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Oscillatory kinetics of gene transcription during the cellular growth

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The negative feedback between mRNA and regulatory-protein production may result in oscillations in the kinetics of gene transcription. If the mRNA and/or protein number are low, the oscillations may be irregular. We present mean-field calculations and Monte-Carlo simulations showing evolution of such oscillations during the cellular growth and division. The oscillations are found to be fairly stable with respect to the cellular growth.

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In cells, the information encoded in deoxyribonucleic acid (DNA) is expressed via a templated polymerization called transcription, in which the genes (segments of the DNA sequence) are used as templates to guide the synthesis of shorter molecules of ribonucleic acid (RNA) [1]. In turn, RNA or, more specifically, messenger RNA (mRNA) serve to direct the synthesis of proteins on ribosomes. The feedback between mRNA and protein production may result in kinetic bistability and oscillations [2, 3]. Physiologically, the bistability in gene transcription is widely used as a key ingredient of regulation of cellular activity. The physiological role of kinetic oscillations in gene transcription is still open for debate.

In terms of conventional mean-field (MF) kinetic equations, the bistability and oscillations in gene transcription are associated with the saddle-node and Hopf bifurcations, respectively. The applicability of the MF concepts is however limited, because the number of mRNA and regulatory proteins is often low and accordingly the gene-transcription kinetics frequently exhibit stochastic behaviour. Instead of bistability, for example, one can observe kinetic bursts which look like huge irregular oscillations. The truly oscillatory kinetics exhibit irregularities as well. Theoretically, the stochastic gene-transcription kinetics are usually simulated by employing the Monte-Carlo (MC) technique. The available MF calculations and MC simulations (see reviews [2, 3], recent publications [4 – 7], and references therein) are focused on the temporal kinetics occurring under steady conditions (for the spatio-temporal effects, see Refs. [8, 9]). In reality, cells however grow, and this process may be relatively rapid. Stem cells, for example, may often divide daily under appropriate conditions. The effect of the cellular growth on the gene-transcription kinetics has theoretically been studied in a few works [10 – 13]. In particular, the author has shown [12, 13] that the growth of cells may suppress the stochastic transcriptional bursts related to bistability. The goal of this Letter is to show the likely evolution of truly oscillatory temporal transcriptional kinetics during the cellular growth.

Kinetic oscillations are possible in the case of transcription of a single gene and also during the interplay of a few different genes. In the former case treated here, kinetic oscillations can be observed provided that the feedback between mRNA and protein production is negative and the suppression of the mRNA production is delayed due to protein conversion [2, 4, 7]. We will analyze one of the simplest generic models of this type, including production of protein P_1 by mRNA (R), conversion of P_1 to P_2 and then to P_3, and suppression of the R production by P_3 (for the earlier MF treatments of such models, see Ref. [7] and references therein).

To describe the kinetics of the mRNA and protein formation and degradation, one can use the mRNA and protein concentrations or numbers. If the MF approximation, these sets of variables are equally convenient if the cellular volume is constant. Moreover, the structures of the equations for these sets of variables are identical in this case. During the cellular growth, the cellular volume increases and due to this reason the structures of the equations for the two sets of variables are different. In the latter case, the use of the mRNA and protein numbers is slightly preferable, because by definition these variables are independent of the cellular volume. For comparison of the MF and stochastic kinetics, the use of the mRNA and protein numbers in the MF equations

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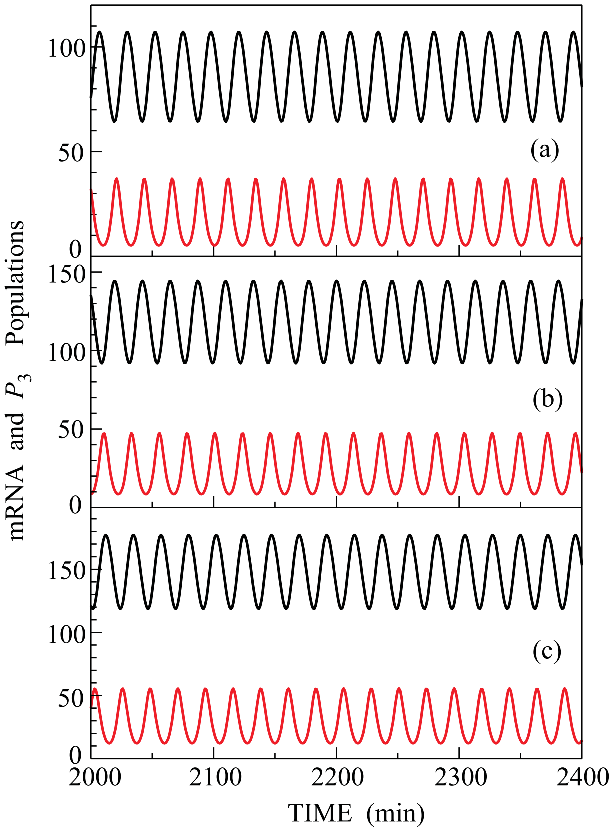

Fig.1. Numbers of R (lower curve) and P_3 (upper curve) as a function of time under the steady conditions according to the MF kinetic Eqs. (2)–(5) with $k_t = 10^5$ min^{-1}, $k_s = 2$ min^{-1}, $k_{12} = 0.2$ min^{-1}, $k_{23} = 0.2$ min^{-1}, $k_R = 0.4$ min^{-1}, $k_{P1} = 0.2$ min^{-1}, $k_{P3} = 0.2$ min^{-1}, $n = 6$, and $v\mathcal{K}_P = 20$ (a), 30 (b) and 40 (c)

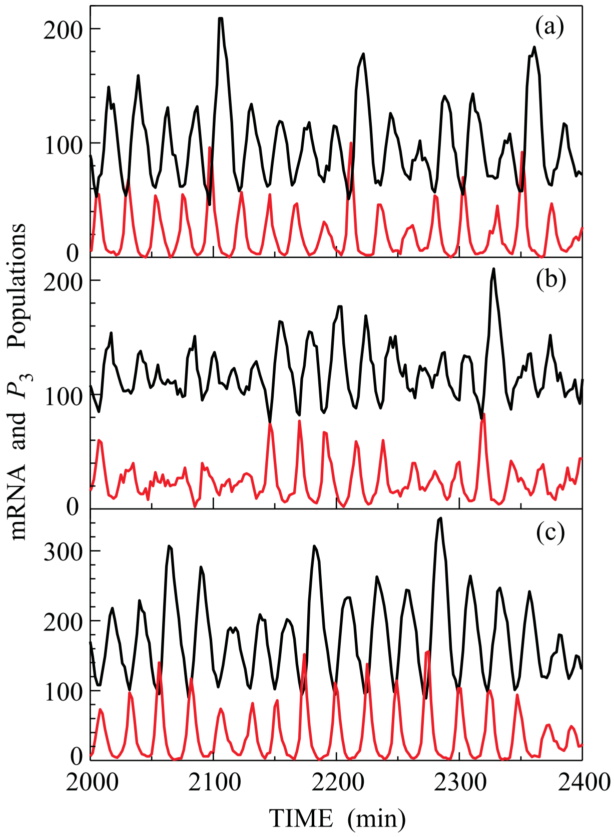

Fig.2. As Fig.1 according to the MC simulations. The time interval between the data points is about 2 min

is preferable as well, because the stochastic kinetics are calculated by operating with these numbers. In addition, the use of the mRNA and protein numbers in the MF equations makes it possible to naturally introduce the algorithms of simulations of stochastic kinetics. For these reasons, we employ the mRNA and protein numbers in the MF equations below.

The gene transcription is performed by RNA polymerase (RNAP). In our analysis, we assume that the association of RNAP with DNA does not limit gene transcription. In addition, the association of P_3 with the regulatory sites and the P_3 detachment from these sites are considered to be rapid. In this case, the conventional MF kinetic equation for the R number is as follows (cf. e.g. Ref. [2])

$$\frac{dN_R}{dt} = k_t \left(\frac{\mathcal{K}_P}{\mathcal{K}_P + N_{P3}/v} \right)^n - k_R N_R, \tag{1}$$

where k_t is the rate constant of the P_3-regulated gene transcription, N_{P3} is the P_3 number, v is the cellular volume, N_{P3}/v is the P_3 concentration, $[\mathcal{K}_P/(\mathcal{K}_P + N_{P3}/v)]^n$ is the probability that all the regulatory sites are free of P_3 (due to this factor the feedback between the R and protein production is negative), n is the number of regulatory sites, $\mathcal{K}_P$ is the constant describing the P_3 association-dissociation equilibrium, and k_R is the R-degradation rate constant.

Taking into account that $\mathcal{K}_P/(\mathcal{K}_P + N_{P3}/v) \equiv v\mathcal{K}_P/(v\mathcal{K}_P + N_{P3})$, we rewrite Eq. (1) as

$$\frac{dN_R}{dt} = k_t \left(\frac{v\mathcal{K}_P}{v\mathcal{K}_P + N_{P3}} \right)^n - k_R N_R. \tag{2}$$

For the P_1, P_2 and P_3 numbers, we use the following equations (cf. Ref. [7])

$$dN_{P1}/dt = k_s N_R - (k_{12} + k_{P1}) N_{P1}, \tag{3}$$

$$dN_{P2}/dt = k_{12} N_{P1} - k_{23} N_{P2}, \tag{4}$$

$$dN_{P3}/dt = k_{23} N_{P2} - k_{P3} N_{P3}, \tag{5}$$

where k_s is the rate constant of P_1 synthesis, k_{12} and k_{23} are the rate constants of conversion $P_1 \to P_2$ and $P_2 \to P_3$, and k_{P1} and k_{P3} are the P_1- and P_3-degradation

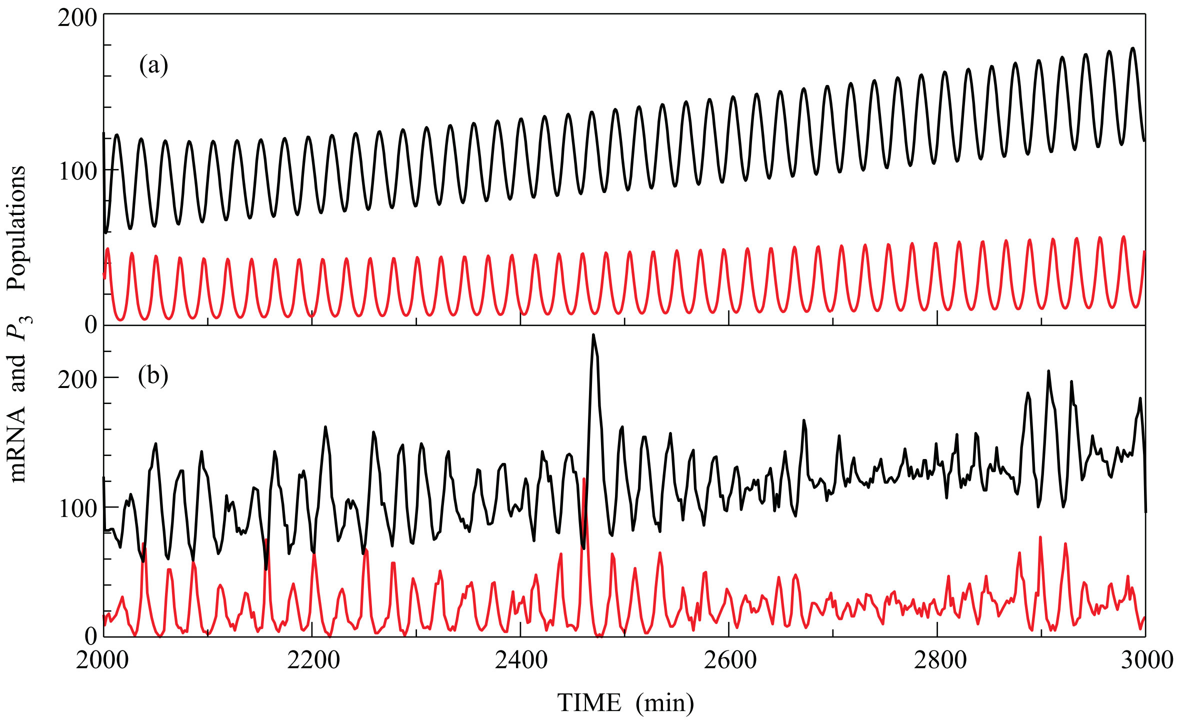

Fig.3. Numbers of R (lower curve) and P_3 (upper curve) as a function of time during one cellular cycle with $t_c = 1000$ min for $v_0\mathcal{K}_P = 20$ (the other model parameters are as in Figs. 1 and 2). The upper and lower panels show the MF and MC kinetics, respectively. For example, we have chosen the cycle occurring between 2000 and 3000 min

rate constants (the P_2 degradation is neglected in order to reduce the number of model parameters).

Typical oscillatory MF kinetics, predicted by Eqs. (2)–(5) with biologically reasonable values of the rate constants in the case when the cellular volume is constant, are shown in Fig.1. The product $v\mathcal{K}_P$ is chosen to be a governing parameter. With increasing $v\mathcal{K}_P$ by a factor of two, the oscillations are seen to persist. The stochastic oscillatory kinetics, calculated with the same parameters by employing the MC algorithm described in Ref. [12], are exhibited in Fig.2. As expected, the stochastic oscillations are rather irregular.

During the growth of a cell, the cellular volume increases, and accordingly some of the constants in Eqs. (1)–(5) may depend on time. Using Eqs. (2)–(5), we assume that all the constants introduced are independent of the cellular volume and accordingly independent of time. For $\mathcal{K}_P$, this assumption is obviously correct, because this constant is related to thermodynamics. For k_t, this is obviously the case as well, because this rate constant characterizes the gene performance. For the other rate constants, this assumption is correct provided the corresponding biochemistry is insensitive to the cellular volume. The latter point has already been discussed in Ref. [12]. For example, we outline the corresponding arguments related to the mRNA-induced protein synthesis. This process takes place on ribosomes and its rate is proportional to the mRNA concentration, N_R/v. With increasing v, the corresponding decrease of the protein synthesis rate is however compensated by increase of the ribosomes size. Thus, the rate constant of the mRNA-induced protein synthesis is expected to be insensitive the cellular volume and accordingly to be independent of time. In contrast, the change of v in the first term of the right-hand part of Eqs. (1) and (2) is inherent and cannot be neglected. For these reasons, we focus our analysis on the latter effect.

To use Eqs. (2), we should specify the dependence of the cellular volume on time. In our treatment, we analyse cycles of the proliferation or differentiation processes. During each cycle, a cell with initial volume v_0 is considered to grow up to volume $2v_0$ and then to divide into two equal parts with the same volumes as in the beginning. In this case, the increase of the cellular volume during the cell cycle is nearly exponential [14], i.e.,

$$v(t) = v_0 \exp(k_g t), \tag{6}$$

where $k_g \equiv (\ln 2)/t_c$ is the growth rate constant, and t_c is the cell-cycle duration. In the end of each cycle (due the cell division), v drops from $2v_0$ to v_0 and then increases again.

The mRNA and protein numbers are reduced by a factor of two in the end of each cycle as well. This procedure mimics the distribution of mRNA and protein between the two daughter cells after the cell division.

In addition, we should take into account DNA replication occurring during cell cycles. Basically, this process represents duplication of genes. In our model, it can be mimicked by increasing k_t by a factor of two at the moment of the gene duplication and then by decreasing k_t back by a factor of two in the end of the cell cycle [13]. For simplicity, we assume that the gene duplication occurs near the end of the cell cycle and accordingly consider that k_t is constant during the whole cycle. If necessary, the gene duplication can easily be performed in simulations at an arbitrary moment of the cell cycle, and we have proved that it does not change our main conclusion.

The MF gene-transcription kinetics, calculated for the case when the cellular volume increases as predicted by Eq. (6) with $t_c = 1000$ min, are shown in Fig.3. The corresponding MC kinetics, calculated by employing the MC algorithm described in Ref. [12], are presented in Fig. 3 as well. During the MC simulations, the increase of the cellular volume was considered to be deterministic as predicted by Eq. (6). This approximation is reasonable, because during the cell growth the fluctuations of the cellular volume are nearly negligible compared to the fluctuations of the mRNA and protein numbers.

The data exhibited in Fig.3 indicate that, as one could expect from the data presented in Figs.1 and 2, the cellular growth does not suppress oscillations. During the cell cycle, the average value of N_{P3} is seen to increase with increasing time. The average value of N_R is nearly constant. The amplitudes of oscillations of N_R and N_{P3} are nearly constant as well.

In summary, our MF and MC calculations indicate that for biologically reasonable kinetic parameters the oscillations in gene-transcription kinetics are fairly stable with respect to the cellular growth.

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