The Third International Symposium on Optimization and Systems Biology (OSB'09)
Zhangjiajie, China, September 20–22, 2009

Response Time and Its Role in Noise Filtering

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Abstract A cell consists of many interacting biomolecular components that form some basic feedback loops, such as positive or negative feedback loops. When biological signals transduce through cascades consisting of various loops they will be affected or even distorted. Especially, how to process various signals buried in various intrinsic and extrinsic noises is an important issue. In this paper, a method on how to cope with these signals will be discussed. A parameter to measure the response time of the signal transduction i.e., $\tau_{0.9}$, and its relationship between the response time and noise filtering will be discussed. Generally speaking, the longer the response time is, the better the ability to filter noises will be. Then we discuss how to enhance the ability to filter noises in a positive or negative feedback loops, and draw a conclusion that coupling feedback loops can enhance the ability.

Keywords signal cycle; response time; noises; filtering noises

1 Introduction

Cells are autonomous entities. Whether to function as single-celled organisms or as a part of higher multicellular organisms, cells must sense their environment and must be able to react to it. Many cellular processes respond abruptly to internal and external variations by using networks of interacting molecules. Over the past decades, the study of detailed models for intracellular networks has become popular. Covalent modification cycles are one of the major intracellular signaling mechanisms both in prokaryotic and eukaryotic organisms [1]. A network can be decomposed into multiple subsystems or modules and subsequently analyzed, therefore a modularity approach has been proposed as a promising rationale for the analysis of large biochemical networks [2, 3].

There exists a basic substrate protein that can be in one of two states: active, e.g., phosphorylated, or inactive, e.g., dephosphorylated, in a signaling cycle, a ubiquitous building block [1]. A kinase catalyzes the substrate protein to make it active, and another enzyme catalyzes the active protein to make it inactive. The concentration of kinase can be regarded as input signal and the concentration of activated protein can be regarded as output signal. The signal can propagate by the cycle that can be frequently organized into cascades in which the activated protein can be considered as a kinase in the next cycle. Four operating regimes, i.e., hyperbolic, signaling-transducing, threshold-hyperbolic, and ultrasensitive steady-state responses have been studied by the total quasi-steady approximation method [1]. It has been shown that different feedback loops have different roles in filtering noises [4, 5].

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In the four regimes discussed in [1], It has been shown that hyperbolic regime is robust to extrinsic fluctuation but generates significant intrinsic noises and loses more information. The ultrasensitive cycles are sensitive to extrinsic kinase and phosphatase fluctuations [6]. However, why different regimes have different roles in dealing with noises is still unknown and need to be discussed further. This paper is organized as follows. In section 2, we will give an introduction to the positive cycle and its functions, and then analyze its response time $\tau_{0.9}$ [4] with the signal amplification. Owing to all kinds of stochastic factors, the noises will be brought about and will affect the transduction of signals. How to filter noises and improve the noise filtering ability will be discussed in section 2. Finally, section 3 concludes the paper.

2 Methods and Results

2.1 Signal cycle

In a signal cycle, there exists a substrate protein, which can be either active or inactive [1]. The substrate can be turned from its initial inactivate state I to an active state A by the catalyst E_1, while another catalyst E_2 turns it in the opposite direction, where E_1 and E_2 are two kinds of enzymes. The substrate toggles between the two states when the enzymes E_1 and E_2 play a role. The transition between the two states I and A catalyzed by the kinase E_1 and phosphatase E_2 forms a cycle. If the enzyme E_1 is regarded as an input signal and A is regarded as an output signal, a signal can be propagated through this cycle.

In order to explore the mechanisms of the signal propagation, it is important to study the relationship between the output, i.e., $A(t)$ and the parameters, e.g., E_1. A dynamical system of differential equations can be be deduced according to the biochemical reactions and the mass action law, but it is difficult to analyze its dynamics theoretically because of its nonlinearity. It is fortunate that the system can be reduced according to the total quasi-steady-state approximation (tQSSA), and the simplified equation takes the form [1]

$$\frac{d\overline{A}(t)}{dt} = k_1 \frac{\overline{E}_1(\overline{S} - \overline{A}(t))}{K_1 + \overline{E}_1 + \overline{S} - \overline{A}(t)} - k_2 \frac{\overline{E}_2 \overline{A}(t)}{K_2 + \overline{E}_2 + \overline{A}(t)}. \tag{1}$$

Here $\overline{E}_1$ can be used to stand for the input signal and $\overline{A}$ for the output signal. The meanings of other parameters can be seen in [1]. When a signal is put into the cycle, it is changed by the module and finally the module puts out a signal as a response to the input signal, so the information is processed by the cycle. The signal cycle consists of the output A and input E_1 and our attention will be focused on the steady-state response and transient dynamics of (1). It can exhibit four regimes which cover all the situations of steady state response, i.e., hyperbolic, signal-transducing, threshold-hyperbolic, and ultrasensitive.

To explore the function of the cycle, it is important to consider the dynamics of $\overline{A}$ over time t. As seen in Fig.1, for different parameter values, the speed of convergence is very different. In other words, in the signal-transducing case, the speed is the fastest, while in the hyperbolic case, it is the slowest. Note that the initial value of A for all the cases is the zero concentration.

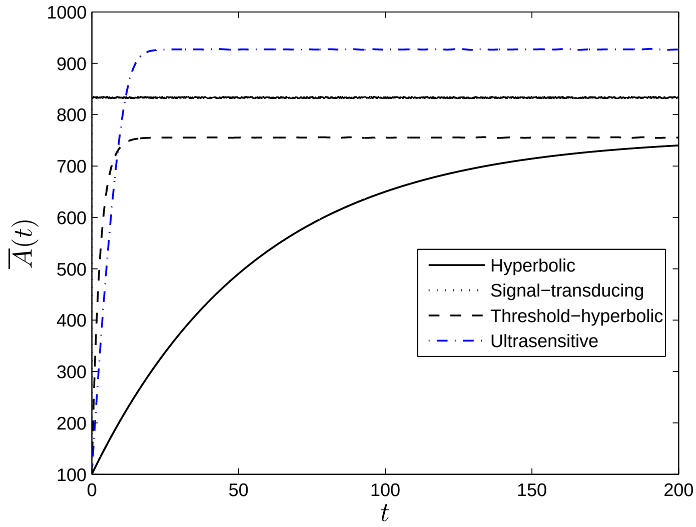

Figure 1: A comparison of the convergence speed for the four operating regimes.

2.2 Response time of signal cycle

It has been known that a response time affects the noises in a signal [4, 7]. The response time is regarded as a transient characteristics of output signal. In order to study the characteristics of the cycle, it is necessary to study both the transient characteristics and the steady state properties in detail as much as possible [8, 9]. Saez-Rodriguez [10] proposed a parameter $\tau_{0.9}$ to measure how fast a system responds to the input roughly and it can be regarded as a response time approximately. The parameter $\tau_{0.9}$ is defined as the time at which 90 percent of the maximal output signal is reached. The response time $\tau_{0.9}$ as a function of the input signal $\overline{E}_1$ for the four operating regimes is shown in Fig.2. The hyperbolic is the slowest and the signal-transducing is the fastest. The response time of the four regimes increases from hyperbolic, ultrasensitive, threshold-hyperbolic, to signal-transducing in turn.

2.3 Noise filtering

There exist noises in nature everywhere and they affect a wide range of biochemical reactions. The signal will be affected by the noises inevitably when it propagates through a cycle. There are many kinds of causes that can induce noises in the transduction of the signal in the cycle. It is well known that random thermal motion originates the fluctuation, which is very common in intracellular signal transduction [11]. It is well known that the causes of the noises mainly come from external and internal perturbations, but we only consider the external noises here. Given any input S without any noise, the system will converge to a steady state in the four operating regimes respectively. When there exists a noise in the input signal, the output will be affected in the transduction.

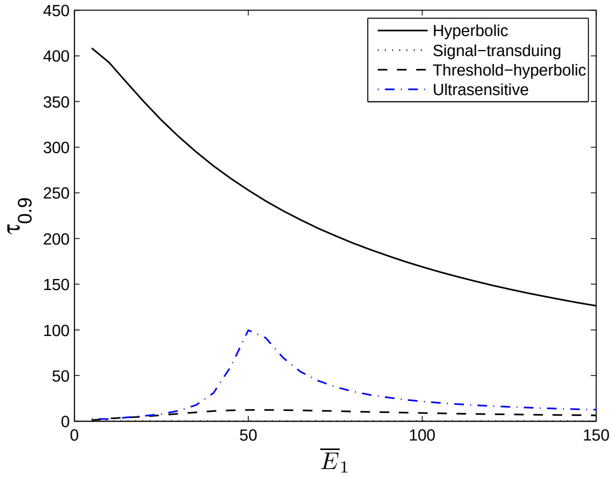

Figure 2: The response time $\tau_{0.9}$ as a function of the input signal $\overline{E}_1$ for the four operating regimes.

When a noisy signal is propagated through the cycle, it is distorted so that we can't get the ideal output signal under the influence of the external noise. Our major task is to filter the noise so as to control the output and make it satisfy certain conditions. A fact has been depicted previously that low-frequency inputs are proxies for longer input activations, whereas high-frequency inputs are proxies for short, transient activations of the cycle and for high-frequency noises [4]. On the one hand, if the frequency of inputs is very low and the response time of the reaction is very short, the noises contained in the signal can be easily filtered out. On the other hand, if the frequency of the input is very high and the response time of the signal is very high, the noises in the cycle is difficult to filtered out relatively, the ability to filter the noise is related to the frequency of the input and the response time of the cycle. Generally speaking, the frequency of an input can be regarded as a fixed number, so the ability to filter noises can be deduced from the response time of a cycle. The longer the response time is, the better the ability to filter noise will be.

If the response time $\tau_{0.9}$ of one cycle is longer than another, the longer should have the better ability to filter noises than the shorter. In order to measure this ability we introduce the noise amplification η which was defined as [5]

$$\eta = \frac{std(X)/<X>}{std(S)/<S>}, \tag{2}$$

where $std(S)$ and $std(X)$ are standard deviation of the input S and output signal X, respectively. $<S>$ and $<X>$ are the mean of the input and output signal, respectively. If $\tau_{0.9}$ of some cycle is very long, the η should be small in general. By comparing the length of response time $\tau_{0.9}$ in the four operating regimes, we found that the response time $\tau_{0.9}$ in the signal-transducing regime is the shortest whereas the hyperbolic is the longest, as shown in Fig.2. The noise amplification η as a function of $\overline{E}_1$ for the four operating regimes is shown in Fig.3. It can be seen that the noise amplification η of the signal-transducing is the biggest while the hyperbolic is the smallest among the four regimes. In other words, the longer the response time $\tau_{0.9}$ is, the smaller the noise amplification η will be. Therefore, the signal cycle with larger response time will have a better ability to filter noises.

However, there exists an exception in an interval from about 20 to 60. In this region, the response time $\tau_{0.9}$ of threshold-hyperbolic is longer than that of the ultrasensitive while the noise amplification η of ultrasensitive is bigger than that of threshold-hyperbolic. However, in other case, the noise amplification and response time have the similar order for both hyperbolic and signal-transducing regimes. Such a phenomenon is related to the gain and will be discussed in future.

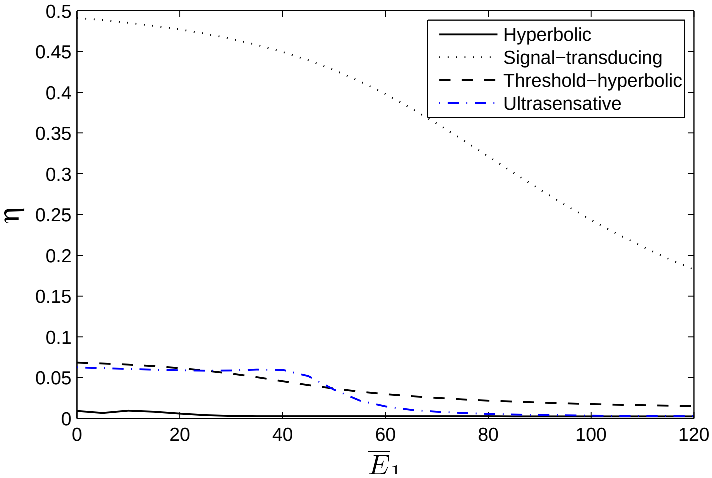

Figure 3: Noises amplification η as a function of $\overline{E}_1$ for the four operating regimes.

2.4 How to improve the filtering ability

The interactions of numerous intercellular biomolecules can induce complex cellular behaviors. These biomolecules interact with each other and form various modules or motifs. One basic module is made up of a positive and a negative feedback loops [9]. In this section, the relationship between the response time and the amplification of a signal will be discussed and some ways to improve the filtering ability will be proposed by the comparison of some basic positive or negative feedback loops about their response time and their noise amplification.

Assume that a positive feedback loop consists of two nodes, X and Y. They activate each other and form a basic motif. The system can be described as

$$\frac{dX}{dt} = V_X(Y/K_{YX})^H/(1+(Y/K_{YX})^H)+S-K_{dX}X(t)+K_{bX}, \quad (3)$$

$$\frac{dY}{dt} = V_Y(X/K_{XY})^H/(1+(X/K_{XY})^H)-K_{dY}Y(t)+K_{bY}, \quad (4)$$

where the parameters V_X and V_Y indicate the the regulatory effect of X and Y, respectively, H indicates the Hill coefficient, the threshold parameter K_{YX} denotes the threshold of Y inducing a significant response of X, the threshold parameter K_{XY} denotes the threshold of X inducing a significant response of Y, K_{dX} and K_{dY} represent the degradation rate constants of X and Y, respectively, K_{bX} and K_{bY} indicate the basal synthesis rates of X and Y, respectively, and S can be regarded as the input signal of the cycle. This loop is denoted as P for the sake of convenience.

Similarly, if X activates Y and Y represses X, they compose a negative feedback loop and it's described as the following equations

$$\frac{dX}{dt} = V_X/(1+(Y/K_{YX})^H)+S-K_{dX}X+K_{bX}, \tag{5}$$

$$\frac{dY}{dt} = V_Y(X/K_{XY})^H/(1+(X/K_{XY})^H)-K_{dY}Y+K_{bY}. \tag{6}$$

We denote this loop as N.

Let S in loops P and N be input signal and there exist noises in the signal. The node X or Y can be regarded as its output. The ability to filter the noises can be measured by the noises amplification and response time. The response time and noise amplification are shown in Fig.4. On the one hand, the response time of a positive loop P is shorter than that of a negative loop N when the input S varies in a certain interval. On the other hand, the noise amplification of the positive loop is higher than that of the negative loop when the input signal varies in the same interval, which means that the positive loop has a better ability to filter noises in the transduction of the signal than that of the negative loop.

Now we consider how to improve the ability to filter noises. We first consider a positive loop P coupled with a negative loop, which is denoted as PN for the sake of convenience, where X and Y compose a positive loop P and Y and Z form a negative loop N. P and N form a motif $PN1$. The equations can be described as

$$\frac{dX}{dt} = \frac{V_X(Y/K_{YX})^H}{1+(Y/K_{YX})^H}-K_{dX}X+K_{bX}+S, \tag{7}$$

$$\frac{dY}{dt} = \frac{V_Y(X/K_{XY})^H}{1+(X/K_{XY})^H+(Z/K_{ZY})^H}-K_{dY}Y+K_{bY}, \tag{8}$$

$$\frac{dZ}{dt} = \frac{V_Z(Y/K_{YZ})^H}{1+(Y/K_{YZ})^H}-K_{dZ}Z+K_{bZ}. \tag{9}$$

Let's consider the variation trend of response time and corresponding noise amplification. It can be easily found that the response time will increase for the coupled motif $PN1$. The noise amplification of $PN1$ is higher than that of P, therefore increasing response time will enhance the ability to filter noise.

We next consider a positive loop coupled with a positive loop. We denote it as $PP1$

and its equations can be described as

$$\frac{dX}{dt} = V_X(Y/K_{YX})^H/(1+(Y/K_{YX})^H)+S-K_{dX}X+K_{bX}, \tag{10}$$

$$\frac{dY}{dt} = V_Y((X/K_{XY})^H+(Z/K_{ZY})^H/(1+(X/K_{XY})^H+(Z/K_{ZY})^H)-K_{dY}Y+K_{bY}, \tag{11}$$

$$\frac{dZ}{dt} = V_Z(Y/K_{YZ})^H/(1+(Y/K_{YZ})^H)-K_{dZ}Z+K_{bZ}, \tag{12}$$

where $V_X = 2$; $V_Y = 2$; $V_Z = 5$; $K_{YX} = 1$; $K_{XY} = 2$; $K_{YZ} = 3$; $K_{dX} = 1$; $K_{ZY} = 1$; $K_{dZ} = 1$; $K_{bX} = 2$; $K_{dY} = 1$; $K_{bZ} = 1$; $K_{bY} = 1$. S is an input signal with some noises.

The response time of the coupled loop PP is longer than that of P while the noise amplification of PP is smaller than that of P. The longer the response time is, the smaller the noise amplification is. Therefore, the response time of such a coupled positive loop increases and its noise amplification decreases. In other words, the ability to filter noises can be enhanced when one positive loop couples another positive loop, as shown in Figs.4A and 4B.

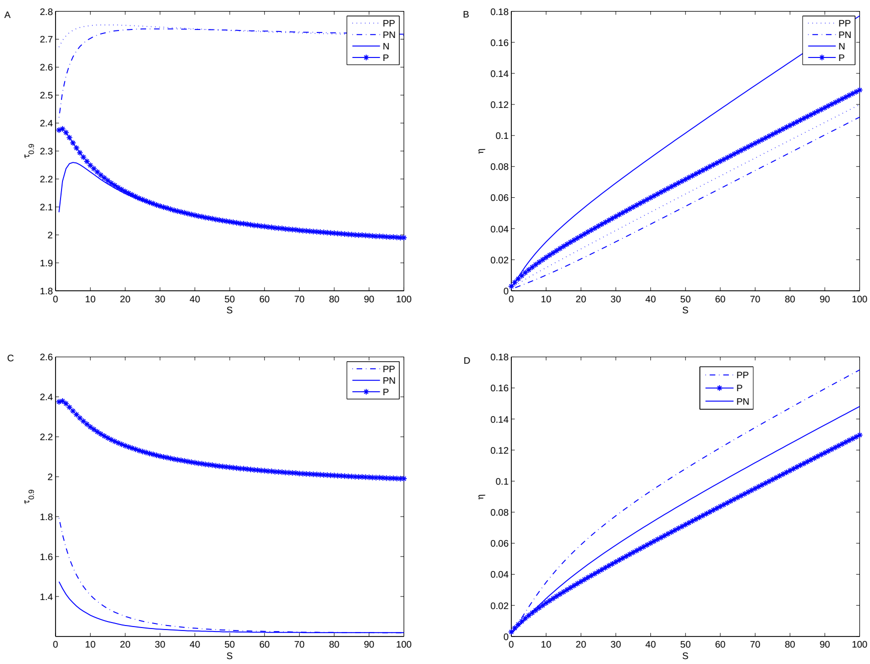

Figure 4: Response times and the noise amplification for different kinds of coupling.

Finally, we consider another type of coupling in which such a positive loop couples anther positive loop or negative loop. At first, the positive loop couples anther positive loop in which Y and Z repress each other. We denote it as $PP2$. Secondly, the positive loop couples a negative loop in which Y represses Z while Z activates Y. We denote it as

*PN*2. The equations describing these tow coupled motifs can be found in Appendix. We simulate such two cases about the response time and the noise amplification (see Figs.4C and 4D). The response time of *PP*2 and *PN*2 are shorter than that of the positive loop *P* when *S* varies in a interval while the noise amplification of *PP*2 and *PN*2 is higher than that of *P*. Therefore the ability to filter noises of such a positive loop can be reduced if it couples a positive loop or a negative loop and form the coupled loops *PP*2 and *PN*2.

From the analysis above a conclusion can be drawn that if a positive feedback loop couples a positive loop or a negative loop and form a cycle that is the same as *PP*1 or *PN*1, the ability to filter noises of the signal positive loop can be enhanced. If a signal feedback loop couples a positive loop or a negative loop and form a cycle that is the same as *PP*2 or *PN*2, the ability to filter noises of the signal positive loop can be deduced.

3 Conclusion and Discussion

In this paper, we mainly discuss the effects of coupled positive or negative feedback on the ability to filter noises. We found that different kinds of feedback have different roles in filtering ability will be. In the first place, a relationship between response time and noise amplification was discussed. It was found that the longer the response time is, the less the noise amplification is and the better the ability to filter noises will be. Using this result, we discuss how to couple a new loop so as to enhance the ability to filter noises by lengthening the response time. We found that different feedback loops have different roles in filtering noises.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Youth Research Grant 10701052) and the Innovation Fund of Shanghai University.

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Appendix 1

The values of its parameters are $V_X = 2; V_Y = 2; V_Z = 5; K_{YX} = 1; K_{XY} = 2; K_{YZ} = 3; K_{dX} = 1; K_{ZY} = 1; K_{dZ} = 1; K_{bX} = 2; K_{dY} = 1; K_{bZ} = 1; K_{bY} = 1;$

Appendix 2

$$\begin{cases} \frac{dX}{dt} = V_X(Y/K_{YX})^H/(1+(Y/K_{YX})^H) + S - K_{dX}X + K_{bX} \\ \frac{dY}{dt} = V_Y((X/K_{XY})^H + (Z/K_{ZY})^H)/(1+(X/K_{XY})^H + (Z/K_{ZY})^H) - K_{dY}Y + K_{bY} \\ \frac{dZ}{dt} = V_Z(Y/K_{YZ})^H/(1+(Y/K_{YZ})^H) - K_{dZ}Z + K_{bZ} \end{cases} \tag{13}$$

The values of its parameters are $V_X = 2; V_Y = 2; V_Z = 5; K_{YX} = 1; K_{XY} = 2; K_{YZ} = 3; K_{dX} = 1; K_{ZY} = 1; K_{dZ} = 1; K_{bX} = 2; K_{dY} = 1; K_{bZ} = 1; K_{bY} = 1;$

Appendix 3

$$\begin{cases} \frac{dX}{dt} = V_X(Y/K_{YX})^H/(1+(Y/K_{YX})^H) + S - K_{dX}X + K_{bX} \\ \frac{dY}{dt} = V_Y((X/K_{XY})^H)/(1+(X/K_{XY})^H + (Z/K_{ZY})^H) - K_{dY}Y + K_{bY} \\ \frac{dZ}{dt} = V_Z/(1+(Y/K_{YZ})^H) - K_{dZ}Z + K_{bZ} \end{cases} \tag{14}$$

The values of its parameters are $V_X = 2; V_Y = 2; V_Z = 5; K_{YX} = 1; K_{XY} = 2; K_{YZ} = 3; K_{dX} = 1; K_{ZY} = 1; K_{dZ} = 1; K_{bX} = 2; K_{dY} = 1; K_{bZ} = 1; K_{bY} = 1;$