

Numerical method to minimize tumor density and drug side effects in cancer treatment regimen

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Abstract

A genetic disorder resulting from epigenetic or genetic alterations in the somatic cells is described as cancer and has uncontrolled cell growth known as tumor. In this paper, Numerical Method is developed based on Patade and Bhalekar approach for the solution of optimal control model of cancer treatment regimen using forward-backward sweep methods. Stability and convergence of the new numerical method are discussed and is found to be of order four, stable and convergent. Results obtained in this study shows that, a high drug strength is infused which destroyed more cancer cells, then the dosage is reduced to minimal level. The drug infusion time is shortened which brings the drug strength to zero in order to reduce toxicity of the drugs. In undergoing cancer treatment regimen using the new numerical method, the destruction of the host normal cells is minimized and simultaneously maximize destruction of cancer cells.

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1 Introduction

Medically termed as a malignant neoplasm, cancer is a genetic disorder that results from genetic or epigenetic alterations in the somatic cells and has uncontrolled cell growth known as tumor [3]. This uncontrolled growth of cells can be attributed to mutations in the signals that regulate the cell cycle of growth and division [9]. Cancer is one of the leading causes of death in the world [9].

There are many things that may increase the chance of having cancer in different parts of the body which include tobacco consumption, poor diet, obesity, lack of physical activity, excessive drinking of alcohol, exposure to ionizing radiation, environmental pollutants, and infection [3], [11]. Inherited genetic defects from patient's parents are also responsible for cancer such as breast, ovarian, colorectal, prostate, skin and melanoma cancer [3]. Cancer can also be resulted from infections which include but not limited to hepatitis B, human papillomavirus infection, Epstein Barr virus, hepatitis C, human papillomavirus infection, immunodeficiency virus (HIV), helicobacter pylori. These factors are at least partly responsible for changing the genes [11].

Attempts to cure or palliate cancer is done through surgery, radiotherapy or chemotherapy. Chemotherapy treatments are type of therapy that may be used to cure or produce palliative relief and symptomatic relaxation in the advance stages of cancer [13]. Chemotherapy is widely used to manage cancer, but its use is restricted for the adverse side-effects of most of the chemotherapeutic drugs [9]. The toxic by-products of some chemotherapeutic drugs are deposited mainly in the liver producing hepatotoxicity, leading to many side-effects like loss of appetite, nausea, vomiting, diarrhea, abdominal cramps and constipation, anemia, fatigue, hyperthermia, loss of hair, etc [9].

In chemotherapy, chemicals are used to treat cancer by stopping or slowing the growth of cancer cells or killing cancer cells or shrink tumors that is causing pain and other problems, but have severe side effects [3], [11]. Chemotherapy regimen involve patients been administered with anticancer drug in cyclic way, during regular weekly or bi-weekly sessions. After the completion of certain cyclic session, treatment is stopped for several fixed periods to allow the patient to rest and their body to re-establish from the toxic effects of anticancer drugs [13]. Cancer cells normally develop new cells quickly than the normal cells and that is why they are the main target of chemotherapy drugs. But, chemotherapy medicine cannot differentiate between the normal cells and the tumor cells, therefore, both healthy and tumor cells are damaged together and this causes adverse side effect. So chemotherapy drugs are given in such a way to balance between curing or controlling the disease by destroying the tumor cells and lessening the side effects on the normal

cells. Chemotherapy is preferred by many for managing cancer, because, most normal cells will recover from the effects of chemo over time, but cancer cells do not recover from the effects of chemo [11].

This study considered the numerical solution to optimal control model for cancer treatment regimen of the form

$$\min_u J[z(t), u(t)] = \int_{t_0}^{T_f} f(t, z(t), u(t)) dt, \quad (1.1)$$

subject to the dynamic system

$$z' = g(t, z(t), u(t)), \quad z(t_0) = x_0, \quad (1.2)$$

where $z(t)$ and $u(t)$ are real valued functions, f and g are differentiable functions. Optimal Control (OC) has been applied in the field of Ordinary Differential Equations (ODEs), Partial Differential Equations (PDEs), Stochastic differential equations, integro differential equations, combination of discrete and continuous systems, to solve problems of physical systems, especially in the areas of aerospace, sciences, engineering, economics, management, biology and medicine [1], [2], [14], [15], [16].

A continuous extended one-step trapezoidal methods is considered by Garret [5] for the solution of optimal control problems, where the control variables are approximated by polynomial functions. Adamu [1] solved optimal control problems by presenting a numerical approach using the indirect method known as the backward forward sweep method. Adamu et al., [15] and Aduroja et al., [15] used block collocation approach to solve optimal control problems using Forward-Backward sweep method.

Lenhart and Workman [7] extensively discussed forward-backward sweep method for the solution of optimal control problem, using 4th order Runge Kutta via Pontryagin's maximum principle. This approach proved to be successful for the solution of optimal control problems, but the derivation of the classical Runge-Kutta method is tedious and complex and the method misbehave when handling stiff problem.

Runge-Kutta (R-K) formulas are among the oldest schemes in numerical analysis [8] and are an important family of iterative methods for the approximation of solutions of ODE's [6], [8], [10]. Runge-Kutta methods are typically single-step methods, however, with multiple stages per step which were first studied by Carle Runge and Martin Kutta [6]. Modern developments are mostly due to John Butcher

improvement and introduction of Butcher tableau. It is easier to write the program for the implementation of this method.

Existing Runge-Kutta schemes suffer from stiffness and computational complexity. Therefore, this study considers a single step trapezoidal method with hybrid point for the development of iterative method following Patade and Bhalekar approach for the solution of optimal control problems using Forward Backward Sweep method.

2 Method

2.1 Development of linear multistep method

This study consider first Boubaker polynomials of the form

$$z(t) = \sum_{n=0}^3 a_n B_n(t), \quad (2.1)$$

where $t \in [a, b]$, $a_n \in \mathbb{R}$ are unknown parameters to be determined. The first Boubaker terms are:

$$\begin{aligned} B_0(t) &= 1, \quad B_1(t) = t, \\ B_2(t) &= t^2 + 2, \quad B_3(t) = t^3 + t. \end{aligned}$$

Interpolating and collocating (2.1) using the points

$$z(t_{n+j}) = z_{n+j}, \quad j = 0; \quad z'(t_{n+j}) = f_{n+j}, \quad j = 0, \frac{51}{100}, 1$$

gives a system of equations

$$TA = U, \quad (2.2)$$

where

$$T = \begin{bmatrix} 3 & 2t_n & t_n^2 & t_n^3 \\ 0 & 2 & 2t_n & 3t_n^2 \\ 0 & 2 & 2t_{n+\frac{51}{100}} & 3t_{n+\frac{51}{100}}^2 \\ 0 & 2 & 2t_{n+1} & 3t_{n+1}^2 \end{bmatrix},$$

$$A = [a_0, a_1, a_2, a_3]^T, \quad U = \left[z_n, f_n, f_{n+\frac{51}{100}}, f_{n+1} \right]^T.$$

Solving the system (2.2) for the unknown parameters and substitute the results into

the approximate solution (2.1) to get the continuous scheme

$$z_{n+t} = \alpha_0(t)z_n + \beta_0(t)hf_n + \beta_{\frac{51}{100}}(t)hf_{n+\frac{51}{100}} + \beta_1(t)hf_{n+1}, \quad (2.3)$$

where the coefficients $\alpha_0(t), \beta_0(t), \beta_{\frac{51}{100}}(t), \beta_1(t)$ are:

$$\alpha_0(t) = 1, \quad \beta_0(t) = \frac{100}{153}t^3 - \frac{151}{102}t^2 + t,$$

$$\beta_{\frac{51}{100}}(t) = \frac{5000}{2499}t^2 - \frac{10000}{7497}t^3, \quad \beta_1(t) = \frac{100}{147}t^3 - \frac{51}{98}t^2.$$

Evaluating Equation (2.3) at point z_{n+1} to get the discrete scheme

$$z_{n+1} = z_n + \frac{h}{14994} \left(2597f_n + 10000f_{n+\frac{51}{100}} + 2397f_{n+1} \right). \quad (2.4)$$

2.2 Development of Runge-Kutta like method

Equation (2.4) can be written as

$$z_{n+1} = z_n + \frac{53h}{306}f_n + \frac{5000h}{7497}f_{n+\frac{51}{100}} + \frac{47h}{294}f_{n+1}. \quad (2.5)$$

Let

$$z = z_{n+1}, \quad (2.6)$$

$$z_0 = f = z_n + \frac{53h}{306}f(t_n, z_n) + \frac{5000h}{7497}f\left(t_{n+\frac{51}{100}}, z_{n+\frac{51}{100}}\right), \quad (2.7)$$

$$N(z_{n+1}) = N(z) = \frac{47h}{294}f(t_{n+1}, z_{n+1}). \quad (2.8)$$

Using 3-terms solution in Daftardar-Gejji and Jafari method series, then

$$z = z_0 + z_1 + z_2, \quad (2.9)$$

where $z_1 = N(z_0)$ and $z_2 = N(z_0 + z_1) - N(z_0)$. Equation (2.9) becomes

$$z = z_0 + N(z_0) + N(z_0 + z_1) - N(z_0)$$

and simplifying it to get

$$z = z_0 + N(z_0 + N(z_0)). \quad (2.10)$$

Substituting (2.6) and (2.7) into (2.10) to get

$$\begin{aligned} z_{n+1} = z_n + \frac{53}{306}hf(t_n, z_n) + \frac{5000}{7497}hf\left(t_{n+\frac{51}{100}}, z_{n+\frac{51}{100}}\right) \\ + N\left(z_n + \frac{53}{306}hf(t_n, z_n) + \frac{5000}{7497}hf\left(t_{n+\frac{51}{100}}, z_{n+\frac{51}{100}}\right) + N\left(z_n + \frac{53}{306}hf(t_n, z_n) + \frac{5000}{7497}hf\left(t_{n+\frac{51}{100}}, z_{n+\frac{51}{100}}\right)\right)\right). \end{aligned} \quad (2.11)$$

$n = 0, 1, 2, \dots$

This can be simplified, by considering Equation (2.8) as

$$\begin{aligned} z_{n+1} = z_n + \frac{53}{306}hf(t_n, z_n) + \frac{5000}{7497}hf\left(t_{n+\frac{51}{100}}, z_{n+\frac{51}{100}}\right) \\ + \frac{47h}{294}f\left(t_{n+1}, z_n + \frac{53}{306}hf(t_n, z_n) + \frac{5000}{7497}hf\left(t_{n+\frac{51}{100}}, z_{n+\frac{51}{100}}\right)\right). \end{aligned} \quad (2.12)$$

Equation (2.12) reduces to

$$z_{n+1} = z_n + \frac{h}{14994}(2597k_1 + 10000k_2 + 2397k_4), \quad (2.13)$$

where

$$\begin{aligned} k_1 &= f(t_n, z_n), \quad k_2 = f\left(t_{n+\frac{51}{100}}, z_{n+\frac{51}{100}}\right), \\ k_3 &= f\left(t_{n+1}, z_n + \frac{53h}{306}k_1 + \frac{5000h}{7497}k_2\right), \\ k_4 &= f\left(t_{n+1}, z_n + \frac{53h}{306}k_1 + \frac{5000h}{7497}k_2 + \frac{47h}{294}k_3\right). \end{aligned}$$

Runge-Kutta properties are tested in order to establish that, the new method is not a Runge-Kutta method. The numerical method is written as

$$z_{n+1} = z_n + h(b_1k_1 + b_2k_2 + b_3k_3 + b_4k_4),$$

while k_i is written as

$$k_i = f(t_j + c_1 h, z_j + h(a_{i1}k_1 + a_{i2}k_2 + a_{i3}k_3 + a_{i4}k_4)), i = 1, 2, 3, 4.$$

The following parameters are extracted from the numerical method:

$$b_1 = \frac{53}{306}, b_2 = \frac{5000}{7497}, b_3 = 0, b_4 = \frac{47}{294}; c_1 = 0, c_2 = \frac{51}{100}, c_3 = c_4 = 1;$$

$$a_{11} = a_{12} = a_{13} = a_{14} = a_{21} = a_{22} = a_{23} = a_{24} = 0,$$

$$a_{31} = \frac{53}{306}, a_{32} = \frac{5000}{7497}, a_{33} = a_{34} = 0, a_{41} = \frac{53}{306}, a_{42} = \frac{5000}{7497}, a_{43} = \frac{47}{294}, a_{44} = 0.$$

Thus the Butcher table for the numerical method is

0	0	0	0	0
$\frac{51}{100}$	0	0	0	0
1	$\frac{53}{306}$	$\frac{5000}{7497}$	0	0
1	$\frac{53}{306}$	$\frac{5000}{7497}$	$\frac{47}{294}$	0
	$\frac{53}{306}$	$\frac{5000}{7497}$	0	$\frac{47}{294}$

For Runge-Kutta method, it is necessary that $\sum_{j=1}^4 a_{ij} = c_i$ [4]. From the parameters,

$a_{31} + a_{32} + a_{33} + a_{34} = \frac{253}{306} \neq c_3$. This shows that numerical method is not Runge-Kutta method.

3 Analysis of the numerical method

3.1 Order of the method

Definition 3.1. *The largest integer p such that*

$$\|h^{-1}T_j\| = O(h^p). \quad (3.1)$$

is called the order of the single step method.

Theorem 3.1. *The new numerical method in (2.13) is of order four.*

Proof. We have

$$k_1 = f_n. \quad (3.2)$$

Using second order Taylor's series, we can write k_2 , k_3 and k_4 as

$$k_2 = f_n + \frac{49h}{4}f_{n,t} + \frac{49h}{8}f_{n,z} + \frac{49h^2}{8}f_{n,tt} + \frac{49h^2}{8}f_{n,tz} + \frac{49h^2}{16}f_{n,zz} + \dots \quad (3.3)$$

$$k_3 = f_n + hf_{n,t} + \frac{h^2}{2}f_{n,tt} + \frac{47h^2}{294}f_nf_{n,tz} + \frac{47h}{294}f_nf_{n,z} + \frac{47h^2}{21168}f_n^2f_{n,zz} + \dots \quad (3.4)$$

$$k_4 = f_n + hf_{n,t} + \frac{h^2}{2}f_{n,tt} + W_4 \left[hf_{n,tz} + f_{n,z} + \frac{h}{4}f_nf_{n,zz} \right] + \dots \quad (3.5)$$

where

$$W_4 = \begin{pmatrix} \frac{47h}{294}f_n + \frac{5000h}{7497} \left(f_n + \frac{49h}{4}f_{n,t} + \frac{49h}{8}f_{n,z} + \frac{49h^2}{8}f_{n,tt} + \frac{49h^2}{8}f_{n,tz} + \frac{49h^2}{16}f_{n,zz} \right) \\ + \frac{53h}{306} \left(f_n + hf_{n,t} + \frac{h^2}{2}f_{n,tt} + \frac{47h^2}{294}f_nf_{n,tz} + \frac{47h}{294}f_nf_{n,z} + \frac{47h^2}{21168}f_n^2f_{n,zz} \right) \end{pmatrix},$$

$$f_n = f(t_n, z_n), \quad f_{n,t} = \left(\frac{\partial f(t, z)}{\partial t} \right)_{(t_n, z_n)}, \quad f_{n,z} = \left(\frac{\partial f(t, z)}{\partial z} \right)_{(t_n, z_n)},$$

$$f_{n,tt} = \left(\frac{\partial^2 f(t, z)}{\partial t^2} \right)_{(t_n, z_n)}, \quad f_{n,zz} = \left(\frac{\partial^2 f(t, z)}{\partial z^2} \right)_{(t_n, z_n)},$$

$$f_{n,tz} = \left(\frac{\partial^2 f(t, z)}{\partial t \partial z} \right)_{(t_n, z_n)}.$$

Using (3.2), (3.3), (3.4) and (3.5) in (2.13), we get

$$\begin{aligned} z_{n+1} = z_n + \frac{h}{14994} & \left[2597f_n + 10000 \left(f_n + hf_{n,t} + \frac{h^2}{2}f_{n,tt} + \frac{47h}{294}f_n \left[hf_{n,tz} + f_{n,z} + \frac{h}{4}f_nf_{n,zz} \right] \right) \right. \\ & \left. + 2397 \left(f_n + hf_{n,t} + \frac{h^2}{2}f_{n,tt} + W_4 \left[hf_{n,tz} + f_{n,z} + \frac{h}{4}f_nf_{n,zz} \right] \right) \right] \end{aligned}$$

$$\begin{aligned}
z_{n+1} = & z_n + hf_n + h^2 \left(\frac{587359}{2204118} f_n f_{n,z} + \frac{253}{306} f_{n,t} \right) \\
& + h^3 \left(\frac{587359}{8816472} f_{n,z^2} f_n^2 + \frac{117077}{26449416} f_n f_{n,z}^2 + \frac{587359}{2204118} f_{n,tz} f_n \right. \\
& \quad \left. + \frac{29375}{44982} f_{n,z}^2 + \frac{39997}{29988} f_{n,t} f_{n,z} + \frac{253}{612} f_{n,t^2} \right) \\
& + h^4 \left(\frac{39997}{29988} f_{n,tz} f_{n,t} + \frac{29375}{22491} f_{n,tz} f_{n,z} + \frac{39997}{59976} f_{n,t^2} f_{n,z} \right. \\
& \quad + \frac{29375}{89964} f_{n,z^2} f_{n,z} + \frac{117077}{13224708} f_n f_{n,tz} f_{n,z} + \frac{39997}{119952} f_n f_{n,z^2} f_{n,t} \\
& \quad \left. + \frac{29375}{179928} f_n f_{n,z^2} f_{n,z} + \frac{2224463}{1904357952} f_n^2 f_{n,z^2} f_{n,z} \right) \\
& + h^5 \left(\frac{117077}{7617431808} f_n^3 f_{n,z^2}^2 + \frac{2224463}{1904357952} f_n^2 f_{n,tz} f_{n,z^2} \right. \\
& \quad + \frac{117077}{26449416} f_n f_{n,tz}^2 + \frac{29375}{179928} f_n f_{n,tz} f_{n,z^2} + \frac{29375}{359856} f_n f_{n,z^2}^2 \\
& \quad + \frac{39997}{239904} f_{n,t^2} f_n f_{n,z^2} + \frac{29375}{44982} f_{n,tz}^2 + \frac{29375}{89964} f_{n,tz} f_{n,z^2} \\
& \quad \left. + \frac{39997}{59976} f_{n,t^2} f_{n,tz} \right) + \dots
\end{aligned}$$

The Taylor's series expansion of exact value $z(t)$ about t_n is

$$\begin{aligned}
z(t_{n+1}) = & z_n + hf_n + h^2 \left(\frac{587359}{2204118} f_n f_{n,z} + \frac{253}{306} f_{n,t} \right) \quad (3.6) \\
& + h^3 \left(\frac{587359}{8816472} f_{n,z^2} f_n^2 + \frac{117077}{26449416} f_n f_{n,z}^2 + \frac{587359}{2204118} f_{n,tz} f_n \right. \\
& \quad \left. + \frac{29375}{44982} f_{n,z}^2 + \frac{39997}{29988} f_{n,t} f_{n,z} + \frac{253}{612} f_{n,t^2} \right) + O(h^4).
\end{aligned}$$

The truncation error gives

$$T_{n+1} = x_{i+1} - x(t_{i+1})$$

$$\begin{aligned}
T_{n+1} = & z_n + hf_n + h^2 \left(\frac{587\,359}{2\,204\,118} f_n f_{n,z} + \frac{253}{306} f_{n,t} \right) \\
& + h^3 \left(\frac{587\,359}{8\,816\,472} f_{n,z^2} f_n^2 + \frac{117\,077}{26\,449\,416} f_n f_{n,z}^2 + \frac{587\,359}{2\,204\,118} f_{n,tz} f_n \right. \\
& \quad \left. + \frac{29\,375}{44\,982} f_{n,z}^2 + \frac{39\,997}{29\,988} f_{n,t} f_{n,z} + \frac{253}{612} f_{n,t^2} \right) \\
& + h^4 \left(\frac{39\,997}{29\,988} f_{n,tz} f_{n,t} + \frac{29\,375}{22\,491} f_{n,tz} f_{n,z} + \frac{39\,997}{59\,976} f_{n,t^2} f_{n,z} \right. \\
& \quad + \frac{29\,375}{89\,964} f_{n,z^2} f_{n,z} + \frac{117\,077}{13\,224\,708} f_n f_{n,tz} f_{n,z} + \frac{39\,997}{119\,952} f_n f_{n,z^2} f_{n,t} \\
& \quad \left. + \frac{29\,375}{179\,928} f_n f_{n,z^2} f_{n,z} + \frac{2\,224\,463}{1\,904\,357\,952} f_n^2 f_{n,z^2} f_{n,z} \right) \\
& + h^5 \left(\frac{117\,077}{7\,617\,431\,808} f_n^3 f_{n,z^2}^2 + \frac{2\,224\,463}{1\,904\,357\,952} f_n^2 f_{n,tz} f_{n,z^2} \right. \\
& \quad + \frac{117\,077}{26\,449\,416} f_n f_{n,tz}^2 + \frac{29\,375}{179\,928} f_n f_{n,tz} f_{n,z^2} + \frac{29\,375}{359\,856} f_n f_{n,z^2}^2 \\
& \quad + \frac{39\,997}{239\,904} f_{n,t^2} f_n f_{n,z^2} + \frac{29\,375}{44\,982} f_{n,tz}^2 \\
& \quad \left. + \frac{29\,375}{89\,964} f_{n,tz} f_{n,z^2} + \frac{39\,997}{59\,976} f_{n,t^2} f_{n,tz} \right).
\end{aligned} \tag{3.7}$$

$$\begin{aligned}
T_{n+1} = & h^5 \left(\frac{117\,077}{7\,617\,431\,808} f_n^3 f_{n,z^2}^2 + \frac{2\,224\,463}{1\,904\,357\,952} f_n^2 f_{n,tz} f_{n,z^2} + \frac{117\,077}{26\,449\,416} f_n f_{n,tz}^2 \right. \\
& + \frac{29\,375}{179\,928} f_n f_{n,tz} f_{n,z^2} + \frac{29\,375}{359\,856} f_n f_{n,z^2}^2 + \frac{39\,997}{239\,904} f_{n,t^2} f_n f_{n,z^2} \\
& \left. + \frac{29\,375}{44\,982} f_{n,tz}^2 + \frac{29\,375}{89\,964} f_{n,tz} f_{n,z^2} + \frac{39\,997}{59\,976} f_{n,t^2} f_{n,tz} \right) + O(h^6).
\end{aligned} \tag{3.8}$$

Hence, the new numerical method is of fourth order. $\square$

3.2 Convergence of the numerical method

Definition 3.2 (12). *A single step method is said to be consistent if*

$$\phi(t, z, 0) = f(t, z). \quad (3.9)$$

Definition 3.3. A single step method is said to be regular if the function $\phi(t, z, h)$ is defined and continuous in the domain $a \leq t \leq b, -\infty < z^j < \infty, i = 1, 2, \dots, n, 0 \leq h \leq h_0$ and if there exist a constant L such that

$$\|\phi(t, z, h) - \phi(t, z^*, h)\| \leq L \|z - z^*\|, \quad (3.10)$$

for every $t \in [t_0, b], z, z^* \in (-\infty, \infty), h \in (0, h_0)$ [12].

Theorem 3.2. Suppose the single step method is regular, then the relation (3.9) is a necessary and sufficient condition for the convergence of the single step method [12].

Theorem 3.3. An iterative method (2.13) is said to be convergent by Theorem 3.2 if the following results hold:

- (i) Consistency holds
- (ii) Regularity holds

Proof (Consistency) Consider the increment function in (2.13),

$$\begin{aligned} \phi(z_n, u_n, h) &= h^{-1} \left(\frac{53h}{306} k_1 + \frac{5000h}{7497} k_2 + \frac{47h}{294} k_3 \right) \\ \phi(z_n, u_n, h) &= \frac{1}{14994} (2597k_1 + 10000k_2 + 2397k_4). \end{aligned} \quad (3.11)$$

If $h = 0$, then

$$\phi(z_n, u_n, 0) = f(t, z). \quad (3.12)$$

Therefore, by Definition 3.2, the method (2.13) is consistent.

Proof. (Regularity) Let $k_1^* = f(t_n, z_n^*)$, $k_2^* = f\left(t_{n+\frac{51}{100}}, z_{n+\frac{51}{100}}^*\right)$, $k_3^* = f\left(t_{n+1}, z_n^* + \frac{53h}{306} k_1^* + \frac{5000}{7497} k_2^*\right)$ and $k_4^* = f\left(t_{n+1}, z_n^* + \frac{53h}{306} k_1^* + \frac{5000h}{7497} k_2^* + \frac{47h}{294} k_3^*\right)$ for every $(t, z), (t, z^*) \in S$ and k_n ($n = 1, 2, 3, 4$) are defined in (2.13).

Since $f(t, z)$ is Lipschitz, we have

$$\begin{aligned}
\|k_1 - k_1^*\| &= \|f(t_n, z_n) - f(t_n, z_n^*)\|, \\
&\leq L \|z_n - z_n^*\|, \\
\|k_2 - k_2^*\| &= \left\| f\left(t_n + \frac{51h}{100}, z_n + \frac{51h}{100}\right) - f\left(t_n + \frac{51h}{100}, z_n^* + \frac{51h}{100}\right) \right\|, \\
&\leq L \|z_n - z_n^*\|, \\
\|k_3 - k_3^*\| &= \left\| f\left(t_{n+1}, z_n + \frac{53h}{306}k_1 + \frac{5000h}{7497}k_2\right) \right. \\
&\quad \left. - f\left(t_{n+1}, z_n^* + \frac{53h}{306}k_1^* + \frac{5000h}{7497}k_2^*\right) \right\|, \\
&\leq L \left(1 + \frac{247h}{294}L\right) \|z_n - z_n^*\| \\
\|k_4 - k_4^*\| &= \left\| \begin{aligned} &f\left(t_n + h, z_n + \frac{53h}{306}k_1 + \frac{5000h}{7497}k_2 + \frac{47h}{294}k_3\right) \\ &- f\left(t_n + h, z_n^* + \frac{53h}{306}k_1^* + \frac{5000h}{7497}k_2^* + \frac{47h}{294}k_3^*\right) \end{aligned} \right\|, \\
&\leq L \|z_n - z_n^*\| + L \left(\frac{53h}{306} \|k_1 - k_1^*\| + \frac{5000h}{7497} \|k_2 - k_2^*\| + \frac{47h}{294} \|k_3 - k_3^*\| \right), \\
&\leq L \left(1 + Lh + \frac{11\,609}{86\,436}L^2h^2\right) \|z_n - z_n^*\|,
\end{aligned}$$

Now using equation (2.13)

$$\begin{aligned}
\phi(z_n, u_n, h) - \phi(z_n, u_n^*, h) &= \frac{1}{14994} \left(2597k_1 + 10000k_2 + 2397k_4 \right. \\
&\quad \left. - 2597k_1^* - 10000k_2^* - 2397k_4^* \right), \\
&= L \left(1 + \frac{47}{294}Lh + \frac{545\,623}{25\,412\,184}L^2h^2 \right) \|z_n - z_n^*\|, \\
&= L' \|z_n - z_n^*\|,
\end{aligned}$$

where $L' = L \left(1 + \frac{47}{294}Lh + \frac{545\,623}{25\,412\,184}L^2h^2 \right)$.

Therefore, the increment ϕ satisfies a Lipschitz condition in z and hence, by Definition 3.3, the method (2.13) is regular. $\square$

Lemma 3.1. *Suppose the function $f(t, z)$ is defined and continuous in the strip*

$S(|t - t_0| \leq a, \|z\| < \infty, a > 0)$ and satisfy Lipschitz condition

$$\|f(t, z) - f(t, z^*)\| \leq L \|z - z^*\| \quad (3.13)$$

for every $(t, z), (t, z^*) \in S$, where L is Lipschitz constant; then, method (2.13) is said to be convergent.

Proof. Since consistency and regularity holds for method (2.13), by Theorem 3.2, it is convergent. $\square$

3.3 Stability of the numerical method

Definition 3.4. *For a method given by the tableau $\frac{c}{b} \left| \frac{A}{b} \right.$, the stability for a $z' = \psi z$ is the set of points in the complex plane satisfying $|R(z)| \leq 1$ [14].*

Theorem 3.4. *For the iterative method (2.13) to be stable, we must have*

$$\left| \frac{\left(1 + \frac{103h\lambda}{153} + \frac{4841h^2\lambda^2}{44982} + \frac{55225h^3\lambda^3}{6353046}\right)}{\left(1 - \frac{1175h^2\lambda^2}{21609} - \frac{50h\lambda}{147} - \frac{55225h^3\lambda^3}{6353046}\right)} \right| \leq 1.$$

Proof Using Definition 3.4. Applying the iterative method (2.13) to the test equation $z' = \lambda z$, we obtain

$$k_1 = \lambda z_n, \quad k_2 = \lambda z_{n+\frac{51}{100}},$$

$$k_3 = \lambda \left[\left(1 + \frac{51h\lambda}{306}\right) z_n + \frac{5000h\lambda}{7497} z_{n+\frac{51}{100}} \right],$$

$$k_4 = \lambda \left[\left(1 + \frac{53h\lambda}{306} + \frac{47h\lambda}{294} + \frac{47h^2\lambda^2}{1764}\right) z_n + \left(\frac{5000h\lambda}{7497} + \frac{117500h^2\lambda^2}{1102059}\right) z_{n+\frac{51}{100}} \right].$$

From (2.13), we can write

$$z_{n+1} = \left(1 + \frac{2497h\lambda}{7497} + \frac{117359h^2\lambda^2}{2204118} + \frac{2209h^3\lambda^3}{518616}\right) z_n + \left(\frac{5000h\lambda}{7497} + \frac{117500h^2\lambda^2}{1102059} + \frac{2761250h^3\lambda^3}{162002673}\right) z_{n+\frac{51}{100}},$$

writing $z_{n+\frac{49}{100}}$ as $\frac{51}{100}(z_{n+1} + z_n)$, then

$$z_{n+1} = \left(1 + \frac{2497h\lambda}{7497} + \frac{117359h^2\lambda^2}{2204118} + \frac{2209h^3\lambda^3}{518616}\right) z_n + \frac{51}{100} \left(\frac{5000h\lambda}{7497} + \frac{117500h^2\lambda^2}{1102059} + \frac{2761250h^3\lambda^3}{162002673}\right) (z_{n+1} + z_n),$$

$$z_{n+1} = \frac{\left(1 + \frac{103h\lambda}{153} + \frac{4841h^2\lambda^2}{44982} + \frac{55225h^3\lambda^3}{6353046}\right)}{\left(1 - \frac{1175h^2\lambda^2}{21609} - \frac{50h\lambda}{147} - \frac{55225h^3\lambda^3}{6353046}\right)} z_n.$$

Now, for stability of numerical method and by Definition (3.4), we must have

$$\left| \frac{\left(1 + \frac{103h\lambda}{153} + \frac{4841h^2\lambda^2}{44982} + \frac{55225h^3\lambda^3}{6353046}\right)}{\left(1 - \frac{1175h^2\lambda^2}{21609} - \frac{50h\lambda}{147} - \frac{55225h^3\lambda^3}{6353046}\right)} \right| \leq 1.$$

4 Numerical experiment

In this section, the new numerical method is used to solve optimal control of the form (1.1) and (1.2) for cancer management. Numerical solutions are given in figure and tabular form. All computations in this section are done with the aid of a written MATLAB codes, which were run on a Window 8.1 computer.

Problem: A cancer management regimen with control to minimize the tumor density and the harmful side effect of the drugs over an interval of time. The tumor is assumed to have Gompertzian growth. The Skipper's log-kill hypothesis which states cell-kill due to chemotherapeutic drugs is examined to be proportional to tumor population. Now, if $N(t)$ is the normalized density of the tumor at time t , then

the model is given by

$$N'(t) = rN(t) \ln \left(\frac{1}{N(t)} \right) - u(t) \delta N(t);$$

where r is the growth rate of the tumor, δ is the magnitude of the dose, and $u(t)$ describes the pharmacokinetics of the drug, i.e., $u(t) = 0$ implies no drug effect and $u(t) > 0$ is the strength of the drug effect. The initial condition is taken to be $N(0) = N_0$, where $0 < N_0 < 1$, as the tumor cells have been normalized. The objective functional used is quadratic, where the cost of the control, representing possible side-effects, and the tumor density N are minimized over a time interval. Finally, we require $u(t) \geq 0$ for all t . The optimal control problem is

$$\min_u J = \int_0^{20} aN^2(t) + u^2(t) dt$$

subject to

$$\begin{aligned} N'(t) &= rN(t) \ln \left(\frac{1}{N(t)} \right) - u(t) \delta N(t), \\ u(t) &\geq 0. \end{aligned}$$

Here, a is a positive weight parameter [7].

Solution 4.1. *Optimality system of the problem is developed by constructing the Hamiltonian as*

$$H = aN^2(t) + u^2(t) + \lambda \left(rN(t) \ln \left(\frac{1}{N(t)} \right) - u(t) \delta N(t) \right).$$

The optimality condition is

$$0 = \frac{\partial H}{\partial u} = -N(t) \delta \Rightarrow u^* = 0.$$

The adjoint equation is

$$\lambda'(t) = -\frac{\partial H}{\partial x} = -r \ln \left(\frac{1}{N(t)} \right) + u(t) \delta + r.$$

Using the optimality system, the numerical code is generated, written in MAT-

LAB R2018a. This problem is solved with $N = 1000$. The results are shown in Figures and Tables. First considering the parameters $r = 0.3$, $a = 3$, $\delta = 0.45$, $N_0 = 0.975$ [7].

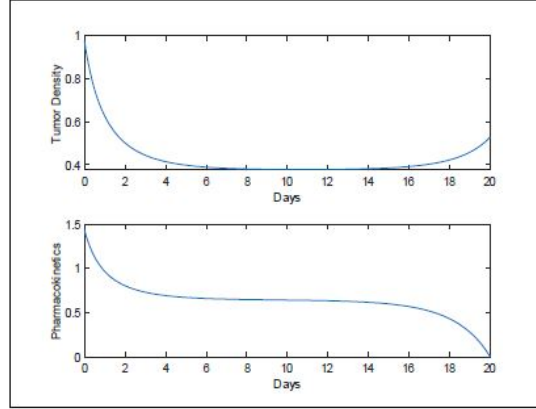


Figure 1: The tumor density and pharmacokinetics of the numerical method $a = 3$, $\delta = 0.45$

Table 1: State and control for case 1

t	State		Control	
	NNM	CRKM [7]	NNM	CRKM [7]
0	0.9750000000000000	0.9750000000000000	1.433706826998135	1.431519487300024
0.1	0.500839379285516	0.505666934475205	0.803368588845305	0.807359115509372
0.2	0.413491710358522	0.418346012470344	0.692013735685715	0.696011945637606
0.3	0.387760017402417	0.392501590925836	0.659157626185285	0.663049282997642
0.4	0.379306324575994	0.383961298332402	0.647484528418595	0.651348032758281
0.5	0.376778902117361	0.381361475491616	0.641447595126311	0.645392567220932
0.6	0.377045342141515	0.381534248673752	0.633885235217778	0.638061381565947
0.7	0.380361998024978	0.384688927101804	0.616201459422975	0.620797910085466
0.8	0.390666267569043	0.394710210763667	0.567993322376923	0.573066317811511
0.9	0.421628254534164	0.425267941054758	0.430117465428098	0.434791866206044
1.0	0.528538228793916	0.532047049218665	0	0

The aim is to minimize the tumor density and drug side effects over a given time interval. The control is the drug strength with its possible side-effects, and the tumor density is the state. From Figure 1 when the magnitude of the dose $\delta = 3$ and positive weight parameter $a = 0.45$ show that, immediately high drug strength is introduced, it drastically reduced the tumor density. The drug strength is then reduced slowly and maintained at a constant level between day 8 and day 14, at this point, the tumor is reduced to its lowest density (0.4). When the drug strength is further reduced to 0 at day 20, the tumor density began to increase again.

From Table 1, it clearly minimize the tumor and the drug side effects better when compared to [7]. Varying the parameters δ

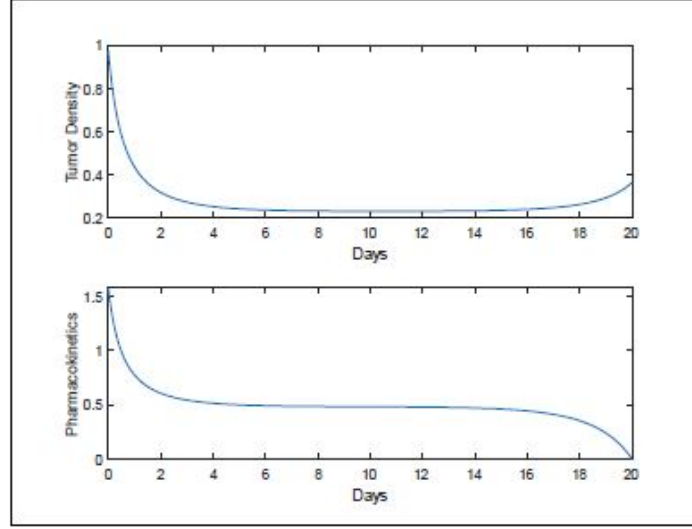


Figure 2: The tumor density and pharmacokinetics of the numerical method for $a = 3$, $\delta = 0.9$.

Table 2: State and control for case 2

State			Control	
t	NNM	CRKM [7]	NNM	CRKM [7]
0	0.975000000000000	0.975000000000000	1.577888180446669	1.574841700801036
0.1	0.316174778473394	0.321535501574790	0.607140277382097	0.611810080427200
0.2	0.250340295480829	0.255249785933422	0.514222152672691	0.518338270123177
0.3	0.234461995575852	0.239159503078733	0.491758637340540	0.495631451262817
0.4	0.230008033592787	0.234610517903486	0.485145080847041	0.488938157245321
0.5	0.228863696436917	0.233409401728040	0.482435483642046	0.486272382635043
0.6	0.229091392749493	0.233557808902514	0.479251884044770	0.483284185170976
0.7	0.230994754817556	0.235290083956162	0.470738364567357	0.475198137206699
0.8	0.237564997246677	0.241502289744987	0.443770662816609	0.448850520235493
0.9	0.260533618010916	0.263848355874142	0.353380082320243	0.358315009284885
1.0	0.361917965094058	0.364635290524031	0	0

In Figure 2, when the magnitude of the dose is maintain at $\delta = 3$ and positive weight parameter varied to $a = 0.9$, the lowest tumor density is reduced up to 0.2. From Table 2, it clearly minimize the tumor and the drug side effects better when

compared to [7]

Now varying the parameters $a = 6, r = 0.3, \delta = 0.45, N_0 = 0.975$

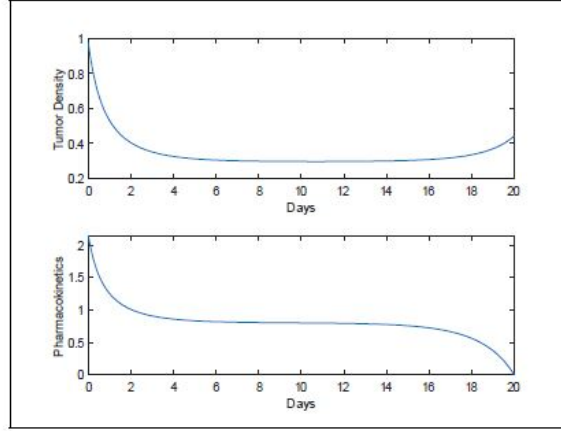


Figure 3: The tumor density and pharmacokinetics of the numerical method $a = 6, \delta = 0.45$

Table 3: State and control for case 3

t	State		Control	
	RKLM	CRKM [7]	RKLM	CRKM [7]
0	0.9750000000000000	0.9750000000000000	2.145893109279030	2.142727839377600
0.1	0.403447602122316	0.408335804379769	1.006668615260192	1.012674278588370
0.2	0.325034006643511	0.329640783423408	0.857133295208174	0.862619610386473
0.3	0.304223090211370	0.308622195107628	0.817397101457904	0.822574837362603
0.4	0.297921588053831	0.302196877601881	0.804601842438389	0.809670968277103
0.5	0.296180286997951	0.300368203948060	0.798757081251958	0.803902166061581
0.6	0.296444118005061	0.300532617139906	0.791713131092871	0.797166532808081
0.7	0.299009083064674	0.302927501090392	0.774118569309370	0.780198373396690
0.8	0.307408503038023	0.311011978928587	0.722322938984285	0.729225238354402
0.9	0.334692031896936	0.337797013107579	0.561623883382889	0.568221726831470
1.0	0.441385751325378	0.444167700807145	0	0

In Figure 3, when the magnitude of the dose is varied to $\delta = 6$ and positive weight parameter maintained at $a = 0.45$, the lowest tumor density is reduced up to 0.3. From Table 1, it clearly minimize the tumor and the drug side effects better when compared to [7].

Therefore, studying Figure 1 to Figure 3, it can be noticed that, the optimal treatment strategy is one of high drug strength early followed by a slow reduction to

no drug treatment on day 20. However, it can be noticed that, the lowered drug strength allows for a slight increase in tumor density after day 14. It can also be observed that when the weight parameter is maintained at $\delta = 3$ and the drug strength increased, the tumor density is reduced to its minimal level, but maintaining the drug strength at $a = 0.45$ and increasing weight parameter does not yield to a better treatment.

Table 1 to Table 3, the state (tumor) was high at the beginning, but as soon as the control (dose of drug) is introduced heavily, the state reduced drastically and became almost constant to one decimal place. But as soon as the control reach zero, the state begin to increase again.

5 Conclusion

In this study, a numerical method is developed based on Patade and Bhalekar approach for the numerical solution of optimal control problem using forward-backward sweep method. The numerical method developed is of order four and verified to be stable and convergent. Codes are written for the implementation of the numerical method using MATLAB R2018a.

Studying the results obtained, it can be noticed that, the optimal treatment strategy is one of high drug strength early followed by a slow reduction to no drug treatment on day 20. It can also be noticed that, the lowered drug strength allows for a slight increase in tumor density after day 14. It is observed that when the weight parameter is maintained at $\delta = 3$ and the drug strength increased, the tumor density is reduced to its minimal level. But maintaining the drug strength at $a = 0.45$ and increasing weight parameter does not yield to a better treatment. Management of cancer using the new numerical method, a high drug strength is infused which destroyed more cancer cells, then the dosage is reduced to minimal level. The drug infusion time is shortened which brings the drug strength to zero in order to reduce toxicity of the drugs. This minimized the destruction of the host cells and simultaneously maximizing the destruction of cancer cells.

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References

- [1] S. Adamu, *Numerical Solution of Optimal Control Problems using Block Method*. Electron. J. Math. Anal. Appl., **11**(2)(2023), 1-12. <http://ejmaa.journals.ekb.eg>.
- [2] S. Adamu, K. Bitrus & H. L. Buhari, *One step second derivative method using Chebyshev Collocation point for the solution of ordinary differential equations*. J. NAMP, **51**(2019), 47-54. <http://nampjournals.org/publications-download/vol51/>.
- [3] A. Alam, U. Farooq, R. Singh, V. P. Dubey, S. Kumar, R. Kumari, K. K. Naik, B. D. Tripathi & K. L. Dhar, *Chemotherapy Treatment and Strategy Schemes: A Review*. Open Acc. J. Toxicol., **2**(5)(2018), OAJT.MS.ID.555600.
- [4] J. C. Butcher, *A history of Runge-Kutta Methods*. Appl. Numer. Math., **20**(1996), 247-260.
- [5] R. R. Garret, *Numerical Methods for Solving Optimal Control Problems*. Tennessee Research and Creative Exchange, University of Tennessee, Knoxville (2015).
- [6] F. B. Hildebrand, *Introduction to Numerical Analysis*. Second Edition, Tata McGraw-Hill Publishing Co. Limited, New Delhi (1972).
- [7] S. Lenhart & J. T. Workman, *Optimal Control Applied to Biological Models*. Chapman & Hall/CRC, London New York (2007).
- [8] H. Musa, I. Saidu & M. Y. Waziri, *A Simplified Derivation and Analysis of Fourth Order Runge Kutta Method*. Int. J. Comput. Appl., **9**(8)(2010), 0975-8887.
- [9] A. Mustapha, A. Ismail, S. U. Abdullahi, O. N. Hassan, P. I. Ugwunnaji & E. B. Berinyu, *Cancer Chemotherapy; A review update of the mechanisms of action, prospects and associated problems*. Biomed. Nat. Appl. Sci., **01**(01)(2021), 001-016.

- [10] M. R. Odekunle, N. D. Oye & S. O. Adey, *A class of inverse Runge-Kutta schemes for the numerical integration of singular problems*. Appl. Math. Comput., **158**(2004), 149-158.
- [11] M. M. Olsen, K. B. LeFebvre & K. J. Brassil, *Chemotherapy and Immunotherapy Guidelines and Recommendations for Practice*. Pittsburgh, PA: Oncology Nursing Society (2019), 61-90.
- [12] J. Patade & S. Bhalekar, *A new numerical method based on Daftardar-Gejji and Jafari technique for solving differential equations*. World J. Model. Simul., **11**(4)(2015), 256-271.
- [13] H. S. Rodrigues, M. T. T. Monteiro & D. F. M. Torres, *Systems Theory: Perspectives, Applications and Developments*. Nova Science Publishers (2014).
- [14] A. A. Salama, *Numerical methods based on extended one-step methods for solving optimal control problems*. Appl. Math. Comput., **183**(2006), 243-250.
- [15] S. Adamu, O. O. Aduroja & K. Bitrus, *Numerical Solution to Optimal Control Problems using Collocations Method via Pontrygin's Principle*. FUDMA J. Sci., **7**(5)(2023), 228-233. <https://doi.org/10.33003/fjs-2023-0705-2016>.
- [16] O. O. Aduroja, S. Adamu, M. Kida & B. H. Lola, *Bi-Basis Function Second Derivative Block Method for the Solution of Optimal Control Problems*. Int. J. Dev. Math., **1**(1)(2024), 16-24. <https://doi.org/10.62054/ijdm/0101.02>.