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Predicting the asymmetric response of a genetic switch to noise

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ABSTRACT

We present a simple analytical tool which gives an approximate insight into the stationary behavior of nonlinear systems undergoing the influence of a weak and rapid noise from one dominating source, e.g. the kinetic equations describing a genetic switch with the concentration of one substrate fluctuating around a constant mean. The proposed method allows for predicting the asymmetric response of the genetic switch to noise, arising from the noise-induced shift of stationary states. The method has been tested on an example model of the *lac* operon regulatory network: a reduced Yildirim–Mackey model with fluctuating extracellular lactose concentration. We calculate analytically the shift of the system's stationary states in the presence of noise. The results of the analytical calculation are in excellent agreement with the results of numerical simulation of the noisy system. The simulation results suggest that the structure of the kinetics of the underlying biochemical reactions protects the bistability of the lactose utilization mechanism from environmental fluctuations. We show that, in the consequence of the noise-induced shift of stationary states, the presence of fluctuations stabilizes the behavior of the system in a selective way: Although the extrinsic noise facilitates, to some extent, switching off the lactose metabolism, the same noise prevents it from switching on.

1. Introduction

Relatively simple biochemical systems regulated at the level of gene expression are capable of a complex dynamic behavior due to their intrinsic nonlinearity. The nonlinear kinetics of the biochemical regulation may result in various patterns of behavior, among which bistability is an extremely interesting one as a source of a switch-like behavior, a common strategy used by biochemical and cellular systems to turn a graded signal into an all-or-nothing response. Another important feature associated with the bistability is hysteresis: in order to switch the system from one steady state to another, the input signal must surpass a given threshold. To switch back, the input signal must be decreased below another (smaller) threshold. This permits a discontinuous evolution of the system along different possible pathways, which may provide the system with an epigenetic (nongenetic) memory (Laurent and Kellershohn, 1999; Casadesus and D'Ari, 2002; Ferrell, 2002).

Recently, growing attention has been focused on the study of stochastic aspects of gene regulation (Austin et al., 2006; Elowitz et al., 2002; Paulsson, 2005; Rosenfeld et al., 2005; Swain et al., 2002; Tsimring et al., 2006). Fluctuations in a gene network are generally divided into 'intrinsic' and 'extrinsic'. This distinction depends on the point of view: we consider the low copy number fluctuations in a single reaction (or set of reactions) under study as the 'intrinsic noise', whereas the 'extrinsic noise' is connected with all the remaining, external processes which are not taken into consideration in detail. The extrinsic noise can originate from low copy number fluctuations in the reactions that are external with respect to the set of processes studied, as well as from other stochastically varying, unknown factors affecting our system.

Reliable functioning of a cell may, on the one hand, require genetic networks to suppress or to be robust to fluctuations (Tabaka et al., 2008; Elowitz et al., 2002; Becskei and Serrano, 2000; Alon et al., 1999). On the other hand, noise offers the opportunity to generate a switch-like behavior (Ozbudak et al., 2004) and a long-term heterogeneity in a clonal population (Elowitz et al., 2002). The presence of fluctuations in nonlinear systems such as genetic networks may induce spontaneous switching between stationary states, emergence of new stationary states and disappearance of the existing ones (Horsthemke and Lefever, 1984).

In this paper we present a simple analytical tool which gives an approximate insight into the stationary behavior of systems undergoing the influence of a weak and rapid noise from one nonlinear source, e.g. kinetic equations where the fluctuations of the concentration of one particular substrate dominate, and where that concentration enters into the equations in a nonlinear function. The proposed method of mean noise expansion allows for predicting the noise-induced shift of stationary states which,

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in case of bistable systems, causes the asymmetric response to fluctuations. This asymmetry may, for example, facilitate switching off a genetic switch but prevent it from switching on. The occurrence of such an effect can give rise to the question of a possible optimization of the genetic switch for functioning in a noisy environment.

We have tested our method on an example model of the *lac* operon. The lactose regulation system in the *Escherichia coli* bacteria is one of the most extensively studied examples of a biological switch: it allows for the maintenance of differences in the phenotype despite the absence of genetic and environmental differences. Monod et al. (1952) discovered the effect of population heterogeneity on the level of an entire bacterial population, whereas Novick and Weiner (1957) identified the same effect on the level of individual *E. coli* cells: in the same external conditions, the bacteria were either able or unable to metabolize lactose. The studies of the expression of β-galactosidase (the enzyme which breaks down the lactose into a simpler sugar) (Novick and Weiner, 1957; Cohn and Horibata, 1959) and of the direct *lac* gene transcription activity at the cellular level (Ozbudak et al., 2004) show that the cells can be in one of two discrete states: either fully induced, with the transcription (and, consequently, enzyme) levels reaching a maximum, or uninduced, with negligible transcription and enzyme levels. The induction may be triggered by applying even a quite short stimulus: a temporary increase in the extracellular lactose level.

Different nonlinear dynamical models of the underlying chemical kinetics were proposed to explain the origins of the switch-like behavior of the lactose utilization network (Laurent and Kellershohn, 1999; Ozbudak et al., 2004). This direction of research has led to a more detailed model proposed by Yildirim and Mackey (2003). It explicitly incorporates all the relevant biochemical processes along with experimentally motivated kinetic constants, and, tested on empirical data, displays a good agreement with experiments. According to this model, the switch-like behavior of the lactose operon results from the bistability of the kinetic equations.

Since the changes of the extracellular lactose concentration are the primary factor which controls the induction and uninduction of the lactose metabolism in *E. coli*, we focus our attention on this, completely external, process influencing the *lac* operon system. Within the example model based on the Yildirim–Mackey framework, we analyze how the weak and rapid Gaussian fluctuations in the extracellular lactose concentration (and their different intensity) affect the *lac* gene expression. We do not take into account the intrinsic fluctuations (modeling their effects deserves a separate study) but our analysis may be the first step to the interpretation of the experimental measurements of stochasticity in *lac* operon expression, in terms of the discrimination between the effects of the intrinsic and extrinsic noises, which is itself a challenging task. It is worth noting that Elowitz et al. (2002) have shown that in systems consisting of several reactions (in particular, also in the *lac* operon system in *E. coli*) the extrinsic noise often gives a much stronger contributionto the gene expression than the intrinsic fluctuations.

Using the proposed method of mean noise expansion, we analytically calculate the noise-induced shift of the stationary states of the model, which gives rise to the asymmetric response of the system to fluctuations: the effective stabilization of the uninduced state and the destabilization of the induced state. We show that the results of the analytical calculation are in excellent agreement with the mean stationary states obtained from the numerical simulation of the noisy system. We also show the consequences of that shift: varying the noise intensity, we measure mean times of the transition between the uninduced and induced states. In this way we check when the system becomes resistant to the fluctuations and when, on the contrary, the fluctuations facilitate the switching between those states.

The paper is organized as follows: in Section 2 we present the analytical method of calculation of the noise-induced shift in stationary states of a system. In Section 3 the example model of the *lac* operon is described. Section 4 presents the results: the application of the analytical method compared to the numerical results (Section 4.1), and changes in the mean times of the transition between the uninduced and induced states being the consequence of the noise-induced shift (Sections 4.2 and 4.3).

2. Theory

The general method of treatment of dynamical systems undergoing the influence of a weak and rapid noise from one nonlinear source, which we present below, can be applied, for example, to the models of genetic regulatory networks. A genetic switch should be described by the equations of chemical kinetics, i.e. neglecting all sources of noise, except one: a fluctuating concentration of a substrate which enters into the equations as a parameter. The concentration of that substrate should fluctuate weakly but rapidly around a constant mean.

Assume that:

(a) The system is described by a set of stochastic differential equations:

$$\frac{d\mathbf{X}}{dt} = \mathbf{F}(\mathbf{X}, h(P_t)). \tag{1}$$

$\mathbf{X}$ can denote here the vector of concentrations of reactants. P_t is a parameter, for example, a concentration of a substrate, which does not depend on $\mathbf{X}$.

(b) P_t is a stochastic process, fluctuating in time t around the mean $\bar{P}$ and having a constant variance $\sigma^2 \ll 1$ (weak fluctuations).

(c) The fluctuations of P_t are rapid enough not to correlate with the time scales of the processes described by System (1). The characteristic time τ_{sys} of the system is given by $1/|Re\,\lambda|$, where λ is the greatest eigenvalue of the Jacobian of (1) (a standard linearization procedure). The characteristic time scale of the process P_t is determined by its correlation time τ. Therefore, $\tau \ll \tau_{sys}$.

(d) P_t enters into the system (1) in the function $h(P_t)$ only.

(e) The deterministic system

$$\frac{d\mathbf{X}}{dt} = \mathbf{F}(\mathbf{X}, h(\bar{P})) \tag{2}$$

with a constant parameter $\bar{P}$ equal to the mean of P_t has steady states $\mathbf{X}^*(\bar{P})$.

If (b) and (c) are fulfilled, we can assume that the trajectories of the stochastic system (1) fluctuate weakly and rapidly around a certain constant average $\langle \mathbf{X}(P_t) \rangle$. This means that the behavior of the system is quasi-stationary, i.e. even if the probability density of $\mathbf{X}(P_t)$ has more than one maxima, the transitions between them are very unlikely. Therefore we will consider only the trajectories which fluctuate around one of the maxima: $\langle \mathbf{X}(P_t) \rangle$ will be then the position of that maximum. Since the fluctuations are weak, the maxima of the probability density of $\mathbf{X}(P_t)$ are close to the steady states of the deterministic system (2).

The response of the system to noise in the parameter P will be a shift of the mean, around which the trajectories of the stochastic system fluctuate, by a small value of Δ with respect to the corresponding steady states of the deterministic system:

$$\langle \mathbf{X}(P_t) \rangle = \mathbf{X}^*(\bar{P} + \Delta). \tag{3}$$