A NOTE ON A ODE MODEL OF MICRO RNA - DEPENDENT REGULATION OF MESSENGER RNA LEVELS

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We study the qualitative behavior (invariance, boundedness and equilibria) of the solutions of a mathematical model describing the dynamics of microRNA AGO complexes and mRNA targets interaction.

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1. Introduction

Consider the following system of differential equations [8]

$$\begin{aligned} \frac{\mathrm{d}x_1}{\mathrm{d}t} &= \alpha_1 - \mu x_1 - \beta\,(S - y_1 - y_2)\,x_1 + \rho_1 y_1 \\ \frac{\mathrm{d}y_1}{\mathrm{d}t} &= \beta\,(S - y_1 - y_2)\,x_1 - \nu_1 y_1 \\ \frac{\mathrm{d}x_2}{\mathrm{d}t} &= \alpha_2 - \mu x_2 - \beta\,(S - y_1 - y_2)\,x_2 + \rho_2 y_2 \\ \frac{\mathrm{d}y_2}{\mathrm{d}t} &= \beta\,(S - y_1 - y_2)\,x_2 - \nu_2 y_2 \end{aligned} \tag{1}$$

where all coeficients are strictly positive. Here α_1, α_2 are the rates of transcription of two distinct species of targeted mRNA, with concentrations x_1 and x_2, respectively; β represents the association rate to the corresponding microRNA-loaded AGO species (having the concentrations y_1 and y_2), while ρ_1, ρ_2 stand for the dissociation rates from the loaded microRNA. S is the total amount of miRNA-loaded AGO and $y_1 + y_2 < S$. Finally, ν_i, $i = \overline{1,2}$ and μ are the elimination rates of the RNAs.

We have adapted the notation from [8], where a brief description of the above mathematical model has been done. Other similar ODE models for mRNA - microRNA interaction have been studied in the literature (see [10], [4], [1], [5], [11], [3]). The case with two messengers and two microRNA species seems to have gained a lot of interest when studying the interaction mechanisms.

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In the sequel, we will analyze the behavior of the system (1) under several assumptions on its coefficients (see [8]). To be more specific, we suppose that

$$\rho_2 \geq \rho_1, \ \ \nu_i - \rho_i = \nu, \ i = \overline{1,2}.$$

2. **Qualitative behavior**

Our goals are: the boundedness of the solutions, the invariance of the positive octant and equilibria.

Remark 2.1. *The above system of differential equations is defined by a polynomial vector field, hence the existence and uniqueness theorem applies to the Cauchy problem associated with (1).*

By using a similar technique as in [6], it can be shown that the positive octant $\mathbb{R}^4_+$ is a positively invariant set for the system.

Proposition 2.1. *The positive octant* $\mathbb{R}^4_+ = (0,\infty)^4$ *is a positively invariant set for the system (1).*

Proof. The proof makes direct use of the following result, contained in Proposition 4.3 in [6]:
Consider the system

$$\dot{c}_k = -a_k(t)c_k + b_k(t), \ \ k = \overline{1,n}. \tag{2}$$

where $a_k(t)$, $b_k(t)$ *are continuous, positive functions on the maximal existence interval for the solutions of (2). Then for any* k *either* $c_k(t) > 0$ *or* $c_k(t) \equiv 0$ *on the whole definition set of the solution.*

To be more specific, rewrite the system (1) as

$$\begin{aligned}
\frac{\mathrm{d}x_1}{\mathrm{d}t} &= -\left(\mu + \beta\left(S - y_1 - y_2\right)\right)x_1 + \alpha_1 + \rho_1 y_1 \\
\frac{\mathrm{d}y_1}{\mathrm{d}t} &= -\left(\beta x_1 + \nu_1\right)y_1 + \beta\left(S - y_2\right)x_1 \\
\frac{\mathrm{d}x_2}{\mathrm{d}t} &= -\left(\mu + \beta\left(S - y_1 - y_2\right)\right)x_2 + \alpha_2 + \rho_2 y_2 \\
\frac{\mathrm{d}y_2}{\mathrm{d}t} &= -\left(\beta x_2 + \nu_2\right)y_2 + \beta\left(S - y_1\right)x_2
\end{aligned}$$

from where, under the obvious notation $c_1 = x_1$, $c_2 = y_1$, $c_3 = x_2$, $c_4 = y_2$ one gets

$$\frac{\mathrm{d}c_k}{\mathrm{d}t} = -a_k(t)c_k + b_k(t), \ \ \ k = 1,2,3, \tag{3}$$

with $a_k(t)$ and $b_k(t)$ taking positive values. Now, one immediately deduces that relation (4.2.4) in [6] holds and the proof follows now straightforward by invoking the result cited at the beginning of the proof. □

Throughout the rest of the paper, by "solution" of the ODE (1) we understand "positive solution".

Proposition 2.2. *The solutions of the ODE model (1) are bounded and can be extended to the real line.*

Proof. The method is based on [7] (Section 4, Chapter 3) and uses a similar technique to that in [5]. By adding the first two equations in (1) we get

$$\frac{\mathrm{d}(x_1+y_1)}{\mathrm{d}t} \leq \alpha_1 - M(x_1+y_1),$$

where $M = \max\{\mu, \nu\}$. Hence $x_1 + y_1$ is bounded. From the addition of the first three equations in (1), one deduces the boundedness of $x_1 + y_1 + x_2$. Thus x_2 is bounded and the rest of the argument goes on in the same manner. □

Equilibria

We are looking for equilibrium points in the positive octant $\mathbf{R}_+^4$. Let us write the corresponding algebraic equations defining the equilibrium points of the system:

$$\begin{aligned} 0 &= \alpha_1 - \mu x_1 - \beta\,(S - y_1 - y_2)\,x_1 + \rho_1 y_1 \\ 0 &= \beta\,(S - y_1 - y_2)\,x_1 - \nu_1 y_1 \\ 0 &= \alpha_2 - \mu x_2 - \beta\,(S - y_1 - y_2)\,x_2 + \rho_2 y_2 \\ 0 &= \beta\,(S - y_1 - y_2)\,x_2 - \nu_2 y_2 \end{aligned} \tag{4}$$

The following result holds.

Theorem 2.1. *For every positive set of parameters α_i, ρ_i, ν_i, $i = \overline{1,2}$, β, μ and S, the system (4) has at least one and at most three solutions $(x_1^*, y_1^*, x_2^*, y_2^*)$ in $\mathbf{R}_+^4$.*

Proof. By adding the first two and the last two equations in (4), one gets

$$\begin{aligned} 0 &= \alpha_1 - \mu x_1 - \nu y_1 \\ 0 &= \alpha_2 - \mu x_2 - \nu y_2 \end{aligned} \tag{5}$$

from where

$$y_1^* = \frac{\alpha_1 - \mu x_2^*}{\nu}, \quad y_2^* = \frac{\alpha_2 - \mu x_2^*}{\nu}. \tag{6}$$

By replacing now y_1 and y_2 in the first and third equations in (4) it results that

$$x_2^* = \frac{A_1}{x_1^*} + B_1 - x_1^* \tag{7}$$

$$x_1^* = \frac{A_2}{x_2^*} + B_2 - x_2^* \tag{8}$$

where

$$A_i = \frac{\alpha_i \nu_i}{\beta\mu}, \quad B_i = \frac{\alpha_1 + \alpha_2 - S\nu}{\mu} - \frac{\nu_i}{\beta}, \quad i = 1, 2.$$

Then, the equilibrium points of the system are the solutions of the following equations

$$x_1^* = \frac{A_2}{\frac{A_1}{x_1^*} + B_1 - x_1^*} + B_2 - \frac{A_1}{x_1^*} - B_1 + x_1^*, \quad y_1^* = \frac{\alpha_1 - \mu x_1^*}{\nu}. \tag{9}$$

Similar formulas hold for x_2 and y_2.
After straightforward algebraic computations, equation (9) can be rewritten as a third degree polynomial equation in x_1^*:

$$p(x_1^*) = (B_1 - B_2){x_1^*}^3 + (A_1 + A_2 + B_1 B_2 - B_1^2){x_1^*}^2 + (A_1 B_2 - 2A_1 B_1)x_1^* - A_1^2. \quad (10)$$

Since $p(0) = -A_1^2 < 0$ and $p(+\infty) > 0$ ($B_1 > B_2$, because $\rho_2 > \rho_1$), it follows that p has at least one positive real root, x_1^*. By subtracting now equation (8) from (7), one deduces that

$$\frac{A_2}{x_2^*} = \frac{A_1}{x_1^*} + (B_1 - B_2) > 0,$$

hence $x_2^* > 0$. The positivity of y_1^*, y_2^* follows immediately by using a similar argument with the second and fourth equation of the system (4).

It results that the system (1) has at least one equlibrium point in the positive octant. But since the polynomial equation (10) might also have three positive real roots, it follows that the system (1) could present at most three equilibrium points. □

3. **Numerical examples. Conclusions.**

As suggested in [8], let us choose the following set of values for the system coefficients: $\alpha_1 = 10$, $\alpha_2 = 1$, $\beta = 3$, $\rho_1 = 2.16$, $\rho_2 = 80.64$, $\nu_1 = 2.32$, $\nu_2 = 80.80$, $\mu = 0.1$ and $S = 70$, respectively.

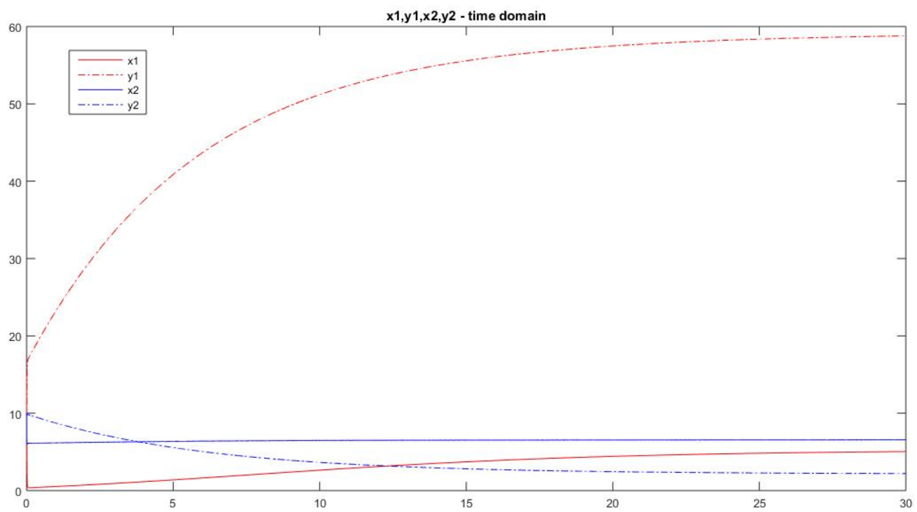

Fig. 1. Typical dynamics

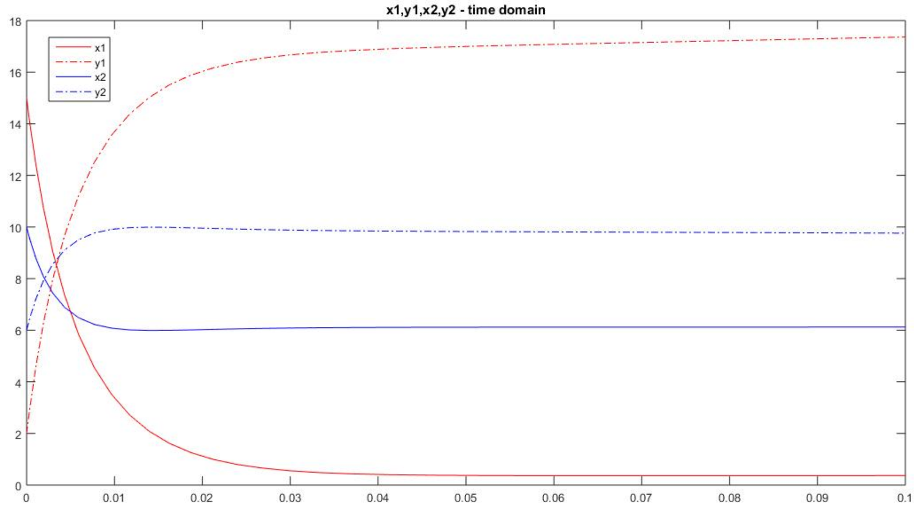

Fig. 2. Transient response: shorter settling times for x_2 and y_2

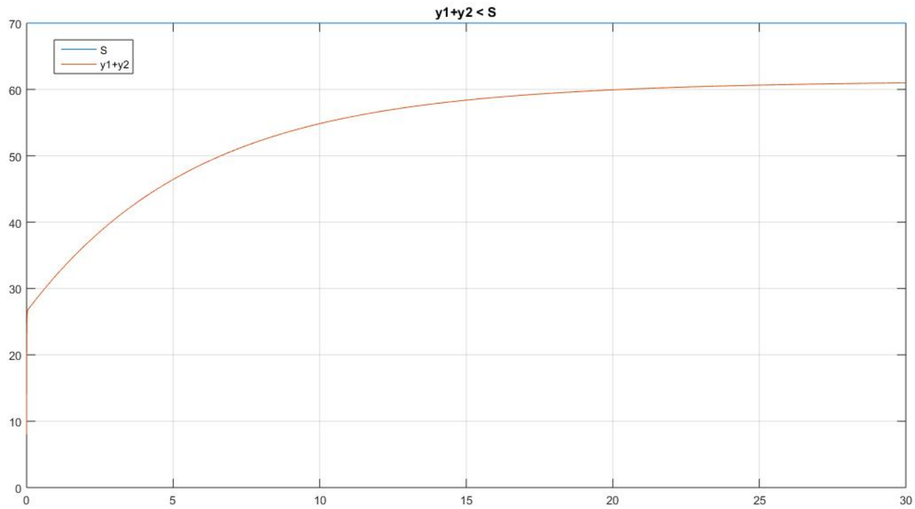

Fig. 3. Limitation of $y_1 + y_2$

By applying a Monte Carlo method one observes that the "other" mRNA targets and their associated AGO microRNA complexes, x_2 and y_2, respectively, are approaching the steady state faster than the mRNA targets x_1 and their associated complexes y_1 - see Figure 2.

Once can also remark (Figure 3) that the amount of microRNA-loaded AGO, $y_1 + y_2$, remains always bounded by S.

Solving the polynomial equation (10), one can easily compute the equilibrium point values: $x_1^* = 5.2873$, $y_1^* = 59.2011$, $x_2^* = 6.5995$, $y_2^* = 2.1253$. These are consistent with steady-state values observed in the simulation results on a sufficiently long time horizon (Figure 1). The numerical experiments suggest that this point is unique, due to the fact that the polynomial $p(x)$ in (10) proved to have for different parameter combinations only one positive real root (and two negative ones).

This comes to confirm that, for a given set of coefficients, there is always a biologically consistent equilibrium point [8]. All these mathematical issues may have a biological relevance in modelling cross-talks in a micro-RNA target network.

Our future work will start by investigating the structural properties of the solutions of equations (4)-(10), in order to identify the (probably unique) biologically relevant equilibrium. Then, we will address Lyapunov stability issues of this equilibrium, aiming to complete the picture of the qualitative behavior of the system in the positive octant.

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