Analysis of Stability, Sensitivity and Simulations of a Model for the Incidence of Microcephaly

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Abstract

The analysis of stability, sensitivity and simulations of a deterministic model is performed for the incidence of Microcephaly, in terms of the basic reproductive number $R_0$. For the simulations, the Maple software and values of the parameters obtained from the literature review are used.

Keywords: Stability, sensitivity, simulation, basic reproductive number, model deterministic, incidence, microcephaly

1 Introduction

At the beginning of 2015, an outbreak of the Zika virus was identified, a flavivirus that is transmitted by the mosquito of the *Aedes* species. By September, a series of reports suggesting an increase in the number of children born with microcephaly in areas affected by the Zika virus began to appear, and Zika virus RNA was identified in the amniotic fluid of two women whose fetuses had microcephaly (head circumference equal to or greater than two standard deviations below the mean for sex and gestational age at birth), according to the findings made by ultrasound done before delivery [1, 2, 3].

Authorities are considering different theories, including a possible association with the onset of Zika virus disease within the region and where the first case
was detected in May 2015 [4]. Interestingly, vertical transmission to the fetus has not been previously reported, although there are two cases of perinatal transmission [5, 6].

Several factors can influence the dynamics of virus transmission, including environmental and climatic factors, interactions between hosts and pathogens, and immunological factors of the population [7, 8, 9, 10].

2 The model

The model of Muñoz et al. (2018) [11] is restarted, with which the stability, sensitivity and simulation analysis is carried out, in terms of the epidemic threshold, basic reproductive number, $R_0$. The model presents the following variables and parameters, $x$: fraction of pregnant women infected with Zika virus, $x_m$: fraction of women in pregnancy whose fetuses have developed microcephaly, $1 - x - x_m$: fraction of susceptible women in pregnancy, $y$: fraction of female mosquitoes carrying Zika virus, $1 - y$: fraction of female mosquitoes not carrying Zika virus, $\lambda_h(t)$: force of the infection in pregnant women, $\lambda_v(t)$: force of the infection in the female mosquito, $\omega_m$: rate of development of microcephaly in the fetuses of pregnant women infected with Zika virus, $\theta$: rate of recovery of women infected with Zika virus, $\mu$: rate of death of the women with fetuses that develop microcephaly, $\epsilon$: rate of death of female mosquitoes by environmental conditions, $\beta$: probability of transmission of Zika virus to to susceptible women in pregnancy, $\sigma$: probability of transmission of Zika virus to non-carrier mosquitoes by the bite of these to pregnant women infected with Zika. The ordinary nonlinear differential equations that interpret the dynamics are:

$$\frac{dx}{dt} = \lambda_h(t)(1 - x - x_m) - \rho x$$  \hspace{1cm} (1)

$$\frac{dx_m}{dt} = \omega_m x - \mu x_m$$  \hspace{1cm} (2)

$$\frac{dy}{dt} = \lambda_v(t)(1 - y) - \epsilon y$$  \hspace{1cm} (3)

where the forces of infection are: $\lambda_h(t) = \beta y$, $\lambda_v(t) = \sigma x$, $\rho = \theta + \omega_m$, $0 < \beta, \sigma < 1$ and $\epsilon, \mu, \theta, \omega_m > 0$. The positive trajectories of this system make epidemiological sense in the region,

$$\Pi = \{(x, x_m, y) \in R^3_+ : \ 0 < x + x_m \leq 1 , \ 0 \leq y \leq 1 \}$$  \hspace{1cm} (4)
Table 1: Parameters of the model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\beta$</th>
<th>$\sigma$</th>
<th>$\epsilon$</th>
<th>$\omega_m$</th>
<th>$\mu$</th>
<th>$\theta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>0.7913</td>
<td>0.7730</td>
<td>0.0352</td>
<td>0.7</td>
<td>0.010</td>
<td>0.0500</td>
</tr>
</tbody>
</table>

3 Basic reproductive number, $R_0$

In epidemiological terms, the basic reproductive number, $R_0$, is defined as the average number of new cases that an infectious person causes in a susceptible population during the average time of infection (infectious period) [12].

Using the mathematical definition, the calculated $R_0$, as the spectral radius of a matrix, called of the next generation, namely, the dominant eigenvalue of said matrix [12, 13, 14, 15],

$$ \tilde{R}_0 = \rho(G) = \max \{\lambda_i\} , \quad i = 1, 2, 3 $$

where $G$: matrix of the next generation, $\rho$: dominant eigenvalue and $\lambda_i$: eigenvalues, obtaining

$$ \tilde{R}_0 = \sqrt{R_0} $$

(5)

donde $R_0 = \frac{\beta \sigma}{\epsilon(\theta + \omega_m)}$.

4 Stability analysis

We start the local stability analysis [16], calculating the equilibrium points, that is, the constant solutions of the system, making the derivatives equal to zero, and solve the non-linear algebraic system, obtaining the equilibrium solution free of infection $E_0 = (0, 0, 0)$ and the prevalence solution $E_1 = (\hat{x}, \hat{x}_m, \hat{y})$,

$$ \hat{y} = \frac{\epsilon(\theta + \omega_m)(R_0 - 1)}{\beta \left[\sigma + \epsilon \left(1 + \frac{\omega_m}{\mu}\right)\right]} , \quad \hat{x} = \frac{\epsilon \hat{y}}{\sigma(1 - \hat{y})} , \quad \hat{x}_m = \frac{\omega_m \epsilon \hat{y}}{\mu \sigma (1 - \hat{y})} $$

with $R_0$ already defined and $R_0 > 1$.

Returning to the stability analysis, we proceed to linearize the nonlinear dynamic system (1)-(3) in the vicinity of a generic equilibrium point $E = (\hat{x}, \hat{x}_m, \hat{y})$,
for which we calculate the Jacobian matrix in $J(E)$,

$$
\begin{pmatrix}
a_{11} & a_{12} & a_{13} \\
\omega_m & -\mu & 0 \\
\sigma(1 - \hat{y}) & 0 & -\sigma\hat{x} - \epsilon
\end{pmatrix}
$$

(6)

where $a_{11} = -\beta\hat{y} - (\theta + \omega_m)$, $a_{12} = -\beta\hat{y}$ and $a_{13} = \beta(1 - \hat{x} - \hat{x}_m)$.

Therefore, the linear system is,

$$
\begin{align*}
\frac{du}{dt} &= -[\beta\hat{y} + (\theta + \omega_m)]u - \beta\hat{y}v + \beta(1 - \hat{x} - \hat{x}_m)w \\
\frac{dv}{dt} &= \omega_m u - \mu v \\
\frac{dw}{dt} &= \sigma(1 - \hat{y})u - [\sigma\hat{x} + \epsilon]w
\end{align*}
$$

By the theorem of Hartman-Grobman (1967) [16], the nonlinear system (1)-(3) is equivalent topologically to the linear system (10)-(12).

Evaluating the matrix (6) at the equilibrium point $E_0 = (0, 0, 0)$, we obtain

$$
J(E_0) = \begin{pmatrix}
-(\theta + \omega_m) & 0 & \beta \\
\omega_m & -\mu & 0 \\
\sigma & 0 & -\epsilon
\end{pmatrix}
$$

(7)

and its corresponding characteristic equation $|J(E_0) - \lambda I| = 0$ is,

$$(\mu + \lambda)[(\theta + \omega_m + \lambda)(\epsilon + \lambda) - \sigma\beta] = 0
$$

(8)

where an eigenvalue is, $\lambda_1 = -\mu$ and $\lambda_2, \lambda_3 = \frac{1}{2}\{-\theta + \omega_m + \epsilon \pm \Omega\}$

where, $\Omega = \sqrt{\delta}$, with $\delta = (\theta + \omega_m + \epsilon)^2 - 4(\theta + \omega_m)\epsilon(1 - R_0)$.

To determine the sign of the roots, we analyze the sign of the discriminant, $\delta$. 
Simplifying is obtained
\[ \delta = (\theta + \omega_m - \epsilon)^2 + 4\sigma \beta > 0 \]

Therefore, \( \lambda_2 < 0 \) and \( \lambda_3 < 0 \). That is, the three eigenvalues have a negative real part. This result leads to the following theorem:

**Teorema 4.1.** If \( R_0 < 1 \), the infection-free equilibrium point \((E_0)\) of the system (1)-(3) is local and asymptotically stable.

For the case \( R_0 = 1 \), we have an eigenvalue \( \lambda_1 = -\mu \) and the characteristic equation
\[ \lambda[\lambda + (\theta + \omega_m + \epsilon)] = 0 \]

has roots (eigenvalues), \( \lambda_2 = 0 \) and \( \lambda_3 = -(\theta + \omega_m + \epsilon) \). That is, the endemicity of the infection is a critical case with a zero eigenvalue.

To analyze the equilibrium point of prevalence, we consider the characteristic equation of the Jacobian matrix (6) evaluated in \( E_1 \),
\[ -[\beta \dot{y} + (\theta + \omega_m + \lambda)(\mu + \lambda)(\sigma \dot{x} + \epsilon + \lambda) + \sigma (1 - \dot{y})(\mu + \lambda) \beta (1 - \dot{x} - \dot{x}_m) - \omega_m \beta \dot{y}(\sigma \dot{x} + \epsilon + \lambda) = 0 \]

Simplifying, we obtain the third degree equation \( \lambda^3 + A\lambda^2 + B\lambda + C = 0 \), with coefficients,
\[ A = \beta \dot{y} + \theta + \omega_m + \sigma \dot{x} + \epsilon + \mu \]
\[ B = [\beta \dot{y} + (\theta + \omega_m)](\sigma \dot{x} + \epsilon + [\beta \dot{y} + (\theta + \omega_m + \sigma \dot{x} + \epsilon)] \mu + \omega_m \beta \dot{y} - \sigma \beta (1 - \dot{y})(1 - \dot{x} - \dot{x}_m) \]
\[ C = [\beta \dot{y} \theta + \omega_m](\sigma \dot{x} + \epsilon) \mu - \sigma \beta (1 - \dot{y})(1 - \dot{x} - \dot{x}_m) \mu + \omega_m \beta \dot{y}(\sigma \dot{x} + \epsilon). \]

The three roots of the cubic equation are negative, if the inequalities of Routh-Hurwitz are met: \( A > 0 \), \( C > 0 \) and \( AB > C \), when \( R_0 > 1 \). In this case, the prevalence solution is local and asymptotically stable; if one of them is not met, the prevalence solution is unstable. This result is summarized in the following theorem:

**Teorema 4.2.** If \( R_0 > 1 \), \( A > 0 \), \( C > 0 \) and \( AB > C \), the equilibrium point of prevalence \((E_1)\) of the system (1)-(3) is local and asymptotically stable, otherwise it is unstable.

## 5 Local sensitivity analysis

Sensitivity allows us to measure the relative change in a variable when a parameter changes. The sensitivity coefficient is the relation of the change of one
of the parameters, while all other parameters remain constant \[17, 18, 19\].

The models are sensitive to input parameters in two different ways: first, the variability associated with a sensitive input parameter is propagated through the model that results in a large contribution to the variability of global production; second, the consequences of the model can be highly correlated with an input parameter so that small changes in the input parameters show significant changes in the output \[17, 18, 19\].

The sensitivity indexes for the basic reproductive number are defined as:

\[
I_{R_0}^P = \frac{\partial R_0}{\partial P} \times \frac{P}{R_0}
\]

where \(P\) represents the parameter. The sensitivity indices for the basic reproductive number were calculated with the expression (9), as shown below:

\[
I_{R_0}^\beta = \frac{\partial R_0}{\partial \beta} \frac{\beta}{R_0} = 1
\]

\[
I_{R_0}^\sigma = \frac{\partial R_0}{\partial \sigma} \frac{\sigma}{R_0} = 1
\]

\[
I_{R_0}^\epsilon = \frac{\partial R_0}{\partial \epsilon} \frac{\epsilon}{R_0} = -1
\]

\[
I_{R_0}^\omega_m = \frac{\partial R_0}{\partial \omega_m} \frac{\omega_m}{R_0} = -\frac{\omega_m}{\theta + \omega_m} = -0.93
\]

and summarized in Table 2. According to the calculated indices, the threshold \(R_0\) is sensitive inversely proportional to the variations in the values of the mortality rate of the mosquito by environmental factors (\(\epsilon\)) and the rate of microcephaly development (\(\omega_m\)) and is sensitive proportionally to changes in the probability of transmission of Zika virus to susceptible pregnant women (\(\beta\)) and to the probability of transmission of the pathogen to the population of non-Zika virus carrying mosquitoes (\(\sigma\)).

<table>
<thead>
<tr>
<th>Indice</th>
<th>(I_\beta)</th>
<th>(I_\sigma)</th>
<th>(I_\epsilon)</th>
<th>(I_\omega_m)</th>
<th>(I_\theta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valor</td>
<td>1.0</td>
<td>1.0</td>
<td>-1.0</td>
<td>-0.93</td>
<td>-0.07</td>
</tr>
</tbody>
</table>

Tabla 1: Sensitivity indexes of \(R_0\).
6 Simulations

The different simulations are carried out in Maple, with the data of the parameters of the model, shown in Table 1. The graphs of Figure 1, show the behavior and differences of the epidemic thresholds $R_0 < 1$ and $\tilde{R}_0$ with respect to the most sensitive parameters proportionally.

![Graphs showing behavior of $R_0$ and $\tilde{R}_0$.](image)

Figure 1: Behavior of $R_0$ and $\tilde{R}_0$, dependents on the probabilities of transmission $\beta$ and $\sigma$.

Figures 2 and 3 show the behavior of the sensitivity indices with respect to the threshold $R_0$.

In the trajectories of Figure 4, the behavior of the populations over time is observed, for the case of prevalence of the infection, when the thresholds $R_0 < 1$ and $\tilde{R}$ are greater than 1; while the second trajectories populations for $R_0 < 1$ and $\tilde{R}_0 < 1$ tend to zero as time passes.
7 Conclusions

From the development of the investigation, it is concluded that the parameters that most influence proportionally in the threshold and consequently in the incidence of the infection are the probabilities of transmission $\beta$ and $\sigma$; while the mortality rate of the mosquito $\epsilon$, is the parameter that most influences inversely proportional, in the behavior of the populations. The results of local
stability agree with the numerical analysis, and show the greatest impact of prevalence of microcephaly.

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References


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