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Two novel aspects of the kinetics of gene expression including miRNAs

Research Article

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Abstract: In eukaryotic cells, many genes are transcribed into non-coding RNAs. Small RNAs or, more specifically, microRNAs (miRNAs) form an abundant sub-class of such RNAs. miRNAs are transcribed as long non-coding RNA and then generated via a processing pathway down to the 20-24-nucleotide length. The key ability of miRNAs is to associate with target mRNAs and to suppress their translation and/or facilitate degradation. Using the mean-field kinetic equations and Monte Carlo simulations, we analyze two aspects of this interplay. First, we describe the situation when the formation of mRNA or miRNA is periodically modulated by a transcription factor which itself is not perturbed by these species. Depending on the ratio between the mRNA and miRNA formation rates, the corresponding induced periodic kinetics are shown to be either nearly harmonic or shaped as anti-phase pulses. The second part of the work is related to recent experimental studies indicating that differentiation of stem cells often involves changes in gene transcription into miRNAs and/or the interference between miRNAs, mRNAs and proteins. In particular, the regulatory protein obtained via mRNA translation may suppress the miRNA formation, and the latter may suppress in turn the miRNA-mRNA association and degradation. The corresponding bistable kinetics are described in detail.

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Keywords: subcellular processes • gene transcription • mRNA and miRNA association and degradation • mRNA translation • stem cells

1. Introduction

To understand the mechanisms that make life possible, one must, first of all, explore the structure and function of the double-stranded deoxyribonucleic acid (DNA) molecule [1]. The key function of DNA or, more specifically, of its fragments identified as genes is to encode and control the heredity of cells. Basically, the expression of this heredity or, in other words, gene expression includes polymerase-mediated gene transcription into messenger ribonucleic acids (mRNAs),

$$\text{Gene} \rightarrow \text{Gene} + \text{mRNA}, \qquad (1)$$

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and mRNA translation by ribosomes into proteins,

$$\text{mRNA} \rightarrow \text{mRNA} + \text{P}. \tag{2}$$

In eukaryotic cells, many genes are transcribed also into non-coding RNAs or, more specifically, microRNAs (miRNAs) [2–4],

$$\text{Gene}_* \rightarrow \text{Gene}_* + \text{miRNA}. \tag{3}$$

All these species degrade,

$$\text{mRNA} \rightarrow \emptyset, \tag{4}$$

$$\text{P} \rightarrow \emptyset, \tag{5}$$

$$\text{miRNA} \rightarrow \emptyset. \tag{6}$$

The numerous biological functions of miRNAs are based primarily on their ability to associate with target mRNAs and to suppress their translation and/or facilitate degradation,

$$\text{mRNA} + \text{miRNA} \rightarrow \text{mRNA} * \text{miRNA} \rightarrow \emptyset. \tag{7}$$

Every step of gene expression represents complex biochemical reaction precisely regulated in one way or another. Despite intensive study, especially in identifying protein-coding genes, the understanding of the genome and its functions is still far from complete, particularly with regard to non-coding RNAs, alternatively spliced transcripts and regulatory sequences [5]. The most recent experimental studies, aimed at large-scale analysis of the genome and regulatory factors, have enabled to assign biochemical functions for 80% of the genome [5] and identified more than one hundred transcription-related factors [6].

Due to abundant feedbacks in gene expression and relatively small populations of each specific RNA and protein in a cell, the kinetics of gene expression are often complex and may exhibit such inherent features as bistability, oscillations, and stochasticity even in the case of the interplay of a few genes. The kinetic models describing various aspects of such kinetics are numerous. Many works are focused on the basic steps of gene expression, including, first of all, gene transcription (see, *e.g.*, Refs. [7–10] and references therein) and mRNA translation (see, *e.g.*, Refs. [11–13] and references therein). The interplay of various steps has also been extensively studied as reviewed with emphasis on stochastic bursts and bistability in simple mRNA-protein networks [14–16], kinetic oscillations in such networks [17, 18], complex mRNA-protein networks [19–22], and networks including mRNAs, proteins and non-coding RNAs [23].

In this article, we scrutinize two novel aspects of the kinetics of gene expression including miRNAs. Specifically, we describe external periodic regulation of the mRNA-miRNA interplay (Section 2) and P-mediated mRNA-miRNA bistability in the context of differentiation of stem cells (Section 3). The motivations of the treatments of these aspects of gene express are given in the beginnings of the corresponding sections.

2. Periodic external regulation

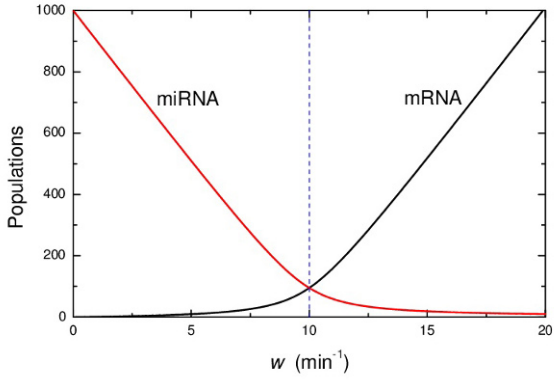


Figure 1. mRNA and miRNA populations as a function of the mRNA synthesis rate under steady-state conditions according to Eqs. (8) and (9) with $u = 10$ min^{-1}, $k = k_* = 0.01$ min^{-1}, and $r = 10^{-3}$ min^{-1}. (This figure is similar to Fig. 1 in Ref. [23].)

2.1. Motivation

As already noted in the Introduction, the feedbacks in gene expression may result in kinetic oscillations. The biochemical role of such oscillations is subtle and often open for debate. One class of oscillations is related to the cell cycle (see, *e.g.*, Refs. [24, 25] and references therein). At present, there are also indications that oscillations in gene expression can be beneficial from other perspectives, *e.g.*, by serving as a powerful means of encoding and transferring information both in time and in space (reviewed in Ref. [26]).

To clarify the role of genetic oscillations, one should understand the mechanisms of how they may arise (reviewed in Refs. [17, 18, 23]) and also their likely effect on the kinetics downstream. One of the scenarios here is that the

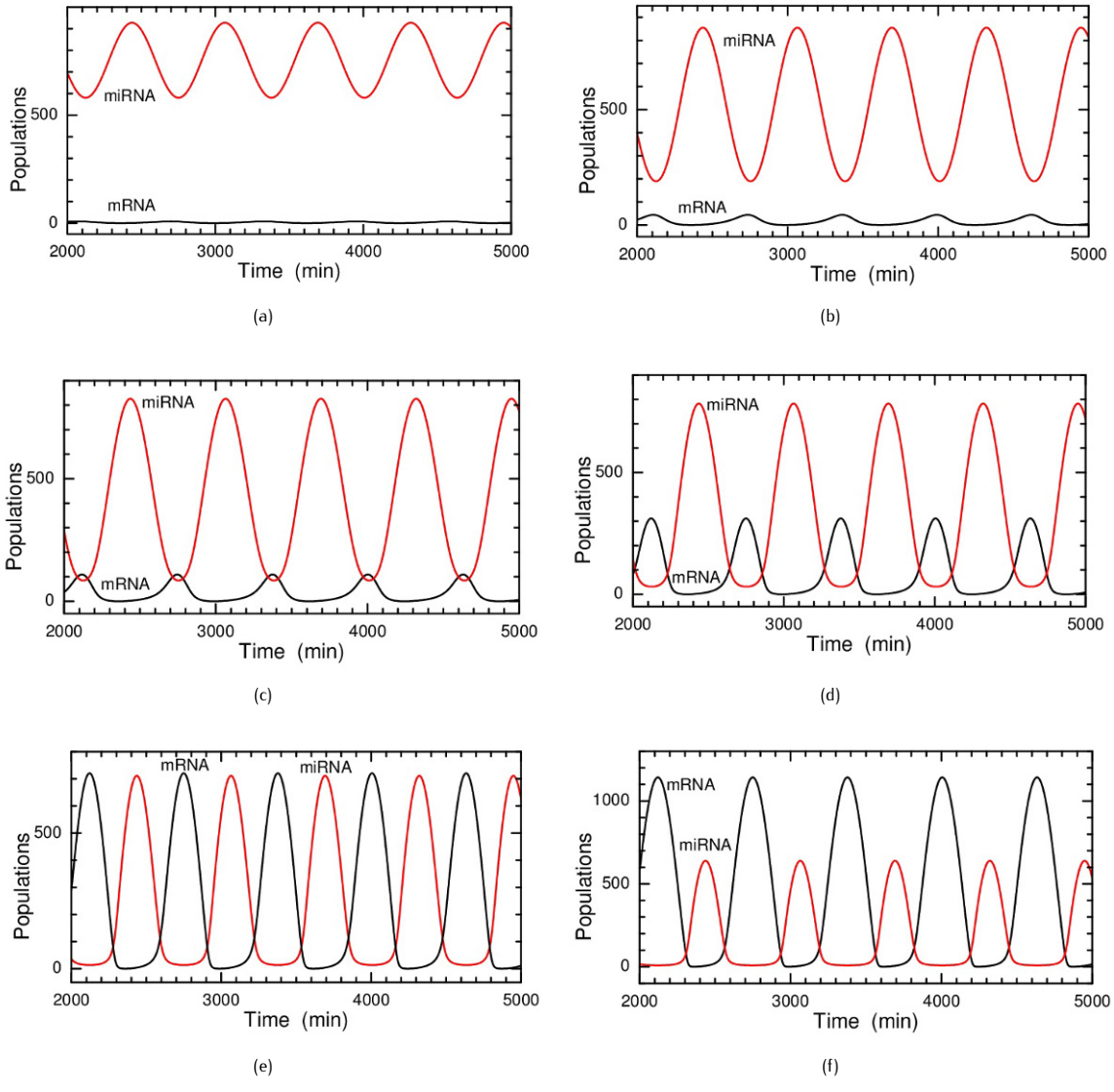


Figure 2. mRNA and miRNA populations as a function of time according to Eqs. (8)-(10) with $\omega = 0.01$ min^{-1}, $u = 10$ min^{-1}, and $w_\circ = 5$ (a), 10 (b), 12 (c), 15 (d), 20 (e), and 25 min^{-1} (f). The other parameters are as in Fig. 1

oscillations in one of the networks result in oscillations in the population of a transcription factor (chemically, the transcription factors are proteins), and the latter induces in turn oscillations downstream via periodic regulation of the gene transcription there. The available studies of this category are focused on periodic perturbation of bistable and oscillatory networks (see, respectively, Refs. [27, 28] and [29–31] and references therein). Complementing those studies, we show here the effect of periodic regulation on the mRNA-miRNA interplay.

2.2. Model

The simplest generic scheme of the mRNA-miRNA interplay includes steps (1), (3), (4), (6), and (7). The corresponding kinetic equations for the intracellular mRNA and miRNA populations, N and N_*, are as follows

$$dN/dt = w - kN - rNN_*, \tag{8}$$

$$dN_*/dt = u - k_*N_* - rNN_*, \tag{9}$$

where w and u are the transcription rates, and r, k and k_* are the rate constants of steps (4), (6) and (7).

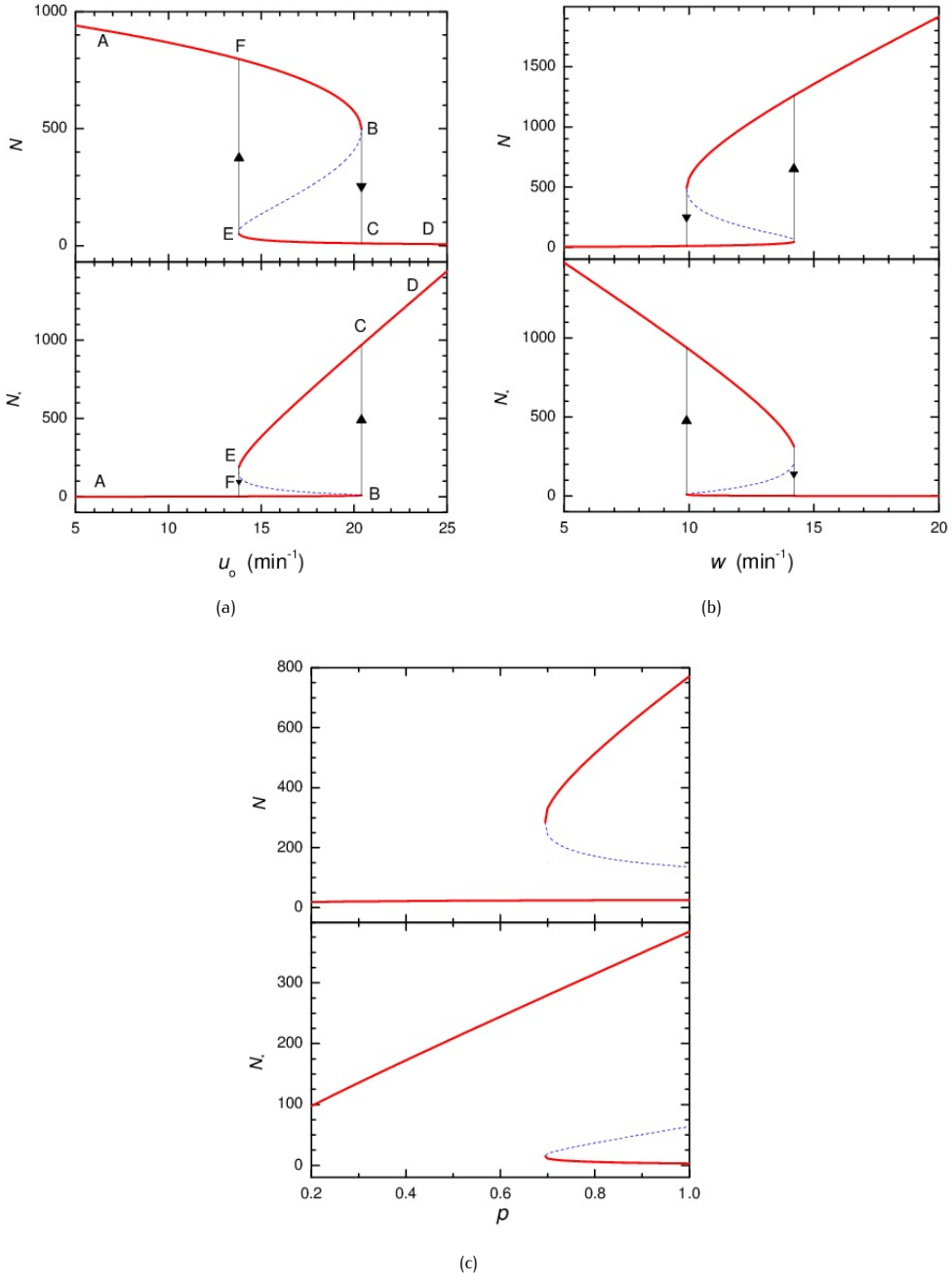


Figure 3. mRNA and miRNA populations (a) as a function of $u_\circ$ for $w = 10$ min^{-1}, (b) as a function of w for $u_\circ = 20$ min^{-1}, and (c) as a function p. The solid and dashed lines correspond to the stable and unstable steady states, respectively. Note that with the parameters chosen (see the text) the P population (not shown) is equal to the mRNA population.

If the association of mRNA and miRNA [step (7)] is fast, the specie produced with lower rate degrades rapidly and almost completely via this step and accordingly its synthesis rate simply reduces the synthesis rate of the specie produced with a higher rate. Specifically, one has $N \simeq (w-u)/k$ and $N_* \simeq 0$ for $w > u$, and $N \simeq 0$ and $N_* \simeq (u-w)/k_*$ for $u > w$. This means that the gene with lower transcription rate is effectively silenced (this effect was widely discussed in the literature [23]). If for example u is fixed and w is used as a governing parame-

ter (Fig. 1), the gene transcribed into miRNA is silenced above the threshold, $w > u$.

Here, we show what will happen in the scheme above if the rate of gene transcription into mRNA or miRNA is periodically regulated by a transcription factor which itself is not perturbed by these species. Taking into account that according to Eqs. (8) and (9) mRNA and miRNA are kinetically symmetric, it is sufficient to present the results for regulation of the rate of the mRNA formation (the results for regulation of the rate of the miRNA formation are similar). We describe this rate as

$$w = \langle w \rangle [1 + \alpha \sin(\omega t)], \qquad (10)$$

where $\langle w \rangle$ is the average value of w, and α and ω are the modulation amplitude and frequency. This periodic modulation of w mimics the effect of the transcription factor (this factor is assumed to be produced in the oscillatory fashion upstream).

If $\alpha \ll 1$ and/or ω is high (compared to the degradation rate constants), the average mRNA and miRNA populations are close to those predicted by Eqs. (8) and (9) in the absence of the periodic perturbation (at $\alpha = 0$), while the amplitudes of oscillations of these populations are small. Under such conditions, Eqs. (8) and (9) in combination with expression (10) can easily be integrated by using the perturbation theory. In particular, one can show that with increasing ω the amplitudes of oscillations of the mRNA and miRNA populations are proportional to $1/\omega$ and $1/\omega^2$, respectively.

The case when the periodic perturbation is not efficient and the amplitudes of oscillations of the mRNA and miRNA populations are small is not of interest, because in this limit the oscillations can easily be smeared by fluctuations. We are interested in the opposite situation when the periodic perturbation is appreciable. To focus on this case, we use $\alpha = 1$ and rewrite expression (10) as

$$w = w_\circ [1 + \sin(\omega t)]/2, \qquad (11)$$

where $w_\circ \equiv 2\langle w \rangle$ is the maximum value of w.

2.3. Results of calculations

Typical results of our calculations performed by employing the model described are shown in Fig. 2 for $u = 10$ min^{-1}, $k = k_* = 0.01$ min^{-1}, $r = 10^{-3}$ min^{-1}, and $w_\circ = 5$, 10, 12, 15, 20, and 25 min^{-1} (for the validation of these parameters, see Section 3.6 in Ref. [23]). To get appreciable periodic perturbation of the mRNA and miRNA populations, we use $\omega = 0.01$ min^{-1} (in this case, we have $\omega = k = k_*$).

With the parameters chosen, our model indicates that, depending on the ratio of u and $w_\circ$, one can distinguish the following three kinetic regimes:

(i) If $w_\circ$ is lower than or equal to u, the model predicts that the miRNA population is appreciable, the oscillations of this population are nearly harmonic, the amplitude of these oscillations is relatively small, while the mRNA population is nearly negligible as shown in Figs.2(a) and 2(b) for $w_\circ = 5$ and 10 min^{-1}, respectively.

(ii) If $w_\circ$ is slightly above u, the oscillations of the miRNA population remain to be nearly harmonic, the amplitude of these oscillations become large, while the mRNA population remains relatively small (see, *e.g.*, Figs. 2(c) and 2(d) for $w_\circ = 12$ and 15 min^{-1}, respectively).

(iii) If $w_\circ$ is appreciably above u, the amplitudes of oscillations of the mRNA and miRNA population are large, and they are shaped as periodic anti-phase pulses (Figs. 2(e) and 2(f) for $w_\circ = 20$ and 25 min^{-1}, respectively). During the periods of large mRNA population, the miRNA population is nearly negligible, and *vice versa*.

3. P-mediated bistability and differentiation of stem cells

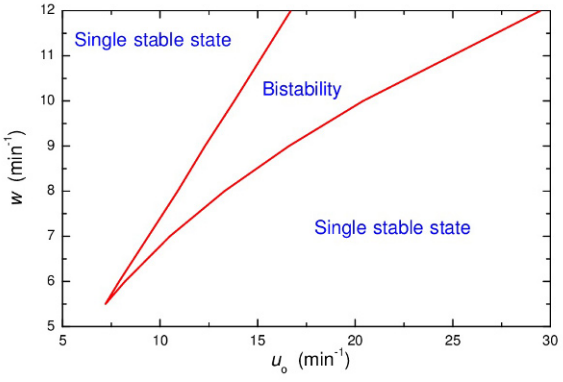


Figure 4. Kinetic phase diagram in the plane of $u_\circ$ and w.

3.1. Motivation

Kinetically, differentiation of a stem cell can be viewed as a transition from one steady state to another steady state [32]. A transition can be intrinsic, *i.e.*, spontaneous or induced by external signals (reviewed in Refs. [32, 33]). Although in reality each steady state is characterized by a multitude of parameters, their specifics are usually believed to be related to the difference in gene expression.

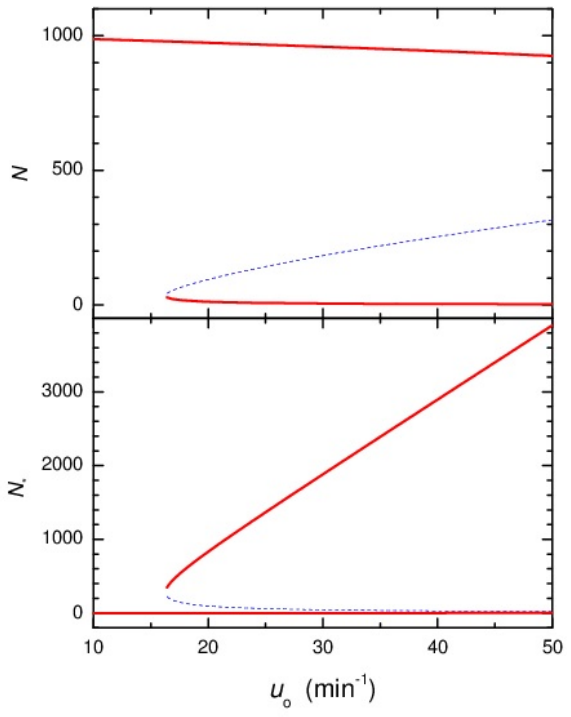


Figure 5. As Fig. 3(a) for $m = 4$.

Mathematically, the existence of different steady states is associated with bistability or multistability. During the last decade, the bistable mean-field kinetic models of gene expression including mRNAs and proteins have been widely used to interpret the signal-induced differentiation [34–49]. Basically, the differentiation is viewed there as a stepwise transition occurring with changing of one of the governing parameters. The mRNA-protein-mediated spontaneous differentiation occurring with a certain probability can be described taking stochasticity into account [45]

More recent experimental studies indicate that the differentiation of stem cells often involves the changes in gene transcription into miRNAs and/or interplay between mRNAs and miRNAs (reviewed in Refs. [50–53]). The advantage of miRNAs is that they often have many target mRNAs, and accordingly the change of the rate of formation of one of miRNAs may result in appreciable changes in the populations of many mRNAs and corresponding proteins. Some of the proteins may play a role of transcription factors and influence in turn the rate of the miRNA formation. During neuronal development, for example, one of the key miRNA, *miR*-124, directs differentiating stem cells into a neuronal phenotype and blocks glia formation [54] (reviewed in Ref. [51]). This miRNA negatively regulates one of the transcriptional repressors (the protein designated as REST) of neuronal genes including *miR*-124 itself. In this section, we present the results of calculations helping to understand what may happen in such cases.

3.2. Model

The model we use for the formation and degradation of mRNA, miRNA and P includes steps (1)-(7). P is assumed to regulate negatively the miRNA formation (as in the case of REST and *miR*-124 in neuronal development). The corresponding kinetic equations for the mRNA, miRNA and P populations, N, N_* and n, in a cell are as follows [23, 55]

$$dN/dt = w - kN - rNN_*, \tag{12}$$

$$dN_*/dt = u_\circ \left(\frac{K}{K+n}\right)^m - k_* N_* - rNN_*, \tag{13}$$

$$dn/dt = \upsilon N - \kappa n, \tag{14}$$

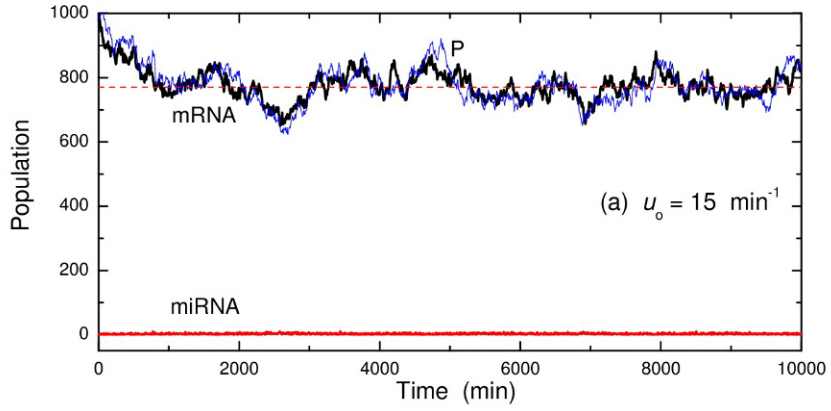
where w is the mRNA formation rate, $u_\circ$ is the maximum miRNA formation rate (*i.e.*, the rate at $n \to 0$), K and m are the parameters describing the negative regulation of the miRNA formation by P (m is the number of regulatory sites, and K is the P-site association constant), υ is the mRNA translation rate constant, r is the rate constant of the mRNA-miRNA association [step (7)], and k, k_* and κ are the rate constants of conventional degradation of mRNA, miRNA and P.

The model outlined above predicts bistability as was earlier shown by using r as a governing parameter [55] (see also Ref. [56]). This parameter is, however, not suitable in the context of cell differentiation, because the latter process is usually believed to include regulation of gene transcription. For this reason, we scrutinize here the model behaviour by employing the transcription rates, $u_\circ$ and w, as governing parameters.

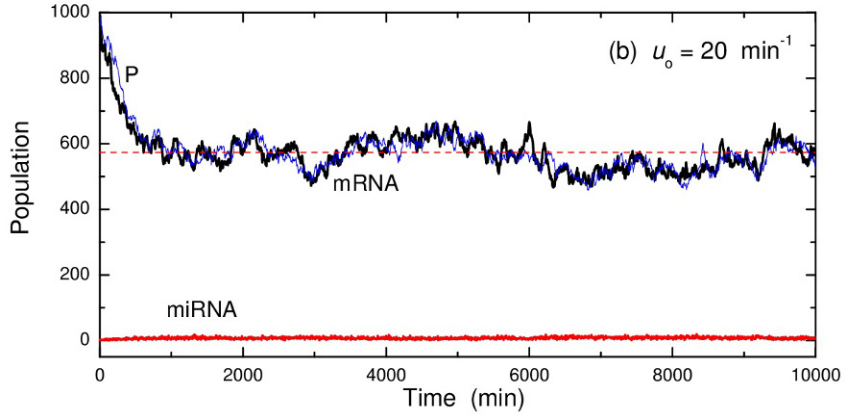
3.3. Results of calculations

The parameters chosen to illustrate the model predictions are: $m = 2$, $K = 500$, $r = 0.001$ min^{-1}, and $\upsilon = k = k_* = \kappa = 0.01$ min^{-1} (for the validation, see Section 3.6 in Ref. [23]). The steady-state kinetics and the corresponding kinetic phase diagram calculated with these parameters are shown in Fig. 3 and 4, respectively. In particular, N and N_* are exhibited as a function of $u_\circ$ in Fig. 3(a) and as a function of w in Fig. 3(b).

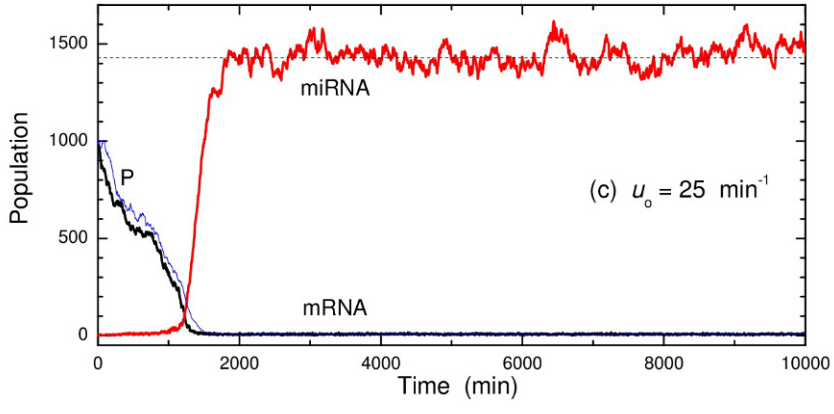
Employing Fig. 3(a), let us consider the situation when initially $u_\circ$ is low, the miRNA population is small, and



(a)



(b)



(c)

Figure 6. Transient Monte Carlo kinetics at $t > 0$. The system is at steady state with $u_\circ = 0$ at $t < 0$ (the other parameters are as in the case of Fig. 3(a)). In this state, the mRNA and P populations are large. At $t = 0$, $u_\circ$ is increased up to 15 (a), 20 (b), or 25 min^{-1} (c) and then kept constant. With increasing time, in agreement with Fig. 3(a), the system either remains in the state with large mRNA and P populations [(a) and (b)] or transits to the state with large miRNA population (c). The interval between the data points is 5 min. The dashed lines show the mean-field steady-state mRNA or miRNA populations [Fig. 3(a)] corresponding to the chosen values of $u_\circ$.

the mRNA and P populations are large, and then $u_\circ$ is increased up to a desirable value due to the regulation by external signals or by a cell-cycle-related transcription factor. The increase of $u_\circ$ corresponds to the motion along line AB. If the desirable value of $u_\circ$ is below that corresponding to point B, the cell will remain in the state with small miRNA population. If, however, the desirable value of $u_\circ$ is above that corresponding to point B, the system will first move along line AB , then jump along line BC to the state with large miRNA population and small mRNA and P populations, and subsequently move along line CD. In the context of our presentation, this jump corresponds to cell differentiation. If initially $u_\circ$ is high, the miRNA population is large, and the mRNA and P populations are small and then $u_\circ$ is decreased, the system will move along line DEFA.

In reality, the signals may regulate the mRNA and miRNA formation rates simultaneously. To illustrate this case, let us consider that these rates are represented as $w = pW$ and $u_\circ = pU_\circ$, where $W = 10$ min^{-1}, $U_\circ = 15$ min^{-1}, and $0 < p \leq 1$ is a governing parameter. With these values of W and $U_\circ$ and $p = 1$, the kinetics are bistable (Fig. 3(a)). The kinetics calculated as a function of p are shown in Fig. 3(c). If p is small, there is a single steady state with negligible population of mRNA. Bistability is observed if p is appreciable ($p \geq 0.69$).

The results presented in Figs. 3 and 4 have been obtained for $m = 2$. With increasing m, the area of the parameter values where one can observe bistability appreciably expands and the kinetic features related to bistability are manifested better [*cf.*, *e.g.*, Figs. 3(a) and 5].

To complement our analysis based on the mean-field kinetic equations (12)-(14), we have simulated the corresponding kinetics by using the Monte Carlo technique or, more specifically, the standard Gillespie algorithm based on the calculation of the total rate of all the possible steps, $w_{\rm tot}$, realization of one of the steps chosen with the probability proportional to its contribution to the total rate, and the increment of time by $|\ln(\rho)|/w_{\rm tot}$, where ρ ($0 < \rho \leq 1$) is a random number (for the details, see Ref. [55]). In the situations when the mRNA, miRNA and P populations are relatively large as, *e.g.*, in the case of Figs. 3-5, the Monte Carlo simulations are in agreement with the mean-field results (see, *e.g.*, Fig. 6). If these populations are small (*e.g.*, below 100), the Monte Carlo kinetics may exhibit stochastic bursts representing transitions between states which are close to the mean-filed steady states [55].

In summary, our calculations illustrate the possible changes in the miRNA, mRNA and protein populations during differentiation of stem cells and may help to understand and interpret this phenomenon. Our analysis has been focused on the case when miRNA has one target. As already noticed, the advantage of miRNAs is that they often have many targets. Our model can easily be generalized to the latter case [57], and our main conclusions remain valid even if the number of targets is large.

4. Conclusion

We have scrutinized two aspects of the mRMA-miRNA interplay including external periodic regulation (Section2) and P-mediated bistability in the context of differentiation of stem cells (Section 3). Finally, we may note that miRNAs may interfere with almost every function of eukaryotic cells [for example, miRNAs are expressed at a high level in the brain in adulthood and participate in normal and abnormal brain functions (reviewed in Refs. [51, 58]; see also a model describing the interplay of membrane voltage and gene expression in neurons [59])]. Many aspects of this interference are open for experimental and theoretical studies.

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