NUMERICAL SOLUTION OF TUMOR-IMMUNE INTERACTION USING 2-POINT BLOCK BACKWARD DIFFERENTIATION METHOD

NOR AIN AZEANY MOHD NASIR

*Institute for Mathematical Research, Department of Mathematics,
Faculty of Science, Universiti Putra Malaysia,
43400 UPM Serdang, Selangor Darul Ehsan, Malaysia
ain_nasir2511@yahoo.com.my*

ZARINA BIBI IBRAHIM

*Institute for Mathematical Research, Department of Mathematics,
Faculty of Science, Universiti Putra Malaysia,
43400 UPM Serdang, Selangor Darul Ehsan, Malaysia
zarina@math.upm.edu.my*

MOHAMED SULEIMAN

*Institute for Mathematical Research, Department of Mathematics,
Faculty of Science, Universiti Putra Malaysia,
43400 UPM Serdang, Selangor Darul Ehsan, Malaysia
zarinabb@math.upm.edu.my*

K. I. OTHMAN

*Department of Mathematics, Faculty of Computer and Mathematical Sciences,
Universiti Teknologi MARA, 40450 Shah Alam,
Selangor Darul Ehsan, Malaysia
khairil@tmsk.uitm.edu.my*

YONG FAEZAH RAHIM

*Institute for Mathematical Research, Department of Mathematics,
Faculty of Science, Universiti Putra Malaysia,
43400 UPM Serdang, Selangor Darul Ehsan, Malaysia
zarinabb@science.upm.edu.my*

In this paper, we consider tumor-immune interaction model systems. The numerical solutions for the tumor-immune interaction system are obtained by using the 2-point Block Backward Differentiation Formula (BBDF) methods developed by Zarina *et al.* in 2007. The numerical results are presented in terms of computational time and accuracy of the solutions.

Keywords: Ordinary Differential Equations; Initial Value Problems; Tumor-Immune Interaction.

1. Introduction

In this paper, we focused on solving systems of first order stiff Ordinary Differential Equations (ODEs). The general form for systems of first order stiff ODEs is given as,

$$Y'_s = AY_s + F_s(t, y_s(t)), \quad Y_s(a) = \eta_s, \quad s = 1, 2, \dots, n. \quad (1)$$

where $Y_s(t) = (Y_1, Y_2, \dots, Y_n)^T$, $\eta_s = (\eta_1, \eta_2, \dots, \eta_n)^T$, A is $m \times m$ matrices with large negative eigenvalues.

Many researchers have proposed numerical methods for solving ODEs such as Chu and Hamilton (1987), Suleiman (1989), Fatunla (1991) and Omar and Suleiman (2003). Although there is extensive literature on using block method for solving Eq. (1), but there are not many works on block methods developed for solving stiff ODEs.

In 2006, Majid and Suleiman (2006) have derived a method which is called 1-point implicit block method of variable stepsize and order (1PVSO) which is presented in the simple form of Adams type. The 1PVSO method is proved to be efficient for solving non-stiff problems within the given tolerance.

Subsequently, Ibrahim *et al.* (2007) have proposed Block Backward Differentiation Formulas (BBDF) specially for solving stiff ODEs. The BBDF method is constructed in backward difference form to approximate two solutions simultaneously in each block. Since the method is in implicit form, the BBDF method is implemented using Newton's iteration which involved the calculation of the Jacobian and the LU decomposition. This BBDF method has been used for solving the Brusselator by Othman *et al.* (2008). The results are shown in Othman *et al.* (2008) to be more efficient when the method is implemented on parallel processors.

Hence, in this paper, we apply the BBDF method for solving tumor-immune interaction model. This mathematical model on tumor-immune interaction is given in Kirschner and Panetta (1998). Most of the tumor-immune interaction equations are stiff ODEs. The aim in this paper is to produce solutions within the user defined tolerance with less computational time. This paper will validate the competency of the BBDF method.

2. Block Backward Differentiation Formula Method

In Ibrahim *et al.* (2007), the derivation of BBDF method are formulated using two backvalues which are t_{n-1} and t_n . The backvalues are used to compute the approximate solutions concurrently at the points t_{n+1} and t_{n+2} . The formulas that have been derived by Ibrahim *et al.* (2007) are as following,

$$\begin{aligned} y_{n+1} &= -\frac{1}{3}y_{n-1} + 2y_n - \frac{2}{3}y_{n+2}^{(p)} + 2hf_{n+1}^{(p)} \\ y_{n+2} &= \frac{2}{11}y_{n-1} - \frac{9}{11}y_n + \frac{18}{11}y_{n+1}^{(p)} + \frac{6}{11}hf_{n+2}^{(p)} \end{aligned} \quad (2)$$

where p is the predicted values. For simplicity, formulas in Eq. (2) can be generally written in the form of,

$$\sum_{j=0}^k A_j y_{n+j} = h \sum_{j=0}^k B_j f_{n+j} \quad (3)$$

with A_j and B_j are r by r matrices, where k is the number of blocks and r is the number of points in block.

Equation (2) is then transform into the form of Eq. (3), which is

$$\begin{bmatrix} 1 & \frac{2}{3} \\ -\frac{18}{11} & 1 \end{bmatrix} \begin{bmatrix} y_{n+1} \\ y_{n+2} \end{bmatrix} = \begin{bmatrix} -\frac{1}{3} & 2 \\ \frac{2}{11} & -\frac{9}{11} \end{bmatrix} \begin{bmatrix} y_{n-1} \\ y_n \end{bmatrix} + h \begin{bmatrix} 2 & 0 \\ 0 & \frac{6}{11} \end{bmatrix} \begin{bmatrix} f_{n+1} \\ f_{n+2} \end{bmatrix}. \quad (4)$$

Next, the Eq. (4) is implemented using $PE(CE)^2$ mode. P and C indicate one application of the predictor or the corrector respectively, and E indicate one evaluation of the function f , given t and y . The numerical solution for solving Eq. (1) is obtained as follows

- (i) The values of predict solutions are computed using predictor equations,
- (ii) Evaluate the values for $e_{n+1,n+2}^{(i+1)} = A^{-1}B$, where $e^{(i+1)} = y_{n+1,n+2}^{(i+1)} - y_{n+1,n+2}^{(i)}$,

$$A = \begin{bmatrix} 1 - 2h \frac{\partial f_{n+1}}{\partial y_{n+1}} & \frac{2}{3} \\ -\frac{18}{11} & 1 - \frac{6}{11} h \frac{\partial f_{n+2}}{\partial y_{n+2}} \end{bmatrix},$$

$$B = \begin{bmatrix} y_{n+1}^{(i)} + \frac{2}{3} h f_{n+1}^{(i)} - \frac{1}{3} y_{n-1}^{(i)} + 2 y_n^{(i)} & \frac{2}{3} y_{n+2}^{(i)} \\ -\frac{18}{11} y_{n+1}^{(i)} & y_{n+2}^{(i)} + \frac{6}{11} f_{n+2}^{(i)} + \frac{2}{11} y_{n-1}^{(i)} - \frac{9}{11} y_n^{(i)} \end{bmatrix}$$

and $\frac{\partial f_{n+1,n+2}}{\partial y_{n+1,n+2}}$ is the Jacobian at ith iteration,

- (iii) the values for $y_{n+1,n+2}^{(i+1)}$ is corrected using the values $e_{n+1,n+2}^{(i+1)}$ obtained from (ii),
- (iv) the values of $e_{n+1,n+2}^{(i+1)} = A^{-1}B$ is calculated using the LU decomposition and solved for the second stage iteration,
- (v) the final values of $y_{n+1,n+2}^{(i+1)}$ is obtained from (iv).

3. The Tumor-Immune Interaction Model

There are many model for tumor-immune dynamic which have been modeled by several researchers such as Kuznetsov *et al.* (1994), DeLisi and Rescigno (1977), Adam (1996) and DeBoer (1985). However, Kirschner and Panetta (1998) have developed a simple model which consist of the interaction between the effector celss, $E(t)$; the tumor cells, $T(t)$ and the cytokine (IL-2), $I_L(t)$. The dynamic model is described as, which is

$$\begin{aligned}\frac{dE}{dt} &= cT - \mu_2 E + \frac{p_1 E I_L}{g_1 + I_L} + s_1 \\ \frac{dT}{dt} &= r_2(T)T - \frac{aET}{g_2 + T} \\ \frac{dI_L}{dt} &= \frac{p_2 ET}{g_3 + T} - \mu_3 I_L + s_2\end{aligned}\tag{5}$$

with initial conditions $E(0) = E_0$, $T(0) = T_0$, $I_L(0) = I_{L_0}$. The parameters in Eq. (5) are defined as follows,

Table 1. Parameters definition.

Parameters	Definition
dE / dt	The rate of change for the effector-cell population
dT / dt	The rate of change for the tumor cells
dI_L / dt	The rate of change for concentration of IL-2
c	The measurement of the antigenicity of the tumor
μ_2	The natural lifespan of the effector cells
p_1	The stimulated effector cells by IL-2 per day
g_1	The concentration of the stimulated effector cells
s_1	External source of effector cells (treatment)
$r_2(T)$	The logistic growth function
a	The strength of the immune response
g_2	The volume loss of the tumor cells
μ_3	The degraded rate of IL-2
s_2	An external input of IL-2 (treatment)
p_2	The stimulated effector cells by interaction with the tumor
g_3	The volume of the stimulated effector cell by interaction with the tumor

In Kirschner and Panetta (1998), the parameters values are given below in the table 2. In this work, we only considered s_1 and s_2 are equal to zero which means, there is no treatment received by the cancer patient. The value of c , the stronger the antigen will produced.

Table 2. Parameters values.

$0 \leq c \leq 0.05$	$\mu_2 = 0.03$	$p_1 = 0.1245$	$g_1 = 2 \times 10^7$
$g_2 = 1 \times 10^5$	$r_2 = 0.18$	$b = 1 \times 10^{-9}$	$a = 1$
$\mu_3 = 10$	$p_2 = 5$	$g_3 = 1 \times 10^3$	

4. Numerical Results

In this section, the numerical results will be tabulated in Table 4 and 5. The BBDF method will be compared with the ode15s and ode23s which runs in Matlab. The notations used in the table are defined as follows,

Table 3. This is the caption for the table. The width of the caption should follow that of the table and centralize if it is less than the table.

Notation	Definition
BBDF	2-point Block Backward Differentiation Formula with fixed stepsize
ode15s	A variable order solver based on the numerical differentiation formulas (NDFs)
Ode23s	A modified Rosenberg formula of order 2
METHOD	Method that being compared
c	The antigenicity of the tumor
H	Stepsize
TIME	Computational time in microseconds

In the literature, the numerical error, *Error* is defined as the difference between the exact analytical solution $y(t_{n+2})$ and its numerical solution y_{n+2} , i.e,

$$Error = |y(t_{n+2}) - y_{n+2}|.$$

However, in practical situations, most applied problems, the analytic solution is unknown. Hence, one way of computing the error is by using the difference between two approximate values at the end point using different stepsize. Therefore, the numerical error, *Error* is given as follows,

$$Error = |y_{n+2}(h) - y_{n+2}(\hat{h})|. \tag{6}$$

where $h = 10^{-3}$ and $\hat{h} = 10^{-5}$. The error and computational time are presented in Table 4 and 5.

Table 4. Numerical results for tumor-immune interaction model.

c	H	METHOD	Error	TIME
0.0	10^{-3}	BBDF	9.27010e-5	7526
		ode15s	9.75492e-4	125000
		ode23s	9.75797e-4	140600
	10^{-4}	BBDF	4.68400e-6	48667
		ode15s	7.97585e -5	218750
		ode23s	1.04014e - 5	187500
	10^{-5}	BBDF	970000e - 7	464695
		ode15s	5.12100e - 6	4484375
		ode23s	2.86021e - 6	4359400

Table 5. Numerical results for tumor-immune interaction model.

<i>c</i>	<i>H</i>	METHOD	Error	TIME
0.025	10^{-3}	BBDF	9.30660e - 5	7798
		ode15s	9.82605e - 4	29690
		ode23s	9.76929e - 4	31300
	10^{-4}	BBDF	3.87500e - 6	49331
		ode15s	982372e - 5	234375
		ode23s	8.19604e - 5	218800
	10^{-5}	BBDF	977000e - 7	467225
		ode15s	7.75505e - 6	4046875
		ode23s	6.60848e - 6	5437500
0.05	10^{-3}	BBDF	1.01065e - 4	7438
		ode15s	1.01073e - 3	15625
		ode23s	1.12065e - 3	25000
	10^{-4}	BBDF	1.48890e - 5	49016
		ode15s	6.32461e - 4	250000
		ode23s	5.11735e - 4	171875
	10^{-5}	BBDF	9.85000e - 7	470719
		ode15s	4.22429e - 6	4656250
		ode23s	3.78190e - 6	4281250

From Table 4 and 5, for all methods, it is obvious that as the stepsize is getting smaller, the error become smaller especially at the last stepsize. The BBDF method outperformed ode15s and ode23s in terms of accuracy. Most of the cases, the error for ode23s is slightly better than the ode15s. In terms of computational time, the BBDF method requires less computational time as compared to ode15s and ode23s. On other hand, ode23s produce less execution time compared to ode15s. The BBDF method produced faster solutions because the method is a block method which obtained two solutions values simultaneously at each iteration while ode23s and ode15s is a one point method.

5. Conclusion

We have shown the efficiency of the BBDF method in terms of accuracy and computational time over the ode23s and ode15s for solving the tumor-immune interaction model. In conclusion, the BBDF method is a reliable method and can be an alternative solver for solving the tumor-immune interaction problems.

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