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Intrinsic noise in post-transcriptional gene regulation by small non-coding RNA

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ABSTRACT

Small non-coding RNA (sRNA) plays very important role in the post transcriptional regulation in various organisms. In complex regulatory networks, highly significant relative fluctuations in RNAs copy numbers can not be neglected due to very small copy number of individual RNA molecules. Here we consider two simple regulation schemes, where one is single target gene regulated by a sRNA and the other is two target mRNAs ($mRNA_R$ and $mRNA_T$) regulated by one sRNA. The Fano factor (a measure of the relative size of the internal fluctuations) formulae of RNA molecules in the post transcriptional regulation are theoretically derived by using of the Langevin theory. For single target gene regulated by a sRNA, it is shown that the intrinsic noise of both mRNA and sRNA approaches the bare Poissonian limit in the regimen of both target RNA silencing and surviving. However, the strong anti-correlation between the fluctuations of two components result in a large intrinsic fluctuations in the level of RNA molecules in the regimen of crossover. For two target mRNAs regulated by one sRNA, in the regimen of crossover, it is found that, with the increasing of transcription rate of target $mRNA_T$, the maximal intrinsic fluctuation of RNA molecules is shifted from sRNA to target $mRNA_R$, and then to target $mRNA_T$. The intrinsic noise intensity of target $mRNA_R$ is determined by both the transcriptional rate of itself and that of sRNA, and independent of the transcriptional rate of the other target $mRNA_T$.

1. Introduction

Since two small RNAs *lin*-4 and *let*-7 were identified in *C. elegans* [1–3], large numbers of small non-coding RNAs (sRNAs) have been found in almost all metazoan genomes [4–6], for example, more than 80 such sRNAs have been found in *E. coli*. sRNA plays very important role in the post transcriptional gene regulation in various organisms range from bacteria to mammals [7–12]. sRNA can regulate the expression of single or multiple target mRNAs by base pairing with the mRNA, pairing of the sRNA and mRNA causes both molecules rapid degradation, and may lead to the post transcriptional gene silencing. A given sRNA molecule is degraded combining with its target instead of being used to regulate other targets, thus, the interaction between the sRNA and its target mRNA is non-catalytic [13–16].

Recently, some kinetic models of post transcriptional gene regulation by sRNAs have been proposed. A non-catalytic mode of gene regulation by *trans*-encoded sRNA was studied through both theoretical analysis and quantitative experiments in *E. coli* by Levine et al. [17,18]. It is demonstrated that there are a threshold-linear response via the irreversible sRNA-mRNA binding, a robust noise resistance characteristic, and a hierarchical cross-talk between targets of sRNA. The sRNA diffuse in the tissue is also explored by using of a mathematical model in Ref. [19]. It is found that mobility of the sRNA generates a sharp interface in the expression profile of its target mRNA. Shimoni et al. [20] studied sRNAs regulating post transcriptional gene expression using the mathematical model and simulation, they showed that regulation by sRNAs is advantageous when fast responses to external signals are needed, and provides fine-tuning of gene expression. In order to quantify the microRNA-mediated effects on its target mRNAs found by experiments [9,10] where microRNA levels are modulated by transfection, a kinetic model of post transcriptional gene regulation by microRNAs have been proposed by Khanin et al. [21], and their model is agreement with a time-course micro-array dataset, and yields a good correspondence between the inferred and experimentally measured decay rates of human target mRNAs.

The dynamic cellular behaviors of genetic regulation processes depend on the interactions between the molecular components, the quantitative parameter values, and the stochastic fluctuations of underlying regulation processes. In general, the cellular biochemical reactions in the regulation process occur far from thermodynamic equilibrium, and the copy number of individual messenger RNAs is often very small (e.g., in bacterial cells like *E. coli*), which leads to highly significant relative fluctuations in messenger RNA copy numbers and also to large fluctuations in protein levels. Recently, the stochastic aspects of biochemical reactions in single cell have become an extensive interesting, and there are large numbers of publications to deal experimentally as well as theoretically with the intrinsically random nature of gene expression [22–35]. On the other hand, to take the stochastic nature of the gene regulation by sRNA into

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account, one has to use the mesoscopic approaches, instead of the macroscopic description where fluctuations are neglected. The first technique is to solve the chemical Master equation of the probability distribution for all the different molecular components [36], however, only in rare cases is it possible to solve the master equation explicitly. Of course, one can choose the Gillespie algorithm [37] to accurately simulate the molecule number trajectories for such stochastic systems. The second method is the linear noise approximation (LNA) of the chemical Master equation. By virtue of this method, the chemical Master equation can be simplified to a linear Fokker–Planck equation by using of van Kampen's Ω-expansion of Master equation, then the statistical properties of stochastic systems can be rapidly charactered [38]. The third technique is the Langevin theory of Swain [39], which provide a solution for small fluctuations around steady state.

Although there are a number of experimental and theoretical studies about the post transcriptional regulation by small non-coding RNAs, little work deals with the intrinsical random nature of sRNA-mediated gene regulation. However, the highly significant relative fluctuations in RNA copy numbers can not be neglected due to very small copy number of individual RNAs (e.g., in *E. coli*). Recently, Mehta et al. [40] showed that transcriptional bursting leads to significantly higher intrinsic noise in sRNA-based regulation than in protein-based regulation in a large range of expression levels. Levine et al. [41] studied noise properties of a gene targeted by a bacterial small RNA, it is found that sRNA-mediated gene silencing is effective in attenuating noise, the phenotypic diversity is induced by noise at the onset of gene expression, and the mutual interaction of RNA molecules gives rise to a bi-modality in growing *E. coli* cells.

In this paper, based on the models of sRNA-mediated gene regulation given by Ref. [17] and the Langevin theory of gene expression given by Ref. [39], we have studied the intrinsic fluctuations of sRNA-mediated gene regulation by using the Fokker-Planck equation of correlated noises, the formulas of Fano factor for RNA molecules, a measure of the relative size of the intrinsic fluctuations of RNA molecules, are analytically derived from the Langevin description of target mRNAs regulated by sRNA around steady-state. Employed the Fano factor formulas presented here, the effects of transcription rate of RNAs and the coupled degradation rate between sRNA and its target gene on intrinsic fluctuations are discussed. In particular, how the transcription rate of RNA molecules and the strength of the interaction parameter between sRNA and its target mRNAs influence the intrinsic noise of gene regulation process. Two post-transcriptional regulation processes that include one target mRNA and two target mRNAs regulated by single sRNA are respectively considered here.

2. Single target gene regulated by one small RNA

Consider a basic model of gene regulation by *trans*-encoded sRNA, which consists of a sRNA and a single species of target mRNA. The biochemical interaction between sRNA and its target gene is described as following

$$\xrightarrow{\alpha_s} \mathrm{sRNA} \xrightarrow{\beta_s} \emptyset, \tag{1}$$

$$\xrightarrow{\alpha_m} \mathrm{mRNA} \xrightarrow{\beta_m} \emptyset, \tag{2}$$

$$\mathrm{sRNA} + \mathrm{mRNA} \xrightarrow{k} \emptyset, \tag{3}$$

where α_s and α_m are the transcription rate of the sRNA molecule and the target gene molecule, β_s and β_m are the degradation rate of sRNA and that of its target gene, respectively, and k is the coupled degradation rate between sRNA and its target gene. When α_s is fixed, both experiment and theory showed that [17,18] there is a threshold response of target gene with the increasing of α_m, and the threshold value is $\alpha_m = \alpha_s$. In the absence of leakage (i.e. $\beta_m\beta_s/k = 0$), the threshold value is not affected by the strength of interaction parameter k.

In the deterministic description that ignores stochastic effects, two variables in the basic scheme of small RNA-mediated gene regulation progress shown by Eqs. (1)–(3) are governed by the macroscopic equations

$$\frac{dS}{dt} = \alpha_s - \beta_s S - kMS, \tag{4}$$

$$\frac{dM}{dt} = \alpha_m - \beta_m M - kMS, \tag{5}$$

where S and M are the molecule number of sRNA and its target mRNA. The steady state amounts M^s and S^s of mRNA and sRNA molecules are accordingly [17]

$$M^s = \frac{\alpha_m - \alpha_s - \lambda + \sqrt{(\alpha_m - \alpha_s - \lambda)^2 + 4\alpha_m\lambda}}{2\beta_m}, \tag{6}$$

$$S^s = \frac{\alpha_s}{\beta_s + kM^s}, \tag{7}$$

where the leakage parameter $\lambda = \beta_m\beta_s/k$.

In the Langevin description, the mRNA and sRNA molecules number in this model are governed by the stochastic equations

$$\frac{dS}{dt} = \alpha_s - \beta_s S - kMS + \xi_1(t), \tag{8}$$

$$\frac{dM}{dt} = \alpha_m - \beta_m M - kMS + \xi_2(t), \tag{9}$$

where $\xi_i(t)$ are random variables, and allow the modelling of thermal fluctuations and stochasticity when appropriately defined. For intrinsic noise, the noise terms in Eqs. (8)–(9) are additive, and for extrinsic noise which can be expected as multiplicative through control parameter of gene regulation process. The statistical properties of random variables ξ_i in Eqs. (8)–(9) at the steady state (M^s,S^s) are given by Eqs. (A6)–(A9) in Appendix A. It should be pointed out that the intrinsic noise intensities are determined by the transcription rate of sRNA and the target gene, respectively, and the cross-correlation strength between noises is determined by the coupled degradation rate and the steady-state values of RNA molecules number.

By using of the Fokker–Planck equation, the stationary mean, variance, and covariance of RNA molecules number are presented in Appendix A. The variance normalized to the steady value of RNA molecules is often called the Fano factor [42], which is a measure of the relative size of the internal fluctuations. From Eqs. (A22) and (A23), the Fano factors of the sRNA and its target mRNA are given by

$$F_{\mathrm{sRNA}} = 1 + \frac{k^2 M^s (S^s)^2}{\alpha_s\left[\beta_s + \beta_m + kM^s + kS^s - k^2 (M^s)^2 S^s/\alpha_m - k^2 M^s (S^s)^2/\alpha_s\right]}, \tag{10}$$

$$F_{\mathrm{mRNA}} = 1 + \frac{k^2 (M^s)^2 S^s}{\alpha_m\left[\beta_s + \beta_m + kM^s + kS^s - k^2 M^s (S^s)^2/\alpha_s - k^2 (M^s)^2 S^s/\alpha_m\right]}. \tag{11}$$

As both the steady value and variance of internal fluctuations are proportional to the volume of the system, the Fano factor is independent of volume. Open systems at thermodynamic equilibrium obey Poisson statistics, and for those the Fano factor is always 1 [38].

By virtue of the theoretical formulas obtained above, one can discuss the steady state properties and the intrinsic fluctuations of the sRNA-mediated gene regulation around the threshold. In Refs. [17,18],

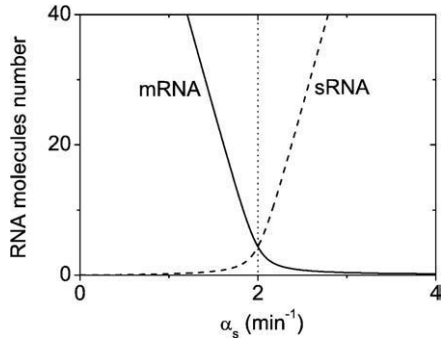

Fig. 1. Stationary mean molecules number as a function of the transcription rate α_s of sRNA. The vertical dot line corresponds to the threshold point where $\alpha_s=\alpha_m$. Parameters: $\beta_m=0.02$ min^{-1}, $\beta_s=0.02$ min^{-1}, $\alpha_m=2$ min^{-1}, $k=0.1$ min^{-1}.

it has been shown that the steady mean number of mRNA exhibits a threshold linear behavior as a function of the mRNA transcriptional rate α_m. When the transcription rate α_m of target mRNA is fixed here, Fig. 1 shows the stationary mean values of sRNA and target mRNA produce an sensitive response to the transcription rate of sRNA around the threshold point $\alpha_s=\alpha_m$ (the vertical dot line in Fig. 1). If the transcription rate of sRNA exceeds the transcription rate of mRNA, then the sRNA can accumulate in the cell, and target message levels can be reduced to very low levels. With increasing of the transcription rate of sRNA, the average number of target mRNA is rapidly decreased around the threshold, which leads to the silence of target mRNA. Therefore, the expression of target mRNA can be classified into three regimens [40]: surviving ($\alpha_s<<\alpha_m$), crossover ($\alpha_s\approx\alpha_m$), and silencing ($\alpha_s>>\alpha_m$). It is also shown that the steady state molecule number of target mRNA rapidly rises when the transcription rate of sRNA drops below the transcription rate of target mRNA. Similar phenomenon was experimentally found in the sRNA control quorum sensing in *Vibrio harveyi* and *Vibrio cholerae* [43], that is, an sensitive increase in *hapR*/*luxR* mRNA levels occurs with decreasing levels of LuxO-P as cell density increases.

The sensitivity by which $\langle M\rangle_{st}$ responds to changes in α_s around the threshold point $\alpha_s=\alpha_m$ in Fig. 1 motivates further analysis. A common measure of the sensitivity of a response to variation in parameter z is the logarithmic gain [44] or sensitivity amplification [45,46] or susceptibility [47] which is defined by

$$\chi_z = \left|\frac{\partial \ln\langle M\rangle_{st}}{\partial \ln z}\right|. \tag{12}$$

Thus,

$$\chi_{\alpha_s} = \frac{\alpha_s}{2\beta_m M^s}\left|1+\frac{\alpha_m-\alpha_s-\lambda}{\sqrt{(\alpha_m-\alpha_s-\lambda)^2+4\alpha_m\lambda}}\right| \tag{13}$$

for the parameter α_s, and

$$\chi_k = \frac{\lambda}{2\beta_m M^s}\left|1-\frac{\alpha_m+\alpha_s+\lambda}{\sqrt{(\alpha_m-\alpha_s-\lambda)^2+4\alpha_m\lambda}}\right| \tag{14}$$

for the parameter k. The susceptibility χ_z (where $z=\alpha_s,k$) measures the relative change in the response of $\langle M\rangle_{st}$ normalized to the relative change in the parameter z.

The effects of parameter α_s on intrinsic fluctuations are shown by Fig. 2. With the increasing of α_s, it is shown that the Fano factors of mRNA and sRNA approach one for low values of α_s, reaches a maximum when α_s is around the threshold, and then decrease back to one for high values of α_s. Moreover, the maximum of Fano factors are increased with the increasing of transcription rate of mRNA α_m. It is interesting that the maximum of Fano factor for mRNA appears when $\alpha_s>\alpha_m$, however, that for sRNA appears when $\alpha_s<\alpha_m$, it means that the variations of internal fluctuation of mRNA and sRNA with increasing α_s are not synchronous around the threshold. The fact, that either F_{sRNA} or F_{mRNA} approaches 1 for both small and large value of α_s, results in the closed curve in F_{sRNA}–F_{mRNA} plane as shown in Fig. 2. To character the relative change in the response of $\langle M\rangle_{st}$ normalized to

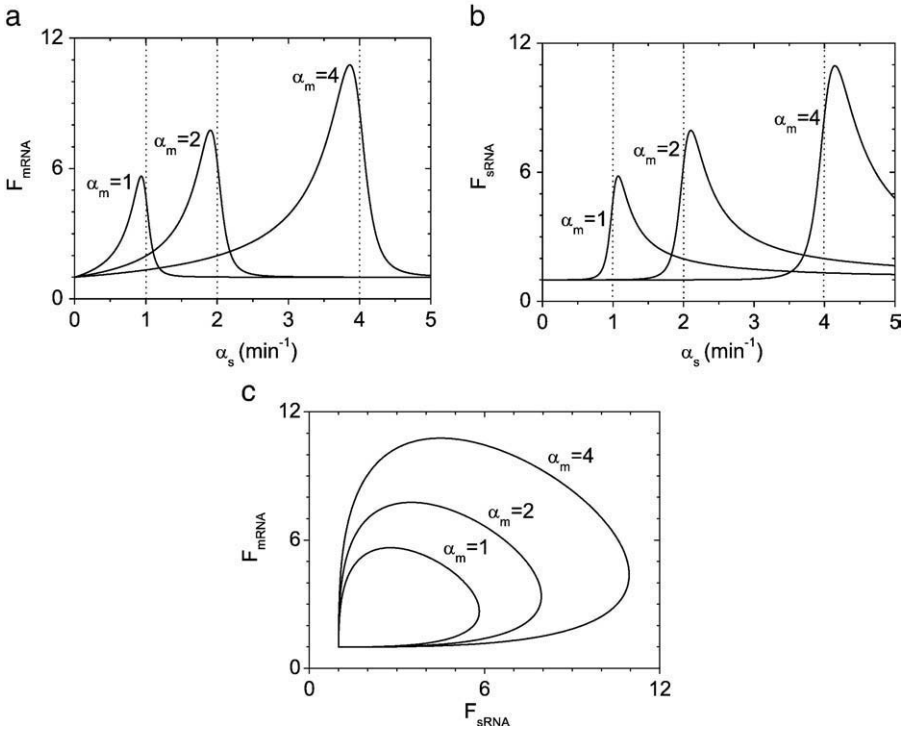

Fig. 2. Fano factor as a function of α_s for different α_m, and the variation in both F_{sRNA} and F_{mRNA} with varying α_s. Parameters: $\beta_s=0.02$ min^{-1}, $\beta_m=0.02$ min^{-1}, $k=0.1$ min^{-1}.

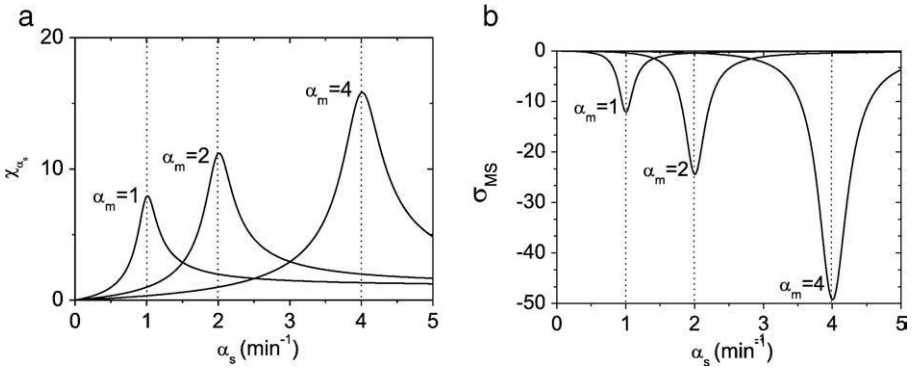

Fig. 3. Susceptibility and covariance of sRNA and its target as a function of α_s for different α_m. The vertical dot lines correspond to the threshold point (where $\alpha_s = \alpha_m$) for different α_m. Parameters: $\beta_m = 0.02\ \text{min}^{-1}$, $\beta_s = 0.02\ \text{min}^{-1}$, $k = 0.1\ \text{min}^{-1}$.

the relative change in the parameter α_s, Fig. 3 shows the susceptibility $\chi_{\alpha s}$ as a function of transcription rate of sRNA. It can be found that, with the increasing of α_s, the susceptibility $\chi_{\alpha s}$ increases first, reaches a maximum at the threshold $\alpha_s = \alpha_m$, and then decreases for large values of α_s. By using of the formula (A24) in Appendix A, the covariance of the sRNA and its target mRNA, which measures the correlation intensity between the fluctuations of two components, is negative as shown in Fig. 3. $\sigma_{ms} = 0$ means that there is no correlation. It is shown that the covariance of the sRNA and its target mRNA has a minimum at $\alpha_s = \alpha_m$, which means that the anti-correlation intensity between the fluctuation of sRNA and that of mRNA is the largest at the threshold value. The magnitude of minimum is increased with the increasing of transcription rate of mRNA.

The effects of coupled degradation rate between target gene and sRNA k on intrinsic fluctuations are shown in Fig. 4. If the parameters α_s, α_m, β_s, and β_m are fixed, with the increasing of coupled degradation rate k, the molecule numbers of both RNA molecules are expected to be rapidly decreased by base pairing of sRNA and mRNA. The Fano factor of mRNA is close to one for low values of k, reaches a maximum, and then decreases for high values of k. Moreover, the maximum of F_{mRNA} increases with the decreasing of the transcription rate of sRNA α_s. However, the Fano factor of sRNA increases and saturates to a plateau value as k increases, and there is no peak phenomenon for the Fano factor of sRNA. The variations of F_{sRNA} and F_{mRNA} with the increasing of k show that the map of F_{sRNA}-F_{mRNA} takes a bell-shaped form due to fact that the Fano factor of sRNA increases and saturates to a plateau value with k increasing. With the increasing of the coupled degradation rate between sRNA and its target gene k, Fig. 5 shows that the susceptibility χ_k is linearly decreased, but the negative correlation (or the covariance) of the sRNA and its target mRNA is increased, and approaches to zero (i.e. the case of un-correlation).

3. Two target mRNAs regulated by one sRNA

For multiple target genes regulated by one *trans*-encoded sRNA, here we consider two target mRNAs (mRNA_R and mRNA_T) regulated

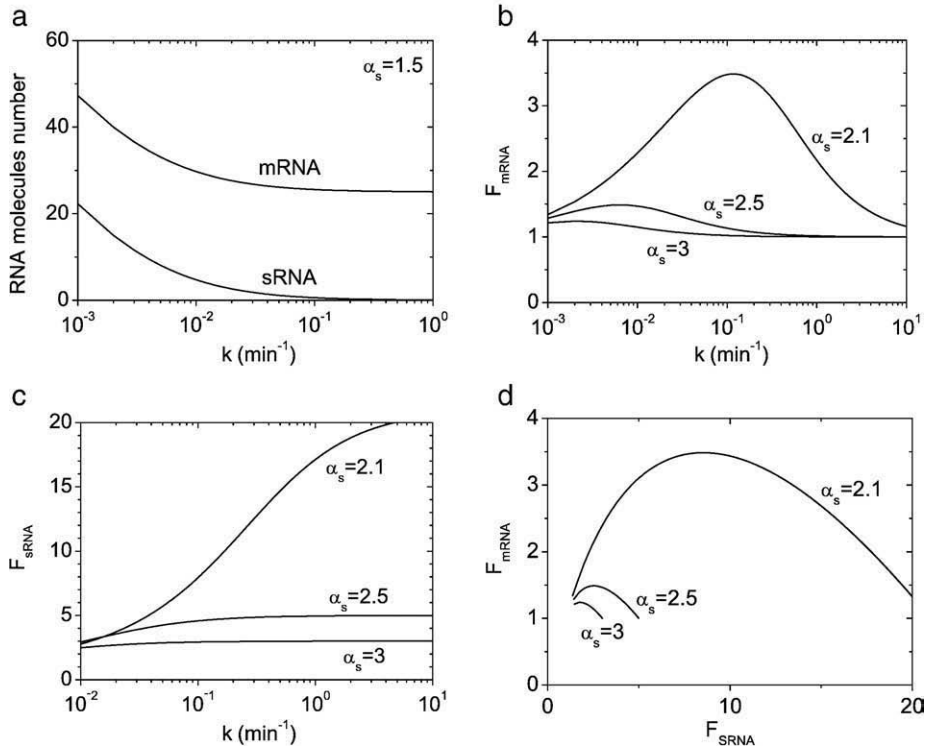

Fig. 4. Stationary mean number of RNA molecules, and Fano factors of mRNA and sRNA as a function of k for different α_s. Variation in both F_{sRNA} and F_{mRNA} with increasing k. Parameters: $\alpha_m = 2\ \text{min}^{-1}$, $\beta_m = \beta_s = 0.02\ \text{min}^{-1}$.

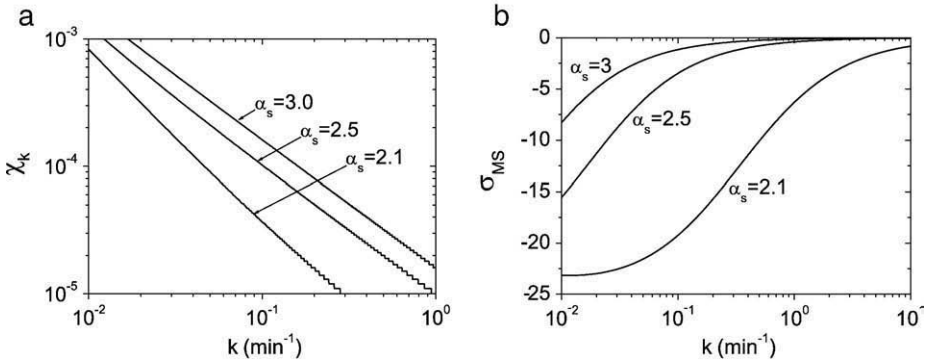

Fig. 5. Susceptibility and covariance of sRNA and its target mRNA as a function of k for different α_s. Parameters: $\alpha_m = 2\ \text{min}^{-1}$, $\beta_m = \beta_s = 0.02\ \text{min}^{-1}$.

by single sRNA, and the biochemical interactions between sRNA and its target genes are described as following

$$\xrightarrow{\alpha_s} \text{sRNA} \xrightarrow{\beta_s} \emptyset, \tag{15}$$

$$\xrightarrow{\alpha_R} \text{mRNA}_R \xrightarrow{\beta_R} \emptyset, \tag{16}$$

$$\xrightarrow{\alpha_T} \text{mRNA}_T \xrightarrow{\beta_T} \emptyset, \tag{17}$$

$$\text{sRNA} + \text{mRNA}_R \xrightarrow{k_R} \emptyset, \tag{18}$$

$$\text{sRNA} + \text{mRNA}_T \xrightarrow{k_T} \emptyset, \tag{19}$$

where α_s and β_s are the transcription rate and the degradation rate of the sRNA, α_R, β_R, α_T, and β_T are transcription rate and the degradation rate of target mRNA$_T$ and mRNA$_R$, respectively. k_R and k_T are the coupled degradation rate between target genes and sRNA. It is assumed that the two target genes are expressed from different promoters, and the parameters for mRNA$_R$ and mRNA$_T$ are changed independently.

In the deterministic description that ignores stochastic effects, three variables in this model are governed by the macroscopic equations

$$\frac{dS}{dt} = \alpha_s - \beta_s S - k_R M_R S - k_T M_T S, \tag{20}$$

$$\frac{dM_R}{dt} = \alpha_R - \beta_R M_R - k_R M_R S, \tag{21}$$

$$\frac{dM_T}{dt} = \alpha_T - \beta_T M_T - k_T M_T S, \tag{22}$$

where S, M_R, and M_T are the molecule number of sRNA and its target mRNAs, respectively. If the degradation rate of target mRNA$_R$ is neglected, $\beta_R = 0$, the steady state amounts M_R^s, M_T^s, and S^s of mRNAs and sRNA are accordingly

$$S^s = \frac{-[(\alpha_R+\alpha_T-\alpha_s)k_T+\beta_s\beta_T]+\sqrt{[(\alpha_R+\alpha_T-\alpha_s)k_T+\beta_s\beta_T]^2-4\beta_s k_T\beta_T(\alpha_R-\alpha_s)}}{2\beta_s k_T}, \tag{23}$$

$$M_R^s = \frac{\alpha_R}{k_R S^s}, \tag{24}$$

$$M_T^s = \frac{\alpha_T}{\beta_T + k_T S^s}. \tag{25}$$

In the Langevin description, the molecules number of mRNAs and sRNA in this model are governed by the stochastic equations

$$\frac{dS}{dt} = \alpha_s - \beta_s S - k_R M_R S - k_T M_T S + \xi_1(t), \tag{26}$$

$$\frac{dM_R}{dt} = \alpha_R - \beta_R M_R - k_R M_R S + \xi_2(t), \tag{27}$$

$$\frac{dM_T}{dt} = \alpha_T - \beta_T M_T - k_T M_T S + \xi_3(t), \tag{28}$$

The statistical properties of random variables ξ_i in Eqs. (26)–(28) at the steady state (S^s,M_R^s,M_T^s) are given by Eqs. (B1)–(B6) in Appendix B.

The Fano factor, a measure of the relative size of the internal fluctuations, of RNA molecules can be derived from Eq. (B23) in Appendix B through the variance normalized to the steady value of RNA molecules:

$$F_s = 1 + \frac{F_s}{F}, \quad F_{M_R} = 1 + \frac{F_R}{F}, \quad F_{M_T} = 1 + \frac{F_T}{F}, \tag{29}$$

where

$$\begin{aligned} F = {} & \frac{\alpha_s}{S^s}\left[-A_R A_T C - A_T B_R k_T S^s - A_R B_T k_R S^s\right] \\ & + \frac{\alpha_R S^s}{(M_R^s)^2}\left[-A_T C k_R M_R^s + B_T k_T^2 M_T^s S^s - B_T k_R^2 M_R^s S^s\right] \\ & - \frac{\alpha_T S^s}{(M_T^s)^2}\left[B_R k_T^2 M_T^s S^s - B_R k_R^2 M_R^s S^s + A_R C k_T M_T^s\right], \end{aligned} \tag{30}$$

$$\begin{aligned} F_s = {} & C\left[A_T B_R k_T S^s + A_R B_T k_R S^s + A_R A_T C\right] \\ & - \frac{\alpha_R}{(M_R^s)^2}\left[-A_T C_R C\frac{\alpha_R}{k_R M_R^s} + C_T B_T \frac{\alpha_T S^s}{M_T^s} + A_T k_T S^s (M_R^s B_R + M_T^s B_T) - C_R B_T \frac{\alpha_R S^s}{M_R^s}\right] \\ & - \frac{\alpha_T}{(M_T^s)^2}\left[A_R k_R S^s (M_R^s B_R + M_T^s B_T) - B_R C_T \frac{\alpha_T S^s}{M_T^s} + C_R B_R \frac{\alpha_R S^s}{M_R^s} - A_R C_T C \frac{\alpha_T}{k_T M_T^s}\right], \end{aligned} \tag{31}$$

$$\begin{aligned} F_R = {} & \frac{\alpha_s}{M_R^s S^s}\left[A_T B_T k_T M_T^s S^s - A_T B_T k_T M_T^s S^s\right] \\ & - \left(\frac{\alpha_s}{M_R^s} - \frac{\alpha_T S^s}{M_T^s M_R^s}\right)\left[-A_T C k_R M_R^s + B_T k_T^2 M_T^s S^s - B_T k_R^2 M_R^s S^s\right] \\ & - \frac{\alpha_T S^s}{(M_T^s)^2 M_R^s}\left[-A_T C k_R M_R^s M_T^s + B_T k_T^2 (M_T^s)^2 S^s - B_T k_R^2 M_R^s M_T^s S^s\right], \end{aligned} \tag{32}$$

$$\begin{aligned} F_T = {} & \frac{\alpha_s}{M_T^s S^s}\left[A_R B_R k_R M_R^s S^s - B_R A_R k_R S^s M_R^s\right] \\ & + \frac{\alpha_R S^s}{(M_R^s)^2 M_T^s}\left[B_R k_T^2 M_T^s M_R^s S^s - B_R k_R^2 (M_R^s)^2 S^s + A_R C k_T M_T^s M_R^s\right] \\ & + \left(\frac{\alpha_s}{M_T^s} - \frac{\alpha_R S^s}{M_R^s M_T^s}\right)\left[B_R k_T^2 M_T^s S^s - B_R k_R^2 M_R^s S^s + A_R C k_T M_T^s\right], \end{aligned} \tag{33}$$

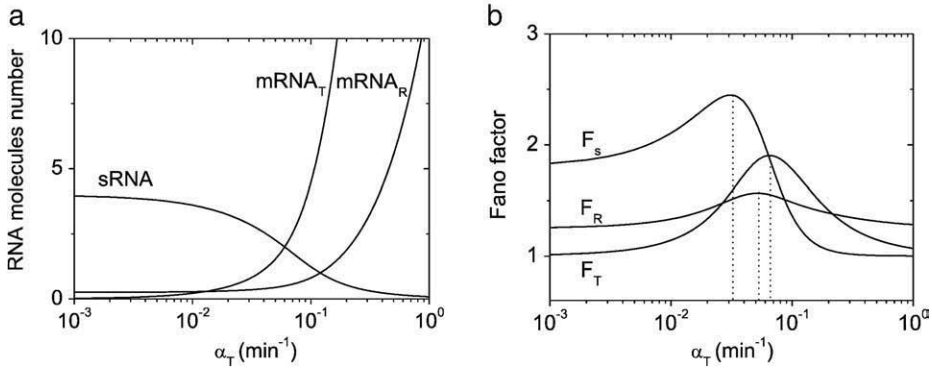

Fig. 6. Stationary mean molecules number and Fano factor of RNA molecules as a function of the transcription rate α_T of mRNA$_T$. The vertical dot lines correspond to a maximum of Fano factor. Parameters: $\alpha_s = 0.1\ \mathrm{min}^{-1}$, $\beta_s = 0.02\ \mathrm{min}^{-1}$, $\alpha_R = 0.02\ \mathrm{min}^{-1}$, $\beta_R = 0\ \mathrm{min}^{-1}$, $k_R = 0.02\ \mathrm{min}^{-1}$, $\beta_T = 0.01\ \mathrm{min}^{-1}$, $k_T = 0.01\ \mathrm{min}^{-1}$.

with

$$C_R = \frac{\alpha_s}{S^s} + \frac{\alpha_R}{M_R^s}, \quad C_T = \frac{\alpha_s}{S^s} + \frac{\alpha_T}{M_T^s}, \tag{34}$$

and A_R, A_T, B_R, B_T, C are given by Eqs. (B24) and (B25) in Appendix B.

Consider the activity of the reporter gene (mRNA$_R$) $\alpha_R < \alpha_s$ is held fixed, while the activity α_T of another target gene (mRNA$_T$) is increased. For simply, β_R is set as zero, and the steady state amounts M_R^s, M_T^s, and S^s of mRNAs and sRNA are given by Eqs. (23)–(25). With α_R fixed, $\alpha_s + \alpha_R$ can be thought as the threshold for the gene expression [17], when α_T is below this threshold, both genes are silenced, and when α_T exceeds the threshold, mRNA molecules of both species survive the sRNA repression. Therefore, the mRNA molecules expression can be classified into three regimens [40]: silenced ($\alpha_T << \alpha_s + \alpha_R$), crossover ($\alpha_T \approx \alpha_s + \alpha_R$), and survive ($\alpha_T >> \alpha_s + \alpha_R$).

The stationary mean molecules number and Fano factor of RNA molecules as a function of the transcription rate α_T of mRNA$_T$ are depicted in Fig. 6 with $\alpha_s = 5\alpha_R$. Both target genes are silenced for very small values of α_T. With the increasing of α_T, mRNA$_T$ starts being expressed first, meanwhile the level of sRNA is decreased, and then mRNA$_R$ starts being expressed. When mRNA$_T$ is highly expressed, the expressions of mRNA$_T$ and mRNA$_R$ grow proportionally to α_T and α_R, respectively, which is qualitatively consistent with the results of Ref. [17]. Fig. 6 also shows that there is a maximum in the Fano factors (or the intrinsic noises) of RNAs in the regimen of crossover ($\alpha_T \approx \alpha_s + \alpha_R$). It is interesting that, with the increasing of α_T, the maximum of Fano factor is first appeared for sRNA, next for mRNA$_R$, and finally for mRNA$_T$. The Fano factor of sRNA is larger than 1 in the regimen of target gene silenced but approaches 1 in the regimen of mRNAs survive. The Fano factor of mRNA$_R$ is larger than 1 in all regimens. The Fano factor of mRNA$_T$ approaches 1 in regimen of both silenced and survive.

The effects of both α_T and α_s on Fano factors of RNA molecules are depicted in Fig. 7. It is shown that the Fano factor of RNA molecules has a maximum in the regimen of crossover. With the increasing of transcription rate α_s of sRNA, the maximum of both F_s and F_T is increased, but that of F_R is decreased. It is interesting that the

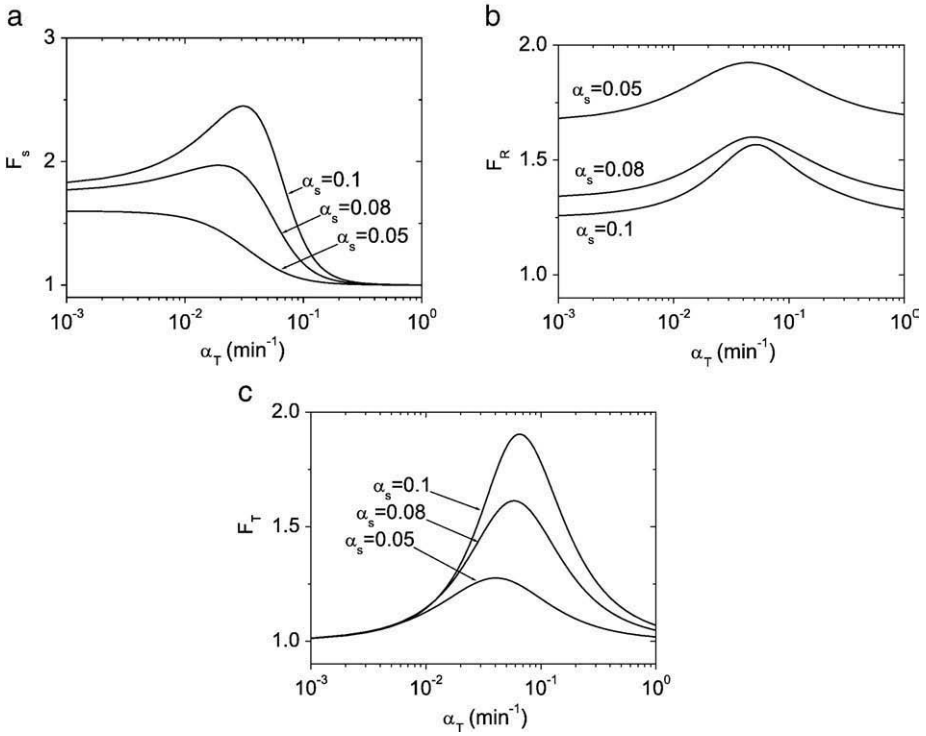

Fig. 7. Fano factors of RNA molecules as a function of α_T for different α_s. Parameters: $\beta_s = 0.02\ \mathrm{min}^{-1}$, $\alpha_R = 0.02\ \mathrm{min}^{-1}$, $\beta_R = 0\ \mathrm{min}^{-1}$, $k_R = 0.02\ \mathrm{min}^{-1}$, $\beta_T = 0.01\ \mathrm{min}^{-1}$, $k_T = 0.01\ \mathrm{min}^{-1}$.

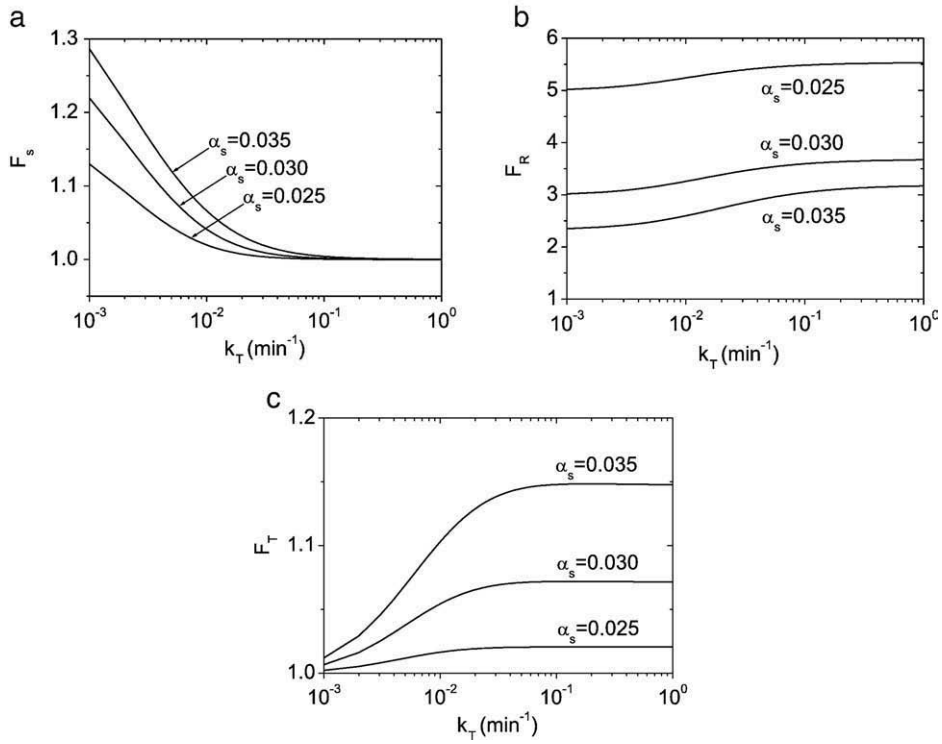

Fig. 8. Fano factors of RNA molecules as a function of k_T for different α_s. Parameters: $\beta_s = 0.02\ \text{min}^{-1}$, $\alpha_R = 0.02\ \text{min}^{-1}$, $\beta_R = 0\ \text{min}^{-1}$, $k_R = 0.02\ \text{min}^{-1}$, $\alpha_T = 0.05\ \text{min}^{-1}$, $\beta_T = 0.01\ \text{min}^{-1}$.

maximum of both F_s and F_T is shifted from left to right with the increasing of α_s, but that of F_R is hardly changed, which means that the intrinsic noise intensity of target mRNA$_R$ is determined by both the transcriptional rate of itself and that of sRNA, and independent of that of the other target mRNA$_T$.

The effects of both k_T and α_s on Fano factors of RNA molecules are depicted in Fig. 8. With the increasing of coupled degradation rate k_T between target mRNA$_T$ and sRNA, the Fano factor of sRNA is decreased and approaches 1, but these of two target genes are increased and saturate to a plateau value. With the increasing of transcription rate α_s of sRNA, the Fano factors of both sRNA and mRNA$_T$ increase, however, that of mRNA$_R$ decreases.

4. Conclusion

Based on the models of sRNA-mediated gene regulation proposed by Levine et al. [17], two models, including single target gene and two target mRNAs regulated by one sRNA, respectively, have been investigated in this paper. The formulas of Fano factor for target mRNAs and sRNA, a measure of the relative size of the intrinsic fluctuations of RNA molecules, are derived from the Langevin approach. By virtue of the formulas presented here, the effects of transcription rate of RNAs and the coupled degradation rate between sRNA and its target gene on intrinsic fluctuations are discussed.

For the model of single target gene regulated by a sRNA, it is found out that (Fig. 2), when the sRNA transcription rate is very high or very low compared with that of target mRNA, the noises of both mRNA and sRNA approach the bare Poissonian limit (i.e. $F_{\text{mRNA}} = F_{\text{sRNA}} = 1$), that is, sRNA-mediated gene silencing is generally effective in attenuating intrinsic noises of RNAs. However, when the two transcription rates are comparable, the strong anti-correlation (or negative correlation in Fig. 3) between the fluctuations of two components result in a large intrinsic fluctuations in the level of RNA molecules. Our results are consistent with these found in very recent work of Levine et al. [41].

For the model of two target mRNAs regulated by one sRNA, in the regimen of crossover, it is found that (Fig. 6), with the increasing of transcription rate of target mRNA$_T$, the maximum of intrinsic fluctuations of RNA molecules is shifted from sRNA to target mRNA$_R$, and then to target mRNA$_T$. With the increasing of transcription rate of sRNA (Fig. 7), the noises of sRNA and mRNA$_T$ is increased, however, that of mRNA$_R$ is decreased. The intrinsic noise intensity of target mRNA$_R$ is determined by both the transcriptional rate of itself and that of sRNA, and independent of that of the other target mRNA. The effects of interaction (coupled degradation rate) of sRNA and its target mRNA$_T$ on intrinsic noises (Fig. 8) show that, when the transcription rates are comparable, the noise of sRNA diminishes and approaches the bare Poissonian limit with the increasing of coupled degradation rate, but the noises of two target genes increase and saturate to a plateau.

The mechanism of post transcriptional gene regulation processes depends on the reaction between various molecules, the quantitative parameters, and the fluctuation levels underlying the genetic circuit. Therefore, it is very important to understand how these elements combine to control biological behaviors. The relationships between the parameter values and the intrinsic fluctuations discussed here are very important properties of the post transcriptional gene regulation process, and we also wish that above theoretical predicts could be proved by using of the similar experimental techniques used in *E. coli* [17].

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Appendix A

The statistical properties (e.g. the mean and the correlation functions) of random variables ξ_i in Eqs. (8) and (9) at the steady state

(M^s,S^s) can be derived under the following two conditions [39]. Condition (i): require the time interval δt to be small enough that only one reaction is occurred in δt, and $\xi_i\delta t$ for $i=1,2$, can only be ± 1 or zero. Let $P(\mu,\nu)$ is the probability that $\xi_1\delta t=u$ and $\xi_2\delta t=v$. At the steady state, from Eqs. (1)–(3) we have $P(1,0)=\alpha_s\delta t$, $P(-1,0)=\beta_s S^s\delta t$, $P(0,1)=\alpha_m\delta t$, $P(0,-1)=\alpha_m M^s\delta t$, and $P(-1,-1)=kM^sS^s\delta t$, and the other $P(u,v)$ identically equal to zero. Therefore, the mean of random variables ξ_i obeys

$$\langle\xi_1\delta t\rangle = (\alpha_s - \beta_s S^s - kM^sS^s)\delta t = 0, \tag{A1}$$

$$\langle\xi_2\delta t\rangle = (\alpha_m - \beta_m M^s - kM^sS^s)\delta t = 0, \tag{A2}$$

and the mean square satisfies

$$\langle\xi_1^2\delta t^2\rangle = (\alpha_s + \beta_s S^s + kM^sS^s)\delta t = 2\alpha_s\delta t, \tag{A3}$$

$$\langle\xi_2^2\delta t^2\rangle = (\alpha_m + \beta_m M^s + kM^sS^s)\delta t = 2\alpha_m\delta t, \tag{A4}$$

$$\langle\xi_1\xi_2\delta t^2\rangle = kM^sS^s\delta t. \tag{A5}$$

Condition (ii): require the steady state values are large enough, then typical fluctuations away from these values will always be small compared to the values themselves. In that case, $\xi_i(t)$ will be uncorrelated with $\xi_i(t')$ for all $|t-t'|>\delta t$. This lack of correlation for $t\neq t'$ can be mathematically described by a delta function. Thus, the statistical properties of random variables ξ_i satisfy

$$\langle\xi_1(t)\rangle = \langle\xi_2(t)\rangle = 0, \tag{A6}$$

with their auto-correlation functions obey

$$\langle\xi_1(t)\xi_1(t')\rangle = 2\alpha_s\delta(t-t'), \tag{A7}$$

$$\langle\xi_2(t)\xi_2(t')\rangle = 2\alpha_m\delta(t-t'), \tag{A8}$$

and the cross-correlations between ξ_i are given by

$$\langle\xi_1(t)\xi_2(t')\rangle = \langle\xi_2(t)\xi_1(t')\rangle = kM^sS^s\delta(t-t'). \tag{A9}$$

The linearization of Eqs. (8) and (9) around steady state (M^s,S^s) leads to

$$\frac{dx_1}{dt} = -(\beta_s + kM^s)x_1 - kS^sx_2 + \xi_1(t), \tag{A10}$$

$$\frac{dx_2}{dt} = -kM^sx_1 - (\beta_m + kS^s)x_2 + \xi_2(t), \tag{A11}$$

where $x_1=S-S^s$ and $x_2=M-M^s$. The Fokker–Planck equation corresponding to the Langevin Eqs. (A10) and (A11) with Eqs. (A6)–(A9) can be written as [48,49]

$$\begin{aligned}\frac{\partial P(x_1,x_2,t)}{\partial t} = &-\frac{\partial}{\partial x_1}\left[-(\beta_s + kM^s)x_1 - kS^sx_2\right]P(x_1,x_2,t)\\ &-\frac{\partial}{\partial x_2}\left[-kM^sx_1 - (\beta_s + kS^s)x_2\right]P(x_1,x_2,t)\\ &+\alpha_s\frac{\partial^2P(x_1,x_2,t)}{\partial x_1^2} + \alpha_m\frac{\partial^2P(x_1,x_2,t)}{\partial x_2^2}\\ &+kM^sS^s\frac{\partial^2P(x_1,x_2,t)}{\partial x_1\partial x_2}.\end{aligned} \tag{A12}$$

The Fokker–Planck equation characterizes the stationary statistics of the sRNA-mediated gene regulation process when the state variables are around the steady state (S^s, M^s).

The moments of $x_i(t)$ $(i=1,2)$ obeys

$$\frac{d}{dt}\langle x_i^n\rangle = \int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty} x_i^n\frac{\partial P(x_1,x_2,t)}{\partial t}dx_1dx_2. \tag{A13}$$

By using of the Fokker–Planck equation (A12) and Eq. (A13), we have

$$\frac{d}{dt}\langle x_1(t)\rangle = -(\beta_s + kM^s)\langle x_1(t)\rangle - kS^s\langle x_2(t)\rangle, \tag{A14}$$

$$\frac{d}{dt}\langle x_2(t)\rangle = -kM^s\langle x_1(t)\rangle - (\beta_m + kS^s)\langle x_2(t)\rangle, \tag{A15}$$

$$\frac{d}{dt}\langle x_1^2(t)\rangle = -2(\beta_s + kM^s)\langle x_1^2(t)\rangle - 2kS^s\langle x_1(t)x_2(t)\rangle - 2\alpha_s, \tag{A16}$$

$$\begin{aligned}\frac{d}{dt}\langle x_1(t)x_2(t)\rangle = &-kM^s\langle x_1^2(t)\rangle - (\beta_s + \beta_m + kM^s + kS^s)\langle x_1(t)x_2(t)\rangle\\ &-kS^s\langle x_2^2(t)\rangle - kM^sS^s,\end{aligned} \tag{A17}$$

$$\frac{d}{dt}\langle x_2^2(t)\rangle = -2kM^s\langle x_1(t)x_2(t)\rangle - 2(\beta_m + kS^s)\langle x_2^2(t)\rangle - 2\alpha_m, \tag{A18}$$

where the following conditions [50]

$$\lim_{x_i\to\pm\infty} P(x_1,x_2,t) = 0, \tag{A19}$$

$$\lim_{x_i\to\pm\infty}\frac{\partial P(x_1,x_2,t)}{\partial x_j} = 0, \text{ for } i,j=1,2, \tag{A20}$$

have been used, and the steady state values of mRNA and sRNA are given by Eqs. (6) and (7), respectively.

At the steady state (i.e., $d\langle x_i^n(t)\rangle/dt=0$), from Eqs. (A14) and (A15), the stationary mean molecules number of mRNA and sRNA are $\langle M\rangle_{st}=M^s$, $\langle S\rangle_{st}=S^s$. The variance $\sigma_{ii}=\lim_{t\to\infty}\langle x_i^2(t)\rangle$ of RNA molecules and the covariance $\sigma_{ij}=\sigma_{ji}=\lim_{t\to\infty}\langle x_i(t)x_j(t)\rangle$ of the sRNA and its target mRNA obeys following matrix equation

$$\begin{pmatrix}-2(\beta_s+kM^s) & -2kS^s & 0\\ -kM^s & -(\beta_s+\beta_m+kM^s+kS^s) & -kS^s\\ 0 & -2kM^s & -2(\beta_m+kS^s)\end{pmatrix}\begin{pmatrix}\sigma_{SS}\\ \sigma_{MS}\\ \sigma_{MM}\end{pmatrix} + \begin{pmatrix}-2\alpha_s\\ -kM^sS^s\\ -2\alpha_m\end{pmatrix} = 0 \tag{A21}$$

thus,

$$\sigma_{SS} = S^s + \frac{k^2M^s(S^s)^3}{\alpha_s\left[\beta_s+\beta_m+kM^s+kS^s-k^2(M^s)^2S^s/\alpha_m-k^2M^s(S^s)^2/\alpha_s\right]}, \tag{A22}$$

$$\sigma_{MM} = M^s + \frac{k^2(M^s)^3S^s}{\alpha_m\left[\beta_s+\beta_m+kM^s+kS^s-k^2M^s(S^s)^2/\alpha_s-k^2(M^s)^2S^s/\alpha_m\right]}, \tag{A23}$$

$$\sigma_{MS} = \sigma_{SM} = \frac{k\alpha_m\alpha_s(M^sS^s)^2}{-\alpha_m\alpha_s(\alpha_mS^s+\alpha_sM^s)+k^2\alpha_s(M^s)^3(S^s)^2+k^2\alpha_m(M^s)^2(S^s)^3}. \tag{A24}$$

Appendix B

The statistical properties of random variables ξ_i in Eqs. (26–28) at the steady state (S^s, M_R^s, M_T^s) can be derived by using of same method of Swain [39]. One has $P(1,0,0)=\alpha_s\delta t$, $P(-1,0,0)=\beta_sS^s\delta t$, $P(-1,-1,0)=k_RM_R^sS^s\delta t$, $P(-1,0,-1)=k_TM_T^sS^s\delta t$, $P(0,1,0)=\alpha_R\delta t$, $P(0,-1,0)=$

$\beta_R M_R^s \delta t$, $P(0,0,1)=\alpha_T \delta t$, $P(0,0,-1)=\beta_T M_T^s \delta t$, and the other $P(u,v,w)$ identically equal to zero. The mean, auto-correlation of random variables ξ_i, and cross-correlation between ξ_i obey

$$\langle \xi_1(t)\rangle = \langle \xi_2(t)\rangle = \langle \xi_3(t)\rangle = 0, \tag{B1}$$

$$\langle \xi_1(t)\xi_1(t')\rangle = 2\alpha_s \delta(t-t'), \tag{B2}$$

$$\langle \xi_2(t)\xi_2(t')\rangle = 2\alpha_R \delta(t-t'), \tag{B3}$$

$$\langle \xi_3(t)\xi_3(t')\rangle = 2\alpha_T \delta(t-t'), \tag{B4}$$

$$\langle \xi_1(t)\xi_2(t')\rangle = \langle \xi_2(t)\xi_1(t')\rangle = k_R M_R^s S^s \delta(t-t'), \tag{B5}$$

$$\langle \xi_1(t)\xi_3(t')\rangle = \langle \xi_3(t)\xi_1(t')\rangle = k_T M_T^s S^s \delta(t-t'). \tag{B6}$$

The linearization of Eqs. (26)–(28) around steady state (S^s, M_R^s, M_T^s) leads to

$$\frac{dx_1}{dt} = (-\beta_s - k_R M_R^s - k_T M_T^s)x_1 - k_R S^s x_2 - k_T S^s x_3 + \xi_1(t), \tag{B7}$$

$$\frac{dx_2}{dt} = -k_R M_R^s x_1 - (\beta_R + k_R S^s)x_2 + \xi_2(t), \tag{B8}$$

$$\frac{dx_3}{dt} = -k_T M_T^s x_1 - (\beta_T + k_T S^s)x_3 + \xi_3(t), \tag{B9}$$

where $x_1 = S - S^s$, $x_2 = M_R - M_R^s$, and $x_3 = M_T - M_T^s$. The Fokker–Planck equation corresponding to the Langevin Eqs. (B7)–(B9) with (B1)–(B6) can be written as

$$\begin{aligned}\frac{\partial P(x_1,x_2,x_3,t)}{\partial t} =& -\frac{\partial}{\partial x_1}[(-\beta_s - k_R M_R^s - k_T M_T^s)x_1 - k_R S^s x_2 - k_T S^s x_3]P(x_1,x_2,x_3,t)\\ &-\frac{\partial}{\partial x_2}[-k_R M_R^s x_1 - (\beta_R + k_R S^s)x_2]P(x_1,x_2,x_3,t)\\ &-\frac{\partial}{\partial x_3}[-k_T M_T^s x_1 - (\beta_T + k_T S^s)x_3]P(x_1,x_2,x_3,t)\\ &+\alpha_s \frac{\partial^2 P(x_1,x_2,x_3,t)}{\partial x_1^2} + \alpha_R \frac{\partial^2 P(x_1,x_2,x_3,t)}{\partial x_2^2} + \alpha_T \frac{\partial^2 P(x_1,x_2,x_3,t)}{\partial x_3^2}\\ &+ k_R M_R^s S^s \frac{\partial^2 P(x_1,x_2,x_3,t)}{\partial x_1 \partial x_2} + k_T M_T^s S^s \frac{\partial^2 P(x_1,x_2,x_3,t)}{\partial x_1 \partial x_3}.\end{aligned} \tag{B10}$$

By using of the Fokker–Planck Eq. (B10), we have

$$\frac{d}{dt}\langle x_1(t)\rangle = -(\beta_s + k_R M_R^s + k_T M_T^s)\langle x_1(t)\rangle - k_R S^s \langle x_2(t)\rangle - k_T S^s \langle x_3(t)\rangle, \tag{B11}$$

$$\frac{d}{dt}\langle x_2(t)\rangle = -k_R M_R^s \langle x_1(t)\rangle - (\beta_R + k_R S^s)\langle x_2(t)\rangle, \tag{B12}$$

$$\frac{d}{dt}\langle x_3(t)\rangle = -k_T M_T^s \langle x_1(t)\rangle - (\beta_T + k_T S^s)\langle x_3(t)\rangle, \tag{B13}$$

$$\begin{aligned}\frac{d}{dt}\langle x_1^2(t)\rangle =& -2(\beta_s + k_R M_R^s + k_T M_T^s)\langle x_1^2(t)\rangle - 2k_R S^s \langle x_1(t)x_2(t)\rangle\\ &-2k_T S^s \langle x_1(t)x_3(t)\rangle - 2\alpha_s,\end{aligned} \tag{B14}$$

$$\frac{d}{dt}\langle x_2^2(t)\rangle = -2k_R M_R^s \langle x_1(t)x_2(t)\rangle - 2(\beta_R + k_R S^s)\langle x_2^2(t)\rangle - 2\alpha_R, \tag{B15}$$

$$\frac{d}{dt}\langle x_3^2(t)\rangle = -2k_T M_T^s \langle x_1(t)x_3(t)\rangle - 2(\beta_T + k_T S^s)\langle x_3^2(t)\rangle - 2\alpha_T, \tag{B16}$$

$$\begin{aligned}\frac{d}{dt}\langle x_1(t)x_2(t)\rangle =& -k_R M_R^s \langle x_1^2(t)\rangle - (\beta_s + \beta_R + k_R S^s + k_R M_R^s + k_T M_T^s)\langle x_1(t)x_2(t)\rangle\\ &-k_R S^s \langle x_2^2(t)\rangle - k_T S^s \langle x_2(t)x_3(t)\rangle - k_R M_R^s S^s,\end{aligned} \tag{B17}$$

$$\begin{aligned}\frac{d}{dt}\langle x_1(t)x_3(t)\rangle =& -k_T M_T^s \langle x_1^2(t)\rangle - (\beta_s + \beta_T + k_T S^s + k_R M_R^s + k_T M_T^s)\langle x_1(t)x_3(t)\rangle\\ &-k_R S^s \langle x_2(t)x_3(t)\rangle - k_T S^s \langle x_3^2(t)\rangle - k_T M_T^s S^s,\end{aligned} \tag{B18}$$

$$\begin{aligned}\frac{d}{dt}\langle x_2(t)x_3(t)\rangle =& -k_T M_T^s \langle x_1(t)x_2(t)\rangle - k_R M_R^s \langle x_1(t)x_3(t)\rangle\\ &-(\beta_R + \beta_T + k_R S^s + k_T S^s)\langle x_2(t)x_3(t)\rangle,\end{aligned} \tag{B19}$$

At the steady state, from Eqs. (B11)–(B13), the stationary mean molecules number of mRNA and sRNA are given by

$$\langle M_R\rangle_{st} = M_R^s, \quad \langle M_T\rangle_{st} = M_T^s, \quad \langle S\rangle_{st} = S^s. \tag{B20}$$

From Eqs. (B15) and (B16), we obtain

$$\langle x_1(t)x_2(t)\rangle_{st} = -\frac{\alpha_R}{k_R M_R^s} - \frac{\alpha_R}{k_R (M_R^s)^2}\langle x_2^2(t)\rangle_{st}, \tag{B21}$$

$$\langle x_1(t)x_3(t)\rangle_{st} = -\frac{\alpha_T}{k_T M_T^s} - \frac{\alpha_T}{k_T (M_T^s)^2}\langle x_3^2(t)\rangle_{st}, \tag{B22}$$

Substituting Eqs. (B21) and (B22) into Eqs. (B14), Eqs. (B17)–(B19) at the steady state, then the variance σ_{ii} of RNA molecules and the covariance σ_{ij} of the sRNA and its target mRNAs obeys following matrix equation

$$\begin{pmatrix} \alpha_s / S^s & -\alpha_R S^s/(M_R^s)^2 & -\alpha_T S^s/(M_T^s)^2 & 0\\ k_R M_R^s & A_R & 0 & k_T S^s\\ k_T M_T^s & 0 & A_T & k_R S^s\\ 0 & B_R & B_T & -C \end{pmatrix} \begin{pmatrix} \sigma_{SS}\\ \sigma_{RR}\\ \sigma_{TT}\\ \sigma_{RT} \end{pmatrix} + \begin{pmatrix} \alpha_s - CS^s\\ M_R^s A_R\\ M_T^s A_T\\ M_R^s B_R + M_T^s B_T \end{pmatrix} = 0, \tag{B23}$$

where

$$A_R = k_R S^s - \left(\frac{\alpha_s}{S^s} + \frac{\alpha_R}{M_R^s}\right)\frac{\alpha_R}{k_R (M_R^s)^2}, \quad A_T = k_T S^s - \left(\frac{\alpha_s}{S^s} + \frac{\alpha_T}{M_T^s}\right)\frac{\alpha_T}{k_T (M_T^s)^2}, \tag{B24}$$

$$B_R = \frac{k_T M_T^s \alpha_R}{k_R (M_R^s)^2}, \quad B_T = \frac{k_R M_R^s \alpha_T}{k_T (M_T^s)^2}, \quad C = \frac{\alpha_R}{M_R^s} + \frac{\alpha_T}{M_T^s}. \tag{B25}$$

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