LMI STABILITY ANALYSIS FOR A MICRO RNA - MESSENGER RNA INTERACTION MATHEMATICAL MODEL

Mircea Olteanu[1] and Radu Ştefan[2]

The micro RNA - messenger RNA dynamics is a topic of constant interest. In this paper we analyze the stability of equilibria of a mathematical model associated to this interaction. After proving the existence and uniqueness of an equilibrium point in the positive ortant, we provide numerically tractable conditions (by using Linear Matrix Inequalities techniques) to check the asymptotic stability of the equilibrium point. An illustrative numerical example is closing the paper along with some conclusions.

Keywords: enzymatic reaction, equilibria, LMI stability, micro RNA
MSC2010: 34D23 37B25 37C10 37C70 37C75

1. Introduction

Consider the following nonlinear system

$$\begin{aligned}
\frac{\mathrm{d}X_i}{\mathrm{d}t} &= b_i - d_iX_i - k_i^+X_iY + k_i^-Z_i, \quad i = \overline{1,N} \\
\frac{\mathrm{d}Y}{\mathrm{d}t} &= \beta - \delta Y - \left(\sum_{i=1}^{N} k_i^+X_i\right)Y + \sum_{i=1}^{N}(k_i^- + K_i)Z_i \\
\frac{\mathrm{d}Z_i}{\mathrm{d}t} &= -(\sigma_i + k_i^- + K_i)Z_i + k_i^+X_iY, \quad i = \overline{1,N}
\end{aligned} \tag{1}$$

Here X_i, Y, Z_i ($i = \overline{1,N}$) denote concentrations in an enzymatic reaction [1], [4], [11], which appears in the study of micro RNA - messenger RNA dynamics (for further details see [5], [2], [7], [6]). The coefficients b_i, d_i, β, δ, k_i^+, k_i^-, K_i and σ_i are all positive.

In a recent paper [10] we studied the dynamics of the interaction between one messenger RNA and several micro RNAs. Here we turn our attention to the situation of several messenger RNAs and one micro RNA and use a standard technique of nondimensionalization (see Section 2) in order to reduce the number of parameters. Although the system structure is different from that in [10], similar results

[1]Professor, Department of Mathematical Methods and Models, Faculty of Applied Sciences, University "Politehnica" of Bucharest, Romania, E-mail: mirolteanu@yahoo.co.uk

[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@acse.pub.ro (corresponding author)

and techniques hold: there exists a unique equilibrium point in the positive ortant (Theorem 2.1) and numerically tractable conditions are employed to check the asymptotic stability of the equilibria, by using Linear Matrix Inequalities techniques. We conclude along a typical numerical example.

2. **Problem statement**

By using a usual technique of nondimensionalization we make the change of variables

$$\begin{aligned} \tau &= \delta\, t \\ u_i &= \frac{d_i}{b_i} X_i \quad i = \overline{1, N} \\ v &= \frac{\delta}{\beta} Y \\ u_i &= \frac{k_i^+}{\sigma_i + k_i^- + K_i} Z_i \quad i = \overline{1, N} \end{aligned}$$

The system (1) can be now rewritten in the new variables τ, u_i, v, w_i as

$$\begin{aligned} \frac{\mathrm{d}u_i}{\mathrm{d}\tau} &= \frac{d_i}{\delta} - \frac{d_i}{\delta} u_i - \frac{\beta k_i^+}{\delta^2} u_i v + \frac{d_i k_i^- (\sigma_i + k_i^- + K_i)}{b_i k_i^+ \delta} w_i, \quad i = \overline{1, N} \\ \frac{\mathrm{d}v}{\mathrm{d}\tau} &= 1 - v - \left(\sum_{i=1}^{N} \frac{b_i k_i^+}{d_i \delta} u_i \right) v + \sum_{i=1}^{N} \frac{(k_i^- + K_i)(\sigma_i + k_i^- + K_i)}{\beta k_i^+} w_i \\ \frac{\mathrm{d}w_i}{\mathrm{d}\tau} &= -\frac{\sigma_i + k_i^- + K_i}{\delta} w_i + \frac{\left(k_i^+\right)^2 b_i \beta}{\delta^2 d_i (\sigma_i + k_i^- + K_i)} u_i v, \quad i = \overline{1, N} \end{aligned} \tag{2}$$

Remark 2.1. *Obviously, the Existence and Uniqueness Theorem applies to both systems (1) and (2); moreover, the positive ortant* $\mathbb{R}_+^{2N+1}$ *is a positively invariant set for these systems - see* [8].

Henceforth we concentrate the study exclusively on the nondimensional system (2).

Let us begin by proving the existence and uniqueness of an equilibrium point in the positive ortant.

Theorem 2.1. *For every set of positive parameters* $b_i, \beta,\ d_i, \delta, \sigma_i,\ k_i^+, k_i^-, K_i,\ i = \overline{1, N}$, *the system (2) has a unique equilibrium point* $(\widetilde{u_i}, \widetilde{v}, \widetilde{w_i})$ *in* $\mathbb{R}_+^{2N+1}$, $i = \overline{1, N}$; *moreover*

$$\widetilde{u_i} \in (0\,,\, 1)\,, \quad \widetilde{v} \in (0\,,\, 1)\,, \quad \widetilde{w_i} \in \left(0\,,\, \frac{\left(k_i^+\right)^2 b_i \beta}{\delta d_i (\sigma_i + k_i^- + K_i)^2} \right).$$

Proof. The algebraic equations defining the equilibria are

$$\frac{d_i}{\delta} - \frac{d_i}{\delta}u_i - \frac{\beta k_i^+}{\delta^2}u_i v + \frac{d_i k_i^-(\sigma_i + k_i^- + K_i)}{b_i k_i^+ \delta}w_i = 0, \quad i = \overline{1,N}, \quad (3)$$

$$1 - v - \left(\sum_{i=1}^{N} \frac{b_i k_i^+}{d_i \delta}u_i\right)v + \sum_{i=1}^{N} \frac{(k_i^- + K_i)(\sigma_i + k_i^- + K_i)}{\beta k_i^+}w_i = 0, \quad (4)$$

$$-\frac{\sigma_i + k_i^- + K_i}{\delta}w_i + \frac{\left(k_i^+\right)^2 b_i \beta}{\delta^2 d_i(\sigma_i + k_i^- + K_i)}u_i v = 0, \quad i = \overline{1,N}. \quad (5)$$

From the last N equations (5) we get

$$w_i = \frac{\left(k_i^+\right)^2 b_i \beta}{\delta d_i(\sigma_i + k_i^- + K_i)^2}\, u_i v, \quad i = \overline{1,N}. \quad (6)$$

Replace w_i in (3) and obtain

$$u_i \left(d_i + \frac{\beta k_i^+(\sigma_i + K_i)}{\delta(\sigma_i + k_i^- + K_i)}v\right) = d_i, \quad i = \overline{1,N},$$

hence

$$u_i = \frac{1}{1 + \frac{\beta k_i^+(\sigma_i + K_i)}{\delta d_i(\sigma_i + k_i^- + K_i)}v}, \quad i = \overline{1,N}. \quad (7)$$

Introduce now the above expressions of u_i and w_i in (4) and get

$$1 - v\left(1 + \sum_{i=1}^{N} \frac{b_i k_i^+ \sigma_i}{d_i \delta\left(\sigma_i + k_i^- + K_i\right) + \beta k_i^+(\sigma_i + K_i)v}\right) = 0. \quad (8)$$

Let $f : \mathbb{R}_+ \to \mathbb{R}$,

$$f(v) = 1 - v\left(1 + \sum_{i=1}^{N} \frac{b_i k_i^+ \sigma_i}{d_i \delta\left(\sigma_i + k_i^- + K_i\right) + \beta k_i^+(\sigma_i + K_i)v}\right);$$

the map f is strictly decreasing:

$$f'(v) = -1 - \sum_{i=1}^{N} \frac{b_i \beta \left(k_i^+\right)^2 (\sigma_i + K_i)\sigma_i}{\left(d_i \delta\left(\sigma_i + k_i^- + K_i\right) + \beta k_i^+(\sigma_i + K_i)v\right)^2} < 0, \quad \forall v \geq 0.$$

Since $f(0) = 1 > 0$ and $f(1) < 0$, equation $f(v) = 0$ has a unique solution $\widetilde{v} \in (0\ ,\ 1)$. Looking now at (7) and (6) the proof is completed. □

3. **Sufficient stability conditions**

Our analysis makes use of Lyapunov's stability theorem in first approximation, by deriving a numerically tractable LMI (Linear Matrix Inequality) sufficient condition.

Translate the system (2) to the origin. The deviations with respect to the equilibrium point $(\widetilde{u_i}, \widetilde{v}, \widetilde{w_i})$ are denoted by

$$x_i = u_i - \widetilde{u_i}, \; y = v - \widetilde{v}, \; z_i = w_i - \widetilde{w_i}, \;\; i = \overline{1,N}.$$

The system in the shifted variables x_i, y, z_i is given by

$$
\begin{aligned}
\frac{\mathrm{d}x_i}{\mathrm{d}\tau} &= \left(\frac{d_i}{\delta} + \frac{\beta k_i^+}{\delta^2}\widetilde{v}\right) x_i - \frac{\beta k_i^+}{\delta^2}\widetilde{u}_i y + \frac{d_i k_i^-(\sigma_i + k_i^- + K_i)}{b_i k_i^+ \delta} z_i - \frac{\beta k_i^+}{\delta^2} x_i y, \quad i = \overline{1, N} \\
\frac{\mathrm{d}y}{\mathrm{d}\tau} &= -\widetilde{v}\sum_{i=1}^{N} \frac{b_i k_i^+}{d_i \delta} x_i - \left(1 + \sum_{i=1}^{N} \frac{b_i k_i^+}{d_i \delta}\widetilde{u}_i\right) y + \\
&+ \sum_{i=1}^{N} \frac{(k_i^- + K_i)(\sigma_i + k_i^- + K_i)}{\beta k_i^+} z_i - \sum_{i=1}^{N} \frac{b_i k_i^+}{d_i \delta} x_i y \qquad (9) \\
\frac{\mathrm{d}z_i}{\mathrm{d}\tau} &= \frac{\left(k_i^+\right)^2 b_i \beta}{\delta^2 d_i(\sigma_i + k_i^- + K_i)}\widetilde{v} x_i + \frac{\left(k_i^+\right)^2 b_i \beta}{\delta^2 d_i(\sigma_i + k_i^- + K_i)}\widetilde{u}_i y - \frac{\sigma_i + k_i^- + K_i}{\delta} z_i + \\
&+ \frac{\left(k_i^+\right)^2 b_i \beta}{\delta^2 d_i(\sigma_i + k_i^- + K_i)} x_i y, \quad i = \overline{1, N}
\end{aligned}
$$

Let us introduce the following notations:

$$
A_i = \frac{\beta k_i^+}{\delta^2}, \;\; B_i = \frac{k_i^-(\sigma_i + k_i^- + K_i)}{b_i k_i^+ \delta}, \;\; C_i = \frac{b_i k_i^+}{d_i \delta},
$$
$$
D_i = \frac{(k_i^- + K_i)(\sigma_i + k_i^- + K_i)}{\beta k_i^+}, \;\; G_i = \frac{\sigma_i + k_i^- + K_i}{\delta}, \quad i = \overline{1, N}
$$

With the above notations, one obtains

$$
\begin{aligned}
\frac{\mathrm{d}x_i}{\mathrm{d}\tau} &= -\left(\frac{d_i}{\delta} + A_i\widetilde{v}\right) x_i - A_i\widetilde{u}_i y + B_i d_i z_i - A_i x_i y, \quad i = \overline{1, N} \\
\frac{\mathrm{d}y}{\mathrm{d}\tau} &= -\widetilde{v}\sum_{i=1}^{N} C_i x_i - \left(1 + \sum_{i=1}^{N} C_i\widetilde{u}_i\right) y + \sum_{i=1}^{N} D_i z_i - \sum_{i=1}^{N} C_i x_i y \qquad (10) \\
\frac{\mathrm{d}z_i}{\mathrm{d}\tau} &= \frac{A_i C_i}{G_i}\widetilde{v} x_i + \frac{A_i C_i}{G_i}\widetilde{u}_i y - G_i z_i + \frac{A_i C_i}{G_i} x_i y, \quad i = \overline{1, N}
\end{aligned}
$$

Notice that the nondimensionalization of the original system leads to the reduction of one parameter.

The translated system (10) reads in matrix form as

$$\left[\begin{array}{c}\dot{x}_1\\ \vdots\\ \dot{x}_N\\ \hline \dot{y}\\ \hline \dot{z}_1\\ \vdots\\ \dot{z}_N\end{array}\right] = \left[\begin{array}{c|c|c} -\operatorname{diag}\left(\frac{d_i}{\delta}+A_i\widetilde{v}\right) & -\begin{bmatrix}A_1\widetilde{u_1}\\ \vdots\\ A_N\widetilde{u_N}\end{bmatrix} & \operatorname{diag}(B_id_i)\\ \hline -\begin{bmatrix}C_1 & \dots & C_M\end{bmatrix}\widetilde{v} & -\left(1+\sum_{i=1}^N C_i\widetilde{u}_i\right) & \begin{bmatrix}D_1 & \dots & D_M\end{bmatrix}\\ \hline \operatorname{diag}\left(\frac{A_iC_i}{G_i}\right)\widetilde{v} & \begin{bmatrix}\frac{A_1C_1}{G_1}\widetilde{u_1}\\ \vdots\\ \frac{A_NC_N}{G_N}\widetilde{u_N}\end{bmatrix} & -\operatorname{diag}(G_i)\end{array}\right]\left[\begin{array}{c}x_1\\ \vdots\\ x_N\\ \hline y\\ \hline z_1\\ \vdots\\ z_N\end{array}\right] + \left[\begin{array}{c}-A_1x_1y\\ \vdots\\ -A_Nx_Ny\\ \hline -\sum_{i=1}^N C_ix_iy\\ \hline \frac{A_1C_1}{G_1}x_1y\\ \vdots\\ \frac{A_NC_N}{G_N}x_Ny\end{array}\right]$$

or, equivalently,

$$\dot{\xi} = M\xi + g(\xi), \tag{11}$$

where $\xi^T = \begin{bmatrix}x_1 & \dots & x_N & y & z_1 & \dots & z_N\end{bmatrix}$, $M = M_0 + \sum_{i=1}^N M_i$,

$$M_0 = \left[\begin{array}{c|c|c} -\operatorname{diag}\left(\frac{d_i}{\delta}\right) & O & \operatorname{diag}(B_id_i)\\ \hline O & -1 & \begin{bmatrix}D_1 & \dots & D_N\end{bmatrix}\\ \hline O & O & -\operatorname{diag}(G_i)\end{array}\right], \quad M_i = m_ir_i^T,$$

$$m_i^T = \left[\begin{array}{ccccc|c|ccccc} \cdots & 0 & -A_i & 0 & \cdots & -C_i & \cdots & 0 & \frac{A_iC_i}{G_i} & 0 & \cdots\end{array}\right],$$

$$r_i^T = \left[\begin{array}{ccccc|c|ccccc} \cdots & 0 & \widetilde{v} & 0 & \cdots & \widetilde{u}_i & 0 & \cdots & 0 & \cdots & 0\end{array}\right],$$

and

$$g(\xi) = \sum_{i=1}^N m_ix_iy.$$

Then the Jacobian matrix associated to the system (10) at a point $\xi \in \mathbb{R}^{2N+1}$ is

$$J(\xi) = M + \sum_{i=1}^{N} m_i(x_i + y), \quad \text{hence} \quad J(0) = M = M_0 + \sum_{i=1}^{N} M_i. \tag{12}$$

Remark 3.1. *The Jacobian matrix associated to the system (10) does not depend on $\widetilde{z}_j$. In order to investigate the stability of the origin for the "translated" system, we make use of Lyapunov's first Theorem* [9]. *To prove that the origin is an asymptotically stable equilibrium point for (10), it is sufficient to check that $J(0)$ is a Hurwitz matrix, or equivalently, there exists a symmetric positive definite matrix P such that*

$$M^T P + PM < 0 \Longleftrightarrow M_0^T P + PM_0 + \sum_{i=1}^{N} r_i p_i^T + \sum_{i=1}^{N} p_i r_i^T < 0, \;\; p_i = Pm_i. \tag{13}$$

For such a P, one can show that

$$r_i p_i^T + p_i r_i^T < r_i r_i^T + p_i p_i^T \leq \lambda_{max}(r_i r_i^T) I_{2N+1} + Pm_i m_i^T P,$$

where $\lambda_{max}(r_i r_i^T)$ denotes the largest eigenvalue of the matrix $r_i r_i^T$. Since

$$\lambda_{max}(r_i r_i^T) = \widetilde{v}^2 + \widetilde{u}_i^{\,2} \leq 2$$

it follows that the LMI (13) is satisfied whenever the following (Riccati) matrix inequality

$$M_0^T P + PM_0 + 2NI_{2N+1} + PBB^T P < 0, \quad \textit{where } B = \begin{bmatrix} m_1 & m_2 & \dots & m_N \end{bmatrix} \tag{14}$$

holds. Equivalently, by using a Schur complement argument the above inequality becomes

$$\begin{bmatrix} M_0^T P + PM_0 + 2NI_{2N+1} & PB \\ B^T P & -I_N \end{bmatrix} < 0. \tag{15}$$

From the above considerations the next important result follows.

Proposition 3.1. *If there exists a symmetric positive definite matrix P satisfying the above LMI (15), then the origin is an asymptotically stable equilibrium point for the translated system (11).*

This last relation is an LMI in the unknown P and can be solved by using existing semidefinite programming software packages.

As we will show in the next section, we have used the *cvx* programming environment developed by Boyd *et. al* [3] and run the SDPT3 semidefinite programming package.

4. **Numerical examples**

Consider $N = 2$ and the following parameters (coefficients): $b_1 = 4, b_2 = 6.5, \beta = 1.5$; $d_1 = 8, d_2 = 12, \delta = 10$; $k_1^+ = 10, k_2^+ = 5$; $k_1^- = 3, k_2^- = 0.1$; $K_1 = 0.8, K_2 = 1$ and $\sigma_1 = 1.5, \sigma_2 = 10$.

In this case the feasibility problem (15) has a positive definite solution

$$P = \begin{bmatrix} 12.3924 & -0.0335 & -1.3116 & 2.4327 & -0.6370 \\ -0.0335 & 10.6937 & -0.3507 & -0.0735 & -0.1067 \\ -1.3116 & -0.3507 & 4.8449 & 4.3219 & 3.8807 \\ 2.4327 & -0.0735 & 4.3219 & 22.2281 & 6.1714 \\ -0.6370 & -0.1067 & 3.8807 & 6.1714 & 16.3932 \end{bmatrix},$$

and the spectrum of P is $\Lambda_P = \{3.0416,\ 10.5606,\ 10.7062,\ 14.5428,\ 27.7011\}$. Furthermore, the spectrum of the left-hand side in (15) is

$$\Lambda = \{-0.0554,\ -0.5517 - 4.7919,\ -6.9898,\ -18.5232,\ -21.7859,\ -20.1738\}$$

confirming that the LMI is fulfilled.

5. **Conclusions**

In this paper we have derived a numerically tractable stability condition for verifying the asymptotic stability of the (unique) equilibrium point exhibited by the nondimensionalized mathematical model of several messenger RNAs and one micro RNA interaction.

Numerical experiments based on the Monte Carlo method show that the sufficiency condition in Proposition 3.1 induces a certain conservatism in the method: if the LMI (15) has no solution, this does not mean that the Jacobian matrix M is unstable. Indeed, for small values of δ, d_1 and d_2 the LMI (15) can become infeasible, while M remains stable.

Acknowledgements: We thank Professors Paul Flondor and Catalin Vasilescu for their helpful comments.

REFERENCES

[1] *M.A. Al-Radhawi and D. Angeli*, New approach to the stability of chemical reaction networks: piecewise linear in rates Lyapunov functions, IEEE Trans. Autom. Control, **61**(2016), 76-89.

[2] *I. Belgacem and J-L Gouze*. Global stability of full open reversible Michaelis-Menten reactions, In *Proceedings of the 8th IFAC Symposium on Advanced Control of Chemical Processes, Furama Riverfront, Singapore*, (2012).

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

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

[5] *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.

[6] *E.H. Flach and S. Schnell*, Stability of open pathways, Mathematical Biosciences, **228** (2010), 147-152.

[7] *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).

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

[9] *V.V. Stepanov and V.V. Nemytskii*, Qualitative Theory of Differential Equations, Dover, 1989.

[10] *M. Olteanu, M and R. Ştefan*, A note on the stability analysis of a class of nonlinear systems - an LMI approach, UPB Sci Bull, 80, issue 4, pp. 3–10.

[11] *C. Vasilescu, M. Olteanu, P. Flondor and G.A. Calin*, Fractal-like kinetics of intracellular enzymatic reactions: a chemical framework of endotoxin tolerance and a possible non-specific contribution of macromolecular crowding to cross-tolerance, Theoretical Biology and Medical Modelling, (2013) (doi:10.1186/1742-4682-10-55).