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OSCILLATORY KINETICS OF GENE EXPRESSION: PROTEIN CONVERSION AND SLOW mRNA TRANSPORT

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The negative feedback between mRNA and regulatory-protein production may result in oscillations in the kinetics of gene expression if the mRNA–protein interplay includes protein conversion. Using a mean-field kinetic model, we show that such oscillations can be amplified due to limitations of the mRNA transport between the nucleus and cytoplasm. This effect may be dramatic for the mRNA population in the nucleus.

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1. INTRODUCTION

The expression of the information encoded in genes is known to occur via a templated polymerization called transcription, in which the genes are used as templates to guide the synthesis of shorter molecules of RNA [1]. Subsequently, many RNAs, or, more specifically, messenger RNAs (mRNA) serve to direct the synthesis of proteins by ribosomes. Another large class of RNA includes noncoding RNAs (ncRNA) [2, 3]. The functions of these RNAs are based on their ability to bind to and modulate the activity of mRNAs and/or proteins [2]. The whole process of gene expression can be regulated at all the steps. Specifically, the gene transcription performed by RNA polymerase during its association with DNA is often controlled by master regulatory proteins. Such proteins associate with DNA and either facilitate or suppress the RNA synthesis.

The positive and negative feedbacks between RNA and protein formation may result in complex kinetic features including bistability and oscillations (see, respectively, reviews [4–6] and [7, 8]). Such features often play a key role in regulation of cellular processes. For this reason, the bistable and oscillatory kinetics of gene expression have long attracted attention, and the current understanding of the general underlying factors is relatively complete. In particular, the kinetic oscillations in the mRNA–protein interplay are believed to be likely if the feedback between mRNA and protein production is negative and the suppression of the mRNA production is delayed due to a few steps of protein conversion (see review [7] and recent simulations [9–11]; for the models including ncRNA, see Ref. [12]). This scenario can be complicated by slow transport of mRNA and protein between the nucleus and cytoplasm. In this work, we show how this transport can influence oscillations. Taking into account that the protein transport is usually faster than that of mRNA [13], we focus our analysis on the mRNA transport.

2. CONVENTIONAL KINETICS

To illustrate the conventional oscillatory kinetics of the mRNA and protein formation, we assume that the feedback between mRNA and protein synthesis is negative, the suppression of the mRNA production is delayed due to protein conversion from one form to another form, and the mRNA and protein transport between the nucleus and cytoplasm is rapid. The last assumption means that mRNA and protein are distributed in the cell at random, and we can operate with the total populations of the interacting species. We analyze one of the simplest generic models of this type, including production of protein P_1 by mRNA (R), con-

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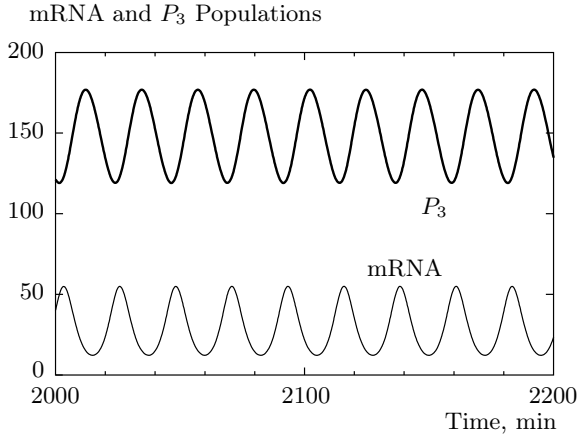

Fig. 1. R and P_3 numbers as functions of time according to Eqs. (1)–(4) with $n = 6$, $K_{P3} = 40$, $k_t = 10^5$ min^{-1}, $k_s = 2$ min^{-1}, $k_{12} = k_{23} = 0.2$ min^{-1}, $k_R = 0.4$ min^{-1}, and $k_{P1} = k_{P3} = 0.2$ min^{-1}

version of P_1 to P_2 and then to P_3, and suppression of the R production by P_3. In particular, the R production is assumed to occur whenever n regulatory sites are free of P_3. The corresponding mean-field kinetic equations for the R, P_1, P_2, and P_3 populations in the cell are given by [11]

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

$$\frac{dN_{P1}}{dt} = k_s N_R - (k_{12} + k_{P1}) N_{P1}, \tag{2}$$

$$\frac{dN_{P2}}{dt} = k_{12} N_{P1} - k_{23} N_{P2}, \tag{3}$$

$$\frac{dN_{P3}}{dt} = k_{23} N_{P2} - k_{P3} N_{P3}, \tag{4}$$

where k_t is the rate constant of the P_3-regulated gene transcription, $[K_{P3}/(K_{P3} + N_{P3})]^n$ is the probability that all the regulatory sites are free of P_3, K_{P3} is the P_3 association–dissociation constant, k_s is the rate constant of P_1 synthesis, k_{12} and k_{23} are the P_1 and P_2 conversion rate constants, and k_M, k_{P1}, and k_{P3} are the degradation rate constants (the P_2 degradation is neglected in order to reduce the number of model parameters).

Typical oscillatory kinetics predicted by Eqs. (1)–(4) with physically reasonable parameters are shown in Fig. 1. Although the protein-conversion-related delay in oscillations plays a constructive role in this case, it simultaneously somewhat damps the feedbacks between different steps. For this reason, the relative changes of the numbers of mRNA and protein copies during the oscillations are relatively small. In particular, the ratio of the minimum and maximum protein numbers is typically ≥ 0.5.

3. INTERPLAY OF CONVERSION AND TRANSPORT

Equations (1)–(4) involving the total mRNA and protein populations imply that the mRNA and protein transport is rapid. In our analysis, we accept this approximation for protein and focus on the mRNA transport. To explicitly include the mRNA transport between the nucleus and cytoplasm into the model, we must specify the transport mechanism. In general, the transport occurs via conventional diffusion in the highly crowded space and penetration through the membrane separating the nucleus and cytoplasm [13, 14]. The relative role of these two channels is often still open for debate. The bistable kinetics of gene expression including the former channel were simulated in Refs. [15–17]. In this work, we assume that the mRNA transport is limited by the penetration through the intracellular membrane. In this case, the nucleus and cytoplasm can be represented by two compartments with volumes αV and βV (V is the cell volume, α is the fraction of the space corresponding to the nucleus, and $\beta \equiv 1-\alpha$), and we can operate with the corresponding mRNA populations, N_{R1} and N_{R2}. The mRNA concentrations in these compartments are $N_{R1}/(\alpha V)$ and $N_{R2}/(\beta V)$. The net rate of the mRNA penetration through the intracellular membrane is proportional to the difference of these concentrations and can be represented as

$$W = \kappa_t \left(\frac{N_{R1}}{\alpha} - \frac{N_{R2}}{\beta}\right),$$

where κ_t is the transport rate constant (this rate constant is proportional to the membrane area and inversely proportional to V). Additionally taking into account that the protein synthesis occurs in the cytoplasm, we extend Eqs. (1)–(4) as

$$\frac{dN_{R1}}{dt} = k_t \left(\frac{K_{P3}}{K_{P3} + N_{P3}}\right)^n - \kappa_t \left(\frac{N_{R1}}{\alpha} - \frac{N_{R2}}{\beta}\right) - k_{R1} N_{R1}, \tag{5}$$

$$\frac{dN_{R2}}{dt} = \kappa_t \left(\frac{N_{R1}}{\alpha} - \frac{N_{R2}}{\beta}\right) - k_{R2} N_{R2}, \tag{6}$$

$$\frac{dN_{P1}}{dt} = k_s^* N_{R2} - (k_{12} + k_{P1}) N_{P1}, \tag{7}$$

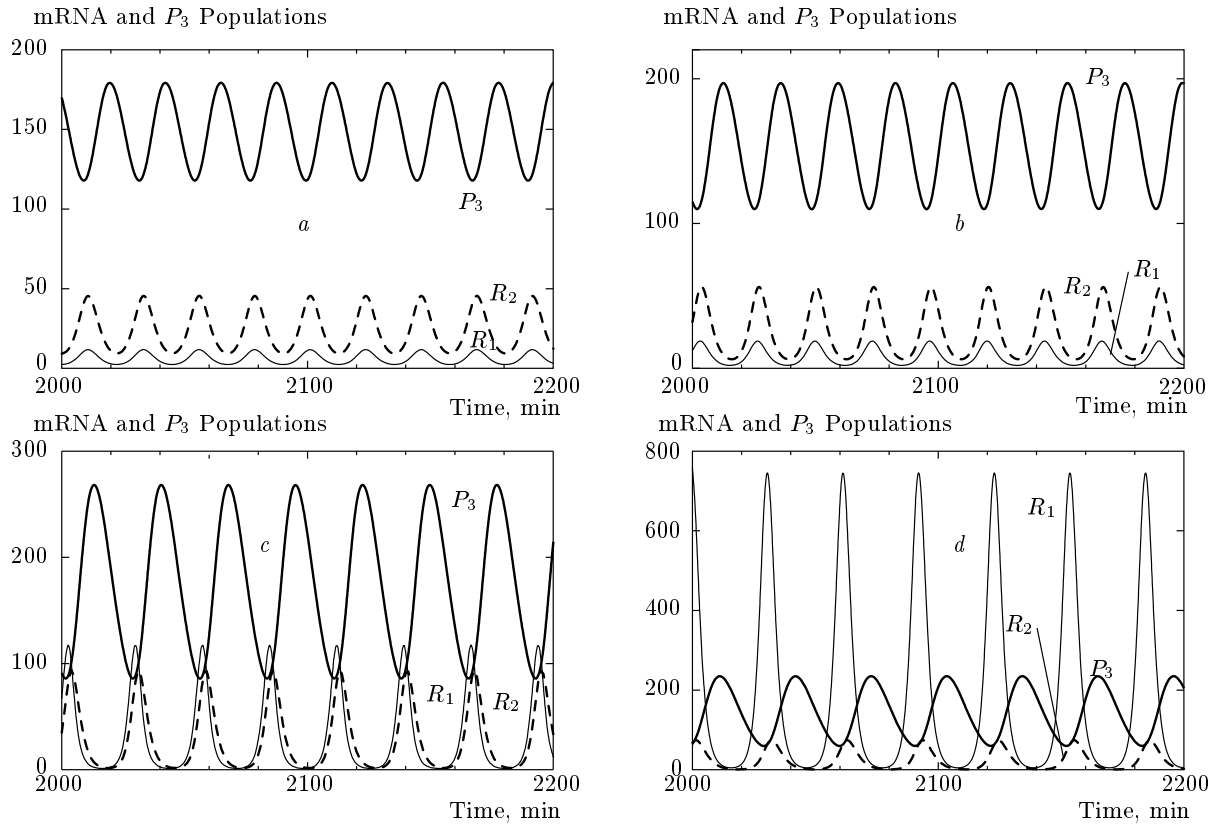

Fig. 2. Populations of mRNA in the nucleus (R_1), mRNA in the cytoplasm (R_2) and P_3 as functions of time according to Eqs. (5)–(9) for $\alpha = 0.2$ and $\kappa_t = 10$ (a), 1 (b), 0.1 (c), and 0.01 min^{-1} (d). The other parameters are as in Fig. 1

$$\frac{dN_{P2}}{dt} = k_{12}N_{P1} - k_{23}N_{P2}, \tag{8}$$

$$\frac{dN_{P3}}{dt} = k_{23}N_{P2} - k_{P3}N_{P3}. \tag{9}$$

All the rate constants (except κ_t) are defined here as in Eqs. (1)–(4).

If the mRNA transport is rapid (i.e., κ_t is sufficiently high), Eqs. (5)–(9) predict the same kinetics as Eqs. (1)–(4). To obtain identical results in this limit, we note that the rate of protein synthesis in Eqs. (5)–(9), $k_s^* N_{R2}$, is proportional to the mRNA population in the cytoplasm, while in Eqs. (1)–(4), this rate, $k_s N_R$, is proportional to the total mRNA population. If the mRNA transport is rapid, these rates must be equal, i.e.,

$$k_s^* N_{R2} = k_s N_R,$$

and in addition we should have

$$N_{R2} = \beta N_R.$$

Therefore, the two rate constants of protein synthesis should be related as $k_s = \beta k_s^*$. With this reservation, we can use the same rate constants in Eqs. (1)–(4) and (5)–(9).

Typical kinetics predicted by Eqs. (5)–(9) are shown in Fig. 2 for $\kappa_t = 10$, 1, 0.1 and 0.01 min^{-1}. For $\kappa_t = 10$ min^{-1}, the kinetics are nearly the same as those predicted by Eqs. (1)–(4) (cf. Figs. 1 and 2). With decreasing κ_t, the amplitude of oscillations is seen to increase. This effect is dramatic for the mRNA population in the nucleus and relatively weak for the mRNA population in the cytoplasm and the protein population.

Taking into account that the limitations in the mRNA transport amplify oscillations, it was interesting to verify whether these limitations can result in oscillations if we exclude protein conversion. The equations corresponding to this scenario are given by

$$\frac{dN_{R1}}{dt} = k_t \left(\frac{K_P}{K_P + N_P}\right)^n - \kappa_t \left(\frac{N_{R1}}{\alpha} - \frac{N_{R2}}{\beta}\right) - k_{R1}N_{R1}, \tag{10}$$

$$\frac{dN_{R2}}{dt} = \kappa_t \left(\frac{N_{R1}}{\alpha} - \frac{N_{R2}}{\beta}\right) - k_{R2}N_{R2}, \tag{11}$$

$$\frac{dN_P}{dt} = k_s^* N_{R2} - k_P N_P. \tag{12}$$

All the rate constants are defined here in analogy with those used Eqs. (5)–(9). Using the same parameters as in Fig. 2, we have found that Eqs. (10)–(12) do not predict oscillations.

4. CONCLUSION

In summary, we have shown that the oscillatory kinetics of gene expression, related to protein conversion, can be amplified due to limitations of the mRNA transport between the nucleus and cytoplasm. This effect may be especially significant for the mRNA population in the nucleus. Finally, we note that our analysis is based on the mean-field kinetic equations. The corresponding Monte Carlo simulations performed by using the standard Gillespie algorithm indicate that the stochastic features do not change our conclusions.

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