*BIO*AUTOMATION, 2009, **13** (4), 127-134

Quasi-Stationary Approximation of a Dynamical Model of microRNA Target Regulation. Part I. Establishment of Time Hierarchy in the Model Dynamics

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Summary: The **Q**uasi-**S**teady-**S**tate **A**pproximation (QSSA) theorem is considered as a basic approach for reduction of dimensionality of a dynamical model of microRNA target regulation. On the basis of previously determined parameters, seven ordinary differential equations of the model are written in a form appropriate to evaluate their terms for further reduction. In accordance with the terminology of the QSSA theorem, it is established that five of the system components are *fast varying* such that the corresponding kinetic equations form an *attached* system. The other two variables are *slow varying* and their kinetic equations form a *degenerate* system.

Keywords: Ordinary differential equations, QSSA theorem, Reduction of dimensionality, MicroRNA target regulation

1. INTRODUCTION

Mature microRNAs (miRNA) are small (21-25 nucleotide) non-coding RNA molecules that influence messenger RNAs (mRNAs). They are estimated to comprise 1–5% of animal genes, making them one of the most abundant classes of regulators. Their widespread and important role in animals is highlighted by recent estimates that up to 30% of an organism's protein-coding genes are subject to miRNA-mediated control and is evidenced by their evolutionary conservation. MiRNAs play a central role in many biological processes, including developmental timing, cell proliferation, apoptosis, metabolism, cell differentiation, and morphogenesis. The mechanism by which miRNAs regulate gene expression is post-transcriptional, possibly influencing the stability, compartmentalization and translation of mRNAs. Most

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computational efforts to understand the post-transcriptional gene regulation by miRNAs have been focused on target prediction tools, as reviewed by Rajewsky [3], while quantitative kinetic modeling of gene regulation by miRNAs has still had a pioneer character. There are only some ODE-based models of gene regulation by miRNAs to this end [1, 2]. In this paper, firstly we modify a minimal ODE-based model for post-transcriptional gene regulation by miRNA, presented in [1]. Towards this end, we do scaling of the modified model mentioned above in order to derive its fast and slow variables in accordance with the QSSA theorem [4].

2. QSSQ THEOREM

In the common case, the mathematical modelling of biomolecular interactions with different time scales leads to dynamical system in the form:

$$\varepsilon \frac{d\vec{x}}{dt} = \vec{f}(\vec{x}, \vec{y}) \tag{2.1}$$

$$\frac{d\vec{y}}{dt} = \vec{g}(\vec{x}, \vec{y}) \tag{2.2}$$

where $\vec{x} \in R^m, \vec{y} \in R^n, 0 < \varepsilon << 1$. Furthermore, for such a system it is introduced the following terminology: The first part of equations, having ε in the numerator, is called *an attached system*, with respect to the other part of equations, which form a *degenerate system*. In this way, the variables of the attached system are called *fast variables* and these of the degenerate system are considered as *slow* ones. The set of both systems form *a complete system*. In accordance with this terminology, the Tichonov's theorem [4] claims that:

The solution of the complete system (2.1-2) tends to the solution of the degenerate system (2.2) at $\varepsilon \to 0$, *if the following conditions are satisfied:*

a) There is an isolated equilibrium (steady state) solution of the attached system (2.1) (i.e. there is not other solution in its neighbourhood).

b) The existing equilibrium solution of the attached system is stable one for every value of the slow variables $\vec{y}$.

c) The initial conditions (states) lie in a region of influence (a basin) of the equilibrium solution of the attached system.

d) The solutions of the complete and attached systems are single-valued and their right hand sides are continuous.

3. A MODIFIED DYNAMICAL MODEL OF miRNA MEDIATED TARGET REGULATION

It is predicted that each miRNA regulates numerous (sometimes hundreds) different types target messenger RNAs. Therefore, in some cases the miRNA itself is likely to become a limiting factor and the potential competing binding sites on target mRNAs need to be taken into account. In this paper, we modify a minimal mathematical model presented in [1] in the case of two targets $\{m_i\}_{i=1}^{N}$. According to Fig. 1 each type of mRNA is being produced with a transcription rate q_i and decays with rate δ_i. The miRNA itself is being produced in the cell with rate p_m and decays with rate δ_m. In addition, mRNA and miRNA (reversibly) make complexes, miRNA & mi, with a forward rate β_i and a reverse rate β_i^-. The complex miRNA & mi decays with rate δ_i^*. Proteins, $\{p_i\}_{i=1}^{N}$ degrade at rate δ_i^P and are being translated at a rate λ_i from free mRNAs, (mi), and with a rate λ_i^* from the complexes, miRNA & mi, which lead also to its decrease. MiRNA exerts its down-regulating effect on the targets by accelerating the degradation rate of the complexes or/and by slowing down the translation rate. The key parameters that are believed to influence the extent of miRNA-mediated target down-regulation, are the fold-changes in mRNA degradation rate δ_i^* / δ_i, and translation rate λ_i^* / λ_i, that depend on specific target mRNA and miRNA base-pairing in and around the seed region. In contrast to investigation made in [1], here we assume that the translation rate $\lambda_i^* / \lambda_i \leq 0{,}001$, i.e the translation rate of the proteins from the complexes miRNA & mRNAs is sufficiently slower than the translation rate from free mRNAs. MiRNA returns to the cytoplasm pool with the rate $q\sum_{i=1}^{N}\delta_i^*$ miRNA & mi, where q is the miRNA turnover rate. In this investigation we consider the case when q=1 in the model, i.e. here the degradation of the microRNA mRNA complex always results in the miRNA returning to the pool.

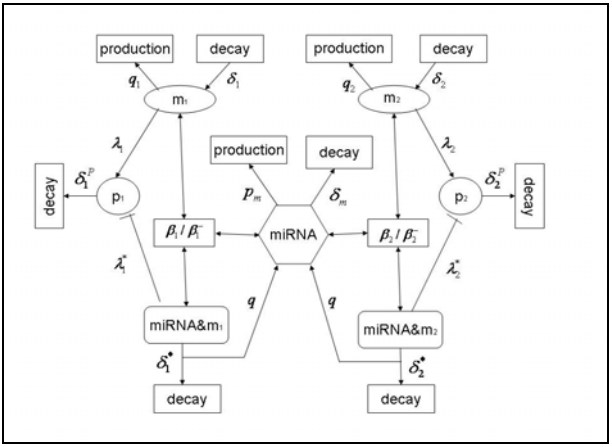

Fig. 1 Graphical representation of microRNA target regulation

According to Figure 1 for two targets, N = 2, the model takes the form:

$$
\begin{aligned}
\frac{dm_1}{dt} &= q_1 - \delta_1 m_1 - \beta_1 m_1(miRNA) + \beta_1^-(miRNA\&\, m_1)\\
\frac{dp_1}{dt} &= \lambda_1 m_1 - \delta_1^p p_1 - \lambda_1^*(miRNA\,\&\, m_1)\\
\frac{dm_2}{dt} &= q_2 - \delta_2 m_2 - \beta_2 m_2(miRNA) + \beta_2^-(miRNA\,\&\, m_2)\\
\frac{dp_2}{dt} &= \lambda_2 m_2 - \delta_2^p p_2 - \lambda_2^*(miRNA\&\, m_2)\\
\frac{d(miRNA)}{dt} &= p_m - \delta_m(miRNA) - \beta_1 m_1(miRNA) + \beta_1^-(miRNA\,\&\, m_1)\\
&\quad - \beta_2 m_2(miRNA) + \beta_2^-(miRNA\,\&\, m_2) +\\
&\quad + \delta_1^* q(miRNA\,\&\, m_1) + \delta_2^* q(miRNA\,\&\, m_2)\\
\frac{d(miRNA\&\, m_1)}{dt} &= \beta_1 m_1(miRNA) - \beta_1^-(miRNA\&\, m_1) - \delta_1^*(miRNA\&\, m_1)\\
\frac{d(miRNA\&\, m_2)}{dt} &= \beta_2 m_2(miRNA) - \beta_2^-(miRNA\&\, m_2) - \delta_2^*(miRNA\&\, m_2)
\end{aligned}
\qquad (3.1)
$$

where m_1 and m_2 are two different types of mRNA molecules, targets of *miRNA*, p_1 and p_2 are proteins, produced by m_1 and m_2, and *miRNA* & m_1 and *miRNA* & m_2 are complexes between *miRNA* and m_1 and m_2, respectively.

In [1] the effect of m_1^{total}, $(m_1^{total} = m_1 + (miRNA \& m_1))$ and p_1 levels are simulated as functions of transcription rate of the second target q_2, for three production rates for miRNA (p_m = 5, 10, 15). For the simulations made in [1] the following numerical values of coefficients of the original form of (3.1) are given:

$$\begin{aligned} &q_1 = 5; \delta_1 = \delta_2 = 1; \beta_1 = \beta_2 = 50; \beta_1^- = \beta_2^- = 0{,}1; \\ &\lambda_1 = \lambda_2 = 2; \delta_1^P = \delta_2^P = 1; \lambda_1^* = \lambda_2^* = 1; \delta_m = 1{,}1; \delta_1^* = \delta_2^* = 5; \end{aligned} \tag{3.2}$$

Taking into account the last numerical values of the coefficients numerical simulations of the system (3.1) at p_m = 5 show that there is complete coincidence between graphics of m_1 and m_2, p_1 and p_2, ($miRNA$ & m_1) and ($miRNA$ & m_2), respectively. This result supposes that difference between numerical values of the system coefficients, denoted by one and the same letters exists. In fact, from a biological point of view it is not possible the corresponding rate constants of two different mRNAs, the proteins, produced by them, and their complexes to have equal numerical values. By this reason we assume that the coefficients, denoted by one and the same letters have different numerical values but they are with one and the same order. According to data given in [1] and our assumptions the numerical values of coefficients of the system (3.1) are as it follows:

$$\begin{aligned} &q_1 = 5; \delta_1 = 1; \ \beta_1 = 50; \beta_1^- = 0{,}1; \lambda_1 = 10; \delta_1^P = 1; \\ &\lambda_1^* = 0.01; q_2 = 10; \delta_2 = 2; \beta_2 = 60; \beta_2^- = 0{,}5; \lambda_2 = 9; \\ &\delta_2^P = 0{,}8; \lambda_2^* = 0.02; \ p_m = 10; \delta_m = 1{,}1; \delta_1^* = 5; \delta_2^* = 6; \end{aligned} \tag{3.3}$$

On the basis of the last values numerical simulation of the model (3.1) is made. Dynamics of mRNAs, proteins, miRNA and miRNA&mRNAs is presented in Fig. 2.

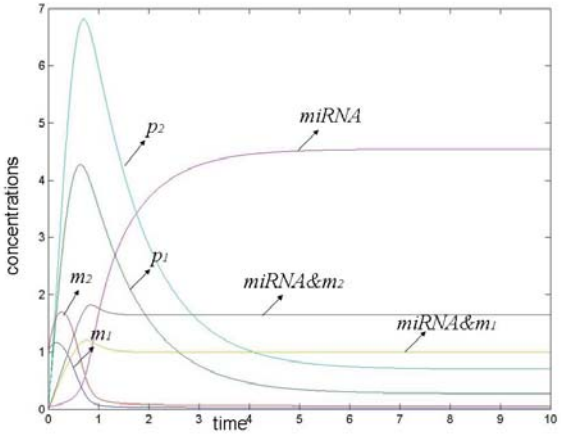

Fig. 2 Graphs of all components of the complete system solution

From Fig. 2, we select the values near the settled (steady state) ones in order to use them as characteristic values of state variables.

$$\begin{aligned} &m_1^0 = 0{,}0263;\ p_1^0 = 0.2731;\ m_2^0 = 0{,}0664;\ p_2^0 = 0.6972; \\ &miRNA^0 = 4{,}5454;\ (miRNA\ \&\ m_1)^0 = 0.9947; \\ &(miRNA\ \&\ m_2)^0 = 1{,}6445; \end{aligned} \tag{3.4}$$

The parameters and concentrations values presented above are given here without units in view of the fact that we do not intend to compare them. What is of interest for us further is to compare neither parameters (some of them having different units) nor concentrations, but the terms in the equations (3.1).

4. SCALING OF THE DYNAMICAL MODEL OF miRNA TARGET REGULATION

In accordance with the scaling procedure, each term in the right hand sides of the system equations mentioned must have an order of 1. For this purpose we introduce *scaling* substitutions for the model variables in the following manner:

$$m_1 = \varepsilon x_1; \quad p_1 = x_2; \quad m_2 = \varepsilon x_3; \quad p_2 = x_4; \quad miRNA = x_5 / \varepsilon; \\ (miRNA \& m_1) = x_6; \quad (miRNA \& m_2) = x_7 / \varepsilon; \tag{4.1}$$

where the small parameter ε = 0.1. Here the new variables x_i (i=1, 2,..., 7) are not dimensionless. Neverthelessp they have an order of 1 (i.e. they change in the interval between 0.1 and 1). The same approach is applied for scaling the model coefficients. The corresponding parameter substitutions have the following form:

$$q_1 = a_1 / \varepsilon; \delta_1 = a_2; \beta_1 = a_3 / \varepsilon^2; \beta_1^- = a_4; \lambda_1 = a_5 / \varepsilon; \\ \delta_1^P = a_6; \lambda_1^* = \varepsilon a_7; q_2 = a_8 / \varepsilon; \delta_2 = a_9; \beta_2 = a_{10} / \varepsilon^2; \\ \beta_2^- = a_{11}; \lambda_2 = a_{12} / \varepsilon; \delta_2^P = a_{13}; \lambda_2^* = \varepsilon a_{14}; p_m = a_{15} / \varepsilon; \\ \delta_m = a_{16}; \delta_1^* = a_{17} / \varepsilon; \delta_2^* = a_{18} / \varepsilon; \tag{4.2}$$

Here the new coefficients α_i (i = 1, 2,…, 18) have the same order, i.e. they chance from 0.1 to 1. After replacing the variable and parameter transformation forms (4.1, 4.2) in (3.1) we obtain the following system:

$$\varepsilon^3 \frac{dx_1}{dt} = \varepsilon a_1 - \varepsilon^3 a_2 x_1 - a_3 x_1 x_5 + \varepsilon^2 a_4 x_6 \tag{4.3}$$

$$\frac{dx_2}{dt} = a_5 x_1 - a_6 x_2 - \varepsilon a_7 x_6 \tag{4.4}$$

$$\varepsilon^3 \frac{dx_3}{dt} = \varepsilon a_8 - \varepsilon^3 a_9 x_3 - a_{10} x_3 x_5 + \varepsilon a_{11} x_7 \tag{4.5}$$

$$\frac{dx_4}{dt} = a_{12} x_3 - a_{13} x_4 - a_{14} x_7 \tag{4.6}$$

$$\varepsilon \frac{dx_5}{dt} = \varepsilon a_{15} - \varepsilon a_{16} x_5 - a_3 x_1 x_5 + \varepsilon^2 a_4 x_6 - \\ - a_{10} x_3 x_5 + \varepsilon a_{11} x_7 + \varepsilon a_{17} x_6 + a_{18} x_7 \tag{4.7}$$

$$\varepsilon^2 \frac{dx_6}{dt} = a_3 x_1 x_5 - \varepsilon^2 a_4 x_6 - \varepsilon a_{17} x_6 \tag{4.8}$$

$$\varepsilon \frac{dx_7}{dt} = a_{10} x_3 x_5 - \varepsilon a_{11} x_7 - a_{18} x_7 \tag{4.9}$$

The presence of a small parameter ε in a part of system equations determines its order. This means in accordance with the terminology

of QSSA theorem we can say that the five equations (4.3), (4.5), (4.7), (4.8) and (4.9) form an *attached* system, and the other two form a *degenerate* one. In the next part of this paper, we investigate some properties of the attached, degenerate and complete systems following from the QSSA theorem.

5. CONCLUSION

The main conclusion from the considerations made in this part of the paper is that time hierarchy exists in the modified by us dynamical model of miRNA target regulation. The separation of fast and slow system variables, made here is needed for further application of the QSSA theorem, presented in the next part of this article.

ACKNOWLEDGEMENTS

The authors thank DAAD -Bulgarian National Science Fund project DO 02-23/05.03.2009. E. Nikolova thanks ESF, OP "Human Resources Development", Grant BG051PO001/07/3.3-02-55/ 17.06.2008 for the financial support.

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