



Available online at <http://scik.org>

Commun. Math. Biol. Neurosci. 2021, 2021:3

<https://doi.org/10.28919/cmbn/5216>

ISSN: 2052-2541

THE CELL-TO-CELL TRANSMISSION OF GUILLAIN-BARRE SYNDROMES: MODELING AND ANALYSIS

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Abstract. Guillain-Barre Syndrome (GBs) is an autoimmune disease that interchangeability of functions immune cells so the immune cells do not work properly. In people with GBs, immune cells destroy healthy cells, thereby reducing the growth rate of healthy cells. One of the causes of GBs is Zika virus infections. GBs in Indonesia has been around since 1859, but this incident is still rarely identified because the symptoms of leg pain and rheumatism have been complained about by many people with various causes. The epidemiological mathematical model for GBs has been modified, with a focus on cell-to-cell interactions, to study the behavior of the GBs transmission by involving healthy cells, infected cells, and immune cells. The mathematical model has considered the role of immune cells in every healthy cell interaction so it can inhibit the interaction of infected cells with healthy cells. The model created is a system of non-linear differential equations with saturated incidence rates. The mathematical model obtained will be analyzed using a dynamical analysis. The stability analysis around the equilibrium point is studied by analyzing the eigenvalues of the Jacobian matrix at the equilibrium point. In the end, the numerical simulation is analyzed to ensure the analytical result. Then the conclusion from the analysis results is described as a solution to the problem.

Keywords: autoimmune; existence; Guillain-Barre syndrome (GBs); stability; Zika.

2010 AMS Subject Classification: 37C25, 37N25, 39A30.

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Received November 16, 2020

1. INTRODUCTION

Guillain-Barre syndrome (GB's) is a neurological disorder called acute poly Neurotherapy one of which is caused by Zika virus infection [1]. The Zika virus (ZIKV) emerging and transmitted by the Aedes mosquito is currently a challenge for health services in countries experiencing outbreaks. ZIKV infection is mild, but in some cases, it may be mild has progressed to neurological disease such as microcephaly in infants and Guillain-Barré (GBS) in adult's syndrome. GBS is an autoimmune disorder that affects peripheral nerves. ZIKV first appeared in South America for several years [1] [2]. The mildest effects of GBs varied considerably, while the most severe effects were maximum within 4 (four) weeks. GB's disease has a variety of cases including acute inflammatory demyelinating polyneuropathy (AIDP) which is common in the Western world. Other types of GBs are acute motor axonal neuropathy (AMAN) which often occurs in Asia and Japan, the Miller-Fisher syndrome (MFS) type, and overlap syndrome between GBs-MFs. Approximately 10% of GBs sufferers experience secondary nerve damage in the first 8 (eight) weeks [2]. Based on the results of the study [2][3], about 5% of patients who were initially diagnosed with GBs, were suffering from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Now, GB's is still one type of severe disease, even though there are treatments for GBs. Approximately 25% of people with GBs need artificial ventilation assistance, 20% of patients are unable to walk for 6 months, and 3-10 patients die. The usual effects of GBs include pain, fatigue, or residual complaints with a period of months or years [2]. Based on data from the ministry of health [3], GBs has existed in Indonesia since 1859. The name Guillain-Barre is taken from two French scientists who suffered from paralysis and then recovered when he received medical treatment. GB's is considered a rare disease because it only affects 1 in 100,000 people each year.

The epidemiological mathematical model of Guillain-Barre Syndrome was proposed in some research. In 2007 Iwami et. al.[4] studied the GBs model to investigate three stages of the disease namely tolerance, flare-up, and dormancy state. Iwami et. al.[5] developed the research by observing the effect of molecular mimicry on disease conditions in 2009. Another research on GBS was conducted by Elettebry et. al. in 2019[6] and Sari et. al.[7] in 2020. Elettebry et. al.

observed changes in model dynamics with four different types of functional immune response. Lisa et al. examine a model by considering cross-reactive immunity and the Holling type II functional immune response. The model building assumption in this study resulted in different observations of dynamic behavior. However, in general, the molecular immune response is the main point in the study of GBs. This becomes more interesting when it is linked to the Zika virus as one of the causes of autoimmune conditions. In this case, Kumar and Delogu's [8] study describes the immune response mechanism that results in autoimmune conditions.

In the case of disease epidemiology, there are several interpretation results obtained when the assumptions are different. In this study, the authors chose the problem formulation of how the dynamic behavior of the epidemiology of GBs, when analyzed analytically and numerically, assumed the rate of occurrence was saturated. This study was conducted to develop an epidemiological model of Guillain-Barre Syndrome with a saturated incidence rate. So that it can enrich the epidemiological model, especially the epidemiological model of GBs.

A modified model for Guillain-Barre Syndrome are studied by identify the interaction between between healthy cell healthy cell (H), infected cell (F), and immune cell (C) [3] [4]. We assume the birth rate of a healthy cell is dynamically growing with parameter α , the interaction between healthy cells and infected cells rates with parameter β_1 , and interactions between healthy cells and immune cells with parameter β_2 . The parameter γ is the rate of immune cell interaction when facing the presence of healthy cells, with parameter v as a speed inhibiting parameter due to the role of immune cells in the systems. Meanwhile, the death rate of the cell population is shown respectively by the parameters μ_1 , μ_2 and μ_3 represents the rate of damage rate of healthy cells, the damage rate to infected cells, and the rate of damage to immune cells. Then a modified model of Guillain-Barre Syndrome is shows in the following system.

$$(1) \quad \begin{aligned} \frac{dH(t)}{dt} &= \alpha H(t) - \frac{\beta_1 H(t)F(t)}{1 + vC(t)} - \frac{\beta_2 H(t)C(t)}{1 + vC(t)} - \mu_1 H(t); \\ \frac{dF(t)}{dt} &= \frac{\beta_1 H(t)F(t)}{1 + vC(t)} - \gamma F(t)C(t) - \mu_2 F(t); \\ \frac{dC(t)}{dt} &= \beta_2 H(t)C(t) + \gamma F(t)C(t) - \mu_3 C(t). \end{aligned}$$

Model (1) is a nonlinear differential equation that does not have an explicit time-dependent solution. Hence, we study these models over a long period of time. By changing the right-hand

side with zero, then the equilibrium point of model (1) are at the following.

$$(2) \quad EP_0 = (0, 0, 0); EP_1 = \left(\frac{\mu_2}{\beta_1}, \frac{\Delta_1}{\beta_1}, 0 \right); EP_2 = \left(\frac{\mu_3}{\beta_2}, 0, \frac{\Delta_1}{\beta_1 + v\Delta_1} \right);$$

$$(3) \quad EP_3 = \left(0, \frac{\mu_3}{\gamma}, -\frac{\mu_2}{\gamma} \right); \text{ and } EP_4 = (F_4, H_4, C_4).$$

Where,

$$\Delta_1 = \alpha - \mu_1, \Delta_2 = 1 + vC_4;$$

$$F_4 = \frac{\mu_3\Delta_1\Delta_2}{(\mu_2\beta_2 + \gamma\Delta_1)\Delta_2 + \gamma\Delta_1}; \text{ and } H_4 = \frac{\mu_3(\mu_2 + \gamma C_4)\Delta_2}{(\mu_2\beta_2 + \gamma\Delta_1)\Delta_2 + \gamma\beta_2 v C_4^2}.$$

2. MATHEMATICAL ANALYSIS

In biological problems, the positivity of the system needs to be analyzed to ensure that the system solution is positive. The following lemma proved that system 1 has positive solutions at infinite times.

Lemma 2.1. *Suppose the model 1 have positive initial values $H(0) \geq 0, F(0) \geq 0, C(0) \geq 0$, then the solution $(H(t), F(t), C(t))$ are positives for all time $t \geq 0$.*

Proof. To prove the positive solution, it is sufficient to show all trajectories of system 1 are nonnegative for time $t > 0$. The first equation of system (1), which is health cells over time t is given by the following inequality.

$$(4) \quad \frac{dH(t)}{dt} \geq - \left(\frac{\beta_1 F(t)}{1 + vC(t)} + \frac{\beta_2 C(t)}{1 + vC(t)} + \mu_1 \right) H(t);$$

By solving the inequality, and taking limit $t \rightarrow \infty$, we have

$$(5) \quad H(t) \geq H_0 \exp \left\{ - \left(\mu_1 t + \int \frac{\beta_1 F(t) + \beta_2 C(t) + \mu_1 v C(t)}{1 + vC(t)} dt \right) \right\}$$

$$(6) \quad \liminf_{t \rightarrow \infty} H(t) \geq 0.$$

Similarly, in the same way, the positivity of equation $F(t)$ and $C(t)$ when t goes to infinity are proved. \square

2.1. Existence of Equilibrium. The existence of an equilibrium point needs to be analyzed to ensure that the observed equilibrium point is in the invariant area. The conditions for the existence of the equilibrium point model 1 can be shown in the following table:

TABLE 1. Existence and Local Stability Condition of the Equilibria

Eq. Point	Existence	Conditions
EP_0	Always Exists	-
EP_1	Exist	$\Delta_1 > 0$
EP_2	Exist	$\Delta_1 > 0$
EP_3	Not Exist	-
EP_4	-	$C_4 \geq 0$

To show the conditions for the existence of point EP_4 , it is necessary to analyze the positivity of C_4 as follows. C_4 is positive root of

$$(7) \quad P(C_4) = \gamma\beta_2\nu C_4^2 - \beta_1 C_4 - \gamma\mu_3(\Delta_1\Delta_2 - \beta_2 C_4)(\mu_2 + \gamma C_4)(\mu_2\beta_2 + \gamma\Delta_1)\Delta_2.$$

The roots of polynomials 7 are

$$C_4 = \frac{-\Delta_1}{\nu\Delta_1 - \beta_2} < 0; \text{ or } C_4 = -\frac{\mu_2}{\gamma} < 0; \text{ or the roots of } Poli(C_4) = \alpha C_4^2 + bC_4 + c = 0,$$

To see the positive root of $Poli(C_4)$ we need to identify the value of $-b/a$ and c/a at the following.

$$C_{41} + C_{42} = -\frac{\gamma\Delta_1 + \mu_2\beta_2}{\gamma\beta_2} < 0 \text{ and } C_{41} \cdot C_{42} = -\frac{\gamma\Delta_1 + \mu_2\beta_2 - \mu_3\beta_1}{\nu\gamma\beta_2}.$$

Then, the polynomials $P(C_4)$ have one positive root.

2.2. Local Stability. The stability of each point identified by analyzing each equilibrium in the following Jacobian matrix: [5] [6]

$$(8) \quad J(H, F, C) = \begin{bmatrix} (\alpha - \mu_1) - \frac{\beta_1 F}{1 + \nu C} & -\frac{\beta_1 H}{1 + \nu C} & \frac{(\beta_1 F + \beta_2 C)\nu H}{(1 + \nu C)^2} - \frac{\beta_2 H}{1 + \nu C} \\ \frac{\beta_1 F}{1 + \nu C} & \frac{\beta_1 H}{1 + \nu C} - \gamma C - \mu_2 & -\frac{\beta_1 \nu H F}{(1 + \nu C)^2} - \gamma F \\ \beta_2 C & \gamma C & \beta_2 H - \gamma F - \mu_3 \end{bmatrix}$$

Furthermore, the stability of each equilibrium point is analyzed by computing the eigenvalues of each Jacobi matrix at each equilibrium point. The local stability at each equilibrium point is described by proving the following Lemmas.

Lemma 2.2. *The equilibrium EP_0 is locally asymptotically stable when $\alpha < \mu_1$.*

Proof. The stability of EP_0 are analyzed by identified the Jacobian of EP_0 .

$$(9) \quad J(EP_0) = \begin{bmatrix} \alpha - \mu_1 & 0 & 0 \\ 0 & -\mu_2 & 0 \\ 0 & 0 & -\mu_3 \end{bmatrix}$$

The eigen value of $J(EP_0)$ are $\alpha - \mu_1, -\mu_2, -\mu_3$, then equilibrium EP_0 is stable when $\alpha \leq \mu_1$. \square

Lemma 2.3. *The equilibrium EP_1 is locally stable (center) when $\alpha = \mu_1$.*

Proof. The Jacobian matrix of EP_1 is

$$(10) \quad J(EP_1) = \begin{bmatrix} 0 & -\mu_2 & -\frac{\mu_2(\beta_2 + v(\alpha - \mu_1))}{\beta_1} \\ \alpha - \mu_1 & 0 & -\frac{(\alpha - \mu_1)(\mu_2 v + \gamma)}{\beta_1} \\ 0 & 0 & \frac{\mu_2 \beta_2 + \gamma(\alpha - \mu_1)}{\beta_1} - \mu_3 \end{bmatrix}$$

Then the eigen values of $J(EP_1)$ are

$$\lambda_1 = \frac{-\mu_3 \beta_1 - \mu_2 \beta_2 - \gamma(\alpha - \mu_1)}{\beta_1},$$

$$\lambda_2 = (\mu_2 \Delta_1) i,$$

$$\lambda_3 = -(\mu_2 \Delta_1) i.$$

According to dynamical analysis theory [6], the equilibrium point EP_1 is stable if $\alpha = \mu_1$. \square

Lemma 2.4. *The equilibrium EP_2 is locally stable (center) if $0 \leq (\alpha - \mu_1) \leq \frac{\beta_2}{v}$ and $\beta_2 \mu_2 - \mu_3 \beta_1 \geq 0$.*

Proof. The Jacobian matrix of EP_2 is $J(EP_2)$. The eigen values of $J(EP_2)$ are

$$\lambda_1 = \frac{1}{\beta_2^2(\beta_2 - v(\alpha - \mu_1))} ((\alpha - \mu_1)(-\mu_3 \beta_1 v(2\beta_2 - v(\alpha - \mu_1))) - \beta_2^2(\gamma + \mu_2 v) - \beta_2^2(\mu_2 \beta_2 - \mu_3 \beta_1)) - 2v\alpha\mu_3\beta_1\beta_2 < 0,$$

$$\lambda_2 = -\mu_3(\alpha - \mu_1)(\beta_2 - v(\alpha - \mu_1))i,$$

$$\lambda_3 = \mu_3(\alpha - \mu_1)(\beta_2 - v(\alpha - \mu_1))i.$$

Hence, the EP_2 is locally stable if $0 \leq (\alpha - \mu_1) \leq \frac{\beta_2}{v}$ and $\beta_2 \mu_2 - \mu_3 \beta_1 \geq 0$. \square

The stability of EP_3 are doesn't identified, because the equilibrium EP_3 is doesn't exist. Then the stability of EP_4 are describe at the following.

Lemma 2.5. *The equilibrium EP_4 is locally asymptotically stable if $\beta_2\mu_2 - \mu_3\beta_1 < 0$ and $\alpha - \mu_1 > 0$.*

Proof. The stability of EP_4 identified by analyze the characteristic polynomial of Jacobian matrix $J(EP_4)$ as follow

$$(11) \quad P(EP_4) = k_3\lambda^3 + k_2\lambda^2 + k_1\lambda + k_0.$$

With,

$$(12) \quad \Delta_3 = \Delta_2(\beta_2\mu_2 + \gamma(\alpha - \mu_1)) + \gamma\beta_2vC_4^2; \Delta_4 = \mu_3\beta_1 + \mu_2\beta_2; \text{ and } \Delta_5 = \mu_2 + \gamma C_4.$$

Where,

$$k_3 = \Delta_2\Delta_3^2;$$

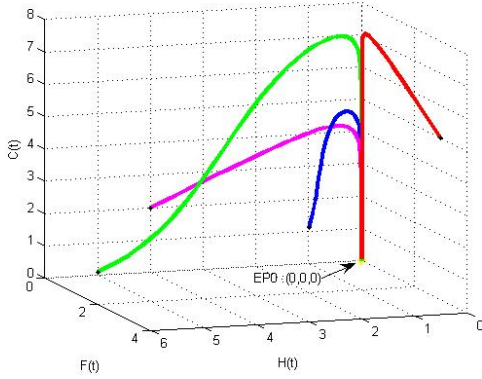
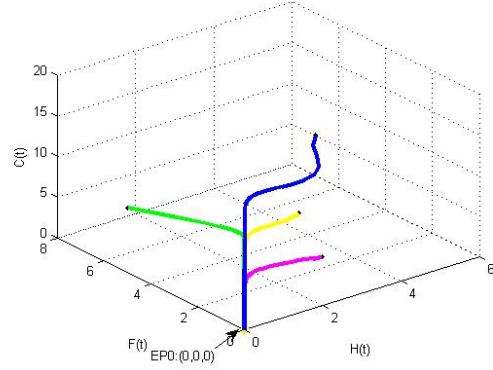
$$k_2 = \Delta_3(\Delta_6(\Delta_2\Delta_4 + \beta_2vC_4^2) + \Delta_1\Delta_2^2\gamma(\Delta_6 - \Delta_1) - \Delta_1\Delta_2\Delta_4 + \beta\gamma C_4(1 - v^2C_4^2) + \mu_2v(1 + \gamma C_4)^2 + \beta_2C_4(1 + \mu_2v(1 + 2\gamma C_4) + v\gamma^2C_4^2)); \text{ and}$$

$$k_0 = -\mu_3C(\Delta_1^2\Delta_2\gamma(\Delta_2\gamma(\Delta_1\gamma + \mu_2\beta_2) + \mu_3\beta_1(\mu_2v - \gamma) + \gamma^3\beta_2C_4(v^3C_4^3 - 3vC_4 - 2)) + \Delta_1\Delta_2(\mu_3\beta_1\beta_2(\gamma^2C_4\Delta_4 + \mu_2v\Delta_5) + \Delta_1\Delta_5\gamma v^2C_4^2) + \Delta_1\Delta_2(\beta_2\gamma(\Delta_4C_4 - \beta_2\mu_2^2 - 5\beta_2\gamma\mu_2C_4 - 2\mu_2\beta_2C_4^2\gamma v\Delta_6)) + \beta_2^2(\mu_2\gamma C_4(2\mu_3\beta_1 - \alpha\mu_2\beta_2) + \mu_2\Delta_4(\mu_2 - vC_4) - v\gamma C_4(3\mu_2 - 2\gamma C_4^2))).$$

By analyzing the positivity of each coefficient on the polynomial $P(EP_4)$, and involving the Routh Hurwitz criterion [7], it can be concluded that the equilibrium point EP_4 is locally stable when $\beta_2\mu_2 - \mu_3\beta_1, \alpha - \mu_1 > 0$, because it satisfy the condition $k_0 > 0; k_3 > 0$; and $k_1k_2 > k_3k_0$. \square

3. NUMERICAL RESULT AND DISCUSSION

The results of the mathematical analysis in the previous chapter need to define numerically involving some parameters. We can relate these parameters to real conditions. For examples, a death rate of cell problems, the death rate of healthy cells is caused by many things such as necrosis, which can be activated by components of the immune system. In the problem of this mathematical model of GB' s disease, we divide the conditions of distribution into several state conditions, according to the Lemma in the mathematical analysis. In the first case we assume the condition $\alpha - \mu_1 \leq 0$, the stable condition for EP_0 by take some parameter value as follows.
Case 1 : $\alpha = 0.5; \beta_1 = 0.1; \beta_2 = 0.1; v = 0.003; \gamma = 0.5; \mu_1 = 0.6; \mu_2 = 0.01; \mu_3 = 0.1$.

(A) Case $\alpha - \mu_1 < 0$ (B) Case $\alpha - \mu_1 = 0$ FIGURE 1. Numerical simulation under condition $\alpha - \mu_1 \leq 0$

In Figure 1 we can see two kinds of condition, when $\alpha - \mu_1 < 0$ and $\alpha - \mu_1 = 0$. In the first simulation, 4 starting points were selected to inform us the trajectory orbit in several initial value. We choose initial value 1 is $(2, 2, 2)$ to assume the initial condition before cell interactions, means the probability of healthy cell, infected cell and immune cells is balance. The second initial value $Iv2 : (4, 0, 2)$ is describe the cell interaction if the initial infected cell without infected cells clearly shows that the cell population is tends to $EP_0 = (0, 0, 0)$. Meanwhile, the third initial value describes cell interactions if there are no healthy cells as the initial value, so that the interaction only occurs between infected cells and immune cells, which interact and tends to EP_0 . In all conditions, it can be seen if the system trajectory will go to point EP_0 . Thus, it can be said that the conditions that have been mentioned cause the system to stabilize to point EP_0 .

Then for case 2 we take some parameter value as follows $\alpha = 0.8; \beta_1 = 0.1; \beta_2 = 0.1; \nu = 0.003; \gamma = 0.5; \mu_1 = 0.01; \mu_2 = 0.01; \mu_3 = 0.1$.

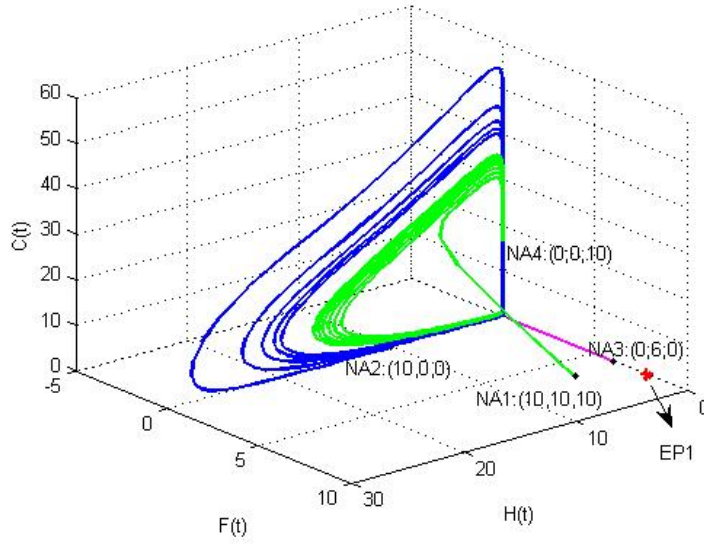


FIGURE 2. Numerical simulation under condition $\alpha - \mu_1 > 0$

In second case, we try to modify the parameter with the condition $\alpha - \mu_1 = 0.79$. By taking some initial values which close to EP_0 and EP_1 , it can be seen that the trajectory is away from point $EP_0 = (0, 1; 7, 9; 0)$, forming a trapping areas in the $F(t)$ and $C(t)$ planes. For two initial value which are initial value 3 : $(0, 0, 10)$ and initial value 4: $(0, 6, 0)$ for $t = 1000$, then the trajectory is tends to $EP_0 = (0; 0; 0)$.

Figure 3 shows the numerical simulation results in case 3. By choosing the following parameter values which are $\alpha = 0.6; \beta_1 = 0.8; \beta_2 = 0.8; \nu = 0.001; \gamma = 0.5; \mu_1 = 0.2; \mu_2 = 0.4; \mu_3 = 0.1$, we can see the behavior of the system around the equilibrium points EP_0 and EP_2 . Based on the simulation in Figure 3 we can see that when the initial value $Iv2 = (1, 1, 1)$, the trajectory will fluctuate around the equilibrium point of EP_2 . When we select the initial value in the $H - C$ plane is $Iv3 = (2, 0, 1)$, the trajectory forms a repeating graph, circling around the equilibrium point EP_2 , but not leading to the equilibrium point. This condition is in accordance with the analytical calculation, where the Jacobian eigenvalues are both complexes. Biologically, this condition states that in conditions there are only healthy cell populations and immune cells are not fully achieved, only close.

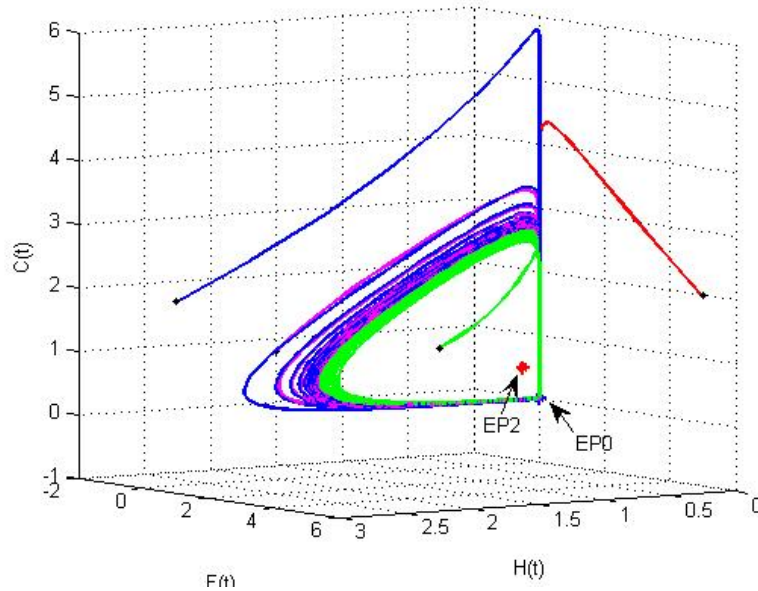


FIGURE 3. Numerical simulation under condition $0 \leq (\alpha - \mu_1) \leq \frac{\beta_2}{\nu}$ and $\beta_2 \geq \frac{\mu_3 \beta_1}{\mu_2}$

In the next case, the orbital behavior will be shown when the parameter values meet the stability requirements of the endemic equilibrium point. Analytically, the endemic conditions can be fulfilled under certain conditions, then we will show the numerical orbital behavior. By selecting the parameter values $\alpha = 1; \beta_1 = 0.5; \beta_2 = 0.2; \nu = 0.001; \gamma = 0.5; \mu_1 = 0.3; \mu_2 = 0.01; \mu_3 = 0$ and the value of $C_4 = 6$ we have the following.

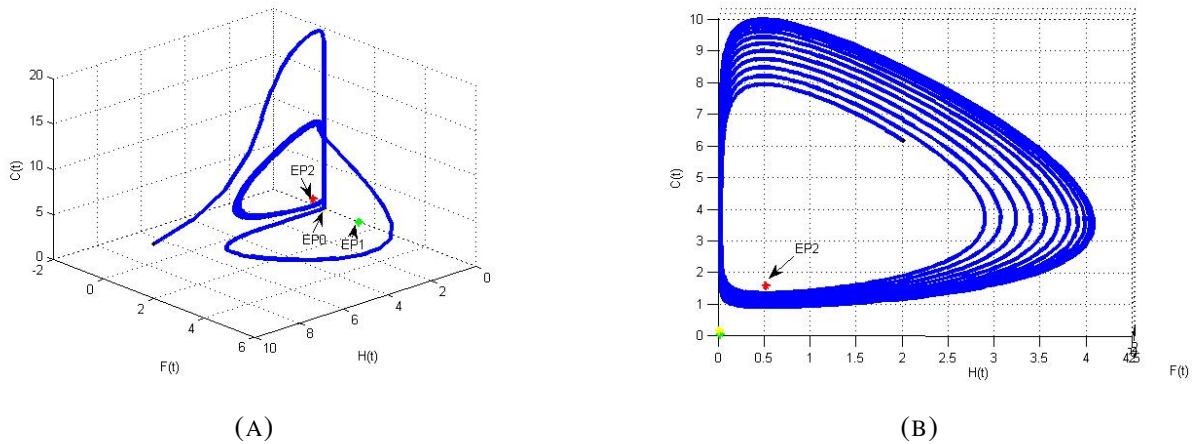


FIGURE 4. Numerical simulation under condition in Lemma 2.5

In Figure 4a we can see the orbital behavior of model 1 with the initial value $(10, 2, 6)$. The orbital behavior will be stable center around the boulder equilibrium point in the $H - C$ plane, the $F - H$ plane, and the $F - C$ plane. By changing the change from the initial value to $(2, 0, 6)$ at the same parameter value, we will obtain Figure 4(b). System 1 will approach the equilibrium point in the $H - C$ plane but not asymptotic, it means that under these conditions, the extinct of infected cells cannot happen. The satisfied conditions for the stability of endemic equilibrium occur and are found analytically. Numerically, the persistence condition for all cell populations is rare to find. It happened only at some initial values.

4. CONCLUSION

Guillain-Barre Syndrome (GBs) is an immune disorder that is quite dangerous because it can have an impact on death. There is no definite cause of these GBs, but one of them GBs is the impact of the Zika virus which attacks adult humans other than pregnant women.

A mathematical model that studies cell-to-cell interactions on the spread of GBs has been constructed in the system (1) involving a population of healthy cells, infected cells, and immune cells. The model formed is a non-linear differential equation with a saturated occurrence rate. The invariant condition has been proven analytically by finding the boundary of the system. The conditions of existence at each equilibrium point are studied in order to show what conditions cause the equilibrium point to be studied.

In this case, the immune response is assumed to be nonlinear so that the baseline reproduction rate is not found. In model (1), the trivial equilibrium point is not always stable. The trivial equilibrium point will be locally stable if the rate of birth of healthy cells is less than the rate of damage to healthy cells. Other conditions change when the opposite symptoms occur, namely when the birth rate of healthy cells is greater than the death rate. There will be several conditions in these conditions followed by changes in other parameters. Meanwhile, the birth rate which is equal to the death rate will cause a stable condition around the equilibrium point in the presence of healthy and infected cells.

The stability condition of the third equilibrium point (the point of equilibrium without infected cells) is obtained analytically and numerically on the condition of certain parameter values. This condition is never precisely acquired or not asymptotically stable, but the orbital

behavior conditions approach the point of stability without infected cells. In the opposite condition, when the growth rate of the cell is greater than the damage rate, followed by other conditions, then analytically and numerically endemic or persistent conditions of all cell populations can be achieved. However, endemic precise conditions are quite rare, because it depends on their initial values. This behavior means that the initial conditions play a role in the fate of the orbital behavior of the system. In other words, eradicating infected cells depends on the initial conditions. Our results suggest that early detection of infection provides a greater chance of cure.

ACKNOWLEDGEMENT

The author would like to thank DRPM RISTEKBRIN for the financial support of the research. Our gratitude also goes to LPPM UIISI for its technical and administrative support.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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