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MicroRNA-mediated incoherent feedforward motifs are robust

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Abstract In this paper, we integrate transcriptional and posttranscriptional regulation into microRNA-mediated incoherent feedforward motifs and analyze their dynamical behaviors and functions. The analysis show that the behaviors of the system are almost uninfluenced by the varying input in certain ranges and the introducing of delay and noise. The results indicate that microRNA-mediated incoherent feedforward motifs greatly enhance the robustness of gene regulation.

Keywords MicroRNA; incoherent; motif; robust

1 Introduction

In the past several years, it is believed that regulation of gene expression, in all organisms, is almost exclusively a task for regulatory proteins. This view reflects the focus on transcriptional regulation and post-translational regulation, other levels of regulation are often considered to be less important. However, as more and more cases of post-transcriptional regulation manifested by small non-coding RNAs are being uncovered, it is recognized that post-transcriptional regulation plays a prominent role in the regulation of cellular processes.

MiRNAs are post-transcriptional regulatory molecules recently discovered in animals and plants. It has been shown that they regulate diverse biological processes ranging from embryonic development to the regulation of neuronal patterning. miRNAs are single-stranded RNA molecules of about 21-23 nucleotides in length, which regulate gene expression. miRNAs are encoded by genes that are transcribed from DNA but not translated into protein (non-coding RNA); instead they are processed from primary transcripts known as pri-miRNA to short stem-loop structures called pre-miRNA and finally to functional miRNA. Mature miRNA molecules are partially complementary to one or more mRNA molecules, and their main function is to downregulate gene expression. They were first described in 1993 by Lee and colleagues in the Victor Ambros lab [1], yet the term microRNA was only introduced in 2001 in a set of three articles in Science [2]. As of early 2008, computational analysis by IBM suggested the existence of as many as 50,000 different miRNAs in the typical mammalian cell, each with perhaps a thousand or more potential targets [3].

In [4], the post-transcriptional regulatory mechanism was investigated by dynamical simulations, and their properties of post-transcriptional regulation by sRNA-mRNA base

pairing were compared with those of transcriptional regulation by protein-DNA interaction and post-translational regulation by protein-protein interaction. It has been shown that there are measurable differences between the three regulation modes and in certain situations regulation by sRNA is advantageous over other regulation modes. But they described and analyzed regulation of a gene as an isolated event. However, regulation of gene expression is often achieved by more complex regulatory patterns, involving various types of regulatory interactions. In [5] computational predictions show that miRNAs are embedded in a large number of gene regulatory networks, in which certain miRNA-containing motifs are recurrent. While almost all miRNAs function through repressing the translation of their target mRNAs, their functions in networks need not be simply repressive, they could have diverse functions depending on the unique gene regulatory network context of individual miRNA-target interactions.

According to above analysis, we describe and discuss miRNA-mediated incoherent feedforward motifs in the first place.

2 Results

Two kinds of miRNA-mediated incoherent feedforward motifs are shown in Figure 1, U, m and T denote the upstream factor, miRNA, and the target gene, respectively.

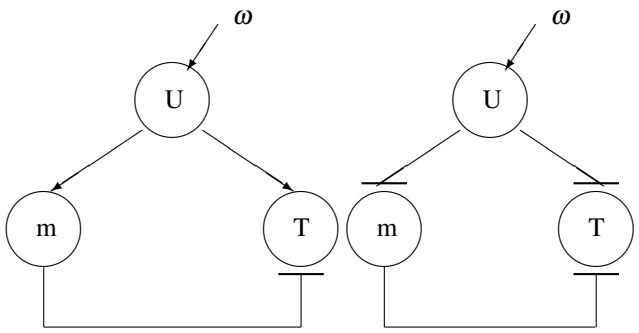

Figure 1: Two kinds of miRNA-mediated incoherent feedforward motifs.

These motifs are recurrent in mammalian gene regulatory networks, one example is c-Myc/E2f1/miR-17-92 network[6, 7].

Next, we mainly describe and analyze the dynamics and functions of the motif I. similar analysis are also done with motif II, and similar results are obtained.

Motif I is described by the following rate equations:

$$\begin{cases} \dot{p}_1 = \alpha_1 w - \beta_1 p_1, \\ \dot{m}_1 = \frac{\alpha_2 p_1^m}{1+p_1^m} - \gamma m_1 m_2 - \beta_2 m_1, \\ \dot{m}_2 = \frac{\alpha_3 p_1^n}{1+p_1^n} - \gamma m_1 m_2 - \beta_3 m_2, \\ \dot{p}_2 = \alpha_4 m_2 - \beta_4 p_2. \end{cases} \tag{1}$$

where p_1, m_1, m_2, p_2 are the number of U, miRNA, mRNA and protein of target gene, respectively. ω is inducer of p_1, α_1 is produce rate of p_1, α_2. α_3 are the transcription rates of miRNA and mRNA, respectively. α_4 is the translation rate of p_2. β_1, β_2, β_3, β_4 are the degradation rates of p_1, m_1, m_2, p_2, respectively. The miRNA base pair with the target mRNA at a rate γ. m and n are coefficients.

The parameter values for these equations are taken as following:

$\alpha_1 = 0.01, \quad \alpha_2 = 0.1, \quad \alpha_3 = 0.02, \quad \alpha_4 = 0.01,$

$\beta_1 = 0.001, \quad \beta_2 = 0.0025, \quad \beta_3 = 0.002, \quad \beta_4 = 0.001,$

$m = 4, \qquad n = 4.$

The transcription rate of miRNA was taken 5 times faster than that of mRNA is based on the high abundance of miRNAs which may be due to duplicated copies of their genes [8]. The simulations are run for a wide range of biologically relevant parameters around the above average values and similar conclusions are obtained.

From figure 2 we can see that when $\omega > 0.1$ This result shows that miRNA regulation make target protein robust to the changes of the inducer ω.

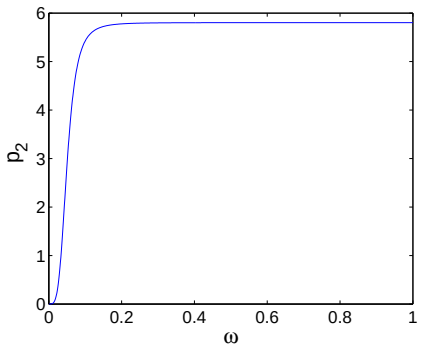

Figure 2: The steady state of p_2 versus ω.

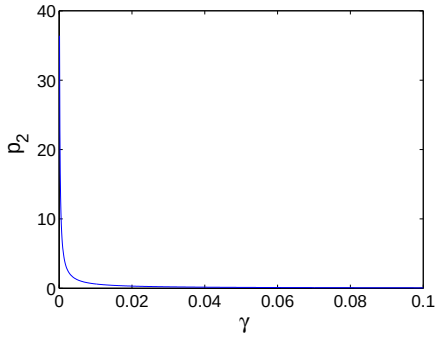

Figure 3: The steady state of p_2 versus γ.

Figure 3 shows that the expression level of p_2 decreases while the base pairing rate increases. The introduction of miRNA regulation plays an important role in repressing the expression of target gene. A very low level of miRNA can silence the expression of p_2.

Next we analyze the upstream regulator U's repression on the target protein as shown in Figure 4 and Figure 5.

Figure 4 and Figure 5 show the level of p_2 for motif I and the feed-forward loop (FFL, a three-gene pattern, is composed of two input transcription factors, one of which regulates the other, both jointly regulating a target gene.)versus time, starting from the time at which the regulation is turned on. In Figure 4, the target protein p_2, miRNA and the upstream factor U are all present in the cell. In Figure 5, The target protein p_2 is present in the cell while the upstream factor U is produced in response to the inducer and the miRNA is produced while the regulation is turned on.

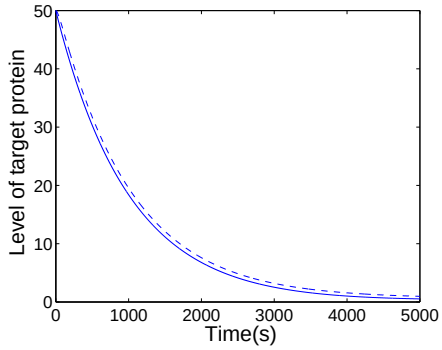

Figure 4: The level of target protein versus time for miRNA-mediated FFL (dash line) and FFL (solid line).

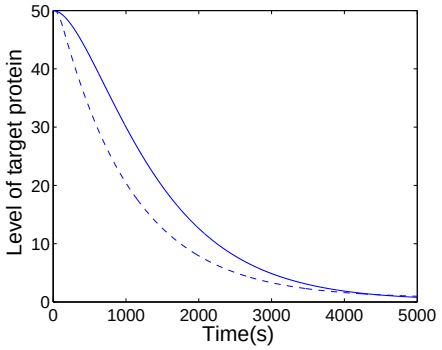

Figure 5: The level of target protein versus time for miRNA-mediated FFL (dash line) and FFL (solid line).

In Figure 4, the response of FFL is faster than miRNA-mediated FFL. In case of FFL, the existing regulator proteins can quickly bind to the target proteins and reduce the level of target proteins. while for miRNA-mediated FFL, the miRNA quickly binds to the mRNA molecules and prevents their translation, but it takes a while for the already existing target proteins to degrade. Thus FFL provides a more efficient regulation.

In Figure 5, miRNA-mediated FFL provide a more efficient regulation. The produced miRNA can quickly base pare with mRNA and prevents its translation, thus quickly decrease the target protein level. While for the FFL, it takes a longer time for the regulator protein of FFL to translate, so the response time is much longer than miRNA-mediated FFL.

Next we introduce time delay in system (1), and obtain the following delay differential equations:

$$\begin{cases} \dot{p}_1 = \alpha_1 w - \beta_1 p_1, \\ \dot{m}_1 = \frac{\alpha_2 p_1(t-\tau_1)^m}{1+p_1(t-\tau_1)^m} - \gamma m_1 m_2 - \beta_2 m_1, \\ \dot{m}_2 = \frac{\alpha_3 p_1(t-\tau_2)^n}{1+p_1(t-\tau_2)^n} - \gamma m_1 m_2 - \beta_3 m_2, \\ \dot{p}_2 = \alpha_4 m_2 - \beta_4 p_2. \end{cases} \tag{2}$$

We run the simulations for a wide range of parameters, the steady state and the response time are almost uninfluenced by the introduction of time delay as shown in Figure 6 and Figure 7, where $\omega = 10$, $\gamma = 0.01$, $\tau_1 = 8$, $\tau_2 = 5$.

Next we add Gaussian noise in system (2):

$$\begin{cases} \dot{p}_1 = \alpha_1 w - \beta_1 p_1, \\ \dot{m}_1 = \frac{\alpha_2 p_1(t-\tau_1)^m}{1+p_1(t-\tau_1)^m} - \gamma m_1 m_2 - \beta_2 m_1 + \eta_1(t), \\ \dot{m}_2 = \frac{\alpha_3 p_1(t-\tau_2)^n}{1+p_1(t-\tau_2)^n} - \gamma m_1 m_2 - \beta_3 m_2 + \eta_2(t), \\ \dot{p}_2 = \alpha_4 m_2 - \beta_4 p_2. \end{cases} \tag{3}$$

where η_1 and η_2 are Gaussian white noise with $\langle \eta_1(t) \rangle = 0$, $\langle \eta_2(t) \rangle = 0$.

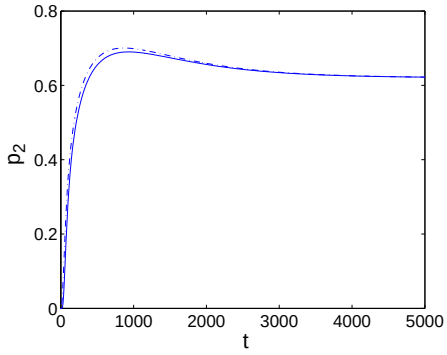

Figure 6: The time evolution of the level of protein p_2 in system(1) (dashed-dotted line) and system (2) (solid line).

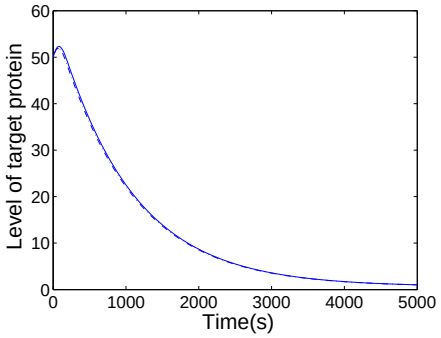

Figure 7: The level of target protein versus time for system (1) (dashed-dotted line) and system(2) (solid line).

Numerical simulations show that motif I is also robust under noisy environments.

3 conclusion

Gene regulatory networks (GRNs) contain significatly recurring subcircuits termed "network motifs" (9, 10, 11). MiRNAs are found experimentally and computationally embedding in a large number of GRNs and form kinds of miRNA-mediated network motifs. By baseparing with mRNAs and thus repress their translation,miRNAs regulate gene expression at post-transcriptional level. Exploration of these motif dynamics will provide a comprehensive view on how gene expression is regulated at the systems level.

In this paper, we investigate the dynamics of the miRNA-mediated incoherent feedforward motifs. The noisy cell environment may cause the target protein fluctuate significantly, we find that the incoherent feedforward motifs are noise-buffering and greatly enhance the robustness of gene regulation. In addition, when the upstream regulator is not present in the cell, miRNA-mediated incoherent feedforward motifs have shorter response time than the FFL thus have an advantage under stress conditions.

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