

Sensitivity Analysis in a Dengue Fever Transmission Model: A fractional order system approach

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Abstract. The main purpose of the study of dengue fever transmission is to be able to determine the best approach to reduce human mortality and morbidity caused by the disease. Therefore, it is essential to identify the relative importance of the different factors that contribute to disease transmission and prevalence. Here, a fractional order epidemiological model describing the dengue fever transmission is presented, as well as the basic reproduction number, denoted by R_0 . The initial disease transmission is highly significant with the basic reproduction number, R_0 . Thus, the needs for conducting an analysis that tells us how sensitive the threshold quantity of R_0 is, with respect to its parameters, is very crucial. The sensitivity analysis is performed to calculate the sensitivity indices of the reproduction number R_0 , that measures the disease transmission and the endemic equilibrium point, that measures disease prevalence to the parameters model. It has been shown that for the reproduction number, the most sensitive parameters are the mortality rate of the adult mosquito and the mosquito biting rate. However, the equilibrium proportion of infected humans is very sensitive to the transition rate from the immature vector stage to the adult stage, and human recovery rate. These suggest that dengue control policies that target the vector population and recovery rate of individuals can be a great resolution in controlling dengue.

1. Introduction

Dengue fever is a mosquito-borne disease that generally exists in tropical and subtropical areas around the globe. The dengue virus is transmitted to human by the bites of *Aedes* mosquito, primarily, *Aedes aegypti*. Dengue is caused by four serologically different viruses known as DEN I, II, III, and IV. Individuals infected by one of the viruses or commonly called serotypes gain a lifetime resistance to it, but short-term immunity to the other serotypes. Millions of dengue cases reported every year, especially in Southeast Asia and the western Pacific, and rapidly increase in Latin America and the Caribbean. Up until today, there is no perfect vaccine available to treat the disease. Controlling and reducing dengue virus transmission are solely depend on vector control and human awareness. [1]

Understanding of the effectiveness and efficiency of various control interventions is vital to construct a reliable dengue control policy. In particular, knowledge of the threshold concepts in



the modelling of infectious disease that contributes to the spread of infection is crucial. In an epidemiological study, the most important threshold concept is the basic reproduction number, denoted by R_0 , that is significant with the initial disease transmission. In general, the sensitivity analysis of the basic reproduction number is performed to identify the relative importance of different parameters to the transmission. Sensitivity analysis of model parameters is crucial in providing the right direction to the public health practitioners in designing the control strategies plan. Chitnis et al [2] have performed a thorough sensitivity analysis on the malaria model by evaluating the sensitivity indices of the basic reproduction number and the endemic equilibrium point. They have discovered the significant parameters contributed to the disease transmission as well as disease prevalence of malaria.

Most of the sensitivity analysis presented in the literature for the epidemic model is of the integer order differential equations [3, 4, 5, 6, 7]. To the best of author knowledge, sensitivity analysis has not been done to the fractional order dengue epidemic model [8, 9, 10]. Other than the goal to determine which parameters are significant in the dengue fever transmission and prevalence, we are also aiming to study the effect of the order on the sensitivity indices of R_0 , and how significant it is in the controlling the disease. In this study, we used the fractional dengue epidemic model proposed by Hamdan and Kilicman [11, 12, 13] to analyze the sensitivity indices of the basic reproduction number with respect to all model parameters. The sensitivity analysis is performed using the normalized forward sensitivity index introduced by Arriola and Hyman [14]. In addition, we numerically determine the sensitivity indices of the endemic point of equilibrium following method used in [2].

2. Model

The dengue epidemic model presented in [11, 12, 13] consists of a system of fractional order differential equations, where human population is divided into three epidemiological states known as; susceptible, H_s , infected, H_i , and recovered, H_r . The total population size is denoted by $H = H_s + H_i + H_r$. Meanwhile, mosquito population is divided into three subgroups namely aquatic stage (for immature population), A_m , susceptible, M_s , and infected, M_i . Here, we will consider both models with the same order dynamics and different order dynamics of the host and vector population. The model for the same order dynamics is represented by the following system of fractional order differential equations:

$$\begin{aligned}
 D^\alpha A_m &= q\phi^\alpha(1 - A_m/C)M - (\sigma_A^\alpha + \mu_A^\alpha)A_m, \\
 D^\alpha M_s &= \sigma_A^\alpha A_m - \frac{b^\alpha \beta_m}{H} M_s H_i - \mu_m^\alpha M_s, \\
 D^\alpha M_i &= \frac{b^\alpha \beta_m}{H} M_s H_i - \mu_m^\alpha M_i, \\
 D^\alpha H_s &= \mu_h^\alpha (H - H_s) - \frac{b^\alpha \beta_h}{H} H_s M_i, \\
 D^\alpha H_i &= \frac{b^\alpha \beta_h}{H} H_s M_i - (\gamma_h^\alpha + \mu_h^\alpha) H_i, \\
 D^\alpha H_r &= \gamma_h^\alpha H_i - \mu_h^\alpha H_r,
 \end{aligned} \tag{1}$$

where $\alpha \in (0, 1)$. The model for different order dynamics is given by the following equations:

$$\begin{aligned}
 D^{\alpha_m} A_m &= q\phi^{\alpha_m}(1 - A_m/C)M - (\sigma_A^{\alpha_m} + \mu_A^{\alpha_m})A_m, \\
 D^{\alpha_m} M_s &= \sigma_A^{\alpha_m} A_m - \frac{b^{\alpha_m}\beta_m}{H} M_s H_i - \mu_m^{\alpha_m} M_s, \\
 D^{\alpha_m} M_i &= \frac{b^{\alpha_m}\beta_m}{H} M_s H_i - \mu_m^{\alpha_m} M_i, \\
 D^{\alpha_h} H_s &= \mu_h^{\alpha_h}(H - H_s) - \frac{b^{\alpha_h}\beta_h}{H} H_s M_i, \\
 D^{\alpha_h} H_i &= \frac{b^{\alpha_h}\beta_h}{H} H_s M_i - (\gamma_h^{\alpha_h} + \mu_h^{\alpha_h})H_i, \\
 D^{\alpha_h} H_r &= \gamma_h^{\alpha_h} H_i - \mu_h^{\alpha_h} H_r,
 \end{aligned} \tag{2}$$

with $\alpha_h, \alpha_m \in (0, 1)$. Since system (1) and (2) monitors human and mosquito population, all the parameters, and state variables are positive. The biological meaning of each parameter of the models is described in Table 1.

Table 1. Descriptions of parameters involved in system (1) and (2)

Parameter	Descriptions	Units
q	proportion of eggs that results in female mosquito	Dimensionless
ϕ	oviposition rate	Time ⁻¹ (day)
C	carrying capacity of the aquatic stage population	Dimensionless
σ_A	transition rate from aquatic stage to adult stage	Time ⁻¹ (day)
μ_A	mortality rate of aquatic stage	Time ⁻¹ (day)
μ_m	mortality rate of mosquito	Time ⁻¹ (day)
μ_h	mortality rate of human	Time ⁻¹ (day)
b	biting rate	Time ⁻¹ (day)
β_m	transmission probability from human to vector	Dimensionless
β_h	transmission probability from vector to human	Dimensionless
γ_h	recovery rate of human	Time ⁻¹ (day)

3. The basic reproduction number R_0 for dengue

The basic reproduction number generally denoted by R_0 , is defined as the average number of secondary infections produced by an infected individual in a completely susceptible population during the mean infectious period [15]. Epidemiologically, the disease will be eliminated when $R_0 < 1$, and when $R_0 > 1$ an epidemic occurs, resulting in a persistent of the disease over time. In this article, the basic reproduction number is derived using the next generation approach. Details of the derivation can be found in [11, 12, 13]. Here, for the same order dynamics model (1), we neglect the assumption that both human and mosquito population do not possess memory. Therefore, the derivation of the basic reproduction number, R_0 , of system (1) following [11, 12] is given by the formula:

$$R_0 = \sqrt{\frac{b^{2\alpha}\beta_m\beta_h C(q\phi^\alpha\sigma_A^\alpha - \mu_m^\alpha(\sigma_A^\alpha + \mu_A^\alpha))}{H\mu_m^{2\alpha}q\phi^\alpha(\gamma_h^\alpha + \mu_h^\alpha)}}. \tag{3}$$

For the different order dynamics, the basic reproduction number, \bar{R}_0 , for system (2), is given by the following equation:

$$\bar{R}_0 = \sqrt{\frac{b^{\alpha_h} b^{\alpha_m} \beta_m \beta_h C (q \phi^{\alpha_m} \sigma_A^{\alpha_m} - \mu_m^{\alpha_m} (\sigma_A^{\alpha_m} + \mu_A^{\alpha_m}))}{H \mu_m^{2\alpha_m} q \phi^{\alpha_m} (\gamma_h^{\alpha_h} + \mu_h^{\alpha_h})}}. \tag{4}$$

4. Baseline parameters

In this article, the numerical computation is performed based on dengue data recorded in Malaysia for year 2016. The parameter values used are determined from the published studies and from the dataset available by the Department of Statistics Malaysia and the Ministry of Health Malaysia. The baseline values and ranges for the parameters described in Table 1 are given in Table 2.

Table 2. Baseline values and ranges for parameters and order of system (1) and (2).

Parameter	Baseline	Range of values	References
q	0.8	0-1	[16, 17]
ϕ	7.5	0-11.2 per day	[16, 17]
σ_A	0.08	0-0.19 per day	[16, 17]
μ_A	0.25	0.01-0.47 per day	[16, 17]
$1/\mu_m$	34	11-56 days	[18]
$1/\mu_h$	75	72-77 years	[19]
b	0.5	0-1 per day	[20]
β_m	0.375	0.35-0.8	[21, 22]
β_h	0.75	0.35-0.8	[21, 22]
γ_h	0.30	0.083-0.33 per day	[18, 16]

5. Sensitivity analysis

5.1. The basic reproduction number, R_0

Sensitivity indices enable us to calculate the relative change in a state variable when a parameter changes [2]. In this study, the sensitivity analysis is conducted using the method defined in [2], which formerly introduced by Arriola and Hyman [14]. The normalized forward sensitivity index of a variable to a parameter is the ratio to the relative change in the variable to the relative change in the parameter. At a time when the variable is defined as the differentiable function of the parameter, the sensitivity index may be interpreted using partial derivatives [2].

Definition 1 [2] *The normalised forward sensitivity index of variable u , that depends differentially on a parameter p , is defined by*

$$\Upsilon_p^u = \frac{\partial u}{\partial p} \times \frac{p}{u}. \tag{5}$$

Since the explicit formula for R_0 is obtained in (3), we can easily compute the analytical expression for the sensitivity of R_0 , based on Definition 1 to all parameters described in Table 1 as,

$$\Upsilon_p^{R_0} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0}. \tag{6}$$

Table 3. Sensitivity indices of R_0 evaluated at the baseline parameter values for $\alpha = 0.9$.

Parameter	Sensitivity index
μ_m	-1.02
b	+0.90
γ_h	-0.52
σ_A	+0.51
β_m	+0.50
β_h	+0.50
q	-0.017
ϕ	-0.011
μ_A	+0.012
μ_h	-1.42×10^{-4}

However, this expression for the sensitivity indices is rather complex. Therefore, the sensitivity indices are evaluated at the baseline parameter values given in Table 2. The sensitivity indices of R_0 to all the parameters in the model (1) are shown in Table 3. The parameters are ordered from most sensitive to least sensitive.

Chitnis et al. in [2] mentioned that the sensitivity index of R_0 with respect to the biting rate parameter (in our case denoted by b), does not depend on the values of the parameters because $\Upsilon_{\sigma_{vh}}^{R_0}$ is always equal to 1. We observed the same result in the fractional order model (1). The sensitivity index of R_0 with respect to b does not depend on the parameter values, but, it is dependent on the order of the derivative α . That $\Upsilon_b^{R_0}$ is always equal to the value of order α . This can be verified with the results in Table 3 and Table 4. However, this is not the case for a system with different order dynamics (2), since the biting rate parameter b is now dependent on two different order, thus, such observation is not valid.

Table 4. Sensitivity indices of R_0 evaluated at the baseline parameter values for $\alpha = 0.6$.

Parameter	Sensitivity index
μ_m	-1.02
b	+0.60
γ_h	-0.52
σ_A	+0.51
β_m	+0.50
β_h	+0.50
q	-0.017
ϕ	-0.011
μ_A	+0.012
μ_h	-1.42×10^{-4}

From the data in Table 3 and 4, it is apparent that the most sensitive parameter is the mortality rate of the mosquito, μ_m ($1/\mu_m$ is the expected lifespan of the mosquito) and the biting rate, b . Other significant parameters include the recovery rate in the human population γ_h , transition rate from aquatic stage to mature stage of the mosquito population σ_A , and transmission probability both from human to vector β_m and from vector to human β_h . The sensitivity indices can be interpreted as, for example, as $\Upsilon_{\mu_m}^{R_0} = -1.02$, if we increase (or decrease) μ_m by 10%, then the basic reproduction number R_0 will be decreasing (or increasing) by approximately 10%. Similarly, as $\Upsilon_{\beta_m}^{R_0} = 0.5$, decreasing (or increasing) β_m by 10% will decrease (or increase)

R_0 by 5%. The obtained results agree with our intuitive expectation.

For system with different order dynamics (2), the sensitivity indices of \bar{R}_0 to all parameters are given in Table 5. We observed that the result is similar to the result in the same order dynamics of system (1), except for the biting rate b and recovery rate γ_h parameter (μ_h is neglected as it is the least sensitive). These two parameters are affected by the change of order on the differential operator.

Table 5. Sensitivity indices of \bar{R}_0 evaluated at the baseline parameter values for $\alpha_m = 0.9$ and $\alpha_h = 0.99, 0.8$.

Parameter	Sensitivity index ($\alpha_m < \alpha_h$)	Sensitivity index ($\alpha_m < \alpha_h$)
μ_m	-1.02	-1.02
b	+0.81	+1.01
γ_h	-0.62	-0.45
σ_A	+0.51	+0.51
β_m	+0.50	+0.50
β_h	+0.50	+0.50
q	-0.017	-0.017
ϕ	-0.011	-0.011
μ_A	+0.012	+0.012
μ_h	-6.23×10^{-5}	-3.53×10^{-4}

Figure 1 shows graphs of infected individuals through parameter variation with order $\alpha = 0.9$. The obtained figures reinforce the sensitivity indices in Table 3. Each plot gives the number of the infected human population using the baseline parameter values specified in Table 2 and the corresponding plot with an increment of 10% in the parameter value. Some parameters like μ_h, ϕ, q, μ_A having a little impact on R_0 and the changes are not graphically noticeable. Thus, we omit their graphs.

5.2. The point of the endemic equilibrium

Here, the local sensitivity analysis of the endemic equilibrium point of model (1) is performed to access the importance of each parameter in the disease prevalence. Disease prevalence is referring to the number of infected cases of a particular disease in a population at a specific location at a particular time [23]. The analysis is associated to the endemic equilibrium point $E_2 = (A_m^*, M_s^*, M_i^*, H_s^*, H_i^*, H_r^*)$, particularly to the size of the infectious human [12]. The sensitivity indices of the endemic equilibrium point are evaluated at the baseline parameter values given in Table 2, using a similar method described in [2] (see Appendix). The calculated sensitivity indices of the endemic equilibrium at the baseline parameters with respect to the model parameters are presented in Table 6.

From Table (6), the most sensitive parameter for infectious human component, H_i , is the transition rate from the aquatic stage to the adult stage of the mosquito population, σ . Any increase in the population of adult female mosquito will increase the infected mosquito, thus, leads to an increase in the infectious human class. Other highly significant parameter is the recovery rate of infected individuals, γ_h , and followed by the biting rate, b , the mortality rate of mosquito, μ_m , and the transmission probability rate from human to mosquito, β_m , and from mosquito to human, β_h . These parameters are also among the important parameter for R_0 .

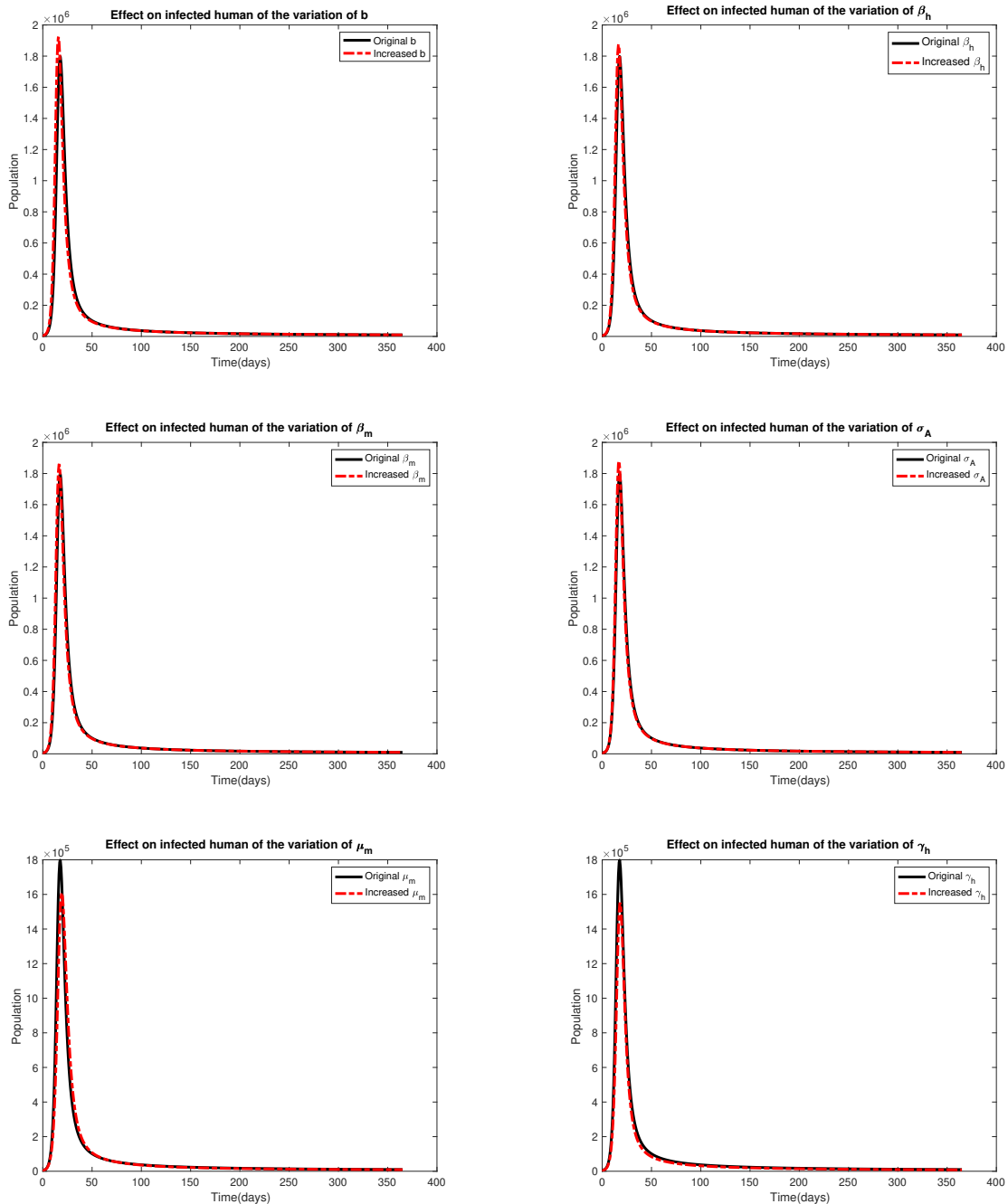


Figure 1. Infected human population with the initial parameter value (solid line) and with an increase of 10% of a specific parameter (dashed line).

6. Discussion and Conclusion

Together these results provide important insights into the contribution to the dengue disease transmission as well as the prevalence of disease. The most important parameter for initial disease transmission is the mortality rate of the mosquito population, μ_m , and this parameter is also highly significant in the disease prevalence. This parameter is certainly become the biggest

Table 6. Sensitivity indices of model (1) of the point of equilibrium.

	A_m	M_s	M_i	H_s	H_i	H_r
q	+0.0542	+0.1658	+0.5721	-0.4973	+0.0923	+0.1626
ϕ	+0.0663	+0.2028	+0.6998	-0.6083	+0.1129	+0.1989
σ_A	+0.1068	+2.7016	+9.3213	-8.1027	+1.5049	+2.6494
μ_A	-0.0696	-0.2129	-0.7347	+0.6386	-0.1186	-0.2088
μ_m	-0.0381	-0.8161	-3.9084	+3.3975	-0.6310	-1.1109
μ_h	0	+0.0002	-0.2003	+0.1271	-0.0906	-0.5194
b	0	-0.0028	+3.7291	-4.0526	+0.7527	+1.3251
β_m	0	-0.0024	+3.2107	-2.7910	+0.5184	+0.9126
β_h	0	-0.0004	+0.5183	-1.2616	+0.2142	+0.4125
γ_h	0	+0.0023	-3.0499	+2.6512	-1.3787	-0.8664

challenge in reducing the transmission rate, as increasing the mortality rate is a whole lot more difficult than reducing it. However, this can be practically done by lowering the natural birth rate of the mosquitoes and also control their frequent blood meals, through the destruction of breeding sites and the use of insecticides. These strategies can also be used to tackle parameter σ_A , which is the most sensitive parameter in the disease prevalence.

The second most important parameter is the mosquito biting rate, b . This parameter cannot be targeted directly through the intervention approaches but can be done by lowering mosquito-human contacts. Clearly, reducing the frequent contacts between humans and mosquitoes, through a reduction in the regularity of mosquito blood meals, as well as the number of bites that a human can tolerate can give a significant effect on the disease transmission. The strategies that can reduce the human-mosquito contact are including the use of insecticide-treated bed nets, mosquito repellent, and indoor residual spraying.

The analysis also shows that the human recovery rate parameter γ_h has an important role in the disease transmission and disease prevalence. This parameter can be reduced through a prompt and effective case management by the health authorities which emphasize immediate and accurate diagnosis of the disease and proper medical treatment of dengue. Furthermore, the transmission probability from an infected human to mosquito β_m and the transmission probability from an infected mosquito to human β_h are also important. Parameter β_m can be treated through current intervention strategies such as the release of genetically modified mosquitoes (GM). While parameter β_h can be managed by, for instance, in Malaysia, fogging will be carried out based on the viral cases reported, hence, would reduce the chances of the infected mosquitoes to transmit the virus to susceptible individuals.

Apart from that, we have observed an interesting result for the proposed fractional order dengue models. The calculated sensitivity indices for model (1) and model (2) indicates that the order of the differential equation has a significant effect on dengue transmission. As the order of the differential equation represents the memory of the population, the targeted interventions to control the disease can be planned accordingly, by taking into consideration every aspect involving memory, especially in the mosquito population. We believe that the research direction initiated in this study can benefit the public health authorities in designing a proper program or policy in the effort of reducing the rising dengue cases.

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Appendix

In this appendix the computation of the sensitivity indices of the point of endemic equilibrium described in [2] is given. By using the formula in (1), the partial derivative of the state variables needs to be evaluated at the endemic equilibrium point with respect to the parameters. The step-by-step computations are given as follow:

- (i) For ease of notation, we suppose that the six state variables at the endemic equilibrium point $E_2 = (A_m^*, M_s^*, M_i^*, H_s^*, H_i^*, H_r^*)$ by x_1, x_2, \dots, x_6 , the parameters $(q, \phi, \dots, \gamma_h)$ by p_1, p_2, \dots, p_{10} , and the six equilibrium equation of the model by

$$\begin{aligned} f_1(x_1, \dots, x_6; p_1, \dots, p_{10}) &= 0, \\ &\vdots \\ f_7(x_1, \dots, x_6; p_1, \dots, p_{10}) &= 0. \end{aligned} \quad (7)$$

- (ii) The partial derivative $\partial x_i / \partial p_j$ for $1 \leq i \leq 6$ and $1 \leq j \leq 10$ for the baseline parameter values is evaluated with the corresponding endemic equilibrium.
- (iii) Taking full derivatives of the six equilibrium equations (7) with respect to the ten parameters, p_j , gives us equations of the form,

$$\frac{df_k}{dp_j} = \sum_{i=1}^6 \left(\frac{\partial f_k}{\partial x_i} \frac{\partial x_i}{\partial p_j} \right) + \sum_{l=1}^{10} \left(\frac{\partial f_k}{\partial p_l} \frac{\partial p_l}{\partial p_j} \right) = 0, \quad (8)$$

for $1 \leq k \leq 6$ and $1 \leq j \leq 10$. However, $\partial p_l / \partial p_j = 0$ if $l \neq j$ so each equation in (8) reduces to

$$\sum_{i=1}^6 \frac{\partial f_k}{\partial x_i} \frac{\partial x_i}{\partial p_j} = - \frac{\partial f_k}{\partial p_j}. \quad (9)$$

- (iv) Equation (9) can be written as the ten linear systems of six coupled equations as follows

$$Az^{(j)} = b^{(j)}, \quad (10)$$

where A is the 6×6 Jacobian matrix of the dengue model (1) with $A_{ki} = \partial f_k / \partial x_i$, $z^{(j)}$ is the unknown 6×1 vector with the i^{th} term of $z^{(j)}$ given by $\partial x_i / \partial p_j$, and $b^{(j)}$ is a 6×1 vector with the k^{th} term given by $-\partial f_k / \partial p_j$.

- (v) Finally, we multiply $\partial x_i / \partial p_j$ by p_j / x_i , as in the Definition 1 of the normalized forward sensitivity index.

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