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MATHEMATICAL MODEL OF COUPLED TRANSCRIPTION, TRANSLATION AND DEGRADATION

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ABSTRACT

S*ynthesis of proteins is one of the most fundamental biological processes, which consumes a significant amount of cellular resources. Despite many efforts to produce detailed mechanistic mathematical models of translation, no basic and simple kinetic model of mRNA lifecycle (transcription, translation and degradation) exists. We present the approximate analytical solution the nonlinear differential equations that describe coupled transcription, translation and degradation. The simple and closed analytical expressions for the amount of mRNA with translation initiation site not occupied by assembling ribosome, mRNA with translation initiation site occupied by assembling ribosome, ribosomes sitting on mRNA synthesizing proteins, proteins have been derived by using homotopy perturbation method for all values of parameter. These results are compared with simulation results and are found to be in good agreement. The obtained results are valid for the whole solution domain.*

Keywords: *Mathematical modeling, Analytical solutions, Non-linear equation, Transcription, Translation and Degradation.*

1. INTRODUCTION

Production of proteins is one of the most fundamental cellular processes, taking up to 75% of cellular resources in terms of chemical energy. In simple microbes [1]. The translation – transcription process with the description of the most basic "elementary" processes consists in:

i) production of mRNA molecules, ii) initiation of these molecules by circularization with help of initiation factors, iii) initiation of translation, recruiting the small ribosomal subunit iv) assembly of full ribosomes v) elongation, i.e. movement of ribosomes along mRNA with production of protein vi) termination of translation vii) degradation of mRNA molecules viii) degradation of proteins

Certain complexity in the mathematical formulation of this process arises when one tries to take into account the phenomenon of polysome [2], when several ribosomes are producing peptides on a single mRNA at the same time. This leads to multiplicity of possible states of mRNA with various numbers of ribosomes and potentially different dynamics, interaction between ribosomes and other difficulties. The process of translation is a subject of mathematical modeling since long time ago [3]. Recent review of existing mathematical model are described in [4]. Nevertheless, no basic and simple kinetic description of the process involving transcription, translation and degradation was suggested until so far.

In the following we start with a 1) detailed mechanistic description of the translation process with explicit representation of every state of translated mRNA, followed by 2) deriving the simplest and basic kinetic model of coupled transcription, translation and degradation, and 3) extending this model in order to take into account various effects.

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The basic model is constructed by 1) correct lumping of the detailed model states and by 2) separating the descriptions of ribosomal turnover and the initiation through introducing a pool of translating ribosomes. The simplest model remains linear under assumption of that the local concentrations of ribosomal subunits or initiation factors remain constant or changes relatively slowly. To avoid non-physiological properties we modify the model by introducing unavoidable delays in the initiation of ribosome and the effects of riboasomes interaction. In this form, the model become more realistic but non-linear in some extension. More complex phenomena related to translation can be taken into account in direct simulatory models of the detailed representation of translation at the cost of more difficult analytical analysis of the model [5].

NOMENCLARURE&UNITS

Symbol	Meaning	Unit	Numerical value
k_1	Rate constant of translation initiated on already initated mRNAs	molecules/sec	0.5
k_2	Rate constant of ribosome assembly, including possible transientarrest of ribosomes before starting translation	molecules/sec	0.01
k_3	Rate including elongation and termination of translation in the absence of miRNA	molecules/sec	0.09
k_d	Rate constant of degradation of mRNA molecules,	molecules/sec	0.5
k_t	Rate constant of production of mRNA molecules,	molecules/sec	0.005
k_{rd}	Rate of ribosome drop-off	molecules/sec	1
k_p	Rate of protein degradation in the absence of miRNA	molecules/sec	2.5
M	Initiated mRNA with free translation	none	none
F	Initiated mRNA with free translation	none	none
R	Number of ribosomes on free-mRNA	none	none
P	Proteins	none	none

2. MATHEMATICAL FORMULATION OF THE PROBLEM

The reaction network describing transcription, translation and mRNA degradation is represented in fig (1)[6].

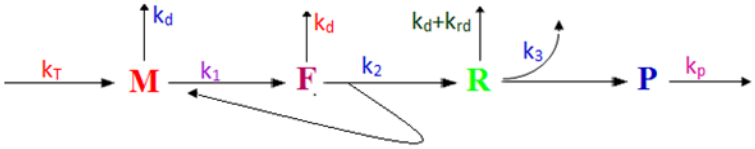


Figure-1

The corresponding rate equation for this model are given by thr following equations:

$$\frac{dM}{dt} = k_t - k_d M - k_1 M + k_2 F \quad (1)$$

$$\frac{dF}{dt} = k_1 M - k_d F - k_2 F \quad (2)$$

$$\frac{dR}{dt} = k_2 F - k_3 R - k_{rd} R - k_d R \quad (3)$$

$$\frac{dP}{dt} = k_3 R - k_p P \quad (4)$$

The initial conditions are when time $t = 0$ $M = M_i, F = F_i, R = R_i, P = P_i$

Where, M is the Initiated mRNA with free translation, F is the Initiated mRNA with translation,

R is the Number of ribosomes on free-mRNA, P is the Proteins, $k_1$is the rate constant of translation is initiated on already initated mRNAs (molecules/sec), k_2 is the rate constant of ribosome assembly, including possible transient arrest of ribosomes before starting translation (molecules/sec). k_3 is the Rate including elongation and termination of translation in the absence of miRNA. In all simulations of translation without miRNA k_t is the rate constant of production of mRNA molecules, k_d is Rate constant of degradation of mRNA molecules, k_{rd} is the Rate of ribosome drop-off and k_p is the Rate of protein degradation in the absence of miRNA

3. SOLUTION OF THE NON-LINEAR INITIAL VALUE PROBLEM USING THE HOMOTOPY PERTURBATION METHOD (HPM)

Non-linear phenomenon plays an important role in applied mathematical and physical science. Explicit solutions of the non-linear equations are the fundamental importance. Various methods for obtaining explicit solutions of non-linear equations have been proposed. Recently many authors have used the HPM for solving various problems and demonstrated the efficiency of the HPM for solving the non-linear problems in various physics and engineering problems [7-9]. This method is the combination of topology and classical perturbation techniques. He used the HPM to solve the Lighthill equation [10], the Diffusing equation [11] and the Blasius equation [12]. The idea has been used to solve non-linear boundary value problems, integral equations and many other problems. The homotopy perturbation method [13-15] is very effective and simple. The HPM is unique in its applicability, accuracy, efficiency uses the imbedding parameter *p* as a small parameter and only a few iterations are needed to search for asymptotic solutions This method is a combination of homotopy in topology and classic perturbation techniques. The HPM is unique in its applicability, accuracy and efficiency. In this method the imbedding parameter p as a small parameter, and only a few iterations are needed to search for an asymptotic solution. Using this method (Appendix A) we can obtain solution to the eqns. (1) - (4) as follows:

$$M(t) = \frac{k_t}{(k_d + k_1)}(1 - e^{-t(k_d+k_1)}) + M_i e^{-t(k_d+k_1)} + \frac{k_2 F_i (e^{-t(k_2+k_d)} - e^{-t(k_d+k_1)})}{(k_1 - k_2)} \tag{5}$$

$$F = F_i e^{-t(k_d+k_2)} + \frac{k_1 k_t}{(k_d+k_1)(k_d+k_2)} - \frac{k_1 k_t e^{-t(k_d+k_1)}}{(k_d+k_2-(k_d+k_1))} + \frac{k_1 M_i (k_d+k_1) e^{-t(k_d+k_1)}}{(k_d+k_2-(k_d+k_1))} + \left[\frac{k_1 k_t}{(k_d+k_2-(k_d+k_1))} - \frac{k_1 k_t}{(k_d+k_2)(k_d+k_1)} - \frac{k_1 M_i (k_d+k_1)}{(k_d+k_2-(k_d+k_1))} \right] e^{-t(k_d+k_2)} \tag{6}$$

$$R = R_i e^{-t(k_3+k_{rd}+k_d)} + \frac{k_2 F_i (e^{-t(k_2+k_d)} - e^{-t(k_{rd}+k_3+k_d)})}{(k_3+k_{rd}-k_2)} \tag{7}$$

$$P = P_i e^{-k_p t} + \frac{k_3 R_i (e^{-k_p t} - e^{-t(k_{rd}+k_3+k_d)})}{(k_3+k_{rd}+k_3-k_p)} \tag{8}$$

4. NUMERICAL SIMULATION

The non-linear differential equations (1)-(4) for the given initial conditions are solved by using homotopy perturbation methods. The function pdex 4 in Matlab software, which is a function of solving boundary value problems was used to solve these equations numerically and the Matlab programs are given in Appendix C of this manuscript. Figures 1, 2, 3 and 4 represent the comparison of analytical results obtained in this work with the numerical results. Upon comparison it is evident that both the results are in good agreement for different values of the reaction and diffusion parameters.

5. RESULTS AND DISCUSSION

Equation (5) to equation (8) represents the simple analytical expression pertaining to the initiated mRNA with free translation, initiated mRNA with translation, number of ribosomes on free-mRNA, proteins respectively. Figure (2) - (5) represents the comparison of analytical and numerical stimulation of the initiated mRNA with free translation M versus time t for different values of parameters k_1, k_2 , k_d , k_t respectively. From figure (2), it is inferred that the initiated mRNA with free translation increases when k_1, k_2 , k_d , k_t increases for some fixed value of other parameters. also initiated mRNA with free translation, initiated mRNA with translation, number of ribosomes on free-mRNA, proteins are always a decresing function for all values of parameters.

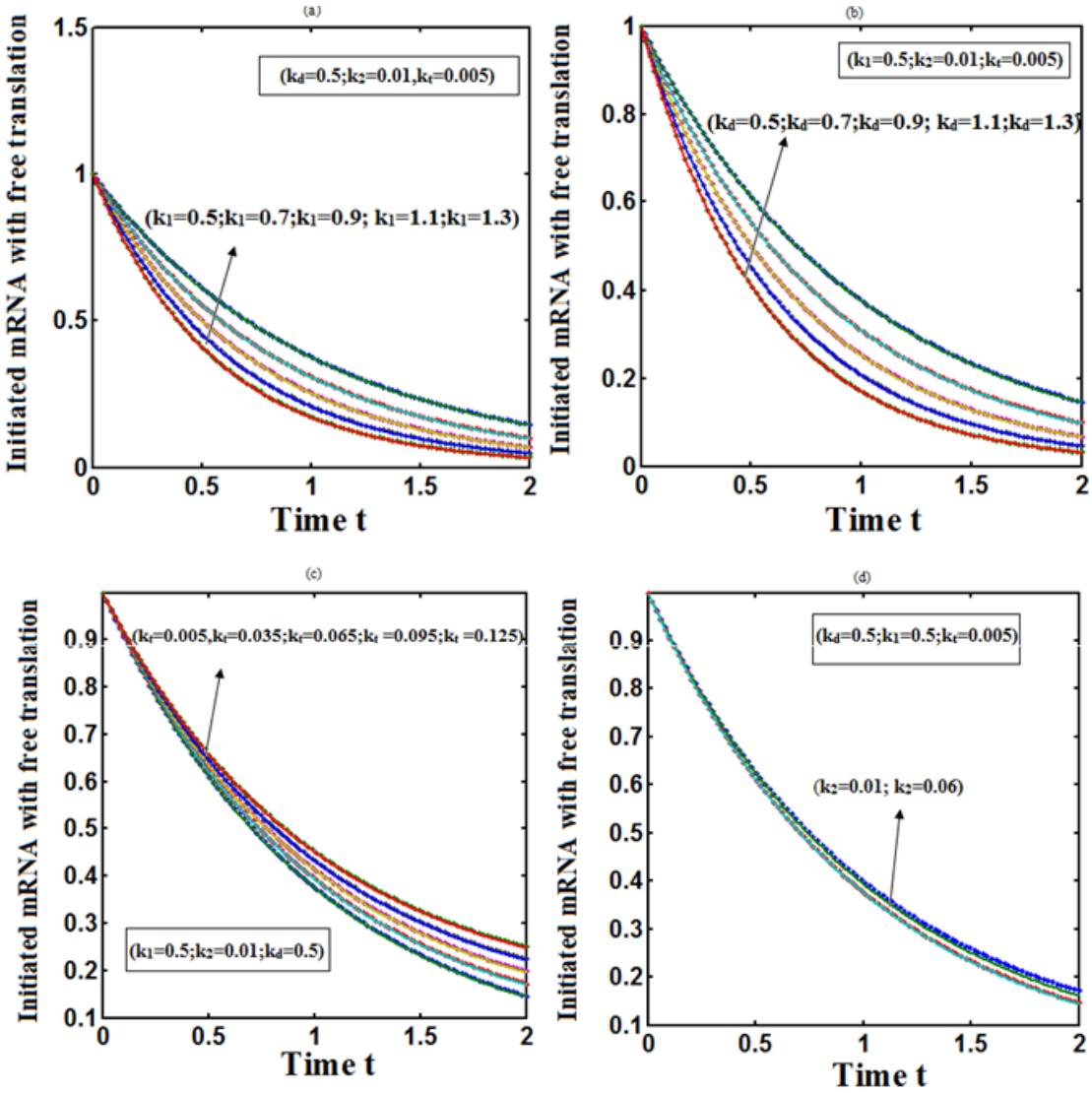
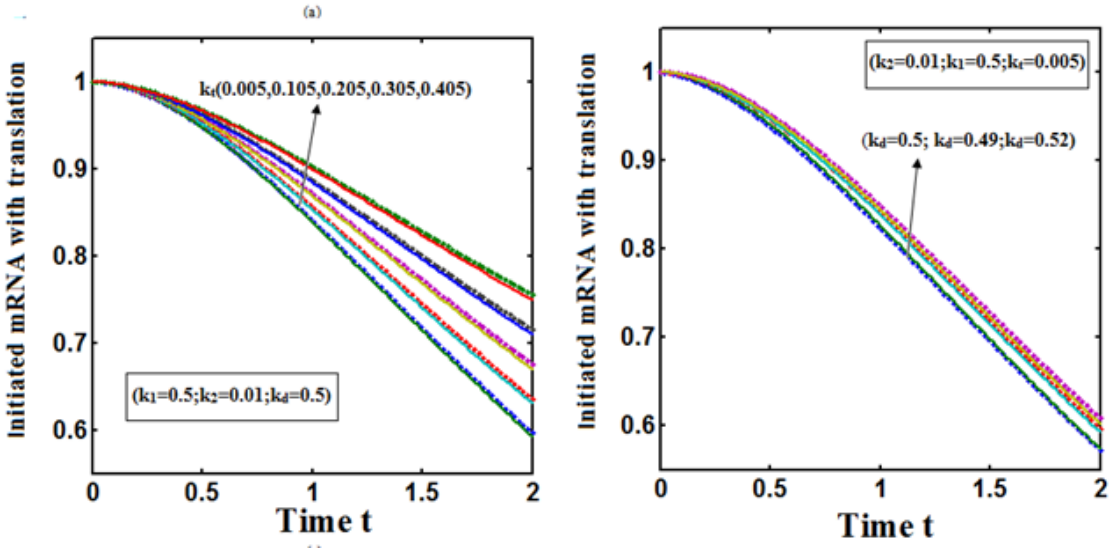


Figure-2

Figure-2: *Comparison of analytical and numerical stimulation of initiated mRNA with free translation M versus time t. The concentration is computed using Enq. (5) for various value of the rate constant of translation is initiated on already initated mRNAs (molecules/sec).The key to the graph: solid line represents the Eqn. (5) and dotted line represents the numerical solution.*



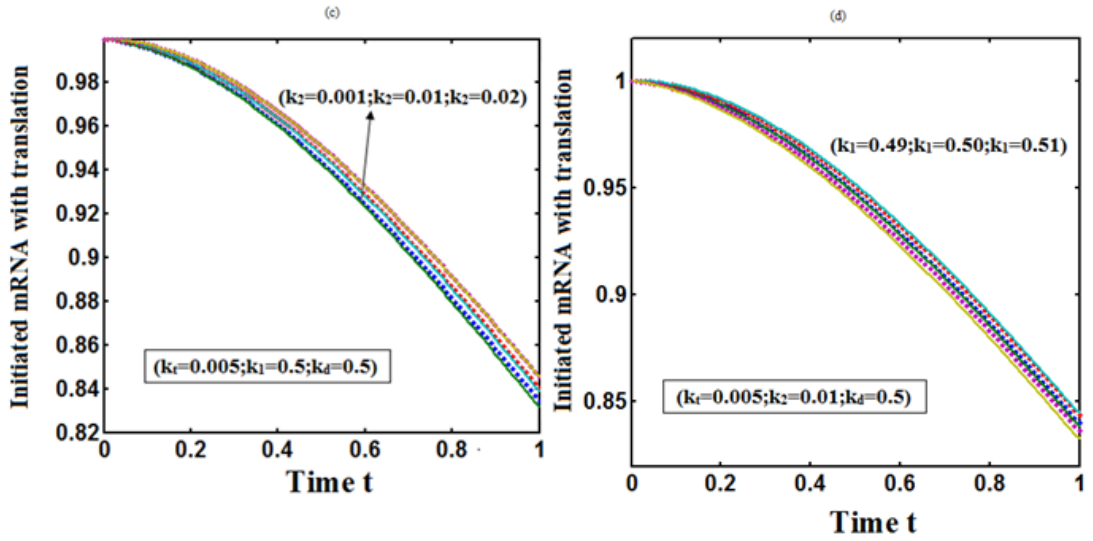


Figure-3

Figure-3: *Comparison of analytical and numerical stimulation of initiated mRNA with translation F versus time t. The concentration is computed using Eqn. (6) for various value of rate constant of production of mRNA molecules. The key to the graph: solid line represents the Eqn. (6) and dotted line represents the numerical solution.*

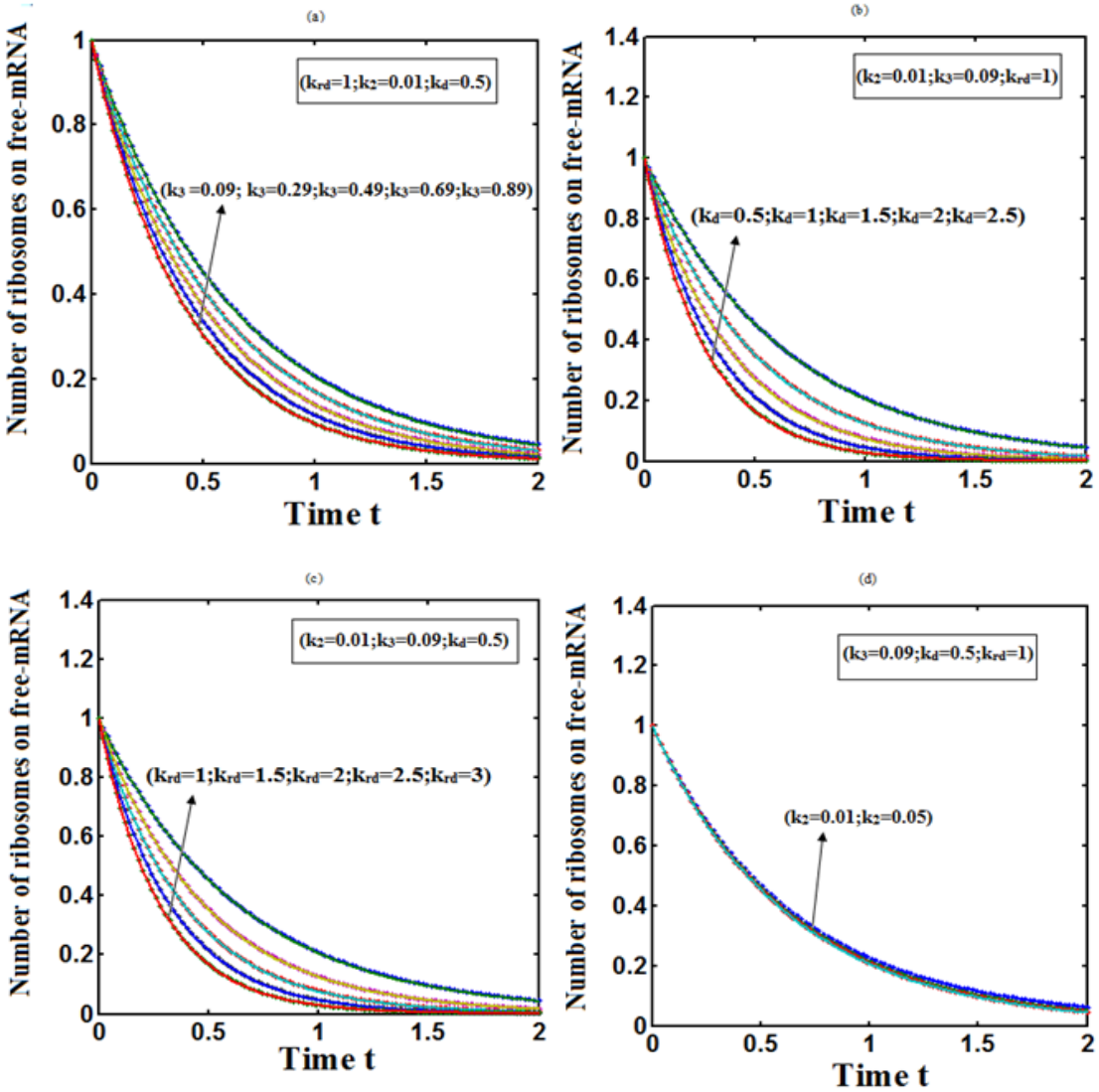


Figure-4

Figure-4: *Comparison of analytical and numerical stimulation of number of ribosomes on free-mRNA R versus time t. The concentration is computed using Eqn. (7) for various value of rate including elongation and termination of translation in the absence of miRNA. In all simulations of translation without miRNA. The key to the graph: solid line represents the Eqn. (7) and dotted line represents the numerical solution.*

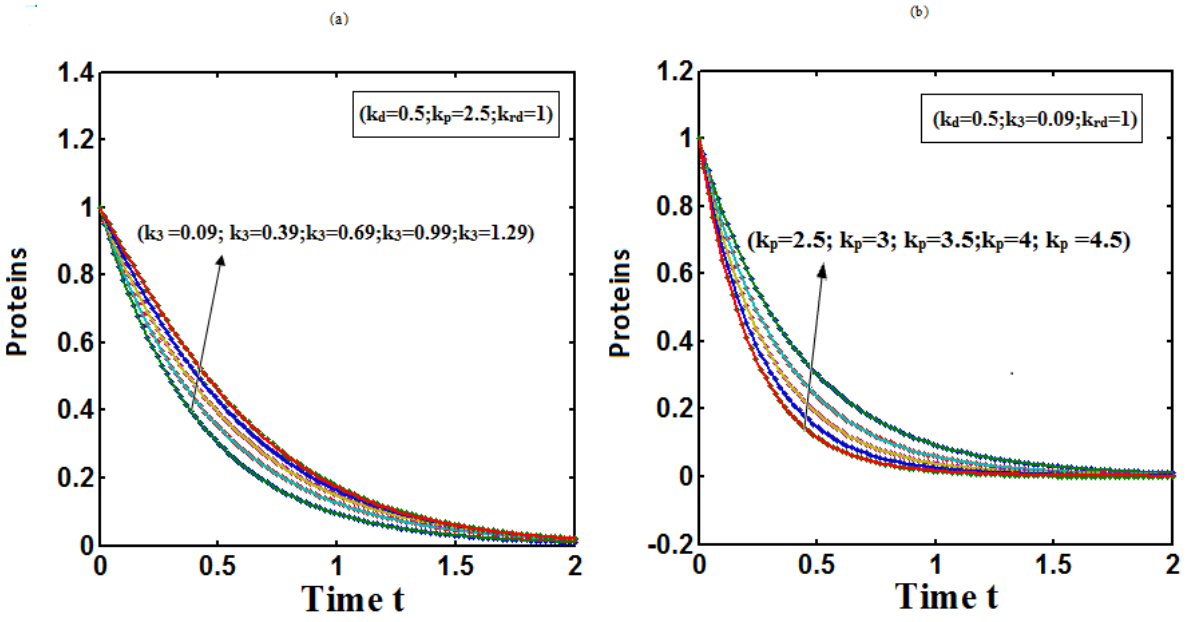


Figure-5

Figure-5: *Comparison of analytical and numerical stimulation of proteins P versus time t. The concentration is computed using Eqn. (8) for various value of rate including elongation and termination of translation in the absence of miRNA. In all simulations of translation without miRNA. The key to the graph: solid line represents the Eqn. (8) and dotted line represents the numerical solution.*

Figure (3) represents the comparison of analytical and numerical stimulation of the initiated mRNA with translation F versus time t for different values of k_1, k_2, k_d, k_t respectively. From figure (3a) & (3d) it is inferred that the initiated mRNA with translation increases when k_1, k_2, k_d, k_t increases for some fixed values of other parameters.

Figure (4) represents the comparison of analytical and numerical stimulation of the number of ribosomes on free-mRNA R versus time t for different values of k_3, k_2, k_d, k_{rd} respectively. From figure (4a) – (4c) it is inferred that the number of ribosomes on free-mRNA increases when all parameters increases.

Figure (5) represents the comparison of analytical and numerical stimulation of the proteins P versus time t for different values of respectively. From figure (5a) & (5b) it is inferred that the proteins increases when k_3, k_2, k_d, k_{rd} increases for some fixed values of other parameters.

CONCLUSION

In this paper, we have presented a mathematical model describing the coupled transcription, translation and degradation. In this work, the time dependent non-linear reaction equation has been solved analytically using homotopy petubration method. The approximate analytical expression for initiated mRNA with free translation, initiated mRNA with translation, number of ribosomes on free-mRNA and proteins for all values of parameters .We obtained a good agreement between numerical and analytical solutions. The analytical expressions are compared to the numerical simulation using Matlab software and satisfactory agreement is noted.

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APPENDIX-A*:* Basic concept of the Homotopy perturbation method (HPM)

To explain this method, let us consider the following function**[1-4]**

$$D_o(u) - f(r) = 0, \qquad r \in \Omega \tag{A.1}$$

with the boundary conditions of

$$B_o\left(u, \frac{\partial u}{\partial n}\right) = 0, \qquad r \in \Gamma \tag{A.2}$$

where D_o is a general differential operator, B_o is a boundary operator, $f(r)$ is a known analytical function and Γ is the boundary of the domain Ω. In general, the operator D_o can be divided into a linear part L and a non-linear part N. The eqn. (A.1) can therefore be written as

$$L(u) + N(u) - f(r) = 0 \tag{A.3}$$

By the Homotopy technique, we construct a homotopy $v(r, p) : \Omega \times [0,1] \to \Re$ that satisfies

$$H(v, p) = (1-p)[L(v) - L(u_0)] + p[D_o(v) - f(r)] = 0. \tag{A.4}$$

$$H(v, p) = L(v) - L(u_0) + pL(u_0) + p[N(v) - f(r)] = 0. \tag{A.5}$$

Where $p \in [0, 1]$ is an embedding parameter, and u_0 is an initial approximation of eqn. (A.1) that satisfies the boundary conditions. From eqns. (A.4) and (A.5), we have

$$H(v,0) = L(v) - L(u_0) = 0 \tag{A.6}$$

$$H(v,1) = D_o(v) - f(r) = 0 \tag{A.7}$$

When p=0, the eqns. (A.4) and (A.5) become linear equations. When p =1, they become non-linear equations. The process of changing p from zero to unity is that of $L(v) - L(u_0) = 0$ to $D_o(v) - f(r) = 0$. We first use the embedding parameter p as a "small parameter" and assume that the solutions of eqns. (A.4) and (A.5) can be written as a power series in p :

$$v = v_0 + pv_1 + p^2 v_2 + \ldots \tag{A.8}$$

Setting $p = 1$ results in the approximate solution of the eqn. (A.1):

$$u = \lim_{p \to 1} v = v_0 + v_1 + v_2 + \ldots \tag{A.9}$$

This is the basic idea of the HPM.

APPENDIX-B: Solution of the boundary value problem eqns. (1) - (4) using the homotopy perturbation method.

In this appendix, we indicate the equations (9) – (14) are derived in this paper. To find the solution of the equations (1) – (4), we construct a Homotopy as follows:

$$(1-p)\left[\frac{dM}{dt} - k_t + (k_d + k_1)M\right] + p\left[\frac{dM}{dt} - k_t + (k_d + k_1)M - k_2 F\right] = 0 \tag{B.1}$$

$$(1-p)\left[\frac{dF}{dt}+(k_d+k_2)F\right]+p\left[\frac{dF}{dt}-k_1M+(k_d+k_2)F\right]=0 \quad (B.2)$$

$$(1-p)\left[\frac{dR}{dt}+(k_3+k_{rd}+k_d)R\right]+p\left[\frac{dR}{dt}-k_2F+(k_3+k_{rd}+k_d)R\right]=0 \quad (B.3)$$

$$(1-p)\left[\frac{dP}{dt}+k_pP\right]+p\left[\frac{dP}{dt}-k_3R+k_pP\right]=0 \quad (B.4)$$

Supposing the approximate solutions of Eqn. (1-4) have the form

$$M=M_0+pM_1+p^2M_2+... \quad (B.5)$$

$$F=F_0+pF_1+p^2F_2+... \quad (B.6)$$

$$R=R_0+R_1p+p^2R_2+... \quad (B.7)$$

$$P=P_0+P_1p+p^2P_2+... \quad (B.8)$$

$$(1-p)\left[\frac{d(M_0+M_1p+.....)}{dt}+(M_0+M_1p+.....)(k_d+k_1)-k_t\right]+$$
$$p\left[\frac{d(M_0+M_1p+.....)}{dt}+(M_0+M_1p+.....)(k_d+k_1)-k_t-k_2(F_0+F_1p+.....)\right]=0 \quad (B.9)$$

$$(1-p)\left[\frac{d(F_0+F_1p+....)}{dt}+(k_d+k_1)(M_0+M_1p+...)\right]+$$
$$p\left[\frac{d(F_0+F_1p+....)}{dt}+(k_d+k_1)(M_0+M_1p+...)-k_1(M_0+M_1p+...)\right]=0 \quad (B.10)$$

$$(1-p)\left[\frac{d(R_0+R_1p+....)}{dt}+(k_{rd}+k_3+k_d)(R_0+R_1p+...)\right]+$$
$$p\left[\frac{d(R_0+R_1p+....)}{dt}+(k_{rd}+k_3+k_d)(R_0+R_1p+...)-k_2(F_0+F_1p+...)\right]=0 \quad (B.11)$$

$$(1-p)\left[\frac{d(P_0+P_1p+....)}{dt}+k_p(P_0+P_1p+...)\right]+$$
$$p\left[\frac{d(P_0+P_1p+....)}{dt}+k_p(P_0+P_1p+...)-k_3(R_0+R_1p+...)\right]=0 \quad (B.12)$$

Substituting the Eqns. (B.5-B.8) respectively into Eqns. (B.1-B.4) and equate the terms with the identical powers of p, we obtain

$$p^0:\frac{dM_0}{dt}+(k_d+k_1)M_0=k_t \quad (B.13)$$

$$p^0:\frac{dF_0}{dt}+(k_d+k_2)F_0=0 \quad (B.14)$$

$$p^0:\frac{dR_0}{dt}+(k_3+k_{rd}+k_d)R_0=0 \quad (B.15)$$

$$p^0:\frac{dP_0}{dt}+k_pP_0=0 \quad (B.16)$$

$$p^1:\frac{dM_1}{dt}+M_1(k_d+k_1)=k_2F_0 \quad (B.17)$$

$$p^1:\frac{dF_1}{dt}+F_1(k_d+k_2)=k_1M_0 \quad (B.17)$$

$$p^1 : \frac{dR_1}{dt} + R_1(k_3 + k_{rd} + k_d) = k_2 F_0 \tag{B.19}$$

$$p^1 : \frac{dP_1}{dt} + P_1 k_p = k_3 R_0 \tag{B.20}$$

solving the above equation using the initial condition

$$M_0(t=0) = M_i,\ F_0(t=0) = F_i,\ \ R_0(t=0) = R_i,\ \ P_0(t=0) = P_i$$
$$and\ \ M_1(t=0) = 0,\ F_1(t=0) = 0,\ \ R_1(t=0) = 0,\ \ P_1(t=0) = 0$$

$$M_0 = \frac{k_t}{(k_d + k_1)}(1 - e^{-t(k_d + k_1)}) + M_i e^{-t(k_d + k_1)} \tag{B.21}$$

$$M_1 = \frac{k_2 F_i (e^{-t(k_2 + k_d)} - e^{-t(k_d + k_1)})}{(k_1 - k_2)} \tag{B.22}$$

$$F_0 = F_i e^{-t(k_d + k_2)} \tag{B.23}$$

$$F_1 = \frac{k_1 k_t}{(k_d + k_1)(k_d + k_2)} - \frac{k_1 k_t e^{-t(k_d + k_1)}}{(k_d + k_2 - (k_d + k_1))} + \frac{k_1 M_i (k_d + k_1) e^{-t(k_d + k_1)}}{(k_d + k_2 - (k_d + k_1))} + \left[\frac{k_1 k_t}{(k_d + k_2 - (k_d + k_1))} - \frac{k_1 k_t}{(k_d + k_2)(k_d + k_1)} - \frac{k_1 M_i (k_d + k_1)}{(k_d + k_2 - (k_d + k_1))} \right] e^{-t(k_d + k_2)} \tag{B.24}$$

$$R_0 = R_i e^{-t(k_3 + k_{rd} + k_d)} \tag{B.25}$$

$$R_1 = \frac{k_2 F_i (e^{-t(k_2 + k_d)} - e^{-t(k_{rd} + k_3 + k_d)})}{(k_3 + k_{rd} - k_2)} \tag{B.26}$$

$$P_0 = P_i e^{-k_p t} \tag{B.27}$$

$$P_1 = \frac{k_3 R_i (e^{-k_p t} - e^{-t(k_{rd} + k_3 + k_d)})}{(k_3 + k_{rd} + k_3 - k_p)} \tag{B.28}$$

Using the two iterations of hpm we get

$$M = M_0 + M_1 = \frac{k_t (1 - e^{-t(k_d + k_1)}) + M_i (k_d + k_1) e^{-t(k_d + k_1)}}{(k_d + k_1)} + \frac{k_2 F_i (e^{-t(k_2 + k_d)} - e^{-t(k_d + k_1)})}{(k_1 - k_2)} \tag{B.29}$$

$$F = F_0 + F_1 = F_i e^{-t(k_d + k_2)} + \frac{k_1 k_t}{(k_d + k_1)(k_d + k_2)} - \frac{k_1 k_t e^{-t(k_d + k_1)}}{(k_d + k_2 - (k_d + k_1))} + \frac{k_1 M_i (k_d + k_1) e^{-t(k_d + k_1)}}{(k_d + k_2 - (k_d + k_1))} + \left[\frac{k_1 k_t}{(k_d + k_2 - (k_d + k_1))} - \frac{k_1 k_t}{(k_d + k_2)(k_d + k_1)} - \frac{k_1 M_i (k_d + k_1)}{(k_d + k_2 - (k_d + k_1))} \right] e^{-t(k_d + k_2)} \tag{B.30}$$

$$R = R_0 + R_1 = R_i e^{-t(k_3 + k_{rd} + k_d)} + \frac{k_2 F_i (e^{-t(k_2 + k_d)} - e^{-t(k_{rd} + k_3 + k_d)})}{(k_3 + k_{rd} - k_2)} \tag{B.31}$$

$$P = P_0 + P_1 = P_i e^{-k_p t} + \frac{k_3 R_i (e^{-k_p t} - e^{-t(k_{rd} + k_3 + k_d)})}{(k_3 + k_{rd} + k_3 - k_p)} \tag{B.32}$$

APPENDIX-C: Matlab/Scilab program is to find the numerical solution of the eqns. (1)-(4)

```
function main1
options= odeset('RelTol',1e-6,'Stats','on');
Xo =[1;1;1;1];
tspan = [0,2];
tic
[t,X] = ode45(@TestFunction,tspan,Xo,options);
toc
figure
holdon
plot(t, X(:,1))
plot(t, X(:,2))
plot(t, X(:,3))
%plot(t, X(:,4))
return
function [dx_dt]= TestFunction(t,x)
k1=.5;k2=.01;kd=.5;kt=.005;krd=1;kp=2.5;k3=.09;
dx_dt(1)=(kt)-(kd*x(1))-(k1*x(1))+(k2*x(2));
dx_dt(2)=(k1*x(1))-(kd*x(2))-(k2*x(2));
dx_dt(3)=(k2*x(2))-(k3*x(3))-(krd*x(3))-(kd*x(3));
dx_dt(4)=(k3*x(3))-(kp*x(4));
dx_dt = dx_dt';
return
```

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