

Constructive role of noise in signal transmissions by biomembrane proteins

A. Fuliński* and P. F. Góra

M. Smoluchowski Institute of Physics, Jagellonian University, Reymonta 4, 30-059 Kraków, Poland

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We discuss new examples of the constructive role of environmental fluctuations in biophysical processes, namely quantitative enhancement and qualitative sharpening of the outgoing signal in the intercellular signal transduction, e.g., in the synaptic links. An experimental check in a chemical flow reactor is suggested.

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I. INTRODUCTION

Although the idea of a *constructive role of noise and fluctuations* seems paradoxical at first sight, the impact of intrinsic noise (spontaneous fluctuations) on various processes is gaining more and more attention. Indeed, for real systems, noise is never strictly zero, and in mesoscopic systems, in particular in biological ones, noise may play a dominant role in the kinetics because more or fewer random fluctuations of physical and chemical parameters are inherent to the environment of biologically important proteins, especially those embedded within membranes of living cells. In fact, the suggestion that “the noise may be a source of order rather than disorder” and that “a biological organism makes use of energy-driven fluctuations for the purpose of signal and free-energy transduction” was put forward about ten years ago by Astumian *et al.* [1]. This suggestion was later discussed in more detail by the present author [2]. Serious discussion of the constructive role of noise in biophysical and biochemical processes began a few years ago [3] and at present it seems to be a well-established idea [4].

The best known phenomena in this respect are the famous stochastic resonance [5] and molecular motors (Brownian ratchets) [6], although there are other manifestations, such as, e.g., noise-induced phase transitions [7], noise-induced resonances [8], fluctuating barrier kinetics [9,10], noise-enhanced stability [11] and synchronization [12], propagation of signals in nonlinear noisy environments [13,14], noise-sustained oscillations in subexcitable media with a threshold [15], etc.

In this paper, we report another phenomenon in which noise helps in transmitting signals. We are going to show that, when the incoming signal (driving field) is coupled to the transmitting process in a multiplicative way, the addition of multiplicative noise improves the outgoing signal (transmitter’s response) both quantitatively and qualitatively. It is noteworthy that in most cases of the constructive role of noises in signal transmission discussed so far, the incoming signal is additive in the transmitter’s kinetics. On the other hand, parametric couplings of the external signal (driving field) to the “transmitter” (kinetic process) exist typically in biological systems, in particular in processes governed by enzymes embedded in cell membranes that are coupled to the membrane electric potential [1,2]. Therefore, the effect dis-

cussed below may be of relevance for signal transduction in living organisms.

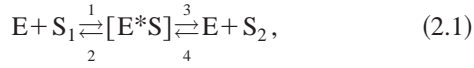
This paper is organized as follows. A biological motivation for considering the type of models discussed in the present paper, as well as their connection with experimental data, is briefly presented in Sec. II. The constructive role of noise in transmitting signals is discussed for a realistic model of a membrane-protein system in the same section, and then for a simplified “skeletal” model in Sec. III. This simplified model, however, offers the possibility of a more thorough analysis. A brief discussion is presented in Sec. IV. A sketch of a proposed experimental verification of the theory presented here is offered in Appendix B, and mathematical details are presented in two other Appendixes.

II. A MEMBRANE-PROTEIN SYSTEM

Random fluctuations and periodic oscillations of physical and chemical parameters are inherent to the environment of many proteins, particularly those embedded within the membranes of living cells. One parameter particularly relevant for membrane enzymes is the membrane potential ψ , which is typically between 50 and 250 mV [2]. The effects of a static external field on enzyme kinetics and thermodynamics are well known. Oscillating, both regular and random, external fields (ac fields) can cause an enzyme to drive a reaction away from equilibrium [1]: The main requirement is that some enzyme conformational transitions be influenced by the field and that the fluctuations in the field be driven by a free-energy dissipating process. As a result, enzymes should be capable of transducing free energy from external fluctuations in their environment. Macroscopic fluctuations of the membrane potential of ± 50 mV have been observed experimentally [1], and even larger stochastic oscillations may well occur in the vicinity of ion channels and membranes. Furthermore, large-amplitude oscillations of the membrane potential are relatively simple to attain experimentally due to the fact that an externally applied field is amplified across closed-cell membranes. These facts present a biological motivation for including large fluctuations in any realistic model of a protein molecule embedded in a cell membrane.

Consider such a molecule (an enzyme E) embedded in the synapse linking the neurons. The protein can be in several distinct internal states. The simplest (two-state) model of the enzyme-governed process, describing the effect of a varying electric field on the action and efficiency of the membrane enzymes [1,2,16,17], can be written schematically as

*Email address: fulinski@if.uj.edu.pl; http://zfs.if.uj.edu.pl



$$\dot{P} = -(k_1 S_1 + k_2 + k_3 + k_4 S_2)P + k_2 + k_3, \quad (2.2)$$

where $P(t)$ is the probability of the enzyme being in the state E [$1 - P(t)$ is the probability of the enzyme being in the state E^*S], S_j are concentrations of substances S_j , and k_j are the effective [18] rate coefficients for processes symbolized by arrows in the scheme (2.2). A crucial property of the model is the dependence of these coefficients on the membrane electric potential $\psi(t) = \psi_e(t) + \xi(t)$, composed of an external field (incoming signal) $\psi_e(t)$ and intrinsic fluctuations $\xi(t)$ [2] (the static part is included in the coefficients α_j):

$$k_j = \alpha_j \exp\{-D_j \psi(t)\}. \quad (2.3)$$

This model, proposed about ten years ago [16] and later extended to include intrinsic fluctuations [2], describes the kinetics of an enzyme cycle under the influence of an alternating (ac) electrical fields. Its main features are (i) the membrane electric potential $\psi(t)$ plays the role of a potential barrier (Arrhenius activation energy), (ii) $\psi(t)$ is composed of an external driving field (input signal) and of intrinsic fluctuations, therefore both the signal and the noise enter the kinetic equation in a multiplicative (nonlinear) way, and (iii) the membrane potential fluctuations are composed of residual (endogenous) noise (mostly thermal) and noise created by the induced activity of nearby ionic channels.

The compatibility of this model with reality has been checked by one of the present authors [2] by comparing its predictions with experimental data on the average current of Na^+ ions pumped by $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ induced by an external (sinusoidal or random) ac field in human erythrocytes [19]. It should be noted that the two-state model without fluctuations of the membrane potential is unable to reproduce these data. A more involved, four-state model has also been proposed [20], but this model without fluctuations cannot reproduce the experimental data either.

We expect that the model (2.2) and (2.3) can also be used for a description of the intercellular signal transmission, e.g., in the synapses linking neurons: Since the model works well

for the transport phenomena, it should describe the system composed of the membrane potential, the protein, and the neurotransmitter at least qualitatively equally well, as the biological mechanisms responsible for the two phenomena are similar [21]. The electric signal (a spike in the membrane potential) causes the membrane protein complex E^*S to release the neurotransmitter S_2 into the synapse space. The latter is caught by proteins on the other side of the synapse, releasing the electric spike(s) in the dendrite(s) of other neuron(s) forming the synapse. In the scheme (2.2), the state $[E^*S]$ is binding (synthesizing) and state E releases the neurotransmitters. Thus the outgoing signal will be proportional to the probability $P(t)$ of the protein being in the state E.

There are no data on the kinetic parameters (α_j , D_j) for synaptic proteins. Therefore, to keep our modeling as realistic (though simplified) as possible, we shall use the values of these parameters determined for another membrane enzyme, viz., $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ [2], expecting them to be not very different from these involved in the signal transmission, the more so that this ATPase is one of the key enzymes responsible for neural conduction. These parameters are $S_1 \alpha_1 = 270 \text{ s}^{-1}$, $\alpha_2 = 4.0 \text{ s}^{-1}$, $\alpha_3 = 0.11 \text{ s}^{-1}$, $S_2 \alpha_4 = 5.4 \text{ s}^{-1}$, $D_1 = -D_2 = 1.74$, and $D_4 = -D_3 = 2.62$. With these values, the characteristic time (relaxation time τ_r) of the kinetics (2.2) is of the order of magnitude of ms.

The fluctuations $\xi(t)$ are approximated by the dichotomous noise,

$$\xi(t) \in \{\Delta, -\Delta\}, \quad \xi^2(t) = \Delta^2, \quad (2.4)$$

$$\langle \xi(t) \rangle = 0, \quad \langle \xi(t) \xi(t + \tau) \rangle = \Delta^2 \exp(-\Lambda \tau). \quad (2.5)$$

Note that since there is an exponential dependence of the rate coefficients (2.3) on the noise, modeling the latter by a Gaussian white noise would be clearly unphysical. Due to the property (2.4), the rate coefficients and the kinetic equation can be written as

$$k_j = \alpha_j \exp(-D_j \psi_e) \left(\cosh D_j \Delta - \frac{1}{\Delta} \xi(t) \sinh D_j \Delta \right), \quad (2.6)$$

$$\dot{P}(t) = -[f_1(t) + f_2(t) \xi(t)]P(t) + f_3(t) + f_4(t) \xi(t). \quad (2.7)$$

with

$$f_1(t) = \alpha_1 S_1 \exp(-D_1 \psi_e(t)) \cosh D_1 \Delta + \alpha_4 S_2 \exp(-D_4 \psi_e(t)) \cosh D_4 \Delta + f_3(t), \quad (2.8a)$$

$$f_2(t) = -\frac{1}{\Delta} [\alpha_1 S_1 \exp(-D_1 \psi_e(t)) \sinh D_1 \Delta + \alpha_4 S_2 \exp(-D_4 \psi_e(t)) \sinh D_4 \Delta] + f_4(t), \quad (2.8b)$$

$$f_3(t) = \alpha_2 \exp(-D_2 \psi_e(t)) \cosh D_2 \Delta + \alpha_3 \exp(-D_3 \psi_e(t)) \cosh D_3 \Delta, \quad (2.8c)$$

$$f_4(t) = -\frac{1}{\Delta} [\alpha_2 \exp(-D_2 \psi_e(t)) \sinh D_2 \Delta + \alpha_3 \exp(-D_3 \psi_e(t)) \sinh D_3 \Delta]. \quad (2.8d)$$

The solution of Eq. (2.7), averaged over the noise, can be found using a theorem by Shapiro and Loginov [22]—see Appendix A for details. Further analysis depends on the shape of the input signal (external driving) $\psi_e(t)$.

A typical situation in the interneuronal signal transmission is the arrival of a single short spike in the action potential (input signal). We shall represent it by the rectangular pulse $\psi_e(t) = b\phi(t)$ with

$$\phi(t) = \begin{cases} 1 & \text{if } t \in [t_i, t_f], \\ 0 & \text{otherwise.} \end{cases} \quad (2.9)$$

In this case, the numerical calculations are rather simple. The influence of the noise (membrane potential fluctuations) on the shape and intensity of the response (outgoing signal), i.e., of $\langle P(t) \rangle$, is shown in Fig. 1 for a relatively long duration (50 ms) of the pulse. It is easily seen that the presence of noise *improves* both the intensity and the shape of the outgoing signal. The increase of intensity depends on the pulse duration. Figure 2 shows the relative gain as the function of impulse width δ : for short pulses (about a few ms), the gain is considerable, about 30%. Figure 1 shows also that, for broader pulses, there is an improvement in the shape of the output signal: the noisy response attains its maximal value faster than the noiseless one. Both of these counterintuitive effects—quantitative enhancement and qualitative sharpening of the outgoing signal—are unexpected new examples of the constructive role of the environmental fluctuations in the biophysical processes.

A similar conclusion can be reached also for the continuous input signal in the form of a sinusoidal wave. The formulas in this case become rather involved and the results for the kinetics (2.7) will be reported elsewhere. Note also that knowing the response of this system to a strictly periodic signal is probably of lesser importance as one seldom encounters such excitations in a realistic biological context.

III. SKELETAL SYSTEM

The phenomenon described above can also be demonstrated in the simplest possible situation (the “skeletal” system) composed of a linear transmitter perturbed by independent Gaussian white noises:

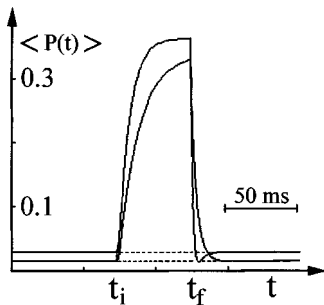


FIG. 1. Shape of outgoing signal in the absence (lower curve, $\Delta^2=0$) and presence (upper curve, $\Delta^2=2.0$) of the noise. Time $t \gg \tau_r$. Note that the noise increases the background (dotted lines). $\Lambda = 4 \text{ ms}^{-1}$.

$$\dot{X}(t) = -[a + f(t) + \eta_1(t)]X(t) + B + \eta_2(t), \quad (3.1)$$

where $a > 0$; B are constants; $\eta_{1,2}(t)$ are the noises,

$$\langle \eta_{i,j}(t) \rangle = 0, \langle \eta_i(t) \eta_j(t') \rangle = D_i^2 \delta_{ij} \delta(t - t'), \quad i, j = 1, 2; \quad (3.2)$$

and $f(t)$ is an external field (the incoming signal) being transmitted. In the following, we will take $f(t)$ to be either the rectangular pulse or the continuous sinusoidal signal; in the latter case the system’s response (the outgoing signal) will be averaged over the initial phase of the incoming signal.

The reason for studying such a simple system as the flow (3.1) is twofold. First, it is clear that if constructive effects of noise appear in such a simple system, they will also appear in more complicated ones, without phase-averaging, in non-linear cases, and for nonequilibrium (colored, coupled, non-Markovian, etc.) noises. Second, such a system can model various chemical reactions and thus can be easily realized experimentally in a flow reactor with variable influxes (see Appendix B and, e.g., [23]), thus allowing for an experimental check of the theory presented here.

A formal solution to Eq. (3.1) reads

$$\begin{aligned} X(t) = & \exp\left[-\int_0^t [a + f(t') + \eta_1(t')] dt'\right] X_0 \\ & + \int_0^t \exp\left[-\int_{t'}^t [a + f(t'') + \eta_1(t'')] dt''\right] \\ & \times [B + \eta_2(t')] dt'. \end{aligned} \quad (3.3)$$

It is easy to see that the response of the system (3.1) to the additive random driving is also random and therefore vanishes in the mean. Thus the term containing η_2 in Eq. (3.3) gives no contribution to the average of $X(t)$, but its effects do not vanish in the correlation $\langle X(t)X(t + \tau) \rangle$,

$$\begin{aligned} \langle X(t) \rangle = & e^{-[a - (1/2)D_1^2]t} \exp\left[a - \int_0^t f(t') dt'\right] X_0 \\ & + B \int_0^t e^{-[a - (1/2)D_1^2](t-t')} \exp\left[-\int_{t'}^t f(t'') dt''\right] dt', \end{aligned} \quad (3.4)$$

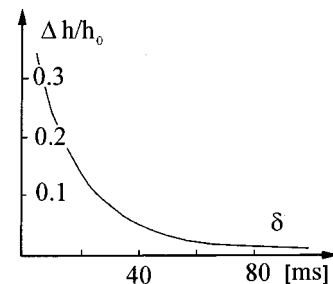


FIG. 2. Relative gain $h(\Delta^2) - h(0)/h(0)$ (h is the maximal height of the outgoing signal, cf. Fig. 1) as a function of the duration $\delta = t_f - t_i$ of the incoming signal.

where the well-known fact has been used that for a Gaussian white noise

$$\left\langle \exp \left[\pm \alpha \int_{t_1}^{t_2} \eta_i(t') dt' \right] \right\rangle = \exp \left[\frac{1}{2} \alpha^2 D_i^2 (t_2 - t_1) \right]. \quad (3.5)$$

Note that for $a < D_1^2$, the system is formally divergent.

Further details depend on the shape of the incoming signal $f(t)$.

A. The rectangular pulse

The incoming signal has the form (2.9). A constant external forcing $B \neq 0$ is now necessary to keep the transmitter in an active state. Calculations with the signal (2.9) are elementary and give

$$\langle X(t) \rangle = e^{-\beta t} X_0 + \frac{B}{\beta} (1 - e^{-\beta t}), \quad (3.6a)$$

$$\begin{aligned} \langle X(t) \rangle &= e^{-\beta t} e^{-b(t-t_i)} X_0 + \frac{B}{\beta} (e^{-\beta(t-t_i)} - e^{-\beta t}) \\ &\quad + \frac{B}{\beta+b} (1 - e^{-(\beta+b)(t-t_i)}), \end{aligned} \quad (3.6b)$$

$$\begin{aligned} \langle X(t) \rangle &= e^{-\beta t} e^{-b(t_f-t_i)} X_0 \\ &\quad + \frac{B}{\beta} (1 + e^{-\beta(t-t_i)} - e^{-\beta(t-t_f)} - e^{-\beta t}) \\ &\quad + \frac{B}{\beta+b} (e^{-\beta(t-t_f)} - e^{-\beta(t-t_i)} e^{-b(t_f-t_i)}), \end{aligned} \quad (3.6c)$$

with $\beta = a - \frac{1}{2} D_1^2$ for $t < t_i$, $t_i < t < t_f$, and $t_f < t$, respectively. Typical responses are shown in Fig. 3. It is clear that for t large enough, the system, prior to the arrival of the pulse, would rest in its stationary state B/β (this is an averaged effect: any specific realization would oscillate randomly around this value), then it would start to grow, and eventually it would start to decay back to the stationary state after the pulse has ended. Note that the magnitude of the response increases with the noise level D_1^2 . However, the skeletal system (3.1) is a poor transmitter, much worse than the protein system of Sec. II; in particular, the shape of the incoming pulse is reproduced badly. This improves slightly for pulses of longer duration [cf. Fig. 3(b)].

B. Oscillatory external driving

In this case, the incoming signal has the form of a sinusoidal wave:

$$f(t) = b \Omega \cos(\Omega t + \phi), \quad (3.7)$$

and we put the constant background $B=0$ as in this case its presence is not necessary for the system to be able to respond. The response of the system, averaged over the noise realizations, is now

$$\begin{aligned} \langle X(t) \rangle &= \left\langle \exp \left[- \int_0^t [a + b \Omega \cos(\Omega t' + \phi) + \eta_1(t')] dt' \right] \right\rangle X_0 \\ &= e^{-[a - (1/2) D_1^2] t} \exp \left[- 2b \sin \frac{1}{2} \Omega t \cos \left(\frac{1}{2} \Omega t + \phi \right) \right] X_0 \\ &= e^{-[a - (1/2) D_1^2] t} \exp \{ b [\sin \phi - \sin(\Omega t + \phi)] \} X_0, \end{aligned} \quad (3.8)$$

where Eq. (3.5) has been used; averaging over η_2 produces a zero mean value. Note that if $D_1^2 > a$, the system is formally divergent. More interesting results can be obtained from the correlations of Eq. (3.3) with Eq. (3.7) and $B=0$. In this case, the correlations approach a stationary state:

$$\begin{aligned} \langle \langle X(t) X(t+\tau) \rangle \rangle &\rightarrow_{t \rightarrow \infty} \langle \langle X^2(\tau) \rangle \rangle_{st} \\ &= D_2^2 e^{-[a - (1/2) D_1^2] \tau} \int_0^\infty dt' e^{-2(a - D_1^2) t'} I_0 \\ &\quad \times \left\{ 4b \sin \left[\frac{1}{2} \Omega (\tau + t') \right] \right\}. \end{aligned} \quad (3.9)$$

Here the $\langle \langle \dots \rangle \rangle$ stands for averaging over realizations of the noises η_1, η_2 first, and then averaging over the initial phase, ϕ , of the incoming signal. I_0 is a modified Bessel function; see Appendix C for details. Although any further quantitative analysis of Eq. (3.9) needs to be done numerically, one thing is clear: $\langle \langle X^2(\tau) \rangle \rangle_{st}$ does not vanish for any $D_2^2 > 0$ even though the average (3.8) decays as time goes to infinity; rather than that, it displays damped oscillations for appropriate values of the parameters.

This result is seemingly paradoxical. Indeed, the additive noise η_2 does not show up *on the average*, but any individual trajectory (realization) feels its presence even for very large times t and fluctuates. These fluctuations are capable of exhibiting correlations echoing signatures of the input signal.

The form of Eq. (3.9) might suggest that the basic frequency has somehow shrunk from Ω to $\frac{1}{2}\Omega$. In fact, this is not the case as the modified Bessel function I_0 has only even powers of its argument in its Taylor expansion, and Eq. (3.9) depends actually on $\sin^2 \frac{1}{2} \Omega \tau$. The original frequency of the driving signal is thus restored.

The correlations are related through the Wiener-Khinchin theorem to the power spectrum of the process $X(t)$. The stationary power spectrum averaged over the initial phase of the incoming signal is

$$S(\omega) = \int_0^\infty \cos(\omega \tau) \langle \langle X^2(\tau) \rangle \rangle_{st} d\tau. \quad (3.10)$$

It is a directly measurable quantity, allowing for an experimental check of the theory presented here. In the transient (short-time) regime, or without the ϕ averaging, the system is nonstationary and the correlation function $\langle X(t) X(t+\tau) \rangle$

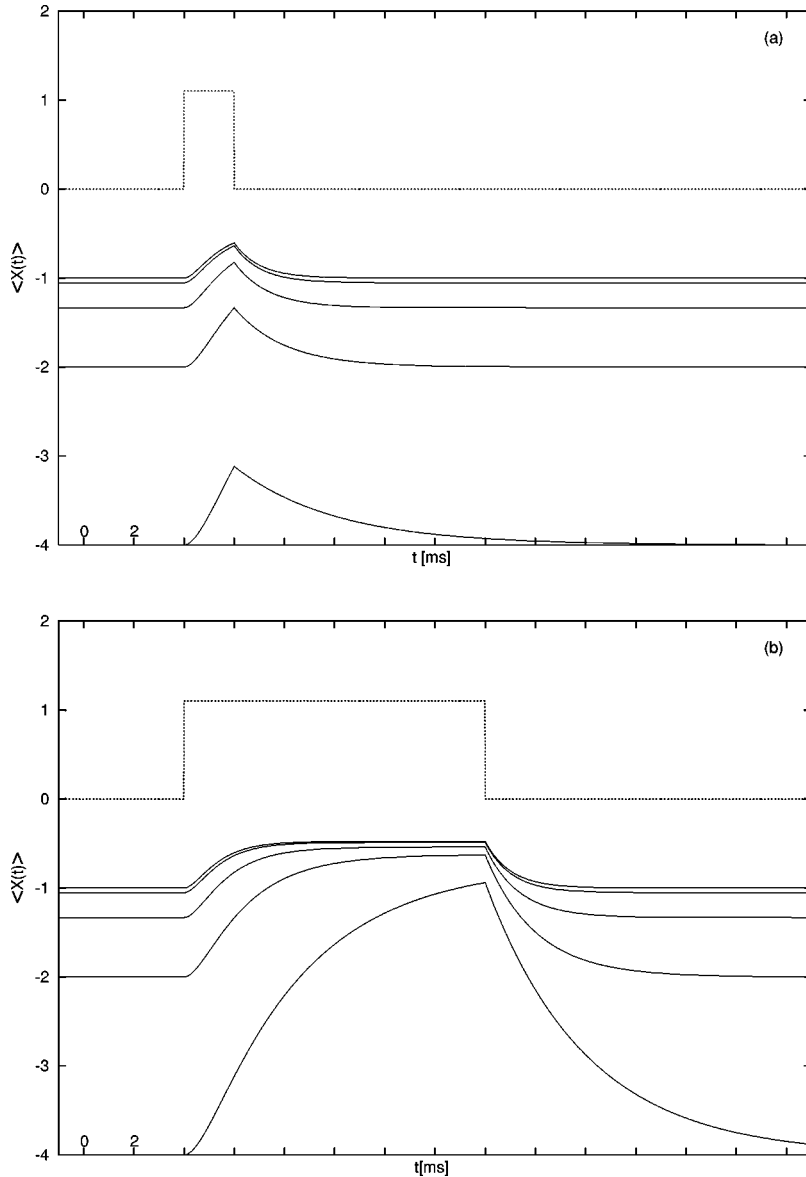


FIG. 3. Response of the skeletal system (3.1) to the pulse input signal averaged over the noise realizations. (a) Dashed line, the incoming signal; solid lines, top to bottom the responses with $D_1^2 = 0.0, 0.1, 0.5, 1.0,$ and $1.5,$ respectively. The signal duration is $t_f - t_i = 2.0.$ Other parameters are $a = B = 1.0, b = 1.1.$ (b) Same as (a) but with signal duration $t_f - t_i = 12.0.$

as well as the corresponding power spectrum depend on time t ; nevertheless, the nonstationary power spectrum is still a directly measurable quantity (see, e.g., [24]).

In the transient regime, the multiplicative noise sharpens the outgoing signal in the absence of the additive noise; this effect is clearly visible even after the averaging over the initial phase, ϕ (Fig. 4). The stationary outgoing periodic signal is also sharpened in the presence of the additive noise (Fig. 5), but the effect is weaker than in the transient regime. Still, in the stationary case an increase in the noise power D_1^2 for 0 to 0.4 results in an increase (weakly exponential) of the signal peak height h of about 35%, and in a decrease (roughly linear) of its width Δ at $\frac{1}{2}h$ of about 18%. The height of the central peak, representing the output noise of the transmitter itself, increases much faster, and the width of it decreases slightly slower than those of the signal peaks. Note also that the correlations depend strongly on the amplitude of the driving signal. For small amplitudes, there are essentially no correlations, just a Debye peak for $\omega = 0.$ For larger values of the amplitude, correlations echoing the

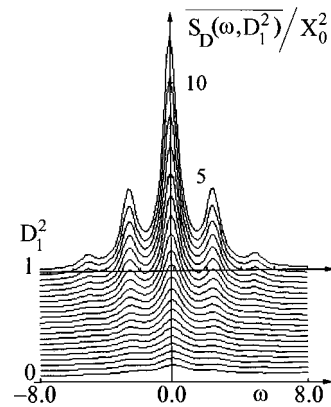


FIG. 4. The effect of sharpening of the transient outgoing signal by multiplicative noise in the absence of additive noise. $a = b = 1, \Omega = 2.5, \Omega t = \pi.$ Overbar means the average over initial phase $\phi.$

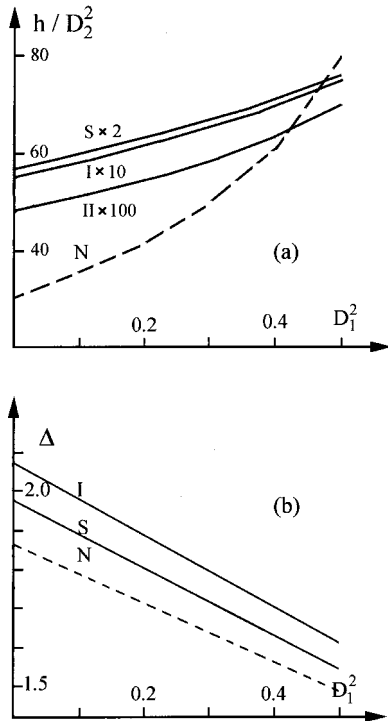


FIG. 5. The effect of sharpening of the stationary outgoing periodic signal by multiplicative noise in the presence of additive noise. (a) Height h (in units of D_2^2), (b) width Δ at $\frac{1}{2}h$ of the main peaks of the stationary frequency spectrum. $a = 1$, $b = 2$, $\Omega = 12$. N denotes the central peak (output noise), S denotes the outgoing signal at frequency Ω , and I and II are its first and second harmonics.

periodicity of the input signal start to show up. For even larger amplitudes, second and even third harmonics of the input signal appear.

Let us compare these results with those for the non- ϕ -averaged case. First, in the absence of the multiplicative noise but with the additive noise present, correlations appear, but they are very weak (Fig. 6). When the multiplicative noise level increases, the correlations become larger (Fig. 7). For large times, the correlations grow even larger and the system exhibits stationary oscillations as a function of time (Fig. 8). A similar effect occurs also when the multiplicative noise is absent but the stationary oscillations are smaller (not plotted) than those with the multiplicative noise present. Figures 6–8 share a common scale for the convenience of the reader. It is clear that without initial phase averaging, the multiplicative noise acts constructively on the correlations as their amplitude gets larger with increasing levels of noise. The correlations are sustained by the additive noise; without it the system would quickly go to a flat zero value.

The multiplicative noise effectively reduces the damping constant a , or lengthens the effective relaxation time, and thus destabilizes the process $X(t)$ and “sensitizes” it to the incoming signal. On the other hand, the action of the additive noise (the sustaining of the output signal) is similar to the effect of the addition of a constant external field B to the right-hand side of Eq. (3.1). However, the effect of the latter would remain visible also in the behavior of the process itself: $\langle X(t) \rangle \neq 0$ for $t \rightarrow 0$ in the presence of the external field.

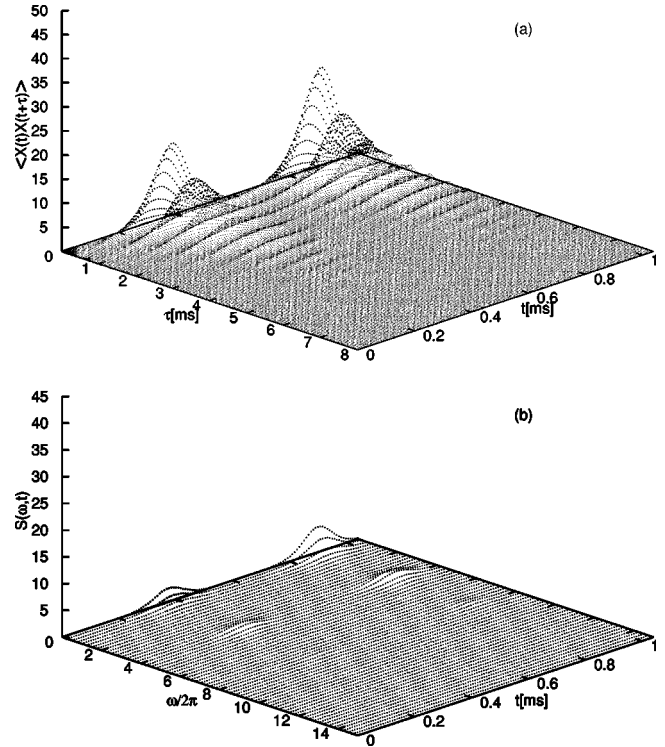


FIG. 6. Time-dependent correlations (a) and the corresponding time-dependent power spectrum (b) of the skeletal system in the absence of the multiplicative noise, $D_1^2 = 0$, not averaged over the initial phase, ϕ . Other parameters are $a = 1$, $b = 1.3$, $\Omega = 12$, $D_2^2 = 1$, $\phi = 0$. Time, t , starts at zero and covers two periods of the input signal.

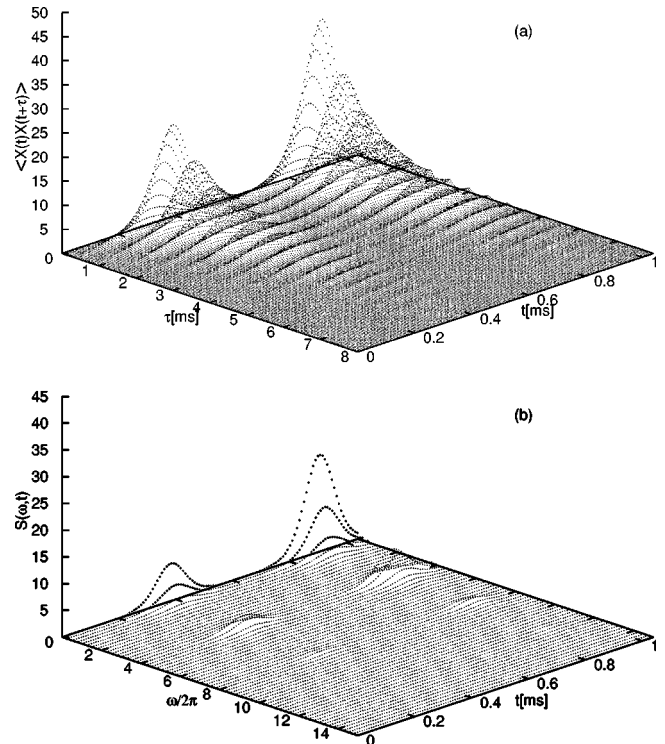


FIG. 7. Same as in Fig. 6, but with $D_1^2 = 0.5$.

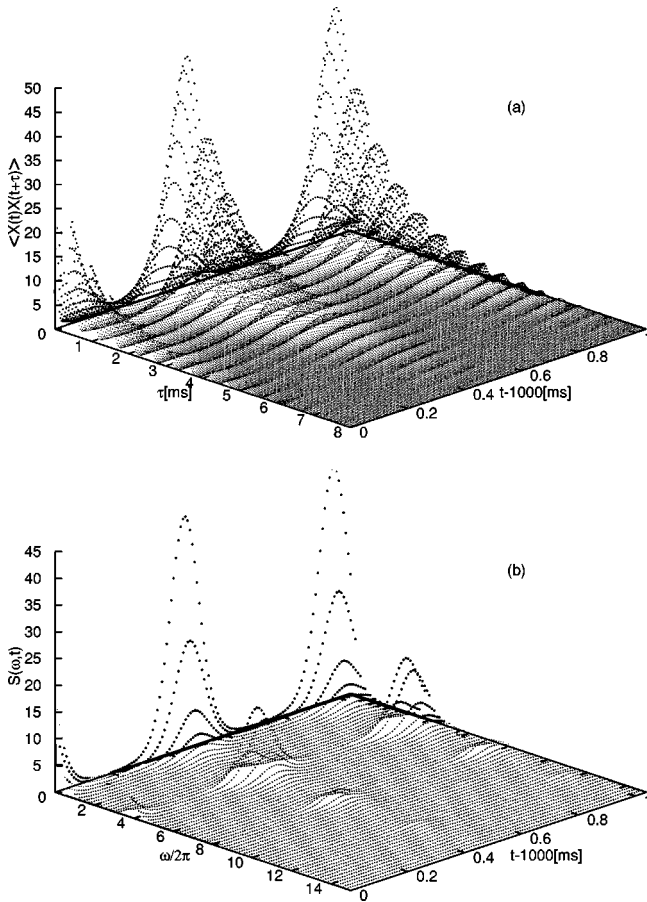


FIG. 8. Same as in Fig. 7, but time, t , starts at $t=1000$ and covers two periods of the input signal. For fixed values of τ in (a) and f in (b), the system exhibits stationary oscillations in t .

IV. DISCUSSION

We have shown that multiplicative noise can enhance, both qualitatively and quantitatively, the output of a realistic model of an enzyme-protein system and of a simplified, but still realistic (cf., Appendix B), “skeletal” system: When the driving field (the incoming signal) is coupled to the transmitting process in a multiplicative way, the addition of a multiplicative noise improves the outgoing signal. In many cases, the constructive role of noise manifests itself only when the fluctuations are of a nonequilibrium nature [6,7]. In this respect, it is worth stressing that the effects reported here are induced also by the Gaussian white noises, which represent standard equilibrium thermal fluctuations, and do not vanish after averaging over the initial phase of the input signal.

These effects are related to the stochastic resonance [5]; this relation will be further clarified elsewhere.

Note that while our model equations of motion (2.7) and (3.1) are formally linear with time-dependent coefficients, a multiplicative coupling between the noise and the system means a “hidden” nonlinearity: The noise is supposed to represent many unobserved degrees of freedom coupled to the transmitting process in a nonlinear manner.

Linear transmitters of periodic or single-pulse, signals can be realized experimentally in simple chemical reactions in a flow reactor with variable influxes [23]. This would allow for

an experimental check of our results on both systems: skeletal, Eq. (3.1); and full, Eq. (2.7).

ACKNOWLEDGMENT

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APPENDIX A: AVERAGE RESPONSE OF THE MEMBRANE-PROTEIN SYSTEM

Given the kinetic equation

$$\frac{dP(t)}{dt} = -[f_1(t) + f_2(t)\xi(t)]P(t) + f_3(t) + f_4(t)\xi(t), \quad (\text{A1})$$

where the noise $\xi(t)$ is defined through Eqs. (2.4) and (2.5), we will now find an expression for the average output $\langle P(t) \rangle$. Obviously,

$$\frac{d}{dt}\langle P(t) \rangle = -f_1(t)\langle P(t) \rangle - f_2(t)\langle \xi(t)P(t) \rangle + f_3(t). \quad (\text{A2})$$

Using the Shapiro-Loginov theorem [22], we find that

$$\frac{d}{dt}\langle \xi(t)P(t) \rangle = -\Lambda\langle \xi(t)P(t) \rangle + \left\langle \xi(t) \frac{dP(t)}{dt} \right\rangle \quad (\text{A3})$$

and we substitute Eq. (A1) in the above expression to get

$$\begin{aligned} \frac{d}{dt}\langle \xi(t)P(t) \rangle &= -\Lambda\langle \xi(t)P(t) \rangle + -f_1(t)\langle \xi(t)P(t) \rangle \\ &\quad - f_2\langle \xi(t)\xi(t)P(t) \rangle + f_4\langle \xi(t)\xi(t) \rangle \\ &= -\Delta^2 f_2(t)\langle P(t) \rangle - [\Lambda + f_1(t)]\langle \xi(t)P(t) \rangle \\ &\quad + \Delta^2 f_4(t), \end{aligned} \quad (\text{A4})$$

where the fact that $\langle \xi(t) \rangle = 0$ and $\xi^2(t) = \Delta^2$ has been used. With abbreviations $u(t) = \langle P(t) \rangle$ and $v(t) = \langle \xi(t)P(t) \rangle / \Delta$ we obtain the following linear equation:

$$\frac{d}{dt} \begin{bmatrix} u \\ v \end{bmatrix} = - \begin{bmatrix} f_1(t) & \Delta f_2(t) \\ \Delta f_2(t) & \Lambda + f_1(t) \end{bmatrix} \begin{bmatrix} u \\ v \end{bmatrix} + \begin{bmatrix} f_3(t) \\ \Delta f_4(t) \end{bmatrix}. \quad (\text{A5})$$

A formal solution to Eq. (A5) reads

$$\begin{bmatrix} u(t) \\ v(t) \end{bmatrix} = e^{-\mathbf{A}(t,0)} \begin{bmatrix} u_0 \\ v_0 \end{bmatrix} + \int_0^t e^{-\mathbf{A}(t,t')} \begin{bmatrix} f_3(t') \\ \Delta f_4(t') \end{bmatrix} dt', \quad (\text{A6})$$

where

$$\mathbf{A}(t,t') = \begin{bmatrix} F_1(t,t') & \Delta F_2(t,t') \\ \Delta F_2(t,t') & \Lambda(t-t') + F_1(t,t') \end{bmatrix}, \quad (\text{A7})$$

$$F_1(t_1,t_2) = \int_{t_2}^{t_1} f_1(t') dt', \quad F_2(t_1,t_2) = \int_{t_2}^{t_1} f_2(t') dt',$$

and $[u_0, v_0]^T$ represent the initial conditions. Eigenvalues of $\mathbf{A}(t,t')$ are

$$\lambda_{\mp} = F_1(t,t') + \frac{1}{2}\Lambda(t-t') \mp \frac{1}{2}\sqrt{\Lambda^2(t-t')^2 + 4\Delta^2 F_2^2(t,t')}. \quad (\text{A8})$$

Note that both these eigenvalues are properly defined for all possible values of t, t' . Diagonalization of $\mathbf{A}(t,t')$, and therefore finding its exponential, is now straightforward,

$$\exp(-\mathbf{A}(t,t')) = e^{-[F_1(t,t') + (1/2)\Lambda(t-t')]} \begin{bmatrix} \frac{1}{2}\mathcal{C}(t,t') + \frac{\Lambda(t-t')}{2\mathcal{F}(t,t')} \mathcal{S}(t,t') & -\frac{2\Delta F_2(t,t')}{\mathcal{F}(t,t')} \mathcal{S}(t,t') \\ -\frac{2\Delta F_2(t,t')}{\mathcal{F}(t,t')} \mathcal{S}(t,t') & \frac{1}{2}\mathcal{C}(t,t') - \frac{\Lambda(t-t')}{2\mathcal{F}(t,t')} \mathcal{S}(t,t') \end{bmatrix}, \quad (\text{A9})$$

where

$$\mathcal{F}(t,t') = \sqrt{\Lambda^2(t-t')^2 + 4\Delta^2 F_2^2(t,t')},$$

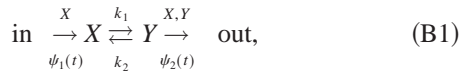
$$\mathcal{C}(t,t') = \cosh\left[\frac{1}{2}\mathcal{F}(t,t')\right], \quad \mathcal{S}(t,t') = \sinh\left[\frac{1}{2}\mathcal{F}(t,t')\right].$$

Finally, collecting all terms, we get

$$\begin{aligned} \langle P(t) \rangle \equiv u(t) = & e^{-[F_1(t,0) + (1/2)\Lambda t]} \left[\left(\frac{1}{2}\mathcal{C}(t,0) + \frac{\Lambda t}{2\mathcal{F}(t,0)} \mathcal{S}(t,0) \right) u_0 - \frac{2\Delta F_2(t,0)}{\mathcal{F}(t,0)} \mathcal{S}(t,0) v_0 \right] \\ & + \int_0^t e^{-[F_1(t,t') + (1/2)\Lambda(t-t')]} \left\{ \left(\frac{1}{2}\mathcal{C}(t,t') + \frac{\Lambda(t-t')}{2\mathcal{F}(t,t')} \mathcal{S}(t,t') \right) f_3(t') - \frac{2\Delta^2 F_2(t,t')}{\mathcal{F}(t,t')} \mathcal{S}(t,t') f_4(t') \right\} dt'. \end{aligned} \quad (\text{A10})$$

APPENDIX B: CHEMICAL REACTIONS MODELED BY THE SKELETAL SYSTEM

Consider a reaction written schematically as



where $\psi_1(t)$ and $\psi_2(t)$ are the influx to and the outflux from the flow reactor [23], respectively. The kinetics is given by

$$\dot{X} = \psi_1(t) - k_1 X + k_2 Y - \psi_2(t) X, \quad (\text{B2})$$

$$\dot{Y} = k_1 X - k_2 Y - \psi_2(t) Y. \quad (\text{B3})$$

It follows immediately that

$$\dot{X} + \dot{Y} = \psi_1(t) - \psi_2(t)(X + Y), \quad (\text{B4})$$

and consequently

$$Y(t) = e^{-\Psi_2(t,0)}(X_0 + Y_0) + \int_0^t e^{-\Psi_1(t,t')} \psi_1(t') dt' - X(t), \quad (\text{B5})$$

where

$$\Psi_i(t,t_1) = \int_{t_1}^t \psi_i(t'') dt''$$

and X_0, Y_0 represent the initial concentrations of the substrates. Plugging Eq. (B5) back into Eq. (B2), we see that

$$\dot{X} = -f_1(t)X + f_2(t), \quad (\text{B6})$$

where $f_1(t), f_2(t)$ are built from the fluxes $\psi_{1,2}$ and the rate constants $k_{1,2}$. Note that Eq. (B6) has a formal structure identical to that of Eq. (3.1).

Concentrations of substrates in a flow reactor can easily be varied, both periodically and randomly. The reaction (B1) can in reality mean conversion of X to Y on a solid catalyst, on an electrode, or induced by light. In the latter two cases, the reaction rates $k_{1,2}$ can further be varied, ran-

domly or in an oscillatory manner, by changing the electrode potential or the intensity of light, thus facilitating the variability of the functions $f_{1,2}(t)$, which in turn should render an experimental check of the theory presented in this paper relatively easy.

APPENDIX C: CORRELATIONS IN THE SKELETAL SYSTEM

The correlation function of a system whose formal solution is given by Eq. (3.3) reads

$$\begin{aligned} \langle X(t)X(t+\tau) \rangle = & \left\langle \exp \left[- \int_0^t dt_1 [a + f(t_1) + \eta_1(t_1)] - \int_0^{t+\tau} dt_2 [a + f(t_2) + \eta_1(t_2)] \right] \right\rangle X_0^2 \\ & + \left\langle \int_0^t dt_1 \int_0^{t+\tau} dt_2 \exp \left[- \int_{t_1}^t dt'' [a + f(t'') + \eta_1(t'')] - \int_{t_2}^{t+\tau} dt'' [a + f(t'') + \eta_1(t'')] \right] \eta_2(t_1) \eta_2(t_2) \right\rangle. \end{aligned} \quad (C1)$$

Since the noises η_1, η_2 are independent and uncorrelated, the mixed terms, which contain a single η_2 , produce a zero average. Furthermore, because $\langle \eta_2(t_1) \eta_2(t_2) \rangle = D_2^2 \delta(t_1 - t_2)$,

$$\begin{aligned} \langle X(t)X(t+\tau) \rangle = & \exp \left[-2 \int_0^t [a + f(t')] dt' - \int_t^{t+\tau} [a + f(t')] dt' \right] \left\langle \exp \left[-2 \int_0^t \eta_1(t') dt' - \int_t^{t+\tau} \eta_1(t') dt' \right] \right\rangle X_0^2 \\ & + D_2^2 \int_0^t dt_1 \int_0^{t+\tau} dt_2 \delta(t_1 - t_2) \left\langle \exp \left[- \int_{t_1}^t dt'' [a + f(t'') + \eta_1(t'')] - \int_{t_2}^{t+\tau} dt'' [a + f(t'') + \eta_1(t'')] \right] \right\rangle. \end{aligned} \quad (C2)$$

Because of the δ term in Eq. (C2), the double integral with $t_1 < t, t_2 > t$ equals zero. Thus

$$\begin{aligned} \langle X(t)X(t+\tau) \rangle = & e^{-2(a-D_1^2)t} e^{-[a-(1/2)D_1^2]\tau} \exp \left[-2 \int_0^t f(t') dt' - \int_t^{t+\tau} f(t') dt' \right] X_0^2 \\ & + D_2^2 \int_0^t dt' \left\langle \exp \left[- \int_{t'}^t dt'' [a + f(t'') + \eta_1(t'')] - \int_{t'}^{t+\tau} dt'' [a + f(t'') + \eta_1(t'')] \right] \right\rangle \\ = & e^{-2(a-D_1^2)t} e^{-[a-(1/2)D_1^2]\tau} \exp \left[-2 \int_0^t f(t') dt' - \int_t^{t+\tau} f(t') dt' \right] X_0^2 \\ & + D_2^2 e^{-2(a-D_1^2)t} e^{-[a-(1/2)D_1^2]\tau} \exp \left[- \int_t^{t+\tau} f(t') dt' \right] \int_0^t dt' e^{2(a-D_1^2)t'} \exp \left[-2 \int_{t'}^t f(t'') dt'' \right]. \end{aligned} \quad (C3)$$

In the derivation of Eq. (C3), in addition to Eq. (3.5), we have used the fact that an average of a product of functions defined on disjoint time intervals factorizes. For instance,

$$\left\langle \exp \left[- \int_0^t \eta(t'') dt'' - \int_0^{t+\tau} \eta(t'') dt'' \right] \right\rangle = \left\langle \exp \left[-2 \int_0^{t+\tau} \eta(t'') dt'' \right] \right\rangle \left\langle \exp \left[- \int_t^{t+\tau} \eta(t'') dt'' \right] \right\rangle.$$

Finally,

$$\begin{aligned} \langle X(t)X(t+\tau) \rangle = & e^{-[a-(1/2)D_1^2]\tau} \exp \left[- \int_t^{t+\tau} f(t') dt' \right] \\ & \times \left\{ e^{-2(a-D_1^2)t} \exp \left[-2 \int_0^t f(t') dt' \right] X_0^2 + D_2^2 e^{-2(a-D_1^2)t} \int_0^t dt' e^{2(a-D_1^2)t'} \exp \left[-2 \int_{t'}^t f(t'') dt'' \right] \right\}. \end{aligned} \quad (C4)$$

We can see that the first term in curly brackets goes to zero as $t \rightarrow \infty$, but the other does not, as the contribution to the integral from the upper limit of integration cancels the exponent in time. We may thus conclude that the additive noise prevents the correlations from decaying as time goes to infinity.

In the case of a sinusoidal input (3.7), the correlation function (C4) can be further averaged over the initial phase of the input signal, ϕ :

$$\begin{aligned} \langle\langle X(t)X(t+\tau)\rangle\rangle &= \frac{1}{2\pi} \int_0^{2\pi} \langle X(t)X(t+\tau)\rangle d\phi \\ &= \frac{X_0^2}{2\pi} e^{-[a-(1/2)D_1^2]\tau-2(a-D_1^2)t} \int_0^{2\pi} \exp\{-\alpha(t+\tau,0)\cos[\beta(t+\tau,0)+\phi]\} d\phi \\ &\quad + \frac{D_2^2}{2\pi} e^{-[a-(1/2)D_1^2]\tau-2(a-D_1^2)t} \int_0^t dt' e^{2(a-D_1^2)t'} \int_0^{2\pi} \exp\{-\alpha(t+\tau,t')\cos[\beta(t+\tau,t')+\phi]\} d\phi, \end{aligned} \quad (\text{C5})$$

where

$$\alpha(t_1, t_2) = 4b \sin \frac{1}{2} \Omega(t_1 - t_2), \quad \beta(t_1, t_2) = \frac{1}{2} \Omega(t_1 + t_2). \quad (\text{C6})$$

Since the integration over ϕ runs over the entire period of the integrands, values of these integrals cannot depend on β , and we can safely set $\beta=0$. An integral representation of the modified Bessel function I_0 ,

$$I_0(z) = \sum_{m=0}^{\infty} \frac{(z/2)^{2m}}{(m!)^2},$$

can then be immediately recognized [25]. After collecting the terms, we get

$$\langle\langle X(t)X(t+\tau)\rangle\rangle = X_0^2 e^{-[a-(1/2)D_1^2]\tau} e^{-2(a-D_1^2)t} I_0(\alpha(t+\tau,0)) + D_2^2 e^{-[a-(1/2)D_1^2]\tau} \int_0^t dt' e^{-2(a-D_1^2)t'} I_0(\alpha(\tau+t',0)). \quad (\text{C7})$$

If $D_1^2 > a$, the system is formally divergent. Denote the integral in Eq. (C7) by $J(\tau, t)$. Note that

$$0 < \int_0^{\infty} dt' e^{-2(a-D_1^2)t'} I_0(\alpha(\tau+t',0)) - J(\tau, t) = \int_t^{\infty} dt' e^{-2(a-D_1^2)t'} I_0(\alpha(\tau+t',0)) \leq \frac{I_0(4b)}{2(a-D_1^2)} e^{-2(a-D_1^2)t} \quad (\text{C8})$$

and we conclude that the correlation function (C7) approaches exponentially a stationary state,

$$\langle\langle X(t)X(t+\tau)\rangle\rangle \rightarrow_{t \rightarrow \infty} D_2^2 e^{-[a-(1/2)D_1^2]\tau} \int_0^{\infty} dt' e^{-2(a-D_1^2)t'} I_0\left\{4b \sin\left[\frac{1}{2}\Omega(\tau+t')\right]\right\}. \quad (\text{C9})$$

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