Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Forecasting of the efficiency of monoclonal therapy in the treatment of CoVID-19 induced by the Omicron variant of SARS-CoV2

Alessandro Nutini a, Juan Zhang b,c, Ayesha Sohail d,e, Robia Arif d, Taher A. Nofal e

a Biology and Biomechanics division., Centro Studi Attività Motorie via di Tiglio 94 Lucca, Italy
b Guangdong ATV Academy for Performing Arts, Dongguan 523710, China
c School of Computer Science, Huabei Normal University, Huabei 235000, China
d Department of Mathematics, Comsats University Islamabad, Lahore Campus 54000, Pakistan
e Department of Mathematics and Statistics, Faculty of Science, Taif University, Taif, Saudi Arabia

ARTICLE INFO

Keywords:
- Omicron
- Monoclonal antibodies
- Delayed dynamics
- Immune response
- COVID-19
- Regression learner

ABSTRACT

On November 26, 2021, the World Health Organization (WHO) announced a new variant of concern of SARS-CoV-2 called Omicron. This variant has biological–functional characteristics such as to make it much faster in the infectious process so as to show an even more intense spread. Although many data are currently incomplete, it is possible to identify, based on the viral biochemical characteristics, a possible therapy consisting of a monoclonal antibody called Sotrovimab. The model proposed here is based on the mathematical analysis of the dynamics of action of this monoclonal antibody and two cell populations: the immune memory cells and the infected cells. Indeed, a delay exists during the physiological immune response and the response induced by administration of Sotrovimab. This manuscript presents that delay in a novel manner. The model is developed with the aid of information based on the chemical kinetics. The machine learning tools have been used to satisfy the criteria designed by the dynamical analysis. Regression learner tools of Python are used as the reverse engineering tools for the understanding of the balance in the mathematical model, maintained by the parameters and their corresponding intervals and thresholds set by the dynamical analysis.

Introduction

On November 26, 2021, the World Health Organization’s Technical Advisory Group on Virus Evolution (TAG-VE, 2021) proposed that variant B.1.1.529 of the SARS-CoV2 virus, known as Omicron, was identified as a variant Of Concern (VOC). The number of nations reporting SARS-CoV-2 Omicron (VOC) infections continues to increase and as of 1st December 2021, there are approximately a total of 352 confirmed cases reported from 27 countries. It is not clear whether the Omicron SARS-CoV-2 is more transmissible or with more severe symptoms than the Delta variant; the Omicron variant includes 30 mutations in the Spike protein, half of which are in the receptor binding domain that cause severe immune leakage from convalescent sera from COVID-19 patients.

These mutations can induce significant changes in the conformation of the Spike protein, which could affect transmissibility, the severity of the CoViD-19 syndrome and the ability to evade immune systems. Although Omicron appears to show a strong tendency to high transmissibility, there is currently no important virological or immunological evidence.

When compared to the Beta or Delta variant, Omicron’s infectivity increases by about ten times [1]. Omicron still uses ACE2 as the main infection receptor and, although it contains 15 mutations in the region of the RBD receptor binding domain (residues Arg339 – Phe541) a comparison to the RBDs of the Beta or Delta variants shows that the binding of the RBD domain itself of the Omicron variant to ACE2 it has a similar binding affinity [2]. Since the binding affinity of RBD to ACE2 is not conspicuously increased, Omicron’s increased infectious capacity could be due to mutations in other areas of the S protein, furthermore, given the high presence of mutations in the RBD region, a sort of "receptor shift" is possible whereby ACE2 may no longer be the infection receptor for Omicron or at least the main means of infection.

Thus, although the binding to the ACE2 receptor is always present at the nanomolar level, compared to the three main variants: Beta, Delta, or D614G, the Omicron variant has more than thirty mutations in protein S and almost half are located in RBD, including a poly-site mutation of bases (PBCS), called P681H, which is affected by the furin enzyme which potentially increases its infectivity [3,4].

In Omicron, then, the receptor-binding motif (438aa-508aa) contains 12 mutations, half of which are located around the N501 at the

* Corresponding author.
E-mail address: ayeshasohail81@gmail.com (A. Sohail).

https://doi.org/10.1016/j.rinp.2022.105300
Received 4 January 2022; Received in revised form 2 February 2022; Accepted 3 February 2022
Available online 26 February 2022
2211-3797/© 2022 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
C-terminus [5–7]. These mutated regions could lead to strong conformational changes that increase immune evasion capabilities: nine of these mutations map the receptor-binding motif (RBM) which is the RBD subdomain that interacts directly with the host receptor, i.e. with ACE2 [8].

The increased infectivity of Omicron resides in an increase in the positive charge at the RBBD end of the protein S which increases the long-range electrostatic attraction between this zone and the negative charge located in the ACE2 contact zone, as hypothesized in a paper by Pawłowski (Pawłowski, 2021) where it is reported as at a distance of about 3 nm, the energy of this interaction is greater than the energy of thermal motion. Furthermore, at no additional cost, the phenomenon can change multipolar interactions during the approach of the molecules. As an innovation in this reasoning, it is hypothesized that these mutations give Omicron an infectious capacity that increases exponentially based on both the approach of the molecules and the presence of a high viral load that can further facilitate these electrostatic interactions modified by the presence of the above mutations. Reported. An initial increase in infectious capacity derives from a possible conformational change which, subsequently, leads to the establishment of greater electrostatic interactions which lead to a "viral coupling" in even shorter times and greater functional adherence to the host. This would allow Omicron both a higher infection rate and a stronger host invasion capacity even for lower viral concentrations than the other variants. The infection process, therefore, always remains multiphase, but with a marked exponential capacity that shortens the infection time and confers a greater capacity for viral "spreading". Undoubtedly, the enhanced infectious capacity of Omicron is linked to these modifications and even if there are no further structural and biochemical data available, we can think that, given that ACE2 is still necessary for its infectivity, vaccination (or therapy) RDB-targeted is still effective, even if partially.

**Therapeutic interactions**

Preliminary reports indicated that the plasma neutralizing activity of individuals vaccinated with Pfizer - BioNTech BNT162b2 is markedly reduced against the Omicron variant of SARS-CoV2 [9,10], which documents a strong, although not complete, evasion of the antibodies induced by this vaccine. One study showed that the vaccine’s efficacy against the disease symptoms of the Omicron variant is lower than the Delta variant [11] and the potential of booster doses to improve this drop in immunization is still underway. Of study. Furthermore, the neutralizing activity of several therapeutic monoclonal antibodies (mAbs) was shown to be decreased or abolished against SARS-CoV-2 Omicron. At the moment, a good therapeutic solution for CoViD-19 from Omicron appears to be the monoclonal antibody Sotrovimab which appears to be quite efficient in treatment [12]; this mAb does not block the ACE2 receptor but targets “non-RBM” epitopes shared among many sarbecoviruses, including SARS-CoV [13].

Although Sotrovimab showed approximately three times reduced neutralizing capacity against Omicron, all other mAbs (specific for RBM) lost their neutralizing activity except for the therapeutic cocktail “COVID-2130 - COVID-2196” for which it was determined. an exceptionally low power. These results support an “antigenic change” in Omicron [14].

Of note, Sotrovimab also showed a less than two-fold reduction in neutralizing activity against Omicron SARS-CoV-2 in vivo compared to the WA1/2020 isolate D614G, as reported in a recent paper on S309, a progenitor mAb of Sotrovimab [15]. Our research group in mathematical models, in collaboration with the BEDSL Lab (Biomedical Engineering and Data Science Group CUI & Lucca Lab), has formulated a mathematical model in which the mAb Sotrovimab interacts with an epitope different from the RBM avoiding the limitation of the hypothetical “antigenic shift” of Omicron, showing a neutralizing capacity sufficient for the treatment of the CoViD-19 syndrome.

| Table 1 | The schematic description of the cellular interactions. |
|---------|--------------------------------------------------------|
| Symbols | Description                                           |
| $C(t)$  | Sotrovimab monoclonal antibody                         |
| $M(t)$  | Memory cells                                           |
| $T(t)$  | Viral infected cells                                   |

Inspired from the existing models [16–23], the proposed mathematical model is based on the dynamic population analysis of two cell types, memory cells and infected cells and the monoclonal antibody Sotrovimab. Delay exists during induced immune response and improvement occurs after administration of Sotrovimab. This article presents this delay in an innovative way. The model is developed with the help of information based on chemical kinetics and machine learning tools were used to meet the criteria designed by the dynamic analysis. Python’s regression learning tools are used as reverse engineering elements for understanding the equilibrium of the mathematical model, maintained by the parameters and related intervals and thresholds set by dynamic analysis.

**Mathematical model**

**Model analysis**

The field of mathematical biology has evolved over the last decades and different computational biology models have been developed and synchronized with the laboratory generated datasets [23–29]. Consider the action of Sotrovimab mAb (C), memory cells (M) and infected cells (T), in a systematic manner as shown in the schematic 1.

We have the system of equations as follows:

$$
\frac{dC}{dt} = (\varphi - \eta - \kappa)C(t) - \delta C(t)T(t) + \delta M(t)T(t),
\frac{dM}{dt} = \kappa \xi C(t) - \mu M(t) - \delta M(t)T(t),
\frac{dT}{dt} = \beta T(t)(1 - \psi T(t)) - \gamma C(t)T(t),
$$

(1)

where the description of compartments $C(t)$, $M(t)$ and $T(t)$ is in Table 1 and the parameters are described in (see Table 3).

**Basic consequences**

The none-negativity of solutions specifies the survival of population. To show that the transmission system (1) to be theoretically feasible, it is necessary to demonstrate that every conditional variable is non-negative $\forall t \geq 0$ the time. Consequently, a solution of the system (1) with non-negative initial value will remain non-negative $\forall t \geq 0$.

**Theorem 1.** Assume that the initial conditions are non-negative of system (1), the solution will remain non-negative for $\forall t > 0$.

**Proof.** From the first equation of system (1) is

$$
\frac{dC}{dt} = (\varphi - \eta - \kappa)C(t) - \delta C(t)T(t) + \delta M(t)T(t)
\geq (\varphi - \eta - \kappa - \delta T(t))C(t)
$$

therefore, by separating the variable $C(t)$ and integrate inequality

$$
C(t) \geq C(0) \exp ((\varphi - \eta - \kappa - \delta T(t))
$$

(2)

which shows that $C(t)$ remain non-negative as long as $C(0)$ is non-negative. Thus proves the non negativity invariant property.

From second equation of system (1) we have

$$
\frac{dM}{dt} = \kappa \xi C(t) - \mu M(t) - \delta M(t)T(t)
\geq -\mu M(t) - \delta M(t)T(t).
$$
whether an infection persists and becomes vanished in population. By the index case, is a fundamental threshold parameter that concludes number, frequently express as average number of infected cells by $E_M$ completely eliminate. The equilibrium saddle point that shows the infected cells from SARS-CoV-2 could not exist for all parameter values. These two equilibrium points exist for all parameter values.

Consequently has following equilibrium points.

By integrating we have $T(t) = T(0) \exp(\beta - \gamma C(t))$. Hence, all the solution are non-negative invariant if initial condition is non-negative.

### Steady states and reproductive number

In this portion, we establish steady states solution by putting the system (1) equal to zero. This calculation specify that the system (1) consequently has following equilibrium points.

$E_0 = (0,0,0)$

$E_1 = (0,0,\frac{1}{\psi})$

These two equilibrium points exist for all parameter values. $E_0$ is saddle point that shows the infected cells from SARS-CoV-2 could not completely eliminate. The equilibrium $E_0$ is exists for all values of parameter in which all population zero.

The endemic equilibrium point $E^* = (C^*, M^*, T^*)$.

Where:

$C^* = \frac{\beta(\mu + \eta - \phi) + \beta \gamma (\zeta + \phi)}{2\gamma \delta}$

$M^* = \frac{\beta \mu (\mu + \eta - \phi)}{2\gamma \delta}$

$T^* = \frac{\beta \mu (\mu + \eta - \phi)}{2\gamma \delta}$

$H_u = \sqrt{\frac{2\gamma \delta}{\beta \mu}} = \frac{\sqrt{2\gamma \delta}}{\beta \mu}$

The reproductive number at $E_1$ is express as $R_1$. The reproductive number, frequently express as average number of infected cells by the index case, is a fundamental threshold parameter that concludes whether an infection persists and becomes vanished in population. By applying operator of next generation to calculate reproductive number. Here we have two matrices $V$ and $F$.

$V = \begin{pmatrix} \frac{\delta}{\psi} + \eta - \phi & -\frac{\beta}{\psi} & 0 \\ 0 & \frac{\beta}{\psi} + \mu \\ -\frac{\beta}{\psi} & 0 & -\frac{\beta}{\psi} \end{pmatrix}$

$F = \begin{pmatrix} -\kappa \xi^2 & 0 & 0 \\ 0 & -\mu \xi & 0 \\ 0 & 0 & \beta \end{pmatrix}$

Sensitivity analysis

The sensitivity is analyzed by taking the derivative of reproductive number $R_1 = \frac{\kappa \psi (\mu + \zeta \theta - \delta)}{(\mu + \delta + \psi (\eta - \phi))}$ with respect to each parameter.

$\frac{dR_1}{dk} = \frac{\psi (\mu + \zeta \theta - \delta)}{(\mu + \delta + \psi (\eta - \phi))}, \quad \frac{dR_1}{d\psi} = \kappa \psi (\mu + \zeta \theta - \delta), \quad \frac{dR_1}{d\mu} = \kappa \psi (\mu + \zeta \theta - \delta), \quad \frac{dR_1}{d\delta} = \kappa \psi (\mu + \zeta \theta - \delta)$

$\frac{dR_1}{d\eta} = \kappa \psi (\mu + \zeta \theta - \delta), \quad \frac{dR_1}{d\phi} = \kappa \psi (\mu + \zeta \theta - \delta)$

It is concluded that the reproductive number is decrease with increment in the death rate of Memory cells and proliferation rate of monoclonal antibodies.

Local stability analysis

The local stability of system (1) at any equilibrium point can be determined by the jacobian matrix at that equilibrium point.

The Jacobian matrix at $E_0$ is

$J_0 = \begin{pmatrix} -\eta - \kappa + \phi & 0 & 0 \\ \kappa \xi^2 & -\mu & 0 \\ 0 & 0 & \beta \end{pmatrix}$
Therefore, $E_0$ is the saddle point and stable manifold on positive xy-plane. It clearly shows that the infected cells from SARS-CoV-2 is not removed completely.

**Theorem 2.** The equilibrium point $E_1$ is locally asymptotically stable if $R_1 < 1$, otherwise unstable.

**Proof.** the Jacobian matrix at $E_1$ is

$$J_1 = \begin{pmatrix} -\frac{\delta}{\varphi} - \eta - \kappa + \varphi & \frac{\delta}{\varphi} & 0 \\ \kappa \varphi & \frac{\delta}{\varphi} - \mu & 0 \\ \frac{\varphi}{\varphi} & 0 & -\delta \end{pmatrix}. \quad (11)$$

The $J_1$ has eigenvalues $\lambda_1 = -\beta, (\lambda_2$ and $\lambda_3$ are given in Box I)

Since all the eigenvalues are strictly negative. Therefore, model (1) is asymptotically stable at $E_1$.

**Theorem 3.** If $R_1 > 1$, the endemic equilibrium point $E^*$ is the locally asymptotically stable.

**Proof.** The Jacobian matrix at $E^*$ is

$$J^* = \begin{pmatrix} F_1 - \lambda & 8T^* & F_2 \\ \kappa \varphi & F_2 - \lambda & -\delta M^* \\ -\gamma T^* & 0 & F_3 - \lambda \end{pmatrix}. \quad (12)$$

Here,

$$F_1 = -\eta - \kappa - \delta T^* + \varphi, \quad F_2 = M^* \delta - C^* \delta, \quad F_3 = -\mu - T^* \delta, \quad F_4 = -\beta - \gamma C^* + 2B T^* \varphi. \quad (13)$$

The characteristic equation of Jacobian matrix is

$$\lambda^3 + \lambda^2 \eta_1 + \lambda \eta_2 + \eta_3 = 0 \quad (14)$$

where the constants are

$$\eta_1 = F_1 + F_3 + F_4, \quad \eta_2 = T^* \left( \kappa \varphi \delta - \gamma F_2 \right) - F_1 F_2 - F_1 (F_3 + F_4), \quad \eta_3 = T^* \left( \gamma \left( M^* \delta \varphi - \delta F_2 \kappa \varphi \right) \right) + \gamma F_1 F_2 F_3. \quad (15)$$

By the condition of Routh–Hurwitz, $E^*$ is locally asymptotically stable if $\eta_1 > 0, \eta_2 > 0$ and $\eta_3 > 0$. Then the polynomial (14) has negative real roots which shows that model (1) at endemic equilibrium point is asymptotically stable if $R_1 > 1$.

**Model with delay**

Sotrovimab is a monoclonal antibody that presents a modification in its Fc segment of two amino acids (LS modification) which increases its half-life and its availability in the respiratory tract through greater involvement of the neonatal Fc receptor [30,31]. This modification allows for longer therapeutic periods. Furthermore, Sotrovimab has been shown to have rather potent immune-mediated viral clearance in vitro [32]. Its target remains protein S but in a “non-RBM” region and common to the subgenus of sarbecoviruses of which the SARS-CoV species belongs [33]. Obviously, this target antigen is also sufficient for the recognition and action of $T$ lymphocytes in conjunction with IFN-$\gamma$.

Assuming this capacity by the monoclonal antibodies receptor modulated on $T_{reg}$ cells, and an antigen-mediated cell proliferation, the recognition of monoclonal antibody is on S protein (“non-RBM” fragment) by en epitope (antigen) that is common to sarbecovirus subgenus, so the $N$ protein is not a target of Sotrovimab.

During this research, we have considered the impact of the immune system on infected cells by Omicron. There is a delay, which is already documented in the introduction.

$$\frac{dC}{dt} = (\varphi - \eta - \kappa) t C(t) - \delta C(t) T(t) + \delta M(t) T(t), \quad (16)$$

$$\frac{dM}{dt} = \kappa \varphi C(t) - \mu M(t) - \delta M(t - \tau) T(t - \tau), \quad (17)$$

$$\frac{dT}{dt} = (\beta - T(t)(1 - \psi) T(t) - \gamma C(t) T(t)). \quad (18)$$

**Local stability analysis at $E_1$**

To examine that model (16) is stable at equilibrium point $E_1$, we linearized the model (16) at equilibrium point $E_1$

$$\frac{dC}{dt} = (\varphi - \eta - \kappa) t C(t) - \delta C(t) T(t) + \delta M(t) T(t), \quad (16)$$

$$\frac{dM}{dt} = \kappa \varphi C(t) - \mu M(t) - \delta M(t - \tau) T(t - \tau), \quad (17)$$

$$\frac{dT}{dt} = (\beta - T(t)(1 - \psi) T(t) - \gamma C(t) T(t)). \quad (18)$$

The characteristic equation is

$$(-\beta - \lambda)(-\lambda - \frac{a - \sqrt{a^2 - 4 \left( (b + B e^{\lambda t}) \right)}}{2B}) \quad (19)$$

$$(-\lambda - \frac{a + \sqrt{a^2 - 4 \left( (b + B e^{\lambda t}) \right)}}{2B}) = 0. \quad (20)$$

Where the constants are

$$a = \delta + \delta \left( e^{\lambda t} + 1 \right) + \psi(\eta + \kappa - \mu - \varphi), \quad b = \delta(\mu \varphi + \delta) + \mu \varphi^2(\eta + \kappa - \varphi) + \varphi \delta(\kappa \varphi + \kappa - \mu). \quad (21)$$

**Parametric optimization with regression learner**

In this manuscript, the mechanism of action of the monoclonal antibodies is visualized as shown in Fig. 1, and the transmission rates are mapped onto the coefficients of the model, with the aid of the machine learning regression learner application [34]. The tools used during the implementation using the python environment are listed in the Table 2.

**Results**

The quantitative results obtained from the mathematical analysis can help to understand the hypothesis. The bifurcation analysis and the intervals for such biological models are of great importance [35]. These results are presented below as:
Local stability analysis at endemic point

Here we examine the stability of endemic equilibrium point $E^*$ at which Jacobian matrix is

$$J^* = \begin{pmatrix} A_1 & A_2 & A_3 \\ A_4 & A_5 & A_6 e^{-\delta t} + A_2 \\ 0 & A_7 e^{-\delta t} + 1 \end{pmatrix}. \quad (19)$$

where:

$$A_1 = -\eta - \kappa - \delta T^* + \varphi < 0, \quad A_2 = T^* \theta, \quad A_3 = M^* \theta - C^* \delta, \quad A_4 = \kappa \xi, \quad A_5 = T^*(-\theta), \quad A_6 = -\gamma T^*, \quad B_1 = -\mu - T^* \theta, \quad B_2 = -M^* \theta. \quad (20)$$

At equilibrium point $E^*$, the characteristic equation of the Jacobian matrix is

$$\lambda^3 + \lambda^2 \alpha_1 + \lambda \alpha_2 + \alpha_3 - e^{-\delta t} (\lambda^2 \beta_1 + \lambda \beta_2 + \beta_3) = 0. \quad (21)$$

where:

$$\alpha_1 = -A_1 - A_3 - A_7, \quad \alpha_2 = -A_4 A_2 - A_1 A_5 + A_4 (A_5 + A_7), \quad \alpha_3 = A_2 (A_4 A_7 - A_6 B_2) + A_1 A_6 A_5 - A_1 A_5 A_7, \quad B_1 = \beta_1, \quad B_2 = (-A_1 - A_3) B_1, \quad B_3 = (A_1 A_7 - A_1 A_6) B_1 + A_1 A_2 B_2. \quad (22)$$

Here we discuss the stability of endemic equilibrium point and Hopf bifurcation conditions of threshold parameter $\tau$. Assume that $\tau = 0$ by applying Routh–Hurwitz criteria we get negative real roots. By the Routh–Hurwitz we have following conditions.

$$a_1 + \beta_1 > 0, \quad a_2 + \beta_2 > 0 \quad (a_1 + \beta_1)(a_2 + \beta_2) > (a_3 + \beta_3).$$

Since delay $\tau$ is increasing continuously, we assume that for some values of delay $\tau > 0$, there exists a real number $\chi$ such that $\chi = i \chi$ is the root of Eq. (21) then, we obtained

$$\beta_1 - \beta_1 \chi^2 = (a_1 \chi^2 + a_3) \cos \tau \chi + a_2 \chi \sin \tau \chi, \quad (23) \beta_2 - \chi^2 = a_2 \chi \cos \tau \chi - (a_1 \chi^2 + a_3) \sin \tau \chi.$$  

By simplifying, we obtain

$$\omega^2 + \omega \gamma_1 + \omega \gamma_2 + \gamma_3 = 0 \chi^2 = \omega. \quad (24)$$

where

$$\gamma_1 = -a_1^2 + \beta_1^2 - 2 \beta_1, \quad \gamma_2 = -a_2^2 - 2a_1 a_3 + \beta_2^2 - 2 \beta_1 \beta_3, \quad \gamma_3 = \beta_2^2 - a_3^2. \quad (25)$$

According to the Descartes' rule of signs Eq. (21) has at least one positive root if $\beta_1^2 - 2 \beta_1 > a_1^2, -a_2^2 - 2a_1 a_3 + \beta_2^2 - 2 \beta_1 \beta_3 < 0$ and $\beta_1^2 > a_3^2$ holds. By eliminating $\sin \tau \chi_0$ form Eq. (23), we have

$$\tau_j = \frac{1}{\chi_0} \arccos(\frac{a_3 \chi_j - x^2 (a_1 \beta_1 + a_3) (a_1 \beta_1 - a_2 \beta_2 - a_1 \beta_3)}{a_1^2 \chi_j^4 + (a_2^2 + 2a_1 a_3) \chi_j^2 + a_3^2} + \frac{2a_j}{\chi_0}) \quad (26)$$

where $j = 0, 1, 2, ...$. By differentiate Eq. (21) with respect to the $\tau$ such that $\chi = \chi_0$, transversality condition in following form is obtained:

$$R(\frac{dA}{d\tau})^{-1} = \frac{\delta_1 \delta_2 - \delta_1 \delta_3}{\delta_1 \delta_4} \quad (27)$$

where

$$\delta_1 = 2a_1^2 \chi_j^2 - 2a_1 a_3 + a_3^2, \quad \delta_2 = 2(\beta_1^2 - 2 \beta_2) \chi_j^2 + \beta_2^2 - 2 \beta_1 \beta_3 + 3 \chi_j^4, \quad \delta_3 = a_3^2 \chi_j^2 + (a_2^2 - a_3 \chi_j^2)^2, \quad \delta_4 = (\chi_j^2 - \chi_j \beta_2)^2 + (\beta_1 - \beta_1 \chi_j^2)^2. \quad (28)$$

Hopf bifurcation will occur if $R(\frac{dA}{d\tau})^{-1} > 0$. This analysis can be summarized by following theorem.

**Theorem 4.** Suppose that $R_i > 1$ if either $\gamma_i < 0$ or $\gamma_i > 0$ and $\gamma_i < 0$, is satisfied and $\chi_0$ is the largest positive value, then endemic equilibrium point $E^*$ of model (16) is asymptotically stable when $\tau < \tau_0$, otherwise unstable. Moreover, model (16) undergoes Hopf bifurcation at equilibrium point $E^*$ when $\tau = \tau_0$.

Intervals

- The characteristic Eq. (18) has one negative root $-\beta$. Following theorems provide sufficient conditions for $E_1$ to be the stable locally.
- **Theorem 5** If $b > \theta(\psi(-\eta - \kappa + \varphi) - \delta)$, then the infection free equilibrium point $E_1$ is locally stable $\forall$ values of the delay parameter.
- **Theorem 6** If $2(b + \theta(\psi(\eta + \kappa) - \varphi) + \delta) > \theta(\psi(-\eta - \kappa - \varphi) + 2 \theta)^2$, then the infection free equilibrium point $E_1$ is locally stable $\forall$ values of the delay parameter.

From Figs. 2 and 3, it is obvious that delay in the onset of virus and during the interaction of memory cells with the infected cells, play an important role. An initial estimate of delay $\tau_{\text{opt}}$, when exceeds, shows remarkable change in virus load relative to $\tau$, i.e. the interaction rate of memory cells and infected cells. Similar behavior is observed for the dynamics of monoclonal antibodies and memory cells as shown in second and third row of numerical results. Here, “$*$” represents the ratio of $C$, $T$ and $M$ to the corresponding starting values for
improved graphical analysis. An interesting observation is made based on the numerical results presented in Figs. 4 and 5, that the change in interaction rate of monoclonal antibodies to the infected cells, for lower and higher values of delay provided almost similar dynamics, except some bifurcation. Although for increased values of $\delta$, there is a lag in case of memory cells and there is a phase lead in case of Omicron infected cells.

Thus, based on the numerical approximations and the biological evidence [10,36], we conclude that the combined action of the monoclonal antibody with memory cells is very particular. The therapy is given when the immune system, and therefore the possible memory, fails to eradicate the infection. The monoclonal antibody (C) reduces the expression of the memory involved in the infection thanks to its therapeutic action against infected cells (T); actually, in the first infectious
Fig. 4. Monoclonal antibodies ($C = \frac{C(t)}{C(0)}$), memory cells ($M = \frac{M(t)}{M(0)}$) and the infected cells ($T = \frac{T(t)}{T(0)}$) for $\tau < \tau_0$, for variation relative to $\delta$.

Fig. 5. Monoclonal antibodies ($C = \frac{C(t)}{C(0)}$), memory cells ($M = \frac{M(t)}{M(0)}$) and the infected cells ($T = \frac{T(t)}{T(0)}$) for $\tau > \tau_0$, for variation relative to $\delta$. 
phase, the memory cells (M) decrease due to the interaction with the infected cells (T). This decrease leads to a therapeutic increase in the presence of the monoclonal antibody (C). It can be hypothesized that the presence of memory cells does not have a specific activity against the Omicron variant so that, in addition to an insufficient presence, there is also a biological activity that presents a strong difficulty in directing its action against Omicron.

Conclusions

The model shown here illustrates a possible antiviral therapy represented by the monoclonal antibody Sotrovimab against the Omicron variant of SARS-CoV-2. The goal of Sotrovimab is to target a “non-RBM” antigen typical of the SARS-CoV viral family which therefore avoids the possible antigenic “shift” imposed by the Omicron variant. Although some of these assumptions are not currently experimentally verifiable parameters, they appear to be deeply interconnected according to a logic based on proven experimental events such as memory induced by monoclonal antibodies therapy or the presence of monoclonal antibodies exhaustion, T cells themselves [37]. Thanks to a local stability analysis conducted on the system of equations of the model (1), it is evident that there is a viral immuno-escape that remains contained thanks to the action of monoclonal antibodies. Furthermore, elements of analysis conducted using a delayed model, evaluates the impact of monoclonal antibodies obtained with the use of Treg cells in viral infection, considering both the exhausted condition and the action of the IFN-γ cytokine in therapy. The quantitative results validate the “monoclonal antibodies and SARS-CoV-2 Omicron hypothesis”. Finally, the model quantifies through computational analysis with Hopf bifurcation, a period of inactivation of memory cells (activated by viral infection) lower than that relating to monoclonal antibodies.

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.

Acknowledgments

The authors received financial support from Taif University Research supports Supporting Project number (TURSP-2020/031), Taif University, Taif, Saudi Arabia. All authors contributed equally to this work.

References

[1] Kumar S, Thambiraj TS, Karuppannan K, Subramaniam G, Omicron and delta variant of SARS-CoV-2: A comparative computational study of spike protein. J Med Virol 2021.
[2] Zhang X, Wu S, Wu B, Yang Q, Chen A, Li Y, Zhang Y, Pan T, Zhang H, He X. SARS-CoV-2 Omicron strain exhibits potent capabilities for immune evasion and viral entry. Signal Transduct Target Ther 2021;6:1–3.
[3] Lubinski B, Fernandes MH, Frazier L, Tang T, Daniel S, Diel DG, Jaimes JA, Amoako D, Karim F, Bernstein M, et al. SARS-CoV-2 Omicron antigenic shift. BioRxiv 2021.
[4] Maison D, Ching L, Shikuma C. Nerurkar. V. Genetic characteristics and interaction with reverse engineering. Prog Biophys Mol Biol 2020.

[10] Wilhelm A, Widera M, Griscomski K, Toptan T, Schenk B, Pallas C, Metzler M, Kohner N, Hoehl S, Heffelfritz FA, et al. Reduced neutralization of SARS-CoV-2 omicron variant by vaccine sera and monoclonal antibodies. MedRxiv 2021.
[11] Andrews N, Stowe J, Kinnebohm F, Tofts S, Rickard T, Gallagher E, Gower C, Kall M, Groves N, O’Connell A-M, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. MedRxiv 2021.
[12] Cameroni E, Saliba C, Bowen JE, Rosen LE, Culap K, Pinto D, De Marco A, Zepeda SK, di Iulio J, Zatta F, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. BioRxiv 2021.
[13] Lempp FA, Soriaga JLB, Montiel-Ruiz M, Benigni F, Noack J, Park Y-J, Bianchi S, Wells AC, Bowen JE, Zhou J, et al. Lectins enhance SARS-CoV-2 infection and influence neutralizing antibodies. Nature 2021;598(7880):542–7.
[14] Cao YR, Wang J, Jian F, Xiao T, Song W, Yismiayi A, Huang W, Li Q, Wang P, An R, et al. B.1.1.529 escapes the majority of SARS-CoV-2 neutralizing antibodies of diverse epitopes. BioRxiv 2021.
[15] VanBlargan LA, Errico JM, Halfmann P, Zost SJ, Crowe JE, Purcell LA, Kawakyo Y, Corti D, Fremont DH, Diamond M. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by several therapeutic monoclonal antibodies. BioRxiv 2021.
[16] Yu Z, Sohail A, Nutini A, Arif R. Delayed modeling approach to forecast the periodic behaviour of SARS-2. Front Mol Biosci 2020;7:386.
[17] Yu Z, Sohail A, Nutini A, Arif R. Delayed modeling approach to forecast the periodic behaviour of SARS-2. Front Mol Biosci 2021:386.
[18] Yu Z, Sohail A, Nofal TA, Tavarez JMR. Explainability of neural network clustering in interpreting the COVID-19 emergency data. Fractals 2021.
[19] Yu Z, Abdel-Salam A-SG, Sohail A, Alam F. Forecasting the impact of environmental stresses on the frequent waves of COVID19. Nonlinear Dynam 2021;106(2):1509–23.
[20] Yu Z, Elahi R, Nutini A, Sohail A, Sait SM. Modeling and simulations of CoVid-19 molecular mechanism induced by cytokines storm during SARS-CoV2 infection. J Molecul Liquids 2021;327:114863.
[21] Yu Z, Arif R, Fahmy MA, Sohail A. Self organizing maps for the parametric analysis of COVID-19 SEIRS delayed model. Chaos Solitons Fractals 2021;150:111202.
[22] Sohail A, Yu Z, Arif R, Nutini A, Nofal TA. Piecewise differentiation of the fractional order CAR-T cells-SARS-2 virus model. Results Phys 2021;105046.
[23] Al-Utaibi KA, Sohail A, Yu Z, Arif R, Nutini A, Abdel-Salam A-SG, Sait SM. Dynamical analysis of the delayed immune response to cancer. Results Phys 2021;26:104282.
[24] Al-Utaibi KA, Idrees M, Sohail A, Arif F, Nutini A, Sait SM. Artificial intelligence to link environmental endocrine disruptors (EDCs) with bone diseases. Int J Model Simul Sci Comput 2021;2250019.
[25] Idrees M, Sohail A. A computational framework and sensitivity analysis for the hormonal treatment of bone. Clin Biomech 2020;75:9–16.
[26] Wang F, Idrees M, Sohail A. “AI-MCMC” for the parametric analysis of the hormonal therapy of cancer. Chaos Solitons Fractals 2021;154:111618.
[27] Idrees M, Sohail A. Bio-algorithms for the modeling and simulation of cancer cells and the immune response. Bio-Algorithms Med-Syst 2021;17(1):55–63.
[28] Nutini A, Sohail A. Deep learning of the role of interleukin il-17 and its action in promoting cancer. Bio-Algorithms Med-Syst 2021;16(4).
[29] Nutini A, Sohail A. Deep learning of the role of interleukin IL-7 and its action in promoting cancer. Bio-Algorithms Med-Syst 2020;1(ahead-of-print).
[30] Ko S-Y, Pegu A, Rudicell RS, Yang Z-y, Joyce MG, Chen X, Wang K, Rao S, Kaeo S, Rodner RD, Taylor JH, et al. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. Nature 2014;514(75)42(5):642–5.
[31] Zalevsky J, Chamberlain AK, Horton IM, Kariki S, Leung IW, Sproule TJ, Lazarv GA, Roopenian DC, Desjarlais JR. Enhanced antibody half-life improves in vivo activity. Nature Biotechnol 2010;28(2):157–9.
[32] Cathcart AL, Havenar-Daughton C, Lempp FA, Ma D, Schmid M, Agostini ML, Guirano B, Rosen L, Tucker H, Dillen J, et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. BioRxiv 2021.
[33] Guo-PC, Huang Y, Lu X, Liu-Y. Coronavirus genomics and bioinformatics analysis. Viruses 2010;2(8):1804–20.
[34] Pan L, Cheng C, Haberkorn U, Dimitrakopoulou-Strauss A. Machine learning-based kinetic modeling: a robust and reproducible solution for quantitative analysis of dynamic PET data. Phys Med Biol 2017;62(9):3566.
[35] Sohail A, Nutini A. Forecasting the timeframe of coronavirus and human cells interaction with reverse engineering. Frog Biophis Mol Biol 2020.
[36] VanBlargan LA, Errico JM, Halfmann P, Zost SJ, Crowe JE, Purcell LA, Kawakyo Y, Corti D, Fremont DH, Diamond M. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by several therapeutic monoclonal antibodies. Nat Med 2021;26:104282.
[37] Kasakovski D, Xu L, Li Y. T cell senescence and CAR-T cell exhaustion in hematological malignancies. J Hematol Oncol 2018;11(1):1–9.