A MATHEMATICAL MODEL ILLUSTRATING THE INHIBITORY EFFECT OF THE MICRO RNA ON THE PROTEIN PRODUCTION

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The present paper introduces a mathematical model for the cross-talking between microRNA and Protein. Studying the qualitative properties of the proposed model, we infer that the microRNA is an inhibitor for the Protein production.

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1. Introduction

For the dynamics between messenger RNA (mRNA), microRNA and Protein we propose the following ODE model:

$$\begin{aligned} \frac{\mathrm{d}m}{\mathrm{d}t} &= b - dm - Am\mu \\ \frac{\mathrm{d}\mu}{\mathrm{d}t} &= \beta - \delta\mu - Bm\mu \\ \frac{\mathrm{d}P}{\mathrm{d}t} &= \frac{\alpha m}{m+K} - \gamma P \end{aligned} \tag{1}$$

Here m is the concentration of messenger RNA, μ the concentration of the micro RNA (which targets the mRNA), while P represents the protein concentration (product). The coefficients A and B are kinetic constants associated with the mass action rates of reaction, γ is the natural protein elimination rate, α is the proportionality factor between mRNA and protein and K is the ususal Michaelis-Menten constant. All these coefficients are naturally strictly positive.

Clearly, the above system of differential equations is a typical enzymatic reaction model, under the Michaelis-Menten hypothesis. The mRNA - microRNA dynamics have been studied in a series of previous papers ([1],[2], [3], [7], [9], [8]).

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In this paper, we focus on the mRNA-Protein interaction in the presence of the microRNA ([10], [14], [15]); this leads to a microRNA-Protein cross-talking analysis. Further, we compare this interaction with the situation where the microRNA is missing.

The main result shows that the microRNA is actually an inhibitor for the protein production.

2. **Equilibria**

The Existence and Uniqueness Theorem can be applied to the Cauchy problem associated to (1), since the system is a polynomial one.

Furthermore, using a similar argument as in [4], by using Proposition 4.3 in [5] once can prove the invariance of the solutions with respect to the positive ortant $\mathbf{R}^3_+$.

With the same technique as in Proposition 3 in [4], it can be shown that the solutions are bounded.

The equilibria of the system are defined by the following system of algebraic equations:

$$\begin{aligned} b - dm - Am\mu &= 0 \\ \beta - \delta\mu - Bm\mu &= 0 \\ \frac{\alpha m}{m+K} - \gamma P &= 0 \end{aligned} \tag{2}$$

Theorem 2.1. *The differential equations system (1) has to equilibrium points, one in the positive, the other one in the negative ortant.*
The equilibrium point in $\mathbf{R}^3_+$ *is given by*

$$m_* = \frac{b}{d + A\mu_*} = \frac{bB - d\delta - A\beta + \sqrt{\Delta}}{2Bd}, \tag{3}$$

$$\textit{where} \quad \Delta = (d\delta + A\beta - bB)^2 + 4b\delta dB > 0 \tag{4}$$

$$\mu_* = \frac{\beta}{\delta + Bm_*} \tag{5}$$

$$P_* = \frac{\alpha\, m_*}{m_* + K} = \frac{\alpha}{\gamma}\, \frac{1}{\delta + \frac{K}{b}(d + A\mu_*)} \tag{6}$$

Proof. From the first two equations in (2) we obtain the following quadratic equation in m:

$$Bdm^2 + (d\delta + A\beta - bB)m - b\delta = 0.$$

Obviously, this equation has two real solutions, one positive and one negative. From here, the expressions for positive (m_*, μ_*, P_*) are straightforward. □

One can easily remark that when m increases (for instance, by raising the production b or diminishing the elimination d) then P_* in (6) will increase as well up to the limit value $\dfrac{\alpha}{\gamma\delta}$ $(b \to \infty,\, d \to 0)$. Assuming there is no interaction with the

microRNA the above formulae reduce to

$$\begin{aligned} m_*^0 &= \frac{b}{d} \\ P_*^0 &= \frac{\alpha\, m_*}{m_* + K} = \frac{\alpha}{\gamma}\, \frac{b}{b\delta + Kd} \end{aligned}$$

Although m_* can become in this case arbitrarily large with $b \to \infty$ and/or $d \to 0$, the protein remains limited to $\dfrac{\alpha}{\gamma}$.

Remark 2.1. *Let us consider the following two cases*

(1) *Dynamics mRNA-Protein in the absence of microRNA. The steady-state value of the protein is*

$$P_*^0 = \frac{\alpha}{\gamma}\, \frac{b}{b\delta + Kd}.$$

(2) *Dynamics mRNA-Protein in the presence of microRNA. The steady-state value of the protein is*

$$P_* = \frac{\alpha}{\gamma}\, \frac{b}{b\delta + Kd + KA\mu_*}$$

Obviously, the steady-state value of the protein is lower in the presence of the microRNA than in the absence of the microRNA.
Moreover

$$\frac{\mathrm{d}P_*}{\mathrm{d}m_*} = \frac{\alpha}{\gamma}\, \frac{1}{(1 + Km)^2} > 0 \tag{7}$$

and, respectively,

$$\frac{\mathrm{d}P_*}{\mathrm{d}\mu_*} = \frac{\alpha}{\gamma}\, \frac{-K\frac{a}{b}}{\left(\delta + \frac{K}{b}(d + A\mu_*)\right)^2} < 0. \tag{8}$$

Hence, as expected, P_* is increasing with respect to m. On the other hand, an important consequence of (7)-(8) is that the steady-state value of the Protein is decreasing with respect to the microRNA.

3. Stability

Theorem 3.1. *The positive equilibrium point (m_*, μ_*, P_*) is a global attractor for system (1) in $\mathbf{R}^3_+$.*

Proof. Since

$$\frac{\alpha m}{m + K} < \alpha,$$

it follows [6] that the stability of system (1) is implied by the stability of following modified system of differential equations

$$\begin{aligned} \frac{\mathrm{d}m}{\mathrm{d}t} &= b - dm - Am\mu \\ \frac{\mathrm{d}\mu}{\mathrm{d}t} &= \beta - \delta\mu - Bm\mu \\ \frac{\mathrm{d}P}{\mathrm{d}t} &= \alpha - \gamma P \end{aligned} \tag{9}$$

We will prove the stability of (9) with respect to the equilibrium point $(m_*, \mu_*, \tilde{P}_*)$, $\tilde{P}_* = \alpha/\gamma$. Let now $\epsilon > 0$; consider the following appropriate function

$$W(m, \mu, P) = -\frac{b}{A}\ln m + \frac{d}{A}m - -\frac{\beta}{B}\ln\mu + \frac{\delta}{B}\mu + m\mu - \alpha\ln P + \gamma P. \tag{10}$$

One can immediately check that the critical points of $W(m, \mu, P)$ given by

$$\frac{\partial W}{\partial m}(m, \mu, P) = -\frac{b}{Am} + \frac{d}{A} + \mu = 0, \quad \frac{\partial W}{\partial \mu}(m, \mu, P) = -\frac{\beta}{B\mu} + \frac{\delta}{B} + m = 0,$$
$$\frac{\partial W}{\partial P}(m, \mu, P) = -\frac{\alpha}{P} + \gamma = 0$$

are verifying the equilibrium set of equations associated to (9). Hence $(m_*, \mu_*, \tilde{P}_*)$ is the unique extreme point of $W(m, \mu, P)$ in $\mathbb{R}^3_+$.
Further, the Hessian matrix is

$$\begin{bmatrix} \frac{b}{Am_*^2} & 1 & 0 \\ 1 & \frac{\beta}{B\mu_*^2} & 0 \\ 0 & 0 & \frac{\alpha}{\tilde{P}_*^2} \end{bmatrix}$$

which is obviously (strictly) positive definite. Hence, $(m_*, \mu_*, \tilde{P}_*)$ is the minimum of $W(m, \mu, P)$ in $\mathbb{R}^3_+$. Let

$$V(m, \mu, P) := W(m, \mu, P) - W(m_*, \mu_*, \tilde{P}_*) > 0, \quad \forall\, (m, \mu, P) \neq (m_*, \mu_*, \tilde{P}_*),$$
$$\forall\, (m, \mu, P) \in \mathbb{R}^3_+.$$

be an appropriate Lyapunov function candidate for the system (9). Its derivative along the trajectories is given by

$$\frac{\mathrm{d}V(m, \mu, P)}{\mathrm{d}t} = -\frac{1}{Am}\left(-\frac{b}{Am} + \frac{d}{A} + \mu\right)^2 - \frac{1}{B\mu}\left(-\frac{\beta}{B\mu} + \frac{\delta}{B} + m\right)^3 - \frac{(\alpha - \gamma P)^2}{P} < 0,$$

for all $(m, \mu, P) \neq (m_*, \mu_*, \tilde{P}_*)$, $(m, \mu, P) \in \mathbb{R}^2_+$. It follows that $(m_*, \mu_*, \tilde{P}_*)$ is a global attractor in $\mathbb{R}^3_+$ for the system (9), and, consequently (m_*, μ_*, P_*) is a global attractor in $\mathbb{R}^3_+$ for the system (1).

□

In order to illustrate the previous theoretical results, time-domain and state-space simulation result are presented below.

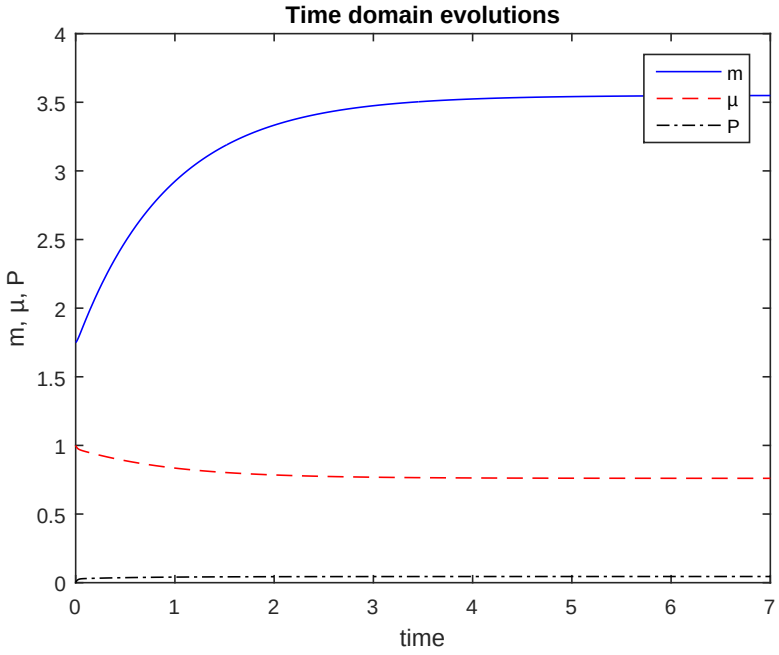

FIGURE 1. Time-domain evolution

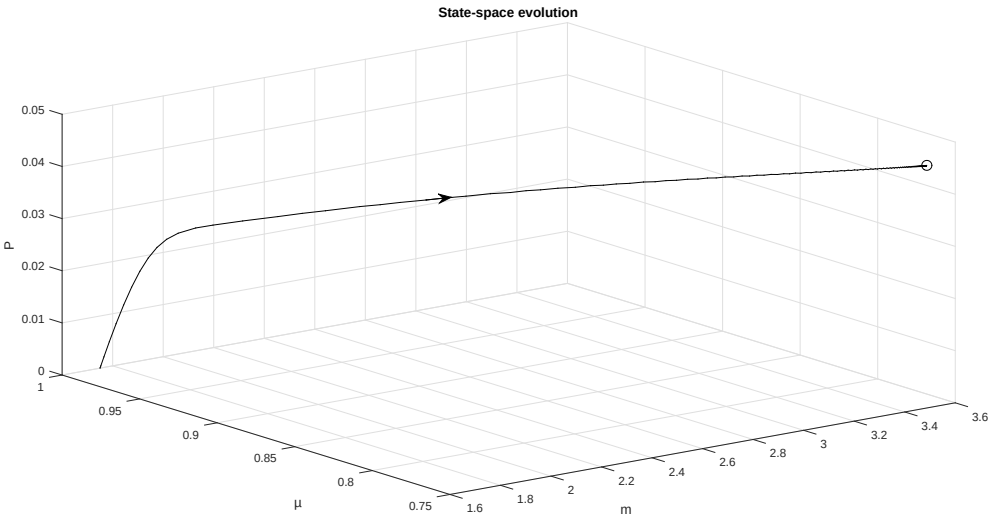

FIGURE 2. State-space trajectory converging to the equilibrium point

4. **Conclusion**

For the proposed model (1) we prove the existence and uniqueness of the positive equilibrium and its stability - global attractor in $\mathbf{R}^3_+$.

As a main conclusion, the steady-state value of the Protein is decreasing with respect to the microRNA.

For a further research, one can consider multiple species of mRNAs, microRNAs and Proteins.

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