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Numerical Solution Model of Brain Tumors Glioblastoma multiforme with Treatment Effect Using Runge Kutta Fehlberg Methods

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ABSTRACT
The mathematical model of glioblastoma multiforme brain tumor (GBM) consists of a population of tumor cells that are sensitive $x(t)$ and the pupulation of cells susceptible to tumor $y(t)$. The effect of treatment on sensitive cells is given by Chemoresistant and pleotropic (d_1), whereas the effect of treatment on susceptible cells is a precursor to prevention in tumor patients (d_2). This article aims to solve the equation of GBM brain tumor model with the effect of treatment using Runge Kutta Fehlberg method. The result of Runge Kutta Fehlberg method has high accuracy and has fulfilled the given error tolerance of 10^{-7}. Numerical solutions show that both populations have met the error tolerance when it reaches 200 days with $\Delta t = 1$. Based on these results, the numerical solution to the effect of treatment using the Runge Kutta Fehlberg method has a good accuracy in solving nonlinear common differential equations of GBM brain tumor mode.

Keywords: *Glioblastoma multiforme (GBM), treatment effect, numerical solution using Runge Kutta Fehlberg method.*

1. INTRODUCTION

The mathematical model of glioblastoma multiforme brain tumor (GBM) consists of growth population of tumor-sensitive cells $x(t)$ and growth population of tumor cells $y(t)$. Bozkurt [1] explains the GBM brain tumor model as follows:

$$\begin{aligned}\frac{dx(t)}{dt} &= r_1 x(t)\big(R_1 - \alpha_1 x(t) - \alpha_2 x([t-1])\big)\\ &\quad + px(t) - \gamma_1 x(t) y([t-1])\\ &\quad - d_1 x(t) x([t])\end{aligned} \tag{1}$$

$$\begin{aligned}\frac{dy(t)}{dt} &= r_2 y(t)\big(R_2 - \beta_1 y(t) - \beta_2 y([t-1])\big)\\ &\quad - d_1 x(t) x([t]) + \gamma_1 x([t]) y(t)\end{aligned}$$

when $t \geq 0$

$$x(-1) = x_{-1}, x(0) = x_0$$

and

$$y(-1) = y_{-1}, y(0) = y_0$$

with x_{-1}, x_0, y_{-1}, dan y_0 is a constant real value and [.] is defined as a function of integers and $x_{-1} \neq 0, x_0 \neq 0$.

The growth population of tumor cells $x(t)$ grew with a tumor growth rate (r_1) of 1.08 cells / day and suppressed by a treatment rate (d_1) of 0.6 cells/day. Treatment effect d_1 is a complex phenomenon using Chemoresistant with one treatment or using pleotropic resistance with multiple treatments. The population of sensitive cells $x(t)$ uses $x([t])$ and $x([t-1])$ which is constant in value with the population capacity (R_1) of 4,704 cells/ml/day. The lower threshold (α_1) and the upper threshold (α_2) population rate of sensitive cells are 0,51 and 0,555 cells/ml/day. The mutation rate (γ_1) of sensitive cells $x(t)$ becomes susceptible cells $y(t)$ of 0.01 cells/day and is affected by the rate of cleavage of tumor cells (p) of 0.192 cells/day [1].

Furthermore, in the growth population cells susceptible to tumor $y(t)$ grow with a tumor growth rate (r_2) of 1.1664 cells/day and suppressed by the

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treatment rate (d_2) of 0.006 cells/day. Treatment effects d_2 is a preliminary procedure of treatment or early steps of prevention in the healing of brain tumor patients. Population of susceptible cells using $y([t])$ and $y([t-1])$ with population capacity (R_2) of 1,232 cells/ml/day. The lower threshold (β_1) and upper threshold (β_2) population rate of susceptible cells are 1,5 and 0,2 cell/ml/day. There is a rate of change of susceptible cells $y(t)$ into sensitive cells $x(t)$ of γ_1 [1].

It is known that the exact solution with reference to the settlement [2] on logistical problems is obtained:

$$x(t) = x(t)e^{((p+r_1R_1)-d_1x([t])-\alpha_2r_1x([t-1])-\gamma_1y([t-1]))t}\left(1 - \beta_1r_2\,y(t)\left(\frac{e^{((p+r_1R_1)-d_1x([t])-\alpha_2r_1x([t-1])-\gamma_1y([t-1]))t}-1}{(p+r_1R_1)-d_1x([t])-\alpha_2r_1x([t-1])-\gamma_1y([t-1])}\right)\right)^{-1} \tag{2}$$

$$y(t) = y(t)e^{\{(p+r_1R_1)-d_1x(t)-\alpha_2r_1x(t-1)-\gamma_1y(t-1)\}t}\left(1 - \beta_1r_2\,y(t)\left(\frac{e^{\{r_2R_2-\beta_2r_2y(t-1)+\gamma_1x(t)-d_2y(t)\}t}-1}{r_2R_2-\beta_2r_2y(t-1)+\gamma_1x(t)-d_2y(t)}\right)\right)^{-1}$$

with,

$$(p+r_1R_1)-d_1x([t])-\alpha_2r_1x([t-1]) - \gamma_1y([t-1]) \neq 0$$

$$r_2R_2-\beta_2r_2y(t-1)+\gamma_1x(t)-d_2y(t) \neq 0$$

2. THEORITICAL REVIEW

2.1. System of Nonlinear Differential Equations Depends on Time

The System of Nonlinear Differential Equations Depends on Time
The ordinary differential equation is a differential equation containing the derivatives of the dependent variable on one independent variable. Ordinary differential equations of the form $F(t, y, \dot{y}, \ddot{y}, \dots, \dot{y}^n) = 0$ are said to be linear if F is linear in the variables l $t, y, \dot{y}, \ddot{y}, \dots, \dot{y}^n$ [3]. In general linear differential equations can be given as follows:

$$a_n(x)y^n + a_{n-1}(x)y^{n-1} + \cdots + a_1(x)\dot{y} + a_0(x)y = f(x) \tag{1}$$

Equation (1) is the n-order differential equation is said to be linear if it has the following characteristics:
a. The dependent variable and its derivative are only one degree.
b. There is no multiplication between the dependent variable and its derivative.
c. The dependent variable is not a transcendent function.

2.2. Runge Kutta Fehlberg Method

According to [4] the Runge Kutta Fehlberg method is the fifth-order Runge Kutta method which has six function evaluations and can achieve accurate accuracy by yielding almost a value close to the analytical settlement value. The general formula of the Fifth Order Runge Kutta method is as follows:

$$y_{i+1} = y_i + \sum_{j=1}^{6} b_jk_j$$

with $j = 1, 2, 3, \dots, 6$; b_j is a constant and k_j is an evaluation function obtained from:

$$k_j = \Delta x\, f(x_i + c_m\Delta x y_i + a_{m1}k_1 + a_{m2}k_2 + \cdots + a_{mm}k_m)$$

Δx is a step size expressed by $\Delta x = x_{i+1} - x_i$ while c_m and a_{mr} are constants with:

$$c_m = \sum_{r=0}^{m} a_{mr}$$

Furthermore, the method of Runge Kutta Fehlberg [5] is formulated as follows:

$$y_{i+1} = y_i + \frac{16}{135}k_1 + \frac{6656}{12825}k_3 + \frac{28561}{56430}k_4 - \frac{9}{50}k_5 + \frac{2}{55}k_6$$

with

$$k_1 = \Delta x f(x_i, y_i)$$

$$k_2 = \Delta x f\left(x_i + \frac{1}{4}\Delta x, y_i + \frac{1}{4}k_1\right)$$

$$k_3 = \Delta x f\left(x_i + \frac{3}{8}\Delta x, y_i + \frac{3}{32}k_1 + \frac{9}{32}k_2\right)$$

$$k_4 = \Delta x f\left(x_i + \frac{12}{13}\Delta x, y_i + \frac{1932}{2197}k_1 - \frac{7200}{2197}k_2 + \frac{7296}{2197}k_3\right)$$

$$k_5 = \Delta x f\left(x_i + \Delta x, y_i + \frac{439}{216}k_1 - 8k_2 + \frac{3680}{513}k_3 - \frac{845}{4104}k_4\right)$$

$$k_6 = \Delta x f\left(x_i + \frac{1}{2}\Delta x, y_i - \frac{8}{27}k_1 + 2k_2 - \frac{3544}{2565}k_3 + \frac{1859}{4104}k_4 - \frac{11}{40}k_5\right)$$

2.3. Error

In numerical methods always used value almost to find a solution that approximates the original solution or can be called a numerical solution. This is the value that causes errors. Errors occur for several reasons:

a. From observation
b. From ignoring something
c. From the tool used
c. From the numerical method used
Error defined as:

$$\varepsilon = |x - x_{t+1}| \quad (4)$$

Where (ε) represents the magnitude of error obtained from the result of almost to the true value. x is a true value and x_{t+1} is an approximation value. The error tolerance is the value of error given so that the value of almost numerical value will be as close as possible to the original value and formulated as:

$$|x - x_{t+1}| < \delta \quad (5)$$

for $\delta < 0$ [6].

3. DISCUSSION

As follows in equation (1) it appears that the equation is a nonlinear equation shown by $\alpha_1 r_1 x(t)^2$ dan $\beta_1 r_2 y(t)^2$ [7]. Equation (1) can then be modified into logistic equations as follows:

$$\frac{dx(t)}{dt} = \big((p + r_1R_1) - d_1x([t]) - \alpha_2 r_1 x([t-1]) - \gamma_1 y([t-1])\big)x(t) \left(1 - \frac{\alpha_1 r_1 x(t)}{(p + r_1R_1) - d_1x([t]) - \alpha_2 r_1 x([t-1]) - \gamma_1 y([t-1])}\right) \quad (3a)$$

$$\frac{dy(t)}{dt} = \big(r_2R_2 - \beta_2 r_2 y([t-1]) + \gamma_1 x([t]) - d_2 y([t])\big)y(t) \left(1 - \frac{\beta_1 r_2 y(t)}{r_2R_2 - \beta_2 r_2 y([t-1]) + \gamma_1 x([t-1]) - d_2 y([t])}\right) \quad (3b)$$

3.1 Settlement of GBM Brain Tumor Equation Model

3.1.1. Brain Tumor GBM with treatment effect (d_1) and (d_2)

The differential equations of GBM equations (3a) and (3b) with treatment effects (d_1) and (d_2) at interval $t \in [0, 200]$ with initial value $x(0) = x_0$and step size $\Delta t = 1$, then obtained for $n = 1,\ x_0 = 0,\ x_1 = 0{,}35$, and $y_0 = 0$ as follows:

$$k_1 = \big((0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0\big)x_1 \left(1 - \frac{0{,}51 \cdot 0{,}08x_1}{(0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0}\right)$$

$$= 0.120414$$

$$k_2 = \left((0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0\right)$$

$$\left(x_1 + \frac{k_1}{4}\right)\left(1 - \frac{0{,}51 \cdot 0{,}08\left(x_1 + \frac{k_1}{4}\right)}{(0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0}\right)$$

$$= 0.13030395635494$$

$$k_3 = \left((0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0\right)$$

$$\left(x_1 + \left(\left(\frac{3}{32}\right)k_1 + \left(\frac{9}{32}\right)k_2\right)\right)$$

$$\left(1 - \frac{0{,}51 \cdot 0{,}08\left(x_1 + \left(\left(\frac{3}{32}\right)k_1 + \left(\frac{9}{32}\right)k_2\right)\right)}{(0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0}\right)$$

$$= 0.136127883420054$$

$$k_4 = \left((0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0\right)$$

$$\left(x_1 + \left(\left(\frac{1932}{2197}\right)k_1 - \left(\frac{7200}{2197}\right)k_2 + \left(\frac{7296}{2197}\right)k_3\right)\right)$$

$$\left(1 - \frac{0{,}51 \cdot 0{,}08\left(x_1 + \left(\left(\frac{1932}{2197}\right)k_1 - \left(\frac{7200}{2197}\right)k_2 + \left(\frac{7296}{2197}\right)k_3\right)\right)}{(0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0}\right)$$

$$= 0.162888195593675$$

$$k_5 = \left((0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0\right)$$

$$\left(x_1 + \left(\left(\frac{439}{216}\right)k_1 - 8k_2 + \left(\frac{3680}{513}\right)k_3 - \left(\frac{845}{4104}\right)k_4\right)\right)$$

$$\left(1 - \frac{0{,}51 \cdot 0{,}08\left(x_1 + \left(\left(\frac{439}{216}\right)k_1 - 8k_2 + \left(\frac{3680}{513}\right)k_3 - \left(\frac{845}{4104}\right)k_4\right)\right)}{(0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0}\right)$$

$$= 0.167457989232798$$

$$k_6 = \left((0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0\right)$$

$$\left(x_1 - \left(\left(\frac{8}{27}\right)k_1 - (2k_2) + \left(\frac{3544}{2565}\right)k_3 - \left(\frac{1859}{4104}\right)k_4 + \left(\frac{11}{40}\right)k_5\right)\right)$$

$$\left(1 - \frac{0{,}51 \cdot 0{,}08\left(x_1 - \left(\left(\frac{8}{27}\right)k_1 - (2k_2) + \left(\frac{3544}{2565}\right)k_3 - \left(\frac{1859}{4104}\right)k_4 + \left(\frac{11}{40}\right)k_5\right)\right)}{(0{,}192 + 0{,}08 \cdot 4{,}704) - 0{,}6x_1 - 0{,}555 \cdot 0{,}08x_0 - 0{,}01y_0}\right)$$

$$= \quad 0.141539080962147$$

So the x_2 value of the equation for $\Delta t = 1$ is:

$$x_2 = \quad x_1 + \left(\left(\frac{16}{135}\right)k_1 + \left(\frac{6656}{12825}\right)k_3 + \left(\frac{28561}{56430}\right)k_4 - \left(\frac{9}{50}\right)k_5 + \left(\frac{2}{55}\right)k_6\right)(1)$$

$$= \quad 0.492368760703149$$

Next, for $t = 1, x_1 = 0.35$, $y_1 = 0.25$, and $y_0 = 0$ is:

$$k_1 = \quad (0.10348 - 0.0168y_0 + 0.01x_1 - 0.06y_1)y_1$$

$$\left(1 - \frac{0.126y_1}{(0.10348 - 0.0168y_0 + 0.01x_1 - 0.06y_1)}\right)$$

$$= \quad 0.0255845$$

$$k_2 = \quad (0.10348 - 0.0168y_0 + 0.01x_1 - 0.06y_1)\left(y_1 + \frac{k_1}{4}\right)$$

$$\left(1 - \frac{0.126\left(y_1 + \frac{k_1}{4}\right)}{(0.10348 - 0.0168y_0 + 0.01x_1 - 0.06y_1)}\right)$$

$$= \quad 0.026218403375271$$

$$k_3 = \quad (0.10348 - 0.0168y_0 + 0.01x_1 - 0.06y_1)\left(y_1 + \left(\left(\frac{3}{32}\right)k_1 + \left(\frac{9}{32}\right)k_2\right)\right)$$

$$\left(1 - \frac{0.126\left(y_1 + \left(\left(\frac{3}{32}\right)k_1 + \left(\frac{9}{32}\right)k_2\right)\right)}{(0.10348 - 0.0168y_0 + 0.01x_1 - 0.06y_1)}\right)$$

$$= \quad 0.02655260871906$$

$$k_4 = \quad (0.10348 - 0.0168y_0 + 0.01x_1 - 0.06y_1)\left(y_1 + \left(\left(\frac{3}{32}\right)k_1 + \left(\frac{9}{32}\right)k_2\right)\right)$$

$$\left(1 - \frac{0.126\left(y_1 + \left(\left(\frac{3}{32}\right)k_1 + \left(\frac{9}{32}\right)k_2\right)\right)}{(0.10348 - 0.0168y_0 + 0.01x_1 - 0.06y_1)}\right)$$

$$= \quad 0.028032080984403$$

$$k_5 = \quad (0.10348 - 0.0168y_0 + 0.01x_1 - 0.06y_1)$$

$$\left(y_1 + \left(\left(\frac{1932}{2197}\right)k_1 - \left(\frac{7200}{2197}\right)k_2 + \left(\frac{7296}{2197}\right)k_3\right)\right)$$

$$\left(1-\frac{0.126\left(y_1+\left(\left(\frac{1932}{2197}\right)k_1-\left(\frac{7200}{2197}\right)k_2+\left(\frac{7296}{2197}\right)k_3\right)\right)}{(0.10348-0.0168y_0+0.01x_1-0.06y_1)}\right)$$

$$= \quad 0.028248863331640$$

$$k_6 = \quad (0.10348-0.0168y_0+0.01x_1-0.06y_1)$$

$$\left(y_1-\left(\left(\frac{8}{27}\right)k_1-(2k_2)+\left(\frac{3544}{2565}\right)k_3-\left(\frac{1859}{4104}\right)k_4+\left(\frac{11}{40}\right)k_5\right)\right)$$

$$\left(1-\frac{0.126\left(y_1-\left(\left(\frac{8}{27}\right)k_1-(2k_2)+\left(\frac{3544}{2565}\right)k_3-\left(\frac{1859}{4104}\right)k_4+\left(\frac{11}{40}\right)k_5\right)\right)}{(0.10348-0.0168y_0+0.01x_1-0.06y_1)}\right)$$

$$= \quad 0.026881545429889$$

So the y_2 value of the equation for $\Delta t = 1$ is:

$$y_2 = \quad y_1+\left(\left(\frac{16}{135}\right)k_1+\left(\frac{6656}{12825}\right)k_3+\left(\frac{28561}{56430}\right)k_4-\left(\frac{9}{50}\right)k_5+\left(\frac{2}{55}\right)k_6\right)(1)$$

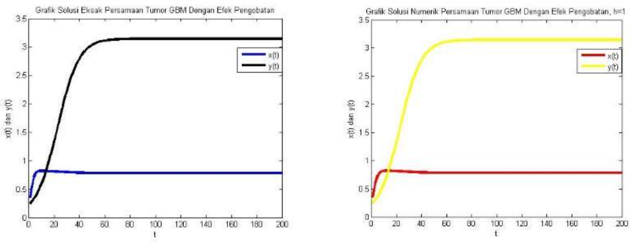
$$= \quad 0.276893316111701$$

The results of numerical solutions, exact solutions, and errors (ε) for equations (3a) and (3b) are given in Table 1.

Table 1. Numerical solutions, exact solutions, and error at equations (3a) and (3b) with treatment effects (d_1) and (d_2)

t	Runge Kutta Fehlberg Method		Exact Solution		Error	
	x_{t+1}	y_{t+1}	$x(t)$	$y(t)$	$\lvert x_{t+1}-x(t)\rvert$	$\lvert y_{t+1}-y(t)\rvert$
$t=0$	0.35	0.25	0.35	0.25	0	0
$t=50$	0.7857699184338	3.0356904749925	0.7857699188538	3.0356904541396	0.00000000042	0.0000000208526
$t=100$	0.7835318957545	3.1444950346134	0.7835318957556	3.1444950345625	0.00000000000	0.0000000000509
$t=150$	0.7835270798256	3.1447246942812	0.7835270798256	3.1447246942811	10^{-13}	0.0000000000001
$t=200$	0.7835270700574	3.1447251600810	0.7835270700574	3.1447251600810	10^{-13}	10^{-13}

Simulation of GBM brain tumor model with the treatment effect given was for $t \in [0, 200]$ and the susceptible tumor cell cells $x(t)$ and $y(t)$ were as follows:



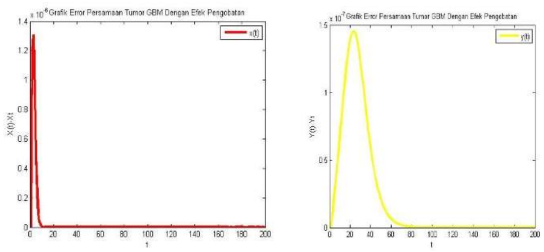
(a) (b)

Figure 1. (a) Exsact Solution of Brain Tumor GBM (b) Numerical Solution of Brain Tumor GBM

Figure 1 (a) explains the growth graph of tumor cells sensitive $x(t)$ from the large error of tolerance given by $\delta = 10^{-7}$it is found that the equation of tumor cells that are sensitive $x(t)$ will be stable on day 141 to day 200 with large cells tumor is between 0,7835270999203 cells/ml to 0,7835270705365 cells/ml.

In the growth of susceptible tumor cells $y(t)$, it is found that the growth of tumor cells susceptible $y(t)$ will be stable on day 167 to day 200 with large cells tumor is between 3,14472510434 cells/ml up to 3.144725160081 cells/ml.

Figure 1 (b) describes numerical rate movement in population growth of sensitive tumor cells $x(t)$ and susceptible cells $y(t)$ using Runge Kutta Fehlberg method at rate $\Delta t = 1$ at $t \in [0, 200]$. Furthermore, the error for equation problems (3a) and (3b) is given in the following Figure 2.



(a) (b)

Figure 2. (a) *Error* Chart $|x_t - x(t)|$ depend on Time (b) *Error* Chart r $|y_t - y(t)|$ depend on Time

Figure 2 (b) describes the magnitude of error in the case of the growth of susceptible cells to tumor $y(t)$. Figure 2 (b) shows that from the given error of tolerance equal to $\delta = 10^{-7}$ it is found that the equation of susceptible tumor cells y(t) will be stable at the 34th iteration until the 200th iteration with the error rate being between 0,0000000976556 to 10^{-13}.

A comparison of the exact solution and the numerical solution using the Runge Kutta Fehlberg equation is given in the following Figure:

The comparison between the exact solution and the numerical solution in Figure 3.2 explains that the solution approach by the Runge Kutta Fehlberg method can be used to approach the exact solution of equations (1) with error tolerance $\delta = 10^{-7}$.

3.2.2. Brain Tumor GBM without treatment effect (d_1)

The results of numerical solutions, exact solutions, and errors (ε) for equations (3a) and (3b) are when $d_1 = 0$ given in Table 2.

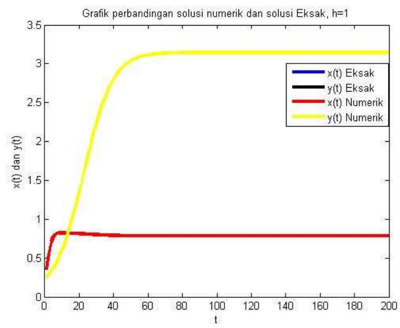
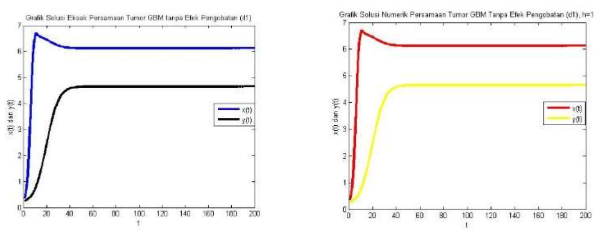


Figure 3. Comparison between the exact solution and the numerical solution chart

Simulation of GBM brain tumor model without the treatment effect d_1 given for $t \in [0, 200]$ were as Figure 4.



(a) (b)

Figure 4. (a) Exact Solution of Brain Tumor GBM (b) Numerical Solution of Brain Tumor GBM

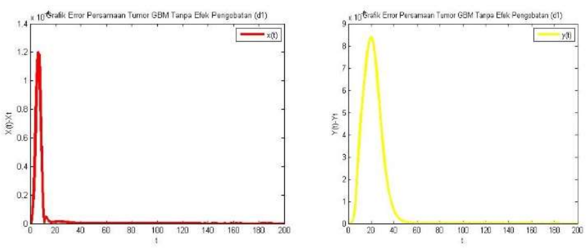
Table 2. Numerical solutions, exact solutions, and error at equations (3a) and (3b) without treatment effects (d_1)

t	Runge Kutta Fehlberg Method		Exact Solution		Error	
	x_{t+1}	y_{t+1}	$x(t)$	$y(t)$	$\lvert x_{t+1}-x(t)\rvert$	$\lvert y_{t+1}-y(t)\rvert$
$t=0$	0.35	0.25	0.35	0.25	0	0
$t=50$	6.1262809343562	4.6433032063880	6.1262809569039	4.6433031358394	0.000000000225477	0.000000000705486
$t=100$	6.1242484819103	4.6534031735414	6.1242484819109	4.6534031735398	0.000000000000006	0.000000000000015
$t=150$	6.1242484146771	4.6534035069593	6.1242484146771	4.6534035069593	10^{-13}	10^{-13}
$t=200$	6.1242484146748	4.6534035069703	6.1242484146748	4.6534035069703	10^{-13}	10^{-13}

Figure 4 (a) explains the growth graph of tumor cells sensitive $x(t)$ without treatment effect d_1. From the large error of tolerance given by $\delta = 10^{-7}$it is found that the equation of tumor cells that are sensitive $x(t)$ will be stable on day 99 to day 200 with large cells tumor is between 6,1242484819109 sel/ml to 6,1242484146748 sel/ml.

In the growth of susceptible tumor cells $y(t)$, it is found that the growth of tumor cells susceptible $y(t)$ will be stable on day 119 to day 200 with large cells tumor is between 4,6534035003691 sel/ml to 4,6534035069703 sel/ml.

Figure 4 (b) describes numerical rate movement in population growth of sensitive tumor cells $x(t)$ without treatment effect d_1 and susceptible cells $y(t)$ using Runge Kutta Fehlberg method at rate $\Delta t = 1$ at $t \in [0, 200]$. Furthermore, the error for equation problems (3a) and (3b) is given in the following Figure:



a)

(a) (b)

Figure 5. (a) *Error* Chart $|x_t - x(t)|$ depend on Time (b) *Error* Chart r $|y_t - y(t)|$ depend on Time

Figure 5 (a) describes the error in the case of growth of tumor cells that are sensitive $x(t)$ without d_1, it is found that the equation of sensitive tumor cells $x(t)$ will be stable at the 43th iteration until the 200th iteration with the error rate being between 0,0000000953660 to 10^{-13}.

Figure 5 (b) describes the magnitude of error in the case of the growth of susceptible cells to tumor $y(t)$. Figure 3.5 (b) shows that from the given error of tolerance equal to $\delta = 10^{-7}$ it is found that the equation of susceptible tumor cells $y(t)$ will be stable at the 49th iteration until the 200th iteration with the error rate being between 0,0000000872009 to 10^{-13}.

A comparison of the exact solution and the numerical solution using the Runge Kutta Fehlberg equation is given in the figure 6.

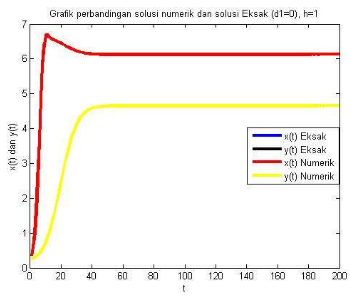


Figure 6. Comparison Between the Exact Solution and the Numerical Solution Chart

The comparison between the exact solution and the numerical solution in Figure 6 explains that the solution by using numerical method with error tolerance $\delta = 10^{-7}$. Show that the solution approach by the Runge Kutta Fehlberg method can be used to approach the exact solution of equations (1) without treatment efffect d_1 reach 10^{-13}.

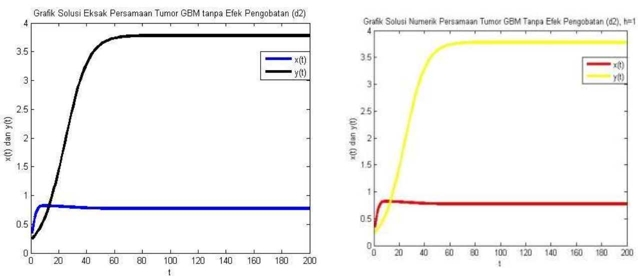
Table 3. Numerical solutions, exact solutions, and error at equations (3a) and (3b) without treatment effects (d_1)

t	Runge Kutta Fehlberg Method		Exact Solution		Error	
	x_{t+1}	y_{t+1}	$x(t)$	$y(t)$	$\lvert x_{t+1} - x(t)\rvert$	$\lvert y_{t+1} - y(t)\rvert$
$t = 0$	0.35	0.25	0.35	0.25	0	0
$t = 50$	0.7774610256746	3.6254604084358	0.7774610246428	3.6254604418472	0.0000000006682	0.0000000333886
$t = 100$	0.7742137000678	3.7830188641103	0.7742137000696	3.78301886402427	0.0000000000018	0.0000000000856
$t = 150$	0.7742070221669	3.7833351118168	0.7742070221669	3.7833351118116	10^{-13}	0.0000000000002
$t = 200$	0.7742070094016	3.7833357163176	0.7742070094016	3.7833357163176	10^{-13}	10^{-13}

3.2.3. Brain Tumor GBM without Treatment Effect (d_2)

The results of numerical solutions, exact solutions, and errors (ε) for equations (3a) and (3b) are when $d_2 = 0$ given in the Table 3.

Simulation of GBM brain tumor model without the treatment effect d_2 given for $t \in [0, 200]$ were as shown in Figure 7.



(a)

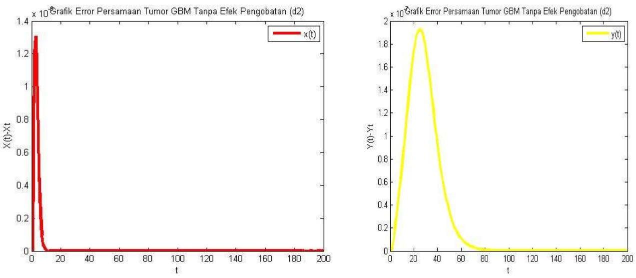
(a) (b)

Figure 7. (a) Exsact Solution of Brain Tumor GBM (b) Numerical Solution of Brain Tumor GBM

Figure 7 (a) explains the growth graph of tumor cells sensitive $x(t)$ without treatment effect d_2. From the large error of tolerance given by $\delta = 10^{-7}$it is found that the equation of tumor cells that are sensitive $x(t)$ will be stable on day 135 to day 200 with large cells tumor is between 0,7742070930267 sel/ml to 0,7742070094016 sel/ml.

In the growth of susceptible tumor cells $y(t)$, it is found that the growth of tumor cells susceptible $y(t)$ will be unstable to day 200 with large cells tumor is 3,7833357163176 sel/ml.

Figure 4 (b) describes numerical rate movement in population growth of sensitive tumor cells $x(t)$ without treatment effect d_2 and susceptible cells $y(t)$ using Runge Kutta Fehlberg method at rate $\Delta t = 1$ at $t \in [0, 200]$. Furthermore, the error for equation problems (3a) and (3b) is given in the following Figure:



(a) (b)

Figure 8. (a) *Error* Chart $\lvert x_t - x(t)\rvert$ depend on Time (b) *Error* Chart r $\lvert y_t - y(t)\rvert$ depend on Time

Figure 8 (a) describes the error in the case of growth of tumor cells that are sensitive $x(t)$, it is found that the equation of sensitive tumor cells $x(t)$ will be stable at the 7th iteration until the 200th iteration with the error rate being between 0,0000000965519 to 10^{-13}.

Figure 8 (b) describes the magnitude of error in the case of the growth of susceptible cells to tumor $y(t)$ without d_2. Figure 8 (b) shows that from the given error of tolerance equal to $\delta = 10^{-7}$ it is found that the equation of susceptible tumor cells $y(t)$ will be stable at the 40th iteration until the 200th iteration with the error rate being between 0,0000000918667to 10^{-13}.

A comparison of the exact solution and the numerical solution using the Runge Kutta Fehlberg equation is given in the following Figure 9.

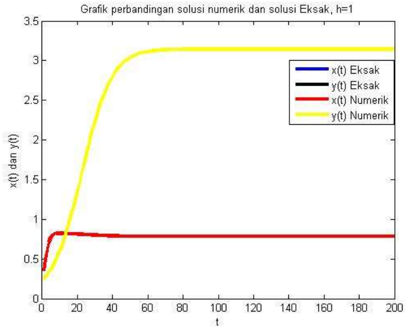


Figure 9. Comparison Between the Exact Solution and the Numerical Solution Chart

The comparison between the exact solution and the numerical solution in Figure 3.6 explains that the solution by using numerical method with error tolerance $\delta = 10^{-7}$. Show that the solution approach by the Runge Kutta Fehlberg method can be used to approach the exact solution of equations (1) without treatment efffect d_2 reach 10^{-13}.

CONCLUSSION

A numerical solution to the effect of treatment using the Runge Kutta Fehlberg method is used to describe numerical behavior in a nonlinear differential equation. The numerical resolution of the GBM brain tumor model results in an approach with a large error of 10^{-13} to the 200th day with $\Delta t = 1$. The GBM brain tumor model that is affected by treatment and without the effect of treatment gives different results. That is, the effect of treatment (d_1) and (d_2) on patients affected by GBM brain tumor will have an impact on tumor growth rate.

REFERENCES

[1] F. Bozkurt, Mathematical Modeling and Stability Analysis of the Brain Tumor Glioblastoma Multiforme (GBM), International Journal of Modeling and Optimization, vol. 4, no. 4, pp. 257-262, 2014.

[2] J. W. Bruce, Exact Solution For Fractional Logistic, Physica A: Statistical Mechanics and its Applications, 2015, pp. 103-108.

[3] S. B. Waluya, Persamaan Diferensial, Yogyakarta: Graha Ilmu, 2006.

[4] E. Kreyzig, Advanced Engineering Mathematics, New York: John Wiley &Sons Inc, 2003.

[5] U. Pagalay and Muhlish, Numerical Solution for Immunology Tuberculosis Model Using Runge Kutta Fehlberg and Adams Bashforth Moulton Method, Jurnal Teknologi (Sains and Engineering), vol. 78, no. 5, pp. 369-372, 2016.

[6] S. D. Conte, Dasar-Dasar Analisis Numerik. Jakarta: Erlangga, 1993.

[7] J. E. Schmitz, A. R. Kansal, and S. Torquato, Acellular automaton model of brain tumor treatment and resistance, Journal of Theoretical Medicine, vol. 4, no. 4, pp.223–239, 2002.