

# Noise helped manifestation of intrinsic frequency: A case study in the mesoscopic hormone signaling system

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## Abstract

The selective sustainment of nonlinear systems to signals is of great significance to signal transduction in living systems. We take hormone signaling as an example, and investigate the sustainment of internal and external signals. Simulation results prove that signals with “intrinsic frequency”, no matter if it is noise induced or external injected, can be selectively sustained by exploiting internal and/or external noise. Both the internal and external noise can optimize the noise-induced signals, and the optimization is rather robust to the disturbance of external signals with other frequencies. These results are of significance for weak signal detection and transduction in the presence of external signals.

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**Keywords:** Noise; Intrinsic frequency; Mesoscopic system

## 1. Introduction

The nontrivial role of noise and disorder in nonlinear systems has been extensively studied during the last two decades. It includes stochastic resonance (SR) [1], noise increased spatial order [2], noise enhanced synchronization [3], noise sustained wave propagation [4], etc. Among these, the most well-known phenomenon is SR, which demonstrates that there exists a “resonant” noise intensity at which the response of a system to a period signal is maximally ordered. It is used well to detect and amplify weak signals in various systems. Further attempts prove that the SR may be remarkably enhanced by embedding one element into a network of elements [5] or injecting certain external signals [6].

In recent years, increasing attention is being shifted to the effect of internal noise that comes from the random fluctuations of the stochastic chemical reaction events in finite-size biochemical systems. It is reported that optimal intracellular calcium signaling appears at a certain size or distribution of the ion-channel clusters [7,8], and internal noise can induce and optimize signals in sub-threshold or supra-threshold systems including neuron spiking [9], circadian clocks [10], genetic regulation [11], etc. It is generally accepted that the strength of the internal noise is inversely proportional to the square root of the number of particles, an indicator of the system size [12]. Therefore, the constructive effect of internal noise is called internal noise stochastic resonance (INSR) or system size resonance. Recently, several investigations have been done to explore the cooperation of internal and external noise in various biological and chemical systems, such as the circadian oscillation [13], intracellular calcium signal [14], surfaces catalytic reactions [15], etc.

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Most of the previous works focus on the exploration of the constructive role of noise in nonlinear systems; however, relatively less efforts are made to find the internal connections of the noise effect with the system intrinsic characters. In this work, we find noise can help to manifest the “intrinsic frequency” by inducing and optimizing internal signals with this frequency, or selectively sustaining external signals with similar frequency. Besides, the noise-induced-optimization of the internal signal is rather robust to the perturbation of other signals.

2. Model

We employ a simple hormone signaling model in a two-coupled cell system, which is proposed by Londergan and Peacock-López [16]. The cells are coupled to each other through a mechanism of mutual feedback, i.e., the two cells (cell<sub>1</sub>(*x, y, z*) and cell<sub>2</sub>(*w, v, u*)) are linked to each other by the concentration of the other one’s product. The inputs of the first internal species in each cell are regulated by the input function  $\sigma_1 = f(u)$  or  $\sigma_2 = f(z)$ . The dimensionless deterministic model for the time evolution of hormone concentrations (denoted by *x, y, z, w, u* and *v*) is introduced as follows:

$$\begin{aligned} \frac{dx}{dt} &= A_1\sigma_1 - xy \\ \frac{dy}{dt} &= xy - \frac{q_1y}{1+y} \\ \frac{dz}{dt} &= \frac{q_1y}{1+y} - k_1z \\ \frac{dw}{dt} &= A_2\sigma_2 - wv \\ \frac{dv}{dt} &= wv - \frac{q_2v}{1+v} \\ \frac{du}{dt} &= \frac{q_2v}{1+v} - k_1u \end{aligned} \tag{1}$$

where *A*<sub>1</sub> and *A*<sub>2</sub> represent the degree or efficiency of input,  $\sigma_1$  and  $\sigma_2$  are governed by  $\sigma_1 = 1/[1 + \exp(b(u - u_0))]$  and  $\sigma_2 = 1/[1 + \exp(c(z - z_0))]$ . *u*<sub>0</sub> and *z*<sub>0</sub> are the critical output concentration. Parameter values used in this work can be found in the caption of Fig. 1. The detailed description of the model and parameters can be found in Refs. [16,17].

For the real living system whose size is very small, the deterministic model is no longer strictly valid due to the existence of internal noise. Mesoscopic stochastic models must be used. Basically, one can describe the reaction system as a birth–death stochastic process governed by a chemical master equation [18], but no practical procedure was found to solve it analytically. A widely used simulation algorithm is the exact stochastic simulation (ESS) method introduced by Gillespie [19], which stochastically determines what is the next reaction step and when it will happen according to the transition rate of each reaction process. For the present model, the eight reaction steps

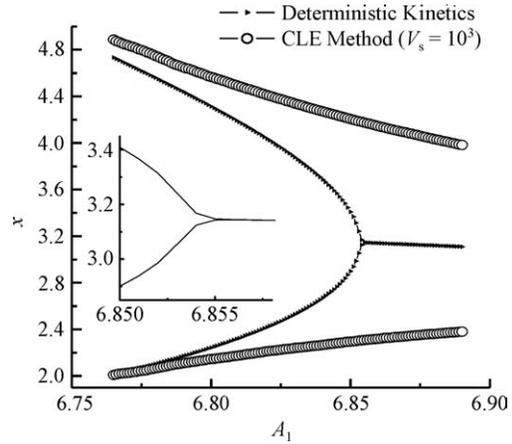


Fig. 1. Bifurcation diagram for the deterministic equation and with the companion of the stochastic oscillation results for *V*<sub>s</sub> = 10<sup>3</sup> obtained from CLE. Parameter values are *A*<sub>2</sub> = 8, *b* = 5, *c* = 1, *u*<sub>0</sub> = 10, *z*<sub>0</sub> = 5, *q*<sub>1</sub> = 10, *q*<sub>2</sub> = 8, *k*<sub>1</sub> = 1 and *k*<sub>2</sub> = 1.2.

and corresponding transition rates are listed in Table 1 (*V*<sub>s</sub> is the system size).

Although ESS has been widely used to study the internal noise effect, it is too time consuming when the system size is large. Therefore, the  $\tau$ -leap method [20] and the chemical Langevin equation (CLE) [21] are developed as an approximation of ESS in the “macro-infinitesimal” time scale system. Hou and his coworkers [11,22] proved that the result of CLE shows good qualitative agreement with the ESS and  $\tau$ -leap method. Therefore, we choose CLE in this work and modulate the internal noise by the system size *V*<sub>s</sub>. For the present model, the CLE reads:

$$\begin{aligned} \frac{dx}{dt} &= (a_1 - a_2) + \frac{1}{\sqrt{V_s}} [\sqrt{a_1}\zeta_1(t) - \sqrt{a_2}\zeta_2(t)] \\ \frac{dy}{dt} &= (a_2 - a_3) + \frac{1}{\sqrt{V_s}} [\sqrt{a_2}\zeta_2(t) - \sqrt{a_3}\zeta_3(t)] \\ \frac{dz}{dt} &= (a_3 - a_4) + \frac{1}{\sqrt{V_s}} [\sqrt{a_3}\zeta_3(t) - \sqrt{a_4}\zeta_4(t)] \\ \frac{dw}{dt} &= (a_5 - a_6) + \frac{1}{\sqrt{V_s}} [\sqrt{a_5}\zeta_5(t) - \sqrt{a_6}\zeta_6(t)] \\ \frac{dv}{dt} &= (a_6 - a_7) + \frac{1}{\sqrt{V_s}} [\sqrt{a_6}\zeta_6(t) - \sqrt{a_7}\zeta_7(t)] \\ \frac{du}{dt} &= (a_7 - a_8) + \frac{1}{\sqrt{V_s}} [\sqrt{a_7}\zeta_7(t) - \sqrt{a_8}\zeta_8(t)] \end{aligned} \tag{2}$$

Here, *a*<sub>1</sub>–*a*<sub>8</sub> are the transition rates per volume as listed in Table 1,  $\zeta_i(t)$  (*i* = 1, . . . , 8) are Gaussian white noises with  $\langle \zeta_i(t)\zeta_j(t') \rangle = \delta_{ij}\delta(t - t')$  and  $\langle \zeta_i(t) \rangle = 0$ .

Integration of Eq. (1) is performed using the explicit Euler method with time step 0.01. With the variation of the control parameter *A*<sub>1</sub>, the system undergoes supercritical Hopf bifurcation (HB) at *A*<sub>1</sub> = 6.858 (Fig. 1). In this work, the control parameter *A*<sub>1</sub> is chosen as 6.89, which is above but close to the bifurcation point. In this case the system (1) is in a stable steady state, that is, no hormone signal exists in the deterministic system. To compare with the

Table 1  
The stochastic processed and transition rate for the system.

Reaction step	Description	Transition rates
$X_0 \rightarrow X$	The input of the first internal species X	$W_1 = a_1 V_s = A_1 \sigma_1 V_s$
$X + Y \rightarrow 2Y$	The enzymatic transformation of X to Y, whose formation is activated by the presence of its product	$W_2 = a_2 V_s = xy V_s$
$Y \rightarrow Z$	The transformation of Y to the final product Z	$W_3 = a_3 V_s = q_1 y / (1 + y) V_s$
$Z \rightarrow \phi$	The decay of external products Z	$W_4 = a_4 V_s = k_1 z V_s$
$W_0 \rightarrow W$	The input of the first internal species W	$W_5 = a_5 V_s = A_2 \sigma_2 V_s$
$W + V \rightarrow 2V$	The enzymatic transformation of W to V, whose formation is activated by the presence of its product	$W_6 = a_6 V_s = wv V_s$
$V \rightarrow U$	The transformation of V to the final product U	$W_7 = a_7 V_s = q_2 v V_s / (1 + v)$
$U \rightarrow \phi$	The decay of external products U	$W_8 = a_8 V_s = k_1 u V_s$

deterministic kinetics, we have also plotted the range of the  $x$  concentration for  $V_s = 10^3$  in Fig. 1. Obviously, the HB point defined in the deterministic kinetics now disappears and stochastic oscillations occur in the case of deterministic steady states. The CLE for this model is integrated by the standard procedure for stochastic differential equations [23] with a time step of 0.01. The hormone signal is detected by the time series of  $x$ . Its signal to noise ratio (SNR) is evaluated by the method provided by Hou and Xin in Ref. [22]. All the quantitative characterization data used in this work are the average of 20 independent runs.

### 3. Results and discussion

#### 3.1. Internal noise-induced signals with “intrinsic frequency”

As predicted in Fig. 1, stochastic signals (Fig. 2(a)) can be induced in the case of steady state in the deterministic limit due to the presence of internal noise. The stochastic oscillations obtained under different values of control parameter  $A_1$  have similar frequency, and it agrees with that of the signal in the deterministic oscillatory area ( $A_1 = 6.855$ ) (Fig. 2(b)). This indicates that the internal noise helps to sustain signals with “intrinsic frequency” in the greater parameter region than predicted by the deterministic model. The internal signal cannot be induced when the noise is too weak (system size is very large), while it will be destroyed when the noise is too strong. Besides, the SNR of these noise-induced signals undergoes a peak with the variation of  $V_s$ , illustrating the occurrence of INSR, as shown in Fig. 2(c). The closer the  $A_1$  is to the HB point, the more prominent is the INSR. However, for the  $A_1$  slightly larger than the HB value, the peak disappears and the SNR curve monotonically increases with the increase in that system size (Fig. 2(c),  $A_1 = 6.855$ ), which demonstrates that the internal noise has lost the nontrivial effect in the deterministic oscillation region [24].

#### 3.2. External noise manifested “intrinsic frequency”

Environmental perturbation is unavoidable in real systems. When external environmental noise is taken into consideration, the external noise term is added in the  $x$  and  $w$

items. Therefore, the first and fourth equations in Eq. (2) read:

$$\begin{aligned} \frac{dx}{dt} &= (a_1 - a_2) + \frac{1}{\sqrt{V_s}} [\sqrt{a_1} \xi_1(t) - \sqrt{a_2} \xi_2(t)] + \Gamma(t) \\ \frac{dw}{dt} &= (a_5 - a_6) + \frac{1}{\sqrt{V_s}} [\sqrt{a_5} \xi_5(t) - \sqrt{a_6} \xi_6(t)] + \Gamma(t) \end{aligned} \quad (3)$$

in which  $\Gamma(t)$  is Gaussian white noise with  $\langle \Gamma_i(t) \Gamma_j(t') \rangle = 2D \delta_{ij} \delta(t - t')$  and  $\langle \Gamma_i(t) \rangle = 0$ . Here,  $D$  is the external noise intensity.

In this case, the “intrinsic frequency” of the noise-induced signals can also be identified (Fig. 3(a)). Compared with the  $D = 0$  case, the internal signal can be further induced in more situations (e.g., when  $V_s > 10^7$  in Fig. 3(a)) with the help of external noise. When  $V_s$  is small, the SNR curves almost overlap. This is because the internal noise dominates and the system is insensitive to external noise. When external noise intensity is in the appropriate range, the SNR curve of the noise-induced internal signal can be further lifted (e.g.,  $D = 10^{-6} - 10^{-3}$  in Fig. 3(a)). This indicates that noise of different origin can cooperate to sustain and optimize the internal signal with “intrinsic frequency”, and some levels of external noise are helpful to hormone signaling in mesoscopic systems.

It can be found in Fig. 3(a) that with the increase in  $D$ , the SNR curves are first enhanced and then depressed. This means that there is also an optimal external noise level at which the stochastic oscillation is best strengthened. The dependence of signal frequency and SNR on  $D$  is also investigated for different choices of  $V_s$  (Fig. 3(b)). When  $V_s$  is very big, i.e., the internal noise is very weak, no signal exists if the external noise is also weak ( $V_s = 10^8$  in Fig. 3(b)). With the increase in  $D$ , a signal with similar frequency as the “intrinsic” one can also be induced. The corresponding SNR has a maximum level at intermediate  $D$ , indicating the occurrence of external noise SR (ENSR). The ENSR phenomenon can be easily identified in relatively big systems. With the decrease of system size, the peak of SNR curves becomes lower, while the SNR for small  $D$  is gradually lifted. This is because the strong internal noise can cooperate with the weak external noise to induce and optimize the internal signals. Once the system size drops to  $10^4$ , the peak disappears and SNR monotonically decreases after the destructive effect of

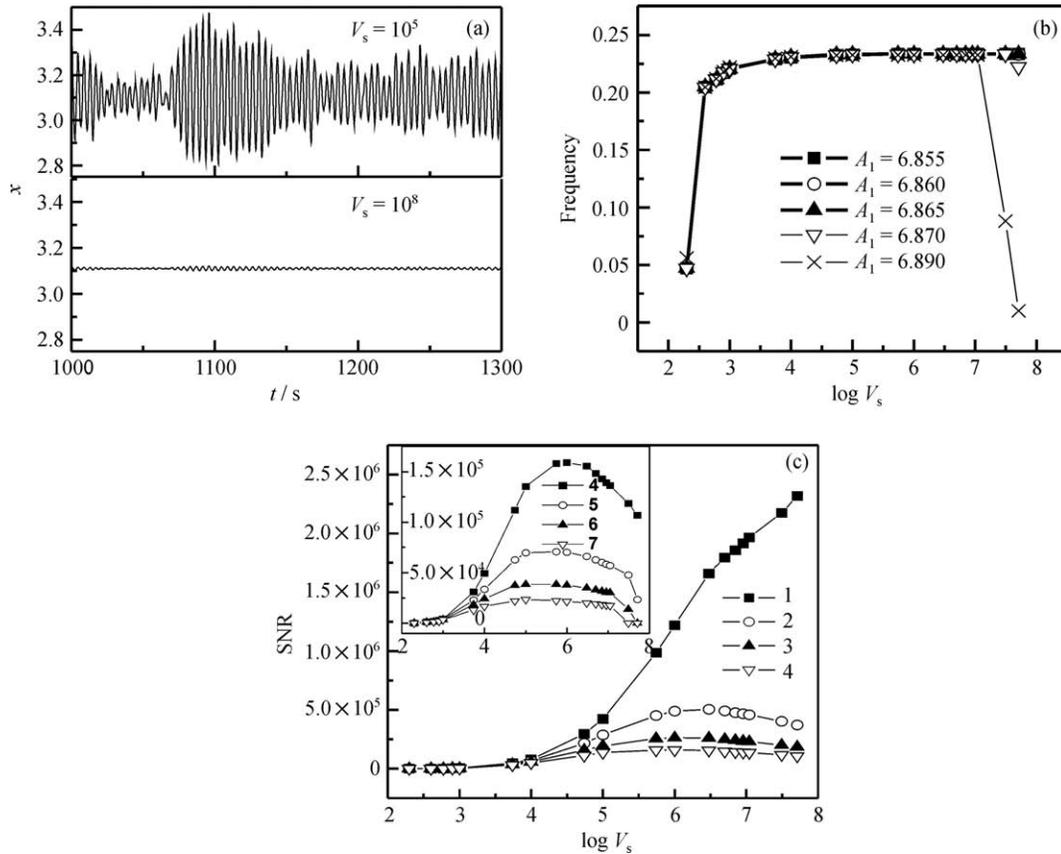


Fig. 2. The “intrinsic frequency” of the internal noise-induced signal. (a) The stochastic oscillation of  $x$  concentration for different system sizes. (b) The dependence of frequency on  $V_s$  for different choices of control parameter  $A_1$ . (c) The dependence of SNR on system size for different choices of control parameter  $A_1$ , lines 1–7 representing the case  $A_1 = 6.855, 6.860, 6.865, 6.870, 6.880, 6.890$  and  $6.900$ , respectively.

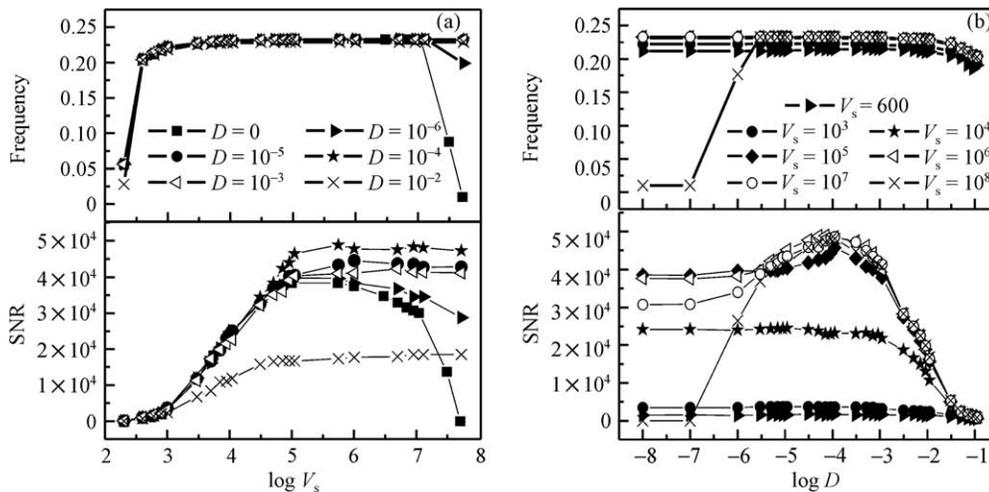


Fig. 3. External noise manifested “intrinsic frequency”. (a) The dependence of internal signal SNR and frequency on  $V_s$ . (b) The dependence of internal signal SNR and frequency on  $D$ .

external noise dominates ( $D > 10^{-3}$ ). Further decreasing  $V_s$ , the curves in the small  $D$  part also dramatically decreased, indicating the internal noise become so strong that no positive role of the external noise can be found.

### 3.3. External signal-manifested “intrinsic frequency”

External signals are ubiquitous in complex living systems. Their influence on the noise-induced signal is also

investigated here. The signal represented by a simple sine wave is introduced in the  $x$  and  $w$  evolution equation, and the first and fourth equations in Eq. (2) take the following form:

$$\begin{aligned} \frac{dx}{dt} &= (a_1 - a_2) + \frac{1}{\sqrt{V_s}} [\sqrt{a_1}\xi_1(t) - \sqrt{a_2}\xi_2(t)] + B \sin(2\pi\omega t) \\ \frac{dw}{dt} &= (a_5 - a_6) + \frac{1}{\sqrt{V_s}} [\sqrt{a_5}\xi_5(t) - \sqrt{a_6}\xi_6(t)] + B \sin(2\pi\omega t) \end{aligned} \quad (4)$$

Here,  $B$  stands for the strength of the signal, and  $\omega$  is its frequency.

Simulation results show that the INSR phenomenon still exists in a large spectrum of  $B$  (Fig. 4(a)). A similar tendency is also obtained for the ENSR case, which is not shown here. These indicate that the optimization of the “intrinsic frequency” signal is rather robust to the presence of other signals. When  $B$  is in the appropriate scope, the influence of external signal frequency on the INSR can also be identified (Fig. 4(b)). The lower the external signal fre-

quency is, the more pronouncedly the INSR will be depressed. The depression is even more apparent when  $\omega$  is close to the “intrinsic frequency”, illustrating “resonant” depressions. A similar situation also appears in the ENSR case (Fig. 4(c)).

The influence of internal noise on external signals is generally trivial. The higher the frequency is, the stronger the signal will be when  $V_s$  is large (Fig. 5(a)). However, the SNR curves for the external signals whose frequency is close to the “intrinsic” one ( $\omega = 0.2$  and  $0.3$ ) are apparently higher when internal noise is weak ( $V_s$  is large). This means the external signals with “intrinsic” frequency may also be selectively sustained. With the cooperation of external noise of appropriate intensity (e.g.,  $D = 10^{-4}$ ), the SNR curves become a plateau in the big  $V_s$  part, indicating that the robustness of the external signal to internal fluctuations is increased. Besides, the SNR of external signals close to the “intrinsic frequency” is even more obviously higher than others (Fig. 5(b)). This suggests noises (or their cooperation) can help to manifest the selective sustainment of “intrinsic frequency” signals, regardless of the signal origin.

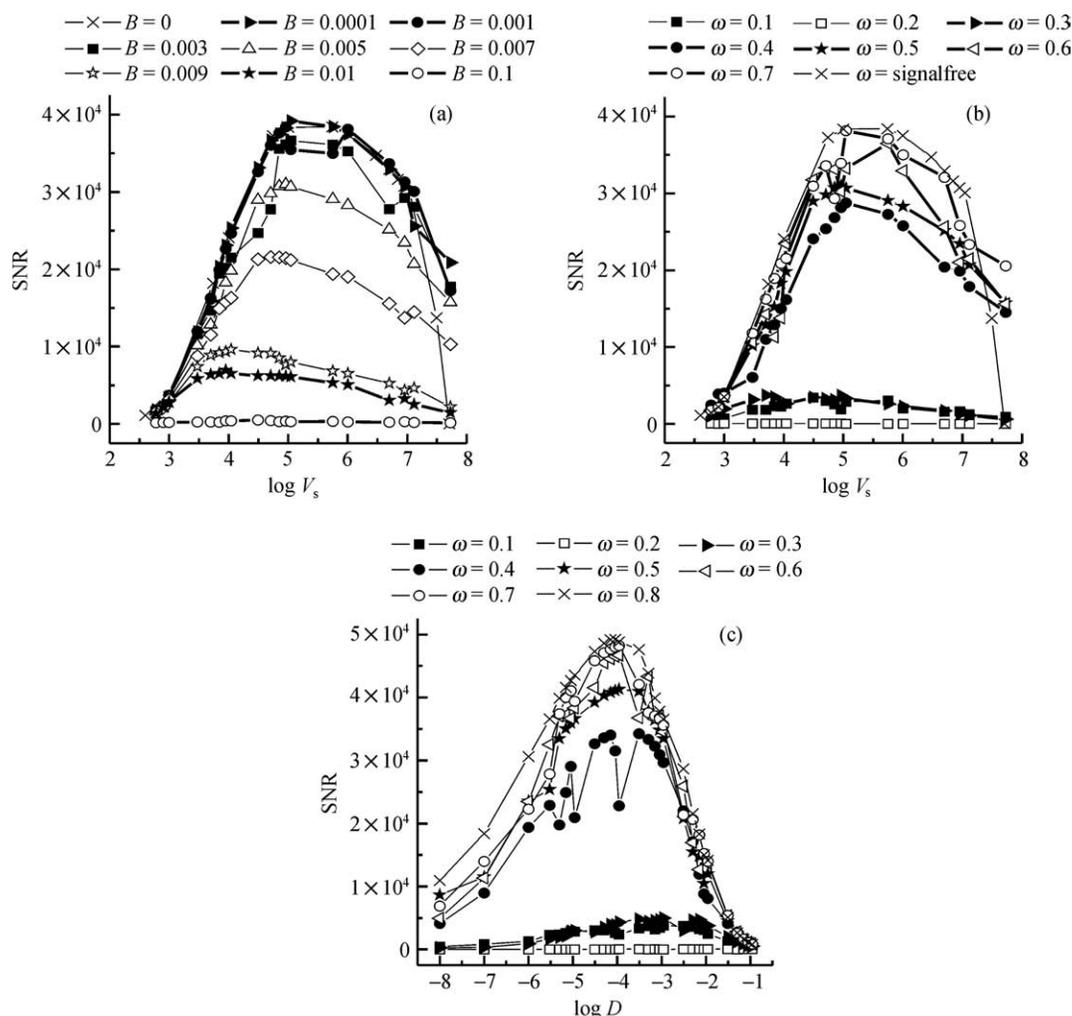


Fig. 4. External signal-manifested “intrinsic frequency”. (a) SNR curves of INSR for different values of  $B$  ( $\omega = 0.5, D = 0$ ). (b) SNR curves of INSR for different values of  $\omega$  ( $B = 0.005, D = 0$ ). (c) SNR curves of ENSR for different values of  $\omega$  ( $B = 0.005, V_s = 10^9$ ).

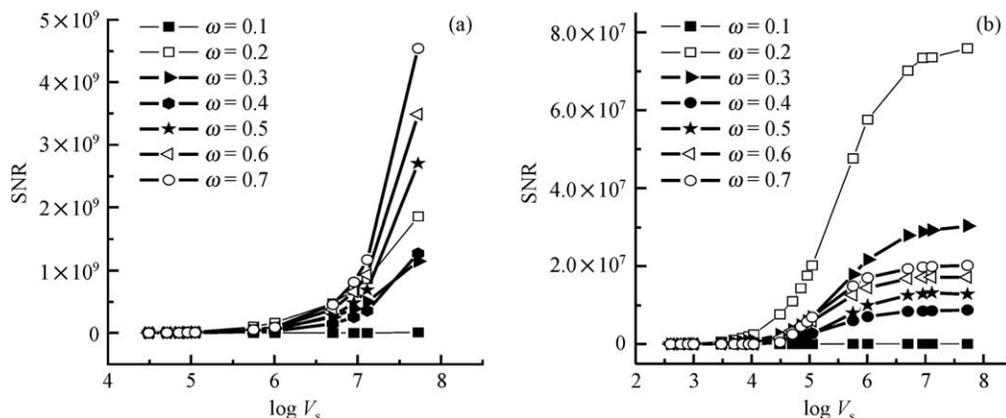


Fig. 5. External noise manifested external signal with “intrinsic frequency” ( $B = 0.005$ ). (a)  $D = 0$ ; (b)  $D = 10^{-4}$ .

#### 4. Summary

In summary, noise helped manifestation of “intrinsic frequency” signals is demonstrated in a mesoscopic hormone signaling system. Simulation results prove that both the internal and external noise can induce and optimize internal signals with “intrinsic frequency”. Their cooperation may further enhance the optimization and enlarge the parameter scope where the internal signal exists. This kind of selective optimization is quite robust to external signals with other frequencies. In fact, the external signal with the frequency similar to the intrinsic one may also be preferably sustained. This means noise can help to manifest the signals with preferred frequency, regardless of their origin. Although the above results are demonstrated in a hormone system here, our further investigations prove that this is a widely existing phenomenon. These results are of significance for weak signal detection and transduction in the presence of other signals.

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