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Non-coding RNAs and complex distributed genetic networks

Research Article

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Abstract: In eukaryotic cells, the mRNA-protein interplay can be dramatically influenced by non-coding RNAs (ncRNAs). Although this new paradigm is now widely accepted, an understanding of the effect of ncRNAs on complex genetic networks is lacking. To clarify what may happen in this case, we propose a mean-field kinetic model describing the influence of ncRNA on a complex genetic network with a distributed architecture including mutual protein-mediated regulation of many genes transcribed into mRNAs. ncRNA is considered to associate with mRNAs and inhibit their translation and/or facilitate degradation. Our results are indicative of the richness of the kinetics under consideration. The main complex features are found to be bistability and oscillations. One could expect to find kinetic chaos as well. The latter feature has however not been observed in our calculations. In addition, we illustrate the difference in the regulation of distributed networks by mRNA and ncRNA.

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Keywords: gene transcription • mRNA translation • association of mRNA and ncRNA • mean-field kinetic equations • bistability and scillations

1. Introduction

The function of genetic networks including many genes can be fairly complex. The understanding of such networks is still limited despite a few decades of studies by biologists, chemists, physicists and mathematicians [1–5]. The main activity in this area has long been focused on the interplay of mRNAs and proteins. In DNA of eukaryotic cells, the sequences or, in other words, genes transcribed into protein-coding RNAs are, however, rare. During the past decade, it has been found that the other parts of DNA of such cells are often transcribed into ncRNAs forming the cornerstone of a regulatory network that operates in concert with the protein network (see recent reviews of long ncRNAs [6–8] and small RNAs obtained by cleavage of long ncRNAs [9–11]). The important role of ncRNAs has been tracked out in a wide variety of cellular processes. For example, thousands of mammalian mRNAs are highly expressed at developmental stages before the expression of small ncRNAs and their levels tend

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to fall as the ncRNAs that target them begin to accumulate [12]. Small RNAs are expressed at high level in the brain and participate in normal and abnormal brain functions [13]. Abnormal levels of ncRNA expression were observed in many types of human cancer [14]. Misexpression of ncRNAs occurs also in many other diseases including diabetes, obesity, heart disease and inflammation [15].

Despite the current boom in experimental investigation of ncRNAs, detailed experimental measurements of the kinetics of gene expression influenced by ncRNAs are still rare. Theoretical studies of such kinetics are focused primarily on the simplest situations without protein-mediated regulation [16–32] or with a single protein-mediated feedback [33–42]. There are also first attempts to describe the kinetics of more complex genetic networks including ncRNAs [43–46]. The structures of the ncRNA-protein interaction networks in six specific systems have been discussed Ref. [47]. The latter work does not, however, include kinetics.

Depending on their structure, complex genetic networks can qualitatively be classified as hierarchical ("autocratic"), intermediate, or distributed ("democratic") [3]. In the first class, a small group of genes controls many other genes. In the third class, all genes act as mutual regulators. The networks belonging to the intermediate class contain both types of regulation. In our previous study [45], we have presented and comprehensively analyzed a kinetic model describing the influence of ncRNAs on a hierarchical two-layer network of genes transcribed into mRNAs (more specific models are related to a cancer network [43] and transcriptional regulation activity of small ncRNAs in *E. coli* during the carbon source transition from glucose to acetate [44]). The genes forming the bottom layer were assumed to be regulated from the top and negatively self-regulated. If the former regulation is positive, the dependence of the RNA populations on the governing parameters is often found to be nonmonotonous. In particular, the model predicts bistability. If the regulation is negative, the dependence of the RNA populations on the governing parameters is monotonous. In particular, the population of the mRNAs, corresponding to the genes forming the bottom layer, is nearly constant. Similar results have been obtained for a hierarchical three-layer network [46].

Our present study is focused on the likely effect of ncRNA on a complex distributed network of genes transcribed into mRNAs. In our analysis, ncRNA is considered to associate with mRNAs and inhibit their translation and/or facilitate degradation. This is one of the key functions of ncRNAs in general and of small ncRNAs in particular (for the other abilities of ncRNAs, see Refs. [6–11]). This function allows ncRNAs to serve as global regulators. To illustrate the corresponding kinetics occurring under steady-state conditions, we use the ncRNA synthesis rate as a governing parameter. In particular, we show the mean-field kinetics observed with increasing and subsequent decreasing this rate. Generally, in calculations of this type the kinetics are expected to exhibit a unique steady state, bistability, oscillations, and/or chaos (for the discussion of stochastic features, e.g., ncRNA-related bursts, see Ref. [32]). The questions we address are: Does our model predict bistability, oscillations, and chaos? How often are these features observed? Is it likely to observe two features, e.g., first bistability and then oscillations for a single set of parameters?

2. Model

The concept of distributed genetic networks has only recently gained empirical support (see, e.g., studies focused on transcriptional variability in clonally related mouse hematopoietic precursor cells [48] (reviewed in Ref. [3]), regulatory networks for five diverse species, from *Escherichia coli* to humans [49], and stem cell transcriptional networks [50]), because its characterization involves genome-wide studies [3]. The validation of any specific model of this category is usually open to debate especially in the cases including ncRNAs. To avoid such debates, here we use a generic model implying a random architecture of mutual protein-regulated regulation.

The reaction scheme under consideration includes synthesis and conventional degradation of ncRNA, n different mRNAs characterized by subscript i ($1 \leqslant i \leqslant n$), and their corresponding proteins (P_i),

$$\mathrm{Gene}_* \rightarrow \mathrm{Gene}_* + \mathrm{ncRNA}, \tag{1}$$

$$\mathrm{Gene}_i \rightarrow \mathrm{Gene}_i + \mathrm{mRNA}_i, \tag{2}$$

$$\mathrm{mRNA}_i \rightarrow \mathrm{mRNA}_i + \mathrm{P}_i, \tag{3}$$

$$\mathrm{ncRNA} \rightarrow \emptyset, \tag{4}$$

$$\mathrm{mRNA}_i \rightarrow \emptyset, \tag{5}$$

$$\mathrm{P}_i \rightarrow \emptyset. \tag{6}$$

In addition, ncRNA and mRNA can associate with subsequent degradation of the ncRNA-mRNA complex,

$$\mathrm{ncRNA} + \mathrm{mRNA}_i \rightarrow \mathrm{ncRNA} * \mathrm{mRNA}_i \rightarrow \emptyset. \tag{7}$$

Concerning the latter step, we note that typically ncRNA has many targets [28]. For this reason, we allow association of ncRNA with each mRNA.

The corresponding mean-field kinetic equations for the ncRNA, mRNA and protein populations, N_*, N_i, and n_i, in a cell are as follows

$$\frac{dN_*}{dt} = w_* - k_* N_* - \sum_i r_i N_* N_i, \tag{8}$$

$$\frac{dN_i}{dt} = w_i - k_i N_i - r_i N_* N_i, \tag{9}$$

$$\frac{dn_i}{dt} = \upsilon_i N_i - \kappa_i n_i, \tag{10}$$

where w_*, w_i, υ_i, k_*, k_i and κ_i are the rates or rate constants of the reactant synthesis and degradation, and r_i are the rate constants of step (7).

To mimic a distributed network, we should specify the protein-mediated regulation of the mRNA synthesis or, in other words, the dependence of the rates of the mRNA synthesis on the protein populations (the other parameters are taken to be constant). In our model, we assume that each gene transcribed into mRNA is governed by two other randomly chosen genes (including self-regulation) via association of the corresponding proteins to the regulatory sites. For simplicity, we consider that the regulatory sites operate independently (for more complex schemes of the regulation of transcription, see, e.g., recent articles [51–54], review [55] and references therein). Each of two proteins governing the transcription of a given gene is assumed to be able to associate with one or two sites. If there are two sites for each protein, the sites are considered to be equivalent. In particular, the mRNA synthesis rate is represented as

$$w_i = w_i^\circ + w_i^r F_{i1}(n_{i1}) F_{i2}(n_{i2}), \tag{11}$$

where w_i° is the so-called basal synthesis rate, w_i^r is the maximum value of the regulated rate, and $F_{i1}(n_{i1})$ and $F_{i2}(n_{i2})$ are the dimensionless functions ($\leqslant 1$) dependent on the populations of proteins (n_{i1} and n_{i2}) regulating a given gene. The former function is defined for positive regulation,

$$F_{i1}(n_{i1}) = \left[\frac{n_{i1}}{K_{i1} + n_{i1}}\right]^m, \tag{12}$$

and for negative regulation,

$$F_{i1}(n_{i1}) = \left[\frac{K_{i1}}{K_{i1} + n_{i1}}\right]^m, \tag{13}$$

where K_{i1} is the association constant, and m (1 or 2) is the number of regulatory sites for a given protein. $F_{i2}(n_{i2})$ is defined by analogy. Physically,

$$\frac{K_{i1}}{K_{i1} + n_{i1}}$$

and

$$\frac{n_{i1}}{K_{i1} + n_{i1}}$$

represent the probabilities that a regulatory site is free or occupied by a protein, respectively.

For example, let us consider that a gene has two regulatory sites for each regulatory protein, and the regulation by one protein is positive while the regulation by another protein is negative. In this case, the transcription rate is given by

$$w_i = w_i^\circ + \frac{w_i^r n_{i1}^2 K_{i2}^2}{(K_{i1} + n_{i1})^2 (K_{i2} + n_{i2})^2}. \tag{14}$$

In combination, steps (1)-(7) and Eqs. (8)-(13) define our model.

3. Details of calculations

To specify the model parameters, we take into account that mRNA and protein degradation usually occurs on the time scale of a few minutes or somewhat longer [56–58], and choose k_i and κ_i at random in the range between 0.05 and 0.15 min^{-1}. For ncRNA, by analogy, we employ $k_* = 0.1$ min^{-1}.

For mRNAs, the basal synthesis rates, w_i°, are selected at random in the range between 1 and 2 min^{-1}. The range of the rates w_i^r was slightly different in different sets of calculations (see Sec. 4 below). Basically, the latter rates were selected to have biologically reasonable mRNA populations.

For the protein synthesis, υ_i are chosen at random in the range between 0.1 and 0.3 min^{-1}. With these parameters, under steady state conditions, the protein population is about two times larger than the mRNA population. To describe association of proteins to the regulatory sites, K_{ij} are selected at random in the range between 100 and 200.

According to the theory of diffusion-limited reactions, the rate constants r_i should be about or lower than 3×10^{-3} min^{-1} [28]. Following this prescription, we choose r_i at random in the range between 0 and 10^{-3} min^{-1}.

The ncRNA synthesis rate, w_*, is used as a governing parameter.

Concerning the number of mRNAs, n, we recall that in cells the whole array of genes transcribed into mRNAs can be divided into many groups so that the protein-mediated interactions inside groups are intensive while the interactions between groups are apparently sporadic. Such groups often contain from 20 to 40 genes. The connectivity can only be appreciable, $m \geqslant 1$, inside these groups. Thus, n should be between 20 and 40. In our calculations

presented below, we use $n = 20$ (the variation of n from 10 to 40 does not add any new bright qualitative features).

For each run of calculations, we choose all the parameters. Then, Eqs. (8)-(10) are integrated (by using the conventional Runge-Kutta method) during relatively long sequential time intervals, Δt (typically, $\Delta t = 1000$ min). After each time interval, w_* is incremented by Δw_* (typically, $\Delta w_* = 1$-3 min^{-1}). The reactant populations obtained at the end of a time interval are used as data points and also as the initial conditions for the subsequent time interval (for the first time interval, we set $w_* = 0$ and define the initial conditions as described below). After reaching a desirable maximum value of w_* (typically, 100-300 min^{-1}), w_* is decremented after each integration interval by Δw_* down to $w_* = 0$. The duration of time intervals was proved to be sufficient in order to reach a steady state corresponding to chosen parameters (if this state exists). The reactant populations obtained in the end of time intervals are shown below as a function of w_*.

As already noted, each run of our calculations started with $w_* = 0$ and accordingly for the first time interval we used $N_*(0) = 0$ as the initial condition for ncRNA and various initial conditions for mRNAs and proteins. All the results presented below were obtained for

$$N_i(0) = \frac{w_i^\circ + w_i^r}{k_i}$$

and

$$n_i(0) = \frac{\upsilon_i N_i(0)}{\kappa_i}.$$

These values represent the maximum possible steady-state mRNA and protein populations. Alternatively, we used $N_i(0) = n_i(0) = 0$. The latter values obviously represent the minimum possible mRNA and protein populations. Typically, the dependence of the data points on w_* was the same for both these initial conditions. In all the examples below where this is not the case, this fact is explicitly noticed. In the case of a complex dependence of the reactant populations on w_*, we employed additional initial conditions, and as a rule this did not add any new features to the kinetics.

The specification above corresponds to the situation where the ncRNA synthesis rate, w_*, is used as a governing parameter. Our calculations are primarily focused on this case. For comparison, we have also analyzed the situation when there is no ncRNA. In the latter case, the maximum regulated rate of the synthesis of one of the mRNAs was employed as a governing parameter. For this mRNA, indicated by $i = 1$, k_1 was set at 0.1 min^{-1}, υ_1 was also set at 0.1 min^{-1}, and w_1^r was increased step by step from 0 to 300 min^{-1} and then decreased back in analogy with the procedure specified in the two paragraphs above. The other parameters were selected as described above.

In experiments, the governing parameter (e.g., w_* or w_1^r) can be systematically changed, for example, by employing external signals. Although our integration strategies mimic two possible scenarios of such changes, a detailed analysis of the response of a cell to signals is beyond the scope of this paper. In our calculations, the governing parameters are varied in order to show the specifics of the kinetics of gene transcription under steady-state conditions.

4. Results of calculations

4.1. With ncRNA

To illustrate the role of ncRNA in the kinetics under consideration, we show (Figs. 1-6) the average mRNA and protein populations,

$$\langle N_i \rangle = \sum_{i=1}^{n} \frac{N_i}{n} \quad \text{and} \quad \langle n_i \rangle = \sum_{i=1}^{n} \frac{n_i}{n},$$

and the ncRNA population, N_*, as a function of w_*. The main reason for the use of the average populations is technical. It allows us to reduce the number of figures (with the figures exhibiting specific populations, the article length would be far beyond the journal specification) and simultaneously to illustrate the complexity of the kinetics (note that bistability, oscillations and chaos are well manifested in this case).

In particular, Fig. 1 shows the typical kinetics in the situation when each of two proteins governing the transcription of a gene is able to associate with one site ($m = 1$) and all these feedbacks are positive. In this case, the kinetics are either bistable (about 60% of runs) or exhibit a single stable steady state (about 40% of runs).

If the association with one site is replaced in the example above by association with two sites ($m = 2$), all the kinetics are already bistable at $w_* = 0$ (Fig. 2). In this case, the results of the calculations depend on the initial conditions. If the initial conditions are chosen so that the system is in the low-active steady state at the beginning of a run, it remains in this state during a whole run (not shown).

If all the feedbacks are negative, the kinetics exhibit a single stable steady state with a monotonous dependence on the reactant populations on w_* (see Figs. 3 and 4 for $m = 1$ and 2, respectively).

Fig. 5 shows the kinetics in the situation where each of two proteins governing the transcription of a gene is able

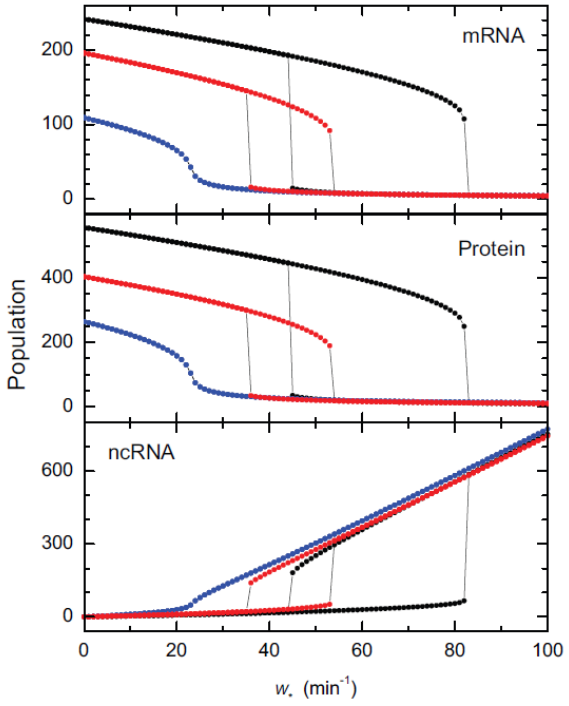

Figure 1. Three runs of the kinetics (two of them are bistable) in the case when each of two proteins governing the transcription of a gene is able to associate with one sites ($m = 1$) and all these feedbacks are positive. The rates w_i^r were chosen at random in the range between 20 and 50 min^{-1}. For the other parameters, see Sec. 3.

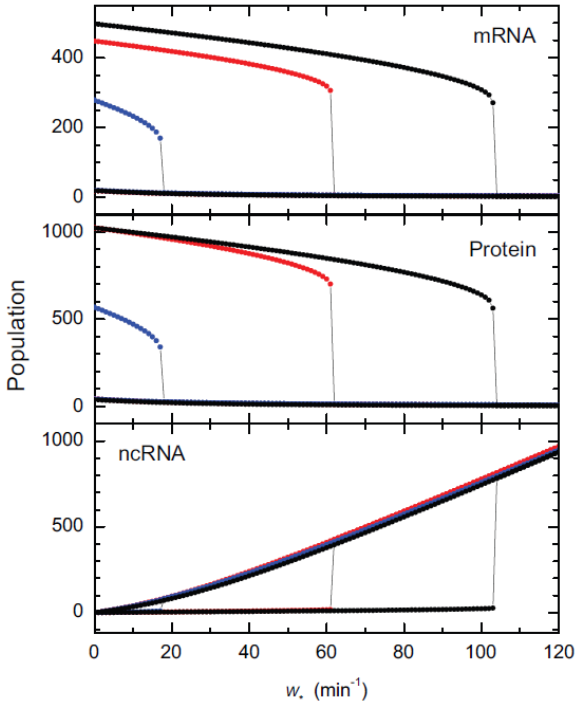

Figure 2. As Fig. 1 for $m = 2$ and w_i^r selected at random in the range between 50 and 100 min^{-1}.

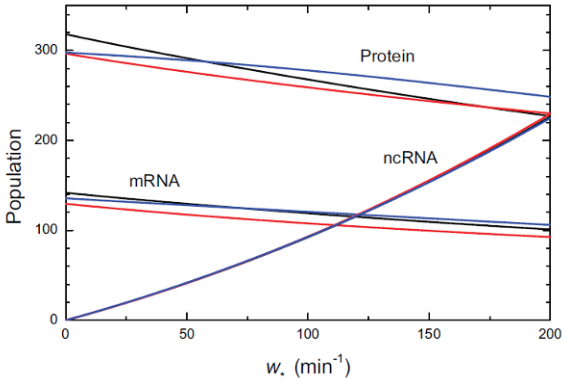

Figure 3. Three runs of the kinetics in the case when each of two proteins governing the transcription of a gene is able to associate with one sites ($m = 1$) and all these feedbacks are negative. The rates w_i^r were chosen at random in the range between 50 and 100 min^{-1}.

to associate with one site ($m = 1$) and each feedback is chosen to be either positive or negative at random with equal probabilities (0.5). In this case, the negative feedbacks dominate, and in analogy with Figs. 3 and 4 there is a single stable steady state.

Fig. 6 exhibits kinetics in the case when each of two proteins governing the transcription of a gene is able to associate with two sites ($m = 2$) and each feedback is either positive or negative with probability 0.5. In this case, the predictions of the model are much richer, and there are at least nine types (Fig. 6a-6i) of kinetics. About 60% of runs exhibit a single steady state with various types of the dependence of the reactant populations on w_* (Fig. 6a-6c). A smaller percentage (about 30%) of the kinetics show various bistable regimes (Fig. 6d-6g). The remaining kinetics (about 10%) are either oscillatory (Fig. 6h) or exhibit oscillations and bistability simultaneously (Fig. 6i). In principle, the kinetics shown in Figs. 6h, 6i could be chaotic. To identify the type of such kinetics, we scrutinized the corresponding runs more explicitly by tracking the dependence of the reactant population on time as, for example, shown in Fig. 7 (note that these and other kinetics were proved to remain invariable with decreasing the integration time step). With an increasing fraction of positive feedbacks, bistable and oscillatory kinetics are observed more often. If for example this fraction is 0.7, the corre-

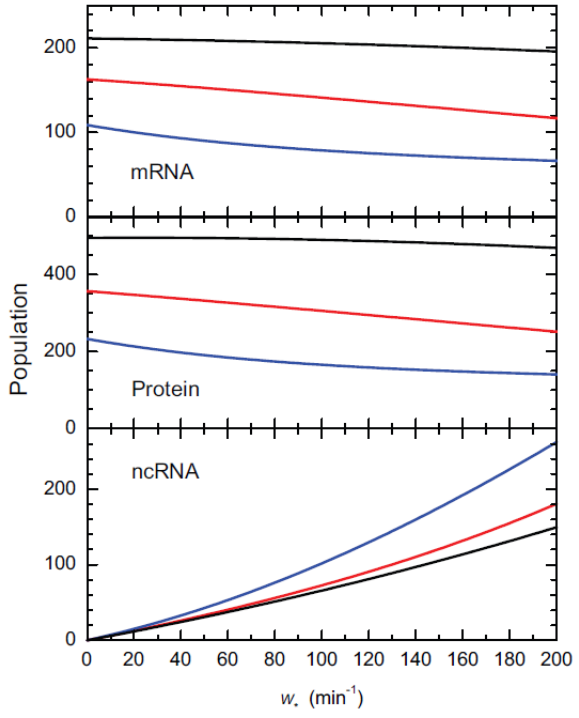

Figure 4. As Fig. 3 for $m = 2$ and w_i^r selected at random in the range between 100 and 200 min^{-1}.

sponding percentages of the kinetics are $\simeq$ 30, 35 and 35%.

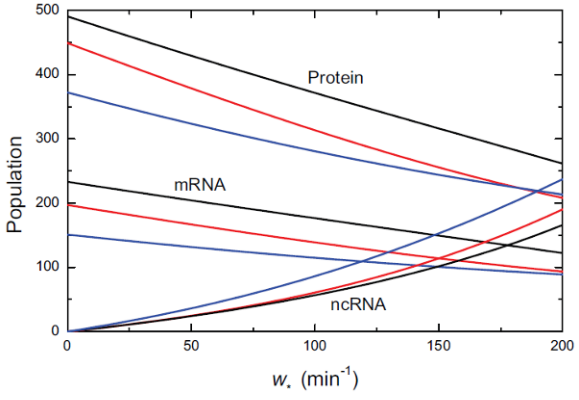

Figure 5. Three runs of the kinetics in the case when each of two proteins governing the transcription of a gene is able to associate with one sites ($m = 1$) and each feedback is either positive or negative with probability 0.5. The rates w_i^r were chosen at random in the range between 50 and 100 min^{-1}.

4.2. Without ncRNA

In the situation when there is no ncRNA, we have used w_1^r as a governing parameter. In this case, the kinetics are expected to be of the same type as those with ncRNA, i.e., one is expected to observe a unique steady state, bistability, and/or oscillations. In reality, there are, however, at least two qualitative distinctions.

First of all, one should bear in mind that in the distributed networks a change in the rate of transcription of one of the genes does not globally influence the network behaviour. For this reason, the variation of w_1^r for mRNA$_1$ results in minor changes in the average population of other mRNAs and proteins with $2 \leqslant i \leqslant n$ (see, e.g., Fig. 8). In contrast, ncRNA is a global regulator and the variation of w_* results in appreciable changes in the average population of mRNAs and proteins (Figs. 1-6).

The second and more subtle distinction is that without ncRNA we have observed either a stable steady state (e.g., about 90% of runs with $m = 2$; Fig. 8) or oscillations (about 10% of runs), while bistability was practically never observed. In contrast, the kinetics with ncRNA exhibit bistability (e.g., Fig. 6). This distinction is also related to the difference of the regulation of the network by ncRNA and mRNA. The variation of w_* globally influences many genes and bistability is usually manifested irrespective of its origin, while the variation of w_1^r effectively influences only a few specific genes and if the bistability originates from other genes it may remain hidden with a high probability.

5. Conclusion

We have shown the likely effect of ncRNA on genetic networks with the distributed architecture. Our main findings are as follows:

(i) Our results (e.g., Fig. 6) are indicative of richness of the kinetics of gene expression including ncRNAs especially compared to the networks with a hierarchial layered architecture [45]. Diverse kinetics are, however, observed only provided that the network connectivity is appreciable.

(ii) The main complex features of the kinetics under consideration are found to be bistability and oscillations. These features are obviously to be expected in nonlinear feedback systems. Our calculations, however, clarify how probable their observation is. If for example each of two proteins governing the transcription of a gene is able to associate with two sites ($m = 2$) and each feedback is either positive or negative with a probability of 0.5, our model predicts that about

60% of runs exhibit a single steady state, a smaller percentage (about 30%) of the kinetics show various bistable regimes, and the remaining kinetics (about 10%) are either oscillatory or exhibit oscillations and bistability simultaneously. Kinetics of the latter type are rare.

(iii) Referring to studies of random Boolean networks [59, 60], one might expect to find kinetic chaos as well. The latter feature, however, was not observed in our calculations. (Concerning this aspect, see also Ref. [61].)

(iv) Our calculations also explicitly show key distinctions between the regulation of the networks by ncRNA and mRNA.

All these findings help us to understand what may happen in distributed genetic networks.

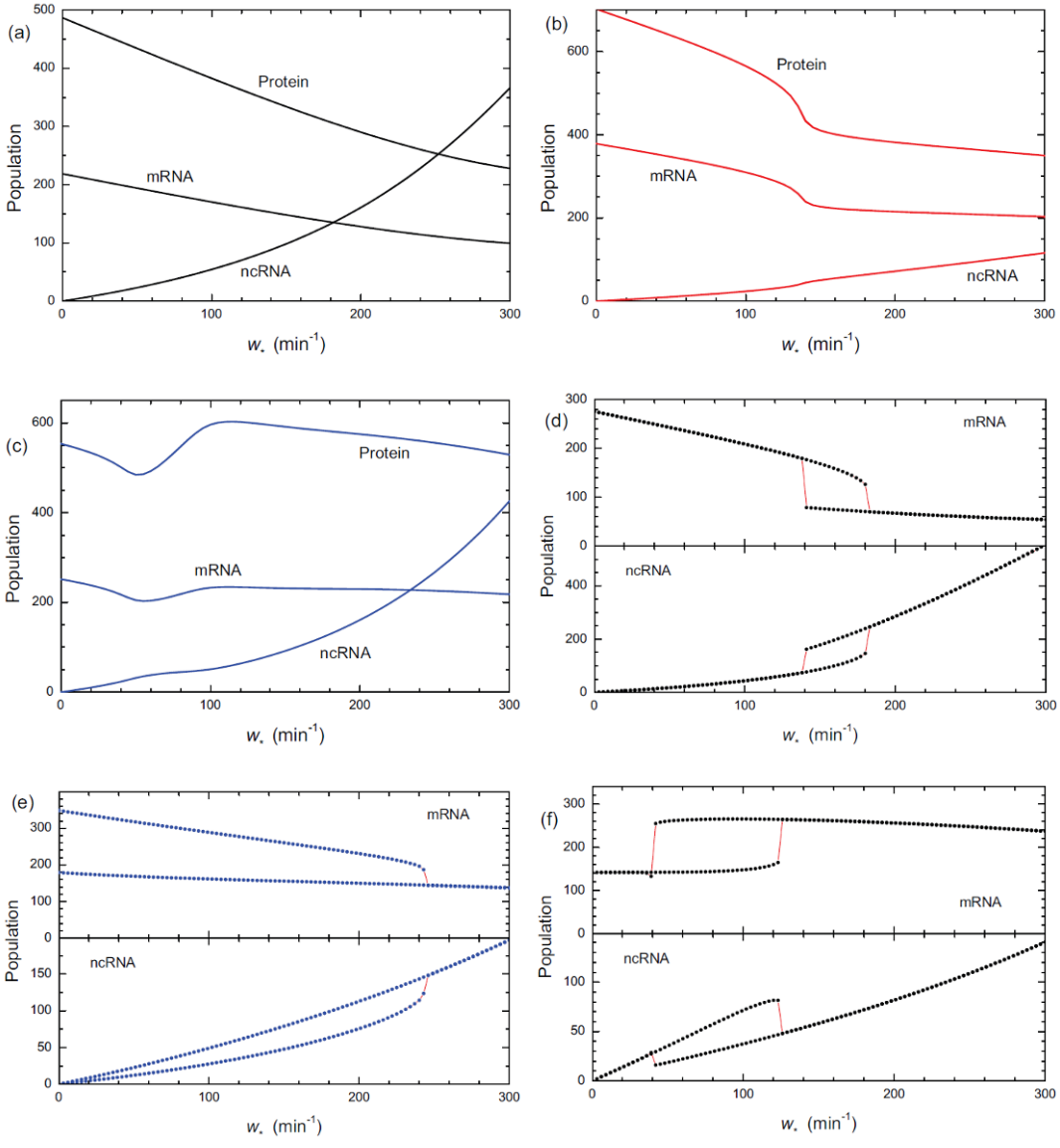

Figure 6. Continued on next page.

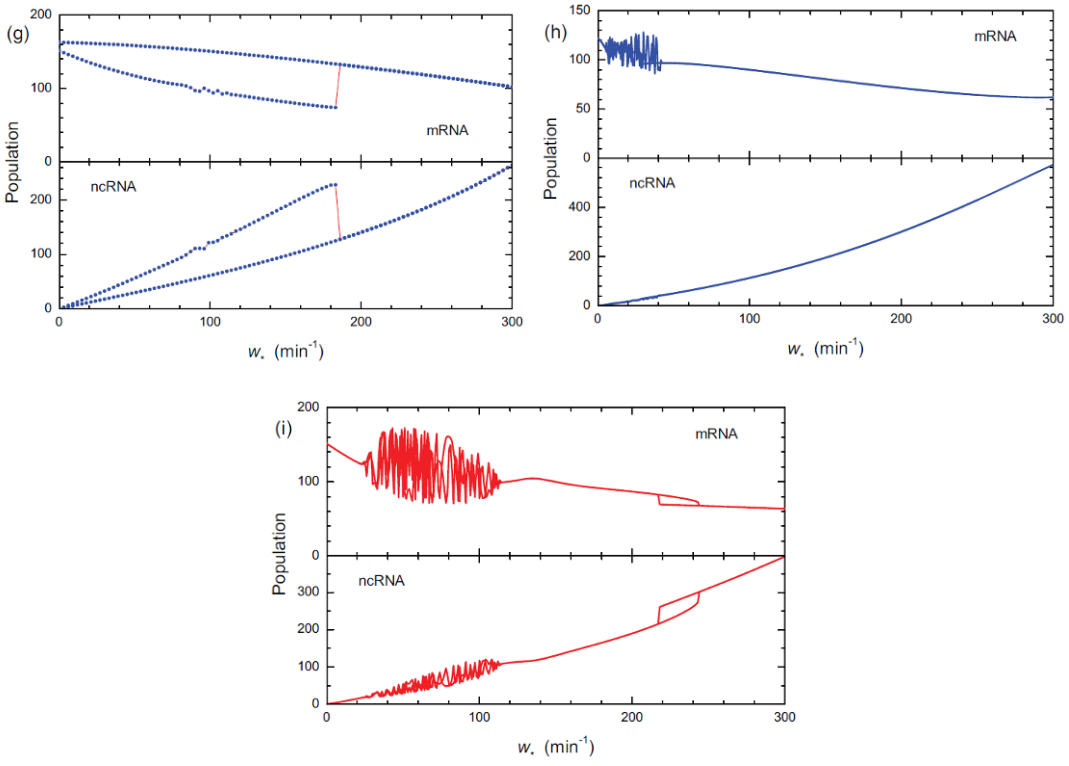

Figure 6. mRNA and ncRNA populations as a function of w_* during nine runs of the kinetics in the case when each of two proteins governing the transcription of a gene is able to associate with two sites ($m = 2$) and each feedback is either positive or negative with probability 0.5. The rates w_i^r were chosen at random in the range between 100 and 200 min^{-1}. Note that the bistable kinetics exhibited in panels (e) and (g) depend on the initial conditions in analogy with those shown in Fig. 2. In case (g), one can notice tiny irregular features at $w_* \simeq 100$ min^{-1}. These features correspond to stable oscillations with a very small amplitude (this was verified by tracking the temporal kinetics in detail). In addition, it is of interest to notice that in case (h) the oscillations in the mRNA populations are appreciable while the oscillations in the ncRNA populations are nearly negligible. This means that ncRNA serves in this case as a trigger for oscillations. [The protein population is not shown (except panels (a-c)), because its dependence on w_* is similar to that of mRNA.]

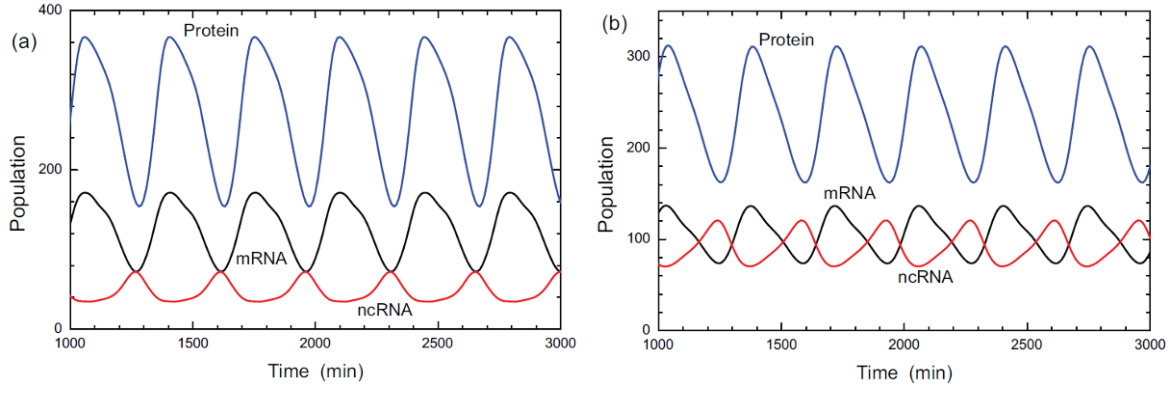

Figure 7. Examples of oscillatory kinetics [for $w_* = 60$ (a) and 100 min^{-1} (b)] corresponding to the diagram shown in Fig. 6i.

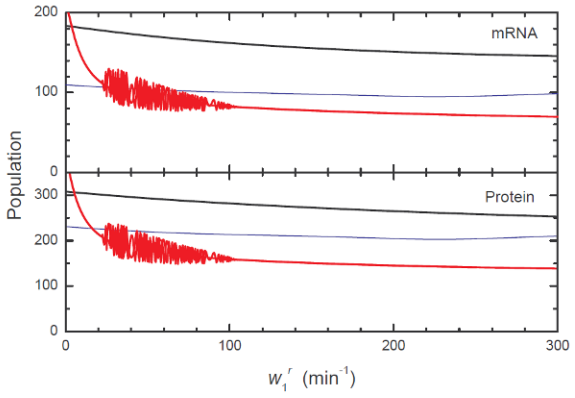

Figure 8. Average populations of mRNA and proteins with $2 \leqslant i \leqslant n$ as a function of w_1^r during three runs (one of them exhibits oscillations) of the kinetics without ncRNA. Each of two proteins governing the transcription of a gene is able to associate with two sites ($m = 2$) and each feedback is either positive or negative with probability 0.5. The rates w_i^r (with $i > 1$) were chosen at random in the range between 100 and 200 min^{-1}. For the other parameters, see the text.

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