The intrinsic stochasticity of gene expression can lead to large variability of protein levels across a population of cells. Variability (or noise) in protein distributions can be modulated by cellular mechanisms of gene regulation; in particular, there is considerable interest in understanding the role of post-transcriptional regulation. To address this issue, we propose and analyze a stochastic model for post-transcriptional regulation of gene expression. The analytical solution of the model provides insight into the effects of different mechanisms of post-transcriptional regulation on the noise in protein distributions. The results obtained also demonstrate how different sources of intrinsic noise in gene expression can be discriminated based on observations of regulated protein distributions.

Post-transcriptional regulation of genes expressed according to the Poisson and Telegraph scenarios. The analytical results obtained provide insight into how different mechanisms of post-transcriptional regulation modulate noise in protein distributions. The results obtained also show how different sources of intrinsic noise in gene expression can be discriminated based on observations of regulated protein burst distributions.

We first analyze how post-transcriptional regulation modifies protein bursts under the Poisson scenario. Several recent studies have focused on the corresponding mean-field and stochastic models, in particular for regulation by small RNAs. These studies have primarily focused on small RNAs which act via irreversible stoichiometric degradation of mRNAs. On the other hand, binding of the post-transcriptional regulator can more generally be considered as a reversible reaction. For this case, and in the limit of large regulator concentrations (see below), we wish to analyze the effects of different mechanisms of post-transcriptional regulation on the
noise in protein burst distributions.

The proposed reaction scheme for our model is shown in Fig.(2A) for a given concentration of the post-transcriptional regulator: the regulator binds mRNA to form a complex with rate $\alpha$; the dissociation rate for the complex is $\beta$. The parameters $k_{p1}$ and $k_{p2}$ are the rates of protein production from the mRNA in free and bound states and $\mu_m$ and $\mu_c$ are the corresponding decay rates. For global post-transcriptional regulators that are present in large numbers, it is a good approximation that binding to the target mRNA does not significantly alter the concentration of the regulator. In this case, fluctuations in regulator concentration can be neglected and the rate $\alpha$ can be taken to be constant.

For the Poisson scenario, the protein burst distribution, $P_b(n)$, corresponds to the number of proteins translated from a single mRNA before it decays. During this process, the mRNA can exist in two states: either free or bound in a complex with the post-transcriptional regulator. Correspondingly, we define the functions $f_1(n, t)$ and $f_2(n, t)$ (generalizing the approach outlined in [16]) which denote the probabilities of finding the mRNA in free and bound states and $\mu_m$ rates. For global post-transcriptional regulators that are form a complex with rate $\alpha$; the dissociation rate for the complex is $\beta$. The parameters $k_{p1}$ and $k_{p2}$ are the rates of protein production from the mRNA in free and bound states and $\mu_m$ and $\mu_c$ are the corresponding decay rates. For global post-transcriptional regulators that are present in large numbers, it is a good approximation that binding to the target mRNA does not significantly alter the concentration of the regulator. In this case, fluctuations in regulator concentration can be neglected and the rate $\alpha$ can be taken to be constant.

For the Poisson scenario, the protein burst distribution, $P_b(n)$, corresponds to the number of proteins translated from a single mRNA before it decays. During this process, the mRNA can exist in two states: either free or bound to the mRNA-target complex. The protein burst distribution is kept the same. The burst distribution for full repression is identical to the geometric distribution with the same mean, whereas $P_b(n)$ for decay modulation and activation deviates significantly from the geometric distribution. Parameters for decay modulation and activation are chosen such that $\frac{\alpha}{\mu_m} = 5$, $\frac{\mu_c}{\mu_m} = 1$, $\frac{\mu_m}{p_m} = 5$, $p_m = 1$ and $\frac{\alpha}{\mu_m} = \frac{\alpha}{\mu_m} = 1$, $k_{p1} = 4$, $p_m = 1$ respectively.

The above equations can be analyzed further using a combination of generating functions and Laplace transforms. Specifically, defining $G_b(z) = \sum_n z^n P_b(n)$ and $F_{1,2}(z, s) = \sum_n z^n \int_0^\infty e^{-st} f_{1,2}(n, t) dt$, we obtain

$$G_b(z) = \lim_{s \to 0} \left( \mu_m F_1(z, s) + \mu_c F_2(z, s) \right)$$

(3)

We now consider the Telegraph scenario wherein multiple mRNAs can be produced during a single burst. In this case, the probability of having $m$ mRNAs in one burst, $P(m)$, is given by a geometric distribution, conditional on the production of at least 1 mRNA [12]

$$P(m) = (1 - p_m)^{m-1} p_m.$$  

(4)

Eq.(4) serves as a general formula for the mRNA burst distribution characterizing both Poisson and Telegraph scenarios. The case $p_m = 1$ correspond to a single mRNA produced every burst (Poisson scenario); whereas if $p_m < 1$, the mean number of mRNAs produced per burst $m_b = 1/p_m$ is greater than 1 (Telegraph scenario). In general, each mRNA will produce a random number of proteins drawn from the distribution $P_b(n)$ (the corresponding generating function $G_b(z)$ is given by Eq.(3)) and furthermore the number of mRNAs in the burst is also a random variable defined by the distribution Eq.(4).

We denote the distribution of proteins produced from all the mRNAs in the burst by $P_b'(n)$. The corresponding generating function $G_b'(z)$ is given by

$$G_b'(z) = \frac{G_b(z)p_m}{1 - G_b(z)(1 - p_m)}. \quad (5)$$

Evaluation of the functions $F_{1,2}(z, s)$ in combination with Eq.(3) and Eq.(4) then leads to the exact expression for $G_b'(z)$, which can be written as

$$G_b'(z) = X \frac{1 - S_1}{z - S_1} + (1 - X) \frac{1 - S_2}{z - S_2} \quad (6)$$

where

$$X = \frac{\sqrt{\Delta} - \left( k_{p1}(\beta + \mu_c) + k_{p2}(\alpha - \mu_mp_m) \right)}{2\sqrt{\Delta}} \quad (7)$$

$$S_{1,2} = 1 + k_{p1}(\beta + \mu_c) + k_{p2}(\alpha + \mu_mp_m) \pm \frac{\sqrt{\Delta}}{2k_{p1}k_{p2}}$$

$$\Delta = \left( k_{p1}(\beta + \mu_c) - k_{p2}(\alpha + \mu_mp_m) \right)^2 + 4\alpha k_{p1}k_{p2}(\beta + \mu_c - \mu_mp_m). \quad (8)$$

The above expression indicates that the distribution of proteins produced in a single burst ($P_b'(n)$) can be
expressed as a weighted sum of two geometric distributions. While the complete expression for \( P_b(n) \) can thus be derived from the results obtained, in some cases, the primary interest is in derived quantities characterizing the noise in protein distributions. For example, several studies have focused on the noise strength (or Fano Factor) \( \sigma_b^2/n_b \). For the protein burst distribution \( P_b(n) \), both the mean and the noise strength can be obtained from the generating function as

\[
\begin{align*}
   n_b &= \frac{k_{p1} (\mu_c + \beta) + k_{p2} \alpha}{\mu_m (\mu_c + \beta) + \mu_c \alpha} \\
   \sigma_b^2/n_b &= 1 + n_b + \frac{2\alpha k_{p2} (k_{p2} \mu_m - k_{p1} \mu_c) + (\alpha k_{p2} + k_{p1} \beta + k_{p1} \mu_c) (\alpha \mu_c + \beta \mu_m + \mu_c \mu_m)}{\mu_m (\mu_c + \beta) + \mu_c \alpha} (8)
\end{align*}
\]

It is noteworthy that Eq. \((7)\) is valid for the most general choice of parameters. To gain additional insight, let us consider specific parameter choices of interest. For example, taking the limit \( \alpha \to 0 \) corresponds to the unregulated protein burst distribution. In this case, we obtain

\[
   G_b'(z) = \frac{\mu_m}{\mu_m + \frac{k_{p2}}{p_m} (1 - z)}, \quad (9)
\]

which corresponds to the generating function of a geometric distribution in agreement with previous studies \[11,12,17,18\]. Of greater interest is the effect of different modes of regulation. While a generally accepted model is that regulator binding prevents ribosome access (i.e. \( k_{p2} = 0 \)), recent studies have shown that small RNAs can also repress gene expression by binding in the coding region significantly downstream of the ribosome binding site \[19\]. In the latter case, regulator binding is not expected to affect the translation rate, but instead alters the mRNA decay rate. To explore the effects of these different regulatory mechanisms on the noise in protein distributions, we consider two special cases for the general results derived above: 1) full repression (\( k_{p2} = 0 \)) and 2) decay modulation (\( k_{p2} = k_{p1} \), \( u_m < u_c \)).

For full repression (in the limit \( k_{p2} \to 0 \)), we have

\[
   G_b'(z) = \frac{\mu_m + \frac{\mu_c \alpha}{\mu_c + \beta} - k_{p1} \mu_m (1 - z)}{\mu_m + \frac{\mu_c \alpha}{\mu_c + \beta}}, \quad (10)
\]

The result is identical to Eq. \((4)\) provided that the mRNA degradation rate is rescaled from \( \mu_m \) to \( \mu_m + \frac{\mu_c \alpha}{\mu_c + \beta} \). Thus the protein burst distribution remains a geometric distribution but with a reduced mean due to lowering of the effective mRNA lifetime. This implies that regulation by full repression results in a protein burst distribution that is identical to that of an unregulated burst distribution with the same mean.

On the other hand for regulation by decay modulation, the burst distribution shows deviations from a geometric distribution (Fig. 2B). To analyze this further, let us focus on the noise strength \( \sigma_b^2/n_b \) in Eq. \((8)\) which, for decay modulation, is given by

\[
   \frac{\sigma_b^2}{n_b} = 1 + n_b + \frac{2\alpha k_{p1} (1 - \theta_1)}{(\alpha + \theta_1 \mu_m + \beta + \theta_1 (\alpha + \mu_m))} = 1 + n_b + \frac{2\alpha k_{p1} (1 - \theta_1)}{(\alpha + \theta_1 \mu_m + \beta + \theta_1 (\alpha + \mu_m))} (11)
\]

where \( \theta_1 = \mu_c/\mu_m > 1 \) and the term \( Q \) quantifies the deviation from the geometric distribution (\( Q = 0 \) for a geometric distribution). Thus for regulation by decay modulation, the noise strength can be tuned by the parameter \( \theta_1 \) resulting in a burst distribution with reduced variance when compared an unregulated burst distribution with the same mean. Eq. \((11)\) indicates that this reduction can be significant since the maximum magnitude for \( Q/n_b \) is 0.5. Such a narrowing of the variance relative to the mean has been previously proposed as a potential function for small RNAs with important implications for canalization of gene expression during development \[20\].

The previous results for repression mechanisms can be contrasted with the effect of post-transcriptional activation of gene expression. The burst distribution for activation also shows significant deviations from a geometric distribution with the same mean (Fig. 2B). For activation due to increased protein production (with \( \mu_c = \mu_m \)), the deviation \( Q \) relative to the burst mean is given by:

\[
   \frac{Q}{n_b} = \frac{2\alpha \theta_2 p_m \mu_m (\theta_2 - 1)}{(\alpha \theta_2 + \beta + \mu_m)^2} (12)
\]

where \( \theta_2 = k_{p2}/k_{p1} \). As \( \theta_2 > 1 \) for activation, the noise will be greater than that of an unregulated burst distribution with the same mean. The value of \( Q/n_b \) depends on the choice of \( \theta_1 \) and \( \alpha \), can be made arbitrarily large. Our results thus indicate that activation of gene expression by small RNAs can potentially lead to large variance in protein distribution, which in turn can give rise to phenotypic heterogeneity that is often beneficial for the organism \[21\].

Eq.\((11)\) also illustrates conditions under which the Poisson and Telegraph scenarios can be distinguished based on observations of protein burst distributions. The unregulated burst distribution is geometric and thus completely determined by its mean value \( n_b = \frac{1}{p_m} (\frac{k_{p1}}{\mu_m}) \). Since there is effectively one measurable quantity \( (n_b) \) for the burst distribution, \( p_m \) cannot be determined given that \( \frac{k_{p1}}{\mu_m} \) is not known \[12\]. Hence the Poisson and Telegraph scenarios cannot be distinguished in this case. However, for the case of decay modulation (with \( k_{p1} = k_{p2} \)), we have an additional measurable quantity: \( Q \). It is of interest to note that \( Q \) depends on \( \frac{k_{p1}}{\mu_m} \), and is independent of \( p_m \). Thus, measurements of \( Q \) and \( n_b \) can be used to determine both \( \frac{k_{p1}}{\mu_m} \) and \( p_m \) and thereby to discriminate between the Poisson and Telegraph scenarios.

The argument above provides a means of determining \( p_m \) provided the interaction parameters such as \( \alpha \),
In general, these parameters are not known, however for regulators such that the dissociation rate $\frac{d}{\mu_m} \to 0$, the following protocol can be used to determine $p_m$: (i) Obtain the mean protein burst levels without regulation, denoted by $n_0$. (ii) Choose a certain regulator concentration. Obtain the mean protein burst level $n_{b1}$ and the corresponding variance. Determine the deviation from a geometric distribution as defined in Eq. (11), which is denoted by $Q_1$ and let $n_1 = n_{b1}/n_0$. (iii) Change the concentration of the regulator, which effectively changes the regulator binding rate $\beta$. Repeat step (ii) and obtain the corresponding quantities denoted by $Q_2$ and $n_2 = n_{b2}/n_0$. Given the five quantities $n_{0,1,2}$ and $Q_{1,2}$, the mean transcriptional burst size $m_b(=1/p_m)$ is given by:

$$m_b = -2n_0n_1n_2 \frac{Q_1(1-n_2) - Q_2(1-n_1)}{Q_1n_1(1-n_2) - Q_2n_2(1-n_1)} \times \frac{(1-n_1)(1-n_2)(n_1-n_2)}{Q_1n_1(1-n_2)^2 - Q_2n_2(1-n_1)^2}$$

Using stochastic simulations, we have verified that the above expression accurately predicts the degree of transcriptional bursting. It should be noted that experimental approaches have been developed recently for direct measurements of mRNA burst distributions and it would be informative to compare results from these direct approaches with estimates from the above protocol.

Finally, we note that the result derived above lead to corresponding analytical expressions for steady-state protein distributions over a population of cells. Recent work has shown that, when protein lifetimes are much longer than mRNA lifetimes, an effective Master equation can be written down for proteins alone. In this approximation, given a geometric distribution for protein bursts, the corresponding steady-state protein distribution is a negative binomial distribution. Given the most general burst distribution obtained above, we derive that the corresponding steady-state distribution is a convolution of two negative binomial distributions. A detailed analysis of the corresponding expressions for the mean and variance will be presented elsewhere.

In summary, we have derived analytical expressions which characterize the noise in protein distributions for a stochastic model of post-transcriptional regulation. It is noteworthy that the expressions provide functional forms for the entire probability distribution (and not just the mean and variance) for arbitrary parameter choices. This knowledge can be a useful input for approaches to infer cellular mechanisms and parameters based on entire distributions. The results also provide insight into how different mechanisms of post-transcriptional regulation can be used to fine-tune the noise in stochastic gene expression with potential implications for studies addressing the evolutionary importance of noise in biological systems. In some limits, the modulated burst distributions can be used to infer the degree of transcriptional bursting and hence to determine the source of intrinsic noise in gene expression. The results derived can serve as building blocks for future studies focusing on regulation of stochastic gene expression.

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