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ncRNA-mediated bistability in the synthesis of hundreds of distinct mRNAs and proteins

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ABSTRACT

The kinetics of gene expression can be bistable due to the feedback between the mRNA and protein formation. In eukaryotic cells, the interplay between mRNAs and proteins can be influenced by non-coding RNAs. Some of these RNAs, e.g., microRNAs, may target hundreds of distinct mRNAs. The model presented here shows how a non-coding RNA can be used as a mediator in order to involve numerous mRNAs and proteins into a bistable network.

1. Introduction

Genetic networks represent one of the best and most important examples of complex networks. Theoretical studies in this field have long been focused on the mRNA and protein interplay (see reviews [1–5]). During the past decade, one of the key discoveries in molecular biology was finding that in eukaryotic cells, in parallel with the formation of mRNAs, gene transcription results in the formation of non-coding RNAs (ncRNAs) or, more specifically, microRNAs (this is one of the most important subclasses of ncRNAs) [6–8]. Such RNAs form a cornerstone of the regulatory network of signalling that operates in concert with the mRNA-protein network and regulates an appreciable part of human genes. The numerous biological functions of ncRNAs are based on their abilities to silence target genes. Specifically, an ncRNA pairs with a target mRNA and then either prevents translation or results in rapid degradation of the ncRNA–mRNA complex.

The identification of the rules of ncRNA target recognition is one the most fundamental challenges in ncRNA biology. For example, microRNAs often recognize their target mRNAs by base-pairing interactions between nucleotides 2–8 of the microRNA (the seed region) and complementary nucleotides in the 3′-untranslated region (3′-UTR) of mRNAs, and each microRNA has hundreds of targets [8]. This rule is widely used in computational algorithms aimed at predicting microRNA targets. However, evidence suggests that perfect seed pairing may not necessarily be a reliable predictor for microRNA interactions, which may explain why some predicted target sites are nonfunctional [8]. Hence, in general, the targets for microRNAs remain to be identified or verified experimentally.

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The understanding of the kinetics of gene expression involving ncRNAs is now limited. The available experimental studies tend to explore tissues, not individual cell types, and do not provide any kinetic information, because the gene expression is usually characterized by using averaged data for cell populations. Good recent examples of more detailed studies can be found e.g. in articles by Selbach et al. [9] and Baek et al. [10]. In the former study, the authors used a proteomic approach to measure changes in synthesis of several thousand proteins in response to transfection of five microRNAs (miR-1, miR-155, miR-16, miR-30a and let-7b) or knockdown of the expression of let-7b in human HeLa cells. In parallel, they quantified mRNA levels using microarrays. In the latter study, Baek et al. separately introduced miR-124, miR-1 and miR-181 into human HeLa cells or, in another set of experiments, deleted mir-223 in mouse neutrophils, and also scrutinized the responsive proteins. The results obtained in these studies show that although due to interaction with mRNAs a single microRNA can repress the production of hundreds of proteins, this repression is relatively mild (about 1.5–2 fold). In another recent study, Bethke et al. [11] show that the *Caenorhabditis elegans* nuclear receptor DAF-12 and its steroidal ligand directly activate promoters of *let-7* microRNA family members to down-regulate the microRNA target *hbl-1*, which drives progression of epidermal stem cells from second to third larval stage patterns of cell division. Their work explicitly identifies microRNAs as components of a hormone-coupled molecular switch that shuts off earlier developmental programs to allow for later ones.

The first kinetic models (see Refs. [12,13] and references therein), proposed recently to describe the interaction of ncRNA with mRNAs, are focused on these species and do not take feedback between the RNA and protein formation into account (note that the results obtained in Ref. [13] complement the experiments by Selbach et al. [9] and Baek et al. [10]). The models predicting bistability [14] and oscillations [15] are focused on the interaction of ncRNA with mRNA of one type. The bistable model [14] implies that the ncRNA synthesis can be suppressed by protein produced via translation of mRNA. This scenario has recently been extended to the case of distinct mRNAs [16]. In this work, we treat an alternative bistable scenario when the synthesis of one of mRNAs can be facilitated by protein produced via translation of this mRNA. Basically, this is a standard ingredient of numerous models describing simple mRNA-protein networks [1,2] (for complex networks, see Ref. [5]). In our model, we add ncRNA and hundreds of distinct mRNAs into this scheme. Our analysis clarifies the conditions when the bistability is possible in this case and may help to understand the function of the switches in gene expression regulated by ncRNAs. In addition, the results presented are of interest from the point of view of general theory of complex bistable systems.

2. Model

Our model includes synthesis of mRNAs of n types (R_i, $1 \le i \le n$),

$$\mathrm{Gene}_i \to \mathrm{Gene}_i + R_i. \tag{1}$$

mRNAs are translated into proteins which may in turn regulate the mRNA production. We analyze the simplest generic situation when only one gene (Gene_1) is positively regulated by protein (P) produced via translation of the corresponding mRNA,

$$R_1 \to R_1 + P. \tag{2}$$

In addition, we take the formation of ncRNA ($\mathcal{R}$) into account,

$$\mathrm{Gene}_* \to \mathrm{Gene}_* + \mathcal{R}. \tag{3}$$

The interaction between ncRNA and mRNAs is considered to occur via their association and degradation,

$$\mathcal{R} + R_i \to \mathcal{R} * R_i \to \emptyset. \tag{4}$$

All these species can also degrade via conventional channels,

$$R_i \to \emptyset, \qquad \mathcal{R} \to \emptyset, \qquad P \to \emptyset. \tag{5}$$

In our treatment, P is considered to facilitate the R_1 synthesis. Specifically, the R_1 formation is assumed to run much faster provided that m regulatory sites of Gene_1 are occupied by P. The P association with and dissociation from the gene are considered to be rapid so that these steps are at equilibrium.

With the specification above, the mean-field kinetic equations for the numbers of R_1, R_i ($2 \ge i \ge n$), P, and $\mathcal{R}$ copies in a cell are as follows

$$\frac{\mathrm{d}N_1}{\mathrm{d}t} = \kappa_b + \kappa_1 \left(\frac{N_P}{K + N_P}\right)^m - k_1 N_1 - r_1 N_1 N_*, \tag{6}$$

$$\frac{\mathrm{d}N_i}{\mathrm{d}t} = \kappa_i - k_i N_i - r_i N_i N_*, \tag{7}$$

$$\frac{\mathrm{d}N_P}{\mathrm{d}t} = \kappa_P N_1 - k_P N_P, \tag{8}$$

$$\frac{\mathrm{d}N_*}{\mathrm{d}t} = \kappa_* - k_* N_* - \sum_{i=1}^{n} r_i N_i N_*, \tag{9}$$