Optimal bang-bang control for variable-order dengue virus; numerical studies

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HIGHLIGHTS

- A novel variable-order nonlinear model of dengue virus is analyzed as an optimal control problem.
- The bang-bang control is suggested to minimize the dose and duration of the intervention for model.
- Necessary conditions for the control problem are derived.
- Two numerical methods are constructed to solve the proposed optimal control problem.
- Comparative studies and numerical simulations are implemented.

ABSTRACT

Introduction: Dengue and Malaria are the most important mosquito-borne viral diseases affecting humans. Fever is transmitted between human hosts by infected female aedes mosquitoes. The modeling study of viral infections is very useful to show how the virus replicates in an infected individual and how the human antibody response acts to control that replication, which antibody playing a key role in controlling infection.

Objectives: Optimal control of a novel variable-order nonlinear model of dengue virus is studied in the present work. Bang-bang control is suggested to minimize the viral infection as well as quick clearance of the virus from the host. Necessary conditions for the control problem are given. The variable-order derivatives are given in the sense of Caputo. Moreover, the parameters of the proposed model are dependent on the same variable-order fractional power. Two numerical schemes are constructed for solving the optimality systems. Comparative studies and numerical simulations are implemented. The variable-order fractional derivative can be describe the effects of long variable memory of time dependent systems than the integer order and fractional order derivatives.

Methods: Both the nonstandard generalized fourth order Runge-Kutta and the nonstandard generalized Euler methods are presented.
Introduction

Dengue and Malaria are the most important mosquito-borne viral diseases affecting humans. Fever is transmitted between human hosts by infected female aedes mosquitoes. The modeling study of viral infections is very useful to show how replication of virus in an infected case and how acts the human antibody. The model presented in this paper confirmed the dynamics of defective interfering particles (DI) with virus. In [1] the authors give quantitative insight into the relationship between antibody levels and the efficiency of viral clearance. In [2], the authors keep the rate of infection and rate of antibody-mediated virus neutralization constant for each serotype and included the immune cell-mediated antibody production, which is triggered by both the free virus and free defective particles. In [4], short fragments of dengue virus (DENV) RNA containing only key regulatory elements at the 3’ and 5’ ends of the genome were recovered from the sera of patients infected with any of the four DENV serotypes. Identical RNA fragments were detected in the supernatant from cultures of Aedes mosquito cells that were infected by the addition of sera from dengue patients, suggesting that the sub-genomic RNA might be transmitted between human and mosquito hosts in defective interfering (DI) viral particles. The authors in [5] conclude that DI particles may be important determinants of the course of acute, self-limiting viral infections and of persistent, slowly progressing viral diseases. In addition, many host reactions may alter the production of DI particles and thus influence the outcome of viral infections.

Recently, optimal control of diseases treatment has become popular in biology. In optimal control problems, it is sometimes the case that a control is restricted to be between a lower and an upper bound. If the optimal control switches from one extreme to the other (i.e., is strictly never in between the bounds), then that control is referred to be a bang-bang solution. Bang-bang controls frequently arise in minimum-time problems. Bang-bang solutions also arise when the Hamiltonian is linear in the control variable; application of Pontryagin’s minimum or maximum principle will then lead to pushing the control to its upper or lower bound depending on the sign of the coefficient of u in the Hamiltonian. In order to find DI particles minimum dose, we used bang-bang control, that should be delivered to minimize viremia duration and height, for more details on advantage of bang-bang control see ([6,7]).

Since integer order derivative is local in nature so it does not contain the complete memory and hence it does not describe the physical behavior of the model. To overcome this challenge, we use the fractional derivative. It is well known that fractional derivative is non-local in nature and due to this characteristic, it contains the whole memory and physical nature of the model. Fractional order models are used to determine the real world problems with a strategic solution. There are many mathematicians in this field, see for example ([21–24]).

On the other side, it is known that variable-order fractional derivative (VOFD) can be describe the effects of long variable memory of time dependent systems, but the integer order derivative can be used to characterize the short memory. Gómez-Aguilar et. al., in [8] studied the advantage of using variable order in the fractional ordinary differential equations (FODE) and proposed a new generalize numerical schemes for simulating variable-order fractional FODE operators with power-law, exponential-law and Mittag–Leffler kernel. Also, Chen et al., in [9] presented an interesting review on variable-order fractional differential equations. Also, Sweilam et al., introduced some numerical studies for variable-order fractional differential equations (VOFDEs), for more details see [10–15]. Recently, Sweilam and AL-Mekhlafi introduced some numerical studies for variable-order optimal control (VOC) models, for more details see [16–18].

The aim of this work is to extend the model of dengue virus which given in [2] to variable-order model with modified parameters. The bang-bang control is suggested to minimize the viral infection as well as quick clearance of the virus from the host. Necessary conditions for the control problem are given. The behavior of the proposed model will be studied by four numerical methods; the generalized Euler method (GEM), the generalized fourth-order Runge–Kutta method (GRK4M), the nonstandard generalized Euler method (NGEM) and the nonstandard generalized fourth-order Runge–Kutta method (NGRK4M). Comparative studies are given.

The rest of this paper is structured as follows: Some mathematical tools of VOFD are given in ‘Notations and Preliminaries’. The proposed VOFD model with bang-bang control is introduced in ‘Model Problem’. Numerical schemes for solving the optimality system are given in ‘Numerical Methods for VOC Model’. Comparative studies and numerical simulations are presented in ‘Numerical Simulations’. In ‘Conclusions’, the conclusions are introduced.

Results: We have successfully applied a kind of Pontryagin’s maximum principle with bang-bang control and were able to reduce the viraemia level by adding the dose of DI particles. The nonstandard generalized fourth order Runge-Kutta method has the best results than nonstandard generalized Euler method. Conclusion: The combination of the variable-order fractional derivative and bang-bang control in the Dengue mathematical model improves the dynamics of the model. The nonstandard generalized Euler method and the nonstandard generalized fourth order Runge-Kutta method can be used to study the variable order fractional optimal control problem simply.

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tional Dengue model with modified parameters, it is more general model than the model given in [2]. The competitive dynamics of the DI particles with virus is in the presence of the antibody response. Infected cells are categorized in two classes according to their stages of infection: early and late. The early infected cells (C_P and C_V) are available for super-infection, but the late cells (C_P and C_VD) are not because of the triggered interferon response and alteration in cell membrane receptor dynamics [2]. We use one control variable u(t), the administration of excess DI particles to the model to reduce the viral infection as well as quick clearance of the virus from the host. Both the variables and parameters of proposed model are given in Tables 1 and 2 respectively. The general model is given as follows:

\[ C_0 D^{(2)}_t C_U = r(t) C_U (1 - \frac{N}{K_U}) - k^{(2)}(V(t) + D(t)) C_U(t) + \sigma^{(2)} C_D(t), \]
\[ C_0 D^{(2)}_t C_D = k^{(1)}(C_U D - C_D V) - \sigma^{(2)} C_D, \]
\[ C_0 D^{(2)}_t C_V = k^{(1)}(C_U V - C_D V) - (\pi_1^{(2)} + \mu^{(2)} C_V) C_V, \]
\[ C_0 D^{(2)}_t C_{VD} = \pi_1^{(2)} V C_V - \rho^{(2)} V C_{VD}, \]
\[ C_0 D^{(2)}_t V = k^{(0)} V + \rho^{(2)} C_U V - (\pi_2^{(2)} C_U + \rho^{(2)} C_V V), \]
\[ C_0 D^{(2)}_t Z = \eta_1^{(2)} Z \frac{u(t)}{v} + \eta_1^{(2)} Z \frac{D(t)}{v} C_U. \]

Let:
\[ N(t) = C_U + C_D + C_V + C_{VD}. \]

**Formulation of VOC bang-bang problem**

In the following, we apply a kind of Pontryagin’s maximum principle given in [3], to determine the necessary conditions for optimal control dengue virus model. Consider the following objective functional [2]:

\[ J(u) = \max_{0 \leq u \leq h} \int_{T_0}^{T_f} \left( \frac{1}{2} a V^2(t) + b C_V(t) + c u(t) \right) dt, \]

subjected to the constraint of the following system:

\[ C_0 D^{(2)}_t C_U = r(t) C_U (1 - \frac{N}{K_U}) - k^{(2)}(V(t) + D(t)) C_U(t) + \sigma^{(2)} C_D(t), \]
\[ C_0 D^{(2)}_t C_D = k^{(1)}(C_U D - C_D V) - \sigma^{(2)} C_D, \]
\[ C_0 D^{(2)}_t C_V = k^{(1)}(C_U V - C_D V) - (\pi_1^{(2)} + \mu^{(2)} C_V) C_V, \]
\[ C_0 D^{(2)}_t C_{VD} = \pi_1^{(2)} V C_V - \rho^{(2)} V C_{VD}, \]
\[ C_0 D^{(2)}_t V = \beta(t) C_U V + \rho^{(2)} C_U V - (\pi_2^{(2)} C_U + \rho^{(2)} C_V V), \]
\[ C_0 D^{(2)}_t Z = \eta_1^{(2)} Z \frac{u(t)}{v} + \eta_1^{(2)} Z \frac{D(t)}{v} C_U. \]

\[ \text{Table 1} \]

| States | Description |
|--------|-------------|
| C_U   | The uninfected target cells. |
| C_D   | The infected cells by defective interfering (DI) particles only. |
| C_V   | The infected cells due to only by virus. |
| C_{VD} | The virus infected. |
| V     | Cells infected by (DI) particles and virus. |
| V_D   | The dynamics of standard virus i.e. viremia level. |
| D     | The defective interfering (DI) particles. |
| Z     | The antibody response, for more details see [2]. |

\[ \text{Table 2} \]

| Symbols | Definitions | Values |
|---------|-------------|--------|
| r(t)    | Intrinsic rate of host cell proliferation. | 15.217^{(2)} |
| k^{(2)}(V(t) + D(t)) C_U | Cellular carrying capacity of proliferation. | 3.505^{(2)} |
| C_U     | Uninfected cells without illness. | 1e^9 |
| N(t)    | Rate of infection per virus. | 2.45e^{-2}^{(2)} |
| T_f     | The rate of mutation of V to D within host cells, turning C_V cells into C_D cells. | 37.651^{(2)} |
| T_0     | Natural rate of clearance for D and V. | 9.562^{(2)} |
| C_D     | Natural rate of loss of DI particles within host cells, turning C_D into C_D cells. | 5.836^{(2)} |
| C_V     | Death rate of infected cells. | 2.426^{(2)} |
| C_{VD}  | Triggered immune rate by D or V, see [2]. | 1.607^{(2)} |
| C_{VD}  | Threshold parameter of the triggered immune cells proliferation. | 2e^{10.12}^{(2)} |
| V_D     | Rate of maturation of C_D cells into C_V cells. | 9.863^{(2)} |
| V_D     | Rate at each C_D cells produces V cells. | 68.503e^{(2)} |
| V_D     | Rate at each C_D cells produces D cells. | 1.782e^{(2)} |
| V_D     | Viramea level on the day of illness. | 3.6e^{1.12} |
| Z_D     | Immune level response without illness. | 0.645e^{-1.12} |

where the constants “a, b and c stand for the weighting constants, whereas T_0 and T_f are the initial and final time respectively. According to ([16,17]) the Hamiltonian is given as follows:

\[ H(C_U, C_D, C_V, C_{VD}, V, D, Z, u, \lambda_i) = \frac{1}{2} (a V^2(t) + b C_V(t)) + c u(t) + \sum_{i=1}^{8} \lambda_i F_i, \]

where, \( \lambda_i \) are the adjoint variables or co-state variables and \( F_i \) is the right hand side of system (5) respectively, \( i = 1, \ldots, 8 \).

The necessary conditions can be obtained by extension the conditions in [3] to variable order fractional as ([16–18]). These can be derived from (4) and (6):

\[ \dot{c}_D D^{(2)}_t \lambda_i(t) = - \frac{\partial H}{\partial g_i}, \quad g_i = \{ V, D, Z, C_U, C_D, C_V, C_{VD} \}. \]

\[ \dot{c}_D D^{(2)}_t C_U(t) = \frac{\partial H}{\partial C_U}, \quad \dot{c}_D D^{(2)}_t C_D(t) = \frac{\partial H}{\partial C_D}, \quad \dot{c}_D D^{(2)}_t C_V(t) = \frac{\partial H}{\partial C_V}, \quad \dot{c}_D D^{(2)}_t C_{VD}(t) = \frac{\partial H}{\partial C_{VD}}, \]

\[ \dot{c}_D D^{(2)}_t V(t) = \frac{\partial H}{\partial V}, \quad \dot{c}_D D^{(2)}_t Z(t) = \frac{\partial H}{\partial Z}, \quad \dot{c}_D D^{(2)}_t \psi(t) = \frac{\partial H}{\partial \psi}, \]

where \( \psi(t) \) is a switching function, it can be negative or positive. A singular control will occur when \( \psi(t) = 0 \). The particular time points, when the changes in sign of the switching function are defined as the switching points, where the duration between the switches are called the bang times [2].

**Theorem 1.** If \( u^* \) is the control variable with corresponding state \( C_U, C_D, C_V, C_{VD}, V, D, Z^* \); then there exist adjoint variables \( \lambda_i^*, i = 1, \ldots, 8 \), satisfies the following:

\[ \text{Table 1} \]

| States | Description |
|--------|-------------|
| C_U   | The uninfected target cells. |
| C_D   | The infected cells by defective interfering (DI) particles only. |
| C_V   | The infected cells due to only by virus. |
| C_{VD} | The virus infected. |
| V     | Cells infected by (DI) particles and virus. |
| V_D   | The dynamics of standard virus i.e. viremia level. |
| D     | The defective interfering (DI) particles. |
| Z     | The antibody response, for more details see [2]. |
(i) adjoint equations:
\[ C_1 D_{x_1}^{(0)} \lambda_1(t) = -\lambda_1(t^2(t_0^2(1 - \frac{N^*}{K_{0}^*}) - \frac{N^*}{K_{0}^*} - k^2(t^2(V^* + D^*))}
- \lambda_2^2 \frac{k^2(t^2D^*)}{K_{0}^*} - \lambda_2^2 \frac{k^2(t^2V^*)}{K_{0}^*}, \]
\[ C_1 D_{x_1}^{(0)} \lambda_2(t) = -\lambda_2^2(t^2 \frac{C_u}{K_{0}^*} - \frac{\sigma(t^2)}{\pi(t^2)} + \lambda_2^2 \frac{(k^2(t^2) + \sigma(t^2)^2) - \lambda_2^2 \frac{k^2(t^2V^*)}{K_{0}^*}}, \]
\[ C_1 D_{x_1}^{(0)} \lambda_3(t) = -bC_0 + \lambda_2^2(t^2 \frac{C_u}{K_{0}^*} + \lambda_3^2 \frac{(k^2(t^2) \pi(t^2) + 1 + \mu(t^2)}{\pi(t^2)} - \lambda_2^2 \frac{\pi(t^2)}{\pi(t^2)} - \lambda_2^2 \frac{(k^2(t^2)D^* + \mu(t^2))}{\pi(t^2)}}, \]
\[ C_1 D_{x_1}^{(0)} \lambda_4(t) = \lambda_4^2 \frac{C_0}{K_{0}^*} - \lambda_2^2 \frac{\pi(t^2)}{\pi(t^2)} + \lambda_2^2 \frac{(k^2(t^2)\pi(t^2)^2 + \delta(t^2)}{\delta(t^2)}}, \]
\[ C_1 D_{x_1}^{(0)} \lambda_5(t) = \lambda_5^2(t^2 \frac{C_u}{K_{0}^*} + \lambda_5^2 \frac{(k^2(t^2) + \delta(t^2)}{\delta(t^2)} - \lambda_2^2 \frac{\theta(t^2)\phi(t^2)}{\phi(t^2)} \lambda_2^2(t^2), \]
\[ C_1 D_{x_1}^{(0)} \lambda_6(t) = -aV^* + \lambda_2^2 \frac{k^2(t^2)C_0^2 + \lambda_6^2 \frac{k^2(t^2)C_0}{k^2(t^2)C_0 + \lambda_6^2 \frac{(k^2(t^2) + \theta(t^2)\phi(t^2)}{\phi(t^2)}}, \]
\[ C_1 D_{x_1}^{(0)} \lambda_7(t) = \lambda_7^2 \frac{(k^2(t^2) + \theta(t^2)\phi(t^2)}){\phi(t^2)} - \lambda_2^2 \frac{\theta(t^2)\phi(t^2)}{\phi(t^2)} \lambda_2^2(t^2), \]
\[ H(C_{0}, C_{1}, C_{2}, C_{3}, C_{4}, C_{5}, C_{6}, C_{7}, u, \lambda_0, \psi(t)) = \psi(t)(t + 1) = 0, \quad \psi(t) < 0. \]

(ii) with transversality conditions:
\[ \lambda_i(T_f) = 0, \quad i = 1, 2, \ldots, 8. \]

(ii) optimality condition:
\[ H(C_{0}, C_{1}, C_{2}, C_{3}, C_{4}, C_{5}, C_{6}, C_{7}, u, \lambda_0, \psi(t)) = \min_{0 \leq t \leq T_f} H(C_{0}, C_{1}, C_{2}, C_{3}, C_{4}, C_{5}, C_{6}, C_{7}, u, \lambda_0, \psi(t)). \]

The switching function
\[ \psi(t) = \frac{dH}{du} = C + \lambda_2. \]
So, \( u^* \) is bang-bang, and
\[ u^* = 0, \quad \psi(t) < 0. \]
\[ u^* = 0, \quad \psi(t) > 0. \]

Proof. By (7), we get the system (10), where \( H' = \frac{1}{2} \frac{d}{dt} V(t) + \frac{C_1}{2} + \frac{C_2}{2}) + c \psi(t^2) + \lambda_1^2 \frac{d(t^2)}{d(t^2)} + \lambda_2^2 \frac{d(t^2)}{d(t^2)} + \lambda_3^2 \frac{d(t^2)}{d(t^2)} + \lambda_4^2 \frac{d(t^2)}{d(t^2)} + \lambda_5^2 \frac{d(t^2)}{d(t^2)} + \lambda_6^2 \frac{d(t^2)}{d(t^2)} + \lambda_7^2 \frac{d(t^2)}{d(t^2)} \]
\[ K_1 = kf(t_n, y_n), \]
\[ K_2 = kf\left(t_n + \frac{1}{2}K_1, y_n + \frac{1}{2}K_1\right), \]
\[ K_3 = kf\left(t_n + \frac{1}{2}K_2, y_n + \frac{1}{2}K_2\right), \]
\[ K_4 = kf\left(t_n + \kappa, y_n + K_3\right), \]

where \( \kappa = \frac{\sigma(t_n)\|\mu\|}{\sigma(t_n)\|\mu\|}. \)

**Stability of NGRK4M**

In order to study the stability of NGRK4M, consider for simplicity the test problem:

\[ c \frac{d^{(2)}y(t)}{dt^2} = v_y(t), \quad 0 < t \leq T, \quad 0 < \alpha(t) \leq 1, \quad v < 0, \quad (17) \]

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**Fig. 1.** Behavior of \( V(t), D(t), \) and \( u(t) \) when \( a = b = c = 1 \) and \( \alpha(t) = 1 - 0.001t \) using GRK4M and NGRK4M.

**Fig. 2.** Behavior of \( V(t), D(t), \) and \( Z(t) \) when \( a = b = c = 1 \) at different values of \( \alpha(t) \) using NGRK4M.
$y(0) = y_0$. We can rewrite Eq. (17) using NGRK4M as follows:

$$y(t_{j+1}) = y(t_j) + \frac{1}{6} \varphi(h)^{t_j} \Gamma(\alpha(t_j + 1)) y(t_j), \; j = 0, 1, \ldots, n - 1.$$ (18)

The stability analysis of NGRK4M is similar to the NGEM method [12], when the terms are regrouped, the following equation is achieved:

$$y(t_{j+1}) = \left(1 + \frac{1}{6} \varphi(h)^{t_j} \Gamma(\alpha(t_j + 1)) \right) y(t_j), \; j = 0, 1, \ldots, n - 1.$$ (19)

Then the stability condition [16] is given as follows:

$$-1 < \left(1 + \frac{1}{6} \varphi(h)^{t_j} \Gamma(\alpha(t_j + 1)) \right) < 1,$$

$$0 < \varphi(h)^{t_j} < 12 \Gamma(\alpha(t_j + 1)) \frac{\Gamma(h)}{\Gamma(h + 1)}.$$

### Numerical simulations

In the following, numerical simulations of the optimality systems (10) and (14) are presented. NGEM and NGRK4M are constructed to simulate these systems using the parameter values in Table 2. So we consider the initials states [2]:

$C_0(0) = 10^6, C_0(0) = 0, C_0(0) = 100, C_0(0) = 0, C_0(0) = 0, C_0(0) = 0, C_0(0) = 0, D_0(0) = 10^3, V_0 = 3.6 \times 10^4$, and $Z_0 = 5.645$. Table 3, shows the reduction values of viraemia level $V(t)$ when weighting constants $a = b = c = 1$, upper bounded $u_0 = 2 \times 10^9$ and $t \in [0, 10]$ which is given as follows:

$$\text{Reduction} = \frac{V_{w, \text{out}} - V_{w, \text{out}}}{V_{w, \text{out}}} \times 100\%,$$

where, $V_{w, \text{out}}$ is viraemia level without bang-bang control treatment and $V_{w, \text{out}}$ is viraemia level with bang-bang control treatment. Fig. 1, illustrates the behavior of the approximate solutions using GRK4M and NGRK4M. Fig. 2, shows the behavior of the state variables $V(t), D(t)$ and $Z(t)$ with bang-bang control treatment and different value of $x(t)$ using NGRK4M. Figs. 3 and 4, show the efficiency of the control treatment based on the densities of uninfected cells, viraemia level, DI particles and antibody particles with and without control. Fig. 3, shows that without treatments, the viraemia level is increasing up to some time. But after treatment of adding DI particles, the concentration of antibody particles are increasing up to some time and viraemia level is decreasing. Fig. 4, shows the effect of control treatment on viraemia and defective particles. Figs. 5 and 6, show the effect of DI high dose which reduce the viraemia and increase antibody particles in host body. Fig. 5, shows the behavior of the state $V(t), D(t), Z(t)$ and the optimal control $u(t)$ at different values of upper bounded when $x(t) = 1 - 0.001t$ and $\varphi(h) = 0.025(1 - e^{-t})$ using NGRK4M. Fig. 6, shows the viraemia controlled treatment and particles defective at different values of upper bounded when $x(t) = 1 - 0.001t$ and $\varphi(h) = 0.025(1 - e^{-t})$ using NGRK4M.

### Conclusions

In the present work, optimal bang-bang control for a novel variable order fractional model of dengue virus is presented. The combination of variable order fractional derivative and optimal control in the model improves the dynamics and increases complexity of the model. We have successfully applied a kind of Pontryagin's
maximum principle with bang-bang control to reduce the viraemia level by adding the dose of DI particles. NGEM and NGRK4M are used to study numerically the control problem. Mathematical analysis for NGEM and NGRK4M are introduced. Comparative studies are done and we can conclude from Table 3 that NGRK4M is the best than GEM, NGEM and GRK4M. Also from Fig. 2, we can conclude that the integer and fractional order models are special cases from the variable order model. Moreover, NGRK4M and NGEM can be used to study the variable order fractional optimal control problem simply.

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Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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