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# Stochastic bistable kinetics of gene transcription during the cell cycle

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The positive feedback between messenger ribonucleic acid (mRNA) and regulatory-protein production may result in bistability of gene transcription. If in addition the mRNA and/or protein numbers in a cell are low, one can observe stochastic transcriptional "bursts" provided that the intracellular conditions are steady. We present Monte Carlo simulations showing what may happen with the bursts under transient conditions during the cell cycle.

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In living cells, the expression of the information encoded in deoxyribonucleic acid (DNA) occurs 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]. Later on, many of these molecules [or, more specifically, messenger RNA (mRNA)] serve to direct the synthesis of proteins on ribosomes. The whole process of gene expression can be regulated at all the steps. In particular, the gene transcription, performed by RNA polymerase (RNAP) 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 mRNA and protein production related to the same gene or different genes may result in complex kinetic behaviour including bistability and oscillations. Mathematically, these phenomena can be described by using conventional mean-field (MF) kinetic equations. In cells, most genes exist at single or low copy numbers, the number of mRNA and regulatory proteins is often low, and accordingly the gene-transcription kinetics may exhibit stochastic features, e.g., transcriptional bursts related to bistability (for direct observation of such bursts, see Ref. [2]). The understanding of these features is obviously of high interest from very different view-points of molecular biology, biochemistry, biophysics, and statistical physics. The corresponding simulations are usually focused on the situations when the gene transcription occurs under steady conditions (see recent reviews [3 – 7], original articles [8 – 10], and references therein).

In realty, cells however grow, and accordingly the conditions for gene transcription are often transient. The studies of the specifics of the stochastic gene transcription under such conditions are just beginning [11, 12]. In particular, we have recently shown [12] that the increase of the cellular volume during the growth may suppress stochastic bursts in gene transcription. The results reported [12] are applicable mainly to the $G_1$ phase of the cell cycle (before the DNA replication), because the model does not include DNA replication. In this Letter, we present Monte Carlo (MC) simulations taking into account the latter process.

In our analysis, we assume that (i) in the beginning of the cell cycle the gene exists in a single copy, (ii) the association of RNAP with DNA does not limit gene transcription, and (iii) the mRNA ($R$) production is activated if $n$ regulatory sites are occupied by proteins ($P$). For this scheme, the conventional MF kinetic equations for the $R$ and $P$ numbers are as follows (cf. e.g. Refs. [4, 12])

$$dN_R/dt = [1 + \theta(t - t_d)]W_1 - k_R N_R, \qquad (1)$$

$$dN_P/dt = k_s N_R - k_P N_P, \qquad (2)$$

where

$$W_1 = k_0 + k_1 \left( \frac{N_P}{K_P v(t)/v_0 + N_P} \right)^n . \qquad (3)$$

The first term in the right-hand part of Eq. (1) describes the $R$-production rate. Specifically, $W_1$ is the $R$-production rate for a single gene. $k_0$ and $k_1$ are the rate constants of the basal and protein-regulated gene transcription. $[N_P/(K_P v(t)/v_0 + N_P)]^n$ is the probability that all the regulatory sites are occupied by $P$

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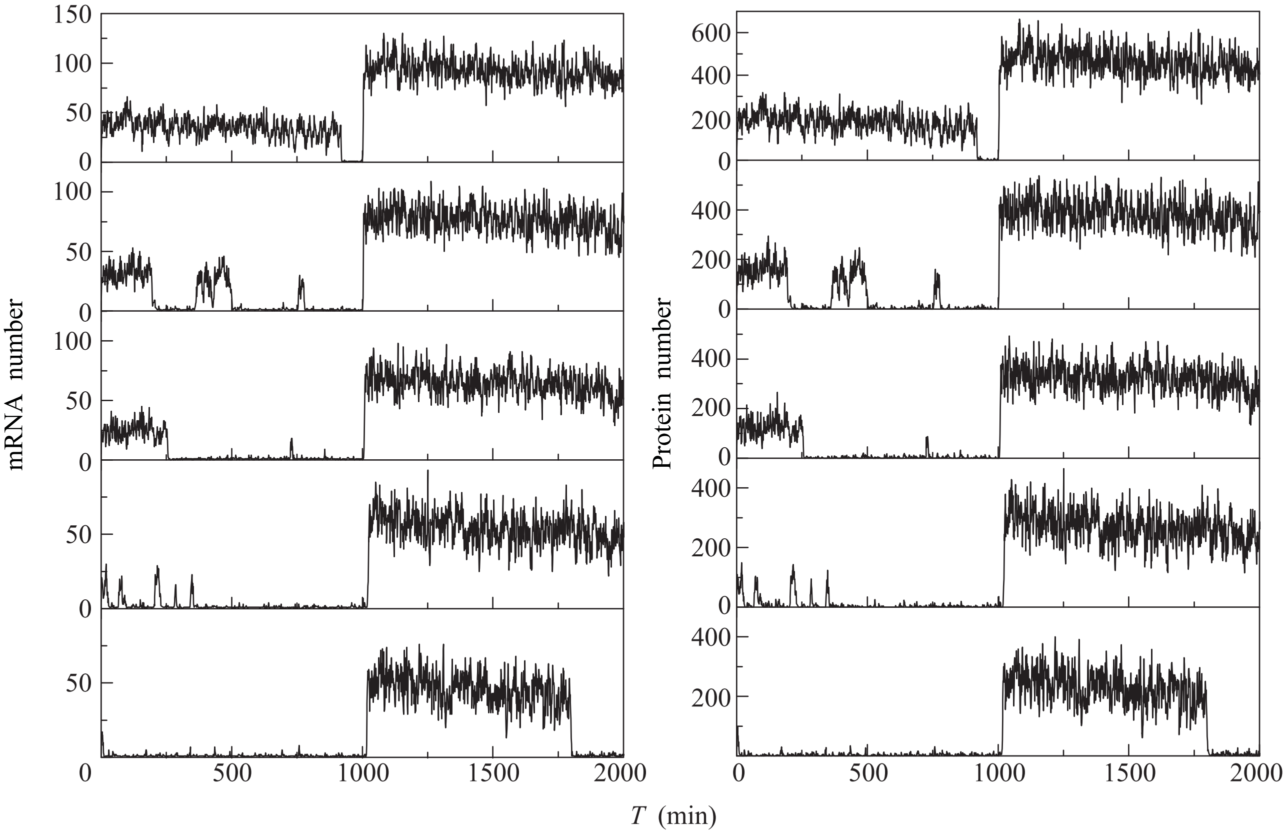


Numbers of mRNA and protein as a function of time during the cell cycle with $t_c = 2000$ min for $t_d = 1000$ min and $k_R = 0.8$, 0.9, 1.0, 1.1, and 1.2 $\text{min}^{-1}$ (from top to bottom)

(due to this factor the feedback between the $R$ and $P$ production is positive). $K_P$ is the protein association-dissociation constant. $v(t) = v_0 \exp(k_g t)$ is the cellular volume [$v_0 \equiv v(0)$ is the initial volume, $k_g \equiv (\ln 2)/t_c$ is the growth rate constant and $t_c$ is the cell-cycle duration]. The gene duplication is considered to occur during the $S$ phase at time $t_d$ and described by employing the Heavyside function $\theta(x)$ [$\theta(x) = 0$ or 1 for $x < 0$ and $x > 0$, respectively]. The use of this function implies that the time interval corresponding to gene duplication is much shorter than $t_c$.

The second term in the right-hand part of Eq. (1) takes the $R$ degradation into account ($k_R$ is the degradation rate constant).

The two terms in the right-hand part of Eq. (2) describe the $P$ synthesis and degradation, respectively ($k_s$ and $k_R$ are the corresponding rate constants).

Under steady-state conditions, the analysis of Eqs. (1) and (2) is trivial. In particular, Eq. (2) yields $N_P = (k_s/k_P)N_R$. Substituting this expression into Eq. (1) and using $v(t) = v_0$, one obtains a non-liner equation. With appropriate kinetic parameters, it predicts bistability provided that $n \geq 2$, and accordingly, with increasing and subsequent decreasing a governing parameter, one can observe a hysteresis loop with stepwise jumps from one stable solution to another. Mathematically, these jumps represent a saddle-node bifurcation (for classification of bifurcations, see Ref. [13]).

The fluctuations of $N_R$ and $N_P$ are, to some extent, equivalent to temporal variation of governing parameters. If $N_R$ and/or $N_P$ are relatively small, the fluctuations may result in irregular switches between the low- and high-reactive states or, in other words, in stochastic transcriptional bursts.

To study stochastic kinetics under transient conditions, we operate with discrete variables $N_P$ and $N_R$ and take into account the elementary steps described above, i.e., $P$ and $R$ production and degradation. In parallel with these steps, $P$ attaches to or detaches from regulatory sites. In our simulations below, $N_P$ is typically not too low, so that the contribution of $P$ attachment and detachment to the $P$ balance is minor, and accordingly we neglect this contribution. In addition, the $P$ attachment and detachment are assumed to be fast and accordingly to be close to equilibrium, so that the effect of $P$ on the

$R$ production rate can be described by using the conventional steady-state approximation, i.e., by employing the MF approximation like in Eq. (3). For the $P$ and $R$ production and degradation steps, we use the standard Monte Carlo algorithm [14] based on calculation of the total reaction rate. Specifically, we have four parallel processes [cf. Eqs. (1), (2)], running with the rates $W_1$ [Eq. (3)], $W_2 = k_R N_R$, $W_3 = k_s N_R$, and $W_4 = k_P N_P$. The total rate of these processes is $W_t = \sum_i W_i$, where $1 \leq i \leq 4$. For given numbers $N_P$ and $N_R$, we choose and execute one of the possible processes (i.e., increase and/or decrease $N_P$ or $N_R$ by one) with probabilities $W_i/W_t$. After each MC trial, time is incremented by $|\ln(\rho)|/W_t$, where $\rho$ $(0 < \rho \leq 1)$ is a random number.

For example, we use here the following biologically reasonable set of parameters: $n = 3$, $K_P = 30$, $k_1 = 50\,\mathrm{min}^{-1}$, $k_0 = 0.01k_1$, $k_s = 1000\,\mathrm{min}^{-1}$, and $k_P = 200\,\mathrm{min}^{-1}$. The duration of the cell cycle is considered to be $t_c = 2000\,\mathrm{min}$ (this value is typical e.g for stem cells). To illustrate general trends, the $R$-degradation rate constant, $k_R$, is employed as a governing parameter.

With the specification above, steady conditions (for $v(t) = v_0$), and in the absence of DNA replication, the model predicts well-developed stochastic transcriptional bursts for $1.0 \leq k_R \leq 1.2$ as shown in detail in Fig.3 in Ref. [12]. With increasing cellular volume in the absence of DNA replication, the bursts are appreciably suppressed (see Fig.4 in Ref. [12]). Typical kinetics with DNA replication (Figure) exhibit novel features. In particular, one can observe relatively low and high transcription rates at $t < t_d$ and $t > t_d$, respectively. In both cases, the bursts are either lacking or not well manifested.

In summary, our Monte Carlo simulations indicate that under transient conditions during a relatively short cell cycle (about 2000 min), the stochastic kinetics of gene transcription may be dramatically different compared to those predicted for steady-state conditions. This may have important consequences for a variety of cellular processes, e.g., for proliferation and differentiation of stem cells (for a review of the corresponding models, see Ref. [15]).

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