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A model for dengue disease with variable human population

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Abstract. A model for the transmission of dengue fever with variable human population size is analyzed. We find three threshold parameters which govern the existence of the endemic proportion equilibrium, the increase of the human population size, and the behaviour of the total number of human infectives. We prove the global asymptotic stability of the equilibrium points using the theory of competitive systems, compound matrices, and the center manifold theorem.

Key words: Dengue – Competitive systems – Global stability – Threshold – Variable population

1 Introduction

In the last 20 years, dengue fever and the severe form of the disease (described for the first time in the 1950s), dengue haemorrhagic fever (DHF) have become the most important arthropod-borne viral disease of humans [18]. At present, the annual estimations of dengue fever range from 50 millions [20] to 100 millions [18] of cases, with approximately 10 000 infant deaths due to the haemorrhagic form of dengue [20].

Dengue fever has been recognized clinically for over 200 years. During the 18th and 19th centuries the spread of the disease was slow, generally by ships carrying breeding populations of *A. aegypti* and susceptible human hosts This pattern changed dramatically during and after World War II. Dengue viruses were spread by viremic military personnel in the Pacific areas, and the vector was spread by vehicles, water storage containers, and tires carrying the larvae of

A. aegypti. The dissemination of the disease was enhanced after the war by rapid population growth and urbanization. Asian cities were characterized by poor sanitation, the necesity of domestic water storage and crowding, creating conditions for the breeding of *A. aegypti* [18]. With the emergence of dengue haemorraghic fever in 1954 the impact of the disease became more pronounced. In the 1970s and 1980s, the incidence of DHF rose to over 250 000 cases per year, and DHF is now the third of fourth leading cause of hospitalization of children in some areas of the Asian continent [18].

Postwar changes in dengue epidemiology in the Americas occured somewhat later than in Asia. The first important outbreak of dengue fever with severe cases occurred in Cuba in 1981 with 116 000 hospitalized patients, 34 000 documented cases of DHF and 158 deaths. During the decade that followed the Cuban epidemic, 14 countries in the Americas have reported confirmed cases of DHF [17, 18].

It is considered that human population growth and the dramatic redistribution of the human population in the urban centers of developing countries have contributed to the introduction and enhancement of dengue fever [1, 12, 17, 18, 24]. In the Americas, for example, the urban population nearly doubled from 1970 to 1990, and during this period dengue emerged as a major problem [18]. Crowding and poor sanitation resulting in the proliferation of inadequate water storage and garbage containers, have been responsible for an enormous proliferation of the *Aedes* mosquitoes.

The assumption of constant population size in epidemiological models, is relatively valid for diseases of short duration with limited effects on mortality. However, this assumption fails to hold for diseases that are endemic in communities with changing population size, and for diseases which raise the mortality rate. In this situation, the effects of the change of population size and induced mortality are far from negligible, and in fact, may have a crucial influence on the dynamics of the disease. Dengue fever may be considered as an example of such a disease, since in regions where it is endemic the annual growth of the population is in general above 2%.

In this paper we continue the modeling of dengue disease started in [9]; here we analyze the effect of variable host population size and disease specific death rate. In section two we formulate the model, assuming that the host population grows exponentially, and has a constant disease death rate.

Using results from the theory of competitive systems we prove the global stability of the disease-free proportion when a certain threshold parameter is less than one. We use the same approach as in [9], which was based upon the results of Li and Muldowney [15], to establish the

global stability of the endemic proportion. We also show, that there is an intrinsic relation between the demographics of the human population and the disease dynamics.

Similar results for epidemic models with variable population have been obtained by several authors, among them, Busenberg and van den Driessche [3], Mena–Lorca and Hethcote [16] for a *SIRS* model with variable population; Busenberg and Vargas [4], Velasco–Hernández [23] for a Chaga's disease model with variable population.

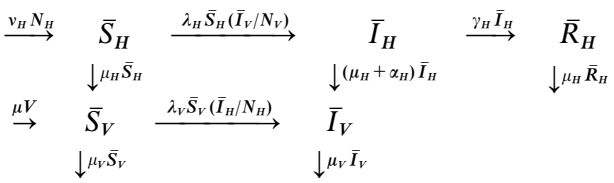
2 Formulation of the model

Denote by N_H and N_V the human and vector population sizes, respectively. We assume that the vector population has constant size with birth and death rate equal to μ_V. For the human population we assume an exponential growth. Then, the human population dynamics without disease is given by

$$\frac{dN_H}{dt} = (v_H - \mu_H)N_H, \qquad N_H(0) = N_{H_0},$$

where v_H and μ_H are the birth and natural death rates, respectively.

Let $\bar{S}_H$, $\bar{I}_H$ and $\bar{R}_H$ denote the total number of susceptibles, infectives, and immunes in the human population, respectively, and $\bar{S}_V$, $\bar{I}_V$ be the total number of susceptible and infective mosquitoes. The immune class in the vector population does not exist, since the mosquitoes never recover from infection, that is, their infective period ends with their death. The model is represented schematically by the following diagram:



In the diagram:

λ_H = effective contact rate between susceptible humans and vectors.
λ_V = effective contact rate between susceptible vectors and humans.
α_H = disease induced death rate of humans.
γ_H = recovery rate of infected humans.
μ_V = mortality rate of vector population.

The effective contact rate λ_H is the average number of contacts per day that would result in infection if the vector is infectious. The effective contact rate λ_H is the product of the average number of bites

per mosquito per day, the proportion of infected bites that results in infection, and the ratio between vector population size and human population size. In the case of variable human population interacting with a vector whose total population remains constant, λ_H should be a variable function of the total human population. However, population growth may be associated with conditions that enhace the effectiveness of vectors in transmitting the disease, thus, we can assume as in [23] that λ_H is constant. This assumption is an approximation that may not be valid for an extended period of time.

The effective contact rate λ_V is the average number of contacts per day that effectively transmit the infection to vectors. λ_V depends on the average number of bites per mosquito per day and the proportion of bites that result in vector infection.

We also assume that the birth and recovery rates are greater than the specific death rate associated with dengue, since as was said in the Introduction the estimated fatality cases are about 10,000 from more than 50 millions of dengue cases.

The above hypotheses lead to the following equations:

$$\begin{aligned}
\bar{S}'_H &= \nu_H N_H - \mu_H \bar{S}_H - \lambda_H \bar{S}_H \frac{\bar{I}_V}{N_V} \\
\bar{I}'_H &= \lambda_H \bar{S}_H \frac{\bar{I}_V}{N_V} - (\gamma_H + \mu_H + \alpha_H)\, \bar{I}_H \\
\bar{R}'_H &= \gamma_H \bar{I}_H - \mu_H \bar{R}_H \\
\bar{I}'_V &= \lambda_V (N_V - \bar{I}_V) \frac{\bar{I}_H}{N_H} - \mu_V \bar{I}_V \\
N'_H &= (\nu_H - \mu_H) N_H - \alpha_H \bar{I}_H \,.
\end{aligned} \tag{2.1}$$

All parameters in this model are non-negative. It is a simple matter to show that equations (2.1) are well-posed, in the sense, that if the initial data $(\bar{S}_H, \bar{I}_H, \bar{R}_H, \bar{I}_V, N_H)$ are in the region R^5_+, then the solutions will be defined for all time $t \geqq 0$ and remain in this region.

Introducing the proportions $S_H = \bar{S}_H/N_H$, $I_H = \bar{I}_H/N_H$, $R_H = \bar{R}_H/N_H$, $I_V = \bar{I}_V/N_V$ in system (2.1), and using the relation $R_H = 1 - S_H - I_H$, we obtain the following system that describes the dynamics of the proportion of individuals in each class

$$\begin{aligned}
S'_H &= \nu_H (1 - S_H) - \lambda_H S_H I_V + \alpha_H S_H I_H \\
I'_H &= \lambda_H S_H I_V - M_H I_H + \alpha_H I_H^2 \\
I'_V &= \lambda_V (1 - I_V)\, I_H - \mu_V I_V
\end{aligned} \tag{2.2}$$

where $M_H = \gamma_H + \nu_H + \alpha_H$. The region

$$\Omega = \{(S_H, I_H, I_V) | 0 \leqq S_H + I_H \leqq 1, 0 \leqq I_V \leqq 1\}$$

is positively invariant for system (2.2). We observe that system (2.2) does not involve $N_H(t)$, and therefore the behaviour of the proportions can be analyzed separately. The population size of each class can be determined from the equation

$$N'_H = (\nu_H - \mu_H - \alpha_H I_H) N_H \tag{2.3}$$

3 Analysis of the model equations

Our first results concern the existence and stability of equilibrium points of system (2.2). For this, we shall use the following threshold parameter:

$$R_0 = \frac{\lambda_H \lambda_V}{M_H \mu_V}. \tag{3.1}$$

Proposition 3.1. *System* (2.2) *always has the disease free equilibrium* $E_0 = (1, 0, 0)$. *If* $R_0 > 1$, *there is a unique endemic equilibrium* $E_1 = (S_H^*, I_H^*, I_V^*)$ *in the interior of* Ω.

Proof. From the first and third equations of system (2.2), the equilibrium points must satisfy the following relations:

$$I_V = \frac{\lambda_V I_H}{\mu_V + \lambda_V I_H}, \tag{3.2}$$

$$S_H = \frac{\nu_H(\mu_V + \lambda_V I_H)}{(\nu_H - \alpha_H I_H)\ (\mu_V + \lambda_V I_H) + \lambda_H \lambda_V I_H}. \tag{3.3}$$

Substituting $I_H = 0$ in equations. (3.2) and (3.3), we obtain $I_V = 0$ and $S_H = 1$. Thus E_0 always exists.

Suppose now that $I_H \neq 0$. Substituting equations. (3.2) and (3.3) in the second equation of system (2.2), we find that I_H satisfies the cubic equation:

$$\begin{aligned} g(I_H) &= \nu_H \lambda_H \lambda_V - [M_H - \alpha_H I_H][(\nu_H - \alpha_H I_H)(\mu_V + \lambda_V I_H) + \lambda_H \lambda_V I_H] \\ &= -\alpha_H^2 \lambda_V I_H^3 + \alpha_H(\lambda_V \nu_H + \lambda_H \lambda_V - \alpha_H \mu_V + \lambda_V M_H)\, I_H^2 \\ &\quad + (\alpha_H \nu_H \mu_V - (\lambda_V \nu_H + \lambda_H \lambda_V - \alpha_H \mu_V) M_H)\, I_H \\ &\quad + \nu_H(\lambda_H \lambda_V - \mu_V M_H). \end{aligned} \tag{3.4}$$

Observe that $\lim_{I_H \to \pm\infty} g(I_H) = \mp \infty$.

In order to be in the interior of Ω, an equilibrium given by (3.2), (3.3), and (3.4) must satisfy the following inequalities:

$$0 < I_H < 1, \tag{3.5}$$

$$0 < \frac{\lambda_V I_H}{\mu_V + \lambda_V I_H} < 1, \tag{3.6}$$

$$0 < \frac{v_H(\mu_V + \lambda_V I_H)}{(v_H - \alpha_H I_H)\ (\mu_V + \lambda_V I_H) + \lambda_H \lambda_V I_H} < 1, \tag{3.7}$$

$$0 < S_H + I_H = 1 - \frac{\gamma_H I_H}{v_H - \alpha_H I_H} < 1. \tag{3.8}$$

The inequality (3.6) follows from (3.5). Since we are assuming that $v_H > \alpha_H$, (3.7) is true if (3.5) holds and $I_H < (\frac{\lambda_H \lambda_V}{\alpha_H \mu_V} - 1)\frac{\mu_V}{\lambda_V}$. Finally, (3.8) follows if $0 < I_H < 1$ and $I_H < \frac{v_H}{\gamma_H + \alpha_H}$.

In order to have the four inequalities mentioned above, we should look for the roots of (3.4) in the interval $(0, I_{H_1})$, where

$$I_{H_1} = min\left\{1, \left(\frac{\lambda_H \lambda_V}{\alpha_H \mu_V} - 1\right)\frac{\mu_V}{\lambda_V}, \frac{v_H}{\gamma_H + \alpha_H}\right\}.$$

If $\frac{\lambda_H \lambda_V}{\alpha_H \mu_V} \leqq 1$, then I_{H_1} is non-positive, and therefore the only equilibrium point in Ω is E_0. Note that this is a special case of $R_0 < 1$.

Suppose now that $\frac{\lambda_H \lambda_V}{\alpha_H \mu_V} > 1$. Then $I_{H_1} > 0$ and straightforward calculations show that $g(I_{H_1}) < 0$.

The local maximum I_{H_2} of $g(I_H)$ is given by

$$I_{H_2} = \frac{\lambda_V v_H + \lambda_H \lambda_V - \alpha_H \mu_V + \lambda_V M_H + \Delta}{3\alpha_H \lambda_V},$$

where

$$\begin{aligned} \Delta = &[(\lambda_V v_H + (\lambda_H \lambda_V - \alpha_H \mu_V) - \lambda_V M_H)^2 \\ &+ \lambda_V(\lambda_V v_H + \lambda_H \lambda_V - \alpha_H \mu_V) M_H + 3\lambda_V \alpha_H v_H \mu_V]^{1/2} \\ &> \lambda_V v_H. \end{aligned}$$

From the above inequality we have

$$I_{H_2} > \frac{\lambda_V v_H + \lambda_H \lambda_V - \alpha_H \mu_V + \lambda_V M_H + \lambda_V v_H}{3\alpha_H \lambda_V} > \frac{v_H}{\alpha_H} \geqq I_{H_1}.$$

Therefore, the maximum of $g(I_H)$ is to the right of the interval $[0, I_{H_1}]$. Since $g(I_{H_1}) < 0$, it can be seen readily that (3.4) has a unique root $I_H^* \in (0, I_{H_1})$, if and only if $g(0) > 0$. But

$$g(0) = v_H(\lambda_V \lambda_H - M_H \mu_V) = \frac{v_H}{M_H \mu_V}(R_0 - 1),$$

therefore, (3.4) has a unique root $I_H^* \in (0, I_{H_1})$ if and only if $R_0 > 1$. □

To analyze the stability of the equilibrium points of equations (2.2) we shall use some results of competitive systems given in Appendix A. In that Appendix we show that system (2.2) is competitive according to the definition given in [21]. Furthermore, we shall use the following property of system (2.2).

Proposition 3.2. *On the boundary of* Ω, *system* (2.2) *has only one* ω*-limit point, which is the equilibrium* E_0. *Moreover for* $R_0 > 1$, E_0 *cannot be the* ω*-limit of any orbit in int*(Ω).

For a proof we refer to [9].

Remark. From Proposition 3.2 it follows that for $R_0 > 1$ system (2.2) is persistent in the sense described in [5].

Next, we analyze the stability of E_0.

Proposition 3.3. *The equilibrium* E_0 *is globally asymptotically stable in* Ω *if* $R_0 \leqq 1$, *and unstable if* $R_0 > 1$.

Proof. Using Theorem A.1 we shall prove the global stability of E_0. Suppose that Γ is a non trivial periodic orbit contained in Ω. By Proposition 3.2, Γ can not be contained in the boundary of Ω. Moreover, since the S_H–axis is an invariant set, the intersection of Γ with this axis must be empty; this implies that there exists $\varepsilon > 0$ such that

$$\Gamma \subset [\bar{a}, \bar{b}] \subset T,$$

where

$$\bar{a} = (0, \varepsilon, \varepsilon), \quad \bar{b} = (1, 1, 1),$$

and T is the unit cube. In this cube, system (2.2) is also competitive, then by Theorem A.1, $[\bar{a}, \bar{b}]$ must contain an equilibrium point, but for $R_0 \leqq 1$, the only equilibrium point in T is E_0 which obviously is not in $[\bar{a}, \bar{b}]$. This eliminates periodic type solutions in Ω, and the global stability of E_0 follows from the Poincaré–Bendixson property for competitive systems [13, 21].

The characteristic equation of the Jacobian of system (2.2) around E_0 is

$$(s + \nu_H)\,[s^2 + (M_H + \mu_V)\,s + M_H \mu_V (1 - R_0)]\,,$$

and we see that E_0 is unstable for $R_0 > 1$. □

Local analysis around the equilibrium E_1 proves that it is locally stable for $R_0 > 1$ (see appendix B for a proof). Global stability is given by the following proposition.

Proposition 3.4. *When $R_0 > 1$, the endemic equilibrium E_1 is globally asymptotically stable in $\Omega - \{(S_H, 0, 0) \mid 0 \leqq S_H \leqq 1\}$. All solutions with initial data $(S_H, 0, 0)$ tend to the disease-free equilibrium E_0.*

Proof. From the transversality of the vector field of system (2.2) on the boundary of $\Omega - \{(S_H, 0, 0) \mid 0 \leqq S_H \leqq 1\}$, we observe that it is enough to show that E_1 is globally asymptotically stable in the interior of Ω. Since system (2.2) is competitive, persistent for $R_0 > 1$ and E_1 is locally asymptotically stable, the result will follow from Theorem A.2 if we show that system (2.2) has the property of stability of periodic orbits (see appendix A for this definition). For this, let $p(t) = (S_H(t), I_H(t), I_V(t))$ be a periodic solution whose orbit Γ is contained in Ω. In accordance with [19] Theorem 4.2, it is enough to prove that the second compound system

$$\bar{X}'(t) = (Df^{[2]}(p(t)))\bar{X}(t)$$

is asymptotically stable, where $Df^{[2]}$ is the second compound matrix of the Jacobian Df. For our system the second compound equation is given by

$$\begin{aligned} X' &= -(\lambda_H I_V + v_H - \alpha_H I_H + M_H - 2\alpha_H I_H)\, X + \lambda_H S_H Y + \lambda_H S_H Z \\ Y' &= \lambda_V (1 - I_V)\, X - (\lambda_H I_V + v_H - \alpha_H I_H + \lambda_V I_H + \mu_V)\, Y + \alpha_H S_H Z \\ Z' &= \lambda_H I_V Y - (M_H - 2\alpha_H I_H + \lambda_V I_H + \mu_V)\, Z. \end{aligned} \tag{3.9}$$

See [9, 15] for more details.

As in [9], we consider the Lyapunov function

$$V(X, Y, Z; S_H, I_H, I_V) = \sup\left(|X|, \frac{I_H}{I_V}\left(|Y| + |Z|\right)\right),$$

where $\|\cdot\|$ is the norm in R^3 defined by

$$\|(X, Y, Z)\| = \sup\{|X|, |Y| + |Z|\}.$$

We obtain the following estimations of the right hand derivative of $|X(t)|$, $|Y(t)|$ and $|Z(t)|$:

$$\begin{aligned} D_+|X(t)| \leqq &-(\lambda_H I_V + v_H - \alpha_H I_H + M_H - 2\alpha_H I_H)|X(t)| \\ &+ \lambda_H S_H \frac{I_V}{I_H}\left(\frac{I_H}{I_V}(|Y(t)| + |Z(t)|)\right), \end{aligned} \tag{3.10}$$

$$D_+|Y(t)| \leqq \lambda_V(1 - I_V)|X(t)| - (\lambda_H I_V + v_H - \alpha_H I_H + \lambda_V I_H + \mu_V) \times |Y(t)| + \alpha_H S_H |Z(t)|, \tag{3.11}$$

$$D_+|Z(t)| \leqq \lambda_H I_V |Y(t)| - (M_H - 2\alpha_H I_H + \lambda_V I_H + \mu_V)|Z(t)|. \tag{3.12}$$

Adding inequalities (3.11) and (3.12), and using the fact that γ_H and $1 - S_H - I_H$ are non–negatives we obtain

$$D_+[|Y(t)| + |Z(t)|] \leqq \lambda_V(1 - I_V)|X(t)| - (v_H - \alpha_H I_H + \lambda_V I_H + \mu_V)(|Y(t)| + |Z(t)|),$$

and therefore

$$\begin{aligned} D_+\left[\frac{I_H}{I_V}(|Y(t)| + |Z(t)|)\right] &= \left(\frac{I'_H}{I_H} - \frac{I'_V}{I_V}\right)\frac{I_H}{I_V}(|Y(t)| + |Z(t)|) \\ &\quad + \frac{I_H}{I_V}D_+(|Y(t)| + |Z(t)|) \\ &\leqq \frac{I_H}{I_V}\lambda_V(1 - I_V)|X(t)| \\ &\quad + \left(\frac{I'_H}{I_H} - \frac{I'_V}{I_V} - v_H + \alpha_H I_H - \lambda_V I_H - \mu_V\right) \\ &\quad \times \frac{I_H}{I_V}(|Y(t)| + |Z(t)|). \end{aligned} \tag{3.13}$$

Let

$$h_1(t) = \lambda_H S_H \frac{I_V}{I_H} - (\lambda_H I_V + v_H - \alpha_H I_H + M_H - 2\alpha_H I_H)$$

and

$$h_2(t) = \frac{I_H}{I_V}\lambda_V(1 - I_V) + \frac{I'_H}{I_H} - \frac{I'_V}{I_V} - v_H + \alpha_H I_H - \lambda_V I_H - \mu_V.$$

Then, from (3.10) and (3.13) it can be shown as in [15] the following inequality

$$D_+ V_1(t) \leqq \sup\{h_1(t), h_2(t)\} V_1(t). \tag{3.14}$$

Rewriting equations (2.2) as

$$-\lambda_H I_V + \alpha_H I_H = \frac{S'_H}{S_H} - \frac{v_H(1 - S_H)}{S_H},$$

$$\frac{\lambda_V I_H}{I_V}(1 - I_V) = \frac{I'_V}{I_V} + \mu_V,$$

$$\frac{\lambda_H S_H I_V}{I_H} = \frac{I'_H}{I_H} + M_H - \alpha_H I_H,$$

and substituting in the expressions for $h_1(t)$ and $h_2(t)$ we obtain

$$\sup\{h_1(t), h_2(t)\} \leqq \frac{I'_H}{I_H} + \frac{S'_H}{S_H} - v_H + \alpha_H I_H \leqq \frac{I'_H}{I_H} + \frac{S'_H}{S_H} - v_H + \alpha_H.$$

Therefore, from (3.14) and Gronwell's inequality we obtain

$$V(t) \leqq V(0)\,(I_H(t) + S_H(t))\,\mathrm{e}^{-(v_H - \alpha_H)t} \leqq V(0)\,\mathrm{e}^{-(v_H - \alpha_H)t},$$

which implies that $V(t) \to 0$ as $t \to \infty$, since by assumption $v_H - \alpha_H > 0$.

Then, system (3.9) is asymptotically stable and therefore the orbit Γ is asymptotically orbitally stable. As was noted before, this proves the global stability of E_1 in $\Omega - \{(S_H, 0,0) : 0 \leqq S_H \leqq 1\}$. □

The second part of the proposition follows immediately.

Next, we analyze the asymptotic behaviour of the total population $N_H(t)$, and the total number of individuals in the epidemiological classes $\bar{S}_H$, $\bar{I}_H$ and $\bar{R}_H$. For this we introduce the parameters

$$R = \begin{cases} \dfrac{v_H}{\mu_H} & \text{if } R_0 \leqq 1 \\ \dfrac{v_H}{\mu_H + \alpha_H I_H^*} & \text{if } R_0 > 1\,, \end{cases} \tag{3.15}$$

$$R_1 = \begin{cases} \dfrac{\lambda_H \lambda_V}{(\gamma_H + \mu_H + \alpha_H)\mu_V} & \text{if } R_0 \leqq 1 \\ \dfrac{\lambda_H \lambda_V S_H^*(1 - I_V^*)}{(\gamma_H + \mu_H + \alpha_H)\mu_V} & \text{if } R_0 > 1. \end{cases} \tag{3.16}$$

First we study the dynamics of solutions whose initial conditions are outside the subspace $\bar{I}_H = \bar{I}_V = 0$. For $R \neq 1$ we have the following results.

Proposition 3.5. *The total population $N_H(t)$ for system* (2.1) *decreases exponentially to zero if $R < 1$ and increases exponentially to ∞* if $R > 1$. *The growth asymptotic rates are $\mu_H(R - 1)$ if $R_0 \leqq 1$, and $(\mu_H + \alpha_H I_H^*)\,(R - 1)$ if $R_0 > 1$.* (See [3] Lemma 3.4.)

Proposition 3.6. *For $R > 1$, $(\bar{S}_H(t), \bar{I}_H(t), \bar{R}_H(t))$ tend, as $t \to \infty$, to $(\infty, 0, 0)$ if $R_1 < 1$ and to (∞, ∞, ∞) if $R_1 > 1$.*

Proof. Since $I'_V(t) \to 0$ as $t \to \infty$, *in the limit, the proportion of infectious mosquitoes is related to the proportion of infectious humans as*

$$I_V = \frac{\lambda_V(1 - I_V)I_H}{\mu_V},$$

thus, the limit form of the equation for $\bar{I}_H(t)$ is given by

$$\bar{I}'_H = (\gamma_H + \mu_H + \alpha_H)\,(R_1 - 1)\bar{I}_H,$$

which implies that $\bar{I}_H(t)$ declines exponentially if $R_1 < 1$, and grows exponentially if $R_1 > 1$.

The solution $\bar{R}_H(t)$ is given by

$$\bar{R}_H = \bar{R}_{H_0} e^{-\mu_H t} + e^{-\mu_H t}\gamma_H \int_0^t \bar{I}_H(s)\, e^{\mu_H s} ds.$$

From the exponential nature of $\bar{I}_H(t)$, it follows that $\bar{R}_H(t)$ declines exponentially if $R_1 < 1$, and grows exponentially if $R_1 > 1$. □

For the case $R = 1$. we have the following proposition.

Proposition 3.7. *Suppose* $R = 1$ *and* $t \to \infty$. *If* $\alpha_H = 0$, $N_H(t)$ *remains fixed at its initial value* N_{H_0} *and* $(\bar{S}_H(t), \bar{I}_H(t), \bar{R}_H(t))$ *tend to* $(N_{H_0}, 0, 0)$ *if* $R_0 \leqq 1$ *and to* $N_{H_0}(S^*_H, I^*_H, R^*_H)$ *if* $R_0 > 1$. *If* $\alpha_H > 0$, $N_H(t)$ *tends to an equilibrium* $N^*_H \geqq 0$ *and* $(\bar{S}_H(t), \bar{I}_H(t), \bar{R}_H(t))$ *tend to* $(N^*_H, 0, 0)$ *for* $R_0 \leqq 1$ *and to* $(\bar{S}^*_H, \bar{I}^*_H, \bar{R}^*_H)$, *for* $R_0 > 1$.

Proof. Suppose $\alpha_H = 0$, then $N'_H(t) = 0$ and thus $N_H(t)$ remains fixed at its initial value N_{H_0}. In this case system (2.1) becomes the model with constant human population studied in [9]. For this system the solutions with initial conditions $\bar{S}_{H_0} + \bar{I}_{H_0} + \bar{R}_{H_0} = N_{H_0}$, tend to $(N_{H_0}, 0, 0)$ if $R_0 \leqq 1$, and to $N_{H_0}(S^*_H, I^*_H, R^*_H)$ if $R_0 > 1$.

Suppose now $\alpha_H > 0$. If $R_0 \leqq 1$, then $v_H = \mu_H$ and the differential equation for $N_H(t)$ becomes

$$N'_H = -\alpha_H \bar{I}_H,$$

which implies that $N_H(t)$ is bounded for all $t > 0$. In this case there exists a line of equilibria along the positive $\bar{S}_H$ axis in the $\bar{S}_H\bar{I}_H\bar{R}_H\bar{I}_V$ space. To prove that all solutions with positive initial conditions approach this line we use the Lyapunov function

$$V = N_H,$$

with orbital derivative

$$\dot{V} = -\alpha_H \bar{I}_H \leqq 0.$$

By the LaSalle–Lyapunov theorem [11], all solutions of (2.1) approach the largest invariant set contained in

$$M_1 = \{(\bar{S}_H, \bar{I}_H, \bar{R}_H, \bar{I}_V) \in R_+^4 \mid \bar{I}_H = 0\}.$$

It can be seen from (2.1), that this set corresponds to the positive $\bar{S}_H$ axis.

Now, for $R_0 < 1$ the equilibria $(N_H^*, 0, 0, 0)$ are neutrally stable, i.e., they have a single zero eigenvalue and the other eigenvalues have negative real part. Therefore, each orbit tends to an equilibrium point (see [2, Proposition 1.1]).

For $R_0 = 1$, the equilibria $(N_H^*, 0, 0, 0)$ have a zero eigenvalue of multiplicity two; in this case, writing the system (2.1) in the normal form and using the center manifold theorem [6], after change of variables and long calculations that we omit here, it can be proved that the equilibria $(N_H^*, 0, 0, 0)$ with $N_H^* > 0$ are unstable [8]. Since $N_H(t)$ is bounded, all solutions except those that lie on the stable manifold of $(N_H^*, 0, 0, 0)$ must approach $(0, 0, 0, 0)$.

If $R_0 > 1$, system (2.1) has a line of equilibria given by $(\bar{S}_H^*, \bar{I}_H^*, \bar{R}_H^*, \bar{I}_V^*)$, where

$$\bar{S}_H^* = \left(\frac{\gamma_H + \mu_H + \alpha_H}{\lambda_H \lambda_V}\right)\left(\frac{\mu_V \alpha_H + \lambda_V r_H}{\alpha_H}\right) N_H^*,$$

$$\bar{I}_H^* = \frac{r_H}{\alpha_H} N_H^*,$$

$$\bar{R}_H^* = \frac{\gamma_H r_H}{\mu_H \alpha_H} N_H^*,$$

$$\bar{I}_V^* = \frac{\lambda_V r_H N_V}{\lambda_V r_H + \mu_V \alpha_H},$$

with $r_H = \nu_H - \mu_H$. These are neutrally stable, and taking the limit form of (2.1), it can be seen that the trajectories are bounded. In this case, we can only say that nearby orbits will approach a unique point in the equilibria line [2]. □

The results for solutions with initial conditions outside the subspace $\bar{I}_H = \bar{I}_V = 0$ are summarized in Table 1. And on the subspace $\bar{I}_H = \bar{I}_V = 0$ we have the following behaviour

Proposition 3.8. *On the subspace* $\bar{I}_H = \bar{I}_V = 0$, *the human population* $N_H(t)$ *grows exponentially if* $R > 1$, *remains constant if* $R = 1$ *and*

Table 1. Threshold criteria and asymptotic behaviour

R	R_0	R_1	N_H	$(S_H, I_H, R_H, I_V) \to$	$(\bar{S}_H, \bar{I}_H, \bar{R}_H) \to$
< 1	$\leqq 1$	< 1[a]	$N_H \to 0$	$(1, 0, 0, 0)$	$(0, 0, 0)$
< 1	> 1	< 1[a]	$N_H \to 0$	$(S_H^*, I_H^*, R_H^*, I_V^*)$	$(0, 0, 0)$
> 1	$\leqq 1$	< 1	$N_H \to \infty$	$(1, 0, 0, 0)$	$(\infty, 0, 0)$
> 1	$\leqq 1$	> 1	$N_H \to \infty$	$(1, 0, 0, 0)$	(∞, ∞, ∞)
> 1	> 1	> 1[a]	$N_H \to \infty$	$(S_H^*, I_H^*, R_H^*, I_V^*)$	(∞, ∞, ∞)
$= 1, \alpha_H = 0$	$\leqq 1$	$\leqq 1$[a]	$N_H = N_{H_0}$	$(1, 0, 0, 0)$	$(N_{H_0}, 0, 0)$
$= 1, \alpha_H = 0$	> 1	$= 1$[a]	$N_H = N_{H_0}$	$(S_H^*, I_H^*, R_H^*, I_V^*)$	$N_{H_0}(S_H^*, I_H^*, R_H^*)$
$= 1, \alpha_H > 0$	< 1	< 1[a]	$N_H \to N_H^*$	$(1, 0, 0, 0)$	$(N_H^*, 0, 0)$
$= 1, \alpha_H > 0$	$= 1$	$= 1$[a]	$N_H \to 0$	$(1, 0, 0, 0)$	$(0, 0, 0)$
$= 1, \alpha_H > 0$	> 1	$= 1$[a]	$N_H \to N_H^*$	$(S_H^*, I_H^*, R_H^*, I_V^*)$	$(\bar{S}_H^*, \bar{I}_H^*, \bar{R}_H^*)$

[a] This condition is automatically satisfied for the values of R_0 and R.

decreases to zero if $R < 1$. *The infective humans* $\bar{I}_H(t)$ *remain constant and equal to zero; the recovered humans* $\bar{R}_H(t)$ *tend exponentially to zero; and the susceptible humans* $\bar{S}_H(t)$ *tend to* $N_H(t)$.

4 Discussion of the threshold parameters

The threshold parameter $R_0 = \frac{\lambda_H \lambda_V}{(\gamma_H + \nu_H + \alpha_H)\mu_V}$ governs whether or not an endemic proportion may exist and be globally stable.

The parameter R is the *basic reproduction number* of the human population, and it has two different values depending on the existence of an endemic proportion, as well as the excess death rate of the disease. When $R_0 \leqq 1$ or $\alpha_H = 0$, $R = \frac{\nu_H}{\mu_H}$, and it represents the net reproduction rate in a population where the disease is absent, or the disease does not raise the mortality rate. When $R_0 > 1$ and $\alpha_H > 0$, $R = \frac{\nu_H}{\mu_H + \alpha_H I_H^*}$, and it is the net reproduction rate when the excess of death due to the presence of the disease is taken into account.

The threshold parameter R_1 governs the growth of the total number of infectious humans and also has two different forms. If $R_0 \leqq 1$, $R_1 = \frac{\lambda_H \lambda_V}{(\gamma_H + \mu_H + \alpha_H)\mu_V}$, and when $R_0 > 1$, $R_1 = \frac{\lambda_H \lambda_V S_H^*(1 - I_V^*)}{(\gamma_H + \mu_H + \alpha_H)\mu_V}$.

The quantity $\tilde{R}_1 = \sqrt{R_1}$ can be interpreted as the average number of secondary infections produced by an infectious individual during its infective period. This follows from the next argument, which we shall give only for the case $R_0 > 1$.

Suppose an infectious human is introduced into a population where there exists an endemic proportion $(S_H^*, I_H^*, R_H^*, I_V^*)$ at

equilibrium. During the infective period this infectious human will produce on average

$$\frac{\lambda_V N_V(1-I_V^*)}{N_H}\,\frac{1}{(\gamma_H+\mu_H+\alpha_H)}$$

new infections in the vector population. Analogously, each infected mosquito infects on average

$$\frac{\lambda_H N_H S_H^*}{N_V}\,\frac{1}{\mu_V}$$

humans during the rest of its life. The geometric mean

$$\tilde{R}_1=\sqrt{\frac{\lambda_V(1-I_V^*)}{(\gamma_H+\mu_H+\alpha_H)}}\,\frac{\lambda_H S_H^*}{\mu_V}$$

is the expected number of secondary cases which one case produces when there exists an endemic proportion at equilibrium. Hence we can say that $\tilde{R}_1$ is the *basic reproduction number of the disease.*

The threshold conditions R and R_1 can be replaced by equivalent conditions involving only the parameters of the model. To find an equivalent expression for R we notice that N_H grows exponentially with asymptotic constant rate $v_H-\mu_H-\alpha_H I_H^*$ when $R_0>1$, Therefore, $N_H\to\infty$ if and only if $\frac{v_H-\mu_H}{\alpha_H}>I_H^*$. Furthermore, for $R_0>1$ and $\alpha_H>0$, $g(I_H)$ defined by (3.4) is positive at $I_H=0$, zero at I_H^* and its local maximum is to the right of $\frac{v_H}{\alpha_H}$. Moreover $g(\frac{v_H}{\alpha_H})<0$. These conditions imply that $\frac{v_H-\mu_H}{\alpha_H}>I_H^*$ if and only if $g(\frac{v_H-\mu_H}{\alpha_H})<0$. Substituting $\frac{v_H-\mu_H}{\alpha_H}$ in the expression for g we obtain the equivalent inequality

$$\frac{v_H\lambda_V}{\mu_H}\left[\frac{\mu_H+\dfrac{(\gamma_H+\mu_H)\lambda_H}{\gamma_H+\mu_H+\alpha_H}}{\lambda_H\lambda_V+\mu_H-\alpha_H\mu_V}\right]>1. \tag{4.1}$$

Defining by Φ the left side of (4.1), we have that $N_H(t)$ grows exponentially if and only if $\Phi>1$. Analogously, $N_H(t)$ decreases to zero if and only if $\Phi<1$, and remains constant when $\Phi=1$.

For the condition $R_1=\frac{\lambda_H\lambda_V S_H^*(1-I_H^*)}{(\gamma_H+\mu_H+\alpha_H)\mu_V}$ we can find also an equivalent expression. Recall that for $R_0>1$ the total number of infectives $\bar{I}_H$ grows exponentially with constant rate given by

$$(\gamma_H+\mu_H+\alpha_H)\left[\frac{\lambda_H\lambda_V S_H^*(1-I_V^*)}{(\gamma_H+\mu_H+\alpha_H)\mu_V}-1\right] \tag{4.2}$$

Substituting $S_H^*(1-I_V^*)$ and using the fact that $g(I_H^*)=0$, (4.2) becomes $v_H-\mu_H-\alpha_H I_H^*$. Therefore, $\bar{I}_H(t)$ grows to infinity if and only if $\Phi>1$, and decreases to zero if and only if $\Phi<1$.

In summary, our threshold parameters could have been

$$R_0 = \frac{\lambda_H \lambda_V}{M_H \mu_V},$$

$$R = \begin{cases} \dfrac{\nu_H}{\mu_H} & \text{if } R_0 \leqq 1 \\ \Phi & \text{if } R_0 > 1, \end{cases}$$

$$R_1 = \begin{cases} \dfrac{\lambda_H \lambda_V}{(\gamma_H + \mu_H + \alpha_H)\mu_V} & \text{if } R_0 \leqq 1 \\ \Phi & \text{if } R_0 > 1. \end{cases}$$

Note that for $R_0 > 1$, the threshold conditions for the behaviour of N_H and $\bar{I}_H$ are the same. Moreover, both populations grow or decay at the same rate.

5 Conclusions

We have formulated a model for dengue disease with variable human population. Since in the regions where dengue is endemic the population grows with an annual rate above 2%, then our model incorporates the effect of variable human population with exponential growth. This model also captures the general features of the transmission of arboviral diseases; thus, our results are more general and can be applied to those diseases as well.

We found three threshold parameters that control the development of the disease and the growth of the human population. The parameter R_0 is the threshold condition for the existence of the endemic proportions of infected humans and infected mosquitoes. On the other hand, the basic reproduction number R_1 controls the asymptotic behaviour of the number of infected humans, in an increasing population, when the infective proportion is tending to zero.

The threshold parameter R controls the growth of the total human population. When $R_0 \leqq 1$ or the disease related death rate α_H is zero, R represents the usual reproduction rate in a disease-free population. When $R_0 > 1$ and $\alpha_H > 0$, R is a measure of how the disease impacts on the population demography. In some cases, this impact may be sufficiently strong to take the population to extinction, as can be observed when the reproduction rate in absence of the disease, $\frac{\nu_H}{\alpha_H}$, is equal to one. Even if the disease dies out, it may be tending to zero so slowly, that it drives the population to extinction (case $\alpha_H > 0$, $R = 1$, $R_0 = 1$).

An interesting case arises when $R = 1$. Here, the asymptotic behaviour of the total population $N_H(t)$ depends on the value of α_H. If $\alpha_H = 0$, $N_H(t)$ remains constant at its initial value N_{H_0}, independently of the proportion of infected individuals. On the other hand, for $\alpha_H > 0$, N_H tends to an equilibrium N_H^*, which depends on the mentioned proportion. Thus, for $R_0 < 1$ (which implies $\nu_H = \mu_H$), $N_H(t)$ will decrease to $N_H^* \leqq N_{H_0}$; and for $R_0 > 1$ (which implies $\nu_H = \mu_H + \alpha_H I_H^*$), $N_H(t)$ will increase or decrease initially, depending if the initial fraction, I_{H_0}, is less or bigger than $\frac{\nu_H - \mu_H}{\alpha_H}$; and then, will tend to N_H^* which can be greater than N_{H_0}.

A basic aspect of these results is that the infective proportion I_H and the total number of infective humans may have different behaviours. Thus, I_H may be tending to a positive endemic value, and yet the total number of infectives tends to zero if the total population is decreasing (case $R < 1, R_0 > 1$). On the other hand, I_H may be tending to zero, and $\bar{I}_H$ will grow exponentially (case $R > 1, R_0 \leqq 1, R_1 > 1$).

Some authors [3, 4, 22] have pointed out that in a nonconstant population, two different policies can be considered: one is to reduce the proportion of infected individuals, and the threshold condition is R_0, and the other policy is to reduce the total number of infectives, and the threshold conditions are R_1 and R.

To get a reduction on the number of infectives in a growing population requires a bigger effort than the one needed to reduce the infective proportion; since in the first case it is necesary to diminish R and R_1, whereas in the second case, it is only necesary to reduce R_0, which in a growing population, is less than R_1.

The discussion above may suggest that the simplest way to control the disease in a growing population is reducing the proportion of infectives. However, we have to consider that the number of hospitalizations and medical services required to attend the infected population can be considerable, even if the infective proportion is relatively small. Gubler [10] mentions that in the Southeast Asian countries, there have been 700 000 children hospitalized with DHF between 1960 and 1986. This figure is not significant compared with the total population of those countries during these years; however, the same author mentions that the economical impact of those hospitalizations has represented an important problem for the region. Unfortunately for these times the problem has increased, Halstead [12] mentions that by the last decade of the XXth century *Aedes aegypti* and the 4 dengue viruses had spread to nearly all countries of the tropical world. Some 2 billion persons live in dengue–endemic areas with tens of millions infected annually. Nearly three million children have been hospitalized with (DHF/DSS) in the past three decades, mainly in South–East Asia.

A Mathematical appendix

In this appendix we give a brief review of some mathematical results on competitive systems. We start with the definition of competitive system given by Smith in [21].

Let $D \subset R^n$ be an open set, and $\bar{x} \to f(\bar{x}) \in R^n$ be a C^1 function defined in D. We consider the autonomous system in R^n given by

$$\bar{x}' = f(\bar{x}). \tag{A.1}$$

System (A.1) is *competitive* in D iff, for some diagonal matrix $H = diag(\varepsilon_1, \ldots, \varepsilon_n)$, where each ε_i is either 1 or -1, $H(DF(\bar{x}))\,H$ has non positive off-diagonal elements for $\bar{x} \in D$, where $DF(\bar{x})$ is the Jacobian of (A.1). It is shown in [21] that, if D is convex, the flow of such a system preserves for $t < 0$ the partial order in R^n defined by the orthant

$$K = \{(x_1, \ldots, x_n) \in R^n : \varepsilon_i x_i \geqq 0\}.$$

The Jacobian DF of system (2.2) is given by:

$$DF = \begin{bmatrix} -v_H - \lambda_H I_V + \alpha_H I_H & \alpha_H S_H & -\lambda_H S_H \\ \lambda_H I_V & -M_H + 2\alpha_H I_H & \lambda_H S_H \\ 0 & \lambda_V(1 - I_V) & -\lambda_V I_H - \mu_V \end{bmatrix}. \tag{A.2}$$

If we choose the matrix H as

$$H = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{pmatrix},$$

we can see that system (2.2) is competitive in Ω with respect to the partial order defined by the orthant

$$K = \{(S_H, I_H, I_V) \in R^3 : S_H \geqq 0, I_H \leqq 0, I_V \geqq 0\}.$$

In [14] and [21], it is proved that three-dimensional competitive systems satisfy the Poincaré–Bendixson property. There is another remarkable property of 3-dimensional competitive systems [13]:

Theorem A.1. *Let Γ be a non-trivial periodic orbit of a competitive system in a convex set $D \subset R^3$, such that*

$$\Gamma \subset [\bar{a}, \bar{b}] \subset D,$$

where $[\bar{a}, \bar{b}] = \{\bar{a} \leqq \bar{x} \leqq \bar{b}\}$ *and* $\leqq$ *is the lexicographic order in* R^3. *Then* $[\bar{a}, \bar{b}]$ *contains an equilibrium point.*

Definition. We say that system (A.1) has the property of stability of periodic orbits, iff the orbit of any periodic solution is asymptotically orbitally stable.

The following result, is the key to establish the global stability of the endemic proportion equilibrium of system (2.2) (see [9, 15]).

Theorem A.2. *Assume that* $n = 3$ *and* D *is convex and bounded. Suppose* (*A*.1) *is competitive, persistent, and has the property of stability of periodic orbits. If* $\bar{x}_0$ *is the only equilibrium point in int*(D), *which is locally asymptotically stable, then it is globally asymptotically stable in int*(D).

B Local stability of E_1

Here we shall prove that E_0 is locally asymptotically stable for $R_0 > 1$. The local stability of the equilibrium E_1 is governed by the Jacobian of system (2.2) evaluated at this point. From system (2.2) we obtain the following relations:

$$S_H^* = \frac{ab}{\lambda_H \lambda_V}, \tag{B.1}$$

$$-\frac{v_H}{S_H^*} = -v_H - \lambda_H I_V^* + \alpha_H I_H^*, \tag{B.2}$$

where

$$a = \lambda_V I_H^* + \mu_V,$$

$$b = M_H(1 - I_H^*).$$

Then the Jacobian can be written as:

$$DF(E_1) = \begin{bmatrix} -\dfrac{\lambda_H \lambda_V v_H}{ab} & \dfrac{\alpha_H ab}{\lambda_H \lambda_V} & -\dfrac{ab}{\lambda_V} \\ \dfrac{\lambda_H \lambda_V I_H^*}{a} & -b + \alpha_H I_H^* & \dfrac{ab}{\lambda_V} \\ 0 & \dfrac{\lambda_V \mu_V}{a} & -a \end{bmatrix}. \tag{B.3}$$

The characteristic equation of (B.3) is given by

$$S^3 + AS^2 + BS + C = 0, \tag{B.4}$$

where

$$A = \frac{\lambda_H \lambda_V \nu_H}{ab} + a + b - \alpha_H I_H^*,$$

$$B = (b - \alpha_H I_H^*)\lambda_V I_H^* + \frac{\lambda_H \lambda_V \nu_H}{b} + \frac{\lambda_H \lambda_V \nu_H}{ab}(b - \alpha_H I_H^*) - b\alpha_H I_H^* - \mu_V \alpha_H I_H^*,$$

$$C = \frac{\lambda_H \lambda_V \nu_H}{b}(b - \alpha_H I_H^*) - \frac{\lambda_H \lambda_V \mu_V}{a}(\nu_H - bI_H^*) - \alpha_H abI_H^*.$$

Since $\gamma_H > \alpha_H$ and $\nu_H > \alpha_H$ then $b - \alpha_H I_H^* > \alpha_H$. From this we see immediately that $A > 0$.

From the first two equations of (2.2) at equilibrium, we have the following relation:

$$bI_H^* = \nu_H - (\nu_H - \alpha_H I_H^*) S_H^* < \nu_H. \tag{B.5}$$

Since $S_H^* < 1$, we also have the relation

$$\lambda_V \lambda_H > ab. \tag{B.6}$$

Therefore, from (B.5) and (B.6) we get

$$B > (b - \alpha_H I_H^*)\lambda_V I_H^* + a\nu_H + \nu_H \alpha_H - \alpha_H bI_H^* - \mu_V \alpha_H I_H^* > 0.$$

Using (B.1) and (B.5), we can write C as

$$C = \frac{\lambda_H \lambda_V \nu_H}{b}(b - \alpha_H I_H^*) - b\mu_V(\nu_H - \alpha_H I_H^*) - \alpha_H abI_H^*.$$

Substituting from (3.4) for $\nu_H \lambda_H \lambda_V$ we obtain

$$C = (\nu_H - \alpha_H I_H^*)\, b\lambda_V I_H^* + \lambda_H \lambda_V bI_H^* - \frac{\nu_H \lambda_H \lambda_V \alpha_H I_H^*}{b} - \alpha_H abI_H^*$$

$$> (\nu_H - \alpha_H I_H^*)\, b\lambda_V I_H^* + \lambda_H \lambda_V (b - 2\alpha_H)\, I_H^*$$

$$> 0.$$

Finally, the following inequality is easy to obtain

$$AB > a\left[\frac{\lambda_H \lambda_V \nu_H}{ab}(b - \alpha_H I_H^*) - b\alpha_H I_H^*\right]$$

$$= \frac{\lambda_H \lambda_V \nu_H}{b}(b - \alpha_H I_H^*) - \alpha_H abI_H^*$$

$$> C.$$

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