Slow and fast dynamics model of a Malaria with Sickle-Cell genetic disease with multi-stage infections of the mosquitoes population

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Abstract. Malaria, which is caused by Plasmodium, is a common disease in tropical areas. There are three types of Plasmodium i.e. Plasmodium Vivax, Plasmodium Malariae, and Plasmodium Falciparum. The most dangerous cases of the Malaria are mainly caused by the Plasmodium Falciparum. One of the important characteristics for the Plasmodium infection is due to the immunity of erythrocyte that contains HbS (Haemoglobin Sickle-cell) genes. The individuals who has the HbS gene has better immunity against the disease. In this paper, we consider a model that shows the spread of malaria involving the interaction between the mosquitos population, the human who has HbS genes population and the human with normal gene population. We do some analytical and numerical simulation to study the basic reproduction ratio and the slow-fast dynamics of the phase-portrait. The slow dynamics in our model represents the response of the human population with HbS gene to the Malaria disease while the fast dynamics show the response of the human population with the normal gene to the disease. The slow and fast dynamics phenomena are due to the fact that the population of the individuals who have HbS gene is much smaller than the individuals who has normal genes.

1. Introduction
Malaria is one of the most common disease which is transmitted by female Anopheles Mosquitos and happens mostly on the tropical areas and also some subtropical areas. According to WHO’s data, it is reported that there are 214 million clinical cases of malaria in the world with 438.000 fatal cases, and about 3.2 billion people at risk. There are more than 30 of 400 species of
Anopheles plays role as the vector of Malaria. The transmission intensity depends on some factors such as the parasite, the vector, the human host and the environment, see [13].

One of the interesting phenomena in Malaria infection is that the individuals who have the Sickle-cells anaemia genetic disease have better endurance against the disease. One of the uniqueness of the Sickle-cell anaemia is that when the Plasmodium falciparum take the actin fibre from erythrocyte to build an intracellular-bridge for transporting protein that is made by the parasite into cell surface, the Sickle-cell will cut that bridge so it can not be used by the Plasmodium, see [1, 9, 12].

In this paper we consider a model of the Malaria transmission which involves the interactions between three populations i.e. the human population with normal genes (AA), the human population with Sickle-cells anaemia genes (AS), and the vector populations. The model is motivated by the study in [5] and [10]. The study in [5] is focused to analyze the interaction between individuals who have normal genes (AA), the individuals who have Sickle-cell genes (AS), and the vector population. However, the analysis in [5] did not consider the transmission process of the disease on the mosquitos population. The authors consider the slow-fast dynamics of the system that show the interactions between the populations.

The transmission process of the disease in the mosquitos population that has been studied in [10] is focused on the interaction dynamics between the human population with normal genes (AA) and the mosquitos population, which are separated into three compartments adopting the classical SIR epidemic model.

In this paper, we combine the human-mosquitos population model in [10] with the HbS cases of the human population. The model contains seven compartments, i.e. the uninfected and infected humans from malaria with genotype AS, the uninfected and infected humans from malaria with genotype AA, the mosquitos which are susceptible with Plasmodium parasites, mosquitos which have Plasmodium parasite in gametocyte form which can not transmit malaria, and mosquitos which can transmit malaria (the Plasmodium parasite is in sporozoite form).

We follow the assumptions in [5], i.e., the malaria infection rate and the malaria-induced death rate of AA individuals are higher than the one in AS individuals, the recovery rate from malaria in AA individuals are lower than in AS individuals, the background mortality rate of AS individuals is higher than AA individuals, the malaria epidemic occurs on a much faster timescale than their progress in sickle-cell gene frequency, and that SS individuals are never born.

2. Construction of the model

The interaction between the individuals with AA and AS genes are each classified into two compartments, i.e. the uninfected \((u_i, i = 1, 2)\) and the infected \((v_i, i = 1, 2)\) individuals by the plasmodium. The mosquitos population is classified into three compartments, i.e., the susceptible mosquitos \((z_1)\), the mosquitos which has plasmodium but do not have ability to transmit the plasmodium \((z_2)\), and the mosquitos which has ability to transmit the plasmodium \((z_3)\). The total population of the mosquitos is \(N_z = z_1 + z_2 + z_3\). The transfer diagram of our system is shown on Figure 1.

We assume that the number of individuals in the human population is \(N\) with \(N = \sum_{i=1}^{2}(u_i + v_i)\) and the density dependency of the birth function is \(B(N) = b(1 - \frac{N}{K})\) where the \(b\) is the birth rate of the human populations. The frequencies of the AA and AS genes are \(p = \frac{u_1 + 2u_2 + v_1 + 2v_2}{2N}\) and \(q = \frac{u_1 + v_1}{2N}\) and the death rate of the human with AA and AS genes are \(m_1 = \mu\) and \(m_2 = \mu + \vartheta\) where \(\mu\) is the natural death rate of the human and the \(\vartheta\) is the extra death rate of the human with AS gene. Lastly, \(P_1 = p^2\) and \(P_2 = 2pq\) show the proportion of the AA genes and AS genes in the human populations.
Based on the transfer diagram in Figure 1, we derive the mathematical model as follows.

\[
\begin{align*}
\frac{du_i}{dt} &= P_iB(N)N - m_iu_i - \beta_{hi}z_3u_i + \gamma_i v_i, \\
\frac{dv_i}{dt} &= \beta_{hi}z_3u_i - (m_i + \gamma_i + \alpha_i)v_i, \quad i = 1, 2, \\
\frac{dz_1}{dt} &= \delta_1 N_z - (\beta_{v_1} v_1 N + \beta_{v_2} v_2 N)z_1 - \delta_2 z_1, \\
\frac{dz_2}{dt} &= (\beta_{v_3} v_1 N + \beta_{v_2} v_2 N)z_1 - \tau z_2 - \delta_2 z_2, \\
\frac{dz_3}{dt} &= \tau z_2 - \delta_2 z_3,
\end{align*}
\]

see the Table 1 on the Appendix for the biological meaning of the parameters in our system.

3. Fast and slow dynamics

In this section, we introduce new variables and parameters transformation. By these transformations, we consider two time scales of the system which show the fast dynamic when the mosquitos population has interaction with individuals with normal genes and slow dynamics when the mosquitos has the interaction with individuals who have Sickle-cell genes.

The fast and slow dynamics on this paper is due to the fact that the individuals who have HbS gene are much smaller than the individuals with normal genes. This situation implies that the population dynamics of the individuals who have HbS gene is much slower compare with the population dynamics of the normal individuals.
Following [5], we assume that \( m_1 < m_2 \), \( \gamma_1 \leq \gamma_2 \), \( \beta_{h_1} \geq \beta_{h_2} \), and \( \alpha_1 \geq \alpha_2 \). Due to the connection with realistic biological parameters the parameters \( m_i, \alpha_i, i = 1, 2 \) and \( b \) are assumed much smaller than the other epidemiological parameters, see [5]. So that we can rescale those parameters, \( m_i = \varepsilon \tilde{m}_i, \quad \alpha_i = \varepsilon \tilde{\alpha}_i, \quad b = \varepsilon b \), where \( \varepsilon \) is a small positive parameter. In [5], the authors define new variables that show the proportion of the human with AA and AS genes, i.e., \( x_i = \frac{y_i}{N}, \quad y_i = \frac{y_i}{N}, \quad w = x_2 + y_2, \quad i = 1, 2 \), where \( x_i, y_i \) show human populations of the respective types and \( w \) is the total frequency of genotype AS. We notice that \( x_1 + y_1 + x_2 + y_2 = 1, x_1 = 1 - y_1 - w, \) and \( x_2 = w - y_2 \). In this case we also consider two time-scales, i.e. the original time \( t \) which is referred as the fast time variable, and \( \tau = \varepsilon t \) which is referred to the slow time variable. Then, we denote '\( t \)' as \( \frac{d}{dt} \) and '\( \tau \)' as \( \frac{d}{d\tau} \).

By using the new variables and the rescaled parameters, we have the transformed systems of System (1) that shows the fast and slow dynamics of the model, i.e.,

\[
\begin{align*}
\frac{dy_1}{dt} &= \beta_{h_1}z_1(1 - y_1 - w) - \gamma_1 y_1 - \varepsilon y_1[(\tilde{m}_1 - \tilde{m}_2)w + \tilde{\alpha}_1(1 - y_1) - \tilde{\alpha}_2 y_2 + (P_1 + P_2) \tilde{b}(1 - \frac{N}{K})], \\
\frac{dy_2}{dt} &= \beta_{h_2}z_1(w - y_2) - \gamma_2 y_2 - \varepsilon y_2[(\tilde{m}_1 - \tilde{m}_2)(w - 1) - \tilde{\alpha}_1 y_1 \\
&\quad + \tilde{\alpha}_2(1 - y_2) + (P_1 + P_2) \tilde{b}(1 - \frac{N}{K})], \\
\frac{dz_1}{dt} &= \delta_1 N z - (\beta_{v_1} y_1 + \beta_{v_2} y_2) z_1 - \delta_2 z_1, \\
\frac{dz_2}{dt} &= (\beta_{v_1} y_1 + \beta_{v_2} y_2) z_1 - \tau z_2 - \delta_2 z_2, \\
\frac{dz_3}{dt} &= \tau z_2 - \delta_2 z_3, \\
\frac{dw}{dt} &= \varepsilon \left( ((1 - w)P_2 - wP_1) \tilde{b}(1 - \frac{N}{K}) + (\tilde{m}_1 - \tilde{m}_2)w(1 - w) \\
&\quad + \tilde{\alpha}_1 y_1 - \tilde{\alpha}_2(1 - w)y_2 \right), \\
\frac{dN}{dt} &= \varepsilon N \left( (P_1 + P_2) \tilde{b}(1 - \frac{N}{K}) - \tilde{m}_1(1 - w) - \tilde{m}_2 w \\
&\quad - \tilde{\alpha}_1 y_1 - \tilde{\alpha}_2 y_2 \right). 
\end{align*}
\] (1)
System (1) shows the fast dynamics, and the system

\[
\begin{align*}
\frac{dy_1}{dt} &= \beta_{h_1} z_3 (1 - y_1 - w) - \gamma_1 y_1 - \varepsilon y_1 ([m_1 - m_2] w + \alpha_1 (1 - y_1)) \\
\frac{dy_2}{dt} &= \beta_{h_2} z_3 (w - y_2) - \gamma_2 y_2 - \varepsilon y_2 ([m_1 - m_2] (w - 1) - \alpha_1 y_1) \\
\frac{dz_1}{dt} &= \delta_1 N z_1 - (\beta_{v_1} y_1 + \beta_{v_2} y_2) z_1 - \delta_2 z_1, \\
\frac{dz_2}{dt} &= (\beta_{v_1} y_1 + \beta_{v_2} y_2) z_1 - \tau z_2 - \delta_2 z_2, \\
\frac{dz_3}{dt} &= \tau z_2 - \delta_2 z_3, \\
\frac{dw}{dt} &= ( ((1 - w) P_2 - w P_1) \bar{b}(1 - \frac{N}{K}) + (m_1 - m_2) w (1 - w) + \alpha_1 y_1 - \alpha_2 (1 - w) y_2, \\
\frac{dN}{dt} &= N (P_1 + P_2) \bar{b}(1 - \frac{N}{K}) - m_1 (1 - w) - m_2 w - \alpha_1 y_1 - \alpha_2 y_2).
\end{align*}
\]

shows the slow dynamics of System (1). We note that \(y_1, y_2, z_1, z_2, z_3\) are the fast variables and \(w, N\) are the slow variables.

In the next section, the fast dynamics of System (1) that is for \(\varepsilon = 0\) will be discussed. We will also analyze the basic reproduction ratio of the system that determine the important parameters which influence the spreads of the disease. In the Numerical Simulation section, we will show the dynamics in full system, that is for \(\varepsilon \neq 0\) and also the slow dynamics of the system, that is the dynamics for \(\varepsilon = 0\) of System (2).

4. The basic reproduction ratio for the fast dynamics

For \(\varepsilon = 0\), we get the new system from the system (1),

\[
\begin{align*}
\frac{dy_1}{dt} &= \beta_{h_1} z_3 (1 - y_1 - w) - \gamma_1 y_1, \\
\frac{dy_2}{dt} &= \beta_{h_2} z_3 (w - y_2) - \gamma_2 y_2, \\
\frac{dz_1}{dt} &= \delta_1 N z_1 - (\beta_{v_1} y_1 + \beta_{v_2} y_2) z_1 - \delta_2 z_1, \\
\frac{dz_2}{dt} &= (\beta_{v_1} y_1 + \beta_{v_2} y_2) z_1 - \tau z_2 - \delta_2 z_2, \\
\frac{dz_3}{dt} &= \tau z_2 - \delta_2 z_3.
\end{align*}
\]

System (3) show the fast dynamics of the Malaria infection processes for the human with AA and AS genes.

By a straightforward calculation, the System (3) has the equilibrium point which represents
For the numerical simulation, we use the similar parameter that being used in [5], In this section we consider the slow dynamics of our model which is represented by System (2).

5. Numerical Simulations for the slow-dynamics

In this section we consider the slow dynamics of our model which is represented by System (2). For the numerical simulation, we use the similar parameter that being used in [5],

\begin{align*}
\beta_{h_1} &= 0.12, \quad \beta_{h_2} = 0.11, \quad \beta_{v_1} = 0.1, \quad \beta_{v_2} = 0.15, \quad \delta_1 = 0.1, \\
\delta_2 &= 0.005, \quad \mu = 0.00004, \quad \nu = 0.00001, \quad \gamma_1 = 0.01, \quad \gamma_2 = 0.01, \\
\alpha_1 &= 0.0001, \quad \alpha_2 = 0.00008, \quad b = 0.00004, \\
K &= 10000, \quad \tau = 0.0001, \quad N_z = 1000.
\end{align*}

where the time variable is on daily scale.

On Figure 2 we show that the solutions will be absorbed by the slow manifold and approach to the equilibrium in very slow time.

The situation can be interpreted as follows. The population of the individuals who has Sickle-cell genetic disease will grow or decay very fast into a certain condition that we call the slow-manifold. In the slow-manifold the population will increase or decrease very slow to reach the steady state condition. The situation is due to the fact that the individuals who have Sickle-cell genes has ability against the plasmodium falciparum infection. On this figure we show the interaction between infected individuals with AA genes and the frequency of the individuals with AS genes.

In those case we found that the solution will tend to the stable equilibrium point. From the position of the equilibrium point, we can conclude that the infected individuals with the normal genes has higher risk for the Plasmodium infection than the individuals with Sickle-cells anaemia.
Figure 2. The dynamics on the slow manifold for System (1) that shows the interaction between the individuals with Sickle-cell genes with the total frequency of the AS genotype for $\varepsilon = 0.01$.

Figure 3. The interaction between the total population of the human and the total frequency of AS genes. The spreads of the disease in AS population grow slowly to reach the equilibrium points, see Figure 3.

In Figure 3, we show that the human population grow rapidly until the carrying capacity where the slow-manifold related to the total frequency of AS genotype appear. The Figure 2 and Figure 3 show the long term behavior of the disease which is represented by the stable equilibrium point. This situation can be interpreted as follows. If the total number of the individuals reaches the carrying capacity, the number of individuals who has HbS genes play role to reduce the spreads of the plasmodium and the disease will be isolated into a certain number of individuals.
6. Concluding remarks
The sickle cells has the gene which prevents the growth of Malaria plasmodium. The slow-manifold in the system can be interpreted as follows. The individuals who has sickle cells anaemia disease has ability to survive from Malaria. So that, the growth of the Malaria in this population is much slower than the normal individuals population. In our model we show the steady state conditions of the spreads of the malaria on those populations that represents the longterm behavior of this disease in such populations. In this case, the number of individuals who has HbS genes play role to reduce the spreads of the plasmodium and the disease will be isolated into a certain number of individuals.

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References
[1] Anwar, C., Musral, Y., 1997, Atlas Parasitologi Kedokteran, Hipokrates, Jakarta.
[2] Anton, H., Rorres C., 2000, Elementary Linear Algebra, Eight Edition, John Wiley and Sons, Inc., New York.
[3] Diekmann, O., Heesterbeek, J.A.P, 2000, Mathematical Epidemiology of Infectious Diseases : Model Building, Analysis, and Interpretation, John Wiley and Sons, Inc., New York.
[4] Diekmann, O., Heesterbeek, J.A.P, Roberts, M.G., 2010, The Construction of Next-generation Matrices for Compartmental Epidemic Models, J. R. Soc. Interface, 7, 873-885.
[5] Feng, Z., Yi, Y., Zhu, H., 2004, Fast and Slow Dynamics and the S-gene Frequency, J Dyn Diff Equat, 16:869 .
[6] Fuller, G., Tarwater, D., 1986, Analytic Geometry, Sixth Editions, Addison-Wesley Publishing Company, Inc, USA.
[7] Kocak, H. and Hole, J.K., 1991, Dynamic and Bifurcation, Springer-Verlag, New York.
[8] Perko, L., 1991, Differential Equation and Dynamical System, Springer-Verlag New York, Inc., USA.
[9] Porth, C. M., 2011, Essentials of Pathophysiology Concepts, Third Edition, Wolters Kluwer Health - Lippincott Williams & Wilkins, China.
[10] Chitnis, N., Cushing, J. M., Hyman, J. M., 2006, Bifurcation Analysis of A Mathematical Model for Malaria Transmission, SIM J. Appl. Math, Vol 67, No. 1, pp.24-45.
[11] Verhulst, F., 1939, Nonlinear differential equations and dynamical systems, Springer-Verlag New York, Inc., USA.
[12] Wahlgren, M., Perlmann, P., 2005, Malaria : Molecular and Clinical Aspects, Harwood Academic Publishers, Singapore.
[13] WHO 2016, Malaria : The Fact Sheet , WHO Media Centre, http://www.who.int/mediacentre/factsheets/fs094/en/
Appendix.
The variables and parameters which is used in the system has been described in Table 1

| Symbol | Description | Symbol | Description |
|--------|-------------|--------|-------------|
| $u_1$  | the number of uninfected people with genotypes AA. | $p$    | the frequencies of the AA gene. |
| $u_2$  | the number of uninfected people with genotypes AS. | $q$    | the frequencies of the AS gene. |
| $v_1$  | the number of infected people with genotypes AA. | $P_1$  | the proportion of the genotypes AA. |
| $v_2$  | the number of infected people with genotypes AS. | $P_2$  | the proportion of the genotypes AS. |
| $N$    | the total population size of humans. | $B(N)$ | a density dependent birth function. |
| $z_1$  | the fraction mosquitos that are susceptible with Plasmodium parasites | $\beta_{h_i}$ | the malaria infection rate of a human of type $i$. |
| $z_2$  | the fraction mosquitos that have Plasmodium parasite (the form is gametocyte) but cant transmit malaria. | $\beta_{v_i}$ | the malaria infection rate of a mosquito from biting people of type $i$. |
| $z_3$  | the fraction mosquitos that can transmit malaria (the Plasmodium parasite’s form is sporozoit) | $\tau$ | the growth rate per capita of mosquitos from the form parasite is gametocyte into sporozoit. |
| $\alpha_i$ | the additional death rate of infected individuals due to malaria. | $\frac{1}{\gamma_i}$ | the average time until a victim of malaria recovers. |
| $\mu$  | the natural death of human. | $\delta_1$ | the birth rate per capita of mosquitos. |
| $\vartheta$ | the extra death rate of AS individuals due to S gene. | $\delta_2$ | the death rate per capita of mosquitos. |
| $K$    | carrying capacity. | $N_z$  | the total population size of mosquitos. |

Table 1. Variables and parameters which are used on the Compartment diagram 1