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Vibrational resonance in a time-delayed genetic toggle switch

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ABSTRACT

Biological oscillators can respond in a surprising way when they are perturbed by two external periodic forcing signals of very different frequencies. The response of the system to a low-frequency signal can be enhanced or depressed when a high-frequency signal is acting. This is what is known as vibrational resonance (VR). Here we study this phenomenon in a simple time-delayed genetic toggle switch, which is a synthetic gene-regulatory network. We have found out how the low-frequency signal changes the range of the response, while the high-frequency signal influences the amplitude at which the resonance occurs. The delay of the toggle switch has also a strong effect on the resonance since it can also induce autonomous oscillations.

1. Introduction

The concept of resonance in physics generally refers to a large increase in the amplitude of the oscillations provoked by a particular external forcing or signal. In nonlinear systems there are many types of resonance, depending on which are the sources that causes them. When the resonance is induced by an stochastic noise, it is called stochastic resonance [1]. In the case that the resonance is produced by a chaotic signal, we say that the system presents a chaotic resonance [2], and finally if the forcing is a high-frequency periodic signal then the phenomenon is called vibrational resonance (VR) [3]. The role of resonances in different biological processes is paramount. For example, stochastic resonance, which has drawn much attention in the past few years, has been found in neural systems [4], crayfish mechanoreceptor cells [5] or the feeding behavior of paddle-fish [6]. However, though VR has been widely studied in physical systems such as lasers [7] and electronic devices [8], only recent attention has been paid to this phenomenon in biology [9–11].

Here, we study VR in a time-delayed genetic network, which is a recurrent control motif [12] in nature. It has been reported that this kind of systems is able to create patterns via quorum sensing [13], modulate immunologic pathways [14] or enhance the oscillations in circadian clocks [15]. Moreover, the variety of dynamical phenomena shown by nonlinear time-delayed systems such as phase synchronization [16], excitation regeneration [17], amplitude death [18], resonance [19,20], etc. makes them a topic of high relevance.

Motivated by the preceding ideas, we present a theoretical and computational study of VR in a time-delayed toggle switch. This work is organized as follows. In Section 2 we explain the main features of the time-delayed toggle switch. First, the original model of the toggle switch is presented. Then, we introduce the delay and analyze its implications. Section 3 is a description of the usual treatment of VR in dynamical systems and how we apply it to our model. In Section 4 we examine the mechanism inducing the VR. Next, we show the effects of the delay on resonance, and we vary the periodic signals too. Finally, in Section 5 we summarize our findings and discuss the role of VR in biological systems.

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2. Description of the model

The genetic toggle switch [22] is a biological system designed to have two possible stable states, in other words, it is a bistable system. It is constructed from two repressible promoters in a mutually inhibitory network. The system can flip between high and low levels of concentration of repressors: when one is high the other one is low, and vice versa. This transition between states can be achieved with chemical or thermal induction, that is, with external signals. The dynamics of the toggle switch can be modeled using dimensionless differential equations. We consider the variables u and v as the concentrations of the two transcription factors involved, and furthermore we introduce the delay in the repressional terms. The equations of the system introducing identical discrete delays in the degradation terms become:

$$\frac{du}{dt} = \frac{\alpha}{1+v^{\beta}} - u(t-\tau), \tag{1}$$

$$\frac{dv}{dt} = \frac{\alpha}{1+u^{\beta}} - v(t-\tau). \tag{2}$$

For simplicity, we assume equal promoter strengths α for both variables and equal repressional cooperativity coefficients β. As it is shown in [22], it is needed that the cooperativity coefficient $\beta \geqslant 2$ to have a bistable system. Also there are some restrictions on the values of α, so by choosing $\alpha = 2.5$ and $\beta = 2$ we get a bistable toggle switch. This election of the parameters will be kept throughout the manuscript. Then, the system presents two symmetric stable equilibria ($e_1 = (0.5, 2),\ e_2 = (2, 0.5)$) and an unstable equilibrium line or separatrix ($u = v$). Interestingly, we have found that a delay τ in the degradation term can induce oscillations in the system. Moreover, we have observed numerically and theoretically that the system presents damped oscillations for $\tau < \tau_{crit}$ and that tuning this delay means tuning the damping coefficient of the oscillations. When the delay is above a certain threshold ($\tau > \tau_{crit}$) the system presents autonomous oscillations. The original work, where VR was first reported [3], was carried out on a bistable damped oscillator. Thereby the time-delayed toggle switch is an extraordinary candidate to make a first study of VR in genetic networks.

3. Methods

Vibrational resonance consists of the optimization of the response of the system to a low-frequency (LF) signal of amplitude A and frequency ω due to a high-frequency (HF) signal of amplitude B and frequency $\Omega \gg \omega$. For the time-delayed toggle switch one can think that the forcing is a thermal bath with oscillating temperature, or an experimental setting with biharmonic variation of the concentration of a chemical inductor, for instance. Our present purpose is to search numerically the phenomenon of VR, so we introduce these two signals to one of the proteins and look at the response of the other one. The system of differential equations that we have to solve is:

$$\frac{du}{dt} = \frac{\alpha}{1+v^{\beta}} - u(t-\tau) + A\sin\omega t + B\sin\Omega t, \tag{3}$$

$$\frac{dv}{dt} = \frac{\alpha}{1+u^{\beta}} - v(t-\tau). \tag{4}$$

The response for the frequency ω is usually defined as the amplitude of the sine and cosine components of the output signal, yielding

$$C_s = \frac{2}{nT}\int_0^{nT} v(t)\sin\omega t dt, \tag{5}$$

$$C_c = \frac{2}{nT}\int_0^{nT} v(t)\cos\omega t dt, \tag{6}$$

where n is the number of complete oscillations of the LF signal and $T = (2\pi/\omega)$ is its period. The numerical values of C_s and C_c are related to the Fourier spectrum of the time series of the variable v computed at the frequency ω. Then, the relation between the output and the forcing signals provides an idea of how the LF signal is being amplified by the HF signal. This is commonly defined by means of the Q factor:

$$Q = \frac{\sqrt{C_s^2 + C_c^2}}{A}h. \tag{7}$$

The usual procedure to search for VR is to compute Q for different amplitudes B of the HF periodic signal [3]. If there is a value of B that maximizes Q, then the VR occurs. This means that there is a particular value of the HF periodic signal that optimizes the response of the system to the weak LF periodic signal.

Our algorithm, developed in MATLAB, accomplish several computational tasks. The different steps are:

- First, we solve the delayed differential equations of the system with the external signals (Eqs. (3) and (4)) using *dde23*. The initial conditions are chosen to be in one of the two symmetric equilibrium states, and the external signals are applied to

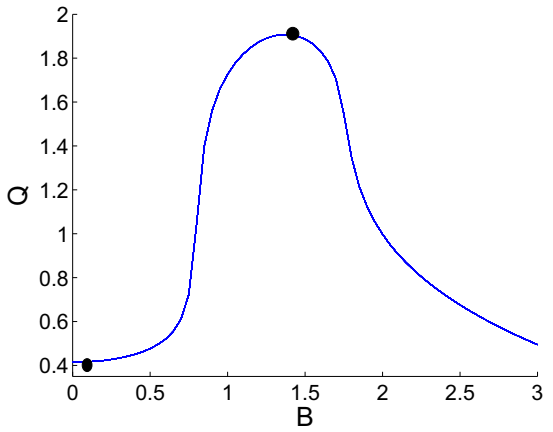

Fig. 1. Typical VR curve, the response of the system Q is plotted vs the amplitude of the HF signal B. The parameters of Eqs. 3,4 are chosen to be $\alpha = 2.5,\ \beta = 2,\ \tau = 0.5,\ A = 0.1,\ \omega = 0.1$ and $\Omega = 5$. These will be the standard parameters along this work if not specified.

the protein at the higher level. This is completely equivalent to solve the delayed differential equations in the absence of external signals with any initial conditions, and then apply the two periodic signals after the transient has vanished.

- After solving the Eqs. (3) and (4) and discarding the transient, we compute the factor Q for a range of different values of the HF intensity B.
- Finally a graph of Q vs B is plotted and, if the parameters are properly chosen, a bell-shaped curve is found (Fig. 1). The maximum of this curve is the optimal match between the LF and HF signals, that is the VR.

4. Results

4.1. Explanation of the mechanism inducing VR

So far, we have seen that it is possible to find VR after having chosen the appropriate parameters. However, it would be interesting to understand why the amplitude is increased and to know what the levels of protein are actually doing. To answer these two questions it is convenient to represent the phase diagram. In this kind of diagram the coordinates give the concentrations of each protein, in such a way that every point represents a state of the system at a given time. In Fig. 2 we can see the trajectories of the system in three different cases. For small values of B the concentration of the protein only oscillates around the low expression state ($B = 0.1$, red line), for very large values of B the low state becomes unstable and the concentration of the protein oscillates around the high expression state ($B = 2.2$, green line). However, for intermediate values of B the concentration of the protein oscillates between the high and the low states, reaching a maximum amplitude for some optimal value of the amplitude $B_{opt} = 1.5$ (blue line). When the system explores both states the amplitude is much larger, thus unveiling an appearance of the VR. In other words, resonance occurs when the concentrations of both proteins switch (oscillate) between the low and the high state. These examples are directly connected to the Fig. 1, where the

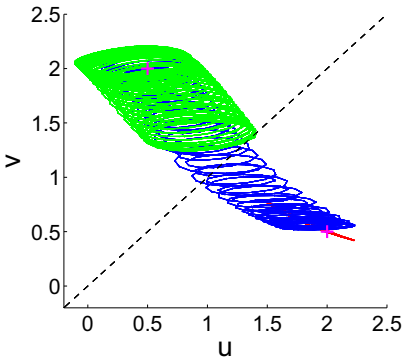

Fig. 2. Phase diagram. The dashed line represents the separatrix ($u = v$) and the magenta crosses are the two equilibria states ($e_1 = (0.5, 2),\ e_2 = (2, 0.5)$). In red $B = 0.1$, only one region below the separatrix is explored; in blue $B = 1.5$, both regions are explored making the amplitude higher (VR); in green $B = 2.2$, only the region above the separatrix is explored. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

amplitude of the oscillations are represented as a function of B. The two plotted dots correspond to the simulations for $B = 0.1$ and $B = 1.5$.

Of course we can also plot directly the concentration of the protein vs time (Fig. 3). When the amplitude of the HF forcing is $B_{opt} = 1.5$, then the oscillations increase their amplitude about four times keeping the same global period. This is shown in Fig. 1.

4.2. Effects of LF/HF signals on VR

To study the dependence of the resonance with the LF signal we can vary its amplitude A and its frequency ω. When we increase the amplitude A the resonance increases as well and the bell-shaped curve gets wider (Fig. 4). There is an upper

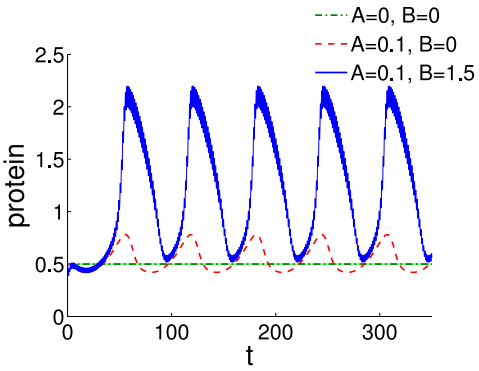

Fig. 3. Oscillations of the protein before introducing any external signal are plotted in dotted line ($A = 0,\ B = 0$), after introducing the LF signal in dashed line ($A = 0.1,\ B = 0$), when both LF and HF signals are introduced in solid line ($A = 0.1,\ B = 1.5$). The amplitude is highly increased when $B = B_{opt}$. The concentrations are given in arbitrary units (A.U.) and the time is given in hours.

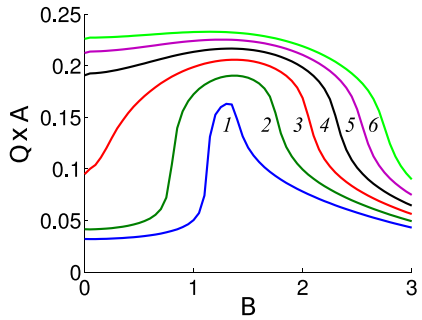

Fig. 4. Resonance curves for different amplitudes of the LF periodic signal A = 0.09, 0.1, 0.11, 0.12, 0.13, 0.14 (curves 1–6 respectively). Note that here we plot $Q \times A$ for clarity of the plot, to avoid crossings of the curves. The shape of the curves remains unaltered, so we can appreciate how the peaks are widened. Above some threshold ($A \gtrsim 0.15$) resonance without tuning occurs.

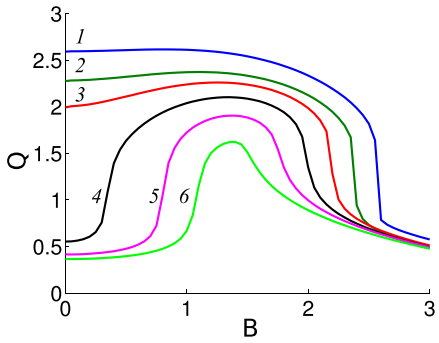

Fig. 5. Response of the system Q when the low frequency ω is varied, ω = 0.02, 0.04, 0.06, 0.08, 0.10, 0.12 for curves 1–6 respectively. Below the threshold ($\omega \lesssim 0.02$) there is resonance without tuning.

limit for A, above which the maximum of the response Q is lost, producing an effect sometimes called resonance without tuning [21]. Changing the frequency ω of the LF signal changes the width of the peak too, but just in the opposite way: for decreasing values of ω the value of Q grows and so does its width. In this case there is a lower limit for ω and below this limit resonance without tuning also occurs (Fig. 5). From these results we can infer that, in general, resonance will be easily achieved for signals with small frequencies and large amplitudes.

The variation of the HF signal changes resonance in a very different manner. Increasing frequencies Ω lead to increasing values of B_{opt} too (Fig. 6). This is important since resonance can be achieved with smaller amplitudes B of the HF force, if its frequency Ω is decreased.

Delving deeper into the effects of the HF signal, we have observed that there is a linear relation between Ω^2 and B_{opt} (Fig. 7). This can be very useful since once we have fixed the parameters of the system, we can tune the amplitude B_{opt} at which VR takes place by tuning the high frequency Ω.

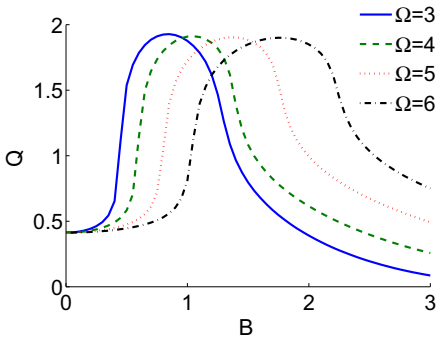

Fig. 6. In this plot Ω is varied keeping the other parameters constant. The VR curve presents a shift in the amplitude of the HF signal B at which resonance occurs. However, the maximum value of Q is barely changed.

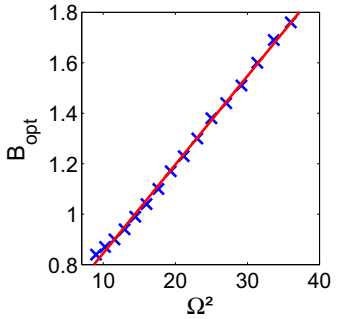

Fig. 7. A relation of the type $B_{opt} \propto \Omega^2$ appears when Ω is varied, keeping the other parameters constant. In this plot 16 points from resonance curves (blue crosses) are fitted to a straight-line (red solid line), with a correlation coefficient $r = 0.9992$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

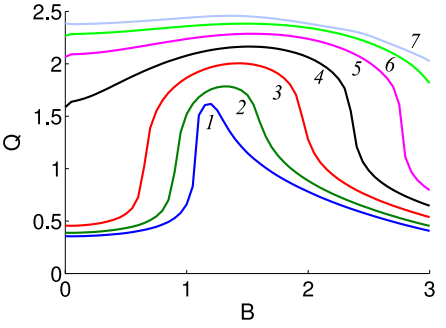

Fig. 8. Effect of the variation of the delay τ in the response of the system, when $\tau < 1$. For the curves 1–7, $\tau = 0.35, 0.45, 0.55, 0.65, 0.75, 0.85, 0.95$. For $\tau > 1$ autonomous oscillations occur.

So far, we have kept the delay constant. However, the strong effect of the delay in the oscillations of the system can also be exploited. When the delay is in a range of values far from the autonomous regime ($\tau < \tau_{crit}$), the variation of τ has qualitatively similar effects to the variation of the amplitude of the slow signal A: over some value of τ the maximum of the curve Q vs B disappears, and VR without tuning is found (Fig. 8).

5. Concluding remarks

In this work it has been shown that under certain conditions LF oscillations can be greatly amplified by a HF signal in a time-delayed toggle switch. It has been reported that oscillations underlay in the heart of many cell processes [23], and the timing involved can vary from minutes [24,25] to days [26], so it is of great importance to know how these low and fast oscillations may couple among them. Here we have also analyzed the different effects of the LF and HF signals on the resonance. The variation of the high frequency Ω produces a shift of the intensity B at which resonance occurs. This is very remarkable since tuning the high frequency allows similar resonances with smaller variations in the concentrations of the proteins. Furthermore, it has been demonstrated that there is a linear dependence between B_{opt} and Ω^2, making it possible to predict the value of the amplitude B_{opt} at which VR will take place. On the other hand, we have seen that the variation of the LF signal changes the width of the peak of resonance. Moreover, we have shown that variations in the amplitude A and variations in the frequency ω had the opposite effect on the resonance: for increasing values of A the resonance increases, but for increasing ω it decreases. This led to a higher (lower) limit for the values of A and ω respectively, and we have seen that above (below) these limits the VR without tuning occurred. In this time-delayed toggle switch, the variation of the delay τ produces a variation in the damping of the system, inducing strong effects on resonance. When the system is far from the autonomous oscillations regime ($\tau < \tau_{crit}$), the effect of the delay on VR is similar to the effect produced by the variation of the amplitude of the LF signal A, including the higher limit above which resonance without tuning is found. The VR is indeed a very interesting mechanism because it can be externally controlled, and can also induce collective behaviors [8], what makes it interesting for both biologists and physicists.

Acknowledgments

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