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Numerical Solution of Mathematical Model of Tumor Immune Response Using Runge-Kutta Fourth Order Method

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Abstract

This study focuses on solving the mathematical model of tumor immune response using the Runge-Kutta fourth order method, a robust numerical approach for ordinary differential equations. The research aims to analyse the dynamic interactions between tumor cells and the immune system, addressing the limitations of analytical methods by applying a numerical solution using MATLAB R2024b software. The Runge-Kutta fourth order method is implemented on the system of ordinary differential equations with specified parameters and initial conditions, providing a numerical solution over a defined time frame. The results reveal that the tumor cell population decreases significantly while the mature lymphocyte population stabilizes, leading to a tumor-free equilibrium. This demonstrates the immune system's effectiveness in eliminating tumor growth under optimal conditions and highlights the accuracy and stability of Runge-Kutta fourth order method in modelling complex biological systems. The study emphasizes the importance of numerical methods in predicting tumor-immune dynamics, offering valuable insights for future applications in immunotherapy and cancer research.

1. Introduction

Cancer is a complex disease and understanding how tumors interact with the immune system is crucial. There are a lot of factors that contribute to elimination and the growth of tumors. Among the factors is how the tumor immune system, also known as lymphocyte responses to the existence of tumor in the body.

[1] emphasized the significance of time delay and noise in shifting tumor dynamics, highlighting the immune system's basal level as a critical factor in tumor elimination. A four-dimensional tumor-immune model was analysed by [2], revealing chaotic behaviour dependent on initial conditions using the differential transformation method. Another study by [3] incorporated interleukin-2 (IL2) and showed that tumor cell populations stabilize over time, showcasing fractional-order derivatives' suitability in modelling long-term tumor-immune interactions. [4] applied Caputo fractional derivatives and the Sumudu transform homotropy perturbation method, effectively capturing tumor-immune dynamics. [5] highlighted the need to balance immune cell levels to prevent tumor escape and autoimmune risks while proposing model improvements for broader applicability.

The Runge-Kutta fourth order method (RK4), derived from the Euler method, is widely used for solving ordinary differential equations (ODEs) due to its accuracy. Zingg [6] developed an RK4 variant with similar accuracy but reduced memory requirements. Chauhan [7] confirmed RK4's superior accuracy over the Euler method, while [8] demonstrated its effectiveness in disease modelling. [9] showed RK4's utility in solving

nonlinear gas flow equations, emphasizing its stability and precision. [10] successfully applied RK4 to model dengue fever spread, confirming its reliability in analysing disease dynamics.

The tumor immune response model, comprising multiple ODEs, captures complex interactions between tumors and the immune system. Previous research by [11] relied solely on analytical methods, leaving a gap in numerical analysis. The RK4, known for its stability and accuracy, is suitable for addressing this gap. MATLAB will be used to implement RK4 for solving the model.

Tumor immune response models use mathematical equations to study the interactions between tumor cells and the immune system, helping to explore factors like immune cell activity, time delays, and treatment effects. These models provide valuable insights into cancer dynamics, enabling researchers to better understand tumor behaviour and design more effective therapies. This study aims to examine the tumor-immune response model, solve it using the RK4, predict future trends, and compare the results with the ode45 solver to ensure accuracy and reliability.

2. Research Methodology

This chapter examines the mathematical expression of the tumor immune response as a system of ODEs. The RK4 technique is detailed to obtain accurate numerical solutions for this complex biological system. Together, these elements demonstrate how to employ computational techniques to systematically investigate tumor-immune dynamics.

2.1 Mathematical Model of Tumor Immune Response

The tumor immune response model, proposed by [11], represents the interaction between tumor cells and T lymphocytes. The model is a system of ODEs that tracks changes in three key populations which are immature T lymphocytes, mature T lymphocytes, and tumor cells. It incorporates parameters like the tumor growth rate, recruitment of lymphocytes, and the rate at which mature lymphocytes eliminate tumor cells. These equations simulate the dynamic interplay between the immune system and tumor growth over time, highlighting how immune cells respond to and suppress tumor progression under specific conditions.

The mathematical modelling of tumor immune response is given by [11];

$$\begin{aligned} \frac{dx}{dt} &= -x + \frac{yz}{1+z}, \\ \frac{dy}{dt} &= \alpha x - \beta y + \gamma \ , \\ \frac{dz}{dt} &= \delta z - zy, \end{aligned} \tag{1}$$

The α is the ratio of the maximum recruitment rate of immature T lymphocytes to the transformation rate from immature to mature T lymphocytes. β ratio of the inactivation rate of mature T lymphocytes to the transformation rate of immature T lymphocytes. γ is the scaled killing rate of tumor cells by mature T lymphocytes, adjusted for the rate of production of young lymphocytes and the squared transformation rate of immature T lymphocytes. δ is the ratio of the tumor growth rate to the transformation rate of immature T lymphocytes. The x represents the number of immature T lymphocytes, y represents the number of mature T lymphocytes and z represents the number of tumor cells. The initial condition for the system is, $x(0) \geq 0, y \geq (0)$ and $z \geq (0)$.

2.2 Runge-Kutta Fourth Order Method.

RK4 is a widely used numerical technique for solving first-order ODEs. Known for its high accuracy and stability, it is particularly effective for systems like the tumor immune response model, where precision is critical [12].

RK4 works by evaluating four slopes at different points within each step: the initial slope (k_1), two estimates at the midpoint (k_2 and k_3), and the slope at the endpoint (k_4). These slopes are combined into a weighted average to calculate the solution at the next step, as given by the RK4 formula:

$$y_{i+1} = y_i + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4) \tag{2}$$

where the slopes are calculated as follows:

$$\begin{aligned} k_1 &= hf(t, x_i, y_i) \\ k_2 &= hf\left(t, x_i + \frac{h}{2}, y_i + \frac{k_1}{2}\right) \\ k_3 &= hf\left(t, x_i + \frac{h}{2}, y_i + \frac{k_2}{2}\right) \\ k_4 &= hf(t, x_i + h, y_i + k_3) \end{aligned} \tag{3}$$

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Here, h is the step size, t_i is the current time, y_i is the current value, and f represents the function defining the ODE.

In this study, RK4 is applied to the tumor immune response model, a system of first-order ODEs. MATLAB software is used to implement RK4 and calculate numerical solutions iteratively for each variable in the system. The results obtained are compared to MATLAB's built-in ode45 solver, known for its adaptive step size and efficiency, to validate the accuracy of RK4. This demonstrates the effectiveness of RK4 in modelling complex biological systems, such as the interactions between tumor cells and immune cells [12].

The RK4 formula for (1) are:

$$\begin{aligned} x_{(i+1)} &= x_i + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4) \\ y_{(i+1)} &= y_i + \frac{1}{6}(l_1 + 2l_2 + 2l_3 + l_4) \\ z_{(i+1)} &= z_i + \frac{1}{6}(m_1 + 2m_2 + 2m_3 + m_4) \end{aligned} \tag{4}$$

where,

$$\begin{aligned} k_1 &= h \cdot f_x(t_i, x_i, y_i, z_i) = h \cdot \left(-x_i + \frac{y_i z_i}{1 + z_i}\right) \\ l_1 &= h \cdot f_y(t_i, x_i, y_i) = h \cdot (-\alpha x_i - \beta y_i + \gamma) \\ m_1 &= h \cdot f_z(t_i, y_i, z_i) = h \cdot (\delta z_i - z_i y_i) \end{aligned} \tag{5}$$

$$\begin{aligned} k_2 &= h \cdot f_x\left(t_i + \frac{h}{2}, x_i + \frac{k_1}{2}, y_i + \frac{l_1}{2}, z_i + \frac{m_1}{2}\right) = h\left(-\left(x_i + \frac{k_1}{2}\right) + \frac{\left(y_i + \frac{l_1}{2}\right)\left(z_i + \frac{m_1}{2}\right)}{1 + \left(z_i + \frac{m_1}{2}\right)}\right) \\ l_2 &= h \cdot f_y\left(t_i + \frac{h}{2}, x_i + \frac{k_1}{2}, y_i + \frac{l_1}{2}\right) = h\left(-\alpha\left(x_i + \frac{k_1}{2}\right) - \beta\left(y_i + \frac{l_1}{2}\right) + \gamma\right) \\ m_2 &= h \cdot f_z\left(t_i + \frac{h}{2}, y_i + \frac{l_1}{2}, z_i + \frac{m_1}{2}\right) = h\left(\delta\left(z_i + \frac{m_1}{2}\right) - \left(z_i + \frac{m_1}{2}\right)\left(y_i + \frac{l_1}{2}\right)\right) \end{aligned} \tag{6}$$

$$\begin{aligned} k_3 &= h \cdot f_x\left(t_i + \frac{h}{2}, x_i + \frac{k_2}{2}, y_i + \frac{l_2}{2}, z_i + \frac{m_2}{2}\right) = h\left(-\left(x_i + \frac{k_2}{2}\right) + \frac{\left(y_i + \frac{l_2}{2}\right)\left(z_i + \frac{m_2}{2}\right)}{1 + \left(z_i + \frac{m_2}{2}\right)}\right) \\ l_3 &= h \cdot f_y\left(t_i + \frac{h}{2}, x_i + \frac{k_2}{2}, y_i + \frac{l_2}{2}\right) = h\left(-\alpha\left(x_i + \frac{k_2}{2}\right) - \beta\left(y_i + \frac{l_2}{2}\right) + \gamma\right) \\ m_3 &= h \cdot f_z\left(t_i + \frac{h}{2}, y_i + \frac{l_2}{2}, z_i + \frac{m_2}{2}\right) = h\left(\delta\left(z_i + \frac{m_2}{2}\right) - \left(z_i + \frac{m_2}{2}\right)\left(y_i + \frac{l_2}{2}\right)\right) \end{aligned} \tag{7}$$

$$\begin{aligned} k_4 &= h \cdot f_x(t_i + h, x_i + k_3, y_i + l_3, z_i + m_3) = h\left(-\left(x_i + \frac{k_2}{2}\right) + \frac{\left(y_i + \frac{l_2}{2}\right)\left(z_i + \frac{m_2}{2}\right)}{1 + \left(z_i + \frac{m_2}{2}\right)}\right) \\ l_4 &= h \cdot f_y(t_i + h, x_i + k_3, y_i + l_3) = h\left(-\alpha\left(x_i + \frac{k_2}{2}\right) - \beta\left(y_i + \frac{l_2}{2}\right) + \gamma\right) \\ m_4 &= h \cdot f_z(t_i + h, y_i + l_3, z_i + m_3) = h\left(\delta\left(z_i + \frac{m_2}{2}\right) - \left(z_i + \frac{m_2}{2}\right)\left(y_i + \frac{l_2}{2}\right)\right) \end{aligned} \tag{8}$$

3. Results and Discussion

This section shows the results of solving the tumor immune response model using RK4. A test problem is examined and numerical results are compared with MATLAB's ode45 solver for validation. The discussion explores the interactions between tumor and immune cells, highlighting the model's accuracy and the effectiveness of the numerical method.

Test Problem

This section demonstrates the solution of mathematical model of tumor immune response using RK4. The system (1) is considered with initial value $x(0) = 6, y(0) = 8$ and $z(0) = 10$. From[11], the values of parameters $\alpha = 0.3, \beta = 0.6, \gamma = 6.2$ and $\delta = 10$ are used where tumor-free equilibrium is stable.

3.1 Numerical Results

In this section, the results of solving the test problem are discussed. The problem is numerically solved by RK4. MATLAB software is used for all the calculations. The problem also is solved by the ode45 solver and compares with RK4's result. Table 1, Table 2 and Table 3 show the results for the numerical solution of the test problem using RK4 and ode45 solver with the absolute error of RK4 for *x(t), y(t)* and *z(t)* respectively.

Table 1 Numerical results of $\boldsymbol{x(t)}$ for the test problem with $\boldsymbol{0 \leq t \leq 10}$ and $\boldsymbol{h = 0.1}$

Time (Days)	RK4	ode45 Solver	Absolute error
0	6	6	0
1	7.955676051573006	7.955397784135918	2.78267E-04
2	9.487973182578182	9.488581637121618	6.08455E-04
3	6.818025375233460	6.822107208251539	4.08183E-03
4	2.787743601208819	2.789450488151460	1.70689E-03
5	1.038154017146408	1.038778085372650	6.24068E-04
6	0.383107778111790	0.383338307566228	2.30529E-04
7	0.141178945837466	0.141210751253535	3.18054E-05
8	0.052019141952717	0.052054655944224	3.55140E-05
9	0.019175329761310	0.019200918047247	2.55883E-05
10	0.007075950182551	0.007086925860905	1.09757E-05

Table 2 Numerical results of $\boldsymbol{y(t)}$ for the test problem with $\boldsymbol{0 \leq t \leq 10}$ and $\boldsymbol{h = 0.1}$

Time (Days)	RK4	ode45 Solver	Absolute error
0	8	8	0
1	10.635026103150874	10.635142024545647	1.15921E-04
2	12.516443458205984	12.516497476574164	5.40184E-05
3	13.449822760202297	13.450391898192345	5.69138E-04
4	13.035060085721915	13.035995999138748	9.35913E-04
5	12.197180865077254	12.197927258447105	7.46393E-04
6	11.497349209731867	11.497841579854576	4.92370E-04
7	11.024189843609889	11.024513312260581	3.23469E-04
8	10.731655170329445	10.731827294763681	1.72124E-04
9	10.559002174076234	10.559098103589273	9.59295E-05
10	10.459788518448773	10.459844333621392	5.58152E-05

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Table 3 Numerical results of $\boldsymbol{z(t)}$ for the test problem with $\boldsymbol{0 \leq t \leq 10}$ and $\boldsymbol{h = 0.1}$

Time (Days)	RK4	ode45 Solver	Absolute error
0	10	10	0
1	18.248859756422803	18.253137757482850	4.27800E-03
2	3.575487757990985	3.575857457396855	3.69699E-04
3	0.161269475861179	0.161344504211755	7.50284E-05
4	0.005820152290382	0.005820967032422	8.14742E-07
5	0.000425084723876	0.000424770839062	3.13885E-07
6	0.000068303896447	0.000068237572412	6.63240E-08
7	0.000019704766890	0.000019673181425	3.15855E-08
8	0.000008292237740	0.000008289157463	3.08028E-09
9	0.000004383193268	0.000004382100623	1.09264E-09
10	0.000002645924362	0.000002645152623	7.71738E-10

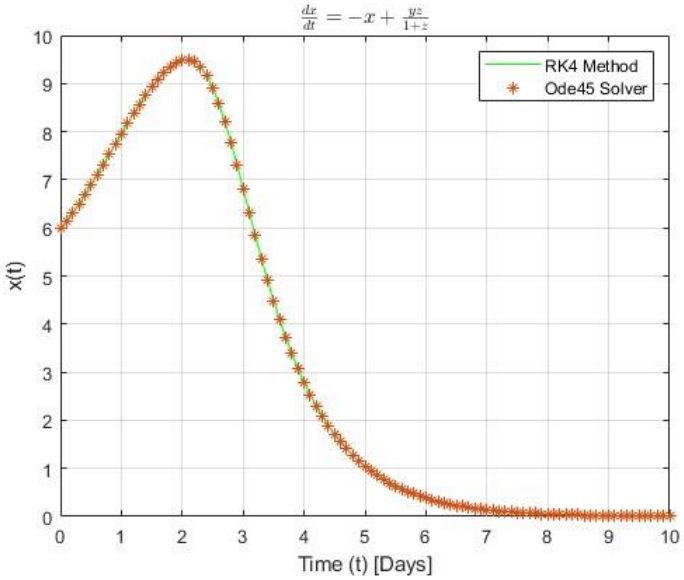

Fig. 1 Graph of Immature Lymphocytes, x(t) with $\boldsymbol{0 \leq t \leq 10}$ and $\boldsymbol{h = 0.1}$ solving using RK4 and ode45 Solver

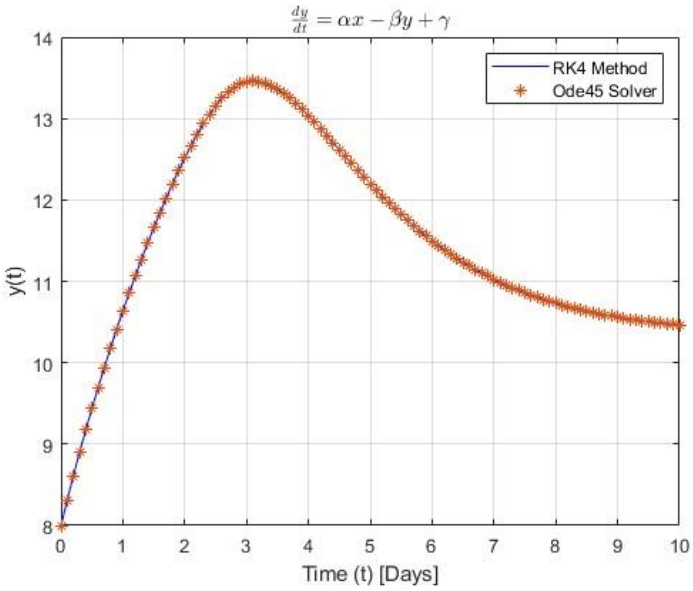

Fig. 2 Graph of mature lymphocytes, y(t) with $\mathbf{0} \leq \boldsymbol{t} \leq \mathbf{10}$ and h=0.1 solving using RK4 and ode45 Solver

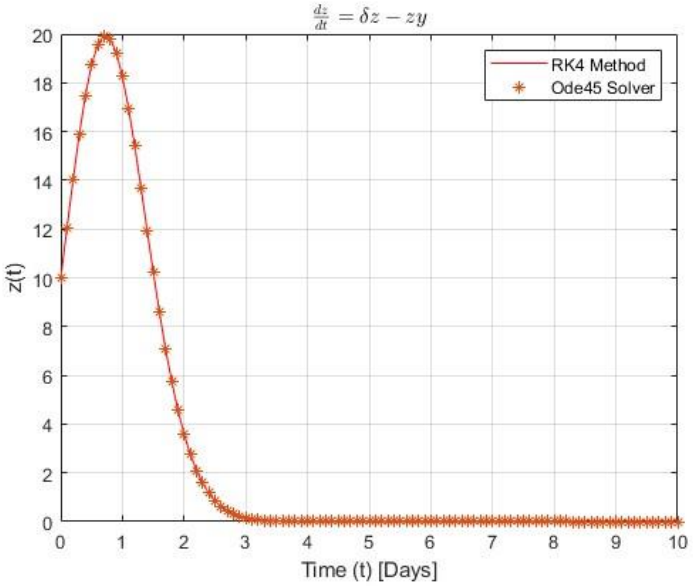

Fig. 3 Graph of tumor cells, z(t) with $\mathbf{0} \leq \boldsymbol{t} \leq \mathbf{10}$ and $\boldsymbol{h} = \mathbf{0.1}$ solving using RK4 and ode45 Solver

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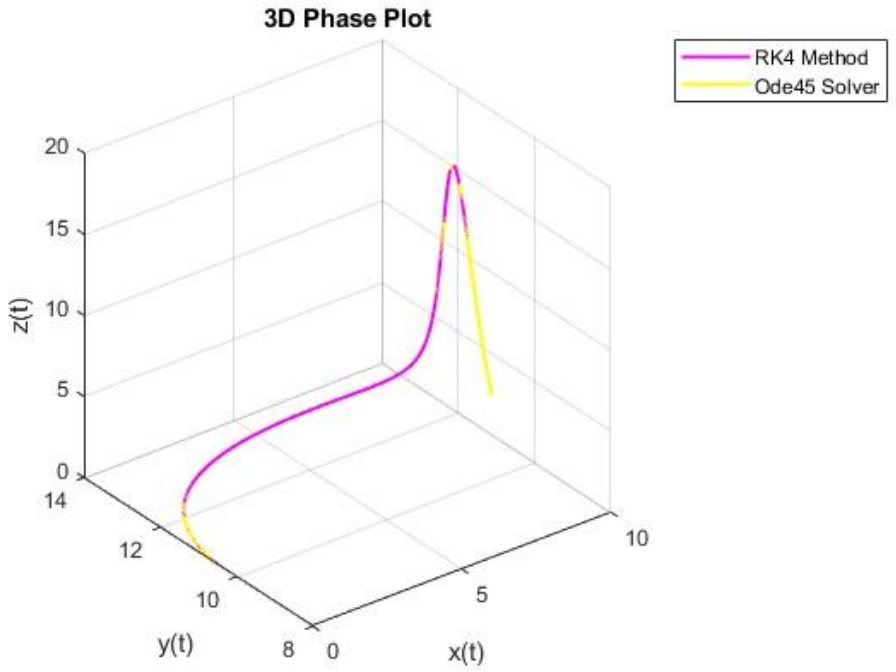

Fig. 4 Graph of mathematical modelling of anti-tumor immune response with $\mathbf{0} \leq \boldsymbol{t} \leq \mathbf{10}$ and $\boldsymbol{h} = \mathbf{0.1}$ solving using RK4 and ode45 Solver

The numerical results obtained from solving the tumor immune response model using the RK4 reveal distinct trends in the interactions between tumor cells and immune cells over time. Beginning with initial values of 6, 8, and 10 for immature lymphocytes, *x(t)*, mature lymphocytes, *y(t)*, and tumor cells, *z(t)*, respectively, the dynamics of these populations show clear patterns.

Fig. 1, Fig. 2 and Fig. 3 represent the dynamic interactions in the tumor-immune response, showing the depletion of immature lymphocytes, *x(t),* the stabilization of mature lymphocytes, *y(t)* and the elimination of tumor cells, *z(t)* over time. Fig. 4 highlights the immune system's coordinated effort to eliminate tumor cells. It shows how immature lymphocytes mature and stabilize, effectively working to clear the tumor and achieve a tumor-free state.

Fig. 1 shows the immature lymphocytes initially increase slightly but decline rapidly, reaching nearly zero by $t = 3$ days. This reflects their transformation into mature lymphocytes, a critical phase in the immune response. Fig. 2 shows the mature lymphocytes rise significantly, peaking at approximately 13 by $t = 3$ days, and then stabilize around 10. This stabilization indicates the immune system maintains a consistent presence of mature lymphocytes, effectively suppressing tumor growth.

Fig. 3 shows the tumor cells show the most dramatic change, decreasing sharply from an initial value of 10 to nearly zero by $t = 3$ days. This trend illustrates the effectiveness of the immune response in eliminating tumor cells and achieving a stable, tumor-free equilibrium. The interplay between the decline in immature lymphocytes, the stabilization of mature lymphocytes, and the near eradication of tumor cells underscores the model's ability to accurately represent the immune system's efficiency.

The accuracy of the RK4 results is further validated through comparison with MATLAB's ode45 solver. For example, at $t = 10$ days, the RK4 calculated value for tumor cells is 2.64592e-06, closely matching the ode45 result of 2.64515e-06, with a minimal absolute error of 7.71738e-10. This consistency confirms the reliability of RK4 for modelling complex biological systems.

In summary, the trends observed in the RK4 results highlight the immune system's capability to suppress and eliminate tumor cells effectively while demonstrating the numerical method's robustness and accuracy. These insights are critical for understanding tumor-immune dynamics and validating the use of RK4 in biological modelling.

4. Conclusion

Based on the results and discussion, the RK4 effectively solved the tumor immune response model, giving a precise illustration of how immune cells and tumor cells interact. The numerical results revealed a significant reduction in tumor cells and stabilization of immune cell populations, demonstrating the immune system's ability to achieve a tumor-free equilibrium under optimal conditions. The comparison with MATLAB's ode45 solver confirmed the accuracy and reliability of RK4 in modelling such dynamic systems.

This study highlights the effectiveness of RK4 in capturing the complex behaviour of biological models, emphasizing its role as a valuable tool for understanding tumor-immune dynamics and guiding future research in immunotherapy and cancer modelling.

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Conflict of Interest

Authors declare that there is no conflict of interest regarding the publication of the paper.

Author Contribution

The authors confirm contribution to the paper as follows: ***study conception and design:*** *Mohamad Najib, Syahirbanun Isa;* ***data collection:*** *Mohamad Najib;* ***analysis and interpretation of results:*** *Mohamad Najib, Syahirbanun Isa;* ***draft manuscript preparation:*** *Mohamad Najib, Syahirbanun Isa. All authors reviewed the results and approved the final version of the manuscript.*

References

[1] L. Han, C. He, and Y. Kuang, "Dynamics of a model of tumor-immune interaction with time delay and noise," *Discrete Continuous Dyn Syst Ser B*, vol. 13, no. 9, pp. 2347–2363, Sep. 2020, doi: 10.3934/dcdss.2020140.

[2] M. A. Padder, Afroz, and A. Khan, "Analysis of Tumor-Immune Response Model by Differential Transformation Method," *Journal of Scientific Research*, vol. 14, no. 1, pp. 243–256, Jan. 2022, doi: 10.3329/jsr.v14i1.55065.

[3] A. Padder, R. Pal, Afroz, and A. Khan, "ANALYSIS OF TUMOR-IMMUNE RESPONSE MODEL BY USING CONFORMABLE FRACTIONAL ORDER DERIVATIVE," *South East Asian Journal of Mathematics and Mathematical Sciences*, vol. 18, no. 3, pp. 393–414, 2022, doi: 10.56827/SEAJMMS.2022.1803.33.

[4] V. Gill Govt College Nalwa Shikaa Samuel, S. Rana Govt College Hisar Yudhveer Singh, V. Gill, S. Samuel, S. Rana, and Y. Singh, "Mathematical analysis of fractional order Tumor-Immune Response Model via an eecient computational technique Mathematical analysis of fractional order Tumor-Immune Response Model via an efficient computational technique," 2023, doi: 10.21203/rs.3.rs-2545282/v1.

[5] S. Sinha, P. Singh, and M. E. Koksal, "Mathematical and Numerical Modelling of Interference of Immune Cells in the Tumor Environment," *Discrete Dyn Nat Soc*, vol. 2023, 2023, doi: 10.1155/2023/9006678.

[6] D. W. Zingg and T. T. Chisholm, "Runge-Kutta methods for linear ordinary differential equations," 1999.

[7] V. Chauhan and P. K. Srivastava, "Computational techniques based on runge-kutta method of various order and type for solving differential equations," *International Journal of Mathematical, Engineering and Management Sciences*, vol. 4, no. 2, pp. 375–386, 2019, doi: 10.33889/ijmems.2019.4.2-030.

[8] L. Simangunsong and S. Mungkasi, "Fourth order Runge-Kutta method for solving a mathematical model of the spread of HIV-AIDS," in *AIP Conference Proceedings*, American Institute of Physics Inc., May 2021. doi: 10.1063/5.0052550.

[9] M. Salah, M. S. Matbuly, O. Civalek, and O. Ragb, "Calculation of Four-Dimensional Unsteady Gas Flow via Different Quadrature Schemes and Runge-Kutta 4th Order Method," *Adv Appl Math Mech*, vol. 16, no. 2, pp. 437–458, 2023, doi: 10.4208/aamm.OA-2021-0373.

[10] S. Side, A. Zaki, and Miswar, "Numerical Solution of the Mathematical Model of DHF Spread using the Runge-Kutta Fourth Order Method," *ARRUS Journal of Mathematics and Applied Science*, vol. 2, no. 2, pp. 92–100, Apr. 2022, doi: 10.35877/mathscience745.

[11] L. Pang, S. Liu, X. Zhang, and T. Tian, "Mathematical modeling and dynamic analysis of anti-tumor immune response," *J Appl Math Comput*, vol. 62, no. 1–2, pp. 473–488, Feb. 2020, doi: 10.1007/s12190-019-01292-9.

[12] S. C. Chapra and R. P. Canale, *Numerical methods for engineers*. McGraw-Hill Higher Education, 2010.