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Noise as a potential controller in antagonist inter-reacting systems

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HIGHLIGHTS

- We propose a stochastic control for the most generic system of antagonist actors.
- The Schögl system of two reactants is equipped with noisy interaction coefficients.
- We show analytically that disorder in such a system can serve a control purpose.
- Potential applications include switches in metabolic and biochemical engineering.
- Besides applications, our results may be important in elucidating the origin of life.

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ABSTRACT

Noise has been recognized as an important factor in a range of physical and informational systems, including the elementary physics of life, such as cellular developments and functions. Here we use a stochastic differential equation to study the effects of noise on a typical system of antagonist actors, the Schlögl model. The phenomena of noise-induced bifurcation are observed. Detailed analysis demonstrates that the region revealing bistability can be modulated by the intensity of noise. This suggests that an external noise source can serve as an engineering tool for controlling antagonist inter-reacting systems in general, and in particular, for manipulating biochemical pathways.

Cellular processes, such as growth, division, motility, and apoptosis – profound examples of the elementary physics of life – are determined by regulatory networks of interacting proteins and genes. These pathways are sets of reactions which convert reactant materials into products at rates dependent on reactant concentrations and concentrations of other chemical components involved. Although most cellular processes are orderly and robust, fluctuations cannot be ignored in living cells [1]; indeed they have been recognized as an important factor in a range of physical and informational systems. Experimental studies demonstrate that genetically identical cells exposed to identical environments can show significant variation in molecular contents and marked distinctions in phenotypic characteristics [2]. This variability has been recognized as the outcome of stochasticity in the gene expression processes (*intrinsic noise*) and that in cellular environments (*extrinsic noise*) [3,4].

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There is growing evidence that noise has crucial effects on a population's heterogeneity, cellular functions, and even the cells' fate [5]. Recently, an interesting phenomenon due to the propagation of noise was identified in a gene cascade network. W. J. Blake et al. demonstrated that increased noise in the transcription process is capable of causing a transition from a monostable expression state to bistable expression states [6]. The phenomenon is referred to as noise induced bifurcation, or stochastic bifurcation. A similar noise induced phenomenon has been found in enzymatic futile cycles [7] and has been considered in synthetic genetic cellular networks [8]. M. Samoilov et al. showed that a wide class of noise can result in bistable switching which is entirely different from the monostable behavior predicted by deterministic calculations [9].

For the biochemical systems studied, several questions remain regarding the bistable behavior observed. Previous studies have mainly focused on the pure stochastic binary state without underlying deterministic bistability. In this paper, we elucidate how external noise affects the dynamics of systems which can present typical bistable behavior deterministically. In particular, we suggest an understanding of stochastic effects on this generic kind of system and provide a clear picture explaining such a noise induced bifurcation. Furthermore, we suggest a potential application of this phenomenon.

1. Model system

We adopt the Schlögl model [10] to study the conversion of a reactant A to B via an intermediate component X. The model is defined as:

$$\begin{aligned} \mathrm{A} + 2\mathrm{X} &\xrightarrow{k_1} 3\mathrm{X}, \\ 3\mathrm{X} &\xrightarrow{k_{-1}} \mathrm{A} + 2\mathrm{X}, \\ \mathrm{X} &\xrightarrow{k_2} \mathrm{B}, \\ \mathrm{B} &\xrightarrow{k_{-2}} \mathrm{X}. \end{aligned} \tag{1}$$

Let x, $\mathcal{A}$, and $\mathcal{B}$ denote the concentration of the inter-reacting agents X, A, and B, respectively. The system is assumed to be open with two infinite reservoirs of A and B, so that the corresponding concentrations $\mathcal{A}$ and $\mathcal{B}$ remain fixed. Based on the reaction kinetics, the rate equation of the concentration x is described by

$$\frac{dx}{dt} = -k_{-1}x^3 + k_1\mathcal{A}x^2 - k_2 x + k_{-2}\mathcal{B}. \tag{2}$$

In a steady state, the solutions obey

$$h(x) \equiv x^3 - ax^2 + kx - b = 0, \tag{3}$$

where $a = k_1\mathcal{A}/k_{-1}$, $k = k_2/k_{-1}$, and $b = k_{-2}\mathcal{B}/k_{-1}$. The system can show one, two, or three non-negative steady states. Here we focus on the conditions within or near the bistable region in which two stable fixed points are separated by an unstable one.

2. Numerical results

We first consider the noise originating from the chemical reaction rate. In biological systems, the system control via single (or several) reaction rates is realizable. For example, a temperature-sensitive cI protein has been applied to a synthetic toggle network, so that the degradation rate is an increasing function of temperature [11]. The modulation process is often accompanied by additional fluctuations dominant over other noise sources [12]. Alternatively, a single biochemical reaction is likely to represent a complex sequence of reactions. It is therefore natural to assume that the reaction rate is affected by fluctuations caused by various internal and external factors [13].

Here we set $k_2(t) = k_2 - \xi(t)$; $\xi(t)$ is a Gaussian white noise with $\langle\xi(t)\rangle = 0$, $\langle\xi(t)\xi(t')\rangle = 2D\delta(t-t')$ and D is the intensity of the noise. The maximum noise intensity used throughout this paper is restricted to the order of 10% of the reaction rates, thus avoiding negative values of the rate constants. The equivalent stochastic differential equation (Langevin equation) [14] of Eq. (2) is

$$\frac{dx}{dt} = f(x) + g(x)\xi(t), \tag{4}$$

in which $f(x) = -k_{-1}h(x)$ and $g(x) = x$. Numerical simulations are performed based on the forward Euler algorithm with a small time step Δt. The iteration of x obeying Eq. (4) can be approximated by [15]: $x_{t+\Delta t} = x_t + f(x_t)\Delta t + g(x_t)W_t + \frac{1}{2}g'(x_t)g(x_t)W_t^2$, where $W_t = (-4D\Delta t \ln\eta_1)^{1/2}\cos(2\pi\eta_2)$, and η_1, η_2 are two independent random numbers distributed with equal probability in the interval $(0, 1)$. $k_{-1} = 0.1$, $k = 1.2$, $a = 2.1$ and $\Delta t = 10^{-4}$ are set if there is no additional emphasis.

We choose $b = 0.20$ and $b = 0.21$ in our simulations. In the deterministic case ($D = 0$), the system with $b = 0.20$ can reveal typical bistable behavior: trajectories initiating from different values of x_0 will asymptotically converge to one of the two stable states, which are separated by an unstable saddle point. With noise affecting the reaction rates, this is however no longer the case. Weaker noise, e.g. $D = 0.005$, sustains the bistability, but causes frequent switching between