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Quasi-Stationary Approximation of a Dynamical Model of MicroRNA Target Regulation. Part II. Application of the QSSA Theorem

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Summary: The QSSA theorem is applied to the dynamical model of microRNA target regulation after special selection of model variables, presented in Part I of this article. On the basis of this theorem the complete model, represented as a system of seven nonlinear ordinary differential equations, is reduced to a degenerate one, comprising only two ordinary differential equations. As a result it is proved that the proteins, produced by miRNAs are identified to play a driving role of the dynamical behaviour of the genetic process investigated, but in post-initial (or quasi-stationary) stage.

Keywords: QSSA theorem, MicroRNA target regulation, Proteins, Post-initial state

1. INTRODUCTION

The term **Q**uasi-**S**teady-**S**tate **A**pproximation (QSSA) is a mathematical method, shortly introduced in Section 2 of this paper. We use it in a sense explained in the work of Schneider and Wilhelm [7]. The method find vast applications in many areas of systems biology, including studies related to cell proliferation, differentiation and the cell cycle [5]. A classical example of dimensionality reduction for nonlinear dynamic systems is the application to Michaelis–Menten type enzyme kinetics [4]. Examples of reversible enzyme catalytic reactions that are well described by reversible kinetic scheme can be found in the literature [1, 3, 8]. An application of QSSA to the reversible case is presented in the work of Tzafriri and Edelman [10]. There, a QSSA for the reversible Michaelis–Menten equation is derived and its validity domain is delineated. In fact, this work presents a more general approach to a QSSA, based on corresponding theorem proved in the work of Tichonov [9]. Our

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aim is to demonstrate that the last theorem in its original form can been also applied to the genetic processes, and especially to a dynamical model of microRNA (miRNA) target regulation. Some initial ideas of the present approach were introduced in the work of Petrov et al. [6].

2. APPLYING QSSA THEOREM TO A DYNAMICAL MODEL OF miRNA TARGET REGULATION

We consider the attached system of equations (4.3), (4.5), (4.7), (4.8) and (4.9), presented in the first part of this paper, under condition that only the variables x_1, x_3, x_5, x_6, x_7 are unknown function of time. The system has a stationary (steady state) solution in the form

$$x_1^0 = \frac{\varepsilon^2 a_1}{\alpha_1^E}; \quad x_3^0 = \frac{\varepsilon^2 a_8}{\alpha_2^E}; \quad x_5^0 = \frac{a_{15}}{a_{16}};$$
$$x_6^0 = \frac{\varepsilon a_1 a_3 a_{15}}{\alpha_1^E a_{16}(\varepsilon a_4 + a_{17})}; \quad x_7^0 = \frac{\varepsilon^2 a_8 a_{10} a_{15}}{\alpha_2^E a_{16}(\varepsilon a_{11} + a_{18})}; \tag{2.1}$$

where

$$\alpha_1^E = \varepsilon^3 a_2 + \frac{a_3 a_{15} a_{17}}{a_{16}(\varepsilon a_4 + a_{17})}; \quad \alpha_2^E = \varepsilon^3 a_9 + \frac{a_{10} a_{15} a_{18}}{a_{16}(\varepsilon a_{11} + a_{18})};$$

In order to analyze stability of the steady state (2.1) we introduce the substitutions

$$x_1 = x_1^0 + \xi_1; \quad x_3 = x_3^0 + \xi_2; \quad x_5 = x_5^0 + \xi_3;$$
$$x_6 = x_6^0 + \xi_4; \quad x_7 = x_7^0 + \xi_5; \tag{2.2}$$

in the attached system of equations (4.3), (4.5), (4.7), (4.8) and (4.9) from Part I. As a result the following variation equations are obtained:

$$\varepsilon^3 \frac{d\xi_1}{dt} = -\varepsilon^3 a_2 \xi_1 - a_3 x_5^0 \xi_1 - a_3 x_1^0 \xi_3 + \varepsilon^2 a_4 \xi_4 \tag{2.3}$$

$$\varepsilon^3 \frac{d\xi_2}{dt} = -\varepsilon^3 a_9 \xi_2 - a_{10} x_5^0 \xi_2 - a_{10} x_2^0 \xi_3 + \varepsilon a_{11} \xi_5 \tag{2.4}$$

$$\varepsilon \frac{d\xi_3}{dt} = -\varepsilon a_{16}\xi_3 - a_3 x_1^0 \xi_3 - a_3 x_5^0 \xi_1 + \varepsilon^2 a_4 \xi_4 \tag{2.5}$$
$$- a_{10} x_3^0 \xi_3 - a_{10} x_5^0 \xi_2 + \varepsilon a_{11}\xi_5 + \varepsilon a_{17}\xi_4 + a_{18}\xi_5$$

$$\varepsilon^2 \frac{d\xi_4}{dt} = a_3 x_5^0 \xi_1 + a_3 x_1^0 \xi_3 - \varepsilon^2 a_4 \xi_4 - \varepsilon a_{17}\xi_4 \tag{2.6}$$

$$\varepsilon \frac{d\xi_5}{dt} = a_{10} x_5^0 \xi_2 + a_{10} x_3^0 \xi_3 - \varepsilon a_{11}\xi_5 - a_{18}\xi_5 \tag{2.7}$$

In order to analyze stability of the last system the corresponding characteristic equation has been written in the following form:

$$\mu^5 + p_1\mu^4 + p_2\mu^3 + p_3\mu^2 + p_4\mu + p_5 = 0 \tag{2.8}$$

where

$$p_1 = \varepsilon^3(a_2 + a_9) + \varepsilon^2 a_4 + \varepsilon(a_{11} + a_{16} + a_{17}) +$$
$$+ a_3(x_1^0 + x_5^0) + a_{10}(x_3^0 + x_5^0) + a_{18}$$

$$p_2 = \varepsilon^6 a_2 a_9 + \varepsilon^3((\varepsilon^2 + 1)a_4 + \varepsilon a_{11} + \varepsilon a_{16} + \varepsilon a_{17} + a_{18} +$$
$$a_{10}x_5^0)(a_2 + a_9) + +\varepsilon^2(\varepsilon a_4 + a_{17})(a_{11} + a_{16}) +$$
$$+ \varepsilon^3 a_2(a_3 x_1^0 + a_{10}x_3^0) + a_3(\varepsilon^3 a_9 + \varepsilon a_{11} + a_{18})(x_1^0 + x_5^0) +$$
$$+ a_{10}(\varepsilon^2 a_4 + \varepsilon a_{17} + a_{18})(x_3^0 + x_5^0) + \varepsilon^2(a_{11}a_{16} + a_4 a_{18}) +$$
$$+ \varepsilon(a_{16} + a_{17})(a_{18} + +x_5^0(a_3 + a_{10})) + a_3 a_{10} x_5^0(x_1^0 + x_3^0)$$

$$p_3 = \varepsilon^8 a_2 a_4 a_9 + \varepsilon^5 a_9 a_{11}(\varepsilon^2 a_2 + a_{17}) +$$
$$+ \varepsilon^6 a_2 a_9(a_{18} + a_3 x_1^0 + a_{10}x_3^0) + \varepsilon^3(\varepsilon^3 a_{11}a_{16} +$$
$$+ \varepsilon^2 a_{16}a_{17} + \varepsilon^2 a_4 a_{18} + \varepsilon a_{10}a_{17}x_3^0 + \varepsilon a_{16}a_{18} +$$
$$\varepsilon a_3 a_{11}x_1^0 + a_3 a_{10}a_{18})(a_2 + a_9) + \varepsilon a_{10}(\varepsilon^4 a_2 a_4 + \tag{2.9}$$
$$+ a_3 a_{17}x_5^0)(x_3^0 + x_5^0) + \varepsilon x_5^0(\varepsilon^3(a_2 a_{10} + a_3 a_9) +$$
$$a_{18}(a_3 + a_{10}))(a_{16} + a_{17}) + \varepsilon^3 a_{11}a_{16}(\varepsilon a_4 + a_{17}) +$$
$$+ \varepsilon^2 a_{16}a_{17}(\varepsilon a_{11} + a_{18}) + \varepsilon^3 a_2 a_3 a_{10}x_5^0(x_1^0 + x_3^0) +$$
$$+ a_3(\varepsilon^2 a_{11}a_{17} + a_{10}a_{18}x_5^0)(x_1^0 + x_5^0) + \varepsilon^2 a_3 a_{16}x_5^0(a_{11} + a_{17})$$

$$p_4 = \varepsilon^5 a_9(\varepsilon^4 a_2 a_4 + \varepsilon^3 a_2 a_{17} + a_3 a_{17} x_5^0)(a_{11} + a_{16}) +$$
$$+ \varepsilon^8 a_2 a_9(a_4 a_{18} + a_{11} a_{16}) + +\varepsilon^5 a_{16}(\varepsilon^2 a_4 a_{11} +$$
$$+ \varepsilon a_4 a_{18} + \varepsilon a_{11} a_{17} + a_{17} a_{18})(a_2 + a_9) + +\varepsilon a_{18}(\varepsilon^6 a_2 a_9 +$$
$$+ x_5^0(\varepsilon^3 a_3 a_9 + \varepsilon^3 a_2 a_{10} + a_3 a_{10} x_5^0))(a_{16} + a_{17}) +$$
$$+ \varepsilon^4 a_9 a_{10} x_3^0(\varepsilon^4 a_2 a_4 + \varepsilon^3 a_2 a_{17} + a_3 a_{17}) +$$
$$+ \varepsilon^3 a_2 a_3 x_1^0(\varepsilon^4 a_9 a_{11} + \varepsilon^3 a_9 a_{18} + a_{10} a_{18} x_5^0) +$$
$$+ \varepsilon^5 a_2 a_4 a_{10} x_5^0(\varepsilon a_{16} + a_{18}) + \varepsilon^2 a_{10} a_{16} a_{17} x_5^0(\varepsilon^3 a_2 + a_{18}) +$$
$$+ \varepsilon^2 a_3 a_{16} a_{17} x_5^0(\varepsilon a_{11} + a_{10} x_5^0) + \varepsilon^2 a_{16} a_{17} x_5^0(\varepsilon a_4 a_{10} + a_3 a_{17})$$

$$p_5 = \varepsilon^2(\varepsilon a_{11} + a_{18})(\varepsilon^4 a_2 a_4 + \varepsilon^3 a_2 a_{17} +$$
$$= a_3 a_{17} x_5^0)(\varepsilon^3 a_9 a_{16} + a_{10} a_{16} a_{18} x_5^0)$$

It can be proved that the Routh-Hurwitz coefficients:

$$\mathbf{D}_1 = p_1; \quad \mathbf{D}_2 = \begin{vmatrix} p_1 & 1 \\ p_3 & p_2 \end{vmatrix}; \quad \mathbf{D}_3 = \begin{vmatrix} p_1 & 1 & 0 \\ p_3 & p_2 & p_1 \\ p_5 & p_4 & p_3 \end{vmatrix};$$
$$\mathbf{D}_4 = \begin{vmatrix} p_1 & 1 & 0 & 0 \\ p_3 & p_2 & p_1 & 0 \\ p_5 & p_4 & p_3 & p_2 \\ 0 & 0 & p_5 & p_4 \end{vmatrix}; \quad \mathbf{D}_5 = \begin{vmatrix} p_1 & 1 & 0 & 0 & 0 \\ p_3 & p_2 & p_1 & 0 & 0 \\ p_5 & p_4 & p_3 & p_2 & p_1 \\ 0 & 0 & 0 & p_4 & p_3 \\ 0 & 0 & 0 & 0 & p_5 \end{vmatrix} \tag{2.10}$$

will have positive signs. In this way according to the well-known Routh-Hurwitz theorem [2] the steady-state solution (2.1) will be stable, which allows us to apply the QSSA theorem. In accordance with this theorem we replace the formulas (2.1) in the equations (4.4) and (4.6) of the degenerate system presented in the previous part of this paper. As a result the system of two independent equations is derived:

$$\frac{dx_2}{dt} = -a_6 x_2 + \frac{\varepsilon^2 a_1}{\alpha_1^E}\left(a_5 - \frac{\varepsilon a_3 a_7 a_{15}}{a_{16}(\varepsilon a_4 + a_{17})}\right)$$
$$\frac{dx_4}{dt} = -a_{13} x_4 + \frac{\varepsilon^3 a_8}{\alpha_2^E}\left(a_{12} - \frac{\varepsilon a_{10} a_{14} a_{15}}{a_{16}(\varepsilon a_{11} + a_{18})}\right) \tag{2.11}$$

Further, we replace the substitutions (4.1-4.2) from Part I in (2.11). In this way an original form of the quasi-steady stationary approximation of the system (3.1) presented in Part I takes the form:

$$\frac{dp_1}{dt} = -\delta_1^p p_1 + \frac{q_1\delta_m(\beta_1^- + \delta_1^*)}{\delta_1\delta_m(\beta_1^- + \delta_1^*) + \delta_1^*\beta_1 p_m}\left[\lambda_1 - \frac{\lambda_1^*\beta_1 p_m}{\delta_m(\beta_1^- + \delta_1^*)}\right]$$
$$\frac{dp_2}{dt} = -\delta_2^p p_2 + \frac{q_2\delta_m(\beta_2^- + \delta_2^*)}{\delta_2\delta_m(\beta_2^- + \delta_2^*) + \delta_2^*\beta_2 p_m}\left[\lambda_2 - \frac{\lambda_2^*\beta_2 p_m}{\delta_m(\beta_2^- + \delta_2^*)}\right] \quad (2.12)$$

Finally the simulations of the complete and reduced systems are made. As it can see from Fig. 1 there is complete coincidence between both systems after third point from the beginning of the process.

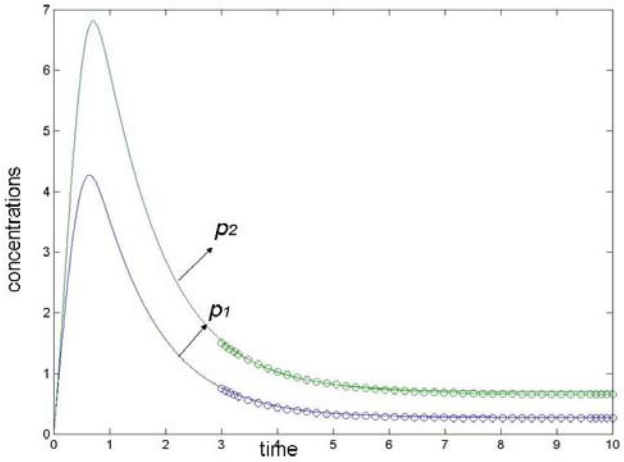

Fig. 1 Coincidence of the graphs of complete (--) and reduced (o) system variables

3. A NEW RELATIONSHIP IN THE DYNAMICAL MODEL OF miRNA TARGET REGULATION NEAR TO ITS QUASI-STATIONARY STATE

From the equations of the reduced system we can derive the following basic relationship: *The rates of protein production evidently will decrease with the increasing constant rate production*

p_m of miRNA, what is not explicitly apparent in the kinetic system of equations (3.1), presented in Part I. The above formulated relationship is apparently demonstrated in the next Fig. 2 and 3, where numerical simulations of protein dynamics are made at three different values of p_m.

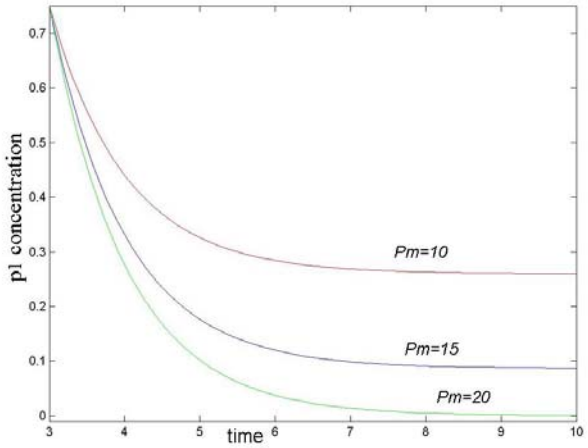

Fig. 2 The behaviour of p_1 at three different values of p_m

Fig. 2 and 3 show the rate of change of the concentrations of proteins p_1 and p_2, respectively at p_m = 10, 15, 20. It is evident that the protein concentrations essentially decrease with the increasing constant rate production p_m of miRNA, which confirms the theoretical conclusion made above. Moreover, as it can see from the Figure 2 at p_m = 20 the concentration of p_1 approaches zero values (about the 10^{-th} time unit after beginning of the process). The last fact supposes that at such a value the miRNA target regulation will be the most successful.

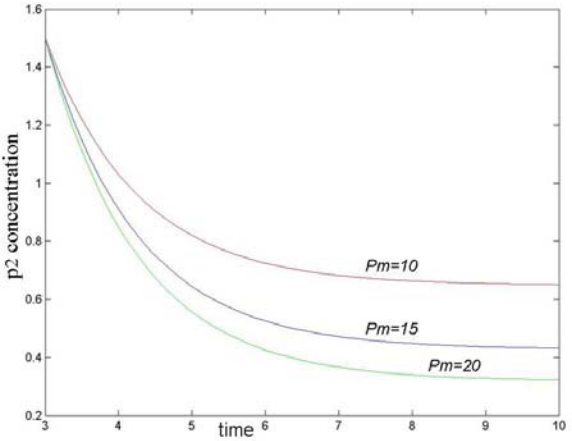

Fig. 3 The behaviour of p_2 at three different values of p_m

4. CONCLUSION

In this part of the paper, the QSSA theorem for quasi-stationary approximation is applied to the scaling dynamical model of miRNA target regulation, presented in Part I. As a result, the proteins produced by miRNAs are identified to play a driving role on the dynamical behaviour of the miRNA target regulation, but in post-initial (or quasi-stationary) stage as it was explained above. This driving role of protein synthesis, however, is parametrically controlled by the production rate of miRNAs in accordance with a basic relationship: the rates of protein synthesis evidently decrease with the increasing constant rate production p_m of miRNA.

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