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Abstract—Noise and stochasticity are ubiquitous within microscopic biological systems. To function stably within such noise, it has been speculated that biological systems exploit noise. However, it was recently proposed that a cell is also equipped with nonlinear dynamics, being properly designed, to effectively suppress such noise. In order to clarify the similarity and difference of the two apparently opposite possibilities, we construct a new mathematical model that can be employed for the comparison. By using the model, we analyze qualitative and quantitative properties of the noise-suppressing and noise-exploiting dynamics.

1. Introduction

One intriguing property of biological systems is the ubiquity of noise and stochasticity in their behaviors. From the viewpoint of engineering, such noise and stochasticity are strong enough to hamper appropriate and stable function of the systems[1, 2, 3]. Nonetheless, biological systems can operate robustly and adapt flexibly in changing environment. This inconsistency between robustness of biological systems against noise and our intuition that man-made systems are sensitive to noise has led to an idea that biological systems may exploit rather than suppress noise for their reliable operation[4, 5]. Stochastic resonance (SR) in biological systems is one example in which noise assists a system to detect very weak signal[6]. Presence of SR has been tested for various biological sensory systems from paddlefish[6] to human vision[7]。

While exploitation of noise has been investigated for the last couple of decades[4], still controversial is whether noise-exploitation is the fundamental design principle of living systems or not. For example, recent molecular biological data has revealed that intracellular networks contain statistically-significant number of negative feedback loops[8], which are the most typical way to suppress noise in engineering systems[9]. Therefore, biological systems seem to actively suppress noise but at the same time they also seem to exploit it.

On this issue, we recently proposed that dynamic Bayesian computation may be conducted by intracellular networks in order to effectively extract environmental information from very noisy signal[10, 11]. On one hand, the Bayesian computation is a mechanism to effectively suppress noise because it is the statistically optimal way to recover or infer the hidden information from noisy observation, On the other hand, however, we also revealed that the Bayesian dynamics is tightly related to noise-induced transition and bifurcation, indicating that dynamic Bayesian computation works as if it exploits noise to amplify small signal[12]. This finding implies that noise-suppression and noise-exploitation are not mutually exclusive but are overlapped concepts.

In this paper, we investigate dynamical properties and efficiency of information processing of noise-induced dynamics by comparing it with SR-like potential-driven dynamics.

2. Dynamic Bayesian information processing

In [10, 11], one of the authors derived optimal intracellular dynamics that can conduct statistically optimal computation of noisy signal. Here, we briefly describe the model introduced there.

Let $x(t)$ be the state to which a cell has to respond. $x(t)$ can be environmental condition or certain intracellular state such as abundance of energy sources, that of antibiotics, or regulatory state of promoter for a specific gene. For simplicity, as in [10], we assume that $x(t)$ has only two discrete states as $x(t) \in \chi \equiv \{\text{off}, \text{on}\}$. Since $x(t)$ such as environmental state changes unpredictably over time, we model the dynamics of $x(t)$ by using two-state Markov process whose transition rate from $x(t) = \text{off}$ to $x(t) = \text{on}$ and that from $x(t) = \text{on}$ to $x(t) = \text{off}$ are r_{on} and r_{off}, respectively[13].

The information on $x(t)$ is transmitted into cell or to other intracellular molecule by stochastic intracellular reactions. One typical reaction is receptor activation where receptors on cell membrane get active stochastically depending on the state of $x(t)$. Because the state of a receptor is generally discrete, we describe it with $s_i(t)$ where $s_i(t) \in \{0, 1\}$. $s_i(t) = 0$ and $s_i(t) = 1$ mean that i-th receptor is active and inactive at t, respectively. Each inactive receptor is assumed to get active with rate $\lambda(x(t))\Delta t$ within interval $(t, t + \Delta t)$. An activated receptor is assumed to get inactive in τ after its activation. The timing of receptor activations is described as $\{t_k : k \in \mathbb{N}\}$ where t_k is the timing of the k-th activation. The trajectory of receptor activity

can also be represented by using Dirac delta function as $y(t) = \sum_k \delta(t - t_k)$. We also assume that the total number of receptors, N_0, is constant.

Under these assumptions on the stochastic change of $x(t)$ and $y(t)$, we can derive posterior probability on $x(t)$ given the time-series of $y(t)$ as $\mathbb{P}(x_t|y_{0:t}) := \mathbb{P}(x, t|\{y(t')|t' \in [0, t]\})$. Since posterior probability is the sufficient statistics on the state of $x(t)$ given the trajectory of $y(t)$, $\mathbb{P}(x_t|y_{0:t})$ can be regarded as information on $x(t)$ that $y(t)$ has.

By following sequential Bayes' theorem, update rule of $\mathbb{P}(x_t|y_{0:t})$ within small interval Δt can be described as

$$\mathbb{P}(x_{t+\Delta t}|y_{0:t+\Delta t}) = \mathbb{P}(y_{t+\Delta t}|x_{t+\Delta t}) \times \frac{\sum_{x(t)\in\chi} \mathbb{P}(x_{t+\Delta t}|x_t)\mathbb{P}(x_t|y_{0:t})}{\mathbb{P}(y_{t+\Delta t}|y_{0:t})}.$$

For sufficiently small Δt, we can obtain

$$\mathbb{P}(y_{t+\Delta t} = y|x_{t+\Delta t} = x) \approx \left[\frac{\lambda(x)N_0\Delta t}{1 - \lambda(x)N_0\Delta t}\right]^y (1 - \lambda(x)N_0\Delta t)$$

$$\mathbb{P}(x_{t+\Delta t} = \tilde{x}|x_t = x) := \mathbb{P}(t + \Delta t, \tilde{x}|t, x) \approx r_{\tilde{x}}\Delta t$$

$$\mathbb{P}(x_{t+\Delta t} = x|x_t = x) := \mathbb{P}(t + \Delta t, x|t, x) \approx 1 - r_{\tilde{x}}\Delta t,$$

where $\tilde{x} = $ off when $x = $ on and $\tilde{x} = $ on when $x = $ off. By taking the limit $\Delta t \to 0$, we approximately obtain

$$\frac{dz(t)}{dt} = z(t)\tilde{z}(t)[\lambda_r N_0 y'(t) - N_0\lambda_d] + r_{on}\tilde{z}(t) - r_{off}z(t), \quad (1)$$

where $z(t) := \mathbb{P}(x_t|y_{0:t})$, $\tilde{z}(t) := 1 - z(t)$, $\lambda_r := \log \frac{\lambda_{on}}{\lambda_{off}}$, $\lambda_d := \lambda_{on} - \lambda_{off}$. In the above equation, $y'(t)$ represents the effective activity of each receptor defined by using indicator function $\mathbf{1}_A$ as $y'(t) \approx \frac{1}{\tau N_0} \sum_k \mathbf{1}_{[t_k, t_k+\tau]}$. Since $y(t)$ and $y'(t)$ contain approximately the same information, we use $y(t)$ to describe $y'(t)$.

Because of the discrete nature of receptor activation, $y(t)$ is an approximation of doubly stochastic Poisson process whose intensity is $\lambda(x(t))$. This property is biologically realistic but mathematically hard to handle analytically. Thus, we approximate Eq. 1 with Wiener process W_t as

$$dz = [\mu(t)z\tilde{z} + \gamma_{on}\tilde{z} - \gamma_{off}z] dt + \sigma z\tilde{z} \circ dW_t, \quad (2)$$

where $\sigma = \sqrt{2\nu/(r_{on} + r_{off})}$, $\mu(t) := (\alpha(t) - \frac{1}{2})\sigma^2$, $\gamma_{on} := r_{on}/(r_{on} + r_{off})$, and $\gamma_{off} := r_{off}/(r_{on} + r_{off})$[12]. ν is defined as

$$\nu := \lambda_{off} N_0[(1 + \beta) \log(1 + \beta) - \beta] \approx \frac{1}{2} \frac{\lambda_d^2 N_0}{\lambda_{off}},$$

where $\lambda_{on} = (1 + \beta)\lambda_{off}$, and $\alpha(t) = 1$ when $x(t) = $ on, and $\alpha(t) = 0$ when $x(t) = $ off. The stationary distribution can be analytically obtained as

$$\mathbb{P}_{st}(z) = \frac{\mathcal{N}}{(z\tilde{z})^2} \exp\left(-\frac{2}{\sigma^2}\left[\frac{\gamma_{off}\tilde{z} + \gamma_{on}z}{z\tilde{z}} + \gamma_d \log \frac{z}{\tilde{z}}\right]\right), \quad (3)$$

where $\mathcal{N}$ is the normalization constant and $\gamma_d = \gamma_{on} - \gamma_{off}$. This representation can be further simplified when $\gamma_{on} = \gamma_{off} = 1/2$ as

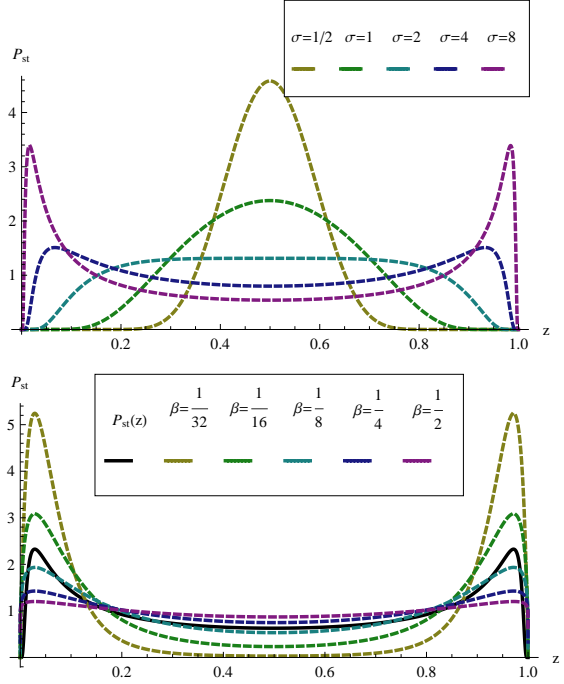$$\mathbb{P}_{st}(z) = \frac{\mathcal{N} \exp\left[-\frac{1}{\sigma^2}\frac{1}{z\tilde{z}}\right]}{(z\tilde{z})^2}.$$

Figure 1: Stationary distribution for different values of parameters. (Upper panel) $\mathbb{P}_{st}^{\mu_0}(z)$ for different σ. The other parameters are $\gamma_{on} = \gamma_{off} = 1/2$, and $\mu_0 = 0$. (Lower panel) $\mathbb{P}_{st}^{\mu_0}(\bar{z})$ for different β. The other parameters are $\gamma_{on} = \gamma_{off} = 1/2$, $\mu_0 = 0$, and $\sigma = 6$.

When $\mu(t)$ is constant over time as $\mu(t) = \mu_0$, then the stationary distribution becomes

$$\mathbb{P}_{st}^{\mu_0}(z) = \frac{\mathcal{N}}{z\tilde{z}} \exp\left(-\frac{2}{\sigma^2}\left[\frac{\gamma_{off}}{z} + \frac{\gamma_{on}}{\tilde{z}} + (\mu_0 + \gamma_d) \log \frac{z}{\tilde{z}}\right]\right). \quad (4)$$

When $\gamma_{on} = \gamma_{off} = 1/2$, we obtain

$$\mathbb{P}_{st}^{\mu_0}(z) = \frac{\mathcal{N} \exp\left[-\frac{1}{\sigma^2}\left[\frac{1}{z\tilde{z}} + 2\mu_0 \log \frac{z}{\tilde{z}}\right]\right]}{z\tilde{z}},$$

which is depicted in the upper panel of Fig. 1.

If we define $F_n(z, \mu) := \mu z\tilde{z} + r_{on}\tilde{z} - r_{off}z$ and $G_n(\bar{z}) := \sigma z\tilde{z}$, then the stationary distribution for constant $\mu(t)$ can be described as

$$\mathbb{P}_{st}^{\mu_0}(z) = \frac{\mathcal{N}}{G_n(z)^2} \exp\left[2 \int^{\bar{z}} \frac{F_n(z', \mu_0) + \sigma G_n(z)\left(\frac{1}{2} - z\right)}{G_n(z')^2} dz'\right].$$

The position of extrema of the stationary distribution, z^*, satisfies

$$\left.\frac{\partial \mathbb{P}_{st}^{\mu_0}(z)}{\partial z}\right|_{z=z^*} = \frac{2\mathbb{P}_{st}^{\mu_0}(z^*)}{G_n(z^*)}\left[-\frac{dG_n(z)}{dz} + \frac{F_n(z^*, \mu_0)}{G_n(z^*)} + \sigma(\frac{1}{2} - z^*)\right],$$

$$= \frac{2\mathbb{P}_{st}^{\mu_0}(z^*)}{G_n(z^*)}\left[\frac{F_n(z^*, \mu_0)}{G_n(z^*)} - \sigma(\frac{1}{2} - z^*)\right] = 0.$$

Thus, z^* can be represented as

$$\mu_0 = \sigma^2(\frac{1}{2} - z^*) - \frac{\gamma_{\text{on}}}{z^*} + \frac{\gamma_{\text{off}}}{\bar{z}^*}, \qquad (5)$$

which is depicted in Fig. 2. If we recognize extrema of stationary distribution as stochastic counterpart of deterministic equilibrium states, this equation describes the nullcline of Eq. 2. In addition, when $\gamma_{\text{on}} = \gamma_{\text{off}} = \gamma$, we can easily verify that the transition of $\mathbb{P}_{st}^{\mu_0}(z)$, i.e., the change in the number of extrema, occurs when $\sigma^2/\gamma = 8$.
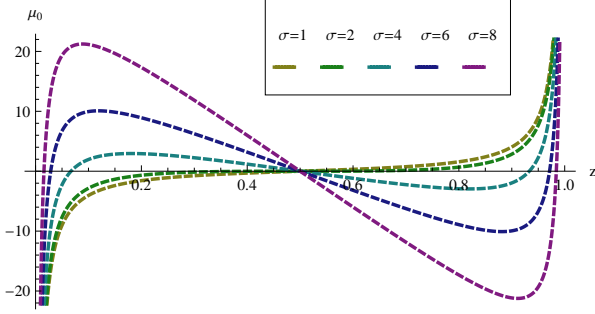

Figure 2: Nullcline (Eq. 5) for different value of σ.

However, if noise intensity is zero, $\sigma = 0$, then Eq. 2 has only single stationary and stable state because $F_n(z) = 0$ has only one solution. Therefore, emergence of new stable state is purely induced by noise[12]. This phenomenon has been known as pure noise-induced transition since 1970s[14]. As clarified in [12], this result indicates that binary information processing by dynamics Bayesian computation naturally accompanies the property to show noise-induced transition, implying that optimal information processing may be linked to noise-induced phenomena.

3. Potential-driven dynamics for Information processing

The relation between Bayesian computation and noise-induced bimodality looks similar to that between stochastic resonance and potential-induced bistability. This similarity naturally raise a question on the difference between these two phenomena. In order to compare Eq. 2 with a potential-induced bistable system, we consider the following dynamics:

$$d\bar{z} = \beta(\mu(t)dt + \sigma dW_t + H(\bar{z})dt), \qquad (6)$$

where $H(\bar{z})$ is the potential of the system. For comparison of the efficiency to extract the information on $\mu(t)$ from the input $\mu(t)dt + \sigma dW_t$, we introduce $\mu(t)dt + \sigma dW_t$ as the external signal to the system in Eq. 6. β is the amplification ratio of the input.

The stationary distribution of $\bar{z}$ for constant $\mu(t)$ as $\mu(t) = \mu_0$ can be described as

$$\mathbb{P}_{st}^{\mu_0}(\bar{z}) = \frac{\mathcal{N}}{G_d(\bar{z})^2} \exp\left[2 \int^{\bar{z}} \frac{F_d(\bar{z}', \mu_0)}{G_d(\bar{z}')^2} d\bar{z}'\right], \qquad (7)$$

where $F_d(\bar{z}, \mu) = \beta(\mu + H(\bar{z}))$ and $G_d(\bar{z}) = \beta\sigma$. The position of extrema of the stationary distribution, $\bar{z}^*$, satisfies

$$\frac{\partial \mathbb{P}_{st}^{\mu_0}(\bar{z})}{\partial \bar{z}}\bigg|_{\bar{z}=\bar{z}^*} = \left[\frac{2F_d(\bar{z}, \mu_0)}{G_d(\bar{z})^2} - \frac{1}{G_d(\bar{z})^2}\frac{\partial G_d(\bar{z})^2}{\partial \bar{z}}\right]_{\bar{z}=\bar{z}^*}$$

$$= \frac{2F_d(\bar{z}^*, \mu_0)}{G_d(\bar{z}^*)^2} = 0.$$

Thus, we have $\mu_0 = -H(\bar{z}^*)$. Since the nullcline of Eq. 2 is $\mu_0 = \sigma^2(\frac{1}{2} - z^*) - \frac{\gamma_{\text{on}}}{z^*} + \frac{\gamma_{\text{off}}}{\bar{z}^*}$, Eq. 6 has the same nullcline as Eq. 2 when

$$H(\bar{z}) = -\sigma^2(\frac{1}{2} - z^*) + \frac{\gamma_{\text{on}}}{z^*} - \frac{\gamma_{\text{off}}}{\bar{z}^*},$$

is satisfied. Then the stationary distribution $\mathbb{P}_{st}^{\mu_0}(\bar{z})$ can be obtained as

$$\mathbb{P}_{st}^d(\bar{z}) = \mathcal{N}\left[\bar{z}^{\gamma_{\text{on}}}(1 - \bar{z})^{\gamma_{\text{off}}}\right]^{2/(\beta\sigma^2)} \exp\left[\frac{2\frac{\mu_0}{\sigma^2}\bar{z} - \bar{z}\bar{z}}{\beta}\right],$$

which is depicted in the lower panel of Fig. 1.

Because intensive search for all possible function $H(\bar{z})$ is not feasible, we compare Eqs. 2 and 6 under the condition that they share the same nullcline structure. Under this condition, β is the only parameter that should be optimized for comparison.
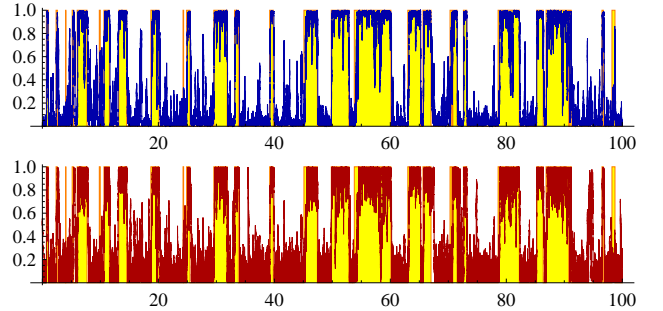

Figure 3: Sample trajectories of Eq. 2 (upper panel, blue) and 6 (lower panel, red). Yellow regions designate that $\alpha(t) = 1$. The parameters are $\gamma_{\text{on}} = \gamma_{\text{off}} = 1/2$, $\sigma = 7.7460$, and $\beta = 1/8$. Because of stiffness of Eq. 6, we added some rules near $z(t) = 0$ or $z(t) = 1$ that can suppress the divergence of simulation. This modification may not influence the result obtained here.

4. Comparison of information processing by noise-induced and potential-driven dynamics

In order to compare the behavior of Eqs. 2 and 6 in response to $\mu(t)$ and $dW(t)$, we simultaneously simulated both equations to which we used the same realization of $\mu(t)$ and $dW(t)$. Figure 3 shows sample trajectories of Eqs. 2 and 6. As easily observed, the trajectory generated by Eq. 6 contains fluctuation with higher frequency than Eq.

2 near $z(t) = 0$ or $z(t) = 1$, suggesting that high frequency noise is not suppressed by the potential induced dynamics.

However, the performance of Eq. 6 depends on the parameter β. We quantified Error rate (ER) of Eq. 2 and Eq. 6 for different values of β as shown in Fig. 4. As clearly observed, Bayesian dynamics (Eq. 2) is always better than Eq. 6 in terms of reconstructing the behavior of $x(t)$ from noisy signal.
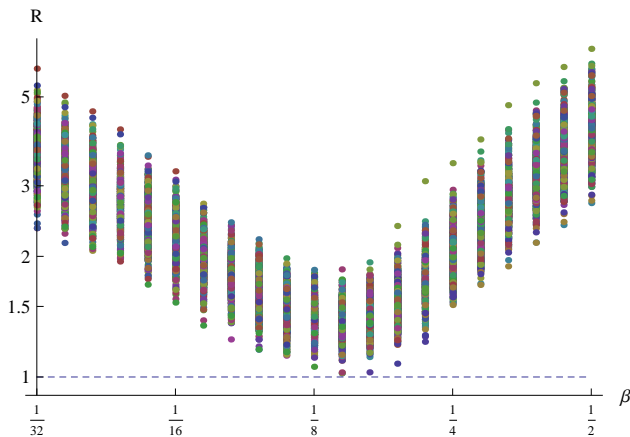

Figure 4: Ratio of error rates of Eq. 2 and Eq. 6. Error rate of a trajectory $z(t)$ is defied as $E(z) := \int |\mathbf{1}_{[1/2,1]}z(t) - \alpha(t)|dt'$ where $\mathbf{1}_A$ is an indicator function of a set A. The ratio R is defined as $R := E(\bar{z})/E(z)$ for each realization of the pair $(x(t), W(t))$. Each points for a given β corresponds to different realization of the pair. The number of points are 800 for a fixed value of β. The other parameters other than β is the same as in Fig. 3. R is always greater than 1 irrespective of realization.

5. Summary and Discussion

In this paper, we investigated the information processing of noisy signal by Bayesian dynamics with noise-induced bimodality and stochastic resonant (SR) dynamics with potential-induced bimodality. Our numerical evaluation indicates that Bayesian dynamics is always better than the stochastic resonant dynamics. Apart from the quantitative difference between Bayesian and SR dynamics, they have other qualitative similarity and differences that will be addressed in the future work.

Acknowledgments

References

[1] M. B. Elowitz and S. Leibler. A synthetic oscillatory network of transcriptional regulators. *Nature*, 403(6767):335–8, January 2000.

[2] M. Ueda and T. Shibata. Stochastic signal processing and transduction in chemotactic response of eukaryotic cells. *Biophysical Journal*, 93:11–20, 2007.

[3] V. Shahrezaei and P.S. Swain. The stochastic nature of biochemical networks. *Current Opinion in Biotechnology*, 19(4):369–74, 2008.

[4] L. Gammaitoni, *et al.* Stochastic resonance. *Reviews of Modern Physics*, 70(1):223–287, 1998.

[5] D. Fraser and M. Kaern. A chance at survival: gene expression noise and phenotypic diversification strategies. *Molecular microbiology*, 71(6):1333–40, 2009.

[6] P. Hanngi. Stochastic Resonance in Biology. *chemphyschem*, 3:285–290, 2002.

[7] K. Kitajo, , *et al.* Behavioral Stochastic Resonance within the Human Brain. *Physical Review Letters*, 90(21), May 2003.

[8] R.Milo, S.Shen-Orr, S.Itzkovitz, N.Kashtan, D.Chklovskii, and U.Alon. Network motifs: simple building blocks of complex networks. *Science (New York, N.Y.)*, 298(5594):824–7, October 2002.

[9] A. Becskei and L. Serrano. Engineering stability in gene networks by autoregulation. *Nature*, 405(6786):590–3, June 2000.

[10] T. J. Kobayashi. Implementation of Dynamic Bayesian Decision Making by Intracellular Kinetics. *Physical Review Letters*, 104(22):228104, June 2010.

[11] T. J. Kobayashi and A. Kamimura. Dynamics of intracellular information decoding. *Physical Biology*, 8:055007, 2011.

[12] T. J. Kobayashi. Connection between Noise-Induced Symmetry Breaking and an Information-Decoding Function for Intracellular Networks. *Physical Review Letters*, 106(22):228101, June 2011.

[13] C. W. Gardiner. *Handbook of Stochastic Methods: for Physics, Chemistry and the Natural Sciences (Springer Series in Synergetics)*. Springer, 2004.

[14] W. Horsthemke and R. Lefever. *Noise-Induced Transitions: Theory and Applications in Physics, Chemistry, and Biology (Springer Series in Synergetics)*. Springer, 2007.