EQUILIBRIA AND STABILITY OF ONE MESSENGER RNA AND TWO MICRO RNA DYNAMICS

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Keywords: ODE model, equilibria, stability, mRNA, microRNA
MSC2010: 34D23 37B25 37C10 37C70 37C75

In this paper we study an ODE model on the microRNA - mRNA dynamics. We prove the existence of two equilibrium points (one with strictly positive components) and obtain a biologically consistent, sufficient asymptotic stability condition for the strictly positive equilibrium.

1. Introduction

In the last decades there was an increased interest in the study of the mRNA-microRNA dynamics ([3], [1], [2],[10],[9], [11], [12]). In [13] we studied ODE models on microRNA - mRNA dynamics. Starting from the mathematical model proposed by Hauser and Zavolan ([7]), in this paper we analyze the dynamics of a one mRNA - two microRNA species. We obtain results on the nature of the equilibria and on stability - Theorems 2.1 and 3.1, respectively, as well as on the crosstalking between the two microRNA species through the mRNA.

Let the following system of differential equations

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= \alpha - \mu x - \beta\left(S - y_1 - y_2\right)x + (\nu_1 - \nu)y_1 + (\nu_2 - \nu)y_2 \\ \frac{\mathrm{d}y_1}{\mathrm{d}t} &= \beta\left(S - y_1 - y_2\right)x - \nu_1 y_1 \\ \frac{\mathrm{d}y_2}{\mathrm{d}t} &= \beta\left(S - y_1 - y_2\right)x - \nu_2 y_2 \end{aligned} \tag{1}$$

The coeficient α is the rate of transcription of the targeted mRNA, with concentrations x, while the coefficient β is the association rate to the corresponding microRNA species (having the concentrations y_1 and y_2). Furthermore, ν_i, $i = \overline{1,2}$ and μ stand for the elimination rates of the microRNAs and ν is the association rate between the

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mRNA and the microRNA species. Naturally, all coefficients are strictly positive, including S - the total amount of microRNA $y_1 + y_2 < S$. It is assumed that $\nu < \nu_1$, $\nu < \nu_2$.

2. Equilibria

By using the same technique as in our previous paper [13], one can show that the solutions of the associated Cauchy problem to (1) exist and are unique, they are bounded and the positive octant $\mathbf{R}^3_+$ is an invariant set.

We start by writing the corresponding algebraic equations defining the equilibria (x^*, y_1^*, y_2^*):

$$\begin{aligned} \alpha - \mu x - \beta\,(S - y_1 - y_2)\,x + (\nu_1 - \nu)y_1 + (\nu_2 - \nu)y_2 &= 0 \\ \beta\,(S - y_1 - y_2)\,x - \nu_1 y_1 &= 0 \\ \beta\,(S - y_1 - y_2)\,x - \nu_2 y_2 &= 0 \end{aligned} \tag{2}$$

From the last two equations in (2) one gets

$$\begin{aligned} y_1^* &= \frac{\beta S \nu 2}{\beta x^*(\nu_1 + \nu_2) + \nu_1\nu_2}\,x^* \\ y_2^* &= \frac{\beta S \nu 1}{\beta x^*(\nu_1 + \nu_2) + \nu_1\nu_2}\,x^* \end{aligned}$$

By replacing now y_1^* and y_2^* in the first equation of (2), the following quadratic equation in x emerges:

$$\mu\beta(\nu_1 + \nu_2)x^2 - [\alpha\beta(\nu_1 + \nu_2) + \beta S(\nu_1\nu_2 - \nu(\nu_1 + \nu_2)) - \mu\nu_1\nu_2]\;x - \alpha\nu_1\nu_2 = 0 \tag{3}$$

This quadratic equation has always two real solutions, one positive and one negative; hence we obtained the following result.

Theorem 2.1. *For every set of strictly positive coeficients α, β, μ, ν, ν_1, ν_2 and S, the system (1) has two equilibrium points, one of them (x^*, y^*, y^*) with strictly positive components.*

Remark 2.1.

(1) *Dividing equation (2) by $\nu_1\nu_2$ and by denoting*

$$\frac{1}{\nu_1} + \frac{1}{\nu_2} = \gamma,$$

the quadratic equation becomes

$$\mu\beta\gamma x^2 - [\alpha\beta\gamma + \beta S(1 - \nu\gamma) - \mu]\;x - \alpha = 0. \tag{4}$$

(2) *It is easy to see that*

$$\nu_1 y_1^* = \nu_2 y_2^*.$$

3. **Stability**

Our main purpose is to investigate the stability properties of the equilibrium point with strictly positive components, since it is the relevant one from the biological perspective. Denote it by (x^*, y_1^*, y_2^*) - as in Theorem 2.1.

The natural approach is to calculate the Jacobian matrix associated to the vector field defining (1) at the equilibrium point (x^*, y^*, y^*) and then to check whether all its three eigenvalues lie in the open complex left half-plane.

In accordance with the equations of system (1), one can easily deduce that

$$J(x,y_1,y_2) = \begin{bmatrix} -\mu-\beta(S-y_1-y_2) & \beta x+\nu_1-\nu & \beta x+\nu_2-\nu \\ \beta(S-y_1-y_2) & -\beta x-\nu_1 & -\beta x \\ \beta(S-y_1-y_2) & -\beta x & -\beta x-\nu_2. \end{bmatrix} \tag{5}$$

Let $A := S - y_1 - y_2 > 0$. The characteristic polynomial of J is calculated as

$$\det(sI_3 - J) = \begin{vmatrix} s+\mu+\beta A & -\beta x-\nu_1+\nu & -\beta x-\nu_2+\nu \\ -\beta A & s+\beta x+\nu_1 & \beta x \\ -\beta A & \beta x & s+\beta x+\nu_2 \end{vmatrix}$$

$$= (s+\mu+\beta A)\left[s^2+(2\beta x+\nu_1+\nu_2)s+(\beta x+\nu_1)(\beta x+\nu_2)-\beta^2x^2\right]+$$
$$-\beta A\left[(-\beta x-\nu_2+\nu)(-\nu_1)+(-\beta x-\nu_1+\nu)(-\nu_2)+(2\beta x-2\nu+\nu_1+\nu_2)s\right]$$
$$= s^3+(\mu+\beta A+2\beta x+\nu_1+\nu_2)s^2+$$
$$\left[\nu_1\nu_2+(\nu_1+\nu_2)(\beta x+\mu)+2\beta\mu x+2\beta A\nu\right]s+(\mu-\beta A)\nu_1\nu_2+(\nu_1+\nu_2)(\mu\beta x+\beta A\nu)$$
$$\overset{not}{=} p(s) = s^3+as^2+bs+c. \tag{6}$$

Applying the Hurwitz criterion to the third order polynomial above (6), one immediately deduces the necessary and sufficient conditions for $p(s)$ having all three roots in the open complex left half-plane: $a > 0$, $b > 0$, $c > 0$ and $ab - c > 0$. The first two inequalities are clearly satisfied since all coefficients (but also A) are strictly positive for all positive values of x, y_1, y_2. The last inequality follows based on the same assumptions after simple, straightforward calculations.

Checking the positivity of c requires a slightly more involved argument. Dividing the inequality $c > 0$ by $\nu_1\nu_2 > 0$ and multiplying it by $x^* > 0$ one gets

$$(\mu-\beta A+\gamma\beta A\nu)x^*+\gamma\beta\mu(x^*)^2 > 0$$

By replacing now $(x^*)^2$ from (4), the above inequality becomes

$$\left[\mu-\beta A(1-\gamma\nu)\right]x^*+\left[\alpha\beta\gamma+\beta S(1-\nu\gamma)-\mu\right]x^*+\alpha > 0 \tag{7}$$

or, equivalently,

$$\left[\alpha\gamma+(S-A)(1-\nu\gamma)\right]\beta x^*+\alpha > 0 \tag{8}$$

Obviously, $S - A > 0$ and with the condition $\nu\gamma < 1$ the last inequality is verified. According to the data in [7], this last condition $\nu(\nu_1+\nu_2) < \nu_1\nu_2$ is biologically consistent. Thus the following results holds:

Theorem 3.1. *For every set of strictly positive coeficients α, β, μ, ν, ν_1, ν_2 and S, such that $\nu(\nu_1 + \nu_2) < \nu_1\nu_2$, the system (1) has an asymptotically stable equilibrium point (x^*, y^*, y^*) in $\mathbf{R}^3_+$.*

4. Numerical examples. Conclusions.

We choose the following set of values for the system coefficients: $\alpha = 8$, $\beta = 3$, $\nu_1 = 4.64$, $\nu_2 = 60.58$, $\nu = 0.32$, $\mu = 1$ and $S = 30$, within the range of values indicated by [7].

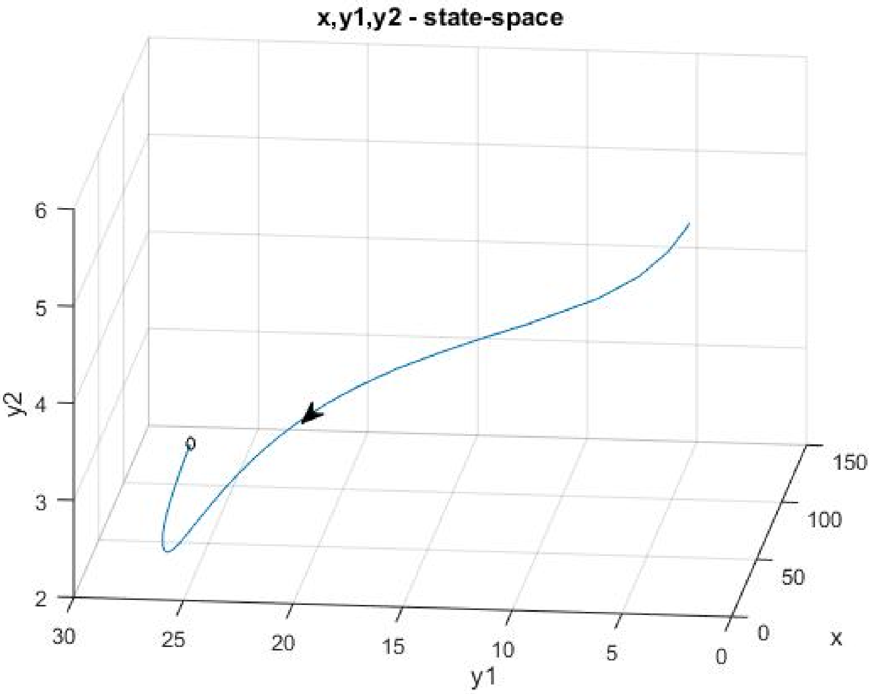

FIGURE 1. Typical dynamics in state-space

Solving the polynomial equation (4), one can easily compute the equilibrium point values: $x^* = 126.35$, $y_1^* = 27.55$, $y_2^* = 2.11$. These are consistent with steady-state values observed in the simulation results on a sufficiently long time horizon (Figure 2).

Thus, we conclude that for any set of strictly positive coefficients, system (1) has a biologically consistent equilibrium point - a relevant fact in the analysis of the cross-talking modeling in a micro-RNA target network.

Please also note (see Figure 3) that the total amount of the two microRNA species, $y_1 + y_2$, remains always bounded by S. In other words, $A = S - y_1 - y_2 > 0$ for every y_1, y_2 on on a given trajectory.

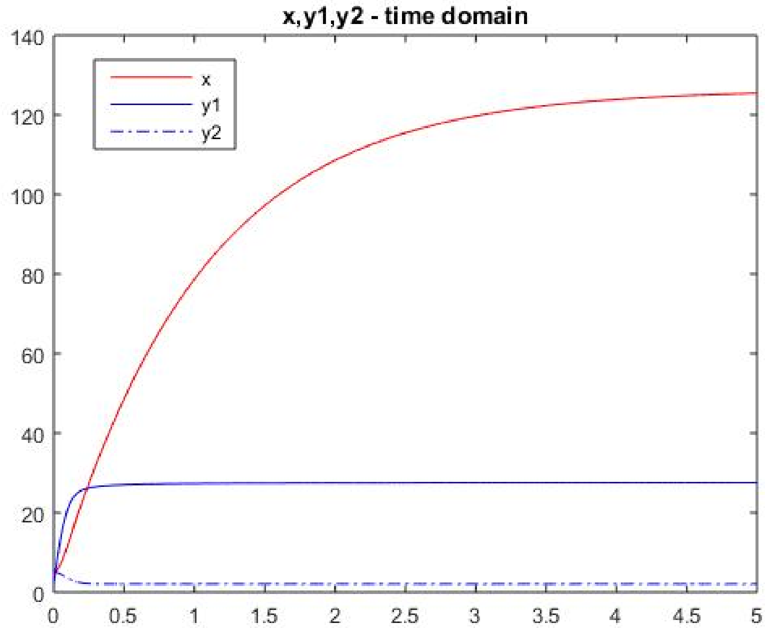

FIGURE 2. Time-domain: shorter settling times for y_1 and y_2

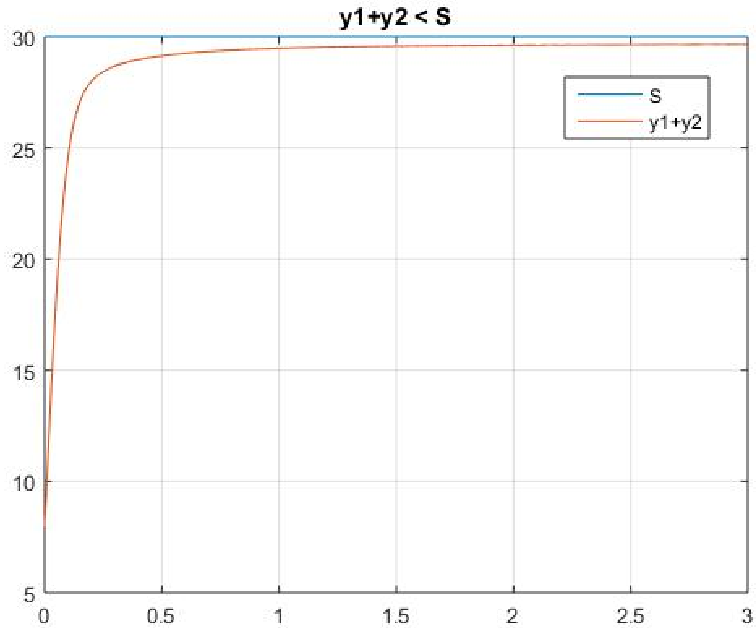

FIGURE 3. Limitation of $y_1 + y_2$

An interesting open problem, which will be addressed in the future, is to prove that the (unique) biologically relevant equilibrium is a global attractor for the positive octant $\mathbf{R}^3_+$. This can be done in a similar manner as in [4]. Alternatively, the stability sufficient condition might be relaxed by employing the LMI approach used in [12].

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