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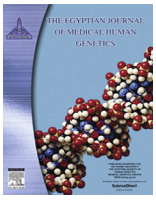

Original article

Fuzzy system model for gene expression

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ABSTRACT

Background: The theoretical information of a gene is contained in cell's genetic materials, namely, DNA, mRNA and proteins. In the synthesis of functional gene products, this information can be expressed in mathematical way.
Aim: In this paper, a fuzzy approach is used to analyse of the behaviour of a gene expression in a cell. The main aim of the present study is to unravel the complexity of gene expression and develop the mathematical model which can be used for better insight of functional gene products.
Subjects and methods: The model for gene expression is obtained in terms of the system of fuzzy differential equations assuming that the transcription and translation processes are taking place in the cell. The Michaelis–Menten's mechanism is incorporated in the model.
Results: The analytic solution for crisp case as well as for fuzzy case is carried out. The sensitivity analysis is also performed and it is observed that the model is highly stable.
Conclusion: The model for gene expression is obtained in terms of system of differential equations involving fuzzy initial values using geometric approach. The numerical results have been obtained for TJK16 strain of E.coli. The semi temporal concentrations profile of DNA, mRNA and protein are obtained and sensitivity analysis has been performed to study the variation in concentrations of DNA, mRNA and protein with respect to variation in transcription and translation rates.

1. Introduction

An individual cell of all living organisms is a complex entity and has scrumptious world in itself. The cell contains DNA, RNA and protein, and these functional products act together in a coordinated manner as a part of the system. Gene is a part or small segment of double stranded DNA sequence that encodes the functional gene products RNA and proteins. Genes are the subunits of DNA which carry the genetic blueprint, that is, they are used to make all the proteins of the needy cell. Every gene contains a particular set of instructions that code for a specific protein. A DNA may contain thousands of genes, for example, a human cell is made up of 46 chromosomes, each of which contains highly condensed and coiled DNA consisting of millions of gene sequences. The genetic information stored in a gene can be read by two process, namely, transcription and translation, where the functional gene product mRNA and protein is produced, respectively. This process, takes place in the cell, is known as gene expression in all living organisms [1,2].

Mathematical modeling of gene expression leads to initial value problem involving differential equation. A system of ordinary differential equations and stochastic processes are reported in the literature to study gene expression and demonstrated a more vast analysis to unravel the complexity of gene regulatory networks mathematically, having with negative feedback as well as positive feedback [3–9]. These models do not involve Michaelis–Menten's mechanism. Sharma and Adlakha proposed a model of gene expression based on Michaelis–Menten's mechanism [10]. Also, Sharma and Adlakha proposed a Markov chain model on gene expression [11]. No attempts is reported in the literature for fuzzy approach with Michaelis–Menten's mechanism to study the gene expression in a cell.

The initial concentration of DNA, mRNA and proteins are not known precisely. This uncertainty of initial values of concentration profiles of DNA, mRNA and proteins poses new challenges for mathematics to develop models for gene expression. To develop a model of such type of dynamical system with uncertainty is quite natural. These models can be developed with differential equations using fuzzy set theory. Many real world problems require the

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solutions of fuzzy differential equations (FDEs) with fuzzy initial conditions.

Chang and Zadeh [12] gave the concept of fuzzy derivative. Kandel and Byatt [13,14] introduced the concept of fuzzy differential equation. The generalisation of Hukuhara derivative [15] of set valued function was given by Puri and Ralescu [16], and in turn it was followed by Kaleva [17,18]. Seikkala [19] demonstrated the fuzzy derivative as an extension of the Hukuhara derivative and fuzzy integral. Due to the unavailability of ample ink-horn term of fuzzy derivative, Hullermeier [20] introduced the notion of fuzzy differential equation as a family of differential inclusions. Further, Buckley and Feuring [21] and Buckley et al. [22] demonstrated the formulation of fuzzy first order differential equation with initial values. Rodriguez-Lopez [23] pay attention towards the comparison results for the solution of fuzzy system of differential equation using Hukuhara derivative. Allahviranloo et al. [24] used the generalised H-differentiability and applied differential transformation method to solve the problem. Further, in view of complex numbers, Xu et al. [25], proposed an α-level sets of a fuzzy system using complex number. Chalco-Cano et al. [26], demonstrated the class of fuzzy differential equation based on Zadeh's extension principle. further, in terms of solution of system of fuzzy differential equations, Gasilov et al. [27] used geometric approach and this geometric approach is followed in this paper to solve the linear system of fuzzy differential equations.

In this paper, a fuzzy set approach is explored to model the non deterministic initial values of concentrations of DNA, mRNA and proteins. These initial values have impact on the processes of transcription and translation, and the whole dynamics of DNA, mRNA and proteins concentrations in the cell. Therefore, fuzzy initial value problem is proposed to study the gene expression. The initial values of DNA, mRNA and proteins are taken to be fuzzy. The model of gene expression is obtained in terms of system of differential equations involving fuzzy initial values and the analytic solution is obtained. The main aim of the present study is to develop the mathematical model for gene expression to unravel the complexity of cell as vitro processes are time consuming and very expensive. The impact of fuzzy initial concentration of DNA, mRNA and protein is analysed numerically which gives significant range of variation in the concentrations of functional gene products. The sensitivity analysis of the model with respect to transcription and translation processes shows that the fuzzy system of gene expression remains stable. Thus, the fuzzy system provides a wide range of the solution of the complex gene expression problem and gives the better insight of the functional gene products. The mathematical formulation is given in next section.

2. Subjects and methods

2.1. Abbreviations

Here the following notations are used:

$w(t)$	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_1	Rate of transcription (microgram/s).
k_2	Rate of translation (microgram/s).
μ_X	Membership function.
$\tilde{w}_0$	Fuzzy initial concentration of DNA.
$\tilde{x}_0$	Fuzzy initial concentration of mRNA.
$\tilde{p}_0$	Fuzzy initial concentration of protein.
$x_{cr(t)}$	Crisp solution.
$\tilde{x}(t)$	Fuzzy solution.
X_α	α-cut of the solution set $\tilde{X}$.

2.2. Mathematical model and method

The graphical representation of a model for gene expression involving two processes transcription and translation is shown in Fig. 1.

The Michaelis–Menten's mechanism is incorporated in the basic model of Chen et al. and Xie [5,6] to obtain the following system of differential equations for gene expression.

$$\frac{dw}{dt} = f(t,w,x,p) = -k_1 w(t), \tag{1}$$

$$\frac{dx}{dt} = g(t,w,x,p) = k_1 w(t) - k_2 x(t), \tag{2}$$

$$\frac{dp}{dt} = h(t,w,x,p) = k_2 x(t), t \geqslant 0. \tag{3}$$

where w, x and p represent DNA, mRNA and protein concentration respectively. Here, k_1 and k_2 represent rates of transcription and translation processes taking place in the cell. Initially, it is assumed that the concentration of $w(t)$, $x(t)$ and $p(t)$ is constant at $t = 0$ denoted by w_0, x_0 and p_0 respectively. Thus, the following initial conditions are imposed based on the physical condition of the cell:

$$w(t) = w_0 \text{ at } t = 0, \tag{4}$$

$$x(t) = x_0 \text{ at } t = 0, \tag{5}$$

$$p(t) = p_0 \text{ at } t = 0. \tag{6}$$

The analytical solution of the above system of differential equations is

$$w(t) = w_0 e^{-k_1 t}, \tag{7}$$

$$x(t) = \frac{w_0 k_1}{k_2 - k_1}\{e^{-k_1 t} - e^{-k_2 t}\} + x_0 e^{-k_2 t}, \tag{8}$$

$$p(t) = w_0\left\{1 + \frac{k_1 e^{-k_2 t} - k_2 e^{-k_1 t}}{k_2 - k_1}\right\} + x_0\{1 - e^{-k_2 t}\} + p_0. \tag{9}$$

But when the initial values of DNA, mRNA and proteins are not precisely known, then fuzzy set approach is used to represent the initial values of DNA, mRNA and protein. Thus, for initial fuzzy values of concentration of DNA, mRNA and proteins, we have following initial conditions:

$$\tilde{w}(t_0) = \tilde{w}_0, \tag{10}$$

$$\tilde{x}(t_0) = \tilde{x}_0, \tag{11}$$

$$\tilde{p}(t_0) = \tilde{p}_0. \tag{12}$$

Here $\tilde{w}_0, \tilde{x}_0$ and $\tilde{p}_0$ respectively, represent the fuzzy values of DNA, mRNA and proteins concentration initially. The system (1), (2) and (3) along with initial condition (10), (11) and (12) leads to fuzzy initial value problem which can be written in matrix notation as given below:

$$\begin{cases} X' = AX \\ X(t_0) = \tilde{B}. \end{cases} \tag{13}$$

where $A = [a_{ij}]$ is an 3×3 crisp matrix and initial conditions, $\tilde{B} = (\tilde{w}_0, \tilde{x}_0, \tilde{p}_0)^T$ is a vector of fuzzy numbers. The differential equations are considered to describe the variation in the concentrations of DNA, mRNA and protein in the cell and fuzzy initial condition is used to incorporate uncertainty at time t_0. Let the initial value vector $\tilde{B} = b_{cr} + \tilde{b}$, where b_{cr} is a vector which denotes the vertex of fuzzy region with the possibility of 1, while $\tilde{b}$ denotes the vertex

Fig. 1. Graphical representation of modelling of gene expressions.

at origin. Now the solution of the given system of fuzzy differential equations can be written in the form of crisp solution and solution with uncertainty, i.e.,

$$\tilde{X}(t) = x_{cr}(t) + \tilde{x}(t). \tag{14}$$

Thus, we have homogeneous system of linear differential equations with fuzzy initial conditions, and let $\tilde{x}(t)$ be the solution of the following homogeneous system involving uncertainty:

$$X' = AX, \tag{15}$$

$$X(0) = \tilde{b} \quad \text{at} \quad t_0 = 0. \tag{16}$$

Let $\tilde{B}_i = (\lambda_i, \phi_i, \varphi_i), i = 1, 2, 3$. So we have $(b_{cr})_i = \phi_i$, and $\tilde{b}_i = \left(\underline{\underline{b_i}}, 0, \overline{\overline{b_i}}\right) = (\lambda_i - \phi_i, 0, \varphi_i - \phi_i)$. Also, let the fuzzy initial vector $\tilde{b}$ can be defined as $\tilde{b} = \left(\underline{\underline{b}}, 0, \overline{\overline{b}}\right)$, which forms a rectangular prism in the coordinate space, i.e., $\tilde{b} = \{b = \alpha_1 f_1 + \alpha_2 f_2 + \alpha_3 f_3 | \alpha_i \in [0, 1];\ f_i = v_i \text{ or } f_i = u_i$ with membership function $\mu_{\tilde{b}}(b) = 1 - \max_{1 \leqslant i \leqslant 3} \alpha_i$ and the values of $v_i = \underline{\underline{b_i}} e_i, u_i = \overline{\overline{b_i}} e_i$, where e_i is the standard basis vector, v_i is lower approximation of initial values and u_i is upper approximation of initial values. Let $q_i(t) = e^{At} v_i$ and $p_i(t) = e^{At} u_i$ then the solution involving uncertainty is

$$\tilde{X} = \{x(t) = x_{cr}(t) + \alpha_1 r_1(t) + \alpha_2 r_2(t) + \ldots + \alpha_n r_n(t) | \alpha_i \in [0, 1]; \\ r_i = q_i \text{ or } r_i = p_i\}, \tag{17}$$

and the membership function is

$$\mu_X(x(t)) = 1 - \max_{1 \leqslant i \leqslant n} \alpha_i \quad \text{where } n = 3. \tag{18}$$

Here, the initial values are triangular fuzzy numbers, then the α-cut of the solution will be determined. The rectangular prism $\tilde{b}$ and its α-cuts can be expressed as

$$\tilde{b} = \left\{c_1 e_1 + c_2 e_2 + \ldots + c_n e_n | c_i \in \left[\underline{\underline{b_i}}, \overline{\overline{b_i}}\right]\right\}, \tag{19}$$

$$b_\alpha = \left\{c_1 e_1 + c_2 e_2 + \ldots + c_n e_n | c_i \in \left[(1-\alpha)\underline{\underline{b_i}}, (1-\alpha)\overline{\overline{b_i}}\right]\right\}. \tag{20}$$

Let $g_i(t) = e^{At} e_i$, then the solution and the α-cuts of the solution can be determined as

$$\tilde{X} = X_0 \text{ with } \mu_X(x(t)) = 1 - \max_{1 \leqslant i \leqslant n} \gamma_i; \text{ and } \gamma_i = \begin{cases} c_i / \overline{\overline{b_i}}, & c_i \geqslant 0; \\ c_i / \underline{\underline{b_i}}, & c_i < 0. \end{cases} \tag{21}$$

$$X_\alpha = \{x(t) = x_{cr}(t) + c_1 g_1(t) + c_2 g_2(t) + \ldots \\ + c_n g_n(t) | c_i \in \left[(1-\alpha)\underline{\underline{b_i}},\ (1-\alpha)\overline{\overline{b_i}}\right]\},\ n = 3. \tag{22}$$

3. Results

The values of the parameters k_1 and k_2 are taken from the literature [6]. The crisp solution of the fuzzy linear differential equation system with crisp initial values $[w_0\ x_0\ p_0]^T = [25\ 25\ 25]^T$ is given below and also shown in the Fig. 2.

$$w_{cr}(t) = 25e^{-0.42t}, \tag{23}$$

$$x_{cr}(t) = 20.18e^{-2.59t} + 4.84e^{-0.42t}, \tag{24}$$

$$p_{cr}(t) = 80.98 + 22.57e^{-2.59t} - 33.41e^{-0.42t}. \tag{25}$$

Form Eq. (22), the initial values are triangular fuzzy numbers which form a fuzzy region in coordinate space. The vertex of the region is $b_{cr} = [25\ 25\ 25]^T$.

$$\begin{bmatrix} \tilde{w}_0 \\ \tilde{x}_0 \\ \tilde{p}_0 \end{bmatrix} = \begin{bmatrix} 20 & 25 & 30 \\ 20 & 25 & 30 \\ 20 & 25 & 30 \end{bmatrix}. \tag{26}$$

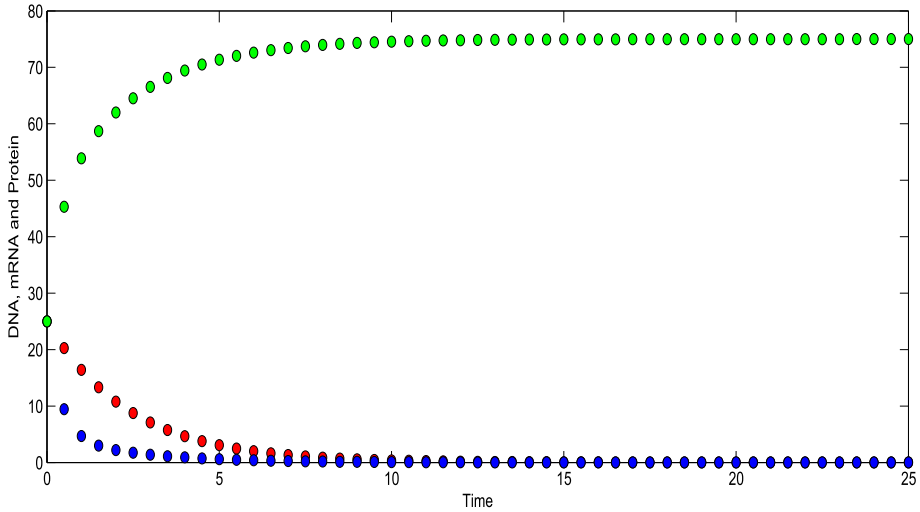

Fig. 2. The crisp solution for concentrations of DNA, mRNA and protein.

Further, for the solution of homogeneous system (15), the vertex will be at origin. We have to find the α-cut of the solution for $\alpha \in [0,1]$. Thus, the initial values can be written as

$$\begin{bmatrix} \tilde{w}_0 \\ \tilde{x}_0 \\ \tilde{p}_0 \end{bmatrix} = \begin{bmatrix} -5 & 0 & 5 \\ -5 & 0 & 5 \\ -5 & 0 & 5 \end{bmatrix} \quad \text{i.e.,} \tag{27}$$

$$\underline{\underline{b}} = \begin{bmatrix} \tilde{w}_0 \\ \tilde{x}_0 \\ \tilde{p}_0 \end{bmatrix} = \begin{bmatrix} -5 \\ -5 \\ -5 \end{bmatrix} = \underbrace{\begin{bmatrix} -5 \\ 0 \\ 0 \end{bmatrix}}_{v_1} + \underbrace{\begin{bmatrix} 0 \\ -5 \\ 0 \end{bmatrix}}_{v_2} + \underbrace{\begin{bmatrix} 0 \\ 0 \\ -5 \end{bmatrix}}_{v_3},$$

$$\overline{\overline{b}} = \begin{bmatrix} \tilde{w}_0 \\ \tilde{x}_0 \\ \tilde{p}_0 \end{bmatrix} = \begin{bmatrix} 5 \\ 5 \\ 5 \end{bmatrix} = \underbrace{\begin{bmatrix} 5 \\ 0 \\ 0 \end{bmatrix}}_{u_1} + \underbrace{\begin{bmatrix} 0 \\ 5 \\ 0 \end{bmatrix}}_{u_2} + \underbrace{\begin{bmatrix} 0 \\ 0 \\ 5 \end{bmatrix}}_{u_3}.$$

where v_1, v_2, v_3, u_1, u_2, u_3 are the support vectors of the prism. The above equation forms a rectangular prism and the general solution of the system of Eq. (15) is

$$\begin{cases} w(t) = c_1 e^{-k_1 t}, \\ x(t) = \frac{c_1 k_1 e^{-k_1 t}}{k_2 - k_1} + c_2 e^{-k_2 t}, \\ p(t) = \frac{c_1 k_2 e^{-k_1 t}}{k_2 - k_1} - \frac{c_2 e^{-k_2 t}}{k_2} + c_3. \end{cases} \tag{28}$$

For some initial point $M(a,b,c)$, the values of the constants can be revealed as

$$\begin{cases} c_1 = a, \\ c_2 = \frac{b(k_2-k_1)-k_1 a}{k_2-k_1}, \\ c_3 = \frac{k_2(k_2-k_1)c + k_2^2 a + b(k_2-k_1) - k_1 a}{k_2(k_2-k_1)}. \end{cases} \tag{29}$$

The α-cut of the solution set $\tilde{X}$ is given below and also shown in the Fig. 3.

$$X_\alpha = \left\{ \begin{bmatrix} w(t) \\ x(t) \\ p(t) \end{bmatrix} = \begin{bmatrix} (25 + c_1)e^{-0.42t} \\ (20.18 - 0.19c_1 + c_2)e^{-2.59t} + (4.84 + 0.19c_1)e^{-0.42t} \\ (22.57 + 0.19c_1 + c_2)e^{-2.59t} + (-33.41 - 0.19c_1)e^{-0.42t} + c_1 + c_2 + c_3 \end{bmatrix} \right\}. \tag{30}$$
$$| -5(1-\alpha) \leqslant c_1 \leqslant (1-\alpha)5, -5(1-\alpha) \leqslant c_2 \leqslant (1-\alpha)5, -5(1-\alpha) \leqslant c_3 \leqslant (1-\alpha)5$$

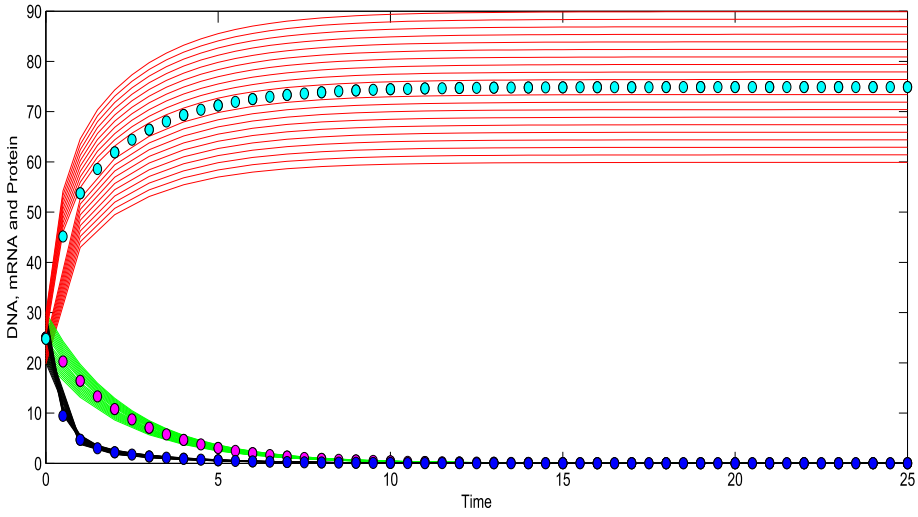

Fig. 3. The graphical representation of α-cut of the solution set $\tilde{X}$.

Table 1
Sensitivity analysis of the model with the parameter k_1 and k_2 respectively, and the initial condition of each DNA, mRNA and protein is 25 microgram. The time is $t = 25$ (in seconds).

	Transcription rate k_1 (microgram/s) 0.42			
	+20%	+50%	−20%	−50%
Transcription rate k_1 (microgram/s)	0.504	0.63	0.336	0.21
DNA concentration (in microgram)	1.3954e−04	6.7828e−06	0.0079	0.1618
mRNA concentration (in microgram)	3.3716e−05	2.1802e−06	0.0012	0.0143
Protein concentration (in microgram)	74.9998	75.0000	74.9910	74.8239
	Translation rate k_2 (microgram/s) 2.59			
Translation rate k_2 (microgram/s)	3.108	3.885	2.072	1.295
DNA concentration (in microgram)	0.0010	0.0010	0.0010	0.0010
mRNA concentration (in microgram)	1.6371e−04	1.2700e−04	2.6637e−04	5.0291e−04
Protein concentration (in microgram)	74.9988	74.9988	74.9987	74.9984

3.1. Sensitivity analysis

The sensitivity analysis, based on transcription and translation rates, is carried out. First, the transcription rate is varied and the translation rate is kept fixed, and then, the transcription rate is kept fixed and the translation rate is varied. The result is given in Table 1, and the solution is portrayed in Figs. 4 and 5, which are showing that the model is highly stable.

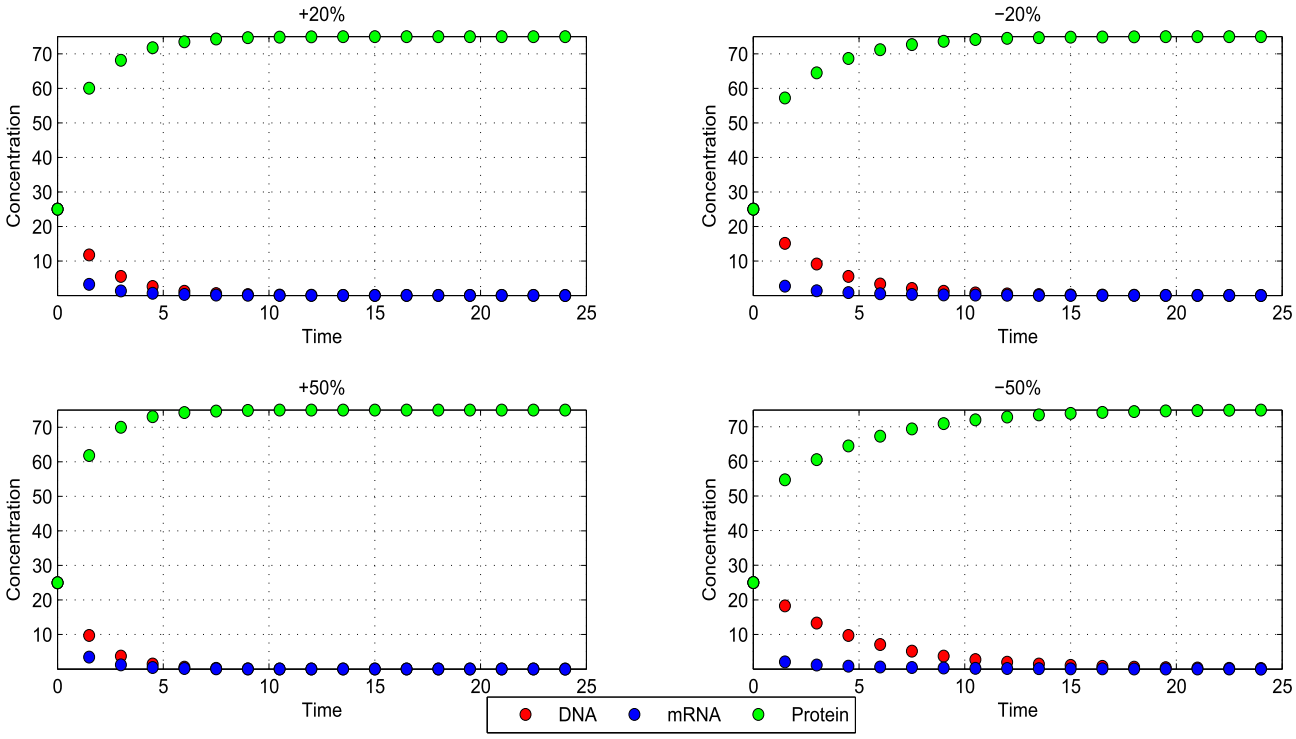

Fig. 4. Sensitivity analysis for the parameter of transcription rate and the graphical representation of the concentrations of DNA, mRNA and protein.

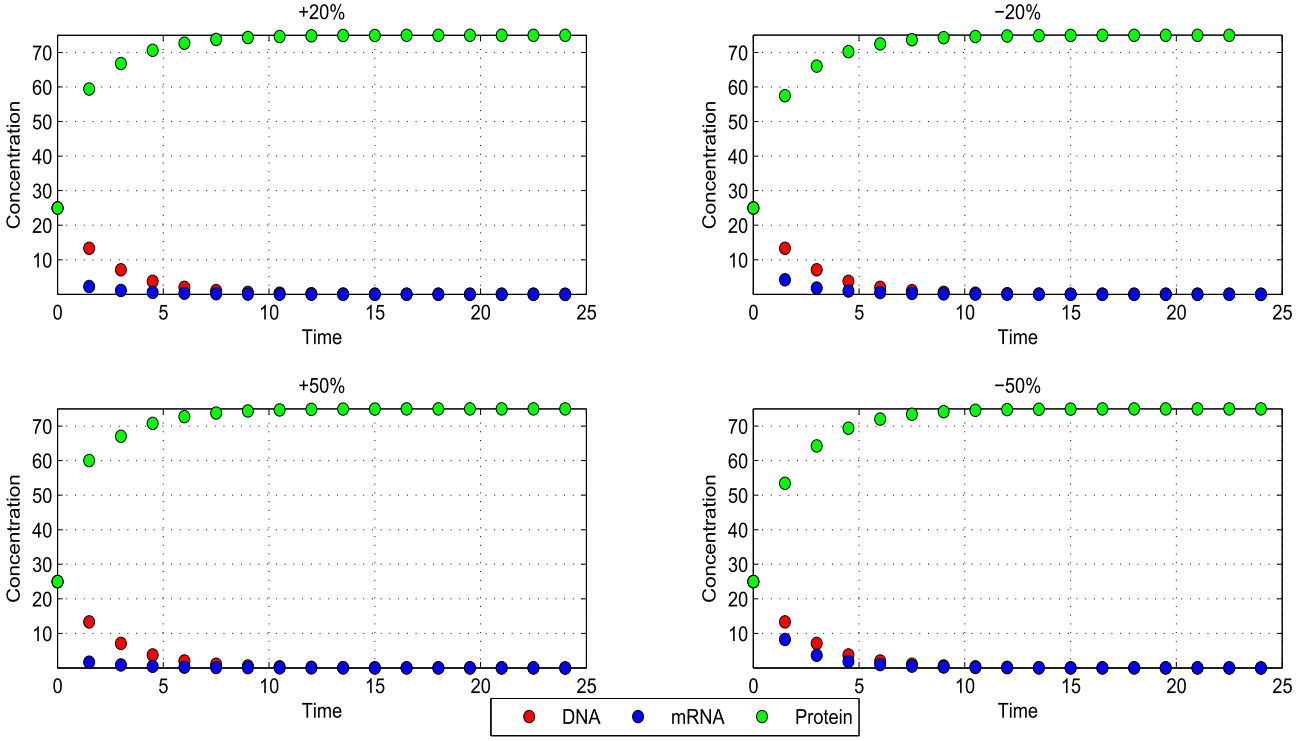

Fig. 5. Sensitivity analysis for the parameter of translation rate and the graphical representation of the concentrations of DNA, mRNA and protein.

4. Discussion

In Fig. 2, analytic solution for crisp case is shown. The concentration profiles of DNA and mRNA are decreasing from $t = 0$ to $t = 12$ seconds and $t = 8$ seconds, respectively, and then they become constant after few seconds. The concentration of protein is increasing from $t = 0$ to $t = 9$ seconds and thereafter becomes constant after few seconds. Thus, the system is stable and achieves steady state in 15 s. In Fig. 3, the fuzzy analytic solution is obtained. The dotted lines show the crisp solution, and the continuous lines below the dotted lines show lower approximation and the continuous lines above the dotted lines show upper approximation of the concentration profiles of DNA, mRNA and proteins. In Table 1, the sensitivity analysis is shown for the transcription and translation processes of gene expression. In Fig. 4, the translation rate is fixed, and the transcription rate is increased by 20% and 50% from its base value respectively in the left parts of the figure and the transcription rate is decreased by 20% and 50% of its base value respectively in the right parts of the figure. It is observed that the system does not burst due to the increment or decrement in the transcription rates which implies that the model is highly stable. The same behaviour of concentrations of DNA, mRNA and protein is seen in Fig. 5 when transcription rate is fixed and the translation rate varies from +20% to −20% and +50% to −50% of its base value. Also, from Table 1, it can be seen that with the increase in the transcription rate, the DNA and mRNA concentration decreases, while the protein concentration increases, and with the decrease in the transcription rate, the DNA and mRNA concentration increases, while the protein concentration decreases. When transcription rate is fixed, with the increase or decrease in the translation rate, the concentration of DNA remains unchanged, but the mRNA concentration decreases with the increase in translation rate and increases with decrease in translation rate respectively. Also, there are slight changes in the protein concentration, up to four decimal, with the variation of translation rate. In both the conditions, the model is highly stable.

5. Conclusion

The fuzzy initial value model is proposed and used to study the gene expression involving transcription and translation processes. On the basis of comparison of fuzzy analytic solution and crisp analytic solution, it is concluded that there is a significant change in concentration profiles of DNA, mRNA and proteins. The initial values of DNA, mRNA and protein concentrations will be different in different conditions and their impact on gene expression has been clearly revealed by the solution of the proposed model. In spite of the significant range of variation of DNA, mRNA and protein concentrations between lower and upper approximation, the system remains stable in the present conditions of the cell taken up in this study. Thus, we can conclude that the control system of the cell keeps the gene expression stable under wide range of variation in the concentrations of DNA, mRNA and protein. Thus, the model gives us better insights of the gene expression involving uncertainty in the initial concentration.

Conflict of interest

The authors declare that they have no conflict of interest.

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Contributors

The first author initiated the research program, carried out the mathematical and statistical analysis with the help of coding in MATLAB software and wrote the manuscript. The second author supervised the project.

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