Research Article

A Novel Dynamic Model Describing the Spread of the MERS-CoV and the Expression of Dipeptidyl Peptidase 4

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The Middle East respiratory syndrome (MERS) coronavirus, a newly identified pathogen, causes severe pneumonia in humans. MERS is caused by a coronavirus known as MERS-CoV, which attacks the respiratory system. The recently defined receptor for MERS-CoV, dipeptidyl peptidase 4 (DPP4), is generally expressed in endothelial and epithelial cells and has been shown to be present on cultured human nonciliated bronchiolar epithelium cells. In this paper, a class of novel four-dimensional dynamic model describing the infection of MERS-CoV is given, and then global stability of the equilibria of the model is discussed. Our results show that the spread of MERS-CoV can also be controlled by decreasing the expression rate of DPP4.

1. Introduction

The Middle East respiratory syndrome (MERS) coronavirus, a newly identified pathogen, causes severe pneumonia in humans, with a mortality of nearly 44%. Human-to-human spread has been demonstrated, raising the possibility that the infection could become pandemic [1]. A colorized electron micrograph shows the coronavirus MERS-CoV acute viral respiratory illness that is characterized primarily by cough, fever, and shortness of breath and is sometimes associated with severe and potentially fatal complications such as pneumonia and kidney failure. The illness was first observed in June 2012 in Jiddah, Saudi Arabia, and soon afterward it was reported in other countries in the Middle East, including Jordan, Qatar, and the United Arab Emirates (UAE). It later was detected in Europe, including cases in France, Germany, Italy, and the United Kingdom; in the North African country of Tunisia; and in countries more distant from the Middle East, including China, Malaysia, South Korea, and the United States. The largest MERS outbreak outside Saudi Arabia occurred in 2015, when an individual who had recently traveled to the Middle East subsequently fell ill in South Korea, transmitting the disease to close contacts. The dissemination of the disease by infected travelers leaving the Middle East suggested that MERS had the potential to escalate into an international public health emergency. The possibility of a pandemic was thought to be impeded, however, by the limited ability of the disease to be passed from one person to another. MERS is caused by a coronavirus known as MERS-CoV, which attacks the respiratory system. The recently defined receptor for MERS-CoV, dipeptidyl peptidase 4 (DPP4), is generally expressed in endothelial and epithelial cells and has been shown to be present on cultured human nonciliated bronchiolar epithelium cells, providing further information on the respiratory tropism of MERS-CoV [2]. Symptoms of illness appear anytime from 2 to 14 days following infection. Cough, fever, and shortness of breath are the primary symptoms, but others such as diarrhea, nausea, vomiting, and myalgia (muscle pain) can also occur. In some persons, infection produces no symptoms or only mild cold-like symptoms, whereas in others, particularly in persons with underlying medical conditions, infection can produce severe illness [3].
It is well-known that dynamic models are still playing important roles in describing the interactions among uninfected cells, free viruses, and immune responses (see, e.g., [4–7]). A three-dimensional dynamic model for viral infection is proposed by Nowak et al. (see, e.g., [5–7]).

\[\begin{align*}
\dot{T} &= \lambda - (\beta D(t)) v(t) T(t) - d T(t), \\
\dot{I} &= (\beta D(t)) v(t) T(t) - d_1 I(t), \\
\dot{V} &= d_1 N I(t) - c v(t).
\end{align*}\]  

(1)

In model (1), \(T(t)\), \(I(t)\), and \(v(t)\) denote the concentration of uninfected cells, infected cells, and free viruses at time \(t\), respectively. The constant \(\lambda > 0\) is the rate at which new uninfected cells are generated (from a pool of precursor cells). The constants \(d > 0\) and \(\beta \geq 0\) are the death rate of uninfected cells and the rate constant characterizing infection of the cells, respectively. The constant \(d_1 > 0\) is the death rate of the infected cells due to viruses or immune responses. The infected cells produce new viruses at the rate \(d_1 N\) during their life, on average having the length \(1/d_1\), where \(N > 0\) is some integer number. The constant \(c > 0\) is the rate at which the viruses are cleared, and the average lifetime of a free virus is \(1/c\).

Figure 1 shows a interaction procedure between uninfected cells and MERS-CoV mediated by DPP4 receptors. Based on basic dynamic model (1) and Figure 1, we propose the following novel four-dimensional dynamic model which describes the spread of the MERS-CoV and the expression of DPP4:

\[\begin{align*}
\dot{T} &= \lambda - (\beta D(t)) v(t) T(t) - d T(t), \\
\dot{I} &= (\beta D(t)) v(t) T(t) - d_1 I(t), \\
\dot{V} &= d_1 N I(t) - c v(t), \\
\dot{D} &= \lambda_1 - \beta_1 (\beta D(t)) v(t) T(t) - \gamma D(t).
\end{align*}\]  

(2)

In model (2), \(D(t)\) represents the concentration of DPP4 on the surface of uninfected cells, which can be recognized by surface spike (S) protein of MERS-CoV (see, e.g., [8]). Infected cells are produced from uninfected cells and free viruses at the rate \((\beta D(t)) v(t) T(t)\). It is assumed that DPP4 is produced from the surface of uninfected cells at the constant rate \(\lambda_1 > 0\). DPP4 is destroyed, when free viruses try to infect uninfected cells, at the rate \(\beta_1 (\beta D(t)) v(t) T(t)\), and is hydrolyzed at the rate \(\gamma D(t)\). Here, \(\beta_1 \geq 0\) and \(\gamma > 0\) are constants. It is assumed that there is no destroyed DPP4 on the surface of infected cells. All other parameters in model (2) have similar biological meanings to that in model (1).

The initial condition of model (2) is given as \(T(0) \geq 0\), \(I(0) \geq 0\), \(v(0) \geq 0\), and \(D(0) \geq 0\). It is not difficult to show that the solution \((T(t), I(t), v(t), D(t))\) with the initial condition is existent, unique, bounded, and nonnegative for all \(t \geq 0\) (in fact, it also has \(T(t) > 0\) and \(D(t) > 0\) for all \(t > 0\)). If \(T(0) > 0\), \(I(0) > 0\), \(v(0) > 0\), and \(D(0) > 0\), it is easily proven that the corresponding solution \((T(t), I(t), v(t), D(t))\) is positive for all \(t \geq 0\).

Furthermore, it can be easily shown that the set

\[\Omega = \{(T, I, v, D) \mid 0 \leq T \leq T_0, I \geq 0, v \geq 0, 0 \leq D \leq D_0, T + I + \frac{a}{N} v \leq \frac{\lambda}{\mu}\}\]

is attractive and positively invariant with respect to model (2), where \(0 < a < 1, \mu = \min\{d_1, (1-a) d_1, c\}\).

The purpose of the paper is to study local and global stability of the equilibria of model (2) by using Roth-Hurwitz criterion and constructing suitable Lyapunov function (see, e.g., [9–13]).

2. Local and Global Stability of the Equilibria

The basic reproductive ratio of the virus for model (2) is \(R_0 = N\beta\lambda\lambda_1/cd_1\). Model (2) always has an infection-free equilibrium \(E_0 = (T_0, 0, 0, D_0) = (\lambda/d, 0, 0, \lambda_1/\gamma)\). If \(R_0 > 1\), model (2) also has unique infected equilibrium \(E^* = (T^*, I^*, v^*, D^*)\), where, for \(\beta_1 = 0\), \(v = v^* = d_1^y (R_0 - 1)/\beta_1\lambda_1\), for \(\beta_1 > 0\), \(v = v^* > 0\) is the positive root of the equation

\[\beta_1 c^2 v^2 - N c \beta (\lambda_1 + \beta_1) v + N c d v (R_0 - 1) = 0,\]

and

\[T^* = \frac{\lambda}{d} - \frac{c v^*}{N d^y}, I^* = \frac{c v^*}{N \beta T^*}, D^* = \frac{c}{N \beta T^*}, v^* = \frac{N \beta (\lambda_1 + \lambda \beta_1) - \sqrt{N^2 \beta^2 (\lambda_1 - \lambda \beta_1)^2 + 4 N \beta_1 \beta c d v (R_0 - 1)}}{2 \beta \beta_1 c}.
\]

First, we have the following result.

Theorem 1. With respect to the set \(\Omega = \{(T, I, v, D) \mid (T, I, v, D) \in \Omega, T > 0, D > 0\}\), the infection-free equilibrium \(E_0 = (T_0, 0, 0, D_0)\) is globally asymptotically stable when \(R_0 < 1\) and globally attractive when \(R_0 = 1\).
Proof. At any equilibrium \((T, I, v, D)\), Jacobian matrix of model (2) is
\[
J = \begin{pmatrix}
-\beta vD - d & -\beta TD & -\beta vT \\
\beta vD & -\beta_1 TD + \beta_1 vT & 0 \\
0 & N\beta_1 & -c \\
-\beta_1 \beta vD & 0 & -\beta_1 \beta TD - \beta_1 \beta vT - \gamma
\end{pmatrix}. \tag{5}
\]
By simple computations, we can get that the characteristic equation at \(E_2\) is \(f(\rho) = (\rho + d)(\rho + c)[(c + d)\rho + \rho_2 \rho + cd_1(1 - R_0)] = 0\). Clearly, if \(R_0 < 1\), all roots of \(f(\rho) = 0\) have negative real parts. Hence, \(E_0\) is locally asymptotic stability by Routh-Hurwitz criterion. If \(R_0 = 1\), \(f(\rho) = 0\) has the zero root \(\rho = 0\) and three negative roots. Hence, \(E_0\) is linearly stable.

Construct the Lyapunov function as follows:
\[
U(T, I, v, D) = T_0 \left( \frac{T}{T_0} - 1 - \ln \frac{T}{T_0} \right) + (1 + \beta_1 I) + \frac{(1 + \beta_1)}{N} v + D_0 \left( \frac{D}{D_0} - 1 - \ln \frac{D}{D_0} \right). \tag{6}
\]
It is clear that \(U\) is continuous on \(\Omega\), and positive definite with respect to \(E_0\) and satisfies condition (ii) of Definition 1.1 in [14] or Lemma 3.1 in [15] on \(\partial\Omega = \Omega \setminus \Omega_1\). Calculating the derivative of \(U\) along the solutions of model (2), we have, for \(t \geq 0\),
\[
\frac{dU}{dt} = \lambda - \beta DvT - dT - T_0 \left( \frac{\lambda}{T} - \beta Dv - d \right) + \beta DvT \notag
\]
\[
+ \beta_1 \beta DvT - \left( 1 + \beta_1 \right) dI + \left( \frac{1 + \beta_1}{N} \right) dNI \notag
\]
\[
- \frac{c v}{N} - \beta_1 \frac{c v}{N} + \frac{\lambda_1}{\gamma} - \beta_1 \beta TDv - \gamma D \notag
\]
\[
- D_0 \left( \frac{\lambda_1}{D} - \beta_1 \beta vT - \gamma \right) \notag
\]
\[
= \frac{\lambda \left( 2 - \frac{T}{T_0} - \frac{T_0}{T} \right) + \lambda_1 \left( 2 - \frac{D}{D_0} - \frac{D_0}{D} \right)}{D_0} \notag
\]
\[
+ \left( \beta DT_0 - \frac{c}{N} \right) + \beta_1 \left( \beta DvT_0 - \beta_1 \frac{c v}{N} \right) \notag
\]
\[
\leq \lambda \left( 2 - \frac{T}{T_0} - \frac{T_0}{T} \right) + \lambda_1 \left( 2 - \frac{D}{D_0} - \frac{D_0}{D} \right) + \frac{c}{N} \left( R_0 - 1 \right) \left( 1 + \beta_1 \right) v. \tag{7}
\]
Clearly, \(dU/dt \leq 0\) on \(\Omega_1\) by \(R_0 \leq 1\). Define \(Q = \{dU/dt = 0 \mid (T, I, v, D) \in \Omega, U(T, I, v, D) < +\infty\}\). Let \(M\) be the largest subset in \(Q\) which is invariant with respect to the set model (2). Hence, we have that \(M \subset Q \subset \{(T, I, v, D) \mid (T, I, v, D) \in \Omega, T = T_0, D = D_0\}\). From the invariance of \(M\) and model (2), we can easily show that \(M = \{E_0\}\). Therefore, it follows from Theorem 1.2 in [14] or Lemma 3.1 in [15] that \(E_0\) is globally attractive. This completes the proof.

For local and global stability of the infected equilibrium \(E^*\), we have the following result.

**Theorem 2.** With respect to the set \(\Omega_2 = \{(T, I, v, D) \mid (T, I, v, D) \in \Omega, T > 0, I > 0, v > 0, D > 0\}\), the infected equilibrium \(E^*\) is locally asymptotically stable when \(R_0 > 1\). In addition, if \((2d_1\mu)^2\gamma_1 \geq \beta_1^2 \lambda_1^2 \lambda N^2\), where \(0 < \alpha < 1\), \(\mu = \min[d_1, (1 - a)d_1, c]\), the infected equilibrium \(E^*\) is globally asymptotically stable.

Proof. The characteristic equation at model (2) at \(E^*\) is
\[
g(\rho) = \rho^4 + a_0 \rho^3 + a_1 \rho^2 + a_2 \rho + a_3 = 0, \tag{8}
\]
where
\[
a_0 = T^* \beta c v v' \beta_1 d_1 + D^* \beta c \gamma v v', \notag
\]
\[
a_1 = T^* \beta c v v' \beta_1 d_1 + T^* \beta d v v' \beta_1 d_1 + D^* \beta c \gamma v^* + D^* \beta c v v' + D^* \beta v v' d_1 + c d_1 + c \gamma + d_1, \tag{9}
\]
\[
a_2 = T^* \beta c v v' \beta_1 + T^* \beta d v v' \beta_1 d_1 + T^* \beta v v' \beta_1 d_1 + D^* \beta c v^* + D^* \beta v v' d_1 + c d + c \gamma + d y + d d_1 + y d_1, \notag
\]
\[
a_3 = \beta_1 \beta v^* T^* + \beta v^* D^* + c + d + \gamma + d_1. \notag
\]
It is obvious that \(a_i > 0\ (i = 0, 1, 2, 3)\). Furthermore, by using Matlab program, it can be shown that \(\Delta_3 = a_1 a_2 a_3 - a_1^2 a_2 - a_2^2 a_3\), which has 20 items in which all items are positive. Hence, \(E^*\) is local asymptotic stability by Routh-Hurwitz criterion.

Construct the Lyapunov function as follows:
\[
W = \beta_1 T^* \left( \frac{T}{T^*} - 1 - \ln \frac{T}{T^*} \right) + \beta_1 I^* \left( \frac{I}{I^*} - 1 - \ln \frac{I}{I^*} \right) + \frac{\beta_1}{N} \left( \frac{v}{v^*} - 1 - \ln \frac{v}{v^*} \right) + D^* \left( \frac{D}{D^*} - 1 - \ln \frac{D}{D^*} \right). \tag{10}
\]
It is clear that \(W\) is continuous on \(\Omega_2\) and positive definite with respect to \(E^*\) and satisfies condition (ii) of Definition 1.1 in [14] or Lemma 3.1 in [15] on \(\partial \Omega = \Omega \setminus \Omega_2\). Calculating
the derivative of W along the solutions of model (2), we have, for $t \geq 0$,
\[
\frac{dW}{dt} = \beta_1 (\lambda - dT) - \beta_1 T^* \left( \frac{\lambda}{T} - \beta_1 D v - d \right) \\
- \beta_1 I^* \left( \frac{\beta_1 D v T}{I} - d_i \right) - \beta_1 v^* \left( \frac{d_i I}{v} - \frac{c}{N} \right) + \lambda_1 \\
- \beta_1 BD v T - \gamma D - D^* \left( \frac{\lambda}{D} - \beta_1 B T v - \gamma \right) \\
- \beta_1 \frac{c v}{N} \\
= \beta_0 \beta D^* v^* T^* + 2 \beta_0 d T^* - \beta_0 d T \\
- \beta_1 T^* \left( \frac{\beta_1 D v T^*}{T} - d_i \right) - \beta_1 d_i I^* \frac{v^*}{v} + \beta_1 \frac{c v}{N} \\
= \left( 2 \beta_1 d T^* - \beta_0 d T - \beta_1 \frac{T^*}{T} d T^* \right) \\
+ \left( 2 \gamma D^* - \gamma D - \frac{D^*}{D} \gamma D \right) \\
+ \left( 2 \beta_0 D v T^* + \beta_0 c v^* + \beta_1 d_i I^* \right) \\
- \beta_0 \beta D^* v^* T^* \frac{D^*}{D} - \beta_0 \beta D^* v^* T^* \frac{T^*}{T} \\
- \beta_0 \beta D v T^* \frac{I}{I} - \beta_0 d_i I^* \frac{v^*}{v} + \beta_0 \beta D v T^* \\
+ \beta_0 \beta D^* T v - \beta_1 \frac{c v}{N} - \beta_1 \beta D v T^* \\
= \beta_0 d T^* \left( 2 - \frac{T^*}{T} - \frac{T^*}{T} \right) + \gamma D^* \left( 2 - \frac{D^*}{D} - \frac{D^*}{D} \right) \\
+ \beta_0 d_i I^* \left( 4 - \frac{T^*}{T} - \frac{D^*}{D} - \frac{\beta_1 T v D^*}{d_i I} - \frac{I^*}{I^*} \right) \\
+ \beta_1 \beta v \left( T D^* + T^* D - T D - \frac{c}{\beta N} \right) \\
= \beta_0 d T^* \left( 2 - \frac{T^*}{T} - \frac{T^*}{T} \right) + \gamma D^* \left( 2 - \frac{D^*}{D} - \frac{D^*}{D} \right) \\
+ \beta_0 d_i I^* \left( 4 - \frac{T^*}{T} - \frac{D^*}{D} - \frac{T v D^*}{T^* v D^*} - \frac{I^*}{I^*} \right) \\
+ \beta_1 \beta v (T D^* + T^* D - T D - T^* D^*) 
\]

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Since the arithmetical mean is greater than or equal to the geometrical mean, we have that $T^*/T + D^*/D + T v D^*/T^* v D^* I + I^*/I^* v - 4 \leq 0$, for any $T_i, I, v, D > 0$, and that $T^*/T + D^*/D + T v D^*/T^* v D^* I + I^*/I^* v - 4 = 0$ only if $T^*/T = D^*/D = T v D^*/T^* v D^* I = I^*/I^* v$. Thus, we have $T = T^*$, $D = D^*$.

On the other hand, notice the inequality in [16]:
\[
-xz^2 + yz \leq -\frac{1}{2} x z^2 + \frac{y^2}{2x} \quad (x > 0, \ y \geq 0, \ z \geq 0). 
\]

We have
\[
-\frac{\beta_0 d}{T} \left( T - T^* \right)^2 - \frac{y}{D} \left( D - D^* \right)^2 \\
- \beta_0 \beta_1 v (D - D^*) \left( T - T^* \right) \\
+ \beta_0 d_i I^* \left( 4 - \frac{T^*}{T} - \frac{D^*}{D} - \frac{T v D^*}{T^* v D^*} - \frac{I^*}{I^*} \right). 
\]

Note that the inequalities $\beta_0 d/2T - D(\beta_0 v)^2/8y \geq 0$ and $y/2D - T(\beta_0 v)^2/8y \geq 0$ are equivalent to the inequalities $4d_0 y \geq \beta_0^2 T D v^2$. Since $T(t) \leq T_0$, $D \leq D_0$, and $v(t) \leq \lambda N/\mu a$ for all $t \geq 0$, we have that the inequality $4d_0 y \geq \beta_0^2 T D v^2$ holds, if the condition $(2d_0 a)^2 / \beta_0^2 \lambda N^2$ in Theorem 2 is satisfied. Therefore, $dW/dt \leq 0$ on $\Omega$.

Define $Q = \{dW/dt = 0 | (T, I, v, D) \in \Omega, W(T, I, v, D) < +\infty \}$. Let $M$ be the largest subset in $Q$ which is invariant with respect to the set of model (2). Hence, we have that $M \subset Q \subset \{(T, I, v, D) | (T, I, v, D) \in \Omega, T = T^*, D = D^* \}$. From the invariance of $M$ and model (2), we can also show that $M = \{E^* \}$. Hence, it follows from Theorem 1.2 in [14] or Lemma 3.1 in [15] that $E^*$ is globally attracting. This completes the proof.

\( \square \)

3. Simulations and Conclusions

Let us first give some numerical simulations on the orbits of model (2). Take the following a set of parameters, $\lambda = \lambda_1 = 1,$
\( \beta = 0.001, \quad d = d_1 = 0.05, \quad N = 1, \quad c = 0.2, \quad \beta_1 = 1, \)
and \( \gamma = 0.11. \) We can compute the values of the infection-free equilibrium \( E_0 = (20, 0, 0, 9.0909) \) and the basic reproductive ratio, \( R_0 = 0.90909 < 1. \) Figure 2(a) shows the trajectory of model (2) with suitable initial condition, which shows that the infection-free equilibrium \( E_0 \) is asymptotically stable.

Let us take \( \gamma = 0.05, \) and all the other parameters are the same as above. We can also compute the values of the infection-free equilibrium \( E_0, \) the infected equilibrium \( E^*, \) and the basic reproductive ratio, \( E_0 = (20, 0, 0, 20), \) \( E^* = (14.142, 5.8579, 1.4645, 14.142), \) and \( R_0 = 2 > 1. \) Figure 2(b) shows orbits of model (2) with suitable initial conditions, which shows that the infected equilibrium \( E^* \) is asymptotically stable. We would like to point out here that, based on the numerical simulations, the condition \((2d\gamma\mu_a)^2 \geq \beta_1\beta_2\lambda_1\lambda^2N^2 \) may be further weakened or even removed.

Finally, by using the basic reproductive ratio \( R_0 = N\beta_1\lambda_1/cd\gamma, \) let us give some simple discussions on the interactions between the protein DPP4 and the virus infection. Usually, in the absence of any drug treatment, all the parameters in model (2) and the corresponding basic reproductive ratio \( R_0 \) can be regarded as relatively fixed constants. If some drug treatment measures are taken, the effectiveness of the treatment can be reflected in the regulation of the parameter \( \gamma. \) For example, by increasing the value of \( \gamma, \) the value of the basic reproductive ratio of \( R_0 \) can be changed from greater than 1 to less than 1. In the numerical simulations in this section, Figure 2(b) shows that the virus infection will be persistent, when \( \gamma = 0.05 \) and \( R_0 = 2 > 1. \) If increasing \( \gamma \) from \( \gamma = 0.05 \) to \( \gamma = 0.11, \) Figure 2(a) shows that the virus infection can be controlled, since \( R_0 = 0.9090 < 1. \)

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Authors’ Contributions**

S. Tang and P. Bai performed local and global stability analysis and the numerical simulations and wrote the manuscript. W. Ma designed the study, developed the methodology of invariance principle, and wrote the manuscript. All authors have read and approved the final manuscript.

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