Response delay as a strategy for survival in fluctuating environment

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Response time-delay is an ubiquitous phenomenon in biological systems. Here we use a simple stochastic population model with time-delayed switching-rate conversion to quantitatively study the biological influence of the response time-delay on the survival fitness of cells living in periodically fluctuating and stochastic environment, respectively. Our calculation and simulation show that for the cells having a slow rate transition into fit phenotype and a fast rate transition into unfit phenotype, the response time-delay can always enhance their fitness during the environment change. Particularly, in the periodic or stochastic environment with small variance, the optimal fitness achieved by these cells is superior to that of cells with reverse switching rates even if the latter exhibits rapid response. These results suggest that the response time delay may be utilized by cells to enhance their adaptation to the fluctuating environment.

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I. INTRODUCTION

Most of living species are exposed to random fluctuations in their environment in the Nature. Environment change can either be periodic, such as day-night interchanges, or be stochastic, such as nutrition supplements in random times. Thus how can a life-form adapt to the fluctuating environment to optimize its fitness within is critical for the species to survive in the nature 1, 2. Recently, with the progresses in the study of the gene regulation networks, the stochastic nature of the gene expression is revealed 3, 4, 5, which is soon considered to further understand optimized fitness of cells. Stochastic gene expression brings the isogenic population to distinct phenotypes which is known as phenotypic heterogeneity 4, 6. Phenotypic heterogeneity is a useful strategy for species to adapt to the fluctuating environment 7. With this concept, various phenomena, including the bacterial persistence 8, 9, 10 and optimized growth rate for the cells living in the fluctuating environment 11, 12, 13, 14, 15, were studied. These authors also considered comparison between the strategy of the heterogeneity in which the switching rate from the fit state to the unfit states in an environment of specific parameters is nonzero and the homogeneity in which the switching rate mentioned above is zero 11, 12, 13, the effects of the static (switching rates do not change with environment) and dynamic (switching rates change with environment) transition between states 12, and the influence of the switching rates on the environment changing rate 14, which are all important for the understanding of the survival of species on earth.

Besides the stochastic gene expression, another important feature of gene regulation networks is time-delay. A time delay usually results from regulated transcription and translation, and leads to behaviors quite different from those without 16. In more complex gene networks, some motifs, such as feed-forward loops and gene cascades, induce time-delays of length even longer than a cell cycle 17, 18, 19. These time-delays have important effects on gene regulatory networks, and there were some assumption that cells can benefit from their time-delay motif in stochastically fluctuating environments 20. However, so far as we know, there is yet no work on the influence of the response time-delay to the fitness of cells living in the fluctuating environment. In this paper, we construct a stochastic population model with time-delayed switching-rate conversation to quantitatively study the biological influence of the response time-delay on the survival of cells in fluctuating environments.

II. MODEL

To study the fitness of cell population, we present a stochastic population model 11, in which environment parameters fluctuate between two different states 21 and 22, and accordingly in which cells display two different phenotypes a and b. Cells of phenotype a are fit for growth in the environment 23 with fast growth rate 24, while those of b is unfit for growth in 23 with slow 24. Situation reverses in the environment 25 as shown in figure 1(a). The environment compensation for the growth of the fit cells is 26, which are all important for the understanding of the survival of species on earth.

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dynamics of the cell numbers in the fit ($n_f$) and unfit ($n_u$) states can be described as

$$\frac{d}{dt}n_f = \gamma_f n_f + k_u n_u - k_f n_f, \quad 0 < t < \tau;$$
$$\frac{d}{dt}n_u = \gamma_u n_u + k_f n_f - k_u n_u, \quad 0 < t < \tau;$$
$$\frac{d}{dt}n_f = \gamma_f n_f + k_f n_f - k_u n_u, \quad \tau < t < T;$$
$$\frac{d}{dt}n_u = \gamma_u n_u + k_f n_f - k_u n_u, \quad \tau < t < T,$$

(1)

where $T$ is the time cells dwell in an environment state before change to the other state. We assume $\tau < T$, which means that dynamic transition condition holds during the switching-rates conversion. When $\tau > T$, switching rates do not convert in this environment state which in fact becomes the static transition. However, static transition can also be a possible choice for cells, and below we consider above situation together.

To investigate the fitness of cells, we consider the time-averaged population growth-rate $\langle \gamma \rangle = \langle \gamma_f f_f(t) + \gamma_u f_u(t) \rangle = \gamma_u + \Delta \gamma f_f(t)$, where $f_f(t) = n_f/\langle n_u + n_f \rangle$, $i = u, f$ is the fraction of cells in the unfit and fit phenotypes in the two environment states respectively. We assume in this model that the fractions of the cells in fit and unfit phenotypes convert when the cells respond to environment changes, that is, if the fraction of the cells in the fit phenotype is $f_f$ just before the environment turnover, it will be $1 - f_u$ after. Hereafter we focus on the time evolution of the $f_f$ and its time-average ($\langle f_f \rangle$) which accounts for the fitness of the cell population. By applying equation (1) the dynamics of $f_f$ can be described by the following equations:

$$\frac{d}{dt}f_f(t) = k_u + (\Delta \gamma - k_u - k_f)f_f - \Delta \gamma f_f^2, \quad 0 < t < \tau;$$
$$\frac{d}{dt}f_u(t) = k_f + (\Delta \gamma - k_u - k_f)f_u - \Delta \gamma f_u^2, \quad \tau < t < T,$$

(2)

In different fluctuating environment conditions, $T$ and $\tau$ can be tuned. We solve equations (2) then average $f_f$ with time to evaluate the influence of response time delay on the survival fitness of cells.

III. RESULT AND DISCUSSION

Figure 1(b) shows two examples of $f_f(t)$ changing with time in periodic and stochastic environments. In the periodic environment state, cells spend a specific time $T$ in each states, while in the stochastic case, the time spent in each states has a mean value $T$. Without losing generality, we set $T = 1$. From the figure we can see that after considering the time delay, in the periodic environment there will be an extra turning point at time $\tau$ after each environment change, while in the stochastic environment, only the environment states with duration time longer than $\tau$ show a state turning point. Those brief environment states with duration time shorter than $\tau$ are filtered as a result of phenotype switching system of cells. The additional turning points of the $f_f(t)$ in different environments and filter out of the short duration environment states in the stochastic environment may introduce intriguing behavior in population fitness of cells with response time-delay, as we show below.

To investigate the influence of response time-delay, we find that the pattern of $f_f(t)$ into the upper graph when $\tau = 0$ is the same as the lower one for $\tau = 1$, and so does when $\tau = 1$, in which $k_u$ denotes the rate switching to the fit state and $k_f$ to the unfit one. Therefore, from figure 1(c), we can see that the pattern of $f_f(t)$ in the upper graph when $\tau = 0$ is the same as the lower one for $\tau = 1$, and so does when $\tau = 1$ and $\tau = 0$. Since $\langle f_f(t) \rangle$ reflects the fitness, we then calculate its averaged value. For these two delayed time discussed above, one can easily notice that the case with larger switching rate to the fit phenotype generally have higher $\langle f_f \rangle$; see figure 2(a). When $0 < \tau < 1$, the tuning point in $f_f(t)$ (figure 1(b), (c)) makes $\langle f_f \rangle$ behaviors quite different from those without time delays. After some mathematical analysis and with the help of numerical solution, we find that $\langle f_f \rangle$ both decrease where $\tau \rightarrow 0^+$ and $1^-$, indicating a maximum at an interme-
Thus results in a steeper slope of the time-averaged fraction of cells in fit phenotype. (a) Time-averaged $f_t$ is plotted with $\tau$. The solid and dash lines denote the case when $k_u = 1.5 > k_f = 0.5$ and $k_f = 1.5 > k_u$, respectively, as $\Delta \gamma = 1$. Two cases of specific time-delays are also shown in the figure. (b) Parameter influence on the time-averaged $f_t$. Here we set $k_u = 1.5$, $\Delta \gamma = 1$, and $k_f \leq k_u$ from 0 to 1.5. Inserts show $k_f > k_u$ from 1.5 to 5.

The results shown above correspond to certain sets of parameters. In all there are three parameters that can be tuned in this model. $\Delta \gamma$ represents the growth compensation in different environment. Large $\Delta \gamma$ indicates much faster cells growth in fit environment than in unfit one, thus it has significant effects on $\langle f_t \rangle$, but limited effects on the trend of $\langle f_t \rangle$ to the time-delay $\tau$. Larger $\Delta \gamma$ induces higher $\langle f_t \rangle$, but make smaller the difference of $\langle f_t \rangle$ induced by different $\tau$. However, an extremum at certain $\tau$ always exist(data not shown). The other two tunable parameters are $k_u$ and $k_f$. They show similar effects in our model(equation 1). Here we first keep $k_u$ fixed and vary $k_f$ to see its influence on the $\langle f_t \rangle$. As shown in figure 2(b), when $k_f = k_u$, exchange of switching rates become trivial in the model, thus delay times have no influence on $\langle f_t \rangle$ and $\langle f_t \rangle$ remains constant at different $\tau$. When $k_f < k_u$, there is a maximum $\langle f_t \rangle$ at a certain $\tau$, even in the homogenetic case when $k_f = 0$.

In addition, in the delayed time ($0 \sim \tau$ with $k_u$), larger $k_u/k_f$ indicates a faster transition into the fit phenotype, thus results in a steeper slope of the $\langle f_t \rangle$ while reaching its maximum, which means more significant influence of response time-delay on increasing the fitness in case of larger $k_u/k_f$ (figure 2(b)). A contrary effect is observed for $k_f > k_u$, which always shows a minimum(figure 2(b) insert). The slope of the decreasing $\langle f_t \rangle$ is steeper with larger $k_f/k_u$, which means the response time-delays also show more significant negative influence on the fitness with larger $k_f/k_u$ (figure 2(b) insert). These results verify that the influence of the response time delay on the fitness of cells is universal and does not strictly depend on state parameters.

These results show some interesting behavior of the response time delay on the fitness of cells. First, if $k_f > k_u$ which means a larger transition rate into fit phenotype in each environment, the best strategy to enhance fitness is to reduce the response time delay, as indicated in figure 2 (b) and larger $k_f/k_u$ introduces a more severe defect in fitness. Second, above results tells us that cells do not always need to adopt $k_f > k_u$ to achieve a higher fitness. If cells use some special strategy to reverse the value of the two switching rates to set $k_u > k_f$, the response time delay can always approve cells’ fitness. Besides, there is a specific delay time $\tau_1$ after which $\langle f_t \rangle$ is larger than what cells can reach without time delay in the similar set of parameters; see figure 2(a). In the region $\tau_1 < \tau < 1$, the response time delays prove to be an effective way for cells of optimizing their fitness. In addition, considering the constant presence of an intrinsic response time-delay in gene networks, there are two switching rates cells can choose. For example, when the delay time is longer than $\tau_2$, a strategy which sets $k_u$ to be the larger one gets a better fitness (figure 2(a)). The parameter-dependence of $\tau_1$ and $\tau_2$ are shown in figure 3(a). The value of $\tau_1$ is always smaller than 1, which confirms the independence of parameters of these effects, relatively. Figure 3(a) also shows a large parameter space to be realized to optimize fitness by response time-delay. Third, the static transition strategy ($\tau > 1$) can be a choice for cells in some special cases. For example, when the systemic time delay is larger than a certain value with $k_f > k_u$ or shorter with $k_u < k_u$ (figure 2(a)), static transition is better than dynamic one in enhancing survival fitness, while in other conditions with the same switching rates, dynamic transition strategy is still an better option. Finally, following the finding that $f_t(t)$ for $\tau = 0$ and 1 are the same while exchanging $k_u$ and $k_f$, we find that after a similar manipulation of $\tau$ with $1 - \tau$ and $k_f$ with $k_u$ in equation 1, this new equation becomes one describing a system with a pre-response time $\tau$. Therefore, the $\langle f_t \rangle$ dependence on the pre-response time $\tau$ in the new equation for $k_f > k_u$ is in fact the same as those with time-delay $\tau$ in the former equation with $k_f < k_u$, which means that an advance-response may induce a better fitness for the population when the cells adopt a faster switching rate to the fit phenotype [22, 23].

Then we consider a simple stochastic environment whose duration-time distribution is described by $T = \sum_{i=1}^n T_i$, where $T_i$ obeys an exponential distribution with
mean value $1/n$. So the mean value of $T$ is 1 and its variance $1/n$. When $n = 1$, $T$ itself obeys an exponential distribution, and when $n \to \infty$, it returns to a deterministic periodic environment state. A general form of $f_t(t)$ is shown in figure 1(b). Our results show, when $n = 1$ and $k_u > k_t$, time delays increase the fitness without reaching a maximum (figure 3(b)). Similarly, after converting the two switching rates to set $k_u < k_t$, $f_t$ monotonically decreases asymptotically to a value with increasing time-delay. However, in contrast to the former results, $\langle f_t \rangle$ for $k_u < k_t$ is always larger than that while $k_u > k_t$. This phenomenon shows that in this stochastic environment the response time-delay is always a defect for the fitness, and tuning $k_u < k_t$ is simply a better strategy [20]. When in cases of larger $n$, results gradually return to the former ones. Results in case of $n = 10$ are shown in figure 3(c), which shows almost all the characteristics we discuss above. These results show that the variance may have significant influence on the cells’ fitness just as the averaged value of the fluctuating environment description. Large variance implies an existence of very short- or very long-duration environment states. Short ones are filtered by the cells’ phenotype switching system as we discussed above, and this effect is similar with the static transition. For the long ones, there are enough time for cells to alter their phenotype with the prescribed switching rates according to the environment change. Therefore, these two effects erase maximum or minimum $\langle f_t \rangle$ induced by time delay, and $\langle f_t \rangle$ monotonously converge to the static value with increasing $\tau$. Similar results hold in non-symmetric periodic environment description. If the ratio of the duration time of the two distinct environment states becomes larger, $\langle f_t \rangle$ of the $k_u < k_t$ also become larger and those of reversed parameters become smaller accordingly. Finally they separate and don’t intersect just as what happens in the $n = 1$ stochastic environment (data not shown).

In this work, we use a simple stochastic population model with time-delayed switching-rates conversion to study the influence of the response time-delay on the fitness of cell population. We find that in some cases such as $k_u > k_t$, time delays can optimize the population fitness, while in other cases, delay time don’t prove to be so positive. We also find that in the stochastically fluctuating environment states, variance may be another important factor determining whether time delay can be an advantage for the population fitness or not. However, since we only considered the exponential distribution of duration time above, other type of stochastic environment should also be considered so as to give a better understanding of population fitness in such environment [20]. Besides, this model only uses the average growth-rate to account for population fitness while neglecting other factors such as energy consumption, thus other environment state factors can be included to give a more comprehensive understanding of the issue, and experimental verification of mentioned results is also needed.

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We have simulated the effect of distinct response delay-time for two environment states, while little influence on the trend of the \( \langle f \rangle \) dependence on \( \tau \) is showed, except the case when the larger \( \tau \) dominates when the system becomes of a static transition. So here we only consider a specific response delay time.