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Delay Differential Equation Model of Gene Expression

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Abstract: In this study, a delay differential equation model of gene expression for both retroviruses and normal cell is proposed to study the dynamics of functional gene products. The model is categorised into two sub-models to understand the characteristics of a cell by incorporating time delays in the processes of gene expression. The first model which is for retroviruses, involves time delay in replication, transcription, reverse transcription and translation processes taking place in the cell, while in the second model which is for normal cell, the time delay in transcription and translation processes are incorporated. A numerical solution is obtained using semi-temporal data set. The impact of time delays on temporal concentration profile of DNA, mRNA and proteins have been analysed which gives better insight into the normal cell as well as retroviruses. Further, sensitivity analysis has been performed for both models to study the behaviour of gene expression in the cell. The results obtained from such models can be useful for biomedical applications.

Keywords: DNA, RNA, proteins, delay differential equations

1. INTRODUCTION

The cell has a very sophisticated control system which dynamically initiates, sustains and terminates the processes of replication, transcription, reverse transcription and translation in the cell. Another vital characteristic of a control system of the cell is its ability to dynamically delay the processes of replication, transcription, reverse transcription and translation in order to regulate the concentrations of DNA, mRNA and proteins. Apart from this, the delay may be caused in these processes of the cell due to some external influence, noise in the cell signal, any abnormality in the environment or due to any disease. The delay in these processes may either be useful to the cell or may have some harmful effects on the cell and the organism. Thus, these delays in the processes may contribute positively to the control system of the cell and its gene expression or it may have a negative impact on the control system of the cell. Experimental investigations have been performed by a number of research workers to study the expression [2, 3, 6, 8]. The experimental investigations are quite expensive and time-consuming, and therefore the scientists have also explored the theoretical approaches to study the gene expression [5, 15, 18, 20, 21, 22].

Further, mathematical modeling plays a vital role for better understanding of the complex real-world problems in every area, for example, supply chain management, inventory theory etc [23]. In terms of differential equations, delay differential equations are more appropriate for modeling of the complex real-world problem, for example, prey-predator model [12, 17], chemostat models [31], circadian rhythms [24], epidemiology [7], the respiratory system [27], tumor growth [28] and neural networks [4]. Thus, delay differential equation is one of the possible approaches to deal and unravel the complexities of real-world problems, and gene

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expression entities are also one of them. According to experimental data, there are some delays in the processes of replication, transcription, reverse transcription and translation to be completed, for example, the transcription process takes about 20 minutes to complete and a model is reported having both transcriptional and translational time delays [13]. Some delay differential equation models are reported in the literature for the study of gene expression [1, 10, 11]. A model with discrete time delay, by using Lindstedt's method and the Hopf bifurcation is reported to study the gene expression [26]. Also, a temporal model, which demonstrates the intracellular signalling using delay differential equations is reported in the literature [25]. Also, some research workers have developed a model with distributed time delay and with translational time delay using the fourth order Runge-Kutta method to study gene expression [9, 16].

Further, in spite of experimental and theoretical investigations, the gene expression has still not been well understood. Thus, in order to have a better understanding of gene expression and control system of the cell, it is necessary to develop models of gene expression involving delays in the processes of a cell. Also, from the literature survey, it is evident that very few attempts are reported in the literature for modeling of gene expression using delay differential equation, and no attempts are reported in the literature for the development of Michaelis-Menten's mechanism-based delay differential equations model to study gene expression. In this paper, two models based on delay differential equation are proposed to study the gene expression. The Michaelis-Menten's mechanism is incorporated in these models. In the first model, the time delay in all four processes replication, transcription, reverse transcription and translation has been considered. In the second model, transcription and translation processes are considered with different time delay. The impact of time delays on the temporal concentration profile of DNA, mRNA and proteins have been analysed with the help of numerical results. The mathematical model is presented in the next section.

2. MATHEMATICAL MODEL

In this section, two different delay differential equation models are proposed for the gene expression in retroviruses and a normal cell, respectively. In order to develop the model, the following assumptions are made:

1. There can be time delays in the processes of replication, transcription, reverse transcription and translation.
2. The variation in the temperature is constant throughout the model, so that, there is no effect of temperature on replication, transcription, reverse transcription and translation processes in the gene.
3. The rates of replication, transcription, reverse transcription and translation processes in the cell lie in the interval $[0, 1]$.
4. A single cell is considered throughout the model, and as the replication of DNA occurs at the time of cell division in the baby cell from the mother cell, it is assumed that the replication occurs in the cell.
5. A single protein is synthesized in a single mRNA transcript.

In the present study, two mathematical models have been proposed using Michaelis-Menten's mechanism. In the first model, the processes of replication, transcription, reverse transcription and translation are incorporated as these processes take place in retroviruses. The first model called "Model-I" is described by the system of delay differential equations $(2.1) - (2.3)$:

$$\frac{dw}{dt} = k_0 w(t-\tau_1) - k_1 w(t-\tau_2) + k_2 x(t-\tau_3), \tag{2.1}$$

$$\frac{dx}{dt} = k_1 w(t-\tau_2) - k_2 x(t-\tau_3) - k_3 x(t-\tau_4), \tag{2.2}$$

$$\frac{dp}{dt} = k_3 x(t-\tau_4), \quad t \geq 0, \tau_i > 0, i = 1,2,3,4. \tag{2.3}$$

Here k_0, k_1, k_2 and k_3 are constants.

In the second model, it is assumed that the replication and reverse transcription processes are absent, and transcription and translation processes are taking place in the cell. In general, the replication process stops taking place in a mature cell and the reverse transcription is absent in a normal cell. In view of the above, the second model is proposed incorporating transcription and translation processes only. The second model called "Model-II" is described by the system of delay differential equations $(2.4) - (2.6)$:

$$\frac{dw}{dt} = -k_1 w(t-\tau_2), \tag{2.4}$$

$$\frac{dx}{dt} = k_1 w(t-\tau_2) - k_3 x(t-\tau_4), \tag{2.5}$$

$$\frac{dp}{dt} = k_3 x(t-\tau_4), \quad t \geq 0, \tau_i > 0, i = 2,4. \tag{2.6}$$

We consider systems of differential equations $(2.1) - (2.3)$ and $(2.4) - (2.6)$ with the initial condition function $\phi\colon\ [-\tau, 0] \to \mathbb{R}^3$, where τ represents time delay. The time delays are taken as positive constants [30]. Further, if all $\tau_i = 0$, then there is no delay in the system and for without delay system, the initial condition is consider as $w(t) = w_0, x(t) = x_0, p(t) = p_0$. Here

$w(t)$	Concentration of DNA in the cell at time t (in second).
$x(t)$	Concentration of mRNA in the cell at time t (in second).
$p(t)$	Concentration of protein in the cell at time t (in second).
k_0	Rate of replication (microgram/second).
k_1	Rate of transcription (microgram/second).
k_2	Rate of reverse transcription (microgram/second).
k_3	Rate of translation (microgram/second).
ϕ	Initial history function.
τ	Time delay.
τ_1	Delay in replication process.
τ_2	Delay in transcription process.
τ_3	Delay in reverse transcription process.
τ_4	Delay in translation process.

For numerical solution, we use the built-in MATLAB programme in the optimization toolbox [19] for both Model-I and Model-II, which is presented in the next section.

3. RESULTS

The rates of replication, transcription, reverse transcription and translation processes will depend on the circumstances and capacity of the cell, and therefore k_0, k_1, k_2 and k_3 can be assigned different values. The data of the strain TJK16 is used to compute the results [6]. Generally, the values of k_0, k_1, k_2 and k_3 lie between $[0, 1]$ [14, 29]. The results obtained for the above system of delay differential equations of both Model-I and Model-II, Table 3.1, along with the comparison study between with time delay and without time delay of both models, are shown in Fig. 3.1 and Fig. 3.2.

Here, four cases are discussed regarding the time lag of replication, transcription, reverse transcription and translation processes, which are shown in Table 3.2. In the first case,

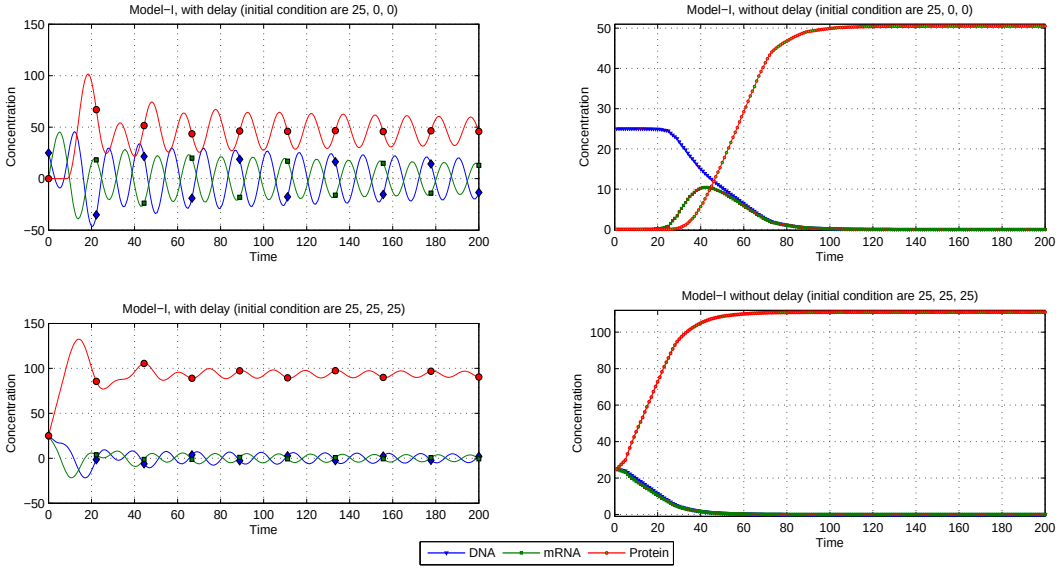

Fig. 3.1. Graphical representation of the solution of the concentrations of DNA, mRNA and protein with time delay in the replication, transcription, reverse transcription and translation processes (both left figures where the initial conditions of DNA, mRNA and protein are (25, 0, 0) and (25, 25, 25) respectively), and without time delay in the replication, transcription, reverse transcription and translation processes are shown (both right figures where the initial conditions of DNA, mRNA and protein are (25, 0, 0) and (25, 25, 25) respectively, of Model-I). The values of parameters are spatio-temporal which exhibit the stability of the system.

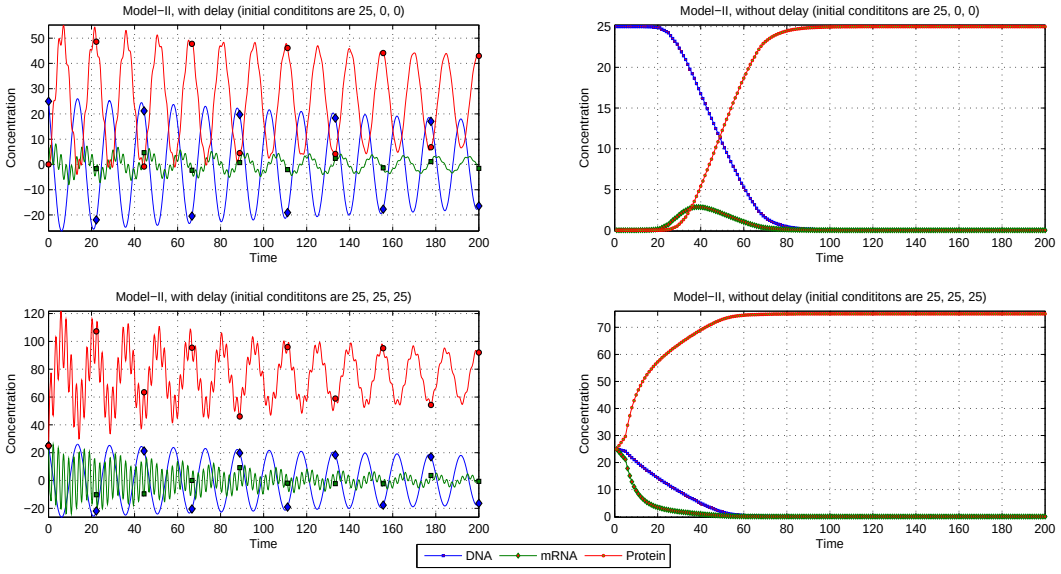

Fig. 3.2. Graphical representation of the solution of the concentrations of DNA, mRNA and protein with time delay in the replication, transcription, reverse transcription and translation processes (both left figures where the initial conditions of DNA, mRNA and protein are (25, 0, 0) and (25, 25, 25) respectively), and without time delay in the replication, transcription, reverse transcription and translation processes are shown (both right figures where the initial conditions of DNA, mRNA and protein are (25, 0, 0) and (25, 25, 25) respectively, of Model-II). The parameter values of transcription and translation rates $K_1 = 0.42, k_3 = 2.59$ respectively, are taken from the literature [29].

Table 3.1. Parameters related to functional gene products DNA, mRNA and protein for strain TJK16 of both models I and II, and the time is t=200 sec.

	Model-I	Model-II
Replication lag τ_1 (in second)	1.7	-
Transcription lag τ_2 (in second)	2.3	3.7
Reverse transcription lag τ_3 (in second)	5.2	-
Translation lag τ_4 (in second)	8.6	0.6
Replication rate k_0 (microgram/second)	0.1425	-
Transcription rate k_1 (microgram/second)	0.4785	0.42
Reverse transcription rate k_2 (microgram/second)	0.2568	-
Translation rate k_3 (microgram/second)	0.3691	2.59
Time t (in second)	200	200

Table 3.2. Parameters related to the time lag in the replication, transcription, reverse transcription and translation processes of functional gene products DNA, mRNA and protein for strain TJK16 at time t=200 sec.

Model-I	$\tau_1 < \tau_2 < \tau_3 < \tau_4$	$\tau_1 > \tau_2 > \tau_3 > \tau_4$	$\tau_1 = \tau_2 > \tau_3 = \tau_4$	$\tau_1 > \tau_2 < \tau_3 < \tau_4$
Replication lag τ_1 (in second)	1.7	7.0	4.2	1.7
Transcription lag τ_2 (in second)	2.3	6.2	4.2	1.2
R. transcri. lag τ_3 (in second)	5.2	3.1	1.9	5.2
Translation lag τ_4 (in second)	8.6	1.9	1.9	8.6
Time t (in second)	200	200	200	200

the time lag of replication, transcription, reverse transcription and translation processes are taken in increasing order as $\tau_1 < \tau_2 < \tau_3 < \tau_4$ respectively. In the second case, the time lag of replication, transcription, reverse transcription and translation processes are taken in decreasing order as $\tau_1 > \tau_2 > \tau_3 > \tau_4$ respectively. In the third case, the time lag of replication process is equal to the transcription process, and the time lag of reverse transcription process is equal to the translation process, which is taken as $\tau_1 = \tau_2 > \tau_3 = \tau_4$. Finally, in the fourth case, the time lag of the replication process is greater than that of the transcription process and in turns lesser than both the reverse transcription and translation processes, which are taken as $\tau_1 > \tau_2 < \tau_3 < \tau_4$.

The above mentioned conditions of time lag for Model-I are taken in the replication, transcription, reverse transcription and translation processes, respectively and the results are shown in Fig. 3.3.

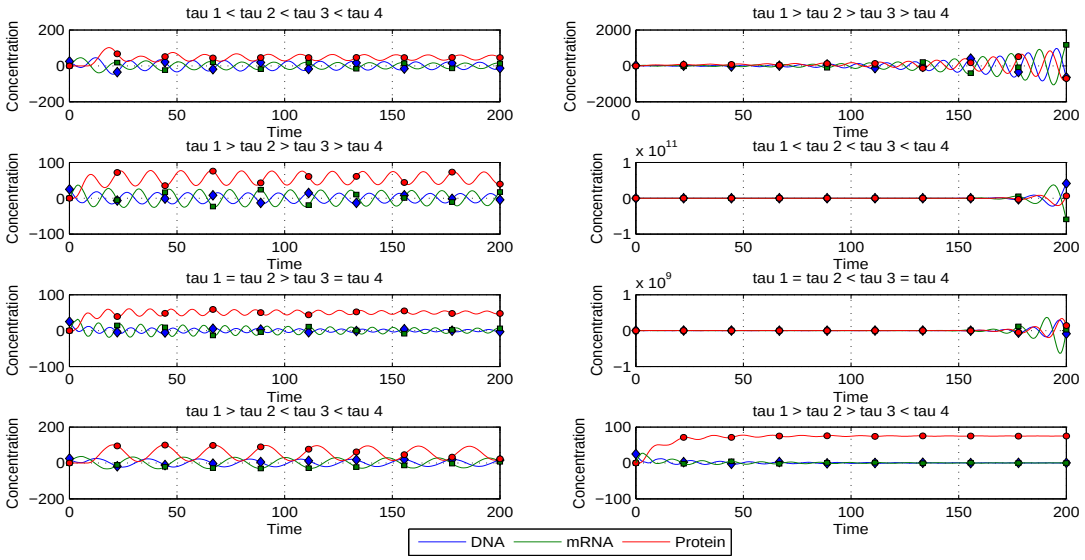

Fig. 3.3. Change in the concentrations profiles of functional gene products with the change in time lags of Model-I. The above graphical representation shows the change in the concentrations of DNA, mRNA and protein with different time lags taken in the replication, transcription, reverse transcription and translation processes, respectively. The left figures show the stability of the model while the right figures except for the fourth one (right lower figure) indicate that the system is not stable and the system bursts. The right figures are generated after reversing the order of time lags corresponding to each left figures, respectively.

4. SENSITIVITY ANALYSIS

The model can be demonstrated precisely using sensitivity analysis. Based on sensitivity, it can be revealed that the particular model is stable, semi-stable or unstable. Regarding this, we consider both models I and II for sensitivity analysis. First, we analyze the sensitivity of both the models based on the rates of replication, transcription, reverse transcription and translation processes. For Model-I, the results are given in Table 4.3 and the graphical solutions are shown in Fig. 4.4, Fig. 4.5, Fig. 4.6 and Fig. 4.7, while for Model-II, the results are shown in Table 4.4, and the graphical solutions are shown in Fig. 4.8 and Fig. 4.9.

Secondly, we analyze the sensitivity of both models based on lags or delays in replication, transcription, reverse transcription and translation processes. For Model-I, the results are given in Table 4.5, and shown in Fig. 4.10, 4.11, 4.12 and 4.13, while for Model-II, the results are given in Table 4.6, and shown in Fig. 4.14 and 4.15.

5. DISCUSSION

In the left parts of Fig. 3.1 we observe the variation in the concentration of DNA, mRNA and protein with delay in the processes and without delay in the processes for the initial values of DNA, mRNA and protein as (25, 0, 0) for a newly born cell and (25, 25, 25) for mature cell, respectively. The oscillations are observed in DNA, mRNA and protein concentrations due to the delays in the processes in replication, transcription, reverse transcription and translation (both left parts of Fig. 3.1), and in case of without delays, the smooth curves are seen in DNA, mRNA and proteins concentrations when the delay is absent in replication, transcription, reverse transcription and translation processes (both right parts of Fig. 3.1). Due to change in the initial values of DNA, mRNA and proteins concentrations from (25, 0, 0) to (25, 25, 25), the small oscillation is observed (both left parts of Fig. 3.1). In case of processes

Table 4.3. Sensitivity analysis of Model-I with the parameter k_0, k_1, k_2 and k_3, respectively, and the initial condition of each DNA, mRNA and protein concentration as 25 micrograms. The value of delays τ_1, τ_2, τ_3 and τ_4 is 1.7, 2.3, 5.2 and 8.6, respectively.

Model-I	Replication rate k_0 (microgram/second) 0.1425			
	+20%	+50%	-20%	-50%
Replication rate k_0 (microgram/second)	0.1710	0.2138	0.1140	0.0713
DNA concentration (in microgram)	-52.3469	2.4164e+03	-0.3831	-5.3790
mRNA concentration (in microgram)	35.1480	-2.6285e+03	0.2160	-7.9647
Protein concentration (in microgram)	144.1702	34.4349	87.6179	96.5009
	Transcription rate k_1 (microgram/second) 0.4785			
Transcription rate k_1 (microgram/second)	0.5742	0.7178	0.3828	0.2393
DNA concentration (in microgram)	126.7853	5.6552e+05	1.8871e+03	-1.7556e+06
mRNA concentration (in microgram)	-93.0348	-4.6064e+05	-1.1285e+03	9.6616e+06
Protein concentration (in microgram)	8.8427	-1.9215e+05	-1.4282e+03	-1.2712e+07
	Reverse transcription rate k_2 (microgram/second) 0.2568			
Reverse transcription rate k_2 (microgram/second)	0.3082	0.3852	0.2054	0.1284
DNA concentration (in microgram)	1.4106e+03	-1.9018e+03	0.2606	488.0431
mRNA concentration (in microgram)	-1.3330e+03	1.6340e+06	-0.0292	-8.5203
Protein concentration (in microgram)	-32.0213	7.4441e+05	90.3924	-416.6525
	Translation rate k_3 (microgram/second) 0.3691			
Translation rate k_3 (microgram/second)	0.4430	0.5537	0.2953	0.1846
DNA concentration (in microgram)	-0.4949	-6.2232e+03	30.9181	-750.3591
mRNA concentration (in microgram)	0.4716	-5.5662e+03	-31.0534	742.9808
Protein concentration (in microgram)	88.9815	1.5255e+03	103.0534	295.4582

without delay, when the initial values of DNA, mRNA and proteins concentrations changes from (25, 0, 0) to (25, 25, 25), the oscillation in the concentration of mRNA has vanished (both right parts of Fig. 3.1). For the proposed Model-II, there are only transcription and translation processes with delays. In Fig. 3.2, the same behaviour of the DNA, mRNA and

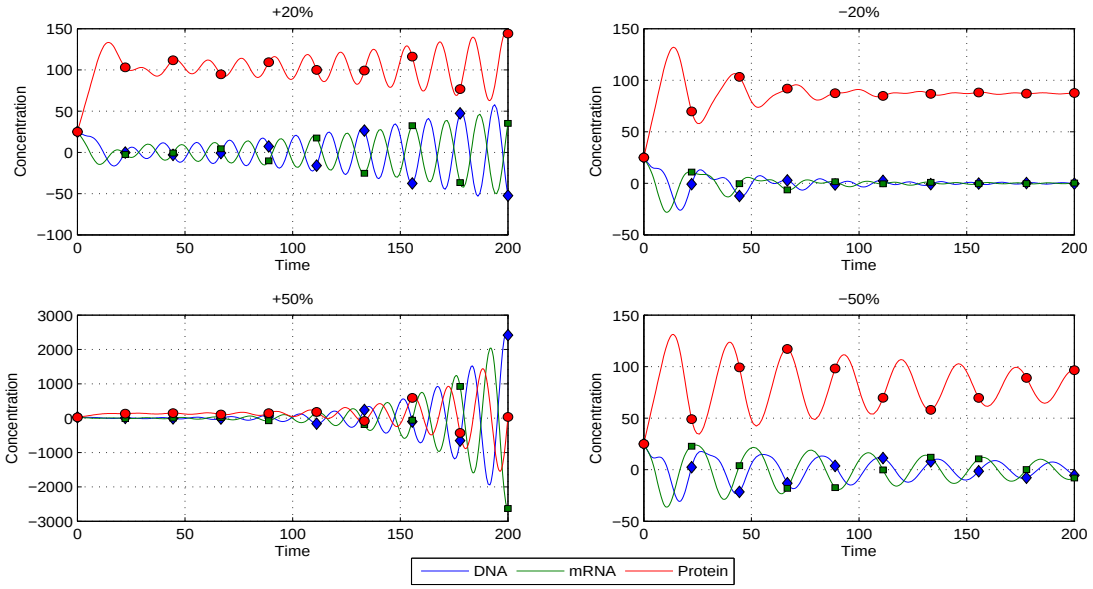

Fig. 4.4. Sensitivity analysis of the parameter replication rate of Model-I with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

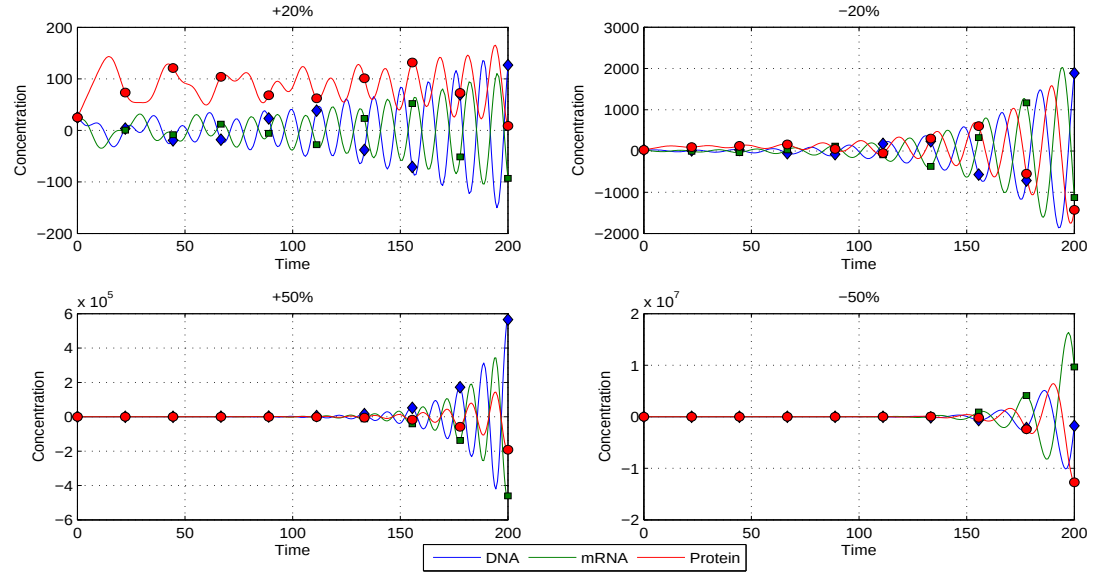

Fig. 4.5. Sensitivity analysis of the parameter transcription rate of Model-I with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

protein concentration profiles are observed as shown in Fig. 3.1 where oscillations occur due to delays in transcription and translation processes and smooth curves are observed due to no delay in transcription and translation processes. The values of concentrations profiles of DNA, mRNA and protein are different in both Fig. 3.1 and Fig. 3.2. Overall, both figures depicted that Model-I and Model-II are stable.

Further, four cases related to delays in the replication, transcription, reverse transcription and translation processes of Model-I are shown in Fig. 3.3. The concentration profiles of DNA, mRNA and protein vary with the change in delays of replication, transcription, reverse

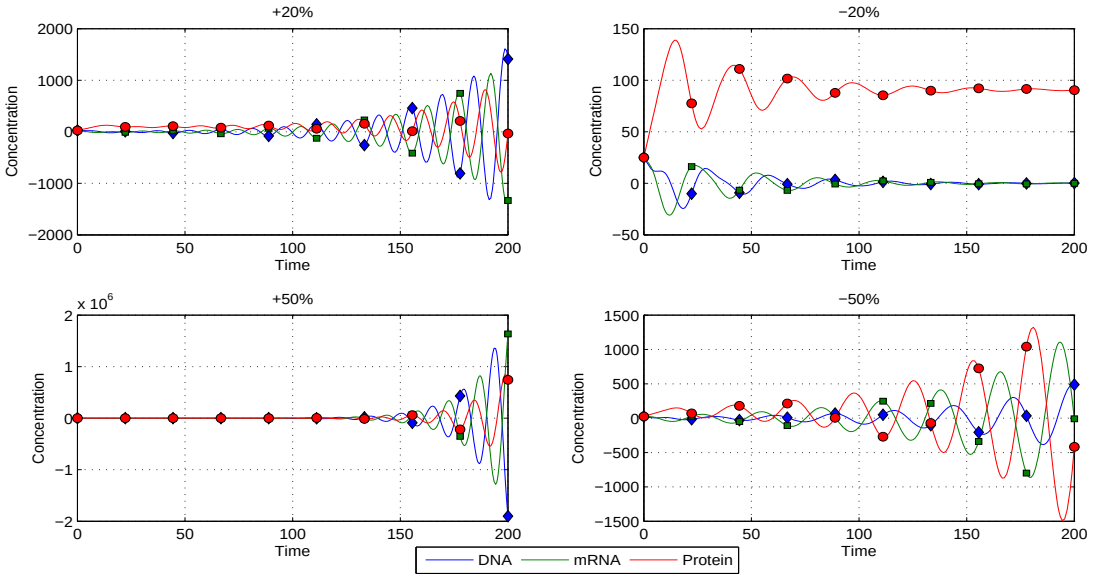

Fig. 4.6. Sensitivity analysis of the parameter reverse transcription rate of Model-I with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

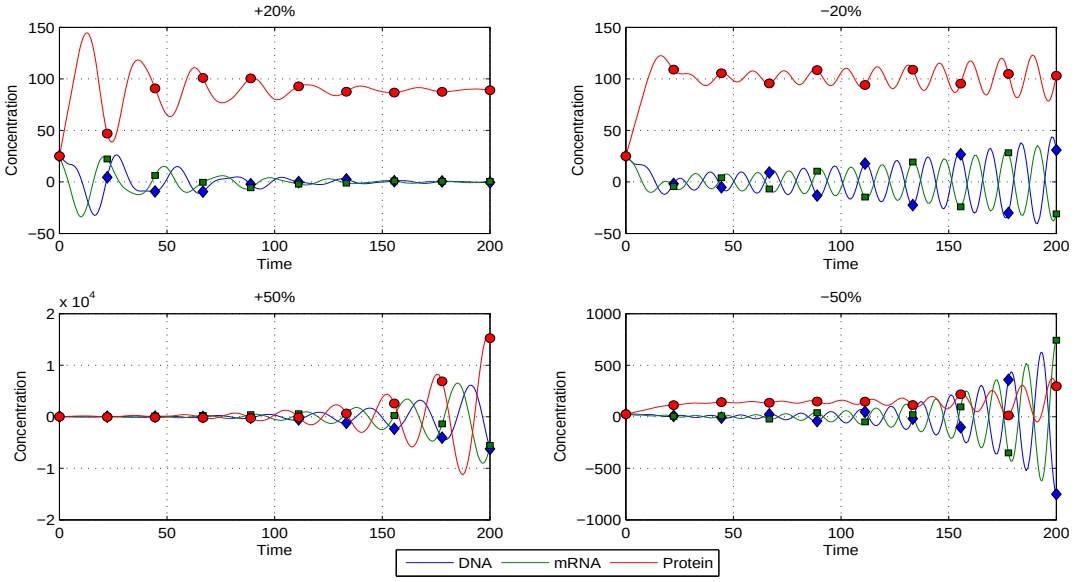

Fig. 4.7. Sensitivity analysis of the parameter translation rate of Model-I with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

transcription and translation processes, respectively. The left four figures along with right lower figure indicate the stability of the model while the figures on right hand side except for the fourth one(right lower figure) indicate that the model is unstable and the system bursts.

The sensitivity analysis of Model-I, Fig. 4.4 shows the concentration profiles of DNA, mRNA and protein when the replication rate increases by 20% and 50%, and decreases by 20% and 50% in the base value. The oscillation decreases with the decrease in the replication rate (both right parts of Fig. 4.4). It is observed from the figure that when the replication rate is lower, the model is stable (both right parts of the Fig. 4.4) while the increase in replication

Table 4.4. Sensitivity analysis of Model-II with the parameter k_1 and k_3, respectively, and the initial condition of each DNA, mRNA and protein concentration as 25 micrograms. The value of delays τ_2 and τ_4 is 3.7 and 0.6, respectively.

Model-II	Transcription rate k_1 (microgram/second) 0.42			
	+20%	+50%	-20%	-50%
Transcription rate k_1 (microgram/second)	0.50	0.63	0.34	0.21
DNA concentration (in microgram)	1.8443e+03	1.3452e+08	-0.0028	5.3398e-11
mRNA concentration (in microgram)	2.7789e+03	3.9139e+06	0.8346	0.8983
Protein concentration (in microgram)	-4.5482e+03	-1.3844e+08	74.1682	74.1017
	Translation rate k_3 (microgram/second) 2.59			
Translation rate k_3 (microgram/second)	3.11	3.89	2.07	1.30
DNA concentration (in microgram)	-16.4334	-16.4334	-16.4106	-16.4070
mRNA concentration (in microgram)	-1.3011e+19	3.2367e+42	-1.5741	-1.8137
Protein concentration (in microgram)	1.3011e+19	-3.2367e+42	92.9847	93.2207

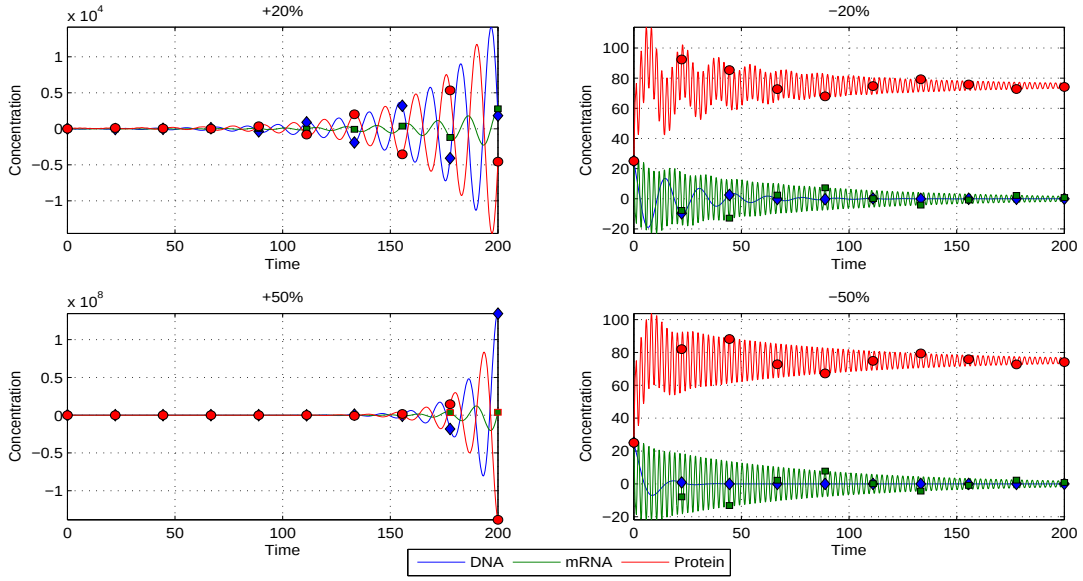

Fig. 4.8. Sensitivity analysis of the parameter transcription rate of Model-II with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

rate causes bursts in the system and the model will be unstable (both left parts of the Fig.

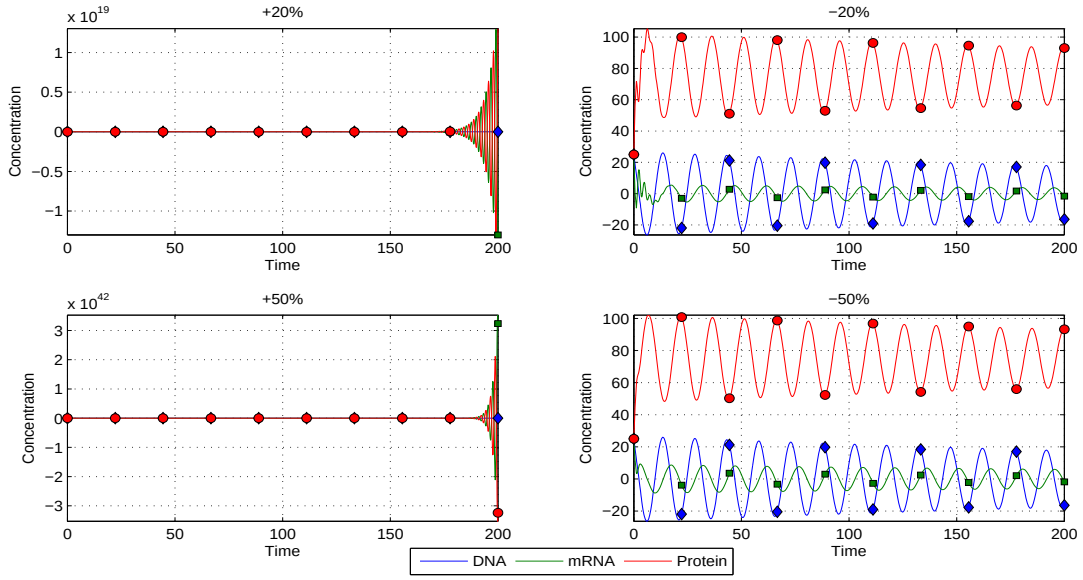

Fig. 4.9. Sensitivity analysis of the parameter translation rate of Model-II with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

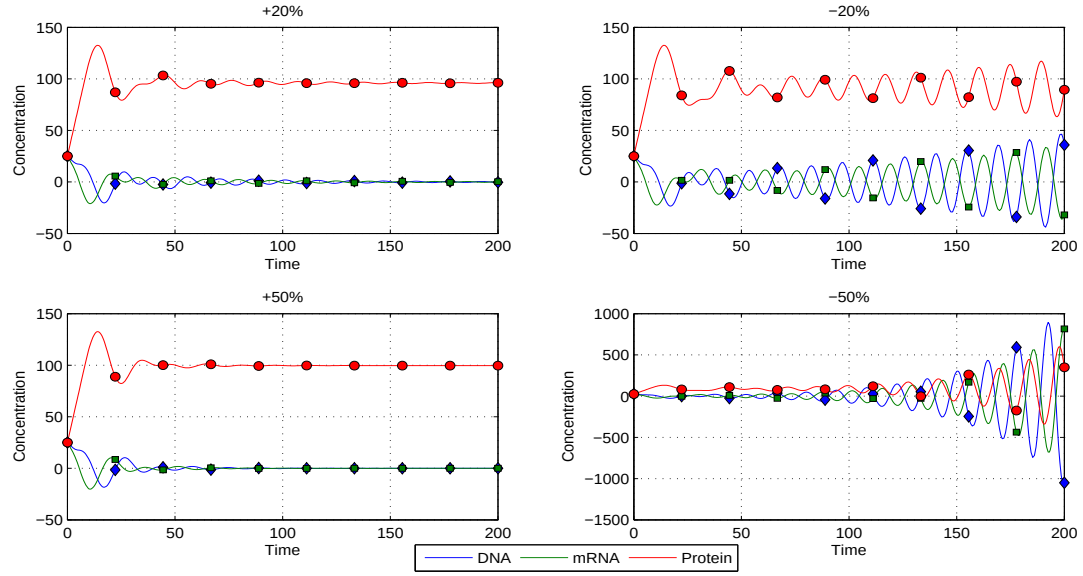

Fig. 4.10. Sensitivity analysis of the parameter replication with time delay for Model-I with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

4.4). In Fig. 4.5, it can be seen that the increase or decrease in transcription rate leads to system burst and makes the model unstable. Thus in Fig. 4.5, the model is highly sensitive as the variation in transcription rate leads to instability. In Fig. 4.6, it is seen that for the small decrease in reverse transcription rate, the model remains stable (right upper part of the Fig. 4.6) but for a substantial and larger amount of decrease in reverse transcription rate, the model becomes unstable (right lower part of Fig. 4.6). Also, the model becomes unstable on increasing the reverse transcription rate (both left parts of Fig. 4.6). In Fig. 4.7, it is observed that the model is stable for a small increase in translation rate (left upper part of Fig. 4.7)

Table 4.5. Sensitivity analysis of Model-I with the parameter τ_1, τ_2, τ_3 and τ_4, respectively, and the initial condition of each DNA, mRNA and protein concentration is 25 micrograms. The value of rates k_0, k_1, k_2 and k_3 are 0.1425, 0.4785, 0.2568 and 0.3691, respectively.

Model-I	Replication lag τ_1 (second) 1.7			
	+20%	+50%	-20%	-50%
Replication lag τ_1 (second)	2.04	2.55	1.36	0.85
DNA concentration (in microgram)	-0.3808	0.0017	35.9046	-1.0507e+03
mRNA concentration (in microgram)	0.2621	2.1784e-04	-31.9812	815.3509
Protein concentration (in microgram)	96.1922	99.6338	89.4417	348.8821
	Transcription lag τ_2 (second) 2.3			
Transcription lag τ_2 (second)	2.76	3.45	1.84	1.15
DNA concentration (in microgram)	-4.3923e+05	-6.3182e+07	0.00029	7.2881
mRNA concentration (in microgram)	4.4777e+05	5.6421e+08	7.0222e-04	-24.9418
Protein concentration (in microgram)	8.0491e+03	-1.5083e+09	96.8251	125.2183
	Reverse transcription lag τ_3 (second) 5.2			
Reverse transcription lag τ_3 (in second)	6.24	7.8	4.16	2.6
DNA concentration (in microgram)	-211.9863	6.6169e+05	0.3168	-2.2200
mRNA concentration (in microgram)	209.0774	-7.9784e+05	-0.1869	-1.6293
Protein concentration (in microgram)	127.0256	-4.6294e+04	89.3957	87.2496
	Translation lag τ_4 (second) 8.6			
Translation lag τ_4 (second)	10.32	12.9	6.88	4.3
DNA concentration (in microgram)	-10.3475	-1.1970e+04	-3.2942e+05	1.5779e+10
mRNA concentration (in microgram)	-8.1428	5.9625e+03	1.1022e+05	-3.3152e+10
Protein concentration (in microgram)	109.7224	8.6237e+03	4.2001e+05	1.7112e+10

but for the larger increase in translation rate, the model becomes unstable (left lower part of Fig. 4.7). Also, with a decrease in translation rate, the increase in the size of oscillations is observed and it leads to instability (both right parts of Fig. 4.7).

For Model-II, in Fig. 4.8, it can be seen that the size of oscillations increases with the increase in the transcription rate causing the system burst, and thus, the model will be unstable (both left parts of Fig. 4.8). Also, the size of oscillations decreases with a decrease

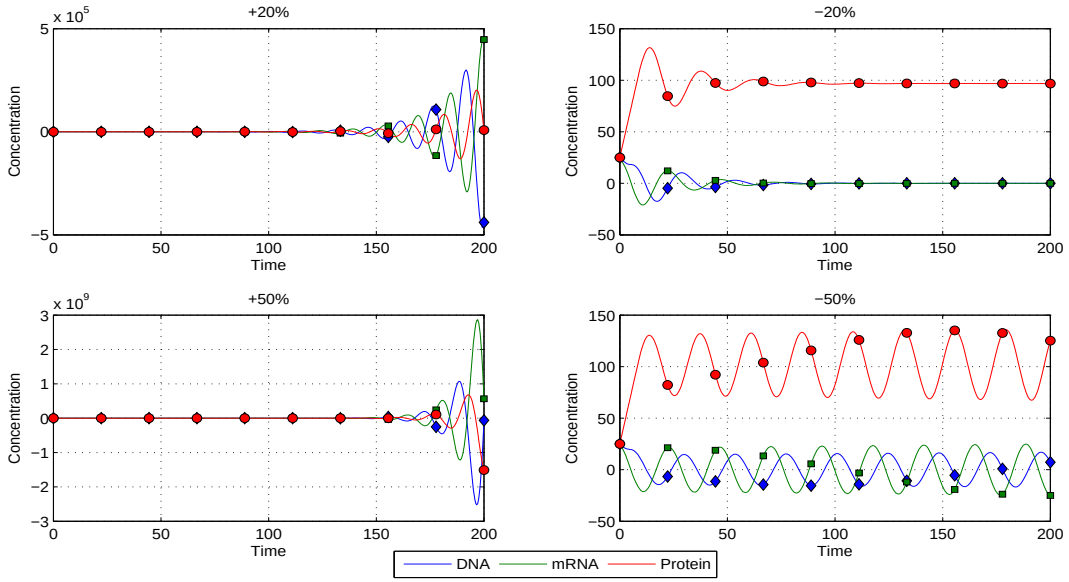

Fig. 4.11. Sensitivity analysis of the parameter transcription with time delay for Model-I with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

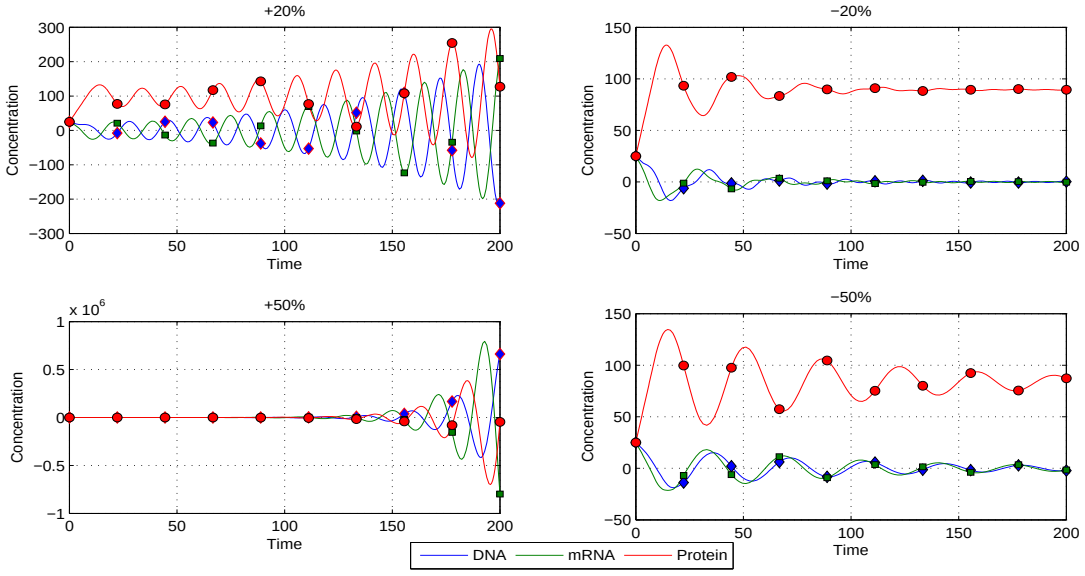

Fig. 4.12. Sensitivity analysis of the parameter reverse transcription with time delay for Model-I with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

in transcription rate and the oscillations converge to make the system stable (both right parts of the Fig. 4.8). In Fig. 4.9, it can be seen that with the decrease in translation rate, the oscillations converge thereby making the model stable (both right parts of Fig. 4.9). But the increase in translation rate leads to an increase in the size of oscillations, thereby making the model unstable (both right parts of the Fig. 4.9).

In Fig. 4.10, it can be seen that the decrease in the time delay in replication process makes the model unstable (both right parts of Fig. 4.10), while model attains stability with the increase in the time delay in replication process (both left parts of Fig. 4.10).

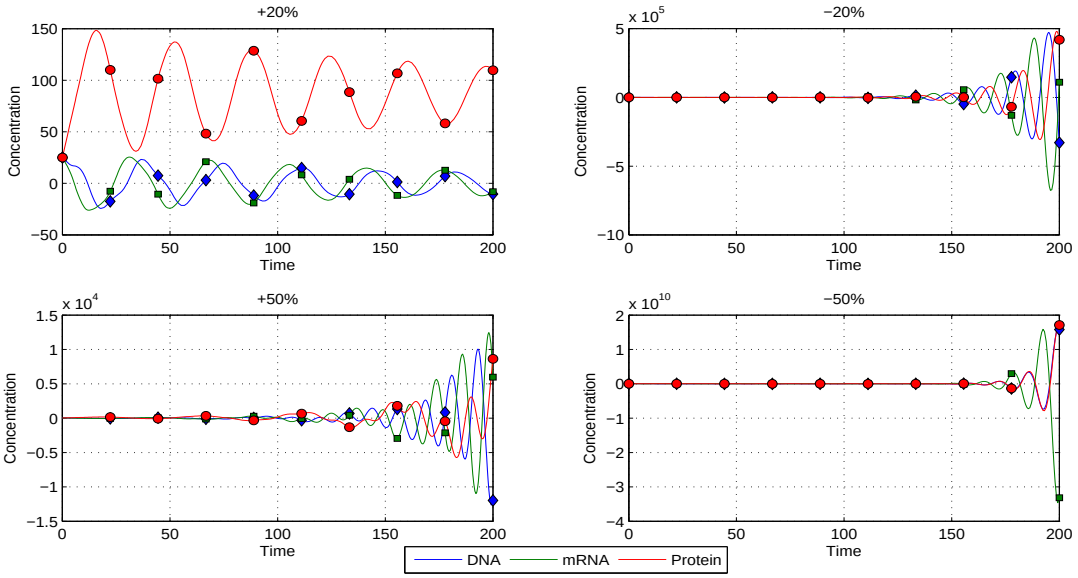

Fig. 4.13. Sensitivity analysis of the parameter translation with time delay for Model-I with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

Table 4.6. Sensitivity analysis of Model-II with the parameter τ_2 and τ_4, respectively. Here the initial values of each DNA, mRNA and protein concentration are 25 micrograms. The value of rates k_1 and k_3 is 0.42 and 2.59, respectively.

Model-II	Transcription lag τ_2 (second) 3.7			
	+20%	+50%	-20%	-50%
Transcription lag τ_2 (second)	4.44	5.55	2.96	1.85
DNA concentration (in microgram)	5.7725e+03	7.6598e+05	-2.1140e-05	7.1306e-23
mRNA concentration (in microgram)	-604.6839	3.2312e+04	0.8043	0.8564
Protein concentration (in microgram)	-5.0929e+03	-7.9822e+05	74.1957	74.1436
	Translation lag τ_4 (second) 0.6			
Translation lag τ_4 (second)	0.72	0.9	0.48	0.3
DNA concentration (in microgram)	-16.4332	-16.4329	-16.4184	-16.4080
mRNA concentration (in microgram)	7.9425e+15	-4.8743e+28	-1.2182	-0.9982
Protein concentration (in microgram)	-7.9425e+15	4.8743e+28	92.6366	92.4061

In Fig. 4.11, it can be seen that the increase in the time delay in transcription process makes the model unstable (both left parts of Fig. 4.11), while a small decrease in the time delay in transcription process, oscillations converge and lead to the stability of the system (right upper part of Fig. 4.11), and further, for a larger decrease in the time delay

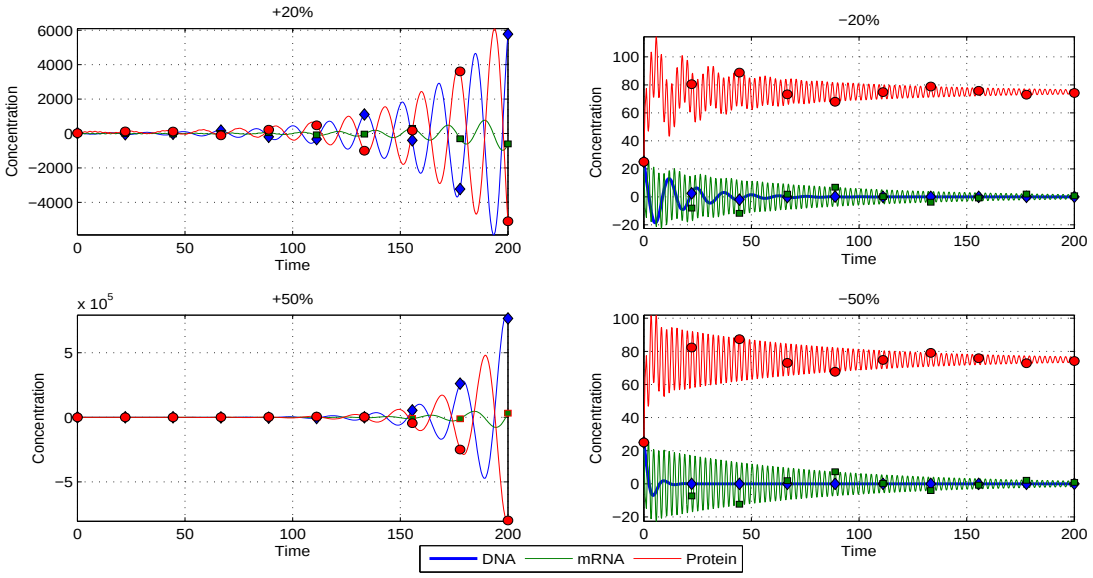

Fig. 4.14. Sensitivity analysis of the parameter transcription with time delay for Model-II with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

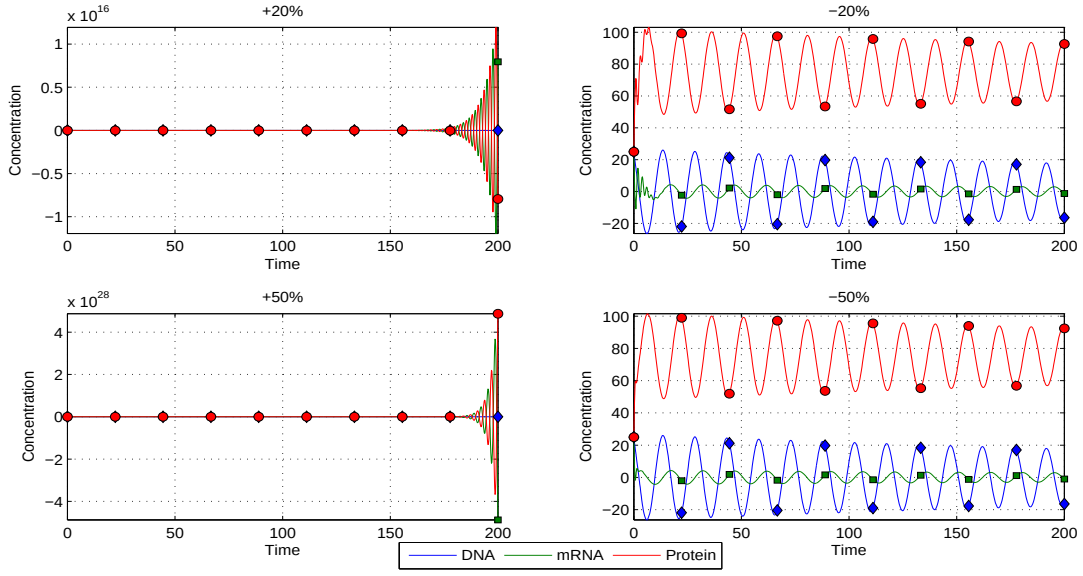

Fig. 4.15. Sensitivity analysis of the parameter translation with time delay for Model-II with an increase of 20% and 50%, and decrease of 20% and 50% in the base value.

in transcription process, model is semi-stable (right lower part of Fig. 4.11). In Fig. 4.12, for the decrease in the time delay in reverse transcription process, the oscillations converge and lead to stability of the system (both right parts of Fig. 4.12), while for the increase in the time delay in reverse transcription process, the model becomes unstable (both left parts of Fig. 4.12). In Fig. 4.13, for the small increase in the time delay in translation process, the oscillations converge and the model becomes stable (left upper part of Fig. 4.13), while a larger increase in the time delay in translation process, leads to instability as oscillations do not converge (left lower part of Fig. 4.13). The decrease in the time delay in translation

process makes the model unstable as oscillations do not converge (both right parts of Fig. 4.13).

For Model-II, in Fig. 4.14, it can be seen that the model is stable as oscillations converge when time delays in transcription process decrease (both right parts of Fig. 4.14), while the model is unstable when the time delays in transcription process increase (both left parts of Fig. 4.14). In Fig. 4.15 it can be seen that when the time delay in translation process increases then the model becomes unstable and due to oscillations in an increasing manner the system bursts (both left parts of Fig. 4.15), while the decrease in the time delay in the translation process causes a decrease in size of oscillations and it makes the system stable (both right parts of Fig. 4.15).

6. CONCLUSION

The proposed model, categorised into two models for retroviruses and normal cell, is employed to study the effect of time delays in the processes of replication, transcription, reverse transcription and translation of the gene expression. It is concluded from the results that the delay in these processes like replication, transcription, reverse transcription and translation causes more dynamic changes in concentrations of DNA, mRNA and proteins in comparison to the system without delay in these processes. The concentration profiles of DNA, mRNA and proteins in the cell for the case without delay are smooth. But the delay in the processes causes the disturbance in the system and therefore the control system of the cell exerts control on these processes to coordinate with each other to regulate the concentration profiles of DNA, mRNA and proteins and thus leads to oscillations. If the delay in these processes is larger, it causes larger disturbances which go beyond the control of the cell thereby making the system unstable. It is concluded that the system is highly sensitive to the rates of these processes replication, transcription, reverse transcription and translation as well as time delay in these processes. The impact of time delays on temporal concentration profile of DNA, mRNA and proteins have been analysed which gives better insight into the normal cell as well as retroviruses. Thus, these two models give us interesting and useful information about the impact of rates of replication, transcription, reverse transcription and translation in presence or absence of time delay in these processes of gene expression which can be useful for various biomedical applications.

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