DYNAMICS OF DENGUE DISEASE

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1. Introduction. In this dissertation we analyze mathematical models for dengue disease to characterize stability properties of equilibria as well as the threshold parameters that determine the existence of endemic or disease–free equilibria.

Dengue fever is a common arboviral disease in tropical regions of the world. It is transmitted to humans by the bite of *Aedes* mosquitoes (*A. aegypti* and *A. albopictus* are the main vectors). Four serotypes of the viruses have been identified, denoted by I, II, II, IV. Infection by any single serotype produces long lasting immunity to it, but apparently only temporary cross immunity to others. The mosquitoes never recover from the infection since their infective period ends with their death.

In the past forty years, a severe form of the disease, dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), has become a major public health problem in Southeast Asia. There is evidence that a similar increase in the disease severity may be occurring in the Americas. No vaccine is available, thus effort to control the disease focus on the vector.

Appropiate mathematical models can provide a qualitative assesment of the risk of the spread of this disease, as well as the effeciveness of the mosquito control methods. To model the transmission of the disease, we use systems of non–linear ordinary differential equations which incorporate the structure of the population imposed by the characteristics of the disease: susceptible, infected and recovered humans, as well as the dynamics of the vector population.

2. Model for arbovirus diseases. In the first chapter we study a general model for the transmission of arbovirus diseases, closed related to the one proposed in [1], [8]. Here, me make a global analysis of the equations. In this model we assume that the human population is constant and only one virus serotype is present.

We denote by S_H and I_H the proportions of susceptible and infectious humans, and by I_V the proportion of infectious mosquitoes. Then the model is given by the following equations:

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$$\begin{aligned} S'_H(t) &= \mu_H(1-S_H) - b\beta_H \frac{N_V}{N_H+m} S_H I_V \\ I'_H(t) &= b\beta_H \frac{N_V}{N_H+m} S_H I_V - (\gamma_H+\mu_H) I_H \\ I'_V(t) &= b\beta_V \frac{N_H}{N_H+m}(1-I_V) I_H - \mu_V I_V, \end{aligned} \tag{2.1}$$

where N_H and N_V are the human and vector populations with constant death rates given by μ_H and μ_V, respectively; b is the rate of biting by a single mosquito (number of bites per unit of time); m is the number of alternative hosts available as blood sources for the mosquitoes; β_H is the proportion of infectious bites on humans that produce an infection; β_V is the porportion of infectious bites that produce infection on vectors and γ_H is the recovery rate in humans.

The region of biological interest

$$\Omega = \{(S_H, I_H, I_V) : 0 \le I_V \le 1,\ 0 \le S_H,\ 0 \le I_H,\ S_H + I_H \le 1\}$$

is positively invariant under the flow induced by (2.1), as the vector field on the boundary does not point to the exterior.

The model has two equilibria:

$$E_0 = (1,0,0) \quad \text{and} \quad E_1 = (S_H^*, I_H^*, I_V^*)$$

where

$$S_H^* = \frac{\beta + M}{\beta + P_0 M}, \quad I_H^* = \frac{P_0 - 1}{\beta + P_0 M}, \quad I_V^* = \frac{\beta(P_0-1)}{P_0(\beta+M)} \tag{2.2}$$

and

$$\beta = \frac{b\beta_V N_H}{\mu_V(N_H+m)}, \quad M = \frac{\gamma_H+\mu_H}{\mu_H}, \quad P_0 = \frac{b^2\beta_H\beta_V N_H N_V}{(N_H+m)^2\mu_V(\gamma_H+\mu_H)}. \tag{2.3}$$

E_0 is the disease–free equilibrium and E_1 corresponds to the endemic value.

The quantity $R_0 = \sqrt{P_0}$ is called the basic reproductive number. It represents the number of secondary cases, that an infective individual can generate during his infectious period, when introduced into a population of susceptibles. This number gives a criterion of the spread of disease.

The following result summarizes the behaviour of system (2.1):

Theorem 2.1 *If $P_0 \le 1$, the only equilibrium point in the feasible region Ω is the disease free–equilibrium, and it is globally asymptotically stable. For $P_0 > 1$ the endemic equilibrium emerges in the region, and it is globally asymptotically stable in $\Omega - \{(S_H,0,0)|0 \le S_H \le 1\}$. On the S_H–axis, the trajectories approach the disease–free equilibrium.*

To prove the global stability of the disease–free equilibrium when $P_0 \le 1$, we came out with a Lyapunov function. For the global stability of the endemic equilibrium we follow the approach of Y. Li and J.S. Muldowney [18] for a $SEIR$ model. This approach uses the

Poincaré–Bendixon property of three–dimensional competitive systems [15, 22], and results for the stability of periodic orbits [20].

Consider the system

$$\overline{x}' = f(\overline{x}) \tag{2.2}$$

where $\overline{x} \in D \subset R^n$.

It is said that (2.2) is *competitive* in D iff for some diagonal matrix $H = diag(\epsilon_1, \epsilon_2, ..., \epsilon_n)$, where each ϵ_i is either 1 or -1, $H(Df(\overline{x}))H$ has non positive off–diagonal elements for $\overline{x} \in D$, where $Df(\overline{x})$ is the jacobian of the system. Hirsch proved [15], that 3–dimensional systems have the Poincaré–Bendixon property. That is, any non empty compact omega limit set that contains no equilibria must be a closed orbit.

A system is *persistent* in the sense described in [4], iff each solution starting in $int(D)$, has the property $\liminf_{t\to\infty} \overline{x}(t)$ is at a positive distance from the boundary of D.

We say that a system has the *property of stability of periodic orbits*, iff the orbit of any periodic solution, if it exists, is asymptotically orbitally stable.

The following theorem is a generalization of the results of Li and Muldowney, and it is the key to prove the global stability of the endemic equilibrium point E_2. Details can be found in [11].

Theorem 2.2. *Assume that $n = 3$ and D is convex and bounded. Suppose the system (2.2) is competitive, persistent, and has the propery of stability of periodic orbits. If $\overline{x}_0$ is the only equilibrium point in int(D), and it is locally asymptotically stable, then it is globally asymptotically stable.*

It is worth to mentioning, that the global stability of the endemic equilibrium, of an SIR model with several populations, has been conjectured [5]. We prove this fact for our two–population problem.

In the dissertation we estimate the basic reproductive number P_0 from serological data for 25 states of México. We find values between one and two.

3. Variable human population. In the regions where dengue disease is endemic the population grows with an anual rate above 2%. Therefore in chapter 2 we assume that the human population grows exponentially, and has a constant disease rate. We have obtain the following model:

$$\begin{aligned}
\overline{S}'_H(t) &= \nu_H N_H - \lambda_H \overline{S}_H I_V - \mu_H \overline{S}_H \\
\overline{I}'_H(t) &= \lambda_H \overline{S}_H I_V - (\gamma_H + \mu_H + \alpha_H)\overline{I}_H \\
\overline{R}'_H(t) &= \gamma_H \overline{I}_H - \mu_H \overline{R}_H \\
I'_V(t) &= \lambda_V (1 - I_V)\frac{\overline{I}_H}{N_H} - \mu_V I_V \\
N'_H(t) &= (\nu_H - \mu_H)N_H - \alpha_H \overline{I}_H,
\end{aligned} \tag{3.1}$$

where $\overline{S}_H$, $\overline{I}_H$, $\overline{R}_H$ denote the number of humans who are susceptible, infectious and recovered, respectively; I_V is the proportion of infected mosquitoes; λ_H, λ_V are the effective contact rates of susceptible humans (mosquitoes) with infectious mosquitoes (humans); ν_H and μ_H the birth and mortality rates of the human population; α_H the disease death rate; and finally μ_V and γ_H are as in section 2.

Remark 1. In this model we assume that the contact rates are independent of the ratio between the vector and human populations. Also we assume that the birth rate ν_H is higher than the disease death rate α_H.

Due to the structure of system (3.1), the corresponding equations for the proportions $S_H = \overline{S}_H/N_H$, $I_H = \overline{I}_H/N_H$, $R_H = \overline{R}_H/N_H$ and I_V do not involve N_H. Also, the equations for the fractions S_H, I_H and R_H are redundant since $S_H + I_H + R_H = 1$. Thus the 3–dimensional system in the $S_H I_H I_V$ space can be analized separately and the total population size dynamics can be determined from the differential equation for N_H. It is easy to prove that the region Ω defined before is positively invariant for the $S_H I_H I_V$ system.

The results are discused in terms of the threshold parameters P_0, R and P_1 given by

$$P_0 = \frac{\lambda_H \lambda_V}{(\nu_H + \gamma_H + \alpha_H)\mu_V},$$

$$R = \begin{cases} \dfrac{\nu_H}{\mu_H} & \text{if } P_0 \leq 1 \\ \dfrac{\nu_H}{\mu_H + \alpha_H I_H^*} & \text{if } P_0 > 1, \end{cases}$$

$$P_1 = \begin{cases} \dfrac{\lambda_H \lambda_V}{(\mu_H + \gamma_H + \alpha_H)\mu_V} & \text{if } P_0 \leq 1 \\ \dfrac{\lambda_H \lambda_V S_H^*(1 - I_V^*)}{(\mu_H + \gamma_H + \alpha_H)\mu_V} & \text{if } P_0 > 1, \end{cases}$$

which govern the existence of the endemic proportion, the increase of the human population and the number of infectious humans, respectively.

The disease–free proportion $E_0 = (1, 0, 0)$ is globally asymptotically stable for $P_0 \leq 1$. To show the local stability of this point, we use local analysis for $P_0 < 1$, and the Center Manifold Theorem [17] for $P_0 = 1$; and to prove the global stability, we use a result on competitive systems given in [16]. For $P_0 > 1$, there exists an endemic proportion $E_1 = (S_H^*, I_H^*, I_V^*) \in int(\Omega)$. Local analysis and Theorem 2.2 prove that all trajectories starting in $\Omega - \{(S_H, 0, 0) | 0 \leq S_H \leq 1\}$ approach E_1 when $P_0 > 1$.

To analyze the asymptotic behaviour of the human population and the total number of individuals in the epidemiological classes, we use Lyapunov functions, the Center Manifold Theorem and classical results on linear non–autonomous systems [7]. The main results for model (3.1) are summaized in Table 1. The proofs can also be found in [12].

As can be observed in Table 1, a basic aspect of these results is that the infectious proportion of humans and the total number of infectious humans may have different behaviour. Thus the infectious proportion of humans may be tending to a positive endemic value, and the total number of infectious humans may be tending to zero if the total population is decreasing (case $P_0 > 1$ and $R < 1$). On the other hand, the infectious proportion of humans may be tending to zero, and the total number of infectious humans will grow exponentially (case $R > 1$, $P_0 \leq 1$ and $P_1 > 1$). Similar results for epidemiological models with variable population have been obtained by several authors, among them, Mena–Lorca and Heth-

Table 1 Threshold criteria and asymptotic behaviour of system (3.1).

R	P_0	P_1	N_H	$(S_H, I_H, R_H, I_V) \to$	$(\overline{S}_H, \overline{I}_H, \overline{R}_H) \to$
< 1	≤ 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	≤ 1	< 1	$N_H \to \infty$	$(1, 0, 0, 0)$	$(\infty, 0, 0)$
> 1	≤ 1	> 1	$N_H \to \infty$	$(1, 0, 0, 0)$	(∞, ∞, ∞)
> 1	> 1	$> 1^a$	$N_H \to \infty$	$(S_H^*, I_H^*, R_H^*, I_V^*)$	(∞, ∞, ∞)
$= 1$, $\alpha_H = 0$	≤ 1	$\leq 1^a$	$N_H = N_{H_0}$	$(1, 0, 0, 0)$	$(N_{H_0}, 0, 0)$
$= 1$, $\alpha_H = 0$	> 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	$= 1^a$	$N_H \to N_H^*$	$(S_H^*, I_H^*, R_H^*, I_V^*)$	$(\overline{S}_H^*, \overline{I}_H^*, \overline{R}_H^*)$

[a] This condition is automatically satisfied for the values of P_0 and R.

cothe [19], Busenberg and van den Driessche [2] for a $SIRS$ model; Busenberg and Vargas [3], Velasco–Hernández [23] for a model of Chagas' disease.

4. Model with two serotypes of virus and variable human population. In chapter 3 we analyze a model for dengue disease with two serotype virus in a variable human population and constant disease death rate. We analyze the factors that allow the invasion and persistence of each serotype virus in a human population, as well as the coexistence levels of both serotypes. The model consists of a non–linear system of nine differential equations that describes the dynamics of the proportions of individuals. Previous models that incorporate the relations among different serotypes or virus strains are given in [6, 9, 10, 13, 21].

$$\begin{aligned}
S_H' &= \nu_H(1 - S_H) - (\lambda_{H_1} I_{V_1} + \lambda_{H_2} I_{V_2}) S_H + (\alpha_{H_1} Y_{H_1} + \alpha_{H_2} Y_{H_2}) S_H \\
I_{H_i}' &= \lambda_{H_i} I_{V_i} S_H - (\nu_H + \gamma_{H_i}) I_{H_i} + (\alpha_{H_1} Y_{H_1} + \alpha_{H_2} Y_{H_2}) I_{H_i} \\
R_{H_i}' &= \gamma_{H_i} I_{H_i} - \sigma_j \lambda_{H_j} I_{V_j} R_{H_i} - \nu_H R_{H_i} + (\alpha_{H_1} Y_{H_1} + \alpha_{H_2} Y_{H_2}) R_{H_i} \\
Y_{H_i}' &= \sigma_i \lambda_{H_i} R_{H_j} I_{V_i} - (\nu_H + \gamma_{H_i} + \alpha_{H_i}) Y_{H_i} + (\alpha_{H_1} Y_{H_1} + \alpha_{H_2} Y_{H_2}) Y_{H_i} \\
I_{V_i}' &= \lambda_{V_i} (I_{H_i} + Y_{H_i})(1 - I_{V_1} - I_{V_2}) - \mu_V I_{V_i},
\end{aligned} \tag{4.1}$$

where $i, j = 1, 2$, $i \neq j$.

In (4.1), S_H denotes the proportion of susceptible humans to both serotypes; I_{H_i} the proportion of primary infectious humans with serotype i; R_{H_i} the proportion of recovered and immune humans from serotype i, susceptible to serotype j, $i \neq j$; Y_i the proportion of secondary infectious humans with serotype i; I_{V_i} the infectious proportion of vectors with serotype i; λ_{H_i}, λ_{V_i} the effective contact rates of susceptible humans (mosquitoes) with infective mosquitoes (humans) with serotype i; γ_{H_i} the recovery rate from serotype i, α_{H_i} the disease death rate due to serotype i; and finally ν_H, μ_H and μ_V are as before.

We assume that primary infections with one serotype may diminish (cross–immunity) or increase (immune enhacement) the susceptibility of the human host to the secondary infection. The parameters σ_i, $i = 1, 2$, simulate this situation ($\sigma_i < 1$ means cross–immunity and $\sigma_i > 1$ immune enhacement).

In this case the region of biological interest becomes

$$\Omega = \{\ (S_H, I_{H_1}, I_{H_2}, R_{H_1}, R_{H_2}, Y_{H_1}, Y_{H_2}, I_{V_1}, I_{V_2}) \in R^9_+ \quad \text{with}$$
$$I_{V_1} + I_{V_2} \leq 1, S_H + I_{H_i} + R_{H_i} + Y_{H_i} \leq 1\ \},$$

which is positively invariant under (4.1).

The existence and stability properties of the equilibrium points of system (4.1)are regulated by the parameters

$$P_i = \frac{\lambda_{H_i}\lambda_{V_i}}{(\nu_H + \gamma_{H_i})\mu_V} \quad i = 1, 2,$$

$$P_0 = max\{P_1, P_2\}.$$

Remark 2. $R_0 = \sqrt{P_0}$ is the basic reproductive number of the disease when there exist two serotypes in the transmission.

If $P_0 < 1$, $E_0 = (1, 0, 0, 0, 0, 0, 0, 0, 0)$ is the only equilibrium in the feasible region Ω and it is locally asymptotically stable. In the case $\sigma_i \leq 1$ we prove, using a Lyapunov function, that it is globally asymptotically stable. When $P_0 > 1$, E_0 becomes an unstable saddle point.

If $P_1 > 1$, there is an equilibrium $E_1 = (S^*_{H_1}, I^*_{H_1}, 0, R^*_{H_1}, 0, 0, 0, I^*_{V_1}, 0) \in \partial\Omega$, where only the serotype one is present. Analysis of the Jacobian of the system reveals that E_1 is locally asymptotically stable if $P_1 > 1$ and

$$P_2 < \frac{P_1}{1 + \dfrac{\sigma_2\gamma_{H_1}M_2}{(\beta_1 + M_1)(\nu_H M_2 + \alpha_{H_2})}(P_1 - 1)}, \tag{4.2}$$

where

$$\beta_i = \frac{\lambda_{V_i}}{\mu_V}, \quad M_i = \frac{\gamma_{H_i} + \nu_H}{\nu_H}, \quad i = 1, 2.$$

Numerical evidence suggests that the conditions above imply global stability of the equilibrium E_1 in the region $\Omega - \{(S_H, I_{H_1}, I_{H_2}, R_{H_1}, R_{H_2}, Y_{H_1}, Y_{H_2}, I_{V_1}, I_{V_2})\ : I_{H_1} > 0, I_{V_1} > 0\}$. Using Lyapunov functions we prove this under the more restrictive conditions $\alpha_{H_i} = 0$, $\sigma_i \leq 1$, $P_2 \leq 1$ and $P_1 > 1$. When (4.2) is not satisfied the equilibrium E_1 is an unstable saddle.

If $P_2 > 1$, there is an analogous equilibrium $E_2 = (S^*_{H_2}, 0, I^*_{H_2}, 0, R^*_{H_2}, 0, 0, 0, I^*_{V_2}) \in \partial\Omega$ where only serotype 2 is present. Analogous stability results to the ones of E_1 are proved.

The regions of stability of the equilibria E_i, $i = 1, 2$, in the parameter space P_1P_2 are disjoint. They change under variations on the susceptibility to the secondary infection and disease related death rates.

If the two conditions

$$\begin{aligned} P_2 &> \frac{P_1}{1 + \dfrac{\sigma_2\gamma_{H_1}M_2}{(\beta_1 + M_1)(\nu_H M_2 + \alpha_{H_2})}(P_1 - 1)} \\ P_1 &> \frac{P_1}{1 + \dfrac{\sigma_1\gamma_{H_2}M_1}{(\beta_2 + M_2)(\nu_H M_1 + \alpha_{H_1})}(P_2 - 1)} \end{aligned} \tag{4.3}$$

are both satisfied, then numerical simulations support the existence and stability of a non trivial equilibrium $E_3 \in int(\Omega)$ at which both serotypes remain endemic. When the disease related death rates α_{H_i} are equal to zero, we prove analytically the existence of E_3.

We find that coexistence of both serotypes is possible for a large range of parameters. As the degree of susceptibility to the secondary infection increases, the system moves from a regime of competitive exclusion (total cross–immunity) in which the strain with higher reproductive number dominates, to a regime of coexistence, in which both serotypes have an increasingly coupled behaviour.

5. Vertical transmission and interrupted feeding in the vector population. In the fourth and last chapter we analyze the impact of vertical transmission and interrupted feeding on the dynamics of the disease. The model is given by the following system:

$$\begin{aligned} S'_H &= \mu_H(1 - S_H) - (\lambda_{H_1} I_{V_m} + \lambda_{H_2} I_V) S_H \\ I'_H &= (\lambda_{H_1} I_{V_m} + \lambda_{H_2} I_V) S_H - (\mu_H + \gamma_H) I_H \\ I'_{V_m} &= q\mu_V (I_{V_m} + L_V + I_V) + \lambda_V I_H (1 - I_{V_m} - L_V - I_V) - (\mu_V + \gamma_{V_m}) I_{V_m} \\ L'_V &= \gamma_{V_m} I_{V_m} - (\mu_V + \gamma_V) L_V \\ I'_V &= \gamma_V L_V - \mu_V I_V \end{aligned} \tag{5.1}$$

in the region

$$\Omega = \left\{ (S_H, I_H, I_{V_m}, L_V, I_V) \in R^5_+ : 0 \leq S_H + I_H \leq 1, 0 \leq I_{V_m} + L_V + I_V \leq 1 \right\}.$$

Here I_{V_m} is the proportion of mosquitoes that have acquired the virus and can transmit it mechanically; L_V the proportion of infected mosquitoes that are in the incubation period (latent); I_V the proportion of infectious mosquitoes; $1/\gamma_{V_m}$ is the average time of permanence of a mosquito in the class I_{V_m} before it becomes latent (this period can be very short); $1/\gamma_V$ is the latent period; q is the proportion of newborns from an infected mosquito that is infectious. The other variables and parameters are as before.

We prove the existence of two equilibria: the disease–free equilibrium $E_0 = (1, 0, 0, 0, 0)$, and the endemic equilibrium $E_1 = (S^*_H, I^*_H, I^*_{V_m}, L^*_V, I^*_V) \in int(\Omega)$. Using results on M–matrices we show the local stability of the disease free equilibrium when the parameter

$$P_0 = \frac{F\lambda_V}{p(\mu_H + \gamma_H)} \tag{5.2}$$

is less than one, where

$$F = \left(\lambda_{H_1} + \frac{\gamma_{V_m}\gamma_V}{\mu_V(\mu_V + \gamma_V)} \lambda_{H_2} \right) \frac{1}{\mu_V + \gamma_{V_m}} \quad and \quad p = 1 - q.$$

We find a Lyapunov function to show the global stability of this equilibrium when $\lambda_{H_1} < \dfrac{\gamma_V}{\mu_V + \gamma_V} \lambda_{H_2}$ and $P_0 \leq 1$. To prove the local stability of the endemic equilibrium for $P_0 > 1$, we use a Krasnoselkii sublinearity technique as was done in [14] for a model with subpopulations.

We find that vertical transmission is more important that the effect of interrupted feeding on the dynamics of the disease. We also find that vertical transmission affects the dynamics of the infectious vectors more than the dynamics of the infectious humans. We conclude that vertical transmission is an important factor in the maintenance of the virus in regions where the human density is low.

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