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Generalized Hukuhara Derivative Approach for Gompertz Tumor Growth with Allee Effect under Fuzzy Environment

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Abstract

In this present study, the tumor growth model using the Gompertz equation with the Allee effect is developed under a fuzzy environment using the Generalized Hukuhara Derivative (GHD) approach. To capture the tumor growth patterns with the Allee threshold, the parameters present in the model vary from time to time, and in real life, it is very difficult to estimate the exact cell count. In this vague situation, the initial condition, coefficient, and both together are taken as the fuzzy number. In this paper, the GHD approach is used to solve the fuzzy tumor growth model in which four different cases are considered with respect to (i)-gH differentiability and (ii)-gH differentiability concept. The main objective of this study is to present a significant reduction in uncertainty while modeling the tumor growth in a fuzzy environment with the Allee effect. Finally, the proposed model and technique are illustrated by numerical simulation and analysis of tumor growth is conducted.

Keywords: Mathematical modeling, gH-Derivative approach, Fuzzy theory, Tumor growth, Allee effect, Differential equation, Soft computing.

1 | Introduction

Mathematical modeling is a significant tool for the quantitative description of physiopathological events in the era of customized oncology [1]. For several decades, mathematical models for tumor growth kinetics have been frequently employed, although they have largely been fitted to an individual or average growth curve. According to traditional tumor growth models, early-stage tumor development dynamics are frequently driven by cell-autonomous proliferation, represented as an exponential rise in cell number. The exponential growth model defines a growth rate that is proportional to the number of cells present and is frequently captured by a single growth rate constant at this stage. Current imaging systems, on the other hand, have a lower detection limit of roughly 1 million cells on a typical CT scan [2]. Recent studies in preclinical animal models and clinical outcomes after tumor excision show that tumor development at low tumor cell densities does not follow the exponential growth paradigm [3]. The dynamics of tumor development have been

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researched clinically and experimentally for decades [4], [5]. One of the most important discoveries of these early investigations is that tumor development is not exponential if examined over a lengthy period (100 to 1000 folds of increase) [6]. Hence, does not match the expectation of an exponential growth pattern. The rate of specific growth declines and the Gompertz model captures this slowdown exceptionally effectively [6]–[8] and a recent study revealed that Cancer cell population growth kinetics at low densities deviate from the exponential growth model and suggests an Allee Effect, which is the biological concept [9]. Benjamin Gompertz introduced the Gompertz model in 1825. The Gompertz model is a growth model that takes into account a diminishing number of survivors. Hence, has been used in various areas such as in fisheries, science, and management [10].

The most often used Gompertzian model is a phenomenological model that incorporates an exponentially decaying growth rate [7], [11], [12]. There is a lot of evidence indicating subclonal interactions among cells in tumors, such as certain subpopulations producing signaling molecules that are important for the development of other subpopulations of cells [13]–[15]. Hence, Cancer cell development, like species cooperation in an ecosystem, is likely to demonstrate cooperative interactions. The Allee effect is a phenomenon that occurs in ecology as a result of cooperative development, such as cooperative predation, feeding, and mating systems. Thus, has been used to inform invasive species control tactics and to forecast how an introduced species would take hold in a new habitat in ecology [16], [17]. Implementing ecological principles to handle tumor growth is gaining popularity to obtain a better understanding of the factors that regulate tumor cell growth at an early stage. This knowledge could aid in improving predictions of initial growth, relapse, and metastasis, as well as guiding therapeutic strategies based on ecological principles to control tumor progression [18]–[23].

The work done by various researchers in the field of mathematical modeling in tumor growth is in a crisp environment i.e., the parameters are considered as a crisp number. Environmental variables that impact population growth are influenced by a variety of elements in numerous settings. So, this impreciseness should be incorporated into the model to create a more appropriate population management plan. One technique to achieve this is to represent the model's parameters in a fuzzy form. Fuzzy theory, introduced by Zadeh [24] in 1965, is a branch of Artificial Intelligence (AI) or soft computing in which a degree of credibility is attained for each set of solutions. Fuzzy theory has gained a great interest in every field of applications with its novel approaches and methods [25]–[32]. Fuzzy Differential Equations (FDEs) are at the core of a type of FL-generalization mathematics known as fuzzy mathematics. A FDE is one in which some of the coefficients, parameters, and/or boundary conditions are supposed to represent a category of fuzzy sets. The fuzzy set class is mostly considered as a subset of the real numbers that consists of normal, fuzzy convex, upper semi-continuous and compactly supported fuzzy subsets. A FDE can alternatively be considered as a subset of granular differential equations. Chang and Zadeh [33] were the first to propose the fuzzy derivative approach and a brief review of FDEs using derivative approaches, see in [34], [35].

FDEs can be solved in various ways, such as, by transforming the FDE into a fuzzy integral equation [36]. The inclusion method is another way in which the supplied differential equation is transformed into a differential inclusion, and the solution is accepted as the α-cut of the fuzzy solution by taking α-cut of the initial value and the solution [37]. Another approach is the Zadeh extension principle. This approach involves first solving the corresponding Ordinary Differential Equation (ODE), then fuzzifying the answer and determining whether or not it is fulfilled [38]. For solving the linear FDE fuzzy Laplace Transform and Lagrange multiplier method can be used [39], [40]. Converting the supplied FDE into two ODEs using the extended Hukuhara differentiability concept is also differential equations using the parametric forms of a fuzzy number[34], [41]. The concept of Generalized Hukuhara Derivative (GHD) was developed to remove the pitfalls of Hukuhara differentiability and this approach was used to smear FDEs. Bede and Stefanini exploited the concept of generalization of Hukuhara difference for compact convex sets and presented generalized Hukuhara differentiability for fuzzy valued functions and demonstrated that this idea of differentiability has links with both weakly and strongly generalized differentiability [41]–[43]. Connections between generalized Hukuhara differentiability and fuzzy derivative under some conditions have also been investigated by researchers in [45].

2 | Background Work

Different work has been done to present tumor growth under a fuzzy environment and hence becomes an emerging area of interest. In [46], tumor growth is shown in a full fuzzy environment by developing a fuzzy partial integro-differential system and providing the difference between approximate and exact solutions. In [47], an adaptive fuzzy back-stepping controller for the MIMO cancer immunotherapy system has been developed to obtain a suitable scheduling scheme for drug dosage to decrease the tumor cells. Based on intuitionistic fuzzy sets and the Invasive Weed Optimization (IWO) method, a fuzzy logic controller for managing intravenous anti-cancer medicine administration has been developed in [48]. Tumor growth pattern under a fuzzy environment using GHD has been revealed in [49]. A mathematical model of tumor growth kinetics with Allee Effect under fuzzy environment has been developed by Khaliq et al. in [34]. That model represents the logistic equation used for model formulation and the GHD approach is utilized to solve the FDEs.

Research related to tumor growth under fuzzy environment has been done by inclusion method; partial integro-differential system method and Gompertz equation with Allee effect in tumor modeling under the crisp environment. Moreover, the literature spots that the Gompertz population model with Allee effect with the initial condition as fuzzy solved by the Rungai Kutta method is present but not implemented to represent the tumor growth; hence, provided the insight and motivation to use the derivative approach under fuzzy environment in the context of tumor growth modeling with both the initial condition and coefficient as fuzzy.

The main objective of this study is to present the significance of reduction in uncertainty while modeling the tumor growth with Allee effect under fuzzy environment with the help of a FDE concept using the GHD. In this proposed work, the Gompertz equation, along with the Allee Effect, is formulated under a fuzzy environment using the derivative concept. The parameters, both the initial condition as well as coefficient, are taken as fuzzy to develop the fuzzy environment. The FDEs are transformed to two crisp differential equations by using GHD concept, which is a more advanced concept for solving FDEs. Based on the literature survey, the potential value of the proposed study is summarised in next section as a novelty.

2.1 | Novelty

Although the contribution of the Gompertz model and Allee effect is satisfactory in tumor growth modeling in a crisp as well as in a fuzzy environment, in this study, some of the fundamental issues are highlighted that will most likely need to be addressed globally.

I. Albeit, there are some publications in the fuzzy environment using the Gompertz model with Allee effect; however, for tumor growth in fuzzy and fuzzy differential approach by GHD concept has not been surfaced out yet.
II. The work as a literature showed that the initial condition had been taken as fuzzy to check the behaviour of the Gompertz growth model. In this work, the application of the Gompertz growth model in tumor growth has been considered with both initial conditions, as well as coefficients as a fuzzy.
III. The applications of gH-derivative are applied in various real-life problems; however, in the current study, the gH-derivative concept is applied first time in tumor growth modeling with Gompertz equation under fuzzy environment along with the Allee Effect.
IV. The proposed model can explain the threshold-like behavior with the help of Allee Effect under a fuzzy environment, which could be very helpful to analyze the growth mechanism clearly hence, claiming novelty.
V. The significance of fuzzy is focused on reducing the ambiguity present in parameters while modeling tumor growth patterns under fuzzy environment through numerical simulation via soft computing.

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3 | Model Construction

3.1 | Gompertz Model of Tumor Growth with Allee Effect under Crisp Environment

The Gompertz model has been applied in tumor modeling and has been shown to reduce tumor growth with tumor size [49]–[53]. The same model with the Allee effect has been also applied in modeling the tumor [55]. The growth rate is calculated by dividing the current population size by the carrying capacity in negative logarithms and is given by

$$\frac{dN}{dt} = -\lambda N \ln\left(\frac{N}{K}\right) \ln(N - a);\ N\ 0) = N_0, \tag{1}$$

where the parameters represented as: N denotes the number of cells K denotes the carrying capacity, λ defines the growth rate, a denotes the Allee threshold and t represents the time.

We obtained K and a the equilibrium levels by setting $\lambda N\ ln\left(\frac{N}{K}\right) \ln N - a) = 0$ and $N\ t) = k$ and $N\ t) = a$ as equilibrium solutions. The Gompertz model with the Allee Effect has two positive equilibrium solutions. The first denotes the highest possible population k, whereas a denotes the second-lowest sustainable population. Due to these two equilibrium solutions, the full growth pattern region is divided into three different sub-regions having interpretation as:

I. In region I, where $0 < N < a$, this condition bears the strong Allee Effect and there is a chance of decaying the solution towards zero. when N is less than Allee threshold a, The Allee Effect term $(N - a)$ becomes negative; hence, the growth becomes negative. Ultimately predicting the population goes to extinction.
II. In region II, where $a < N < K$, this condition bears the weak Allee Effect, and there exist two cases such as when N is near a but larger than a, the Allee Effect term $(N - a)$ slowdowns the net growth but remains positive. Such a scenario can be seen in the normal logistic model also. When N is much larger than a, the term $(N - a)$ becomes negligible and the cell population begins to behave like an exponential growth model.
III. In region III, where $N > K$, in this case also, the solutions decay towards K seen in the logistic model.

3.2 | Gompertz Model of Tumor Growth with Allee Effect under Fuzzy Environment

By taking the impreciseness on the parameters of *Eq. (1)*, as a fuzzy, we get the FDE as:

$$\frac{\widetilde{dN}}{dt} = \lambda N \ln\left(\frac{N}{K}\right) \ln(N - a) \text{ Where } \lambda, N, \text{ are fuzzy.} \tag{2}$$

I. Fuzziness in the initial condition: The transformed model using the differentiability concept, when $N(t)$ is (i)-gH Differentiable in *Eq. (2)*.

$$\frac{dN_1(t,\alpha)}{dt} = \lambda_1 N_1\ t,\alpha) \ln\left[\frac{N_2}{K}(t,\alpha)\right] \ln(N_1\ t,\alpha) - a). \tag{3}$$

$$\frac{dN_2(t,\alpha)}{dt} = \lambda_2 N_2\ t,\alpha) \ln\left[\frac{N_1}{K}(t,\alpha)\right] \ln(N_2\ t,\alpha) - a). \tag{4}$$

With initial conditions $N_1\ t_o,\alpha) = N_{o1}(\alpha)$ and $N_2\ t_o,\alpha) = N_{o2}(\alpha)$.

The transformed model using the differentiability concept, when $N(t)$ is (ii)-gH Differentiable in *Eq. (2)*.

$$\frac{dN_2(t,\alpha)}{dt} = \lambda_1 N_1\ t,\alpha)\ \ln\left[\frac{N_2}{K}(t,\alpha)\right]\ln(N_1\ t,\alpha) - a). \tag{5}$$

$$\frac{dN_1(t,\alpha)}{dt} = \lambda_2 N_2\ t,\alpha)\ \ln\left[\frac{N_1}{K}(t,\alpha)\right]\ln(N_2\ t,\alpha) - a). \tag{6}$$

With initial conditions $N_1\ t_o,\alpha) = N_{o1}(\alpha)$ and $N_2\ t_o,\alpha) = N_{o2}(\alpha)$.

II. Fuzziness in coefficient: The transformed model using the differentiability concept, when $N(t)$ is (i)-gH Differentiable in *Eq. (2)*.

$$\frac{dN_1(t,\alpha)}{dt} = \lambda_1\ \alpha)N_1\ t,\alpha)\ \ln\left[\frac{N_2}{K}(t,\alpha)\right]\ln(N_1\ t,\alpha) - a). \tag{7}$$

$$\frac{dN_2(t,\alpha)}{dt} = \lambda_2\ \alpha)N_2\ t,\alpha)\ \ln\left[\frac{N_2}{K}(t,\alpha)\right]\ln(N_2\ t,\alpha) - a). \tag{8}$$

With initial conditions $N_1\ t_o,\alpha) = N_o$ and $N_2\ t_o,\alpha) = N_o$.

The transformed model using the differentiability concept, when $N(t)$ is (ii)-gH Differentiable in *Eq. (2)*.

$$\frac{dN_2(t,\alpha)}{dt} = \lambda_1\ \alpha)N_1\ t,\alpha)\ \ln\left[\frac{N_2}{K}(t,\alpha)\right]\ln(N_1\ t,\alpha) - a). \tag{9}$$

$$\frac{dN_1(t,\alpha)}{dt} = \lambda_2\ \alpha)N_2\ t,\alpha)\ \ln\left[\frac{N_1}{K}(t,\alpha)\right]\ln(N_2\ t,\alpha) - a). \tag{10}$$

With initial conditions $N_1\ t_o,\alpha) = N_o$ and $N_2\ t_o,\alpha) = N_o$.

III. Fuzziness in both initial condition and coefficient: The transformed model using the differentiability concept, when $N(t)$ is (i)-gH Differentiable in *Eq. (2)*.

$$\frac{dN_1(t,\alpha)}{dt} = \lambda_1\ \alpha)N_1\ t,\alpha)\ \ln\left[\frac{N_2}{K}(t,\alpha)\right]\ln(N_1\ t,\alpha) - a). \tag{11}$$

$$\frac{dN_2(t,\alpha)}{dt} = \lambda_2\ \alpha)N_2\ t,\alpha)\ \ln\left[\frac{N_1}{K}(t,\alpha)\right]\ln(N_2\ t,\alpha) - a). \tag{12}$$

With initial conditions $N_1\ t_o,\alpha) = N_{o1}(\alpha)$ and $N_2\ t_o,\alpha) = N_{o2}(\alpha)$.

The transformed model using the differentiability concept, when $N(t)$ is (ii)-gH Differentiable in *Eq. (2)*.

$$\frac{dN_2(t,\alpha)}{dt} = \lambda_1\ \alpha)N_1\ t,\alpha)\ \ln\left[\frac{N_2}{K}(t,\alpha)\right]\ln(N_1\ t,\alpha) - a). \tag{13}$$

$$\frac{dN_1(t,\alpha)}{dt} = \lambda_2\ \alpha)N_2\ t,\alpha)\ \ln\left[\frac{N_1}{K}(t,\alpha)\right]\ln(N_2\ t,\alpha) - a). \tag{14}$$

With initial conditions $N_1\ t_o,\alpha) = N_{o1}(\alpha)$ and $N_2\ t_o,\alpha) = N_{o2}(\alpha)$.

4 | Numerical Simulation

Fuzziness in both initial condition and coefficient

When $N(t)$ is (i)-gH differentiable, the model transformed using this differentiability concept as:

$$\frac{d_{N_1}(t,\alpha)}{dt} = \lambda_1\ \alpha)N_1\ t,\alpha)\ln\left[\frac{N_2\ t,\alpha)}{K}\right]\ln N_1\ t,\alpha) - a).$$

$$\frac{d_{N_2}(t,\alpha)}{dt} = \lambda_2\ \alpha)N_2\ t,\alpha)\ln\left[\frac{N_1\ t,\alpha)}{K}\right]\ \ln N_2\ t,\alpha) - a).$$

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With initial condition $N_1\ t_0,\alpha) = N_{01}(\alpha)$s and $N_2\ t_0,\alpha) = N_{02}\ \alpha)$:

Take $\mathrm{N\ O}) = \ 0.46, 0.51, 0.66),$

$\lambda = \ 0.016, 0.026, 0.031),$

$K = 7, t \in [0,1000], a = 2.$

$$\frac{dN_1(t,\alpha)}{dt} = \ 0.016 + 0.01\alpha)N_1\ t,\alpha)\ln\left[\frac{N_2}{7}\ t,\alpha)\right]\ \ln N_1\ t,\alpha) - 2).$$

$$\frac{dN_2(t,\alpha)}{dt} = \ 0.031 - 0.005\ \alpha)N_2\ t,\alpha)\ln\left[\frac{N_1}{7}\ t,\alpha)\right]\ \ln N_2\ t,\alpha) - 2).$$

With initial conditions$N_1\ 0,\alpha) = 0.46 + 0.05\alpha$ and $N_2\ 0,\alpha) = 0.66 - 0.15\alpha$.

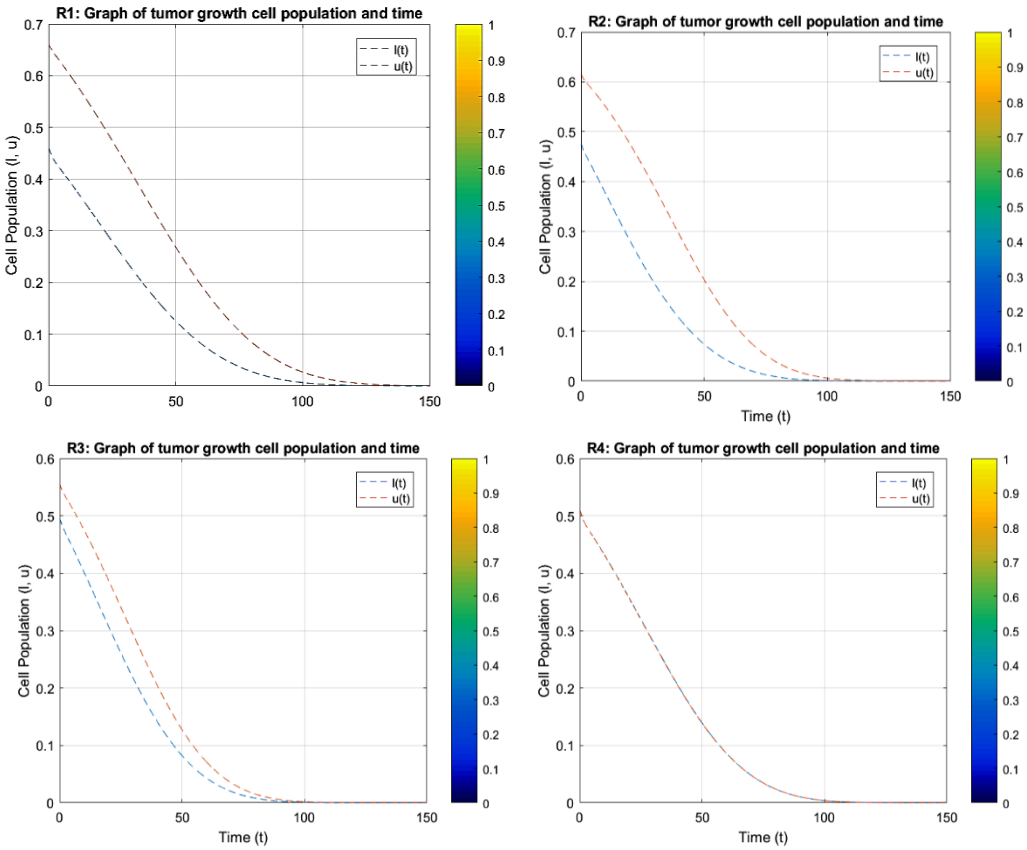

Fig. 1. In this figure, for the initial condition less than the Allee threshold, the growth decays towards 0 with time.

For different values of $\alpha = 0, 0.3, 0.7,$ the growth curves are shown when $N(t)$ is (i)-gH differentiable and the solution $N_1(t,\alpha) \le N_2(t,\alpha)$ for $t \in [0,120]$ and for $\alpha = 1$, both $N_1\ t,\alpha) = N_2(t,\alpha)$for all t and finally approaches to 0.

When $N(t)$ is (ii)-gH differentiable, the model transformed using this differentiability concept as:

$$\frac{d_{N_2}(t,\alpha)}{dt} = \lambda_1\ \alpha)N_1\ t,\alpha)\ln\left[\frac{N_2\ t,\alpha)}{K}\right]\ln N_1\ t,\alpha) - a).$$

$$\frac{d_{N_1}(t,\alpha)}{dt} = \lambda_2\ \alpha)N_2\ t,\alpha)\ln\left[\frac{N_1\ t,\alpha)}{K}\right]\ \ln N_2\ t,\alpha) - a).$$

With initial conditions $N_1\ t_0,\alpha) = N_{01}(\alpha)$ and $N_2\ t_0,\alpha) = N_{02}\ \alpha)$:

Take N O) = 0.46, 0.51, 0.66),

$\lambda =$ 0.016, 0.026, 0.031),

K = 7, t ϵ [0,1000], a = 2.

$$\frac{dN_2(t,\alpha)}{dt} = 0.016 + 0.01\alpha)N_1\ t,\alpha)\ln\left[\frac{N_2}{7}\ t,\alpha)\right]\ \ln N_1\ t,\alpha) - 2).$$

$$\frac{dN_1(t,\alpha)}{dt} = 0.031 - 0.005\ \alpha)N_2\ t,\alpha)\ln\left[\frac{N_1}{7}\ t,\alpha)\right]\ \ln N_2\ t,\alpha) - 2).$$

With initial conditions $N_1\ 0,\alpha) = 0.46 + 0.05\alpha$ and $N_2\ 0,\alpha) = 0.66 - 0.15\alpha$.

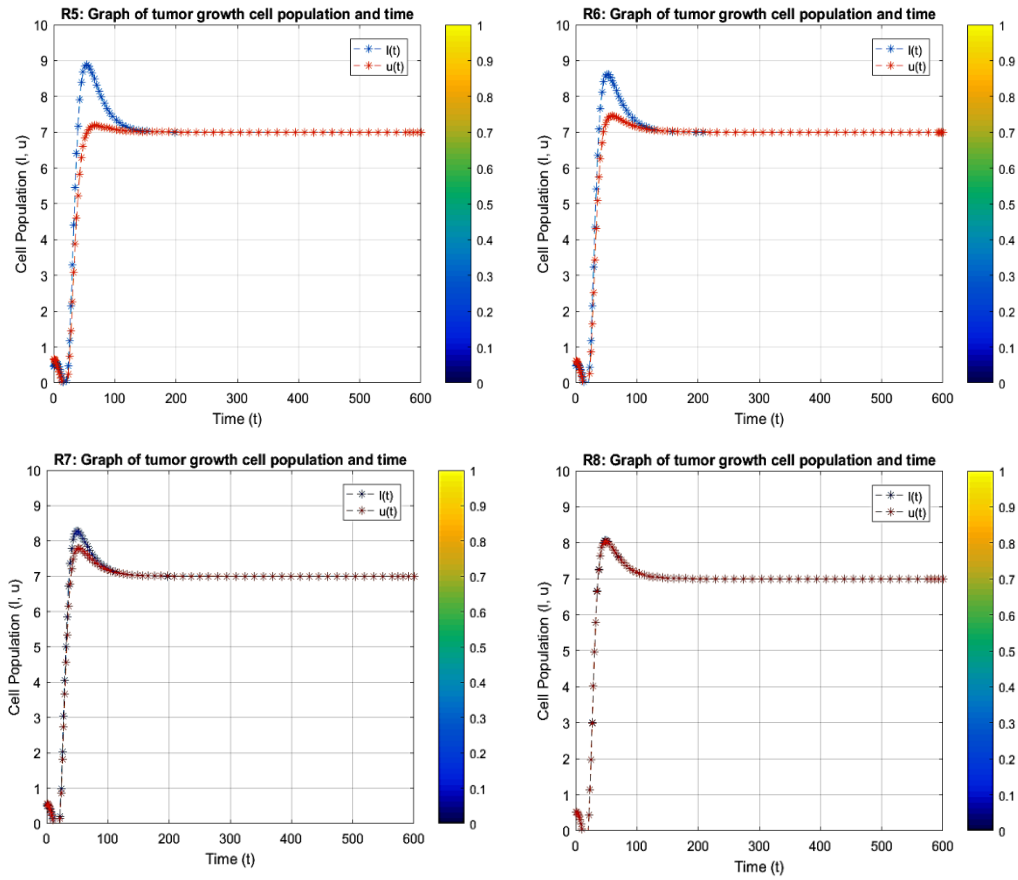

Fig. 2. In this figure, the growth is limited and decaying towards carrying capacity.

When $N(t)$ is (ii)-gH differentiable, for $\alpha = 0, 0.3, 0.7$, the solution $N_1(t,\alpha) \geq N_2(t,\alpha)$ for $t \in [0,150]$ and for $\alpha = 1$, both $N_1\ t,\alpha) = N_2(t,\alpha)$ for all t.

5 | Results and Discussion

The findings revealed that the involvement of the Allee Effect affects the growth path potentially. When $N(t)$ is (i)-gH differentiable, the Allee threshold is greater than the initial value and bears a strong Allee Effect, which slows down the growth exponentially towards 0 for different values of α through R1-R4 as expected. However, When $N(t)$ is (ii)-gH differentiable with the same Allee threshold, the result shows the rising growth towards carrying capacity through R5-R8. Also, in this case, the results revealed that if the population is greater than the carrying capacity, the growth shows decay towards the carrying capacity. The results revealed the realistic situation of tumor growth patterns under fuzzy environment using Gompertz equation.

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With the help of gH-differentiability, the tumor growth with the Allee Effect under fuzzy environment is analyzed in realistic way. The full growth pattern shown by the Gompertz model in tumor growth is revealed in this study using fuzzy mathematics. Application of GHD in tumor growth proved successful in showing growth patterns.

6 | Comparision between the Gompertz growth Model and the Gompertz Growth Model with the Allee Effect

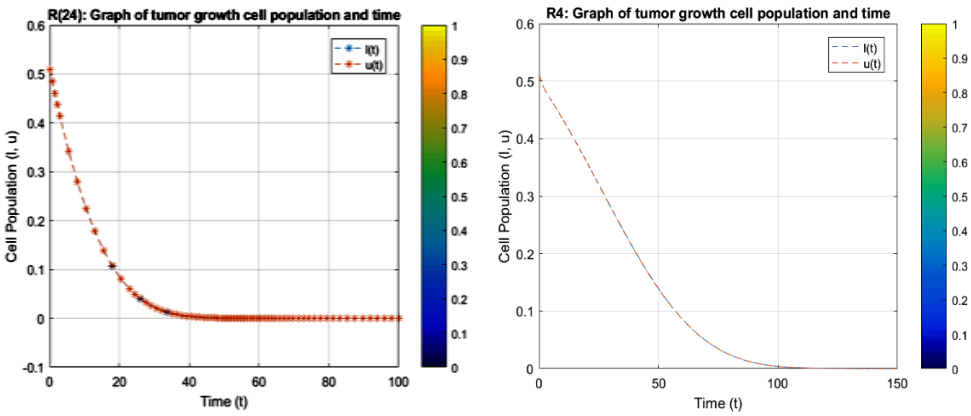

Fig. 3. Comparision graphs of tumor growth Gompertz model and Gompertz model in the presence of Allee Effect under uncertainty.

Comparision between the fuzzy Gompertz model shown in [43], [49] and the Fuzzy Gompertz model along with Allee effect is demonstrated in *Fig. 3*. Fuzzy Gompertz model shows the decline in tumor growth with time in R (24) and shows saturation at time 40. However, Gompertz tumor model with the Allee Effect under the fuzzy environment in R (4) shows a decline but with a very inflection point and shows saturation at time 100. Since, the fuzzy Gompertz model covers less decline area of burden as compared to the fuzzy Gompertz model with the Allee Effect with time, as shown in *Fig. 3*. Gompertz model with Allee Effect revealed an efficient result as compared to Gompertz model. Hence, it could be enhanced the treatment strategies by implementing the Allee Effect in therapies.

7 | Conclusion and Future Insights

For the tumor growth model using the Gompertz equation with the Allee Effect, the initial value and coefficient affect the solution potentially. The initial value less than the Allee threshold will cause the decaying of growth towards zero hence indicating the eradication of tumor cells. Gompertz model with Allee Effect in tumor growth insights many approaches towards treatment process. Fuzzy mathematics helped in reducing the uncertainty of parameters and showed the threshold behaviour of tumor growth around the Allee threshold. The GHD method successfully revealed the full growth pattern using the Gompertz equation with the Allee Effect.

With the help of this study, future work includes the different fuzzy techniques such as generalization of fuzzy called neutrosophic and interval-valued neutrosophic approach in the same model can be implemented in order to analyze the growth patterns. Different derivative concepts with the neutrosophic approach could enhance the results efficiently. Moreover, further research could be focused on considering the all parameters together as fuzzy in which carrying capacity could be captured under full a fuzzy mechanism. The Fractional derivatives concept will be a tremendous outcome of future research for the same model. The behavior of growth curves for the weak Allee Effect, that is, when the initial condition is greater than Allee threshold and one parameter having the dual property of weak as well as strong Allee Effect under some conditions, would be future research of this proposed work. The Stability criterion of the model can be also be discussed in future research for the same. The efficiency and accuracy of the

proposed model could be tested on experimental data; hence, it could be the more interesting to provide the importance of soft computing technology in real-life problems.

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