Dynamics of Macrofages and Cytokines after Myocardial Infarction

Usman Pagalay[1], Luluk Handayani[2], Abdullah Azzam[3]
[1,2,3]Department of Mathematics, Faculty of Science and Technology,
Universitas Islam Negeri Maulana Malik Ibrahim Malang, Indonesia. 65144

{usmanpagalay@yahoo.co.id[1], lulukhandayani68@gmail.com[2], abdullahazzamt11@gmail.com[3]}

Abstract. The mathematical model of populations of Macrophages and Cytokines after Myocardial Infraction explains the macrophages activation following by cytokines secretion in the left ventricle. Those models appears to be a system of six simultaneous non-linear ordinary differential equations, involving inactivated macrophages $M_u(t)$, classical activated macrofages $M_1(t)$, alternative activated macrophages $M_2(t)$, interleukin-10 $I_{10}(t)$, TNF-α $T_\alpha(t)$ and interleukin-1 $I_1(t)$. The method used in this article is numerical Runge-Kutta method with computer assistance for obtaining the numerical solution and gathering several informations including the crucials of cytokines on the development of macrophages.

Keywords: *Mathematical model, Macrophage, Cytokines, Myocardial Infraction.*

1 Introduction

Myocardial infarction is a disease found in the myocardia, this symptom is present in myocytes in the process of necrosis (cell death) and acute inflammation due to prolonged ischemia (lack of oxygen). Myocardial infarction occurs when the blood flowing to the part of the heart muscle is blocked .

Cardiac macrophages react to myocardial ischemia causing a significant increase in the number of macrophages in death. Monocytes are produced in the bone marrow and spleen after myocardial infarction and enter the infarct area then differentiate into macrophages [3]. Macrophages play the role of innate immune defenses and are involved in tissue remodeling and repair. See [4].

Activation of macrophages consists of two different sets of Ly-6chigh macrophages or classically activated macrophages and Ly-6clow macrophages or alternatively activated macrophages. The mathematical model of macrophage activation in the left ventricle remodeling after myocardial infarction which was presented in [14] explains that the classically activated macrophages secrete proinflammatory cytokines namely IL-1 and TNF-α, whereas alternatively activated macrophages produce anti-inflammatory cytokines, IL-10 [14]. The model became a reference in this study.

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2 Material and Methods

The mathematical model proposed in [14] is the following :

$$
\begin{aligned}
\frac{dM_u(t)}{dt} &= M - k_2 M_u(t)\frac{I_1(t)}{I_1(t)+c_{I1}} - k_3 M_u(t)\frac{T_\alpha(t)}{T_\alpha(t)+c_{T_\alpha}} \\
&\quad - k_4 M_u(t)\frac{I_{10}(t)}{I_{10}(t)+c_{I10}} - \mu M_u(t) \\
\frac{dM_1(t)}{dt} &= k_2 M_u(t)\frac{I_1(t)}{I_1(t)+c_{I1}} + k_3 M_u(t)\frac{T_\alpha(t)}{T_\alpha(t)+c_{T_\alpha}} + k_{11}\, M_2(t) \\
&\quad - k_1 M_1(t) - \mu M_1(t) \\
\frac{dM_2(t)}{dt} &= k_4 M_u(t)\frac{I_{10}(t)}{I_{10}(t)+c_{I10}} + k_1 M_1(t) - k_{11} M_2(t) - \mu M_2(t) \\
\frac{dI_{10}(t)}{dt} &= k_5 M_2(t)\frac{c_1}{c_1 + I_{10}(t)} - d_{I10} I_{10}(t) \\
\frac{dT_\alpha(t)}{dt} &= (k_6 M_1(t) + \lambda M_c)\frac{c}{c + I_{10}(t)} - d_{T\alpha} T_\alpha(t) \\
\frac{dI_1(t)}{dt} &= (k_7 M_1(t) + \lambda M_c)\frac{c}{c + I_{10}(t)} - d_{I1} I_1(t)
\end{aligned}
\tag{2.1}
$$

Table 2. 1 Parameter Values for Mathematical Model (see [14])

Parameter	Value	Units	Interpretation
μ	0.2	Per day	Emigration from macrofages
k_1	0.075	Per day	Transition constant from M_1 to M_2
k_{11}	0.05	per day	Transition constant from M_2 to M_1
k_2	0.1	ml/pg/day	Activation constant of macrofages M_1 by I_1
c_{I10}	5	pg/ml	Effectivity of I_{10}
c_{I1}	10	pg/ml	Constant I_1
k_3	1	cell/ml	Activation constant of macrofages M_1 by secretion from T_α
c	25	pg/ml	Effectivity of I_{10} as an inhibitor of T_α
c_1	100	pg/ml	Effectivity of self-inhibitority of I_1
k_4	0.3	cell/ml	Constant of macrofages M_2
k_5	5 x 10^{-4}	Pg/sel/day	Secretion constant of I_{10} by M_2
k_6	7 x 10^{-4}	pg/cell/day	Secretion constant from M_1 and miosit
k_7	5 x 10^{-4}	pg/cell/day	Secretion constant of I_1
d_{I10}	2,5	Per day	Decay rate of I_{10}
$d_{T\alpha}$	55	Per day	Deposition rate of secretion T_α
d_{I1}	10,5	Per day	Deposition rate of I_1
λ	5 x 10^{-6}	Pg/ml/cell/day	Secretion rate T_α by miosit

$M_u(0)$	2000		Initial value
$M_1(0) = M_2(0)$	0		Initial value
$I_1(0) = I_2(0) = I_3(0)$	0.1		Initial value

The system of equations (2.1) is a system of ordinary nonlinear differential equations that requires a special method in solving them. One of them is the runge-kutta method. The Runge Kutta method was developed by Carl Runge and Wilhelm Kutta in order to mimic the results of the Taylor series approach [12]. To get accurate results, a small Δx or h is needed, in the use of a small Δx it causes a longer count time. The Runge Kutta method is an alternative to the Taylor series method that provides greater accuracy of results and without having to perform differential analytics repeatedly [13].

The fourth Order Runge Kutta Method is the following

$$y_{i+1} = y_i + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

where

$$k_1 = f(x_i, y_i)$$
$$k_2 = f(x_i + \frac{h}{2}, y_i + \frac{h}{2}k_1)$$
$$k_3 = f(x_i + \frac{h}{2}h, y_i + \frac{1}{2}k_2)$$
$$k_4 = f(x_i + h, y_i + hk_3)$$

In the practical situation, it is often useful to optimize the accuration of calculation of numerical Runge-Kutta method by using the better composition in the method via (4,5) explicit formula. The Dormand-Prince pair which has been addopted to be an accurate Modified-Runge-Kutta-based numerical algorithm, called ODE45 algorithm, is a one-step method for calculating the completion of $y(t_n)$ used one solution at the previous time point, $y\ (t_{n-1})$. Due to the bettter accuracy, we will use this algorithm along with MATLAB to obtain the desired numerical behavior of the system [11].

The main objective of this article is, however, to obtain the clues and insight of how population of interleukins gives influence to the population of macrofages. The tuning of the rate of change of interleukin is hypotesized to give the significant-simultaneous change to to the real time rate of change of macrofages. To reach the objective, we first obtain the fixed point semi-analitically and numerically. Further, in the following section, we give an interpretation and numerical result as the clue to approximate the long-term behavior of the system.

3 Results and Discussion

The fixed points of the system (2.1) is obtained analitically and will be denoted by $M_u^*, M_1^*, M_2^*, I_{10}^*, T_a^*$, and I_1^*. We constrained the solution to satisfy

$$\frac{dM_u}{dt} = 0,\ \frac{dM_1}{dt} = 0, \frac{dM_2}{dt} = 0, \frac{dI_{10}}{dt} = 0, \frac{dT_\alpha}{dt} = 0 \text{ dan } \frac{dI_1}{dt} = 0 \qquad (3.1)$$

Further we have

$$0 = M - k_2 M_u^* \frac{I_1^*}{I_1^* + c_{I1}} - k_3 M_u^* \frac{T_\alpha^*}{T_\alpha^* + c_{T_\alpha}} - k_4 M_u^* \frac{I_{10}^*}{II_{10}^* + c_{I10}} - \mu M_u^*$$

$$
\begin{aligned}
0 &= k_2 M_u^* \frac{I_1^*}{I_1^* + c_{I1}} + k_3 M_u^* \frac{T_\alpha^*}{T_\alpha^* + c_{T_\alpha}} + k_{11} M_2^* - k_1 M_1^* - \mu M_1^* \\
0 &= k_4 M_u^* \frac{I_{10}^*}{I_{10}^* + c_{I10}} + k_1 M_1^* - k_{11} M_2^* - \mu M_2^* \\
0 &= k_5 M_2^* \frac{c_1}{c_1 + I_{10}^*} - d_{I10} I_{10}^* \\
0 &= (k_6 M_1^* + \lambda M_c) \frac{c_1}{c_1 + I_{10}^*} - d_{T\alpha} T_\alpha^* \\
0 &= (k_7 M_1^* + \lambda M_c) \frac{c_1}{c_1 + I_{10}^*} - d_{I1} I_1^*
\end{aligned}
\tag{3.2}
$$

Hence, we obtain the following

$$
\begin{aligned}
M_u^* &= \frac{M}{k_2 \frac{I_1^*}{I_1^* + c_{I1}} + k_3 \frac{T_\alpha^*}{T_\alpha^* + c_{T_\alpha}} - k_4 \frac{I_{10}^*}{I I_{10}^* + c_{I10}} + \mu} \\
M_1^* &= \frac{M_u^* \left(k_2 \frac{I_1^*}{I_1^* + c_{I1}} + k_3 \frac{T_\alpha^*}{T_\alpha^* + c_{T_\alpha}} \right) + k_{11} M_2^*}{k_1 + \mu} \\
M_2^* &= \frac{k_4 M_u^* \frac{I_{10}^*}{I_{10}^* + c_{I10}} + k_1 M_1^*}{k_{11} + \mu} \\
I_{10}^* &= \frac{k_5 M_2^* \frac{c_1}{c_1 + I_{10}^*}}{d_{I10}} \\
T_\alpha^* &= \frac{(k_6 M_1^* + \lambda M_c) \frac{c_1}{c_1 + I_{10}^*}}{d_{T\alpha}} \\
I_1^* &= \frac{(k_7 M_1^* + \lambda M_c) \frac{c_1}{c_1 + I_{10}^*}}{d_{I1}}
\end{aligned}
\tag{3.3}
$$

By subtituting the parameter values from Table 2.1, and setting the value of $c_{T\alpha}$(evectivity constant of T_α) to be 0.5 pg/ml, M_c (density of miosit) to be 10^{-5} cell/ml and the differentiation of monosit to be 10000 cell/ml, with computational help of MATLAB, we have the following result for fixed point.

$$
\begin{aligned}
(M_u^*, M_1^*, M_2^*, I_{10}^*, T_\alpha^*, I_1^*) = (&15554.76376, \\
&21735.24401, 12079.99222, 2.48047, 0.25166, 0.94158)
\end{aligned}
$$

Using 4th-order Runge-Kutta method we obtain the following numerical result for the relatively long time behavior of each variable:

Tabel 3. 2 Numerical Solution of the Mathematical Model using 4th-order Runge-Kutta Method

Time (Day)	$M_u(t)$	$M_1(t)$	$M_2(t)$
$t = 0.01$	2093.056813729	2.272394661	0.119855577
$t = 0.02$	2186.899948707	4.473082276	0.243480504
$t = 0.03$	2281.204731533	5.562888925	0.370104752
$t = 0.04$	2375.736830751	6.232096788	0.499160281
⋮	⋮	⋮	⋮
$t = 90$	15554.763527729	21735.245246907	12709.990494324
Time (Day)	$I_{10}(t)$	$T_\alpha(t)$	$I_1(t)$
$t = 0.01$	0.097531286	0.057741975	0.090039515
$t = 0.02$	0.095124126	0.033356539	0.081082224
$t = 0.03$	0.092777017	0.019285294	0.073024315
$t = 0.04$	0.090488488	0.011165999	0.065773645
⋮	⋮	⋮	⋮
$t = 90$	2.480470719	0.251660894	0.941588383

As the comparison, the result obtained by ODE45 algorithm is the following:

Tabel 3. 3 Numerical Solution of the Mathematical Model using ODE45 Algorithm

Time (Day)	$M_u(t)$	$M_1(t)$	$M_2(t)$
$t = 0.01$	2093.053122763	2.731087883	0.119853320
$t = 0.02$	2186.894825080	4.478208005	0.243478402
$t = 0.03$	2281.119943114	5.568190065	0.370104197
$t = 0.04$	2375.732629731	6.232951441	0.499162945
⋮	⋮	⋮	⋮
$t = 90$	15554.764065455	21735.245051221	12709.990152284
Time (Day)	$I_{10}(t)$	$T_\alpha(t)$	$I_1(t)$
$t = 0.01$	0.097531286	0.057703220	0.090039483
$t = 0.02$	0.095124126	0.033308284	0.081082181
$t = 0.03$	0.092777017	0.019240813	0.073024274
$t = 0.04$	0.090488489	0.011139440	0.065773625
⋮	⋮	⋮	⋮
$t = 90$	2.480470654	0.25167585240	0.941588583

The initial values for the system are $M_u(0) = 2 \times 10^3$ cells / ml, $M_1(0) = 0$ cells / ml and $M_2(0) = 0$ cells / ml. Using this initial condition, inactive macrophages population increases at t <10 and decreases at t <20, furthermore, the population of inactive macrophages is constantly constant. On the otherhand, the population of classically activated macrophages has increased at t <20 and alternative activated macrophages have increased since t <25, as time goes on, the populations of both tend to be constant. The 4th-order Runge Kutta method-based graph assisted by the program matlab shows that the value of $M_u(t)$ tends to be fixed arround 15554.763527729 cells / ml, $M_1(t)$ tends to be fixed arround 21735.245246907 cells / ml, $M_2(t)$ tends to be fixed arround 12709.990494324 cells / ml. Whereas in the graph the results using

ODE45, we have $M_u(t)$ tends to be fixed arround 15554.764065455 cells / ml $M_1(t)$ tends to be fixed arround 21735.245051221 cells / ml, and $M_2(t)$ tends to be fixed arround 12709.990152284 cells / ml (see Fig. 1).

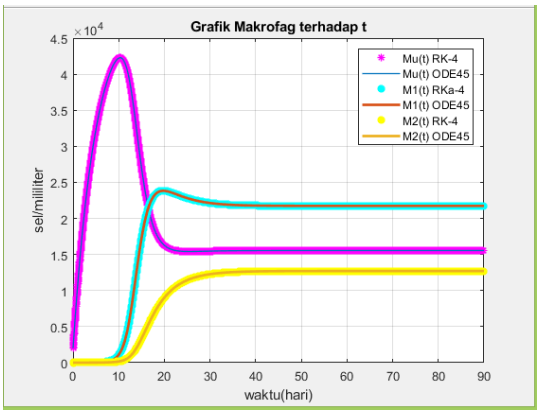

Fig. 1. Numerical Solution of $M_u(t), M_1(t), M_2(t)$ on $t = 90$

Next, we set $I_1(0) = I_{10}(0) = T_\alpha(0) = 0.1$ pg / ml. Changes in the concentration of IL-1, IL-10 and TNF-α have increased since t <30 and then the concentration of each cytokine tends to be constant. The graph of the results using the 4th-order Runge-Kutta method shows values of IL-1, IL-10 and TNF-α, that is $I_{10}(t)$ is asymptotic towards 2.480470719 pg / ml, T_α(t) is asymptotic towards 0.251660894 pg / ml, $I_1(t)$ is asymptotic towards 0.941588383 pg / ml. Whereas in the graph the results of ODE45 $I_{10}(t)$ is asymptotic towards 2.480470654 pg / ml, $T_\alpha(t)$ is asymptotic towards 0.25167585240 pg / ml, $I_1(t)$ is asymptotic towards 0.941588583 pg / ml (see Fig. 2).

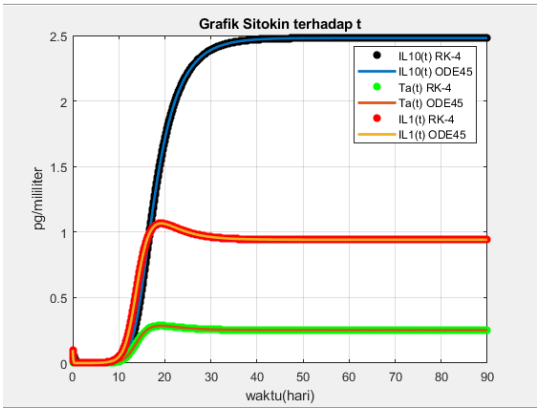

Fig. 2. Numerical Solution of $I_1(t), I_{10}(t), T_\alpha(t)$ on $t = 90$

To see the effect of the rate of growth of cytokines on the population of macrophages, constant values were given for $\dot{I_{10}}$(t), $\dot{T_\alpha}$(t), and $\dot{I_1}$(t) by 0.1 pg / ml and 0.0001 pg / ml, respectively.

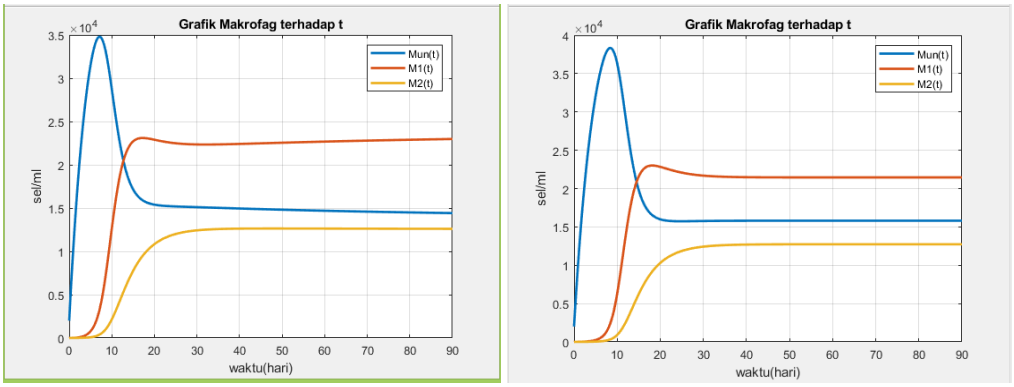

Fig. 3. Numerical Solution for macrofages with $\dot{I_1}(t) = 0.1$ (left), and with $\dot{I_1}(t) = 0.0001$ (right)

In Fig. 3, the influence of tuning the growth-rate for the variable $I_1(t)$ tunrs out to be unsignificant. It doesn't massively change the whole population of macrofages. the inactive macrophages M_u(t) increases until the 8th day and then decreases since day 9. While, the population of classically activated macrophages M_1(t) increases up to day 90. Alternative activated macrophages M_2(t) increases along certain period and tends to be constant until the 90th day.

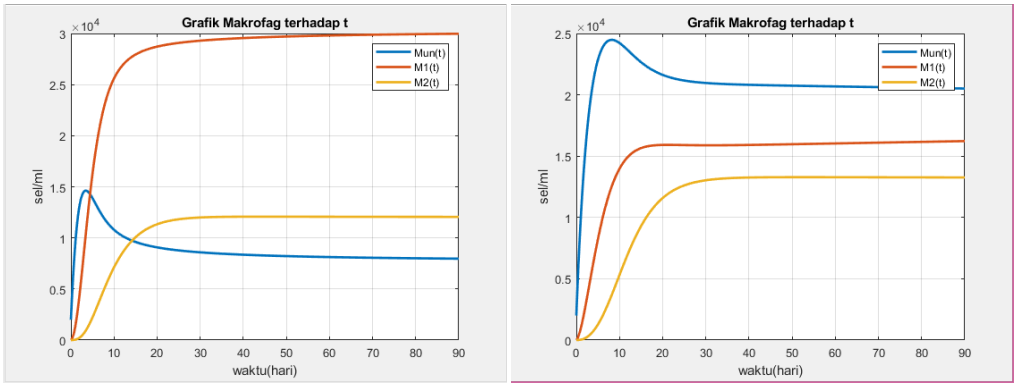

Fig. 4. Numerical Solution for macrofages with $\dot{T_\alpha}(t) = 0.1$ (left), and with $\dot{T_\alpha}(t) = 0.0001$ (right)

In Fig. 4, we can observe that the inactive macrophages M_u(t) increases until the third day and starts to decrease at day 4. The growth occurred in the population of classically activated macrophages M_1(t) until the 90th day. Meanwhile the decaying phenomena occurred in the population of alternative activated macrophages M_2(t) and also tends to be constant towards the 90th day. Based on the graph it can be concluded that giving a relatively high growth-rate for T_α(t) in about 0.1 units results in a significant growth in M_1(t) and decay in M_u(t). While giving a relatively low growth-rate for T_α(t) in about 0.0001 units in implies that the population of each macrophages increases and tends constant.

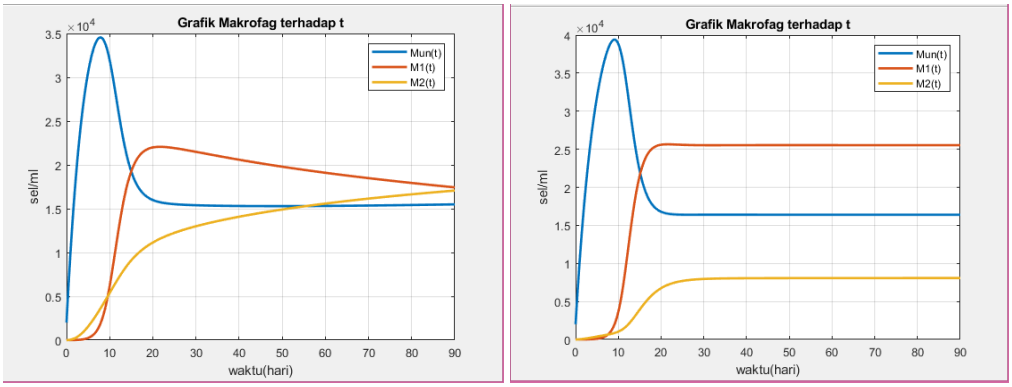

Fig. 5. Numerical Solution for macrofages with $\dot{I_{10}}(t) = 0.1$ (left), and with $\dot{I_{10}}(t) = 0.0001$ (right)

In the figure above, we observe that the inactive macrophages M_u(t) increases until the 8th day and then decreases on day 9. The growth occurs in the population of alternatively activated macrophages M_2(t) until the 90th day. Meanwhile the classically activated macrophages M_1(t) have increased until the 20th day and have decreased until the 90th day. Based on the graph it can be concluded that giving a growth-rate value for I_{10} in about 0.1 units results in a significant growth for M_2(t) and a decay for M_1(t) and M_u(t). While giving a growth-rate value for I_{10} in about 0.0001 implies that the population of macrophages tends to be constant, in other words it does not result in a significant increase or decrease.

4 Conclusion

Based on the results of the simulation of mathematical models of macrophages and cytokines after myocardial infarction using the 4th-order numerical Runge Kutta method and ODE 45 from t = 0 to t = 90 with the size of the steps h = 0.01, it can be concluded that the solutions of the two methods are close together and almost the same, that can be observed by a graph of the solution of both methods. Giving a constant value of 0.1 on I_1(t) and T_α(t) affects the increase in M_1(t), while giving a relatively large value to the rate of change I_1(t) and T_α(t) produces a significant effect on M_1(t), and giving a relatively large value for I_{10}(t) produces a significant effect on M_2(t).

References

[1] Bober, W. Numerical and Analytical Methods with Matlab for Engineers and Scientists. New York: CRC Press. (2013).

[2] Djojodiharjo, H. Numerical Method. Jakarta: PT. Gramedia Main Library. (2000)

[3] Dutta, P. d. Monocytes in Myocardial Infarction. *HHS Public Access*, 1066-1070. (2015).

[4] Gombozhapova, A., et al. Machropage Activation and Polarization in Post-Infraction Cardiac Remodeling. Journal of Biomedical Science, 13-24. (2017).

[5] Kartono. Persamaan Diferensial Biasa. Semarang: Graha Ilmu. (2011).

[6] Kharab, A., & Guenther, R. B. An Introduction to Numerical Methods A Matlab Approach. Boca Raton-London: CRC Press. (2011).
[7] Munir. *Metode Numerik.* Bandung: Informatika. (2007).
[8] Pagalay, Usman. Optimal control of innate immune response on lung-macrophages in pneumonia. AIP Conference Proceedings. 2084, (1). 020009 (2019).
[9] Pagalay, Usman. Optimal Control of Innate Immune Response in Infected Lung-Macrophages by Streptococcus Pneumoniae. Symposium of Biomath, pp. 68. (2018).
[10] Pagalay, Usman. Dynamic Analysis of Mathematical Model of Glucose, Insulin Concentration, and Beta Select Cycles of Diabetes Mellitus Disease. Proceedings of the International Conference on Green Technology 8 (1), 413-420. (2017).
[11] Sahid. Introduction to Numerical Computing with Matlab. Yogyakarta: Andi Offset. (2005).
[12] Suarga. *Komputasi Numerik.* Makasar: Andi Yogyakarta. (2012).
[13] Triatmodjo, B. *Metode Numerik Dilengkapi dengan Program Komputer.* Yogyakarta: Beta Offset. (2002).
[14] Wang, Y., et al. Mathematical Modeling and Stability Analysis of Machropage Activation in Left Ventricular Remodeling Post-Myocardial Infarction. BMC Geonomics, 1471-2164. (2012).
[15] Weinberger, T., & Schulz, C. Myocardial Infarction: A Critical Role of Macrophages In Cardiac Remodeling. Frontiers in Physiology, 107. (2015).