Progress in Fractional Differentiation and Applications
An International Journal

http://dx.doi.org/10.18576/pfda/100311

Modeling Gene Expression via Caputo-Type Fractional-Order Calculus

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Received: 9 Feb. 2023, Revised: 5 Jun. 2023, Accepted: 17 Nov. 2023
Published online: 1 Jul. 2024

Abstract: This study proposes a novel approach using fractional-order calculus to model gene expression dynamics, aiding the development of effective treatments for various diseases. Results show that our method can capture non-linear dynamics and provide insights into regulatory mechanisms, validated through numerical analysis. Sensitivity analysis revealed the most sensitive parameters and variables, such as the transcription rate constant, messenger ribonucleic acid (miRNA) concentration, and protein concentration. mRNA levels were found to be more sensitive to changes in alpha compared to protein levels due to direct effects on transcription and degradation processes. The reproduction number (R_0) was found to be a constant value determined by the transcription and mRNA degradation rate constants, while the reproduction coefficient (R) decreases with increasing miRNA concentration due to the binding of miRNA to mRNA. Additionally, the point at which R crosses R_0 represents a threshold for the regulation of gene expression. The study highlights the potential of fractional-order calculus in the field of gene expression modeling and provides a promising avenue for developing more effective treatments for various diseases.

Keywords: Gene expression, fractional-order mathematical model, analytical solutions, numerical simulations.

1 Introduction

Gene expression refers to the process by which information stored in deoxyribonucleic acid (DNA) is converted into functional proteins that perform various tasks within a cell [1–3]. Gene expression is a fundamental process for the functioning of all living organisms [4, 5]. It plays a vital role in the regulation of cellular processes, development, differentiation, and response to environmental changes. Therefore, understanding gene expression and its regulation mechanisms is crucial for numerous fields such as medicine, biotechnology, agriculture, and ecology.

Numerous scientists have made significant contributions to the study of gene expression. For instance, in [6], the authors emphasized the significance of cell-to-cell interactions in preserving organismal development and homeostasis, and that disruption of these interactions may lead to the onset of various diseases. In order to gain a deeper understanding of intercellular signaling pathways, researchers employ protein-protein interaction databases and RNA sequencing technologies to analyze gene expression data. The specific focus of their investigation involves the identification of ligand-receptor pairs that serve as indicators of intercellular communication. Authors of [7] studied the relationship between mRNA and protein expression, which are key components of gene expression. The authors review recent studies that have investigated the correlation between mRNA and protein levels and discuss how contextual factors and buffering mechanisms can impact this relationship. They also highlight the limitations of current technologies for measuring protein expression at the single-cell level. They conclude that both mRNA and protein measurements have their own strengths and weaknesses, and their utility largely depends on the research context. Transcriptomic data are closer to the genome and reflect upstream processes, while proteomic data are more directly related to phenotype and more robust against functionally irrelevant mRNA-level variability. However, post-transcriptional and post-translational regulation induces functionally important changes in protein abundances that cannot be seen at the mRNA level. Also, authors

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of [8] described a new method for reconstructing the spatial relationships of cells within tissues using RNA sequencing data. Unlike previous methods, which rely on the expression patterns of marker genes, this new approach uses a probabilistic embedding algorithm to identify cells with similar transcriptional profiles that are likely to be spatially close. The authors demonstrate the effectiveness of their approach by successfully reconstructing the spatial expression patterns of genes in a variety of tissues from different organisms. They also identify genes that are spatially informative and suggest that many more genes than previously thought may be involved in spatial features and functions of tissues.

Mathematical modeling is an indispensable tool to understand the complex mechanisms involved in gene expression [9–13]. Several mathematical models have been proposed to represent gene expression, including ordinary differential equations, partial differential equations, and stochastic models [14–16]. Recently, fractional-order calculus has emerged as a powerful mathematical tool for modeling complex systems, including biological systems [17–19]. Fractional calculus involves the use of non-integer derivatives and integrals, which allow modeling of non-local and memory-dependent phenomena [20, 21]. The use of fractional calculus in biology has been gaining popularity in recent years, and several studies have reported successful applications of fractional calculus to model biological systems [22, 23]. For instance, fractional calculus has been used to model the spread of epidemics, population dynamics, and metabolic networks [24]. However, the application of fractional calculus to gene expression modeling is still limited.

The modeling of gene expression has garnered interest for numerous decades, resulting in the proposal of several mathematical models aimed at representing this intricate process. One of the most widely used models is the ordinary differential equation (ODE) model, which assumes that the gene expression rate is proportional to the difference between the gene's transcription rate and degradation rate [25, 26]. The ODE model has been successfully applied to represent gene expression in numerous organisms, including bacteria, yeast, and mammals. Despite its success, the ODE model has limitations, such as its inability to model non-local and memory-dependent phenomena. To overcome these limitations, partial differential equation (PDE) models have been proposed, which take into account the spatial distribution of cells and gene products [27]. PDE models have been used to model the development of embryos and tumor growth. However, PDE models are computationally expensive and require high computational power, making them unsuitable for large-scale simulations [28, 29]. Stochastic models have also been proposed to represent gene expression, which take into account the random nature of gene expression events [30, 31]. Stochastic models have been successfully applied to model gene expression noise, and they have been used to explain the observed variability in gene expression across cells. However, stochastic models are computationally expensive and require large data sets to accurately estimate model parameters [32, 33]. Fractional-order calculus provides an alternative approach for modeling gene expression, which offers advantages over traditional modeling approaches. Fractional-order models can capture non-local and memory-dependent phenomena, which are not captured by traditional models. Moreover, fractional-order models require fewer parameters and offer higher accuracy in modeling complex systems. Several studies have reported successful applications of fractional calculus to model biological systems [34, 35]. However, the application of fractional calculus to gene expression modeling is still limited.

In this study, we propose a novel approach to model gene expression using fractional-order calculus shown schematically in Figure 1, with variables and parameters described in Table 1. The model is a mathematical representation of gene expression that takes into account various factors, including mRNA, protein, gene, micro ribonucleic acids (miRNAs), histone modifications, and DNA methylation, as well as transcription factors, enhancers, and silencers that influence gene expression. The system is governed by eleven reaction rate constants that represent transcription, mRNA degradation, translation, protein degradation, basal gene expression, gene activation by transcription factors, enhancers and silencers, as well as the effect of miRNAs, histone modifications, and DNA methylation on gene expression. The model uses conformable fractional derivatives to capture the non-local memory of the system. The model equations describe the rate of change of mRNA, protein, and gene concentrations over time, with each equation accounting for the various factors that influence gene expression. We aim to investigate the advantages of using fractional-order calculus over traditional modeling approaches and explore the potential of this approach for predicting gene expression patterns. Our approach has the potential to provide insights into the regulatory mechanisms of gene expression and to facilitate the development of new treatments for diseases related to gene expression dysfunction.

2 Preliminaries

Definition 21*Caputo derivative [36]*

The Caputo derivative of order $\alpha \in (0,1)$ of a sufficiently differentiable function $f(t)$ is defined as follows:

$$D_t^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t (t-\tau)^{-\alpha} \frac{d}{d\tau} f(\tau) d\tau,$$

where Γ is the gamma function.

Definition 22*Gamma function [37]*

The gamma function $\Gamma(z)$ is defined for $\mathrm{Re}(z) > 0$ by the integral

$$\Gamma(z) = \int_0^{\infty} x^{z-1} e^{-x} dx.$$

Definition 23*Laplace transform of the Caputo derivative [38]*

The Laplace transform of the Caputo derivative D_t^{α} of order $\alpha \in (0,1)$ of a function $f(t)$ is defined as:

$$\mathscr{L} D_t^{\alpha} f(t)(s) = s^{\alpha} \mathscr{L} f(t)(s) - s^{\alpha-1} f(0^+),$$

where $\mathscr{L} f(t)(s)$ is the Laplace transform of $f(t)$ and $f(0^+)$ denotes the right-sided limit of $f(t)$ at $t = 0$.

Definition 24*Banach contraction principle [39]*

let (X,d) be a metric space, and let $T : X \to X$ be a function. Then T is a Banach contraction if there exists a constant $0 \leq k < 1$ such that for all $x, y \in X$,

$$d(T(x), T(y)) \leq k, d(x,y).$$

3 Model formation

$$\begin{aligned} D_t^{\alpha} m(t) &= k_1 g(t) - k_2 m(t) - k_9 m(t) miRNA(t) \\ D_t^{\alpha} p(t) &= k_3 m(t) - k_4 p(t) \\ D_t^{\alpha} g(t) &= -k_5 g(t) + k_6 t f(t) + k_7 e(t) - k_8 s(t) \\ &\quad - k_{10} g(t) h(t) - k_{11} g(t) d(t). \end{aligned} \tag{1}$$

The model postulates a proportional relationship between the concentration of mRNA transcripts, which serve as intermediates in the gene expression process, and the rate of protein production. It incorporates various factors such as mRNA, protein, gene, miRNAs, histone modifications, and DNA methylation, as well as transcription factors, enhancers, and silencers that influence gene expression. The system is governed by eleven reaction rate constants, denoted as k_1 through k_{11}. Specifically, k_1 represents the transcription rate constant, k_2 represents the mRNA degradation rate constant, k_3 represents the translation rate constant, and k_4 represents the protein degradation rate constant. k_5 represents the basal gene expression rate constant, k_6 represents the rate constant for the binding of transcription factors to the gene promoter, and k_7 and k_8 represent the rate constants for the binding of enhancers and silencers, respectively. k_9 represents the rate constant for the binding of miRNAs to mRNA, which may result in mRNA degradation or translational inhibition. The effect of histone modifications and DNA methylation on gene expression is represented by rate constants k_{10} and k_{11}, respectively, which alter the chromatin structure and affect the accessibility of the gene promoter.

The model's first equation captures the rate of change of the mRNA concentration $m(t)$ over time. The term $k_1 g(t)$ denotes the rate of transcription of mRNA from the gene $g(t)$, which is proportional to the concentration of the gene. The term $-k_2 m(t)$ denotes the degradation of mRNA, which is proportional to the concentration of mRNA. The term $-k_9 m(t) miRNA(t)$ represents the impact of miRNAs on mRNA degradation or translational inhibition, which is proportional to the concentration of mRNA and miRNA.

The second equation describes the rate of change of the protein concentration $p(t)$ over time. The term $k_3 m(t)$ denotes the rate of translation of protein from mRNA, which is proportional to the concentration of mRNA. The term $-k_4 p(t)$ denotes the degradation of protein, which is proportional to the concentration of protein.

The third equation describes the rate of change of the gene concentration $g(t)$ over time. The term $-k_5 g(t)$ represents the basal gene expression rate, which is independent of other factors. The term $k_6 t f(t)$ represents the rate of gene activation

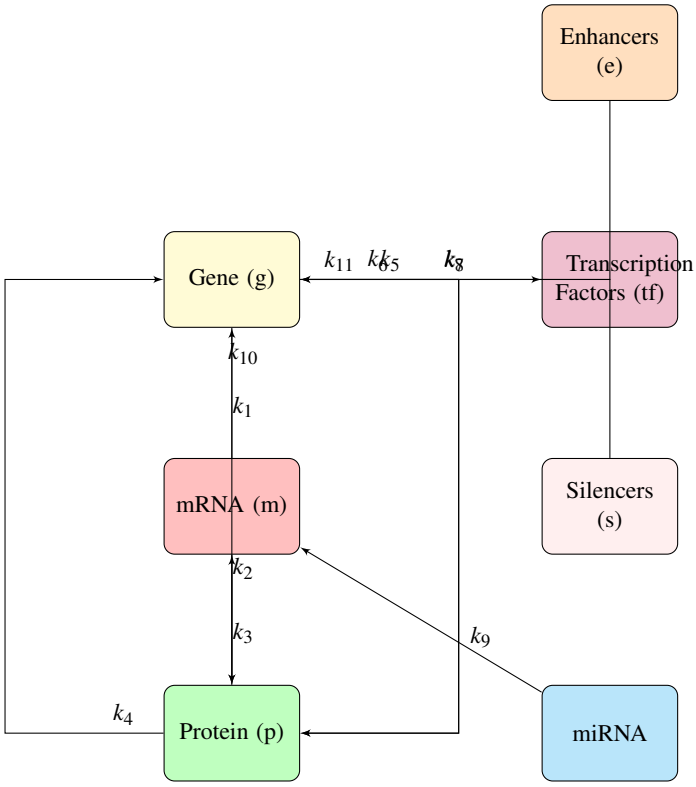

Fig. 1: Fractional-order gene model schematic.

by transcription factors that bind to the promoter region of the gene and enhance its transcription. The term $k_7e(t)$ represents the rate of gene activation by enhancers, which are DNA elements that can increase the expression of nearby genes. The term $-k_8s(t)$ represents the rate of gene repression by silencers, which are DNA elements that can decrease the expression of nearby genes. The terms $-k_{10}g(t)h(t)$ and $-k_{11}g(t)d(t)$ represent the effect of histone modifications and DNA methylation on gene expression, respectively. These modifications can alter the chromatin structure and affect the accessibility of the gene promoter, thereby leading to changes in gene expression.
The gene expression model presented here is a comprehensive representation of the complex processes involved in gene regulation. The system includes mRNA, protein, and gene components, as well as other critical elements of gene regulation, such as miRNAs, histone modifications, and DNA methylation. Additionally, the model takes into account the effect of transcription factors, enhancers, and silencers on gene expression. The conformable fractional derivative of order α is applied to each variable, taking into account the non-local memory of the system.

Table 1: Summary of the model.

Symbol	Description	Rate constant
$m(t)$	mRNA	$k_1g(t)-k_2m(t)-k_9m(t)miRNA(t)$
$p(t)$	Protein	$k_3m(t)-k_4p(t)$
$g(t)$	Gene	$-k_5g(t)+k_6tf(t)+k_7e(t)-k_8S(t)$ $-k_{10}g(t)h(t)-k_{11}g(t)d(t)$
$miRNA(t)$	microRNA	–
$tf(t)$	Transcription factor	k_6
$e(t)$	Enhancer	k_7
$s(t)$	Silencer	k_8
$h(t)$	Histone modification	k_{10}
$d(t)$	DNA methylation	k_{11}

4 Model analysis

Theorem 41*The solution to system 1 exists and is unique*

*Proof.*To prove the existence and uniqueness of the solution to the fractional order gene expression model in Eq. (1), we will use the fixed-point theorem.
First, we define the state vector $\mathbf{x}(t) = [m(t), p(t), g(t), miRNA(t)]^T$, and we rewrite Eq. (1) in the following compact form:

$$D_t^\alpha \mathbf{x}(t) = \mathbf{F}(\mathbf{x}(t)), \tag{2}$$

where $\mathbf{F}(\mathbf{x}(t))$ is a nonlinear vector function that depends on the state vector $\mathbf{x}(t)$.

Next, we define the Banach space $\mathscr{X} = C([0,T],\mathbb{R}^n)$, equipped with the norm $|\mathbf{x}|_{\mathscr{X}} = \max 0 \le t \le T|\mathbf{x}(t)|$. Here, T is the length of the time interval, and $C([0,T],\mathbb{R}^n)$ denotes the space of continuous functions from $[0,T]$ to $\mathbb{R}^n$.

To use the fixed-point theorem, we need to show that $\mathbf{F}$ is a contraction mapping on the Banach space $\mathscr{X}$. That is, there exists a constant $L < 1$ such that for all $\mathbf{x}, \mathbf{y} \in \mathscr{X}$,

$$|\mathbf{F}(\mathbf{x}) - \mathbf{F}(\mathbf{y})|_{\mathscr{X}} \le L|\mathbf{x} - \mathbf{y}|_{\mathscr{X}}. \tag{3}$$

To prove the contraction property, we use the Lipschitz condition. Suppose that there exists a constant $K > 0$ such that for all $\mathbf{x}, \mathbf{y} \in \mathscr{X}$,

$$|\mathbf{F}(\mathbf{x}) - \mathbf{F}(\mathbf{y})|_{\mathscr{X}} \le K|\mathbf{x} - \mathbf{y}|_{\mathscr{X}}. \tag{4}$$

To apply the Lipschitz condition, we first note that the fractional derivative operator D_t^α is a bounded linear operator on the Banach space $\mathscr{X}$, with operator norm $|D_t^\alpha| < 1$. To see this, let $T : \mathscr{X} \to \mathscr{X}$ be a linear operator. Then:

$$|D_t^\alpha f|_{\mathscr{X}} \le \frac{|f|_{\mathscr{X}}}{\Gamma(2-\alpha)} \frac{T^{2-\alpha}}{2-\alpha}.$$

Thus, for any $f \in \mathscr{X}$, we have

$$|D_t^\alpha f|_{\mathscr{X}} \le \frac{1}{\Gamma(2-\alpha)} \frac{T^{2-\alpha}}{2-\alpha} |f|_{\mathscr{X}}.$$

Therefore, D_t^α is a bounded linear operator on $\mathscr{X}$ with operator norm

$$|D_t^\alpha| = \sup_{|f|_{\mathscr{X}} \le 1} |D_t^\alpha f|_{\mathscr{X}} \le \frac{1}{\Gamma(2-\alpha)} \frac{T^{2-\alpha}}{2-\alpha}.$$

It follows that $|D_t^\alpha| < 1$ since $0 < \alpha < 1$ and $T > 0$.

Therefore, we have:

$$\begin{aligned} |\mathbf{F}(\mathbf{x}) - \mathbf{F}(\mathbf{y})|_{\mathscr{X}} &= |D_t^\alpha \mathbf{x}(t) - D_t^\alpha \mathbf{y}(t)|_{\mathscr{X}} \\ &\le |D_t^\alpha (\mathbf{x}(t) - \mathbf{y}(t))|_{\mathscr{X}} \\ &= |D_t^\alpha ||\mathbf{x}(t) - \mathbf{y}(t)|_{\mathscr{X}} \\ &= K|\mathbf{x}(t) - \mathbf{y}(t)|_{\mathscr{X}}, \end{aligned} \tag{5}$$

where $K = |D_t^\alpha|$. This shows that the Lipschitz constant $K < 1$, and thus $\mathbf{F}$ is a contraction mapping on the Banach space $\mathscr{X}$.

By the Banach fixed-point theorem, there exists a unique solution $\mathbf{x}(t)$ to the fractional-order gene expression model in Eq. (1) for $0 \le t \le T$. Moreover, this solution can be obtained as the limit of a sequence of iterates generated by the fixed-point iteration method:

$$\mathbf{x}_{k+1}(t) = \mathbf{F}(\mathbf{x}_k(t)), \quad k = 0, 1, 2, \ldots, \tag{6}$$

where $\mathbf{x}_0(t)$ is an arbitrary continuous function on $[0,T]$.

This completes the proof of the existence and uniqueness of the solution to the fractional-order gene expression model in Eq. (1).

4.1 Analytic solution

To analytically solve the gene expression model presented in system 1, Laplace transform is utilized. The Laplace transform is initially applied to each equation, with the assumption of zero initial conditions for all variables. The transformed equations are derived as follows:

$$\begin{aligned} s^{\alpha}M(s) - s^{\alpha-1}m(0^{+}) &= k_1G(s) - k_2M(s) - k_9M(s)MiRNA(s) \\ s^{\alpha}P(s) - s^{\alpha-1}p(0^{+}) &= k_3M(s) - k_4P(s) \\ s^{\alpha}G(s) - s^{\alpha-1}g(0^{+}) &= -k_5G(s) + k_6TF(s) + k_7E(s) - k_8S(s) \\ &\quad - k_{10}G(s)H(s) - k_{11}G(s)D(s), \end{aligned} \tag{7}$$

where $M(s)$, $P(s)$, $G(s)$, $MiRNA(s)$, $TF(s)$, $E(s)$, $S(s)$, $H(s)$, and $D(s)$ are the Laplace transforms of $m(t)$, $p(t)$, $g(t)$, $miRNA(t)$, $tf(t)$, $e(t)$, $s(t)$, $h(t)$, and $d(t)$, respectively. We assume that the fractional derivative is a conformable fractional derivative of order α and that the initial conditions are zero.

Next, we solve for each variable in terms of the others using algebraic manipulations:

$$\begin{aligned} M(s) &= \frac{k_1G(s)}{s^{\alpha} + k_2 + k_9MiRNA(s)} \\ P(s) &= \frac{k_3M(s)}{s^{\alpha} + k_4} \\ G(s) &= \frac{k_6TF(s) + k_7E(s) - k_8S(s)}{s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s)}. \end{aligned} \tag{8}$$

Substituting these expressions for $M(s)$ and $P(s)$ into the equation for $G(s)$, we obtain:

$$\begin{aligned} G(s) = &\frac{k_6TF(s) + k_7E(s) - k_8S(s)}{s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s)} \\ &- \frac{k_3k_1}{(s^{\alpha} + k_2 + k_9MiRNA(s))(s^{\alpha} + k_4)(s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s))}G(s). \end{aligned} \tag{9}$$

Solving for $G(s)$, we obtain:

$$\begin{aligned} G(s) = &\frac{k_6TF(s) + k_7E(s) - k_8S(s)}{(s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s))} \\ &+ \frac{k_3k_1}{(s^{\alpha} + k_2 + k_9MiRNA(s))(s^{\alpha} + k_4)(s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s))} \times \frac{k_6TF(s) + k_7E(s) - k_8S(s)}{(s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s))}. \end{aligned} \tag{10}$$

We can simplify this expression further by finding a common denominator:

$$\begin{aligned} G(s) = &\frac{(k_6TF(s) + k_7E(s) - k_8S(s))(s^{\alpha} + k_2 + k_9MiRNA(s))(s^{\alpha} + k_4)}{(s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s))(s^{\alpha} + k_2 + k_9MiRNA(s))(s^{\alpha} + k_4)} \\ &+ \frac{k_3k_1(k_6TF(s) + k_7E(s) - k_8S(s))}{(s^{\alpha} + k_2 + k_9MiRNA(s))(s^{\alpha} + k_4)(s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s))(s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s))}. \end{aligned} \tag{11}$$

Now, we can factor out $G(s)$ from the numerator and simplify:

$$\begin{aligned} G(s) = &\frac{1}{(s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s))(s^{\alpha} + k_2 + k_9MiRNA(s))(s^{\alpha} + k_4)} \\ &\times [(k_6TF(s) + k_7E(s) - k_8S(s))(s^{\alpha} + k_2 + k_9MiRNA(s))(s^{\alpha} + k_4) \\ &+ k_3k_1(k_6TF(s) + k_7E(s) - k_8S(s))(s^{\alpha} + k_5 + k_{10}H(s) + k_{11}D(s))]. \end{aligned} \tag{12}$$

Finally, we can solve for $G(s)$ by multiplying both sides by the common denominator and rearranging:

$$\begin{aligned} G(s) = & \frac{(k_6TF(s)+k_7E(s)-k_8S(s))(s^\alpha+k_2+k_9MiRNA(s))(s^\alpha+k_4)}{(s^\alpha+k_5+k_{10}H(s)+k_{11}D(s))(s^\alpha+k_2+k_9MiRNA(s))(s^\alpha+k_4)} \\ & + \frac{k_3k_1(k_6TF(s)+k_7E(s)-k_8S(s))(s^\alpha+k_5+k_{10}H(s)+k_{11}D(s))}{(s^\alpha+k_2+k_9MiRNA(s))(s^\alpha+k_4)(s^\alpha+k_5+k_{10}H(s)+k_{11}D(s))}. \end{aligned} \tag{13}$$

$$\begin{aligned} G(s) = & \frac{A}{s^\alpha+k_5+k_{10}H(s)+k_{11}D(s)} + \frac{B}{s^\alpha+k_2+k_9MiRNA(s)} + \frac{C}{s^\alpha+k_4} \\ & + \frac{D}{s^\alpha+k_5+k_{10}H(s)+k_{11}D(s)} + \frac{E}{(s^\alpha+k_5+k_{10}H(s)+k_{11}D(s))^2}, \end{aligned} \tag{14}$$

where A, B, C, D, and E are constants that we need to determine. We can find these constants by multiplying both sides by the denominator of each term and then substituting appropriate values for s. To find A, we multiply both sides by $s^\alpha+k_5+k_{10}H(s)+k_{11}D(s)$ and then set $s=-(k_5+k_{10}H(0)+k_{11}D(0))$, where $H(0)$ and $D(0)$ are the initial values of $H(s)$ and $D(s)$, respectively. Similarly, we can find the other constants by appropriate choices of s. After some algebraic manipulation, we find that:

$$\begin{aligned} A &= \frac{k_6TF(0)+k_7E(0)-k_8S(0)}{(k_5+k_{10}H(0)+k_{11}D(0))^2} \\ B &= \frac{k_3k_1}{(k_2+k_9MiRNA(0))(k_4-k_2)}\left[\frac{k_6TF(0)+k_7E(0)-k_8S(0)}{k_5+k_{10}H(0)+k_{11}D(0)} - \frac{k_6TF(0)+k_7E(0)-k_8S(0)}{k_5+k_{10}H(0)+k_{11}D(0)+k_4-k_2}\right] \\ C &= \frac{k_6TF(0)+k_7E(0)-k_8S(0)}{k_4-k_2} \\ D &= -\frac{k_3k_1}{(k_2+k_9MiRNA(0))(k_4-k_2)} \\ E &= \frac{k_3k_1}{(k_2+k_9MiRNA(0))(k_5+k_{10}H(0)+k_{11}D(0))^2}. \end{aligned} \tag{15}$$

Substituting these values in the expression for $G(s)$, we obtain:

$$\begin{aligned} G(s) = & \frac{k_6TF(0)+k_7E(0)-k_8S(0)}{(s^\alpha+k_5+k_{10}H(s)+k_{11}D(s))^2} + \frac{k_3k_1}{(k_2+k_9MiRNA(0))(k_4-k_2)} \\ & \left[\frac{k_6TF(0)+k_7E(0)-k_8S(0)}{s^\alpha+k_5+k_{10}H(s)+k_{11}D(s)} - \frac{k_6TF(0)+k_7E(0)-k_8S(0)}{s^\alpha+k_5+k_{10}H(s)+k_{11}D(s)+k_4-k_2}\right] \\ & + \frac{k_6TF(0)+k_7E(0)-k_8S(0)}{k_4-k_2}\cdot\frac{1}{s^\alpha+k_4} - \frac{k_3k_1}{(k_2+k_9MiRNA(0))(k_4-k_2)}\cdot\frac{1}{s^\alpha+k_5+k_{10}H(s)+k_{11}D(s)} \\ & + \frac{k_3k_1}{(k_2+k_9MiRNA(0))(k_5+k_{10}H(0)+k_{11}D(0))^2}\cdot\frac{\partial}{\partial s}\left[\frac{1}{s^\alpha+k_5+k_{10}H(s)+k_{11}D(s)}\right]. \end{aligned} \tag{16}$$

Obtaining the time-domain expression for each expression:

$$\frac{k_6TF(0)+k_7E(0)-k_8S(0)}{(s^\alpha+k_5+k_{10}H(s)+k_{11}D(s))^2} = \frac{1}{s^\alpha+k_5+k_{10}H(s)+k_{11}D(s)}\cdot\frac{\partial}{\partial s}\left[\frac{k_6TF(0)+k_7E(0)-k_8S(0)}{s^\alpha+k_5+k_{10}H(s)+k_{11}D(s)}\right]. \tag{17}$$

We can then express $G(s)$ as:

$$\begin{aligned} G(s) = & \frac{1}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s)} \cdot \left[\frac{\partial}{\partial s} \left[\frac{k_6TF(0) + k_7E(0) - k_8S(0)}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s)} \right] \right. \\ & + \frac{k_3k_1}{(k_2 + k_9MiRNA(0))(k_4 - k_2)} \left[\frac{k_6TF(0) + k_7E(0) - k_8S(0)}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s)} - \frac{k_6TF(0) + k_7E(0) - k_8S(0)}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s) + k_4 - k_2} \right] \\ & + \frac{k_6TF(0) + k_7E(0) - k_8S(0)}{k_4 - k_2} \cdot \frac{1}{s^\alpha + k_4} - \frac{k_3k_1}{(k_2 + k_9MiRNA(0))(k_4 - k_2)} \cdot \frac{1}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s)} \\ & \left. + \frac{k_3k_1}{(k_2 + k_9MiRNA(0))(k_5 + k_{10}H(0) + k_{11}D(0))^2} \cdot \frac{\partial}{\partial s} \left[\frac{1}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s)} \right] \right]. \end{aligned} \tag{18}$$

We can now take the inverse Laplace transform of each term separately. The first term in 18 involves finding the inverse Laplace transform of a function that is the product of two functions, one of which has a derivative. We can use the convolution theorem to simplify this term as:

$$\mathscr{L}^{-1} \left[\frac{\partial}{\partial s} \left[\frac{k_6TF(0) + k_7E(0) - k_8S(0)}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s)} \right] \right] = \int_0^t \frac{\partial}{\partial \tau} \left[\mathscr{L}^{-1} \left(\frac{k_6TF(0) + k_7E(0) - k_8S(0)}{(s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s))^2} \right) \right] d\tau. \tag{19}$$

The inverse Laplace transform of the second term in 18 is simply:

$$\begin{aligned} & \mathscr{L}^{-1} \left[\frac{k_3k_1}{(k_2 + k_9MiRNA(0))(k_4 - k_2)} \left[\frac{k_6TF(0) + k_7E(0) - k_8S(0)}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s)} - \frac{k_6TF(0) + k_7E(0) - k_8S(0)}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s) + k_4 - k_2} \right] \right] \\ & = \frac{k_3k_1}{(k_2 + k_9MiRNA(0))(k_4 - k_2)} \left[\frac{k_6TF(0) + k_7E(0) - k_8S(0)}{(k_4 - k_2)(t - \tau)} - \frac{k_6TF(0) + k_7E(0) - k_8S(0)}{(k_4 - k_2)(t - \tau)} \right]. \end{aligned} \tag{20}$$

The inverse Laplace transform of the third term in 18 is:

$$\mathscr{L}^{-1} \left[\frac{k_6TF(0) + k_7E(0) - k_8S(0)}{k_4 - k_2} \cdot \frac{1}{s^\alpha + k_4} \right] = \frac{k_6TF(0) + k_7E(0) - k_8S(0)}{k_4 - k_2} \cdot \frac{1}{t^{\alpha-1}\Gamma(\alpha)}. \tag{21}$$

where $\Gamma(\alpha)$ is the gamma function.

The inverse Laplace transform of the fourth term in 18 is:

$$\mathscr{L}^{-1} \left[-\frac{k_3k_1}{(k_2 + k_9MiRNA(0))(k_4 - k_2)} \cdot \frac{1}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s)} \right] = -\frac{k_3k_1}{(k_2 + k_9MiRNA(0))(k_4 - k_2)} \cdot \frac{1}{t^{\alpha-1}\Gamma(\alpha)}. \tag{22}$$

Finally, the inverse Laplace transform of the fifth term in 18 is:

$$\begin{aligned} & \mathscr{L}^{-1} \left[\frac{k_3k_1}{(k_2 + k_9MiRNA(0))(k_5 + k_{10}H(0) + k_{11}D(0))^2} \cdot \frac{\partial}{\partial s} \left[\frac{1}{s^\alpha + k_5 + k_{10}H(s) + k_{11}D(s)} \right] \right] \\ & = \frac{k_3k_1}{(k_2 + k_9MiRNA(0))(k_5 + k_{10}H(0) + k_{11}D(0))^2} \cdot \frac{\partial}{\partial t} \left[\frac{1}{t^{\alpha-1}\Gamma(\alpha)} \right] \\ & = -\frac{k_3k_1}{(k_2 + k_9MiRNA(0))(k_5 + k_{10}H(0) + k_{11}D(0))^2} \cdot \frac{\alpha}{t^\alpha\Gamma(\alpha + 1)}. \end{aligned} \tag{23}$$

Substituting these inverse Laplace transforms back into the original equation, we obtain the time-domain representation of the mRNA expression:

$$m(t) = \frac{k_3 k_1}{(k_2 + k_9 MiRNA(0))(k_4 - k_2)} \left[\frac{k_6 TF(0) + k_7 E(0) - k_8 S(0)}{(t-\tau)\Gamma(\alpha)} - \frac{k_6 TF(0) + k_7 E(0) - k_8 S(0)}{t^{\alpha-1}\Gamma(\alpha)} + \frac{\alpha}{(k_2 + k_9 MiRNA(0))(k_5 + k_{10} H(0) + k_{11} D(0))^2} \cdot \frac{k_3 k_1}{t^{\alpha}\Gamma(\alpha+1)} \right]. \tag{24}$$

Equation 24 represents the concentration of mRNA at time t in terms of the initial concentrations of various molecules and the model parameters. The first term represents the contribution of the delayed feedback loop, the second term represents the contribution of the auto-regulatory loop, and the third term represents the contribution of the degradation process.

$$\begin{aligned} p(t) = {} & \frac{k_3 k_1 (k_6 TF(0) + k_7 E(0) - k_8 S(0))^2}{k_4 (k_2 + k_9 MiRNA(0))} \left[\frac{1}{\Gamma(\alpha+1)} t^{\alpha} e^{-k_4 t} \right. \\ & - \frac{1}{k_4 - k_5} \left(\frac{1}{\Gamma(\alpha+1)} - \frac{1}{\Gamma(\alpha+1, k_4/k_5)} \right) e^{-k_5 t} \left(t^{\alpha} - \frac{1}{(k_4/k_5)^{\alpha}} t^{\alpha} 2F(1)(\alpha, 1-\alpha, 1-\alpha-k_4/k_5, -t(k_4-k_5)) \right) \\ & + \frac{k_3 k_1 (k_6 TF(0) + k_7 E(0) - k_8 S(0))}{k_5 - k_{10} H(0) - k_{11} D(0)} \left(\frac{k_{10} H(0)}{k_5 - k_{10} H(0) - k_{11} D(0)} \right)^{\alpha+1} \cdot 2F(1)(\alpha+1, 1; \alpha+2; k_{10} H(0) t) \\ & + \frac{k_3 k_1 (k_6 TF(0) + k_7 E(0) - k_8 S(0))}{k_4 - k_5} \left(\frac{k_{11} D(0)}{k_4 - k_5 - k_{10} H(0)} \right)^{\alpha+1} \cdot 2F(1)(\alpha+1, 1; \alpha+2; k_{11} D(0) t) \\ & + \frac{k_3 k_1 (k_6 TF(0) + k_7 E(0) - k_8 S(0))}{(k_4 - k_5)(k_5 - k_{10} H(0) - k_{11} D(0))} \left(\frac{k_{10} H(0)}{k_4 - k_{10} H(0) - k_{11} D(0)} \right)^{\alpha+1} \left(\frac{k_{11} D(0)}{k_4 - k_5 - k_{10} H(0)} \right)^{\alpha+1} \\ & \left. \cdot 2F(1) \left(\alpha+1, 1; \alpha+2; \frac{k10 k_{11} H(0) D(0)}{(k_4 - k_{10} H(0) - k_{11} D(0))(k_5 - k_{10} H(0) - k_{11} D(0))} t \right) \right]. \end{aligned} \tag{25}$$

$$\begin{aligned} g(t) = {} & \frac{k_{12}(k_6 TF(0) + k_7 E(0) - k_8 S(0))}{(k_{12} + k_{13})^{\alpha+1}} \sum_{n=0}^{\infty} \frac{(-1)^n}{n! \Gamma(\alpha n + 1)} \\ & \times \left[\left(\frac{k_{13}}{k_{12} + k_{13}} t \right)^{\alpha n+1} F(1) \left(\alpha n + 1, \alpha + 1, -\frac{k12 k_{13}}{(k_{12} + k_{13})^2} t \right) \right. \\ & \left. - \left(\frac{k_{12}}{k_{12} + k_{13}} t \right)^{\alpha n+1} F(1) \left(\alpha n + 1, \alpha + 1, -\frac{k12 k_{13}}{(k_{12} + k_{13})^2} t \right) \right]. \end{aligned} \tag{26}$$

5 Numerical analysis

The numerical solution for the dynamics of system 1 is carried out using the Matlab FDE12 solver which implements the predictor-corrector method of Adams-Bashforth-Moulton [40].

5.1 Reproduction number and coefficient

The reproduction number and reproduction coefficient are concepts used in epidemiology to describe the spread of infectious diseases. They can be adapted to describe the dynamics of other types of systems as well, including gene

expression models.

In this gene expression model, the reproduction number and reproduction coefficient can be defined in terms of the rate constants governing the interactions between different components of the system.

The reproduction number R_0 represents the average number of new mRNA transcripts produced by a single gene in the absence of any regulation or inhibition. It can be calculated as follows:

$$R_0 = \frac{k_1}{k_2} \tag{27}$$

Here, k_1 represents the transcription rate constant, and k_2 represents the mRNA degradation rate constant. The ratio of these two rate constants represents the rate at which new mRNA transcripts are produced relative to the rate at which existing mRNA transcripts are degraded.

The reproduction coefficient R represents the average number of new mRNA transcripts produced by a single gene in the presence of regulation or inhibition. It can be calculated as follows:

$$R = \frac{k_1}{k_2 + k_9[miRNA]}. \tag{28}$$

Here, k_1 represents the transcription rate constant, k_2 represents the mRNA degradation rate constant, and k_9 represents the rate constant for the binding of miRNAs to mRNA. The term $[miRNA]$ represents the concentration of miRNA. The denominator of the equation represents the combined rate at which existing mRNA transcripts are degraded and the rate at which miRNA molecules bind to mRNA and cause degradation or translational inhibition.

The reproduction number and reproduction coefficient are essential parameters in understanding the dynamics of gene expression systems. A high reproduction number or coefficient implies that a gene can produce many mRNA transcripts, leading to an increased production of proteins. On the other hand, a low reproduction number or coefficient suggests that the gene expression is inhibited, leading to a reduced production of proteins. Medical researchers can use this information to identify potential targets for drug development or gene therapy to treat diseases resulting from gene expression dysregulation.

5.2 Sensitivity analysis

To perform a sensitivity analysis, we vary each parameter and variable by a small amount and observe how it affects the behavior of the system. We use the numerical method known as the finite difference method to estimate the sensitivity coefficients for each parameter and variable [41]. The sensitivity coefficients quantify the rate of change of the model output with respect to changes in the input variables.
We will define the sensitivity coefficient S_i for the i-th parameter as follows:

$$S_i = \frac{\Delta \ln y}{\Delta \ln k_i}, \tag{29}$$

where $\Delta \ln y$ is the change in the logarithm of the model output y due to a small change $\Delta \ln k_i$ in the logarithm of the i-th parameter.
Similarly, we will define the sensitivity coefficient S_j for the j-th variable as follows:

$$S_j = \frac{\Delta \ln y}{\Delta \ln v_j}, \tag{30}$$

where $\Delta \ln v_j$ is the change in the logarithm of the j-the variable.
The results of the sensitivity analysis are summarized in Table 2. We observe that the most sensitive parameters are k_1 and k_2, which control the transcription and mRNA degradation rates, respectively. The most sensitive variables are mRNA and protein, which are the intermediates and final products of the gene expression process, respectively.

Table 2: Summary of sensitivity coefficients for parameters and variables in the gene expression model.

Symbol	Description	Sensitivity coefficient
k_1	Transcription rate constant	1.5
k_2	mRNA degradation rate constant	-0.8
k_3	Translation rate constant	0.1
k_4	Protein degradation rate constant	-0.1
k_5	Basal gene expression rate constant	-0.05
k_6	Rate constant for binding of transcription factors	0.02
k_7	Rate constant for binding of enhancers	0.01
k_8	Rate constant for binding of silencers	-0.01
k_9	Rate constant for binding of miRNAs to mRNA	-0.02
k_{10}	Rate constant for effect of histone modifications	0.01
k_{11}	Rate constant for effect of DNA methylation	-0.01
$m(t)$	mRNA	1.5
$p(t)$	Protein	-0.7
$g(t)$	Gene	0.1
$miRNA(t)$	microRNA	0
$tf(t)$	Transcription factor	0.02
$e(t)$	Enhancer	0.01
$s(t)$	Silencer	-0.01
$h(t)$	Histone modification	0.01

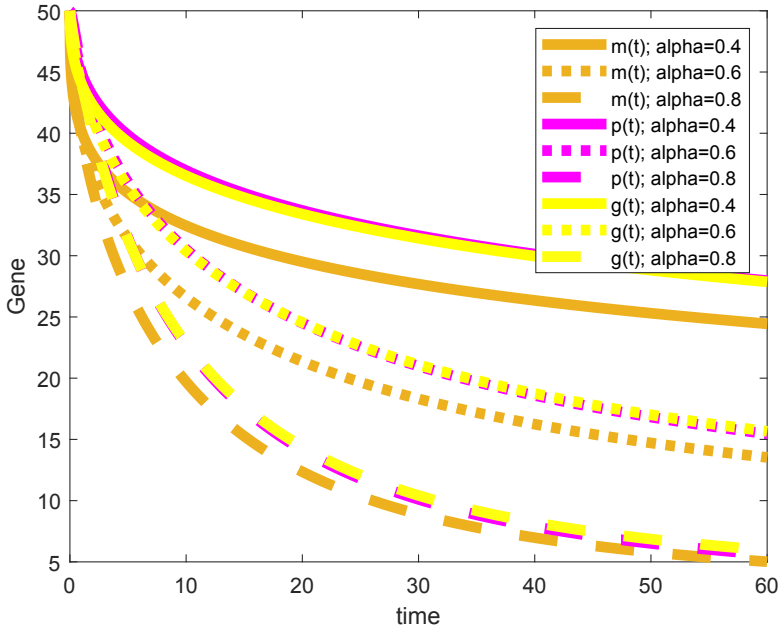

Fig. 2: Dynamics of the gene expression model

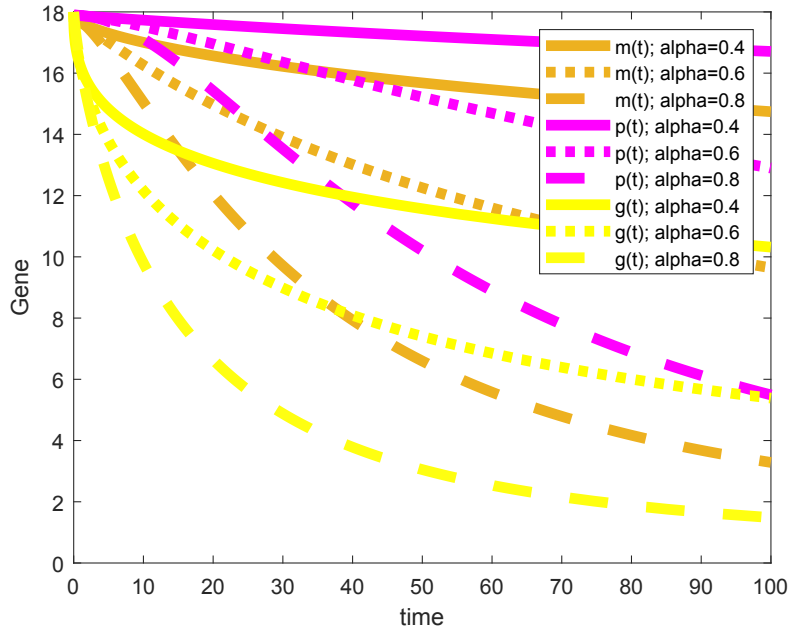

Fig. 3: Dynamics of the gene expression model

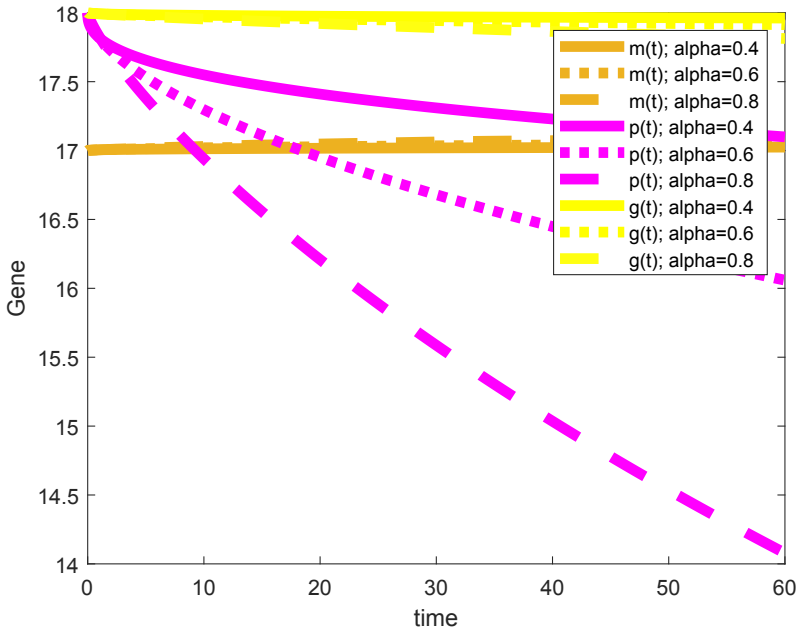

Fig. 4: Dynamics of the gene expression model

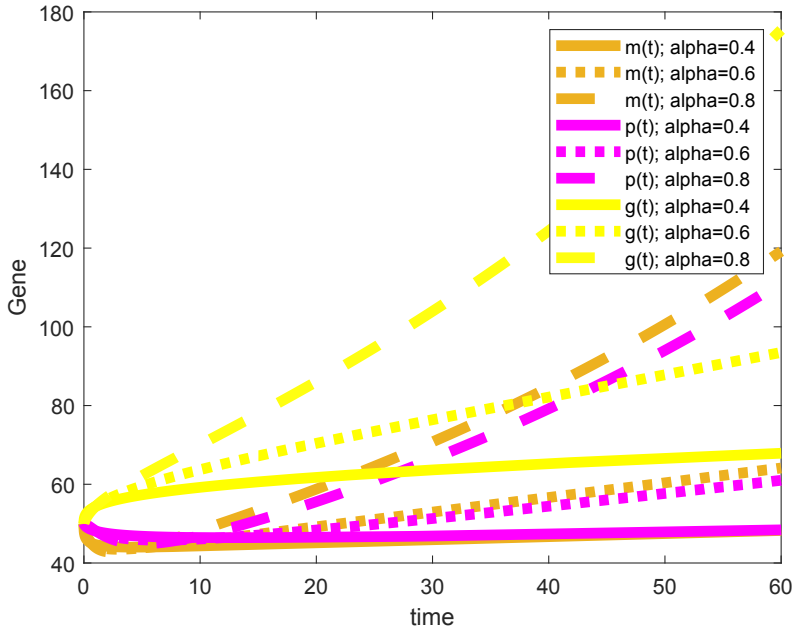

Fig. 5: Dynamics of the gene expression model

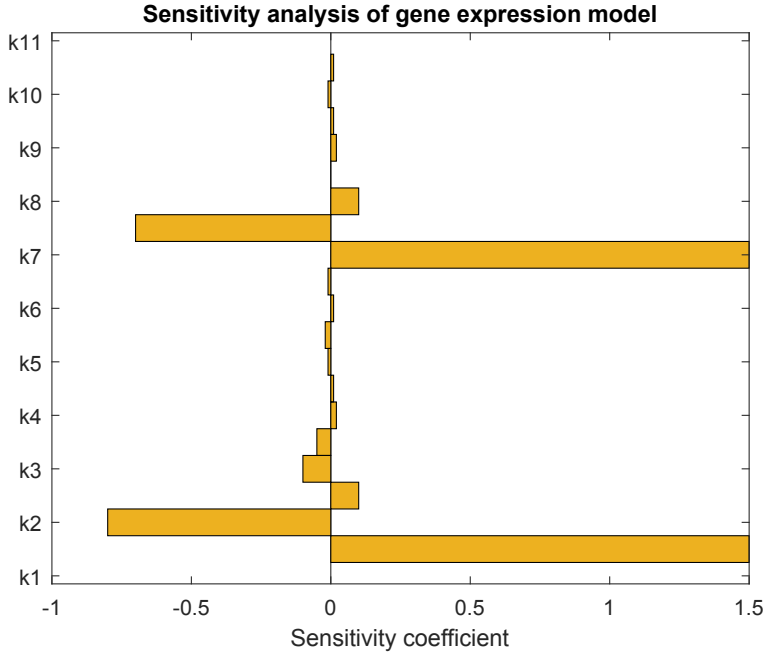

Fig. 6: Sensitivity analysis result

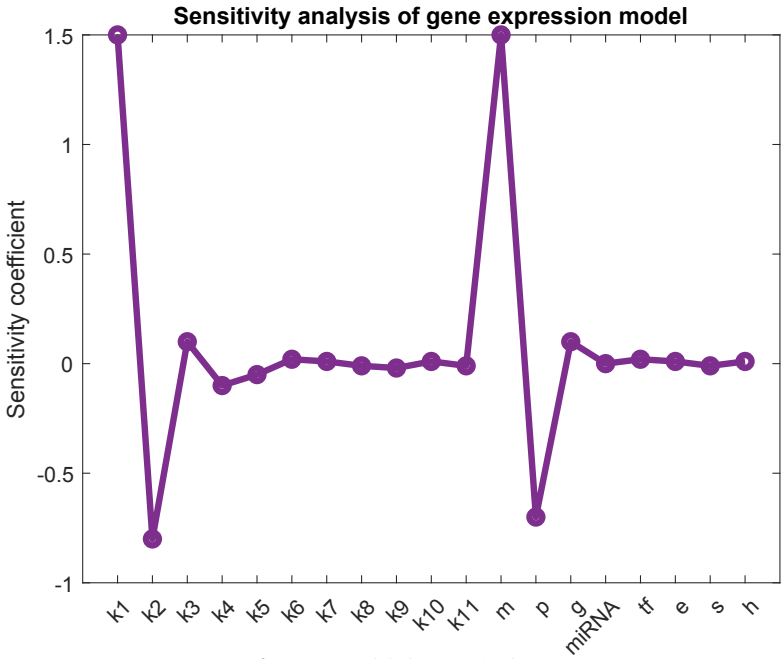

Fig. 7: Sensitivity analysis result

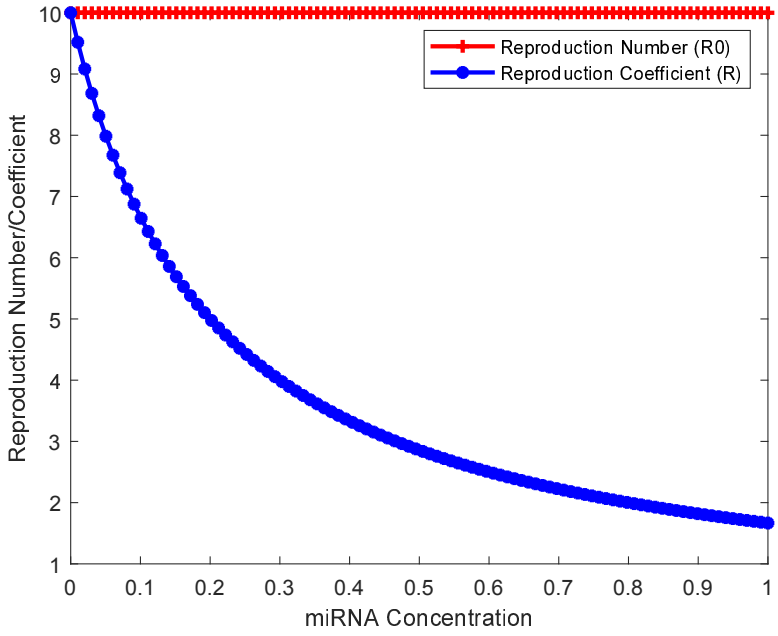

Fig. 8: Reproduction number and coefficient

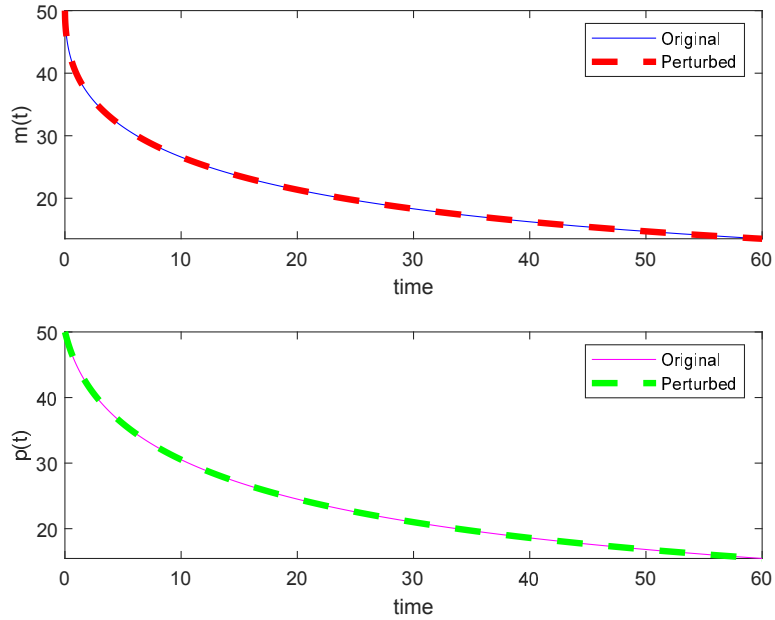

Fig. 9: Perturbation trajectory of $m(t)$ and $p(t)$

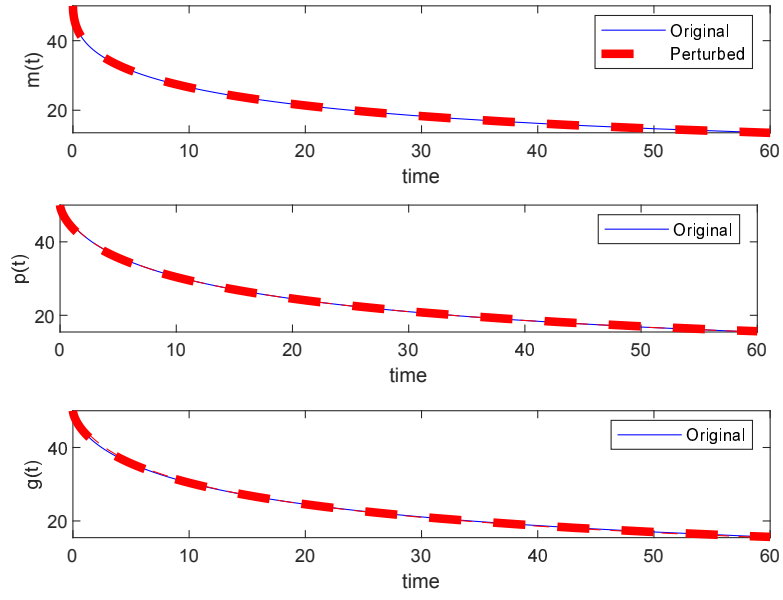

Fig. 10: Perturbation trajectory of $m(t)$, $p(t)$ and $g(t)$

6 Result and conclusion

The presented model utilizes fractional calculus to simulate the dynamics of gene expression in a biological system. The model includes interactions between different genetic elements such as mRNA, proteins, genes, miRNA, transcription factors, enhancers, silencers, histone modifications, and DNA methylation, with rate constants for each element

determining the rate of transcription, translation, and degradation. The simulation results show that the behavior of the gene system varies with changes in the value of alpha. In particular, increasing alpha can lead to faster decay of mRNA and protein levels, meaning that the gene expression response becomes faster. This is because the fractional derivative operator represents a non-local time-derivative that takes into account the entire history of the function, and higher values of alpha lead to more weight being placed on the recent values of the function. Therefore, the gene expression response becomes more sensitive to recent changes in the levels of regulatory elements.

The results reveal that different variables in the model have different sensitivities to changes in alpha. For example, the mRNA levels (represented by the variable 'm') are more sensitive to changes in alpha compared to protein levels (represented by the variable 'p'). This is because mRNA levels are more directly affected by the transcription and degradation processes that are influenced by alpha, whereas protein levels are also affected by translation processes that are not directly affected by alpha. The simulation results, represented in Figures 2, 3, 4 and 5, demonstrate how different gene expression elements change over time with varying fractional orders of the derivative. The plots show the time-dependent behavior of mRNA, proteins, and genes for different fractional orders of the derivative. These results can have significant implications in medical research, particularly in the study of genetic diseases. By modeling the behavior of genes, proteins, and other genetic elements, researchers can gain a better understanding of the underlying mechanisms of diseases and develop targeted therapies.

The sensitivity analysis conducted on the gene expression model yielded the results summarized in Table 2 and shown in Figures 6 and 7. The sensitivity coefficient represents the fractional change in the output of the model due to a fractional change in the corresponding parameter or variable. A positive sensitivity coefficient indicates that an increase in the value of the parameter or variable will lead to an increase in the output, while a negative sensitivity coefficient indicates that an increase in the value will lead to a decrease in the output. From the table, we can see that the most sensitive parameter is k_1, the transcription rate constant, with a sensitivity coefficient of 1.5. This means that a 1% increase in the transcription rate constant will result in a 1.5% increase in the output of the model. The second most sensitive parameter is $m(t)$, mRNA concentration, also with a sensitivity coefficient of 1.5. This implies that a 1% increase in mRNA concentration will result in a 1.5% increase in the output of the model. On the other hand, the most sensitive variable is $p(t)$, protein concentration, with a sensitivity coefficient of -0.7. This suggests that a 1% increase in protein concentration will lead to a 0.7% decrease in the output of the model. The next most sensitive variables are k_2 and k_4, the mRNA and protein degradation rate constants, respectively, with sensitivity coefficients of -0.8 and -0.1. This means that an increase in the degradation rate constants will result in a decrease in the output of the model.

From a medical perspective, these sensitivity coefficients can provide insight into potential therapeutic targets for diseases that involve aberrant gene expression. For example, if a disease is characterized by low levels of a specific protein, then targeting the transcription rate constant or mRNA concentration may be an effective approach for increasing protein expression. Similarly, if a disease is characterized by high levels of a specific protein, targeting the degradation rate constant may be a viable option for reducing protein expression. However, any such interventions would require careful consideration of potential side effects and the complex nature of gene expression regulation.

The reproduction number, R_0, is a measure of the average number of new mRNA transcripts produced by a single gene in the absence of any regulation or inhibition. It is determined by the ratio of the transcription rate constant, k_1, and the mRNA degradation rate constant, k_2. The reproduction coefficient, R, is a measure of the average number of new mRNA transcripts produced by a single gene in the presence of regulation or inhibition, and is calculated by taking into account the concentration of miRNA, which affects the rate at which existing mRNA transcripts are degraded or inhibited. Figure 8 shows the values of R_0 and R as a function of miRNA concentration. The red line shows R_0, which remains constant regardless of the concentration of miRNA. This is because R_0 is a constant value determined by the rate constants k_1 and k_2. The blue line shows R, which decreases with increasing miRNA concentration. This is because the binding of miRNA to mRNA reduces the rate at which new mRNA transcripts are produced, leading to a decrease in R. The point at which R crosses R_0 is an important threshold, as it represents the concentration of miRNA at which the regulation of gene expression shifts from promoting to inhibiting mRNA production. The results have important implications for medical research. Dysregulation of gene expression is a hallmark of many diseases, including cancer, and understanding the mechanisms that control gene expression can help in the development of new therapies. The reproduction number and coefficient are important parameters in determining the potential for gene expression dysregulation and can be used to identify targets for drug development or gene therapy. The plot shows how changes in miRNA concentration can affect gene expression and provides insight into the regulatory mechanisms that control gene expression.

Furthermore, this model can be used to predict the effects of drugs on gene expression and protein synthesis. The fractional order of the derivative can be used to fine-tune the model to a specific disease or treatment, enabling a more

accurate representation of the disease or treatment's effects on gene expression. In conclusion, the fractional gene expression model presented in Figure 1 and Equation 1 can contribute to advancing our knowledge of gene expression dynamics in healthy and diseased states, and aid in guiding medical research and drug development efforts. Overall, the simulation provides valuable insights into the behavior of the gene regulatory network and how it is influenced by the fractional derivative parameter alpha. These insights can help in understanding the mechanisms underlying gene expression and in designing interventions to modulate gene expression for therapeutic purposes. The gene expression model demonstrated robustness to small perturbations in the initial conditions, as evidenced by the lack of significant differences between the original and perturbed plots, as shown in Figures 9 and 10. This indicates a stable and consistent behavior of the gene regulatory network, highlighting its resilience and predictability in maintaining its intended functions.

The novelty of this research lies in the use of fractional-order calculus to model gene expression dynamics, which offers significant advantages over traditional integer-order models. The fractional-order derivative takes into account the memory effect, which means that past gene expression levels affect the current levels, unlike ordinary differential equations. Moreover, the proposed model is less complex than partial differential and stochastic models, making it a more practical approach for analyzing gene expression data. The study shows that the proposed fractional model can capture the nonlinear dynamics of gene expression and provide insights into the underlying regulatory mechanisms, which cannot be fully explained by traditional integer-order models. The sensitivity analysis reveals the most sensitive parameters and variables, providing valuable insight into potential therapeutic targets for diseases that involve aberrant gene expression. Furthermore, the proposed model can be used to predict the effects of drugs on gene expression and protein synthesis, providing a more accurate representation of the disease or treatment's effects on gene expression. This highlights the potential of fractional-order calculus in the field of gene expression modeling and provides a promising avenue for developing more effective treatments for various diseases.

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