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Article:

Probing noise in gene expression and protein production

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We derive exact solutions of simplified models for the temporal evolution of the protein concentration within a cell population arbitrarily far from the stationary state. We show that monitoring the dynamics can assist in modeling and understanding the nature of the noise in gene expression. We analyze the dispersion of the process, i.e., the ratio of the variance to the mean at arbitrary time, and introduce a measure, the fractional protein distribution, which can be used to probe the phase of transcription of DNA into mRNA.

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I. INTRODUCTION

Advances in experimental techniques, which enable the direct observation of gene expression in individual cells, have demonstrated the importance of stochasticity in gene expression, the translation into proteins of the information encoded within DNA [1–5]. Such variability can lead to deleterious effects in cell function and cause diseases [6]. On the positive side, stochasticity in gene expression confers on cells the ability to be responsive to unexpected stresses and may augment growth rates of bacterial cells compared to homogeneous populations [7]. Disentangling the various contributions to production fluctuations is complicated by the recent finding that different stochastic processes yield the same response in the variance in protein abundance at stationarity [8]. A population of isogenic cells growing under the same environmental conditions can exhibit protein abundances that vary greatly from cell to cell. The sources of variability have been identified at multiple levels [9–13], with transcription and translation playing a major role under certain circumstances [14–16].

The low concentration of reactants potentially has two important consequences: the first is that fluctuations around the mean can be large; the second is that the nature of the stochastic noise should be taken into account in some detail because one may not simply invoke the central limit theorem [17], which leads to the universal and ubiquitous Gaussian noise. Thus, two genes expressed at the same average abundance can produce protein populations with different Fano factors $F(t) = \text{var}[x(t)]/\langle x(t) \rangle$, where $\text{var}[x(t)]$ and $\langle x(t) \rangle$ are the variance and the mean of the protein concentration $x(t)$, respectively [18]. We show here that two distinct models, one taking into account the detailed nature of the noise and the other following from an application of the central limit theorem, yield exactly the same stationary solution for the distribution of proteins in isogenic cells under the same environmental conditions. The applicability of the central limit theorem arises from the fact that the stochasticity in gene expression results from the large number of available components which entangle a lot of different mechanisms within a cell. The exact dynamical solution of these two simplified models demonstrates the value of monitoring the dynamics for understanding the nature of the noise in a cell.

II. MODEL

We make the simplified assumption that the kinetics of gene expression can be described approximately by four rate constants: k_1 and k_2 are the transcription and translation rates, respectively, and γ_1 and γ_2 are the degradation rates for mRNA and proteins, respectively. It has been found experimentally that proteins are produced in bursts [5,18–20] with an exponential distribution of the protein concentration produced in a given event. We will assume that transcription pulses are Poisson events and that the probability distribution that in a single event $I > 0$ proteins are produced, $w(I)$, is approximated by $w(I) = \frac{\gamma_1}{k_2} e^{-(\gamma_1/k_2)I}$, where k_2/γ_1 is the translation efficiency, i.e., the mean number of proteins produced in a given burst. Here we consider a simple model for the production of proteins without memory and aging of molecules. Using the specific burst distribution given above allows one to obtain the shape of the protein distribution even far from stationarity. Under these assumptions, the stochastic equation that governs the single-variable dynamics of gene expression can be written as

$$\dot{x}(t) = \delta - \gamma_2 x(t) + \Lambda(t). \tag{1}$$

This pseudoequation describes the real-time stochastic evolution of gene expression through a deterministic part and a stochastic term $\Lambda(t)$, which will be defined later on. Here x is a continuous variable that represents the protein concentration within a cell. For the sake of generality, we have added the constant δ, which can be incorporated into the average noise. However, although $\delta > 0$ can account for important effects in ecological systems [25], we will show in the following that it does not play a significant role under the burstlike production of proteins.

In order to understand the nature of the noise for the gene expression case, let us consider the random variable, I_k, that is a measure of the number of proteins in the kth transcription event, where $k = 1, 2, \ldots, n$. A key quantity of interest is $\sum_{k=1}^{n(t)} I_k \equiv \Lambda(t)\Delta t$, where $n(t)$, the number of events in the time interval $(t, t+\Delta t)$, is a random variable independent of both x and the I_ks. As in the experiment, let us postulate that: (i) the I_ks are independent and identically distributed with exponential distribution; and (ii) the probability of n events occurring during the time interval Δt is given by the Poisson distribu-

tion $q_n(\Delta t) = (k_1 \Delta t)^n \exp(-k_1 \Delta t)/n!$. The distribution of $\Lambda(t)$ that we use in Eq. (1) can be explicitly calculated (see Appendix A) and leads to the following expression for the cumulants: $\langle\langle \Lambda(t_1) \cdots \Lambda(t_n) \rangle\rangle = n! k_1 (k_2/\gamma_1)^n \prod_{i=2}^{n} \delta(t_i - t_1)$ for $n \geq 2$ and $\langle \Lambda(t) \rangle = k_1 k_2/\gamma_1$, independent of time.

Because the cumulants are delta functions, the noise is still white (events are uncorrelated if they occur at different times); however the noise is no longer Gaussian because cumulants with n greater than two are nonzero.

The master equation that describes this burstlike process is [17]

$$\frac{\partial p(x,t)}{\partial t} = -\frac{\partial}{\partial x}[(\delta - \gamma_2 x)p(x,t)] + k_1 \int_0^x w(x-y)p(y,t)dy$$
$$- k_1 p(x,t), \quad (2)$$

where $p(x,t) \equiv p(x,t|x_0,0)$ is the conditional probability that the protein concentration has a value x at time t given that it has a value x_0 at time 0; and $w(x) = \frac{\gamma_1}{k_2} e^{-(\gamma_1/k_2)x}$.

Equation (2) can be easily understood as follows. The first term in the right-hand side is simply related to the deterministic motion given by the first two terms in Eq. (1) and it is independent of the nature of the noise term. The second and third terms are related to the probability per unit time to jump from a population of size y to a population of size x, $w(x-y)$, given that k_1 is the transition rate for a transcription event. The stationary solution of this model was already known [21,22] with $\delta=0$. For arbitrary $\delta>0$, the stationary solution is

$$p_s(x) = \left(\frac{\gamma_1}{k_2}\right)^{k_1/\gamma_2} \frac{\Theta(x - \delta/\gamma_2)}{\Gamma(k_1/\gamma_2)} \left(x - \frac{\delta}{\gamma_2}\right)^{k_1/\gamma_2 - 1} e^{-(\gamma_1/k_2)(x - \delta/\gamma_2)},$$
$$(3)$$

where $\Theta(x)$ is the step function equal to 1 when $x>0$ and zero otherwise. This distinctive feature is a sharp signature of the nature of the noise even in the stationary solution but is present only when $\delta \neq 0$. However, as shown in the fit to the stationary solution in Fig. 1, the singularity, if it exists, is easily masked by other noise effects, leading to a rounding effect.

III. ALTERNATIVE MODEL

Although experiments on gene expression [5,18] are consistent with a burstlike protein production, steady-state distributions of protein abundances are equally compatible with alternative explanations. In fact, because mRNA is unstable compared to protein lifetime ($\gamma_1 \gg \gamma_2$), one can assume that transcripts give rise to a constant flux of proteins f and subsequently any protein degrades at a constant rate γ_2. Because of the great amount of available molecules, one can apply the central limit theorem and suppose that the amplitude of fluctuations is simply proportional to $\sqrt{x}$. Within this framework there is no burstlike production; nevertheless the stationary solutions that one obtains for a burstlike process, including that of the extended autoregulation model [23,24], are also obtained in models with appropriately chosen random multiplicative Gaussian noise (see Appendix C). Within this sce-
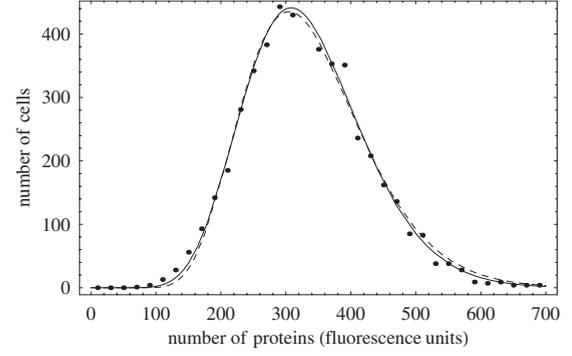
FIG. 1. The stationary distribution of proteins in a prokaryotic cell population taken from Ref. [18] fitted to Eq. (3) with $\delta=0$ or $\delta/\gamma_2 = 60.3$ (dashed). The best fit parameters are $\gamma_1/k_2 = 0.038$, $k_1/\gamma_2 = 12.88$ ($\chi^2 \simeq 6100$), and $\gamma_1/k_2 = 0.030$, $k_1/\gamma_2 = 8.33$ ($\chi^2 \simeq 8700$), respectively. From the experimental data it is hard to distinguish between the steady-state distributions predicted by Eq. (3) with $\delta=0$ and $\delta>0$.

nario the stochastic evolution of the protein concentration $x(t)$ is governed by the equation

$$\dot{x}(t) = f - \gamma_2 x(t) + \sqrt{Dx(t)}\,\eta(t), \quad (4)$$

where $\eta(t)$ is a Gaussian white noise with autocorrelation $\langle \eta(t)\eta(t')\rangle = 2\delta(t-t')$. Note that the same equation could be obtained on setting $\langle \Lambda(t) \rangle = f$ and $\langle\langle \Lambda(t)\Lambda(t')\rangle\rangle \equiv \langle \Lambda(t)\Lambda(t')\rangle - \langle \Lambda(t)\rangle\langle \Lambda(t')\rangle = 2Dx(t)\delta(t-t')$ in Eq. (1) with all higher-order cumulants being identically zero. Note that the square root of the multiplicative noise in Eq. (4) is not introduced *ad hoc*. It has its roots in the central limit theorem and can also be justified on the basis of other general considerations about the discrete nature of the process. In fact, on temporal scales much larger than the mRNA lifetime, the protein production can be suitably described by a birth and death process whose rates are proportional to the number of available molecules. Accordingly, the fluctuations of this discrete Markov process can be well described by the multiplicative noise term present in Eq. (4) in the continuum limit, i.e., when a large number of molecules is present. In addition, because the noise goes to zero when $x(t)=0$, it also prevents the random variable $x(t)$ from becoming negative.

We point out that in ecology Eq. (4) is useful for studying the evolution of tropical forests [25], where the detailed nature of the stochastic noise is not important because of the relatively large numbers of trees of a given species. In the field of finance, Eq. (4) has been used to study the evolution of interest rates (the Cox-Ingersoll-Ross model [26]), where analogous considerations on fluctuations can be made. On defining $f \equiv k_1 k_2/\gamma_1$ and $D \equiv \gamma_2 k_2/\gamma_1$, Eq. (4) yields the same stationary state as in Eq. (2) with $\delta=0$, i.e., Equation (3). The mean protein concentration at stationarity is $k_1 k_2/\gamma_1\gamma_2$ and the Fano factor at stationarity is k_2/γ_1, relations that are consistent with previous findings [18]. In order to take into account the effects of feedback in a system undergoing autoregulation, one can introduce the physically transparent modification $f \rightarrow Dc(x)$, where c is a response function which can be modeled as having two distinct limit-
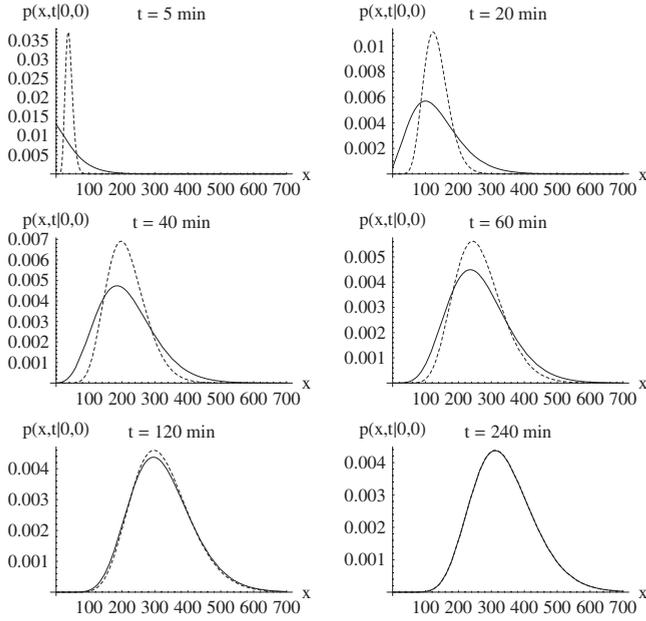
FIG. 2. Protein distribution dynamics for different types of noise and with the same initial condition, i.e., $x_0=0$ proteins at $t=0$. The dashed curve is for the multiplicative Gaussian noise, i.e., Eq. (4) with $f \equiv k_1 k_2/\gamma_1$ and $D \equiv \gamma_2 k_2/\gamma_1$ (see Appendix C); whereas the solid curve is for the non-Gaussian noise, i.e., for Eq. (5). In both cases the parameters are $\delta=0$, $\gamma_2/D=\gamma_1/k_2=0.038$, $f/D=k_1/\gamma_2$ $=12.88$ and we have set $\gamma_2^{-1}=40$ min, $\gamma_1^{-1}=2$ min.

ing values at zero and at infinity with the latter being smaller than the former. Even in this situation, we obtain the same stationary distribution with bistability as in Ref. [22]. Despite this much more realistic analysis, the final stationary protein distribution is experimentally indistinguishable from Eq. (3) with $\delta=0$. Thus, a theoretical modeling of the stationary state of protein production provides little insight into the microscopic nature of the noise that leads to stationarity.

IV. TEMPORAL EVOLUTION

These results raise the question whether the agreement between the stationary solutions of the theoretical models and experiments are in fact a direct probe of the nature of the microscopic noise and whether the asymmetric stationary solutions derive from a careful consideration of the bursty nature of the noise. In order to circumvent the indistinguishability of steady states, one can look into empirical protein abundances far from stationarity, for which we provide analytical formulas. Thus we turn now to a study of the dynamics of Eq. (2), which is a powerful probe of the noise effects. We have derived (see Appendix B) the solution at arbitrary time (Fig. 2),

$$
p(x,t) = e^{-k_1 t}\delta(x-\xi_t) + \Theta(x-\xi_t)\frac{k_1\gamma_1}{k_2\gamma_2}(e^{\gamma_2 t}-1)e^{-k_1 t}
$$
$$
\times \exp\left[-\frac{\gamma_1}{k_2}e^{\gamma_2 t}(x-\xi_t)\right]
$$
$$
\times {}_1F_1\left(\frac{k_1}{\gamma_2}+1,2;\frac{\gamma_1}{k_2}(e^{\gamma_2 t}-1)(x-\xi_t)\right), \quad (5)
$$
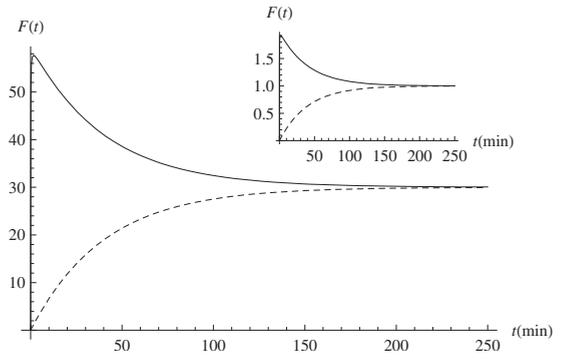
FIG. 3. Fano factor dynamics with the same initial condition, i.e., $x_0=0$ proteins at $t=0$. The solid curves are for the non-Gaussian noise case, i.e., $F(t)=\text{var}[x(t)]/\langle x(t)\rangle$ is obtained from Eq. (5) with $\delta=0$; the dashed curves are for the multiplicative Gaussian noise, i.e., $F(t)$ is calculated with the analytical solution of Eq. (4). The parameters ($k_1=0.01$, $k_2=15$ min^{-1}) in the main figure correspond to an infrequent production of large bursts, whereas the ones (k_1 $=0.3$, $k_2=0.5$ min^{-1}) used in the inset give rise to small bursts produced frequently. In both cases we have set $\gamma_1^{-1}=2$ and γ_2^{-1} $=40$ min.

where ${}_1F_1(a,b;x)$ is the confluent hypergeometric function [27] and $\xi(t) \equiv x_0 e^{-\gamma_2 t}+\frac{\delta}{\gamma_2}(1-e^{-\gamma_2 t})$ is the solution of the deterministic part of the equation, i.e., without the noise.

Interestingly, one obtains a distribution of proteins with a cutoff along the interval $[0,\xi_t]$ at any time whenever $\delta>0$. The stochasticity plays a major role when the mean number of bursts per cell cycle is very small, i.e., $k_1/\gamma_2 \ll 1$. In this case, the solution in Eq. (5) can be approximated by replacing ${}_1F_1(1,2;z)$ with $(e^z-1)/z$ (see Ref. [27] and Appendix B). On using Eq. (5), one can calculate the evolution of the Fano factor, $F(t)$, starting from an arbitrary initial amount of proteins. This time evolution is highly sensitive to the nature of the stochasticity. Figure 3 vividly shows the distinct dependence of the initial dynamics of $F(t)$ on the nature of the noise. Note that, at stationarity, the distinct types of stochasticity are indistinguishable. Interestingly, within the temporal transient, the fluctuations deviate from Poisson behavior, whereas, at stationarity, both models predict a Poissonian Fano factor for genes with high transcription and low translation rates and $\lim_{t\to\infty} F(t)=k_2/\gamma_1 \simeq 1$.

V. FRACTIONAL PROTEIN DISTRIBUTION

Another measurable quantity that directly probes the protein distribution and its temporal evolution is the fractional protein distribution (FPD), $\mathcal{P}(\rho,t)$, i.e., the probability that at time t the ratio $x(t)/x(0)$ is equal to ρ, where $x(t)$ and $x(0)$ are the protein concentrations at time $t>0$ and $t=0$, respectively. Unlike the stationary distribution in Eq. (3) with δ $=0$, the FPD can exhibit a distinctive signature of the nature of the burstlike noise even under stationary conditions: it has an interval in which it identically vanishes and this, in principle, can be experimentally observed. This quantity can be defined at arbitrary times (see Appendix D): if the initial distribution is the steady state given by Eq. (3) with $\delta=0$, then at $t>0$ the FPD is

$$\mathcal{P}(\rho,t) = e^{-k_1 t}\delta(\rho - e^{-\gamma_2 t}) + \left(\frac{k_1}{\gamma_2}\right)^2 \frac{e^{-k_1 t}(e^{\gamma_2 t} - 1)\Theta(\rho - e^{-\gamma_2 t})}{[1 + e^{\gamma_2 t}(\rho - e^{-\gamma_2 t})]^{k_1/\gamma_2 + 1}}$$

$$\times {}_2F_1\left(\frac{k_1}{\gamma_2} + 1, \frac{k_1}{\gamma_2} + 1, 2; \frac{(e^{\gamma_2 t} - 1)(\rho - e^{-\gamma_2 t})}{1 + e^{\gamma_2 t}(\rho - e^{-\gamma_2 t})}\right), \quad (6)$$

where ${}_2F_1(a,b,c;x)$ is the standard hypergeometric function [27]. Thus, according to Eq. (6), under the burst process hypothesis we predict that (i) the FPD vanishes between 0 and $e^{-\gamma_2 t}$ even though the system is at stationarity, an effect which ought to be detectable for time scales less than or of the order of $1/\gamma_2$, (ii) the FPD depends on k_1 and γ_2 only, (iii) at very large time separation there is only one free parameter, the ratio k_1/γ_2, and the FPDs predicted by the Gaussian and non-Gaussian noises become the same (see Appendix D).

The analogous time-dependent solutions for the Gaussian white noise can be compared with Eqs. (5) and (6) (see Appendix D).

The closer the system is to its steady state, the more difficult it is to distinguish among the effects of gestation, senescence and burstlike production. Thus an experimental protocol capable of analyzing the cell population and its time evolution with different initial conditions would be helpful to disentangle the nature of stochastic noise. At early times, the evolution of the distribution is strongly affected by the specific mechanisms involved in the dynamics. At this stage, different distributions of interarrival times between events or burst sizes produce nonstationary distributions that are very different, and the distinctive effects of noise, deterministic driving forces, or coupling of degrees of freedom can be elucidated. Different conditions at initial times propagate into the early temporal evolution in strongly different ways according to the different effects of involved mechanisms, but inexorably lead to the same distribution for large time separation.

VI. CONCLUSION

In summary, we have shown that fits to experimental data of the stationary solution do not discriminate between different types of noise. However, the temporal evolution of the probability distribution of protein or fractional protein concentration under stationary conditions as well as the evolution of the Fano factor can be used as a powerful probe of the noise effects of protein production. We have shown that the full time dependence of the analytical solution of the model proposed in [22] with burstlike protein production events presents a singularity. This singularity is absent in the corresponding model with Gaussian multiplicative noise.

APPENDIX A: DEFINITION OF THE NON-GAUSSIAN WHITE NOISE

In this section we wish to exploit the burst hypothesis of protein production in gene expression in order to derive its probability distribution.

Let $x_1, x_2, \ldots, x_n$ be n-independent one-burst processes with only positive increments. Let us suppose that they are identically distributed, so they have the same jump transitions, say a probability density function $w(x)$ with $x \geq 0$. Let us further assume that the burst processes occur in time according to a Poisson distribution $q_n(t) = (k_1 t)^n \exp(-k_1 t)/n!$, where k_1 is the transcription rate.

Because any burst produces x_i proteins according to the distribution $w(x)$, we are interested in the distribution of the random variable $\xi(t) = \Sigma_{i=1}^n x_i$, i.e., the total amount of proteins produced from $t=0$ through $t>0$, where we are assuming that n bursts have been occurred in a time t. The characteristic function for the process $\xi(t)$ is

$$\langle e^{iz\xi(t)}\rangle = \sum_{n=0}^{\infty}\langle e^{iz\xi(t)}|n \text{ events by } t\rangle \text{prob}[n \text{ events by } t]$$

$$= \sum_{n=0}^{\infty}[g(z)]^n q_n(t), \quad (A1)$$

where we have used the independence of any one-burst process and we have used the definition

$$g(z) \equiv \langle e^{izx_j}\rangle = \int_0^{\infty} e^{izx}w(x)dx, \quad (A2)$$

for any $j = 1, \ldots, n$. Because we are using the Poisson distribution $q_n(t)$, one obtains

$$\langle e^{iz\xi(t)}\rangle = e^{k_1 t(g(z)-1)}. \quad (A3)$$

Thus the characteristic function of $\xi(t)$ in Eq. (A1) defines the following integral equation for the distribution $p(x,t) = \langle \delta(x - \xi(t))\rangle$:

$$\int_0^{\infty} e^{izx}p(x,t)dx = \sum_{n=0}^{\infty}[g(z)]^n q_n(t). \quad (A4)$$

By direct substitution one can verify that a solution is

$$p(x,t) = q_0(t)\delta(x) + q_1(t)w(x) + q_2(t)\int_0^x w(x-y)w(y)dx$$

$$+ \cdots = \sum_{n=0}^{\infty} q_n(t)\underbrace{w(x) \diamond w(x) \diamond \cdots \diamond w(x)}_{\text{n-fold convolution}}, \quad (A5)$$

where $\delta(x)$ is a Dirac delta and the symbol "$\diamond$" stands for a convolution of $w(x)$'s.

Now we use the particular jump distribution $w(x) = \lambda e^{-\lambda x}$ ($\lambda \equiv \gamma_1/k_2$). Hence

$$g(z) = \frac{\lambda}{\lambda - iz}, \quad (A6)$$

and the calculations for the nth convolution ($n \geq 1$) result in

$$\lambda^n \frac{x^{n-1}}{(n-1)!}e^{-\lambda x}. \quad (A7)$$

Thus we obtain with $q_n(t) = (k_1 t)^n \exp(-k_1 t)/n!$

$$p(x,t) = e^{-k_1 t}\delta(x) + \frac{e^{-k_1 t - \lambda x}}{x}\sum_{n=1}^{\infty}\frac{(k_1 t \lambda x)^n}{(n-1)! \, n!}$$

$$= e^{-k_1 t}\delta(x) + \frac{t}{x}e^{-k_1 t - \lambda x}\frac{\partial}{\partial t}I_0(2\sqrt{k_1 t \lambda x})$$

$$= e^{-k_1 t}\delta(x) + \frac{e^{-k_1 t - \lambda x}}{x}\sqrt{k_1 t \lambda x}I_1(2\sqrt{k_1 t \lambda x}), \quad \text{(A8)}$$

where $I_\nu(z)$ is the modified Bessel function of the first kind [27], whose definition is

$$I_\nu(x) = \sum_{n=0}^{\infty}\frac{(x/2)^{\nu+2n}}{n! \, \Gamma(\nu+n+1)}.$$

By exploiting this definition, one can see that in Eq. (A8) there is no divergence at $x=0$. We can also calculate all the moments

$$\langle \xi^n(t)\rangle = \frac{n!}{\lambda^n}k_1 t e^{-k_1 t}{}_1F_1(n+1,2;k_1 t) + e^{-k_1 t}\delta_{n,0}, \quad \text{(A9)}$$

where ${}_1F_1(a,b;x)$ is the confluent hypergeometric function [27] and $n=0,1,2,\dots$.

Now we can consider the fundamental stochastic differential equation which defines the model in the main text,

$$dx(t) = \left(\delta - \frac{x(t)}{\tau}\right)dt + d\xi(t), \quad \text{(A10)}$$

where $\tau \equiv \gamma_2^{-1}$ and $\xi(t)$ is the noise whose probability distribution is given by Eq. (A8). Finally, in order to recover Eq. (1) in the main text, one can formally write $d\xi(t)=\Lambda(t)dt$. The master equation which governs the process defined by Eq. (A10) is Eq. (2) in the main text.

APPENDIX B: THE SOLUTION OF THE MASTER EQUATION

The main goal of this section is to obtain the fundamental solution of the integrodifferential equation that describes the evolution of the protein concentration within a population of isogenic cells under the burst hypothesis [Eq. (2) in the main text],

$$\frac{\partial p(x,t)}{\partial t} = -\frac{\partial}{\partial x}\left[\left(\delta - \frac{x}{\tau}\right)p(x,t)\right] + \frac{1}{\theta}\int_0^x w(x-y)p(y,t)dy$$
$$- \frac{1}{\theta}p(x,t), \quad \text{(B1)}$$

where $\theta \equiv k_1^{-1}$, $\tau \equiv \gamma_2^{-1}$, $\delta \geq 0$, $w(x)$ is a probability density function and $p(x,t) \equiv p(x,t|x_0,0)$ is the conditional probability that the protein concentration has a value x at time t given that it has a value x_0 at time 0. Note that Eq. (B1) exhibits two temporal scales, θ and τ, which are related to transcription and protein dilution, respectively.

The probability flux determined by Eq. (B1) is

$$j(x,t) = \left(\delta - \frac{x}{\tau}\right)p(x,t) + -\frac{1}{\theta}\int_0^x \int_0^z w(z-y)p(y,t)dzdy$$
$$+ \frac{1}{\theta}\int_0^x p(y,t)dy, \quad \text{(B2)}$$

where we assume that $\lim_{x\to\infty}j(x,t)=0$ for any $t>0$. The flux at $x=0$ is simply

$$j(0,t) = \delta \lim_{x\to 0^+}p(x,t), \quad \text{(B3)}$$

where $\lim_{x\to 0^+}xp(x,t)=0$ due to the integrability of $p(x,t)$ at $x=0$. By Laplace transforming Eq. (B1) with respect to x, one obtains

$$\frac{\partial\omega(s,t)}{\partial t} = j(0,t) - \frac{s}{\tau}\frac{\partial\omega(s,t)}{\partial s} - bs\omega(s,t) + \frac{[\rho(s)-1]\omega(s,t)}{\theta}, \quad \text{(B4)}$$

where $\rho(s) \equiv \int_0^\infty w(x)e^{-sx}dx$ is supposed to be finite. We are interested in the time-dependent reflecting solution of Eq. (B1), so $j(0,t)=0$ and the characteristic equations for Eq. (B4) get

$$dt = \frac{\tau ds}{s} = \frac{\theta d\omega}{\omega(\rho(s)-1-\delta\theta s)}, \quad \text{(B5)}$$

which can be easily solved. The solutions may be written as follows:

$$se^{-t/\tau} = s_0, \quad \text{(B6)}$$

$$\omega(s) = \omega_0 \exp\left[\frac{\tau}{\theta}\int_{s_0}^s \frac{\rho(\sigma)-1}{\sigma}d\sigma - \delta\tau(s-s_0)\right], \quad \text{(B7)}$$

where s_0, ω_0 are arbitrary constants. If we choose an arbitrary well-behaved function $\phi(x)$ such that $\phi(s_0)=\omega_0$, one can write down the general solution of Eq. (B4),

$$\omega(s,t) = \phi(se^{-t/\tau})\exp\left[\frac{\tau}{\theta}\int_{se^{-t/\tau}}^s \frac{\rho(\sigma)-1}{\sigma}d\sigma - \delta\tau(s-se^{-t/\tau})\right]. \quad \text{(B8)}$$

Since the initial condition is $p(x,0)=\delta(x-x_0)$, we have $\omega(s,0)=e^{-sx_0}$, thereby one can determine the function $\phi(x)$, finally achieving

$$\ln\omega(s,t) = -(\delta\tau + x_0 e^{-t/\tau} - \delta\tau e^{-t/\tau})s + \frac{\tau}{\theta}\int_{se^{-t/\tau}}^s \frac{\rho(\sigma)-1}{\sigma}d\sigma. \quad \text{(B9)}$$

By using the translation theorem which holds for Laplace transforms [28], we may study only the function

$$\Omega(s,t) = \exp\left[\frac{\tau}{\theta}\int_{se^{-t/\tau}}^s \frac{\rho(\sigma)-1}{\sigma}d\sigma\right]. \quad \text{(B10)}$$

We are interested in solving Eq. (B1) with $w(x)=\lambda e^{-\lambda x}$, where $\lambda \equiv \gamma_1/k_2$ is the translation efficiency as defined in the

main text. So $\rho(s) = \lambda/(\lambda+s)$ and $\Omega(s,t)$ becomes

$$\Omega(s,t) = \left(\frac{s e^{-t/\tau} + \lambda}{s + \lambda} \right)^{\tau/\theta}. \quad \text{(B11)}$$

It turns out that one can analytically calculate the inverse Laplace transform of $\Omega(s,t)$ (see below), and then one can finally achieve the fundamental solution of Eq. (B1), which is

$$p(x,t|x_0,0) = e^{-t/\theta}\delta(x - \xi_t) + \Theta(x - \xi_t)\frac{\tau\lambda}{\theta}e^{-t/\theta}(e^{t/\tau} - 1)$$

$$\times \exp[-\lambda e^{t/\tau}(x - \xi_t)]$$

$$\times {}_1F_1\left(\frac{\tau}{\theta} + 1, 2; \lambda(e^{t/\tau} - 1)(x - \xi_t) \right), \quad \text{(B12)}$$

where $\xi_t \equiv x_0 e^{-t/\tau} + \delta\tau(1 - e^{-t/\tau})$, ${}_1F_1(a,b;x)$ is the confluent hypergeometric function [27], $\Theta(x)$ is the step function which is equal to one for $x \geq 0$ and zero otherwise, and $\delta(x)$ is a Dirac delta. It is worth noting that Eq. (B12) exhibits a cutoff along the interval $[0, \xi_t)$ at any time whenever $\delta > 0$, thus the probability is generally continuous but not differentiable (at $x = \xi_t$). One may also achieve the steady-state solution of Eq. (B1) by using the leading term of the asymptotic representation of the confluent hypergeometric function [27], i.e.,

$${}_1F_1(a,b;x) \simeq \frac{\Gamma(b)}{\Gamma(a)}e^x x^{-(b-a)}, \quad \text{(B13)}$$

when $x \gg 1$ and $a, b \neq 0, -1, -2, \dots$. Thus the normalized solution at stationarity is

$$p_s(x) = \frac{\lambda^{\tau/\theta}}{\Gamma(\tau/\theta)}\Theta(x - \delta\tau)(x - \delta\tau)^{\tau/\theta - 1}e^{-\lambda(x - \delta\tau)}. \quad \text{(B14)}$$

In Fig. 1 in the main text we show $p_s(x)$ for different values of δ and we compare it with experimental data obtained in a *prokaryotic* cell population: the agreement is excellent. When the mean number of bursts per cell cycle is very small, one obtains $\tau/\theta \ll 1$ and we can expand Eq. (B12) in powers of τ/θ. In this case, the solution in Eq. (B12) reads

$$p(x,t|x_0,0) = e^{-t/\theta}\delta(x - \xi_t) + \left(\frac{\tau}{\theta} \right)\frac{\Theta(x - \xi_t)}{x - \xi_t}(\exp[-\lambda(x - \xi_t)$$

$$- t/\theta] - \exp[-\lambda e^{t/\tau}(x - \xi_t) - t/\theta]) + O((\tau/\theta)^2), \quad \text{(B15)}$$

where we have used (see Ref. [27])

$${}_1F_1(1,2;z) = \frac{e^z - 1}{z}. $$

Laplace transform

In this section we calculate the inverse Laplace transform of Eq. (B11). In order to get it we study the function

$$\Phi(x) \equiv \frac{1}{2\pi i}\int_{k-i\infty}^{k+i\infty} \left(\frac{as + \lambda}{bs + \lambda} \right)^c e^{sx}ds, \quad \text{(B16)}$$

where $x > 0$, $k > 0$, $0 < a < b$, $\lambda > 0$, and $c > 0$. On using the variable $z \equiv (as + \lambda)/\bar{z}$, with $\bar{z} \equiv \lambda(1 - a/b) > 0$, one obtains

$$\Phi(x) \equiv \frac{e^{-\lambda x/a}}{a}\left(\frac{a}{b} \right)^c \frac{\bar{z}}{2\pi i}\int_{z'-i\infty}^{z'+i\infty} \left(1 - \frac{1}{z} \right)^{-c} e^{(x\bar{z}/a)z}dz, \quad \text{(B17)}$$

where $z' > 1$. We can also write

$$\left(1 - \frac{1}{z} \right)^{-c} = \sum_{n=0}^{\infty} \frac{(c)_n}{n!}\frac{1}{z^n}, \quad \text{(B18)}$$

when $|z| > 1$ and $(c)_n \equiv c(c+1)\cdots(c+n-1)$, $(c)_0 \equiv 1$. The series in Eq. (B18) is absolutely and uniformly convergent if $|z| > 1$; thus it can be integrated term by term

$$\sum_{n=0}^{\infty} \frac{(c)_n}{n!}\int_{z'-i\infty}^{z'+i\infty} \frac{e^{(x\bar{z}/a)z}}{z^n}dz = 2\pi i\delta\left(\frac{x\bar{z}}{a} \right)$$

$$+ \sum_{n=1}^{\infty} \frac{(c)_n}{n!}\left(\frac{x\bar{z}}{a} \right)^{n-1}\int_{\sigma'-i\infty}^{\sigma'+i\infty} \frac{e^{\sigma}}{\sigma^n}d\sigma, \quad \text{(B19)}$$

where $\sigma' > 1$ and we used

$$\delta(x) = \frac{1}{2\pi i}\int_{z'-i\infty}^{z'+i\infty} e^{xz}dz.$$

In Eq. (B19) the integral may be evaluated along a simple closed path that encircles the origin within which the integrand has a pole of order n at $z = 0$. Thus, by applying the residue theorem, one obtains

$$\oint \frac{e^{\sigma}}{\sigma^n}d\sigma = \frac{2\pi i}{(n-1)!}. \quad \text{(B20)}$$

Therefore Eq. (B19) gets

$$\frac{1}{2\pi i}\sum_{n=0}^{\infty} \frac{(c)_n}{n!}\int_{z'-i\infty}^{z'+i\infty} \frac{e^{(x\bar{z}/a)z}}{z^n}dz = \delta\left(\frac{x\bar{z}}{a} \right) + \sum_{n=1}^{\infty} \frac{(c)_n}{n!}\frac{(x\bar{z}/a)^{n-1}}{(n-1)!}. \quad \text{(B21)}$$

We may use the definition and the properties of the confluent hypergeometric function [27] to rewrite this latter relation as follows:

$$\sum_{n=1}^{\infty} \frac{(c)_n}{n!}\frac{(x\bar{z}/a)^{n-1}}{(n-1)!} = \frac{\partial}{\partial(x\bar{z}/a)}{}_1F_1(c,1;x\bar{z}/a)$$

$$= c\,{}_1F_1(c+1,2;x\bar{z}/a), \quad \text{(B22)}$$

and finally reaching the equation

$$\Phi(x) = \frac{e^{-\lambda x/a}}{a}\left(\frac{a}{b} \right)^c \bar{z}\left[\delta\left(\frac{x\bar{z}}{a} \right) + c\,{}_1F_1(c+1,2;x\bar{z}/a) \right], \quad \text{(B23)}$$

We can obtain the solution in Eq. (B12) on setting $a = e^{-t/\tau}$, $b=1$, $c=\tau/\theta$ and by using the translation theorem which holds for the Laplace transforms.

APPENDIX C: THE GAUSSIAN WHITE NOISE CASE

Let us consider the fundamental equation of the main text for the number of proteins at time t, $x(t)$, within an isogenic cell population,

$$\dot{x}(t) = \delta - x(t)/\tau + \Lambda(t), \tag{C1}$$

where $\tau \equiv \gamma_2^{-1}$ and

$$\langle \Lambda(t) \rangle = f,$$

$$\langle\langle \Lambda(t)\Lambda(t') \rangle\rangle \equiv \langle \Lambda(t)\Lambda(t') \rangle - \langle \Lambda(t) \rangle\langle \Lambda(t') \rangle = 2Dx(t)\delta(t-t'). \tag{C2}$$

Because we suppose that all the other cumulants are negligible, Eq. (C2) defines a multiplicative Gaussian white noise and on using the Itô prescription [17], one can prove that Eq. (C1) with Eq. (C2) is equivalent to the following Fokker-Planck equation:

$$\dot{p} = \partial_x[(x/\tau - f - \delta)p] + D\partial_x^2(xp). \tag{C3}$$

In this case the constant δ only shifts the average number of proteins, so we can assume that $\delta=0$ without lack of generality. In Eq. (C3) $p \equiv p(x,t|x_0,0)$ is the conditional probability that the protein concentration has a value x at time t given that it has a value x_0 at time 0, i.e., $\int_n^{n+\Delta n} p(x,t|x_0,0)dx$ is the fraction of cells with protein population between n and $n+\Delta n$; furthermore, $f \equiv k_1 k_2/\gamma_1$ and $D \equiv \gamma_2 k_2/\gamma_1$. Setting $\dot{p} = 0$, one obtains the stationary solution of Eq. (C3),

$$p_{stat}(x) = (D\tau)^{-f/D}\Gamma(f/D)^{-1}x^{f/D-1}e^{-x/D\tau}, \tag{C4}$$

where $\Gamma(x)$ is the gamma function [27]. This solution is equivalent (with $\delta=0$) to Eq. (3) of the main text, which has been derived on using a non-Gaussian white noise that embodies the burst hypothesis.

One can also obtain the time-dependent solution of Eq. (C3) with reflecting boundary conditions and with initial population equal to x_0. One can find all the details of the derivation in [29], here we write down only the final expression

$$p(x,t|x_0,0) = \left(\frac{1}{D\tau}\right)^{f/D} x^{f/D-1} e^{-x/D\tau} \frac{\left[\left(\frac{1}{D\tau}\right)^2 x_0 x e^{-t/\tau}\right]^{1/2-f/2D}}{1 - e^{-t/\tau}}$$

$$\times \exp\left[-\frac{\frac{1}{D\tau}(x+x_0)e^{-t/\tau}}{1-e^{-t/\tau}}\right] I_{f/D-1}\left[\frac{\frac{2}{D\tau}\sqrt{x_0 x e^{-t/\tau}}}{1-e^{-t/\tau}}\right]. \tag{C5}$$

In Fig. 2 of the main text we have compared the behavior of this equation with that in Eq. (5) of the main text. Unlike this latter, Eq. (C5) has no any cutoff neither at finite times nor at stationarity.

APPENDIX D: THE FRACTIONAL PROTEIN DISTRIBUTION

The fractional protein distribution (FPD), $\mathcal{P}_{FPD}(\rho,t)$, is defined as the probability that at time t the ratio $x(t)/x(0)$ is equal to ρ, where $x(t)$ and $x(0)$ are the protein concentrations within a population of isogenic cells at time $t>0$ and $t=0$, respectively. The system can be initially prepared according to any kind of probability density function, $p_{init}(x_0)$, nevertheless because we are interested in FPD at stationarity, we are using Eqs. (5) and (6) of the main text, i.e., the time-dependent reflecting solution and the stationary probability distribution with $\delta=0$, respectively. Thus, by definition the FPD is

$$\mathcal{P}_{FPD}(\rho,t) = \langle \delta(\rho - x/x_0) \rangle$$

$$= \int_0^\infty dx_0 \int_0^\infty dx\, p_{stat}(x_0)p(x,t|x_0,0)\delta(\rho - x/x_0), \tag{D1}$$

where $\rho > 0$, $t > 0$, and $\delta(x)$ is a Dirac delta. Notice that $\mathcal{P}_{FPD}(\rho,0) = \delta(\rho-1)$ and

$$\lim_{t \to +\infty} \mathcal{P}_{FPD}(\rho,t) = \int_0^\infty dx_0 x_0 p_{stat}(x_0)p_{stat}(\rho x_0)$$

$$= \frac{\Gamma(2\beta)}{\Gamma^2(\beta)}\frac{\rho^{\beta-1}}{(\rho+1)^{2\beta}}, \tag{D2}$$

where $\beta = k_1/\gamma_2$ and $\Gamma(\beta)$ is the standard gamma function [27]. Note that Eq. (D2) has a peak for $\rho > 0$ only when $\beta > 1$, whereas when $0 < \beta < 1$ there is an integrable singularity at $\rho = 0$. Furthermore, because the Gaussian and non-Gaussian noises have the same steady state, they both have the same FPD when $t \to +\infty$.

When substituting Eqs. (3) and (5) of the main text in Eq. (D1) and performing some simple manipulations, one gets

$$\mathcal{P}_{FPD}(\rho,t) = e^{-t/\theta}\delta(\rho - e^{-t/\tau}) + \Theta(\rho - e^{-t/\tau})\frac{\tau}{\theta}\frac{\lambda^{\tau/\theta+1}}{\Gamma(\tau/\theta)}e^{-t/\theta}$$

$$\times (e^{t/\tau} - 1)\int_0^\infty dx x^{\tau/\theta}\exp[-\lambda x(1 + e^{t/\tau}(\rho - e^{-t/\tau}))]$$

$$\times {}_1F_1\left(\frac{\tau}{\theta} + 1, 2; \lambda(e^{t/\tau} - 1)(\rho - e^{-t/\tau})x\right), \tag{D3}$$

where $\theta \equiv k_1^{-1}$, $\tau \equiv \gamma_2^{-1}$, $\lambda \equiv \gamma_1/k_2$. On exploiting the formula 7.621.4 in [30] for the integral, one can come up with Eq. (6) of the main text, which is independent on λ. When the mean number of bursts per cell cycle is very small, one obtains $\tau/\theta \ll 1$ and we can expand Eq. (6) of the main text in powers of τ/θ. In this case, the solution reads

$$\mathcal{P}_{FPD}(\rho,t) = e^{-t/\theta}\delta(\rho - e^{-t/\tau}) + - \left(\frac{\tau}{\theta}\right)^2\frac{\Theta(\rho - e^{-t/\tau})e^{-t/\theta}}{\rho - e^{-t/\tau}}$$

$$\times \ln\left(\frac{1 + \rho - e^{-t/\tau}}{1 + e^{t/\tau}(\rho - e^{-t/\tau})}\right) + O[(\tau/\theta)^3], \tag{D4}$$

where we have used (see Ref. [27])

$$_2F_1(1,1,2;z) = -\frac{\ln(1-z)}{z}.$$

Along the same lines one can obtain the FPD for the Gaussian white noise. Thus, substituting the time-dependent reflecting solution in Eq. (C5) and the steady state in Eq. (C4), one comes up with the final expression

$$\mathcal{P}_{\mathrm{FPD}}(\rho,t) = \frac{2^{f/D-1}}{\sqrt{\pi}}\frac{\Gamma\left(\frac{f}{D}+\frac{1}{2}\right)}{\Gamma\left(\frac{f}{D}\right)}\frac{(\rho+1)}{\rho}\frac{(e^{t/\tau})^{f/2D}}{1-e^{-t/\tau}}$$

$$\times\left(\frac{\sinh\left(\frac{t}{2\tau}\right)}{\rho}\right)^{f/D+1}\left(\frac{4\rho^2}{(\rho+1)^2e^{t/\tau}-4\rho}\right)^{f/D+1/2},$$

$$(\mathrm{D5})$$

where $f \equiv k_1 k_2 / \gamma_1$, $\tau \equiv \gamma_2^{-1}$ and $D \equiv \gamma_2 k_2 / \gamma_1$. Note that in this case $\mathcal{P}_{\mathrm{FPD}}(\rho,t)$ is much simpler than Eq. (6) in the main text and depends only on $f/D = k_1/\gamma_2$ and τ. In Fig. 4 we have compared the FPD for the non-Gaussian white noise [Eq. (6) in the main text] and Eq. (D5), which have the same steady state.
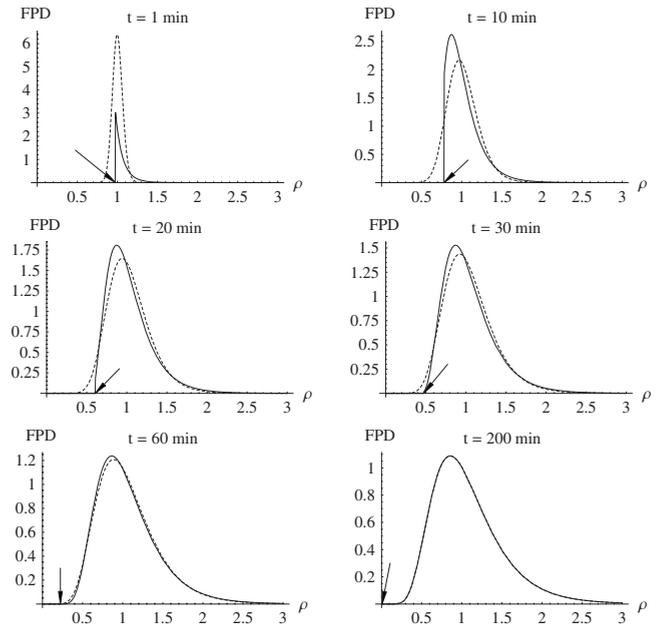
FIG. 4. Fractional protein distribution (FPD). The dashed curve is for the Gaussian noise case, i.e., Eq. (D5) with $f \equiv k_1 k_2 / \gamma_1$ and $D \equiv \gamma_2 k_2 / \gamma_1$; whereas the solid curve is for the non-Gaussian noise case, i.e., Eq. (6) in the main text. The arrow indicates the cutoff point. Note, however, that extrinsic noise could tend to smooth out the discontinuity. In both cases $k_1/\gamma_2 = 12.88$ and we have set $\gamma_2^{-1} = 40$ min.

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