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The effects of input noise on a simple biochemical switch

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Many biological processes are controlled by biomolecular switches which themselves are regulated by various upstream chemical molecules (the input). Understanding how input noise affects the output stochastic switching process is of significant interest in various biophysical systems like gene regulation, chemosensing, and cell motility. Here, we propose an exactly solvable model where the noisy input signal arises from a simple birth-death process and directly regulates the transition rates of a downstream switch. We solve the joint master equations to analyze the statistical properties of the output switching process. Our results suggest that the conventional wisdom of an *additive input-output noise rule* fails to describe signaling systems containing a single molecular switch, and instead, the most important effect of input noise is to effectively reduce the on rate of the switch.

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A broad range of biological processes are regulated by certain switching systems where biochemical molecules randomly flip between on and off states under the regulation of other molecules (kinases, ligands, *etc.*). For example, gene transcription depends on whether DNA promoters are occupied by specific transcription factors [1, 2]; in eukaryotic chemotaxis, accurate sensing of chemical gradients is achieved by using chemoreceptors to detect spatial differences in chemical concentrations [3]. Very often, the number of input molecules is quite small and the stochasticity of the input signal, due to molecular diffusion [4] or random births and deaths of molecules [5, 6], is not negligible. This leads to a central question: what is the role of input noise in a biochemical switching system. Previous studies on this topic mostly used the Langevin approach with a linear-noise approximation and/or the fluctuation-dissipation theorem [6–11]. These approaches assume that the fluctuations of input signals are very small such that one can linearize the input noise in the chemical Langevin equation. This Taylor-expansion treatment typically, unless there are correlations [12], leads to the widely accepted *additive noise rule*, i.e., the output variance is the sum of the intrinsic variance of the switch and a contribution from the extrinsic noise. It is often overlooked, however, that this additive noise rule can fail in the case of a single switch which has a strict upper bound on the variance.

Here, we study a simple two-state switch regulated by a fluctuating chemical input. Our treatment does not rely on the aforementioned approximations, but instead on exact solutions of the master equation. To explicitly capture the discreteness and randomness of the number of input molecules, we model the input $X(t)$ as generated from a Markov birth-death process where the birth and death rates are denoted by α and β , respectively (Fig. 1A). Clearly, the equilibrium distribution of the input molecules, denoted by C_n , is Poisson with mean $\mu \equiv \alpha/\beta$ and variance $\sigma^2 \equiv \alpha/\beta = \mu$, i.e.,

$$C_n(X(t \rightarrow \infty) = n) = \mu^n e^{-\mu} / n!. \quad (1)$$

$X(t)$ is nonnegative, mean-reverting, and also stationary,

with limit covariance, $\lim_{t \rightarrow \infty} \langle X(t), X(t+s) \rangle = \sigma^2 e^{-\beta|s|}$. Thus, the relaxation time of $X(t)$ is β^{-1} . It is convenient to choose a time scale by setting $\beta = 1$ so that both the mean and variance are determined by α (i.e., $\alpha = \mu = \sigma^2$). Then, we have $\alpha = \mu^2/\sigma^2$, which can be interpreted as the *signal-to-noise ratio*.

We assume that the number of input particles, $X(t)$, directly regulates the transition rates of a downstream switch, the states of which in continuous time constitute the output process, $Y(t)$. For the simplest reaction scheme (Fig. 1A), the rate for the molecular switch to turn on is given by $k_{\text{on}}X(t)$ and the rate for it to turn off is k_{off} . Let $P_n(t)$ (and $Q_n(t)$) be the probability to find the switch in the on (and off) state together with exactly n input molecules at time t . Since the input birth-death dynamics is independent of the switch states, we must have $P_n + Q_n = C_n$. Although $Y(t)$ alone is not Markovian, the joint process $(X(t), Y(t))$ is. We can write down the joint master equations for P_n and Q_n as

$$\begin{aligned} \frac{dP_n}{dt} = & k_{\text{on}}nQ_n - k_{\text{off}}P_n + \alpha P_{n-1} - \alpha P_n \\ & + (n+1)P_{n+1} - nP_n, \end{aligned} \quad (2)$$

$$\begin{aligned} \frac{dQ_n}{dt} = & k_{\text{off}}P_n - k_{\text{on}}nQ_n + \alpha Q_{n-1} - \alpha Q_n \\ & + (n+1)Q_{n+1} - nQ_n. \end{aligned} \quad (3)$$

In equilibrium, from $Q_n \equiv C_n - P_n$ and Eq. (2), we get

$$(k_{\text{on}}n + k_{\text{off}} + \alpha + n)P_n - \alpha P_{n-1} - (n+1)P_{n+1} = k_{\text{on}}nC_n, \quad (4)$$

which reduces to $P_1 = (k_{\text{off}} + \alpha)P_0$ at $n = 0$. Thus, if we find the solution for P_0 , the expression of P_1 immediately follows and the general solution for P_n is easily determined by Eq. (4). We introduce the generating function, $G(z) = \sum_{n=0}^{\infty} z^n P_n$, to transform Eq. (4) into

$$(k_{\text{on}}+1)zG' + (k_{\text{off}}+\alpha)G - \alpha zG - G' = k_{\text{on}}\alpha z e^{\alpha(z-1)}, \quad (5)$$

which contains a regular (power-law) singular point at $z_s \equiv (k_{\text{on}}+1)^{-1}$, so that generically,

$$G(z) \sim (z - z_s)^{-\lambda}, \quad \lambda \equiv z_s(k_{\text{off}} + \alpha - \alpha z_s). \quad (6)$$

Choosing the boundary condition to eliminate the possible singularity at z_s , we find an integral solution:

$$G(z) = \int_{z_s}^z \frac{k_{\text{on}} \alpha e^{-\alpha z_s x}}{x - z_s} \left| \frac{x - z_s}{z - z_s} \right|^h \exp\left(\frac{k_{\text{on}} \alpha x + \alpha z}{k_{\text{on}} + 1}\right) dx \quad (7)$$

where $h \equiv z_s^2(k_{\text{on}}k_{\text{off}} + k_{\text{on}}\alpha + k_{\text{off}})$. In particular, this directly gives $P_0 = G(z=0)$. Moreover, the equilibrium probability to find the switch in the on state is given by $P_{\text{on}} = \sum_{n=0}^{\infty} P_n = G(z=1)$, which we will examine for different limits later on.

If the input is fixed at a constant level (i.e. $X(t) = \alpha$), the output $Y(t)$ is clearly a two-state Markov (or random telegraph) process with the forward rate, $K_+ \equiv k_{\text{on}}\alpha$, and the backward rate, $K_- \equiv k_{\text{off}}$. Since k_{off} is independent of $X(t)$, the input noise will only affect the chance for the switch to turn on. One can calculate the mean waiting time, τ_n , for the switch to turn on given that it starts from being off with n particles initially. We first write the backward Kolmogorov equation for $\rho_n(t)$, which denotes the probability density for the switch (starting with n particles) to exit the off state at time t :

$$\begin{aligned} \rho_n(t) = & [1 - (\alpha + n + k_{\text{on}}n) dt] \rho_n(t - dt) \\ & + \alpha \rho_{n+1}(t - dt) dt + n \rho_{n-1}(t - dt) dt + k_{\text{on}} n \delta(t), \end{aligned}$$

where the first term represents the probability of nothing happening so that the exit has to be at $t - dt$, the second the probability that there is currently a birth so that the exit has to be at $t - dt$ from the $n + 1$ particle state, the third the probability that there is a death, and the last term represents the boundary condition using the Dirac delta function. This equation can be expanded and reorganized to the following differential equation,

$$\frac{d\rho_n}{dt} = -(\alpha + n + k_{\text{on}}n) \rho_n + \alpha \rho_{n+1} + n \rho_{n-1} + k_{\text{on}} n \delta(t). \quad (8)$$

To calculate the mean first passage time, we multiply both sides of Eq. (8) by t and integrate over all t , yielding

$$(\alpha + n + k_{\text{on}}n) \tau_n = \alpha \tau_{n+1} + n \tau_{n-1} + 1. \quad (9)$$

By defining $f_n \equiv \tau_n \alpha^n / n!$, Eq. (9) can be simplified to

$$(k_{\text{on}}n + n + \alpha) f_n - (n + 1) f_{n+1} - \alpha f_{n-1} = \alpha^n / n! \quad (10)$$

which looks quite similar to Eq. (4) and can be transformed into a differential equation by introducing $F(z) = \sum_{n=0}^{\infty} z^n f_n$. The solution is immediate:

$$F(z) = \int_{z_s}^z \frac{z_s}{x - z_s} \left| \frac{x - z_s}{z - z_s} \right|^{z_s^2 k_{\text{on}} \alpha} \exp\left(\frac{k_{\text{on}} \alpha x + \alpha z}{k_{\text{on}} + 1}\right) dx. \quad (11)$$

The mean waiting time in equilibrium for the switch to turn on is $\bar{\tau} = \sum_n \tau_n C_n = \sum_n f_n e^{-\alpha} = F(1) e^{-\alpha}$ or

$$\bar{\tau} = \int_{z_s}^1 \frac{e^{-\alpha} z_s}{x - z_s} \left(\frac{x - z_s}{1 - z_s} \right)^{z_s^2 k_{\text{on}} \alpha} \exp\left(\frac{k_{\text{on}} \alpha x + \alpha}{k_{\text{on}} + 1}\right) dx. \quad (12)$$

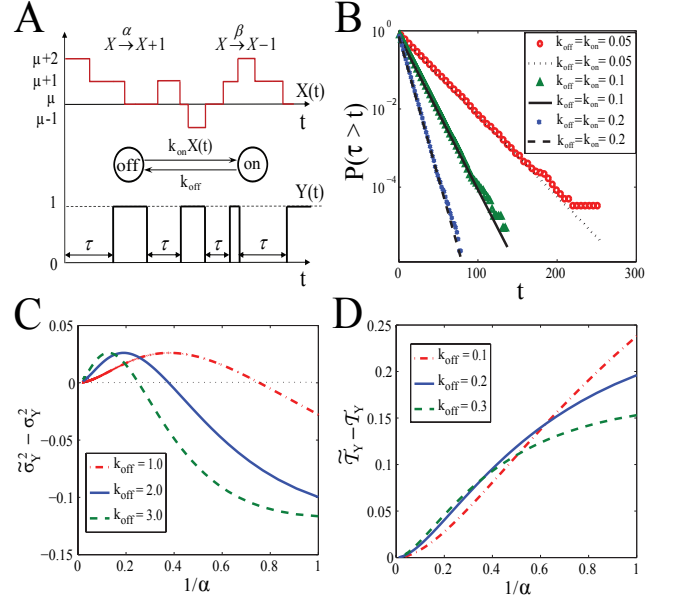


FIG. 1: (color online). (A) Schematic representation of our model. (B) $P(\tau > t)$ versus t , with fixed $\alpha = 1$ and $\beta = 1$ but different k_{on} and k_{off} . Symbols represent simulation results, while lines denote $P(\tau > t) = \exp(-\tilde{k}_{\text{on}}\alpha t)$. (C) $\sigma_Y^2 - \sigma_Y^2$ versus $1/\alpha$ from theory, where we choose $\beta = 1, k_{\text{on}} = 1$, and different values of k_{off} . (D) $\bar{\tau}_Y - \tau_Y$ versus $1/\alpha$ from theory, for $\beta = 1, k_{\text{on}} = 0.1$, and different k_{off} .

In the slow switch limit ($k_{\text{on}}\alpha \ll \beta = 1$), we can evaluate the integral of Eq. (12) by expanding its exponential term around $k_{\text{on}}\alpha$. To leading order, this gives $\bar{\tau} \approx (z_s k_{\text{on}}\alpha)^{-1}$, which is obviously larger than the average time, $K_+^{-1} = (k_{\text{on}}\alpha)^{-1}$, for the on transition in the constant input model. Thus, for our noisy input model, we can define an effective on rate, $\tilde{k}_{\text{on}} \equiv z_s k_{\text{on}}$. Correspondingly, we can define an effective forward rate $\tilde{K}_+ \equiv \tilde{k}_{\text{on}}\alpha$ which, in terms of K_+ , can be written as:

$$\tilde{K}_+ \equiv z_s K_+ = \frac{\alpha K_+}{\alpha + K_+} = \left(\frac{1}{\alpha} + \frac{1}{K_+} \right)^{-1} < K_+. \quad (13)$$

To analyze the effect of input noise, we vary α and simultaneously fix the forward rate $K_+ = k_{\text{on}}\alpha$ such that the mean on-state occupancy for the constant input model, $K_+/(K_- + K_+)$, remains constant. In contrast, the mean on-state occupancy for our noisy input model is $\tilde{K}_+/(K_- + \tilde{K}_+)$ which is less than $K_+/(K_- + K_+)$ by Eq. (13). This means that the input noise will effectively suppress the on state by prolonging the average time for the switch to turn on. The larger the noise, the more the suppression. Our Monte-Carlo simulations reveal that the switch's off-state residence times (τ) are still, to good approximation, distributed exponentially, $P(\tau > t) \approx \exp(-\tilde{k}_{\text{on}}\alpha t)$, as shown in Fig. 1B. Thus, $Y(t)$ in this case can be well approximated as a two-state Markov process with transition rates $\tilde{k}_{\text{on}}\alpha$ and k_{off} . Likewise, we can evaluate $P_{\text{on}} = G(1)$ by Taylor expansion in

this slow switch limit, yielding

$$P_{\text{on}} \approx \frac{k_{\text{on}}\alpha}{k_{\text{on}}k_{\text{off}} + k_{\text{on}}\alpha + k_{\text{off}}} = \frac{\tilde{k}_{\text{on}}\alpha}{\tilde{k}_{\text{on}}\alpha + k_{\text{off}}}, \quad (14)$$

consistent with the result $\bar{\tau} \approx 1/(\tilde{k}_{\text{on}}\alpha)$. So the variance of $Y(t)$ is $\tilde{\sigma}_Y^2 = P_{\text{on}}(1 - P_{\text{on}}) \approx \tilde{k}_{\text{on}}\alpha k_{\text{off}}/(\tilde{k}_{\text{on}}\alpha + k_{\text{off}})^2$. In contrast, the output variance for the constant-input model is $\sigma_Y^2 = k_{\text{on}}\alpha k_{\text{off}}/(k_{\text{on}}\alpha + k_{\text{off}})^2$. Their difference $\tilde{\sigma}_Y^2 - \sigma_Y^2$ is plotted as a function of α^{-1} for fixed k_{on} in Fig. 1C. For small noise ($\alpha = \mu^2/\sigma^2 \gg 1$), we find

$$\tilde{\sigma}_Y^2 - \sigma_Y^2 \approx \frac{k_{\text{off}}[k_{\text{on}}\alpha - 2k_{\text{off}}(2 + k_{\text{on}})]}{k_{\text{on}}\alpha^2} + \mathcal{O}\left(\frac{1}{\alpha^3}\right). \quad (15)$$

Eq. (15) shows that the input noise contributes in a non-additive way to the output variance [13]; the contribution can be negative when $\alpha < 2k_{\text{off}}(1 + 2k_{\text{on}}^{-1})$. This seemingly surprising result has a simple explanation: a two-state switch at any moment is just a Bernoulli random variable and hence its variance is strictly upper bounded by one quarter. From Eq. (14) and Fig. 1B, one can see that the net effect of input noise is to reduce the on rate from k_{on} to \tilde{k}_{on} . This turns out to be a general feature for any two-state (single) switch system, no matter how the input process is defined or whether the switch exhibits an ultra-sensitive response through cooperativity. We will elaborate on this point elsewhere. Returning to our noisy input model, the output autocorrelation time is $\tilde{\mathcal{T}}_Y \approx (\tilde{k}_{\text{on}}\alpha + k_{\text{off}})^{-1}$, which is obviously larger than $\mathcal{T}_Y \equiv (k_{\text{on}}\alpha + k_{\text{off}})^{-1}$, the output autocorrelation time for the constant-input model. In the limit $\alpha \gg k_{\text{off}}/k_{\text{on}}$, we find that $\tilde{\mathcal{T}}_Y - \mathcal{T}_Y \approx \alpha^{-1} + \mathcal{O}(\alpha^{-2})$. So $\tilde{\mathcal{T}}_Y$ increases with the relative level of input noise ($\alpha^{-1} = \sigma^2/\mu^2$) when the mean of X is much larger than the dissociation constant $K_d \equiv k_{\text{off}}/k_{\text{on}}$; see Fig. 1D. Consider an integration of the output signal $Y(t)$ over a time window T (assuming $T \gg \mathcal{T}_Y$). The output noise after temporal averaging is:

$$\text{Var}\left(\frac{1}{T} \int_0^T Y(t) dt\right) \simeq \frac{2\tilde{\mathcal{T}}_Y}{T} \tilde{\sigma}_Y^2, \quad (16)$$

which may still decrease with the relative level of input noise α^{-1} , just as $\tilde{\sigma}_Y^2$ does (Fig. 1C). All the above results show that the *additive noise rule* is an incomplete characterization of the input-output noise relationship for a single switch system. Finally, we calculate the mean number of particles given that the switch is on,

$$N_{\text{on}} = \frac{\sum_n n P_n}{\sum_n P_n} = \frac{G'(1)}{G(1)} = \alpha \left(\frac{1}{P_{\text{on}}} - \frac{k_{\text{off}}}{k_{\text{on}}\alpha} \right). \quad (17)$$

Using our result for P_{on} in the slow switch limit, we get

$$N_{\text{on}} \approx \alpha \left(1 + \frac{k_{\text{off}}}{\alpha} \right) = \alpha + k_{\text{off}} > \alpha. \quad (18)$$

Thus, input noise can increase N_{on} significantly if k_{off} is relatively large. The average number of particles given

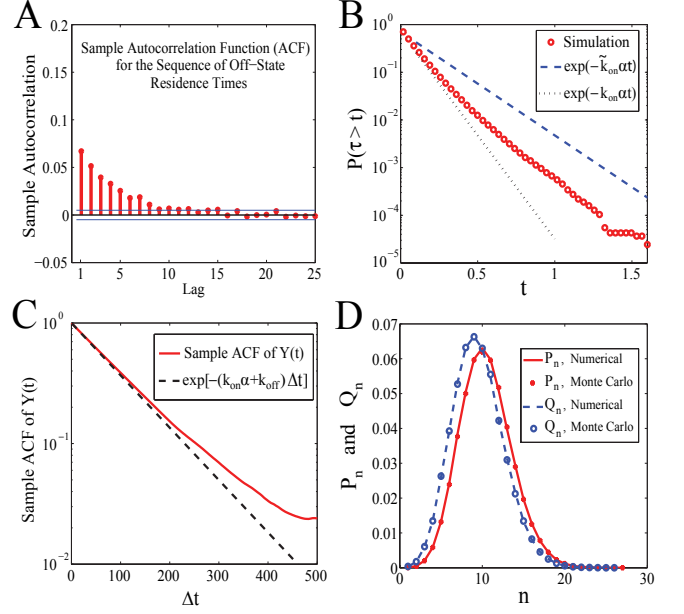


FIG. 2: (color online). We choose $\alpha = 10$, $\beta = 1$, $k_{\text{on}} = 1$, and $k_{\text{off}} = 10$. (A) Sample ACF of the sequence of the off-state residence times. (B) Distribution of the off-state residence times. (C) Sample ACF of $Y(t)$. (D) P_n and Q_n versus n .

that the switch is off, denoted by N_{off} , is found as well:

$$N_{\text{off}} = \frac{\sum_n n Q_n}{\sum_n Q_n} = \frac{\mu - G'(1)}{1 - G(1)} = \frac{k_{\text{off}}}{k_{\text{on}}} \frac{P_{\text{on}}}{1 - P_{\text{on}}}, \quad (19)$$

which, in the slow switch limit, gives

$$N_{\text{off}} \approx K_d \frac{\tilde{k}_{\text{on}}\alpha}{k_{\text{off}}} = z_s \alpha = \frac{\alpha}{1 + k_{\text{on}}} < \alpha. \quad (20)$$

Thus, we have $N_{\text{off}} < N_{\text{on}}$ in general.

In the fast switch limit ($k_{\text{on}}\alpha \gg \beta = 1$), the approximate expression for Eq. (12) is found to be

$$\bar{\tau} \approx \frac{e^{-\tilde{k}_{\text{on}}\alpha}}{\tilde{k}_{\text{on}}\alpha} + \frac{e^{-\tilde{k}_{\text{on}}\alpha}}{k_{\text{on}} + 1} \left[1 + \sum_{j=1}^{\infty} \frac{(\tilde{k}_{\text{on}}\alpha)^j}{j \cdot j!} \right]. \quad (21)$$

For fixed α and $k_{\text{on}} \rightarrow \infty$, we have $\tilde{k}_{\text{on}} \rightarrow 1$ and hence $\bar{\tau} \rightarrow e^{-\alpha}/\alpha$ which is just the time to leave the $n = 0$ state times the probability of being in the $n = 0$ state. Looking at the maximal noise limit ($\alpha \ll 1$), we can restrict our attention to $n = 0$ and $n = 1$. This results in a simple Markov chain model where one can easily calculate,

$$P_0 \approx \frac{k_{\text{on}}\alpha}{k_{\text{off}}^2 + k_{\text{off}} + k_{\text{on}}\alpha + k_{\text{off}}k_{\text{on}}}, \quad (22)$$

such that the overall probability to find the switch on is

$$P_{\text{on}} \approx P_0 + P_1 \approx \frac{(k_{\text{off}} + \alpha + 1)k_{\text{on}}\alpha}{k_{\text{off}}^2 + k_{\text{off}} + k_{\text{on}}\alpha + k_{\text{off}}k_{\text{on}}}. \quad (23)$$

Unlike the case of a slow switch, the successive off-state residence times are slightly correlated with each other (Fig. 2A), as a natural result of the temporal correlation in the input process. The distribution of these off-state residence times, $P(\tau)$, is not exponential (Fig. 2B), especially at the head, although its tail decays exponentially at the rate $\tilde{k}_{\text{on}}\alpha$. In Fig. 2C, we draw the sample *autocorrelation function* (ACF) for the simulated output path. Clearly, the ACF of $Y(t)$ exhibits a much longer tail than what one expects from the constant input model, demonstrating a long-term memory in $Y(t)$. All the above results (Fig. 2A-C) show that the output process is strongly non-Markovian in the fast switch limit. As a last illustration of the interdependence of input and output, we plot in Fig. 2D the equilibrium conditional distributions, P_n and Q_n , which are obtained either directly by running Monte-Carlo simulations or indirectly by numerically evaluating Eq. (7) and applying Eq. (4). Clearly, Fig. 2D shows $N_{\text{off}} < N_{\text{on}}$.

Our results may have broad biological implications. The effects of input noise on the output may be quite different, depending on the input relaxation time β^{-1} compared to the typical switching time scale \mathcal{T}_Y . The rate β can represent either the degradation of input particles or molecular diffusion which removes input particles from a particular space for chemical reaction. If molecular diffusion is the biophysical basis for β , then faster diffusion will make the input noise less appreciable, consistent with the Berg-Purcell formula for concentration sensing limits [4, 11, 14, 15]. Many biological processes may be classified into this scenario where input fluctuations are of little impact. For example, switching of DNA promoters usually occurs at a time scale much longer than

the characteristic diffusion time of transcription factors, providing a temporal averaging opportunity to suppress the input noise. Eukaryotic gradient sensing is another example where the chemoattractant diffuses so fast that we can ignore the input diffusive noise when considering cellular gradient sensing capacities [14, 16]. Nonetheless, there exist biological cases where the input relaxes much slower than the biochemical switch flips its states. Take for example the bacterial flagellar motors which rotate either clockwise or counterclockwise for chemotactic movements. The probability of clockwise motor spinning depends sharply on the concentration of CheY-P in *E. coli* [17]. The correlation time of the input CheY-P level is dominated by slow methylation kinetics and measures 10 ~ 30 seconds [18]. This is much longer than the typical switching time of the flagellar motors which is approximately 1 second [17, 18]. Therefore, input noise in this system is expected to have interesting effects on the motor switching statistics, as experimentally revealed in [17] and theoretically explored in [18].

In summary, we have studied a solvable stochastic model to examine how input fluctuations affect a simple biochemical switch. Our results show that the presence of input noise does not necessarily increase the output variance. It does however act to suppress the on state. We also demonstrate that the presence of memory effects can induce non-exponential statistics in the output switching process. It is interesting to extend our current model by incorporating other effects such as feedbacks and cooperativity. Work in this direction is underway.

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