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Frequency analysis of splicing regulation

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Abstract— **In the past decades, mathematical modelers developed a huge literature to model and analyze gene networks under both deterministic and stochastic formalisms. Such literature is predominantly focused on modeling transcriptional and translational regulation, while the development of proper mathematical frameworks to model and study post-transcriptional regulation via splicing and its connection with transcriptional and translational regulation are almost missing. Nowadays, it is becoming of paramount importance the need for modeling post-transcriptional regulation via splicing especially for bacteria or viruses. However, current literature is focused on investigating splicing regulation at steady state and none of them have the purpose to investigate gene networks behavior in the frequency domain, thus providing only a partial investigation about the system dynamical response. The aim of this work is to theoretically investigate a simple gene network subjects to splicing regulation with/without negative feedback control under a frequency domain perspective. This study showed the pivotal role of the burst size, as well as splicing conversion rates to modulate the noise and the power spectrum response. It also shows an interesting behavior under the frequency domain induced by the merging effect of burst size, splicing conversion rates and negative feedback strength.**

I. INTRODUCTION

State of the art approaches to model deterministic and stochastic gene networks focus on modelling transcriptional and translational regulations. However, a theoretical extensive investigation to deal with the post-transcriptional regulation via splicing is still pretty much unexplored. As far as we know, there are only four works that theoretically investigate the dynamical modeling of splicing regulation at steady state [1], [2], [3], [4]. However, such works do not account for the investigation in the frequency domain of splicing regulation under open loop or feedback regulation scenarios. The stochastic analysis of gene networks is of paramount importance for properly understanding the features of gene expression dynamics. Moreover, it is very likely that the pre-mRNA intrinsic stochasticity becomes relevant given that the pre-mRNA copy number (CN) is usually very low [1]. However, understanding the steady state behavior of gene networks does not necessarily give an exhaustive comprehension of their dynamical features. Frequency analysis adds further important insights with especial regards to systems subject to feedback control. Developing a general approach to model post-transcriptional regulation via splicing and its connection with transcriptional regulation has become of great importance nowadays. This is particularly significant to study pathogens (e.g., bacteria and viruses). Noteworthy is the case of modeling DNA viruses and retroviruses which make extensive use of the splicing control. This is the case of the HIV [6] or of the human papillomavirus (HPV) that makes use of the splicing regulation during its entire lifecycle [7]-[12]. This work aims at extending and studying some preliminary works available in the literature [2], [3] about stochastically modeling the post-transcriptional regulation via splicing. In this work we will infer the steady state moment behaviors of a simple splicing gene network with and without a negative feedback regulation and we will further investigate its behavior in the frequency domain by the aid of the noise power spectrum analysis. As far as we know, this is the first work that stochastically investigates the splicing regulation under a frequency domain approach.

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II. METHODS

A. Model

The major mechanisms and noteworthy features of the gene network model are reported below and depicted in Fig.1:

- only one mRNA isoform is spliced from the pre-mRNA. Moreover, we made the simplifying assumption that the mRNA coincides with its own protein, when we consider the feedback autoregulation.
- we both consider a linear open loop model and a negative feedback regulation of the mRNA on its own pre-mRNA.
- stochastic bursts in the pre-mRNA expression are modeled through the aid of a stochastic variable (called Burst) that accounts for the stochastic burst size.
- the conversion of the pre-mRNA into the mRNA implies the loss of a pre-mRNA molecule to produce an mRNA molecule. This is one of the peculiar novelty and differences with a classical model based on the transcription of the mRNA and its translation into a protein.
- In general, the pre-mRNA splicing gives rise to two or more mRNA isoforms having two or more branches of mRNAs and related proteins generated from the pre-mRNA, as reported in some few studies [2], [3]. In this work, we consider, for the sake of simplicity, the splicing of just one mRNA isoform.

B. Biochemical equations

The biochemical equations related to the model in Fig. 1 are reported in Table I. The state variables of the model are the copy numbers [CN] of the pre-mRNA (pr) and the mRNA (m). Transition rates are reported in Table I and, in particular: S is the synthesis of the pre-mRNA; k_r, δ_p are the

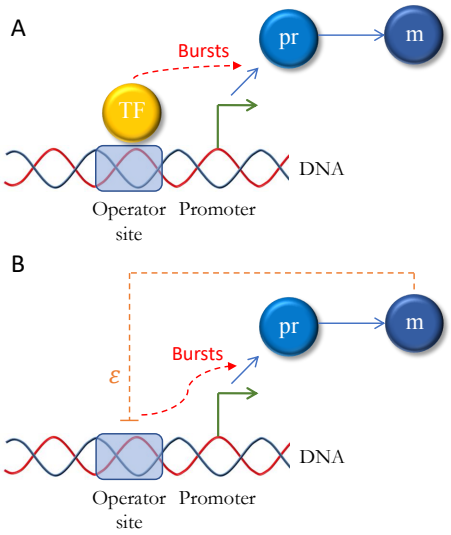

Fig. 1. Gene expression model. The pre-mRNA (pr) is transcribed and subsequently spliced into a mRNA. We consider an open loop structure (A) and a negative feedback structure (B) where the mRNA is the promoter transcriptional regulator. ε represents the negative feedback strength. The effects of bursts in the pre-mRNA (due to the transcription factor (TF) in the open loop structure or due to the protein) gene expression are condensed as a stochastic variable, called Burst, which is a re-scaling factor for the pre-mRNA copy number, hence representing the stochastic burst size.

degradations of the pre-mRNA and the mRNA, respectively; k_m is the conversion rates of the pre-mRNA into the mRNA. The degradation rate k_r accounts for the degradation of the pre-mRNA or, alternatively, for its conversion to other,not explicitly modeled, mRNAs (different from m). *Burst* is a stochastic variable that accounts for the burst size, as further explained in the following sections.

TABLE I
BIOCHEMICAL MODEL REACTIONS AND TRANSITION RATES

Event	Update	Transition rate
pre-mRNA synthesis	$p_r \to p_r + Burst$	$S(m)$
pre-mRNA degradation	$p_r \to p_r - 1$	$k_r\, p_r$
mRNA/protein m production	$\begin{cases} p_r \to p_r - 1 \\ m \to m + 1 \end{cases}$	$k_m p_r$
mRNA/protein m degradation	$m \to m - 1$	$\delta_m m$

C. Chemical Master Equation (CME)

The CME [13] for the entire system of biochemical reactions, reported in Table I takes the following form

$$\begin{aligned}\frac{dp_{\mathbf{n}}}{dt} =& S(m)\left(\sum_{i=0}^{p_r} P[Burst=i]\,p_{p_r-i,m} - p_{\mathbf{n}}\right) \\ &+ k_r\left[(p_r+1)\,p_{p_r+1,m} - p_r p_{\mathbf{n}}\right] \\ &+ k_m\left[(p_r+1)\,p_{p_r+1,m-1} - p_r p_{\mathbf{n}}\right] \\ &+ \delta_m\left[(m+1)\,p_{m+1,p_r} - m p_{\mathbf{n}}\right]\end{aligned} \tag{1}$$

where $p_{\mathbf{n}} = P(\mathbf{n};t) = P(pr,m;t)$ represents the total joint probability of the chemical species. The variable *Burst* is a random variable, as in [2], modeling the burst size of the pre-mRNA expression, with probability distribution

$$p_{Burst} = P\left[Burst = i\right], i \in \mathrm{N} \tag{2}$$

in particular, when $P[Burst=1]=1$ and $P[Burst=i, i\neq 1]=0$, the pre-mRNA is under constitutive expression.

D. Differential equations of the CME statistical moments

The system of ordinary differential equations (ODEs) of the first statistical moments takes the following form

$$\frac{dE\left[p_r\right]}{dt} = E\left[S(m)\right]E\left[Burst\right] - \left(k_r + k_m\right)E\left[p_r\right] \tag{3}$$

$$\frac{dE\left[m\right]}{dt} = k_m E\left[pr\right] - \delta_m E\left[m\right] \tag{4}$$

The system of ODEs for the second statistical moments takes the form

$$\begin{aligned}\frac{dE\left[p_r^2\right]}{dt} =& E\left[S(m)\right]E\left[Burst^2\right] + 2E\left[S(m)p_r\right]E\left[Burst\right] \\ &+ \left(k_r + k_m\right)\left(E\left[p_r\right] - 2E\left[p_r^2\right]\right)\end{aligned} \tag{5}$$

$$\frac{dE\left[m^2\right]}{dt} = k_m E\left[p_r\right] + 2k_m E\left[p_r m\right] + \delta_m\left(E\left[m\right] - 2E\left[m^2\right]\right) \tag{6}$$

$$\begin{aligned}\frac{dE\left[p_r m\right]}{dt} =& E\left[S(m)\,m\right]E\left[Burst\right] + k_m\left(E\left[p_r^2\right] - E\left[p_r\right]\right) \\ &- \left(k_r + k_m + \delta_m\right)E\left[p_r m\right]\end{aligned} \tag{7}$$

where $E[\cdot]$ is the expectation operator.

It is well known that the general statistical moments, $E[x^r]$, and correlations, $E[x_i x_j]$ (as in [4]) can be written as

$$E\left[x^r\right] = \sum_{x=0}^{\infty} x^r p_x \tag{8a}$$

$$E\left[x_i x_j\right] = \sum_{x_i=0}^{\infty}\sum_{x_j=0}^{\infty} x_i x_j p_{x_i,x_j} \tag{8b}$$

where p_x is the marginal probability of the variable x and $p_{xi,xj}$ the marginal joint probability for x_i and x_j variables, respectively, both derived from the total probability p_n, given from the CME. Taking the derivative on both terms of Eqs. 8 and applying the CME (Eq. 1) we can derive the general form of the ODEs for the statistical moments and correlations (as in [4]).

In the case of feedback regulation the synthesis rate of the pre-mRNA, $S(m)$ is a nonlinear function of the mRNA regulation. Being the feedback regulation of the studied model a negative feedback, we can consider the synthesis rate $S(m)$ as a monotonically decreasing function of the mRNA, $m(t)$. Linear noise approximation (LNA) [14] has been used in order to linearize the pre-mRNA synthesis rate $S(m)$ about the steady state average number of mRNA molecules $E^{ss}[m]$, as similarly done in [14], where $E^{ss}[\cdot]$ stands for the

expectation operator at steady state. LNA is valid as long as the stochasticity in mRNA copy number is contained, i.e., the state trajectory remains close to the steady state equilibrium. We can apply the linear noise approximation by using Taylor expansion of the $S(m)$ as follows

$$S(m) \approx S(E^{ss}[m]) \left[1 - \varepsilon \left(\frac{m(t) - E^{ss}[m]}{E^{ss}[m]}\right)\right] \tag{9}$$

where $S(E^{ss}[m])$ is the mean transcription rate, around the equilibrium. The dimensionless constant

$$\varepsilon = -\frac{E^{ss}[m]}{S(E^{ss}[m])} \frac{dS(m)}{dm}|_{m(t)=E^{ss}[m]} > 0 \tag{10}$$

represents the strength of the negative feedback induced by the mRNA on the promoter regulation.

E. Steady state moments and correlations

In this section we report the steady state means, variances and some correlations from the system of differential equations Eqs.3-7.

The steady state means are

$$E^{ss}[p_r] = \frac{S(E^{ss}[m])\, E[Burst]}{k_m + k_r} \tag{11}$$

$$E^{ss}[m] = \frac{k_m}{\delta_m} E^{ss}[p_r] \tag{12}$$

where $E^{ss}[\cdot]$ stands for the expectation operator at steady state.

The steady state variances and correlation are

$$Var^{ss}[p_r] = \left\{ \frac{\delta_m[(B+1) + \varepsilon(\varepsilon+1)] + (B+1)(\varepsilon+1)}{(\varepsilon+1)(\delta_m + k_m + k_r)} + \frac{\delta_m k_r \varepsilon^2}{k_m(\varepsilon+1)(\delta_m + k_m + k_r)} \right\} E^{ss}[p_r] \tag{13}$$

$$Var^{ss}[m] = \left\{ \frac{\delta_m(\varepsilon+1) + k_m + k_r}{(\varepsilon+1)(\delta_m + k_m + k_r)} + \frac{B k_m^2}{(\varepsilon+1)(\delta_m + k_m + k_r)} \right\} E^{ss}[m] \tag{14}$$

$$Cov^{ss}[m\, p_r] = \left\{ \frac{\delta_m B}{(\varepsilon+1)(\delta_m + k_m + k_r)} - \frac{\varepsilon\, \delta_m (k_m + k_r)}{(\varepsilon+1)(\delta_m + k_m + k_r)} \right\} E^{ss}[m] \tag{15}$$

where $Var^{ss}[\cdot]$ and $Cov^{ss}[\cdot]$ stand for the variance and the covariance at steady state, respectively, and where B is defined as

$$B = \frac{E[Burst^2] - E[Burst]}{2E[Burst]} \tag{16}$$

as similarly defined in [2]. In this case, B represents a sort of Fano factor [4] of the burst size.

Notice that, in the Eqs.13-15, we have split the steady state second moments into two contributions, one of them related to the Bursts through the Burst factor B.

F. Noise power spectra

In the previous sections we have derived the mean and variance-covariance matrices in the time domain, and especially at steady state. In this section we are interested to derive the noise power spectra of the chemical species in order to study the system behavior in the frequency domain. Firstly, we need to derive the autocorrelations, being the power spectra the Fourier transform of the autocorrelations. To calculate the autocorrelation functions we will follow the method reported in [15]. In particular, we define the set of correlation functions as follows

$$R_{x_i x_j}(t) = E[\Delta x_i(0) \Delta x_j(t)] \tag{17}$$

where x_i is the copy number (CN) of a general chemical species and where Δx_i is the instantaneous deviation away from the steady state mean values

$$\Delta x_i(t) = x_i(t) - E^{ss}[x_i] \tag{18}$$

The steady state variance-covariance matrix, derived in the previous section, can be written in terms of Δx_i as follows

$$Cov^{ss}(x_i, x_j) = E[\Delta x_i \Delta x_j] \tag{19}$$

and the steady state variances are the diagonal elements of the previous covariance matrix

$$\sigma_i^2 = Cov^{ss}(x_i, x_i) = E\left[\Delta x_i^2\right]. \tag{20}$$

Correlation functions are subject to the following properties

$$R_{x_i x_j}(t) = R_{x_i x_j}(-t), \quad R_{x_i x_j}(0) = Cov^{ss}(x_i, x_j), \quad R_{x_i x_j}(\infty) = 0. \tag{21}$$

It can be proved [15] that, for linear systems, the previously defined correlation functions satisfy the following linear system of ODEs

$$\frac{dR_{x_q x_i}(t)}{dt} = \sum_j F_{ij} R_{x_q x_j}(t) \tag{22}$$

This is a particular version of a regression theorem [15], where F_{ij} is the matrix of the biochemical equations transition rates. Noteworthy is that, in general, $R_{x_i x_j}(t) \neq R_{x_j x_i}(t)$ for $i \neq j$, i.e., the correlation functions are not symmetric, as proved in [15]. However, the steady state covariance matrix is symmetric [15], hence $Cov^{ss}(x_i, x_j) = Cov^{ss}(x_j, x_i)$. We notice that the regression theorem can only be used for linear systems. In our scenario, we can still apply the regression theorem to the approximated version of the feedback-based system through LNA, since it will still be linear around the equilibrium.

To solve Eq. 22 the use of Laplace transform is the more convenient choice, since it will lead to a simple formula to calculate the noise power spectra without the need to explicitly calculate the Fourier transform of the correlations. The initial conditions will be $R_{x_q x_i}(0) = Cov^{ss}(x_q, x_i) = E^{ss}[x_q x_i] - E^{ss}[x_q] \cdot E^{ss}[x_i]$, where $E^{ss}[x_i]$ and $E^{ss}[x_q x_i]$ are the steady state first and second moments, calculated in the

previous sections. By taking the Laplace transform of Eq. 22 it can be shown that

$$s\tilde{R}_{x_q x_i}(s) - Cov^{ss}(x_q, x_i) = \sum_j F_{ij} \tilde{R}_{x_q x_j}(s) \tag{23}$$

where we define

$$\tilde{R}_{x_i x_j}(s) = \int_0^\infty R_{x_i x_j}(t) e^{-st} dt \tag{24}$$

By using the previously reported theory, and take into account that $R_{x_i x_j}(t) \neq R_{x_j x_i}(t)$ for $i \neq j$, we can perform the Laplace transform of the system of the correlation functions for the model in Fig.1

$$s\tilde{R}_{p_r p_r}(s) - \sigma^2_{p_r} = -(k_r + k_m)\tilde{R}_{p_r p_r}(s) \tag{25}$$

$$s\tilde{R}_{p_r m}(s) - Cov^{ss}(p_r, m) = k_m \tilde{R}_{p_r p_r}(s) - \delta_m \tilde{R}_{p_r m}(s) \tag{26}$$

$$s\tilde{R}_{mm}(s) - \sigma^2_m = k_m \tilde{R}_{m p_r}(s) - \delta_m \tilde{R}_{mm}(s) \tag{27}$$

$$s\tilde{R}_{m p_r}(s) - Cov^{ss}(m, p_r) = -(k_r + k_m)\tilde{R}_{m p_r}(s) \tag{28}$$

By solving the system of Eqs. 25-28 we obtain the Laplace transformations of the autocorrelations of the chemical species

$$\tilde{R}_{p_r p_r}(s) = \frac{Var^{ss}[p_r]}{s + k_m + k_r} \tag{29}$$

$$\tilde{R}_{mm}(s) = \frac{Var^{ss}[m]}{s + \delta_m} + \frac{k_m Cov^{ss}(m, p_r)}{(s + k_m + k_r)(s + \delta_m)} \tag{30}$$

Noise power spectra can be defined as follows [15]

$$S_{x_i x_i}(\omega) = E\left[|\Delta x_i(\omega)|^2\right] = 2\int_0^\infty R_{x_i x_i}(t)\cos(\omega t)\, dt, \tag{31}$$

where $\Delta x_i(\omega)$ is the Fourier transform of $\Delta x_i(t)$.

By considering the Eq. 23 and Eq. 24 it is straightforward to prove the following formula

$$S_{x_i x_i}(\omega) = \tilde{R}_{x_i x_i}(i\omega) + \tilde{R}_{x_i x_i}(-i\omega). \tag{32}$$

With such formula we avoid the direct calculation of the Fourier integral.

We can now calculate the noise power spectra of the model's chemical species, starting from the autocorrelations in the Laplace domain (Eqs.29,30) and inserting the steady state variances and covariance derived in Eqs.13-15

$$\frac{S_{p_r p_r}(\omega)}{E^{ss}[p_r]} = \frac{2\delta_m k_m (k_m + k_r)\left[(B+1) + \varepsilon(\varepsilon+1)\right]}{k_m(\varepsilon+1)(\delta_m + k_m + k_r)\left[\omega^2 + (k_m + k_r)^2\right]} + \frac{2\delta_m k_m \left[\delta_m k_r \varepsilon^2 + k_m (B+1)(\varepsilon+1)(k_m + k_r)\right]}{k_m(\varepsilon+1)(\delta_m + k_m + k_r)\left[\omega^2 + (k_m + k_r)^2\right]} \tag{33}$$

$$\frac{S_{mm}(\omega)}{E^{ss}[m]} = \frac{2\,\delta_m \left[(k_m + k_r)(k_m(B+1) + k_r) + (\varepsilon+1)\,\omega^2\right]}{(\varepsilon+1)(\delta_m^2 + \omega^2)\left[\omega^2 + (k_m + k_r)^2\right]} \tag{34}$$

G. Limit cases

In the open loop scenario, (i.e., in the limit when the negative feedback strength $\varepsilon = 0$) we obtain the following simplifying steady state variances, correlation and noise power spectra

$$\lim_{\varepsilon \to 0} Var^{ss}[p_r] = (B+1)\, E^{ss}[p_r] \tag{35}$$

$$\lim_{\varepsilon \to 0} Var^{ss}[m_i] = \left\{1 + \frac{B k_m^2}{(\delta_m + k_m + k_r)}\right\} E^{ss}[m_i] \tag{36}$$

$$\lim_{\varepsilon \to 0} E^{ss}[m\, p_r] = \frac{\delta_m B}{(\delta_m + k_m + k_r)} E^{ss}[m_i] \tag{37}$$

$$\lim_{\varepsilon \to 0} \frac{S_{p_r p_r}(\omega)}{E^{ss}[p_r]} = \frac{2\,(B+1)\,(k_m + k_r)}{\omega^2 + (k_m + k_r)^2} \tag{38}$$

$$\lim_{\varepsilon \to 0} \frac{S_{mm}(\omega)}{E^{ss}[m]} = \frac{2\,\delta_m \left[(k_m + k_r)(k_m(B+1) + k_r) + \omega^2\right]}{(\delta_m^2 + \omega^2)\left[\omega^2 + (k_m + k_r)^2\right]} \tag{39}$$

III. Implementation

Simulations were performed in MATLAB 2020b. All the simulations were performed with nominal parameters reported in Table II, unless differently specified. In the previously discussed cases, unless differently specified, the bursts were assumed to follow a geometric distribution of the form:

$$P(Burst = r) = \frac{1}{1 + E[Burst]} \left(\frac{E[Burst]}{1 + E[Burst]}\right)^r, \quad r = 0, 1, 2, \ldots . \tag{40}$$

In this particular scenario it can be proved that $Burst = E[Burst]$.

TABLE II
Model parameters

Parameters	Value	Unit of measure	Reference
S	2	$[CN min^{-1}]$	[4]
k_m	0.5	$[CN min^{-1}]$	[4]
δ_m	0.033	$[min^{-1}]$	[4]
k_r	0.1	$[min^{-1}]$	[4]

IV. Results

From Eqs.13,14 we can notice how the higher the burst size, B, the higher the variances of both the pre-mRNA and the mRNA, hence the higher the stochasticity, as already proved in [4]. However, we can notice how the higher the negative feedback strength the higher the variance of the pre-mRNA (Eq.13). This is because a higher negative feedback strength ε, induces a decrease of the pre-mRNA copy number, hence increasing the stochasticity. Moreover, the higher the negative feedback strength, the lower the variance of the mRNA, especially that regarded the burst contribution (Eq.14). However, a more comprehensive study about the noise rejection by different feedback mechanisms, in a similar system, is already present in the literature [14],

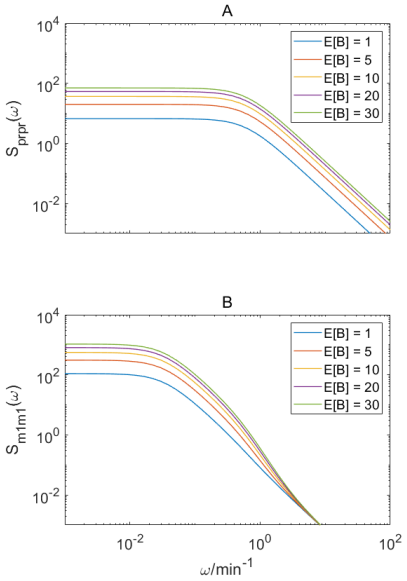

Fig. 2. Noise power spectra of p_r pre-mRNA (A) and m mRNA (B) for different values of the burst size, under an open loop scenario (i.e., without feedback regulation).

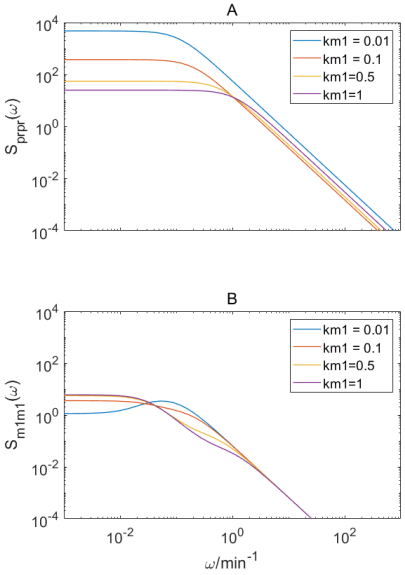

Fig. 4. Noise power spectra of p_r pre-mRNA (A) and m mRNA (B) for different values of the splicing conversion rate k_m, under a scenario with a strong negative feedback regulation (feedback strength $\varepsilon = 100$).

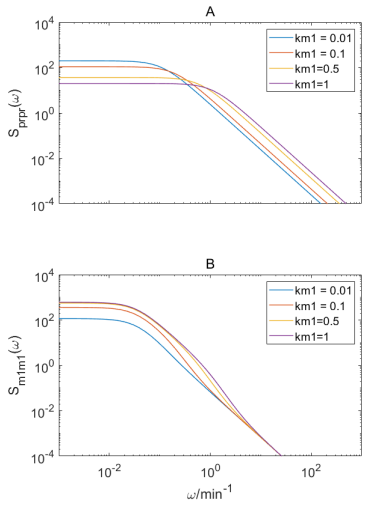

Fig. 3. Noise power spectra of p_r pre-mRNA (A) and m mRNA (B) for different values of the splicing conversion rate k_m, under an open loop scenario (i.e., without feedback regulation).

although it doesn't focus on showing the derivation of the steady state second moments and it does not discuss the contribution of the bursts and of the negative feedback on the steady state variances.

Let's now focus on the frequency domain response of the system which represents the major purpose of the current study. By looking at the noise power spectra, for the open loop context, we can notice how both the pre-mRNA and the mRNA behave as low pass filters were the cutoff frequency of the mRNA is lower than the cutoff frequency of the pre-mRNA (Fig.2). This suggests, as well known in the literature, that the mRNA is affected by a lower stochasticity compared to the pre-mRNA. We can also observe how the higher the burst size, B, the higher the magnitude of the power spectra of both the pre-mRNA and the mRNA. This proves the quite intuitive fact that the higher the burstiness the more amplified the stochasticity and the higher the autocorrelation of the chemical species (Fig.2). We can also notice that for lower frequency contents the power spectra are both affected by the burst size, while for higher frequencies ($\omega > 10^0$) the mRNA power spectrum is invariant to the burst size (Fig.2). This is because for higher frequencies the system behavior is dominated by the noise related to the mRNA conversion and degradation processes. From Fig.3 we can observe that the splicing conversion rate, k_m, modulates the cutoff frequency of the pre-mRNA frequency response but it does not alter the cutoff frequency of the mRNA response. However, the higher the splicing conversion rate, k_m, the higher the mRNA power spectrum magnitude and the lower the power spectrum magnitude of the pre-mRNA. Indeed, the higher the splicing conversion rate, the lower the pre-mRNA copy number. Similarly to what happens in Fig.2, the power spectrum of the mRNA becomes invariant to the splicing conversion rate for high frequencies (Fig.3B).

The pre-mRNA power spectrum magnitude is amplified by a strong negative feedback regulation due to the consequent decrease of the pre-mRNA abundance by the negative feedback control, while it strongly decreases the mRNA power spectrum magnitude (Fig.4). In particular, for low splicing conversion rates (e.g., $k_m = 0.01$) the power spectrum of the mRNA peaks around intermediate frequencies (i.e., around $\omega = 10^{-1}$). The latter fact suggests that for a proper window of frequencies the noise variance will increase by the effect of the negative feedback regulation, when the splicing conversion rates are sufficiently small. Such effect occurs for

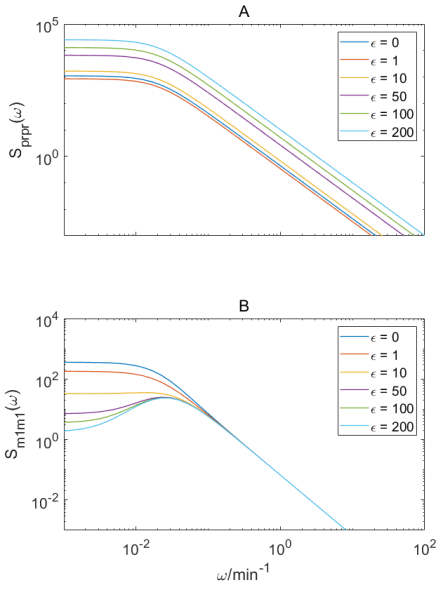

Fig. 5. Noise power spectra of p_r pre-mRNA (A) and m mRNA (B) for different values of the splicing conversion rate k_m, for different negative feedback regulation strengths.

sufficiently high negative feedback strengths, as shown in Fig.5.

V. Discussion

In this work we have theoretically investigated a simple gene network related to the splicing regulation where we have considered the conversion of a pre-mRNA into an mRNA/protein. We have considered both an open loop and a negative feedback regulation scenarios and we have derived the steady state first and second moments of the pre-mRNA and the mRNA from the Chemical Master Equation of the gene network. We have also shown how the presence of bursts increases the stochastic noise variance of both the pre-mRNA and mRNA and that the higher the negative feedback strength the higher the pre-mRNA noise variance and the lower the mRNA noise variance. Thanks to the steady state moments it was possible to derive the noise power spectra of the chemical species where it was proved that the pre-mRNA stochasticity is higher than the stochasticity of the related mRNA. Burst size and splicing conversion rates are key ingredients affecting both the power spectra of the pre-mRNA and mRNA, however the frequency response of the mRNA becomes invariant to both burst size and splicing conversion rates for high frequencies. It was finally proved the important action of the negative feedback regulation in reducing the total noise of the mRNA. However, under low splicing conversion rates, the negative feedback amplifies the noise under a proper frequency window, as similarly found for classical feedback regulations between mRNA and proteins [16]. This latter fact could be justified by analyzing the power spectra together with the system transfer function response, as similarly done in [16]. In particular, it could be shown that also for system subject to splicing regulation the presence of a negative feedback reduces the system phase margin, hence approaching system instability by the effect of the splicing conversion rate which is diminishing. This aspect could open future interesting investigations to better understand the frequency domain behavior of more complex splicing regulations, under the effect of different structures of feedback regulations.

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