Supplemental Material

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

Xiaojun Bai [1,2,†], Sizhe Wang [1,3,†], Xin Zhang [1,2,4] and Haohua Wang [1,2,*]

[1] School of Mathematics and Statistics, Hainan University, Haikou 570228, China;
15737315201@163.com (X.B.); 13566245642@163.com (X.Z.)
[2] Key Laboratory of Engineering Modeling and Statistical Computation of Hainan Province, Hainan University, Haikou 570228, China
[3] The School of Mathematics, Tianjin University, Tianjin 300072, China; tjuwangsz@163.com
[4] School of Cyberspace Security, Hainan University, Haikou 570228, China
* Correspondence: huazi8112@hainanu.edu.cn
† These authors contributed equally to this work.

Proof of Main theorem

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*

$$x_1^s = \langle p \rangle = \frac{K_0}{2K_p}\left[\left(\frac{2\langle B\rangle(K_m+d)}{d}+1\right)^{\frac{1}{l_p}}-1\right],$$

$$x_2^s = \langle m \rangle = \frac{K_0}{2(K_m+d)}\left[\left(\frac{2\langle B\rangle(K_m+d)}{d}+1\right)^{\frac{1}{l_p}}-1\right].$$

Otherwise, if Process2 has memory($l_m \neq 1$ *and* $l_p = 1$), *then the steady states of products can be expressed as*

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

Proof: based on the theory of approximate approximation by 3.1 linear noise[1-4], then the rate equation corresponding to the Markov response network constructed above can be expressed as:

$$\frac{dx}{dt} = SK(x), \tag{S.1}$$

$x=(\langle p\rangle,\langle m\rangle)=(x_1,x_2)^T$ is a column vector. $S=(s_{ij})_{2\times4}=\begin{pmatrix}B & -1 & 1 & 0\\ 0 & 1 & -1 & -1\end{pmatrix}$ 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) The process of transcription and synthesis of proteins by kinetochores has a memory, and the other processes have no memory（$l_p\neq1$ and $l_m=1$）, The effective transfer rate for each process at this point is[3-6]:

$$K_1(x)=\frac{(K_px_1+K_mx_2+dx_2)(K_0)^{l_p}}{(K_0+K_px_1+K_mx_2+dx_2)^{l_p}-(K_0)^{l_p}},K_2(x)=K_px_1,K_3(x)=K_mx_2,K_4(x)=dx_2.$$

The steady state of the system is denoted by x^s and is given by equation (S.1) in the following form: $\begin{cases}\langle B\rangle K_1+K_3=K_2,\\ K_3+K_4=K_2\end{cases}$, simplifies to get:

$$\langle B\rangle K_1=K_4. \tag{S.2}$$

The equation $K_3+K_4=K_2$ can be derived: $(K_m+d)x_2=K_px_1$, We obtain $x_1=\frac{(K_m+d)x_2}{K_p}$ and substitute into(S.2),we get:

$$\frac{\langle B\rangle(K_px_1+K_mx_2+dx_2)(K_0)^{l_p}}{(K_0+K_px_1+K_mx_2+dx_2)^{l_p}-(K_0)^{l_p}}=dx_2$$

The simplification gives:

$$x_1^s=\langle p\rangle=\frac{K_0}{2K_p}\left[\left(\frac{2\langle B\rangle(K_m+d)}{d}+1\right)^{\frac{1}{l_p}}-1\right],$$

$$x_2^s=\langle m\rangle=\frac{K_0}{2(K_m+d)}\left[\left(\frac{2\langle B\rangle(K_m+d)}{d}+1\right)^{\frac{1}{l_p}}-1\right].$$

(2) Biochemical processes that convert proteins to polymerized proteins have memory and other processes do not（$l_m\neq1$ and $l_p=1$）

The effective transfer rate for each process at this point is:

$$K_1(x)=K_0,K_2(x)=\frac{(K_0+K_mx_2+dx_2)(K_px_1)^{l_m}}{(K_0+K_px_1+K_mx_2+dx_2)^{l_m}-(K_px_1)^{l_m}},K_3(x)=k_mx_2,K_4(x)=dx_2.$$

The steady state of the system is denoted by x^s. It is obtained from equation (S.1)

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

The simplification gives: $\langle B \rangle K_1 = K_4$.

From $K_3 + K_4 = K_2$ we get $\langle B \rangle K_0 = dx_2$, which simplifies to: $x_2 = \dfrac{\langle B \rangle K_0}{d}$.

From(S.2)we get $(K_m + d)x_2 = \dfrac{(K_0 + K_m x_2 + dx_2)(K_p x_1)^{l_m}}{(K_0 + K_p x_1 + K_m x_2 + dx_2)^{l_m} - (K_p x_1)^{l_m}}$, which simplifies to:

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

End of the proof!

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[3, 7-10]:*

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

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

Otherwise, if Process2 has memory($l_m \neq 1$ *and* $l_p = 1$), *the two noises is:*

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

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

Proof: It is known from theorem 1 that (1) the steady state of a stochastic biochemical reaction system at the time $l_p \neq 1$ and $l_m = 1$ is:

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

By 3.1 Linear Noise Approximation Theory. At this point,

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

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

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

Where, $\gamma = K_0 + dx_2 + K_m x_2 + K_p x_1$.

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

Here,

$$K_2 = K_p x_1^s = \frac{K_0}{2}[(\frac{2\langle B \rangle (K_m + d)}{d})^{\frac{1}{l_p}} - 1],$$

$$K_3 = K_m x_2^s = \frac{K_0 K_m}{2(K_m + d)}[(\frac{2\langle B \rangle (K_m + d)}{d})^{\frac{1}{l_p}} - 1],$$

$$K_4 = dx_2^s = \frac{K_0 d}{2(K_m + d)}[(\frac{2\langle B \rangle (K_m + d)}{d})^{\frac{1}{l_p}} - 1].$$

From the equation, $A_s \Sigma_s + \Sigma_s A_s^T + D_s = 0.$ we get the following system of equations and relations:

$$\begin{cases} 2(\langle B\rangle\dfrac{\partial K_1}{\partial x_1}-K_p)\sigma_{11}+2(\langle B\rangle\dfrac{\partial K_1}{\partial x_2}+k_m)\sigma_{12}=-(\langle B\rangle K_4+K_2+K_3), \\ (\langle B\rangle\dfrac{\partial K_1}{\partial x_1}-K_p)\sigma_{12}+(\langle B\rangle\dfrac{\partial K_1}{\partial x_2}+K_m)\sigma_{22}+k_p\sigma_{11}-(K_m+d)\sigma_{12}=K_2+K_3, \\ 2K_p\sigma_{12}-2(K_m+d)\sigma_{22}=-2K_2 \end{cases} \tag{S.3}$$

$$\sigma_{22}=\frac{K_p}{K_m+d}\sigma_{12}+\frac{K_2}{K_m+d},\sigma_{11}=\frac{-(\langle B\rangle\dfrac{\partial K_1}{\partial x_2}+K_m)}{(\langle B\rangle\dfrac{\partial K_1}{\partial x_1}-K_p)}\sigma_{12}-\frac{(\langle B\rangle K_4+K_2+K_3)}{2(\langle B\rangle\dfrac{\partial K_1}{\partial x_1}-K_p)}. \tag{S.4}$$

The relation (S.4) is brought into the system of equations (S.3). We get:

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

This leads to the noise of synthesized proteins in the biological model of this paper:

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

The noise for generating polymerized proteins in biological models is:

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

(2) the steady state of a stochastic biochemical reaction system at time $l_m\neq 1$ and $l_p=1$, is：

$$x_1{}^s=\frac{(1+\langle B\rangle)k_0d+\langle B\rangle k_0k_m}{dk_p[(\dfrac{(1+\langle B\rangle)d+\langle B\rangle k_m}{\langle B\rangle(k_m+d)}+1)^{\frac{1}{l_2}}-1]},x_2{}^s=\frac{\langle B\rangle k_0}{d}.$$

It is clear from theorem 1: $A=(A_{ij})=\begin{pmatrix}-\dfrac{\partial K_2(x)}{\partial x_1} & -\dfrac{\partial K_2(x)}{\partial x_2}+K_m \\ \dfrac{\partial K_2(x)}{\partial x_1} & \dfrac{\partial K_2(x)}{\partial x_2}-K_m-d\end{pmatrix}$,

$$D=(D_{ij})=\begin{pmatrix} \frac{\langle B\rangle K_0(\langle B\rangle d+2K_m+d)}{d} & -\frac{\langle B\rangle K_0(2K_m+d)}{d} \\ -\frac{\langle B\rangle K_0(2K_m+d)}{d} & 2\frac{\langle B\rangle K_0(K_m+d)}{d} \end{pmatrix}.$$

Here：

$$\frac{\partial K_2(x)}{\partial x_1}=\frac{(K_p x_1)^{l_m}(K_p l_2(K_p x_1)^{l_m-1}-K_p l_m(\gamma)^{l_m-1})(\gamma-K_p x_1)}{((K_p x_1)^{l_m}-(\gamma)^{l_m})^2}-\frac{K_p l_m(K_p x_1)^{l_m-1}(\gamma-K_p x_1)}{(K_p x_1)^{l_m}-(\gamma)^{l_m}},$$

$$\frac{\partial K_2(x)}{\partial x_2}=-\frac{(K_p x_1)^{l_m}(d+K_m)}{(K_p x_1)^{l_m}-(\gamma)^{l_m}}-\frac{(K_p x_1)^{l_m} l_m(d+K_m)(\gamma-K_p x_1)(\gamma)^{l_m-1}}{((K_p x_1)^{l_m}-(\gamma)^{l_m})^2}.$$

where $\gamma=K_0+dx_2+K_m x_2+K_p x_1$. From equation $A_s\Sigma_s+\Sigma_s A_s^T+D_s=0.$

we get the following system of equations and relations:

$$\begin{cases} 2(-\frac{\partial K_2}{\partial x_1})\sigma_{11}+2(-\frac{\partial K_2}{\partial x_2}+K_m)\sigma_{12}=-\frac{\langle \mathrm{B}\rangle K_0(\langle B\rangle d+2K_m+d)}{\mathrm{d}}, \\ (-\frac{\partial K_2}{\partial x_1})\sigma_{12}+(-\frac{\partial K_2}{\partial x_2}+K_m)\sigma_{22}+\frac{\partial K_2}{\partial x_1}\sigma_{11}+(\frac{\partial K_2}{\partial x_2}-K_m-d)\sigma_{12}=\frac{\langle \mathrm{B}\rangle K_0(2K_m+d)}{\mathrm{d}}, \\ 2\times\frac{\partial K_2}{\partial x_1}\sigma_{12}+2(\frac{\partial K_2}{\partial x_2}-K_m-d)\sigma_{22}=-2\times\frac{\langle \mathrm{B}\rangle K_0(K_m+d)}{\mathrm{d}} \end{cases} \quad \text{(S.5)}$$

$$\sigma_{11}=\frac{K_m-\frac{\partial K_2}{\partial x_2}}{\frac{\partial K_2}{\partial x_1}}\sigma_{12}+\frac{\langle B\rangle K_0(\langle B\rangle d+2K_m+d)}{2\times\frac{\partial K_2}{\partial x_1}\times d}, \quad \text{(S.6)}$$

$$\sigma_{22}=\frac{\frac{\partial K_2}{\partial x_1}}{(K_m+d-\frac{\partial K_2}{\partial x_2})}\sigma_{12}+\frac{\langle B\rangle K_0(K_m+d)}{d(K_m+d-\frac{\partial K_2}{\partial x_2})}. \quad \text{(S.7)}$$

Substituting relation (S.6)and(S.7) into the system of equations (S.5), we can get:

$$\sigma_{12}=\frac{\langle B\rangle K_0[d(K_m+d+\frac{\partial K_2}{\partial x_2})-\langle B\rangle d(K_m+d-\frac{\partial K_2}{\partial x_2})]}{2\times d^2(\frac{\partial K_2}{\partial x_2}-K_m-d-\frac{\partial K_2}{\partial x_1})}.$$

The noise of synthesized proteins in the model in this paper is:

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

The noise in the stochastic biochemical reaction system to generate polymerized proteins is:

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

The proof is complete!

Reference

1. Cao, Z. X.; Grima, R. Linear mapping approximation of gene regulatory networks with stochastic dynamics. *Nat. Commun.* **2018**, *9*, 15.
2. Chen, L. Y.; Wang, Y.; Liu, J. R.; Wang, H. H. Coloured noise induces phenotypic diversity with energy dissipation. *Biosystems* **2022**, *214*, 12.
3. Deng, Q. Q.; Chen, A. M.; Qiu, H. H.; Zhou, T. S. Analysis of a non-Markov transcription model with nuclear RNA export and RNA nuclear retention. *Math. Biosci. Eng.* **2022**, *19* (8), 8426-8451.
4. Deng, Q. Q.; Zhou, T. S. Memory-Induced Bifurcation and Oscillations in the Chemical Brusselator Model. *Int. J. Bifurcation Chaos* **2020**, *30* (10), 14.
5. Chen, A. M.; Qiu, H. H.; Tian, T. H.; Zhou, T. S. Generalized fluctuation-dissipation theorem for non-Markovian reaction networks. *Phys. Rev. E* **2022**, *105* (6), 14.
6. Zhang, J. J.; Zhou, T. S. Markovian approaches to modeling intracellular reaction processes with molecular memory. *Proc. Natl. Acad. Sci. U. S. A.* **2019**, *116* (47), 23542-23550.
7. Huang, L. F.; Yuan, Z. J.; Liu, P. J.; Zhou, T. S. Feedback-induced counterintuitive correlations of gene expression noise with bursting kinetics. *Phys. Rev. E* **2014**, *90* (5), 14.
8. Maleki, F.; Becskei, A. An open-loop approach to calculate noise-induced transitions. *J. Theor. Biol.* **2017**, *415*, 145-157.
9. Singh, A.; Bokes, P. Consequences of mRNA Transport on Stochastic Variability in Protein Levels. *Biophys J* **2012**, *103* (5), 1087-1096.
10. Yang, X. Y.; Luo, S. H.; Zhang, Z. Q.; Wang, Z. H.; Zhou, T. S.; Zhang, J. J. Silent transcription intervals and translational bursting lead to diverse phenotypic switching. *Phys. Chem. Chem. Phys.* **2022**, *24* (43), 26600-26608.