Computational approach of tumor growth in human body with a significant technique the rough set

Arvind Kumar Sinha¹, Nishant Namdev²*
¹,²Department of Mathematics, National Institute of Technology Raipur C.G., India.

*Corresponding author’s e-mail address: aksinha.maths@nitrr.ac.in, nishantnamdev84@yahoo.in

Abstract. Tumors are the most threatening issue everywhere throughout the world. The development of tumor cells is dubious in the human body because of its unusual phenomena. The Rough set is a rising and the most special mathematical device to manage uncertain circumstances. A scientific model is given for tumor cells population development with carrying capacity and by the Rough set in uncertain circumstances. In this methodology, the mathematical analysis of the nonlinear behavior of tumor cells population is set up via carrying capacity and simulation by using Euler’s method. The accuracy of the carrying capacity of the number of tumors cells 99.53% correct according to our model. The paper is an interface between mathematical modeling, numerical computation, simulation, and implementation of application on biomedical systems, which is an oriented idea to biology. Keywords: tumor, carrying capacity, tumor growth, rough set, non-linear behavior.

1. Introduction
Tumors are the most threatening issue everywhere throughout the world. It is the fundamental driver of death of human life and puts a substantial burden on the medical system because of the endless characteristics. Tumors are gathering of diseases incorporating isolated cells improvement with the likelihood to develop to a different part of the body [1] [2]. These show up distinctively in connection to benign tumors, which do not grow to various parts of the body [2]. Possible signs and responses of the tumor cell development contain a bump, abnormal passing on, and weight loss [3]. Tumors are perceived by specific symptoms and indications or screening tests [1].

Over the earlier decades, a consistent advancement related to tumor research has been performed [4]. Numerous scientific models are used to support, appreciate, and treat the tumor. Models are used to perceive how tumors form [5] and shape [6-8]. They are used to streamline or even modify the modern approach [4] [9], prognosticate the suitability of different prescriptions [10], or a mix of different medicines [11-13] and give knowledge into the development of resistance from medication. Numerous examinations are done to improve the capacity and to deliver a result of the immediate medical care for tumors [14-15].

This article concentrates on the ordinary differential equation (ODE) model for the nonlinear behavior of tumor cell enlargement in the human body. Different ODE models are proposed to address tumor growth and are reliably utilized to make assumptions regarding the sufficiency of development.
medication [10] [16] [17-18]. The uncontrolled development of cells that attack close-by parts of our body causes tumor growth [10]. The behavior of the tumor cells describes by a system of differential equations with time-dependent coefficients [19] [20].

The analytical dynamics of nonlinear behavior of tumor cell growth have not been studied in uncertain situations by the Rough set, which is a useful asset to consider the conduct of tumor cell development in any suspicious circumstance. Along these lines, in this scientific model, the dynamics of nonlinear behavior of tumor cells and carrying capacity is given with simulation by using Euler’s method in MATLAB. A relation between the number of tumor cells and carrying capacity is established and also validated by the Rough set. The complete workflow of the mathematical model of tumor cell growth and validation using the Rough set is in Figure 1.

Figure 1. The workflow of the mathematical approach of tumor cells growth with validation using the Rough set.

2. Materials and methods
2.1 Data source and collection
Experimental data for EAT (Ehrlich ascites tumors) in a mouse and the results of approximation using the logistic equation for \( K = 150 \times 10^7 \) and \( \theta = 0.6 \) which is obtained from (Krug and Taubert, 1985) [21] [22].

2.2 Mathematical Approach of Tumors Cells Growth
The measure of disease cells in tumors is difficult to survey in perspective on unsurprising changes in time. The number of tumor cells increases, and the number of cells die liable to the considered time distinction. It allows us to expect the cell cycle length of an individual tumor cell is twenty-four hours. By then, through the range of one day, the probability that the cell isolates are close 100%. We can acknowledge that the likelihood of this cell to partition inside the time length of one hour is 1/24. In reality, the right number of cells in a tumor cell population not known, so the population level can explicitly imply the above case. It is accepted that all cells partition once if \( dt = \) twenty-four hours. So also, if \( dt = \) one hour, just a small amount of cell in the population (around 1/24) is relied upon to separate [23].

2.3 Mathematical Analysis of nonlinear behaviour of tumors cells in terms of carrying capacity
To find the number of diseased cells in the tumor in a human body is a hard task because of constant changes in tumor growth with time [23]. The number of cells changes according to time,
\[
\frac{dS}{dt} = S(t)[e(t) - f(t)] \quad \ldots (1)
\]
\[
\frac{dS}{dt} = \theta(t)S(t) \quad \ldots (2)
\]

where \( S \) stands the number of tumor cells concerning time \( t \) (in days), \( e \) and \( f \) respectively producing and dying tumor cells, \( \frac{dS}{dt} \) is the per capita growth rate of tumor cells population, \( e(t) - f(t) = \theta(t) \)
and \( \theta(t) \) is the function that controls the growing the population of cells and strongly connected with access to nutrient and space availability.

A per capita tumor cell development, subject to tumors size and concerning carrying limit \( K \), is given by the logistic model [24].

\[
\frac{dS}{dt} = \theta S\left(\frac{K - S}{S}\right)
\]
Also equivalent to
\[
\frac{dS}{dt} = \theta S\left(1 - \frac{S}{K}\right) \quad \ldots (3)
\]

at \( S(t = 0) = S_0, K(t = 0) = K_0 \)

So, we obtain,
\[
S = \frac{KS_0}{S_0 + (K - S_0)e^{\theta t}} \quad \ldots (4)
\]

Let \( f(S) = \theta(1 - \frac{S}{K}) \) and if the growth of tumor cell will be exponential and in a real-life situation, it is not possible the growth of cells exponentially because after some time growth of the cells will reach to constant position so now from equation (3),

\[
\frac{dS}{dt} = Sf(S) \quad \ldots (5)
\]

The carrying limit \( K \) is considered as a variable representing the tumor cell growth.

\[
\frac{dK}{dt} = \theta S^{2/3} \quad \ldots (6)
\]

The fraction \( \frac{2}{3} \) has taken because the carrying capacity is proportional to the tumor surface [25].

2.4 Maximum size of tumor cell
For the solution of the carrying capacity, now from the system (6),

\[
\frac{dK}{dt} = \theta S^{2/3}
\]

So, putting the value of the \( S \) in the above equation, we obtain,

\[
\frac{dK}{dt} = \theta \left\{ \frac{KS_0}{S_0 + (K - S_0)e^{\theta t}} \right\}^{2/3}
\]

We simplify this equation, and we obtain
\[ K = \left( \gamma t + K_0 \frac{1}{2B_0} K_0^{-\frac{1}{3}} \right)^{\frac{3}{2}} \left( 3(1 - \frac{2}{3} e^{-\alpha t}) \frac{1}{2B_0} e^{-\beta t} \right) \ldots (7) \]

In the above expression, since \( K \) is carrying capacity of tumor cells, it shows that \( K \) is the maximum number of tumor cells in the human body at any part; it means, it forms a tumor of the maximum size.

3. Result of the model
The equation (7) shows the expression of the carrying capacity. The number of cells increases with time (days), and after some time growth of the number of tumor cells reaches the constant state (Figure 2). If the growth of tumor cells reaches the carrying capacity, then a few cells from the tumor leaves and make another tumor. In the case of the absence of the dead cells, the tumor cells grow at a rate proportional to the current population of the tumor cells.

4. The Rough set
The Rough set is concerned with the characterization and examination of imprecise data information and considered as one of the principal non-statistical methodologies in information investigation [26-27]. The concept of the Rough set has turned into an effective method in different issues, for example, representation of uncertain learning, information investigation, and assessment of data [27-29].

4.1 Validation with the Rough set
The data that we have taken is more appropriate data for explaining to our model because we only need the approximate number of tumor cells growth with time (days) for the validation of the model, and in searching for the estimated number of tumor cells with time, we found this experimental data in the exact form. The data is reliable and most suitable for work; that is why we have used it for the model. This work can be applied to the same type of experimental data. The data set of the number of tumor cells and its approximation is taken, and by using Rough Set Exploration System (RSES 2.2.2) [30], we found that the number of tumor cells increases with time (days) and after sometime growth of the tumors cells shows the constant behavior (Figure 3).

4.2 The mechanism used for the Rough set
A Rough set is a scientific apparatus that can be used to administer with imperfect learning and uncertain situations. The main principle of the Rough set is the indiscernibility association, which is used to estimate to what degree things are like or related. From (Krug and Taubert, 1985) [21] [22], we have two attributes (i.e., number of tumor cells and time) for one object. The number of tumor cells which are below the carrying limit belongs to the lower approximation, and some of the cells that cross the carrying limit belong to the upper limit. That gives us a Rough set. So, here, the dynamics of growth of tumor cells is dealt with the Rough set. We take the data set (Krug and Taubert, 1985, [21] [22]) of approximate values of the number of tumor cells with time, and we found the relation of the number of tumor cells with time (Figure 3). We found the relationship through the simulation process (Figure 2) that is the same as the relation that generated through the Rough Set Exploration System (RSES 2.2.2) (Figure 3).

4.3 The result from the Rough set
By using the approximate values of the number of tumor cells (Krug and Taubert, 1985, [21] [22]) and the Rough Set Exploration System (RSES 2.2.2), the relationship found between the number of tumor cells and time, that shows the number of tumor cells increases with time, and after some time, it reaches the constant state (Figure 3).
4.4 General statistics for the “number of cells of tumor” attribute

Using the Rough set, the statistics for the “number of cells of tumor” attribute are seen. Here, the mean value of the number of cells of tumors is 94.317, the standard deviation is 58.47, the lower limit of values is 3.33, and the upper limit of values is 149.3 in Table 1. The maximum number of cells growth values (i.e., 8) is in the range between 134.703 and 149.3, and the minimum number of cells growth values (i.e., 0) is in the range between 32.524 and 47.121 and 76.315 and 90.912 for the number of cells of tumor attribute in Figure 4 (A).

4.5 General statistics for the “time” attribute

Using the Rough set, we can see the statistics for the “time” attribute. Here, the mean value of time is 8.5, the standard deviation is 5.339, the lower limit of values is 0, and the upper limit of values is 17 in Table 2. The maximum number of values (i.e., 2) are in the range ([0, 1.7], [1.7, 3.4], [3.4, 5.1], [6.8, 8.5], [8.5, 10.2], [11.9, 13.6], [13.6, 15.3] and [15.3, 17.2]) and the minimum number of values (i.e., 1) are in the range ([5.1, 6.8] and [10.2, 11.9]) for the time attribute Figure 4 (B).

5. Conclusion and Discussion

Tumors are the primary reason for death and put a massive load on the medical system because of the chronic characteristics of the disease and typically undesirable effects produced by many of the treatments. The Rough set is involved with the characterization and examination of imprecise data information and considered as one of the principal non-statistical methodologies in information investigation.

The fundamental assumptions from various references of international reputed research articles are taken and formulated the mathematical model of nonlinear tumor cells growth in the human body, which validated by using the Rough set. We found that the relation between the number of tumor cells and time that the number of tumor cells increases, and after some time, it reaches to constant state (Figure 2). The Rough set for the validation of the model applied and found the result using the Rough Set Exploration System (RSES 2.2.2) that the relationship between the number of tumor cells and time, that the number of tumor cells increases with time, and after some time it reaches the constant state (Figure 3).

The result from the simulation process using MATLAB and the Rough Set Exploration System (RSES 2.2.2) is the same, i.e., the number of tumor cells increases with time, and after some time, it reaches the carrying capacity that is the growth of tumor cells reaches the constant state.

Further, experimentally, the results of approximation using the logistic equation for \[ K = 150 \times 10^7 \] \[ [21] \[22] \], and in our model, we have obtained the estimate of the number of tumor cells \(( \approx 149.30 \times 10^7 \) \) in the simulation process. So our model is only differing from \( K = 0.7 \times 10^7 \) significant digits, and we have obtained the accuracy of carrying capacity of the number of tumor cells 99.53\% correct in the body according to our model.

Therefore, these advances offer novel insights for tumor growth, which further supports research in tumor cell dynamics.
Table 1. General statistics of the “number of tumor cells” attribute

| General Statistics         | Attributes          | Attribute range                  |
|----------------------------|---------------------|----------------------------------|
| Number of objects: 18      | Number of tumor cells | Lower limit of values: 3.33     |
| Number of attributes: 2    | Status: condition   | Upper limit of values: 149.3    |
|                            | Type: numeric       |                                  |
|                            | Precision: 4        |                                  |
|                            | Mean: 94.317        |                                  |
|                            | Standard deviation: 58.47 |                          |
|                            | Minimum: 3.33       |                                  |
|                            | Maximum: 149.3      |                                  |

Table 2. General statistics of the “time” attribute

| General Statistics         | Attributes          | Attribute range                  |
|----------------------------|---------------------|----------------------------------|
| Number of objects: 18      | Time                | Lower limit of values: 0         |
| Number of attributes: 2    | Status: condition   | Upper limit of values: 17        |
|                            | Type: numeric       |                                  |
|                            | Precision: 4        |                                  |
|                            | Mean: 8.5           |                                  |
|                            | Standard deviation: 5.339 |                        |
|                            | Minimum: 0          |                                  |
|                            | Maximum:17          |                                  |

Figure 2. The number of tumor cells increases with time, and after some time, it reaches the constant state.

Figure 3. The number of tumor cells increases with time, and after some time, it reaches the constant state by the Rough set exploratory system (2.2.2).
Figure 4 (A). Attribute value interval for the “number of tumor cells” attribute

Figure 4 (B). Attribute value interval for the “time” attribute

Figure 4 (A) - (B): The bar diagrams found from the Rough set using the parameters, number of tumor cells and time (A) attribute value interval for the “number of tumor cells” attribute which shows that the maximum number of tumor cells growth values (i.e., 8) is in the range between 134.703 and 149.3 and the minimum number of cells growth values (i.e., 0) are in the range between 32.524 and 47.121 and 76.315 and 90.912 for the number of cells of tumor attribute; (B) attribute value interval for the “time” attribute which shows that the maximum number of values (i.e., 2) are in the range between [0, 1.7], [1.7, 3.4], [3.4, 5.1], [6.8, 8.5], [8.5, 10.2], [11.9, 13.6], [13.6, 15.3] and [15.3, 17] and the minimum number of values (i.e., 1) are in the range between [5.1, 6.8] and [10.2, 11.9] for the time attribute.

Acknowledgments
The authors are extremely thankful, to the Department of Mathematics, NIT Raipur (C. G.), India for providing facilities, space and an opportunity for the work.

Conflict of Interest
The authors declare that there is no conflict of interest.

References
[1] Clark W H 1991 Tumour progression and the nature of cancer Br. J. Cancer 64 631–644. Doi: 10.1038/bjc.1991.375
[2] Elder D E, Rodeck U, Thurin J, Cardillo F, Clark WH, Stewart R and Herlyn M 1989 Antigenic profile of tumor progression stages in human melanocytic nevi and melanomas Can. Research 49 5091–5096.
[3] Kerbel R S, Waghorne C, Korczak B, Lagarde A and Breitman M L 1988 Clonal dominance of primary tumours by metastatic cells: genetic analysis and biological implications Can. Surveys 7 597–629.
[4] Batmani Y and Khaloozadeh H 2013 Optimal drug regimens in cancer chemotherapy: A multi-objective approach Comp. Bio. Medicine 43 2089–95. Doi: 10.1016/j.compmied.2013.09.026.
[5] Huang X, Ning J and Wahed A S 2014 Optimization of individualized dynamic treatment regimes for recurrent diseases Stat. Medicine 33 2363–78. Doi: 10.1002/sim.6104.
[6] Elias J, Dimitrio L, Clairambault J and Natalini R 2014 The p53 protein and its molecular network: Modelling a missing link between dna damage and cell fate BiochimBiophys Acta Proteins Proteomics 1844 232–47. Doi: 10.1016/j.bbapap.2013.09.019.
[7] Laird A K 1965 Dynamics of tumour growth: Comparison of growth rates and extrapolation of growth curve to one cell Br. J. Cancer 19 278–91. Doi: 10.1038/bjc.1965.32.
[8] Laird A K 1964 Dynamics of tumors growth Br. J. Cancer 13 490–502. Doi:
[9] Brodin N P, Vogelius I R, Eriksson T B, AlRosenschold P M, Maraldo M V, Aznar M C, Specht L and Bentzen S M 2014 Optimizing the radiation therapy dose prescription for pediatric medulloblastoma: Minimizing the life years lost attributable to failure to control the disease and late complication risk Acta Oncologica \textbf{53} 462–70. Doi: 10.3109/0284186X.2013.858824.

[10] Ercan B, İlhanO and SenolK 2019 Dynamical behaviour of fractional order tumor model with Caputo and conformable fractional derivative Chaos, Solitons & Fractals \textbf{123} 43-51. Doi: https://doi.org/10.1016/j.chaos.2019.03.032.

[11] Panetta J C 1998 A mathematical model of drug resistance: Heterogeneous tumors Math. Biosciences \textbf{147} 41–61. Doi: 10.1016/S0025-5564(97)00080-1.

[12] Sakode C M, Padhi R, Kapoor S, Rallabandi V P S and Roy P K 2014 Multimodal therapy for complete regression of malignant melanoma using constrained nonlinear optimal dynamic inversion Biomed. Sig. Pro. Control \textbf{13} 198–211. Doi: 10.1016/j.bspc.2014.04.010.

[13] De Pillis L G, Gu W and Radunskaya A E 2006 Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations J. Theo. Biology \textbf{238} 841–62. Doi: 10.1016/j.jtbi.2005.06.037.

[14] Rihan F A, Lakshmanan S and Maurer H 2019 Optimal control of tumor-immune model with time-delay and immuno-chemotherapy Appl. Math. Computation \textbf{353} 147-165. Doi: https://doi.org/10.1016/j.amc.2019.02.002.

[15] Huang Y, Zhang Z and Hu B 2017 Bifurcation for a free-boundary tumor model with angiogenesis Nonli. Anal.: Re. Wor. Applications \textbf{35} 483-502. Doi: https://doi.org/10.1016/j.nonrwa.2016.12.003.

[16] Jin Y, Yuanshun T and Robert A C 2019 Modelling effects of a chemotherapeutic dose response on a stochastic tumor-immune model Chaos, Solitons & Fractals \textbf{123} 1-13. Doi: https://doi.org/10.1016/j.chaos.2019.03.029.

[17] Parajdi L 2014 Modeling the treatment of tumor cells in a solid tumor J. Nonli. Sci. Applications \textbf{7} 188-195.

[18] Alavi S A, Norabadi J and Arjmand M 2012 Optimal Control Brain Tumor System with Drog and Its Stability J. Math. Comp. Science \textbf{4} 473 – 486.

[19] Zheng J and Cui S 2019 Analysis of a tumor-model free boundary problem with a nonlinear boundary condition J. Math. Anal. Applications \textbf{478} 806-824. Doi: https://doi.org/10.1016/j.jmaa.2019.05.056.

[20] Kassem M A E H, Hemeda A A and Abdeen M A 2020 Solution of the tumor-immune system by differential transform method J. Nonli. Sci. Applications \textbf{13} 9–21. Doi: 10.22436/jnsa.013.01.02.

[21] Krug H and Taubert G 1985 Zur praxis der anpassung der logistischen function an das wachstum experimenteller tumoren Arch. Geschwulstforsch \textbf{55} 235–244.

[22] Forys U and Czochra A M 2003 Logistic equations in tumour growth modelling, Int. J. Appl. Math. Comput. Science \textbf{13} 317–325.

[23] Enderling H and Chaplain A J M 2014 Mathematical modeling of tumor growth and treatment Curr Pharm Design \textbf{20} 4934-40. Doi: 10.2174/13816128196661125150434.

[24] Hahnfeldt P, Panigrahy D, Folkman J and Hlatky L 1999 Tumors development under angiogenic signaling: a dynamical theory of tumors growth, treatment response, and postvascular dormancy Can. Research \textbf{59} 4770-5.

[25] Iwata K, Kawasaki K and Shigesada N 2000 A dynamical model for the growth and size distribution of multiple metastatic tumors J. Theo. Biology \textbf{203} 177–86.

[26] Jain M and Bhatia M P S 2014 A rough set based approach to classify node behavior in mobile Ad hoc networks J. Math. Comp. Science \textbf{11} 64-78.
[27] Polkowski L 2002 *Advance in soft computing: Rough sets mathematical foundations* (Physical-Verlag A Springer-Verlag Company). Doi: 10.1007/978-3-7908-1776-8.

[28] Peters G, Lingras P and Slezak D 2012 *Rough sets selected methods and applications in management and engineering* (Springer). Doi: 10.1007/978-1-4471-2760-4.

[29] Lin T Y and Cercone N1997 *Rough sets and data mining analysis of imprecise data* (Springer). Doi: 10.1007/978-1-4613-1461-5

[30] RSES 2.2 *User’s Guide* 2005 Warsaw University. http://logic.mimuw.edu.pl/~rses.