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On a stochastic gene expression with pre-mRNA, mRNA and protein contribution ☆

Ryszard Rudnicki [a], Andrzej Tomski [b,*]

[a] Institute of Mathematics, Polish Academy of Sciences, Bankowa 14, 40-007 Katowice, Poland
[b] Institute of Mathematics, Jagiellonian University, Łojasiewicza 6, 30-348 Kraków, Poland

HIGHLIGHTS

- We model stochastic gene expression with pre-mRNA, mRNA and protein contribution.
- This mechanism is mathematically based on Piece-wise Deterministic Markov Process.
- We show that if the initial distribution of the process has a density, then it stabilizes in time with some invariant density.
- We find a set on which the invariant density is supported.
- We investigate bistability state and the existence of limit cycle in the adiabatic limit.

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ABSTRACT

In this paper we develop a model of stochastic gene expression, which is an extension of the model investigated in the paper [T. Lipniacki, P. Paszek, A. Marciniak-Czochra, A.R. Brasier, M. Kimmel, Transcriptional stochasticity in gene expression, J. Theor. Biol. 238 (2006) 348–367]. In our model, stochastic effects still originate from random fluctuations in gene activity status, but we precede mRNA production by the formation of pre-mRNA, which enriches classical transcription phase. We obtain a stochastically regulated system of ordinary differential equations (ODEs) describing evolution of pre-mRNA, mRNA and protein levels. We perform mathematical analysis of a long-time behavior of this stochastic process, identified as a piece-wise deterministic Markov process (PDMP). We check exact results using numerical simulations for the distributions of all three types of particles. Moreover, we investigate the deterministic (adiabatic) limit state of the process, when depending on parameters it can exhibit two specific types of behavior: bistability and the existence of the limit cycle. The latter one is not present when only two kinds of gene expression products are considered.

1. Introduction

Gene expression and its regulation is a very complex process, which takes place in the cells of living organisms, especially in eukaryotes (Maniatis and Reed, 2002). It is widely known that this process depends on the behavior of crucial substances, called transcription factors (TFs) and chromatin architecture. Our investigation is based on the idea of Lipniacki et al. (2006), where a simplified diagram of gene expression was presented. It was mentioned there that genes fluctuate randomly between their activity or inactivity status and transcripts are produced in bursts. Stochastic effects at the initial stage are very strong compared to both the matter production and degradation processes, so we consider the noise of Markov-type origin merely at the activation stage. These claims were verified and analyzed through the years (Blake et al., 2003; Friedman et al., 2006; Kepler and Elston, 2001; Kim and Marioni, 2013; Pedraza and Paulsson, 2008). The whole scheme describes expression of a single gene, assuming it has n copies, but further analyze was performed in the case of one copy only. After activation of the gene (which is initiated by binding to the promoter region some of TFs), mRNA transcription and protein translation phases follow. At first, mature mRNA is produced in the nucleus, then it is transported from the nucleus to the cytoplasm, where the second phase takes place. As a result, new proteins are born.

In the mentioned class of models, not only transcription and translation evolution were considered, but also biological degradation of both types of the particles: mRNA and protein. All the processes were recognized as continuous, so the planar system of ordinary linear differential equations were used to represent the

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* Corresponding author.
E-mail addresses: ryszard.rudnicki@us.edu.pl (R. Rudnicki), andrzej.tomski@im.uj.edu.pl (A. Tomski).

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0022-5193/

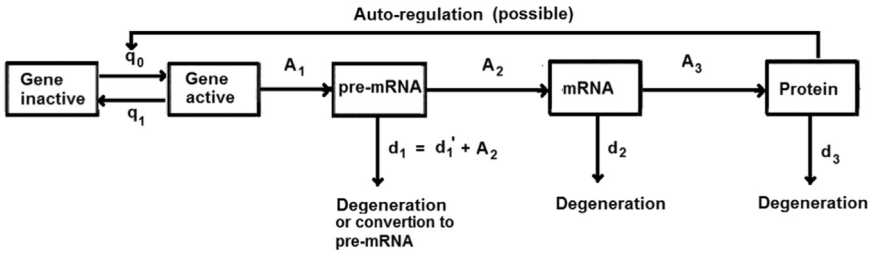

Fig. 1. An extended scheme of (auto-regulated) gene expression.

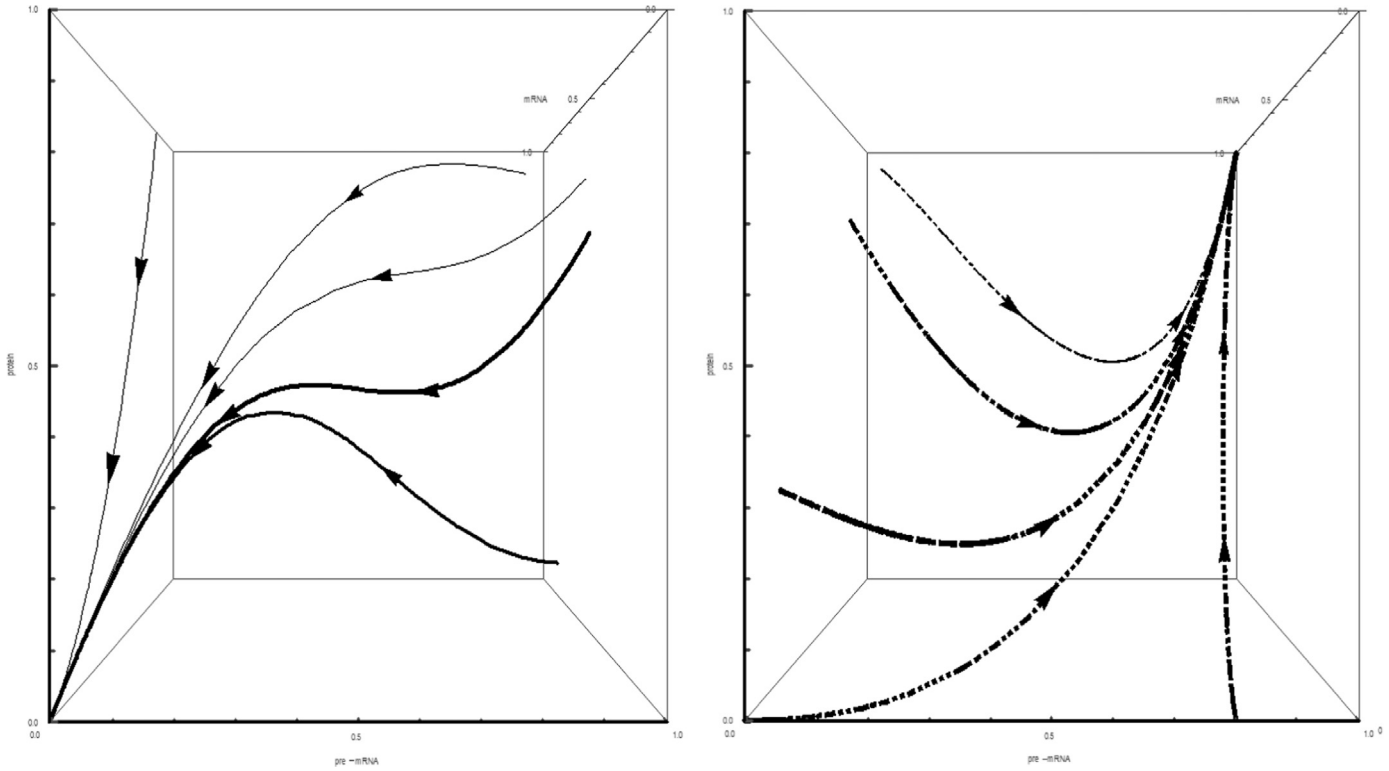

Fig. 2. A sample solutions of Eq. (4) for $a=2, b=3, i=0$ (left) and $a=2, b=3, i=1$ (right).

dynamics of fluctuations in the level of certain type particles. Moreover, first equation included stochastic "switch" component, being responsible for the control of gene activity status. This system has been identified in Bobrowski et al. (2007) as a Piece-wise Deterministic Markov Process (PDMP), introduced by Davis (1984). However, after reflection on these results, an important question arises: to what extent does the two-stage model fits the current state of biological knowledge? Would adding another stage make description of the gene expression more precise? Finally, will the problem be much more complicated if we add the third stage? In the mentioned work of Lipniacki et al. (2006) there is a remark that translated mRNA particle must get through some further processing before a new, mature protein is formed. Besides that, plenty of thematic books; Lodish et al. (2012), Watson et al. (2013) and publication sources; Cui et al. (2014), Yap and Makeyev (2013) claiming that at least one additional phase, called primary transcript (or pre-mRNA) processing should be taken into account. Actually, in eukaryotic genes, after the activation signal, the DNA code is transformed into pre-mRNA form of transcript. Then, the non-coding sequences (introns) of transcript are cut off. This action is combined with other modifications widely known as RNA processing. Only then we get a functional form of mRNA, which is transferred into the cytoplasm, where during the third phase, translation phase, mRNA is decoded into a protein. In short, we consider three-phase model of gene expression with three main components, i.e. three variables x_1, x_2, x_3 describing evolution of pre-mRNA, mRNA and protein levels. Firstly, we assume that pre-mRNA molecules are produced at the rate $A_1\gamma(t)$, where A_1 is a constant and we introduce a stochastic binary valued function $\gamma(t)\in\{0,1\}$ which marks, at time $t\geq 0$, if the gene is in active ($\gamma(t)=1$) or inactive ($\gamma(t)=0$) state. This function will be described in detail in Section 2.4. The mRNA production rate is equal to $A_2x_1(t)$, where A_2 is a constant and $x_1(t)$ denotes the number of pre-mRNA molecules at time t. Similarly, the protein translation takes the place at the rate $A_2x_1(t)$, where $x_2(t)$ denotes the number of mRNA molecules at time t. Moreover, all three types of particles undergo the degradation process. The total lost of pre-mRNA particles is given by $d_1x_1=d_1'x_1+A_2x_1$, where the constant d_1' is the degradation rate of pre-mRNA particles and another constant A_2 is the rate of converting pre-mRNA into mRNA particles. It means that $d_1=d_1'+A_2$ should be treated as the total degradation rate of pre-mRNA particles. This concept takes into consideration that pre-mRNA is converted to mRNA (Lipniacki et al., 2007), in contrast to mRNA which serves as a template for mRNA synthesis, but is not degraded during the synthesis. Thus, in other cases we use standard description, i.e. the constants d_2 and d_3 denote, respectively, mRNA and protein degradation rates. This expansion of the previous, simplified diagram of gene expression depicted in