e^{\langle \lambda \rangle t'} \langle \Delta_{t_1''} \cdots \Delta_{t_i''} \Delta_{t'} \rangle \\ &\quad \times dt_1'' \cdots dt_i'' dt' =: s^{(1)} + s^{(2)} + \cdots, \end{aligned} \tag{A16}$$

where the exponential inside of the expectation value has been expanded into its Taylor series. The terms $\langle \Delta_{t_1''} \cdots \Delta_{t_i''} \rangle$ are the centralized i-time moments of α_t. These provide a series for the mean promoter occupancy $\langle s \rangle$. The first order, $s^{(1)}$, vanishes because of $\langle \Delta_{t'} \rangle = 0$. The second order contains the two-time-covariance, $\langle \Delta_{t_1''}, \Delta_{t_2''} \rangle = \langle \alpha_{t_1''}, \alpha_{t_2''} \rangle$. Namely, this order reads

$$s^{(2)} = -\frac{(j^+)^2 j^-}{\langle \lambda \rangle} \int_{-\infty}^0 \int_{t'}^0 e^{\langle \lambda \rangle t'} \langle \alpha_{t''}, \alpha_{t'} \rangle dt'' dt'. \tag{A17}$$

This order will be termed *noise correction*; when referring to the whole series Eq. (A16)—where, in fact, all orders correct for fluctuations—the term *moment expansion* will be used. Inserting the above result into the definition of the promoter occupation yields

$$\begin{aligned}\langle s \rangle &= s^{(0)} + s^{(2)} + \cdots \\ &\approx \frac{\langle \alpha \rangle}{\langle \alpha \rangle + J} - \frac{\langle \alpha \rangle}{\langle \alpha \rangle + J} \frac{j^+ j^-}{\langle \alpha \rangle + J} \int_{-\infty}^0 \int_{t'}^0 e^{\langle \lambda \rangle t'} \langle \alpha_{t''}, \alpha_{t'} \rangle dt'' dt'. \end{aligned} \tag{A18}$$

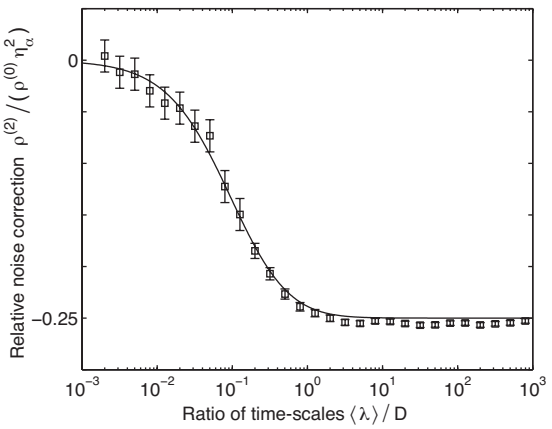

FIG. 5. Relative correction to the mean-field description as a function of the time scales of promoter, $\langle \lambda \rangle$, and the transcription factor D. Shown is the analytical expression (solid line) and numerical simulations. The relative noise correction vanishes if the regulator noise is faster than the binding kinetics, $\langle \lambda \rangle / D \ll 1$ and approaches a stationary value of $-0.25\,\eta_\alpha^2$ for the biologically relevant case of fast binding dynamics. In this limit, the stationary is given by the adiabatic noise correction Eq. (8) as presented in the main text. In this plot, external noise was modeled with a two-time-covariance of $\langle \xi_t, \xi_{t'} \rangle = \sigma_\xi^2 e^{-d|t-t'|}$, where, in this case, $D/d=10$. Error bars denote the standard deviation of the numerical estimator based on the finite simulation length. The small yet statistically significant deviation from the analytical expression stems from the second-order truncation of the series in Eq. (A16).

For the case of exponentially decorrelating external noise, the behavior of this expression is depicted in Fig. 5 as a function of the ratio of the decorrelation time scales of the promoter, $\langle \lambda \rangle$, and α. Figure 5 demonstrates that the noise corrections present an excellent approximation to the mean occupation over all orders of magnitude. Furthermore, it can be seen that the noise correction vanishes if the dynamics of α is faster than the promoter and reaches a plateau in the opposite limit. As this situation is biologically relevant and allows a suggestive interpretation we will explicitly derive simplified equations for this limit.

Adiabatic limit. If the process α_t is slow compared to $\langle \lambda \rangle = j^+ \langle \alpha \rangle + j^-$, Eq. (A14), can be assumed to be equilibrated on the time scale of changes in α_t. For a stationary process α_t the i-time moments $\langle \Delta_{t_1''} \cdots \Delta_{t_i''} \rangle$ necessarily vanish for every pair $|t_i - t_j| \to \infty$. The maximal decay rate is given independently of ξ_t by the dampening $-D\alpha_t$ according to Eq. (A8).

Thus for $\langle\lambda\rangle \gg D$, the factor $e^{\langle\lambda\rangle t'}$ in Eq. (A16) decays so rapidly that the integral over the $i+1$-time moments can be linearly approximated by $\mu_\alpha^{(i+1)} t^i$ and the expression simplifies to

$$\begin{aligned}\langle\zeta\rangle &\approx -\frac{j^+ j^-}{\langle\lambda\rangle}\sum_{i=0}^{\infty}\frac{(-j^+)^i}{i!}\mu_\alpha^{(i+1)}\int_{-\infty}^{0} e^{\langle\lambda\rangle t'}(-t')^i dt' \\ &= -j^-\sum_{i=0}^{\infty}\frac{\mu_\alpha^{(i+1)}}{i!}\frac{(j^+)^{i+1}}{\langle\lambda\rangle}\partial^i_{\langle\lambda\rangle}\int_{-\infty}^{0} e^{\langle\lambda\rangle t'} dt' \\ &= \sum_{i=1}^{\infty}\frac{\mu_\alpha^{(i)}}{i!}\partial^i_{\langle\alpha\rangle}\frac{J}{\langle\alpha\rangle+J} = \sum_{i=2}^{\infty}\frac{\mu_\alpha^{(i)}}{i!}h^{(i)}(\langle\alpha\rangle), \qquad \text{(A19)}\end{aligned}$$

from which it follows that

$$\rho_1 = \langle s\rangle = \sum_{i=0}^{\infty}\frac{\mu_\alpha^{(i)}}{i!}h^{(i)}(\langle\alpha\rangle), \qquad \text{(A20)}$$

where $h^{(i)}$ denotes the ith derivative of $h(\alpha)=\alpha/(\alpha+J)$. This is identical to the expansion Eq. (7) in the main text. The intuitive notion of this result is that for sufficiently fast operator equilibration the occupation s can be approximated by the steady state of the SDE, Eq. (A14), $s_t \approx h(\alpha_t)$. Then it follows that

$$\rho_1 = \int_0^{\infty} h(\alpha) f(\alpha) d\alpha. \qquad \text{(A21)}$$

Evaluating this integral after expanding $h(\alpha)$ about the expectation value $\langle\alpha\rangle$ yields the series Eq. (A20) where $h^{(i)}(\langle\alpha\rangle)/i!$ can be interpreted as the Taylor coefficients. Note, however, that this intuitive derivation faces the problem that the Taylor series does only converge on a subset of $\mathbb{R}^+$.

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