Research Article

A Comprehensive Survey on Various Mathematical Modeling Techniques used for Tumor Dynamics

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Abstract

Mathematical modeling has gained significant attention recently due to its increased utilization rate of many applications. Estimating the growth of tumor size and resistance, drug resistance and tumor dynamics are the most challenging and demanding processes in the medical field. Hence, the mathematical modeling techniques are suitable options for characterizing the effect of cancer-based on the tumor dynamics. In the existing works, different types of mathematical modeling techniques have been deployed to quantify the measurements of the tumor. This paper aims to comprehensively review various mathematical modeling techniques used to estimate the tumor's growth with its treatment therapies. The main intention of this work is to investigate the formulations and operating functions of various mathematical modeling techniques. In addition to that, the comparative analysis between various mathematical modeling techniques is also presented in this work for selecting the most suitable model for tumor dynamics and treatment resistance. Based on this study, it is examined that the fuzzy modeling technique can analyze the effects of different elements for estimating the growth of tumors in the fields like biology, genetics, and ecology.

INTRODUCTION

Mathematical models (Jarrett et al., 2018;Vakil&Trappe, 2019) are mainly used for analyzing the dynamical processing and explosion of cancer/tumor-affected cells. The main reason for deploying these models is to accurately predict the size of the tumor for providing optimized treatments to the patients. In the present days, canceris one of themost deadly diseases among many people across the world (Kłusek et al.,

2019) and is a highly challenging task to detect the disease. Mathematical modeling is the most suitable solution for tumor identification and treatment therapies in the biological field. Because the mathematical models (Rihan&Velmurugan, 2020) are highly robust that can accurately detect the tumor affected cells. Also, the mathematical modeling techniques (Vaghi et al., 2020) incorporated with the computational approaches are widely used in many application systems for simulating the growth of the tumor, cellular automata, and mutational heterogeneity. In conventional works, there are different types of mathematical modeling techniques (Benzekryet al., 2017) have been developed for tumor identification and treatment. The ordinary and partial differential equations have been computed concerning the operating functions in these mathematical models. The different types of mathematical modeling techniques (Farayola et al., 2020) used for the tumor identification system are listed as follows:

1. Fuzzy modeling with differential and delay equations.
2. Population growth mathematical models
3. Linear growth mathematical models
4. Exponential growth mathematical models
5. Logistic models
6. Stochastic mathematical models
7. Deterministic mathematical models
8. Game theory

These techniques (Drexleret al., 2019; Heidbuechelet al., 2020; Bocharovet al., 2020) are mainly used to identify the tumor's growth, proliferation cycle, prediction of cancer-affected cells, and treatment therapies. This research intends to conduct a detailed survey to analyse the different types of mathematical models used for tumor identification and treatment. The major objectives behind this work are as follows:

⌡ To investigate the formulations and operating functions of various mathematical modeling techniques used in the biological field.
⌡ To study various mathematical modelling approaches' parameters and computing functions with their usage and applications.

⌡ To select the most suitable technique among all other methodologies based on the computational complexity and evolutions.

The remaining sections of this paper are systematized as follows: some of the existing mathematical modeling techniques used for simulating the tumor dynamics are investigated and the detailed analysis of various mathematical modeling techniques with their computational functions is discussed in Section I. The comparative analysis between the different types of mathematical modeling techniques used for tumor dynamics and resistance modeling is illustrated in Section II. Finally, the overall paper is summarized with its obtainment and future work in Section III.

RELATED WORKS

Typically, mathematical modeling is considered one of the most useful and effective tools for simulating the dynamics of complex systems and real-time experiments.

Enderlin and Chaplin (Enderling&Chaplain, 2014) intended to utilize the mathematical modeling technique to analyse tumors' growth effectively. Here, some ordinary differential mathematical equations have been used, which helps to identify the tumor-affected cells with the time changes. This paper states that the Partial Differential Equation (PDE) is the most suitable mathematical modeling technique for efficiently simulating cancer cells' invasion and metastatic spread. Moreover, the extracellular matrix has been constructed in this model based on logistic growth, non-linear diffusion, production, and decay parameters. *Unni, et al* (Unni et al., 2019) suggested a new mathematical modeling technique for simulating the tumor dynamics using partial differential equations. Here, the stability of this model was validated with the use of optimal parameters. This technique could be more helpful for predicting and eliminating the cancer cells, where the key parameters are the killer cells, tumor cells, cytotoxic cells, and dendritic cells.

Moreover, the stability of this model was assessed by solving the quadratic equations with the equilibrium point. *Khajanchi, et al* (Khajanchi et al., 2019) suggested the mathematical modeling system for designing the tumor-immune competitive system based on three different parameters: tumor cells, cytotoxic cells, and helper cells. Here, the local stability analysis was also conducted by constructing the variational matrix. *Harmuth, et al* (Hormuth et al., 2020) recommended a quantitative imaging technique for analyzing the growth of tumor dynamics. The stages involved in this work were preprocessing, model calibration, model selection, and model prediction, where the model parameters have been mainly updated for reducing the error value. Based on the estimated parameter, the growth of the tumor was computed by applying the forward evaluation model. Both the lowest and highest ranked models were considered for evaluation during the prediction process. *Shu, et al* (Shu et al., 2020) utilized an enhanced mathematical modeling technique for accurately predicting the tumor-affected cells based on the functions of macrophages. Here, the simple mathematical modeling technique has been considered for estimating the growth of the tumor, and this model comprises the parameters of the population of tumor-affected cells, M1 macrophages, and M2 macrophages. Then, these equations have been obtained by using the logistic pattern model.

I. ANALYSIS OF VARIOUS MATHEMATICAL MODELING TECHNIQUES

This section discusses the different types of mathematical modeling techniques related to tumor dynamics and cancer cell prediction analysis with their working functionalities. Typically, mathematical modeling is one of the most extensively used techniques for supporting the earlier prediction of tumor/cancer cells, which also helps to provide appropriate treatment for making low-risk factors. For this purpose, enormous mathematical modeling approaches have been implemented in the conventional works, including the types of fuzzy modeling, basic growth modeling, stochastic modeling, deterministic modeling, and game theory. Then, the applicability of these mathematical modeling techniques have been assessed based on the following key parameters:

1. Scope
2. Accuracy
3. Complexity
4. Stability
5. Computation
6. Consistency

Moreover, these parameters are considered for designing efficient mathematical modeling techniques.

A. Fuzzy Based Mathematical Modeling

In the present days, fuzzy systems are widely used as a tool in many medical diagnosis application systems due to their benefits of accurate measurements and qualitative modeling. The main intention of formulating the fuzzy differential equations is, it can solve the uncertainty problem and is more suitable for all types of mathematical equations like linear/non-linear. Also, it provides a recognized way for modeling the uncertainty of information to the dynamic situation. The major advantages of using this method are better numerical evaluation, accurate outcomes, and uniqueness of the solution. *Abbasnejad* (Abbasnejad, 2015) suggested a new mathematical modeling technique for analyzing chemical drug concentration, where the fuzzy Lyapunov stability and differential equations have been utilized. The main aim of this work was to detect cancer-affected cells for analyzing the effect of chemical drugs on the human body. For this purpose, fuzzy differential equations have been utilized in this work, which helps to accurately estimate the drug concentration level of the human body.
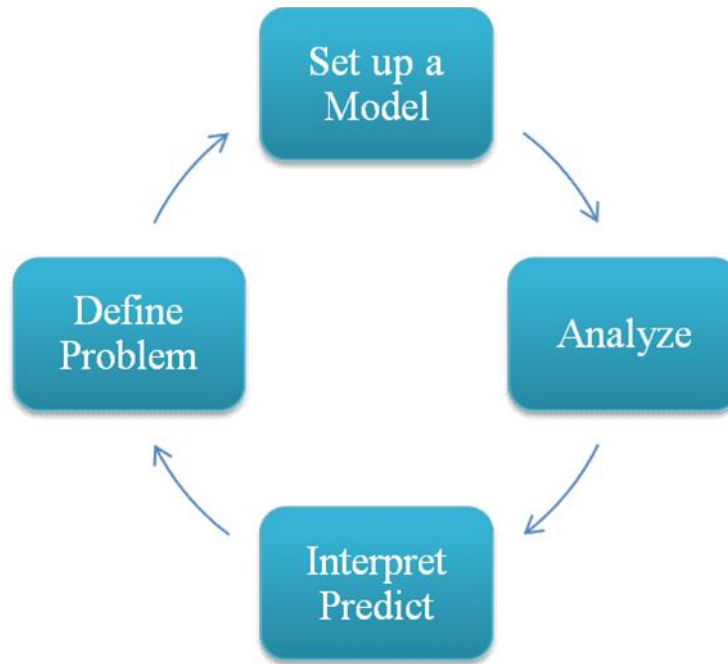
Figure 1:Steps involved in fuzzy differential equations

In addition to that, the Lyapunov direction method was also used to increase the global stability of the dynamic system with balanced parameters. The optimal balancing point was predicted for preventing the re-growth of parameters used in the system. *Rooka and Ghasemi*(Rooka&Ghasemi, 2018) suggested a fuzzy fractional sliding model controlling technique for estimating tumor cell drug concentration and dynamics. Here, the Mittag-Leffler function was computed based on the laplacian transformation technique. Moreover, it intended to simplify the process of Lyapunov function estimation for quantifying the toxicity of drugs. The main advantages of this technique were ensuring the stability of the system and increased convergence. Also, the performance of this system has been assessed based on the error dynamics. Moreover, it provided the dynamic solution for the drug administration process based on the equilibrium point.

Nobile, et al (Nobile et al., 2020) employed a fuzzy modeling technique for predicting the cancer cells based on the global optimal solution. The major factors of this work were as follows: to predict the system's dynamic behaviour and to determine the set of system components. This work mentioned that the Dynamic Fuzzy rule-based Model (DFM) was a computational mathematical modeling technique mainly used to analyse the complex system's behaviour based on the uncertainty parameters. Here, the cellular components have been defined for predicting the growth condition. The global fitness function $F(\pi)$ of DFM has been estimated to the number of perturbation parameters.

⨼ At sample time instant $\Delta > 0$, $t_b + \Delta \leq t_e$, where the $F(\pi)$ lies between the range of $t_b + \Delta$.
⨼ Here, the neighborhood function has been randomly modified based on the new parameter obtained from the linguistic term, $\pi_i' = \eta_p(\pi_i)$.

The major advantages of this model were increased flexibility and reduced complexity. The different types of fuzzy models used in many real-time application systems are listed as follows:

1. Fuzzy differential equations
2. Fuzzy delay differential equations

These types of fuzzy equations are used to solve the problems related to biological fields such as medical cybernetics, fuzzy tumor analysis, and other tumor dynamics.

B. Basic Growth Model

Benzekry, et al (Benzekry et al., 2014) implemented a classical mathematical modeling technique for estimating the growth of the tumor, in which statistical modeling was used for measuring the error. Then, the descriptive power of each model has been utilized for assessing the identifiability of attributes, based on this value, the future tumor growth could be accurately forecasted. In this work, some other mathematical modeling techniques used for identifying the tumor growth were discussed, which includes the follows:

⌡ Logistic and Gompertz models
⌡ Exponential linear models
⌡ Dynamic carrying capacity
⌡ Von Bertalanffy and power law
⌡ Population-based approaches
⌡ Individual approaches

In which, the logistic model is computed to the growth of population $\frac{1}{T}\frac{dT}{dt}$ as shown below:

$$\begin{cases} \frac{dT}{dt} = aT\left(1 - \frac{T}{K}\right) \\ V(t = 0) = 1mm^3 \end{cases} \quad (1)$$

Where, *a* indicates the coefficient value, and this model is mainly used to estimate tumor volume growth. Similar to that, the Gompertz model is calculated as follows:

$$\begin{cases} \frac{dV}{dt} = ae^{-\beta t}(T) \\ T(t = 0) = 1mm^3 \end{cases} \quad (2)$$

Where, *a* represents the initial proliferation value, and β indicates the exponential decay. Then, the exponential linear models are estimated as shown below:

$$\begin{cases} \frac{dT}{dt} = a_0 T, & t \leq \tau \\ \frac{dT}{dt} = a_1, & t > \tau \\ T(t = 0) & V_0 \end{cases} \quad (3)$$

Where, a_0 and a_1 are the coefficients of the linear space and T_0 is the initial volume. Consequently, the dynamic carrying capacity mode is estimated as shown below:

$$\begin{cases} \frac{dT}{dt} = aT\log\left(\frac{K}{T}\right) \\ \frac{dK}{dt} = bT^{2/3} \\ T(t = 0) = 1\,mm^3, K(t = 0) = K_0 \end{cases} \quad (4)$$

Then, the von Bertalanffy and power-law model are represented as follows:

$$\frac{dT}{dt} = aT^\gamma - bT \quad (5)$$

In paper (Hadjiandreou et al., 2013), the Gompertz-type-based mathematical modeling approach has been utilized to analyse the tumor's growth using an optimal therapeutic strategy. Here, the pharmacokinetic model is also utilized to examine drug distribution effects. For avoiding the drug toxicity concentration, this work suggests the weight loss modeling, where the density of the tumor has been assessed. In addition to that, the side effect index is also employed for quantifying the toxicity of drug concentration.

C. Stochastic Models

Yin, et al (Yin et al., 2019) conducted a detailed review of various mathematical modeling techniques used to analyse tumor dynamics. To characterize this, the different types of equations such as ordinary mathematical models, partial differential equations, and algebraic models have been examined in this paper. In paper (Kozłowska et al., 2018), the stochastic mathematical modeling technique has been used for analyzing the effect of platinum chemotherapy and

resistance accumulation based on the tumor size. Typically, two stochastic models are used to predict the tumor cells, including the stochastic Gompertz and stochastic logistic model. This paper aims to present a survey on various stochastic and deterministic mathematical modeling techniques used for drug discovery. Also, it intends to select the most suitable drug disease model based on the parameters of versatility and realistic. The stochastic differential equation is defined as follows:

$$\begin{cases} dS_c = G_i \cdot S_c \cdot \left(1 - \frac{(S_c + R_c)}{Tr_{me}}\right) \cdot dT - M_p \cdot S_c \cdot dT - D_c' \cdot S_c \cdot dT + \sigma_1 \cdot S_c \cdot dCD_1 - d_i \cdot A \cdot S_c \cdot dSD_1 \\ D_c' = D_c \cdot \frac{C_D}{D_i + C_D} \end{cases} \quad (6)$$

Where, dS_c indicates the death rate of sensitive cells, G_r defines the growth rate, S_c denotes the sensitive cells, R_c denotes the resistance cells, d indicates the constant death value, Tr_{me} is the maximum treatment effect, M_p represents the mutation probability, D_c' is the shrinkage rate constant, C_D defines the concentration level of drug, σ_1 is the diffusion rate, dCD_1 represents the stochastic cell diffusion in a small interval (Wiener process), d_r is the dissemination rate, A indicates the angiogenesis, and dSD_1 defines the stochastic dissemination value.

D. Deterministic Models

In the deterministic models (Tabassum et al., 2019), different types of mathematical modeling techniques are used to analyse the growth of tumor cells. The main reason for using the deterministic models is to examine the behavior of tumor cells based on the perturbation of parameters. The tumors are assumed to grow exponentially in these models, predicted using the Gompertz law or the logistic curves. Due to the side effects of drugs, the tumor cells have grown and their size may change with these effects. The general deterministic model equations are defined as follows:

$$\begin{cases} \frac{dS_c}{dT} = (G_r - d - D_c) \cdot S_c \\ \frac{dR_c}{dT} = (G_r - d) \cdot R_c + M_p \cdot S_c \end{cases} \quad (7)$$

$$\begin{cases} \frac{dS_c}{dT} = (G_r \cdot (1 - M_p) - d - D_c) \cdot S_c \\ \frac{dR_c}{dT} = (G_r - d) \cdot R_c + G_r \cdot M_p \cdot S_c \end{cases} \quad (8)$$

$$\begin{cases} \frac{dS_c}{dT} = (G_r - D_c \cdot Dose) \cdot S_c \\ \frac{dR_c}{dT} = G_r \cdot R_c + G_r \cdot M_p \cdot S_c \end{cases} \quad (9)$$

$$\begin{cases} \frac{dS_c}{dT} = (G_{r1} - M_{p1} \cdot D_{c1} \cdot C_D) \cdot S_c + M_{p2} \cdot R_c \\ \frac{dR_c}{dT} = (G_{r2} - M_{p2}) \cdot R_c + M_{p1} \cdot R_c \end{cases} \quad (10)$$

In paper (Salgia et al., 2018), the stochastic and deterministic mathematical modeling techniques have been utilized for the cancer detection system. Here, it is stated that these techniques are most suitable for research related to the drug development process. Also, the carrying capacity is estimated to the growth rate and tumor burden at varying time instances. In addition to that, some other differential models are also utilized to analyse individual cells' effects. *Jordao, et al* (Jordão & Tavares, 2017) derived the deterministic mathematical models for analyzing cancer-affected cells' targeting therapies. In this paper, various updated mathematical modeling techniques have been investigated for tumor dynamics.

E. Game Theory

Gluzman, et al (Gluzman et al., 2020) constructed a dynamic framework model to find suitable treatment strategies by solving the Hamilton-Jacobo-Bellman equation. The main intention of this paper is to estimate the optimal value for adaptive policies by using the game theory-based mathematical modeling technique. The objective

functions are estimated based on the key factors of total treatment time, cost function, value function, and boundary conditions. *Pacheco, et al* (Pacheco et al., 2014) suggested the evolutionary game theory-based mathematical modeling technique for estimating the growth of tumor cells. Here, the main reason for using the game theory approach is, it helps to construct an efficient and convenient framework structure for capturing the frequency of dynamics. *Archetta and Pienta*(Archetti& Pienta., 2019) applied the game theory approach for identifying cancer-affected cells based on evolutionary proof therapies. The game theory is a strategic interaction that helps solve many complex optimization problems by estimating the fitness value. It is estimated as follows:

$$G(i) = \sum_{PC_j} \cdot Payoff(ij) = 1 - CR_i - CT_i + (1 - PC_i) \cdot R_i \quad (11)$$

$$\bar{G} = \sum PC_i \cdot G(i) \quad (12)$$

$$\frac{dPC_i}{dT} = PC_i \cdot (G(i) - \bar{G}) \quad (13)$$

Where, $G(i)$ indicates the fitness type of i^{th}cell, PC_i and PC_j are the proportion of cells, CR_i defines the cost of resistance, CT_i indicates the cost as the product of treatment, and R_i is the level of interaction between the susceptible cells of tumor.

II. RESULTS AND DISCUSSION

This section presents the comparative analysis between various mathematical modeling techniques used in the biological environment. Table 1 compares the mathematical modeling techniques with their description and appropriate computational parameters.

Table 1. Comparative analysis between different mathematical modeling techniques

Author & Year	Mathematical Model	Description	Parameter Computations
Sun & Hu, 2018Spoloar et al., 2021 Ganusov et al., 2020 Wang &Deisboeck, 2019 Sadegh et al.,2021	Dynamic Fuzzy rules based Modeling (DFM)	It is mainly used to analyze the behavior of complex heterogeneous systems. Here, the linguistic variables are used to determine the fuzzy set of rules.	1. Inner variables 2. Outer variables 3. User-defined functions 4. Membership functions
Vinothini and Kavitha, 2020 Souza et al., 2020 Bekisz& Geris, 2020 Piretto et al., 2019	Fuzzy delay differential equations	It is a kind of differential equation that comprises the time lag used for life science modeling. Also, it plays a vital role in the dynamics of the population.	1. Uncertainty of distribution 2. Uniqueness of solution 3. Derivatives of unknown functions

Unni et al., 2019 Mahlbacher, et al., 2019 Phan et al., 2020 Perrillat et al., 2019	Population growth model	It is more suitable for providing solutions to the population dynamics problem. Also, it is mainly used to realize the intricacy of biological invasions. Here, the growth of populations highly depends on the log or exponential, decline or transitional, plateau or stationary.	1. Population size 2. Natality 3. Mortality 4. Immigration 5. Emigration
Nanmaran ,2017 Ghanizadeh et al., 2021 Rajalakshmi& Ghosh, 2018	Logistic growth model	In this model, the growth of the population highly depends on the particular group. It provides the optimal solution based on the carrying capacity with the positive constants.	1. Carrying capacity 2. Positive constants 3. Capita birth rate
Bilous et a., 2019 Johnsonet al., 2019 Schlicke et al., 2021 Kuznetsov et al., 2021	Exponential growth model	It is one of the simplest mathematical modeling approaches, which provides the solution based on the intrinsic rate of increase.	1. Constant rate 2. Intrinsic rate 3. Population size 4. Population growth
Belkhir et al., 2021 Grigorenkoet al., 2020 Lai et al.,2020 Cunningham et al., 2018	Lotka-Volterra Model	This modeling is mainly used for representing the complex relationship with prey. Here, the fuzzy differential equations are applied to obtain the solutions.	1. Prey population size 2. The growth rate of populations 3. Number of predators 4. Positive real parameters
Wolflet al., 2021 West et al., 2019 Khajanchi& Banerjee, 2017	Game theory	This type of mathematical modeling is extensively used to provide solutions to the tumor dynamics problem underneath combination therapies.	1. Payoff 2. Probability of cell number 3. Proportion of cells 4. Fitness function

Kuznetsov& Kolobov, 2018 Dorraki et al., 2020	Basic growth models	Here, ordinary differential equations have been used for simulating the models. It helps to prioritize the tumor dynamics based on the growth patterns.	1. Tumor heterogeneity 2. Carrying capacity 3. Tumor proliferation function 4. Delayed time 5. Linear growth rate 6. Coefficients of quadratic growth rates
Idrees et al., 2021 Tabassumet al.,2019 Salgia et al., 2018	Stochastic models	This model is more adopted for analyzing the branching process. Here, the markovian property has been utilized to assess the tumor's growth. Then, the probability of resistance could be estimated to the probability generation function.	1. Sensitive cells 2. Resistant cells 3. Probability generating function 4. Fitness of resistant cells 5. Population growth 6. Expected cell numbers
Sheergojri et al., 2021 Alameddine et al., 2018	Deterministic models	In this model, deterministic differential equations have been utilized to analyze drug resistance. It is mainly used to control the total count of resistant mutations obtained from the single resistant/sensitive cells.	1. Growth rate constant 2. Sensitive cells 3. Resistant cells 4. Mutation rate
Rivaset al., 2019 Bonyah&Zarin, 2020	Integral differential equations	It is mainly used to characterize the state of cancer resistance. Also, it describes the dynamics of cancer cells to the resistance and time.	1. Cell division 2. Treatment effect 3. Cell mutation

III. Conclusion

The mathematical modeling techniques have received much attention in many applications in biology.This paper intends to analyze the effects of various mathematical modeling techniques used for tumor dynamics and treatment resistance. The study is conducted based on the different types of elements, and behavior predictions used in various mathematical modeling techniques. Based on this study, it is inferred that the fuzzy differential, delay differential, partial differential, and partial integral differential equations have been widely applied in many mathematical modeling techniques. Also, it helps to accurately estimate the growth and size of tumor dynamics based on its similarity variables. Moreover, many studies have mentioned that fuzzy-based mathematical modeling techniques are the most suitable solution for tumor dynamics and treatment resistance activities. Hence, the fuzzy-based mathematical modeling technique can be used in our future work to estimate the tumor's growth with its appropriate treatment resistance activities.

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