Constructive role of noise in p53 regulatory network

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ABSTRACT

We study the effect of noise on p53 regulatory network, the core of a cell’s modulator for switching between survival and apoptosis. We find that the fluctuations, originating from stochastic expression of p53-responsive genes, introduce marked advantages for the system to sense external stimuli and sustain the function of switches. The coherence between a stimulus and the system’s response undergoes a maximum with the raise of noise level, indicating the occurrence of stochastic resonance. The biological significance of our results is discussed.

Fig. 1. Schematic diagram of the p53/Mdm2/Akt regulatory network. Arrows, horizontal bars, “p”, and “deg” denote stimulatory interactions, inhibitory influences, phosphorylation, and degradation, respectively.

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Since the pioneering work by Elowitz et al. [1], the study of noise in biochemical pathways has inspired many experimental and theoretical studies. Noise can be either intrinsic or extrinsic. The former arises from the stochasticity of gene expression, while the later results from the interactions of the system with other noisy pathways or its varying environment. These different sources now can be well identified and quantified by using fluorescence microscopy.

Traditionally the noise has been considered as a destructive factor for signal transduction, and therefore most previous works have focused on the design of pathways which can reduce or resist the fluctuations [2]. In the present paper we explore another possibility: whether a biochemical system can benefit from the existing noise? To answer this question, we adopt a specific crosstalk, the p53 regulatory network, as our working system.

The tumor suppressor protein, p53, is a major regulator of preserving genomic integrity in mammals and plays a crucial role in the origins of cancer [3]. The central core of the p53 pathway consists of two feedback loops, one is a negative feedback (p53-Mdm2-p53) whereas the other is positive (p53-Akt-Mdm2-p53) (Fig. 1). The negative loop initiates with the transcription of Mdm2 in a cytoplastic form. To be translocated into the nucleus, Mdm2 should be phosphorylated by active Akt kinase (Atkp). In the nucleus, the phosphorylated Mdm2 (Mdm2p) catalyzes the p53 for ubiquitination and degradation and then closes the loop. On the other hand, Mdm2 cytoplasm-nuclear shuttle is antagonized by p53 via a long pathway involving the mediator Akt. We simplify the loop by assuming that Mdm2p is inhibited by p53 via the mediator Akt. Denoting [p53], [Akt], [Atkp], [Mdm2], and [Mdm2p] as x, y, yp, z, andzp, respectively, then we have the following differential equations based on biochemical kinetics [4]:

\[
\begin{align*}
\frac{dx}{dt} &= k_0 - v_2(x, z_p) - k_{d0}x + f(t), \\
\frac{dy_p}{dt} &= v_1(y) - v_{m1}(y_p) - v_{m3}(x, y_p), \\
\frac{dz_p}{dt} &= v_4(y_p, z) - v_m(z_p) - d_{M2}z_p, \\
\frac{dz}{dt} &= s_M + v_5(x) - v_4(y_p, z) + v_m(z_p) - d_Mz + \sqrt{D}\xi(t),
\end{align*}
\]
in which \( v_1(y) = k_1 y/(j_1 + y) \), \( v_{m_1}(y_p) = k_{m_1} y_p/(j_{m_1} + y_p) \),
\( v_2(x, y_p) = k_2 y_p/(j_2 + x) \), \( v_{m_3}(x, y_p) = k_{m_3} y_p/(j_{m_3} + y_p) \),
\( v_4(y_p, z) = k_4 y_p/(j_4 + z) \), \( v_{m_4}(z_p) = k_{m_4} y_p/(j_{m_4} + z_p) \), and
\( v_5(x) = k_5 x^2/(j_5^2 + x^2) \). Total concentration of Akt_{tot}, [Akt_{tot}] = y + y_p, is chosen as a constant. Values of parameters (\( k_i, j_i, n, \) etc.) for the model are listed in Ref. [5]. Euler method has been used to solve Eq. (1).

Stimulus, resulting from external stresses or other cellular pathways, is simplified as a periodical signal, \( f(t) = a \cos(\omega t) \). Because the intrinsic noise is generated by the discrete nature of expression of p53-responsive genes [1], the Gaussian white noise \( \xi(t) \) of strength \( D \) is used to mimic the fluctuations in the transcription process of Mdm2, which is induced by p53. Additionally independent noisy-terms appended to other variables have also been studied. However, they do not alter the characteristics of the phenomena reported below.

In healthy cells, p53 is normally kept to a low concentration under the control of Mdm2. When cells suffer stresses, e.g. DNA damage and oncogene stimulation, the p53 level rises resulting in a cascade of gene expression which causes cell cycle arrest, DNA repair, or cell senecence. Ultimately, if the damage is irreparable, the programmed cell death will be initiated by p53 regulated mechanisms. Contrarily, the kinase Akt averts cell death by inhibiting some pro-apoptotic proteins. The cross-talk involving p53 and Akt then regulates the cellular survival-apoptosis switches [3,4].

The studied model can capture the aforementioned functions appropriately. In the absence of stimuli and noise, i.e., \( a = D = 0 \), the regulatory network presents robust bistability in the region of \([\text{Akt}_{\text{tot}}] \in (0.67, 1.15) \) [4]. The stable point with higher concentration of p53, which would terminally cause the death of cells, is referred to as the apoptotic state. The other focus presenting lower concentration of p53 indicates the normal situation or the survival state of cells. The resonant switches of p53 between the two states in response to a stimulus \( (a \geq 0.005) \) therefore provide a control mechanism to kill cancerous cells and keep normal (recovered) cells alive.

When the stimulus is subthreshold (e.g. \( a = 0.0045 \)), the system fails to sense the stimuli and the p53 level is entrained around the surviving state. With the introduction of noise, it is no longer the case. Weaker noise induces negligible fluctuations (Fig. 2(a)). If the noise strength is further increased, fluctuations would evoke occasional jumps into the apoptotic state (Fig. 2(b)). Ultimately, an optimal noise would cause a significant ordering between the p53 level and the periodical stimuli (Fig. 2(c)), i.e. the noise provides a constructive effect in sensing a weaker stimulus, thus sustaining the resonant apoptosis-survival switches. If the noise is over-amplified, the resonance would be destroyed.

The mechanism of the aforementioned results can be understood as follows: the noise enhances the possibility of threshold crossing and thereby improves the network’s resonant response to a subthreshold stimulus. Such a phenomena is reminiscent of stochastic resonance (SR) [6]. To describe the phenomenon more quantitatively, we adopt a signal-to-noise ratio (SNR) [6], which is defined as the ratio of the signal power divided by the noise power at the frequency \( \omega_0 \) of the stimulus, to characterize the degree of resonance. As illustrated in Fig. 3, with the raise of \( D \) the performance of the SNR undergoes a maximum, revealing the typical characteristic of SR. Dropping the amplitude of stimuli results in a higher threshold of noise required for jumping between two foci, but does not otherwise alter the SR phenomenon.

We further analyze the robustness of the resonant switches depending on the bifurcation parameter, \([\text{Akt}_{\text{tot}}] \in (0.7, 1.0)\), the system can perform the resonant switches in response to a stimulus \( a = 0.0060 \), but otherwise is entrained in one of the two foci and becomes malfunctioned. However, when the stochastic effect is taken into account \((D = 10^{-2})\), the region in which the p53 reveals resonant switches is extremely enlarged \([\text{Akt}_{\text{tot}}] \in (0.7, 1.7)\). In other words, the introduced noise is beneficial for maintaining the basal function of the regulatory network over a broader range of parameter values. The upper threshold of the resonant switches region \((\text{Akt}_{\text{tot}}^\text{up})\) approximates a logarithm function of noise intensity \( D \) [7], while the lower threshold keeps invariant. The inset of Fig. 3 plots SNR versus noise levels using the parameters within the newly emerged switches region. The SNR profile reveals typical characteristic of SR implying that the enhanced robustness arises from the aforementioned SR mechanism. Similar phenomenon of noise enhancing robustness persists for other system parameters, including \( k_0 \) and \( k_{d0} \).

In brief, we have demonstrated that in biochemical networks noise could not only have a pivotal role in sensing subthreshold stimuli but also make the desired property, the responding survival-apoptosis switches, easier to obtain. These theoretical anticipations imply that gene regulatory networks are potentially able to exploit the inherent stochasticity in living cells.

References

[5] Parameters used in the model mainly come from Ref. [4]: \( k_0 = 0.1 \mu \text{M/min}, \ k_{d0} = 0.05 \text{min}^{-1}, \ j_1 = 0.15 \mu \text{M/min}, \ j_0 = 0.2 \mu \text{M/min}, \ j_{m1} = 0.1 \mu \text{M}, \ k_2 = 0.055 \text{min}^{-1}, \ j_2 = 0.1 \mu \text{M}, \ j_{m2} = 7.05 \text{min}^{-1}, \ j_{m3} = 2.5 \mu \text{M}, \ k_{d2} = 0.018 \mu \text{M/min}, \ d_{Dp} = 0.015 \text{min}^{-1}, \ d_{Ap} = 0.015 \text{min}^{-1}, \ D_0 = 10 \text{min}^{-1}, \ j_4 = 0.3 \mu \text{M}, \ k_{d4} = 0.2 \mu \text{M/min}, \ j_{m4} = 0.1 \mu \text{M}, \ k_5 = 0.024 \mu \text{M/min}, \ j_5 = 1 \mu \text{M}, \ n = 3, \ [\text{Akt}_{\text{tot}}] = 0.9 \mu \text{M}.
[7] In the region of \( D \in [10^{-9}, 10^{-5}] \), the logarithm function approximates \( \text{Akt}_{\text{tot}}^\text{up} = 3.26 + 0.29 \ln(D) + 0.01 \ln(D)^2 \).