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Molecular-Memory-Induced Counter-Intuitive Noise Attenuator in Protein Polymerization

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Abstract: Gene expression comprises many asymmetric and complex processes. Transcriptional details revealed by the whole genome indicate that genes resort to transcriptional bursting and accumulate molecular memory. However, it is still unclear how the interplay of transcriptional bursting and memory regulates robustness and expression noise. Here, we consider a model of multiple coupled processes of protein polymerization to focus on decoding the effect of molecular memory. Using non-Markovian transformation technology, we first define the memory index to measure the correlation window of expression to decipher the mechanism of regulation. The results indicate that memory from synthesis can amplify expression noise, while memory originating from polymerization can reduce the lower bound of the noise of gene products; that is, the memory from different sources plays distinct regulatory roles to induce non-symmetry. Moreover, it is counterintuitive that the dual regulation from memory and bursting expression can directly suppress system noise, violating the principle that transcriptional bursting enhances noise. Our results not only provide a theoretical framework for investigating the function of memory but also imply that expression noise is not part of a half-power relationship with, nor mediated by, memory.

Keywords: molecular memory; non-Markov modeling; feedback; bursting; expression noise

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1. Introduction

Transcription and protein synthesis are the two core components of gene expression [1,2]. Amazingly, by undergoing the series of biochemical reactions verified in the whole genome, including nucleus retention, chromatin state switching, positive or negative feedback, transcriptional bursting, and protein polymerization, the cell can achieve its biological function and maintain stability [3,4]. One must always simplify or omit these intermediate details to construct a Markov or symmetric model that demonstrates the expression process according to the assumption of Markovian, which thus does not reflect the actual situation whereby every biochemical process essentially involves multiple-step reactions [5,6]. Different from the classical Markovian process, the multi-step biochemical process may be the source of molecular memory leading to non-Markov kinetic problems or asymmetric stochastic processes [7,8]. Therefore, it is important to decipher the mechanism of expression stability to remeasure expression noise, as well as assess the effect of memory on noise and the regulation of the interplay of transcriptional bursting and memory on the asymmetric process [9–12].

Molecular memory may originate from a distinct biochemical process [13–15]. One such process is nuclear retention, which implies that the transcription product pauses for a short time in the nucleus and expires at a random time [16,17]. The nucleus retention rate

(p_r) often reflects a relatively large interval, that is, $p_r \in (5\%, 95\%)$, implying that protein synthesis in the cytoplasm can be illustrated as $K_0 = K_E(1 - p_r)$; K_E denotes the nuclear pore escape rate of gene transcription [18]. In general, the nuclear pore escape rate is always much faster than the nuclear retention rate [18–20]; that is, we can directly omit the retention process. However, the presence of nuclear retention causes the process from transcription initiation to translation to be essentially a multistep reaction process, not a one-step biochemical reaction, an assumption that we often adopt. Furthermore, the functional proteins in the nucleus are always present in the form of a multimer, and they must achieve polymerization in order to obtain a dimer protein or polymer protein [5,11,21,22]. It is known that protein polymerization often obeys the principle of the Michaelis–Menten equation, and the most striking feature of this equation is that there is an intermediate instantaneous product that can decompose into a reaction substrate and biomarker protein [23]; namely, protein polymerization also entails the multistep biochemical reaction, which can cause protein polymerization to be an asymmetric process. In fact, non-Markovian expression can be described by its memory character or memory index to distinguish it from the classical Langevin jump process. Therefore, we can define different memory indexes with distinct time windows to simulate transcription and protein polymerization in order to calculate expression noise, defined as the variance divided by the square of the mean, to then assess expression stability [13,18]. Of note, this is the first tentative study to regulate expression stability from the perspective of time, rather than using the traditional method from the perspective of strength or space.

Generally, the non-Markovian process can be analyzed through the two methods of protein synthesis and regulation. We can view it as a generalized jump process and equivalently transform it into a random walk with a memory window (the autocorrelation window). In this way, we can directly analyze the renewal process, which is a classical result of the stochastic process, and this is an idea related to queuing theory with arbitrary service time distribution [7,8,14,15]. Here, it is difficult to determine the service time distribution due to the contradiction between the non-Markovian process and the assumption of independence in queuing theory. Alternatively, we can also resort to the framework of the equivalent topological approximation to obtain the corresponding Markovian process coupled with some specific parameters, including the memory index, fluctuation strength, stimuli strength, upstream signal mediation, and so on [21,24,25]. According to this equivalent approximation, we can characterize the non-Markovian process via a generalized chemical master equation or Fokker–Planck equation by regulating a specific parameter, for example, the memory index, to cover different time scales. Of course, this is the core mechanism yielding the memory index or the function of the effective switching rate [13,15,18], and this framework can be applied to a larger range because of its operability and the ubiquitous Brownian motion.

Here, we investigate a typical post-regulation motif with a feedback loop including nucleus retention and protein polymerization. The emergence of nucleus retention and protein polymerization can directly cause expression to be a non-Markovian process. We employ the framework of the equivalent topological approximation to define the effective switching rate function and thus illustrate the non-Markovian process [13,15,18]. Notably, we use non-exponential waiting time distribution (Gamma distribution) to model the dwell time of nucleus retention and protein polymerization by omitting the detailed pilot process due to the difference in time scales, enabling us to obtain a computational model for assessing the effect of memory on the expression mean and noise with promoter feedback [8,13,15,18,26]. The results indicate that molecular memory can significantly affect the expression mean and noise of protein synthesis during gene transcription. Different molecular memories then lead to distinct degrees of stabilizing noise intensity, inducing the peak value of transcription protein drift to produce stochastic focus; the existence of molecular memory can directly change the biological function of the feedback loop, i.e., the interplay between the memory and bursting expression can suppress the expression noise and attenuate the lower bound of noise, as opposed to the classical finding report

that the larger the burst size is, the higher the expression noise will be. Specifically, the different sources of memory can play distinct roles in the post-transcription regulation; that is, memory originating from synthesis can boost direct expression noise, whereas memory from polymerization could suppress the noise, implying that memory originating from different sources may possess completely different sets of biological functions.

In summary, deciphering the regulatory effects of molecular memory on expression stability is key to understanding the biological function of the expression time processes and their correlation, as well as the non-symmetry of expression. We consider the motif of protein polymerization with bursting transcription in a non-Markovian environment from the points of view of nucleus retention or polymerization. It is reassuring that deciphering the regulation of memory may represent a milestone in gene expression, with the finding that it cannot operate in the experiment from the viewpoint of time.

2. Method

2.1. Model

The complex processes of gene transcription are becoming increasingly clear as the existing processes for studying gene transcription mature [3,4]. Here, we consider nucleus export and protein polymerization with a positive feedback loop, finding that the polymeric protein can positively regulate transcription. We focus on the regulation mechanism related to how memory originating from multiple coupled biochemical reactions in the above two complex sectors affects expression stability in two distinct cases, that is, memory from nucleus retention and from protein polymerization, respectively. Based on these premises, we have constructed a schematic diagram of the gene transcription model, shown in Figure 1. It is composed of four processes, that is, Process 1—In the ON state, promoter transcription synthesizes proteins; Process 2—proteins form polymers; Process 3—polymerized proteins form proteins under the action of the promoter (reverse reaction of process 2) and cause feedback to the promoter; Process 4—polymerized proteins are degraded away. Notably, the four motifs can directly form an asymmetric cascade whereby the genetic information transmits from transcription to protein synthesis. Considering the effect of feedback, we also want to determine whether this motif network is symmetric, that is, whether the expression details can be omitted or are illustrated via a Markovian process.

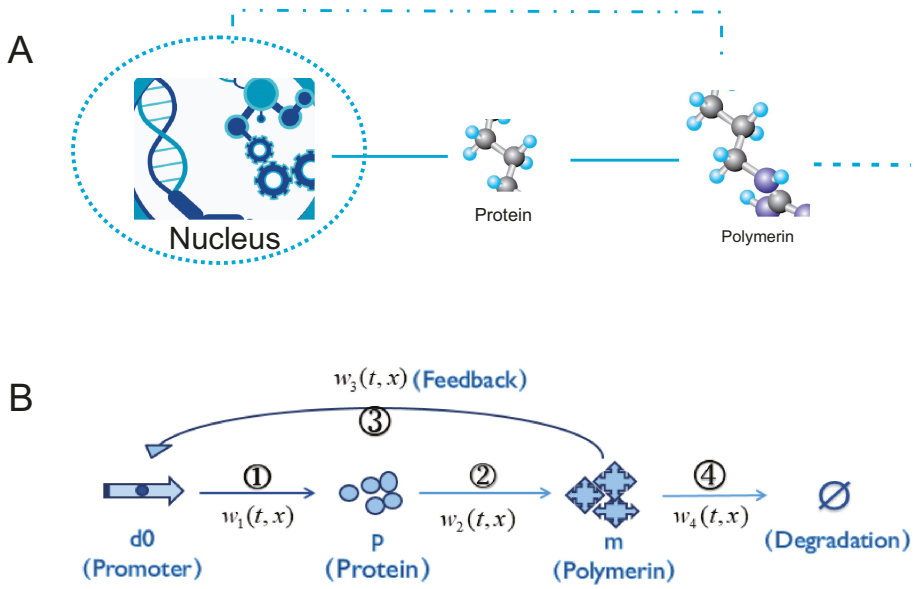

Figure 1. Schematic diagram of gene transcription model. (**A**) The representative reaction network; (**B**) The biochemical reaction denoted by numbers. The different colors symbols imply the distinct reaction substrates.

The four-step network and the corresponding stochastic biochemical reaction system can be described as $R_i(1 \le i \le 4)$. The simplified positive feedback self-regulatory model of single gene transcription in the ON state can be illustrated as follows:

$$R_1 : d_0 \overset{W_1(t,x)}{\rightarrow} d_0 + Bp, R_2 : p \overset{W_2(t,x)}{\rightarrow} m,$$
$$R_3 : m + d_0 \overset{W_3(t,x)}{\rightarrow} d_0 + p, R_4 : m \overset{W_4(t,x)}{\rightarrow} \phi,$$

where $W_1(t,x), W_2(t,x), W_3(t,x)$ and $W_4(t,x)$ represent the probability density functions of the waiting time distributions for the transcription of the promoter to generate proteins, the synthesis of polymers from proteins, the feedback of polymerized proteins to the promoter, and the degradation of polymerized proteins, respectively. d_0 is promotion, B represents transcription burst with continuous distribution ($prob\{B = i\} = \alpha_i$, $(\alpha_i > 0, i = 1, 2, 3 \ldots)$), and $\langle B \rangle$ is the mean burst size. Note that if $\langle B \rangle = 0$, then the promoter is in the OFF state, while $\langle B \rangle > 0$ means that the promoter is in the ON state. p and m represent proteins and protein polymers, respectively. Without loss of generality, we consider the transient processes of nucleus retention and protein polymerization, that is, the residual time of state-switching at every state obeys the Gamma distribution within the memory window

$$W_1(t,x) = \left[\Gamma(l_p)\right]^{-1} t^{l_p - 1} (K_0)^{l_p} e^{-K_0 t}, W_2(t,x) = \left[\Gamma(l_m)\right]^{-1} t^{l_m - 1} \left(K_p x_1\right)^{l_m} e^{-K_p x_1 t},$$

All other biochemical reactions are one-step processes, and the dwell time between states takes the exponential distribution $W_3(t,x) = K_p x_1 e^{-K_p x_1 t}$, $W_4(t,x) = K_m x_2 e^{-K_m x_2 t}$ and $W_5(t,x) = d x_2 e^{-d x_2 t}$. Here, K_0 is the average transcription rate, K_p is the average synthesis rate of polymerized proteins, K_m is the feedback strength of polymerized proteins to promoters, d is the average degradation rate of polymerized proteins, and l_p and l_m are the memory index of the reaction process. Obviously, if $l_p(l_m)$ is equal to one, the waiting time distribution $W_i(t,x)$ degenerates into the exponent distribution, and the above model can change into the classical Markovian expression process due to its lack of memory, implying our model can account for the reported results [13,15,18].

2.2. Equivalent Transformation of Non-Markov into Markov Systems

Molecular memory during biochemical reactions leads to non-Markovian kinetic problems for stochastic biochemical reaction systems, and the original Markov theoretical solutions will no longer be applicable.

Lemma 1. *Define the effective jump rate $K_i(x)$ for each reaction process as follows:*

$$K_i(x) = \frac{\int_0^{+\infty} W_i(t,x) \left[\prod_{j \ne i} \int_t^{\infty} W_j(t';x) dt'\right] dt}{\int_0^{+\infty} \left[\prod_{j=1}^{4} \int_t^{\infty} W_j(t';x) dt'\right] dt}, (1 \le i \le 4).$$

As a result, the non-Markovian stochastic biochemical reaction system is converted into a Markovian system.

Proof. The general proof of this lemma is offered using our model. For each memorized biochemical reaction process $R_i(1 \le i \le 4)$, we suppose $\widetilde{M}_i(t;x)$ is the Laplace transform of the memory function $M_i(t;x)$. $p(x;t)$ is the state probability distribution of protein polymers m at moment t of the stochastic biochemical reaction system. $\widetilde{p}(x;t)$ is the Laplace transform of $p(x;t)$. $\widetilde{\varphi}_i(s;x)$ is the Laplace transform of $\varphi_i(t;x)$. The following equation then holds:

$$\widetilde{M}_i(s;x) = \frac{s\widetilde{\varphi}_i(s;x)}{\left[1 - \sum_{i=1}^{4} \widetilde{\varphi}_i(s;x)\right]},$$

Here, $\varphi_i(t;x) = W_i(t;x)\prod_{k\neq i}\left[1-\int_0^t W_k(t';x)dt'\right], (1 \le i \le 4)$. From this, we can infer that the chemical master equation in the sense of the Laplace transform can be expressed in the following form:

$$\begin{aligned} s\widetilde{p}(x;s) - p(0;s) = &\left(\sum_{i=0}^{x_1} \alpha_i {E_1}^{-i} - I\right)\left[\widetilde{M_1}(s;x)\widetilde{p}(x;s)\right] + \left(E_1{E_2}^{-1} - I\right)\left[\widetilde{M_2}(s;x)\widetilde{p}(x;s)\right] + \\ &\left({E_1}^{-1}E_3 - I\right)\left[\widetilde{M_3}(s;x)\widetilde{p}(x;s)\right] + (E_4 - I)\left[\widetilde{M_4}(s;x)\widetilde{p}(x;s)\right] = 0. \end{aligned} \tag{1}$$

Note that we find that there is always a limit to the Laplace variation of the memory function, as $s \to 0$, and we denote this limit function as $K_i(x)$. Then, $K_i(x)$ can be expressed explicitly by use of the previously given waiting time distribution $W_i(t,x), (1 \le i \le 4)$, as follows:

$$K_i(x) = \frac{\int_0^{+\infty} W_i(t,x)\left[\prod_{j\neq i}\int_t^{\infty} W_j(t';x)dt'\right]dt}{\int_0^{+\infty}\left[\prod_{j=1}^{4}\int_t^{\infty} W_j(t';x)dt'\right]dt}, (1 \le i \le 4)$$

$K_i(x)$ is the effective jump rate for each biochemical reaction $R_i (1 \le i \le 4)$. The non-Markovian stochastic biochemical reaction system is converted into a Markov stochastic biochemical reaction system: $\begin{matrix} d_0 \overset{K_1(x)}{\to} d_0 + Bp, p \overset{K_2(x)}{\to} m, \\ m + d_0 \overset{K_3(x)}{\to} d_0 + p, m \overset{K_4(x)}{\to} \phi \end{matrix}$. The corresponding chemical master equation for this martensitic reaction system is as follows ($p(x)$ is the dynamic density probability function corresponding to the steady-state probability density function $p(x,t)$):

$$\begin{aligned} &(\sum_{i=0}^{x_1} \alpha_i {E_1}^{-i} - I)[K_1(s;x)p(x)] + (E_1{E_2}^{-1} - I)[K_2(x)p(x)] + \\ &({E_1}^{-1}E_3 - I)[K_3(x)p(x)] + (E_4 - I)[K_4(x)p(x)] = 0. \end{aligned} \tag{2}$$

At this point, we find that the forms of (1) and (2) are the same. That is, the two reaction systems have the same chemical master equation when in a steady state, which means that the two steady-state behaviors are identical. The proof is thus complete. □

3. Theoretical Analysis

3.1. Small Noise Approximation

First, the chemical master equation of the corresponding Markov reaction network system constructed by the stochastic biochemical reaction system is

$$\begin{aligned} \tfrac{\partial p(x,t)}{\partial t} &= (\sum_{i=0}^{x_1} \alpha_i {E_i}^{-i} - I)[K_1(x)p(x,t)] + (E_1{E_2}^{-1} - I)[K_2(x)p(x,t)] \\ &\quad + ({E_1}^{-1}E_3 - I)[K_3(x)p(x,t)] + (E_4 - I)[K_4(x)p(x,t)]. \end{aligned}$$

Second, let x_1 denote the concentration of protein p synthesized via gene transcription, x_2 denote the concentration of protein m synthesized via gene transcription, $x_1 = \lim_{\substack{p\to\infty \\ \Omega\to\infty}} p/\Omega$, $x_2 = \lim_{\substack{m\to\infty \\ \Omega\to\infty}} m/\Omega$, and Ω be the volume of the biochemical reaction system. Then, the rate equation corresponding to the Markov reaction network above can be expressed as

$$\frac{dx}{dt} = SK(x), \tag{3}$$

where $x = (x_1, x_2)^T$ is a column vector. $S = (s_{ij})_{2\times 4} = \begin{pmatrix} B & -1 & 1 & 0 \\ 0 & 1 & -1 & -1 \end{pmatrix}$ is a matrix, and $K(x) = (K_1(x)K_2(x), K_3(x), K_4(x))^T$ is the column vector of the effective jump rate of the reaction process. The steady-state or equilibrium state of the system described by

Equation (3) can be expressed as $x^s = ({x_1}^s, {x_2}^s)^T$. This is determined by solving a system of algebraic equations $SK(x^s) = 0$, that is,

$$\begin{gathered}\langle B\rangle K_1(x^s) + k_3(x^s) = k_2(x^s),\\ k_2(x^s) = k_3(x^s) + k_4(x^s).\end{gathered}$$

Finally, the Fokker–Planck equation for determining the steady state of the ensuing biochemical system takes a solution of the following form:

$$\prod(z) = \frac{1}{\sqrt{(2\pi)^3 \det(\Sigma_s)}} \exp(-\frac{1}{2} z^T {\Sigma_s}^{-1} z).$$

Here, the matrix $\sum_s = \left(\left\langle (X - X^s)^T (X - X^s) \right\rangle\right) \equiv (\sigma_{ij})$ (covariance matrix) is obtained by solving the following Lyapunov matrix equation:

$$A_s \Sigma_s + \Sigma_s {A_s}^T + D_s = 0. \tag{4}$$

Note that the diagonal elements of the matrix Σ_s reflect the variances in the state variables of the stochastic biochemical system, and the average concentrations of the reacting substances are approximated by $\langle X\rangle = x^s$. The result Σ_s obtained from Equation (3) is an extension of the linear noise approximation. Here,

$$A = (A_{ij}) = \begin{pmatrix} \langle B\rangle \frac{\partial K_1}{\partial x_1} - \frac{\partial K_2}{\partial x_1} + \frac{\partial K_3}{\partial x_1} & \langle B\rangle \frac{\partial K_1}{\partial x_2} - \frac{\partial K_2}{\partial x_2} + \frac{\partial K_3}{\partial x_2} \\ \frac{\partial K_2}{\partial x_1} - \frac{\partial K_3}{\partial x_1} - \frac{\partial K_4}{\partial x_1} & \frac{\partial K_2}{\partial x_2} - \frac{\partial K_3}{\partial x_2} - \frac{\partial K_4}{\partial x_2} \end{pmatrix},$$

$$D = (D_{ij}) = \begin{pmatrix} \langle B\rangle^2 K_1 + K_2 + K_3 & -K_2 - K_3 \\ -K_2 - K_3 & K_2 + K_3 + K_4 \end{pmatrix}.$$

3.2. Stable States of Synthesized Proteins Induced by Molecular Memories

Theorem 1. *If the transcription has memory and other processes have no memory ($l_p \neq 1$ and $l_m = 1$), then the homeostasis of the synthesized protein can be expressed as*

$$\begin{aligned} {x_1}^s = \langle p\rangle &= \tfrac{K_0}{2K_p}\left[\left(\tfrac{2\langle B\rangle(K_m+d)}{d} + 1\right)^{\frac{1}{l_p}} - 1\right],\\ {x_2}^s = \langle m\rangle &= \tfrac{K_0}{2(K_m+d)}\left[\left(\tfrac{2\langle B\rangle(K_m+d)}{d} + 1\right)^{\frac{1}{l_p}} - 1\right]. \end{aligned} \tag{5}$$

Otherwise, if Process 2 has memory ($l_m \neq 1$ and $l_p = 1$), then the steady states of products can be expressed as

$${x_1}^s = \langle p\rangle = \frac{K_0(d + \langle B\rangle d + \langle B\rangle K_m)}{dK_p\left[\left(\frac{(1+\langle B\rangle)d + \langle B\rangle K_m}{\langle B\rangle\langle K_m + d\rangle} + 1\right)^{\frac{1}{l_m}} - 1\right]}, {x_2}^s = \langle m\rangle = \frac{\langle B\rangle k_0}{d}.$$

Proof. According to the rate equation (Equation (3)),

$$\frac{dx}{dt} = SK(x),$$

$x = (\langle p\rangle, \langle m\rangle) = (x_1, x_2)^T$ is a column vector. $S = (s_{ij})_{2\times 4} = \begin{pmatrix} B & -1 & 1 & 0 \\ 0 & 1 & -1 & -1 \end{pmatrix}$ is the stoichiometric matrix. $K(x) = (K_1(x), K_2(x), K_3(x), K_4(x))^T$ is a column vector of effective jump rates during biochemical reactions.

(1) Process 1 has a memory and the other processes have no memory ($l_p \neq 1$ and $l_m = 1$). The effective transfer rate for each process is as follows (for more details, refer to Supplementary Materials):

$$K_1(x) = \frac{(K_p x_1 + K_m x_2 + dx_2)(K_0)^{l_p}}{(K_0 + K_p x_1 + K_m x_2 + dx_2)^{l_p} - (K_0)^{l_p}}, K_2(x) = K_p x_1, K_3(x) = K_m x_2, K_4(x) = dx_2. \tag{6}$$

The steady state of the system is denoted by x^s, and is given by Equation (3), satisfying

$$\begin{cases} \langle B \rangle K_1 + K_3 = K_2, \\ K_3 + K_4 = K_2 \end{cases} \tag{7}$$

which can be simplified to the equation

$$\langle B \rangle K_1 = K_4. \tag{8}$$

By substituting Equation (6) into Equation (7), we derive $(K_m + d)x_2 = K_p x_1$. Combining with Equation (8) yields $\frac{\langle B \rangle \left(K_p x_1 + K_m x_2 + dx_2\right)(K_0)^{l_p}}{\left(K_0 + K_p x_1 + K_m x_2 + dx_2\right)^{l_p} - (K_0)^{l_p}} = dx_2$.

Then, we can obtain the steady solution of two products:

$$\begin{aligned} {x_1}^s = \langle p \rangle &= \tfrac{K_0}{2K_p}\left[\left(\tfrac{2\langle B \rangle (K_m + d)}{d} + 1\right)^{\frac{1}{l_p}} - 1\right], \\ {x_2}^s = \langle m \rangle &= \tfrac{K_0}{2(K_m + d)}\left[\left(\tfrac{2\langle B \rangle (K_m + d)}{d} + 1\right)^{\frac{1}{l_p}} - 1\right]. \end{aligned}$$

(2) Here, if Process 2 only has memory ($l_m \neq 1$ and $l_p = 1$), then the effective transfer rate is as follows (for more details, refer to Supplementary Materials):

$$K_1(x) = K_0, K_2(x) = \frac{(K_0 + K_m x_2 + dx_2)(K_p x_1)^{l_m}}{(K_0 + K_p x_1 + K_m x_2 + dx_2)^{l_m} - (K_p x_1)^{l_m}}, K_3(x) = k_m x_2, K_4(x) = dx_2.$$

The steady state of the system can also be denoted by x^s, satisfying

$$\begin{cases} \langle B \rangle K_1 + K_3 = K_2, \\ K_3 + K_4 = K_2 \end{cases}$$

We can simplify the above equations as $(K_m + d)x_2 = \frac{(K_0 + K_m x_2 + dx_2)\left(K_p x_1\right)^{l_m}}{\left(K_0 + K_p x_1 + K_m x_2 + dx_2\right)^{l_m} - \left(K_p x_1\right)^{l_m}}$, yielding

$${x_1}^s = \langle p \rangle = \frac{K_0(d + \langle B \rangle d + \langle B \rangle K_m)}{dK_p\left[\left(\frac{(1 + \langle B \rangle)d + \langle B \rangle K_m}{\langle B \rangle \langle K_m + d \rangle} + 1\right)^{\frac{1}{l_m}} - 1\right]}, {x_2}^s = \langle m \rangle = \frac{\langle B \rangle k_0}{d}.$$

The proof is thus complete. □

3.3. Expression Noise of Synthesized Proteins Induced by Molecular Memories

Theorem 2. *If Process 1 has a memory and other processes have no memory ($l_p \neq 1$ and $l_m = 1$), then the noise of expression products can be expressed as*

$$\eta_p = \frac{\sigma_{11}}{\langle X_1 \rangle^2} = \frac{2{K_p}^2\left(K_2 + K_3 + BK_4 + 2\frac{\partial K_1}{\partial x_2}B\sigma_{12} + 2K_m\sigma_{12}\right)}{{K_0}^2\left(-1 + \left(1 + \frac{2B(d + K_m)}{d}\right)^{\frac{1}{l_p}}\right)^2\left(-\frac{\partial K_1}{\partial x_1}B + K_p\right)}, \tag{9}$$

$$\eta_m = \frac{\sigma_{22}}{\langle X_2 \rangle^2} = \frac{4(d+K_m)\left(K_2+K_p\sigma_{12}\right)}{{K_0}^2\left(-1+\left(1+\frac{2B(d+K_m)}{d}\right)^{\frac{1}{l_p}}\right)^2}.$$

Otherwise, if Process 2 has memory ($l_m \neq 1$ and $l_p = 1$), the two noises are

$$\eta_p = \frac{\sigma_{11}}{\langle X_1 \rangle^2} = \frac{d\left(-1+\left(\frac{d+2Bd+2BK_m}{Bd+BK_m}\right)^{\frac{1}{l_m}}\right)^2 {K_p}^2\left(B^2dK_0+BK_0(d+2K_m)+2d\left(-\frac{\partial K_2}{\partial x_2}+K_m\right)\sigma_{12}\right)}{2\frac{\partial K_2}{\partial x_1}{K_0}^2(d+Bd+BK_m)^2},$$

$$\eta_m = \frac{\sigma_{22}}{\langle X_2 \rangle^2} = \frac{B^2{K_0}^2\left(BK_0(d+K_m)+\frac{\partial K_2}{\partial x_1}d\sigma_{12}\right)}{d^3\left(-\frac{\partial K_2}{\partial x_2}+d+K_m\right)}.$$

Proof. Theorem 1 provides the steady solution with reference to the rate equation. If Process 1 has memory ($l_p \neq 1$ and $l_m = 1$), we derive the following (for more details, refer to Supplementary Materials):

$${x_1}^s = \frac{K_0}{2K_p}[(\frac{2\langle B\rangle(K_m+d)}{d}+1)^{\frac{1}{l_m}}-1], {x_2}^s = \frac{K_0}{2(K_m+d)}[(\frac{2\langle B\rangle(K_m+d)}{d}+1)^{\frac{1}{l_m}}-1].$$

In this stationary state, we can calculate the Jacobian matrix, as follows:

$$A = (A_{ij}) = \begin{pmatrix} \langle B\rangle\frac{\partial K_1(x)}{\partial x_1}-K_p & \langle B\rangle\frac{\partial K_1(x)}{\partial x_2}+K_m \\ K_p & -K_m-d \end{pmatrix},$$

$$\frac{\partial K_1(x)}{\partial x_1} = -\frac{{K_0}^{l_p}K_p}{{k_0}^{l_p}-(\gamma)^{l_p}} - \frac{{K_0}^{l_p}K_p l_1(dx_2+K_mx_2+K_px_1)(\gamma)^{l_p-1}}{({K_0}^{l_p}-(\gamma)^{l_p})^2},$$
$$\frac{\partial K_1(x)}{\partial x_2} = -\frac{{K_0}^{l_p}(d+K_m)}{{K_0}^{l_p}-(\gamma)^{l_p}} - \frac{{K_0}^{l_p}l_1(d+K_m)(dx_2+K_mx_2+K_px_1)(\gamma)^{l_p-1}}{({K_0}^{l_p}-(\gamma)^{l_p})^2}.$$

where $\gamma = K_0+dx_2+K_mx_2+K_px_1$, $D = (D_{ij}) = \begin{pmatrix} \langle B\rangle K_4(x)+K_2(x)+K_3(x) & -K_2(x)-K_3(x) \\ -K_2(x)-K_3(x) & 2K_2(x) \end{pmatrix}$.

Here,

$$K_2 = K_p{x_1}^s = \tfrac{K_0}{2}[(\tfrac{2\langle B\rangle(K_m+d)}{d})^{\frac{1}{l_p}}-1]$$
$$K_3 = K_m{x_2}^s = \tfrac{K_0K_m}{2(K_m+d)}[(\tfrac{2\langle B\rangle(K_m+d)}{d})^{\frac{1}{l_p}}-1]$$
$$K_4 = d{x_2}^s = \tfrac{K_0d}{2(K_m+d)}[(\tfrac{2\langle B\rangle(K_m+d)}{d})^{\frac{1}{l_p}}-1].$$

According to Equation (4), we have

$$\begin{cases} 2(\langle B\rangle\frac{\partial K_1}{\partial x_1}-K_p)\sigma_{11}+2(\langle B\rangle\frac{\partial K_1}{\partial x_2}+k_m)\sigma_{12} = -(\langle B\rangle K_4+K_2+K_3), \\ (\langle B\rangle\frac{\partial K_1}{\partial x_1}-K_p)\sigma_{12}+(\langle B\rangle\frac{\partial K_1}{\partial x_2}+K_m)\sigma_{22}+k_p\sigma_{11}-(K_m+d)\sigma_{12} = K_2+K_3, \\ 2K_p\sigma_{12}-2(K_m+d)\sigma_{22} = -2K_2 \end{cases} \quad (10)$$

and can obtain the following relations:

$$\sigma_{22} = \frac{K_p}{K_m+d}\sigma_{12}+\frac{K_2}{K_m+d}, \sigma_{11} = \frac{-(\langle B\rangle\frac{\partial K_1}{\partial x_2}+K_m)}{(\langle B\rangle\frac{\partial K_1}{\partial x_1}-K_p)}\sigma_{12}-\frac{(\langle B\rangle K_4+K_2+K_3)}{2(\langle B\rangle\frac{\partial K_1}{\partial x_1}-K_p)}. \quad (11)$$

Combining Equation (10) with (11), we derive

$$\sigma_{12} = \frac{2(\langle B\rangle \frac{\partial K_1}{\partial x_1} - K_p)(K_m + d)(K_2 + K_3) - [K_p(K_m + d)(\langle B\rangle K_4 + K_2 + K_3) - 2K_2(\langle B\rangle \frac{\partial K_1}{\partial x_1} - K_p)(\langle B\rangle \frac{\partial K_1}{\partial x_2} + K_m)]}{(\langle B\rangle \frac{\partial K_1}{\partial x_1} - K_p - K_m - d)(\langle B\rangle \frac{\partial K_1}{\partial x_1} K_m + \langle B\rangle \frac{\partial K_1}{\partial x_1} d - dK_p + \langle B\rangle \frac{\partial K_1}{\partial x_2} K_p)}.$$

We can then derive the noise of products as follows:

$$\eta_p = \frac{\sigma_{11}}{\langle X_1\rangle^2} = \frac{2{K_p}^2\left(K_2 + K_3 + BK_4 + 2\frac{\partial K_1}{\partial x_2} B\sigma_{12} + 2K_m\sigma_{12}\right)}{{K_0}^2\left(-1 + \left(1 + \frac{2B(d+K_m)}{d}\right)^{\frac{1}{l_p}}\right)^2\left(-\frac{\partial K_1}{\partial x_1} B + K_p\right)},$$

$$\eta_{\mathrm{m}} = \frac{\sigma_{22}}{\langle X_2\rangle^2} = \frac{4(d + K_m)\left(K_2 + K_p\sigma_{12}\right)}{{K_0}^2\left(-1 + \left(1 + \frac{2B(d+K_m)}{d}\right)^{\frac{1}{l_p}}\right)^2}.$$

Similarly, if Process 2 has memory ($l_m \neq 1$ and $l_p = 1$), we can also derive the noise of expression products (for more details, refer to Supplementary Materials), that is,

$$\eta_p = \frac{\sigma_{11}}{\langle X_1\rangle^2} = \frac{d\left(-1 + \left(\frac{d+2Bd+2BK_m}{Bd+BK_m}\right)^{\frac{1}{l_m}}\right)^2 {K_p}^2\left(B^2dK_0 + BK_0(d + 2K_m) + 2d\left(-\frac{\partial K_2}{\partial x_2} + K_m\right)\sigma_{12}\right)}{2\frac{\partial K_2}{\partial x_1}{K_0}^2(d + Bd + BK_m)^2},$$

$$\eta_{\mathrm{m}} = \frac{\sigma_{22}}{\langle X_2\rangle^2} = \frac{B^2{K_0}^2\left(BK_0(d + K_m) + \frac{\partial K_2}{\partial x_1} d\sigma_{12}\right)}{d^3\left(-\frac{\partial K_2}{\partial x_2} + d + K_m\right)}.$$

The proof is thus complete. □

4. Numerical Results

4.1. Transcription Memory Suppresses the Expression Mean While Amplifying Noise ($l_p \neq 1$ and $l_m = 1$)

Although Theorems 1 and 2 give the analytical solutions of the steady mean and expression noise, the nonlinearity of these solutions obscures the relationship between the memory and expression mean and the noise of protein polymers. In order to understand the regulation of memory, we simulate the mean and noise of protein polymers whose analytical formations are presented in Equations (5) and (9), respectively. Firstly, Figure 2a illustrates that the steady mean of protein polymers is a monotonically decreasing function of l_p, meaning the memory index is larger, and the mean is smaller. Considering the presence of the nucleus retention rate, the dwell time in the cell nucleus is stochastic but proportional to the memory index. This means that nuclear retention naturally reduces the amount of protein polymers formed by transcription. Conversely, we can conclude that the smaller the nuclear retention is, the higher the expression efficiency of polymerized proteins will be. Considering that the proportion of mature RNA translocated into the cytoplasm is about 7 to 3, we set the nuclear retention rate as either $p_r = 0.2$ or $p_r = 0.25$ [16]. Inevitably, the positive feedback amplifies the expression noise. With the increase in the memory index, we can obtain two factors to increase the expression noise, that is, the mean reduction induced by memory and the noise increase modulated by the positive feedback loop (Figure 2b).

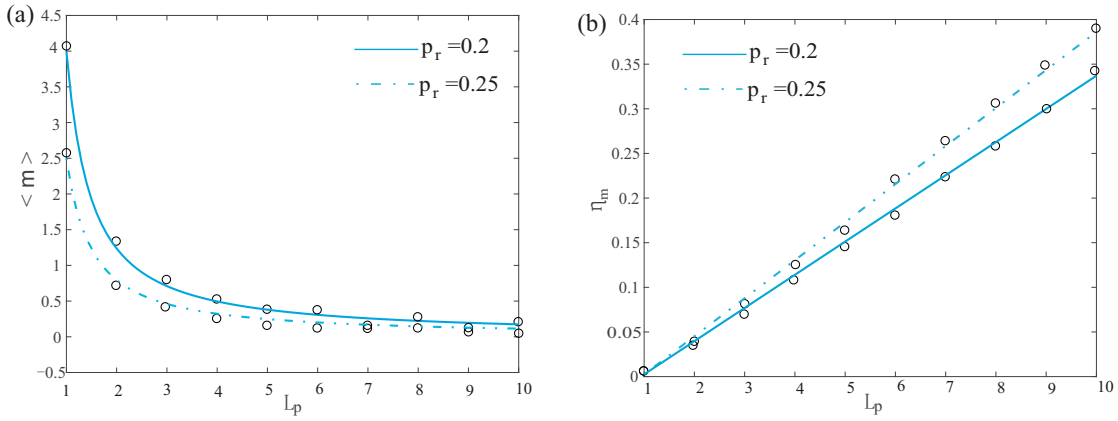

Figure 2. Effect of molecular memory l_p on polymerized proteins m, refers to (**a**). (**b**) The solid line represents the theoretical results obtained via smaller noise approximation. The hollow circles indicate the numerical results obtained using the Gillespie algorithm (the visualization of numerical results is operated in Matlab 2022a). Parameters are set as $\langle B \rangle = 1, p_r = 0.2, K_0 = 4, K_p = 1, K_m = 1, d = 1$ (the solid line) and $\langle B \rangle = 1, p_r = 0.25, K_0 = 4, K_p = 0.9, K_m = 0.8, d = 1$ (the dashed line).

Despite a small error, the results obtained via the small noise approximation (solid line) are fairly consistent with those obtained using the Gillespie algorithm (hollow circles). The findings that the memory can reduce the expression mean of the protein polymer and amplify the noise have varying implications, agreeing with some other reported experimental observations [18,27–29]. Therefore, transforming non-Markovian processes with memory into an equivalent Markovian process represents a tried and true method of defining an effective switching rate function.

4.2. The Interplay of Memory and Transcription Bursting Attenuates the Noise ($l_p \neq 1$ and $l_m = 1$)

Next, we consider how the interplay of memory and transcription bursting regulates the expression stability. It is well known that positive feedback can increase expression noise, which is verified in Figure 2. However, the occurrence of transcription bursting alters this conclusion (Figure 3). In Figure 3, we investigate the dual effects of the interplay of memory and transcription burst on noises with increases in the mean burst size. Figure 3a illustrates that the protein noise is a monotonically decreasing function of the feedback strength (k_m), coinciding with the biological function of the positive feedback loop. Also, we can see that the noise increases on the whole with the increasing memory index of the transcription process. Moreover, it is interesting that the value of noise exhibits a descending trend with the increase in the mean burst size from 1 (left subgraph in Figure 3a) to 3 (right subgraph in Figure 3a).

Furthermore, Figure 3b demonstrates the relationship between transcription noise and the synthesis rate of polymerized proteins (k_p). It is very clear that noise is a monotonically increasing function of the synthesis rate, i.e., the actual degeneration of the protein can linearly affect the abundance of proteins and thus amplify the expression noise. Also, memory can further promote the enlarging effect, which we can see by comparing the three lines in each subgraph of Figure 3b.

The enlarging effect of memory also pertains to the polymer protein, as shown in Figure 4. A significant difference here is that the noise does not show a linear relationship with the synthesis rate (Figure 4b), implying that the polymerization process is more complex than the degradation. Actually, we often assume that degradation involves first-order kinetics (we also made this assumption here), but the polymerization process involves multi-step reactions that are the source of molecular memory. In order to account for this, we must understand the regulation mechanism of memory.

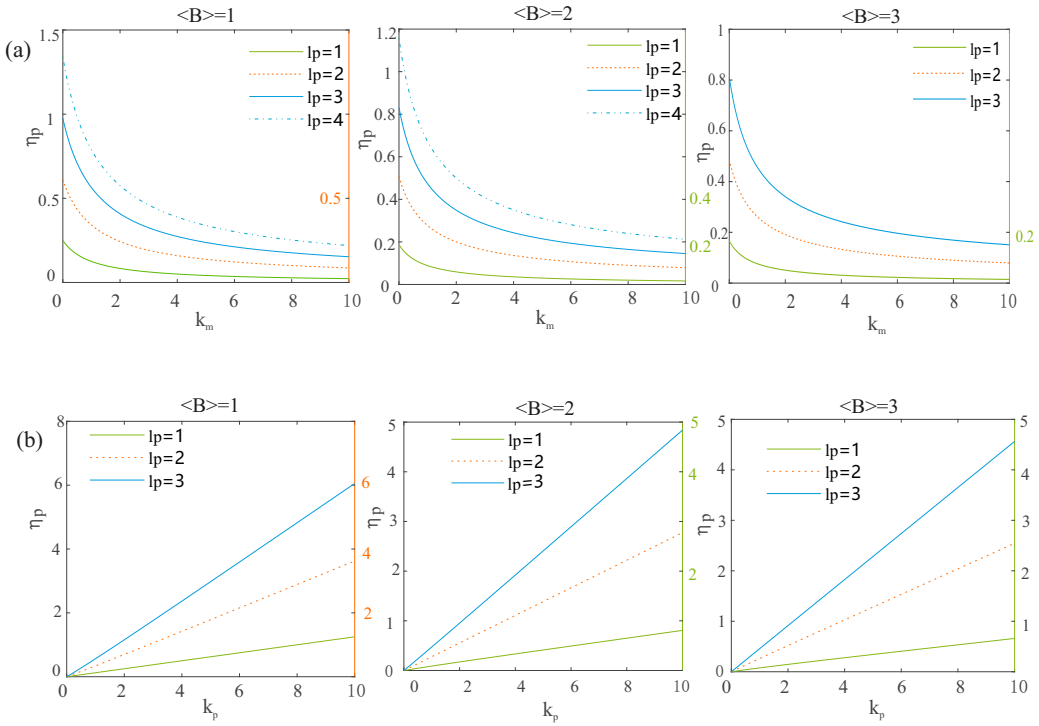

Figure 3. The effect of the rate of gene transcription to form polymerized proteins K_m (and the rate of feedback of polymerized proteins to promoters K_p, refers to (**b**)) on the noise of synthesized proteins η_p under the dual influence of molecular memory l_p and transcriptional bursts B, refers to (**a**). ((**a**,**b**) The parameters are set to: $p_r = 0.2, K_E = 5, K_p = 1, d = 1$. From left to right: $\langle B \rangle = 1, 2, 3$).

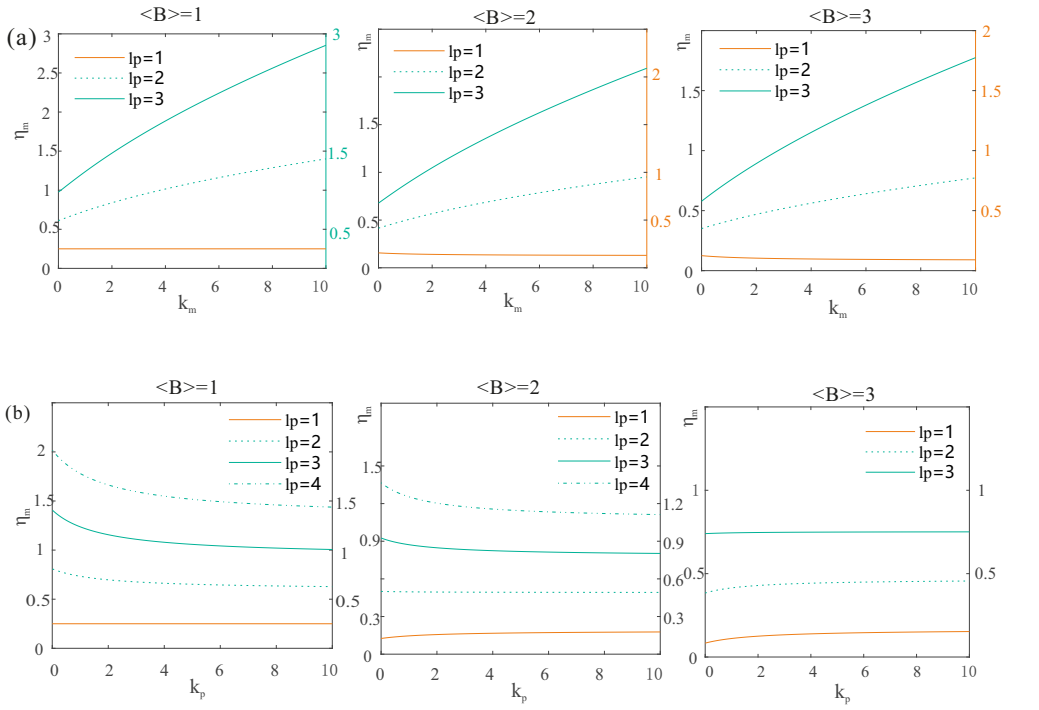

Figure 4. The effect of the rate of polymerization K_p (and the rate of feedback from the protein polymer to the promoter K_m, refers to (**a**)) on the noise of synthesized proteins η_m under the combined influence of molecular memory l_p and transcriptional burst B, refers to (**b**). The parameters are set to: $p_r = 0.2, K_E = 5, K_p = 1, d = 1$. From left to right: $\langle B \rangle = 1, 2, 3$.

Comparing Figures 3 and 4, we can observe that the noise decreases as a whole with the increase in mean burst size ($\langle B \rangle$) from 1 to 3 (from left to right). It is very clear that the larger the burst size is, the larger the noise will be, which has been reported in previous research [9,18]. Here, we have derived a counter-intuitive result that even if the mean burst size increases, the noise remains suppressed (refer to the stable value in the right vertical axis in each subgraph). These results indicate that there is a tradeoff between the memory and the expression burst that regulates the expression stability, that is, we can infer a double-ended regulation strategy that stabilizes the expression network in the time domain and the space domain, respectively. The reported experiment has verified that the regulation in the space domain is effective [1,9,11,30,31], e.g., increasing the abundance of the transcription factor to promote the transcription [18], changing the structure of the cell microenvironment to achieve phase switching, and increasing cell-to-cell communication to obtain phenotypic heterogeneity [9]; however, it is rare to regulate cell stability in the time domain. Here, we can see that although our results are simple, they provide an opportunity for regulation in the time domain.

4.3. Polymerization Memory Attenuates the Noise ($l_p = 1$ and $l_m = 1$)

Different from transcription memory, memory originating from the polymerization process suppresses noise (Figure 5). Specifically, Figure 5a,b demonstrate the relationships between expression noise and feedback strength (k_m) and synthesis rate (k_p), respectively. Actually, we see here that the protein noise is also a monotonically decreasing function of feedback strength, elucidating the general law of the positive feedback loop. Also, memory can further enhance the attenuation of noise—we see that the lower bound of noise becomes increasingly smaller when comparing the three lines in Figure 5a (from the green line to the dashed blue line to the solid blue line), meaning that memory may be a noise attenuator, and that cells can use the memory to retain expression stability. In general, we know that the noise always remains in the half-power form, and the regulation of memory may urge diversification in this relationship. Considering the source of polymerization memory, we can infer that post-transcription regulation is indispensable to maintaining cell stability, and the existence of intermediate transient products is a requisite for expression.

Contrarily, Figure 5a,b show that noise remains a monotonically, linearly increasing function of the synthesis rate (k_p), and memory also suppresses the lower bound of noise. Comparing Figure 5 with Figure 3, we can see that the memory has distinct functions because of its different sources. It is noteworthy that the appearance of memory does indeed directly reshape the bursting kinetics of expression noise.

Next, we further consider the expression kinetics of downstream polymer proteins. The numeric results are shown in Figure 6. We also investigate the relationship between the expression noise of polymer proteins and the two parameters, that is, the feedback strength and synthesis rate. It is clear that memory is still a noise attenuator and that increasing the burst size (from left to right, the burst size increases from 1 to 3) can suppress the entirety of polymer protein noise (Figure 6a). The most notable difference is that the nonlinearity becomes more and more apparent, as shown in Figure 6b, implying that burst kinetics always regulate the expression stability in a nonlinear way, and the memory can accelerate this regulation. It should be noted that the superiority of nonlinearity is essential to producing stochastic focus or defocus, and this mechanism has been reported many times [6,9,18,32]. Here, the interruption of memory may alter the progress of this nonlinearity, that is, we can not only reshape the half-power relationship of expression noise, but also mediate expression stability in the time domain.

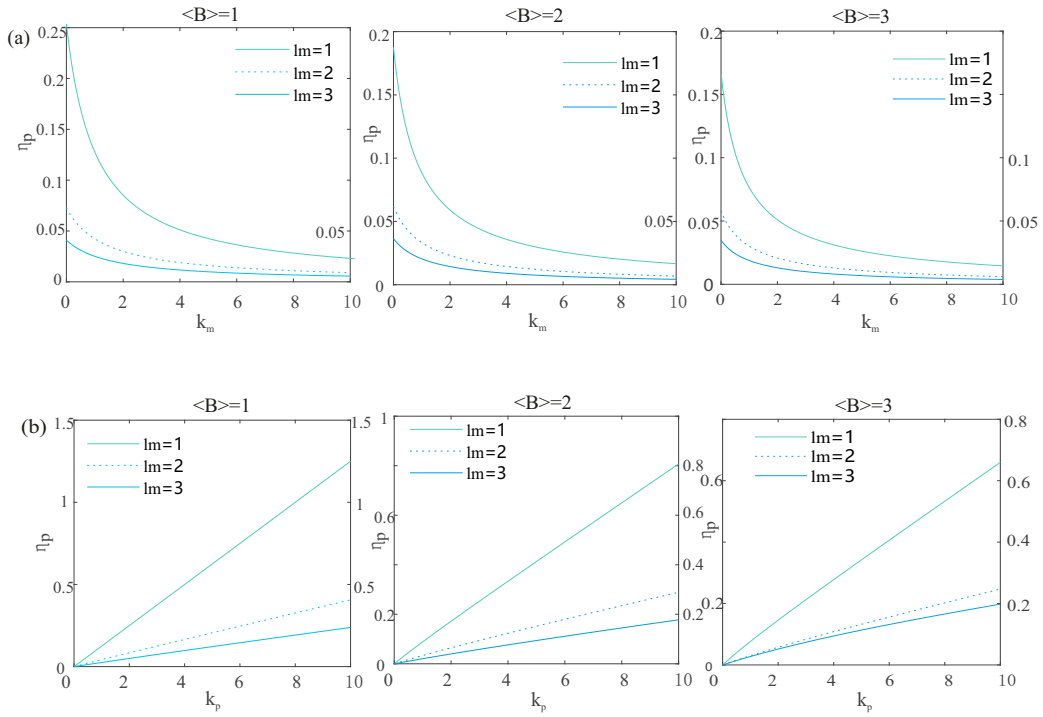

Figure 5. The effect of the rate at which genes are transcribed to form polymerized proteins K_p (and the rate of feedback from polymerized proteins to the promoter K_m, refers to (**a**)) on the noise of synthesized proteins η_p under the combined influence of molecular memory l_m and bursting B, refers to (**b**). The parameters are set to: $p_r = 0.2, K_E = 5, K_p = 1, d = 1$. From left to right: $\langle B \rangle = 1, 2, 3$.

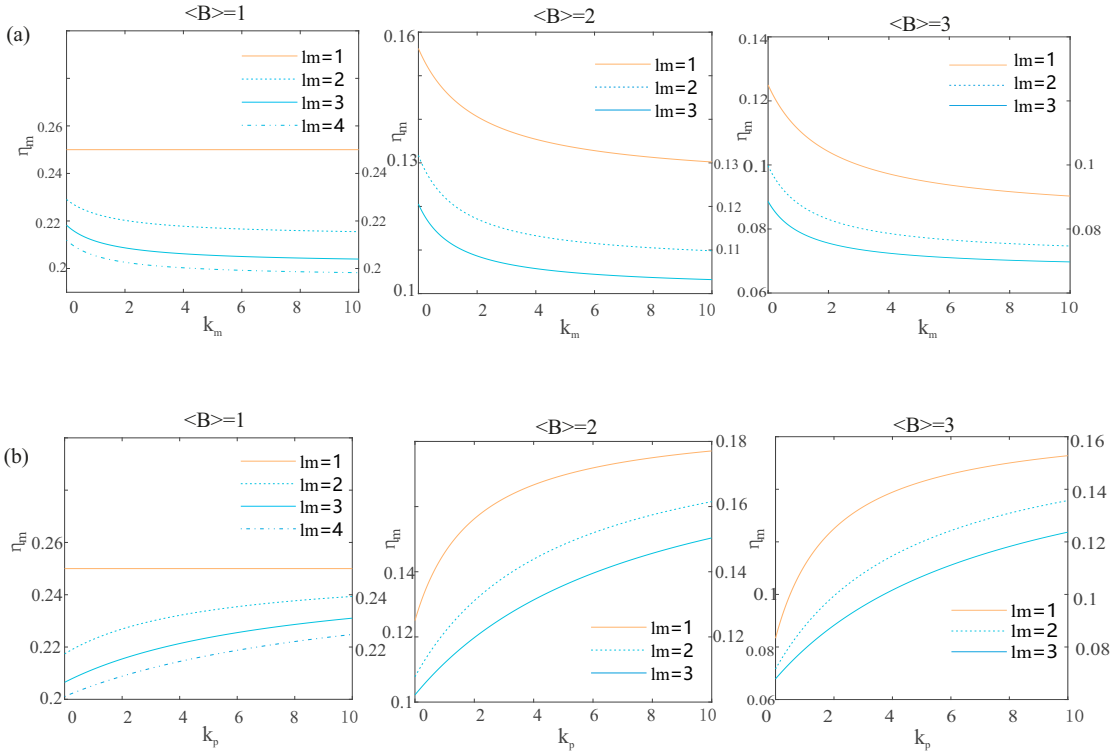

Figure 6. The effect of the rate of transcription of genes to form polymerized proteins K_p (and the rate of feedback of protein polymers to the promoter K_m, refers to (**a**)) on the noise of synthesized proteins η_m under the combined influence of molecular memory l_m and bursting B, refers to (**b**). The parameters are: $p_r = 0.2, K_E = 5, K_p = 1, d = 1$. From left to right: $\langle B \rangle = 1, 2, 3$.

5. Discussion and Conclusions

Deciphering the biological function of molecular memory is a popular topic in system biology. However, memory has different sources, and various multi-step biochemical reactions can directly result in memory. We want to know whether there is a mechanism by which cells can use the memory to maintain expression stability. Here, we propose a positive feedback expression model that couples nucleus retention with protein polymerization. Via non-Markovian transformation, we obtain a topologically equivalent Markovian process that expounds upon the regulation of memory and helps us understand the non-symmetry of the expression process. The results indicate that memory from distinct sources has different functions. Specifically, transcription memory inhibits the expression mean, but increases the noise, and when combined with transcription burst, it can reduce noise on the whole by a wide margin. The situation is nearly the opposite for polymerization memory, which plays the role of an attenuator and can reduce the lower limit of noise. Also, it can directly change the noise amplifier function of transcription bursting to decrease the level of expression, leading to a counterintuitive correlation between the two.

The presence of memory would imply that the expression process does not follow the assumptions of the Markovian theory, and different values of memory indicate distinct time scales and time windows. The above counterintuitive result implies that the same biological motif may have hugely different functions because of the inconsistency in time scales. A recent cancer cell experiment found that some biomarker proteins may bidirectionally regulate the tumor progress, such as the IFN-γ signal [33], the AGO2 protein [34], the MAPK activator [35], etc. Here, we also observe that memory originating from distinct sources has very distinct roles in the given expression network; it can not only amplify noise, but it can also suppress noise by regulating the memory index. Moreover, the involvement of memory can also mediate the function of bursting. The dual function may be achieved by regulating time or memory, rather than the previous traditional approach of regulating space. Furthermore, an inner tradeoff may occur between memory and expression stability, implying that we can control the timescale window to maintain the noise. Nowadays, it is very clear that noise may be detrimental to cells' survival but is also a vital clue to decoding life activity [6,15,24,36,37]. It seems likely that there is a suitable time window for comprehensively understanding the biological function of expression noise.

Also, the stochastic process involves a distinct memory window, or autocorrelation, which leads to the asymmetric or non-Markovian process. How to cope with the non-Markovian problem remains an open issue. Here, a novel idea is proposed of constructing a method with a process that is topologically equivalent to that of the non-Markovian process by defining the effective transition rate. In so doing, we can easily extend this method to solve larger-scale networks by ignoring the processes that we always previously omitted, such as multi-step degradation, the binding of the transcription factor, and the more detailed protein polymerization process.

Finally, it is important to state that the relative range of variation in the formation of proteins and polymers at the level of gene transcription may be large for different biological cells [18]. In addition, the theoretically predicted noise of proteins and polymers formed by gene transcription may be overestimated due to biological regulation, and this may differ from the theoretical assumptions made here; further, the classical noise formula calculations used in the computation of noise expression are often more burdensome than the exact-noise calculations [9]. In this case, there is some fluctuation in the noise corresponding to the protein synthesis of polymers and their feedback to promoters, even when the average burst size is fixed. Furthermore, the synthesizing and polymerizing of proteins occur simultaneously in gene expression, and as we said, gene transcription entails a multi-step process; nuclear retention, gene shearing, positive or negative feedback states, the switching of ON or OFF state switches, the complexity of the promoter, and a variety of external environmental factors all have an impact on the reaction processes of stochastic biochemical systems. Therefore, the theoretical results of our model may differ from the results of different experiments, within the range of error tolerance [9,18,30]. We

should next investigate transcription and protein polymerization to a greater degree of detail, including assessments of transcription burst frequency, the switching between ON and OFF states, and the bi-directional regulation of transcription factors, which will lead to more abundant and interesting experimental results.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/sym16030315/s1.

Author Contributions: H.W., X.B. and S.W. proposed and designed this study, performed all the numerical simulations described in the paper, interpreted the results, and wrote the paper. X.Z., S.W., X.B. and H.W. performed an analytical treatment of a non-Markovian system. All authors contributed to the discussions. All authors have read and agreed to the published version of the manuscript.

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