

Analysis of Noise Sensitivity of Attractor Selection

大阪大学 大学院情報科学研究科 ライプニッツ賢治 (Kenji Leibnitz)
Graduate School of Information Science and Technology,
Osaka University

筑波大学 大学院システム情報工学研究科 香田正人 (Masato Koda)
Graduate School of Systems and Information Engineering,
University of Tsukuba

Abstract

In this paper we study the essential dynamics of a system referred to as attractor selection. This model is based on the dynamical and self-adaptive behavior of gene regulatory networks found in biological cells and we apply the methodology of stochastic sensitivity analysis. Our goal is to investigate the fundamental mathematical relationship between the dynamics of the interactions between a system state vector corresponding to an on/off behavior of protein regulation and the cell growth rate function.

1 Introduction

Noise is a common phenomenon that is ubiquitous and can be found everywhere in nature, as well as many in engineered systems. In biological systems, noise is often manifested in the random motion of molecular particles or the spike trains of firing neurons in the brain. On the other hand, in engineered systems, such as communication networks, different user behavior and heterogeneous devices interacting with each other are often the cause that fluctuations appear. Especially, in the design of complex systems on nano-scale [1] it is therefore highly desirable to understand and exploit the beneficial properties induced by noise, such as the reduction of complexity or higher robustness to failures [2].

Biological cells are not deterministic in their dynamics, but are influenced by the inherent fluctuations which govern their reaction to external influences. In general, the interaction between cells is controlled through signaling molecules, which are propagated among cells. Intercellular communication over close proximity is performed by the diffusion of first messenger molecules that are emitted from one cell and bound by the receptors of neighboring cells. Since these molecules can not penetrate the membrane of the receiving cells, receptors at the membrane bind these molecules and cause an internal chemical reaction over *signal transduction networks* that are pre-encoded pathways in the cell. These transduction networks can be regarded as pre-programmed responses to frequently occurring events in the environment and they trigger a biochemical reaction within the cell to result in a certain expression of genes that is reflected in the activation of proteins in an on/off manner. *Gene expression* is, therefore, essential to the way a cell reacts to environmental changes in terms of external nutrients that are provided to the cell. However, due to the almost infinite number of possible conditions that a cell may be exposed to, there can only be a finite number of stored pathways and the question arises

to how the cell reacts to possible environmental conditions for which no such pathway exists. This problem is experimentally discussed in [3] and we use their mathematical formulation to provide a framework for studying the sensitivity of the basic dynamical model. In this paper, our goal is to investigate the fundamental relationship between the dynamics of the system state (protein concentration levels) and the feedback function (cell growth or activity) using the framework of *stochastic sensitivity analysis* [4].

The remainder of this paper is organized as follows. We first discuss the underlying biological model of gene expression and the basic mathematical formulation in Section 2. By investigating the stochastic sensitivity of the kinetics of the dynamical systems in Section 3, we establish a relationship between the cell activity and the dynamics of gene expression. Our intention is to provide a framework for mathematically characterizing the sensitivity of the system in a generalized form to define appropriate functions and criteria for implementation in robust, noise-tolerant systems. As target application we consider the self-adaptive and fully distributed control of information networks [5].

2 Attractor Selection Model

In this section, we briefly summarize the fundamental behavior of attractor selection and provide an introduction to the biological background and the original mathematical model. The attractor selection method was introduced by Kashiwagi et al. in [3] by formalizing the results from experimental studies when exposing mutually inhibitory operons of *Escherichia Coli* cells to different media where nutrients are available in the environment or not. In molecular biology, such experiments are carried out by synthetically modifying the genetic structure of cells by attaching a fluorescence protein to their operons. The level of fluorescence can be measured to obtain empirical results in the long term dynamics when exposed to a certain environmental condition.

2.1 Biological Background

Let us now describe in greater detail the background of the underlying biological model. In [3], the original model was derived from experiments of a bistable switch of two mutually inhibitory operons in *E. Coli* cells. An *operon* is a unit in the protein transcription process that creates messenger RNA (mRNA) and consists of an operator, a promoter, and the associated structural genes.

In general, cells alter their gene expression through their regulatory network, which induces a change in expression as response to environmental changes or external signals. The regulatory network is essentially a network of activating or inhibiting genes and it is controlled through specialized signal transduction networks to quickly react to frequently occurring signals. Thus, a specific program in the transduction network is activated if a certain environmental event is detected. However, the number of possible environmental changes can be so large that a transduction pathway can not exist for all possible cases, but the adaptation toward a stable expression state is nevertheless achieved.

In order to study this phenomenon, Kashiwagi et al. used in [3] a synthetic gene network composed of two mutually inhibitory operons that were respectively attached with a *green fluorescence protein* (GFP) and *red fluorescence protein* (RFP) to visualize their dynamics. Exposure to a neutral medium resulted in a single monostable attractor,

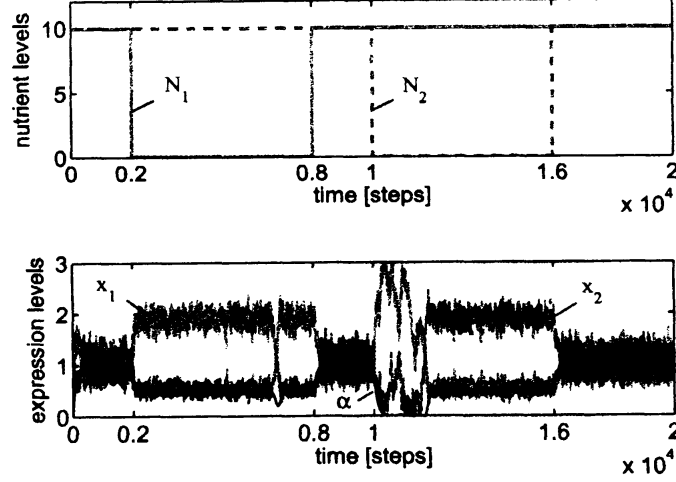


Figure 1: Simulation of dynamics of network with two mutually inhibitory operons

where the mRNA concentrations of both operons showed only weak expression. On the other hand, when the network was exposed to a medium that was lacking either one of the key nutrients, it resulted in a bistable condition with two attractors, one with high green and low red fluorescence expression and vice versa. Thus, the former single stable attractor with weak expression became unstable and fluctuations due to the noise inherent in gene expression caused the system to shift toward either one of the attractors due to their mutually inhibitory behavior.

A mathematical model of this phenomenon was derived in [3], describing the dynamics of the mRNA concentrations $x_i(t)$ of each operon $i = 1, 2$.

$$\begin{aligned} \frac{d}{dt} x_1(t) &= \frac{S(\alpha)}{1 + x_2^2(t)} - D(\alpha) x_1(t) + \eta_1(t) \\ \frac{d}{dt} x_2(t) &= \frac{S(\alpha)}{1 + x_1^2(t)} - D(\alpha) x_2(t) + \eta_2(t) \end{aligned} \quad (1)$$

The functions $S(\alpha)$ and $D(\alpha)$ are the rate coefficients of the synthesis and degradation of cell growth, respectively, and can be defined over a function α , which represents the *cell activity*. The values $\eta_i(t)$ are used for modeling the intrinsic noise in gene expression.

$$S(\alpha) = \frac{6\alpha}{2 + \alpha} \quad D(\alpha) = \alpha \quad (2)$$

The activity dynamics is explained in the supplemental material of [3] and defined using a classical model for cell growth rate [6].

$$\frac{d}{dt} \alpha(t) = \frac{P}{\prod_{i=1}^2 \left[\left(\frac{\theta_i}{x_i(t) + N_i} \right)^{n_i} + 1 \right]} - C \alpha \quad (3)$$

An example of a numerical simulation is illustrated in Fig. 1, using the same parameter set as specified in [3]. Here, $P = C = 0.01$ are the production and consumption rates of

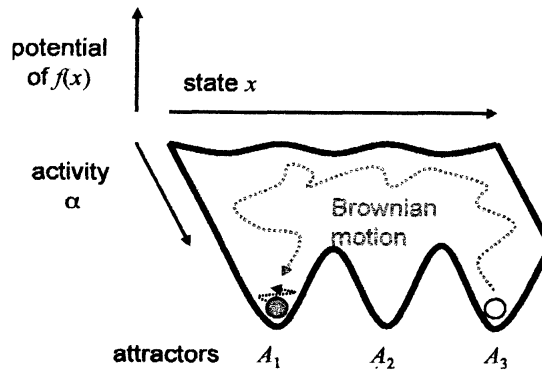


Figure 2: Principle of attractor selection dynamics

activity, $N_i \in \{0, 10\}$ represent the external supplementation of the respective nutrients, $\theta_i = 2$ are the thresholds of nutrient production, and $n_i = 5$ are their sensitivities, for $i = 1, 2$. The upper figure shows the nutrient availability over time, whereas the lower figure depicts the expression levels of the two operons. Notice that roughly between time 10000 and 12000, the system state lies outside the basin of the proper attractor, so the activity decreases to 0 (black line marked by α) and a random walk is performed until the system finally approaches the proper attractor.

2.2 Generalized Model of Attractor Selection

In Section 2.1, a mathematical model was discussed using stochastic differential equations that show the basic reaction and it was observed that convergence to attractors is achieved under certain environmental conditions. However, as biological systems do not instantly adapt to environmental changes, they are driven by the inherent noise in gene expression causing the orbit of the dynamical system to approach an attractor through feedback and fluctuations. For the sake of mathematical tractability, we only discuss in this section a one-dimensional formulation that captures the basic dynamical behavior of the system, see Eqn. (4). As we will show later, our study can be easily extended to a higher dimensional case. For a further discussion of multi-dimensional attractor selection systems, we refer to [3, 7, 8].

$$\frac{d}{dt}x(t) = f(x(t))\alpha + \eta(t) \quad (4)$$

In Eqn. (4), function f defines the attractors and depends on the system state $x(t)$ at time t . Function $\alpha : \mathbb{R} \rightarrow [0, 1]$ represents the activity or growth rate of the system. The term $\eta(t)$ represents the system-inherent fluctuation, which we assume to be zero-mean white Gaussian noise with a standard deviation σ . Before we analyze the system in greater detail, let us examine the essential behavior in Eqn. (4). The function $f(x(t))$ characterizes the attractors of the system to which its state will converge, regardless of small perturbations introduced by $\eta(t)$. However, as α approaches 0, the influence of the first summand diminishes, leaving the entire dynamics influenced only by the noise term, essentially resulting in a random walk in phase space.

Figure 2 illustrates the general principle of attractor selection. The horizontal axis represents the internal state $x(t)$ and three attractors exist as A_1 , A_2 , and A_3 . The orbit

of the system is currently within the influence of the rightmost attractor A_3 . If this solution is no longer suitable due to the influence from some environmental factor, the activity function α decreases, leading to a “flatter” potential landscape defined by $f(x(t))$ on the vertical axis. Given that the noise term is unchanged, the system will be driven away from its current attractor and perform a random walk in the phase space. Once the system approaches a more suitable attractor (in this case A_1), the system will become again more deterministic and its state will remain at this attractor in spite of the still existing noise terms. In order to appropriately define the functions f and α for application as self-adaptive control mechanism, we investigate their sensitivity in Section 3.

3 Sensitivity Analysis of Attractor Selection

In the following, we consider the abstract form of the attractor selection equation introduced in Eqn. (4). We distinguish two cases with regard to α . The first case simply assumes $\alpha(t)$ to be only a function of time and independent of the state $x(t)$. Secondly, we include the influence of $x(t)$ and consider in Section 3.2 that we have a function of the type $\alpha(x(t), t)$.

3.1 Time-Dependent Activity Function

Let us now consider that $\alpha(t)$ is simply a function of time and independent of the system state $x(t)$, see Eqn. (5).

$$\frac{d}{dt}x(t) = f(x(t))\alpha(t) + \eta(t) \quad (5)$$

In this case, activity is influenced only by an external source. Eqn. (5) can thus be interpreted as a variation of the *simulated annealing* technique [9], which is closely related to the considered system. However, while in simulated annealing the noise amplitude is gradually reduced over time, we have here an always constant noise influence in the system and the switching to a new attractor is controlled by the dynamics of the activity $\alpha(t)$.

We define the *variation* or *drift* of the system by the operator δ , such that

$$\delta f(x(t)) = \frac{f(x(t) + \delta x(t)) - f(x(t))}{\delta x(t)} \delta x(t) = \frac{\partial f(x(t))}{\partial x(t)} \delta x(t). \quad (6)$$

This leads to the following equation for describing the dynamics of the fluctuations of the state.

$$\frac{d}{dt}\delta x(t) = \alpha(t) \frac{\partial f(x(t))}{\partial x(t)} \delta x(t) + f(x(t)) \delta \alpha(t) + \delta \eta(t) \quad (7)$$

Equation (7) shows us that there are two (independent) driving forces for the dynamics of the state behavior given by the last two summands on the right hand side of Eqn. (7). Thus, we can consider two sensitivities, a *noise sensitivity* $\delta x(t)/\delta \eta(t)$ and a *parameter function sensitivity* $\delta x(t)/\delta \alpha(t)$.

Let us follow the argumentation as in [10, 11] and introduce an *adjoint function* $\phi(t)$. We can then multiply Eqn. (7) on both sides with $\phi(t)$ and obtain

$$\phi(t) \frac{d}{dt}\delta x(t) = \alpha(t) \phi(t) \frac{\partial f(x(t))}{\partial x(t)} \delta x(t) + \phi(t) f(x(t)) \delta \alpha(t) + \phi(t) \delta \eta(t). \quad (8)$$

If we define T as the time of interest, we can integrate both sides as

$$\int_0^T \phi(t) \frac{d}{dt} \delta x(t) dt = \int_0^T \left[\alpha(t) \phi(t) \frac{\partial f(x(t))}{\partial x(t)} \delta x(t) + \phi(t) f(x(t)) \delta \alpha(t) + \phi(t) \delta \eta(t) \right] dt \quad (9)$$

and apply integration by parts on the term on the left hand side of Eqn. (9) to remove the dependence on $d\delta x(t)/dt$. By replacing the left hand side of Eqn. (9), we now have

$$\begin{aligned} & \left[\phi(t) \frac{d}{dt} \delta x(t) \right]_0^T - \int_0^T \frac{d\phi(t)}{dt} \delta x(t) dt \\ &= \int_0^T \left[\alpha(t) \phi(t) \frac{\partial f(x(t))}{\partial x(t)} \delta x(t) + \phi(t) f(x(t)) \delta \alpha(t) + \phi(t) \delta \eta(t) \right] dt \end{aligned} \quad (10)$$

which can be rewritten by inserting the limits 0 and T of the integration as

$$\begin{aligned} & \phi(T) \delta x(T) - \phi(0) \delta x(0) - \int_0^T \frac{d\phi(t)}{dt} \delta x(t) dt \\ &= \int_0^T \left[\alpha(t) \phi(t) \frac{\partial f(x(t))}{\partial x(t)} \delta x(t) + \phi(t) f(x(t)) \delta \alpha(t) + \phi(t) \delta \eta(t) \right] dt. \end{aligned} \quad (11)$$

Since we can assume that there is initially no perturbation, i.e., $\delta x(0) = 0$, this leads us to the final formulation as shown in Eqn. (12).

$$\begin{aligned} & \phi(T) \delta x(T) \\ &= \int_0^T \left[\frac{d\phi(t)}{dt} + \alpha(t) \frac{\partial f(x(t))}{\partial x(t)} \right] \delta x(t) dt + \int_0^T \phi(t) f(x(t)) \delta \alpha(t) dt + \int_0^T \phi(t) \delta \eta(t) dt \end{aligned} \quad (12)$$

Let us now specify the adjoint function $\phi(t)$ by the following differential equation

$$\frac{d\phi(t)}{dt} = -\alpha(t) \frac{\partial f(x(t))}{\partial x(t)} \phi(t) \quad (13)$$

such that the first summand on the right hand side of Eqn. (12) is eliminated, and define the boundary condition $\phi(T) = 1$. Thus, we now have the simplified form of

$$\delta x(T) = \int_0^T \phi(t) f(x(t)) \delta \alpha(t) dt + \int_0^T \phi(t) \delta \eta(t) dt. \quad (14)$$

With Eqn. (14), we can now easily obtain the functional derivatives

$$\frac{\delta x(T)}{\delta \alpha(t)} = \phi(t) f(x(t)) \quad \frac{\delta x(T)}{\delta \eta(t)} = \phi(t) \quad (15)$$

which describe the sensitivity of the system state in terms of the adjoint function $\phi(t)$. It should be noted that the functional derivative means that both time variables t and T may differ and the formulation in Eqn. (15) is directly represented by the definition of the functional derivatives. Basically, these terms indicate how a past change of a parameter value affects the current system state. If we know the sensitivity with respect to noise, we can directly obtain the sensitivity to the dynamics of the parameter function.

3.2 State-Dependent Activity Function

The previous section considered simply the time-dependent dynamics of the growth function $\alpha(t)$. This implies that the activity is in fact independent of the system state. However, a more realistic assumption is when $\alpha(x(t), t)$ is a function of the system state. This corresponds to the case where the system's output actually influences the activity, see Eqn. (16).

$$\frac{d}{dt}x(t) = f(x(t))\alpha(x(t), t) + \eta(t) \quad (16)$$

The dynamics of the perturbation of state $x(t)$ can be now formulated as follows.

$$\begin{aligned} \frac{d}{dt}\delta x(t) &= \delta f(x(t))\alpha(x(t), t) + f(x(t))\delta\alpha(x(t), t) + \delta\eta(t) \\ &= \left[\frac{\partial f(x(t))}{\partial x(t)}\alpha(x(t), t) + f(x(t))\frac{\partial\alpha(x(t), t)}{\partial x(t)} \right] \delta x(t) + \delta\eta(t) \end{aligned} \quad (17)$$

In order to evaluate Eqn. (17), we need to decompose $x(t)$ to its reference trajectory $\bar{x}(t)$, which describes the “average” dynamical behavior and can be obtained by experiments or simulations, and its perturbation $\delta x(t)$.

$$x(t) = \bar{x}(t) + \delta x(t) \quad (18)$$

Inserting $\bar{x}(t)$ into Eqn. (17), we now obtain

$$\begin{aligned} \frac{d}{dt}\delta x(t) &= \left[\frac{\partial f(\bar{x}(t))}{\partial x(t)}\alpha(\bar{x}(t), t) + f(\bar{x}(t))\frac{\partial\alpha(\bar{x}(t), t)}{\partial x(t)} \right] \delta x(t) + \delta\eta(t) \\ &= A(\bar{x}(t))\delta x(t) + \delta\eta(t). \end{aligned} \quad (19)$$

We can repeat the same method as in Section 3.1, by multiplying Eqn. (19) with an adjoint function $\phi(t)$ and integrating by parts.

$$\begin{aligned} \phi(t) \frac{d}{dt} \delta x(t) &= \phi(t) A(\bar{x}(t)) \delta x(t) + \phi(t) \delta\eta(t) \\ \Leftrightarrow \int_0^T \phi(t) \frac{d}{dt} \delta x(t) dt &= \int_0^T \phi(t) A(\bar{x}(t)) \delta x(t) dt + \int_0^T \phi(t) \delta\eta(t) dt \\ \Leftrightarrow [\phi(t) \delta x(t)]_0^T &= \int_0^T \left[\frac{d\phi(t)}{dt} + \phi(t) A(\bar{x}(t)) \right] \delta x(t) dt + \int_0^T \phi(t) \delta\eta(t) dt \\ \Leftrightarrow \phi(T) \delta x(T) &= \int_0^T \phi(t) \delta\eta(t) dt \end{aligned}$$

Defining the adjoint function dynamics as

$$\frac{d\phi(t)}{dt} = -\phi(t) A(\bar{x}(t)) \quad (20)$$

as well as setting again the boundary condition $\phi(T) = 1$ leads to a sensitivity value that only depends on the perturbation of the noise terms $\eta(t)$.

$$\delta x(T) = \int_0^T \phi(t) \delta \eta(t) dt \quad (21)$$

With Eqn. (21), we can now easily obtain the functional derivative expressing the noise sensitivity.

$$\frac{\delta x(T)}{\delta \eta(t)} = \phi(t) \quad (22)$$

4 Numerical Evaluations

Let us now consider some numerical experiments of the previously discussed stability analysis. So far we only considered generic formulations of the involved functions, but now need to take specific functions into account. For this we use a definition as given in [7] for an N -dimensional system state. Let function f be defined as

$$f(x_i(t)) = S \left(\sum_{j=1}^N w_{ij} x_j(t) \right) - x_i(t) \quad i = 1, \dots, N \quad (23)$$

where S is a sigmoid function, such as the logistic function in Eqn. (24), where c is a constant.

$$S(z) = \frac{1}{1 + e^{-cz}} \quad (24)$$

For the sake of simplicity, we assume in the following that $N = 2$. We assume the weights w_{ij} to be self-activatory ($w_{ij} = 1$ for $i = j$) and mutually inhibitory ($w_{ij} = -1$ for $i \neq j$), as well as constant over time as shown in the weight matrix $\mathbf{W} = (w_{ij})_{2 \times 2}$ below.

$$\mathbf{W} = \begin{pmatrix} 1 & -1 \\ -1 & 1 \end{pmatrix} \quad (25)$$

Although we now consider a two-dimensional system, the formulation of the adjoint function can be done in the same manner as in Eqn. (13) for each $i = 1, 2$ independently.

4.1 Time-Dependent Activity Function

As we are mostly interested in the behavior when a system that is currently dominated by noise influence converges to an attractor, we make the assumption that activity α is simply a monotonically growing function in this study with $\alpha(0) = 0$ and $\lim_{t \rightarrow \infty} \alpha(t) = 1$ with parameter β indicating its steepness.

$$\alpha(t) = \tanh(\beta t) \quad (26)$$

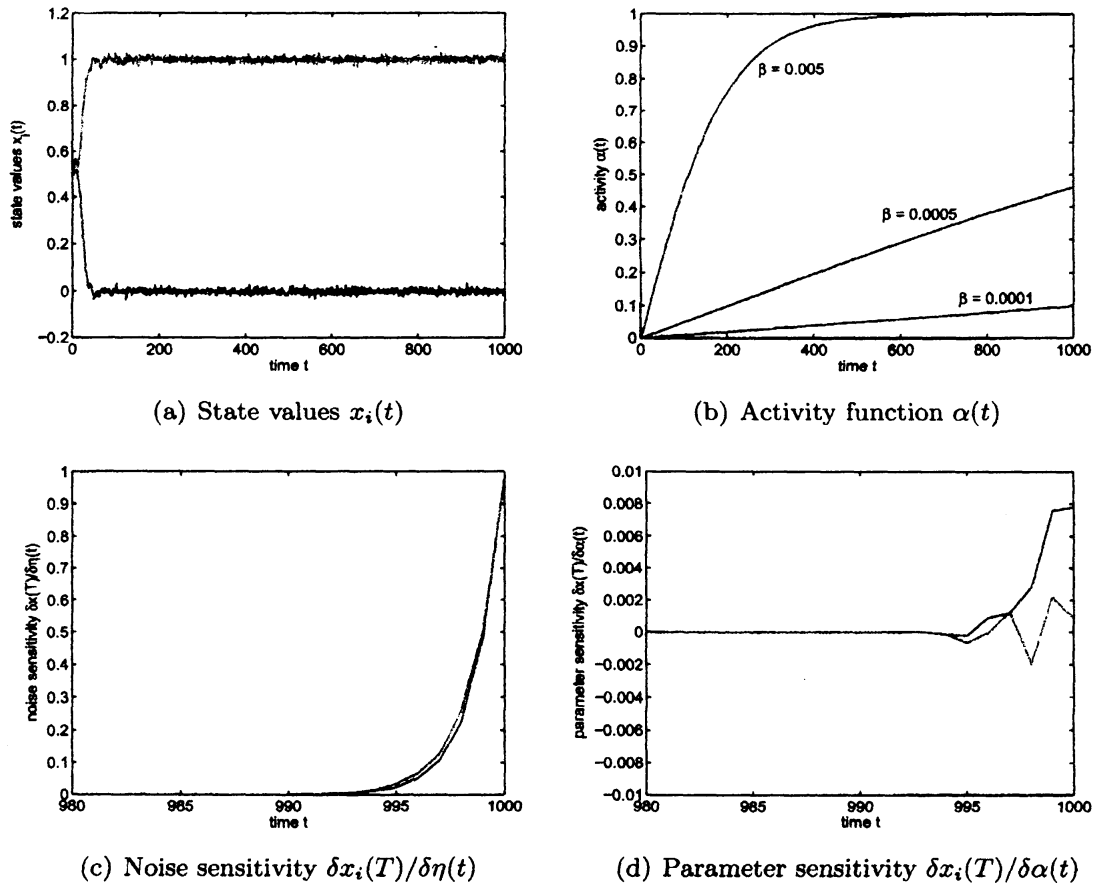


Figure 3: Numeric evaluation of two-dimensional state dynamics and its sensitivities

We now perform a numeric evaluation of the state dynamics in the two-dimensional case and compute the noise and parameter function sensitivities as described in Section 3.1, see Fig. 3. The observation time was selected as $T = 1000$ time steps and the noise standard deviation is $\sigma = 0.01$. Figure 3(a) shows the dynamic evolution of the states $x_i(t)$ over time for $\beta = 0.005$. Due to their mutually inhibitory definition, one of the states increases from the initial condition $x_i(0) = 0.5$ for $i = 1, 2$ due to the noise term and reaches 1, while the other reaches 0. Since both attractors at $(0, 1)^T$ and $(1, 0)^T$ are stable, noise influences which attractor is eventually reached. The activity function $\alpha(t)$ slowly increases over time from 0 to 1, but its effect on the convergence becomes already negligible once $\alpha(t)$ becomes sufficiently large. Figure 3(b) also shows how the parameter β influences the speed that function $\alpha(t)$ converges.

When we look at the sensitivities in Figs. 3(c) and 3(d), it becomes obvious that only the immediate past from the observation time T plays an actual role. Both figures just show a small window of the last 20 time steps prior to T for $\beta = 0.005$. Noise sensitivity reduces exponentially toward the past, i.e., the influence of prior fluctuations becomes less important as time passes. The sensitivity to the parameter function in Fig. 3(d) even shows only very minor influence since $\alpha(t)$ in Fig. 3(b) has converged by the time T well to its target level at 1 for $\beta = 0.005$.

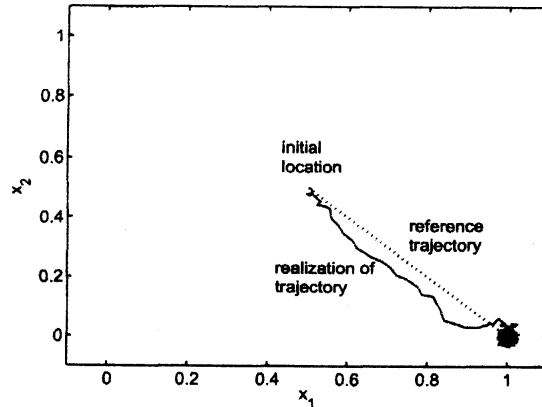
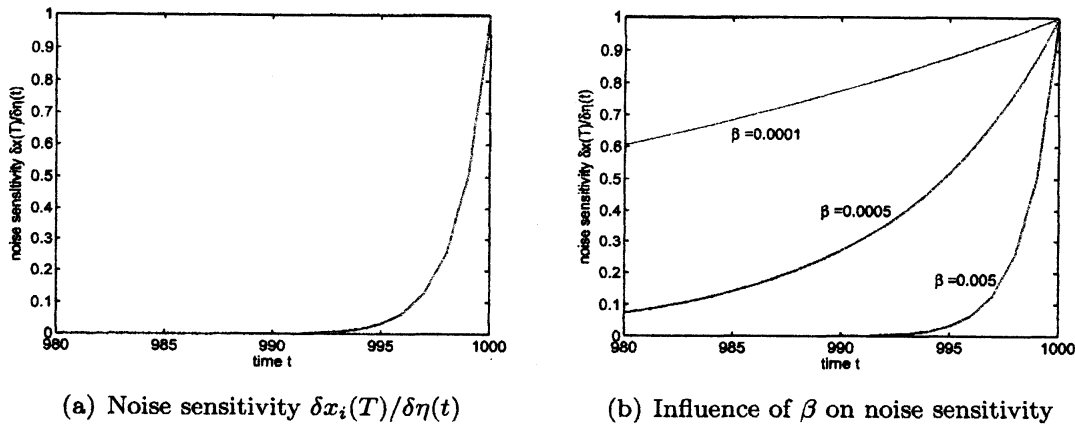


Figure 4: Phase plot of realization of state-dependent activity function



(a) Noise sensitivity $\delta x_i(T)/\delta \eta(t)$

(b) Influence of β on noise sensitivity

Figure 5: Noise sensitivity for state-dependent activity at $T = 1000$

4.2 State-Dependent Activity Function

Finally, let us examine the more realistic case where the state $x(t)$ actually influences the activity function $\alpha(x(t), t)$. We define the activity function to be controlled as

$$\alpha(x(t), t) = \tanh(\beta x_1(t) t) \quad (27)$$

which makes the system state attracted to $(1, 0)^T$. The reference trajectory is indicated in Fig. 4 as the dotted direct line from the initial point at $(0.5, 0.5)^T$ to the attractor at $(1, 0)^T$, where the system will remain in spite of the small perturbations by $\eta(t)$.

Figure 5 shows the numerical results for the same parameter settings as in Section 4.1. In Fig. 5(a) we can recognize that the computation of Eqn. (22) yields almost the identical results as when the activity α is simply a function of time (Fig. 3(c)). The reason for this behavior can be interpreted as follows. Since the considered system has only two attractors, its dynamics is already very close to the reference trajectory, especially at the considered noise amplitude. Furthermore, the observation time T and the activity adaptation rate β play an important role on how sensitive the system is toward noise. This is illustrated in Fig. 5(b) for different values of β . The smaller β gets, the higher the

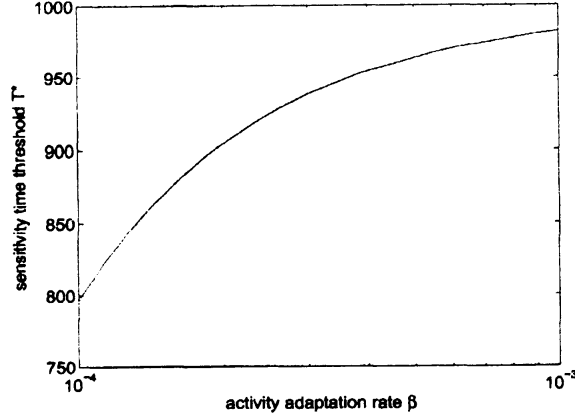


Figure 6: Sensitivity time threshold for different β

noise sensitivity becomes, since activity remains for a longer time at a lower level. If at the observation instant T the system state has already settled at an attractor, the impact of fluctuations in the past becomes less important.

This phenomenon is further investigated in Fig. 6, where we define the threshold T^* as the time instant where $\phi_i(T^*)$ falls below 0.01. The figure shows the relationship between the activity adaptation rate β and T^* for the previously considered system at $T = 1000$. We can see that if activity does not adapt fast enough, past fluctuations will influence the system's state for a much longer period.

5 Conclusion

In this work, we discussed the fundamental mathematical properties of the dynamics of attractor selection inspired from biological gene expression. In general, attractor selection dynamically switches between a “deterministic mode”, where the system converges to its nearest attractor and a “random mode”, where the potential landscape is flattened by the activity term. We used the formal methodology of sensitivity analysis to mathematically derive the relationship between the system state and the influencing noise terms and activity parameter function. Furthermore, we considered two different types of activity functions, one which is simply a function of time and another one which is dependent on the current system state. Numerical evaluations showed that it is possible to compute the sensitivities and that there is a high interdependence between the adaptation rate of the activity function, which in turn governs the system state's convergence and the noise amplitude. This requires further detailed analytical studies in order to fine-tune a system such that a better convergence can be designed for an implementation as a self-adaptive control method in autonomous communication networks. Noise-driven mechanisms provide an important approach to designing robust adaptation mechanisms, e.g. *Subconscious Noise Reaction* in neural network learning as discussed in [12], and in the future we intend to combine the attractor selection methodology with the Langevin-learning rule for updating the weight matrix. This would enable us to combine short-term dynamics through attractor selection with an adaptation of the attractors through learning the long-term changes in the environment.

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