THE EFFECTIVENESS OF RUNGE-KUTTA METHOD OF ORDER NINE TO SOLVE THE IMMUNITY MODEL FOR INFECTION OF MYCOBACTERIUM TUBERCULOSIS

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Abstrak. *Model sistem kekebalan tubuh terhadap infeksi Mycobacterium tuberculosis telah dikembangkan dan dikemas dalam bentuk sistem persamaan diferensial biasa non linier order satu. Model tersebut sangat komplek sehingga memerlukan metode numerik untuk menyelesaikannya. Salah satu metode numerik yang yang efektif adalah metode Runge-Kutta. Penelitian ini akan merumuskan formula metode Runge-Kutta order sembilan, dan menentukan sifat dari metode tersebut sebelum merumuskannya, serta menganalisis konvergensi dan efektivitas dari metode Runge-Kutta order sembilan bila dibandingkan dengan metode Adam Bashforth-Moulton order sembilan. Metode dikatakan efektif dan efisien bila error yang terjadi pada metode dalam menyelesaikan model semakin kecil (menuju nol) dan waktu yang dibutuhkan metode untuk menyelesaikan model matematika semakin sedikit. Hasil penelitian menunjukkan bahwa metode Runge-Kutta order sembilan lebih efisien dan efektif dibandingkan metode Adam Bashforth-Moulton order sembilan dalam menyelesaikan model sistem kekebalan tubuh terhadap infeksi Mycobacterium tuberculosis.*

Kata kunci : *Metode Runge-Kutta order sembilan, konvergensi, efektivitas, model sistem kekebalan tubuh terhadap infeksi Mycobacterium tuberculosis.*

INTRODUCTION

Most of problems in our life can be solved by mathematics. One example is in medical science. Mathematics is used to determine the spread of viruses, bacteria and the spread of infectious and non-infectious diseases. They are represented by mathematical models. One of infectious diseases caused by bacteria are tuberculosis. Based on the facts in the WHO (World Health Organization) report, the disease often attacks the old age human. This is caused by decreased the immunity in old age so that Avner Friedman, Joanne Turner, and Barbara Szomolay developed a model of the influence of age on immunity to infection with Mycobacterium tuberculosis [11].

The model is represented by a system of ordinary differential equations first order non-linier that is very complex. The model on the immunity to infection with *Mycobaterium tuberculosis* includes the relationships between the three populations of bacteria, two macrophage populations, four populations of cytokines, and two populations of T cells that is expressed by system of ordinary differential equation first order non-linier. The model are given by equation (1)-(11).

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$$\begin{aligned}
\frac{dB_I}{dt} &= \alpha_I B_I(1-\frac{B_I^2}{B_I^2+(NM_I)^2})+k_1n_3M_R\frac{B_E}{B_E+c_1}- \\
&\quad k_2NM_I\frac{B_I^2}{B_I^2+(NM_I)^2}-n_1k_3B_I\frac{I_\gamma}{I_\gamma+c_2}+ \\
&\quad n_2k_4B_A\frac{I_{10}}{I_{10}+c_3I_\gamma+c_4}, \qquad (1)\\
\frac{dB_A}{dt} &= \alpha_A B_A-n_2k_4B_A\frac{I_{10}}{I_{10}+c_3I_\gamma+c_4}+n_1k_3B_I\frac{I_\gamma}{I_\gamma+c_2} \\
&\quad -n_2\mu_{MA}B_A, \qquad (2)\\
\frac{dB_E}{dt} &= \alpha_E B_E-k_1n_3M_R\frac{B_E}{B_E+c_1}+k_2NM_I\frac{B_I^2}{B_I^2+(NM_I)^2}- \\
&\quad k_5M_AB_E+n_2\mu_{MA}B_A, \qquad (3)\\
\frac{dM_I}{dt} &= k_1M_R\frac{B_E}{B_E+c_1}-k_2M_I\frac{B_I^2}{B_I^2+(NM_I)^2}-k_3M_I\frac{I_\gamma}{I_\gamma+c_2}+ \\
&\quad k_4M_A\frac{I_{10}}{I_{10}+c_3I_\gamma+c_4}-\mu_{MI}M_I, \qquad (4)\\
\frac{dM_A}{dt} &= -k_4M_A\frac{I_{10}}{I_{10}+c_3I_\gamma+c_4}+k_3M_I\frac{I_\gamma}{I_\gamma+c_2}-\mu_{MA}M_A+ \\
&\quad k_6M_R\frac{B_E}{B_E+c_5}\frac{I_\gamma}{I_\gamma+c_6}, \qquad (5)\\
\frac{dI_{10}}{dt} &= k_7M_I\frac{c_7}{I_{10}+c_7}-\mu_{10}I_{10}, \qquad (6)\\
\frac{dI_{12}}{dt} &= k_8M_A\frac{c_8}{I_{10}+c_8}+k_9M_R\frac{B_E}{B_E+c_9}-\mu_{12}I_{12}, \qquad (7)\\
\frac{dI_2}{dt} &= k_{10}T_4-(k_{11}T_4+k_{12}T_8)\frac{I_2}{I_2+c_{10}}-\mu_2I_2, \qquad (8)\\
\frac{dI_\gamma}{dt} &= (\lambda_u(t)+\lambda_y(t)T_8)\frac{I_{12}}{I_{12}+c_{11}}-\mu_\gamma I_\gamma, \qquad (9)\\
\frac{dT_4}{dt} &= \lambda_z(t)M_AI_{12}+k_13T_4\frac{I_2}{I_2+c_{10}}-\mu_{T4}T_4, \qquad (10)\\
\frac{dT_8}{dt} &= \lambda_x(t)(M_A+M_I)I_{12}+k_14T_8\frac{I_2}{I_2+c+10}-\mu_{T8}T_8 \qquad (11)
\end{aligned}$$

The estimation of initials values and parameters values of the model are gotten based on the result of research were done by Avner Friedman, Joanne Turner and Barbara Szomolary [11].

The model can't be solved by analytical method so that we must use the numerical method to solve it. One of the effective numerical method is the Runge-Kutta method. The level of this method is higher than Euler method, because this method has a high precision. The advantages of this method is the technique is more accurate because it has small truncation and integration errors [10]. Runge-Kutta method can be developed to a higher order. Many previous research have developed Runge-Kutta method. Runge-Kutta method that has been found is third order Runge-Kutta (Asih, 2001), fourth order Runge-Kutta (Faisol, 2001), fifth order Runge-Kutta (Yustica, 2010), sixth order Runge-Kutta (Bukaryo, 2012), seventh order Runge-Kutta (shodiq, 2012) [15], and Eighth order Runge-Kutta (Ardhilia, 2013).

Runge-Kutta Method has three characteristics, that are:

1. Runge-Kutta method is one-step method, to obtain $y_{(m+1)}$ it need only the values at an earlier point, x_m,y_m;
2. based on Taylor series, Runge-kutta method is up to h^p, where p is different for different methods and it is called order of method;
3. Runge-Kutta method does not require the evaluation of any derivative $f(x, y)$, but only function f itself.

Definition 1. Runge-Kutta method is defined by:

$$y_{n+1} = y_n + h\sum_{i=1}^{m} b_i k_i, \quad where\ k_i = f(x_n + c_i h, y_n + h\sum_{j}^{i-1} a_{ij}k_j),$$

with the asumption : $c_i = \sum_{j=1}^{m} a_{ij}, dan \sum_{i=1}^{m} b_i = 1, \quad i = 1, 2, \ldots, m$. The value of a, b, c can be expressed by Butcher Array table below.

$$\begin{array}{c|ccccc}
0 & & & & & \\
c_2 & a_{21} & & & & \\
c_3 & a_{31} & a_{32} & & & \\
\vdots & \vdots & \vdots & \ddots & & \\
c_m & a_{m1} & a_{m2} & \cdots & a_{mm-1} & \\
\hline
 & b_1 & b_2 & \cdots & b_{m-1} & b_m
\end{array}$$

Based on previous studies, Runge-Kutta method with a higher order will be more effective if it was compared to the Runge-Kutta with a lower order. One such case, the Fifth Order Runge-Kutta method is more effective than the sixth order Runge-Kutta Method [19]. Runge-Kutta method with higher order is also more effective than other methods with lower order. One such case, the Seventh order Runge-Kutta Method is more effective than the sixth order Adam Bashforth-Moulton method [15].

Research to determine the effectiveness of the Runge-Kutta method if it is compared with other method and the same order has not been done. In this paper, we will analyze the effectiveness of the ninth order Runge-Kutta method to solve a model on the immunity to infection with *Mycobaterium tuberculosis* and compare it with the ninth order Adam Bashforth-Moulton method.

RESEARCH METHOD

Research method of this research is deductive axiomatic and experiment. This research use the existed definitions and theorems to determine the characters of Ninth Order Runge-Kutta method and to formulate the formula of it. The exited definitions and theorems are taken form Lambert (1997) [12], Fausett (2008) [9], and Dafik (1999) [4]. Experiment method is used to analyze efficiency and effectivenes of Ninth Order Runge-Kutta method if it is compared with Ninth Orders Adam Bashforth-Moulton method.

THE RESULTS OF RESEARCH

Lemma 1. *Ninth Order Runge-Kutta Method has the following character :*

$$\sum_{i=1}^{m} b_i = 1, \quad where\ m = 9 \tag{12}$$

$$\sum_{i=2}^{m} b_i c_i^p = \frac{1}{p+1}, \quad for\ p = 1, 2, 3, ..., m-1 \tag{13}$$

$$\sum_{i=3}^{m-1} b_i \Big(\sum_{j=2}^{i-1} c_j^q a_{ij}\Big) = \frac{1}{(q+1)(q+2)}, \quad for\ q = 1, 2, 3, ..., m-3 \tag{14}$$

Proof. Based on definition (1), ninth order Runge-Kutta method is defined by :
$y_{n+1} = y_n + h\sum_{i=1}^{m} b_i k_i$, where m = 9, then $y_{n+1} = y_n + h(b_1k_1 + b_2k_2 + b_3k_3 + b_4k_4 + b_5k_5 + b_6k_6 + b_7k_7b_8k_8 + b_9k_9)$.
We use expansion of Taylor series to compare it with y_{n+1} and it is needed $y^{(1)}(x_n)$, ..., $y^{(9)}(x_n)$. To make easier, we suppose $J = f_x + ff_y$, $K = f_{xx} + 2ff_{xy} + f^2f_{yy}$, $L = f_{xxx} + 3ff_{xxy} + 3f^2f_{xyy} + f^3f_{yyy}$, $M = f_{xxxx} + 4ff_{xxxy} + 6f^2f_{xxyy} + 4f^3f_{xyyy} + f^4f_{yyyy}$, $N = f_{xxxxx} + 5ff_{xxxxy} + 10f^2f_{xxxyy} + 10f^3f_{xxyyy} + 5f^4f_{xyyyy} + f^5f_{yyyyy}$, $O = f_{xxxxxx} + 6ff_{xxxxxy} + 15f^2f_{xxxxyy} + 20f^3f_{xxxyyy} + 15f^4f_{xxyyyy} + 6f^5f_{xyyyyy} + f^6f_{yyyyyy}$, $P = f_{xxxxxxx} + 7ff_{xxxxxxy} + 21f^2f_{xxxxxyy} + 35f^3f_{xxxxyyy} + 35f^4f_{xxxyyyy} + 21f^5f_{xxyyyyy} + 7f^6f_{xyyyyyy} + f^7f_{yyyyyyy}$, $Q = f_{xxxxxxxx} + 8ff_{xxxxxxxy} + 28f^2f_{xxxxxxyy} + 56f^3f_{xxxxxyyy} + 70f^4f_{xxxxyyyy} + 56f^5f_{xxxyyyyy} + 28f^6f_{xxyyyyyy} + 8f^7f_{xyyyyyyy} + f^8f_{yyyyyyyy}$. And then we

get the derivate of $y(x_n)$ that are $y^{(1)} = f$, $y^{(2)} = J$, $y^{(3)} = K + Jf_y$, $y^{(4)} = L + Kf_y$, $y^{(5)} = M + Lf_y$, $y^{(6)} = N + Mf_y$, $y^{(7)} = O + Nf_y$, $y^{(8)} = P + Of_y$, $y^{(9)} = Q$.
The expansion of $y(x_{n+1})$ is done by subtitute $y^{(1)}, y^{(2)}, ..., y^{(9)}$ to Taylor series, that is:

$$\begin{aligned} y(x_{n+1}) &= y(x_n) + hf + \frac{1}{2!}h^2 J + \frac{1}{3!}(K + Jf_y) + \frac{1}{4!}h^4(L + Kf_y) + \frac{1}{5!}h^5(M + Lf_y) \\ &+\frac{1}{6!}h^6(N + Mf_y) + \frac{1}{7!}h^7(O + Nf_y) + \frac{1}{8!}h^8(P + Of_y) \\ &+\frac{1}{9!}h^9 Q + \frac{1}{10!}h^{10}y^{(10)}(x_n) + ... \end{aligned} \tag{15}$$

The expansion of $k_1, k_2, k_3, k_4, \ldots k_9$ is done by rule of two variables Taylor series expansion [9] and subtitute it to y_{n+1}. So, by compare $y(x_{n+1})$ with y_{n+1} we will get the characteristic of ninth order Runge-Kutta method.□

Corollary 1. *The formula of ninth order Runge-Kutta method (RK9A)*

$$\begin{aligned} y_{n+1} &= y_n + \frac{h}{105.000}(5062k_1 + 27.357k_2 + 1.260k_3 + 1.275k_4 + 35.050k_5 \\ &-16.800k_6 + 19.440k_7 + 27.273k_8 + 5.083k_9) \end{aligned}$$

where,

$$\begin{aligned} k_1 &= f(x_n, y_n) \\ k_2 &= f(x_n + \frac{h}{6}, y_n + \frac{h}{6}k_1) \\ k_3 &= f(x_n + \frac{h}{3}, y_n + \frac{h}{6}(k_1 + k_2)) \\ k_4 &= f(x_n + \frac{h}{3}, y_n + \frac{h}{3}(-k_1 + k_2 + k_3)) \\ k_5 &= f(x_n + \frac{h}{2}, y_n + \frac{h}{10}(k_1 + 2k_2 + k_3 + k_4)) \\ k_6 &= f(x_n + \frac{2h}{2}, y_n + \frac{h}{48}(-10k_1 + 2k_2 + 25k_3 + 9k_4 + 6k_5)) \\ k_7 &= f(x_n + \frac{2h}{3}, y_n + \frac{h}{240}(65k_1 + 27k_2 + 27k_3 - 8k_4 + 93k_5 - 44k_6)) \\ k_8 &= f(x_n + \frac{5h}{6}, y_n + \frac{h}{5.4546}(-13.291k_1 + 24.768k_2 + 942k_3 + 3.336k_4 + \\ &22.542k_5 + 6.612k_6 + 546k_7)) \\ k_9 &= f(x_n + h, y_n + \frac{h}{5.083}(-4.844k_1 + 984k_2 + 2.912k_3 + 125k_4 + 296k_5 \\ &+1.008k_6 + 102k_7 + 4.500k_8)) \end{aligned}$$

Proof. To proof it, we must solve the Lemma (1), in order we get the value of matrix coefficient. It is solved by determine the value of $c_1, c_2, c_3, ..., c_9$ such as we get the value of $b_1, b_2, \ldots, b_9$ that is satisfy with $c_i = \sum_{j=1}^{9} a_{ij}$ and $\sum_{i=1}^{9} b_1 = 1$. the determination are $c_2 = \frac{1}{6}$, $c_3 = \frac{1}{3}$, $c_4 = \frac{1}{3}$, $c_5 = \frac{1}{2}$, $c_6 = \frac{2}{3}$, $c_7 = \frac{2}{3}$, $c_8 = \frac{5}{6}$, and $c_9 = 1$. To get the value of a_{32}, a_{42}, a_{43}, ..., we must modified the Eq.(14) become $\sum_{i=2}^{8} c_i^k (\sum_{j=i+1}^{9} b_j a_{ji}), \quad k = 1, 2, ..., 6$ because Eq.(14) is very complex by suppose $\sum_{j=i+1}^{9} b_j a_{ji} = A$ for $i = 2$, $\sum_{j=i+1}^{9} b_j a_{ji} = B$ for $i = 3$ up to $\sum_{j=i+1}^{9} b_j a_{ji} = G$ for $i = 8$. Then we get a new equation system by find the value of A, B, C, D, $\ldots, G$ to get the value of coefficient matrix that contain a_{32}, a_{42},.... Based on the Runge-Kutta properties that are $c_i = \sum_{j=1}^{9} a_{ij}$ dan $\sum_{i=1}^{9} b_1 = 1$, the coefficient matrix can be expressed by Butcher array at table (1). □

Table 1: Coefficient matrix Ninth Order Runge-Kutta Method (RK9A)

0	0								
$\frac{1}{6}$	$\frac{1}{6}$	0							
$\frac{1}{3}$	$\frac{1}{6}$	$\frac{1}{6}$	0						
$\frac{1}{3}$	$\frac{-1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	0					
$\frac{1}{2}$	$\frac{1}{10}$	$\frac{2}{10}$	$\frac{1}{10}$	$\frac{1}{10}$	0				
$\frac{2}{3}$	$\frac{-10}{48}$	$\frac{2}{48}$	$\frac{25}{48}$	$\frac{9}{48}$	$\frac{6}{48}$	0			
$\frac{2}{3}$	$\frac{65}{240}$	$\frac{27}{240}$	$\frac{27}{240}$	$\frac{-8}{240}$	$\frac{93}{240}$	$\frac{-44}{240}$	0		
$\frac{5}{6}$	$\frac{-13.291}{54.546}$	$\frac{24.768}{54.546}$	$\frac{942}{54.546}$	$\frac{3.336}{54.546}$	$\frac{22.542}{54.546}$	$\frac{6.612}{54.546}$	$\frac{546}{54.546}$	0	
1	$\frac{-4.844}{5.083}$	$\frac{984}{5.083}$	$\frac{2.912}{5.083}$	$\frac{125}{5.083}$	$\frac{296}{5.083}$	$\frac{1.008}{5.083}$	$\frac{102}{5.083}$	$\frac{4.500}{5.083}$	0
	$\frac{5.062}{105.000}$	$\frac{27.357}{105.000}$	$\frac{1.260}{105.000}$	$\frac{1.275}{105.000}$	$\frac{35.050}{105.000}$	$\frac{-16.800}{105.000}$	$\frac{19440}{105.000}$	$\frac{27.273}{105.000}$	$\frac{5.083}{105.000}$

The formula above is said RK9A method, because from the effect of Lemma (1), we can to get the new formula with the same c_1, c_2, ... , c_9 but different a_{31}, a_{32}, a_{41}, and so on. The RK9A method is ninth order Runge-Kutta method with determination value $c_1 = 0$, $c_2 = \frac{1}{6}$, $c_3 = \frac{1}{3}$, $c_4 = \frac{1}{3}$, $c_5 = \frac{1}{2}$, $c_6 = \frac{2}{3}$, $c_7 = \frac{2}{3}$, $c_8 = \frac{5}{6}$, and $c_9 = 1$, and with maximal matrix coefficient. The other formula of ninth order Runge-Kutta method is called RK9B method that has the same c_1, c_2, ... , c_9 but it has minimal matrix coefficient.

Corollary 2. *The formula of ninth order Runge-Kutta method (RK9B) is expressed by Butcher array at table (2)*

Table 2: Matriks koefisien Runge-Kutta Order Sembilan (RK9B)

0	0								
$\frac{1}{6}$	$\frac{1}{6}$	0							
$\frac{1}{3}$	$\frac{-368}{21}$	$\frac{125}{7}$	0						
$\frac{1}{3}$	$\frac{-13}{51}$	0	$\frac{10}{17}$	0					
$\frac{1}{2}$	$\frac{641}{1402}$	0	0	$\frac{30}{701}$	0				
$\frac{2}{3}$	$\frac{47}{28}$	0	0	0	$\frac{-85}{84}$	0			
$\frac{2}{3}$	$\frac{407}{648}$	0	0	0	0	$\frac{25}{648}$	0		
$\frac{5}{6}$	$\frac{44.705}{54.546}$	0	0	0	0	0	$\frac{125}{9.091}$	0	
1	$\frac{583}{5.083}$	0	0	0	0	0	0	$\frac{4.500}{5.083}$	0
	$\frac{5.062}{105.000}$	$\frac{27.357}{105.000}$	$\frac{1.260}{105.000}$	$\frac{1.275}{105.000}$	$\frac{35.050}{105.000}$	$\frac{-16.800}{105.000}$	$\frac{19440}{105.000}$	$\frac{27.273}{105.000}$	$\frac{5.083}{105.000}$

Theorem 1. *Ninth order Runge-Kutta method is convergent method because it satisfy* $\|e_n\| \leq \frac{h^9 M_{10}}{10!\breve{L}}(e^{(x_n-x_0)\breve{L}} - 1)$, *where* $\breve{L}$ *is Lipschitz constant.*

Proof. Global error is determined based on the definition of Global error [6], $e_n = y(x_n) - y_n$ such as $e_{n+1} = y(x_{n+1}) - y_{n+1}$,
$e_{n+1} = e_n + h(y^{(1)}(x_n) - y_n^{(1)}) + \frac{1}{2!}h^2(y^{(2)}(x_n) - y_n^{(2)}) + \frac{1}{3!}h^3(y^{(3)}(x_n) - y_n^{(3)}) + \frac{1}{4!}h^4(y^{(4)}(x_n) - y_n^{(4)}) + \frac{1}{5!}h^5(y^{(5)}(x_n) - y_n^{(5)}) + \frac{1}{6!}h^6(y^{(6)}(x_n) - y_n^{(6)} + \frac{1}{7!}h^7(y^{(7)}(x_n) - y_n^{(7)}) + \frac{1}{8!}h^8(y^{(8)}(x_n) - y_n^{(8)}) + \frac{1}{9!}h^9(y^{(9)}(x_n) - y_n^{(9)}) + \frac{h^{10}}{10!}y^{(10)}(\eta)$
Based on Lipschitz condition [3] and assume $|y^{(10)}(\eta)| < M_{10}$, then we get $\|e_{n+1}\| \leq \|e_n + hL_1e_n + \frac{1}{2!}h^2L_2e_n + \frac{1}{3!}h^3L_3e_n + \frac{1}{4!}h^4L_4e_n + \frac{1}{5!}h^5L_5e_n + \frac{1}{6!}h^6L_6e_n + \frac{1}{7!}h^7L_7e_n + \frac{1}{8!}h^8L_8e_n + \frac{1}{9!}h^9L_9e_n + \frac{h^{10}}{10!}M_{10}\|$. Based on norm vector definition [3], we get $\|e_{n+1}\| \leq (1+h\breve{L})\|e_n\| + \frac{h^{10}}{10!}M_{10}$, $\breve{L} =$ *konstanta Lipschitz*. in fact, $\|e_0\| = 0, \|e_1\| \leq \frac{h^{10}}{10!}M_{10}, \|e_2\| \leq (1 + h\breve{L})\frac{h^{10}}{10!}M_{10} + \frac{h^{10}}{10!}M_{10}, \|e_3\| \leq (1+h\breve{L})(1+h\breve{L})\frac{h^{10}}{10!}M_{10} + (1+h\breve{L})\frac{h^{10}}{10!}M_{10} + \frac{h^{10}}{10!}M_{10}, \ldots, \|e_n\| \leq (1+(1+h\breve{L})+(1+h\breve{L})^2+\ldots+(1+h\breve{L})^{n-1})\frac{h^{10}}{10!}M_{10}$. So, we get $\|e_n\| \leq \frac{h^9 M_{10}}{10!\breve{L}}(1+h\breve{L})^n - 1$. Because of h, $(1 + h\breve{L})^n \leq e^{nhl}$, $h = \frac{x_n - x_0}{n}$, $\breve{L} > 0$,$(1 + h\breve{L})^n \leq e^{nhl}$, $h = \frac{x_n - x_0}{n}$, then

$\lim_{h\to 0} \|e_n\| \leq \lim_{h\to 0} \frac{h^9 M_{10}}{10!\check{L}}(e^{(x_n-x_0)\check{L}} - 1) = 0$. So, ninth order Runge-Kutta method is convergence method. $\square$

Simulation Result

In this section we describe simulation result based on the gotten solution by ninth order Runge-Kutta method to solve model on the immunity to infection with *Mycobacterium tuberculosis*.

The models include the interaction between 3 populations of bacteria, 2 populations of macrophages, 4 concentrations of cytokines, and 2 population of T lymphocytes, that are T CD4+ and T $CD8^+$. On the graph BI population, population of intracellular bacteria in young mice and old mice since the beginning infected increase drastically, but in young mice, it decreases after nearly 15×10^5 cell/ml and old mice continue to rise until it reaches $2,3 \times 10^6$ cell/ml. The population of extracellular bacteria in young mice and old mice increase up to $1,8 \times 10^5$, but extracellular bacteria load of young mice decrease up to 7×10^4, and in old mice, it decrease up to $1,5 \times 10^5$. the both of extracellular bacteria stabilize after 40 days. Populations of activated bacteria in young mice and old mice increased drastically since 15 days of infection, and young mice faster than old mice in stabilize. This fact caused the old age human easily attacked tuberculosis.

The concentrate of IL-10 in old mice is more than young mice. The increased of IL-10 can decrease the immunity to activate bacteria so that it increase activated macrophage. This fact caused the old age human easily attacked tuberculosis. The function of $IFN-\gamma$ is to disable infected macrophage so that it is become activated macrophage that is active to disable Mycobacterium tuberculosis. The concentrate of $IFN-\gamma$ in old mice is less than young mice. This fact also caused the old age human easily attacked tuberculosis.

Efficiency of Ninth Order Runge-Kutta Method

Ninth Order Runge-Kutta and Adams Bashforth-Moulton method are convergent because the error of both method are close to zero. In addition to the graph convergence, it also produced the number of iterations and time are presented in Table 3.

Table 3 shows that any value specified tolerance, RK9B method requires more iterations than the methods RK9A, and the method most require iterations to reach

Table 3: Table of Efisiensi

Indikator	Tol (e)	young mice			old mice		
		RK9A	RK9B	ABM9	RK9A	RRK9B	ABM9
Iteration	10^{-1}	92.820	92.816	**93.848**	91.247	91.267	**91.310**
	10^{-3}	133.477	133.482	**133.517**	123.179	123.212	**123.265**
	10^{-5}	174.115	174.128	**174.165**	154.930	154.978	**155.036**
time (secon)	10^{-1}	181,459	**45,3339**	126,440	167,529	**42,9780**	108,9810
	10^{-3}	241,0210	**71,3069**	184,8760	217,4330	**63,1020**	152,9460
	10^{-5}	315,7600	**110,9940**	284,7000	280,9410	**90,5720**	213,2840

the tolerance is ABM9 method. So that we can say that Runge-Kutta method with matrix coefficient value minimal requires more iterations than Runge-Kutta method with matrix coefficient value maximal. However, based on Table 5, RK9B method takes less time than the RK9A method. This is because the ninth order Runge-Kutta relies on a previous step, ie k_1 affect k_2, k_2 influence k_3, and so on. In Methods RK9A value of k_2 is affected k_1, k_3 if influenced k_1 and k_2, k_4 is influenced k_1, k_2, and k_3, and so on, each worth k_i is affected all values of k in advance (k_{i-1}, k_{i-2},..., k_1). While, because the coefficient matrix of the RK9B method is minimal then the value of k_4 is only influenced k_1 and k_3, k_5 is only affected k_1 and k_4, the value of k_i is only affected by two k ie k_1 and k_{i-1}, so that ABM9 method needs more time than the RK9B method.

Then, ninth order Runge-Kutta metode which be compared with ABM9 is RK9B method. Table 5 shows that RK9B method needs the least amount of time than the ABM9 method. so, we can conclude that Ninth Order Runge-Kutta method is more effective than ninth order Adam Bahforth-Moulton.

Effectiveness of Ninth Order Runge-Kutta Method

The data generated from the execution of the effectiveness of such errors are presented in Table 6. Based on the table, iterations that are used to analyze the effectiveness of the ninth order Runge-Kutta method than Ninth Order Adam Bashforth-Moulton is 10.000, 50.000, 100.000, 115.000, 125.000, 150.000, 175.000, and 200.000. At iteration 10.000 to 100.000, it can not be determined the most effective method, because at the 10.000 iterations, ABM9 method has the smallest error, whereas at 50.000 and 100.000 iterations the smallest error occurs in the method RK9B. But at iteration 115.000, and so on indicate that the method RK9A has the smallest error. It can be concluded that the ninth order Runge-Kutta more effective than Ninth Order Adam

Bashforth-Moulton methods to solve a model on the immunity to infection with *Mycobacterium tuberculosis*.

Table 4: Effectiveness in young mice

Iteration (n)	*Error*		
	RK9A	RK9B	ABM9
10.000	76,171886	76,183000	**76,169763**
50.000	12,412641	**12,411799**	12,447050
100.000	4,436146$\times10^{-2}$	**4,434942**$\times10^{-2}$	4,451410$\times10^{-2}$
115.000	**8,113087**$\times10^{-3}$	8,113704$\times10^{-3}$	1,530210$\times10^{-2}$
125.000	**2,613003**$\times10^{-3}$	2,613837$\times10^{-3}$	2,624033$\times10^{-3}$
150.000	**1,537487**$\times10^{-4}$	1,538936$\times10^{-4}$	1,545185$\times10^{-4}$
175.000	**9,044539**$\times10^{-6}$	9,058975$\times10^{-6}$	9,097000$\times10^{-6}$
200.000	**5,322508**$\times10^{-7}$	5,331821$\times10^{-7}$	5,355000$\times10^{-7}$

Table 5: Effectiveness in old mice

Iteration (n)	*Error*		
	RK9A	RK9B	ABM9
10.000	41,216065	**41,188425**	41,189464
50.000	**27,851661**	27,869678	27,935266
100.000	**2,846000**$\times10^{-2}$	2,856079$\times10^{-2}$	2,875000$\times10^{-2}$
115.000	**5,213087**$\times10^{-3}$	5,214104$\times10^{-3}$	6,730210$\times10^{-3}$
125.000	**7,680794**$\times10^{-4}$	7,718964$\times10^{-4}$	7,778736$\times10^{-4}$
150.000	**2,045277**$\times10^{-5}$	2,058641$\times10^{-5}$	2,075871$\times10^{-5}$
175.000	**5,424954**$\times10^{-7}$	5,471520$\times10^{-7}$	5,518000$\times10^{-7}$
200.000	**1,443548**$\times10^{-8}$	1,443549$\times10^{-8}$	1,444000$\times10^{-7}$

CONCLUSION

Based on the results of the discussion, we can conclude that:

1. Ninth Order Runge-Kutta method has the following character:

$$\begin{aligned}
\sum_{i=1}^{m} b_i &= 1, \quad where\ m = 9 \\
\sum_{i=2}^{m} b_i c_i^p &= \frac{1}{p+1}, \ for\ p = 1, 2, 3, ..., m-1 \\
\sum_{i=3}^{m-1} b_i (\sum_{j=2}^{i-1} c_j^q a_{ij}) &= \frac{1}{(q+1)(q+2)}, \ for\ q = 1, 2, 3, ..., m-3
\end{aligned}$$

2. The formula of Ninth Order Runge-Kutta method (RK9A) is:

$$
\begin{aligned}
y_{n+1} &= y_n + \frac{h}{105.000}(5062k_1 + 27.357k_2 + 1.260k_3 + 1.275k_4 + 35.050k_5 \\
&\quad -16.800k_6 + 19.440k_7 + 27.273k_8 + 5.083k_9)
\end{aligned}
$$

   where,

$$
\begin{aligned}
k_1 &= f(x_n, y_n) \\
k_2 &= f(x_n + \frac{h}{6}, y_n + \frac{h}{6}k_1) \\
k_3 &= f(x_n + \frac{h}{3}, y_n + \frac{h}{6}(k_1 + k_2)) \\
k_4 &= f(x_n + \frac{h}{3}, y_n + \frac{h}{3}(-k_1 + k_2 + k_3)) \\
k_5 &= f(x_n + \frac{h}{2}, y_n + \frac{h}{10}(k_1 + 2k_2 + k_3 + k_4)) \\
k_6 &= f(x_n + \frac{2h}{3}, y_n + \frac{h}{48}(-10k_1 + 2k_2 + 25k_3 + 9k_4 + 6k_5)) \\
k_7 &= f(x_n + \frac{2h}{3}, y_n + \frac{h}{240}(65k_1 + 27k_2 + 27k_3 - 8k_4 + 93k_5 - 44k_6)) \\
k_8 &= f(x_n + \frac{5h}{6}, y_n + \frac{h}{5.4546}(-13.291k_1 + 24.768k_2 + 942k_3 + 3.336k_4 + \\
&\quad 22.542k_5 + 6.612k_6 + 546k_7)) \\
k_9 &= f(x_n + h, y_n + \frac{h}{5.083}(-4.844k_1 + 984k_2 + 2.912k_3 + 125k_4 + 296k_5 \\
&\quad +1.008k_6 + 102k_7 + 4.500k_8))
\end{aligned}
$$

3. Ninth order Runge-Kutta is convergent method because it satisfy : $\|e_n\| \leq \frac{h^9 M_{10}}{10!\check{L}}(e^{(x_n - x_0)\check{L}} - 1)$, where $\check{L}$ is Lipschitz constant.

4. Ninth Order Runge-Kutta is more efficient and more effective than Ninth Order Adam Bashforth-Moulton to solve a model on the immunity to infection with *Mycobacterium tuberculosis*

REFERENCES

[1] Adhimah, Isrokotul. 2011. *Model Matematika Pada Sistem Kekebalan Tubuh Terhadap Infeksi Mycobacterium tuberculosis dengan Pengaruh Usia.* not published (Thesis). Malang: Universitas Islam Negeri Maulana Malik Ibrahim.

[2] Conte, Samuel. 1993. *Dasar-Dasar Analisis Numerik.* Jakarta: Erlangga.

[3] Dafik. 1998. *Metode Numerik I.* Jember: Universitas Jember.

[4] Dafik. 1999. *Persamaan Differensial biasa(PDB): Masalah nilai awal dan nilai batas.* Jember : FKIP Universitas jember.

[5] Dafik. 2008. *Pengantar Persamaan Differensial Parsial dan Solusi Analitik.* Jember : Universitas jember.

[6] Dafik . 2009. *Metode Numerik dan Aplikasinya.* Jember: FKIP Universitas Jember.

[7] Dafik . 2010. Metode Numerik dalam Menyelesaikan Fungsi-Fungsi Aproksimasi. Jember: FKIP Universitas Jember.

[8] Faisol, A. 2001. *Penerapan Metode Runge-Kutta Order Empat Untuk Menyelesaikan Model Penyebaran Virus Dengue Oleh Nyamuk Aedes aegypti.* Not published (Thesis). Jember: Universitas Jember.

[9] Fausett,Lauren V . 2008. *APPLIED NUMERICAL ANALYSIS USING MATLAB second edition.* USA :Pearson Education Inc.

[10] Finizio dan Gladas. 1988. *Ordinary Differential Equation with Modern Application.*Jakarta: Erlangga.

[11] Friedman, A., Turner, J., dan Szomolay, B. 2008. *A Model on the Influence of Age on Immunity to Infection with Mycobacterium tuberculosis.* NIH Public Access. Exp Gerontol. 43(4). Hal 275-285.

[12] Lambert, JD. 1997.*Numerical Methods for Ordinary Differential Systems.* New York: JOHN WILEY and SONS.

[13] Sahid. 2005. *Pengantar Komputasi Numerik dengan MATLAB.*Yogyakarta: ANDI OFFSET.

[14] Shampine, L.F. 1994. *Numerical Solution Of Ordinary Differential Equation.* London: Chapman and Hall.

[15] Shodiq, Lukman Jakfar. 2012. *Efektifitas Metode Runge-Kutta Orde Tujuh Terhadap Motode Multistep Adams Orde Enam pada Model Penyebaran Penyakit Tuberkulosis* (not published). Thesis. Jember: Fakultas Keguruan dan Ilmu Pendidikan Universitas Jember.

[16] Susanti, N.I. 2010. *Efefktifitas Metode Multistep Linier (MML) Implisit Order Lima Untuk Menyelesaiakan Model Persamaan Penyebaran Bakteri Leptospira* (not published). Thesis. Jember: Fakultas Keguruan dan Ilmu Pendidikan Universitas Jember.

[17] Universitas Jember. 2012. *Pedoman Penulisan Karya Ilmiah.* Jember: Badan Penerbit Universitas Jember.

[18] Yanse, Nina Made Nova. 2012. *Efektifitas Metode Adam Bashforth Moulton Order Sembilan dalam Menganalisis Model Penyebaran Penyakit Demam Berdarah Dengue (DBD).*(not published). Thesis. Jember: Fakultas Keguruan dan Ilmu Pendidikan Universitas Jember.

[19] Yustica, Ayu. 2010. *Efektifitas Metode Runge-Kutta Order Lima Untuk Menyelesaikan Model Penyebaran Virus Avian Influenza (flu burung).*(not published). Thesis. Jember: Fakultas Keguruan dan Ilmu Pendidikan Universitas Jember.

Internet

[20] Hidayat,Yuristiarso.2011.*Jatim catat kasus TBC naik 30%.* http://www.bisnisjatim.com /index.php/2011/03/28/jatim-catat-kasus-tbc-naik-30/.(30 Juni 2012).

[21] Medicastore .2011. *Penyakit TBC.*http://medicastore.com/tbc/penyakit_tbc.htm. (9 Agustus 2012).

[22] Moler, Cleve. 2000. *MATLAB News & Notes-Winter 2000.* http://www.mathworks.-com/company/newsletters/news_notes/clevescorner/winter2000.cleve.html. (6 Maret 2013).

[23] Vivanews. 2012. *Kasus TBC Indonesia Peringkat Empat Dunia.* http://nasional. news.viva.co.id/news/read/315414-kasus-tbc-di-ri-terbesar-nomor-empat-dunia. (22

Juli 2012).

[24] WHO. 2012. *Global tuberculosis report*.http://www.who.int/topics/tuberculosis/en/.(29 Juni 2012).

[25] Wikipedia. 2012. *Tuberkulosis*.http://id.wikipedia.org/wiki/Mycobacterium-tuberculosis. (8 Agustus 2012).