

LOCAL STABILITY OF DENGUE MODEL USING THE FRACTIONAL ORDER SYSTEM WITH DIFFERENT MEMORY EFFECT ON THE HOST AND VECTOR POPULATION

by

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In this study, we formulate a fractional order dengue model by considering different order dynamics on human and mosquito population. The order of the differential equation is associated with the index of memory. Both human and mosquito carry a different value of order to showcase the different memory effect implies to each of them in the transmission process. Local stability of the equilibria is obtained based on the threshold parameter related to the basic reproduction number, denoted by R_0 . Finally, numerical simulations of the model are conducted to study the dynamical behavior of the system.

Key words: dengue fever, fractional, local stability, epidemiology

Introduction

Dengue is a serious mosquito-viral infection caused by four distinct, but closely related virus serotypes identified as DEN-I, DEN-II, DEN-III, and DEN-IV. Dengue is endemic in at least 128 countries, mostly in the tropical and subtropical regions De Los Reyes and Escaner [1]. The virus is transmitted to humans thru the bite of the *Aedes* female mosquito, namely *Aedes aegypti* (primary vector), and *Aedes albopictus*. The *Aedes* mosquito normally lives in the urban and suburban regions, where containers that can keep the water inside, serve as their breeding sites, Gumel [2]. Individuals who recover from one of the dengue serotypes will gain a lifetime resistance against that serotype, but, only partial or momentary immunity to the other serotypes.

Removing and monitoring *Aedes* mosquitoes is not a stress-free task since they have adaptations to the environment that make them highly resistance or capable to immediately recover to their original numbers after disruptions resulting from natural disasters such as droughts or human interferences. One of the adaptations is the ability of the eggs to tolerate dryness and to survive without water for several months on the inner walls of containers [3]. These are the consequences of the memory and learning behavior of mosquitoes that become the fundamental aspects of their ecology. Thus, entomological factors should be included in the study of any vector-borne disease, for a better understanding and interpretation of the transmission dynamics.

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For many years, deterministic mathematical models for the dengue transmission includes model with control measure, vertical or horizontal transmission, age-structured and stage-structured were developed using the system of ODE [4-13]. However, the integer order models are not the best candidates to integrate memory and learning behavior of either human or mosquito on the transmission dynamics of the disease. The biological studies on the vector-borne disease such as dengue and malaria in [14-16] shown that memory and associative learning behavior of the mosquito or insects, in general, are crucial in the disease transmission. A potential generalization of the ODE system would be a system that carries information about its prior state. Since the behavior of the solution of a fractional derivative is non-local, memory can be included in a dynamical process [17, 18] and the memory can be associated with the order of the derivative [19]. Therefore, the fractional order compartmental system is found to be a proper model to study the transmission of the dengue virus. The fractional order derivative has been found to be a great success in study the nature of a system not only in infectious diseases, but also in thermal dynamics [20, 21], and control system.

Pooseh *et al.* [22] and Diethelm [23] were among the first few researchers that proposed a fractional order dengue model, and they showed that the proposed models are well-fit with the real data. While Sardar *et al.* [24, 25] revealed that their improved fractional order model with a different value of the order for the host and vector population translates the real phenomena of dengue outbreaks in a more sensible sense. As the memory of the vector increased, the disease transmission became more severed. Meanwhile, as the memory of human increased, the intensity of dengue outbreaks reduced. However, none of the existence fractional dengue model incorporated the aquatic stages of the vector (*i. e.* eggs, larva, pupa) into the compartmental model of the mosquito, in which involved in the whole transmission of the disease. Also, the natural explanations of the model parameter and its solutions in terms of the order (memory) demands more investigation. Hamdan and Kilicman in [26] proposed a simple fractional order dengue model included the entomological parameter of the vector population (aquatic phase) and consider only the same order dynamic for human and mosquito population.

In this paper, we extend the previous work in [26] but considering a different order dynamics for both human and mosquito population and all the dimension parameters are assumed to be memory dependent.

Model formulation

Fractional calculus involves integrals and derivatives in the form of any positive arbitrary real orders not restricted to a fraction. The word fractional is reserved only for historical reason [27]. There are several definitions of fractional operators in the literature. The most common definitions of the fractional derivative are the Riemann-Liouville, Caputo, and Grunwald-Letnikov. In this paper, the Caputo's definition will be used since the classical initial conditions can be applied directly without confronting any difficulty when obtaining the solution.

Definition 1. The Caputo derivative of fractional order α of a function $f : R^+ \rightarrow R$ is defined by:

$$D_C^\alpha f(x) = \frac{1}{\Gamma(n-\alpha)} \int_a^x \frac{d^n f}{d\varepsilon^n}(\varepsilon)(x-\varepsilon)^{n-\alpha-1} d\varepsilon \quad (1)$$

where α is the order of the derivative with $n-1 < \alpha < n$ and $n = [\alpha] + 1$. The $\Gamma(n-\alpha)$ is the Euler gamma function defined by the Euler integral:

$$\Gamma(n - \alpha) = \int_0^{\infty} t^{n-\alpha-1} e^{-t} dt \quad (2)$$

where $t^{n-\alpha-1} = e^{(n-\alpha-1)\log(t)}$.

The total human population is assumed to be constant and represented by H . It is distributed into three parts specifically called susceptible human, $H_s(t)$, infected human, $H_i(t)$, and recovered/immune human, $H_r(t)$. Correspondingly, the total mosquito population, M , is assumed to be constant and subdivided into susceptible mosquito, $M_s(t)$, and infected mosquito, $M_i(t)$. The recovered class population is not considered for the mosquito population since their lifespan is very short. In addition, the aquatic stage of the mosquito involving egg, larvae, and pupa is included and denoted by $A_m(t)$. The system of fractional order differential equation of a different order dynamics concerning human and mosquito population is given by:

$$\begin{aligned} D^{\alpha_m} A_m &= q\phi^{\alpha_m} \left(1 - \frac{A_m}{C}\right) M - (\sigma_A^{\alpha_m} + \mu_A^{\alpha_m}) A_m \\ D^{\alpha_m} M_s &= \sigma_A^{\alpha_m} A_m - \frac{b^{\alpha_m} \beta_m}{H} M_s H_i - \mu_m^{\alpha_m} M_s \\ D^{\alpha_m} M_i &= \frac{b^{\alpha_m} \beta_m}{H} M_s H_i - \mu_m^{\alpha_m} M_i \\ D^{\alpha_h} H_s &= \mu_h^{\alpha_h} (H - H_s) - \frac{b^{\alpha_h} \beta_h}{H} H_s M_i \\ D^{\alpha_h} H_i &= \frac{b^{\alpha_h} \beta_h}{H} H_s M_i - (\gamma_h^{\alpha_h} + \mu_h^{\alpha_h}) H_i \\ D^{\alpha_h} H_r &= \gamma_h^{\alpha_h} H_i - \mu_h^{\alpha_h} H_r \end{aligned} \quad (3)$$

where $\alpha_m, \alpha_h \in (0,1)$ is the order. All parameters are assumed to be non-negative and the biological meaning of each parameter are listed in tab. 1. Since $H = H_s + H_i + H_r$, then we can have $H_r = H - H_s + H_i$, thus system of eq. (3) can be reduced to the following system:

$$\begin{aligned} D^{\alpha_m} A_m &= q\phi^{\alpha_m} \left(1 - \frac{A_m}{C}\right) M - (\sigma_A^{\alpha_m} + \mu_A^{\alpha_m}) A_m \\ D^{\alpha_m} M_s &= \sigma_A^{\alpha_m} A_m - \frac{b^{\alpha_m} \beta_m}{H} M_s H_i - \mu_m^{\alpha_m} M_s \\ D^{\alpha_m} M_i &= \frac{b^{\alpha_m} \beta_m}{H} M_s H_i - \mu_m^{\alpha_m} M_i \\ D^{\alpha_h} H_s &= \mu_h^{\alpha_h} (H - H_s) - \frac{b^{\alpha_h} \beta_h}{H} H_s M_i \\ D^{\alpha_h} H_i &= \frac{b^{\alpha_h} \beta_h}{H} H_s M_i - (\gamma_h^{\alpha_h} + \mu_h^{\alpha_h}) H_i \end{aligned} \quad (4)$$

Lemma 2. The closed set

$$\begin{aligned} \Omega &= \{(A_m, M_s, M_i, H_s, H_i) \in \mathbb{R}_+^5 : 0 \leq H_s + H_i = K ; 0 \leq M_s + M_i \leq V_1 \\ &V_1 \geq \frac{\sigma_A^{\alpha_m} A_m}{\mu_m^{\alpha_m}} ; 0 \leq A_m \leq V_2 \text{ and } V_2 \geq q\phi^{\alpha_m} M\} \end{aligned}$$

Table 1. Nomenclature

Parameter	Biological meaning
q	Proportion of eggs that results in female mosquito
ϕ	Oviposition rate
σ_A	Transition rate from aquatic stage to adult
μ_A	Per capita mortality rate of aquatic stage
$1/\mu_m$	Average lifespan of adult mosquito
$1/\mu_h$	Average lifespan of human
b	Mosquito biting rate
β_m	Transmission probability from human to vector
β_h	Transmission probability from vector to human
γ_h	Recovery rate in the human population
C	Mosquito carrying capacity
ρ	Density

where

$$R_m = \frac{q\phi^{\alpha_m}\sigma_A^{\alpha_m}}{\mu_m^{\alpha_m}(\sigma_A^{\alpha_m} + \mu_A^{\alpha_m})}$$

The R_m is biologically interpreted as the basic offspring of the vector population. These two equilibrium is known as the disease-free equilibrium. We are interested in E_1 as this equilibrium is biologically realistic since the mosquito population exists.

The basic reproduction number, R_0 , is computed using the next-generation matrix approach where:

$$R_0 = \rho(FV^{-1}) \quad (8)$$

where F is the new infection terms matrix and V is the transition terms. The basic reproduction number, R_0 , corresponds to system of eqs. (3) is given:

$$R_0 = \sqrt{\frac{b^{\alpha_m} b^{\alpha_h} \beta_m \beta_h \sigma_A^{\alpha_m} C \left(1 - \frac{1}{R_m}\right)}{H \mu_m^{2\alpha_m} (\gamma_h^{\alpha_h} + \mu_h^{\alpha_h})}} \quad (9)$$

According to [5], based on the basic reproduction number, R_0 , in the integer order cases, a new case of dengue can only happen after two bites from the same *Aedes* mosquito. Whereas, in the fractional derivative case in eq. (10), we observed that the new case of dengue is dependent on the order α . In other words, we can say that the new case of dengue depends on the memory of both human and mosquito population.

The third equilibrium is called positive endemic equilibrium and is given by $E_2^* = (A_m^*, M_s^*, M_i^*, H_s^*, H_i^*)$ where:

is positively invariant with respect to model of eqs. (4).

Proof. The prove is similar to the proof in [26].

Theoretical analysis

Equilibrium points

The equilibrium points of the reduced system (4) are obtained by equating the derivative to zero, and in our case yielding to three equilibrium points.

$$E_0 = (0, 0, 0, H, 0) \quad (5)$$

$$E_1 = (\tilde{A}_m, \tilde{M}_s, 0, H, 0) \quad (6)$$

where \tilde{A}_m and \tilde{M}_s are given:

$$\tilde{A}_m = C \left(1 - \frac{1}{R_m}\right) \text{ and } \tilde{M}_s = \frac{\sigma_A^{\alpha_m} \tilde{A}_m}{\mu_m^{\alpha_m}} \quad (7)$$

$$\begin{aligned}
 A_m^* &= C \left(1 - \frac{1}{R_m} \right) \\
 M_s^* &= \frac{\sigma_A^{\alpha_m} C \left(1 - \frac{1}{R_m} \right) \left[b^{\alpha_m} \beta_m \mu_h^{\alpha_h} + \mu_m^{\alpha_m} (\gamma_h^{\alpha_h} + \mu_h^{\alpha_h}) R_0^2 \right]}{\mu_m^{\alpha_m} R_0^2 K_1} \\
 M_i^* &= \frac{\sigma_A^{\alpha_m} C \left(1 - \frac{1}{R_m} \right) b^{\alpha_m} \beta_m \mu_h^{\alpha_h} (R_0^2 - 1)}{\mu_m^{\alpha_m} R_0^2 K_1} \\
 H_s^* &= \frac{HK_2}{K_2 + \mu_m^{\alpha_m} (\gamma_h^{\alpha_h} + \mu_h^{\alpha_h}) (R_0^2 - 1)} \\
 H_i^* &= \frac{H \mu_m^{\alpha_m} \mu_h^{\alpha_h} (R_0^2 - 1)}{K_2 + \mu_m^{\alpha_m} (\gamma_h^{\alpha_h} + \mu_h^{\alpha_h}) (R_0^2 - 1)}
 \end{aligned} \tag{10}$$

with $K_1 = b^{\alpha_m} \beta_m \mu_h^{\alpha_h} + \gamma_h^{\alpha_h} + \mu_h^{\alpha_h}$ and $K_2 = b^{\alpha_m} \beta_m \mu_h^{\alpha_h} + \mu_m^{\alpha_m} (\gamma_h^{\alpha_h} + \mu_h^{\alpha_h})$. For E_2^* to be biologically meaningful, all the co-ordinates need to be positive. Obviously, A_m^* and M_s^* are positive. Meanwhile, for the other components to be positive, $R_0 > 1$. Thus, leads to the following result.

Theorem 3. The reduced system of eq. (4) with regards to model (3), has a unique positive endemic equilibrium $E_2^* = (A_m^*, M_s^*, M_i^*, H_s^*, H_i^*)$ if $R_0 > 1$.

Local stability

The linear stability of the equilibrium points can be established similar to the case in the system of ODE using the basic reproduction number R_0 . To examine further the stability of the equilibria of system of eq. (4), we apply the fundamental theorem established by Matignon [28].

Theorem 4. [29] Consider the following commensurate fractional order system:

$$\begin{aligned}
 D^\alpha x(t) &= f[t, x(t)] \\
 x(t_0) &= x_0
 \end{aligned} \tag{11}$$

where D^α is the Caputo's derivative of the order $0 < \alpha \leq 1$ and $f[t, x(t)]: \mathbb{R}^+ \times \mathbb{R}^n \rightarrow \mathbb{R}^n$ is a vector field. The equilibrium points of this system are locally asymptotically stable if all eigenvalues λ_i of the Jacobian matrix evaluated at the equilibrium point satisfy the following condition:

$$|\arg \lambda_i| > \frac{\alpha\pi}{2} \tag{12}$$

We obtain the following results for the local stability of the disease-free equilibrium and endemic equilibrium of system (4).

Theorem 5. The disease-free equilibrium E_1 is locally asymptotically stable if $R_0 < 1$ and unstable otherwise.

Proof. Following *Theorem 4*, to prove the local stability of E_1 , it is sufficient to show that all eigenvalues of the Jacobian matrix of system of eqs. (4) evaluated at E_1 have non-positive real parts. The Jacobian matrix of the system evaluated at the equilibrium point, E_1 is given:

$$J(E_1) = \begin{bmatrix} -R_m(\sigma_A^{\alpha_m} + \mu_A^{\alpha_m}) & 0 & 0 & 0 & 0 \\ \sigma_A^{\alpha_m} & -\mu_m^{\alpha_m} & 0 & 0 & -\frac{b^{\alpha_m} \beta_m}{H} \tilde{M}_s \\ 0 & 0 & -\mu_m^{\alpha_m} & 0 & \frac{b^{\alpha_m} \beta_m}{H} \tilde{M}_s \\ 0 & 0 & -b^{\alpha_h} \beta_h & -\mu_h^{\alpha_h} & 0 \\ 0 & 0 & b^{\alpha_h} \beta_h & 0 & -(\gamma_h^{\alpha_h} + \mu_h^{\alpha_h}) \end{bmatrix} \quad (13)$$

The calculated eigenvalues are $\lambda_1 = -R_m(\sigma_A^{\alpha_m} + \mu_A^{\alpha_m})$, $\lambda_2 = -\mu_m^{\alpha_m}$, $\lambda_3 = -\mu_h^{\alpha_h}$. The other two eigenvalues are determined by the roots of the quadratic equation:

$$\lambda^2 + (\mu_m^{\alpha_m} + \gamma_h^{\alpha_h} + \mu_h^{\alpha_h})\lambda + \mu_m^{\alpha_m}(\gamma_h^{\alpha_h} + \mu_h^{\alpha_h})(1 - R_0) = 0 \quad (14)$$

From the characteristic polynomial in eq. (15), to get negative real roots, $R_0 < 1$. Thus, tells us that E_1 is locally asymptotically stable if $R_0 < 1$, and unstable when $R_0 > 1$.

In *Theorem 3* we showed that the positive endemic equilibrium exists if $R_0 > 1$. Now, we will determine the condition for the local stability of the endemic equilibrium. According to *Theorem 4*, the local stability of the endemic equilibrium point E_2^* can be determined by showing all the eigenvalues of the following Jacobian matrix satisfy the condition in (13):

$$J(E_2^*) = \begin{bmatrix} -M_1 & 0 & 0 & 0 & 0 \\ \sigma_A^{\alpha_m} & -M_2 & 0 & 0 & M_3 \\ 0 & M_2 - \mu_m^{\alpha_m} & -\mu_m^{\alpha_m} & 0 & -M_3 \\ 0 & 0 & -M_4 & -M_5 & 0 \\ 0 & 0 & M_4 & M_5 - \mu_h^{\alpha_h} & -M_6 \end{bmatrix} \quad (15)$$

where

$$M_1 = \frac{-q\phi^{\alpha_m} M}{C} - (\sigma_A^{\alpha_m} + \mu_A^{\alpha_m}), \quad M_2 = \lambda_m^* + \mu_m^{\alpha_m}, \quad M_3 = \frac{b^{\alpha_m} \beta_m M_s^*}{H} \quad (16)$$

$$M_4 = \frac{b^{\alpha_h} \beta_h H_s^*}{H}, \quad M_5 = \lambda_h^* + \mu_h^{\alpha_h}, \quad M_6 = \gamma_h^{\alpha_h} + \mu_h^{\alpha_h}$$

and λ_m^* and λ_h^* is the force of infection from human to mosquito and the force of infection from mosquito to human, respectively,

$$\lambda_m^* = \frac{b^{\alpha_m} \beta_m H_i^*}{H}, \quad \lambda_h^* = \frac{b^{\alpha_h} \beta_h M_i^*}{H} \quad (17)$$

The characteristic equation of $J(E_2^*)$ is given:

$$(t + \mu_m^{\alpha_m}) \left[t + (\gamma_h^{\alpha_h} + \mu_h^{\alpha_h}) \right] (t^3 + a_1 t^2 + a_2 t + a_3) = 0 \quad (18)$$

where a_1, a_2 , and a_3 are given:

$$\begin{aligned}a_1 &= M_1 + M_2 + M_5 \\a_2 &= M_5(M_1 + M_2) + M_1M_2 \\a_3 &= M_1M_2M_5 + M_3M_4(1 - M_2) + M_3M_4\mu_m^{\alpha_m}\end{aligned}\quad (19)$$

If $p(x) = x^3 + a_1x^2 + a_2x + a_3$. Let $D(p)$ be the discriminant of a polynomial $p(x)$, then:

$$D(p) = - \begin{vmatrix} 1 & a_1 & a_2 & a_3 & 0 \\ 0 & 1 & a_1 & a_2 & a_3 \\ 3 & 2a_1 & a_2 & 0 & 0 \\ 0 & 3 & a_1 & a_2 & 0 \\ 0 & 0 & 3 & 2a_1 & a_2 \end{vmatrix} = 18a_1a_2a_3 + (a_1a_2)^2 - 4a_3a_1^3 - 4a_2^3 - 27a_3^2 \quad (20)$$

Following El-Shahed and Alsaedi in [30], we have the following proposition:

Proposition 6. One assumes that E_2^* exist in \mathbb{R}_+^3 .

- If the discriminant of $p(x)$ which is $D(p)$ is positive and Routh-Hurwitz is satisfied, that is $D(p) > 0$, $a_1 > 0$, $a_3 > 0$ and $a_1a_2 > a_3$, then E_2^* is locally asymptotically stable.
- If $D(p) < 0$, $a_1 > 0$, $a_2 > 0$, $a_1a_2 = a_3$ and $\alpha \in [0, 1)$, then E_2^* is locally asymptotically stable.
- If $D(p) < 0$, $a_1 < 0$, $a_2 < 0$ and $\alpha > 2/3$, then E_2^* is unstable.
- The necessary condition for E_2^* to be locally asymptotically stable is, $a_3 > 0$.

Numerical results

In this section, numerical simulations are conducted to exemplify the theoretical analysis done in section *Theoretical analysis*. Also, several results of different values of α are presented to observe the consequences of using different parameter α on both human and mosquito population on the dynamics of the fractional order dengue model of eq. (3). To simulate the dengue model (3), we apply the method established in [31]. The parameters value used are the same as in [26] and the initial conditions are given (tab. 2) as follows based on the reported cases of dengue in Selangor, Malaysia in 2013 [32].

According to fig. 1, the disease-free equilibrium E_1 changes from being stable to unstable at $R_0 = 1$. This behavior is called forward bifurcation. The main features of this type of bifurcation are that the non-existence of the endemic equilibrium nearby the disease-free equilibrium when $R_0 < 1$ and a low level of endemicity when R_0 is slightly beyond unity [2]. Therefore, the requirement of $R_0 < 1$ is necessary and sufficient to eliminate the disease for model of eq. (3).

Figures 2 and 3 show that when $R_0 < 1$, the solutions approach the disease-free equilibrium and when $R_0 > 1$, the solutions move towards the endemic equilibrium.

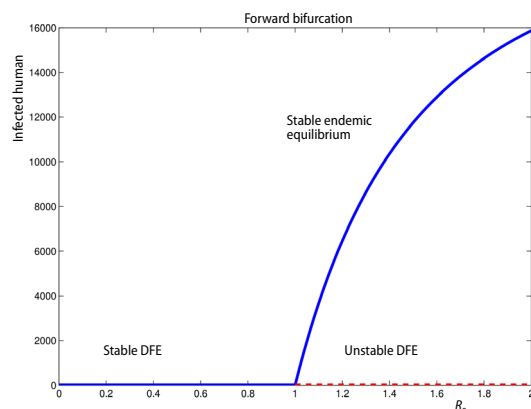


Figure 1. Bifurcation diagram for the infected human population of the system (3)

Table 2. Initial conditions for system of eqs. (4)

Variable	Value
$A_m(0)$	17370000
$M_s(0)$	23160000
$M_i(0)$	2316000
$H_s(0)$	5766148
$H_i(0)$	23852

librium, respectively. Thus, verified *Theorem 5* in section *Theoretical analysis*. From these figures, different dynamics are observed when different order is assigned to the host and vector compartmental model. At the aquatic stage of the mosquito population, the trajectories suggest that by having α_m, α_h between 0 and 1 and making $\alpha_h < \alpha_m$, the population of the aquatic form of the vector is decreasing. As a result of this, we can observe that the number of infectious mosquitoes is also decreasing, thus, reducing the number of the infected human population. Meanwhile, in the endemic case where the disease is persists, when $\alpha_m < \alpha_h$, we can see that the number of the susceptible human population drop and the infected human population is at the highest value.

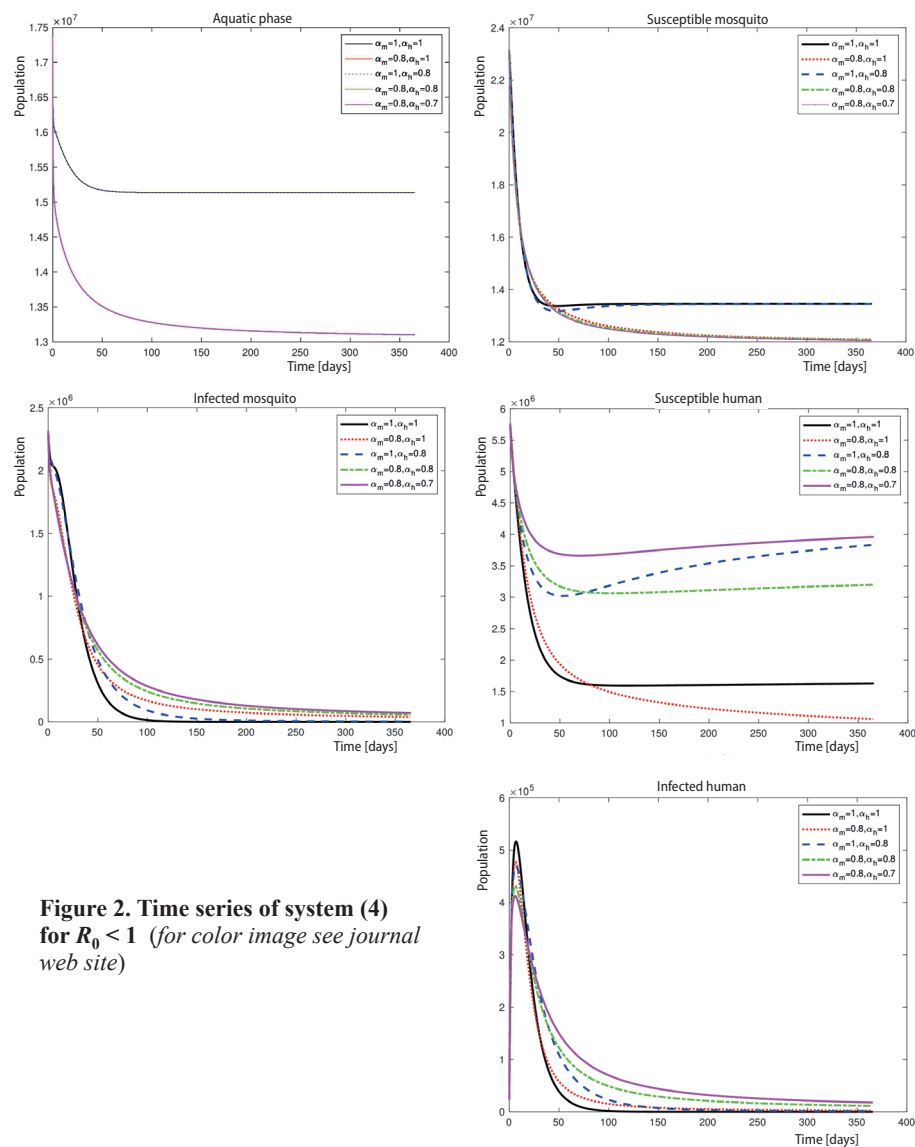


Figure 2. Time series of system (4) for $R_0 < 1$ (for color image see journal web site)

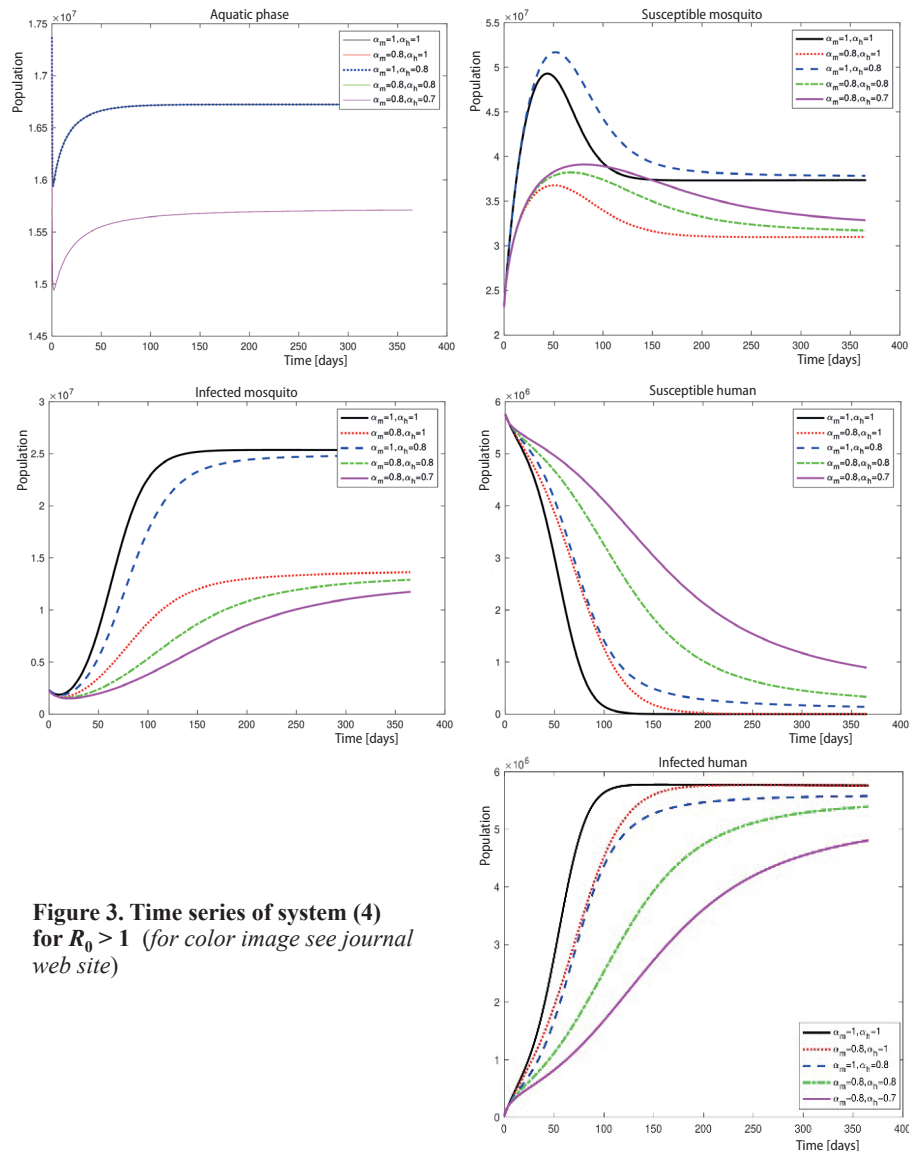


Figure 3. Time series of system (4) for $R_0 > 1$ (for color image see journal web site)

Since the order of the differential equation is interpreted as the index of memory, making $\alpha_{m,h} \rightarrow 0$, means that the memory of the particular population is increase. Thus, the results tell us that memory in human and mosquito population is significant in the disease transmission. In particular, increasing the memory of the mosquito population will increase the mosquito abundance, hence, increase the dengue transmission rate. Whereas, increasing the memory of the human population will slow down the transmission rate. This result numerically interprets the experimental results in [14, 16] and in agreement with the study in [24].

It is worth to mention that solutions of the fractional order in figs. 2 and 3 required more time to converge to the steady state compared to the integer order solution. This numerically explained the fact that exponential stability cannot be used to characterize the asymptotic stability of fractional differential systems [33].

Conclusion

In this paper, we extend the fractional order dengue model in [26] by considering a different order dynamics on human and mosquito population. For our fractional order model, we proved that the disease-free equilibrium is locally asymptotically stable when $R_0 < 1$. The basic reproduction number R_0 corresponds to the proposed model indicates that the index of memory represent by order α has a significant contribution in the disease transmission. In the fractional order model, it is not necessary for a new case of dengue to happen after two bites of the same mosquito. Other factors can lead to the occurrence of new cases and such factors can be associated with the memory of both human and mosquito population.

The memory in vector population is related to their blood feeding behavior like the selection of host location and host choice of mosquito which is not a random process and depend upon its prior experience [34, 35]. Besides, memory and learning behavior in mosquitoes are also significant for selection of their breeding site. Meanwhile, in the human population, the memory can be associated with the experience and awareness in treating the breeding site of the dengue mosquitoes. Increasing the awareness of the people in the community in treating and controlling the dengue transmission will eventually help the government to get rid of the breeding site of the mosquito. Thus, can reduce the dengue cases in the community within the reasonable time frame.

The proposed fractional order dengue model is believed to be more realistic and significant to the real-life situation of dengue disease compared to the integer order model. This study can give a good insight to the experimentalist and public health practitioners in designing their experiments and control strategies in order to eradicate the disease in the community. This model can be improved by including different serotypes and environmental factors such as rainfall and temperature. Thus, we reserved these in our future study.

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