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Self-induced Stochastic Resonance in MicroRNA Regulation of a Cancer Network*

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Abstract The transcription factors (TFs) EF2 and Myc, which participate in the control of cell proliferation and apoptosis and can act as oncogenes or tumor suppressors depending on their levels of expression, are inhibited at the posttranscriptional level by some microRNAs (miRs). The consequences of coupling between these TFs and miRs were investigated by using a mathematical model, which predicted these miRs can play a critical role in regulating the position of the off-on switch in EF2/Myc protein levels and determining the levels of these proteins. In this work, we study the properties of switching behavior induced by stochastic fluctuations. Based on the Kramers escape rate in statistic dynamics, we derive the following conclusion: when the noise increases to reach the threshold, the stochastic resonance will appear, and the E2F/Myc and miR-17-92 will burst, which may result in the increase of the probability for the system to enter the state of cancer. The average bursting period for the E2F/Myc and miR-17-92 will decrease as the noise intensity increases. These phenomena induced by small noise not only reveal the possible mechanism of the biological processes but also can be used to control cancer progress, e.g. by perturbing small noise.

Keywords Self-induced Stochastic Resonance; MicroRNA; Noise; Limit Cycle.

1 Introduction

Since V.Ambros et al firstly discovered the microRNAs (miRs) [5], the biologists are more and more aware of the importance, and these microRNAs as well as their characters are more and more investigated. Today, we have known that miRs are small noncoding RNAs, 18-24 nt in length, that are predicted to regulate the expression of approximately one-third of all human genes[6, 7]. Experimental data show that a microRNA can target tens to hundreds of genes and a gene can also be targeted by many miRs. In particular, miRs participate many activities of cell processes on development and diseases, which can act as tumor suppressors or oncogenes.

Y.Shimoni et al [8] show that the primary role of miRs is to modulate or fine-tune the dynamics of regulatory networks. W.C.Cho et al [9] indicate that abnormal miR expressions correlate with cancer development. He et al [10] found the oncogenic activity of

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miR-17-92. Some experiments show the over-expression of miR-17-92 in several tumors, including cancers of breast, lung, colon, stomach, pancreas and prostate [11, 12]. Among the experimentally validated targets of miR-17-92 cluster members, the transcription factors (TFs) Myc, E2F1, E2F2 and E2F3 often act as oncogenes or tumor suppressors in the mammalian G1-S regulatory network. Some evidences show that these TFs can also induce the transcription of miR-17-92[13]. In the following, we will focus on the regulatory network involving Myc/E2F/miRs, viewing E2F, Myc and miRs as members of a control node in the network (see Figs.1 and 2). The deterministic dynamics of this network had been investigated by Friedman et al [2], who proposed a new concept *cancer zone*, and predicted some dynamical behaviors. In this work, stressing on the importance of noise, we will study the behaviors of switching dynamics induced by small noise, which not only results in critical phase transition in the cancer network but also provides insight into the possible mechanism of microRNA regulations. We also investigate how the small noise as well as stochastic resonance affects the mutation in the cancer network.

2 Mathematical model of a cancer network mediated by miR-17-92

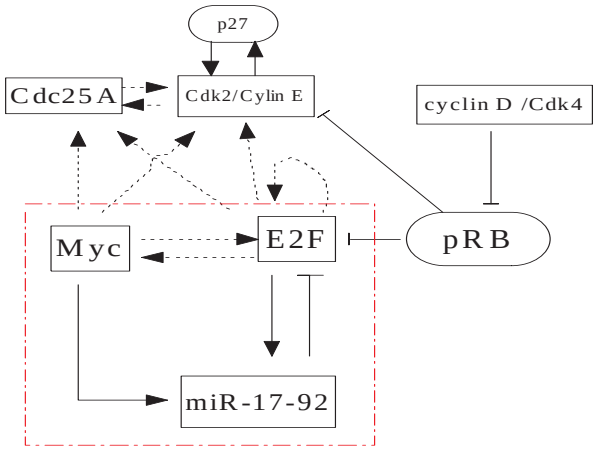

Figure 1: A cancer network related with Myc/E2F/miR-17-92.This cancer network is part of the mammalian G1-S regulatory network. The red box indicates the interplay between Myc, E2F and miR-17-92.

For convenience, we simplify the model from the mammalian G1-S regulatory network, and consider only the interaction between Myc, E2F and miR-17-9. Since the Myc and E2F act both as oncogene or tumor suppressor, both clusters of TFs can be viewed as one node in the model, and the regulatory network can be reduced to a model with two components (see Fig.2). The node p represents the TFs, Myc and E2Fs, while the node m represents the miR-17-92. The dynamics of this model with stochastic fluctuations at the transcriptional level can be described by Eq.(1).

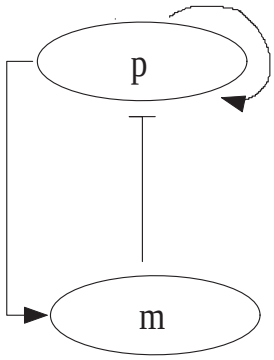

Figure 2: The abstract model for the cancer network

$$\begin{aligned}
\frac{dp(t)}{dt} &= \alpha + \frac{k_1 p^2(t)}{\Gamma_1 + p^2(t) + \Gamma_2 m(t)} - \delta p(t) + \sqrt{D}\xi(t) \\
\frac{dm(t)}{dt} &= \beta + k_2 p(t) - \gamma m(t) \\
&< \xi(t) >= 0, \;\; < \xi(t)\xi(t') >= \delta(t-t')
\end{aligned} \tag{1}$$

For Eq.(1), the value of Γ_2 is a measure of the efficiency of miR inhibition of protein expression, α stands for constitutive protein expression due to the signal transduction pathway stimulated by growth factors present in the extracellular medium.δ represents degradation rate of p, β represents p-independent constitutive transcription of m, γ is the degradation rate of m, k_2 is the Synthesis rate of m, and D is the noise intensity. For simplification, Eq.(1) can be rewritten as a nondimensional model (see Eq.(2))

$$\begin{aligned}
\frac{d\phi(\tau)}{d\tau} &= a + \frac{k\phi^2(\tau)}{r_1 + \phi^2(\tau) + r_2 u(\tau)} - \phi(\tau) + \sqrt{D_1}\xi(\tau) \\
\frac{du(\tau)}{d\tau} &= \varepsilon(1 + \phi(\tau) - u(\tau)) \\
&< \xi(\tau)\xi(\tau') >= \delta(\tau - \tau')
\end{aligned} \tag{2}$$

where $\varepsilon = \frac{\gamma}{\delta}$, $\tau = \delta t$, $\phi = \frac{k_2}{\beta} p$, $u = \frac{\gamma}{\beta} m$, $a = \frac{k_2}{\delta\beta}\alpha$, $k = \frac{k_1 k_2}{\delta\beta}$, $r_1 = \frac{k_2^2}{\beta^2}\Gamma_1$, $r_2 = \frac{k_2^2}{\beta\gamma}\Gamma_2$.

In following, we investigate the dynamical behaviors and show how the small amplitude noises induce the phase transition away from steady state. Because miRs are often more stable than protein, $\varepsilon << 1$. Hence, there is a large time-scale separation in the deterministic part of the dynamics governed by the second equation of Eq.(2). We can view the variable ϕ as fast variable and u as slow variable. To investigate the effect of small amplitude noise, we first study the deterministic part of Eq.(2).

The equilibrium of Eq.(2), which are determined by equating the right-hand sides to zero when $D_1 = 0$. After eliminating u, we obtain the following cubic polynomial whose non-negative roots are noted as ϕ_e:

$$\phi_e^3 + c_2\phi_e^2 + c_1\phi_e + c_0 = 0 \tag{3}$$

where

$$c_2 = r_2 - a - k \tag{4}$$
$$c_1 = r_1 + r_2 - ar_2 \tag{5}$$
$$c_0 = -a(r_1 + r_2) \tag{6}$$

Eq.(2) has three positive roots if the parameters satisfy the following condition:

$$T = \{(c_2, c_1, c_0) \in R^3 | c_2 < 0, c_1 > 0, c_0 < 0, K_3 < 0\} \tag{7}$$

where

$$K_3 = 27c_0^2 + 4c_0c_2^3 - 8c_2c_1c_0 - 8c_2c_1c_0 - c_1^2c_2^2 + 4c_1^3 \tag{8}$$

Thus the necessary (but not sufficient)condition for the existence of three steady states of the model is :

$$r_2 - k < a < 1 + \frac{r_1}{r_2} \tag{9}$$

In reference [2], Friedman, et.al, show that there are bistability in the above system. As we know, when the system lies in one of steady states, if there is a stimulus so that the potential overpasses the energy barrier between stable state and unstable state, the phase transition will arise, and the system state will pass from stable manifold to unstable manifold. In this article, we find that the small amplitude noise can induce this phase transition. Actually, from the theory of Krammers escape rate [2, 4], this process happens at Kramers rate for small noise and $\varepsilon << 1$ as follows

$$\kappa = \frac{\omega}{2\pi}\exp(\frac{-\Delta V(u)}{D_1}) \tag{10}$$

where $\Delta V(u)$ is the $u-$dependent energy barrier to be crossed to initiate the escape from the slow manifold. For this escape rate, there is a $u = u_0$ satisfying $\Delta V(u_0) \to D_1 \log \varepsilon^{-1}$ as $\varepsilon, D_1 \to 0$

When the small noise is absent in Eq.(2) and $\varepsilon << 1$, the system relaxes quickly to the stable manifold, the stable and unstable manifolds can be obtained by solving $a + \frac{k\phi^2}{r_1+\phi^2+r_2u} - \phi = 0$ for ϕ. Assume that $\phi_{1+}(u)$ and $\phi_{2+}(u)$ are stable manifold and $\phi_{-}(u)$ is the unstable manifold.

When the noise is small in amplitude and $\varepsilon \to 0$, the second equation of system (2) reduces to $\frac{du}{d\tau} = 0$ which indicates that u is frozen on the $O(1)$ fast-time scale. On this time scale, the dynamics is governed by the first equation for ϕ in system (2) in which u can be viewed as a fixed parameter. And this equation can be viewed as the motion of particle in the potential, i.e. write it as:

$$\frac{d\phi}{d\tau} = -\frac{\partial V(\phi,u)}{\partial \phi} + \sqrt{D_1}\xi \tag{11}$$

where $V(\phi,u)$ is given by

$$V(\phi,u) = (a+k)\phi - \frac{1}{2}\phi^2 + \frac{kr_2u - kr_1}{\sqrt{r_1+r_2u}} \arctan\left(\frac{\phi}{\sqrt{r_1+r_2u}}\right) \tag{12}$$

From the theory of Krammers escape rate, when

$$\Delta V(u) = V(\phi_{1+}(u)) - V(\phi_{-}(u)) \to D_1 \log(\varepsilon^{-1}) \tag{13}$$

we can obtain the threshold value u_0 for u, and $\Delta V(u_0) = D_1 \log(\varepsilon^{-1})$.

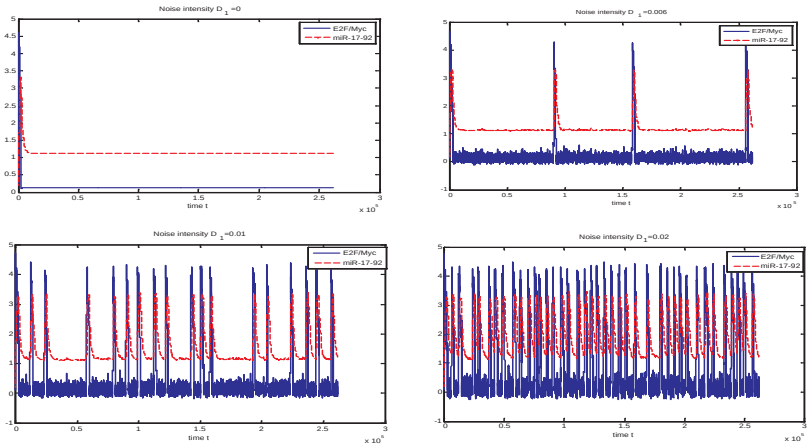

Figure 3: Numerical solution of the stochastic differential equation for $a = 0.1, r_1 = 1, r_2 = 1.8, k = 5, \varepsilon = 0.01, D_1 = 0, 0.006, 0.01, 0.02$

According to the relation on escape rate, we know that the threshold value of u is governed by the amplitude of noises and the ratio between degration rate of m and p (i.e, ε), and period of limit cycle is also governed by ε and D_1. When the energy reaches energy barrier, the limit cycle of the system appears. Hence, the matching of time-scales implied by $\Delta V(u_0) \to D_1 \log \varepsilon^{-1}$ is precisely the resonance mechanism in the standard stochastic resonance.

To better understand how the E2F/Myc/miR-17-92 regulate the cancer network, we integrate Eq.(2) using Euler-Maruyama Method[15]. Fig.3 shows the time series for different realizations of the different noises, and shows a train of large amplitude spikes in

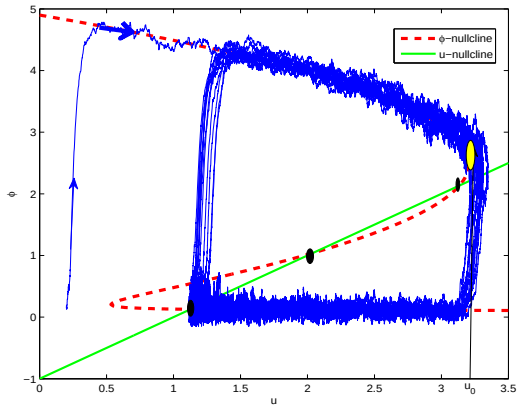

Figure 4: Phase plane plot showing the corresponding limit cycle (almost deterministic). Green line and red line are the ϕ- and u-nullclines, respectively. Black ellipses are the equilibria. Yellow ellipse is the threshold of energy escaping

the fast variable. It is clear that the spikes are bursting in a almost periodic fashion, with the their amplitudes and other characteristics being approximately the same at each time. Fig.3 also shows that the average period for which these spikes occur decreases as the noise intensity increases. In the cancer network, these spikes correspond to the burst of E2F/Myc and miR-17-92, i.e, the overexpression of these oncogenes, and can cause the cell to enter the cancer state. Fig.4 shows how the noise induces the stochastic resonance and forms a limit cycle, when the energy in Eq.(12) reaches the energy barrier. Clearly, the variables ϕ and u burst suddenly and leave the steady state. This represents that the small amplitude noise can induce the phase transition of oncogenes of the cancer network, and causes the oncogene escape from the steady state and enters the bursting state, thus resulting in the overexpression of these oncogenes. The phenomenon in Fig.4 means that when the noise intensity matches the energy barrier, i.e, stochastic resonance occurs, the oncogenes burst so that the cell may move the cancer state.

3 Discussion

E2F and Myc play the important role in mammalian G1-S regulatory network, and often are mediated by miR-17-92. In this study, it shows that MYc, E2F and miR-17-92 can burst suddenly even with small amplitude noise from the viewpoint of nonlinear dynamics. This small noise can cause the energy to reach the energy barrier and to make E2F, Myc and miR-17-92 away from the steady state, to enter the abnormal state (i.e, cancer state or enter the cancer zone [2]), which results in the cancer cell. In addition, we show that the average period for which these TFs burst decreases as the noise intensity increases, i.e, as the noise intensity decreases, the probability of burst occurring will be more small. Hence, based on the numerical analysis, the small noise may possibly enhance the cancer state by increasing the probability in the mammalian G1-S regulatory

network. Hence, the self-induced stochastic resonance and the matching of times scales implied by (13), play an important role in this cancer network, make the relationship between energy barrier and noise intensity reach the coherence state, and affect the mutation of the biological network [1].

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