Attenuation of transcriptional bursting in mRNA transport

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Received 23 July 2009
Accepted for publication 12 November 2009
Published 21 December 2009
Online at stacks.iop.org/PhysBio/7/016005

Abstract
Because of the stochastic nature of biochemical processes, the copy number of any given type of molecule inside a living cell often exhibits large temporal fluctuations. Here, we develop analytic methods to investigate how the noise arising from a bursting input is reshaped by a transport reaction which is either linear or of the Michaelis–Menten type. A slow transport rate smoothes out fluctuations at the output end and minimizes the impact of bursting on the downstream cellular activities. In the context of gene expression in eukaryotic cells, our results indicate that transcriptional bursting can be substantially attenuated by the transport of mRNA from nucleus to cytoplasm. Saturation of the transport mediators or nuclear pores contributes further to the noise reduction. We suggest that the mRNA transport should be taken into account in the interpretation of relevant experimental data on transcriptional bursting.

1. Introduction
Molecular binding and chemical modifications underlying intracellular processes are intrinsically stochastic. They give rise to temporal fluctuations and cell-to-cell variations in the number of molecules of any given type, mask genuine signals and responses, and generally contribute to the phenotypic diversity in a population of genetically identical individuals [1–3]. Various characteristics of such noise have been under intense quantitative study in the past few years [4, 5]. One of the focal points of the discussion is how the noise propagates along a biological pathway. It has been shown that in cases where the dynamics of the upstream molecules is not affected by the downstream processes (e.g., in gene transcription and translation), a ‘noise addition rule’ generally applies, i.e., each process in the pathway contributes to the overall noise strength in a statistically independent fashion [6, 7]. Modifications to this rule in molecular circuits with feedbacks or ‘detection’ capabilities as in signalling have been examined by Tănase-Nicola et al [8].

In metabolic pathways and other transport processes, however, the upstream molecule is passed on to the downstream pool in a modified form. The conservation of mass and/or number of molecules in the reaction sets new rules on noise propagation. In a recent work, Levine and Hwa considered this problem in the steady state of a metabolic network [9]. Their results show that fluctuations in the number of intermediate metabolites are generally uncorrelated to each other, upstream or downstream along a pathway or across branches. This, of course, does not exclude dynamic correlations which can be quite nontrivial in driven processes [10]. The full dynamic description of stochastic transport through a network is a very challenging task which has not been fully solved even for a linear pathway [11], though suggestions have been made to reduce the complexity of the problem through an adiabatic coarse-graining procedure [12]. A case of interest in the present context is bursty input, where the molecules to be transported are produced in batches separated by long silent intervals. Well-known examples of such behavior include the transcriptional and translational bursting [2, 13] and vesicular transport [14]. In eukaryotic gene expression, a large number of mRNAs are produced over a short period of time and followed by a long silent period as a result of the chromatin remodeling. In prokaryotes, burst of
protein copy number can occur as the result of short lifetime of an mRNA transcript. Nutrient uptake in endocytosis can also be viewed as a burst event: endocytic vesicle transports and releases a large number of extracellular molecules to the target site.

In this paper, we examine the attenuation of bursting noise in a two-compartment model with a stochastic transport channel. The model is motivated by a recent experimental and theoretical work by Raj et al [15] on the mRNA copy number fluctuations in mammalian cell gene expression. The experiments show that the total number of mRNA transcripts produced in a single burst event ranges from a few tens to hundreds. It was argued that such large bursts, if unattenuated, could harm the progression of normal cellular activity [16] due to their large perturbations to the cytoplasmic mRNA and protein levels. A suggestion was made by Raj et al that the latter could be avoided if the overall protein copy number is kept high by a low protein degradation rate. However, no distinction between nuclear and cytoplasmic mRNAs was made in their work. A more complete study should include a discussion of the mRNA transport out of the nucleus. As we show in this work, a sufficiently slow nuclear mRNA processing and export process can substantially attenuate mRNA bursting and minimize its impact on the downstream protein population.

Supporting this view, an earlier kinetic study of mammalian cell mRNA splicing and nuclear transport has shown that the nuclear dwelling (or retention) time of an mRNA molecule can be comparable to its lifetime in the cytoplasm [17]. This is evidenced in the time required to reach the respective steady-state levels for the mRNAs residing in the nucleus and in the cytoplasm, which were measured separately in the experiment. Consistent with this observation, both studies also concluded that, on average, about 10–40% of mRNA are retained in the nucleus. In this respect, the one-compartment model of Raj et al, which considers only the total mRNA copy number in a cell, overestimates fluctuations in the actual number of mRNAs in the cytoplasm that participate in the translation process. While the attenuation of high-frequency noise in transport processes is generally expected [6, 18, 19], we present here quantitative estimates of the noise reduction factor as a function of the ratio between nuclear and cytoplasmic mRNAs.

To establish a reasonable model, let us first examine the typical fate of a single mRNA: the mRNA is synthesized in bursts at the transcription site and almost simultaneously processed into an mRNA-protein (mRNP) complex [20, 21]; the mRNP complex diffuses inside the nucleus [22–24], eventually reaches one of the nuclear pores and exits with the help of export mediators [25, 26]; the mRNA degrades in the cytoplasm. Therefore, our model includes three processes: the transcriptional bursting in the nucleus, the mRNA transport and the mRNA decay in the cytoplasm. We shall assume that the mRNA transport to the cytoplasm is much slower than the diffusion process, so that the spatial inhomogeneity of the mRNA molecules in the two compartments can be ignored.

The detailed kinetic process of mRNA export through the nuclear envelope is rather complicated and involves a number of intermediate steps [27, 28]. A related problem which has been considered in the literature is protein translocation through a single nanopore [29–33]. In the present work, we shall take a phenomenological approach and assume that, on time scales over which the mRNA populations in the two compartments undergo substantial change, mRNA export can be effectively described as a two-step process that includes a reversible attachment to the rate-limiting export mediator within or on the nuclear membrane, and a subsequent irreversible export reaction to the cytoplasm, i.e., it follows the Michaelis–Menten (MM) kinetics. The treatment of multiple-channel transport can be further divided into two regimes. In the linear regime, the export mediators and nuclear pores are abundant as compared to the transported mRNA. Consequently, the export events are independent of each other. Nonlinear transport corresponds to a situation where queuing of nuclear mRNA takes place due to a limited number of transport mediators or nuclear pores. Since the linear case is much easier to treat mathematically and can also serve as a limiting case for the more general nonlinear transport, we will consider it first.

This paper is organized as follows. In section 2, we introduce the chemical master equations that govern the time-dependent distribution of mRNA copy numbers in the two compartments. In the case of linear transport, exact expressions for the copy number fluctuations in a steady-state situation are obtained. The MM transport in the weak noise limit can be treated using the linear noise approximation (LNA) [34]. A novel independent burst approximation (IBA) is introduced to treat the MM transport in the strong fluctuations regime.

The main results of our calculation are summarized in section 3. The noise strength of cytoplasmic mRNA is expressed in terms of the average burst size and the ratio of the mean nuclear and cytoplasmic mRNA copy numbers, which are measurable in experiments. Quite generally, the extent of burst attenuation is governed by the rate of transport. The slower the mRNA transport, the smaller the noise in the cytoplasmic mRNA number. In the case of the MM transport, the saturation effect of transport mediators or nuclear pores further reduces mRNA copy number fluctuations in the cytoplasm. The accuracy of the analytic predictions is verified in stochastic simulations. In section 4, based on these findings, we suggest a revision of the parameters estimated by Raj et al for the bursting and decay dynamics of mRNA in their experiments. Some mathematical details are relegated to appendices.

2. Methods

The transport event involves two compartments, usually with different volumes which result in different concentrations even in [15], obtained a diffusion constant \( D = 0.03 - 0.06 \, \mu m^2 \, s^{-1} \) [23]. Given that the diameter of the CHO nucleus is about 5 \( \mu m \), the time needed for the mRNP complexes to disperse throughout the nucleus is of the order of a few minutes, much shorter than the nuclear dwelling time of several hours.  

4 The study by Vargas and colleagues on the diffusion of mRNA particles in the nucleus of the Chinese hamster ovary (CHO) cell, the same system used
when the number of molecules is the same. To step aside this problem and to be more clear, we measure the amount of mRNA in copy number rather than concentration and define all the reaction rates mesoscopically (by scaling the macroscopic counterparts with volumes). Such a treatment (we will not explicitly refer to specific units for variables and parameters in the following calculations) also facilitates the application of chemical master equations. Then we can start safely by introducing the methods for the simplest case: linear transport.

2.1. Linear transport

Transcriptional bursting is a result of switching between the active state $A$ and the inactive state $I$ of a given gene. The nuclear mRNA population, denoted by $M_n$, is produced from the gene in its active state. To faithfully describe the bursting, we write the relevant reactions, as often done in many previous works [2, 15], as

$$I \xrightarrow{\lambda} A, \quad A \xrightarrow{\gamma} I, \quad A \xrightarrow{\mu} A + M_n. \quad (1)$$

Here $\lambda$ and $\gamma$ are the rates of gene activation and inactivation respectively, and $\mu$ is the transcription rate. Using $M_c$ to denote the cytoplasmic mRNA, we define the linear transport and cytoplasmic decay of mRNA as

$$M_n \xrightarrow{k} M_c, \quad M_c \xrightarrow{\delta} \emptyset. \quad (2)$$

Here $k$ is the rate of the transport reaction, which is assumed to be irreversible, and $\delta$ is the degradation rate of cytoplasmic mRNA. The decay of mRNA in the nucleus is ignored [17].

The state of the system is specified by the activation state of the gene ($A$ or $I$) and the copy numbers $m_n$ and $m_c$ of the nuclear and cytoplasmic mRNAs, respectively. Let $P_\xi(m_n, m_c, t), \xi = A, I$, be the probability of such a state at time $t$. Its time evolution obeys the chemical master equations,

$$\frac{dP_A(m_n, m_c, t)}{dt} = \lambda P_I(m_n, m_c, t) - \gamma P_A(m_n, m_c, t) + \mu (\varepsilon_a^{-1} - 1) P_A(m_n, m_c, t) + k (\varepsilon_c^{-1} - 1) m_n P_A(m_n, m_c, t) + \delta (\varepsilon_c - 1) m_c P_A(m_n, m_c, t), \quad (3)$$

$$\frac{dP_I(m_n, m_c, t)}{dt} = \gamma P_A(m_n, m_c, t) - \lambda P_I(m_n, m_c, t) + \mu (\varepsilon_a^{-1} - 1) m_n P_I(m_n, m_c, t) + \delta (\varepsilon_c - 1) m_c P_I(m_n, m_c, t), \quad (4)$$

where $\varepsilon$ is the step operator defined by its effect on arbitrary functions of $m_n$ and $m_c$: $\varepsilon_n^{\pm 1} f(m_n, m_c, t) = f(m_n \pm 1, m_c, t)$ and $\varepsilon_c^{\pm 1} f(m_n, m_c, t) = f(m_n, m_c \pm 1, t)$.

The first moments or mean values of $m_n$ and $m_c$ can be obtained by multiplying equations (3) and (4) by $m_n$ and $m_c$ in turn, and summing over all $m_n, m_c$ and gene states:

$$\frac{d\langle m_n \rangle}{dt} = \mu \langle P_A \rangle - k \langle m_n \rangle, \quad (5)$$

$$\frac{d\langle m_c \rangle}{dt} = k \langle m_n \rangle - \delta \langle m_c \rangle. \quad (6)$$

Here $\langle \cdot \rangle$ denotes average over the distribution, and $p_A(t) = \sum_m P_A(m_n, m_c, t)$ is the probability that the gene is in the active state. The following equation is easily seen from the gene activation dynamics (1):

$$\frac{dp_A}{dt} = \lambda (1 - p_A) - \gamma p_A. \quad (7)$$

Equations (5)–(7) are equivalent to the macroscopic rate equations given by the mass-action law due to the linearity of the process. Setting the right-hand side of these equations to zero, we obtain the steady-state relations for the average mRNA flux: $J = \mu \rho_A = \mu \lambda / (\lambda + \gamma) = k \langle m_n \rangle = \delta \langle m_c \rangle$.

In the following discussion, we will focus on the burst limit where $\mu$ and $\gamma$ are significantly larger than all other reaction rates. The steady-state probability $\rho_A$ goes to zero but the mRNA synthesis rate $J = \mu \rho_A = \lambda / (\lambda / \gamma + 1)$ remains finite. Gene activation in this case follows a Poisson process at a rate $\lambda$. The number of mRNA copies $b$ produced in each activation event is a random variable that satisfies the geometric distribution: $G(b) = (\mu / \gamma)^b (1 + \mu / \gamma)^{-b-1}$ [35]. In terms of the mean mRNA copy number produced in each burst, $\langle b \rangle = \mu / \gamma$, we have

$$J = \lambda \langle b \rangle = k \langle m_n \rangle = \delta \langle m_c \rangle. \quad (8)$$

A similar procedure as above yields the second moments of mRNA copy numbers in the steady state:

$$\langle m_n^2 \rangle = \langle m_n \rangle^2 + \langle (b + 1) \rangle \langle m_n \rangle, \quad (9)$$

$$\langle m_n m_c \rangle = \langle m_n \rangle \langle m_c \rangle + \langle b \rangle \langle m_n \rangle \langle m_c \rangle, \quad (10)$$

$$\langle m_c^2 \rangle = \langle m_c \rangle^2 + \langle (b + 1) \rangle \langle m_c \rangle - \langle b \rangle \langle m_n \rangle \langle m_c \rangle / \langle m_n \rangle + \langle m_c \rangle. \quad (11)$$

It is customary to measure temporal variations of population size in a stationary process using the noise strength (also known as the Fano factor), defined as the variance over average [6, 13, 36]:

$$\frac{\sigma_{m_n}^2}{\langle m_n \rangle} = \langle b \rangle + 1, \quad (12)$$

$$\frac{\sigma_{m_c}^2}{\langle m_c \rangle} = \langle b \rangle + 1 - \langle b \rangle \langle m_n \rangle + \langle m_c \rangle. \quad (13)$$

For the Poissonian fluctuation arising from the simplest case where molecules are produced one by one with a constant probability and degraded linearly, the noise strength is unity [37, 38]. When the synthesis is burst like and the degradation is still linear, the noise strength becomes $\langle b \rangle + 1$, which is much larger than the Poissonian fluctuation [39]. This is the case for the nuclear mRNA population (equation (12)), and for the mRNA without transport, as in the prokaryotic cells. Equation (13), on the other hand, shows that although the transport event follows a random process, the noise strength of the cytoplasmic mRNA that propagates directly to protein noise is actually reduced. The amount of reduction is controlled by the ratio $\langle m_n \rangle / (\langle m_n \rangle + \langle m_c \rangle)$, which increases with decreasing transport rate $k$. 

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2.2. Michaelis–Menten-type transport

Accumulation of the mRNAs in the nucleus may lead to a saturation effect that changes the transport dynamics when the number of export mediators or nuclear pores becomes limiting. This prompts us to study a more general mechanism of transport that takes the transport capacity into account. The resulting process can be cast in the form of the well-known Michaelis–Menten model.

To simplify the discussion, we consider here only one source of constraint, say the limited number of one kind of export mediators denoted by \( E \), and treat the rest of the export mediators (including the nuclear pores) in the process to be non-rate-limiting. Thus, the transport process of mRNA can be described as

\[
M_n + E \xrightleftharpoons{k_1}{k_2} EM_n \rightarrow E + M_c,
\]

where \( k_1 \) and \( k_2 \) are the binding and unbinding rates respectively, and \( k_3 \) is the export rate. This is similar to the MM model for enzymatic reaction.

The analysis presented below is based on the ‘fast equilibration’ approximation, in which \( EM_n \) is treated as a transition state rather than an accumulation point in the mRNA export. For this to be true, the lifetime of the complex \( EM_n \) should be significantly shorter than the total nuclear dwelling time, i.e., either the Michaelis constant \( K_m = (k_2 + k_3)/k_1 \) is much greater than one, or \( k_3 \) is much smaller than the other two rates. Under this assumption, the \( EM_n \) population remains in quasi-equilibrium with the nuclear population \( m_n \) which varies on a much slower time scale as compared to the decomposition time of the complex \( EM_n \).

Because of the small copy number of the nuclear mRNA and the transporter \( E \), we distinguish the free \( M_n \) from the bound ones and define the total number of nuclear mRNAs as \( m_n = m_{nf} + c \), where \( m_{nf} \) is the number of free \( M_n \) and \( c \) is the number of the complexes. The total number of \( E \), including both free and bound ones, is denoted by \( e \). The usual rate equation approach for the complex yields

\[
k_1 m_{nf}(e - c) - (k_2 + k_3)c = 0
\]

when quasi-equilibrium is established. Hence the mean complex number is given by

\[
c = e \frac{m_{nf}}{K_m + m_{af}}.
\]

On the other hand, through an exact analysis, Levine and Hwa [9] obtained a modified expression in the limit \( k_3 \to 0 \),

\[
c = e \frac{m_n}{K + m_n},
\]

where \( K = K_m + e \). The two expressions converge to the exact result in both the linear regime \( m_n \ll K \) and the saturated regime \( m_n \gg K \). They differ only in the crossover regime \( m_n \approx K \), where no exact result is available in the general case, though either of the two can be used as approximate expressions.

Using equation (16), we write the transport flux as

\[
v(m_n) = k_3 c = \frac{v_{\text{max}} m_n}{K + m_n},
\]

where \( v_{\text{max}} = k_3 e \). Following the fast equilibration assumption, we may now describe the mRNA export under the MM kinetics using the reduced description (2) with an effective transport coefficient \( k = v_{\text{max}}/(K + m_n) \) that decreases with increasing \( m_n \). Again, taking the burst limit for the mRNA production, we arrive at the following master equation for the joint distribution of \( m_n \) and \( m_c \):

\[
\frac{dP(m_n, m_c, t)}{dt} = \sum_{i=0}^{m_n} \lambda G(b) P(m_n - b, m_c, t)
\]

\[
- \sum_{i=0}^{m_n} \lambda G(b) P(m_n, m_c, t)
\]

\[
+ (e - 1) v(m_n) P(m_n, m_c, t)
\]

\[
+ \delta(e - 1) m_c P(m_n, m_c, t).
\]

Since the nonlinear function \( v(m_n) \) in the MM transport does not allow for the closure of equations for the second moments of the distribution, approximate treatment of the master equation is necessary.

The two limiting situations \( m_n \gg \langle b \rangle \) and \( m_n \ll \langle b \rangle \) call for separate considerations. In the former case, the contribution of each burst event on the total nuclear mRNA population is small, so that perturbative treatment around the average \( \langle m_n \rangle \) is appropriate. The latter case, however, corresponds to the situation where the nuclear mRNA from each burst event is essentially cleared before the next one arrives. The two cases are treated separately below.

2.2.1. Linear approximation. We first consider the weak fluctuation case \( m_n \gg \langle b \rangle \). A general scheme to perform the noise calculations is the van Kampen’s \( \Omega \) expansion whose lowest order terms reproduce the macroscopic rate equations and the next order terms yield a linear Fokker–Planck equation (FPE), which is often called the linear noise approximation [34]. In appendix A we derive the noise strengths under the LNA. Here, we outline a more direct yet equivalent way to obtain the results.

The approximation we introduce is to replace (17) with its linear expansion at \( m_n = \langle m_n \rangle \):

\[
v \approx v_{\text{eff}}(m_n + m_0).
\]

Here \( v_{\text{eff}} = v_{\text{max}} K/(K + \langle m_n \rangle^2) \) and \( m_0 = \langle m_n \rangle^2/K \).

Substituting (19) into (18), we obtain moments of the distribution \( P(m_n, m_c, t) \) in the same way as in section 2.1. In fact, equations (8)–(11) remain valid if we make the substitution \( k \to k_{\text{eff}} \) and \( m_n \to m_n + m_0 \). After rearranging the terms, we obtain

\[
\frac{\sigma_{m_n}^2}{\langle m_n \rangle} = \left( \frac{\langle m_n \rangle}{K} + 1 \right) (\langle b \rangle + 1),
\]

\[
\frac{\sigma_{m_c}^2}{\langle m_c \rangle} = \langle b \rangle + 1 - \langle b \rangle \frac{\langle m_n \rangle}{k_{\text{eff}}(m_n)} + \langle m_n \rangle.
\]

Note that the condition \( \langle m_n \rangle \gg \langle b \rangle \) indeed implies \( \sigma_{m_n}^2/\langle m_n \rangle^2 \ll 1 \) (i.e., fluctuations of \( m_n \) remain small as compared to \( \langle m_n \rangle \)) when the channel operates not too close to saturation (that is, \( \langle m_n \rangle \) is smaller or of the order of \( K \)). In the nearly saturated case \( \langle m_n \rangle \gg K \), equation (20) is still applicable if \( \langle b \rangle < K \). Otherwise one may encounter anomalous fluctuations that require a more careful treatment.
2.2.2. Independent burst approximation. In the case $\langle m_n \rangle \ll \langle b \rangle$, the mRNA produced in a given burst has sufficient time to exit the nucleus before the next burst arrives. It is then appropriate to consider the independent burst approximation, where individual burst events contribute additively to $m_n(t)$ and $m_c(t)$:

$$m_n(t) = \sum_{i<t} \xi(b_i, t - t_i),$$

$$m_c(t) = \sum_{i<t} \eta(b_i, t - t_i).$$

(22)

(23)

Here $b_i$ is the size of the $i$th burst which takes place at $t_i$, and $\xi(b, t)$ and $\eta(b, t)$ are the number of mRNAs in the nucleus and in the cytoplasm, respectively, generated by a single burst of size $b$ at $t = 0$.

Three independent stochastic processes contribute to the statistical properties of the time series $m_n(t)$ and $m_c(t)$: (i) the time of the burst events $t_i$, which we assume to be Poisson at a rate $\lambda$; (ii) the size $b_i$ of individual bursts which follow the geometric distribution $G(b)$; and (iii) the stochastic nature of the MM transport and mRNA decay in the small copy number regime. In the following discussion we shall focus on the noise effects due to processes (i) and (ii), while neglecting stochasticity in (iii). The latter approximation is justified by noting that the most significant contributions to the quantities computed below are from the period when $\xi(b, t)$ and $\eta(b, t)$ are large and their relative fluctuations are small. Denoting by $x(b, t) = \langle \xi(b, t) \rangle$ and $y(b, t) = \langle \eta(b, t) \rangle$, we obtain the following expressions for the moments:

$$\langle m_n \rangle = \sum_b G(b) \int_0^\infty x(b, t) \lambda \, dt,$$

$$\langle m_n^2 \rangle = \langle m_n \rangle^2 + \sum_b G(b) \int_0^\infty x^2(b, t) \lambda \, dt,$$

$$\langle m_c \rangle = \sum_b G(b) \int_0^\infty y(b, t) \lambda \, dt,$$

$$\langle m_c^2 \rangle = \langle m_c \rangle^2 + \sum_b G(b) \int_0^\infty y^2(b, t) \lambda \, dt,$$

$$\langle m_n m_c \rangle = \langle m_n \rangle \langle m_c \rangle + \sum_b G(b) \int_0^\infty x(b, t) y(b, t) \lambda \, dt.$$ 

(24)

(25)

(26)

(27)

(28)

Under the MM transport (17), the dynamical equations for $x(b, t)$ and $y(b, t)$ are given by

$$\frac{dx}{dt} = -v_{\text{max}} \frac{x}{K + x},$$

$$\frac{dy}{dt} = v_{\text{max}} \frac{x}{K + x} - \delta y,$$

(29)

(30)

with the initial condition $x(b, 0) = b$ and $y(b, 0) = 0$.

As shown in appendix B, the sum and integrals in equations (24) and (25) can be worked out exactly to give

$$\langle m_n \rangle = \frac{\lambda}{v_{\text{max}}} (b + K + \frac{1}{2}),$$

$$\langle m_n^2 \rangle = \frac{\lambda}{v_{\text{max}}} (b + 1) \left[ (b + K + \frac{1}{2})^2 + \frac{1}{2} \right].$$

(31)

\[
\sigma_{m_n}^2 = \frac{\langle m_n^2 \rangle - \langle m_n \rangle^2}{\langle m_n \rangle} = \frac{\lambda}{v_{\text{max}}} \left[ 2(b + K + \frac{3}{2}) + \frac{1}{2} \right].
\]

(32)

Hence,

$$\frac{\sigma_{m_n}^2}{\langle m_n \rangle} = (b + \frac{1}{2}) \left[ (b + K + \frac{3}{2}) + \frac{1}{2} \right].$$

(33)

The mean value of $m_c$ can be obtained from flux balance, i.e., $\lambda(b) = \delta \langle m_c \rangle$ or $\langle m_c \rangle = (\lambda/\delta)(b)$. The calculation of $\langle m_c^2 \rangle$ is a bit more involved which we relegate to appendix B. Assuming $\delta \ll v_{\text{max}}$, the decay time of an mRNA molecule is much longer than the fastest release time of one mRNA to the cytoplasm, we may write the result in the form

$$\frac{\sigma_{m_c}^2}{\langle m_c \rangle} = (b + \frac{1}{2}) \Psi(u, w),$$

(34)

where $u = (b + \frac{1}{2})/v_{\text{max}}$ and $w = K b / v_{\text{max}}$. The function $\Psi$ is given by

$$\Psi(u, w) = \int_0^1 dx \int_0^1 dx_1 e^{\frac{w \ln(x/x_1)}{1 + u (x_1 - x)}}.$$ 

(35)

Since the integrand is less than 1, we have $\Psi(u, w) \leq 1$.

We have not managed to find a closed-form expression for $\Psi(u, w)$, but the integral can be worked out in the two limiting cases: (i) $u = 0$, $\Psi(0, w) = 1/(1 + w)$ and (ii) $w = 0$, $\Psi(u, 0) = 1/(1 + u)$. These two expressions also set upper bounds for $\Psi(u, w)$ in general. An approximate expression that is consistent with the two limits and also verified by numerical integration of (35) is given by

$$\Psi(u, w) \simeq \frac{1}{1 + u + w}.$$ 

(36)

In terms of $\langle m_n \rangle$ and $\langle m_c \rangle$ and with the help of (31) and the flux balance condition, equation (34) can be rewritten as

$$\frac{\sigma_{m_c}^2}{\langle m_c \rangle} \simeq \frac{(b + \frac{1}{2})}{1 + \frac{\langle m_n \rangle}{\langle m_c \rangle}}.$$ 

(37)

3. Results and discussion

Let us first summarize the analytical results derived in section 2 when the average burst size $\langle b \rangle \gg 1$. In general, noise strength of mRNA copy number in the two compartments can be expressed in the form

$$\frac{\sigma_{m_n}^2}{\langle m_n \rangle} = \alpha \langle b \rangle + 1,$$

$$\frac{\sigma_{m_c}^2}{\langle m_c \rangle} = \frac{\langle b \rangle}{1 + \beta \langle m_n \rangle / \langle m_c \rangle} + 1.$$ 

(38)

(39)

For the linear model, we have $\alpha = \beta = 1$. In the MM case where the transporter may become the bottleneck in the process, $\alpha = \beta = 1 + (m_n) / K$ if the slow transport leads to the nuclear accumulation of mRNA, i.e., $\langle m_n \rangle \gg \langle b \rangle$. In the opposite limit $\langle m_n \rangle \ll \langle b \rangle$, where there is nuclear clearance between successive burst events, $\alpha \simeq 1 + \langle b \rangle / (K + \langle b \rangle)$ and $\beta \simeq 1$. 5
The general trend of noise attenuation on the cytoplasmic mRNA due to delay in nuclear transport is now clear. Retention of the mRNA inside the nucleus decreases the effective burst size and hence the noise strength of the cytoplasmic mRNA. Even at a fixed ratio of \( \langle m_n \rangle / \langle m_c \rangle \), further reduction of the noise is possible in the nonlinear MM transport when \( \langle m_n \rangle \) is greater than both the dissociation constant \( K \) and burst size \( \langle b \rangle \). On the other hand, the independent burst approximation yields a \( \beta \) value close to 1, extending the validity of the linear model when the noise strength of \( m_c \) is considered as a function of the ratio of mean copy numbers \( \langle m_n \rangle / \langle m_c \rangle \).

Fluctuations in the nuclear mRNA level, on the other hand, exhibit a somewhat different behavior. The parameter \( \alpha \) that characterizes the noise strength of \( m_c \) reaches the minimum value 1 in the linear model, but increases when the saturation effect in the MM transport kicks in. Thus, queuing results in an enhanced fluctuation upstream of the transport channel.

To check the accuracy of the analytic results under parameter values that broadly correspond to the mammalian cell gene expression experiments mentioned above, we have carried out simulations of the stochastic MM transport defined by (14), following the Gillespie’s exact algorithm [40]. The unit of time is chosen such that the mRNA decay rate \( \delta = 1 \). The number of transport channels is set to \( e_i = 10 \). We fix the average mRNA production rate \( \lambda \langle b \rangle \) relative to the mRNA decay rate \( \delta \) such that the mean cytoplasmic mRNA copy number \( \langle m_c \rangle = \lambda \langle b \rangle / \delta = 40 \). For easy comparison with the experimental measurements and analytic results, we also fix the mean nuclear mRNA copy number \( \langle m_n \rangle = 20 \). With these parameter values, the noise strengths in the linear model are given by \( \sigma^2_{m_n} / \langle m_n \rangle = \langle b \rangle + 1 \) and \( \sigma^2_{m_c} / \langle m_c \rangle = \frac{2}{3} \langle b \rangle + 1 \), respectively. Simulations are then performed to examine the effect of channel saturation on the noise strengths by varying the MM parameters \( k_1 \) and \( k_3 \) in such a way that the mean nuclear mRNA copy number stays at the value set above. The unbinding rate of the mRNA-transporter complex \( EM_a \) is fixed at a low value \( k_2 = 0.1 \).

Figure 1 shows a comparison of simulation data (open circles) and analytic results under the LNA (solid line) and the IBA (dashed line). Plots on the upper panel show the noise strength of nuclear mRNA as a function of the Michaelis constant \( K_m = (k_2 + k_3) / k_1 \). Fluctuations in \( m_n \) grow as the saturation effect becomes more prominent on the low \( K_m \) side. An opposite trend is seen in the fluctuations of the cytoplasmic mRNA copy number \( m_c \) shown in plots on the lower panel. As expected, the LNA results (solid line) agree well with the simulation data (circles) in the weak burst regime ((a) and (d)), in which case the overall noise strength (as compared to the mean mRNA copy number) is weak. On the other hand, the IBA results (dashed line) represent a better approximation in the strong burst regime ((c) and (f)).

Therefore each of the two approximations performs reasonably well in its respective regime of validity and is complementary to each other.

Figure 2 shows the actual distribution ((a) and (c)) and sample time course ((b) and (d)) of the nuclear and cytoplasmic mRNA copy numbers, respectively, generated from simulations at \( K_m = 6.5 \). Other model parameters are the same as that of figures (b) and (e), which represent

\[ 5 \text{ The dashed lines in the lower panel of figure 1 are obtained by evaluating the integral (35) numerically. Direct application of (37) yields nearly identical results.} \]
a borderline case for the two approximate treatments. It is seen from figure 2(b) that $m_n$ falls below $K = 16.5$ most of the time, so approximating the MM transport by a linear expansion at $m_n = \langle m_n \rangle$ is too crude. On the other hand, there are occasional overlaps of the mRNA produced in successive bursts. These have the effect of slowing down the mRNA transport than what is assumed in the IBA, leading to a somewhat lower $m_n$ noise as seen in the left part of figure 1(e).

We have also examined the validity of equation (17) for the mean transport flux. At a given number $c$ of complexes $EM_n$, the expected mRNA export flux is $k_3 c$. Therefore $v(m_n)$ can be obtained in the simulations from the conditional average of $c$ at a given $m_n$. As shown in figure 3, equation (17) (dashed line) fits the simulation data (dots) very well when $K_m \gg \langle m_n \rangle$ (c), but quite poorly in the regime $K_m \ll \langle m_n \rangle$ (a). Surprisingly, the classic MM equation (15), suitably modified to be considered as a function of $m_n$, agrees with the numerical result extremely well for both large and small values of $K_m$. Note that equation (17) was derived under the quasi-equilibrium approximation $k_3 \ll k_1, k_2$ which does not hold in the present case. This inaccuracy may also contribute to the discrepancy between our analytic results and simulation data at small $K_m$ in figure 1.

4. Conclusions and outlook

The main conclusion of our work is that the nuclear envelope, which sets a natural barrier for the exodus of mature mRNA to the cytoplasm in an eukaryotic cell, can significantly attenuate the effect of transcriptional bursting on the downstream protein population. The extent of the noise reduction on the cytoplasmic mRNA copy number is controlled by the transport efficiency. A high transport rate has a weak effect on noise reduction and essentially brings one back to the one-compartment model considered previously. On the other hand, a low transport rate turns the nucleus into a buffer for the bursting noise, thereby reducing the temporal variation of the mRNA copy number in the cytoplasm. The noise-reduction effect is more dramatic in the saturated regime under the Michaelis–Menten dynamics where, due to the limited availability of transport channels, the mRNA export becomes a Poisson process unaffected by the bursty input.
Our results can be used to re-estimate the mean mRNA burst size in the experiment by Raj and his colleagues. Take the linear transport as an example, the noise strength of the total mRNA copy number in the cell can be obtained from equations (9)–(11):

$$\frac{\sigma_n^2}{\langle m_n \rangle} = \langle b \rangle + 1 + \langle b \rangle \frac{\langle m_n \rangle}{\langle m_n \rangle + \langle m_c \rangle}.$$  (40)

Thus the average burst size $\langle b \rangle$ can be obtained from the measured total mRNA fluctuations and the ratio $\langle m_n \rangle / \langle m_c \rangle$ of nuclear to cytoplasmic mRNA. If 30% of the mRNA accumulate in the nucleus, the burst size should be 83% of that estimated from the model without transport. With the help of the two-compartment models, it would be interesting to revisit the single-molecule experiment data of Raj et al to gain a more complete view of the role of transport on the characteristics of the mRNA noise generated by transcriptional bursting.

Previous studies suggest that for eukaryotes, such as *S. cerevisiae* [2], *Dictyostelium* [41] and mammalian cells [15], transcriptional bursting is a dominant source of the noise from the internal molecular circuits known as the ‘internal noise’. It is interesting to note that the stress-related genes, which demand a fast response and an accelerated export rate, are noisier than the essential house-keeping genes such as proteasome genes [42]. In our limited transport capacity model described by the MM dynamics, the downstream noise is indeed stronger in the linear regime and weaker in the saturated regime. The linear regime also allows for a faster response to external stimulus as there is no queuing effect. In this respect, one cannot help but wonder whether special processing and export channels are in place in the nucleus for the fast release of stress response genes without congestion.

Finally, we would like to mention that noise propagation through capacity-limited channels with a bursty input is a general phenomenon not limited to the transcriptional bursting, and hence the discussions initiated here can be of broader significance. A somewhat peculiar behavior associated with the limited-capacity transport is that, as the extent of channel saturation increases while maintaining the same average transport current, the noise level of the upstream population increases while that of the downstream population decreases (see figure 1). This counterintuitive phenomenon is neither stochastic resonance (SR) nor stochastic focusing (SF) proposed by Paulsson et al [37, 38]. SR is usually related to periodic signal detection, where the signal noise is typically external, while SF exploits signal noise to make a gradual response mechanism work more like a threshold mechanism. Here, the interesting phenomenon we observe is due to a quite different mechanism: the degradation of upstream species and production of downstream species share a common reaction (here transport), whose effective order at the steady state can be tuned from zero to one by a combination of reaction parameters.

**Acknowledgments**

We would like to thank HG Liu and XQ Shi for helpful discussions. LPX would like to thank the Physics Department, Hong Kong Baptist University where part of the work was carried out for the hospitality. This work was supported by the National Natural Science Foundation of China under grant 10629401 and by the Research Grants Council of the HKSAR under grant HKBU 2016/06P.

**Appendix A. The Ω expansion**

Equations (20) and (21) can be equivalently derived using the more formal $\Omega$ expansion which applies when fluctuations of $m_n$ and $m_c$ are weak. ($\Omega$ here stands for the system volume.) To set the notation straight, the rate equation for the copy number $x_i$ of molecule $i$ (i.e., $m_n$ or $m_c$ in the present case) is given by

$$\frac{dx_i}{dt} = \sum_q S_{iq} V_q = (S \cdot V),$$  (A.1)

where $S_{iq}$ is the stoichiometric coefficient of molecule $i$ in reaction $q$ and $V_q$ (which depends on the copy numbers in general) is the propensity of reaction $q$. Stochasticity in the problem is assumed to be due to fluctuations in the propensity $V_q$ with a strength set at $V_q^{1/2}$ due to the underlying Poisson process.

In the large volume limit and for the steady state, the joint distribution of the $x_i$’s, which satisfies the Fokker–Planck equation, can be approximated by a Gaussian centered at the solution to the equation $dx/dt = S \cdot V = 0$. The width of the distribution is parametrized by a covariance matrix $C$ which satisfies equation [43]:

$$AC + CA^T + B = 0.$$  (A.2)

Here

$$A_{ij} = \frac{\partial (S \cdot V)_i}{\partial x_j}, \quad B_{ij} = \sum_q V_q S_{iq} S_{jq},$$  (A.3)

all evaluated at the steady state. Specializing on our two-component problem, there are three reactions: the bursting reaction leading to the production of $m_n$, the MM transport reaction for nuclear export and the mRNA decay in the cytoplasm. Simple calculations yield

$$A = \begin{pmatrix} -\frac{v_{max} K}{(K + \langle m_n \rangle)} & 0 \\ \frac{v_{max} K}{(K + \langle m_n \rangle)} & -\delta \end{pmatrix}$$  (A.5)

Application of (A.4) yields

$$B_{11} = \frac{v_{max} \langle m_n \rangle}{K + \langle m_n \rangle} + \sum_b \lambda G(b) b^2$$

$$= \frac{v_{max} \langle m_n \rangle}{K + \langle m_n \rangle} + \lambda \langle b^2 \rangle$$

$$= 2\lambda \langle b \rangle + \langle b^2 \rangle.$$  (A.6)

In the last step, we have used the flux-balance condition and $\langle b^2 \rangle = 2\langle b \rangle^2 + \langle b \rangle$. Other matrix elements of $B$ can be obtained as

$$B_{12} = B_{21} = -\lambda \langle b \rangle, \quad B_{22} = 2\lambda \langle b \rangle.$$  (A.7)
Substituting the values of $A$ and $B$ into equation (A.2) gives

$$\sigma_{m_a}^2 = C_{11} = \frac{\langle m_n \rangle (\langle m_n \rangle + K)}{K} (\langle b \rangle + 1),$$

(A.8)

$$\langle m_a m_c \rangle - \langle m_n \rangle \langle m_c \rangle = C_{12} = C_{21} = \frac{\langle b \rangle \langle m_n \rangle \langle m_c \rangle}{K + \langle m_n \rangle + \langle m_n \rangle},$$

(A.9)

$$\sigma_{m_c}^2 = C_{22} = \langle m_c \rangle (\langle b \rangle + 1) - (\langle b \rangle \langle m_n \rangle \langle m_c \rangle) \frac{K + \langle m_n \rangle + \langle m_n \rangle}{K + \langle m_n \rangle + \langle m_n \rangle},$$

(A.10)

from which equations (20) and (21) follow.

### Appendix B. Integrals in the independent burst approximation

A convenient way to carry out the integrals in (24)–(27) is to convert them into integration over $x$, which decreases monotonically from its initial value $b$ to 0 in a single burst event, with the help of (29) and (30). Following this procedure, we may write

$$\int_{0}^{\infty} dt \ x(b, t) = - \int_{0}^{b} \frac{dx}{dx/\delta} = \int_{0}^{b} \frac{K + x}{\delta/\lambda} \ dx = \frac{1}{\lambda} \left( K b + \frac{1}{2} b^2 \right).$$

(B.1)

$$\int_{0}^{\infty} dt \ x^2(b, t) = - \int_{0}^{b} \frac{x^2 dx}{dx/\delta} = \int_{0}^{b} x \frac{K + x}{\delta/\lambda} \ dx = \frac{1}{\lambda} \left( K b^2 + \frac{1}{3} b^3 \right).$$

(B.2)

To perform the averaging over $b$, we make use of the following results for the geometric distribution:

$$\langle b^2 \rangle = \langle b \rangle (1 + 2 \langle b \rangle),$$

$$\langle b^3 \rangle = \langle b \rangle (1 + 6 \langle b \rangle + 6 \langle b \rangle^2).$$

With the help of these results, (31) and (32) are readily obtained.

The dependence of $y$ on $x$ follows the equation,

$$\frac{dy}{dx} = \frac{dy/\delta}{dx/\delta} = -1 + \frac{\delta}{\lambda} \left( 1 + \frac{K}{x} \right) y,$$

(B.3)

which can be integrated to give

$$y(x) = \int_{x}^{b} dx_1 e^{\delta (x-x_1)/\lambda + \delta \ln(x/x_1)}.$$  

(B.4)

where $\lambda \equiv \delta K/\lambda_{\text{max}}$.

As a check, let us first consider

$$\int_{0}^{\infty} dt \ y = \int_{0}^{b} \frac{K + x}{\lambda_{\text{max}} x} \ y.$$

(B.5)

Using equation (B.3) and noting that $y(x = b) = y(x = 0) = 0$, we obtain

$$\int_{0}^{b} \frac{K + x}{\lambda_{\text{max}} x} \ y = \delta^{-1} \int_{0}^{b} \left( 1 + \frac{dy}{dx} \right) dx = b/\delta.$$  

(B.6)

Hence,

$$\langle m_c \rangle = \lambda \langle b \rangle / \delta,$$

(B.7)

which is nothing but the conservation law.

We now consider

$$\int_{0}^{\infty} dt \ y^2 = \int_{0}^{b} y \delta^{-1} \left( \frac{dy}{dx} + 1 \right) dx = \delta^{-1} \int_{0}^{b} y \ dx.$$  

(B.8)

Using equation (B.4) and performing the substitution $x \rightarrow bx$, we obtain

$$\int_{0}^{\infty} dt \ y^2 = \frac{b^2}{\delta} \int_{0}^{1} dx \int_{0}^{1} dx_1 e^{b(b/x_{\text{max}})(x-x_1) + \delta \ln(x/x_1)}.$$  

(B.9)

The averaging over $b$ can now be readily carried out. Using the result $\sum_{b=0}^{\infty} b^2 a^b = a(1 + a)/(1 - a)^3$, we obtain

$$\sum_{b} G(b) \int_{0}^{\infty} dt \ y^2(b, t) = \delta^{-1} \int_{0}^{1} dx \int_{0}^{1} dx_1 e^{u \ln(x/x_1)} a(1 + a)/(1 - a)^3.$$  

(B.10)

Here $a = (b) e^{(x-x_1)/\lambda_{\text{max}}}/(1 + (b))$.

To avoid run-away accumulation of mRNAs in the nucleus, we require $\lambda \langle b \rangle < \lambda_{\text{max}}$. Therefore $\langle m_c \rangle < \lambda_{\text{max}} / \delta$. Note that $\langle m_c \rangle > 1$ automatically implies $\delta / \lambda_{\text{max}}$ to be a small quantity. In this case, we can approximate $a \approx (b)(1 + (x - x_1)\delta/\lambda_{\text{max}})/(1 + (b))$. Consequently,

$$\sum_{b} G(b) \int_{0}^{\infty} dt \ y^2(b, t) = \frac{(b)(1 + \frac{1}{\delta})}{\lambda} \Psi(u, w).$$  

(B.11)

where $u = (b)\delta/\lambda_{\text{max}}$ and $\Psi(u, w)$ is given by (35).

Finally, the integral in equation (28) can be rewritten in the form

$$\int_{0}^{\infty} dt \ x(b, t) y(b, t) = \int_{0}^{b} \delta \left( \frac{dy}{dx} + 1 \right) dx = \frac{b^2}{2\delta} - \delta^{-1} \int_{0}^{b} y \ dx.$$  

(B.12)

Comparing with (B.8) and using (B.11), we obtain

$$\sum_{b} G(b) \int_{0}^{\infty} dt \ x(b, t) y(b, t) = \frac{(b)(1 + \frac{1}{\delta})}{\lambda} \left[ 1 - \Psi(u, w) \right].$$  

(B.13)

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