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RESEARCH ARTICLE

MODELING AND SENSITIVITY OF DENGUE VIRAL DYNAMICS

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ABSTRACT

In this paper we focus on describing the dynamics of dengue virus, using a compartment type model with time delay that occurs during the production of antibodies. We study the dynamics of healthy cells, infected cells, B-cells of the human body, viruses and antibodies where immunity is provided by the activation of B cells into plasma cells and maturation of plasma cells into antibodies (humoral immune response). Stability regions are identified with respect to the external variables and it is observed as the virus burst rate increases, the stability regions would decrease. Further, a sensitivity index is introduced to find the parameters that have a high impact on the reproduction number R0. In addition results indicate as the conversion rate of healthy cells into infected cells increases, the viral load in the body and the antibody production also increases which agrees with theory presented on humoral immune response and the viral load goes to negligible levels within 7-14 days as observed in dengue infection.

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INTRODUCTION

Dengue continues to be one of the world's fastest growing vector-borne diseases, with a 30-fold increase in disease incidence over the last 50 years. It is transmitted to humans through the bite of an infected female Aedesaegypti mosquito. Dengue can be mainly found intropical and sub-tropical regions around the world, particularly in urban and semi-urban areas. But over time, with increasing globalization and the geographic spread of inhabitants mosquitoes, dengue infection has steadily penetrated every corner of the world (Clark and Gubler; Guzmán and Kourí, 2004). The World Health Organization (WHO) estimates that there are currently 50-100 million dengue infections worldwide every year, and almost half of the worlds' population lives in countries where dengue is endemic. The spectrum of dengue infection ranges from asymptomatic infection to death. There are four distinct closely related viruses designated as serotypes (DEN-1, DEN-2, DEN-3, DEN-4) that cause dengue of varying severity in humans. Though the classic form of the disease known as Dengue Fever (DF) causes flu-like symptoms and is non-life-threatening, its more severe forms as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) can be fatal especially in children. Recovery from one virus provides lifelong immunity against that virus but not against the other viruses (Rodrigues *et al.,* 2012). The first outbreak of dengue in Sri Lanka occurred in 1965 and the first major epidemic was reported in 1989 and since then it has become endemic. Eventhough almost all the districts in Sri Lanka have reported dengue cases, urban areas such as Colombo, Gampaha, Kalutara and Kandy districts have recorded the highest number of cases. The disease has a seasonal trend where two peaks of dengue occur following monsoon rains in June-July and October-December (Epidemiology Unit Ministry of Health Sri Lanka; Sirisena and Noordeen 2014). Majority of individuals who experience dengue infection have asymptotic infection or mild disease which is usually cleared from the body within 7-14 days after onset of fever by a complex immune response process (Gujarati and Ambika, 2014; Nuraini, 2009; PAHO, 1994). Only a few would proceed to severe stages. With close monitoring of key indicators, the development of severe manifestation can be detected on time. But due to the large number of patients admitted during a dengue epidemic and with lack of laboratory facilities, specialized staff and medical professionals in Sri Lanka, closely monitoring and keeping track of each individual patient's illness becomes intensely demanding, and thus the critical period can go unnoticed which

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results in unfortunate deaths. Though there are currently no vaccines available against dengue, understanding the viral dynamics in human body will help in developing interventions such as antiviral drugs or vaccines against dengue. For this we must first understand the multistage cellular process that occurs during the infection. When an infected mosquito bites a person, it injects the dengue virus into the bloodstream. The virus then infects the nearby skin cells and multiplies inside a type of dendritic cell called Langerhans cells. The infected cells will release a signaling protein called interferons which may interfere with viral proliferation and limit the spread of the virus. Then the infected Langerhans cells travel to the lymph nodes and alert the immune system to trigger the immune response as an infection is growing in the body (Host Response to the Dengue Virus).During its journey, the dengue virus infects more cells, including those in the lymph nodes and bone marrow, macrophages in both the spleen and liver, and monocytes in the blood. This whole process is illustrated in Fig.1.

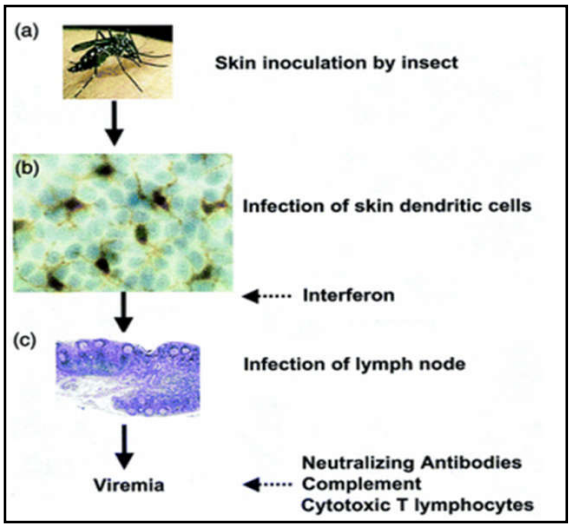

Fig. 1. cellular process that occurs during dengue infection1

The spread and increase of the virus results in viremia, a condition in which there is a high level of dengue virus in the bloodstream (Host Response to the Dengue Virus). The body's defense against any infectious organism or any invading pathogens is the immune system, which is made up of two parts. The first one, called the innate immune system provides an immediate, but non-specific response, but it does not provide a person with long-term immunity against an invading pathogen since it contains no memory (Host Response to the Dengue Virus; Nikin-Beers, 2014).The second part of the immune system, the adaptive immune system, produces cells that specifically and efficiently target the virus and infected cells (Host Response to the Dengue Virus). The adaptive immune system produce antibody-secreting B cells (humoral immune response) and cytotoxic T cells (cell-mediated immune response) both of which are responsible to clear the infection and provide life-long immunity against a pathogen (Host Response to the Dengue Virus; Nikin-Beers, 2014; Wahala and de Silva, 2011;Janeway CA *et al.,* 2001). The schematic representation of the human immune system is shown in Fig.2.

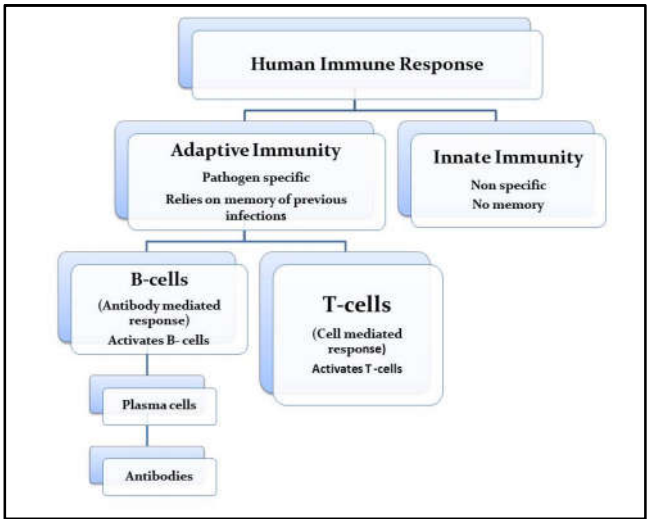

Fig. 2. Human immune system

As soon as the body learns that the cells are infected with dengue virus, it triggers the innate immune response by alerting two types of white blood cells-monocytes and macrophages which normally attack any invading pathogens. But instead of destroying the virus antigens, both types of cells get infected by the dengue virus. Hence the virus tricks the immune system and spreads throughout the body (Host Response to the Dengue Virus). Thus we will focus on the adaptive immune response since it plays a more prominent role in dengue viral infection. Once the adaptive immune response starts fighting the dengue infection, the antigens present on virus particles activates B-cells, which mature into plasma cells which then produce antibodies called IgM and IgG(Gujarati and Ambika, 2014; Host Response to the Dengue Virus). These antibodies travel though the blood stream and bind to the antigens making them non-infectious. The cytotoxic T cells recognize and kill cells that are infected with pathogens. (Gujarati and Ambika, 2014; Host Response to the Dengue Virus; Nikin-Beers, 2014).The external appearance of this whole process is onset of fever along with symptoms such as headaches, muscle or joint pain, rash and so on which is termed as an acute febrile illness that gets cured within 7-14 days (Gujarati and Ambika, 2014; Murphy and Whitehead, 2011). Mathematical modeling on epidemiology of dengue has been widely studied but mathematical models on cell dynamics concerning dengue has not yet been paid much attention in literature. In this paper we focus on describing the dynamics of dengue virus for primary dengue infection, using a compartment type model with time delay that occurs during the production of antibodies. We study the dynamics of healthy cells, infected cells, B-cells of the human body, viruses and antibodies (Gujarati and Ambika, 2014). In this model it is assumed that immunity is provided by humoral immune response where activated B cells proliferate and mature into plasma cells which then produce antibodies. Stability and sensitivity of the model are discussed with respect to external variables such as production rate of antibodies, the conversion rate of healthy cells into infected cells due to the interaction with virus and virus burst rate. Further, stability regions are identified with respect to the external variables and sensitivity of the reproduction number R_0 is discussed.

The Model

The model presented in (Gujarati and Ambika, 2014) epitomizes a within-host primary infection dynamical model that incorporates time delays which occur from various steps involved during antibody production. It was expanded using the basic model proposed by May and Nowak (Nowak and May, 2000). We assume that only one serotype of dengue virus circulates in an infected host and the virus infects monocytes, macrophages, dendritic cells and hepatocytes in the blood stream.

The model for within host dengue viral infection with humoral immune response is given by

$$\begin{aligned}
\frac{dS}{dt} &= \mu - \alpha S - aSV \\
\frac{dI}{dt} &= aSV - \beta I \\
\frac{dV}{dt} &= kI - \gamma V - pAV \\
\frac{dB}{dt} &= \eta - \delta B + cBV \\
\frac{dA}{dt} &= fH(t-\tau_1)B(t-\tau_2) - qAV - \kappa A
\end{aligned} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where S -healthy cells (monocytes, macrophages, dendritic cells, hepatocytes or mast cells), I -infected cells, V -Dengue virus particles, B -B lymphocytes and A -neutralizing antibodies. The description of the parameters along with the baseline parameter values are given in Table 1. For this model the basic reproduction ratio R_0 is defined as the average number of secondary infected cells generated by a single infected cell placed in an uninfected cell population.Using the next generation method, we obtain the basic reproduction ratio

$$R_0 = \frac{a\mu k}{\alpha\beta\gamma} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Stability of the model

Once a patient recovers from dengue fever, the virus is completely removed from the body and the antibodies produced persists in the body for a long time.

Paper (Gujarati and Ambika, 2014) discuss about the infection free solutions and their stability over a long time period. For this in (Gujarati and Ambika, 2014)the model (1) is solved for all equilibrium values. Once virions enter the body, they start multiplying in infected cells and burst out in large numbers. The production of antibodies depends on the number of virus particles present and hence on infected cells. Thus we consider the parameters, a , the rate at which healthy cells are converted to infected cells due to their interaction with virus particles (a is directly proportional to R_0) and f , the production rate of antibodies and identify regions of stability in the parameter plane $f-a$ for a given value of $k-$virus burst rate. The regions in Fig.3are colour coded using the maximum values of the real parts of the eigenvalues obtained from the characteristic equation in (Gujarati and Ambika, 2014) for disease free equilibrium state. The dark blue region at the end of the spectrum in each figure denotes negative eigenvalues and hence implies that the system is in stable equilibrium in those regions for a given k value. Similarly in other regions, the eigenvalues are positive and hence the system is unstable in those regions. One can see from the figures (3a), (3b), (3c) and (3d) as the virus burst rate k increases, the stability regions decreases. Because for a higher value of k, the other conditions must be strong enough for the system to be stable.

Thus as k increases, it will be stable only for higher values of f and lower values of a . In (Gujarati and Ambika, 2014) it is found that the eigenvalues have negative real parts when $R_0 > 1$ and $f > (R_0 - 1)\frac{\kappa\delta\gamma}{p\eta}$. Fig.4 shows the variation of R_0 in the parameter plane $a-k$. The system is unstable in the dark blue region where $R_0 < 1$.

Sensitivity Analysis

Sensitivity analysis tells us how robust the model responses are with respect to perturbations in model parameters and helps us identify the parameters which are important in controlling model output. It is a valuable tool for guiding experimental analysis, model reduction and parameter estimation (Zi, 2011). In most biological models, lack of precise parameter values becomes a major issue.

Table 1. Description of the parameters

Parameter Symbol	Parameter Description	Value
μ	Production rate of healthy cells	10
α	Death rate of healthy cells	0.05
a	Rate at which healthy cells are converted to infected cells due to their interaction with virus particles	0.001
β	Death rate of infected cells	0.5
k	Burst rate of virus particles	2
γ	Rate at which virus particles degrade	0.5
p	Rate at which virus particles are neutralized by antibodies	0.001
η	production rate of B-lymphocytes	10
δ	Death rate of B-lymphocytes	0.049
c	Rate at which B-lymphocytes are stimulated by virus particles	0.001
f	Rate at which stimulated B-cells(Plasma cells) produce antibodies	8
q	Rate at which antibody virus complex affects the antibody growth	0.001
κ	Rate at which free antibodies degrade	0.051
τ_1	Time period required for the 1st production of antibodies after the virus and B-cells interact	3
τ_2	Time required to produce antibodies from plasma cells	0

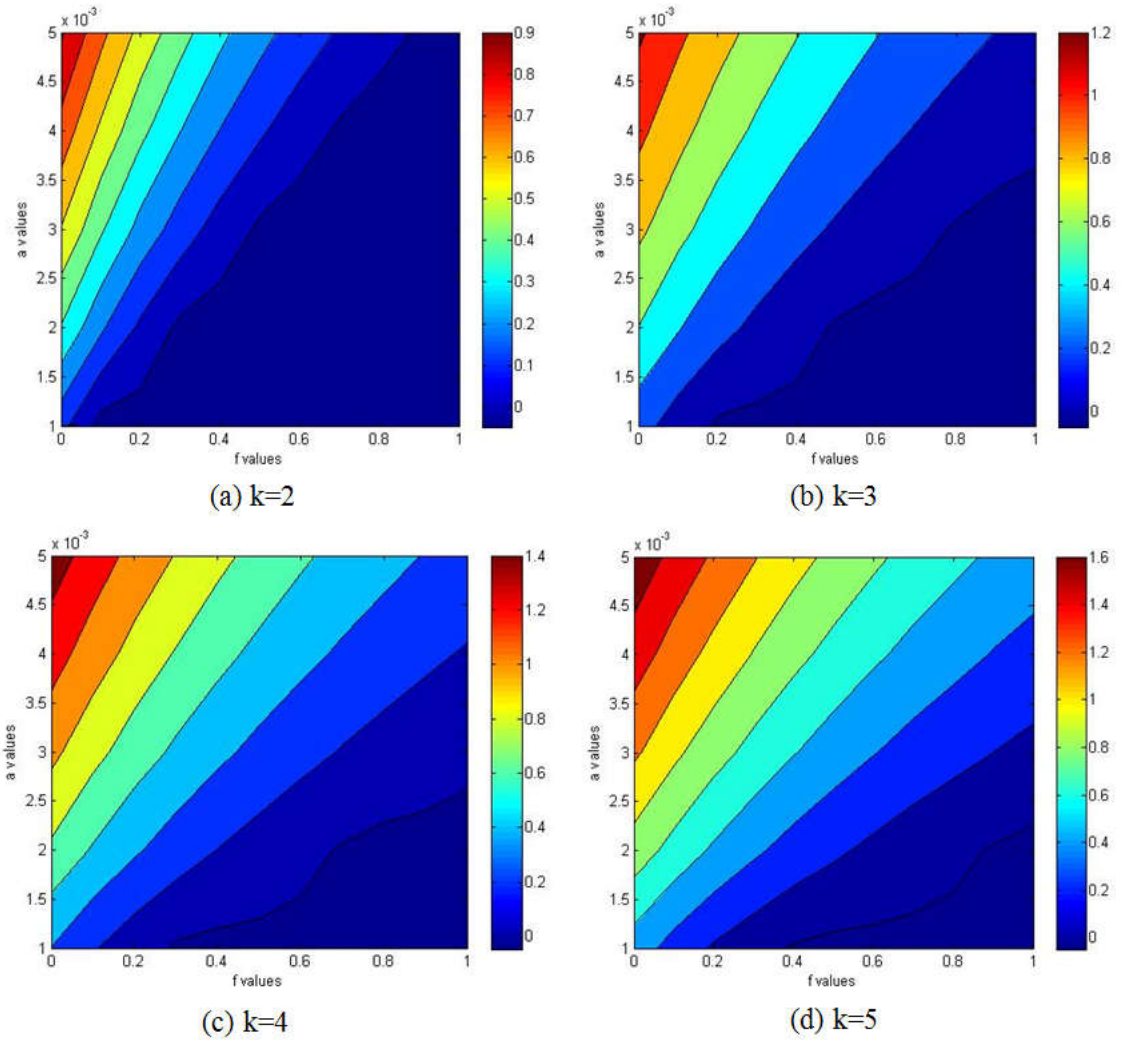

Fig. 3: The parameter plane $f-a$ indicating the stability regions for different k values. The numerical values of the parameter used are: μ=10, α=0.05, a=0.001, β=0.5, κ=0.051, γ=0.5, p=0.001, η=10, δ=0.049, c=0.001, q=0.001

The uncertainty of the parameter values can be addressed using sensitivity analysis (Summer, 2010). Based on the results that we obtained for stability criteria of the model, we are motivated to analyze the sensitivity of R_0 and to identify the parameters that have a high impact on R_0. For this we used the normalized forward sensitivity index (Rodrigues *et al*., 2013) which is defined as the ratio of the relative change in R_0 to the relative change in the parameter. If R_0 is a differentiable function of the parameter, the sensitivity index can be defined using partial derivatives.

Definition 1. The normalized forward sensitivity index of R_0 that depends differentiably on a parameter p, is defined by (Rodrigues *et al.,* 2013)

$$r_p^{R_0} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0} \qquad \text{..... (3)}$$

Using the explicit formula (2) for R_0, we derive analytical expressions for the sensitivity of R_0 with respect to each parameter that comprise it. The sensitivity indices are evaluated at the baseline parameter values and are given in Table 2.

Table 2. Sensitivity indices of R_0 evaluated for the parameter value

Parameter	Sensitivity index
a	+1
μ	+1
k	+1
α	-1
β	-1
γ	-1

For example $r_a^{R_0} = +1$ means increasing (or decreasing) a by 10% increases (or decreases) R_0 by 10%. Since $r_\alpha^{R_0} = -1$ if α is increased by 10%, R_0 decreases by 10%.

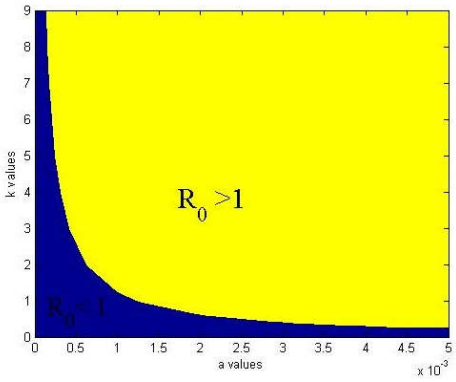

Fig.4. Stability region for R_0

RESULTS AND DISCUSSION

The model parameters one at a time by a small amount from the baseline values and the effect of individual perturbations on the model variables are noted. A highly sensitive parameter would display a high impact on model responses for a small perturbation in model parameter. Fig.5 shows the sensitivity of viral dynamics to the model parameters, varying one parameter at a time. Only the most significant parameters are graphically presented. Each graph represents the change in state variables using the assigned parameter values taken from literature, given in Table 1 and the corresponding curves with a specific parameter increase of 10%. Changes in the parameters a and k reflect the same kind behaviour on all state variables.

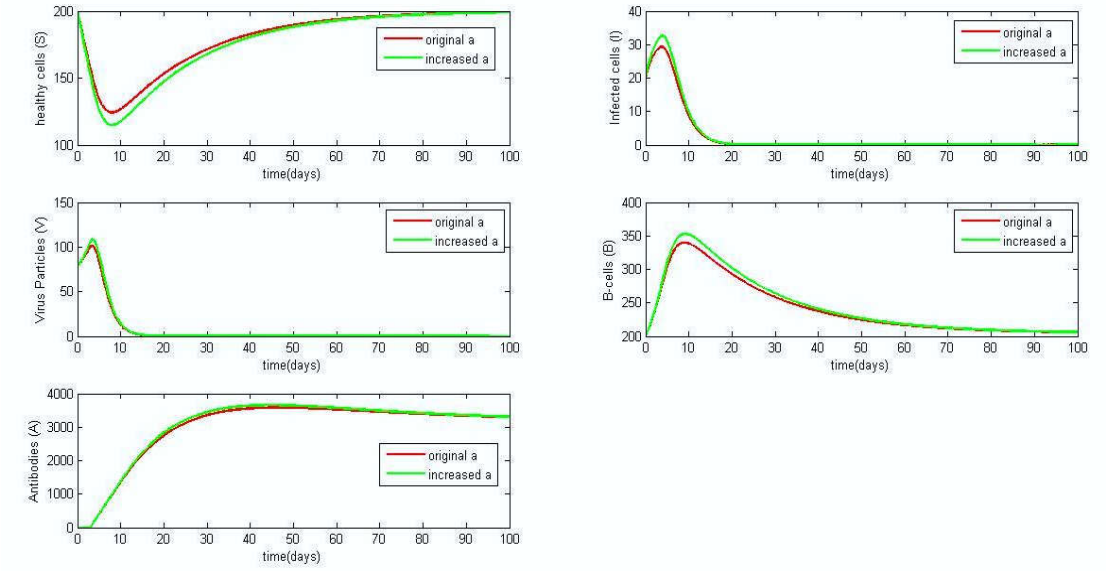

Fig. 5a: The dynamics of S, I, V, B, A for the variation of a

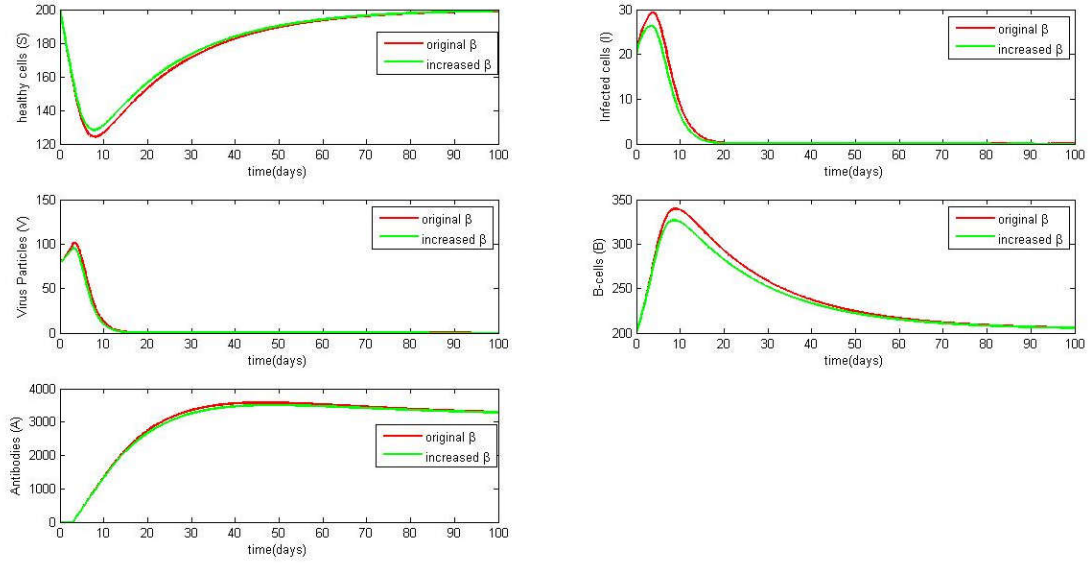

Fig. 5b: The dynamics of S, I, V, B, A for the variation of β

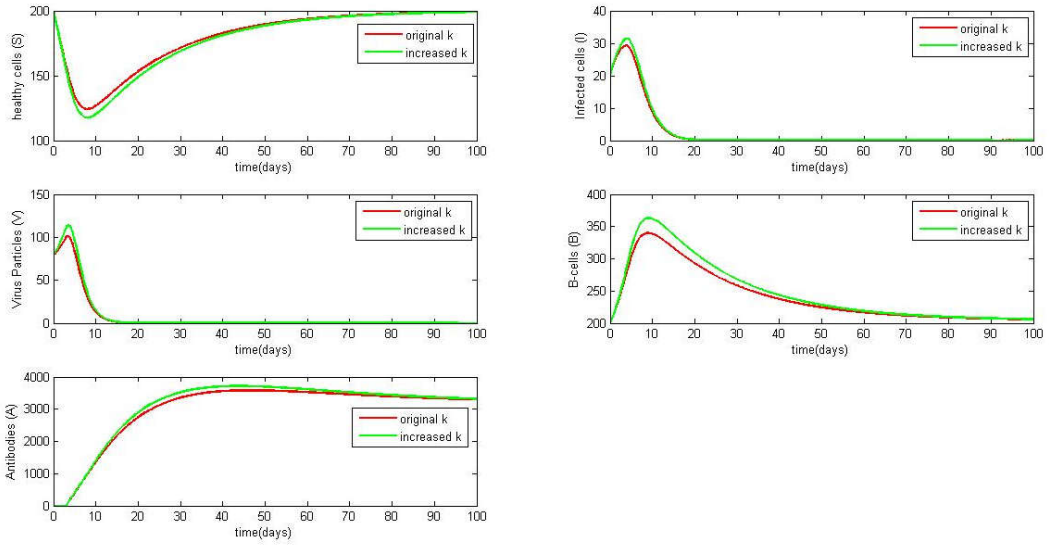

Fig. 5c: The dynamics of S, I, V, B, A for the variation of k

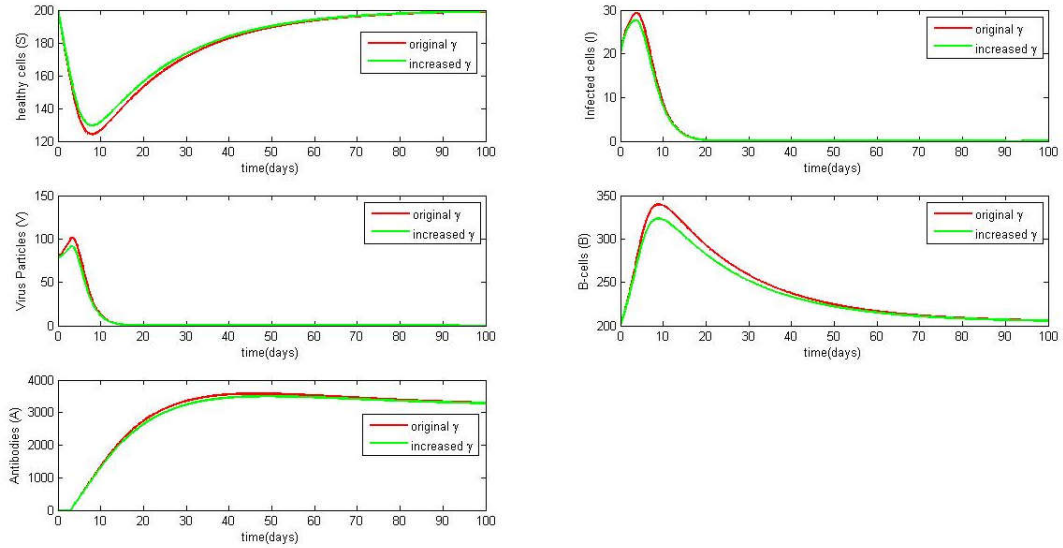

Fig. 5d: The dynamics of S, I, V, B, A for the variation of γ

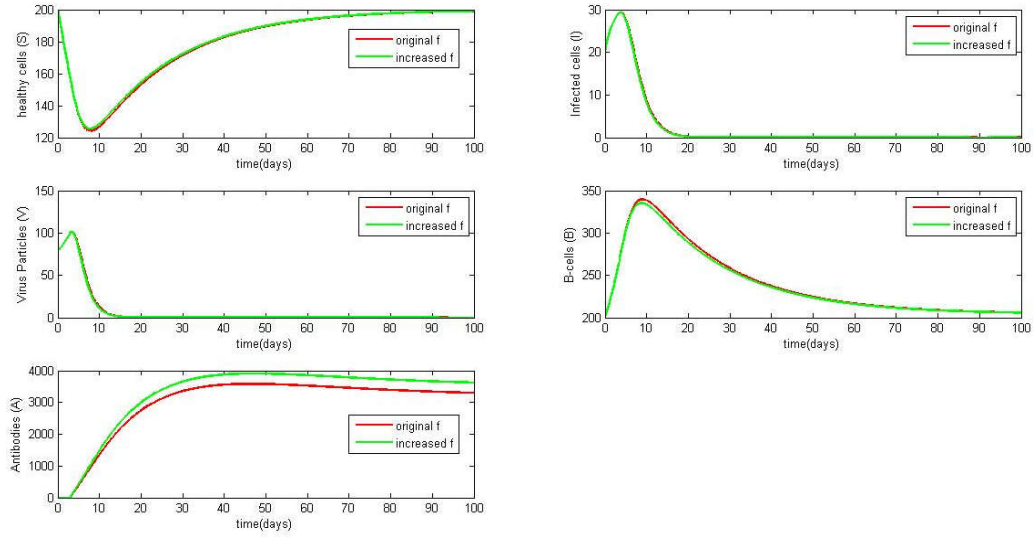

Fig.5e: The dynamics of S, I, V, B, A for the variation of f

Figure 5: The sensitivity of viral dynamics to the model parameters

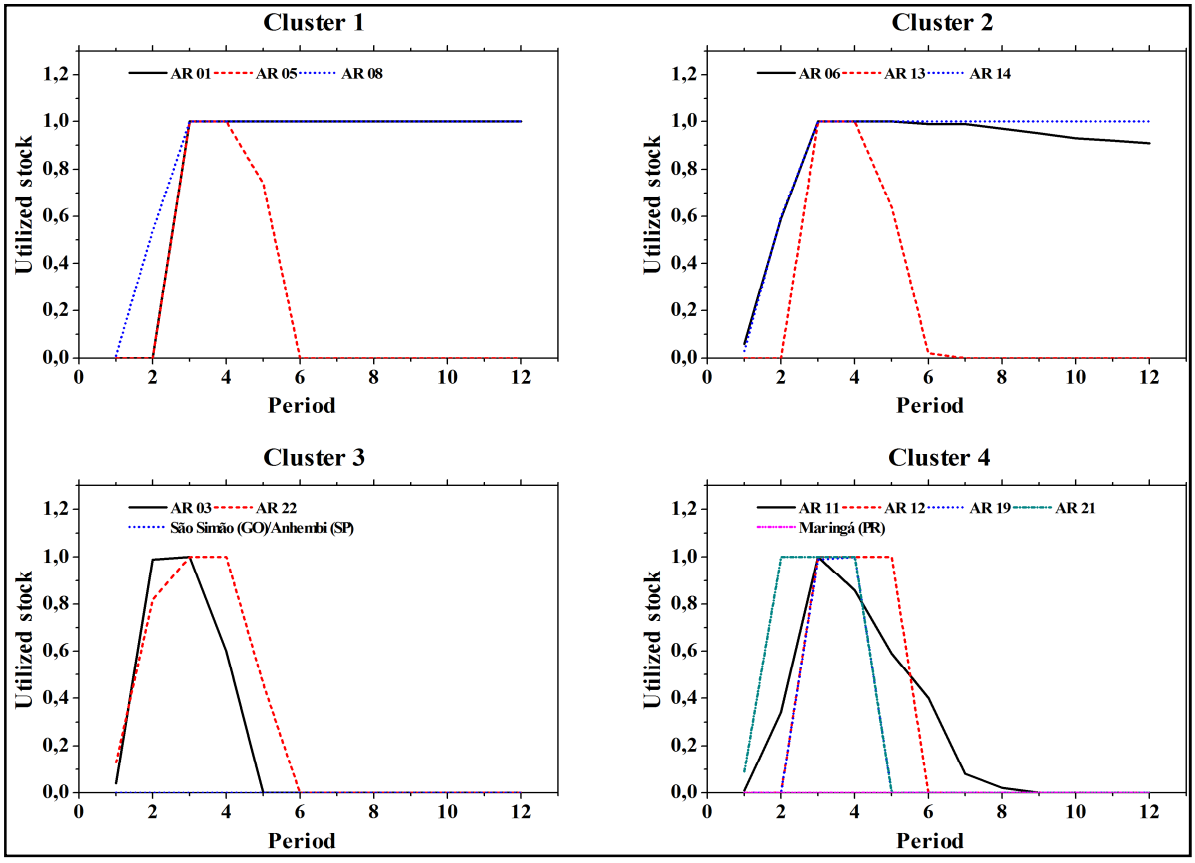

Figure 8. Stock's behavior to MCDF scenario

As a and k increases, the healthy cell population, S, decreases to a minimum value and then increases to its equilibrium value. Infected cells, I, Virus particles, V and B-cells show similar kind of behaviour. With increasing a and k, they increases to a maximum value and then decreases to its equilibrium value of 0. So does the antibodies, which increases and reaches equilibrium after some time period. It is noticeable that for high values of k, there is a higher load of virus and proportionally a high load of antibodies which agrees with our theory on humoral immune response. It is clear from Fig.5b that as the natural death rate of infected cells, β increases, the number of infected cells decreases and since virus multiplies within infected cells, number of virus particles present also decrease. Since B-cells are stimulated by virus particles, they would also decrease producing less number of antibodies. The same phenomenon can be observed for increase in death rate of virus particles γ. Increasing f has a contra effect on the dynamics of S, I, V, B and A compared to the variation of a and k. Increasing the parameter f, makes S and A to increase I, V and B to decrease. The rest of the parameters do not show any significant sensitivity towards viral dynamics and the changes are not graphically perceptible. Here we vary all parameters at once by 10% from the baseline values and note the effect of on the model variables. When all parameters are increased by 10%,healthy cells, S, increase and decrease at a rate higher than the original rate. The infected cells, I, virus particles, V, B-cells, B and antibodies, A increases to its maximum at a higher rate and then decreases at a higher rate than the original rate. Thus when all parameters are increased by 10%, we may get rid of the infection a little faster from the body but the infection can become more severe as the maximum of infected cells and virus particles is higher than for the original parameters. When all parameters are decreased by 10%, healthy cells increase to its equilibrium value much slowly and it takes more time for the production of antibodies. Also the time taken for the body to get rid of the infection is more than in the case of original parameter values.

Conclusion

The model considered in this paper is based on humoral or antibody mediated immune response as it is the most relevant immunity system in the context of dengue. Our results indicate that as the virus burst rate increases, other conditions in the body must be strong enough to eliminate the disease completely from the body. It is also noticeable that for higher virus burst rates, there is a high load of virus and proportionally a high load of antibodies which agrees with the theory on humoral immune response. By studying the sensitivity indices of the basic reproduction number R_0, one can determine the relative importance of the model parameters in the evolution of within-host dengue infection. Such analysis can provide acute information for public health officials, medical practitioners and decision makers who may have to

deal with an infectious disease in reality. Also we can see even if we vary all parameters at once, it does not significantly affect the model outcomes. Our results imply that in general the virus gets cleared with 7-14 days which is observed in clinical literature. The model can be improved by incorporating the absorption effect that considers the absorption of pathogens into the uninfected cells. Also if a relationship between the model parameters and available clinical data can be established the model can be easily validated against the available data.

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