# AN EXPONENTIAL STABILITY TEST FOR A MESSENGER RNA–MICRO RNA ODE MODEL

Mircea OLTEANU[1] and Radu ŞTEFAN[2]

*In this paper we obtain a numerically tractable test (sufficient condition) for the exponential stability of the unique positive equilibrium point of an ODE system. The result (Theorem 3.1) is based on Lyapunov theory and Linear Matrix Inequalities techniques. The ODE model is related to the messengerRNA-microRNA interaction.*

**Keywords:** ODE model, Lyapunov stability, enzymatic reaction, micro RNA
**MSC2010:** 34D23 37B25 37C10 37C70 37C75

## 1. Introduction

Consider the following ODE matematical model

$$\begin{aligned} \frac{\mathrm{d}m_i}{\mathrm{d}t} &= b_i - d_i m_i - \left(\sum_{j=1}^{M} k_{ij}^{+}\mu_j\right) m_i + \sum_{j=1}^{M} k_{ij}^{-} c_{ij}, \quad i=\overline{1,N} \\ \frac{\mathrm{d}\mu_j}{\mathrm{d}t} &= \beta_j - \delta_j \mu_j - \left(\sum_{i=1}^{N} k_{ij}^{+} m_i\right)\mu_j + \sum_{i=1}^{N}(k_{ij}^{-}+\kappa_{ij})c_{ij}, \quad j=\overline{1,M} \\ \frac{\mathrm{d}c_{ij}}{\mathrm{d}t} &= -(\sigma_{ij}+k_{ij}^{-}+\kappa_{ij})c_{ij} + k_{ij}^{+} m_i \mu_j, \quad i=\overline{1,N}, j=\overline{1,M}. \end{aligned} \tag{1}$$

The notation is the usual one, as in the original papers [4] and [5]: $m_i$ ($i=\overline{1,N}$) represent the concentrations of the messengerRNAs, $\mu_j$ ($j=\overline{1,M}$) are the concentrations of the microRNAs, while $c_{ij}$ stand for the concentrations of the complexes. Let us remark that $d_i$, $\delta_j$ and $\sigma_{ij}$ are the elimination rates of the messengerRNAs, microRNAs and complexes, respectively. The kinetic constants associated with the mass action rates of the enzymatic reactions are $k_{ij}^{+}$, $k_{ij}^{-}$ and $\kappa_{ij}$. Finally, $b_i$ and $\beta_j$ stand for the transcription rates of the messengerRNAs and microRNAs, respectively. We assume throughout the paper that all coeficients are strictly positive.

[1]Professor, Department of Mathematical Methods and Models, Faculty of Applied Sciences, University "POLITEHNICA" of Bucharest, Romania, E-mail: mircea.olteanu@upb.ro

[2]Professor, Department of Automatic Control and Systems Engineering, Faculty of Automatic Control and Computer Science, University "POLITEHNICA" of Bucharest, Romania, E-mail: radu.stefan@upb.ro (corresponding author)

During the last years, such mathematical models received a lot of attention in the literature (see [7], [4], [2], [9], [3]). The case with two messenger and two micro RNA species appears to be relevant for many issues raised by the interaction mechanisms. Therefore we decided to concentrate here exclusively on the situation when $M = N = 2$. In this case (1) rewrites as a system with 8 equations

$$\begin{aligned} \frac{\mathrm{d}m_i}{\mathrm{d}t} &= b_i - d_i m_i - \left(k_{i1}^+\mu_1 + k_{i2}^+\mu_2\right) m_i + \left(k_{i1}^- c_{i1} + k_{i2}^- c_{i2}\right), \quad i = 1,2 \\ \frac{\mathrm{d}\mu_j}{\mathrm{d}t} &= \beta_j - \delta_j\mu_j - \left(k_{1j}^+ m_1 + k_{2j}^+ m_2\right)\mu_j + \left((k_{1j}^- + \kappa_{1j})c_{1j} + (k_{2j}^- + \kappa_{2j})c_{2j}\right) j = 1,2 \\ \frac{\mathrm{d}c_{ij}}{\mathrm{d}t} &= -(\sigma_{ij} + k_{ij}^- + \kappa_{ij})c_{ij} + k_{ij}^+ m_i\mu_j, \quad i,j = 1,2. \end{aligned} \tag{2}$$

Further, we will analyze the behavior of the above system (2) under the Quasi Steady State Assumption (QSSA). To be more specific, this means that

$$\frac{\mathrm{d}c_{ij}}{\mathrm{d}t} = 0, \quad \text{or, equivalently,} \quad c_{ij} = \frac{k_{ij}^+}{\sigma_{ij} + k_{ij}^- + \kappa_{ij}} m_i\mu_j, \quad i,j = 1,2.$$

The QSSA is consistent with the experimental fact that complexes often reach the steady-state (equilibrium) much faster than the RNA species (see [4], [5]). Under this hypothesis, we get the following ODE model comprising four equations

$$\begin{aligned} \frac{\mathrm{d}m_1}{\mathrm{d}t} &= b_1 - d_1 m_1 - \left(a_{11}\mu_1 + a_{12}\mu_2\right) m_1 \\ \frac{\mathrm{d}m_2}{\mathrm{d}t} &= b_2 - d_2 m_2 - \left(a_{21}\mu_1 + a_{22}\mu_2\right) m_2 \\ \frac{\mathrm{d}\mu_1}{\mathrm{d}t} &= \beta_1 - \delta_1\mu_1 - \left(\alpha_{11} m_1 + \alpha_{21} m_2\right)\mu_1 \\ \frac{\mathrm{d}\mu_2}{\mathrm{d}t} &= \beta_2 - \delta_2\mu_2 - \left(\alpha_{12} m_1 + \alpha_{22} m_2\right)\mu_2 \end{aligned} \tag{3}$$

where

$$a_{ij} = \frac{\sigma_{ij} + \kappa_{ij}}{\sigma_{ij} + k_{ij}^- + \kappa_{ij}} k_{ij}^+, \tag{4}$$

$$\alpha_{ij} = \frac{\sigma_{ij}}{\sigma_{ij} + k_{ij}^- + \kappa_{ij}} k_{ij}^+. \tag{5}$$

Obviously, $\alpha_{ij} < a_{ij} < k_{ij}^+$.

**Remark 1.1.**

(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 (3). Moreover, the solutions are bounded (see* [5]*).*

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

We shall prove the existence of a unique equilibrium point in the positive ortant of $\mathbf{R}^4$ and then give conditions for the exponential stability of this equilibria.

## 2. Equilibria

The equilibrium points are the solutions of the following system of equations:

$$\begin{aligned} m_i &= \frac{b_i}{d_i + a_{i1}\mu_1 + a_{i2}\mu_2}, \; i = 1,2, \\ \mu_j &= \frac{\beta_j}{\delta_j + \alpha_{1j} m_1 + \alpha_{2j} m_2}, \; j = 1,2. \end{aligned} \tag{6}$$

The following existence and uniqueness result holds.

**Theorem 2.1.** *For every positive set of parameters $b_i, \beta_j, d_i, \delta_j, \sigma_{ij}, k_{ij}^+, k_{ij}^-$ and $\kappa_{ij}$, $i, j = 1,2$, the system (6) has a unique solution $(m_1^*, m_2^*, \mu_1^*, \mu_2^*)$ with $m_i \in \left(0\,,\,\frac{b_i}{d_i}\right)$ and $\mu_j \in \left(0\,,\,\frac{\beta_j}{\delta_j}\right)$, $i, j = 1,2$.*

*Proof.* Consider the maps

$$\begin{aligned} g_i(m_i, \mu_1, \mu_2) &= m_i \left(d_i + a_{i1}\mu_1 + a_{i2}\mu_2\right), \; i = 1,2, \\ h_j(m_1, m_2, \mu_j) &= \mu_j \left(\delta_j + \alpha_{1j} m_1 + \alpha_{2j} m_2\right), \; j = 1,2. \end{aligned}$$

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

$$\begin{aligned} g_i(m_i, \mu_1, \mu_2) &= b_i, \; i = 1,2, \\ h_j(m_1, m_2, \mu_j) &= \beta_j, \; j = 1,2. \end{aligned}$$

Let us first notice that for any $i, j = 1,2$

$$\frac{\partial g_i}{\partial m_i} > 0, \; \frac{\partial h_j}{\partial \mu_j} > 0, \; \frac{\partial g_i}{\partial \mu_j} > 0 \text{ and } \frac{\partial h_j}{\partial m_i} > 0.$$

From system (6), at equilibrium, the uniqueness results from

$$\frac{\partial m_i}{\partial \mu_j} < 0, \; \frac{\partial \mu_j}{\partial m_i} < 0, \; i, j = 1,2.$$

Then observe that $g_i(0, \mu_1, \mu_2) = 0$ and that $g_i(\frac{b_i}{d_i}, \mu_1, \mu_2) > b_i$, hence for every pair $(\mu_1, \mu_2) \in \mathbf{R}_+^2$ there exist unique $m_1^* = m_1^*(\mu_1, \mu_2) > 0$ and $m_2^* = m_2^*(\mu_1, \mu_2) > 0$ such that $g_i(m_i, \mu_1, \mu_2) = b_i$, $i = 1,2$.

Considering now the system $h_j\left(m_1^*(\mu_1, \mu_2), m_2^*(\mu_1, \mu_2), \mu_j\right) = \beta_j$, $j = 1,2$, one gets

$$\begin{aligned} h_1\left(m_1^*(0, \mu_2), m_2^*(0, \mu_2), 0\right) &= 0 \\ h_1\left(m_1^*(\frac{\beta_1}{\delta_1}, \mu_2), m_2^*(\frac{\beta_1}{\delta_1}, \mu_2), \frac{\beta_1}{\delta_1}\right) &> \beta_1. \end{aligned}$$

Thus there exists a unique $\mu_1^* = \mu_1^*(\mu_2)$ such that $h_1\left(m_1^*(\mu_1^*, \mu_2), m_2^*(\mu_1^*, \mu_2), \mu_1^*\right) = \beta_1$. By a similar reasoning it follows that the last equation

$$h_2\left(m_1^*(\mu_1^*, \mu_2), m_2^*(\mu_1^*, \mu_2), \mu_2\right) = \beta_2$$

has also a unique solution $\mu_2^* \in \left(0\,,\,\frac{\beta_2}{\delta_2}\right)$ and the proof is completed. □

## 3. **Exponential stability of the equilibrium point**

The analysis of the stability properties of the origin will make use of the classical Lyapunov's stability theorems. Introduce a quadratic form as a Lyapunov function candidate, that is, $V(z) = z^T P z$. We will derive an LMI (Linear Matrix Inequality) sufficient condition in terms of $P$ which ensures the exponential stability of the equilibrium point. The solution is then obtained by using the *cvx* programming environment developed by Boyd *et. al* [1] and running the SDPT3 semidefinite programming package.
Translate first the system (3) to the origin. Define the deviations with respect to the equilibrium point in Theorem 2.1 as $x_i := m_i - m_i^*$, $y_j := \mu_j - \mu_j^*$, $i, j = 1, 2$ and let $z^T := [x_1\ x_2\ y_1\ y_2]$. Then write the equivalent translated system as

$$\dot{z} = Az + g(z), \tag{7}$$

where

$$A = \begin{bmatrix} -\widetilde{d_1} & 0 & -a_{11}m_1^* & -a_{12}m_2^* \\ 0 & -\widetilde{d_2} & -a_{21}m_1^* & -a_{22}m_2^* \\ -\alpha_{11}\mu_1^* & -\alpha_{21}\mu_1^* & -\widetilde{\delta_1} & 0 \\ -\alpha_{12}\mu_2^* & -\alpha_{22}\mu_2^* & 0 & -\widetilde{\delta_2} \end{bmatrix},$$

$$\widetilde{d_1} = d_1 + a_{11}\mu_1^* + a_{12}\mu_2^*, \qquad \widetilde{d_2} = d_2 + a_{21}\mu_1^* + a_{22}\mu_2^*,$$
$$\widetilde{\delta_1} = \delta_1 + \alpha_{11}m_1^* + \alpha_{21}m_2^*, \qquad \widetilde{\delta_2} = \delta_2 + \alpha_{12}m_1^* + \alpha_{22}m_2^*$$

and $g : \mathbf{R}^4 \to \mathbf{R}^4$ is defined by

$$g_1(x_1, x_2, y_1, y_2) = -\left(a_{11}y_1 + a_{12}y_2\right) x_1, \qquad g_2(x_1, x_2, y_1, y_2) = -\left(a_{12}y_1 + a_{22}y_2\right) x_2,$$
$$g_3(x_1, x_2, y_1, y_2) = -\left(\alpha_{11}x_1 + \alpha_{21}x_2\right) y_1, \qquad g_4(x_1, x_2, y_1, y_2) = -\left(\alpha_{12}x_1 + \alpha_{22}x_2\right) y_2.$$

**Proposition 3.1.**
*For every $r > 0$, there exists $\gamma_r > 0$ such that*

$$\|g(z)\| \le \gamma_r \|z\|, \ \ \forall \|z\| < r. \tag{8}$$

*Proof.* Let $r > 0$ and assume that $\|z\| < r$. Then

$$g_1^2(z) = \left(a_{11}y_1 + a_{12}y_2\right)^2\ x_1^2 \le \left(a_{11} + a_{12}\right)^2\ r^2\, x_1^2.$$

One can also bound from above in the same manner $g_i^2(z)$, $i = \overline{2, 4}$. Define

$$\gamma_r := r\,\sqrt{\max\{(a_{11} + a_{12})^2, (a_{21} + a_{22})^2, (\alpha_{11} + \alpha_{21})^2, (\alpha_{12} + \alpha_{22})^2\}} \tag{9}$$

Then, we see that

$$\|g(z)\|^2 = \sum_{i=1}^{4} g_i^2(z) \le \gamma_r^2\,\|z\|^2,$$

hence $\|g(z)\| \le \gamma_r \|z\|, \ \ \forall \|z\| < r$.

□

Now we can state the main result of the section.

**Theorem 3.1.** *If there exist a positive definite matrix of appropriate dimensions* $P > 0$ *and positive real numbers* $c > 0$, $\gamma > 0$, *all depending on* $A$, *such that*

$$\begin{bmatrix} A^T P + PA + cP + \gamma^2 I & P \\ P & -I \end{bmatrix} < 0, \tag{10}$$

*then the origin is an exponentially stable equilibrium point for the system (7).*

*Proof.* Consider the quadratic Lyapunov function candidate $V(z) = z^T P z$. According to a standard Lyapunov stability result (see Chapter 9 in [8]), the exponential stability of the origin is guaranteed if the derivative of $V(z)$ along the trajectories of the system verifies

$$0 > -cV(z) > \dot{V}(z) = z^T \left(A^T P + PA\right) z + g^T(z) P z + z^T P g(z),$$

or, equivalently,

$$z^T \left(A^T P + PA + cP\right) z + z^T P g(z) + g^T(z) P z < 0. \tag{11}$$

Let $z \in \mathbf{R}^4$ and let $r > 0$ such that $\|z\| < r$; Proposition 3.1 applies and (8) holds. It follows that whenever the inequality below

$$z^T \left(A^T P + PA + cP\right) z + z^T P g(z) + g^T(z) P z + \gamma_r^2 z^T z - g^T(z) g(z) < 0 \tag{12}$$

or, equivalently,

$$\begin{bmatrix} z^T & g^T(z) \end{bmatrix} \begin{bmatrix} A^T + PA + cP + \gamma_r^2 I & P \\ P & -I \end{bmatrix} \begin{bmatrix} z \\ g(z) \end{bmatrix} < 0$$

is satisfied for a given $P = P^T > 0$ and $c > 0$, then the origin is exponentially stable. Hence it is sufficient that the LMI (10) holds.

□

As it was already mentioned, the inequality (10) is an LMI in the unknown $P$ and parameters $c$ and $\gamma$, and can be solved by using existing semidefinite programming software packages. If a solution exists, then automatically the equilibrium point in Theorem 2.1 is an exponentially stable equilibrium for the system (3).

## 4. Numerical examples. Conclusions.

Consider the following parameters (coefficients): $b_1 = 4, b_2 = 8, \beta_1 = 1.5, \beta_2 = 1$; $d_1 = 5, d_2 = 2.8, \delta_1 = 8, \delta_2 = 6.7$; $k_{11}^+ = 8.2, k_{12}^+ = 0.5, k_{21}^+ = 0.3, k_{22}^+ = 4.8$; $k_{11}^- = 0.3, k_{12}^- = 0.1, k_{21}^- = 2, k_{22}^- = 1.2$; $\kappa_{11} = 0.8, \kappa_{12} = 1, \kappa_{21} = 1.3, \kappa_{22} = 0.5$ and $\sigma_{11} = 1.5, \sigma_{12} = 3.8, \sigma_{21} = 7, \sigma_{22} = 10$.
In this case the feasibility problem (10) has a positive definite solution ($\Lambda$ denotes here the spectrum):

$$P = \begin{bmatrix} 3.8925 & -0.1070 & -0.9507 & -0.1833 \\ -0.1070 & 1.2117 & 0.0251 & -0.7505 \\ -0.9507 & 0.0251 & 3.7720 & 0.0755 \\ -0.1833 & -0.7505 & 0.0755 & 2.5543 \end{bmatrix}, \ \Lambda_P = \{0.866, 2.841, 2.923, 4.800\}.$$

Furthermore, the LMI is fulfilled since the spectrum of the left-hand side in (10) is $\Lambda = \{-68.4193, -64.2490, -31.6846, -3.3227, -0.0544, -0.3398, -0.8601, -0.9551\}$. As expected, $A$ is stable with $\Lambda_A = \{-17.8122, -12.1811, -5.4813, -2.8975\}$.

We have also noticed that if the values of $d_i$ or $\delta_j$, $i, j = 1, 2$ are small enough, the LMI (10) is not feasible anymore, but $A$ remains stable. For instance, by taking $d_1 = 2$ we do not get a solution for $P$ anymore, but $\Lambda_A = \{-13.8627, -17.9746, -3.4381, -2.8929\}$ still belongs to the left complex half-plane. This only shows that this type of sufficient LMI conditions always contain a certain degree of conservatism, implicitly present in the numerical procedure: if (10) is not feasible, this does not imply that the matrix $A$ or the origin are not (exponentially) stable.

A sufficient condition for exponential stability of the single positive equilibrium point of an ODE system modeling messengerRNA - microRNA interaction has been derived. This condition can be verified numerically in a sound manner.

## REFERENCES


[1] *S. Boyd and L. Vandenberghe*, Convex Optimization, Cambridge University Press, 2004.

[2] *J. Eilertsen and S. Schnell*, The standard, reverse and total Quasi-Steady-State Approximations revised: Timescale, small parameters, normal forms and singularities in enzyme kinetics. Preprint, November 2019.

[3] *M. Feinberg*, The existence and uniqueness of steady states for a class of chemical reaction networks, Arch. Ration. Mech. Anal., **132** 1995, 311-370.

[4] *M. Figliuzzi, E. Marinari and A. De Martino*, MicroRNAs as a selective channel of communication between competing RNAs: a steady-state theory, Biophysical Journal, **104** 2013, 1203-1213.

[5] *P. Flondor, M. Olteanu and R. Ştefan.* Qualitative analysis of an ODE Model of a Class of Enzymatic Reactions, Bull Math Biology, **80** 2018, 32-45 (`doi: 10.1007/s11538-017-0360-8`).

[6] *A. Halanay and V. Răsvan*, Application of Liapunov Methods in Stability, Springer Science + Business Media, Dordrecht, 1993.

[7] *J. Hausser and M. Zavolan* Identification and consequences of miRNA-target interactions–beyond repression of gene expression [published correction appears in Nat Rev Genet. 2014 Oct;15(10):702]. Nat Rev Genet. 2014; 15(9):599-612. doi:10.1038/nrg3765

[8] *H. N. Khalil*, Nonlinear Systems, 3rd Edition Prentice Hall, 2002.

[9] *M. Olteanu and R. Ştefan* A note on the stability analysis of a class of nonlinear systems - an LMI approach U.P.B. Sci. Bull., Series A, Vol. **80**, Iss. 4, pp. 3-10, 2018.