Fractional Order Analysis of the Activator Model for Gene Regulation Process

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Abstract: Mathematical modeling for gene regulation process is very important for future prediction and control of diseases on the hereditary level. This paper presents a complete fractional dynamical analysis for an activator gene regulation model. The study of the system's phase planes portraits and the variables' transient responses starting from different initial points are presented and discussed. The effect of the fractional parameter within the differential operator is investigated. The simulation results show that the fractional parameter (α) is effective in the process of synthesizing proteins and the gene regulation process stability.

1 INTRODUCTION

Mathematical modeling is becoming a vital tool for molecular cell biology (MCB). Thus, it is of paramount importance for life scientists to have a solid background in the relevant mathematical techniques, to enable them to participate in the construction, analysis, and critique of published models.

Biological systems are complex systems and the higher levels of complexity emerge from collective behaviour and rising properties at multiple levels. At initial stages, this requires the analysis of large quantities of low level data, which is either acquired by direct measurements or by accessing a variety of sources. It is very important to understand and clarify the dynamic of gene regulatory networks. Various mathematical models have been developed to clarify those complex biochemical systems. Each modeling technique has its focal points and drawbacks and that has to be taken into consideration when creating mathematical model, where the proposed model has to provide good insight into gene regulation process and be valuable for predicting of some possible mutations or any other change (Ahmet and David, 2011), (Santo and Francesco, 2012).

Gene expression is the process by which the hereditary code of a gene is used for synthesizing proteins and producing the structures of the cell. Genes that code for amino acid sequences are named as 'structural genes'. Gene expression process includes two main stages known as 'Transcription and translations'. Transcription is the creating of messenger RNA (mRNA) by the enzyme RNA polymerase, and the processing of the resulting mRNA molecule. But, translation is the use of mRNA to direct synthesizing proteins, and the subsequent posttranslational preparing for the protein molecule. There are some genes are responsible for the production of other forms of RNA and play a role in translation, including transfer RNA (tRNA) and ribosomal RNA (rRNA) (Donald and Charlotte, 2016).

The mathematical model to be studied is a fractional mathematical model. The concept of Fractional Calculus (FC) is basically a generalization of ordinary differentiation to the non integer case, where the integrals and derivatives are of an arbitrary order. First introduced by (Ross, 1975), FC was soon regarded as a major research point by scientists from various fields. This is because it proved to be exceptionally well suited in modeling and describing the complex nature of real world problems (Kilbas, and Trujillo, 2006) (e.g. MCB), in comparison to local derivatives.

The main contribution of this paper is introducing a fractional model for the gene expression process. A complete mathematical analysis of the fractional

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differential operator for the gene regulation process with the effect of activators is presented. The exact solution of the fractional model and studying the stability conditions are discussed. The effect of the fractional parameter α on the system performance is taken into consideration.

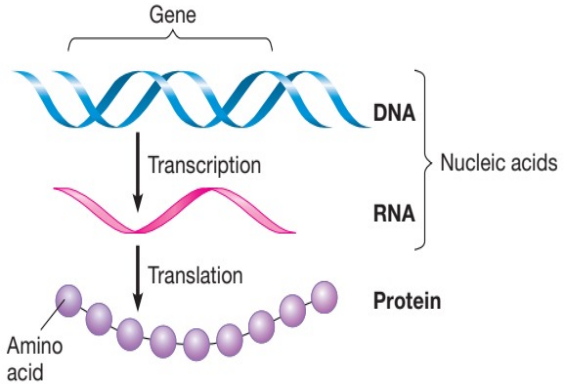
This paper is organized as follows: Section 2 introduces the gene expression process, Transcription and translation. Section 3 presents a fractional analysis model for the gene regulation process using activator. The results and discussion are shown in section 4. Finally, section 5 concludes this work.

2 GENE EXPRESSION PROCESS

The main principle of molecular biology is describing the structure of deoxyribonucleic acid (DNA) and the process of synthesizing proteins. These proteins are synthesized in a process called gene expression. The gene expression process is performed in two steps known as transcription (DNA → RNA) and translation (RNA → Proteins) as shown in figure 1(a).

In transcription process, enzymes use one of the strands of DNA within a gene as a template to create a messenger RNA (mRNA). This process can be executed in four steps (Ana and Želimir, 2012): (i) promoter recognition (ii) chain initiation (iii) mRNA chain elongation and (iii) chain termination and regulation can occur at each step. Producing RNA polymerase using proteins is named as transcription factors (TF), binds to a specific sequence within the gene, which is called the promoter and prices the two strands apart. One of the strands acts as a template strand, or antisense strand, which means that it will be used to produce the mRNA. The other strand is a non-template strand or a sense strand (Ana and Želimir, 2012).

RNA polymerase does not need a primer; it simply initiates mRNA generation at the start codon, and then moves downstream along the gene in a process called elongation. This is very similar to the way DNA polymerase synthesizes DNA as it moves along the template strand, the main difference here is that RNA is being produced. Termination occurs when RNA polymerase reaches the end of the gene, and the enzyme withdraws from the gene and the DNA with it the data encoded within the gene, and after a few quick adjustments during RNA processing it will leave the nucleus, where all the hereditary material or chromatin is and move into the cytoplasm, where it will meet a ribosome. This is where translation happens (Ana and Želimir, 2012).



(a)

$$Gene \xrightarrow[Transcr.]{} mRNA \xrightarrow[Transl.]{} Protein$$

$$mRNA \xrightarrow[Degard.]{} \phi$$

$$Protein \xrightarrow[Degard.]{} \phi$$

(b)

Figure 1: (a) transcription and translation (Martha, 2017) (b) Gene expression.

During translation the mRNA acts as a code for a particular protein, this occurs since each set of three bases on the mRNA, which known as codons, will be coded for a particular transfer RNA (tRNA), and match the mRNA sequence by the complementary sequence of amino acids carried by another sort of RNA called transfer RNA (tRNA). They are utilized to encode the 20 standard amino acids. The generated amino acids add together to form a peptide chain shaping the desired protein, then the mRNA molecule corrupts. The same produced mRNA can be translated many times (Samar, 2018).

3 FRACTIONAL MODELING

The constitutive gene expression has been summarized in figure 1(b). When gene expression is unregulated, it is said to be constitutive, and the gene is always on. Using the law of mass action, a model for constitutive expression as in (Guy, 2018) given as:

$$\begin{aligned} m' &= k_1 - d_1 m \\ p' &= k_2 m - d_2 p \end{aligned} \tag{1}$$

Where m and p represent the produced mRNA and protein, respectively. k_1 and k_2 are the constitutive transcription and translation rates, respectively. Also, d_1 and d_2 are the mRNA and protein degradation rates, respectively.

The constitutive transcription rate in case of the gene whose transcription is activated by the activator $A^n/(k^n + A^n)$; which is known as the hill function. It is found that the shape of the hill function for modeling the transcriptional activation of the gene expression analysis is a function of the amount of the activator A. This function appears in the dynamics of m· ; and it can be derived from considering it to very quickly reach its steady state.

The following model is commonly used to describe activator controlled gene transcription (Samar, 2018), (Guy, 2018).

$$m\cdot = k_1 \frac{A^n}{k^n + A^n} - d_1 m$$
$$p\cdot = k_2 m - d_2 p \quad (2)$$

Where k is the activation coefficient and n is the number of the activators that need cooperatively bind the promoter to trigger the activation of the gene expression.

The usual Caputo fractional time derivative of order α, is given as in (Miller and Ross, 1993), (Caputo, 1967) by:

$${}_a^C D_t^\alpha f(t) = \frac{1}{\Gamma(\alpha - 1)} \int_a^t \frac{f(\tau)}{(t-\tau)^\alpha} d\tau \quad (3)$$

The aim of the current work is to solve the fractional version of the above dynamical system, given by:

$$D^\alpha \begin{bmatrix} m(t) \\ p(t) \end{bmatrix} = \begin{bmatrix} -d_1 & 0 \\ k_2 & -d_2 \end{bmatrix} \begin{bmatrix} m(t) \\ p(t) \end{bmatrix} + k_1 \begin{bmatrix} a_k \\ 0 \end{bmatrix} \quad (4)$$

where $a_k = \frac{A^n}{k^n + A^n}$. This system can be written in a matrix form:

$$D^\alpha \boldsymbol{X}(t) = A\boldsymbol{X}(t) + \boldsymbol{B} \quad (5)$$

where α is the fractional order of the fractional system and it is equal to a real number between 0 and 1. The general solution of the fractional dynamical system (4) as in (Odibat, 2010), has the following form:

$$\boldsymbol{X_G}(t) = \boldsymbol{X_P}(t) + \boldsymbol{X_C}(t) \quad (6)$$

First, to find the particular solution $\boldsymbol{X_P}(t)$, which is assumed to be constant, depending on the constant non-homogeneous part,

$$D^\alpha \boldsymbol{X_P}(t) = A\boldsymbol{X_P}(t) + \boldsymbol{B} \quad (7)$$

Due to the previous Caputo definition (3), $D^\alpha \boldsymbol{X_P} = 0$, then,

$$\boldsymbol{X_P} = -\frac{a_k}{d_1} \begin{bmatrix} 1 \\ k_2/d_2 \end{bmatrix} \quad (8)$$

Second, the homogeneous solution of the fractional order of the studied dynamical system with two dimensions can be calculated from the following equation (Odibat, 2010),

$$\boldsymbol{X_C}(t) = C_1 \boldsymbol{u}_1 E_\alpha(\lambda_1 t^\alpha) + C_2 \boldsymbol{u}_2 E_\alpha(\lambda_2 t^\alpha) \quad (9)$$

where $\boldsymbol{u}_{1,2}$ and $\lambda_{1,2}$ are the eigenvectors and the eigenvalues of the coefficient matrix $\boldsymbol{A}$, respectively. The arbitrary constants depend on the initial conditions of the system, $m(0) = 0$ and $p(0) = 0$. Ultimately, the general solution takes the form:

$$m(t) = \frac{a_k}{d_1} - \left[\frac{a_k}{d_1} - m(0)\right] E_\alpha(-d_1 t^\alpha) \quad (10a)$$

$$p(t) = \frac{a_k k_2}{d_1 d_2} + \left[\frac{a_k}{d_1} - m(0)\right] \frac{k_2}{(d_1 - d_2)} E_\alpha(-d_1 t^\alpha) + \frac{p(0) d_1 d_2 - p(0) d_2^2 - a_k k_2 + m(0) d_2 k_2}{d_2 (d_1 - d_2)} E_\alpha(-d_2 t^\alpha) \quad (10b)$$

4 RESULTS AND DISCUSSION

The general solution of the mRNA (m) and the protein (p) are plotted in Figure 2 at the parameter values as in [8], such that $a_k = 416.7$, $d_1 = 41.6$, $d_2 = 83.3$ and $k_2 = 41.6$, for $\alpha = \{0.3, 0.5, 0.7, 1.0\}$.

4.1 Stability Analysis

The stability of the fractional gene regulation system can be deduced from the stability conditions $\tau^2 - 4\Delta > 0$, $\tau > 0$ and $\Delta > 0$. The parameter $\tau = -d_1 - d_2$ is the trace of the coefficient matrix **A** and $\Delta = d_1 d_2$ is the value of the determinant **A**. The stability analysis has been studied for different values of α and for different initial points.

The system's phase plane portrait and the variables' transient responses starting from different initial points are shown in figure 2. Figure 2 shows that the system reaches the same fixed point, $(m^* = a_k/d_1,\ p^* = a_k k_2/d_1 d_2)$ for different values of α and for different initial points $\big(m(0), p(0)\big)$. Also, the figure shows that as the value of α decreased, the relation curve between m and p near to be linear.

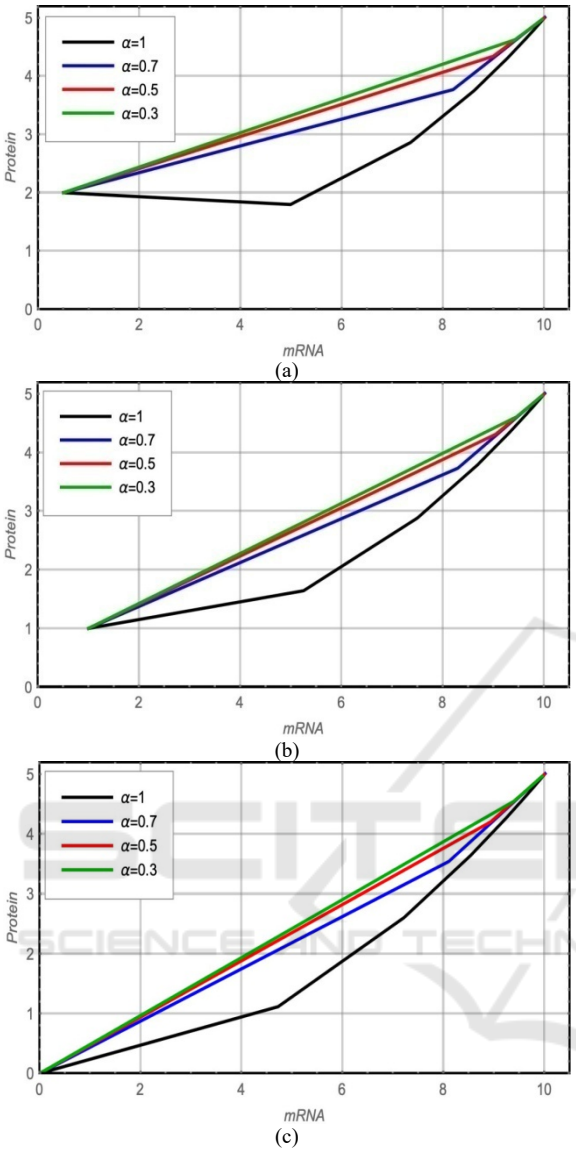


Figure 2: Phase plane portrait (a) m(0)=0 and p(0)=0. (b) m(0)=1 and p(0)=1.(c) m(0)=0.5 and p(0)=2.

4.2 Fractional Parameter Analysis

Studying the effect of the fractional parameter α on the system behavior is presented in figures 3 and 4. To study the behaviour of mRNA and protein at small-time interval t, the graphs are plotted for $\log(m)$ and $\log(P)$ in figure 3 and figure 4 respectively. From figure 3(b) and figure 4(b), it is clear that the rising time of mRNA (m) and protein (P) decreases with increasing the value of α which improves the system stability.

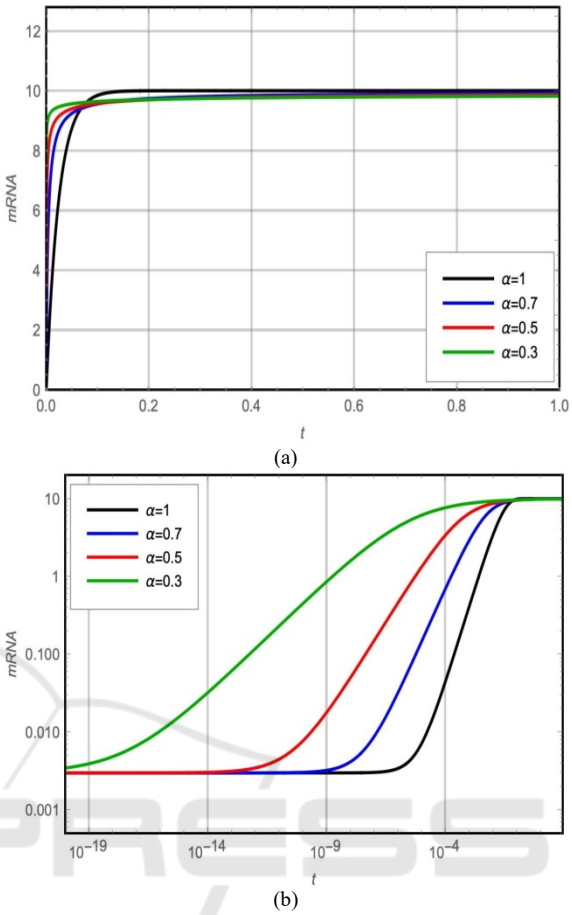


Figure 3: Fractional solution of m(t). (a) Linear plot (b) Logarithmic plot.

5 CONCLUSIONS

This paper presents the modeling of a fractional differential operator on the gene regulation process. A complete fractional dynamical system for an activator gene regulation model using the exact solution of the fractional model is introduced and discussed. The study of the systems' phase plane portrait and the variables' transient responses starting from different initial points are discussed. Moreover, the effect of the fractional parameter α on the system stability and its transient response is presented. Results show that the parameter α is effective in describing mRNA and Protein , and it causes variance especially at a small interval of t. These results and analysis may be helpful for the future genetic studies in case of availability of laboratory data.

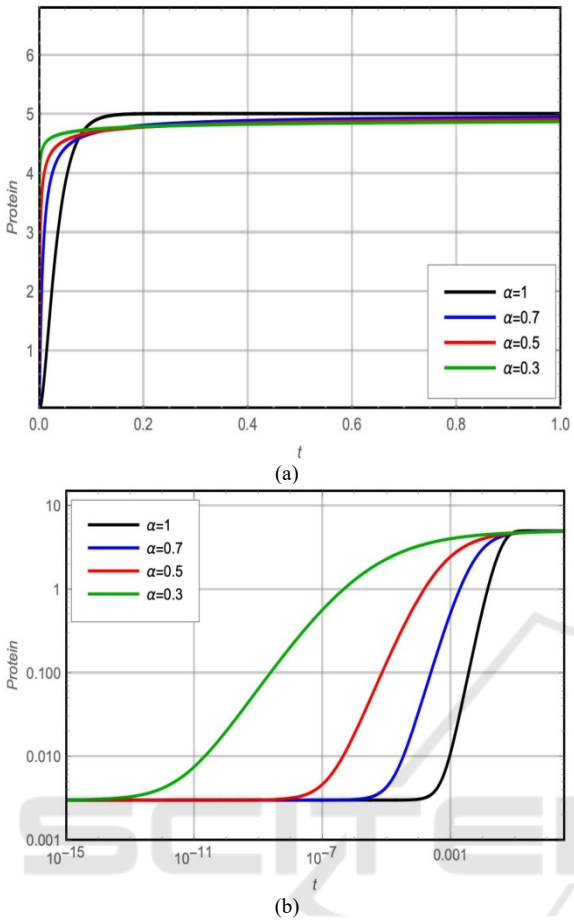


Figure 4: Fractional solution of p(t). (a) Linear plot (b) Logarithmic plot.

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