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Mathematical modeling of host response to dengue virus and antibody dependent enhancement

Modelagem da resposta do hospedeiro ao vírus da dengue e reforço dependente de anticorpos

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Resumo

Por muitos anos, os quatro sorotipos do vírus da dengue têm causado doença variando de assintomática à dengue grave e potencialmente fatal em milhões de pessoas por ano. A primeira infecção por dengue fornece uma proteção para a vida toda contra a reinfecção com o mesmo sorotipo, mas apenas proteção parcial contra outros sorotipos. Acredita-se que os anticorpos existentes contra um sorotipo pode aumentar a gravidade da doença, um fenômeno conhecido como *Reforço dependente de anticorpo*. Nesta tese, nosso foco foi o tratamento matemático da interação entre o sistema imunológico e vírus da dengue. Primeiramente, desenvolvemos um modelo matemático da resposta imune adaptativa ao vírus da dengue na infecção primária, onde se considera que a ativação da resposta imune celular e humoral é mediada pela diferenciação de células auxiliadoras Th. Conclui-se que o vírus da dengue é eficazmente eliminado pela resposta imunológica celular, se ocorrer uma intensa proliferação de células citotóxicas. Caso contrário, em uma proliferação fraca, o vírus da dengue é removido por uma proliferação potente de células B ativadas ou/e a inibição da ativação de células auxiliadoras Th1. Além disso, as simulações com dados clínicos mostram que a atividade citotóxica é inibida no início da infecção, enquanto que as células B ativadas realizam a primeira resposta imunológica, o que pode ser uma estratégia do vírus da dengue para se propagar no corpo. Após a primeira etapa, formulamos um modelo matemático para explorar o reforço dependente de anticorpos na segunda infecção pelo vírus da dengue e determinamos um limiar para o parâmetro de proliferação das células B de memória. É possível ver que acima deste parâmetro, a elevada proliferação dos anticorpos não neutralizantes aumenta a possibilidade de formação do complexo anticorpo-antigêno, levando consequentemente, a uma maior probabilidade de opsonização por células imunitárias, enquanto que abaixo desse parâmetro ou as partículas virais são eliminadas ou atingem o nível mínimo. Finalmente, usamos um método direto de Lyapunov para estudar a estabilidade global de um modelo de dinâmica de vírus considerando uma resposta imune humoral e celular. Observamos que, se o número líquido de vírus é menor ou igual a um, o equilíbrio livre de vírus é globalmente e assintoticamente estável. A estabilidade global do equilíbrio com presença de vírus foi estabelecida se a taxa de entrada viral nas células de alvo for menor ou igual a um.

Palavras-chave: Vírus da Dengue. Reforço dependente de anticorpos. Sistema imunológico adaptativo. Método direto de Lyapunov.

Abstract

For many years, the four serotypes of dengue virus have caused asymptomatic to severe and potentially fatal dengue disease in millions of individuals each year. The first dengue infection provides a protection for life against reinfection with the same serotype, but only partial protection against other serotypes. It is believed that existing antibodies against one serotype may increase the severity of the disease, a phenomenon known as *antibody dependent enhancement*. In this thesis, we focus on the mathematical treatment of the interaction between the immune system and dengue virus. First, we develop a mathematical model of the adaptive immune response to dengue virus in the primary infection, in which it is considered that the differentiation of the helper cell mediates the activation of the cellular and humoral immune response. We conclude that the dengue virus is effectively eliminated by the cellular immune response if there exists an intense proliferation of cytotoxic cells. By contrast, in a weak proliferation, the dengue virus is removed by a potent proliferation of activated B cells and/or the inhibition of the activation of Th1 helper cells. Further, the simulations with clinical data demonstrate that cytotoxic activity is inhibited at the beginning of infection, whereas the activated B cells perform the first immune response, which could be a dengue virus strategy for spreading throughout the body. Second, we formulate a mathematical model to explore the antibody-dependent enhancement of dengue disease. We found a threshold for the proliferation parameter of B memory cells. We can see that above this threshold, the high proliferation of non-neutralizing antibodies increases the possibility that antibody-antigen complex will form. Consequently, opsonization by immune cells would become more likely, whereas those below this threshold or the viral particles are either eliminated or reach the minimum level. Finally, we use a Lyapunov direct method to study the global stability of a model of virus dynamics while considering the humoral and cellular immune responses. We found that if the net number of viruses is less than or equal to one, the virus-free equilibrium is globally asymptotically stable. By contrast, the global stability of virus-presence equilibrium is established if the viral entrance rate in the target cells is less than or equal to one.

Keywords: Dengue virus. Antibody dependent enhancement. Adaptive immune system. Direct Lyapunov method.

Contents

Introduction

Dengue is an endemic viral disease present in more than 100 countries, with approximately 50–100 million new infections occurring annually. Dengue exerts a huge impact on the economy because it directly affects the population and health systems, and its incidence has increased 30-fold in the past decade [1]. Dengue virus (DENV) is a virus of the family Flaviviridae that is transmitted by the bite of an infected female mosquito of the species *Aedes aegypti* or *Aedes albopictus* [2],[3]. A dengue infection could be asymptomatic or symptomatic. When it is symptomatic, it is called dengue fever or severe dengue (dengue hemorrhagic fever and dengue shock syndrome). Dengue fever includes a high fever and at least two of the following symptoms: severe headache, pain behind the eyes, muscle and joint pain, nausea, vomiting, swollen glands or rash. Symptoms usually last for 2–7 days. Severe dengue is most serious manifestation of the disease due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment, which need proper medical care to prevent complications and reduce the risk of death [4],[5]. There are four serotypes of DENV (DENV-1, DENV-2, DENV-3 and DENV-4), and all can generate the clinical manifestations described above. A primary dengue infection provides protection for life against reinfection with the same serotype, but only partial protection against other serotypes. Generally, most primary infections are dengue fever and few develop severe dengue, but epidemiological studies suggest that a secondary infection by a different serotype of DENV could increase the risk of severe dengue [4],[6]. Furthermore, severe dengue could occur in primary DENV infections of infants born to dengue-immune mothers [7], [8].

When a DENV-infected female mosquito feeds on a healthy person, it inoculates some amount of DENV. The initial targets of the virus are the most common skin cells, the keratinocytes [9],[10]. The virus replicates in the dendritic cells of the skin, the Langerhans cells [11], [12], [13],[14]. These cells are specialized in antigen presentation. They belong to the skin's immune system and transport antigens to regional lymph nodes. In this journey to the lymph nodes, the white cells–monocytes and macrophages–try to destroy the pathogen and are consequently infected by DENV [15],[16]. The rise and spread of the virus results in viremia. Once the innate immune system is unable to stop the DENV, the immune system looks for another strategy, which is normally called adaptive immune response, a fundamental immune response to the recovery of any disease. Generally, the adaptive immune response is activated by the Th helper cells, which are in turn activated and differentiated by the stimulus of antigen-presenting cells. The infected cells produce and release cytokines that help the immune system to recognize and protect DENV-infected and uninfected cells, respectively. Based on the types of cytokine production, Th cells are

categorized as Th1 and Th2. Activated Th1 produces IFN-γ, IL-2, and IL-12, whereas Th2 produces IL-4, IL-5, IL-10, and IL-13 [17]. If the Th cell differentiates into a Th1 cell, it will activate macrophages and cytotoxic T cells, a process known as cellular immune response that is responsible for eliminating the intracellular pathogens, i.e. killing the infected cells. However, if a Th helper cell differentiates into a Th2 cell, it can stimulate B cells to make most classes of antibodies. This is known as a humoral immune response, and it defends the host from extracellular pathogens. Therefore, getting a cellular and/or humoral immune response will depend on how Th helper cells are differentiated. The immunologic responses in dengue disease have been reported in an activated Th1-type cytokine response in dengue fever and an activated Th2-type cytokine response in severe dengue [18]. A person previously infected with DENV has antibodies against this serotype for life. However, for the remaining three serotypes, immunity is lost after a short time and the person becomes susceptible [19]. Studies show that a person exposed to a different serotype of DENV a second time is more likely to develop severe dengue compared to those who have not been exposed [20], [21]. Generally, the B and T memory cells remain in the body to react to pathogens responsible for earlier infections. However, it seems these antibodies are not effective against another DENV serotype. By contrast, the infection is worse. The first researchers who observed this were Dr. Scott Halstead and colleagues who called this phenomenon as *antibody dependent enhancement* (ADE) [6]. In vitro studies show that the ADE works in the following way: the preexistent antibodies from a previous DENV infection bind to the dengue virus antigens, especially to E or prM antigens, but these are unable to neutralize the virus. This antigen-antibody complex is better opsonized via Fc receptor-bearing cells such as monocytes and macrophages, which are major replication cells in vivo that could increase the titer of the virus in the blood [22].

In this thesis, the aim is to study the mathematical dynamics of dengue virus and the immune system by trying to express the principal process of the immune system to stop the spread of dengue virus in primary and secondary infections. In the chapter 1, we develop a mathematical model to describe the immune response to dengue virus when there is no previous infection. In this model, we consider the fact that cellular and humoral immune responses are activated by the differentiation of helper T cells, and we evaluate the contribution of each immune response to the clearance of dengue virus. In chapter 2, we propose a mathematical model to study the antibody-dependent enhancement. In this model, we consider the existence of an immunological memory that defends against a certain dengue serotype. It is shown when there will be a strong increase in the viral load and infected cells, which will depend on an immunological threshold. In chapter 3 we propose a mathematical simplification of the model in chapter 1 and study the global stability using the direct Lyapunov method. Finally, we discuss the conclusions of this thesis and the future work arising from these studies are discussed in chapter 4.

1 Mathematical model of the immune response to dengue virus

Abstract. Dengue disease is caused by an infected mosquito's bite and manifests in different clinical symptoms. The complexity of the pathogenesis of dengue virus and the limitations of biological models have been barriers to completely understanding this disease. To address this concern, we developed a mathematical model of the immune response to dengue virus, which evaluated the impact of cellular and humoral immune responses. We also performed global sensitivity analysis and parameter estimation using clinical data. We concluded that to prevent instability and control the viral load, a strong proliferation of cytotoxic cells must prevail. However, if there exists a weak proliferation of cytotoxic cells, the way to avoid instabilities is to either inhibit the differentiation of T helper cells into Th1 cells or increase the proliferation of B cells. In addition, our results based on clinical data showed that cellular response is inhibited initially but strongly activated later, which could be a spreading strategy of the virus that is not completely effective because of the strong proliferation of cytotoxic activity to stop the infection in target cells.

1.1 Introduction

Dengue virus belongs to the virus family Flaviviridae and genus flavivirus, which includes yellow fever, West Nile virus fever, Japanese encephalitis virus fever, tick-borne encephalitis virus and Zika virus. There are four DENV serotypes (DENV-1, DENV-2, DENV-3 and DENV-4), which are transmitted by the bite of an infected female mosquito of the species *Aedes aegypti* or *Aedes albopictus*. After dengue virus is inoculated into the skin, a small battle to stop the virus is initiated by our innate immune system. Unfortunately, not all battles are won, and it will depend on many factors influencing the disease, like host genetics, virulence, the strain of the virus and host immunity [23]. Generally, it is accepted that the major target cells are dendritic cells and monocytes/macrophages. Infection of these cells induces cytokine production and cell activation and maturation [24],[25]. The chemical signaling of infected cells activates the humoral and cellular immune responses, which are crucial in the protection and clearance of DENV. In relation to the humoral immune response, the process starts when the B cells are activated. Once the activated B cells improve affinity, they are going to differentiate into plasma cells. These, in turn, will release the antibodies that are crucial mechanisms in the neutralization of DENV infectivity. A similar process occurs for cellular immune response. The activated T cells proliferate, and these cells will kill the cells infected by dengue virus. These

cytotoxic cells are necessary and decisive for clearing dengue virus. Actually, there are few mathematical models of dengue virus that describe the interaction between dengue virus and the target cells or the interaction of dengue virus, the target cells and the immune system [26],[27],[28],[29].Beyond taking into account dengue virus and target cells, our model considers the T helper cells and how their differentiation into Th1 or Th2 influences the immune response. The aim of this paper is to investigate and asses the implications of humoral and cellular immune responses in the dengue viral clearance. To do this, we assume that there are no previous antibodies from a primary dengue infection.

1.2 Model formulation

We consider an infection by DENV and a possible reaction of adaptive immune response. In this way, the model considers: the target cells S, infected cells I, dengue virus V, and the cells of immune system, the helper cells $Th0$, $Th1$ and $Th2$ denoted by T_0, T_1 and T_2, B and CD8+ cells in rest and activated states; B_r, T_{cr} and B_a, T_{ca} represents these states. The target cells S are produced in the bone marrow at rate k_s, have death rate μ_s, and got infected at rate $\beta_{_I}$. These infected cells I have an additional death rate by apoptosis $\mu_{_I}$. The dengue virus V has death rate μ_v, and its number increases proportionally to the presence of infected cells I at rate $N_1(\mu_s + \mu_{_I})$, where N_1 is the number of virus particles released on average by a productively infected cell during its lifetime. Besides, we considerer that more than one particle of virus are trying to infect each cell. This number is denoted by N_2. So the simplest model, considering these descriptions is

$$\begin{aligned}
\frac{dS}{dt} &= k_s - \beta_{_I} SV - \mu_s S \\
\frac{dI}{dt} &= \beta_{_I} SV - (\mu_s + \mu_{_I})I \\
\frac{dV}{dt} &= N_1(\mu_s + \mu_{_I})I - N_2\beta_{_I} SV - \mu_v V.
\end{aligned}$$

If the innate immune system is not able to stop the disease, then the infected cells travel to lymph node to activate the adaptive immune response. The different signals emitted by the infected cells and the innate immune response will differentiate the helper cells into helper cells Th1 or Th2, which in turn will activate a balanced humoral and cellular immune responses to try stop the dengue infection. The helper cells T_0 are produced in the bone marrow at rate k_0 and are capable of differentiating into T_1 by the signalization of cytokine IL-12 and into T_2 by the cytokine IL-4. In our model we consider that this differentiation is possible by the presence and the stimulus of infected cells and virus, at rates γ_1 and γ_2 respectively. The death rate of these helper cells are μ_0, μ_1 and μ_2. The resting B_r cells are produced in the bone marrow at rate k_r and are stimulated by the

signals emitted by the T_2 cells at rate α_r and decay at μ_r. The activated B_a cells are going to proliferate in the presence of dengue virus at rate α_a and decay at rate μ_a. The proliferation of B_a cells allow these cells to improve its affinity, which means that they are effective to clear the dengue infection, we consider that this happen at rate α_v. In the same way the CD8+ cells T_{cr} are activated by the cells T_1 at rate α_{cr} and have death rate μ_{cr}. The activated cells T_{ca} have cloning rate α_{ca} and decay at rate μ_{ca}; those T_{ca} cells receiving the correct signal will perform the lysis of infected cells at rate $\alpha_{_I}$. Consequently the model considering a humoral and cellular immune responses is

$$\begin{aligned}
\frac{dS}{dt} &= k_s - \beta_{_I} SV - \mu_s S \\
\frac{dI}{dt} &= \beta_{_I} SV - \alpha_{_I} IT_{ca} - (\mu_s + \mu_{_I})I \\
\frac{dV}{dt} &= N_1(\mu_s + \mu_{_I})I - N_2\beta_{_I} SV - \alpha_v B_a V - \mu_v V \\
\frac{dT_0}{dt} &= k_0 - \gamma_1 T_0 I - \gamma_2 T_0 V - \mu_0 T_0 \\
\frac{dT_1}{dt} &= \gamma_1 T_0 I - \mu_1 T_1 \\
\frac{dT_2}{dt} &= \gamma_2 T_0 V - \mu_2 T_2 \\
\frac{dB_r}{dt} &= k_r - \alpha_r B_r T_2 - \mu_r B_r \\
\frac{dB_a}{dt} &= \alpha_r B_r T_2 + \alpha_a B_a V - \mu_a B_a \\
\frac{dT_{cr}}{dt} &= k_{cr} - \alpha_{cr} T_{cr} T_1 - \mu_{cr} T_{cr} \\
\frac{dT_{ca}}{dt} &= \alpha_{cr} T_{cr} T_1 + \alpha_{ca} T_{ca} I - \mu_{ca} T_{ca}.
\end{aligned} \tag{1.1}$$

The set of biological interest is given by

$$\mathcal{A} = \left\{ P \in \mathbb{R}^{10}_{+} : N_1 S + NI + V + T_0 + T_1 + T_2 + \frac{\alpha_v}{\alpha_a}(B_r + B_a) + \theta\,(T_{cr} + T_{ca}) \leqslant \frac{\bar{k}}{\delta} \right\}, \tag{1.2}$$

where $P = (S, I, V, T_0, T_1, T_2, B_r, B_a, T_{cr}, T_{ca})$, $N = (N_1 + N_2)$, $\theta = \dfrac{N\alpha_{_I}}{\alpha_{ca}}$, $\bar{k} = k_0 + N_1 k_s + \dfrac{\alpha_v}{\alpha_a} k_r + \theta k_{cr}$ and $\delta = \min\left\{ \mu_s, \mu_v, \mu_0, \mu_1, \mu_2, \mu_r, \mu_a, \mu_{cr}, \mu_{ca}, \dfrac{N_2(\mu_s + \mu_{_I})}{N} \right\}$.

Lemma 1.1. *The set $\mathcal{A}$ is positively invariant with respect to system (1.1).*

Proof. let $P_0 \in \mathcal{A}$ be the initial condition of the system (1.1) and

$$\Phi = N_1 S + NI + V + T_0 + T_1 + T_2 + \frac{\alpha_v}{\alpha_a}(B_r + B_a) + \theta\,(T_{cr} + T_{ca})\,. \tag{1.3}$$

Taking the derivative of Φ with respect to t, we have:

$$\frac{d\Phi}{dt} = N_1 k_s - N_1 \mu_s S - N_2(\mu_s + \mu_I)I - \mu_v V + k_0 - \mu_0 T_0 - \mu_1 T_1 - \mu_2 T_2 + \frac{\alpha_v}{\alpha_a}\left[k_r - (\mu_r B_r + \mu_a B_a)\right] + \theta\left[k_{cr} - (\mu_{cr} T_{cr} + \mu_{ca} T_{ca})\right],$$

which can be written as

$$\frac{d\Phi}{dt} + N_1 \mu_s S + N_2(\mu_s + \mu_I)I + \mu_v V + \mu_0 T_0 + \mu_1 T_1 + \mu_2 T_2 + \frac{\alpha_v}{\alpha_a}(\mu_r B_r + \mu_a B_a) + \theta(\mu_{cr} T_{cr} + \mu_{ca} T_{ca}) = \bar{k},$$

where $\bar{k} = k_0 + N_1 k_s + \dfrac{\alpha_v}{\alpha_a} k_r + \theta k_{cr}$.

If we choose $\delta = \min\left\{\mu_s, \mu_v, \mu_0, \mu_1, \mu_2, \mu_r, \mu_a, \mu_{cr}, \mu_{ca}, \dfrac{N_2(\mu_s + \mu_I)}{N}\right\}$, we conclude that,

$$\frac{d\Phi}{dt} + \delta\Phi \leqslant \bar{k},$$

then

$$\Phi \leqslant \frac{\bar{k}}{\delta} + \left(\Phi(0) - \frac{\bar{k}}{\delta}\right) e^{-\delta t}, \text{ for all } t \geqslant 0,$$

wich implies

$$\Phi \leqslant \frac{\bar{k}}{\delta}.$$

□

1.3 Mathematical analysis

The immune system is very complex and every disease generates different immune responses and challenges for the researchers, but there are some well known reactions, like the inhibition of differentiation between the helper cells T_1 and T_2. This inhibition occurs by chemical signaling; the T_1 cells are inhibited by the citokines IL-4 and IL-10 which are produced by the T_2 cells, which in turn, can be inhibited by citokines IFN-γ produced by the T_1 cells. In the model the action of those citokines is not considered explicitly, instead of, we contemplate its action in the parameters γ_1 and γ_2. Therefore in the model (1.1) we study initially two scenarios: a) The T_2 cells are going to inhibit completely the differentiation into cells T_1, this means that the parameter of differentiation of T_0 cells into T_1 has to be zero, i.e. $\gamma_1 = 0$ (This situation will generate a type of immune response which is known as humoral immune response); b) The total inhibition of the T_2 cells by T_1 will happen when the parameter of differentiation of T_0 cells into T_2 is zero,

i.e. $\gamma_2 = 0$ (This type of response is known as cellular immune response). This section is divided into three topics: in the subsection 1.3.1 we present an analysis of the model considering the humoral immune response, in the subsection 1.3.2 the cellular immune response is studied, finally in the subsection 1.3.3 we present the mathematical analysis of the model considering both immune responses.

1.3.1 Humoral immune response to dengue virus

We consider a total inhibition of T_1 cells, therefore it is considered a humoral immune response when the parameter $\gamma_1 = 0$. The model is

$$\begin{aligned}
\frac{dS}{dt} &= k_s - \beta_{_I} SV - \mu_s S \\
\frac{dI}{dt} &= \beta_{_I} SV - (\mu_s + \mu_{_I})I \\
\frac{dV}{dt} &= N_1(\mu_s + \mu_{_I})I - N_2\beta_{_I} SV - \alpha_v B_a V - \mu_v V \\
\frac{dT_0}{dt} &= k_0 - \gamma_2 T_0 V - \mu_0 T_0 \\
\frac{dT_2}{dt} &= \gamma_2 T_0 V - \mu_2 T_2 \\
\frac{dB_r}{dt} &= k_r - \alpha_r B_r T_2 - \mu_r B_r \\
\frac{dB_a}{dt} &= \alpha_r B_r T_2 + \alpha_a B_a V - \mu_a B_a.
\end{aligned} \tag{1.4}$$

1.3.1.1 Virus-free equilibrium for humoral model

The model has the virus-free equilibrium $P_{h0} = \left(\frac{k_s}{\mu_s}, 0, 0, \frac{k_0}{\mu_0}, 0, \frac{k_r}{\mu_r}, 0\right)$. The characteristic polynomial evaluated at point P_{h0} is

$$p_h(\lambda) = \prod_{\vartheta}(\lambda+\mu_\vartheta)\left[\lambda^2 + \left(\mu_s + \mu_{_I} + \mu_v + \frac{\beta_{_I}\, k_s\, N_2}{\mu_s}\right)\lambda + (\mu_s + \mu_{_I})\left(\mu_v + \frac{\beta_{_I}\, k_s\, N_2}{\mu_s} - \frac{\beta_{_I}\, k_s\, N_1}{\mu_s}\right)\right],$$

with $\vartheta \in \{0, 2, s, r, a\}$. Observe that the last term of the polynomial inside the brackets can be written as,

$$(\mu_s + \mu_{_I})\mu_v\,(1 - R_0)\,,$$

where $R_0 = \dfrac{\beta_{_I}(N_1 - N_2)k_s}{\mu_v\mu_s}$. To prove stability at this point, it is necessary that the roots of previous polynomial at P_{h0} be negative or have negative real part. Then by the Routh Hurwitz criteria [30] (pg 230), the virus-free equilibrium P_{h0} is locally asymptotically stable, if the coefficients of polynomial of second degree are positives, i.e. if $R_0 < 1$ and it is unstable if $R_0 > 1$. We summarize these considerations in the following theorem

Theorem 1.1. *The virus-free equilibrium P_{h0} is locally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$.*

1.3.1.2 Virus-presence equilibrium for humoral model

The model has a virus-presence point $(S^*, I^*, V^*, T_0^*, T_2^*, B_r^*, B_a^*)$, which exists if $R_0 > 1$, with

$$\begin{aligned}
S^* &= \frac{k_s}{\beta_I V^* + \mu_s} \\
I^* &= \frac{\beta_I k_s V^*}{(\mu_I + \mu_s)(\beta_I V^* + \mu_s)} \\
T_0^* &= \frac{k_0}{\gamma_2 V^* + \mu_0} \\
T_2^* &= \frac{\gamma_2 k_0 V^*}{\mu_2(\gamma_2 V^* + \mu_0)} \\
B_r^* &= \frac{k_r \mu_2(\gamma_2 V^* + \mu_0)}{(\alpha_r k_0 + \mu_2\mu_r)\gamma_2 V^* + \mu_0\mu_2\mu_r} \\
B_a^* &= \frac{\alpha_r \gamma_2 k_0 k_r V^*}{(\mu_a - \alpha_a V^*)[(\alpha_r k_0 + \mu_2\mu_r)\gamma_2 V^* + \mu_0\mu_2\mu_r]}.
\end{aligned} \tag{1.5}$$

The last equation of (1.5) has biological sense if it is positive, so we need to have $V^* < \frac{\mu_a}{\alpha_a}$. The values of V^* are the roots of the third degree polynomial

$$P_h(V) = \mu_v(\mu_a - \alpha_a V)[(\alpha_r k_0 + \mu_2\mu_r)\gamma_2 V + \mu_0\mu_2\mu_r][\mu_s(R_0 - 1) - \beta_I V] - \alpha_v\alpha_r\gamma_2 k_0 k_r V(\beta_I V + \mu_s).$$

This polynomial has a unique root in the interval $\left(0, \frac{\mu_a}{\alpha_a}\right)$. To show this, note that the coefficient of term V^3 is positive. Then $P_h(V) \to +\infty$ if $V \to +\infty$ and $P_h(V) \to -\infty$ if $V \to -\infty$, besides

$$P_h(0) = \mu_s\mu_v\mu_0\mu_2\mu_r\mu_a(R_0 - 1) > 0,$$

and

$$P_h\left(\frac{\mu_a}{\alpha_a}\right) = -\alpha_v\alpha_r\gamma_2 k_0 k_r \frac{\mu_a}{\alpha_a}\left(\beta_I \frac{\mu_a}{\alpha_a} + \mu_s\right) < 0.$$

Therefore, the polynomial P_h has one negative root in $(-\infty, 0)$ and two positive roots, one in the interval $\left(0, \frac{\mu_a}{\alpha_a}\right)$ and the other in $\left(\frac{\mu_a}{\alpha_a}, \infty\right)$.

Then this virus-presence equilibrium always exists for $R_0 > 1$, besides, in the polynomial P_h, it is possible to observe that if $\alpha_a \to \infty$, then $V \to 0$. This means that it is always possible to decrease the viral load V when the proliferation of B_a cells is big.

Remark 1.1. *Note that for $R_0 < 1$, the polynomial P_h has no positive roots less than $\frac{\mu_a}{\alpha_a}$. In fact, let's write*

$$P_h = P_{3h} - P_{2h},$$

with $P_{3h} = \mu_v(\mu_a - \alpha_a V)[(\alpha_r k_0 + \mu_2\mu_r)\gamma_2 V + \mu_0\mu_2\mu_r][\mu_s(R_0 - 1) - \beta_I V]$ and $P_{2h} = \alpha_v\alpha_r\gamma_2 k_0 k_r V(\beta_I V + \mu_s)$. It is clear that the polynomial P_{3h} has two negative roots,

$\frac{\mu_s(R_0-1)}{\beta_I}$, $-\frac{\mu_0\mu_2\mu_r}{(\alpha_r k_0+\mu_2\mu_r)\gamma_2}$ *and one positive,* $\frac{\mu_a}{\alpha_a}$. *Whereas that the polynomial* P_{2h} *has the roots* $-\frac{\mu_s}{\beta_I}$ *and* 0. *All these considerations implies that the equation* $P_{3h}(V) = P_{2h}(V)$ *has a positive root greater than* $\frac{\mu_a}{\alpha_a}$, *and two negative, as we can see in the following figure.*

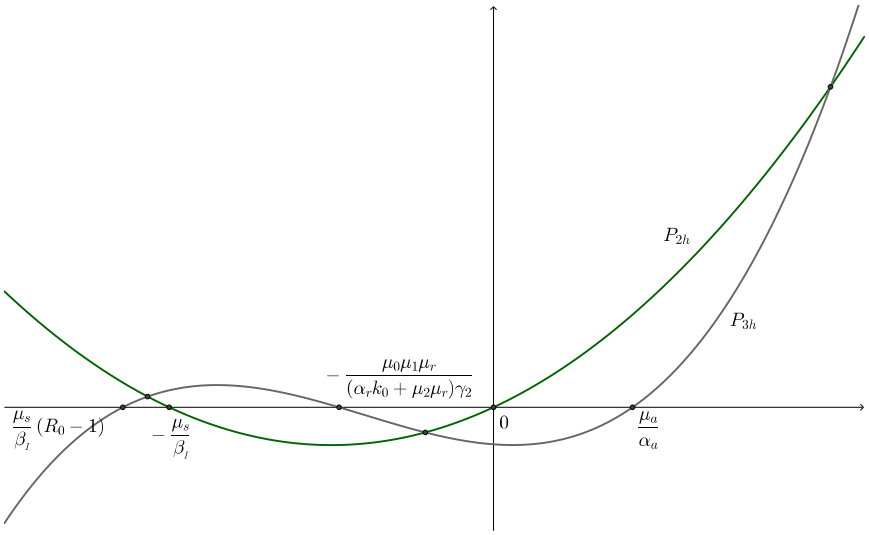


Figure 1 – This shows that for $R_0 < 1$, there is no a positive root less than $\frac{\mu_a}{\alpha_a}$

The stability analysis of virus-presence equilibrium is done by numeric simulations. The characteristic polynomial evaluated at this point is

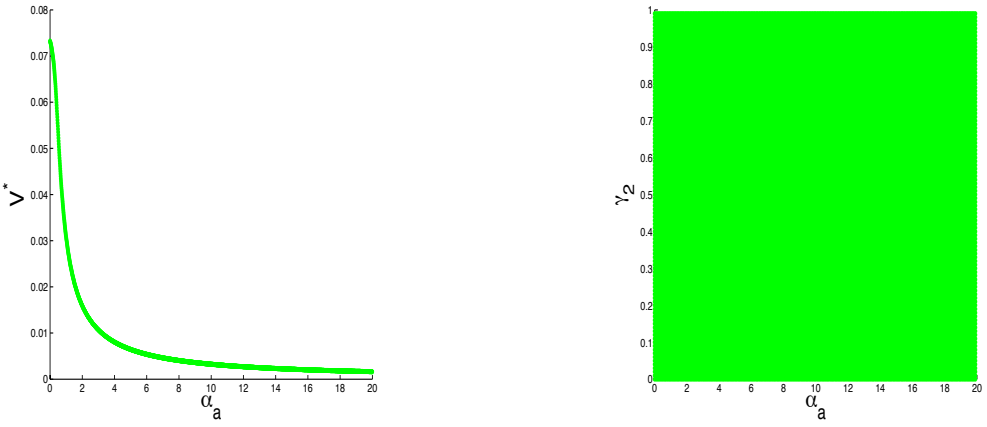
$$(x+\mu_2)(x+\alpha_r T_2^*+\mu_r)(x+\gamma_2 V^*+\mu_0)(x^4+a_1x^3+a_2x^2+a_3x+a_4),$$

where

$$\begin{aligned}
a_1 &= (\beta_I V^* + 2\mu_s + \mu_I + \beta_I S^* N_1 + \mu_a - \alpha_a V^*)\\
a_2 &= (\beta_I V^* + \mu_s)(\mu_s+\mu_I) + \beta_I S^* N_1 \mu_s + \beta_I S^*(N_1-N_2)\beta_I V^*\\
&\quad - (\alpha_a V^* - \mu_a)(\beta_I V^* + 2\mu_s + \mu_I + \beta_I S^* N_1) + \alpha_a B_a^* \alpha_v V^*\\
a_3 &= \alpha_a B_a^* \alpha_v V^*(\beta_I V^* + 2\mu_s + \mu_I) + \beta_I S^*(\mu_s+\mu_I)(N_1-N_2)\beta_I V^*\\
&\quad - (\alpha_a V^* - \mu_a)\left[(\beta_I V^* + \mu_s)(\mu_s+\mu_I) + \beta_I S^* N_1 \mu_s + \beta_I S^*(N_1-N_2)\beta_I V^*\right]\\
a_4 &= \alpha_a B_a^* \alpha_v V^*(\beta_I V^* + 2\mu_s + \mu_I) - (\alpha_a V^* - \mu_a)\beta_I S^*(\mu_s+\mu_I)(N_1-N_2)\beta_I V^*.
\end{aligned}$$

The above polynomial has three negative roots and the others depend on the fourth degree polynomial. This polynomial satisfies the necessary condition of Ruth-Hurwitz criteria ($a_1,\ a_2,\ a_3,\ a_4 > 0$), because $N_1 > N_2$ and $V^* < \frac{\mu_a}{\alpha_a}$. For the sufficient condition ($a_3(a_1a_2-a_3)-a_1^2a_4 > 0$) were done numerical simulations varying the principal parameters,

the parameter of activation of activation of B cells, γ_2, and the parameter of proliferation of the activated B cells, α_a. Figure 2a shows the values of equilibrium V^* when α_a varies and the green (gray) color represents local stability of the virus-presence equilibrium. It is possible to see that for high values of α_a, the viral load is decreased, while in the figure 2b it is represented the local stability of virus-presence equilibrium when the parameters γ_2 and α_a vary.



(a) (b)

Figure 2 – (a) The figure shows the viral load equilibrium V^* as a function of the parameter of proliferation of B_a cells, α_a. The green(gray) color represents the local stability of virus-presence equilibrium for this α_a values. Note that the equilibrium is always locally asymptotically stable and the viral load is decreased when the proliferation parameter α_a is raised. (b) The figure shows that for whatever parameters γ_2 and α_a, the humoral sub-model is locally asymptotically stable. The parameters used for this simulations are presented in Table 1 (pg 23).

1.3.1.3 Discussion

In this subsection, it is considered a sub-model of immune response to control dengue virus, by assuming that there exists a inhibition for the cellular immune response and consequently, the humoral immune response is activated to fight against dengue virus. In our simulations we found that the parameter of proliferation α_a affects drastically the viral load but it does not alter the local stability of the virus-presence equilibrium. This means that the humoral immune response controls effectively the spread of dengue virus, by rising the action of activated B cells which will assure a greater amount of clones with better affinity that will differentiate into plasma cells and release antibodies to stop the spread of dengue virus.

1.3.2 Cellular immune response to dengue virus

In this subsection we consider the inhibition by chemistry signaling induced by T_1 cells against differentiation of the cells T_0 into the cells T_2. This means that the model (1.1) is reduced to the cellular immune response model, given by

$$\begin{aligned}
\frac{dS}{dt} &= k_s - \beta_{_I} SV - \mu_s S \\
\frac{dI}{dt} &= \beta_{_I} SV - \alpha_{_I} I T_{ca} - (\mu_s + \mu_{_I}) I \\
\frac{dV}{dt} &= N_1(\mu_s + \mu_{_I}) I - N_2 \beta_{_I} SV - \mu_v V \\
\frac{dT_0}{dt} &= k_0 - \gamma_1 T_0 I - \mu_0 T_0 \\
\frac{dT_1}{dt} &= \gamma_1 T_0 I - \mu_1 T_1 \\
\frac{dT_{cr}}{dt} &= k_{cr} - \alpha_{cr} T_{cr} T_1 - \mu_{cr} T_{cr} \\
\frac{dT_{ca}}{dt} &= \alpha_{cr} T_{cr} T_1 + \alpha_{ca} T_{ca} I - \mu_{ca} T_{ca}.
\end{aligned} \tag{1.6}$$

1.3.2.1 Virus free equilibrium for the cellular model

The model has a virus-free equilibrium which is denoted by $P_{c0} = \left(\frac{k_s}{\mu_s}, 0, 0, \frac{k_0}{\mu_0}, 0, \frac{k_{cr}}{\mu_{cr}}, 0\right)$. The characteristic polynomial evaluated at point P_{c0} is

$$p_c(\lambda) = \prod_{\varpi} (\lambda + \mu_\varpi) \left[\lambda^2 + \left(\mu_s + \mu_{_I} + \mu_v + \frac{\beta_{_I}\, k_s\, N_2}{\mu_s} \right) \lambda + (\mu_s + \mu_{_I}) \mu_v \,(1 - R_0) \right],$$

with $\varpi \in \{0, 1, s, cr, ca\}$ and $R_0 = \dfrac{\beta_{_I}(N_1 - N_2) k_s}{\mu_v \mu_s}$. Then, by the Routh Hurwitz criteria [30] (pg 230), the virus-free equilibrium P_{h0} is locally asymptotically stable if the coefficients of polynomial of second degree are positive, i.e., if $R_0 < 1$ and it is unstable if $R_0 > 1$. We summarize these considerations in the following theorem

Theorem 1.2. *The virus-free equilibrium P_{c0} is locally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$.*

1.3.2.2 Virus presence equilibrium for cellular model

The model (1.6) presents a unique virus-presence equilibrium point when $I^* < \frac{\mu_{ca}}{\alpha_{ca}}$ and $R_0 > 1$. This point is denoted by $(S^*, I^*, V^*, T_0^*, T_1^*, T_{cr}^*, T_{ca}^*)$, with

$$\begin{aligned}
S^* &= \frac{k_s}{\beta_I V^* + \mu_s} \\
I^* &= \frac{(N_2\beta_I S^* + \mu_v)V^*}{\sigma_1} \\
T_0^* &= \frac{k_0\sigma_1}{(N_2\beta_I S^* + \mu_v)\gamma_1 V^* + \mu_0\sigma_1} \\
T_1^* &= \frac{\gamma_1 k_0(N_2\beta_I S^* + \mu_v)V^*}{\mu_1[(N_2\beta_I S^* + \mu_v)\gamma_1 V^* + \mu_0\sigma_1]} \\
T_{cr}^* &= \frac{k_{cr}\mu_1[(N_2\beta_I S^* + \mu_v)\gamma_1 V^* + \mu_0\sigma_1]}{(N_2\beta_I S^* + \mu_v)\sigma_2 V^* + \mu_0\mu_1\mu_{cr}\sigma_1} \\
T_{ca}^* &= \frac{\alpha_{cr}\gamma_1 k_0 k_{cr} V^*(N_2\beta_I S^* + \mu_v)}{[\mu_{ca} - \alpha_{ca} I^*][(N_2\beta_I S^* + \mu_v)\sigma_2 V^* + \mu_0\mu_1\mu_{cr}\sigma_1]};
\end{aligned} \tag{1.7}$$

where $\sigma_1 = N_1(\mu_s + \mu_I)$, $\sigma_2 = (\alpha_{cr}k_0 + \mu_1\mu_{cr})\gamma_1$, and V^* is a solution of the equation

$$P_c(V^*) = \chi_c(V^*) - g_c(V^*) = 0, \tag{1.8}$$

with

$$\begin{aligned}
\chi_c(V) &= \mu_v[\mu_s(R_0 - 1) - \beta_I V]h_1(V)h_2(V) \\
h_1(V) &= [(\mu_{ca}\sigma_1 - \alpha_{ca}\mu_v V)(\beta_I V + \mu_s) - \alpha_{ca}N_2\beta_I k_s V] \\
h_2(V) &= [N_2\beta_I k_s\sigma_2 V + (\mu_v\sigma_2 V + \mu_0\mu_1\mu_{cr}\sigma_1)(\beta_I V + \mu_s)] \\
g_c(V) &= \alpha_I\alpha_{cr}\gamma_1 k_0 k_{cr} N_1 V(\beta_I V + \mu_s)(N_2\beta_I k_s + \mu_s\mu_v + \mu_v\beta_I V)^2.
\end{aligned}$$

The equation (1.8) has five solutions, but only two are real and positive and just one positive solution satisfies $R_0 > 1$ and $I^* < \frac{\mu_{ca}}{\alpha_{ca}}$. To prove this, note that the polynomial g_c has three negative roots and $g_c(0) = 0$. Besides, the polynomial χ_c is a product of one degree polynomial and two second degree polynomial. Then it has five roots, two positive and three negative because the second degree polynomial h_2 has all its coefficients positive which means that all its roots are negatives or has negative real part and the polynomial h_1 has one positive root and the other negative. Then the positive roots of χ_c are

$$V_1 = \frac{\mu_s}{\beta_I}(R_0 - 1),$$

and

$$V_2 = \frac{1}{2}\left(\frac{\mu_{ca}}{\alpha_{ca}}\frac{\sigma_1}{\mu_v} - \frac{\mu_s}{\beta_I} - N_2\frac{k_s}{\mu_v} + \sqrt{\left(\frac{\mu_{ca}}{\alpha_{ca}}\frac{\sigma_1}{\mu_v} - \frac{\mu_s}{\beta_I} - N_2\frac{k_s}{\mu_v}\right)^2 + 4\frac{\mu_{ca}}{\alpha_{ca}}\frac{\sigma_1\mu_s}{\beta_I\mu_v}}\right),$$

note that V_2 is always positive $\left(\frac{1}{2}\left(a+\sqrt{a^2+b}\right) > 0 \text{ for all } a \in \mathbb{R} \text{ and } b > 0\right)$. Now remembering that the polynomial g_c is always positive for $V > 0$, so the positive roots of P_c are between the positive roots of χ_c. In fact

$$P_c(0) = \chi_c(0) - g_c(0) = \mu_v \mu_s (R_0 - 1) h(0) > 0,$$

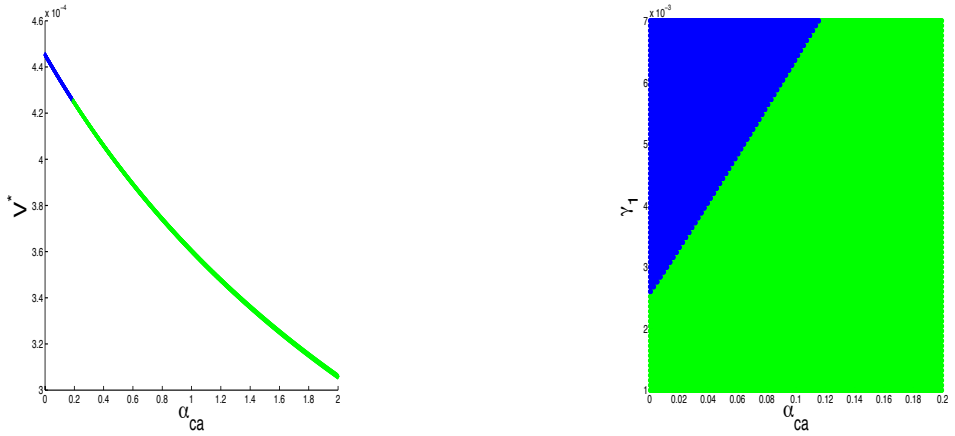
because $R_0 > 1$ and $h_c(0) > 0$. Besides

$$P_c(V_i) = \chi_c(V_i) - g_c(V_i) = -g_c(V_i) < 0, \text{ for } i = 1, 2.$$

This means that in the interval $(0, V_i)$ for $i = 1, 2.$, exists a positive root of the polynomial P_c. Meanwhile if we impose the requirement that I^* has to be less than $\frac{\mu_{ca}}{\alpha_{ca}}$, then from second equation of (1.7), we have $V^* < V_2$. It means that in the interval $(0, V_2)$ there exists a positive root of polynomial P_c. Additionally, the coefficient of term V^5 is positive, consequently $P \to +\infty$ when $V \to +\infty$. Then in the interval (V_2, ∞) there exists another positive root, but it is not feasible.

Remark 1.2. *Similarity to the remark 1.1, for $R_0 < 1$, the polynomial P_c has no positive roots less than V_2. Because the polynomial χ_c has just one positive root, V_2 and the others negative. Whereas that the polynomial g_c has a zero as root and the others negative. Then the equation $\chi_c(V) = g_c(V)$ has a positive root greater than V_2 and the others are negative.*

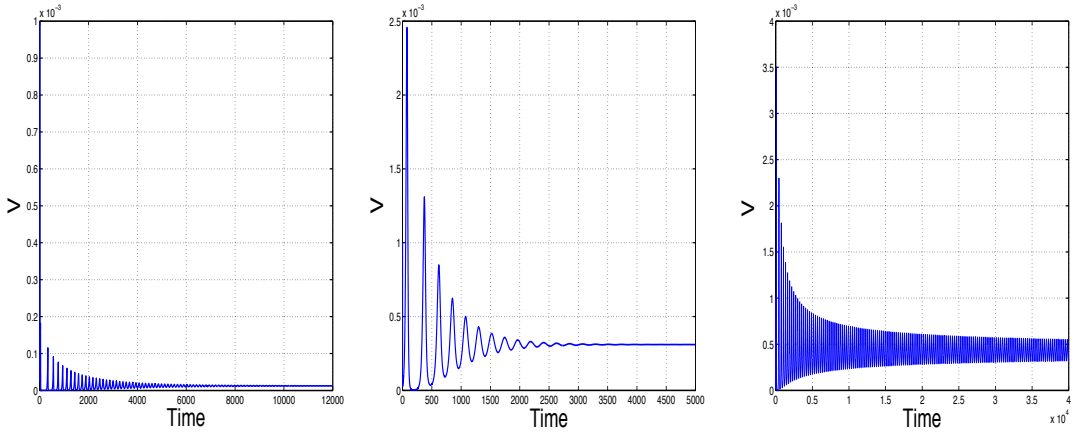
The virus-presence equilibrium (1.7) is locally asymptotically stable for some parameters. For example in the figure 3a, we can see that if the parameter of proliferation of T_{ca} cells, α_{ca}, is low, there exists instability (blue (black) color), but if it is high, the system is locally asymptotically stable and the viral load decreases as this parameter raises (see figure 3a green(grey) color). On the other hand, if we vary the differentiation parameter of the T_0 cells into T_1 cells, γ_1, and the proliferation parameter α_{ca} (see Figure 3b), we can infer that to obtain stability when the parameter γ_1 is high, the parameter of proliferation α_{ca} has to be high too (green(grey) color). But if the parameter α_{ca} is high, not necessarily the parameter γ_1 has to be high.



(a) (b)

Figure 3 – (a) The figure shows the viral load V^* as function of proliferation parameter α_{ca}. The color indicate the stability in the virus-presence equilibrium, the blue(black) color designate the unstable region, meanwhile the green(grey) color the stable region. (b) This sub-figure presents the local stability of the system (1.6) when the differentiation parameter of T_0 cells into T_1, γ_1 and proliferation parameter α_{ca} are varied. The parameters used for this simulations appear in table 1.

In the figure 4 we observe the rise of oscillations as the parameter α_{ca} is decreased. When the parameter α_{ca} is varied, the system loses stability and a periodic orbit is expected. In the next subsection we proof that there exists a Hopf bifurcation in relation to the parameter α_{ca}.



(a) $\alpha_{ca} = 190$ (b) $\alpha_{ca} = 1.9$ (c) $\alpha_{ca} = 0.19$

Figure 4 – The figure shows the viral dynamics in relation to proliferation parameter of T_{ca} cells. If this parameter is raised, the viral load is reduced to very low levels and the system is locally asymptotically stable, but if the parameter α_{ca} is too small, the system loses stability and a limit cycle emerges. The parameters used for this simulations are presented in Table 1

1.3.2.3 Hopf bifurcation

We can prove the existence of a hopf bifurcation if the transversality condition (definition 1.1) and the first Lyapunov coefficient (lemma 1.2) are different of zero. To do this, we start finding the function F defined in appendix 1.A.1 in equation (1.12). Initially, the Jacobian is computed at the virus-presence equilibrium (1.7) to obtain

$$A = \begin{pmatrix} M & N \\ L & Q \end{pmatrix},$$

with

$$M = \begin{pmatrix} -\beta_I V^* - \mu_s & 0 & -\beta_I S^* \\ \beta_I V^* & -\alpha_I T_{ca}^* - \mu_s - \mu_i & \beta_I S^* \\ -\beta_I N_2 V^* & (\mu_s + \mu_i)\ N_1 & -\beta_I N_2 S^* - \mu_v \end{pmatrix} N = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\alpha_I I^* \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$L = \begin{pmatrix} 0 & -\gamma_1 T_0^* & 0 \\ 0 & \gamma_1 T_0^* & 0 \\ 0 & 0 & 0 \\ 0 & \alpha_{ca} T_{ca}^* & 0 \end{pmatrix} Q = \begin{pmatrix} -\gamma_1 I^* - \mu_0 & 0 & 0 & 0 \\ \gamma_1 I^* & -\mu_1 & 0 & 0 \\ 0 & -\alpha_{cr} T_{cr}^* & -\alpha_{cr} T_1^* - \mu_{cr} & 0 \\ 0 & \alpha_{cr} T_{cr}^* & \alpha_{cr} T_1^* & \alpha_{ca} I^* - \mu_{ca} \end{pmatrix}.$$

Now compute the functions $\bar{B}$ and C defined in the appendix 1.A.1 by the equations (1.13) and (1.14) respectively. Therefore $C(x, y, z) = 0$ and $\bar{B}(x, y) = (\bar{B}_1(x, y), \ldots, \bar{B}_7(x, y))^T$, with

$$\bar{B}_1(x, y) = -\beta_I (x_1 y_3 + x_3 y_1) \qquad \bar{B}_2(x, y) = \beta_I (x_1 y_3 + x_3 y_1) - \alpha_I (x_2 y_7 + x_7 y_2)$$
$$\bar{B}_3(x, y) = -N_2 \beta_I (x_1 y_3 + x_3 y_1) \qquad \bar{B}_4(x, y) = -\gamma_1 (x_2 y_4 + x_4 y_2)$$
$$\bar{B}_5(x, y) = \gamma_1 (x_2 y_4 + x_4 y_2) \qquad \bar{B}_6(x, y) = -\alpha_{cr} (x_5 y_6 + x_6 y_5)$$
$$\bar{B}_7(x, y) = \alpha_{ca} (x_2 y_7 + x_7 y_2) + \alpha_{cr} (x_5 y_6 + x_6 y_5).$$

Using the parameters in table 1, the virus-presence equilibrium of the cellular model (1.6) is $x_0 = (1.8998, 0.0056, 4.2529 \times 10^{-4}, 0.9949, 0.0051, 0.7294, 0.0933)$ and the Jacobian A at this point has eigenvalues

$$\lambda_1 = -5.4305 \qquad \lambda_2 = -0.0471$$
$$\lambda_3 = -0.0171 \qquad \lambda_4 = -0.0110$$
$$\lambda_5 = -0.0110 \qquad \lambda_{6,7} = \pm 0.0241 i.$$

From equations (1.15)-(1.17) defined in the appendix 1.A.1, the eigenvectors q and p are

$$q = \begin{pmatrix} 0.1495 + 0.3787i \\ 0.0530 - 0.0807i \\ 0.0039 - 0.0062i \\ 0.0192 + 0.0307i \\ -0.0192 - 0.0307i \\ 0.7447 \\ -0.4365 - 0.2776i \end{pmatrix} \quad p = \begin{pmatrix} -3.0278 \times 10^{11} - 5.02557 \times 10^{13}i \\ 8.5927 \times 10^{15} - 6.2925 \times 10^{15}i \\ 2.668 \times 10^{15} + 1.9567 \times 10^{15}i \\ 5.0382 \times 10^{13} - 1.4947 \times 10^{13}i \\ 1.6255 \times 10^{16} + 1.8577 \times 10^{16}i \\ 1.1371 \times 10^{14} + 1.2995 \times 10^{14}i \\ -3.4652 \times 10^{14} + 1.151 \times 10^{15}i \end{pmatrix}.$$

Parameter	Value	Units
	Parameters common to both sub-models	
k_s	0.033	$C \times d^{-1}$
k_0	0.011	$C \times d^{-1}$
β_I	0.87	$C^{-1} \times d^{-1}$
μ_s	0.017	d^{-1}
μ_I	0.033	d^{-1}
μ_v	2	d^{-1}
μ_0	0.011	d^{-1}
N_1	8	
N_2	2	
	Parameters for cellular sub-model	
k_{cr}	0.011	$C \times d^{-1}$
α_I	0.8	$C^{-1} \times d^{-1}$
γ_1	0.01	$C^{-1} \times d^{-1}$
α_{cr}	0.8	$C^{-1} \times d^{-1}$
α_{ca}	0.1912001193283	$C^{-1} \times d^{-1}$
μ_1	0.011	d^{-1}
μ_{cr}	0.011	d^{-1}
μ_{ca}	0.033	d^{-1}
	Parameters for humoral sub-model	
k_r	0.056	$C^{-1} \times d^{-1}$
α_v	0.08	$C^{-1} \times d^{-1}$
γ_2	0.84	$C^{-1} \times d^{-1}$
α_r	0.7	$C^{-1} \times d^{-1}$
α_a	0.04	$C^{-1} \times d^{-1}$
μ_2	0.011	d^{-1}
μ_r	0.011	d^{-1}
μ_a	0.033	d^{-1}

Table 1 – Parameter of the humoral and cellular immune response model. For the value of parameter α_{ca} there exists a Hopf bifurcation in cellular sub-model.

Once we calculate the function F and the vectors p and q, we need to know if the pair of complex-conjugate eigenvalues crosses the imaginary axis with nonzero speed, i.e. if the Transversality condition is verified.

Transversality condition From equation (1.18) defined in the appendix 1.A.1, we can see that we need to compute $A'(\alpha_{ca})$, and this implies that we need to compute $\frac{dV}{d\alpha_{ca}}$. In order to do this, let us consider the equation (1.8) expliciting the dependence on $alpha_{ca}$, i.e. $P_c(V(\alpha_{ca}), \alpha_{ca}) = 0$, then

$$\frac{dV}{d\alpha_{ca}} = -\frac{\frac{\partial P}{\partial \alpha_{ca}}}{\frac{\partial P}{\partial V}} = -\frac{\frac{\partial \chi_c}{\partial \alpha_{ca}}}{\frac{\partial P}{\partial V}}.$$

From this formula we can compute the derivatives of $S, T_0, T_1, T_{cr}, T_{ca}$ with respect to α_{ca}, to obtain

$$A'(\alpha_{ca}) = \begin{pmatrix} M'(\alpha_{ca}) & N'(\alpha_{ca}) \\ L'(\alpha_{ca}) & Q'(\alpha_{ca}) \end{pmatrix},$$

and

$$\langle p, A'(\alpha_{ca})q \rangle = -3.4327 \times 10^{13} + 1.1823 \times 10^{13} i.$$

From the equation (1.18) we have that the trasnversality condition is

$$\mu'(\alpha_{ca}) = -3.4327 \times 10^{13}.$$

First Lyapunov coefficient To find the first Lyapunov coefficient we start calculating the vectors q_1 and q_2 defined in the lemma 1.2, to obtain

$$q_1 = \begin{pmatrix} 0.2573 \\ -0.0446 \\ -0.0045 \\ 0.0375 \\ -0.0375 \\ -0.0718 \\ 0.0084 \end{pmatrix}, \quad q_2 = \begin{pmatrix} 0.0243 - 0.0103i \\ -0.0539 - 0.1256i \\ -0.0070 - 0.0091i \\ 0.0022 - 0.0008i \\ -0.0022 + 0.0008i \\ 0.0630 - 0.0398i \\ -0.0564 + 0.0694i \end{pmatrix},$$

and from equation (1.19) we have

$$l_1(\alpha_{ca}) = -6.4531 \times 10^{13}.$$

Hence the Hopf bifurcation is supercritical and the limit cycle is stable (see figure 5).

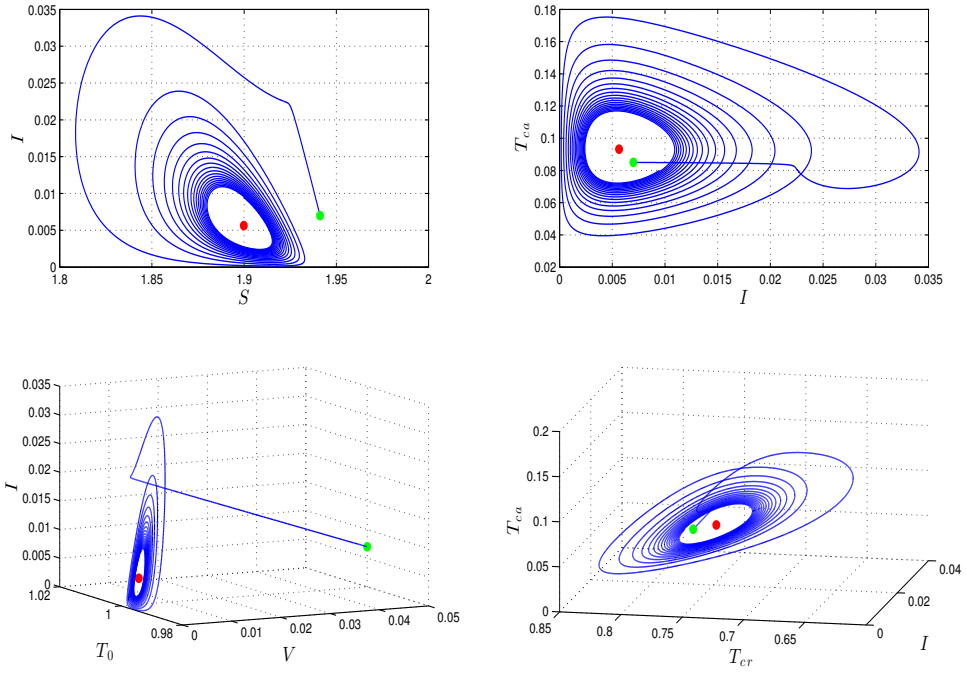


Figure 5 – The figure shows the stable limit cycle in the cellular immune response model. The red(black) dot is the virus-presence equilibrium point and the green(grey) dot is the initial condition of the system.

1.3.2.4 Discussion

Here we evaluate a sub-model considering that there is an inhibition of the T_2 cells, which means that there is a cellular immune response. In this situation we found that the proliferation of activated cytotoxic cells T_{ca} is the most important parameter of this sub-model and the model stability and virus presence control depend on this parameter. If the parameter α_{ca} is raised, the local stability is assured. Besides, the infected cells and viral load are decreased by effect of large number of cytotoxic cells. Meanwhile if the α_{ca} is small, the model stability is compromised and for a particular value of this parameter there exists a supercritical Hopf bifurcation. The parameters used in this model are not necessarily realistic and may have not a specific meaning for dengue virus disease .

1.3.3 Humoral and cellular immune response to dengue virus

In this section we discuss the joint action of the humoral and the cellular immune responses of the model (1.1). First we analyze the local stability of virus-free equilibrium and we give an interpretation for R_0. Second we review the existence of virus-presence equilibrium, and we use parameters from medical literature to perform sensitive global analysis and parameter estimation using viral load from dengue patients. Finally, we analyze the influence in the general model (1.1) of the sub-models considered in the last two subsections.

1.3.3.1 Stability of virus-free equilibrium

Let P_0 be the virus-free equilibrium point which is obtained when we assume that non particle of dengue virus is in the body, i.e., $V = 0$, then

$$P_0 = \left(\frac{k_s}{\mu_s}, 0, 0, \frac{k_0}{\mu_0}, 0, 0, \frac{k_r}{\mu_r}, 0, \frac{k_{cr}}{\mu_{cr}}, 0\right).$$

For this point, the local stability is analyzed, and the threshold R_0 is obtained. To prove the local stability at point P_0, we show that the eigenvalues of the Jacobian matrix of the system (1.1) at P_0 are negative or have negative real part . The characteristic polynomial evaluated at point P_0 is $p(\lambda) = |A - \lambda I_{3\times 3}||B - \lambda I_{7\times 7}|$, where

$$A = \begin{pmatrix} -\mu_s & 0 & -\dfrac{\beta_I\, k_s}{\mu_s} \\ 0 & -\mu_s - \mu_I & \dfrac{\beta_I\, k_s}{\mu_s} \\ 0 & (\mu_s + \mu_I)\, N_1 & -\dfrac{\beta_I\, k_s\, N_2}{\mu_s} - \mu_v \end{pmatrix},$$

$$B = \begin{pmatrix} -\mu_0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\dfrac{\alpha_r\, k_r}{\mu_r} & -\mu_r & 0 & 0 & 0 \\ 0 & 0 & \dfrac{\alpha_r\, k_r}{\mu_r} & 0 & -\mu_a & 0 & 0 \\ 0 & -\dfrac{\alpha_{cr}\, k_{cr}}{\mu_{cr}} & 0 & 0 & 0 & -\mu_{cr} & 0 \\ 0 & \dfrac{\alpha_{cr}\, k_{cr}}{\mu_{cr}} & 0 & 0 & 0 & 0 & -\mu_{ca} \end{pmatrix}.$$

The roots of polynomial $p(\lambda)$ are given by $-\mu_s,\ -\mu_0,\ -\mu_1,\ -\mu_2,\ -\mu_r,\ -\mu_a,\ -\mu_{cr},\ -\mu_{ca}$ and by the solutions of following polynomial of second degree:

$$\lambda^2 + \left(\mu_s + \mu_I + \mu_v + \frac{\beta_I\, k_s\, N_2}{\mu_s}\right)\lambda + (\mu_s + \mu_I)\mu_v\,(1 - R_0)\,.$$

where $R_0 = \dfrac{\beta_I(N_1 - N_2)k_s}{\mu_v\mu_s}$. Then by the Routh Hurwitz criteria [30] (pg 230), the virus-free equilibrium P_0 is locally asymptotically stable if the coefficients of polynomial of second degree are positive, i.e. if $R_0 < 1$ and it is unstable if $R_0 > 1$. We summarize these considerations in the following theorem.

Theorem 1.3. *The virus-free equilibrium P_0 is locally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$.*

Basic reproduction number of virus We are considering that an infected mosquito feeds on a healthy person. In this process it inoculates an amount of dengue virus in the body, and the infection depends on the different reactions of the immune system to stop or decline the infection, so it's natural ask if the infection is going to spread or not. The number R_0 found in last theorem can tell us when the infection by dengue virus is going to progress ($R_0 > 1$) or when the virus will be cleared ($R_0 < 1$).

This number can be interpreted as follow: One virus during its average lifetime, $\dfrac{1}{\mu_v}$, infects one target cell, with rate $\beta_I\dfrac{k_s}{\mu_s}$. This cell releases N_1 virus, but N_2 virus will infect one cell with rate $\left(\beta_I\dfrac{k_s}{\mu_s}\right)$. The term of entrance of virus into target cells N_2 in general is at least one or less than the number of virus released by the infected cells N_1, i.e., $1 \leqslant N_2 < N_1$. Then R_0 is the net number of viruses produced by one virus.

1.3.3.2 Virus presence equilibrium

In the proof of theorem 1.3, it is possible to see that the basic reproductive number R_0 is a parameter of bifurcation. When $R_0 > 1$ the system has two more equilibria which depend on the positive solutions of a function of V, but just one of this solution is biologically feasible (positive). Let $P_1 = (S^*, I^*, V^*, T_0^*, T_1^*, T_2^*, B_r^*, B_a^*, T_{cr}^*, T_{ca}^*)$ be the

feasible point, the equations describing this point are:

$$\begin{aligned}
S^* &= \frac{k_s}{\beta_{_I} V^* + \mu_s} \\
I^* &= \frac{\phi(V^*)V^*}{N_1(\mu_{_I} + \mu_s)} \\
T_0^* &= \frac{k_0 N_1(\mu_{_I} + \mu_s)}{\psi(V^*)} \\
T_1^* &= \frac{\gamma_1 k_0 \phi(V^*)V^*}{\mu_1 \psi(V^*)} \\
T_2^* &= \frac{\gamma_2 k_0 N_1(\mu_{_I} + \mu_s)V^*}{\mu_2 \psi(V^*)} \\
B_r^* &= \frac{k_r \mu_2 \psi(V^*)}{\alpha_r \gamma_2 k_0 N_1(\mu_{_I} + \mu_s)V^* + \mu_r \mu_2 \psi(V^*)} \\
B_a^* &= \frac{-\varphi(V^*) + \sqrt{\varphi(V^*)^2 + 4(\mu_a - \alpha_a V^*)\xi\eta V^{*2}}}{2(\mu_a - \alpha_a V^*)\xi V^*} \\
T_{cr}^* &= \frac{k_{cr}\mu_1 \psi(V^*)}{\theta\phi(V^*)V^* + \mu_{cr}\mu_1 \bar{\sigma}(V^*)} \\
T_{ca}^* &= \frac{\alpha_{cr} k_{cr} \gamma_1 k_0 \phi(V^*)V^*}{(\mu_{ca} - \alpha_{ca} I^*)\{\theta\phi(V^*)V^* + \mu_{cr}\mu_1 \bar{\sigma}(V^*)\}},
\end{aligned} \tag{1.9}$$

where

$$\begin{aligned}
\xi &= \mu_r \mu_2 \gamma_1 \alpha_v \\
\eta &= \alpha_r k_r \gamma_2 k_0 N_1(\mu_{_I} + \mu_s) \\
\theta &= (\alpha_{cr}\gamma_1 k_0 + \mu_{cr}\mu_1\gamma_1) \\
\varphi(V^*) &= (\mu_a - \alpha_a V^*)\left\{ \frac{\eta}{k_r} V^* + \mu_r\mu_2[\gamma_1(N_2\beta_{_I} S^* + \mu_v)V^* + (\gamma_2 V^* + \mu_0)N_1(\mu_{_I} + \mu_s)] \right\} \\
\phi(V^*) &= \frac{\alpha_v\left(-\varphi(V^*) + \sqrt{\varphi(V^*)^2 + 4(\mu_a - \alpha_a V^*)\xi\eta V^{*2}}\right)}{2(\mu_a - \alpha_a V^*)\xi V^*} + \frac{N_2\beta_{_I} k_s}{(\beta_{_I} V^* + \mu_s)} + \mu_v \\
\psi(V^*) &= \gamma_1\phi(V^*)V^* + (\gamma_2 V^* + \mu_0)N_1(\mu_{_I} + \mu_s) \\
\bar{\sigma}(V^*) &= (\gamma_2 V^* + \mu_0)N_1(\mu_{_I} + \mu_s),
\end{aligned}$$

and the values of V are solutions of the equation

$$\chi(V) = \chi_1(V)\chi_2(V)\chi_3(V) - g(V) = 0, \tag{1.10}$$

where

$$\begin{aligned}
\chi_1(V) =&[((N_1 - N_2)\beta_I k_s - \mu_v(\beta_I V + \mu_s))2(\mu_a - \alpha_a V)\xi V - \alpha_v \bar{B}_a(\beta_I V + \mu_s)] \\
\chi_2(V) =&[(\mu_{ca} N_1(\mu_I + \mu_s) - \alpha_{ca}\mu_v V)(\beta_I V + \mu_s) - \alpha_{ca} N_2 \beta_I k_s V]2(\mu_a - \alpha_a V)\xi - \alpha_{ca}\alpha_v \bar{B}_a(\beta_I V + \mu_s) \\
\chi_3(V) =&\{[\theta(N_2\beta_I k_s + \mu_v(\beta_I V + \mu_s))V + \mu_{cr}\mu_1\bar{\sigma}(\beta_I V + \mu_s)]2(\mu_a - \alpha_a V)\xi + \theta\alpha_v \bar{B}_a(\beta_I V + \mu_s)\} \\
g(V) =&\xi b\left[(N_2\beta_I k_s + \mu_v(\beta_I V + \mu_s))2(\mu_a - \alpha_a V)\xi V + \alpha_v \bar{B}_a(\beta_I V + \mu_s)\right]^2 2(\mu_a - \alpha_a V)(\beta_I V + \mu_s) \\
\bar{B}_a =&2(\mu_a - \alpha_a V)\xi V B_a \\
b =&N_1\alpha_I\alpha_{cr}k_{cr}\gamma_1 k_0.
\end{aligned}$$

The equation (1.10) shows two positive points for V, but just one is feasible if we impose the restrictions $V^* < \dfrac{\mu_a}{\alpha_a}$ and $I^* < \dfrac{\mu_{ca}}{\alpha_{ca}}$. The next figures show some numeric examples of the function defined in (1.10). We consider the next cases: $\alpha_{ca} > \alpha_a$ (figure 6), $\alpha_{ca} = \alpha_a$ (figure 7) and $\alpha_{ca} < \alpha_a$ (figure 8). In all these three cases, there exists just one feasible solution.

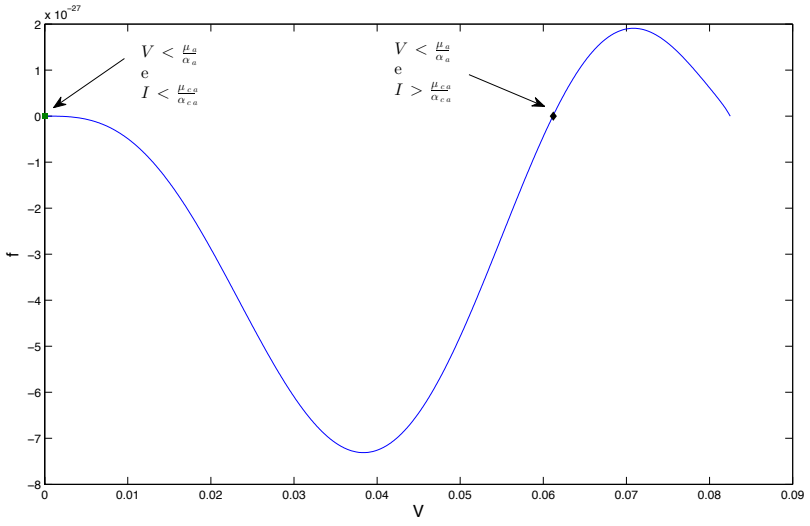


Figure 6 – Graph of the function defined in (1.10) when $\alpha_{ca} > \alpha_a$. In this case, there exist two points satisfying $V < \dfrac{\mu_a}{\alpha_a}$, but just one of these points meets the inequality $I < \dfrac{\mu_{ca}}{\alpha_{ca}}$. The feasible point is $V = 2.594 \times 10^{-6}$, $I = 3.489 \times 10^{-5}$, while the thresholds are $\dfrac{\mu_a}{\alpha_a} = 8.25 \times 10^{-2}$ and $\dfrac{\mu_{ca}}{\alpha_{ca}} = 8.25 \times 10^{-5}$.

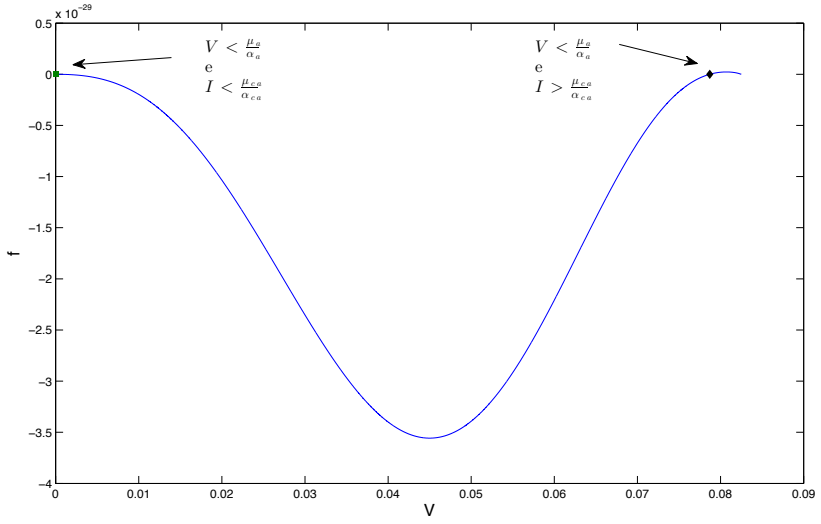


Figure 7 – Graph of the function defined in (1.10) when $\alpha_{ca} = \alpha_a$. There exists just one point that satisfies the constraints, $V < \dfrac{\mu_a}{\alpha_a}$ and $I < \dfrac{\mu_{ca}}{\alpha_{ca}}$. The values of the point are $V = 5.2519 \times 10^{-6} < \dfrac{\mu_a}{\alpha_a} = 8.25 \times 10^{-2}$ and $I = 7.87 \times 10^{-2} < \dfrac{\mu_{ca}}{\alpha_{ca}} = 8.25 \times 10^{-2}$

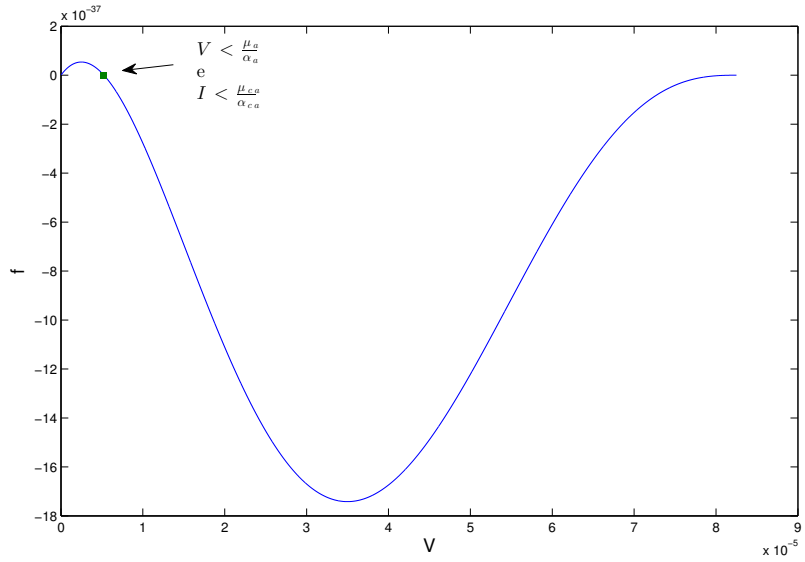


Figure 8 – Graph of the function defined in (1.10) when $\alpha_{ca} < \alpha_a$. In this situation there exists just one possible point satisfying $V < \dfrac{\mu_a}{\alpha_a}$ and $I < \dfrac{\mu_{ca}}{\alpha_{ca}}$. The point is $V = 5.2512 \times 10^{-6}$ and $I = 7.0632 \times 10^{-5}$, while the thresholds are $\dfrac{\mu_a}{\alpha_a} = 8.25 \times 10^{-2}$ and $\dfrac{\mu_{ca}}{\alpha_{ca}} = 8.25 \times 10^{-5}$.

1.3.3.3 Numerical simulation

Parameters of the model

The half life of the monocytes/macrophages in vivo is between 1 to 2 months [31], so we assume the value $\mu_s = \frac{1}{60} = 0.017$. The activated macrophages has a half life of 7 days and because the virus induces apoptosis [32],[33], the death rate of the infected cells is taken as $\mu_I = 0.2$. There are in average 4×10^5 monocytes per milliliter of blood in humans [34], this will be the initial quantity of monocytes $S(0)$, so this implies that $k_s = \mu_s S(0) = 6.8 \times 10^3$. In healthy humans, the cells $CD4+$ and $CD8+$ survive in average 87 and 77 days, respectively [35], it means that the death rate μ_0, μ_1, μ_2 have the value 0.011 and $\mu_{cr} = 0.013$. The initial values of $T_0(0)$ and $T_{cr}(0)$ are 1×10^6 per milliliter of blood, which are the average quantities of T cells per milliliter of blood [34], thus $k_0 = \mu_0 T_0(0) = 1.1 \times 10^4$ and $k_{cr} = \mu_{cr} T_{cr}(0) = 1.3 \times 10^4$. The activated cells $CD8+$ have half life of a month approximately [36], then $\mu_{ca} = 0.03$. The B cells in rest have half life between 2 and 4 days and more than 6 weeks if they are activated [17], which implies $\mu_r = 0.25$ and $\mu_a = 0.02$ respectively. The quantity of B cells per milliliter of blood is around of 2×10^6 [34], thus $B(0) = 2 \times 10^6$, and as before we have $k_r = \mu_r B(0) = 5 \times 10^5$. The virus released by one infected cells is $N_1 = 5 \times 10^4$ [37],[31], and we assume that the value $N_2 = 2$. A summary of these parameters is in the table 2

Parameter	Value	Units	Reference
k_s	6.8×10^3	$(mL \times day)^{-1}$	[31], [34]
k_0	1.1×10^4	$(mL \times day)^{-1}$	[35], [34]
k_r	5×10^5	$(mL \times day)^{-1}$	[34]
μ_s	0.017	day^{-1}	[31]
μ_I	0.2	day^{-1}	[32],[33]
μ_0	0.011	day^{-1}	[35]
μ_1	0.011	day^{-1}	[35]
μ_2	0.011	day^{-1}	[35]
μ_r	0.25	day^{-1}	[17]
μ_a	0.02	day^{-1}	[17]
μ_{cr}	0.013	day^{-1}	[35]
μ_{ca}	0.03	day^{-1}	[36]
N_1	5×10^4		[31], [37]
N_2	2		

Table 2 – Parameters used in the model

1.3.3.4 Global uncertainty and sensitivity analysis

In mathematical models there are frequently many unknown parameters, therefore an important questions that must be answered concern with relationship of these parameters with the model outputs, in particular which ones contribute most to output variability, and which ones require additional research or are insignificant. These questions can be answered using uncertainty and sensitivity analysis. We use the Latin hypercube sampling (Lhs) and Partial rank correlation coefficients (Prcc) and extended fourier amplitude sensitivity test (Efast) to assess global uncertainty and sensitivity analysis following the methodology proposed in [38], a short description of this methods can be found in the appendix 1.A.2 and 1.A.3. The days analyzed were the second and seventh day after infection, because these are crucial in dengue infections: the onset of infection and the clearance. The parameters selected to perform global uncertainty and sensitivity analysis, were $\beta_{_I}$, α_v, γ_1, γ_2, α_r, α_{cr} and μ_v. We do not know the threshold of these parameters except for the mortality rate of dengue virus μ_v. The four serotypes of dengue virus have half life between 2.5 to 7.5 hours [39]. The results of Lhs/Prcc for variable V show that in the day two, the effect of infection rate $\beta_{_I}$ is positively correlated (0.800394) with the viral load V. It means that if we increase this parameter then the viral load will rise, while the action of antibodies against virus α_v, the differentiation rate of T helper cells into Th2, γ_2, and activation of the B cells, α_r, have negative correlations -0.78303, -0.62821, and -0.59711, respectively. The Lhs/Prcc for variable V in the day seven show an interesting fact: the infection rate $\beta_{_I}$, the cytotoxic action rate $\alpha_{_I}$ and the differentiation rate of T helper cells into Th1 γ_1 are negatively correlated (see table 3). The negative correlation of parameters $\alpha_{_I}$ and γ_1 is clear because the cytotoxic action rate $\alpha_{_I}$ helps to decrease the infected cells and the differentiation rate γ_1 activates the T_1 cells which are crucial for the activation of cytotoxic activity. While that for the negative correlation of parameter $\beta_{_I}$, we can say that if we increase the infection rate, there are more infected cells helping the T_0 cells to differentiate into Th1 cells that are capable of activating the cytotoxic activity of the T_{ca} cells. This suggest that cytotoxic activity is more important for the clearance of infection. Similar things happen with the infected cells (see table 4). The results of sensibility analysis Efast are quite similar to Lhs/Prcc. The parameters with high first order (S_i) and total order S_{T_i} sensitivity index are $\beta_{_I}$, α_v and γ_2 in the second day, and in the seventh day, three became important $\alpha_{_I}$, γ_1 and α_{cr} (see table 5), the same occur with the infected cells (data not shown).

Time	β_I	α_v	γ_2	α_r	α_I	γ_1
2	0.800394^{**}	-0.78303^{**}	-0.62821^{**}	-0.59711^{**}		
7	-0.63696^{**}	—	—	—	-0.35573^{**}	-0.42147^{**}

Table 3 – The Lhs with $N = 800$ and Prcc for the virus V in the days two and seven. $^{**}p < 0.01$

Time	β_I	α_v	γ_2	α_r	α_I	γ_1
2	0.90099^{**}	-065448^{**}	-0.5645^{**}	-0.55954^{**}		
7	-0.6318^{**}	—	—	—	-0.37803^{**}	-0.42181^{**}

Table 4 – The Lhs with $N = 800$ and Prcc for the infected cells I in the days two and seven. $^{**}p < 0.01$

	β_I	α_v	γ_2	α_I	γ_1	α_{cr}
S_i						
2	0.0124^{**}	0.0542^{**}	0.0083^{*}	—	—	—
7	0.0135^{*}	0.0143^{**}	0.0126^{*}	0.0135^{*}	0.0265^{**}	0.0131^{*}
S_{T_i}						
2	0.6521^{**}	0.8805^{**}	0.6246^{*}	—	—	—
7	0.8706^{*}	0.8751^{**}	0.8589^{*}	08731^{**}	08694^{**}	0.8538^{*}

Table 5 – The Efast with $Ns = 600$ for the virus V in the days two and seven. $^{*}p < 0.05$, $^{**}p < 0.01$

1.3.3.5 Parameter estimation

To perform parameter estimations we use real data of primary dengue fever of patients with DENV1, DENV2 and DENV3. These data show the quantity of dengue virus RNA in plasma (they can be accessed in the supplementary data of [29]). We used the parameters of table 2 and genetic algorithm to find the best set of unknown parameters (β_I, α_v, γ_1, γ_2, α_r, α_a, α_{cr}, α_{ca}, μ_v) (see the appendix 1.A.4 for a short explanation). The table 6 shows the parameters estimated from data. In all the estimations we got high values for the proliferation parameter (α_{ca}) of activated T_{ca} cells in relation to the proliferation parameter (α_a) of B_a cells, whereas the differentiation of T_0 cells into T_1 or T_2 cells is almost of the same order, which implies that the control of viral load and infected cells are obtained mostly by the cytotoxic activity but not exclusively. Indeed, we can see in the fittings of these parameters in the Figures 10 and 11 that there is a little inhibition of activated T_{ca} cells and a strong response of B_a cells in the beginning of dengue infection. This could be a strategy of dengue virus to spread the virions, because it will activate a greater amount of B cells which will turn into plasma cells and release antibodies with not high affinity which may facilitate the opsonization of pathogen. The clearance of the

dengue virus happens when the antibodies improve its affinity and the cytotoxic cells get the right chemical signal. This allow the infected cells destruction to prevent release of new virus, this happens approximately in the four day (see Figures 10 and 11).

Parameters	DENV-1	DENV-2	DENV-3	Units
β_I	5×10^{-8}	2.37×10^{-8}	5×10^{-8}	$\frac{mL}{day}$
α_v	1.2×10^{-5}	2.34×10^{-5}	1.21×10^{-5}	$\frac{mL}{day}$
γ_2	1.0×10^{-7}	2.48×10^{-5}	1.43×10^{-5}	$\frac{mL}{day}$
α_r	1.6×10^{-7}	1.8×10^{-5}	1.61×10^{-5}	$\frac{mL}{day}$
α_a	2.94×10^{-10}	2.1×10^{-12}	2.0×10^{-13}	$\frac{mL}{day}$
α_I	1.6×10^{-5}	2.28×10^{-5}	1.41×10^{-5}	$\frac{mL}{day}$
γ_1	1.13×10^{-4}	2.38×10^{-5}	1.3×10^{-5}	$\frac{mL}{day}$
α_{cr}	1.21×10^{-7}	2.2×10^{-5}	1.41×10^{-5}	$\frac{mL}{day}$
α_{ca}	4.89×10^{-7}	3.16×10^{-9}	4.0×10^{-11}	$\frac{mL}{day}$
μ_v	3.3	3.5	3.3	$\frac{1}{day}$

Table 6 – Parameters estimated from patients data with dengue fever with serotypes 1, 2 and 3 (DENV-1, DENV-2 and DENV-3).

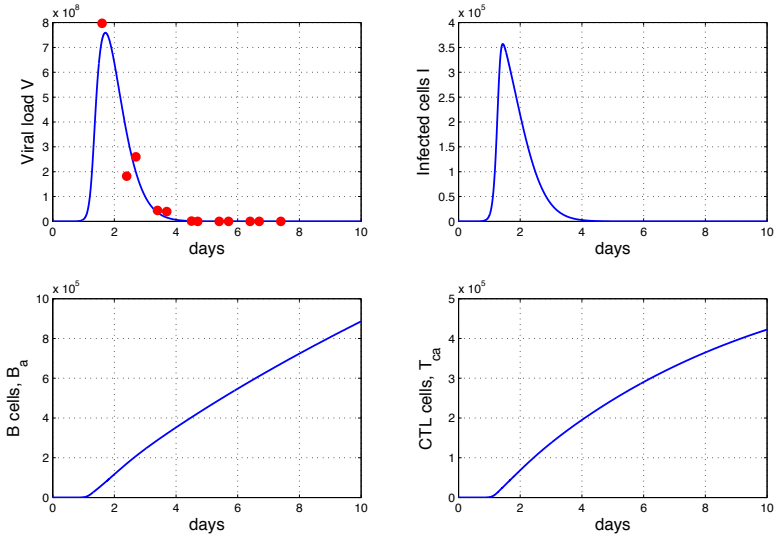


Figure 9 – The figure shows the virus, infected cells and immune response dynamics of primary dengue fever with virus serotype 1. The red points indicated the viral load data. There exists a high response of B cells compared to T cells.

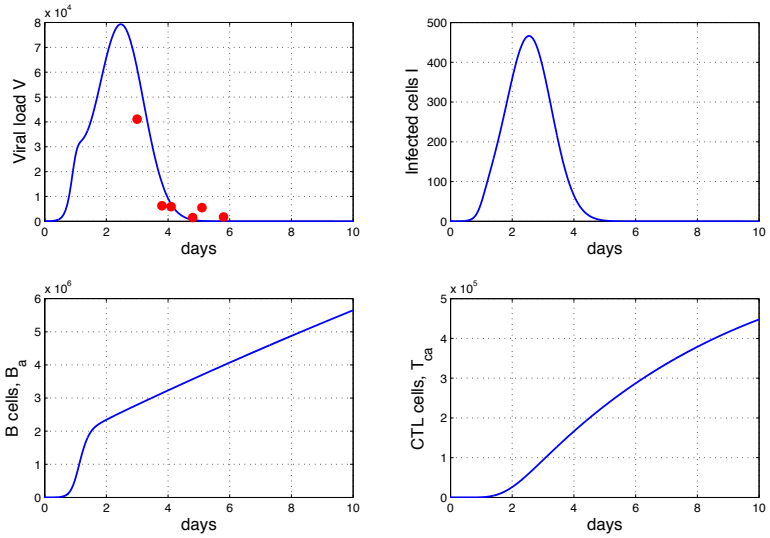


Figure 10 – The figure shows the virus, infected cells and immune response dynamics of primary dengue fever with virus serotype 2. The red points indicated the viral load data. There exists a high response of B cells compared to T cells. It is possible to observe that the response of T cells start after the B cells, showing a possible inhibition of this immune response.

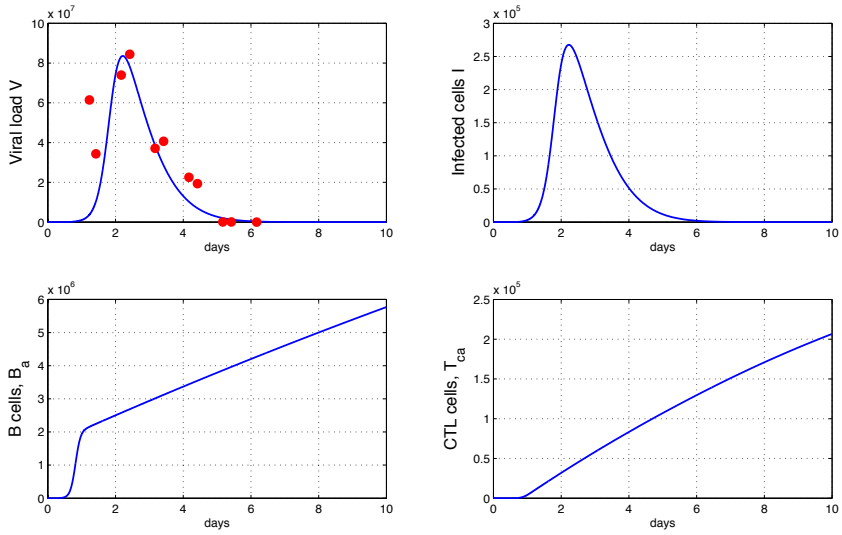
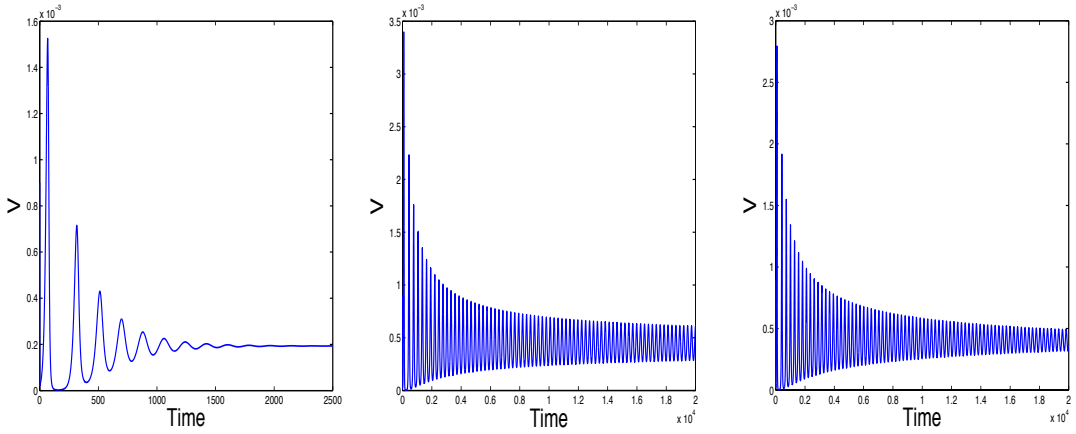


Figure 11 – The figure shows the virus, infected cells and immune response dynamics of primary dengue fever with virus serotype 3. The red points indicated the viral load data. There exists a high response of B cells compared to T cells and the cellular immune response is inhibited initially but strongly activated in the end.

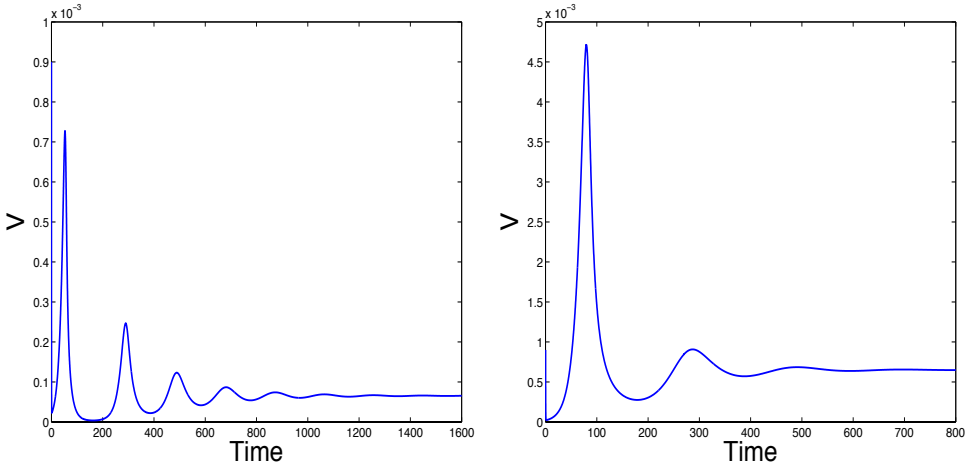
1.3.3.6 Instabilities

In this subsection, we connect the influence in the general model (1.1) of humoral and cellular sub-models analyzed in subsections 1.3.1 and 1.3.2. In particular, we discuss how the instability in the sub-model of cellular immune response studied in the subsection 1.3.2 affects the general model (1.1). In order to do this, we use the parameters in table 1, and the proliferation parameters of activated B_a and T_{ca} cells are varied. In the figure 12a, we can see that high values of parameter α_{ca} are enough to avoid oscillations, while low values of this parameter lead the system to experiment instability (see Figure 12b) and it is not possible to keep the viral load in low levels. In this situation, the influence of the cytotoxic activity is fundamental for the control of increase in the viral load. Then the proliferation parameter T_{ca} cell should be large enough compared to proliferation parameter of B_a cell. On the other hand, if there exists a weak cytotoxic response represented in a fragile proliferation T_{ca} cells but a high proliferation of B_a cells, we have three situations: first, if the proliferation parameter α_a is not too high, it is not possible to avoid the oscillations (see Figure 12c). Second, if the parameter α_a is big enough, the oscillations disappear and the infection is controlled (see Figure 13a). Third, there is another possibility to control the infection when there is a weak cytotoxic activity. This is the inhibition of T_0 differentiation into T_1, i.e., $\gamma_2 \gg \gamma_1$, with γ_1 small enough (see Figure 13b). In this situation the general model (1.1) will have the same asymptotic behavior of the humoral sub-model. All this means that the sub-model of cellular immune response is that which most affects the dynamics of the general model. Also with a high proliferation of T_{ca} cells, it is possible to decrease the viral load to the level which laboratory tests can not detect the dengue virus in the body, although mathematically, the viral load will always be nonzero. However, when the proliferation of B_a cells is not high enough, the humoral immune response will not completely stop the infection by dengue virus and it is necessary to use different strategies, like a inhibition of differentiation of cells T_0 into T_1 cells. This means that the dynamics is acting asymptotically as a humoral sub-model. In figure 14, we show clearly how the stability of the model (1.1) is strongly affect by the proliferation of cytotoxic activated cells T_{ca}. In figure 14a, we can see that high values of parameter α_{ca} are enough to assure stability. Meanwhile, if this parameter is small, it is necessary high values of parameter α_a. In figure 14b, it is presented the situation where the proliferation parameter α_{ca} of cytotoxic cells is small. Therefore, we can see that, in order to get stability it is necessary to increase the proliferation parameter of B_a cells, α_a, and at the same time it is necessary to decrease the values of activation parameter of T_1 cells, γ_1. This means that, in order to get an effective humoral response, it is necessary a inhibition of activity cellular or at least a weak activation.



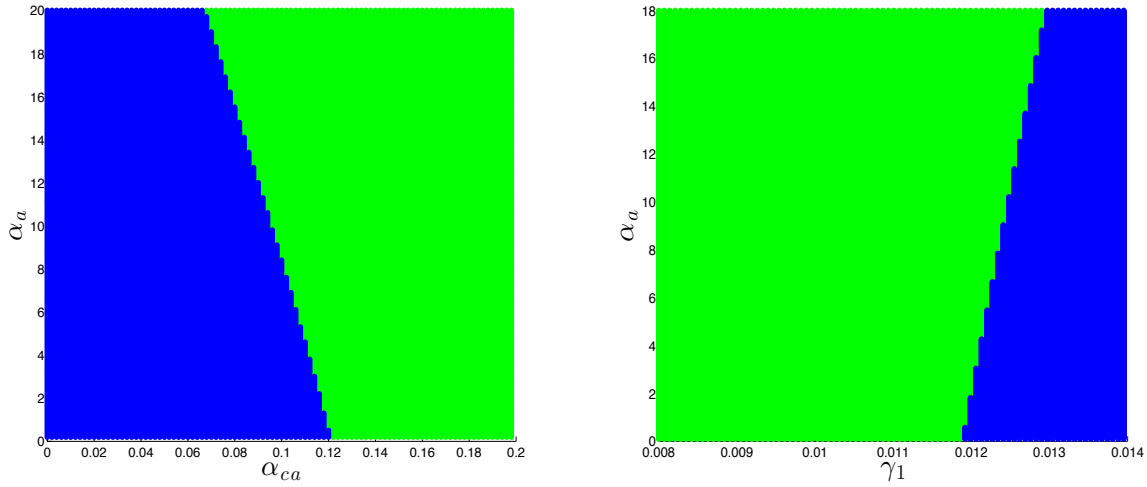
(a) $\alpha_{ca} = 6 > \alpha_a = 0.5$ (b) $\alpha_{ca} = 0.06 < \alpha_a = 0.5$ (c) $\alpha_{ca} = 6 \times 10^{-3} < \alpha_a = 50$

Figure 12 – The figure shows the viral dynamics. (a) In this figure we consider that the proliferation parameter of T_{ca} cells is much bigger than proliferation parameter of B_a cells. In this situation the stability of the model is not affected and the viral load is decreased. (b) This figure shows a drastically reduction of parameter α_{ca} compared to α_a, but still greater. In this case we have instability and the possibility of a limit cycle. This means that cytotoxic activity cause a strong influence in the decline of viral load. (c) in this figure, we consider an increase of proliferation(α_a) of B_a cells and the parameter α_{ca} remains small. This increase is not enough to prevent oscillations and control or decrease the viral load.



(a) $\alpha_{ca} = 6 \times 10^{-3} < \alpha_a = 500$ (b) $\alpha_{ca} = 6 \times 10^{-3} < \alpha_a = 50$, with $0.01 \times \gamma_1$

Figure 13 – The figure shows the viral dynamics, and represents the way how the immune system acts with a weak cellular immune response to control the infection. (a) In this situation, in order to avoid the oscillations, it is necessary a strong humoral immune represented in the proliferation of B_a cells (b) This case represents a strategy of the immune system against the non possibility to reduce the viral load only by the increasing the proliferation of B cells, for which it is necessary a inhibition of differentiation of T_0 cells into T_1 cells. This implies in a reduction of parameter γ_1 and $\gamma_2 \gg \gamma_1$.



(a) (b)

Figure 14 – The figure shows the local stability of general model (1.1). The blue (black) color represents instability and the green (grey) color represents stability. (a) The proliferation parameter of B_a cells, α_a, and proliferation parameter of T_{ca}, α_{ca}, are able to vary. High values of parameter α_{ca} ensure stability in the model but high values of α_a not necessarily generates stability. (b) The figure shows that to avoid instability with values of parameter α_a it is necessary small values of parameter γ_1

1.4 Conclusion

In the present study, we developed a mathematical model of interaction between the immune system and dengue virus, which is a complex interaction that is little understood. We proposed a model in which the cellular and humoral immune responses depend on the differentiation of Th0 helper cells into Th1 and Th2. Our findings show that the dynamic of the general model is mostly affected by the cellular immune response. A strong cellular immune response will be enough to control the viral load and avoid oscillations. Meanwhile, a weak response in the proliferation of cytotoxic cells will generate oscillations and the possibility of a limit cycle. There exist two ways to change this behavior. The first is a strong proliferation of active B cells, which will generate an improvement in the fitting of antibodies to stop the infection. The second is inhibition of the differentiation of cells Th0 into Th1, which means that activation of cytotoxic cells would be low. In this way, the immune response would predominantly be the humoral immune response, and the dynamical system will act as the the humoral sub-model, which has no oscillations.

By using the parameters from the medical literature and performing fittings of unknown parameters through the use of clinical data on dengue fever, we show that there is more proliferation of cytotoxic cells than B cells. This is evident in the values of the proliferation parameter of activated cytotoxic cells, α_{ca}. which are higher than the values

of the proliferation parameter of activated B cells, α_a. These values assure the control of infection, avoid oscillations and suggest a dominant cellular immune response in relation to the humoral immune response. Besides, the simulations showed that the initial humoral immune response is faster than the cellular immune response at the onset of infection, but the cellular immune response is stronger in clearance. This means that the cellular immune response is inhibited in the onset of infections as a possible strategy used by the virus to spread through the body, because the large number of activated B cells will release low affinity antibodies which may facilitate the opsonization of pathogen and it may be a clue to answer why the antibodies can help in enhance second infections. In fact, in vitro studies of dengue infections in dendritric cells reported a notably suppressed proliferation of T cells [40],[41], and some studies with patients showed an increase CD8+ T cell counts later in the course of disease [42],[43]. Other models considering the role of cytokines have to be considered to better analyze the role of the CD8+ T cells in the control of the viral replication and the balance between humoral and cellular immune responses.

1.A Appendix

1.A.1 Hopf bifurcation

Consider the system of ordinary differential equation in the way

$$\dot{x} = f(x, \alpha_{ca}), \tag{1.11}$$

where $x \in \mathbb{R}^n$ and $\alpha_{ca} \in \mathbb{R}$. If we make Taylor expansion of f around the equilibrium point $x = x_0$, we obtain

$$F(x) = A\,x + \frac{1}{2}\bar{B}(x,x) + \frac{1}{6}C(x,x,x) + O(\|x\|^4), \tag{1.12}$$

where $A = f_x(x_0, \alpha_{ca})$, $\bar{B}(x,x)$ and $C(x,x,x)$ are functions defined by

$$\bar{B}_i(x,y) = \sum_{j,k=1}^{n} \left.\frac{\partial^2 f_i(\xi)}{\partial\xi_j\partial\xi_k}\right|_{\xi=x_0} x_j y_k \tag{1.13}$$

$$C_i(x,y,z) = \sum_{j,k,l=1}^{n} \left.\frac{\partial^3 f_i(\xi)}{\partial\xi_j\partial\xi_k\partial\xi_l}\right|_{\xi=x_0} x_j y_k z_l,\ i = 1,\ldots,n. \tag{1.14}$$

we assume that $A = f_x(x_0, \alpha_{ca})$ has its eigenvalues with the property $\mathrm{Re}(\lambda_i) < 0$, $i = 3,\ldots,n$ and $\lambda_{1,2} = \pm i\,\omega_0$.
Once we calculate the function F, we need to know if the pair of complex-conjugate eigenvalues crosses the imaginary axis with nonzero speed, this condition is named as Transversality condition and its definition is presented above.

Transversality condition

Definition 1.1. *Let A be a real matrix $n \times n$ which depends on the parameter α ($A(\alpha)$) with a simple pair of eigenvalues $\lambda_{1,2}(\alpha) = \mu(\alpha) \pm i\omega(\alpha)$ and $\mu(\alpha_0) = 0$, $\omega(\alpha_0) > 0$. We define the transversality condition by*

$$\mu'(\alpha_0) \neq 0.$$

There is another way to compute the transversality condition, by using the Projection method for center manifold computation [44](pg 175). First, Let $q \in \mathbb{C}^n$ be a complex eigenvector corresponding to λ_1

$$Aq = i\omega_0 q, \quad A\bar{q} = -i\omega_0\bar{q}. \tag{1.15}$$

Introduce also the adjoint eigenvector $p \in \mathbb{C}^n$ having the properties

$$A^T p = -i\omega_0 p, \quad A^T\bar{p} = -i\omega_0\bar{p}, \tag{1.16}$$

and satisfying the normalization

$$\langle p, q\rangle = 1, \tag{1.17}$$

where $\langle p, q\rangle = \overline{p}^T \cdot q = \sum_i \overline{p_i} q_i$. Once we computed the vectors p and q, we can use the next lemma to compute the transversality condition (This result appears in the book [44] as an exercise in pg 189)

Lemma 1.2. *Let $A(\alpha)$ the matrix defined in 1.1 then the transversality condition can be compute by*

$$\mu'(\alpha_0) = \mathrm{Re}\langle p, A'(\alpha_0)q\rangle, \tag{1.18}$$

where q and p are eigenvectors satisfying the equations (1.15) to (1.17).

Proof. Suppose that $q(\alpha)$ and $p(\alpha)$ are eigenvectors of the eigenvalues $\lambda_{1,2}(\alpha) = \mu(\alpha) \pm i\omega(\alpha)$. Then differentiating with respect to α the equation

$$A(\alpha)q(\alpha) = \lambda_1(\alpha)q(\alpha),$$

we obtain

$$A'(\alpha)q(\alpha) + A(\alpha)q'(\alpha) = \lambda_1'(\alpha)q(\alpha) + \lambda_1(\alpha)q'(\alpha).$$

Computing the scalar product with p in both sides, we have

$$\begin{aligned}
\langle p, A'(\alpha)q(\alpha) + A(\alpha)q'(\alpha)\rangle &= \langle p, \lambda_1'(\alpha)q(\alpha) + \lambda_1(\alpha)q'(\alpha)\rangle \\
\langle p, A'(\alpha)q(\alpha)\rangle + \langle p, A(\alpha)q'(\alpha)\rangle &= \langle p, \lambda_1'(\alpha)q(\alpha)\rangle + \langle p, \lambda_1(\alpha)q'(\alpha)\rangle \\
\langle p, A'(\alpha)q(\alpha)\rangle + \langle A^T(\alpha)p, q'(\alpha)\rangle &= \lambda_1'(\alpha)\langle p, q(\alpha)\rangle + \lambda_1(\alpha)\langle p, q'(\alpha)\rangle.
\end{aligned}$$

Evaluating the previous equation in $\alpha = \alpha_0$, we obtain

$$\langle p, A'(\alpha_0)q\rangle + \langle A^T(\alpha_0)p, q'(\alpha_0)\rangle = \lambda_1'(\alpha_0)\langle p, q\rangle + i\omega_0(\alpha_0)\langle p, q'(\alpha_0)\rangle,$$

and, from the equations (1.16)-(1.17), results in

$$\begin{aligned}
\langle p, A'(\alpha_0)q\rangle + \langle -i\omega_0(\alpha_0)p, q'(\alpha_0)\rangle &= \lambda_1'(\alpha_0) + i\omega_0(\alpha_0)\langle p, q'(\alpha_0)\rangle \\
\langle p, A'(\alpha_0)q\rangle + i\omega_0(\alpha_0)\langle p, q'(\alpha_0)\rangle &= \lambda_1'(\alpha_0) + i\omega_0(\alpha_0)\langle p, q'(\alpha_0)\rangle.
\end{aligned}$$

Then

$$\lambda_1'(\alpha_0) = \langle p, A'(\alpha_0)q\rangle, \text{ and } \mu'(\alpha_0) = \mathrm{Re}\langle p, A'(\alpha_0)q\rangle.$$

□

First Lyapunov coefficient The First Lyapunov coefficient is a number that indicate that certain combination of Taylor coefficients of the right-hand sides of the system (up to and including third-order coefficients) does not vanish.

Definition 1.2. *The first Lyapunov coefficient is given by*

$$l_1(\alpha_0) = \frac{1}{2\omega_0}\,\mathrm{Re}\left[\langle p, C(q,q,\bar{q})\rangle - 2\langle p, \bar{B}(q,q_1)\rangle + \langle p, \bar{B}(\bar{q},q_2)\rangle\right], \tag{1.19}$$

where $q_1 = A^{-1}\bar{B}(q,\bar{q})$ *and* $q_2 = (2i\omega_0 I_n - A)^{-1}\bar{B}(q,q)$.

Remark 1.3. *A deduction of the first Lyapunov coefficient* $l_1(\alpha)$ *can be found in [44] (pg 178).*

Theorem 1.4 (Hopf bifurcation)**.** *Consider the system*

$$\dot{x} = f(x,\alpha),\ x \in \mathbb{R}^n,\ \alpha \in \mathbb{R},$$

with f *smooth function of* (x,α)*. For* α *near to* α_0*, let* x_0 *be the equilibrium point with eigenvalues*

$$\lambda_{1,2}(\alpha) = \mu(\alpha) \pm i\omega(\alpha),$$

which satisfies $\mu(\alpha_0) = 0$ *and* $\omega(\alpha_0) > 0$*, and the other eigenvalues are negatives. If the following conditions hold*

- $l_1(\alpha_0) \neq 0$,
- $\mu'(\alpha_0) \neq 0$,

Then, there are invertible coordinate that depends on the parameter α *and a time reparameterization transforming, where the system (1.11) can be reduced in the central manifold to*

$$\frac{d}{d\,\tau}\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \beta & -1 \\ 1 & \beta \end{pmatrix}\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + s(y_1^2 + y_2^2)\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} + O(\|y\|^4), \tag{1.20}$$

where $\beta = \dfrac{\mu(\alpha)}{\omega(\alpha)}$ *and* $s = sgn(l_1(\alpha_0))$*. [45](pg 353)*

Definition 1.3. *If* $l_1(\alpha_0) < 0 (l_1(\alpha_0) > 0)$*, the bifurcation is named supercritical Hopf bifurcation (subcritical), and the limit cycle is stable (unstable).*

1.A.2 Latin hypercube sampling and Partial rank correlation coefficient

Latin hypercube sampling (LHS) is a stratified sampling without replacement technique and belongs to the Monte Carlo class of sampling methods. The random parameter distributions are divided into N equal probability intervals, which are then sampled. N represents the sample size. The choice for N should be at least k+1, where k is the number of parameters varied, but usually much larger to ensure accuracy. For each parameter is chosen a probability density function (pdf) (i.e. normal, uniform, lognormal, etc.). If biological knowledge exists suggesting a more frequent or expected value for a parameter, a normal pdf would be the best choice. Otherwise, the choice is a uniform distribution. The sampling is done by randomly selecting values from each pdf. A matrix is generated (called LHS matrix) that consists of N rows for the number of simulations (sample size) and of k columns corresponding to the number of varied parameters. N model solutions are then simulated, using each combination of parameter values (each row of the LHS matrix). The model output of interest is collected for each model simulation. Different model outputs can be studied if more than one model output is of interest [38].

We selected the parameters β_I, α_v, γ_1, γ_2, α_r, α_{cr} and μ_v and $N = 800$ to perform the LHS. The parameters α_a and α_{ca} were not selected because they were analyzed in the subsection 1.3.3.6 and we know the influence in the model.

To define Partial rank correlation coefficient (PRCC), we start defining:
Correlation coefficient: is a number that quantifies some type of correlation and dependence between two or more random variables.
Rank correlation coefficient: the study of relationships between rankings of different variables or different rankings of the same variable.
Partial correlation coefficient: is a number that measures the degree of association between two random variables, with the effect of a set of controlling random variables removed.
Finally we define:
Partial Rank Correlation coefficient: Is the partial correlation on rank-transformed data.

So in the model (1.1), we are interested to know what is the relationship of virus load V and the infected cells I with the parameters β_I, α_v, γ_1, γ_2, α_r, α_{cr} and μ_v. In this way we perform LHS and PRCC to assess the sensitivity of our outcome variable to parameter variation the results are discussed in subsection 1.3.3.4.

1.A.3 Extended fourier amplitude sensitivity test

The extended fourier amplitude sensitivity test (efast) is a method to perform global sensitivity analysis which evaluates the relative importance of input variable and model parameters on the evolution over time of the model state variables. Efast is a variance decomposition method and use spectral analysis to decomposes the output variance. The total number of model simulations made for efast is given by $N = N_s \times k \times N_r$, where N_s is the samples per search curve, k is the number of parameters and N_r is the number of search curves (resampling). We choose $Ns = 600$, $k = 10$, $N_r = 5$, to perform efast to the model (1.1). The codes that are available in <http://malthus.micro.med.umich.edu/lab/usadata/>, give us the first-order sensitivity S_i and total-order sensitivity S_{T_i} of each input parameter with the significance for the output variable. [46], [38].

To perform LHS/PRCC and EFAST we used the codes of methodology proposed in [38] and can be accessed in the link <http://malthus.micro.med.umich.edu/lab/usadata/>

1.A.4 Genetic Algorithm

The function to minimize is $f(V, \Upsilon) = (V - V_{data})^2$, where V is the viral load solution of the system (1.1), V_{data} are the data of viral load of patients and Υ are the unknown parameters $\Upsilon = (\beta_I, \alpha_v, \gamma_1, \gamma_2, \alpha_r, \alpha_a, \alpha_{cr}, \alpha_{ca}, \mu_v)$, where $\beta_I \in (\beta_{Imin}, \beta_{Imax})$, $\alpha_v \in (\alpha_{vmin}, \alpha_{vmax}), \ldots, \mu_v \in (\mu_{vmin}, \mu_{vmax})$. The first step is transform each parameter in binary and form a string called chromosome. Let be Γ the binary representation of Υ. Then

$$\Gamma = (\beta_{I2}\alpha_{v2}\gamma_{12}\gamma_{22}\alpha_{r2}\alpha_{a2}\alpha_{cr2}\alpha_{ca2}\mu_{v2}).$$

will be the chromosome, which has just 1's and 0's and $\beta_{I2}, \alpha_{v2}, \gamma_{12}, \gamma_{22}\alpha_{r2}, \alpha_{a2}, \alpha_{cr2}, \alpha_{ca2}, \mu_{v2}$ are the binary representation of parameters. This chromosome has length $m = \sum_{i=1}^{9} m_i$, where m_1 is the smallest integer such that $(\beta_{Imax} - \beta_{Imin}) \times 10^p < 2^{m_1} - 1$, m_2 is the smallest integer such that $(\alpha_{vmax} - \alpha_{vmin}) \times 10^p < 2^{m_2} - 1, \ldots,$ m_9 is the smallest integer such that $(\mu_{vmax} - \mu_{vmin}) \times 10^p < 2^{m_9} - 1$ and p is the is the decimal places for the parameters. Each m_i is the length of binary string of parameters. Now we start the algorithm

1. **Initial population**
   We create a random population P_0 of chromosomes, where each chromosome is a binary string of length $m = \sum_{i=1}^{9} m_i$. We suppose that this initial population has n chromosomes. i.e
   $$P_0 = \{\Gamma_0^1, \ldots, \Gamma_0^n\}$$

2. **Evaluation function**
   In this step we evaluate the function f at each element of the population P_0, it means $f(V, \Upsilon^i)$, where Υ^i is the decimal representation of Γ_0^i, $i = 1, \ldots, n$.

3. **Next Population**
   In this step we select the next population to apply the genetic operator (crossover and mutations).

   - **Selection method**
     To select the population we apply the tournament selection method, which consists in select randomly some number k of chromosome and selects the minimum of the set $\{f(V, \Upsilon^{J_1}), \ldots, f(V, \Upsilon^{J_k})\}$ of k elements, where J is a subset of k elements ($J \subset \{1, 2, \ldots, n\}$), into the next generation. This process is repeated n times. Obviously, some chromosomes would be selected more than once. Now, we apply the crossover and mutations operators to this selected population.

   - **Crossover operator**
     This operator apply recombination in the chromosomes. We give the probability of crossover p_c. This probability give us the expected number $p_c \times n$ of chromosomes, which undergo the crossover operation. The process of crossover function in the following way: for each chromosome in the (new) population, we generate a random number r from the range $[0, 1]$. If $r < p_c$, we select this chromosome for crossover.

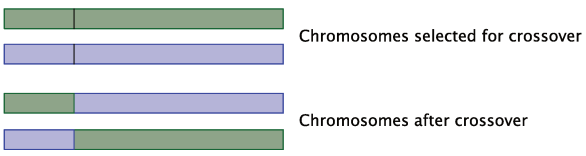


Figure 15 – The one-point crossover in two chromosome.

If the number of selected chromosomes is even, we can pair them easily. If the number of selected chromosomes were odd, we would either add one extra chromosome or remove one selected chromosome, this choice is made randomly as well. The operator explained here is known as one-point crossover. There are other crossover operator as: Two-point crossover, Uniform crossover and half uniform crossover.

- **Mutation operator**
  This operator apply alterations in the elements of chromosomes (changes of 0 for 1 or vice versa). We give the probability of mutation p_m. This probability give us the expected number of mutated elements $p_m \times m \times_n$. The process to perform the mutation operator is similar to the crossover operator: For each chromosome in the current (i.e., after crossover) population and for each element within the chromosome, is generated a random number r from the range $[0, 1]$. If $r < p_m$, then mutate the element.

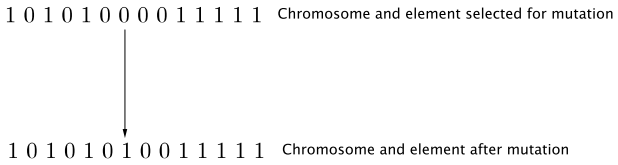


Figure 16 – The mutation operator.

4. After all the above steps, we have created the first generation: population P_1. Now just repeat the steps 2 and 3 to P_1, and the process goes up to the desired generations.

A detailed explanation of genetic algorithms can be found in [47]. The algorithm adapted and used in the simulations can be accessed in the link <http://people.csail.mit.edu/gbezerra/Code/GA/ga.m>

2 Mathematical model of antibody dependent enhancement in dengue disease

Abstract. We developed a mathematical model to explore the different situations in which antibody dependent enhancement in dengue disease could occur. The model has a virus-free equilibrium that is locally asymptotically stable but could be unstable depending on the region of immune parameters. The instability of this point implies in the rise of viral load and infected cells. Further, there is a locally asymptotically stable virus-presence equilibrium. We analyzed when the viral load increases or reaches the minimum viral level. We found that high proliferation parameter levels of cross-reactive antibodies increases the viral load, and even if the basic reproductive number is less than one, there exists a large chance of an increase dependent on the proliferation of cross-reactive antibodies and the initial viral load.

2.1 Introduction

The mechanism by which the viral production of target cells is altered by the presence of serotype-cross-reactive antibodies is a serological phenomenon called antibody-dependent enhancement (ADE) [48]. The first studies about ADE were conducted about 15 years after the World War II by the virologists Kjellen [49] and Hawkes [50], but this phenomenon only became important when the epidemiologist/virologist Halstead proposed a relationship between epidemiology, cross-reactive antibodies and dengue disease severity [51],[52],[53]. Actually there is a very large number of disease that show ADE in vitro and vivo, including HIV, Influenza A, Measles and Dengue [54]. In dengue disease, the major target cells are macrophages, monocytes, and dendritic cells. After a primary dengue infection, the immunological memory will raise cross-reactive antibodies that cannot block the infection and can enhance the infection by a different virus type. In fact, there is much evidence that the Fcγ receptors, which are proteins on the surface of some cells like macrophages and monocytes that bind to the antigen-antibody complex, might facilitate viral entry in cells and increase dengue viral replication [55]. It was recently inferred that immunological memory for dengue virus is cross-reactive to Zika virus and might develop ADE [56], which will be a challenge in research on vaccines against dengue and Zika virus.

Here we propose a mathematical model of ADE in dengue infection based on the biological mechanism involved in this phenomenon and try to capture the possible scenarios in which the ADE happens. There exist few mathematical models that consider the viral dynamics of dengue virus and even fewer that treat the second infections by

dengue virus [57],[28]. The difference in our mathematical approach is that we considered the principal actors in the ADE: B memory cells, dengue virus and macrophages. It is assumed that the antigen-antibody complex will be engulfed by the macrophages and that a portion of this binding will generate infection. This formulation allowed us to determine a proliferation parameter threshold of B memory cells in which the ADE does not happen and represent the scenery when there is no expectation of infection ($R_0 < 1$). However, with a high level of the parameter of proliferation of B cells and a high initial viral load will trigger an increase in the viral load.

2.2 Model formulation

In the model, we consider the existence of an immunological memory to one of the four serotypes of dengue virus. This memory is represented by B memory cells, that will respond quickly and effectively to the dengue virus encountered previously, but weakly to the three others. We assume that these cells are maintained in a constant level rate $k_{_B}$ by the immune system, proliferate in the presence of antigen at rate $\alpha_{_B}$ and have death rate $\mu_{_B}$. Once B memory cells recognize the pathogen, which is denoted by V, they differentiate into plasma cells and release antibodies. These antibodies will bind to the pathogen, and we consider that it happens at rate proportional to the presence of B cells. Thus, $\alpha_1 BV$ will be the binding of antibodies to the pathogen which is known as antigen-antibody complex (or immune complex), where α_1 is the formation rate of antigen-antibody complex. The macrophages S are produced by the bone marrow at rate k_s and have half life of $\dfrac{1}{\mu_s}$. These cells may react in two ways: by direct phagocytosis of virus, a slow process promoted by pseudopods, or by opsonization of antigen-antibody complex which facilitate the phagocytosis. Due to imperfect action of antibodies against another serotypes of dengue virus, some cells became infected, i.e, virus can replicate in these cells, releasing new virus. The concentration of these infected cells is denoted by I and has a death rate $\mu_{_I}$. The direct phagocytosis of virus is described by the term $\alpha_v SV$, where α_v is the slow rate of phagocytosis. The opsonization process is mediated or facilitated by the receptors $Fc\gamma r$ that are present in macrophages. Therefore the antigen-antibody complex is quickly phagocited when it is bound to the $Fc\gamma r$ receptors. This process is described by $\alpha_2(\alpha_1 BV)S$, where α_2 is the fast rate of phagocytosis. We define $\alpha_c = \alpha_1 \times \alpha_2$ as phagocytosis rate of antigen-antibody complex. By a imperfect cross-reactive immune response to heterologous serotype of dengue virus, a portion of these effector cells can become infected, i.e. $\rho\alpha_c BVS$, with $0 < \rho < 1$. The effective cross-reactive immune response to homologous serotype of dengue virus is considered when $\rho = 0$. It could happen that some infected macrophages kill the pathogen. It means that these macrophages are target of the dengue virus again, and this happens at rate σ. The other portion $(1-\rho)\alpha_c BVS$ becomes a type of target cells $\hat{S}$ and these cells quickly transform

back to the target cells S, with rate $\alpha_{\hat{S}}$. The concentration of virus is proportional to the quantity of virus released by infected cells after its death, γI and the virus decay at rate μ_v. Furthermore, once the free virus form the antigen-antibody complex it will be engulfed by the macrophages. Thus, we assume that the macrophages engulf more than one immune complex, that is, $N\alpha_c BVS$. Therefore, the system of differential equations is

$$\begin{aligned}
\frac{dB}{dt} &= k_{_B} + \alpha_{_B} BV - \mu_{_B} B \\
\frac{dS}{dt} &= k_s + \sigma I - (\alpha_c BV + \mu_s)S + \alpha_{\hat{S}}\hat{S} \\
\frac{d\hat{S}}{dt} &= (1-\rho)\alpha_c BVS - \alpha_{\hat{S}}\hat{S} \\
\frac{dI}{dt} &= \rho\alpha_c BVS - (\sigma + \mu_{_I})I \\
\frac{dV}{dt} &= \gamma I - N\alpha_c BVS - (\alpha_v S + \mu_v)V.
\end{aligned}$$

In the third equation of previous system, we can see that the transition of $\hat{S}$ to S is instantaneous, so we can consider this equation in equilibrium. This means that $\alpha_{\hat{S}}\hat{S} = (1-\rho)\alpha_c BVS$ and our system becomes

$$\begin{aligned}
\frac{dB}{dt} &= k_{_B} + \alpha_{_B} BV - \mu_{_B} B \\
\frac{dS}{dt} &= k_s + \sigma I - (\rho\alpha_c BV + \mu_s)S \\
\frac{dI}{dt} &= \rho\alpha_c BVS - (\sigma + \mu_{_I})I \\
\frac{dV}{dt} &= \gamma I - N\alpha_c BVS - (\alpha_v S + \mu_v)V.
\end{aligned} \tag{2.1}$$

The solutions of the model (2.1) with initial conditions in $\mathbb{R}^4_+$ are always positive and limited if they are in the set:

$$\Omega = \left\{ P \in \mathbb{R}^4_+ : \frac{\gamma}{\mu_{_I}} S + \left(\frac{\gamma}{\mu_{_I}} + \frac{N}{\rho}\right) I + V \leqslant \frac{\bar{k}}{\delta}, B \leqslant \frac{k_{_B}}{\zeta} \right\}, \tag{2.2}$$

where $P = (B, S, I, V)$, $\bar{k} = \dfrac{k_s \gamma}{\mu_{_I}}$, $\delta = \min\left\{\mu_s, \mu_v, \dfrac{\frac{N}{\rho}(\sigma + \mu_{_I})}{\left(\frac{\gamma}{\mu_{_I}} + \frac{N}{\rho}\right)}\right\}$, and ζ satisfy $\zeta := \mu_{_B} - \alpha_{_B}\dfrac{\bar{k}}{\delta} > 0$.

Lemma 2.1. *The set Ω is positively invariant with respect to system (2.1).*

Proof. Let $f : \mathbb{R}_+ \to \mathbb{R}_+$, the function defined by $f(t) = \dfrac{\gamma}{\mu_{_I}} S(t) + \left(\dfrac{\gamma}{\mu_{_I}} + \dfrac{N}{\rho}\right) I(t) + V(t)$.

Taking the derivative of function f with respect to t, we have

$$\begin{aligned}\frac{df}{dt} &= \frac{\gamma}{\mu_I}k_s - \mu_s\frac{\gamma}{\mu_I}S - \frac{N}{\rho}(\sigma+\mu_I)I - \alpha_v VS - \mu_v V \\ &\leqslant \frac{\gamma}{\mu_I}k_s - \mu_s\frac{\gamma}{\mu_I}S - \frac{N}{\rho}(\sigma+\mu_I)I - \mu_v V,\end{aligned}$$

this can be write as

$$\frac{df}{dt} + \mu_s\frac{\gamma}{\mu_I}S + \frac{N}{\rho}(\sigma+\mu_I)I + \mu_v V \leqslant \frac{\gamma}{\mu_I}k_s.$$

If $\bar{k} = \dfrac{k_s\gamma}{\mu_I}$ and $\delta = \min\left\{\mu_s, \mu_v, \dfrac{\frac{N}{\rho}(\sigma+\mu_I)}{\left(\frac{\gamma}{\mu_I}+\frac{N}{\rho}\right)}\right\}$, then $\dfrac{df}{dt} + \delta f \leqslant \bar{k}$. Therefore $f(t) \leqslant \dfrac{\bar{k}}{\delta}$, for $t \geqslant 0$.

The last inequality implies that $V(t) \leqslant \dfrac{\bar{k}}{\delta}$, for $t \geqslant 0$, and it is always possible to choose the parameters μ_B, α_B, and δ, such that

$$\mu_B - \alpha_B\frac{\bar{k}}{\delta} > 0. \tag{2.3}$$

Taking into account this considerations and the first equation of system (2.1) we have

$$\frac{dB}{dt} + \left(\mu_B - \alpha_B\frac{\bar{k}}{\delta}\right)B \leqslant \frac{dB}{dt} + (\mu_B - \alpha_B V)\,B = k_B.$$

Then $\dfrac{dB}{dt} + \zeta B \leqslant k_B$, where $\zeta = \mu_B - \alpha_B\dfrac{\bar{k}}{\delta}$, which implies $B \leqslant \dfrac{k_B}{\zeta}$ for $t \geqslant 0$. □

2.3 Analysis of the model

2.3.1 Virus-free equilibrium and stability

Corresponding to absence of infection by dengue virus, we have the equilibrium point $W_0 = (B_0, S_0, 0, 0)$, where $B_0 = \dfrac{k_B}{\mu_B}$ and $S_0 = \dfrac{k_s}{\mu_s}$. We call this point the virus-free equilibrium. The characteristic polynomial of the Jacobian matrix evaluated at W_0 has two negative roots: $-\mu_s$, $-\mu_B$ and two roots that depend on the sign of independent term of next polynomial:

$$\lambda^2 + d\lambda + (\mu_I+\sigma)\left(\frac{N\alpha_c k_s k_B}{\mu_s\mu_B} + \mu_v + \alpha_v\frac{k_s}{\mu_s}\right) - \frac{\alpha_c k_s k_B\rho\gamma}{\mu_s\mu_B},$$

where $d = \left(\sigma + \mu_I + \mu_v + \alpha_v \frac{k_s}{\mu_s} + \frac{N\alpha_c k_s k_B}{\mu_s \mu_B}\right)$. Note that the independent term can be written in the form $\frac{(\alpha_v k_s + \mu_v \mu_s)(\mu_I + \sigma)}{\mu_s}\left(1 - R_0\right)$, where

$$R_0 = \alpha_c \frac{\frac{k_B}{\mu_B}\frac{k_s}{\mu_s}\left[\rho\frac{\gamma}{(\mu_I+\sigma)} - N\right]}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)}. \tag{2.4}$$

Then by Routh Hurwitz criteria [30] (pg 230), the virus-free point W_0 is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$. The local stability of this point is stated in theorem 2.1.

The number R_0 can be interpreted in the following way. The average period of time that one virus survives and circulates freely without being phagocytosed by macrophages is

$$\frac{1}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)}.$$

The binding of virus with antibodies produced by all memory cells during this time is

$$\alpha_1 \times \frac{1}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)} \times \frac{k_B}{\mu_B}$$

and

$$\alpha_2 \times \left[\alpha_1 \frac{1}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)} \frac{k_B}{\mu_B}\right] \frac{k_s}{\mu_s},$$

is the fast phagocytosis of antigen-antibody complex by macrophages which is mediated by the $Fc\gamma r$ receptors. Therefore, $\alpha_c \frac{\frac{k_B}{\mu_B}\frac{k_s}{\mu_s}}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)}$, with $\alpha_c = \alpha_1 \times \alpha_2$, is the engulfment of one virus by macrophages trough antigen-antibody complex during the average time of free circulating. Further, $\alpha_c \frac{\frac{k_B}{\mu_B}\frac{k_s}{\mu_s}}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)} \rho$ is the fraction of macrophages that will produce virus. Consequently the average number of virus produced by productive macrophages during the life span is $\alpha_c \frac{\frac{k_B}{\mu_B}\frac{k_s}{\mu_s}}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)} \rho \frac{\gamma}{(\mu_I + \sigma)}$. However the average number of virus engulfed by macrophages is $\alpha_c \frac{\frac{k_B}{\mu_B}\frac{k_s}{\mu_s}}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)} N$. Then R_0 is the net number of virus produced by one virus.

Theorem 2.1. *The point W_0 is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$. Where R_0 is given by (2.4)*

2.3.2 Fold Bifurcation

In the proof of the Theorem 2.1, we can see that when $R_0 = 1$, the characteristic polynomial has a zero eigenvalue and the others are negative. Thus the point W_0 is not hyperbolic, so we don't have any information about its stability. For the study of the stability in this point W_0 at $R_0 = 1$ we can use theory of central manifold to prove that there exists a fold bifurcation. To do this we chose μ_I, as bifurcation parameter, so $R_0 = 1$ at $\mu_I = \mu_I^* = \dfrac{\rho\gamma\alpha_c \frac{k_B}{\mu_B}\frac{k_s}{\mu_s}}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right) + N\alpha_c \frac{k_B}{\mu_B}\frac{k_s}{\mu_s}} - \sigma$. Using the projection method for center manifold computation [44] (pg 488), we can prove that the dynamics of system (2.1) is locally topologically equivalently in the central manifold to the dynamics of the equation $\dot{u} = \frac{1}{2}au^2 + O(u^3)$. In the appendix 2.A.1, we prove that $a > 0$. Therefore the fold bifurcation warrants the existence of one virus-presence equilibrium near to point W_0, for $\mu_I^* < \mu_I < \mu_I^* + \epsilon$ (this situation represents $R_0 < 1$) , $\epsilon > 0$, which is unstable, besides we can say that for $\mu_I^* - \epsilon < \mu_I < \mu_I^*$ (this situation represents $R_0 > 1$), there will be a quickly increase of the viral load.

2.3.3 Virus-presence equilibrium

The virus-presence equilibrium is defined by the point $W_1 = (B^*, S^*, I^*, V^*)$, where

$$
\begin{aligned}
B^* &= \frac{Q-1}{Q-R_0}\frac{k_B}{\mu_B} \\
S^* &= \frac{1}{1 + \frac{\mu_I\alpha_c\rho k_B}{\mu_s(\mu_I+\sigma)\alpha_B}\frac{(R_0-1)}{(Q-R_0)}}\frac{k_s}{\mu_s} \\
I^* &= \frac{1}{1 + \frac{\mu_s(\mu_I+\sigma)\alpha_B}{\mu_I\alpha_c\rho k_B}\frac{(Q-R_0)}{(R_0-1)}}\frac{k_s}{\mu_I} \\
V^* &= \frac{R_0-1}{Q-1}\frac{\mu_B}{\alpha_B},
\end{aligned}
$$

and $Q = \dfrac{k_B\mu_v\mu_I\rho\alpha_c}{\alpha_B(\alpha_v k_s + \mu_v\mu_s)(\mu_I+\sigma)}$.

The number Q can be written in the form: $Q = \dfrac{\frac{\alpha_c\frac{k_B}{\mu_B}}{\left(\alpha_v\frac{k_s}{\mu_s}+\mu_v\right)\mu_s}\rho\frac{\mu_I}{(\mu_I+\sigma)}}{\frac{1}{\mu_v}\alpha_B\frac{1}{\mu_B}}$. We can interpreted its numerator and denominator as follow:

- In the numerator, the term

$$
1 \times \alpha_1 \times \frac{1}{\left(\alpha_v\frac{k_s}{\mu_s} + \mu_v\right)} \times \frac{k_B}{\mu_B}, \tag{2.5}
$$

was described before as the rate at which one virus, during its average period of time, that survives and circulates freely without being phagocytosed by macrophages $\frac{1}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)}$, is linked to the antibodies $\frac{k_B}{\mu_B}$, forming the complex antigen-antibody. The term

$$\alpha_1 \frac{1}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)} \frac{k_B}{\mu_B} \times \alpha_2 \times \frac{1}{\mu_s}, \tag{2.6}$$

is the rate at which one macrophage in its average life $\frac{1}{\mu_s}$ engulfs the complex antigen-antibody. Then, the term

$$\alpha_1 \frac{1}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right)} \frac{k_B}{\mu_B} \alpha_2 \frac{1}{\mu_s} \times \rho, \tag{2.7}$$

is the infection rate of one macrophage that in its average life $\frac{1}{\mu_s}$ have engulfed the complex antigen-antibody and

$$\frac{\alpha_c \frac{k_B}{\mu_B}}{\left(\alpha_v \frac{k_s}{\mu_s} + \mu_v\right) \mu_s} \rho \times \frac{\mu_I}{(\mu_I + \sigma)}, \tag{2.8}$$

will be the death probability of infected macrophages that have not released virus .

- The denominator $\frac{1}{\mu_v} \alpha_B \frac{1}{\mu_B}$ is the proliferation rate of B memory cells by the stimulus of antigen.

In the definition of virus-presence equilibrium W_1, we can see that it has biological meaning if $Q < R_0 < 1,$ or $Q > R_0 > 1$. Furthermore if $R_0 \approx 1$, then

$$B^* \approx \frac{k_B}{\mu_B},\ S^* \approx \frac{k_s}{\mu_s},\ I^* \approx 0,\ V^* \approx 0. \tag{2.9}$$

This situation is the fold bifurcation described in the section 2.3.2, because when we have $Q < R_0 < 1$ and $R_0 \approx 1$, we really have $\mu_I \approx \mu_I^*$ ($\mu_I^* < \mu_I < \mu_I^* + \epsilon$), which implies that the point W_1 is unstable and all the solutions converge to free virus point W_0. Observe that, if $\mu_I \to \mu_I^{*+}$, the parameter Q decrease and R_0 increase, so this is not a good situation. On the other hand, for $Q > R_0 > 1$ and $R_0 \approx 1$, we have that $\mu_I \approx \mu_I^*$ ($\mu_I^* - \epsilon < \mu_I < \mu_I^*$), the point W_0 is unstable and the virus-presence W_1 is stable. This situation is ideal because if $\mu_I \to \mu_I^{*-}$, the parameter Q increases and R_0 decreases and the level of infected cells and virus is almost zero by the effect of apoptosis increase.

On the other hand, if $Q \approx R_0$ and $R_0 \neq 1$, we have

$$B^* \to +\infty,\ S^* \approx 0,\ I^* \approx \frac{k_s}{\mu_I},\ V^* \approx \frac{\mu_B}{\alpha_B}.$$

This is the worst case because the infected cells and virus reach the maximum levels. Besides for $Q > R_0 > 1$, and if $Q \to \infty$, we can see that

$$B^* \approx \frac{k_{_B}}{\mu_{_B}},\ S^* \approx \frac{k_s}{\mu_s},\ I^* \approx 0,\ V^* \approx \frac{(\alpha_v k_s + \mu_v \mu_s)(\mu_{_I} + \sigma)\mu_{_B}(R_0 - 1)}{k_{_B}\mu_v \mu_{_I} \rho \alpha_c}.$$

In this situation there is a benefit for the cross-reactive immune response if Q is big and $R_0 > 1$, because the infected cells reach a minimum level.

From previous considerations, we can see that when Q is incremented and $Q > R_0$ there is always a benefit for immune system; because the infected cells and/or virus load decrease. In fact we shall see that, in order to eliminate the infection or to prevent a strong infection, we will require $Q > R_0$.

Let us see which are the situations where we obtain an increment in the parameter Q. The possibilities are: the numerator increases or the denominator decreases. The numerator can increase if the parameter α_c is raised. The problem of this situation is that R_0 will raise too, and this means that the productions of virus increases. So is not the better idea to rise this parameter, and, similarity the parameter ρ. Another situation where the numerator can increase is when the parameter $\mu_{_I}$ is increased. The feature of this situation is that R_0 will decrease. In fact, we discussed this situation after the equation (2.9). We concluded that if apoptosis parameter $\mu_{_I}$ is increased until $\mu_{_I}^*$, then Q will raise until Q^* and $R_0 \to 1$. This implies in a decrease of dengue virus and the infected cells by increment of parameter Q. The denominator will decrease (which means that the parameter Q increases), if the parameter of proliferation of B memory cells, $\alpha_{_B}$, decreases. In fact we shall show that the parameter $\alpha_{_B}$ will have substantial implications in the increase of the infection.

In the next figure 17, we present a scheme about the existence of equilibrium points with respect to the parameters Q and R_0. Note that when $Q < R_0 < 1$, there is coexistence with the point W_0.

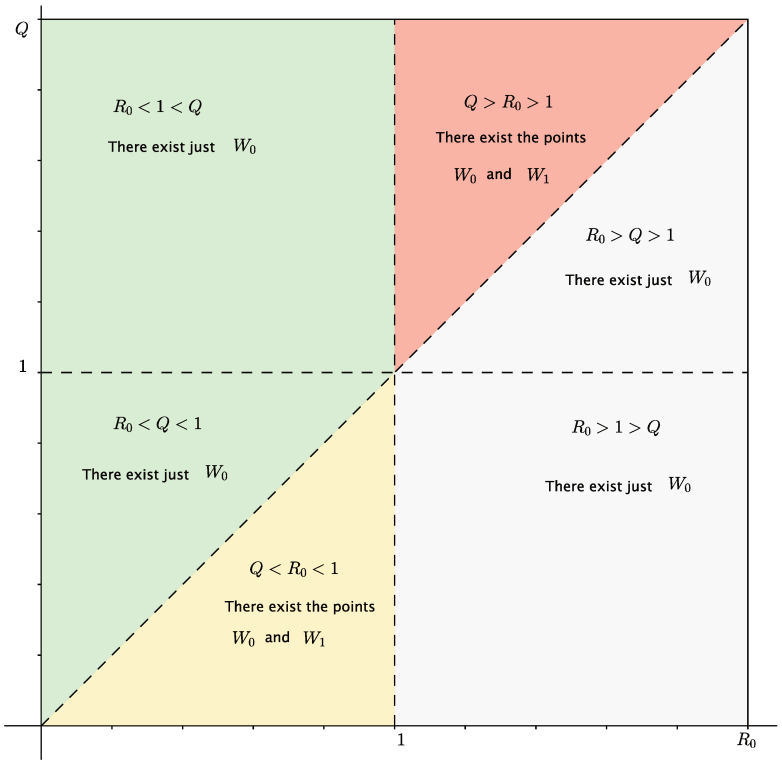


Figure 17 – The figure shows the existence of equilibrium points with respect to parameters Q and R_0

2.3.4 Stability of virus-presence equilibrium W_1 when $Q < R_0 < 1$ and $Q > R_0 > 1$

The local stability of the point W_1 is characterized by the roots of the characteristic polynomial of matrix Jacobian of system (2.1) evaluated at point W_1, this polynomial is:

$$\lambda^4 + S_3(W_1)\lambda^3 + S_2(W_1)\lambda^2 + S_1(W_1)\lambda + S_0(W_1), \tag{2.10}$$

where

$$
\begin{aligned}
S_3(W_1) &= \mu_{_B}\frac{Q-R_0}{Q-1} + \alpha_c\,\rho\,V^* + \mu_s + A\\
S_2(W_1) &= \mu_{_B}\frac{Q-R_0}{Q-1}\left(\alpha_c\,\rho\,B^*\,V^* + \mu_s + A\right) + \alpha_B\,N\alpha_c\,B^*\,V^*\,S^*\\
&\quad + (\mu_{_I}+\mu_v)\alpha_c\,\rho\,B^*\,V^* + \mu_s A\\
S_1(W_1) &= \mu_{_B}\mu_s\frac{Q-R_0}{Q-1}\left[\mu_{_I}+\sigma+\alpha_v\,S^*+\mu_v\right] + \mu_{_B}\mu_s N\alpha_c\,B^*\,S^*\\
&\quad + \left[k_{_B}(\mu_{_I}+\mu_v)\rho\,\alpha_c - \alpha_{_B}\alpha_v\rho\alpha_c\,B^*\,V^*\,S^*\right]V^*\\
&\quad + \left\{\mu_v\mu_{_I}\rho\,B^* - \left[\gamma\rho - N(\mu_{_I}+\sigma)\right]\alpha_{_B}B^*\,S^*\right\}\alpha_c V^*\\
S_0(W_1) &= \mu_{_B}(\alpha_v k_s + \mu_v\mu_s)(\mu_{_I}+\sigma)(R_0-1),
\end{aligned}
$$

and $A = \mu_{_I} + \sigma + N\alpha_c\,B^*\,S^* + \alpha_v\,S^* + \mu_v$.

2.3.4.1 Stability analysis of the point W_1 when $Q < R_0 < 1$

As we see in the figure 17, when $Q < R_0 < 1$, there exist two points: the point W_0 which is locally asymptotically stable by Theorem 2.1 and the point W_1, which is unstable by Theorem 2.2 .

Theorem 2.2. *The point W_1 is unstable if $Q < R_0 < 1$.*

Proof. In the characteristic polynomial (2.10), the coefficients $S_3(W_1)$, $S_2(W_1)$ are positive and $S_0(W_1)$ is negative for $Q < R_0 < 1$. Therefore, independently of signal of coefficient $S_1(W_1)$, the polynomial has just one change of signal. Then the Descartes' rule of signs warrants the existence of one positive root, which implies that the point W_1 is unstable if $Q < R_0 < 1$. □

If R_0 remains constant and Q is able to vary, we can see that the only way it happens is when $\alpha_{_B}$ varies, because $\dfrac{\mu_{_I}}{(\mu_{_I}+\sigma)} < 1$ and the other parameters depend on R_0. So if $\alpha_{_B}$ is large enough we have $Q < R_0$ and if it is small, we have $Q > R_0$. We analyze the stability of system (2.1) when $Q < R_0 < 1$ and $1 > Q > R_0$

In figure 18, we plot the stability relationship between Q and the equilibrium V^* and B^* respectively, when R_0 remains constant and Q varies. It is possible to observe that the point W_1 is a separatrix of stability for the point W_0. It means that if we put a initial condition below this point the infection will be eliminated, but if we put a initial condition above this point we have a strong increase in the viral load.

The antibodies will help in the elimination of dengue virus, if they are below of B^* or they will help to increase the viral load and infected cells, if they are above of B^* (see figure 18b). There is another problem, if the proliferation parameter, $\alpha_{_B}$, is too big,

the region where cross-reactive immune response can eliminate the dengue virus will be decreased and there is more likely to rise the viral load by ADE (see figure 18a).

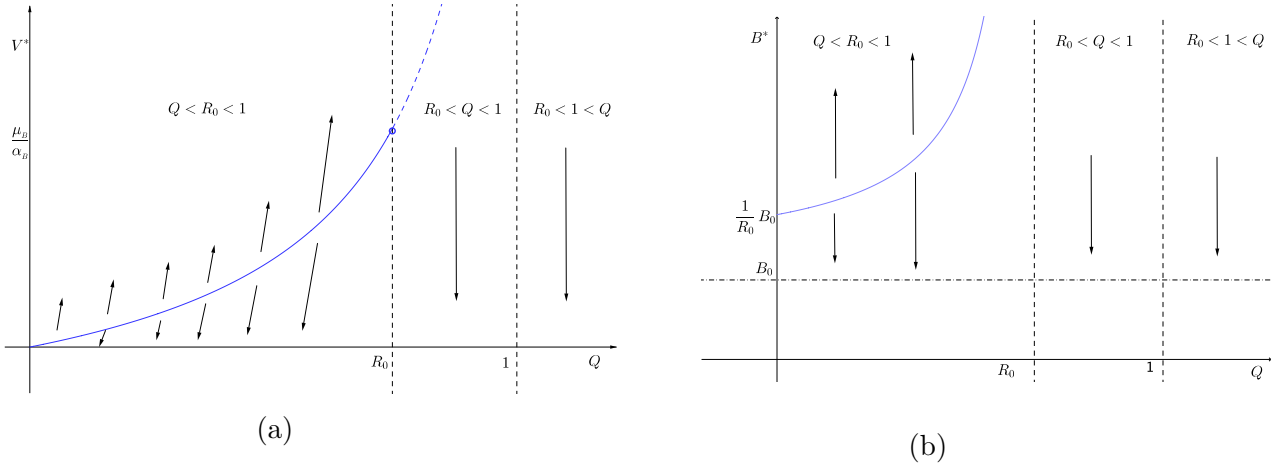


Figure 18 – (a) The figure shows the virus-presence point V^* as function of parameter Q, when $R_0 < 1$ remains constant. The arrows indicate the dynamic of dengue virus V. We can see that if parameter Q is small($\alpha_{_B} \to \infty \Rightarrow Q \to 0$), the by any initial viral load above of V^*, our immune system will not be able to eliminate the virus, which means that the antibodies are enhancing the infection. While that if parameter Q is not too small (the parameter $\alpha_{_B}$ is not too big), the immune system will tolerate greater initial viral load and will be able to eliminate the virus. (b) The figure shows B^* cells as function of parameter Q, when $R_0 < 1$ remains constant. The arrows indicate the dynamics of B cells. When $Q < R_0 < 1$, the dengue virus will be eliminate for initial values of B cells below of B^*, but if this initial value will be above of B^*, the virus will not be eliminated, and a strong increase of dengue virus could be happen by ADE. Further, it could be worst if the parameter $\alpha_{_B}$ is too big, because $1 > R_0 >> Q \longrightarrow$ and the region where the immune system eliminate the virus is decreased. For $R_0 < Q < 1$ we have total elimination of the dengue virus, observe that in this situation the parameter $\alpha_{_B}$ has not to be too big.

2.3.4.2 Stability analysis of the point W_1 when $Q > R_0 > 1$

Theorem 2.3. *The point W_1 is locally asymptotically stable if $Q > R_0 > 1$.*

Proof. To get the local stability of the point W_1, first we define $S_i(W_1) := S_i$ for $i = 0, \ldots, 4$. We have to prove that the coefficients of polynomial characteristic (2.10) satisfy, for $Q > R_0 > 1$, the following Routh–Hurwitz conditions:

$$S_3 > 0, S_2 > 0, S_1 > 0, S_0 > 0 \tag{2.11}$$

$$S_1 S_2 S_3 - S_1^2 > S_3^2 S_0. \tag{2.12}$$

The condition (2.11) is easily checked by S_3, S_2, and S_0. A proof of $S_1 > 0$ can be found in appendix 2.A.2. Since the condition (2.11) is valid for $Q > R_0 > 1$, the inequality (2.12) can written as

$$\frac{1}{S_2}\left(\frac{S_3 S_0}{S_1} + \frac{S_1}{S_3}\right) < 1. \tag{2.13}$$

For $Q > R_0 > 1$, we have, $\dfrac{S_3 S_0}{S_1} < \dfrac{S_2}{2}$ and $\dfrac{S_1}{S_3} < \dfrac{S_2}{2}$ (see a proof in Appendix 2.A.3). This implies that the point W_1 is locally asymptotically stable.

□

As in subsection 2.3.4.1, we vary Q and let R_0 constant. In figure 19b, we can see that if the parameter of proliferation $\alpha_{_B}$ is too small, then Q increases and therefore B^* asymptotically approaches the value B_0 and viral load is the lowest possible $\left(V^* \to \dfrac{(\alpha_v k_s + \mu_v \mu_s)(\mu_{_I} + \sigma)\mu_{_B}(R_0 - 1)}{k_{_B}\mu_v \mu_{_I} \rho \alpha_c}\right)$. On the contrary, if $\alpha_{_B}$ increases up to a threshold $\widehat{\alpha_{_B}}$, such that $Q \to R_0$, we will have the greatest value for viral load $V^* \to \dfrac{\mu_{_B}}{\alpha_{_B}}$ and $B^* \to +\infty$ (see figure 19a). This is a clear example of antibodies mediation in the intensity of infection.

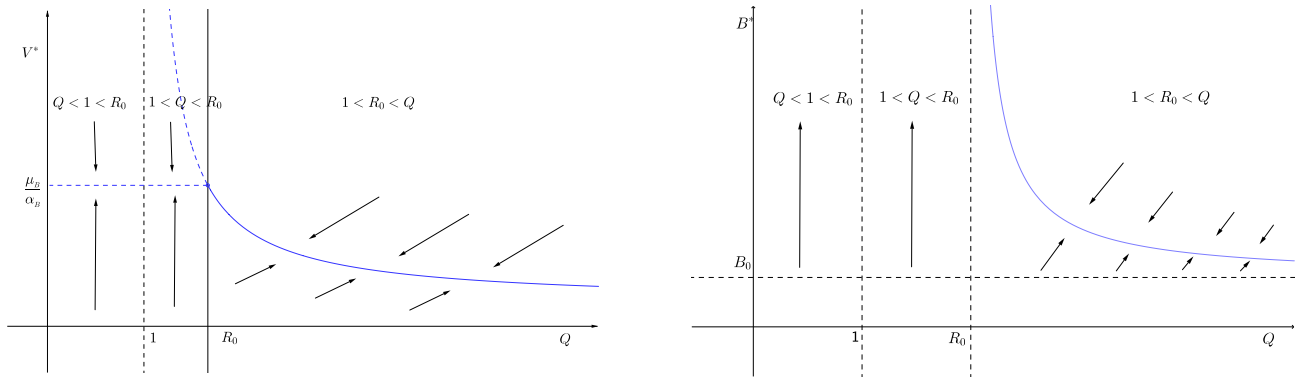


Figure 19 – (a) The figure shows V^* cells as function of parameter Q, when $R_0 > 1$ remains constant. The arrows indicate the dynamics of dengue virus V. In this case there is no elimination of virus, even there is a possibility of increase the viral load if $Q \approx R_0$ (which means α_B is big). (b) The figure shows B^* cells as function of parameter Q, when $R_0 > 1$ remains constant. Arrows indicate the dynamic of B cells. When $Q > R_0 > 1$, there is not chance of virus elimination, but if the parameter α_B is small, the B cells and the viral load V^* will be smaller. Besides, if the parameter α_B grows to a threshold such that $Q \approx R_0$, the B cells blowup and viral load will increase, and again we have the antibody dependent enhancement.

2.4 Discussion

2.4.1 Antibody dependent enhancement

We have noticed the importance of parameter Q in the increment of viral load. We analyze three situations in which it happens: $Q < R_0 < 1$, $R_0 > Q > 1$ and $Q > R_0 > 1$.

In the figure 18a, it is examined the situation $Q < R_0 < 1$. It is possible to observe that for initial viral load above to V^*, the viral load will increase without limit. This situation is more evident when Q is close to zero, which means that α_B is too big. It implies that for a little initial viral load V_0, we will have a fast rise of the virus, which is a clear evidence in the mediation of enhancement of infection by the antibodies. The problem is that the range of this initial viral load is decreased by action of proliferation parameter of B cells. Which means that the immune system will tolerate even less initial viral load.

When $Q > R_0 > 1$, the situation is a little different, by any initial viral load, the cross-reacive immune response is not able to eliminate the virus and the viral load will be increased by the action of proliferation of B cells, as we can see in the figure 19a. It means that while the parameter of proliferation α_B is increased, the viral load will be increased and the situation is worst when $Q \to R_0^+$, because the viral load and the

number of infected cells will be the highest possible.

For $R_0 > Q > 1$, we do not have virus-presence equilibrium, the only thing we know is that the virus-free equilibrium is unstable. But we can study the asymptotic behavior of the model (2.1). Initially we show that $B \to +\infty$, in fact, in this region, the equation (2.3) is violated for the parameter $\alpha_{_B}$, because to have $R_0 > Q$, we need

$$\alpha_{_B} > \frac{\mu_{_B}\mu_v}{\left[\gamma - \frac{N}{\rho}(\sigma + \mu_{_I})\right]\frac{k_s}{\mu_{_I}}}.$$

However, from equation (2.3) we have

$$\alpha_{_B} < \frac{\mu_{_B}\min\left\{\mu_s, \mu_v, \frac{\frac{N}{\rho}(\sigma+\mu_{_I})}{\left(\frac{\gamma}{\mu_{_I}}+\frac{N}{\rho}\right)}\right\}}{\gamma\frac{k_s}{\mu_{_I}}}.$$

Which is impossible, because

$$\mu_v \geqslant \min\left\{\mu_s, \mu_v, \frac{\frac{N}{\rho}(\sigma + \mu_{_I})}{\left(\frac{\gamma}{\mu_{_I}} + \frac{N}{\rho}\right)}\right\}$$

besides

$$\gamma > \gamma - \frac{N}{\rho}(\sigma + \mu_{_I}) \Longrightarrow \frac{1}{\gamma - \frac{N}{\rho}(\sigma + \mu_{_I})} > \frac{1}{\gamma}.$$

Then

$$\frac{\mu_{_B}\mu_v}{\left[\gamma - \frac{N}{\rho}(\sigma + \mu_{_I})\right]\frac{k_s}{\mu_{_I}}} > \frac{\mu_{_B}\min\left\{\mu_s, \mu_v, \frac{\frac{N}{\rho}(\sigma+\mu_{_I})}{\left(\frac{\gamma}{\mu_{_I}}+\frac{N}{\rho}\right)}\right\}}{\gamma\frac{k_s}{\mu_{_I}}}.$$

Now we know that $B \to +\infty$, so we need to know the asymptotic behavior of the other variables. From the equation one and two of the model (2.1), and remembering that S, I and V are limited in the Ω set, we have

$$\frac{1}{B}\frac{dB}{dt} = \frac{k_{_B}}{B} + \alpha_{_B}V - \mu_{_B}, \text{ if } B \to +\infty \text{ then } V \to \frac{\mu_{_B}}{\alpha_{_B}}$$
$$\frac{1}{B}\frac{dS}{dt} = \frac{1}{B}k_s + \frac{1}{B}\sigma I - \rho\alpha_c VS - \frac{1}{B}\mu_s S, \text{ if } B \to +\infty \text{ then } S \to 0.$$

By adding the equation two and three of the model (2.1), we obtain

$$\frac{d(S+I)}{dt} = k_s - \mu_s S - \mu_{_I} I. \text{ How } S \to 0, \text{ if } B \to +\infty \text{ then}$$
$$\frac{d(I)}{dt} \approx k_s - \mu_{_I} I, \text{ which implies } I \to \frac{k_s}{\mu_{_I}}.$$

Then we concluded that for $R_0 > Q > 1$, the viral load and infected cells are drastically affected by te increment of the parameter of proliferation of B memory cells, which is another evidence that the our model represent the mediation of antibodies in the increase of dengue infection.

2.4.2 Effective cross-reactive immune response

In the past sections, it is possible to observe that when $Q > R_0$, there is always a benefit for an adequate cross-reactive immune response, because the viral load is either completely cleared ($1 > Q > R_0$) or it reaches the lowest level possible ($Q >> R_0 > 1$). For $Q > R_0$, we need that the proliferation of B cells is not increased up to the threshold $\alpha_{_B}^{**}$, it means

$$\alpha_{_B} < \alpha_{_B}^{**},$$

where $\alpha_{_B}^{**} = \dfrac{\mu_{_B}\mu_v\mu_{_I}\rho}{\left[\rho\frac{\gamma}{(\mu_{_I}+\sigma)} - N\right]k_s(\mu_{_I}+\sigma)}$. But if $R_0 > 1$, there is not chance of elimination. Besides, if $\alpha_{_B}$ is too close $\alpha_{_B}^{**}$ ($\alpha_{_B} \approx \alpha_{_B}^{**}$), there will be increase of viral load by the antibody dependent enhancement, as described in the figure 19a. So to avoid this situation we need the parameter $\alpha_{_B}$ to be small ($\alpha_{_B} << \alpha_{_B}^{**}$). There is another immune system strategy to raise the parameter Q and reduce the viral load. This is by the increment in the apoptosis of infected cells ($\mu_{_I} \to \mu_{_I}^{*-}$), the effect of this situation is a decline in the net number of virus $R_0 \approx 1$. It will have an enormous impact in the infected cells and the virus because $I^* \approx 0$ and $V^* \approx 0$.

Now if $R_0 < 1$ and $Q > R_0$, there is elimination of virus, but what should be the amount of proliferation $\alpha_{_B}$ of B cells for this to happen?. To answer this question, it is needed distinguish two cases: $1 > Q > R_0$ and $Q > 1 > R_0$. For $1 > Q > R_0$, it is needed that the proliferation $\alpha_{_B}$ of B cells satisfies

$$\alpha_{_B}^{*} < \alpha_{_B} << \alpha_{_B}^{**},$$

where $\alpha_{_B}^{*} = \dfrac{k_{_B}\mu_v\mu_{_I}\rho\alpha_c}{(\alpha_v k_s + \mu_v\mu_s)(\mu_{_I}+\sigma)}$. On the other hand, if $Q > 1 > R_0$, the proliferation rate of B cells has not to be too big and it has to be controlled. In terms of the parameters this happens when

$$\alpha_{_B} < \min\left\{\alpha_{_B}^{*}, \alpha_{_B}^{**}\right\}.$$

In this ideal situation ($R_0 < 1$ and $Q > R_0$), for any initial viral load (V_0), the immune system will eliminate the pathogen, i.e. $(B_0, S_0, 0, V_0) \to W_0$.

2.5 Conclusion

In the current study, we proposed a mathematical model to study ADE in dengue disease at an early stage. The model considers an existing immunological memory acquired from a past infection by one of the serotypes of dengue virus. We showed that there exists a high dependence between infection and the proliferation of B cells. There is a threshold for the parameter of proliferation of B cells at which our immune system will clear dengue virus and a threshold at which the mediation of antibodies will increase the infection of cells(antibody-dependent enhancement). If we could control this parameter, we could stop the infection or avoid a strong increase of viral load and infected cells. It is interesting to note that even for $R_0 < 1$, there is a probability that the viral load will increase. In fact, we showed that even for a small initial inoculation of the dengue virus, a rise in the viral load is always possible and depends on how big is the parameter of proliferation of B cells, $\alpha_{_B}$. These observations are in agreement with studies that suggest that in the second infection by dengue virus, there is a favorable increase of the serotype-cross-reactive B cells from primary dengue infection [58], [59] that could contribute to the risk of severe dengue disease [60],[61]. These results have to be read carefully because this model only takes into account the initial stage and does not consider the response of adaptive immune response. However, this was our exact goal for this study because we believe that the initial stage of the second infection is crucial for the course of dengue infection, and understanding it from different point of view may be will be important for future research.

2.A Appendix

2.A.1

The system (2.1) has a fold bifurcation when $R_0 = 1$ or $\mu_{_I} = \mu_{_I}^*$. To prove this, it is enough to use the projection method for center manifold computation [44] (pg 488). Then is necessary compute the sign of a, we start looking for vectors p and q, such that

$$J(W_0)q = 0, \;\; J(W_0)^T p = 0, \;\; < p, q >= 1,$$

where J is the Jacobian matrix of system (2.1), and $< p, q >= \sum_{i=1}^{4} p_i q_i$. After some calculations we have

$$q = \begin{pmatrix} 1 \\ q_2 \\ \dfrac{\mu_s}{\mu_{_I}} q_2 \\ \dfrac{\mu_{_B}^2}{\alpha_{_B} k_{_B}} \end{pmatrix}, \qquad p = \frac{1}{< p, q >} \begin{pmatrix} 0 \\ 0 \\ 1 \\ \dfrac{\mu_{_I} + \sigma}{\gamma}, \end{pmatrix}, \tag{2.14}$$

where, $q_2 = \dfrac{\mu_{_I} \rho(\alpha_v k_s + \mu_v \mu_s)\mu_{_B}^2}{\mu_s^2 \alpha_{_B} k_{_B}[\gamma\rho - N(\mu_{_I} + \sigma)]}$. Now the sign of a is computing using the formula $a =< p, B(q, q) >$, where $\bar{B}(x, y) = (\bar{B}_1(x, y), \ldots, \bar{B}_4(x, y))^T$ is defined in the equation (1.13).Then

$$\begin{aligned}
\bar{B}_1(x, y) &= \alpha_{_B} (x_1 y_4 + x_4 y_1) \\
\bar{B}_2(x, y) &= -\rho\alpha_c \frac{k_s}{\mu_s} (x_1 y_4 + x_4 y_1) - \rho\alpha_c \frac{k_{_B}}{\mu_{_B}} (x_2 y_4 + x_4 y_2) \\
\bar{B}_3(x, y) &= -B_2(x, y) \\
\bar{B}_4(x, y) &= -N\alpha_c \frac{k_s}{\mu_s} (x_1 y_4 + x_4 y_1) - \left(N\alpha_c \frac{k_{_B}}{\mu_{_B}} + \alpha_v \right) (x_2 y_4 + x_4 y_2) .
\end{aligned}$$

Therefore

$$a =< p, \bar{B}(q, q) >= \frac{2}{< p, q >} \frac{\mu_{_B}}{\alpha_{_B} B_0} \left\{ \left[\rho - \frac{N(\mu_{_I} + \sigma)}{\gamma} \right] \alpha_c S_0 + q_2 \left[\frac{(\alpha_v k_s + \mu_v \mu_s)(\mu_{_I} + \sigma)}{\gamma k_s} \right] \right\} > 0,$$

Then the system has a subcritical fold bifurcation.

2.A.2

To prove that the coefficient S_1 is always positive for $Q > R_0 > 1$, first we see that using the equations of equilibrium W_1 we have

$$\begin{aligned}
\rho\alpha_c\, B^*\, V^*\, S^* = (\mu_{_I} + \sigma)I^* &\leqslant (\mu_{_I} + \sigma)\frac{k_s}{\mu_s} \\
[\gamma\rho - N(\mu_{_I} + \sigma)]B^*\, S^* = (\alpha_v\, S^* + \mu_v)(\mu_{_I} + \sigma)\frac{1}{\alpha_c} &\leqslant \left(\alpha_v\,\frac{k_s}{\mu_s} + \mu_v\right)(\mu_{_I} + \sigma)\frac{1}{\alpha_c} \\
B^* &> \frac{k_{_B}}{\mu_{_B}},
\end{aligned}$$

taking in account this inequalities we have

$$\begin{aligned}
S_1 \geqslant\ & \mu_{_B}\mu_s\frac{Q - R_0}{Q - 1}\left[\mu_{_I} + \sigma + \mu_v + \alpha_v\, S^*\right] + \mu_{_B}\mu_s N\alpha_c\, B^*\, S^* \\
&+ \left[k_{_B}(\mu_{_I} + \mu_v)\rho\,\alpha_c - \alpha_{_B}\alpha_v(\mu_{_I} + \sigma)\frac{k_s}{\mu_s}\right] V^* \\
&+ \left[\mu_v\mu_{_I}\rho\,\frac{k_{_B}}{\mu_{_B}} - \left(\alpha_v\,\frac{k_s}{\mu_s} + \mu_v\right)(\mu_{_I} + \sigma)\frac{\alpha_{_B}}{\alpha_c}\right]\alpha_c V^*.
\end{aligned}$$

From $Q > 1$, we have, $k_{_B}\rho\,\alpha_c > \left(\alpha_v\,\dfrac{k_s}{\mu_s} + \mu_v\right)(\mu_{_I} + \sigma)\dfrac{\alpha_{_B}}{\mu_v\mu_{_I}}$, then

$$\begin{aligned}
S_1 \geqslant\ & \mu_{_B}\mu_s\frac{Q - R_0}{Q - 1}\left[\mu_{_I} + \sigma + \mu_v + \alpha_v\, S^*\right] + \mu_{_B}\mu_s N\alpha_c\, B^*\, S^* \\
&+ \left[\frac{(\mu_{_I} + \mu_v)}{\mu_v\mu_{_I}}\left(\alpha_v\,\frac{k_s}{\mu_s} + \mu_v\right) - \alpha_v\frac{k_s}{\mu_s}\right](\mu_{_I} + \sigma)\alpha_{_B} V^* \\
&+ \left[\frac{1}{\mu_{_B}}Q - 1\right]\left(\alpha_v\,\frac{k_s}{\mu_s} + \mu_v\right)(\mu_{_I} + \sigma)\frac{\alpha_{_B}}{\alpha_c}\,\alpha_c V^*,
\end{aligned}$$

the death rates $\mu_{_I}$ and $\mu_{_B}$ are always less than or equal to one, it means that $\dfrac{1}{\mu_{_I}} \geqslant 1$ and $\dfrac{1}{\mu_{_B}} \geqslant 1$, then $S_1 > 0$.

2.A.3

We are going to prove that for $Q > R_0 > 1$, we have $\dfrac{S_3 S_0}{S_1} < \dfrac{S_2}{2}$ and $\dfrac{S_1}{S_3} < \dfrac{S_2}{2}$. To prove that $\dfrac{S_3 S_0}{S_1} < \dfrac{S_2}{2}$, we have to prove $2S_0S_3 - S_1S_2 < 0$. First we start writing $S_0 = S_{01} + S_{02}$ and $S_1 = S_{11} + S_{12}$, where

$$
\begin{aligned}
S_{01} &= \mu_{_B}\frac{Q-R_0}{Q-1}\mu_v\mu_{_I}\alpha_c\,\rho\,B^*\,V^*\\
S_{02} &= -\alpha_{_B}V^*[(\alpha_v\,S^*+\mu_v)\mu_s(\mu_{_I}+\sigma)+\alpha_v\mu_{_I}\alpha_c\,\rho\,B^*\,V^*S^*]\\
S_{11} &= \mu_{_B}\mu_s\frac{Q-R_0}{Q-1}\left[\mu_{_I}+\sigma+\alpha_v\,S^*+\mu_v\right]+\mu_{_B}\mu_sN\alpha_c\,B^*\,S^*\\
S_{12} &= \left[k_{_B}(\mu_{_I}+\mu_v)\rho\,\alpha_c-\alpha_{_B}\alpha_v\rho\alpha_c\,B^*\,V^*\,S^*\right]\,V^*\\
&\quad+\left\{\mu_v\mu_{_I}\rho\,B^*-\left[\gamma\rho-N(\mu_{_I}+\sigma)\right]\alpha_{_B}B^*\,S^*\right\}\,\alpha_cV^*.
\end{aligned}
$$

Note that, S_{11} and S_{12} are positive as shown in 2.A.2, and $S_{02}S_3<0$, then $2S_0S_3-S_1S_2=2S_{01}S_3-S_{11}S_2+2S_{02}S_3-S_{12}S_2$, is equal to

$$
\begin{aligned}
2S_0S_3-S_1S_2 &= \left[\mu_{_B}\frac{Q-R_0}{Q-1}\right]^2\left[2\mu_v\mu_{_I}\alpha_c\,\rho\,B^*\,V^*-\mu_s(\mu_{_I}+\sigma+\alpha_v\,S^*+\mu_v)(\alpha_c\,\rho\,B^*\,V^*+\mu_s+A)\right]\\
&\quad+\mu_{_B}\frac{Q-R_0}{Q-1}\Big\{2\mu_v\mu_{_I}\alpha_c\,\rho\,B^*\,V^*(\alpha_c\,\rho\,V^*+\mu_s+A)\\
&\qquad-(\mu_{_I}+\sigma+\alpha_v\,S^*+\mu_v)[\alpha_{_B}\,N\alpha_c\,B^*\,V^*\,S^*+(\mu_{_I}+\mu_v)\alpha_c\,\rho\,B^*\,V^*+\mu_sA]\\
&\qquad-\mu_{_B}\mu_sN\alpha_c\,B^*\,S^*(\alpha_c\,\rho\,B^*\,V^*+\mu_s+A)\Big\}\\
&\quad-\mu_{_B}\mu_sN\alpha_c\,B^*\,S^*[\alpha_{_B}\,N\alpha_c\,B^*\,V^*\,S^*+(\mu_{_I}+\mu_v)\alpha_c\,\rho\,B^*\,V^*+\mu_sA]+2S_{02}S_3-S_{12}S_2,
\end{aligned}
$$

From $Q>R_0>1$, we have $\dfrac{Q-R_0}{Q-1}<1$ and $\left(\dfrac{Q-R_0}{Q-1}\right)^2<\dfrac{Q-R_0}{Q-1}<1$, then

$$
\begin{aligned}
2S_0S_3-S_1S_2 &\leqslant -\mu_{_B}^2\mu_s\left[\frac{Q-R_0}{Q-1}\right]^2(\mu_{_I}+\sigma+\alpha_v\,S^*+\mu_v)(\alpha_c\,\rho\,B^*\,V^*+\mu_s+A)\\
&\quad-\mu_{_B}\frac{Q-R_0}{Q-1}\Big\{2\alpha_{_B}V^*[(\alpha_v\,S^*+\mu_v)\mu_s(\mu_{_I}+\sigma)+\alpha_v\mu_{_I}\alpha_c\,\rho\,B^*\,V^*S^*]\\
&\qquad+(\sigma+\alpha_v\,S^*)[\alpha_{_B}\,N\alpha_c\,B^*\,V^*\,S^*+(\mu_{_I}+\mu_v)\alpha_c\,\rho\,B^*\,V^*+\mu_sA]\\
&\qquad+(\mu_{_I}+\mu_v)[\alpha_{_B}\,N\alpha_c\,B^*\,V^*\,S^*+\mu_sA]\\
&\qquad+\mu_{_B}\mu_sN\alpha_c\,B^*\,S^*(\alpha_c\,\rho\,B^*\,V^*+\mu_s+A)\Big\}\\
&\quad-\mu_{_B}\mu_sN\alpha_c\,B^*\,S^*[\alpha_{_B}\,N\alpha_c\,B^*\,V^*\,S^*+(\mu_{_I}+\mu_v)\alpha_c\,\rho\,B^*\,V^*+\mu_sA]-S_{12}S_2<0.
\end{aligned}
$$

Next, to prove that $\dfrac{S_1}{S_3}<\dfrac{S_2}{2}$, we can see that $\dfrac{S_1}{S_3}<\dfrac{S_2}{2}\iff 2S_1-S_2S_3<0$ then,

$$
\begin{aligned}
2S_1-S_2S_3 &= 2\mu_{_B}\mu_s\frac{Q-R_0}{Q-1}\left[\mu_{_I}+\sigma+\alpha_vS^*+\mu_v\right]+2\mu_{_B}\mu_sN\alpha_cB^*S^*\\
&\quad+2\left[k_{_B}(\mu_{_I}+\mu_v)\rho\,\alpha_c-\alpha_{_B}\alpha_v\rho\alpha_c\,B^*\,V^*\,S^*\right]\,V^*\\
&\quad+2\left\{\mu_v\mu_{_I}\rho\,B^*-\left[\gamma\rho-N(\mu_{_I}+\sigma)\right]\alpha_{_B}B^*\,S^*\right\}\,\alpha_cV^*\\
&\quad-\left[\mu_{_B}\frac{Q-R_0}{Q-1}\,(\alpha_c\,\rho\,B^*\,V^*+\mu_s+A)+\alpha_{_B}\,N\alpha_c\,B^*\,V^*\,S^*\right.\\
&\quad\left.+(\mu_{_I}+\mu_v)\alpha_c\,\rho\,B^*\,V^*+\mu_sA\right]\left[\mu_{_B}\frac{Q-R_0}{Q-1}+\alpha_c\,\rho\,V^*+\mu_s+A\right],
\end{aligned}
$$

After some calculations we have

$$
\begin{aligned}
2S_1 - S_2S_3 = &-2\alpha_{_B}\alpha_v\rho\alpha_c B^*V^*S^*V^* - (\mu_{_I}^2+\mu_v^2)\alpha_c\,\rho\,B^*V^* - 2[\gamma\rho - N(\mu_{_I}+\sigma)]\alpha_{_B}\,\alpha_c\,B^*V^*S^* \\
&- \mu_{_B}\frac{Q-R_0}{Q-1}\left[\mu_{_B}\frac{Q-R_0}{Q-1}\,(\alpha_c\,\rho\,B^*\,V^*+\mu_s+A) + \alpha_B\,N\alpha_c\,B^*\,V^*\,S^*\right] \\
&- (\alpha_c\,\rho\,V^*+A)\left[\mu_{_B}\frac{Q-R_0}{Q-1}\,(\mu_s+A) + \alpha_B\,N\alpha_c\,B^*\,V^*\,S^* + \mu_sA\right] \\
&- (\sigma + N\alpha_c\,B^*\,S^* + \alpha_v\,S^*)\left[\mu_{_B}\frac{Q-R_0}{Q-1} + \mu_{_I} + \mu_v\right]\alpha_c\,\rho\,B^*\,V^* \\
&- \mu_s\left[\mu_{_B}\frac{Q-R_0}{Q-1}\,(\alpha_c\,\rho\,B^*\,V^*+\mu_s) + \alpha_B\,N\alpha_c\,B^*\,V^*\,S^* + (\mu_{_I}+\mu_v)\alpha_c\,\rho\,B^*\,V^* + \mu_sA\right] < 0.
\end{aligned}
$$

3 Global dynamics of humoral and cellular immune responses to virus infection

Abstract. We studied the global stability of a model of virus dynamics with consideration of humoral and cellular immune responses . We used a Lyapunov direct method to get sufficient conditions for the global stability of virus-free and virus-presence equilibriums. First, we analyzed the model without an immune response and found that if the reproductive number of virus is less than or equal to one, the virus-free equilibrium is globally asymptotically stable. However, for the virus-presence equilibrium, global stability is obtained if the virus entrance rate in the target cells is less than one. We analyze the model with humoral and cellular immune responses and found similar results. The difference is that in the reproductive number of virus and in the virus entrance rate in the target cells there is the presence or action of humoral and cellular immune response, which means that the adaptive immune response will stop or control the rise of the infection.

3.1 Introduction

Global stability analysis in models of within-host viral infections has been addressed in particular cases. In [62], the authors proved global stability using an extension of the Poincaré–Bendixson theorem for the class of three-dimensional competitive systems. In [63], the authors used the direct Lyapunov method to demonstrate global stability. The same was done in a model with a Beddington-DeAngelis functional response [64]. On the other hand, there are models that consider the immune response [65], [66], [67] showing the global stability analysis. All of these models are just considered humoral or cellular immune response. In our model, besides considering virus entrance rate in the target cells, we also study the humoral and cellular immune responses. None of the cited models consider this approach. In this way, using a direct Lyapunov method, we show the global stability of a model of virus dynamics without immune response. Further, we gave conditions for global stability analysis of model considering the humoral and cellular immune responses. The organization of this paper is as follows. In section 3.2, we present the model formulation of the model with immune response and the positive invariant set. The global stability analysis of model without an immune response is presented in section 3.3. Finally, in section 3.4, we study the global stability analysis of model with humoral and cellular immune responses.

3.2 Model Formulation

Denote by S, I, V, B and T the target cells, infected cells, dengue virus, B cells and the cytotoxic T cells, respectively. The cells S are produced in bone marrow by a constant rate k_s. The target cells are chronically infected at rate β_I and die at a rate μ_s, the lysis of this infected cells occur by action of the cytotoxic CD8+ cells T at rate α_I and die by apoptosis at rate μ_I. We assume that diverse chemical signals will activate the B cells and the cytotoxic T cells, these cells in the beginning of this activation have not high affinity, which means that they are not efficient to clear the dengue infection, so by somatic hypermutations, they become step by step with better affinity(fit) to stop or kill the virus. Therefore we consider that after some time, this specialization is maintained at constant rate k_B and k_T, and they are going to proliferate in the presence of dengue virus at rate α_B and by the presence of infected cells at rate α_T. The virus amount is considered proportional to the released virus by the infected cells after its death $N_1(\mu_s + \mu_I)I$, where N_1 is the number of virions released by infected cell and more than one particle of virus will try to infected each cell denoted by N_2, here we assume that this value is less than half of number of virions released, i.e., $N_2 < \frac{N_1}{2}$, the action of antibodies against the virus is considered proportional to the amount of B cells at rate α_v and finally the virus decay at rate μ_v. The differential equations describing the interactions of dengue virus and the immune system are given by

$$\begin{aligned}
\frac{dS}{dt} &= k_s - \beta_I SV - \mu_s S \\
\frac{dI}{dt} &= \beta_I SV - \alpha_I IT - (\mu_s + \mu_I)I \\
\frac{dV}{dt} &= N_1(\mu_s + \mu_I)I - N_2\beta_I SV - \alpha_v BV - \mu_v V \\
\frac{dB}{dt} &= k_B + \alpha_B BV - \mu_B B \\
\frac{dT}{dt} &= k_T + \alpha_T TI - \mu_T T.
\end{aligned} \tag{3.1}$$

The positively invariant set for the model (3.1) is given by

$$\Omega = \left\{ P \in \mathbb{R}^5_+ : N_1 S + NI + V + \frac{\alpha_v}{\alpha_B} B + \frac{N\alpha_I}{\alpha_T} T \leqslant \frac{k}{\delta} \right\}, \tag{3.2}$$

where $P = (S, I, V, B, T)$, $N = (N_1 + N_2)$, $k = N_1 k_s + \frac{\alpha_v}{\alpha_B} k_B + \frac{N\alpha_I}{\alpha_T} k_T$ and $\delta = \min\left\{ \mu_s, \mu_v, \mu_B, \mu_T, \frac{N_2(\mu_s + \mu_I)}{N} \right\}$.

Lemma 3.1. *The set Ω is positively invariant with respect to system (3.1).*

Proof. let $P_0 = (S(0), I(0), V(0), B(0), T(0)) \in \Omega$ the initial condition of the system (3.1) and $\Theta(t)$ the function defined by

$$\Theta = N_1 S + NI + V + \frac{\alpha_v}{\alpha_{_B}} B + \frac{N\alpha_{_I}}{\alpha_{_T}} T,$$

taking the derivative of Θ with respect to t, we have:

$$\frac{d\Theta}{dt} = N_1 k_s - N_1 \mu_s S - N_2(\mu_s + \mu_{_I})I - \mu_v V + \frac{\alpha_v}{\alpha_{_B}}\left(k_{_B} - \mu_{_B} B\right) + \frac{N\alpha_{_I}}{\alpha_{_T}}\left(k_{_T} - \mu_{_T} T\right),$$

this can be written as

$$\frac{d\Theta}{dt} + N_1 \mu_s S + N_2(\mu_s + \mu_{_I})I + \mu_v V + \frac{\alpha_v}{\alpha_{_B}} \mu_{_B} B + \frac{N\alpha_{_I}}{\alpha_{_T}} \mu_{_T} T = k,$$

where $k = N_1 k_s + \dfrac{\alpha_v}{\alpha_{_B}} k_{_B} + \dfrac{N\alpha_{_I}}{\alpha_{_T}} k_{_T}$. If we choose $\delta = \min\left\{\mu_s, \mu_v, \mu_{_B}, \mu_{_T}, \dfrac{N_2(\mu_s + \mu_{_I})}{N}\right\}$, we conclude that,

$$\frac{d\Theta}{dt} + \delta\Theta \leqslant k,$$

then

$$\Theta \leqslant \frac{k}{\delta} + \left(\Theta(0) - \frac{k}{\delta}\right) e^{-\delta t}, \text{ for all } t \geqslant 0,$$

wich implies

$$\Theta \leqslant \frac{k}{\delta}.$$

□

In next sections we analyze the model without immune response and the model considering humoral and cellular immune responses 3.1.

3.3 Analysis of model without immune response

If there is not immune response, we have the next model

$$\begin{aligned} \frac{dS}{dt} &= k_s - \beta_{_I} SV - \mu_s S \\ \frac{dI}{dt} &= \beta_{_I} SV - (\mu_s + \mu_{_I})I \\ \frac{dV}{dt} &= N_1(\mu_s + \mu_{_I})I - N_2\beta_{_I} SV - \mu_v V. \end{aligned} \tag{3.3}$$

for this model we studied the global stability of equilibrium points.

3.3.1 Equilibrium Points for model (3.3)

The virus-free equilibrium is $P_{0w} = \left(\frac{k_s}{\mu_s}, 0, 0\right)$, and a virus-presence equilibrium $P_w = (S_w^*, I_w^*, V_w^*)$, where

$$\begin{aligned} S_w^* &= \frac{k_s}{\mu_s}\frac{1}{R_0} \\ I_w^* &= \frac{k_s}{(\mu_s + \mu_I)}\left(1 - \frac{1}{R_0}\right) \\ V_w^* &= \frac{\mu_s}{\beta_I}(R_0 - 1), \end{aligned}$$

and

$$R_{0w} = \frac{\beta_I \left[N_1 - N_2\right] k_s}{\mu_v \mu_s}. \tag{3.4}$$

3.3.2 Global stability of virus-free equilibrium P_{0w}

Theorem 3.1. *For $R_{0w} \leqslant 1$, the virus-free point P_{0w} is globally asymptotically stable.*

Proof. We use the direct Lyapunov method in this proof. Let L_1 the function defined as follows $L_1 : \Omega_1 \to \mathbb{R}$, where

$$\Omega_1 = \{(S, I, V) : S > 0, I \geqslant 0, V \geqslant 0\}$$

and

$$L_1 = (N_1 - N_2)\int_{\frac{k_s}{\mu_s}}^{S} \frac{\zeta - \frac{k_s}{\mu_s}}{\zeta} d\zeta + N_1 I + V.$$

It is easily to check that $L_1(P_{0w}) = 0$ and $L_1 > 0$ in $\Omega_1 - \{P_{0w}\}$. Besides the orbital derivative of L_1 along solutions of the system 3.3, it is given by

$$\begin{aligned} \dot{L}_1 = (N_1 - N_2)\left(1 - \frac{k_s}{\mu_s S}\right)\left(k_s - \beta_I SV - \mu_s S\right) + N_1\Big[\beta_I SV - (\mu_s + \mu_I)I\Big] \\ + \Big[N_1(\mu_s + \mu_I)I - N_2\beta_I SV - \mu_v V\Big], \end{aligned}$$

which is equivalent to

$$\dot{L}_1 = -(N_1 - N_2)\mu_s S\left(1 - \frac{k_s}{\mu_s S}\right)^2 + (R_0 - 1)\mu_v V.$$

From last equation $\dot{L}_1 < 0$, in $\Omega_1 - \{P_{0w}\}$ if and only if $R_{0w} \leqslant 1$. Then we conclude that the virus-free point P_{0w} is globally asymptotically stable.

□

3.3.3 Global stability of virus-presence equilibrium P_w

The existence of the equilibrium P_w is assured if $R_{0w} > 1$, and we are going to prove that P_w is globally asymptotically stable if the virus entrance in the target cells is less than or equal to one i.e, $\frac{N_2\beta_I k_s}{\mu_v\mu_s} \leqslant 1$. For this purpose, we define the function $L_2 : \mathbb{R}^3_+ \to \mathbb{R}$, where

$$L_2 = (N_1 - N_2)\int_{S^*_w}^{S} \frac{\zeta - S^*_w}{\zeta}d\zeta + N_1\int_{I^*_w}^{I} \frac{\zeta - I^*_w}{\zeta}d\zeta + \int_{V^*_w}^{V} \frac{\zeta - V^*_w}{\zeta}d\zeta. \tag{3.5}$$

This type of function was proposed by Goh in [68].

Theorem 3.2. *The virus-presence equilibrium P_w is globally asymptotically stable if*

$$\frac{N_2\beta_I k_s}{\mu_v\mu_s} \leqslant 1. \tag{3.6}$$

Remark 3.1. *The conditions $R_{0w} > 1$ and $\frac{N_2\beta_I k_s}{\mu_v\mu_s} \leqslant 1$, give us a threshold for the parameter β_I: $\beta^*_I < \beta_I \leqslant \beta^{**}_I$, where $\beta^*_I = \frac{\mu_v\mu_s}{[N_1 - N_2]\,k_s}$ and $\beta^{**}_I = \frac{\mu_v\mu_s}{N_2 k_s}$. The existence of values of β_I satisfying this inequality is guaranteed by the condition $N_2 < \frac{N_1}{2}$.*

Proof. First we start the proof that the orbital derivative of function L_2 is negative in $\mathbb{R}^3_+ - \{P_w\}$. Taking the derivative of function L_2 along trajectories of system (3.3), we have

$$\begin{aligned}\dot{L}_2 = (N_1 - N_2)\left(1 - \frac{S^*_w}{S}\right)\left(k_s - \beta_I SV - \mu_s S\right) + N_1\left(1 - \frac{I^*_w}{I}\right)\left[\beta_I SV - (\mu_s + \mu_I)I\right] \\ + \left(1 - \frac{V^*_w}{V}\right)\left[N_1(\mu_s + \mu_I)I - N_2\beta_I SV - \mu_v V\right].\end{aligned} \tag{3.7}$$

From the equilibrium equations, we have

$$k_s = \beta_I S^*_w V^*_w + \mu_s S^*_w, \quad \mu_v = (N_1 - N_2)\beta_I S^*_w, \quad (\mu_s + \mu_I) = \frac{\beta_I S^*_w V^*_w}{I^*_w}. \tag{3.8}$$

Substituing the last equations into (3.7), it turns into

$$\dot{L}_2 = \left[N_2\beta_I V^*_w - (N_1 - N_2)\mu_s\right] S^*_w\left(\frac{S^*_w}{S} + \frac{S}{S^*_w} - 2\right) - N_1\beta_I S^*_w V^*_w\left(\frac{S^*_w}{S} + \frac{S}{S^*_w}\frac{V}{V^*_w}\frac{I^*_w}{I} + \frac{V^*_w}{V}\frac{I}{I^*_w} - 3\right). \tag{3.9}$$

From the fact that arithmetic mean is greater than or equal to geometric mean, i.e.

$$\sum_{i=1}^{n}\frac{x_i}{n} \geqslant \sqrt[n]{\prod_{i=1}^{n} x_i}, \tag{3.10}$$

we have $\frac{S_w^*}{S} + \frac{S}{S_w^*} \geqslant 2$ and $\frac{S_w^*}{S} + \frac{S}{S_w^*}\frac{V}{V_w^*}\frac{I_w^*}{I} + \frac{V_w^*}{V}\frac{I}{I_w^*} \geqslant 3$.

Then $\dot{L}_2 < 0$, if $\left[N_2\beta_{_I}V_w^* - (N_1 - N_2)\mu_s\right]S_w^* \leqslant 0$, in fact, from equations (3.8), we can write

$$\left[N_2\beta_{_I}V_w^* - (N_1 - N_2)\mu_s\right]S_w^* = N_2(k_s - \mu_s S_w^*) - \frac{\mu_v\mu_s}{\beta_{_I}} \leqslant N_2k_s - \frac{\mu_v\mu_s}{\beta_{_I}},$$

and by the inequality (3.6), we have

$$\left[N_2\beta_{_I}V_w^* - (N_1 - N_2)\mu_s\right]S_w^* \leqslant \frac{\mu_v\mu_s}{\beta_{_I}}\left(\frac{N_2\beta_{_I}k_s}{\mu_v\mu_s} - 1\right) \leqslant 0.$$

Then $\dot{L}_2 < 0$ in $\mathbb{R}^3_+ - \{P_w\}$. Besides $L_2(P_w) = 0$ and $L_2 > 0$ in $\mathbb{R}^3_+ - \{P_w\}$. Therefore the point P_w is globally asymptotically stable.

□

3.4 Stability analysis of model with immune response

3.4.1 Equilibrium Points for model 3.1

Here we show the existence of virus-free equilibrium and virus-presence equilibrium. In fact setting the system (3.1) equal to zero and making some operations we can write:

$$S = \frac{k_s}{\beta_{_I}V + \mu_s} \tag{3.11}$$

$$I = \frac{\beta_{_I}SV}{\alpha_{_I}T + (\mu_s + \mu_{_I})} \tag{3.12}$$

$$V = \frac{N_1(\mu_{_I} + \mu_s)I}{(N_2\beta_{_I}S + \alpha_vB + \mu_v)} \tag{3.13}$$

$$B = \frac{k_{_B}}{\mu_{_B} - \alpha_{_B}V} \tag{3.14}$$

$$T = \frac{k_{_T}}{\mu_{_T} - \alpha_{_T}I}, \tag{3.15}$$

These equations have biological meaning if we have $I < \frac{\mu_{_T}}{\alpha_{_T}}$ and $V < \frac{\mu_{_B}}{\alpha_{_B}}$. Now putting the equations (3.11) and (3.12) into equation (3.13) we obtain

$$V = \frac{k_sN_1(\mu_{_I} + \mu_s)\beta_{_I}V}{\left[N_2\beta_{_I}k_s + (\alpha_vB + \mu_v)(\beta_{_I}V + \mu_s)\right]\left[(\alpha_{_I}T + (\mu_s + \mu_{_I})\right]},$$

from this equation we obtain

$$V = 0 \tag{3.16}$$

or

$$[N_2\beta_I k_s + (\alpha_v B + \mu_v)(\beta_I V + \mu_s)][(\alpha_I T + (\mu_s + \mu_I)] = k_s N_1(\mu_I + \mu_s)\beta_I. \tag{3.17}$$

$V = 0$ implies the existence of a virus-free point which can be call P_0, and has the coordinates

$$P_0 = \left(\frac{k_s}{\mu_s}, 0, 0, \frac{k_B}{\mu_B}, \frac{k_T}{\mu_T}\right).$$

For the existence of virus-presence equilibrium, we have to show that the equation (3.17) have one solution such that $V < \frac{\mu_B}{\alpha_B}$. In fact, let's rewrite the equation (3.17), and call q the polynomial:

$$\begin{aligned} q(V) = &[(N_2\beta_I k_s + \mu_v\mu_s + \mu_v\beta_I V)(\mu_B - \alpha_B V) + \alpha_v k_B(\beta_I V + \mu_s)]\,[\alpha_I T + \mu_s + \mu_I] \\ &- k_s N_1(\mu_s + \mu_I)\beta_I(\mu_B - \alpha_B V), \end{aligned} \tag{3.18}$$

it is easy to see that

$$\begin{aligned} q(0) = \left(1 - R_0\right)\left(\alpha_I\frac{k_T}{\mu_T} + \mu_s + \mu_I\right)\left(\alpha_v\frac{k_B}{\mu_B} + \mu_v\right)\mu_s\mu_B < 0, \text{if } R_0 > 1, \\ q\left(\frac{\mu_B}{\alpha_B}\right) > 0, \end{aligned}$$

where R_0 is defined in the equation (3.33) in the appendix 3.A.1. Then there is one solution V such that $0 < V < \frac{\mu_B}{\alpha_B}$. We can write the equations (3.11)-(3.15) in function of V, for this purpose, we substitute the equation (3.15) into the equation (3.12) to obtain

$$c_1 I^2 - c_2 I + c_3 = 0, \tag{3.19}$$

where $c_1 = \alpha_T(\mu_s + \mu_I)$, $c_2 = (k_T\alpha_I + \mu_T(\mu_s + \mu_I) + \alpha_T\beta_I SV)$, $c_3 = \mu_T\beta_I SV$. This equation has two solutions but just one satisfies our requirements, in fact

$$I = \frac{c_2 \pm \sqrt{c_2^2 - 4c_1c_3}}{2c_1}.$$

These two solutions have to be real, positive and less than $\frac{\mu_T}{\alpha_T}$. First, they are real because the term inside of root is always positive, in fact

$$\begin{aligned}\left[k_T\alpha_I + \mu_T(\mu_s+\mu_I) + \alpha_T\beta_I SV\right]^2 - 4\alpha_T(\mu_s+\mu_I)\mu_T\beta_I SV &= (k_T\alpha_I)^2 + 2k_T\alpha_I\mu_T(\mu_s+\mu_I)\\ &+ 2k_T\alpha_I\alpha_T\beta_I SV\\ &+ \left[\alpha_T\beta_I SV - \mu_T(\mu_s+\mu_I)\right]^2,\end{aligned}$$

Second, they are positive, because $c_2^2 > c_2^2 - 4c_1c_3$, for $c_1 > 0$, $c_3 > 0$. So they are real, and positive. To show that just one meet the condition $I < \frac{\mu_T}{\alpha_T}$, we see that this is true if

$$\frac{\left[k_T\alpha_I - \mu_T(\mu_s+\mu_I) + \alpha_T\beta_I SV\right] \pm \sqrt{c_2^2 - 4c_1c_3}}{c_1} < 0, \tag{3.20}$$

so the unique possibility for I is

$$I = \frac{c_2 - \sqrt{c_2^2 - 4c_1c_3}}{2c_1}.$$

Then there exists the virus-presence point $P^* = (S^*, I^*, V^*, T^*, B^*)$, for $R_0 > 1$, where:

$$S^* = \frac{k_s}{\beta_I V^* + \mu_s} \tag{3.21}$$

$$I^* = \frac{c_2 - \sqrt{c_2^2 - 4c_1c_3}}{2c_1} \tag{3.22}$$

$$B^* = \frac{k_B}{\mu_B - \alpha_B V^*} \tag{3.23}$$

$$T^* = \frac{k_T}{\mu_T - \alpha_T I^*}, \tag{3.24}$$

and the root of the polynomial (3.18) such that $0 < V^* < \frac{\mu_B}{\alpha_B}$ and $I^* < \frac{\mu_T}{\alpha_T}$.

3.4.2 Stability of virus-free equilibrium

Here we present the stability of virus-free point P_0

Theorem 3.3. *For $R_0 \leqslant 1$, the virus-free point P_0 is globally asymptotically stable.*

Proof. Let $\Omega_3 = \{(S, I, V, B, T) : S > 0, I \geqslant 0, V \geqslant 0, B > 0, T > 0\}$ and $L_3 : \Omega_3 \to \mathbb{R}$ be the function defined as follow:

$$L_3 = a_1\int_{\frac{k_s}{\mu_s}}^{S}\frac{\zeta - \frac{k_s}{\mu_s}}{\zeta}d\zeta + a_2 I + a_3 V + \frac{\alpha_I}{\alpha_T}a_2\int_{\frac{k_T}{\mu_T}}^{T}\frac{\zeta - \frac{k_T}{\mu_T}}{\zeta}d\zeta + \frac{\alpha_v}{\alpha_B}a_3\int_{\frac{k_B}{\mu_B}}^{B}\frac{\zeta - \frac{k_B}{\mu_B}}{\zeta}d\zeta, \tag{3.25}$$

with $a_1 = N_1(\mu_s+\mu_I)-N_2\left(\alpha_I\dfrac{k_T}{\mu_T}+\mu_s+\mu_I\right)$, $a_2 = N_1(\mu_s+\mu_I)$, $a_3 = \left(\alpha_I\dfrac{k_T}{\mu_T}+\mu_s+\mu_I\right)$. It is clear that $L_3(P_0) = 0$ and $L_3 > 0$ in $\Omega_3 - P_0$. Now we prove that $\dot{L}_3 < 0$, in fact

$$\begin{aligned}\dot{L}_3 = {} & a_1\left(1-\frac{\frac{k_s}{\mu_s}}{S}\right)\left(k_s-\beta_I SV-\mu_s S\right)+a_2\Big[\beta_I SV-\alpha_I IT-(\mu_s+\mu_I)I\Big]\\ & + a_3\Big[N_1(\mu_s+\mu_I)I-N_2\beta_I SV-\alpha_v BV-\mu_v V\Big]\\ & + \frac{\alpha_I}{\alpha_T}a_2\left(1-\frac{\frac{k_T}{\mu_T}}{T}\right)\left(k_T+\alpha_T TI-\mu_T T\right)+\frac{\alpha_v}{\alpha_B}a_3\left(1-\frac{\frac{k_B}{\mu_B}}{B}\right)\left(k_B+\alpha_B BV-\mu_B B\right).\end{aligned}$$

After some calculations, we have that

$$\begin{aligned}\dot{L}_3 = {} & -a_1\mu_s S\left(1-\frac{\frac{k_s}{\mu_s}}{S}\right)^2+a_3\left(\alpha_v\frac{k_B}{\mu_B}+\mu_v\right)V\Big[R_0-1\Big]-\frac{\alpha_I}{\alpha_T}a_2\mu_T T\left(1-\frac{\frac{k_T}{\mu_T}}{T}\right)^2\\ & -\frac{\alpha_v}{\alpha_B}a_3\mu_B B\left(1-\frac{\frac{k_B}{\mu_B}}{B}\right)^2.\end{aligned}$$

Then $\dot{L}_3$ is negative in $\Omega_3 - P_0$ if $R_0 \leqslant 1$. Therefore the point P_0 is globally asymptotically stable for $R_0 \leqslant 1$. □

3.4.3 Global stability of virus-presence equilibrium

In this section, we proved the global stability of virus-presence equilibrium P^* using a direct Lyapunov method. Let $L_4 : \mathbb{R}^5_+ \to \mathbb{R}$ defined as follows

$$\begin{aligned}L_4 = {} & a\int_{S^*}^{S}\frac{\zeta-S^*}{\zeta}d\zeta+b\int_{I^*}^{I}\frac{\zeta-I^*}{\zeta}d\zeta+\int_{V^*}^{V}\frac{\zeta-V^*}{\zeta}d\zeta\\ & +\frac{\alpha_I}{\alpha_T}b\int_{T^*}^{T}\frac{\zeta-T^*}{\zeta}d\zeta+\frac{\alpha_v}{\alpha_B}\int_{B^*}^{B}\frac{\zeta-B^*}{\zeta}d\zeta.\end{aligned}\tag{3.26}$$

where $a = \left(\dfrac{N_1(\mu_s+\mu_I)I^*}{\beta_I S^*V^*}-N_2\right)$, $b = \dfrac{N_1(\mu_s+\mu_I)I^*}{\beta_I S^*V^*}$. This type of function was proposed by Goh in [68].

Theorem 3.4. *The virus-presence equilibrium P^* is globally asymptotically stable if*

$$\frac{N_2\beta_I k_s}{\left(\alpha_v \frac{k_B}{\mu_B} + \mu_v\right)\mu_s} \leqslant 1. \tag{3.27}$$

Remark 3.2. *The conditions $R_0 > 1$ and $\frac{N_2\beta_I k_s}{\left(\alpha_v \frac{k_B}{\mu_B} + \mu_v\right)\mu_s} \leqslant 1$, give us a threshold for the parameter β_I: $\beta_I^* < \beta_I \leqslant \beta_I^{**}$, where $\beta_I^* = \frac{\left(\alpha_v \frac{k_B}{\mu_B} + \mu_v\right)\mu_s}{\left[\frac{(\mu_s+\mu_I)}{\left(\alpha_I \frac{k_T}{\mu_T}+\mu_s+\mu_I\right)}N_1 - N_2\right]k_s}$ and $\beta_I^{**} = \frac{\left(\alpha_v \frac{k_B}{\mu_B} + \mu_v\right)\mu_s}{N_2 k_s}$. The existence of β_I satisfying this inequality is guaranteed by the condition $N_2 < \frac{N_1}{2}$.*

Proof. we start showing that the derivative of function L_4 defined in (3.26) is negative along trajectories of system (3.1), if (3.27) holds. In fact, taking the derivative of function L_4 along trajectories of system (3.1), we have

$$\begin{aligned}\dot{L}_4 = {} & a\left(1 - \frac{S^*}{S}\right)\left(k_s - \beta_I SV - \mu_s S\right) + b\left(1 - \frac{I^*}{I}\right)\left[\beta_I SV - \alpha_I IT - (\mu_s + \mu_I)I\right] \\ & + \left(1 - \frac{V^*}{V}\right)\left[N_1(\mu_s + \mu_I)I - N_2\beta_I SV - \alpha_v BV - \mu_v V\right] \\ & + \frac{\alpha_I}{\alpha_T} b\left(1 - \frac{T^*}{T}\right)\left(k_T + \alpha_T TI - \mu_T T\right) + \frac{\alpha_v}{\alpha_B}\left(1 - \frac{B^*}{B}\right)\left(k_B + \alpha_B BV - \mu_B B\right).\end{aligned} \tag{3.28}$$

From the equilibrium equations (3.11)-(3.15), we have

$$\begin{aligned} k_s &= \beta_I S^*V^* + \mu_s S^*, \qquad \mu_v = \frac{(N_1 - N_2)\beta_I S^*V^* - N_1\alpha_I T^*I^* - \alpha_v B^*V^*}{V^*}, \\ (\mu_s + \mu_I) &= \frac{\beta_I S^*V^* - \alpha_I T^*I^*}{I^*}, \quad k_T = \mu_T T^* - \alpha_T T^*I^*, \qquad k_B = \mu_B B^* - \alpha_B B^*V^*. \end{aligned} \tag{3.29}$$

Substituing the last equations into (3.28), it turns into,

$$\begin{aligned}\dot{L}_4 = &-a\mu_s S^*\left(\frac{S^*}{S}+\frac{S}{S^*}-2\right)+a\beta_I S^*V^*\left(2-\frac{S^*}{S}-\frac{I}{I^*}-\frac{S}{S^*}\frac{V}{V^*}\frac{I^*}{I}+\frac{V}{V^*}\right)\\&+N_2\beta_I S^*V^*\left(-\frac{I}{I^*}-\frac{S}{S^*}\frac{V}{V^*}\frac{I^*}{I}+\frac{V}{V^*}+\frac{S}{S^*}\right)\\&+N_1\beta_I S^*V^*\left(\frac{I}{I^*}-\frac{V}{V^*}-\frac{I}{I^*}\frac{V^*}{V}+1\right)\\&+N_1\alpha_I T^*I^*\left(\frac{V}{V^*}-\frac{I}{I^*}-1+\frac{V^*}{V}\frac{I}{I^*}\right)\\&+b\alpha_I T^*\left(I^*-\frac{\mu_T}{\alpha_T}\right)\left(\frac{T}{T^*}+\frac{T^*}{T}-2\right)\\&+\alpha_v B^*\left(V^*-\frac{\mu_B}{\alpha_B}\right)\left(\frac{B}{B^*}+\frac{B^*}{B}-2\right).\end{aligned}\tag{3.30}$$

From equation (3.12) we have

$$a=\left(N_1\frac{(\mu_s+\mu_I)I^*}{\beta_I S^*V^*}-N_2\right)=N_1-N_2-N_1\frac{\alpha_I T^*I^*}{\beta_I S^*V^*},\tag{3.31}$$

taking the equation (3.31) into (3.30) implies

$$\begin{aligned}\dot{L}_4 = &\left(N_2\beta_I V^*-a\mu_s\right)S^*\left(\frac{S^*}{S}+\frac{S}{S^*}-2\right)\\&-(\mu_s+\mu_i)I^*N_1\left(\frac{S^*}{S}+\frac{S}{S^*}\frac{V}{V^*}\frac{I^*}{I}+\frac{V^*}{V}\frac{I}{I^*}-3\right)\\&+b\alpha_I T^*\left(I^*-\frac{\mu_T}{\alpha_T}\right)\left(\frac{T}{T^*}+\frac{T^*}{T}-2\right)\\&+\alpha_v B^*\left(V^*-\frac{\mu_B}{\alpha_B}\right)\left(\frac{B}{B^*}+\frac{B^*}{B}-2\right).\end{aligned}\tag{3.32}$$

Now note that, from the equations (3.29), the first term of equation (3.32) can be written as

$$N_2\beta_I S^*V^*-a\mu_s S^*=N_2(k_s-\mu_s S^*)-\frac{\alpha_v B^*+\mu_v}{\beta_I}\mu_s\leqslant N_2k_s-\frac{\alpha_v B^*+\mu_v}{\beta_I}\mu_s,$$

and in view of $B^*\geqslant\dfrac{k_B}{\mu_B}$ and the inequality (3.27), we have

$$N_2\beta_I S^*V^*-a\mu_s S^*\leqslant N_2k_s-\frac{\alpha_v\frac{k_B}{\mu_B}+\mu_v}{\beta_i}\mu_s=\frac{\alpha_v\frac{k_B}{\mu_B}+\mu_v}{\beta_i}\mu_s\left[\frac{N_2\beta_I k_s}{\left(\alpha_v\frac{k_B}{\mu_B}+\mu_v\right)\mu_s}-1\right]\leqslant 0.$$

Due to the fact $N_2\beta_{_I}S^*V^* - a\mu_s S^* \leqslant 0$, $V^* < \dfrac{\mu_B}{\alpha_{_B}}$, $I^* < \dfrac{\mu_{_T}}{\alpha_{_T}}$ and remembering that arithmetic mean is greater than or equal geometric mean $\left(\sum_{i=1}^{n}\dfrac{x_i}{n} \geqslant \sqrt[n]{\prod_{i=1}^{n} x_i}\right)$, we have $\dot{L}_4 < 0$ in $\mathbb{R}^5_+ - \{P^*\}$. Additionally, we have that $\dot{L}_4(P^*) = 0$ and $L_4 > 0$ in $\mathbb{R}^5_+ - \{P^*\}$. Then P^* is globally asymptotically stable in $\mathbb{R}^5_+$.

□

Remark 3.3. *If in the model we assume that the number of virus entry in the target cells $N_2\beta_{_I}SV$ is included into the virus loss $\mu_v V$, i.e., assume $N_2 = 0$. Then we avoid the restriction (3.27) and the virus-presence equilibrium P^* is globally asymptotically stable if $R_0 > 1$, with the same Lyapunov function (3.26) and the same proof.*

3.5 Discussion

In this study, we determined the global stability of a mathematical model of a viral dynamic when there is no immune response and when there are humoral and cellular immune responses. Using the direct Lyapunov method, we showed that the virus-free point of the model with or without immune response is globally asymptotically stable, if the reproductive number of virus is less than or equal to one–i.e. whatever the initial viral load, the virus will be cleared. In the first case, we can argue that the innate immune response is acting to stop the viral load from increasing. Of course, in the second case, we can argue that the adaptive immunity is an effective response to control the virus and infected cells. Further, we determined the global stability of the virus-presence equilibrium whenever the viral entrance rate in the healthy cells is less than or equal to one. This condition is almost the same for the two models. The difference is that the immune response controls the rise of this viral entrance rate. In this situation not matter how much is the initial viral load the result will be always a virus persistence.

3.A Appendix

3.A.1

To compute the basic reproductive number of the model (3.1) with immunity, we use [69], [70] to form the next generation matrix, then

$$F = \begin{bmatrix} 0 & \beta_{_I}\dfrac{k_s}{\mu_s} \\ N_1(\mu_{_I}+\mu_s) & -N_2\beta_{_I}\dfrac{k_s}{\mu_s} \end{bmatrix}, \quad V = \begin{bmatrix} \alpha_{_I}\dfrac{k_{_T}}{\mu_{_T}}+(\mu_{_I}+\mu_s) & 0 \\ 0 & \alpha_v\dfrac{k_{_B}}{\mu_{_B}}+\mu_v \end{bmatrix},$$

$$FV^{-1} = \begin{bmatrix} 0 & \beta_{_I}\dfrac{k_s}{(\alpha_v\frac{k_{_B}}{\mu_{_B}}+\mu_v)\mu_s} \\ N_1\dfrac{(\mu_{_I}+\mu_s)}{\alpha_{_I}\frac{k_{_T}}{\mu_{_T}}+(\mu_{_I}+\mu_s)} & -N_2\beta_{_I}\dfrac{k_s}{(\alpha_v\frac{k_{_B}}{\mu_{_B}}+\mu_v)\mu_s} \end{bmatrix}.$$

From last matrix we have that the polynomial characteristic is

$$\lambda^2 - \left(-N_2\beta_{_I}\frac{k_s}{(\alpha_v\frac{k_{_B}}{\mu_{_B}}+\mu_v)\mu_s}\right)\lambda - N_1\frac{(\mu_{_I}+\mu_s)}{\alpha_{_I}\frac{k_{_T}}{\mu_{_T}}+(\mu_{_I}+\mu_s)}\beta_{_I}\frac{k_s}{(\alpha_v\frac{k_{_B}}{\mu_{_B}}+\mu_v)\mu_s}.$$

We can not use [70], but we can use an extended conjecture which is in the appendix 3.A.2. Then we have

$$R_0 = \frac{\beta_{_I}\left[\frac{(\mu_s+\mu_{_I})}{\left(\alpha_{_I}\frac{k_{_T}}{\mu_{_T}}+\mu_s+\mu_{_I}\right)}N_1 - N_2\right]k_s}{\left(\alpha_v\frac{k_{_B}}{\mu_{_B}}+\mu_v\right)\mu_s}. \tag{3.33}$$

Similarity, if the humoral and cellular immune response is not present, the basic reproductive number of the model 3.3 is

$$R_{0w} = \frac{\beta_{_I}\left[N_1-N_2\right]k_s}{\mu_v\mu_s}. \tag{3.34}$$

The unique difference with the before number R_0, is that the immune activity is not present in the control of free viral particles and infected cells.

3.A.2

Conjeture 3.1. *Let the characteristic polynomial of order n corresponding to the next generation matrix FV^{-1} be written as*

$$\Lambda(\lambda) = \lambda^n - a_{n-1}\lambda^{n-1} - \cdots - a_1\lambda - a_0,$$

with $a_i \geqslant 0$, $i = 0,\ldots,k$ and $a_j \leqslant 0$, $j = k+1,\ldots,n-1$. Let R_0 denote the spectral radius of the next generation matrix, that is, $R_0 = \rho(FV^{-1})$ and

$$R_0^* = a_0 + \cdots + a_{n-1}.$$

Then R_0^* is a threshold value for the disease to take off or die out in the sense that:

1. $R_0^* < 1$ *if and only if* $R_0 < 1$
2. $R_0^* = 1$ *if and only if* $R_0 = 1$
3. $R_0^* > 1$ *if and only if* $R_0 > 1$

Proof. Is the same proof of conjecture 1 in [70] (pg 103) □

4 Conclusions and future work

This chapter presents the conclusions of the thesis and outlines directions for future research.

In the chapter 1, we proposed a mathematical model describing the adaptive immune response to dengue virus in primary infection. In this model, the infected cells and viruses send chemical signals to facilitate the differentiation of helper cells into helper cells $Th1$ and $Th2$, which are crucial to the activation and balance of cellular and humoral immune responses. The viral load and the infected cells are greatly reduced when an intense cellular immune response occurs. On the other hand, if there is an inadequate proliferation of cytotoxic cells, it is impossible to stop the viral increase with a cellular immune response alone. This situation can be controlled by a powerful proliferation of activated B cells or a reduction in the activation of Th1 cells, which perform a balanced humoral and cellular immune response to stop the infection. Based on clinical data, the fitting process suggests a predominant cellular immune response by the strongest proliferation of cytotoxic activated cells, which assures the control of the dengue viral load. The dynamic of humoral and cellular immune response represented in the activated B and T cells indicates an initial reaction from antibodies in early states of infection but a strong cytotoxic activity in the clearance period. We conclude that this situation is a strategy of dengue virus uses to spread throughout the body because the inhibition of cytotoxic activity allows the antibodies without good fit to bind to the pathogen and maybe facilitate opsonization.

In the chapter 2, we discussed the secondary infection by a heterogeneous dengue virus and the antibody dependent enhancement by formulating a mathematical model. This model tries to explain when the antibody dependent enhancement could take place or what situations it can happen in. We found a threshold for the proliferation parameter of B memory cells at which it is possible to see the intervention of antibodies in clearing or increasing the viral load. With a few inoculations of dengue virus, it is possible to develop a strong disease. We believe that this happens because a huge proliferation of these non-neutralizing antibodies increases the possibility that an antibody-antigen complex will form. This would make opsonization by immune cells more likely. Therefore, the control of this threshold is fundamental to the evolution of the disease.

In the chapter 3, we proposed a simplification of the model in chapter 1 . We used the direct Lyapunov method to show the stability analysis and established the global stability of virus-free equilibrium provided that the net number of virus is less than or equal to one. This means that the humoral and cellular immune responses are acting in complete balance to stop the disease. The global stability of disease equilibrium is established if the

viral entrance rate in the healthy cells is less than or equal to one. However, in a situation where virus-presence always mathematically exists, it is possible to increase the humoral and cellular immune response to reduce the viral load and number of infected cells

Future work

About direct Lyapunov method. In the proof of Lemma 1.1, we defined a function (1.3), if we use this function to construct the function $L_{P_1} : \mathcal{A} \to \mathbb{R}$ in the form

$$L_{P_1} = \Phi - \Phi^* - \Phi^* \ln \frac{\Phi}{\Phi^*}$$

or

$$L_{P_1} = \frac{1}{2}(\Phi - \Phi^*)^2.$$

Then we can prove that in the next two sets

a)

$$\mathcal{A}_1 = \big\{P \in \mathcal{A} : S \leqslant S^*, I \leqslant I^*, V \leqslant V^*, T_0 \leqslant T_0^*, T_1 \leqslant T_1^*, T_2 \leqslant T_2^*, \\ B_r \leqslant B_r^*, B_a \leqslant B_a^*, T_{cr} \leqslant T_{cr}^*, T_{ca} \leqslant T_{ca}^*\big\}.$$

b)

$$\mathcal{A}_2 = \big\{P \in \mathcal{A} : S \geqslant S^*, I \geqslant I^*, V \geqslant V^*, T_0 \geqslant T_0^*, T_1 \geqslant T_1^*, T_2 \geqslant T_2^*, \\ B_r \geqslant B_r^*, B_a \geqslant B_a^*, T_{cr} \geqslant T_{cr}^*, T_{ca} \geqslant T_{ca}^*\big\}.$$

we have $L_{P_1}(P_1) = 0$, $L_{P_1} > 0$ in $\mathcal{A}_i - \{P_1\}$, $i = 1, 2$ and $\dot{L}_{P_1} < 0$, where P_1 is the disease equilibrium of model (1.1). From last deduction and from all the attempts to prove the global stability or local stability for disease equilibrium of model (1.1), we prove the next theorem

Theorem 4.1. *Let f be a function Lipschitz and*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n. \tag{4.1}$$

Suppose that there exists a point $x^* \neq 0$, such that $f(x^*) = 0$ and there exists $a_i > 0$ such that $\Phi = \sum_{i=1}^{n} a_i x_i$ and $\dot{\Phi} = \sum_{i=1}^{n} a_i \dot{x}_i = \alpha - \sum_{i=1}^{n} b_i x_i$, where $b_i \geqslant 0$ and at least one is different of zero. Define the function L by

$$L_1 = \frac{1}{2}(\Phi - \Phi^*)^2 \tag{4.2}$$

or

$$L_2 = \Phi - \Phi^* - \Phi^* \ln \frac{\Phi}{\Phi^*}. \tag{4.3}$$

then the orbital derivative of function L along the trajectories of system (4.1) is negative in the sets $\Omega_1 = \{x_i \in \mathbb{R} : 0 < x_i \leqslant x_i^*\}$ or $\Omega_2 = \{x_i \in \mathbb{R} : x_i \geqslant x_i^*\}$

Proof. Taking the derivative of (4.2) along the trajectories of the system (4.1) we have

$$\dot{L}_1 = \dot{\Phi}\ (\Phi - \Phi^*)\,. \tag{4.4}$$

We perform the proof just for (4.2), because $\dot{L}_2 = \dfrac{1}{\Phi}\dot{L}_1$. Note that $\dot{\Phi} = \alpha - \sum_{i=1}^{n} b_i x_i$ and $\alpha = \sum_{i=1}^{n} b_i x_i^*$, then $\dot{\Phi} = -\sum_{i=1}^{n} b_i(x_i - x_i^*)$. Besides

$$(\Phi - \Phi^*) = \sum_{i=1}^{n} a_i(x_i - x_i^*).$$

Therefore the equation (4.4) can be express in the next way

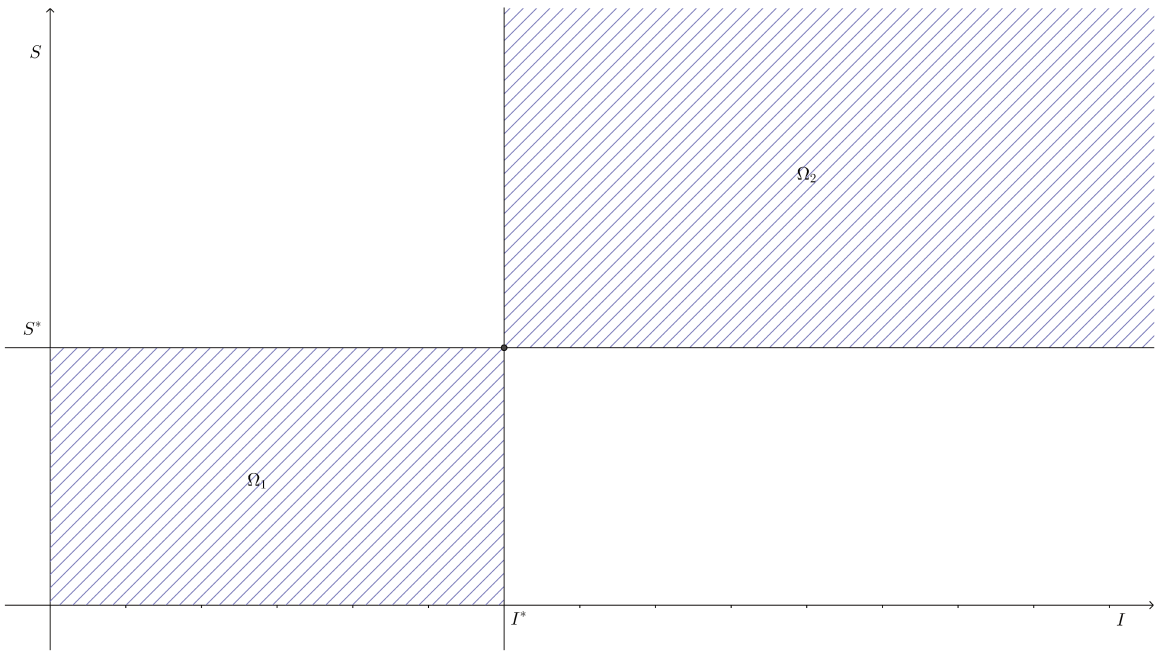
$$\dot{L}_1 = -\sum_{i=1}^{n} a_i b_i (x_i - x_i^*)^2 - \sum_{j=1}^{n}\left[a_j(x_j - x_j^*)\sum_{i=1, i\neq j}^{n} b_i(x_i - x_i^*)\right].$$

The first finite series in the last equation is always negative, meanwhile the last finite series is negative for $0 < x_i \leqslant x_i^*$ or $x_i \geqslant x_i^*$, $i = 1, \ldots, n$. Then $\dot{L}_1 < 0$ in the sets Ω_1 or Ω_2. □

For example consider the general SI system

$$\dot{S} = k_s - g(S, I) - \mu_s S$$
$$\dot{I} = g(S, I) - \mu_I I.$$

If a nontrivial equilibrium point (S^*, I^*) exists, then the function Φ in theorem is $\Phi = S + I$, because $\dot{\Phi} = k_s - \mu_s S - \mu_I I$. The most interesting thing is that to get $\dot{L} < 0$ in the regions Ω_1 and Ω_2, there is not restriction for the function g .



Another example can be

$$\begin{aligned}\dot{S} &= k_s - g(S,I) - \mu_s S \\ \dot{I} &= g(S,I) - \mu_I p(I) \\ \dot{V} &= \alpha p(I) - \mu_v V\end{aligned}$$

The function Φ is given by $\Phi = S + I + \frac{\mu_I}{\alpha} V$. The theorem suggest a geometric characteristic of this kind of models which could be explored to get a global stability.

Genetic algorithm. Develop a possible algorithm similar or better than genetic algorithm (ga) based in the immune system. The ga uses the idea of mutation and crossover for improve the optimization process. My idea is to use the mechanism of adaptive immune system to develop an algorithm. If we see the adaptive immune system as a machine making some task. This machine is trying to learn which is the best way to develop it, by using the adaptive immune response. The challenge is how insert the differentiation process of helper cells as well as the proliferation and affinity of B and T cytotoxic cells in the algorithm.

Control theory. It is interesting to see that in all the immune response, the adaptive process is the best instrument to stop any disease, although this tool is not always effective. In this way we could use the control theory to look for the best or more efficient cellular and humoral immune response against a viral infection. Besides in the model of antibody dependent enhancement, we can insert a control to prevent that the non neutralizing antibodies for the E and prM antigens bind the virus and maybe stop or avoid this phenomenon.

Stochastic model. In the implementation of adaptive immune response is evident the participation of Th helper cells in the balance a humoral and cellular immune responses. If we consider the chemical signals for differentiation of Th helper cells into Th1 and Th2 as a probabilistic process, maybe we could get a more realistic adaptive immune response.

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Glossary

adaptive immune response : Part of the immune system that uses antigen receptors and adapts or "learns" to recognize specific antigens, and retains a memory of those antigens to speed up future responses.

affinity : A measure of the degree of interaction between two molecules, such as an antigen and antibody or a hormone and its receptor.

antibody : Protein produced by the immune system in response to the presence in the body of antigens: foreign proteins or polysaccharides such as bacteria, bacterial toxins, viruses, or other cells or proteins. Such antigens are capable of inflicting damage by chemically combining with natural substances in the body and disrupting the body's processes. The body contains hundreds of thousands of different white blood cells called B lymphocytes, each capable of producing one type of antibody and each bearing sites on its membrane that will bind with a specific antigen. When such a binding occurs, it triggers the B lymphocyte to reproduce itself, forming a clone that manufactures vast amounts of its antibody.

antigen : Any substance that causes the production of antibodies; now, more generally, anything that is recognized by antibodies or by the antigen receptors of lymphocytes.

antigen-antibody complex : A complex of antibody with its specific antigen, which forms when antigen and antibody come together. It is in this form that foreign antigens are most effectively scavenged by phagocytic cells and thus removed from the body.

antigen-presenting cells : Cells that process protein antigens into peptides and present them on their surface in a form that can be recognized by lymphocytes.

apoptosis : Death of cells triggered by extracellular signals or genetically programmed events. Also known as programmed cell death.

cytokine : Signal molecules secreted by various cell types, which regulate the intensity and duration of immune response and mediate cell-to-cell communication.

cytotoxic cells : T cells that are activated to kill target cells.

Fc receptor-bearing cells : An Fc receptor is a protein found on the surface of certain cells, that contribute to the protective functions of the immune system. A Fc receptor-bearing cells are cells with this protein.

immunological memory : The capacity of the immune system to respond more rapidly and vigorously to a pathogen that has been encountered previously.

innate immune system : That part of the immune system that that is relatively nonspecific and immediate: it does not change or adapt to specific pathogens.

lymph node : Small organs, distributed throughout the body, in which an adaptive immune response can develop.

lysis : The dissolution or destruction of cells, including microorganisms; disruption of tissue structure under the influence of enzymes and other lytic agents.

macrophages : White blood cells (activated monocytes) that protect the body against infection and foreign substances by breaking them down into antigenic peptides recognized by circulating T cells.

opsonization : The process by which bacteria and other cells are altered in such a manner that they are more readily and more efficiently engulfed by phagocytes .

phagocytosis : The process of ingestion and digestion by cells of solid substances, for example, other cells, bacteria, bits of necrotic tissue, foreign particles .

serotype : Microorganisms differing in the type of surface antigens.

T helper cell : A type of lymphocyte that matures in the thymus and "helps" other lymphocytes by providing a second signal for costimulation.

Th1 cells : T helper cells that secrete a characteristic set of cytokines (such as interleukin-2 and interferon gamma) and tend to encourage a cellular response.

Th2 cells : T helper cells that secrete a characteristic set of cytokines (such as interleukin-4 and interleukin-10) and tend to encourage a humoral response.

viremia : The presence of a virus in the bloodstream.