Extrinsic Noise and Heavy-Tailed Laws in Gene Expression

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Noise in gene expression is one of the hallmarks of life at the molecular scale. Here we derive analytical solutions to a set of models describing the molecular mechanisms underlying transcription of DNA into RNA. Our ansatz allows us to incorporate the effects of extrinsic noise—encompassing factors external to the transcription of the individual gene—and discuss the ramifications for heterogeneity in gene product abundance that has been widely observed in single cell data. Crucially, we are able to show that heavy-tailed distributions of RNA copy numbers cannot result from the intrinsic stochasticity in gene expression alone, but must instead reflect extrinsic sources of variability.

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Transcription is one of the canonical examples of a stochastic process in biology; and as the first step in gene expression, is of fundamental biophysical importance. Stochasticity leads to significant heterogeneity between cells subject to identical conditions [1], observable through single-cell analysis methods that provide distributions of transcript copy numbers across ensembles of cells [2,3]. It is possible to model transcriptional processes using stochastic master equation descriptions, reminiscent of those in statistical physics [4,5]. The most popular models for transcription describe the effects of intrinsic noise: stochasticity arising from the Markovian nature of molecular binding, unbinding, synthesis, and decay.

The search for the causes of heterogeneity has been based on such models [6]; analyses were based either on the form of the distributions [2,7–11], or on the relationships between the moments tracked over varying conditions, or multiple genes [12,13]. Such early studies concluded that intrinsic noise alone could explain experimental observations; however, more recently a somewhat murkier picture has emerged in which it has been accepted that static observations cannot always enable accurate inference of the underlying dynamics [14,15]. A particular challenge comes in decoupling the effect of extrinsic noise, which has been widely reported from direct measurements [16–18]. While certain experimental [19] and numerical [20] studies have demonstrated that extrinsic noise can give rise to qualitatively similar results to intrinsic noise alone, incorporating these effects into mathematical descriptions has proven difficult.

Here we present a framework in which to do exactly this, capturing the joint effects of intrinsic and extrinsic noise on the distributions of transcript abundance. We confirm through analytic solutions that in many cases both the distributions and the moment scaling behavior may be indistinguishable from situations with purely intrinsic noise. However we also obtain a key identifier of extrinsic noise as a heavy-tailed copy number distribution, demonstrating that such distributions are consistent with experimental measurements.

The most widely used model for stochastic RNA transcription initiation is the telegraph process, originally detailed in [21] and discussed in recent reviews [20,22]. In the slightly generalized form we consider here, a gene is either active or inactive, states that may be associated with transcription factor binding [19] or mechanical effects on transcription [23]. When active, mRNA is transcribed as a Poisson process with rate K_1, while when inactive, basal transcription may still occur at lower rate, K_0. The mRNA degradation is modeled by a first-order Poissonian degradation process with rate, δ, while switching between the two states occurs at rates ν_0 (turn off) and ν_1 (turn on), see Fig. 1(a). This leads to a Markov process for the copy number n of the mRNA molecules at time t and gene state i, with an associated master equation for the probability $p_i(n,t)$.

$$\begin{aligned}(\forall\, n \geq 1)\partial_t p_i(n,t) = &-(\nu_{i'} + K_i + \delta n)p_i(n,t) \\ &+ \delta(n+1)p_i(n+1,t) \\ &+ K_i p_i(n-1,t) \\ &+ \nu_i p_{i'}(n,t). \end{aligned} \tag{1}$$

Here, $i \in \{0,1\}$, $i' = 1 - i$ and for $n = 0$ terms involving $n-1$ are set to 0.

The master equation Eq. (1) for this "leaky gene" model coincides with [[24], Eqs. (2),(3)], though a steady state solution is not given there; biologically it is widely applicable as basal expression has been reported in many systems [25,26], including those exhibiting Polycomb repression [27,28]. When $K_0 = 0$, the equation reduces

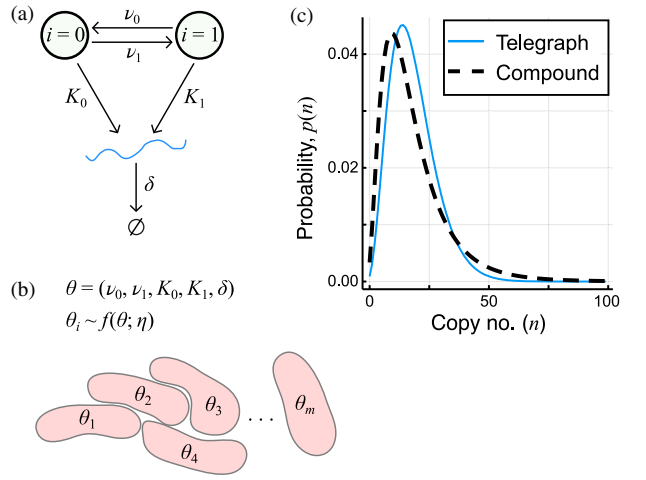

FIG. 1. The leaky telegraph model (a), captures intrinsic noise due to inherent stochasticity and burstiness. The compound model (b) considers that each cell is subject to different model parameters, leading to greater variability and a heavier-tailed distribution across the population (c).

to that given in [[21], Eq. (5)]. Following the generating function method [29,30], it can be shown that the stationary probability mass function (pmf) is given by [31]:

$$\tilde{p}(n) = \frac{1}{n!}\sum_{r=0}^{n}\left[\binom{n}{r} K_1^{n-r} e^{-K_1} w^r \frac{\nu_0^{(r)}}{(\nu_0+\nu_1)^{(r)}} \times {}_1F_1(\nu_0+r, \nu_0+\nu_1+r, -w)\right], \quad (2)$$

where $w := K_0 - K_1$, and rates are scaled so that $\delta = 1$. Here, for real number x and positive integer n, the notation $x^{(n)}$ abbreviates the rising factorial of x, while ${}_1F_1$ denotes the confluent hypergeometric function [32].

A useful limiting case of this generalized model is obtained when the active state of the gene is extremely rare ($\nu_0 \gg \nu_1$), and the degradation rate is sufficiently small ($K_1, \nu_0 \gg \delta$). This model simultaneously encompasses the two well-known extremes of very bursty transcription and constitutive transcription, as we now explain.

The steady-state solution is again obtained by employing the generating function method [29,30]. The resulting stationary pmf is simply that for an independent sum of the negative binomial and Poisson random variable, and can be derived as [31]:

$$\tilde{p}(n) = \frac{1}{n!}\sum_{s=0}^{n}\left[\binom{n}{s} \frac{\Gamma[\nu_1/\delta + (n-s)]}{\Gamma(\nu_1/\delta)(n-s)!} \times (1-r)^{(n-s)} r^{\nu_1/\delta} \frac{e^{-K_0/\delta} K_0^s}{\delta^s}\right], \quad (3)$$

where $r := \nu_0/(\nu_0+K_1)$. When $K_0 = 0$, corresponding to bursty gene expression, Eq. (3) is the pmf for $\mathrm{NegBin}(\nu_1/\delta, r)$, agreeing with the solution of [33]. When $K_1 = 0$ (or indeed is kept constant and $\nu_0 \to \infty$) the burst height parameter $r = \nu_0/(\nu_0+K_1)$ becomes 1, and the steady state solution Eq. (3) agrees with the solution for constitutive gene expression, $\mathrm{Pois}(K_0/\delta)$. Similarly, when $K_0 = 0$, we recover the following analytical expression for the telegraph model [39,40]:

$$\tilde{p}(n) = \frac{K_1^n \nu_1^{(n)}}{n!(\nu_0+\nu_1)^{(n)}} {}_1F_1(\nu_1+n, \nu_0+\nu_1+n, -K_1). \quad (4)$$

The telegraph model for transcription describes the effect of intrinsic noise at the level of a single gene, yet the process will often also be influenced by other sources of variability. Such extrinsic noise has been widely observed experimentally [16–18,41], and considered theoretically [42–45], but incorporating these effects into the master equations has generally proven challenging. The approach we take is to consider the model parameters themselves to vary between cells, and therefore to be drawn from probability distributions [25,46] [see Fig. 1(b)]. The mRNA copy number then follows a compound distribution,

$$\tilde{q}(n;\eta) = \int \tilde{p}(n;\theta) f(\theta;\eta) d\theta, \quad (5)$$

where θ is the vector of parameters $[\nu_0, \nu_1, K_0, K_1]$ and the distribution f is a multivariate distribution for θ with hyperparameters η. This model is valid provided that parameter values are static for individual cells but vary across an ensemble of cells according to f, or change substantially slower (adiabatically) than the transcriptional dynamics [34,47]. For the remainder of the Letter, when it is clear from the context that only one rate of transcription is being considered, we will use K in place of K_0 or K_1.

Typical sources of extrinsic variability for each parameter are given in Table I, along with comments on their expected features. Many of these sources of variability are related to protein abundances, which are well understood to vary over much longer timescales than mRNA [48], justifying the adiabatic assumption. Most extrinsic factors may also be categorized as either "local" or "global," denoting whether the effect would be confined to a few specific genes or would be widespread. As a general rule, locally extrinsic noise may arise due to regulatory pathways and will act on the switching rates.

Global effects are more likely to act on the rate K and furthermore are likely to be multiplicative in nature. A result of the central limit theorem in the log domain is that the multiplication of positive random variables will tend towards a log-normal distribution which is heavy tailed [49–51] and consistent with experimental observations [52]; this has important practical implications.

An alternative to the log-normal is the gamma distribution, which has also been demonstrated to arise from some

TABLE I. Interpretation of the parameters in the model and their sources of variation. "P" refers to extrinsic sources dependent on protein abundances, "L" specifies a source of variability local to one or a small number of genes, while "G" refers to more cell-wide influences.

	Interpretation	Sources of variability	
ν_1	Activating TF binding	Activating TF abundance	P, L
	Repressive TF unbinding	Repressive TF abundance	P, L
	Supercoiling relief	Topoisomerase abundance	P, G
ν_0	Activating TF unbinding	Activating TF abundance	P, L
	Repressive TF binding	Repressive TF abundance	P, L
K	Transcription rate	RNApol abundance	P, G
		Sigma factor abundance	P, G
		Polycomb repression	G, L
		Resource availability	G
		Energy availability	G
δ	Degradation rate	Ribonuclease abundance	P, G

processes governing protein abundance [53]. If we take $K \sim \text{Gamma}(\alpha, \beta)$, the compound distribution $\tilde{q}(n; \alpha, \beta)$ can be obtained analytically in two key cases.

When $\tilde{p}(n)$ is taken to be the telegraph model [Eq. (4)], it can be shown that the resulting distribution coincides with the steady-state protein number distribution found in [54]. The result is particularly striking in the special case of constitutive transcription, where $\tilde{p}(n) = \text{Pois}(K/\delta)$. In this situation, the compound distribution yields the negative binomial distribution,

$$\tilde{q}(n; \alpha, \beta) = \text{NegBin}\left(\alpha, \frac{\beta}{1+\beta}\right), \tag{6}$$

which is notably of the same form as that arising from very bursty transcription, with distribution $\text{NegBin}(\nu_1/\delta, r)$.

While these specific results arise from choosing a Gamma distributed K, this form of the distribution is qualitatively similar to many other distributions with only positive support and thus popular in the description of stochastic molecular processes [55–57]. Moreover, very similar qualitative results arise if different extrinsic distributions are chosen [31]. Thus, given a finite number of experimental data, number distribution alone cannot distinguish between intrinsic and extrinsic sources of noise. More specifically one cannot differentiate between constitutive expression with extrinsic noise, and bursty expression without extrinsic noise, although the negative binomial is often used as evidence for the latter [2,9].

Another key issue for comparison with experimental data is whether or not the moments of compound distributions converge [50]. We can provide simple formulæ for all moments—provided they exist—of the copy number distribution [Eq. (4)] under extrinsic noise on the transcription rate K. Noise in K is of particular relevance, as will become apparent in due course. Let $X = X_K$ denote a random variable from $\tilde{p}(n; K)$ [from Eq. (4)] and $Y = Y_\eta$ a random variable from the compound distribution $\tilde{q}(n; K)$ [from Eq. (5)]. It can be shown that the nth moment of Y is given by

$$E(Y^n) = \sum_{i=1}^{n} \frac{\nu_1^{(i)_\delta}}{\delta^i (\nu_0 + \nu_1)^{(i)_\delta}} S(n, i) E(K^i), \tag{7}$$

where $S(n, i)$ is a Stirling number of the second kind [58]; the notation $x^{(n)_y}$ abbreviates $x(x+y), \ldots, [x+y(n-1)]$ for real numbers x, y, and positive integer, n. It follows from Eq. (7) that if the first two moments of the compounding distribution $f(K; \eta)$ are known, then the mean, variance, and Fano factor of the compound distribution $\tilde{q}(n; \eta)$ can be easily calculated. From Eq. (7), and noting that $S(1,1) = S(2,1) = S(2,2) = 1$, the Fano factor of $\tilde{q}(n; \eta)$ is given by

$$\text{FF}(Y) = 1 - \frac{\nu_1}{\delta(\nu_0+\nu_1)} E(K) + \frac{\nu_1+\delta}{\delta(\nu_0+\nu_1+\delta)} \frac{E(K^2)}{E(K)}. \tag{8}$$

It is also possible to obtain formulæ for the nth moments and Fano factor in the case for constitutive expression with extrinsic noise on K, as well as in the case for bursty expression with extrinsic noise on K. In the former, we can alternatively obtain a formula for the Fano factor from Eq. (8) by taking $[\nu_1/(\nu_0+\nu_1)] = 1$ (corresponding to $\nu_1 \to \infty$, or $\nu_0 \to 0$). This gives

$$\text{FF}(Y) = 1 + \frac{1}{\delta} \frac{\text{Var}(K)}{E(K)}. \tag{9}$$

It has previously been suggested that the universal scaling between the mean and Fano factor, observed across various organisms, can be attributed to intrinsic noise but not extrinsic noise [12]. However, the observed scaling is entirely consistent with the analytical solutions for the Fano factor. Equation (8) shows that Fano factor of the compound distribution $\tilde{q}(n; K)$ depends only on $E(K)$ and $\text{Var}(K)$ [or equivalently $E(K^2)$] and the values of the parameters ν_0, ν_1, δ. Letting c denote the coefficient of variation, $\sigma(K)/E(K)$, for the noise distribution, $f(K; \eta)$, and noting that $E(K^2)/E(K) = (1+c^2)E(K)$, Eq. (8) becomes

$$1 - \frac{\nu_1}{\delta(\nu_0+\nu_1)} E(K) + \frac{\nu_1+\delta}{\delta(\nu_0+\nu_1+\delta)} (1+c^2) E(K). \tag{10}$$

The situation $E(Y) \to 0$ corresponds to $\nu_0 \to \infty$, which from Eq. (10) straightforwardly gives $\text{FF}(Y) \to 1$.

Equation (10) allows us to make further direct comparisons between experimental observations and analytic scaling expressions for purely intrinsic noise [12]. Figure 2(a) shows qualitatively identical behavior of the

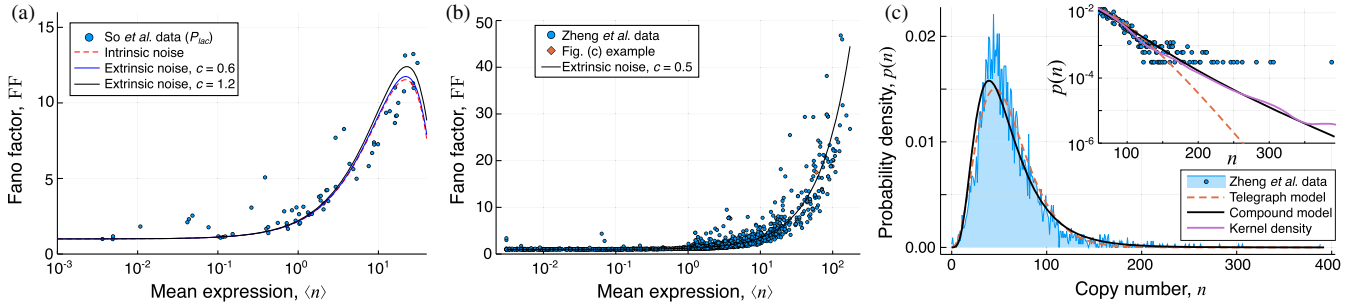

FIG. 2. In (a), the parameters for the intrinsic noise curve are $E(K) = K = 54$, $\nu_1 = 0.86$, and $\delta = 1$. Parameter values for the extrinsic noise curves are given in Table I of the Supplemental Material [31]. (a) The Fano factor of the compound distribution as a function of the mean mRNA copy number [given by Eq. (10)], varied by tuning the parameter ν_0. Different values of c are plotted against the universal noise scaling curve (intrinsic noise only) given in [12]. Data is the P_{lac} promoter also from [12]. (b) The Fano factor as a function of the mean copy number for constitutive expression with log-normal noise [given by Eq. (8)]. For comparison the mammalian data of [35] is plotted. (c) Compound and telegraph models fitted to experimental data from [35]. The particular gene is highlighted in (b).

Fano factor as a function of the mean mRNA copy number for values of c close to 1. We remark that, as in [12], the mean is varied by regulating ν_0 only. It is straightforward to demonstrate that similar agreement is also observed for the scaling of the squared coefficient of variation [31].

We next examine the effect of extrinsic noise on the noise scaling curve in the case for constitutive transcription, again considering only noise on K. Here we find that the mean copy number $E(Y)$ is equal to $E(K)$. Thus, from Eq. (9), scaling the Fano factor with mean copy number is dependent only on the noise distribution of K. If the coefficient of variation is fixed at c as the noise distribution on K is varied, then the Fano factor is given by $1 + c^2E(K)$, which is linear in $E(Y) = E(K)$. This again yields qualitatively the same behavior, and is displayed in Fig. 2(b) alongside mammalian data for comparison [35]. The observations after Eq. (6) are pertinent here: with $c = 1/\sqrt{\nu_1}$, identical noise scaling behavior arises from the two extremes—constitutive expression with extrinsic noise and bursty expression without noise. This had eluded earlier studies relying on simulations alone.

Thus far, extrinsic noise, as modelled by the compound distribution, exhibits behavior that is similar to, and, in fact, indistinguishable from, intrinsic noise alone. We now present a potential qualitative identifier for extrinsic noise: we show that contrary to previous claims [40], intrinsic noise alone never leads to a heavy-tailed copy number distribution, but find many cases in which extrinsic noise does so. Formally, we take heavy tailed to mean that the moment generating function (mgf) [29] is undefined for positive t, which implies that the tail of the distribution decays more slowly than that of the exponential distribution.

If K and δ are fixed, then the copy number is maximized when the gene remains permanently active, which has distribution Poisson(K/δ) and is not heavy tailed. Intuitively then, no compounding of ν_0 and ν_1 alone can result in a heavy-tailed distribution. A more robust argument is obtained by establishing the following inequality for the telegraph model [31]: for all positive t,

$$M_{\mathrm{Pois}(\frac{\nu_1}{\nu_0+\nu_1}\frac{K}{\delta})}(t) \le M_{\tilde{p}}(t) \le M_{\mathrm{Pois}(\frac{K}{\delta})}(t), \tag{11}$$

where M_g denotes the mgf for distribution g. In particular, $M_{\tilde{p}}(t)$ is bounded above by a Poissonian mgf that does not depend on ν_0 or ν_1. Thus $\tilde{p}(n)$ itself is not heavy tailed, and we require compounding of K or δ to make it so. On the other hand, *any* extrinsic noise on K or δ that renders the mgf for Pois$\{[\nu_1/(\nu_0+\nu_1)](K/\delta)\}$ undefined, will also result in $M_{\tilde{p}}(t)$ being undefined and the resulting compound distribution will be heavy tailed. One particular example is if $K \sim \log\text{-normal}(\mu, \sigma)$, but our results are general and do not depend on this particular choice. We use the following well-known property of mixture distributions, here interpreted in the context of Eq. (5),

$$M_{\tilde{q}}(t) = E_\theta[M_{\tilde{p}(;\theta)}(t)]. \tag{12}$$

From this and Eq. (11) it follows that the compounding integrand is bounded below by

$$\exp\left(\frac{\nu_1}{\nu_1+\nu_0}\frac{K}{\delta}(e^t-1)\right)\frac{1}{\sqrt{\sigma 2\pi}K}\exp\left(-\frac{\ln^2(K-\upsilon)}{2\sigma^2}\right), \tag{13}$$

which diverges to infinity as $K \to \infty$ provided $t > 0$. Thus log-normal extrinsic noise on K renders the compound distribution $\tilde{q}(n;\mu,\sigma)$ heavy tailed; cf. Fig. 2(c). These results extend to the leaky gene model, with log-normal noise on K_1 (conditional on $K_0 < K_1$), as it is trivial that $K_0 > 0$ only increases the probability of large copy number in comparison to the standard telegraph model. This result also naturally extends to constitutive expression with log-normal noise, since this is simply a particular case of the leaky gene model.

For bursty expression we require $\nu_0 \gg \nu_1, \delta$, so consider extrinsic noise on K only. The effect of extrinsic noise here is qualitatively different to the other cases: we observe that the mgf for the negative binomial distribution is given by

$$M_{\mathrm{nb}}(t) = \left(\frac{r}{1-(1-r)e^t}\right)^{\nu_1/\delta},$$

for $t < -\ln(1-r) = -\ln[K/(K+\nu_0)]$, and is infinite otherwise, where $r = \nu_0/(\nu_0+K)$. Thus, the range of positive t for which $M_{\mathrm{nb}}(t)$ is finite approaches 0 as $K \to \infty$, implying that any unbounded distribution $f(K;\eta)$ leads to the moment generating function of the compound distribution

$$M_{\tilde{q}}(t) = \int_0^\infty M_{\mathrm{nb}}(t) f(K,\eta) dK$$

being undefined for positive t. A wide range of extrinsic noise models on K can therefore lead to a heavy-tailed compound distribution for bursty transcription.

It had been noted before that transcript abundance distributions appear heavy tailed [59–61]. Our statistical analysis [36] finds ample evidence in many genes from the published mammalian data in Fig. 2(b) [31,35]. Furthermore, comparing the distributions shows that a compound model with log-normal noise fits the observed distribution including the heavy tail in a manner that an intrinsic noise model cannot, as exemplified in Fig. 2(c).

Noise has been intriguing and frustrating biologists to almost equal degree. Even confined to the context of gene expression alone, there is a vast literature. From epigenetic factors controlling the accessibility of genes for transcription, to understanding the role of transcriptional noise in cell fate decision making, theoretical analysis has mostly relied on stochastic simulations.

Crucially, we have been able to jointly consider the effects of intrinsic and extrinsic noise and how this relates to empirical observations including the probability distribution for mRNA copy number and the observed Fano factor scaling [12]. Further to this, we have demonstrated that extrinsic noise is required to explain observations of heavy-tailed distributions, which intrinsic noise alone cannot produce. While heavy-tailed distributions have been indicated in a number of biological contexts including in bacterial chemotaxis [62,63], this is the first result we are aware of describing an explanation for heavy-tailed distributions of molecular copy numbers. Given the notoriously noisy environment within cells and the intricate organization of gene regulatory networks, noise extrinsic to a given gene (or gene model) is almost certainly ubiquitous. The framework and results provided here allow us to get a better, more detailed handle on the origins and implications of noise in molecular systems and beyond, and how these should be studied experimentally.

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