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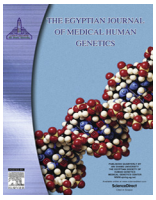

Original article

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

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