Abstract: In this study, a singly diagonally implicit block backward differentiation formula (SDIBBDF) was proposed to approximate solutions for a dynamical HIV infection model of CD4+ T cells. A SDIBBDF method was developed to overcome difficulty when implementing the fully implicit method by deriving the proposed method in lower triangular form with equal diagonal coefficients. A comparative analysis between the proposed method, BBDF, classical Euler, fourth-order Runge-Kutta (RK4) method, and a Matlab solver was conducted. The numerical results proved that the SDIBBDF method was more efficient in solving the model than the methods to be compared.

Keywords: backward differentiation formulas; block multistep method; CD4+ T cell; HIV infection; singly diagonally implicit

1. Introduction

Based on global HIV/AIDS statistics by [1], there were about 36.9 million individuals living with HIV in 2017. Approximately around 1.8 million people worldwide developed a new infection with the virus in the same year, with an estimation of 5000 new infections each day. The spread of HIV not only affects the individual’s health, but the impacts can also be experienced in households, societies, and the growth and economic development of nations. Regardless of these challenges, there have been successes and promising signs, thanks to advances in our scientific understanding on HIV/AIDS, and besides preventative measures and treatment, along with years of significant effort by the health community worldwide and leading government and civil society organizations, the number of newly infected individuals has declined over the years.

According to [2], HIV is a virus that is spread through certain bodily fluids that attack the CD4 cells, specifically or often called T cells, which are related to the body’s immune system. The cells’ count gives a clear picture on the efficiency of the immune system. The CD4+ T cells are white blood cells that fight infection, which means that the more you have them, the better. These are the cells that the HIV kills. As the virus infection grows, the number of these cells decreases. When the CD4 count drops to below 200, a person can be diagnosed with AIDS. A normal range for CD4 cells is around 500–1500. Usually, the CD4 cell count rises when the HIV virus is controlled with an effective treatment.

A model for the infection of HIV into the human immune system was introduced by [3], which consists of three variables; free virus particles, uninfected cells, and infected cells. The proposed model was later extended in [4] by considering four variables which divided the infected cells into latently and actively infected cells. However, [5] managed to reduce the model in [4] into a system of three ordinary differential equations (ODEs) with an assumption that all infected cells are capable of...
creating the virus. Thus, this paper considers the following mathematical model for the HIV infection of CD4\(^+\)T cells:

\[
\begin{align*}
\frac{dT}{dt} &= \lambda - \mu T + rT \left(1 - \frac{T}{T_{\text{max}}}\right) - kVT, \\
\frac{dI}{dt} &= kVT - \rho I, \\
\frac{dV}{dt} &= N\rho I - \tau V,
\end{align*}
\]

where \(T(t), I(t),\) and \(V(t)\) signify the concentration of healthy CD4\(^+\)T cells, a concentration of infected CD4\(^+\)T cells, and a concentration of a virus population of CD4\(^+\)T cells by HIV in the blood, respectively, at time \(t\). Other parameters and constants involved are described in Table 1.

\begin{table}[h]
\centering
\caption{List of variables and parameters involved for viral spread.}
\begin{tabular}{ll}
\hline
Dependent variables & Parameters & constants \\
\hline
\(T\) & Uninfected CD4\(^+\)T cells population size & \(1.0 \times 10^{-1}\ \text{day}^{-1}\ \text{mm}^{-3}\) \\
\(I\) & Infected CD4\(^+\)T cells density & \(2.0 \times 10^{-2}\ \text{day}^{-1}\) \\
\(V\) & Initial density of HIV RNA & \(3 \ \text{day}^{-1}\) \\
\hline
\(\lambda\) & Source term for uninfected CD4\(^+\)T cells & \\
\(\mu\) & Natural death rate of CD4\(^+\)T cells & \(2.0 \times 10^{-2}\ \text{day}^{-1}\) \\
\(r\) & Growth rate of CD4\(^+\)T cells population & \(3 \ \text{day}^{-1}\) \\
\(T_{\text{max}}\) & Maximal population level of CD4\(^+\)T cells & \(1.5 \times 10^{3}\ \text{mm}^{-3}\ \text{day}^{-1}\) \\
\(k\) & Rate of CD4\(^+\)T cells become infected with virus & \(2.7 \times 10^{-3}\ \text{mm}^{-3}\ \text{day}^{-1}\) \\
\(\rho\) & Blanket death rate of infected CD4\(^+\)T cells & \(3.0 \times 10^{-1}\ \text{day}^{-1}\) \\
\(N\) & Number of virions produced by infected CD4\(^+\)T cells & \(10 \ \text{mm}^{-3}\) \\
\(\tau\) & Death rate of free virus & \(2.4 \ \text{day}^{-1}\)
\end{tabular}
\end{table}

According to [5], when the virus is absent, the T cell population has a stable state value of:

\[
T_0 = \frac{r - \mu T + \sqrt{(r - \mu T)^2 + 4r\lambda T_{\text{max}}^{-1}}}{2rT_{\text{max}}^{-1}}.
\]

Hence, the only possible preliminary states for infection by free virus particles are:

\[
T(0) = T_0, \quad I(0) = I_0, \quad V(0) = V_0.
\]

This paper aims to develop a block multistep method for solving the HIV infection of a CD4\(^+\)T cells model. Efficiency of the method is analyzed by comparing it with a fully implicit multistep method (BBDF by [6]) and explicit one-step methods (RK4 and Euler’s method).

The outline of the paper is organized with derivation of the SDIBBDF method in Section 2 which will give the basic idea on how the block multistep works. Section 3 will provide the implementation of the derived method for the proposed dynamical model. This section presents the numerical results between the SDIBBDF, BBDF, RK4, Euler’s method and a Matlab solver. Analysis of the results obtained are also provided in the section. Overall findings of the research are concluded in Section 4.

2. Singly Diagonally Implicit Block Backward Differentiation Formulas

In this section, we will apply the two-point Singly Diagonally Implicit Block Backward Differentiation Formulas (SDIBBDF) to the mathematical model of ODEs shown in (1). The motivation in deriving the SDIBBDF method comes from the singly diagonally implicit method that is commonly used by researchers of RK fields. The works on singly diagonally implicit RK (SDIRK) methods were initially introduced by [7] by referring a method as singly diagonally implicit when its diagonal elements are equal, \(a_{ii} = \gamma\). Thus, the stored LU factorization of a single such matrix can be used
repeatedly, which will result in only one Jacobian evaluation and one LU decomposition for each time step [8]. These properties contribute to the efficiency of the method in approximating solutions.

In order to accelerate the computational process, the block method is introduced by [9]. The idea is to develop $k-$blocks where each block contains an $r-$point approximation at each iteration of the algorithm. The BBDF method was developed by [6], which had proved to outperform the results obtained by a non-block variable step variable order BDF method by [10].

The two-point block multistep method is illustrated in Figure 1. Solutions for $y_{n+1}$ and $y_{n+2}$ were computed concurrently in a block by using previous blocks with two points. Points $x_{n-1}$ and $x_n$ are the backvalues used as initial points to evaluate solutions at $x_{n+1}$ and $x_{n+2}$.

![Figure 1](image)

**Figure 1.** The two-point Singly Diagonally Implicit Block Backward Differentiation Formulas (SDIBBDF) method of constant step size.

The SDIBBDF method is derived by using the following linear difference operator,

$$L_{s}(y(x): h) = \left( \sum_{j=0}^{k+s-1} \alpha_{j-1,s} y_{n+j-1} \right) - h \beta_{k+s-1,s} y_{n+s},$$

(2)

where $k = 2$ and $\alpha_{ii} = \gamma$. Next, we substitute $s = 1, 2$ for points $y_{n+1}$ and $y_{n+2}$, respectively, into Equation (2) and expanded it to obtain the following approximate relation of the operator.

$$\alpha_{-1,1} y_{n-1} + \alpha_{0,1} y_n + \gamma y_{n+1} - h \beta_{1,1} y'_{n+1} = 0,$$

$$\alpha_{-1,2} y_{n-1} + \alpha_{0,2} y_n + \alpha_{1,2} y_{n+1} + \gamma y_{n+2} - h \beta_{2,2} y'_{n+2} = 0.$$  

(3)

Next, we let:

$$A_0 = \begin{bmatrix} \alpha_{-1,1} \\ \alpha_{-1,2} \end{bmatrix}, A_1 = \begin{bmatrix} \alpha_{0,1} \\ \alpha_{0,2} \end{bmatrix}, A_2 = \begin{bmatrix} \gamma \\ \alpha_{1,2} \end{bmatrix}, A_3 = \begin{bmatrix} 0 \\ \gamma \end{bmatrix}, B_2 = \begin{bmatrix} \beta_{2,1} \\ 0 \end{bmatrix}, B_3 = \begin{bmatrix} 0 \\ \beta_{3,2} \end{bmatrix}.$$  

(4)

Equation (4) is then substituted into the following formula

$$C_q = \frac{1}{q!} \sum_{j=0}^{k-1} j! A_j - \frac{1}{(q-1)!} \sum_{j=2}^{k-1} j!^{-1} B_j.$$  

(5)

Since the proposed method is designed for order 2, hence we expand Equation (5) for $q = 0, 1, 2$ where $C_0$ is only considered for $A_j$.

By using Maple programming, we solved $C_0, C_1$ and $C_2$ simultaneously to obtain the coefficients of the SDIBBDF method for both $y_{n+1}$ and $y_{n+2}$. Then, the coefficients obtained were substituted into (3), and we let $y' = f(x, y)$. By rearranging the equation, we formed the general corrector formula of the SDIBBDF method, as shown below.

$$\frac{1}{2} y_{n-1} - 2 y_n + \frac{3}{2} y_{n+1} = h f_{n+1},$$

$$\frac{1}{2} y_{n} - 2 y_{n+1} + \frac{3}{2} y_{n+2} = h f_{n+2}.$$  

(6)
Although the method derived is not fully implicit (singly diagonally implicit) when implemented in block form, each formula in Equation (6) is implicit, which requires the estimated value of $f_{n+s}$ in order to approximate the solution for $y_{n+s}$. Therefore, the predictor formula is developed.

The predictor formula for the first point, $y_{n+1}^{(p)}$, and the second point, $y_{n+2}^{(p)}$, of the SDIBBDF method shown in Equation (6) are derived by using the backvalues of $x_n$, $x_{n-1}$, and $x_{n-2}$ as the interpolating points. The Lagrange interpolating polynomial of the method is given as follows:

$$P(x) = P(x_{n+1} + sh)$$
$$= L_{k,m}(x)y(x_n) + ... + L_{k,k}(x)y(x_{n-k})$$
$$= \sum_{m=0}^{k} L_{k,m}(x)y(x_{n-m})$$  \hspace{1cm} (7)

where

$$L_{k,m} = \prod_{i=0, i \neq m}^{k} \frac{x - x_{n-i}}{x_{n-m} - x_{n-i}}, \hspace{0.5cm} m = 0, 1, ..., k$$  \hspace{1cm} (8)

and $k$ is the number of the backvalue proposed. Thus, substituting $s = 0$ and 1 into Equation (8) gives the following predictor formula for each point, respectively.

$$y_{n+1}^{(p)} = y_{n-2} - 3y_{n-1} + 3y_n,$$
$$y_{n+2}^{(p)} = 3y_{n-2} - 8y_{n-1} + 6y_n.$$  \hspace{1cm} (9)

The SDIBBDF method was applied in PECE mode, where the implementation of its predictor and corrector formula is denoted as $P$ and $C$, respectively, while $E$ is the evaluation of function $f(x, y)$. The sequence of the computational process for the block method in PECE mode shown below is executed in parallel.

$$P: y_{n+1}^{(s)} \rightarrow E: f_{n+1}^{(s)} \rightarrow C: y_{n+1}^{(s+1)} \rightarrow E: f_{n+1}^{(s+1)},$$
$$P: y_{n+2}^{(s)} \rightarrow E: f_{n+2}^{(s)} \rightarrow C: y_{n+2}^{(s+1)} \rightarrow E: f_{n+2}^{(s+1)}.$$  \hspace{1cm} (10)

Further details on a block multistep method can be found in [6].

3. Results of Numerical Simulation

The performance of numerical simulation for HIV infection of CD4$^+$ T cells is outlined in this section. We had introduced an analytical tool in the previous section to conduct qualitative analysis of the dynamical model proposed. Based on [11], the values of parameters and constants of the model described in (1) are shown.

Values in Table 1 were substituted into (1) to get:

$$\frac{dT}{dt} = 1.0 \times 10^{-1} - 2.0 \times 10^{-2}T + 3T\left(1 - \frac{T + I}{1.5 \times 10^3}\right) - 2.7 \times 10^{-3}VT,$$
$$\frac{dI}{dt} = 2.7 \times 10^{-3}VT - 3.0 \times 10^{-1}I,$$
$$\frac{dV}{dt} = 3.0I - 2.4V.$$  \hspace{1cm} (11)
Next, we let $y_1 = T$, $y_2 = I$, and $y_3 = V$ into (11) to obtain the following test problem:

$$
\begin{align*}
    y_1'(t) &= -2.0 \times 10^{-3} y_2^2(t) - 2.0 \times 10^{-3} y_1(t)y_2(t) - 2.7 \times 10^{-3} y_1(t)y_3(t) \\
    &\quad + 2.98y_1(t) + 0.1, \\
    y_2'(t) &= 2.7 \times 10^{-3} y_1(t)y_3(t) - 3.0 \times 10^{-1} y_2(t), \\
    y_3'(t) &= 3y_2(t) - 2.4y_3(t), \\
\end{align*}
$$

(12)

with $y_1(0) = 0.1$, $y_2(0) = 0.0$ and $y_3(0) = 0.1$ for the interval of $0 \leq t \leq 1$.

To measure the efficiency of the proposed method, we compared the numerical results with existing methods as presented in Tables 2–4. Numerical results for the SDIBBDF and BBDF methods were computed by using the C++ program, while numerical results for RK4 and Euler’s method were obtained from [11].

### Table 2. Numerical results for concentration of uninfected T cells, $T(t)$.

| t      | SDIBBDF           | BBDF         | RK4          | EULER       |
|--------|-------------------|--------------|--------------|-------------|
| 0.0    | 0.1000000000000000 | 0.1000000000000000 | 0.1000000000000000 | 0.1000000000000000 |
| 0.2    | 0.2090205532222125 | 0.2162665954333766 | 0.2087297222454430 | 0.2066396850000000 |
| 0.4    | 0.4065545236060797 | 0.4050981887697551 | 0.4059409955447710 | 0.3455020000000000 |
| 0.6    | 0.7648420298033937 | 0.7365813304773389 | 0.7635801781341750 | 0.6050020000000000 |
| 0.8    | 1.4150679653076676 | 1.3965775540613832 | 1.4119574363577000 | 1.0420600000000000 |
| 1.0    | 2.5840259154129843 | 2.3865826219889092 | 2.5867778755778800 | 1.7779900000000000 |

### Table 3. Numerical results for concentration of HIV RNA, $V(t)$.

| t      | SDIBBDF           | BBDF         | RK4          | EULER       |
|--------|-------------------|--------------|--------------|-------------|
| 0.0    | 0.1000000000000000 | 0.1000000000000000 | 0.1000000000000000 | 0.1000000000000000 |
| 0.2    | 0.0619225726474935 | 0.0638429946616157 | 0.0618798121706440 | 0.0577610000000000 |
| 0.4    | 0.0383177394040220 | 0.0385396728096125 | 0.0382948730795908 | 0.0333660000000000 |
| 0.6    | 0.0237164787182014 | 0.0244756054303048 | 0.0237045402752520 | 0.0192790000000000 |
| 0.8    | 0.0146863853079351 | 0.0147827377616151 | 0.0146803506585660 | 0.0111450000000000 |
| 1.0    | 0.0091490338048673 | 0.0094989136078710 | 0.0091008270878710 | 0.0064500000000000 |

### Table 4. Numerical results for concentration of infected T cells, $I(t)$.

| t      | SDIBBDF           | BBDF         | RK4          | EULER       |
|--------|-------------------|--------------|--------------|-------------|
| 0.0    | 0.0000000000000000 | 0.0000000000000000 | 0.0000000000000000 | 0.0000000000000000 |
| 0.2    | 0.0000060459344453 | 0.0000058406917327 | 0.0000060315204770 | 0.0000059531387000 |
| 0.4    | 0.0000131823896412 | 0.0000130303451230 | 0.0000131530315000 | 0.0000128846300000 |
| 0.6    | 0.0000212573455944 | 0.0000214442550764 | 0.0000212106240460 | 0.0000206134400000 |
| 0.8    | 0.0000302184570008 | 0.0000302550927739 | 0.0000301518386990 | 0.0000290605600000 |
| 1.0    | 0.0000399547343565 | 0.0000382638392925 | 0.0000399426147800 | 0.0000382160400000 |

The results presented in Tables 2–4 are illustrated in graphical form by using Maple, as shown in figures below. The graphs also present the solutions plot by the Maple solver. Figures 2–4 represent the local variations of variables $T(t)$, $V(t)$, and $I(t)$, respectively.

The graphs show that the results produced by Euler’s method are slightly diverged from those obtained by Maple solver for each of the variables over time. Nevertheless, the SDIBBDF method is in better agreement with the RK4 method and Maple solver than the fully implicit BBDF method.

In Figure 2, we can observe that the concentration of susceptible T cells rises along $t$. Once the CD4$^+$ T cells were infected with HIV, the depletion of HIV RNA particles in the blood decreased rapidly in a short period of time, as analyzed in Figure 3. This resulted in the rapid growth of infected T cells, as shown in Figure 4.
Figure 2. Graph for concentration of uninfected T cells, $T(t)$, between comparing methods.

Figure 3. Graph for concentration of HIV RNA, $V(t)$, between comparing methods.
Subsequent studies by [12,13] verified that the HIV was selectively infected and destroyed the CD4⁺T cells in vitro. In addition, the numbers of circulating CD4⁺T cells in HIV⁺ subjects predicted the onset of explicit immunodeficiency. Furthermore, [14] also agreed that an overpoweringly weakened cellular immune response due to a reduction of CD4⁺T cells and loss of CD4⁺T cell function was the primary cause of immunodeficiency present in the infected subjects. Further evidence for this hypothesis came from the study of experimental infections of non-human primates with certain strains of chimeric simian or human immunodeficiency viruses (SHIV).

4. Conclusions

In this study, the SDIBBDF method was derived and successfully applied to solve the dynamical model for the HIV infection of CD4⁺T cells. Approximate solutions obtained by the proposed method were compared with the BBDF, RK4, and Euler’s method when solving the model. From the graphs, we can conclude that the solutions approximated by the proposed method very much agrees with the solutions obtained from the RK4 method and Maple solver.

On the other hand, the SDIBBDF method is an advanced tool that can be easily applied to the system of linear and nonlinear ODEs, as well as the dynamical system. In addition, the computational process was conducted efficiently with an advanced C++ programming language.

Therefore, the SDIBBDF method can be applied as an alternative solver for the HIV infection of a CD4⁺T cells model.

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