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RESEARCH PAPER

Model Reduction for Non-linear Protein Translation Pathways Using Slow and Fast Subsystems

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A B S T R A C T:

This paper reviews the mechanisms of miRNA model where mathematical models of miRNA translation are suggested to describe the dynamics of protein synthesis. In this regard, we use the idea of quasi steady state approximation (QSSA) for separating model equations into slow and fast subsystems. This separation is based on a proper scaling that we have used in this study. The suggested technique provides one to minimize the model elements and gives some analytical approximate solutions. Accordingly, the equation of slow manifold can be calculated from the simplified model. The slow manifold is sufficiently close to the analytical solutions when the slow-fast parameter becomes smaller. We apply three types of model coefficient analysis including, elasticity coefficients, flux control coefficients and concentration control coefficients. These techniques have three main goals. The first goal quantifies the sensitivity of reaction rates to the change of concentrations or parameters. The second goal is to measure the change of a flux along model pathways in response to a change in model reaction rates. The third goal is to calculate the change of concentrations while responding to a change in reaction rates.

KEY WORDS: miRNA protein translation, Mathematical modeling, Slow and fast subsystems, Quasi steady state approximation, Elasticity and control coefficients.
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1. INTRODUCTION :

Cells can be found in skin, muscles and bones. All of those cells include billions of proteins and enzymes. Indeed, proteins are fundamental of molecular for each living creature on the Earth (Cooper, 2000). There is an important part in cells that is called MicroRNA. MicroRNAs are a type of post-transcriptional well organized non-coding RNAs lately discovered in plants and animals. It has been shown that they regulate various biological procedures ranging from the embryotic development to the regularization of neural network model (Xu *et al*., 2009).

MicroRNAs (miRNAs) are 20 to 22 nucleotide RNAs that modulate the operation of eukaryotic mRNAs and have an important role in evolution, virus infection, stress responses, and cancer (Nissan and Parker, 2008). MicroRNAs are single-stranded RNA molecules of about 21 to 23 nucleotides in length, which modulate gene expression (Xu *et al*., 2009). There are some functions of miRNAs such as prevent translation of mRNAs,contributing mRNA and deadenylating progress (Eulalio *et al*., 2008, Filipowicz *et al*., 2008, Jackson and Standart, 2007, Valencia-Sanchez *et al*., 2006).

There are some main functions of MicroRNA where the most important function is related to gene expression regulation. For the first time, they were described in 1993 (Lee *et al*., 1993). In the

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Victor Ambros lab, and still the term microRNA was only introduced in 2001 (Ruvkun, 2001). As of early 2008, computational analysis by IBM proposed the existence of 50000 dissimilar microRNAs in the typical mammalian cell, each with perhaps a thousand or more possible targets (Glaser, 2008). Accordingly, MicroRNAs are recently well thought out as key regulators of a wide variety of biological pathways, including development, differentiation and on cogenesis.

Currently, remarkable advancement was made in understanding of microRNA functions, biogenesis and mechanisms of action.

The RISC effector complex and mature microRNAs are incorporated, which includes as a key component an Argonaut protein. MicroRNAs affect gene expression by guiding the RISC complex toward particular target mR NAs. It can be seen that there is a big controversial to determine the exact mechanism of this inhibition (Zinovyev *et al*., 2010); see Figure 1.

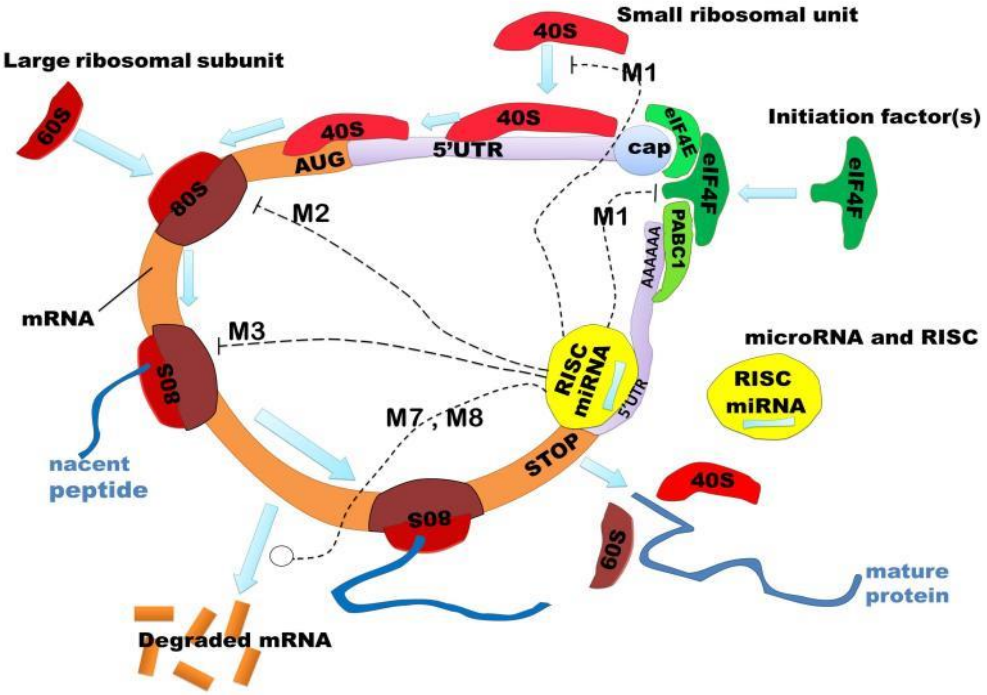


Figure 1: Protein translation process with microRNA mechanisms

In last decades, many possible mechanisms of microRNA have been recognized. The most of all documented mechanisms are negative post - transcriptional regulation of mRNA by mRNA translation inhabitancy and/or mRNA rotting. Whereas, there are some possibilities show that miRNAs might also act at the decomposition stage. There are also some studies in the present literature about to determine and decide which mechanism and in which situations has a control role in living cells. It is clear that some experimental systems handling with the same pairs of miRNA and mRNA. They can provide contentious evidences about which is the actual mechanism of translation subdue noticed in the experiment (Zinovyev et *al.*, 2013).

mRNA translation is an important procedure in cell signaling pathways that can be seen in many systems of biology. In this procedure, the genetic sequences are translated from mRNA to protein by ribosome translocation, after the genetic information included in DNA is transcribed to the mRNA. There are three important components in the mRNA translation process: the mRNA (genetic template), the ribosome (assembly machinery), and the aminoacyl transfer RNAs (aa-tRNAs).

mRNA protein translation is theoretically divided into three levels: initiation, elongation and termination. At the initiation stage, the ribosome first attaches to the mRNA then reads the mRNA codon by codon (from the 5' end of the mRNA to the 3' end). At the elongation stage, it recruits the

appropriate aa-tRNA and unites the latest amino acid into the nascent muster chain, releases the discharged tRNA. At the last stage of protein translation, the completed protein from the mRNA when the ribosome reaches the end of the mRNA eventually are released (Lewin, 2007).

There is a long history of mathematical modeling of mRNA. Models for mRNA then have been developed in recent years with the evolution of systems and synthetic biology. The various constructs of models for mRNA translation are introduced at various levels of abstraction (Zhao and Krishnan, 2014).

In this study, we give a detailed description for mathematical modelling of miRNA that describing the process of protein translation. We simply reviewed the previous study of miRNA protein translation given in (Zinovyev *et al.*, 2013). Then, we use quasi steady state approximation to separate equations into slow and fast subsystems and identifying some analytical approximate solutions for state variables. Finally, elasticity and control coefficient are calculated for the model network to identify effect of reaction rates, parameters and state variables on model dynamics.

2. Model Equations of miRNA

To explain the effect of microRNA interference with translation initiation factors, a non-linear version of the translation model was proposed. It explicitly takes into account recycling of initiation factors (eIF4F) and ribosomal subunits (40S and 60S).

The model has six chemical species *40S*, *60S*, *eIF4F*, *F*, *A*, and *R* and four chemical reactions, all considered to be irreversible; see Figure 2.

The model reactions are given below:
1. *40S* + *eIF4F* ⟶ *F*, assembly of the initiation complex (rate k_1).
2. *F* ⟶ *A*, some late and cap-independent initiation steps, such as scanning the 5'UTR for the start codon *A* (rate k_2).
3. *A* ⟶ *R*, assembly of ribosomes and protein translation (rate k_3).
4. 80S ⟶ 60S + 40S, recycling of ribosomal subunits (rate k_4).

We use stoichiometric vectors, reaction rates and mass action law to define the model equations (Khoshnaw, 2015a, Khoshnaw *et al*., 2016, Khoshnaw, 2015b).

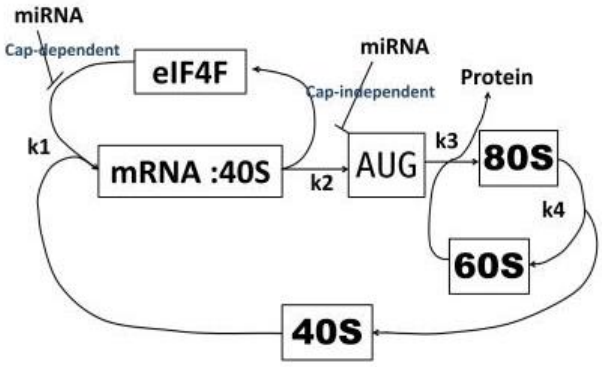


Figure 2: The model pathways for non-linear protein translation.

The model is described by the following system of nonlinear differential equations:

$$\begin{aligned}
\frac{d[40S](t)}{dt} &= -k_1[40S][eIf\,4F] + k_4[R],\\
\frac{d[eIF\,4F]}{dt} &= -k_1[40S][eIf\,4F] + k_2[F],\\
\frac{d[F](t)}{dt} &= k_1[40S][eIf\,4F] - k_2[F],\\
\frac{d[A](t)}{dt} &= k_2[F] - k_3[A][60S], \qquad (1)\\
\frac{d[60S]}{dt} &= -k_3[A][60S] + k_4[R],\\
\frac{d[R]}{dt} &= k_3[A][60S] - k_4[R],\\
Psynth(t) &= k_3[A](t).
\end{aligned}$$

System (1) contains three independent conservations laws:

$$\begin{aligned}
&[F]+[40S]+[A]+[R]=[40S]_0,\\
&[F]+[eIF\,4F]=[eIF\,4F]_0, \qquad (2)\\
&[60S]+[R]=[60S]_0,
\end{aligned}$$

where $[40S]_0$, $[60S]_0$ and $[eIF\,4F]_0$ are total amounts of small, big ribosomal subunits and the

initiation factor respectively. The following assumptions on the model parameters and initial variable states were suggested:

$$k_4 << k_1, k_2, k_3,$$
$$k_3 >> k_1, k_2, \quad (3)$$
$$[eIF4F]_0 << [40S]_0,$$
$$[eIF4F]_0 < [60S]_0 < [40S]_0.$$

More details and descriptions about the model equations and the proposed assumptions can be found in (Zinovyev *et al*., 2013).

3. Fast and Slow Subsystems for miRNA Model

Quasi steady state approximation (QSSA) is an important technique in systems biology. The method can be applied for nonlinear models to classify such systems into fast and slow subsystems and identify some analytical approximate solutions. More details about the QSSA method can be seen in (Khoshnaw, 2015a, Khoshnaw *et* al., 2016, Khoshnaw, 2015b). Based on conservation laws (2), we can remove the following variables:

$$eIF4F = [eIF4F]_0 - F,$$
$$60S = [60S]_0 - R, \quad (4)$$
$$A = [40S]_0 - 40S - F - R.$$

Then, system (1) becomes

$$\frac{d[40S](t)}{dt} = k_1[40S]F - k_1[eIF4F]_0[40S] + k_4R,$$
$$\frac{d[F](t)}{dt} = k_1[eIF4F]_0[40S] - k_1[40S]F - k_2F, \quad (5)$$
$$\frac{d[R](t)}{dt} = k_3[40S]_0[60S]_0 - k_3[60S]_0[40S] - k_3[60S]_0F$$
$$+ k_3[40S]R + k_3FR + k_3R^2 - (k3[60S]_0 + [40S]_0 + k_4)R.$$

By introducing the following new variables

$$x = \frac{[40S]}{[40S]_0}, y = \frac{F}{[eIF4F]_0}, z = \frac{R}{[eIF4F]_0}$$

and $\tau = k_1[eIF4F]_0 t.$ (6)

System (5) takes the form

$$\frac{dx}{d\tau} = x(y-1) + \rho z,$$
$$\varepsilon\frac{dy}{d\tau} = x(1-y) - \alpha_1 y, \quad (7)$$
$$\varepsilon\frac{dz}{d\tau} = \alpha_2(1-x) - \alpha_3 y + \alpha_4 xz + \varepsilon\alpha_4 yz$$
$$+ \varepsilon z^2 - (\alpha_3 + \alpha_4 + \rho)z,$$

where

$$\varepsilon = \frac{[eIF4F]_0}{[40S]_0}, \rho = \frac{k_4}{k_1[40S]_0}, \alpha_1 = \frac{k_2}{k_1[40S]_0},$$
$$\alpha_2 = \frac{k_3[60S]_0}{k_1[eIF4F]_0}, \alpha_3 = \frac{k_3[60S]_0}{k_1[40S]_0} \text{ and } \alpha_4 = \frac{k_3}{k_1}.$$

According to conditions (3),

$\rho = \frac{k_4}{k_1[40S]_0} \to 0$ when $k_4 << k_1$. Then, system (7) is completely on the form of slow and fast subsystems with six parameters. By applying QSSA technique, the system can be simplified when limit $\varepsilon \to 0$, the system takes the form

$$\frac{dx}{d\tau} = x(y-1) + \rho z, \quad (8a)$$
$$0 = x(1-y) - \alpha_1 y, \quad (8b)$$
$$0 = \alpha_2(1-x) - \alpha_3 y + \alpha_4 xz - (\alpha_3 + \alpha_4)z. \quad (8c)$$

We can analytically solve equations (8b) and (8c) for *y* and *z* in terms of *x*,

$$y = \frac{x}{\alpha_1 + x}, \quad (9a)$$
$$z = \frac{\alpha_3 x - \alpha_2(1-x)(\alpha_1 + x)}{(\alpha_4 x - \alpha_4 - \alpha_3)(\alpha_1 + x)}. \quad (9b)$$

Therefore, the approximate solution of system (7) is sufficiently close to the manifold M_0, where M_0 is defined as follows:

$$M_0 = \{(x, y, z) : x \in [0,1], \quad y = \frac{x}{\alpha_1 + x},$$
$$z = \frac{\alpha_3 x - \alpha_2(1-x)(\alpha_1 + x)}{(\alpha_4 x - \alpha_4 - \alpha_3)(\alpha_1 + x)}\}.$$

Thus, we obtain the following reduced differential equation close to the manifold M_0,

$$\frac{dx}{d\tau} = \frac{x^2}{\alpha_1 + x} - x. \qquad (10)$$

The above equation can be solved analytically.

The implicit solution of the separable differential equation takes the form

$$\alpha_1 \ln(x) + x = 1 - \alpha_1 \tau. \qquad (11)$$

$$[40S](t) = 1 + \frac{k_2}{k_1}\ln([40S]_0) - k_2[eIF4F]_0\, t - \frac{k_2}{k_1}\ln([40S](t)),$$

$$F(t) = \frac{[eIF4F]_0[40S](t)}{[40S](t) + \frac{k_2}{k_1}},$$

$$R(t) = \frac{[eIF4F]_0[60S]_0[40S](t) + [60S]_0([40S](t) - [40S]_0)(k_1[40S](t) + k_2)}{([40S](t) + \frac{k_2}{k_1})([40S](t) - [40S]_0 - [60S]_0)},$$

$$[eIF4F](t) = \frac{k_2[eIF4F]_0}{k_1[40S] + k_2},$$

$$[60S](t) = [60S]_0 - \frac{[eIF4F]_0[60S]_0[40S](t) + [60S]_0([40S](t) - [40S]_0)(k_1[40S](t) + k_2)}{([40S](t) + \frac{k_2}{k_1})([40S](t) - [40S]_0 - [60S]_0)},$$

$$A(t) = [40S]_0 - [40S](t) - \frac{[eIF4F]_0[40S](t)}{[40S] + \frac{k_2}{k_1}} - \frac{[eIF4F]_0[60S]_0[40S](t) + [60S]_0([40S](t) - [40S]_0)(k_1[40S](t) + k_2)}{([40S](t) + \frac{k_2}{k_1})([40S](t) - [40S]_0 - [60S]_0)},$$

$$Psynth(t) = k_3([40S]_0 - [40S](t) - \frac{[eIF4F]_0[40S](t)}{[40S] + \frac{k_2}{k_1}} - \frac{[eIF4F]_0[60S]_0[40S](t) + [60S]_0([40S](t) - [40S]_0)(k_1[40S](t) + k_2)}{([40S](t) + \frac{k_2}{k_1})([40S](t) - [40S]_0 - [60S]_0)}).$$

4. Analytical Approximate Solutions

In this section, the analytical solutions for the original model (1) are calculated. This is based on equations (11), (9), (6) and (4). All analytical solutions are given below:

It is obvious that the slow manifold M_0 is normally hyperbolic and stable. We assume that the functions $G_1(y,z)$ is the left side of equation (8b) and $G_2(y,z)$ is the left side of equation (8c). This means

$$G_1(y,z) = x(1-y) - \alpha_1 y, \qquad (12)$$

$$G_2(y,z) = \alpha_2(1-x) - \alpha_3 y + \alpha_4 xz - (\alpha_3 + \alpha_4)z.$$

Then, the Jacobian matrix of G_1 and G_2 is given:

$$J=\begin{pmatrix}\frac{\partial G_1}{\partial y} & \frac{\partial G_1}{\partial z}\\ \frac{\partial G_2}{\partial y} & \frac{\partial G_2}{\partial z}\end{pmatrix}=\begin{pmatrix}-(\alpha_1+x) & 0\\ -\alpha_3 & \alpha_4 x-\alpha_4-\alpha_3\end{pmatrix}.$$

The characteristic equation $\det(J-\lambda I)=0$ can be solved analytically to find the eigenvalues of the Jacobian matrix. We obtained the following eigenvalues:

$$\lambda_1=-(\alpha_1+x),$$
$$\lambda_2=\alpha_4 x-\alpha_4-\alpha_3.$$

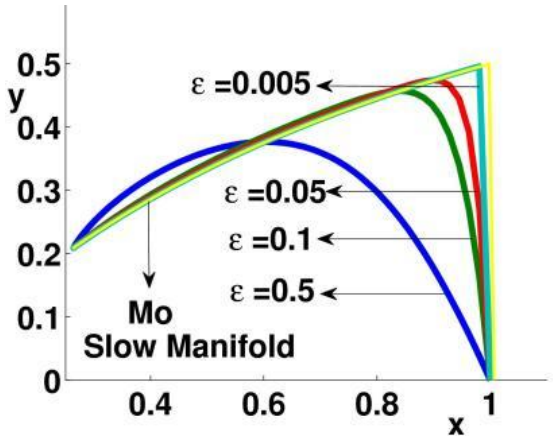
It is clear that the first eigenvalue is negative. It means $\lambda_1<0$ since

$x=\frac{[40S]}{[40S]_0}>0$ and $x=\frac{k_2}{k_1[40S]_0}>0$ .The other eigenvalue is also negative $\lambda_2<0$

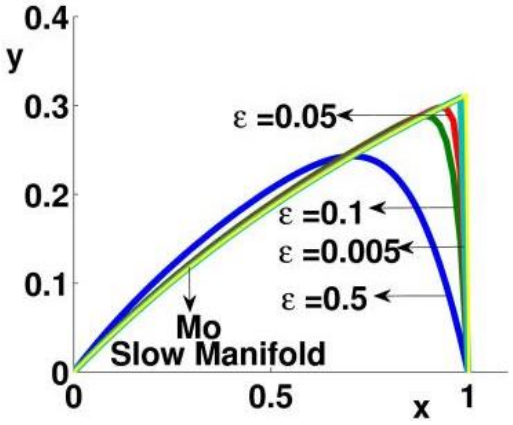
because $\alpha_3=\frac{k_3[60S]_0}{k_1[40S]_0}$ and $\alpha_4=\frac{k_3}{k_1}, k_3>>k_1,$

and $x\in[0,1]$.

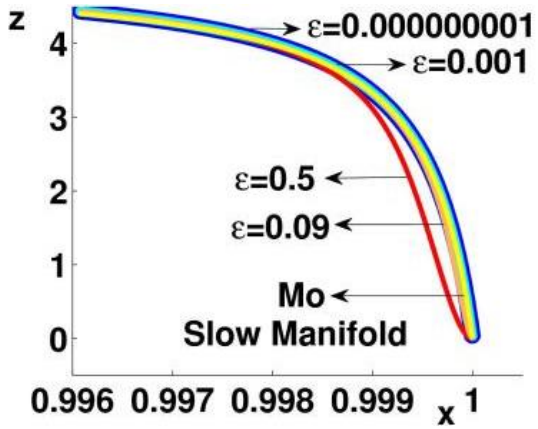
Since eigenvalues have negative real parts $\mathrm{Re}(\lambda_i)<0$, for i = 1, 2 then the slow manifold M_0 is stable. And the approximate solutions of equations (7) for different values of the small parameter ε can be expressed in Figure 3. The approximate solutions are sufficiently close to M_0 when the slow-fast parameter becomes smaller. We have compared the species concentrations of reduced model (10) and the full model (dimensionless form); see Figure 4.



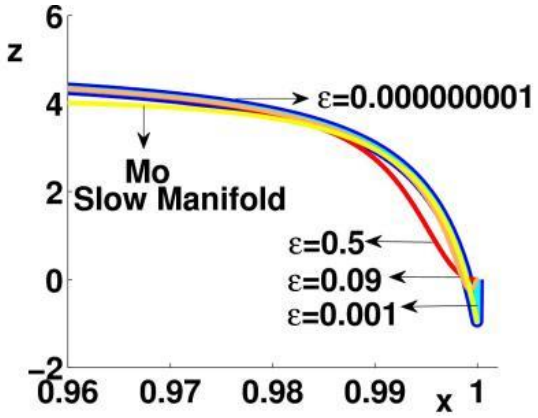
a) $\rho=1,\alpha_1=1,\alpha_2=3,\alpha_3=2$ and $\alpha_4=4$



b) $\rho=0.001,\alpha_1=2.2,\alpha_2=3,\alpha_3=2$ and $\alpha_4=4$



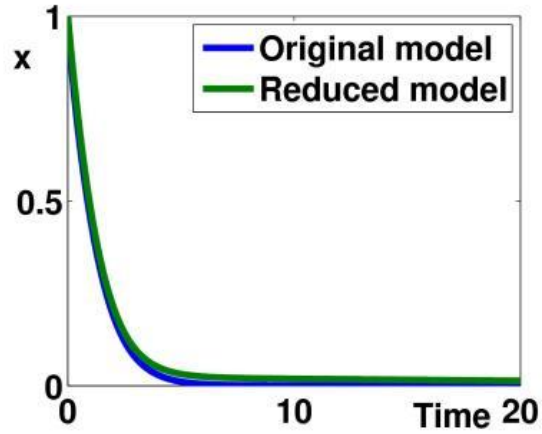
c) $\rho=0.0000000001,\alpha_1=0.0002,\alpha_2=25000000,$ $\alpha_3=0.25$ and $\alpha_4=500$



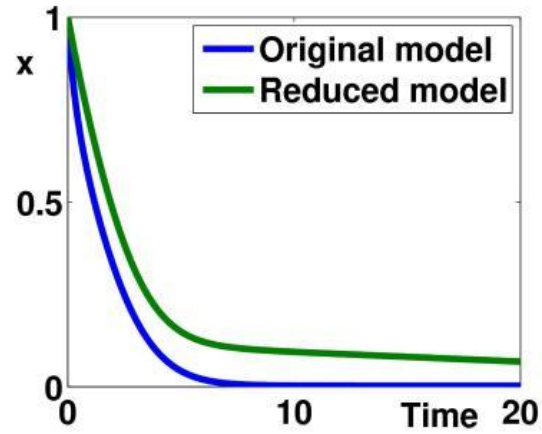
d) $\rho=0.00000001,\alpha_1=0.002,\alpha_2=250,\alpha_3=0.25$

and $\alpha_4=50$

Figure 3: Approximate solutions of equations (7) with slow manifold M_0.



a) $\rho = 0.001, \alpha_1 = 2.2, \alpha_2 = 3, \alpha_3 = 2$ and $\alpha_4 = 4$



b) $\rho = 0.005, \alpha_1 = 0.5, \alpha_2 = 3, \alpha_3 = 2$ and $\alpha_4 = 4$

Figure 4: Reduced model (10) and the full model (dimensionless form).

5. Elasticity and Control Coefficients for MicroRNA Model

The power to change metabolism states in response to an outer signaling is called metabolic control. It is measurable in terms of influence of the metabolic response to external factors. This is happened without any idea about the purpose /function/mechanism of the response (Newsholme and Start, 1973). The control structure of a metabolic pathway can be quantitatively characterized by metabolic control analysis (MCA). This is a mathematical frame work for describing metabolic, signaling, and genetic pathways. MCA quantifies how variables, such as fluxes and species concentrations, depend on network parameters. In particular, if MCA describes how networks depend on their properties, is called control coefficients. In addition, if MCA depending on its local properties, is called elasticities. By means of control and elasticity coefficients, the control coefficient is the fractional change in metabolic concentration (Puigjaner *et al*., 1997). Metabolic control analysis is an important step forward to determine the complexity of dynamic changes of species in a complex metabolic system (Li *et al*., 2010, Teusink *et al.*, 2000). There are three main types of coefficient analysis. The first one is elasticity coefficients that quantify the sensitivity of a reaction rate to the change of concentration or a parameter. The second type is flux control coefficients that measure the change of a flux along a pathway in response to a change in the reaction rates. The last one is concentration control coefficients that calculate the change of concentration of some metabolite species S_i in response of a change in the rate of a reaction (Newsholme and Start, 1973).

5.1. Elasticity

Elasticity coefficients are used in economics, physics, chemistry, or more generally in mathematics as a definition of point elasticity. The rate of reaction is affected by many different factors, such as pH, temperature, reactant and product concentrations and etc. The elasticity is defined effectively by factors on the reaction rates. Elasticities in biochemistry theory called kinetic orders and describe how sensitive a reaction rate is to changes in reactant, product and effector concentrations (Kacser *et al.*, 1995, Klipp *et al*., 2008, Sauro *et al*., 1987). The elasticity coefficient is the fractional change in the net rate for an individual substrate, with everything else is kept fixed (Puigjaner *et al*., 1997). The main equation of elasticity coefficient given by

$$E_{s_i}^{v_i} = \frac{\partial v}{\partial s}\frac{s}{v},$$

where v_i is reaction rate and s_i is concentration of species. The equation of elasticity measures the change of v_i in response to a change in s_i, while everything else is kept fixed. If we have substrate *S*, inhibition *I* and activation *A* in a pathway then some quantitative amounts can be considered.

There are some typical values for elasticity coefficients that satisfy the following inequalities:

$$E_s^v = \frac{\partial v}{\partial s}\frac{s}{v} > 0, \quad E_p^v = \frac{\partial v}{\partial p}\frac{p}{v} < 0.$$

That means more substrates are required to have fast rates, while more products give slower rates. In addition, if there are given inequalities

$$E_A^v = \frac{\partial v}{\partial A}\frac{A}{v} > 0, \quad E_I^v = \frac{\partial v}{\partial I}\frac{I}{v} < 0.$$

This gives us fast reaction rates required the higher activator concentration, whereas slow reaction rates are depended on the higher inhibitor concentration (Newsholme and Start, 1973).

5.2. Control Coefficients for MicroRNA Model.

A control coefficient quantifies the relative steady state change in a system variable, e.g. metabolite concentration *S* or pathway flux *J*, in response to a relative change in a parameter. We have two main control coefficients, they are concentration control coefficients and flux control coefficients (Kacser *et al*., 1995, Klipp *et al*., 2008, Sauro *et al*., 1987). The equation of flux control coefficients is defined below

$$C_{v_i}^J = \frac{\dfrac{dJ}{dp}\dfrac{p}{J}}{\dfrac{\partial v_i}{\partial p}\dfrac{p}{v_i}} = \frac{d\ln(J)}{d\ln(v_i)} = \frac{dJ}{dv_i}\frac{v_i}{J}.$$

The equation of concentration control coefficients is given by

$$C_{v_i}^s = \frac{\dfrac{ds}{dp}\dfrac{p}{s}}{\dfrac{\partial v_i}{\partial p}\dfrac{p}{v_i}} = \frac{d\ln(s)}{d\ln(v_i)} = \frac{ds}{dv_i}\frac{v_i}{s}.$$

The flux control coefficient $C_{v_i}^s$ gives the relative small change in (a system variable) concentration with small change in pathway flux *J*. The word flux *J* also used to describe the rate of the system. Therefore, changing in the concentration can be fluctuated between increasing and decreasing (Li *et al*., 2010, Teusink *et al*., 2000). Flux coefficients usually vary from 0 to 1. The concentration control coefficient $C_{v_i}^s$ gives the relative change in metabolite concentration *S*. The concentration control coefficients can have large values. They can also vary from negative to positive and small to large value (Li *et al*., 2010, Teusink *et al*., 2000).

Furthermore, there is a relationship between control coefficients and elasticity. The flux control summation theorem was discovered independently by Kacser/Burns group and Heinrich/Rapoport group in the early 1970s and late 1960s respectively. The flux control summation theorem implies that metabolic fluxes are systemic properties and that their control is shared by all reactions in the system. When a single reaction changes its control of the flux this is compensated by changes in the control of the same flux by all other reactions. The two important equations are proposed as follows:

$$\sum_i C_{v_i}^J = 1 \quad \text{and} \quad \sum_i C_{v_i}^s = 0.$$

The connectivity theorems are specific relationships between elasticities and control coefficients. They are useful because they highlight the close relationship between the kinetic properties of individual reactions and the system properties of a pathway. Two basic sets of theorems exist, one for flux and another for concentrations. The concentration connectivity theorems are divided again depending on whether the system species S_n is different from the local species S_m.

$$\sum_i C_{v_i}^J E_s^{v_i} = 0,$$

$$\sum_i C_{v_i}^{S_n} E_{S_m}^{v_i} = 0, \qquad n \neq m$$

$$\sum_i C_{v_i}^{S_n} E_{S_m}^{v_i} = -1 \qquad n = m.$$

5.3. Model Results

For system (1), we have the following reaction rates

$$v_1 = k_1[40S][eIF\,4F], v_2 = k_2 F, v_3 = k_3 A[60S]$$

and $v_4 = k_4 R.$

The following elasticity equations are calculated for system (1):

$$E^{v_1}_{[40S]} = \frac{\partial v_1}{\partial [40S]} \frac{[40S]}{v_1} =$$

$$k_1[eIF\,4F]\frac{[40S]}{k_1[40S][eIF\,4F]} = 1,$$

$$E^{v_2}_{[40S]} = E^{v_3}_{[40S]} = E^{v_4}_{[40S]} = 0,$$

$$E^{v_1}_{[eIF\,4F]} = 1, E^{v_2}_{[eIF\,4F]} = E^{v_3}_{[eIF\,4F]} = E^{v_4}_{[eIF\,4F]} = 0,$$

$$E^{v_1}_{[60S]} = E^{v_2}_{[60S]} = E^{v_4}_{[60S]} = 0, E^{v_3}_{[60S]} = 1, \qquad (13)$$

$$E^{v_1}_{F} = E^{v_3}_{F} = E^{v_4}_{F} = 0, E^{v_2}_{F} = 1,$$

$$E^{v_1}_{A} = E^{v_2}_{A} = E^{v_4}_{A} = 0, E^{v_3}_{A} = 1,$$

$$E^{v_1}_{R} = E^{v_2}_{R} = E^{v_3}_{R} = 0, E^{v_4}_{R} = 1.$$

In general, if an elasticity value is positive then reaction rates are increased. On the other hand, if elasticity value is negative then reaction rates are decreased. For the chemical reaction rates in system (1), we assume that [40S], [eIF4F] and [60S] are fixed boundary species. Therefore, the pathway can reach a steady state. Then, we can calculate the control coefficients for the remaining sates F, A and R. The model has some control coefficient equations based on summation and connectivity theorem as below:

$$C^{J}_{v_1} + C^{J}_{v_2} + C^{J}_{v_3} + C^{J}_{v_4} = 1,$$

$$C^{F}_{v_1} + C^{F}_{v_2} + C^{F}_{v_3} + C^{F}_{v_4} = 0,$$

$$C^{A}_{v_1} + C^{A}_{v_2} + C^{A}_{v_3} + C^{A}_{v_4} = 0,$$

$$C^{R}_{v_1} + C^{R}_{v_2} + C^{R}_{v_3} + C^{R}_{v_4} = 0,$$

$$C^{J}_{v_1}E^{v_1}_{F} + C^{J}_{v_2}E^{v_2}_{F} + C^{J}_{v_3}E^{v_3}_{F} + C^{J}_{v_4}E^{v_4}_{F} = 0,$$

$$C^{J}_{v_1}E^{v_1}_{A} + C^{J}_{v_2}E^{v_2}_{A} + C^{J}_{v_3}E^{v_3}_{A} + C^{J}_{v_4}E^{v_4}_{A} = 0,$$

$$C^{J}_{v_1}E^{v_1}_{R} + C^{J}_{v_2}E^{v_2}_{R} + C^{J}_{v_3}E^{v_3}_{R} + C^{J}_{v_4}E^{v_4}_{R} = 0, \qquad (14)$$

$$C^{F}_{v_1}E^{v_1}_{A} + C^{F}_{v_2}E^{v_2}_{A} + C^{F}_{v_3}E^{v_3}_{A} + C^{F}_{v_4}E^{v_4}_{A} = 0, F \neq A$$

$$C^{F}_{v_1}E^{v_1}_{R} + C^{F}_{v_2}E^{v_2}_{R} + C^{F}_{v_3}E^{v_3}_{R} + C^{F}_{v_4}E^{v_4}_{R} = 0, F \neq R$$

$$C^{A}_{v_1}E^{v_1}_{F} + C^{A}_{v_2}E^{v_2}_{F} + C^{A}_{v_3}E^{v_3}_{F} + C^{A}_{v_4}E^{v_4}_{F} = 0, A \neq F$$

$$C^{A}_{v_1}E^{v_1}_{R} + C^{A}_{v_2}E^{v_2}_{R} + C^{A}_{v_3}E^{v_3}_{R} + C^{A}_{v_4}E^{v_4}_{R} = 0, A \neq R$$

$$C^{R}_{v_1}E^{v_1}_{F} + C^{R}_{v_2}E^{v_2}_{F} + C^{R}_{v_3}E^{v_3}_{F} + C^{R}_{v_4}E^{v_4}_{F} = 0, R \neq F$$

$$C^{R}_{v_1}E^{v_1}_{A} + C^{R}_{v_2}E^{v_2}_{A} + C^{R}_{v_3}E^{v_3}_{A} + C^{R}_{v_4}E^{v_4}_{A} = 0, R \neq A$$

$$C^{F}_{v_1}E^{v_1}_{F} + C^{F}_{v_2}E^{v_2}_{F} + C^{F}_{v_3}E^{v_3}_{F} + C^{F}_{v_4}E^{v_4}_{F} = 0, n = m$$

$$C^{A}_{v_1}E^{v_1}_{A} + C^{A}_{v_2}E^{v_2}_{A} + C^{A}_{v_3}E^{v_3}_{A} + C^{A}_{v_4}E^{v_4}_{A} = 0, n = m$$

$$C^{R}_{v_1}E^{v_1}_{R} + C^{R}_{v_2}E^{v_2}_{R} + C^{R}_{v_3}E^{v_3}_{R} + C^{R}_{v_4}E^{v_4}_{R} = 0, n = m.$$

By substituting the elasticity values in equations (13) into equations (14), the following results are obtained

$$C_{v_1}^J = 1, C_{v_2}^J = C_{v_3}^J = C_{v_4}^J = 0,$$

$$C_{v_1}^F = 1, C_{v_2}^F = -1, C_{v_3}^F = C_{v_4}^F = 0,$$

$$C_{v_1}^A = 1, C_{v_3}^A = -1, C_{v_2}^A = C_{v_4}^A = 0,$$

$$C_{v_1}^R = 1, C_{v_4}^R = -1, C_{v_2}^R = C_{v_3}^R = 0.$$

According to flux control coefficients $C_{v_2}^J = C_{v_3}^J = C_{v_4}^J = 0$, this means that second, third and the last step of reactions have not any effect on model fluxes. On the other hand, the control coefficient $C_{v_1}^J = 1$, this gives us the first reaction rate has a strong effect on the model fluxes. In other words, the model steady state fluxes are controlled by v_1.

Furthermore, concentration control coefficients quantify how variables, such as species concentrations, depend on reaction rates. In this study, it can be more precisely concluded that there is no any relative change in F, A and R regarding to reaction rates v_2, v_3 and v_4. While, there is a significant change in F, A and R with respect to v_1.

6. Conclusions

The non-linear model of miRNA protein translation including seven species and four parameters has been studied. Mass action law and classical chemical kinetics under constant rates are used for modelling the system. We have introduced some new variables to reduce the number of model species and parameters. We proposed QSSA to analyze the fast variables and calculate slow manifolds. As a result, the analytical approximate solutions are sufficiently close to the manifolds when the slow-fast parameter becomes smaller. The analytical approximate solutions give some effective results particularly provided us understanding about global dynamics. It can be also noticed that there is a good agreement between the simplified and the original model dynamics.

Results in this study show some interesting points. The first point is that how variables, such as fluxes and species concentrations, depend on network parameters. Another point is that how reaction rates are sensitive to changes in reactant, product and concentrations. The proposed techniques will be applied to a wide range of complex miRNA mechanisms.

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