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Modeling the crossover behavior of the bacterial infection with the COVID-19 epidemics

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ABSTRACT

To explore the crossover linkage of the bacterial infections resulting from the viral infection, within the host body, a computational framework is developed. It analyzes the additional pathogenic effect of Streptococcus pneumonia, one of the bacteria that can trigger the super-infection mechanism in the COVID-19 syndrome and the physiological effects of innate immunity for the control or eradication of this bacterial infection. The computational framework, in a novel manner, takes into account the action of pro-inflammatory and anti-inflammatory cytokines in response to the function of macrophages. A hypothetical model is created and is transformed to a system of non-dimensional mathematical equations. The dynamics of three main parameters (macrophages sensitivity κ, sensitivity to cytokines η and bacterial sensitivity ϵ), analyzes a "threshold value" termed as the basic reproduction number R_0 which is based on a sub-model of the inflammatory state. Piece-wise differentiation approach is used and dynamical analysis for the inflammatory response of macrophages is studied in detail. The results shows that the inflamatory response, with high probability in bacterial super-infection, is concomitant with the COVID-19 infection. The mechanism of action of the anti-inflammatory cytokines is discussed during this research and it is observed that these cytokines do not prevent inflammation chronic, but only reduce its level while increasing the activation threshold of macrophages. The results of the model quantifies the probable deficit of the biological mechanisms linked with the anti-inflammatory cytokines. The numerical results shows that for such mechanisms, a minimal action of the pathogens is strongly amplified, resulting in the "chronicity" of the inflammatory process.

Introduction

The severe acute respiratory syndrome due to the Corona virus has evolved into a pandemic that is among the most serious in modern history, critically affecting health systems around the world.

The CoVID-19 syndrome, resulting from the SARS-CoV2 viral infection, has also shown events of superinfection and concomitant bacterial co-infection that are highly critical in patients hospitalized in intensive care. It is observed that the mortality rate worsened during the frequent waves of COVID-19 and the pathological events, collateral to the viral infection, increased.

The acute respiratory distress syndrome (ARDS) in CoVID-19 is initiated by the SARS-CoV2 virus, which subsequently leads to inflammation-driven lung injury [1].

Secondary bacterial infections are well-described processes that are "collateral" in viral diseases. Such infections are believed to be responsible for the "morbidity" as well as the "mortality" in viral ARDS [2].

Secondary bacterial infections are generally referred to as superinfections, while the term co-infection is intended to describe simultaneous virus infection. Both, the co-infections and the superinfections have been described in COVID-19 patients [3].

Data on bacterial superinfections of COVID-19 pneumonia is limited and new evidence is currently emerging [4]. A recent review concluded that the rate of bacterial superinfections is quite low, exposing the idea that frequent use of broad-spectrum antimicrobials is counterproductive [5]; however, the presence of associated pulmonary

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aspergillosis (CAPA) has been reported in various cases of critical CoVID-19 syndrome [6].

It is still an open problem since the accurate linkage of the tendency of the concomitant bacterial and viral infections, in critically ill, CoVID-19 patients, is poorly understood [5]. Although it is reported by different research labs that the increased mortality in critical cases of COVID-19 patients is partly due to "secondary-infections" (in addition to the strong viral presence in the lower respiratory tract leading to lung lesions and the ARDS [7,8]).

Superinfection, therefore, appears to be an important risk factor for mortality in patients with CoVID-19 although, currently there is limited understanding of the related clinical situations [9].

Rapid diagnosis of co-infections and superinfections can help to improve survival and to administer targeted antimicrobial therapy, allowing further control of the patient's prognosis and avoiding further collateral damage [10].

An interesting study by Buehler et al. [11] detected lung pathogens ten days after admission to the ICU; the most frequently isolated bacteria per patient were Enterococcus spp., Enterobacter/Citrobacter and Klebsiella spp.

Additionally, Streptococcus pneumonia, Streptococcus anginosus, Escherichia coli, Enterobacter spp., Citrobacter spp., Pseudomonas aeruginosa, and Burkholderia cepacia have been found.

Although some studies conclude that bacterial superinfections do not play an important role in disease severity and therapy, the results of the study by Buehler et al. question this conclusion and during the investigated cohort, the isolation of respiratory bacteria was associated with a more severe COVID-19 syndrome with longer disease courses and with the adoption of invasive mechanical ventilation which resulted in prolonged stays in intensive care [11].

Based on these studies, we can admit that SARS-CoV2 infection, like other respiratory viral infections, predispose patients to co-infections and superinfections and these lead to an increase in the severity of the disease and mortality.

Various types of antibiotics such as azithromycin have been used for the prevention and treatment of secondary bacterial infections in patients with a viral respiratory infection such as SARS-CoV2 and although antibiotics do not directly affect this virus, such viral respiratory infections often cause bacterial pneumonia to a limit that, it is possible to think that some patients die from bacterial superinfection rather than from the virus itself [12].

Currently, a considerable number of bacterial strains are resistant to various antibiotics such as the aforementioned azithromycin and excessive use without clinical control could make other antibiotics less effective as well.

Therefore, in assessing the clinical status of a patient with severe COVID-19 syndrome, both viral coinfection and secondary bacterial superinfection should be considered as critical risk factors for COVID-19 severity and mortality rates. Furthermore, it is strongly recommended to consider the resistance to antibiotics, that may take place due to their excessive use. Streptococcus pneumoniae is one of the various bacteria that cause superinfection in conjunction with COVID-19 syndrome. It is a gram-positive bacterium belonging to the genus Streptococcus and a cause of bacterial pneumonia.

Although the contribution of the respiratory microbiota to SARS-CoV2 infection and pathogenesis has not been extensively studied [13], interesting work by Lewnard et al. [14] suggests a potential interaction between this pneumococcus and the SARS-CoV2 virus.

The results reported by this study are in agreement with other works that suggest that the pathogenicity of respiratory viruses can be modified by the bacterial load that leads to a defect in the functioning of the physical barriers, to a dysfunction of the immune responses, and delays in the restoration of homeostasis [15]. Evidence that commensal upper respiratory tract bacteria promote viral infection has been evident as early as 1987 [16] with scientific work demonstrating how enzymes expressed by bacteria, including pneumococcal species [17], improve the replication and pathogenicity of a virus such as influenza.

For this reason, it is worth considering the hypothesis of Lewnard et al. [14] that takes into account the action of Streptococcus pneumoniae as an additional pathogenic element, and the net effect may be the growth of pathogens, that increases the pathology in an immune-mediated manner and thus increases the morbidity.

Furthermore, an evaluation of the previous (or concomitant presence of pneumococcus) SARS-CoV2 infection is associated with different immune responses, to this virus, that could further clarify the host-mediated interaction mechanisms between pneumococci and SARS-CoV2 itself.

Pathogenic cycle of streptococcus pneumonia superinfection in COVID-19 syndrome

Streptococcus pneumoniae (also called pneumococcus) is a Gram-positive bacterium commensal of the respiratory tract, and the infection is possible in conditions of chronic disease or immunosuppression. This type of bacterium is responsible for the onset of various diseases, including bacterial pneumonia, ear infections, sinus infections, bacteremia, and sepsis up to meningitis with a high fever.

Although the pathological effects of this infection are known, the true burden of disease caused by pneumococcus is uncertain as these disorders can be caused by a variety of different organisms and are often treated without bacteriological diagnosis of the cause; in order to have a better prognosis of the disease and a specific and early therapy, it would therefore be advisable to have a better diagnosis or a highly effective vaccine to provide a more faithful picture of the pneumococcal disease burden and to confirm that the current values are underestimated [18].

Pneumococci are highly adapted commensals and their main reservoir sits on the mucosal surface of the hosts' upper airways, allowing for transmission. As noted above, these bacteria can cause serious disease when they manage to invade essentially "sterile" sites such as the middle ear spaces, lungs, bloodstream and meninges. Transmission, colonization and invasion depend on Streptococcus pneumoniae's remarkable ability to evade or exploit host inflammatory and immune responses [19].

This pneumococcus has appeared as a secondary pathogen, during the SARS-CoV2 superinfections, this further complication has led to a greater number of hospitalizations and to increasingly critical clinical conditions [9,20,21].

Moreover, it is very likely that SARS-CoV2 infection facilitates pneumococcal superinfection [14] and that there are molecular mechanisms that provide for this facilitation. The mechanism of inflammation that pneumococcal infection creates is, in the case of SARS-CoV2, very particular because it is affected by the immune response to the virus which, in some way, accentuates the superinfection condition.

Streptococcus pneumoniae, through the activation of the MAPK/ERK pathway, induces an inflammatory state that is fueled by the production of proinflammatory cytokines by the effectors of the immune system such as macrophages, already activated by the COVID-19 syndrome, which in turn produce, further secretion of proinflammatory cytokines via the "cytokines storm" [22–24]. This condition is amplified by a further production of these cytokines implicit in the pathological condition triggered by the SARS-CoV2 virus which is further increased by the exposure of the LPS antigen (lipopolysaccharide) typical of pneumococcus (Fig. 1).

Superinfection with Streptococcus pneumoniae, therefore, constitutes an additional pathological stimulus which, in addition to inducing additional bacterial pneumonia, leads to an even more severe and widespread inflammatory condition. Understanding the superinfection model, therefore, can lead to greater therapeutic precision in the case of superinfections related to the COVID-19 syndrome and to a prevention activity that can allow a reduction in the number of hospitalizations.

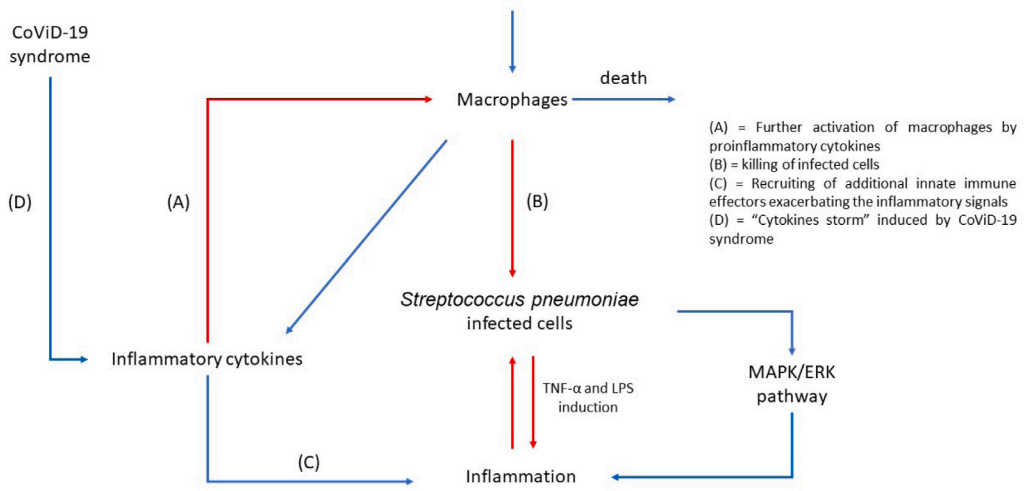

Fig. 1. Schematic description of SARS-2 inflammatory action.

For this reason, we have worked on a model of Streptococcus pneumoniae superinfection secondary to SARS-CoV2 infection that tends to clarify, quantitatively, and qualitatively, some parameters of immune response that are referable to the additional inflammatory state that could constitute additional damage and a critical element in hospitalized patients with severe COVID-19 syndrome.

Computational framework

Here, we state some basic definitions and important lemmas, and other theorems for both sorts of incommensurate and commensurate model of fractional order that is suitable to define the analytical results of model.

Definition. The Caputo fractional derivative of order α where $\alpha \in (n-1, n)$, as n is a natural number for the function $K \in C^n$ is given as follows

$$ {}^{C}D_t^{\alpha}(K(t)) = \frac{1}{\Gamma(n-1)} \int_0^t \frac{K^{(n)}\varkappa}{(1-\varkappa)^{\alpha-n+1}} d\varkappa. \tag{1}$$

where γ is a gamma function. ${}^{C}D_t^{\alpha}(K(t)) \to K'(t)$ as $\alpha \to 1$.

Definition. Fractional integral of α order of function $h : R^+ \to R^+$ define by as follows

$$ I_t^{\alpha}(K(t)) = \frac{1}{\Gamma(\alpha)} = \int_0^t (t-\varkappa)^{\alpha-1} K(\varkappa) d\varkappa. \tag{2}$$

Definition. The equilibrium point for this model is defined as:

$$ {}^{C}D_t^{\alpha}(Y(t)) = K(t, Y(t)), \alpha \in (0, 1) \tag{3}$$

iif $K(t, Y^*) = 0$.

Analysis of model

The variables of model are alveolar macrophage population (A), inflammatory cytokine concentrations (I), anti-inflammatory cytokine concentrations (C), and bacterial population (B). The non dimensional mathematical equations of the model are

$$\begin{aligned}
{}^{C}D_t^{\alpha} A &= 1 + \frac{\kappa I}{1+\beta I} - A, \\
{}^{C}D_t^{\alpha} I &= AB + \gamma \left(\frac{\eta A}{(1+I)(C+1)} - 1 \right) I, \\
{}^{C}D_t^{\alpha} C &= \sigma A I - \psi C, \\
{}^{C}D_t^{\alpha} B &= \mu(\epsilon - \mathrm{I})B.
\end{aligned} \tag{4}$$

Table 1
Description of the variables.

Symbols	Biological meanings
$A(t)$	Alveolar macrophage population
$I(t)$	Inflammatory cytokine concentrations
$C(t)$	Anti-inflammatory cytokine concentrations
$B(t)$	Bacterial population

With the initial conditions $(A(0), C(0), I(0), B(0)) \geq 0$. The biological description of parameters is described in the table. In this computational model, three parameters play an important role.

- The first parameter is macrophage sensitivity κ; in absence of infection plays an important part in defining the intensity of long-term inflammation Macrophage sensitivity, i.e. it defines the intensity of macrophage recruitment and it is decided by the concentration of inflammatory cytokine. This parameter, therefore, is a pre-existing value in the inflammatory regime and is a characteristic of the phagocytic cell population.
  The dynamics of the parameter κ is such that its increase also implies a slight increase in the concentration of inflammatory cytokines which, in turn, provides for an increase in the population of macrophages. This cycle involves an increase in the level of inflammation.
- The second is sensitivity to cytokines η, which helps us to analyze the long-term systemic situation. the parameter η can be referred to the presence of inflammatory cytokines in the absence of the pathogen, thus attributing a basal value to the physiological action of these cytokines. The sensitivity to cytokines η is therefore directly proportional to the inflammatory cytokines produced by self-induction.
- The third parameter is bacterial sensitivity ϵ, which refers to the resolution of the pathological event (infection removed) or to a chronicity of the same. This value is based on bacterial growth during infection and the consequent increase in the colonization capacity of the host. If the infection is not eradicated, the growth of the bacterial population can exceed the defensive efficiency of the macrophage population increasing the pathological condition. In the present analysis, this does not happen and the macrophage population is at least able to contain the infection if not neutralized.

The description of variables an parameters are given in Tables 1 and 2.

Table 2
Summary of parameters.

Symbols	Biological Meanings
κ	Macrophage sensitivity
η	Cytokine sensitivity
ϵ	Bacterial sensitivity
β	Saturation constant for inflammatory cytokine

Positivity of model solution

Based on the above considerations and admitting a positive biological function exerted by the immune system, we can assume R_+^3 to shows the positivity of the model solution we have following equation

$$R_+^4 = \{y(t) \in R^4 | y(t) \geq 0\}, y(t) = (A, I, C, B)^T \tag{5}$$

For more analysis the succeeding lemma is essential.

Lemma. *Assume that*
$y(t) \in [a, b]$ *and* ${}^C D_t^\alpha y(t) \in (a, b]$ *then,*

$$y(t) = y(a) + \frac{1}{\Gamma(\alpha)} {}^C D_t^\alpha y(\varkappa)(t-a)^\alpha \tag{6}$$

with condition $a \leq \varkappa \leq t$, *for all* $t \in (a, b]$.

Corollary. *Consider that*
$F(t) \in C[a, b]$ *and* ${}^c D_t^\alpha y(t) \in (a, b]$, *where* $\alpha \in (0, 1]$.

Then

- $y(t)$ is non-increasing for ${}^c D_t^\alpha y(t) \leq 0$ for all $t \in (a, b)$,
- $y(t)$ is non-decreasing for ${}^c D_t^\alpha y(t) \geq 0$ for all $t \in (a, b)$.

Theorem 1. *The model (4) has the solution* $Y(t) \in$ *sum for all* $Y(t_0) = (A_0, I_0, C_0, B_0) \in \sum$ *with initial condition for all* $t \geq 0$.

Proof. Assume the region

$$\sum = \{(A, I, C, B) \in R^3 : \max\{|A|, |I|, |C|, |B|\} \leq \Omega\}. \tag{7}$$

where Ω is non negative number. suppose map $Y(\varkappa) = (Y_1(\varkappa), Y_2(\varkappa), Y_3(\varkappa), Y_4(\varkappa))$ where $Y = (A, I, C, B)$ and $Y' = (A, I, C, B)$.

$$\begin{aligned}
Y_1(\varkappa) &= 1 + \frac{\kappa I}{1+\beta I} - A,\\
Y_2(\varkappa) &= AB + \gamma\left(\frac{\eta A}{(1+I)(C+1)} - 1\right) I,\\
Y_3(\varkappa) &= \sigma A I - \psi C,\\
Y_4(\varkappa) &= \mu(\epsilon - \mathrm{I})B.
\end{aligned} \tag{8}$$

For any $\varkappa, \varkappa' \in \sum$

$$\|Y(\varkappa) - Y(\varkappa')\| = |Y_1(\varkappa) - Y_1(\varkappa')| + |Y_2(\varkappa) - Y_2(\varkappa')| + |Y_3(\varkappa) - Y_3(\varkappa')|. \tag{9}$$

Where

$$\begin{aligned}
|Y_1(\varkappa) - Y_1(\varkappa')| &= \left|\frac{I\kappa}{1+\beta I} - \frac{I'\kappa}{1+\beta I'} - (A - A')\right|\\
&\leq \left|\frac{I\kappa}{1+\beta I} - \frac{I'\kappa}{1+\beta I'}\right| - |A - A'|\\
&\leq K_1 \beta\kappa |(I - I')^2| - |A - A'|
\end{aligned} \tag{10}$$

$$\begin{aligned}
|Y_2(\varkappa) - Y_2(\varkappa')| &= \left|AB + \gamma\left(\frac{\eta A}{(1+I)(C+1)} - 1\right) I\right.\\
&\quad \left. - \left(A'B' + \gamma\left(\frac{\eta A'}{(1+I')(C'+1)} - 1\right) I'\right)\right|\\
&\leq |A - A'||B' + A|B - B'| + \gamma\eta\varrho\left(|A - A'|I\right.\\
&\quad \left. + \left(I' - I\right) A'\right) - \gamma|I - I'|
\end{aligned} \tag{11}$$

$$\begin{aligned}
|Y_3(\varkappa) - Y_3(\varkappa')| &= \left|\psi\left(C - C'\right) + \sigma\left(I'\left(A - A'\right) + A\left(I - I'\right)\right)\right|\\
&\leq \psi|C - C'| + \sigma\left(I'|A - A'| + A|I - I'|\right).
\end{aligned} \tag{12}$$

$$\begin{aligned}
|Y_4(\varkappa) - Y_4(\varkappa')| &= \left|\mu(\epsilon - I)B - \mu\left(\epsilon - I'\right)\right|\\
&\leq \mu\epsilon|B - B'| - \mu|I'|B - B'| + B|I - I'|.
\end{aligned} \tag{13}$$

adding values from Eqs. (10), (11), (12) and (13) in Eq. (9) we get

$$\begin{aligned}
\|Y(\varkappa) - Y(\varkappa')\| &\leq \left(B + I\gamma\eta\varrho + \sigma I'\right)|A - A'|\\
&\quad + \left(\gamma\eta\varrho A' + A\sigma + \frac{\beta\kappa\left(I - I'\right)}{(1+I\beta)(1+\beta I')} - B\mu - \gamma\right)|I - I'|\\
&\quad + \psi|C - C'| + \left(A' - \mu I' + \mu\epsilon\right)|B - B'|\\
&= Y_1|A - A'| + Y_2|I - I'| + Y_3|C - C'| + Y_4|B - B'|\\
&\leq Y\|\gamma - \gamma'\|.
\end{aligned} \tag{14}$$

Where $Y = \min\{Y_1, Y_2, Y_3, Y_4\}$ and $Y_1 = \left(B + I\gamma\eta\varrho + \sigma I'\right)$, $Y_2 = \gamma\eta\varrho A' + A\sigma + \frac{\beta\kappa(I-I')}{(1+I\beta)(1+\beta I')} - B\mu - \gamma$, $Y_3 = \psi$ and $Y_4 = A' - \mu I' + \mu\epsilon$. Hence, $Y(\varkappa)$ obeys Local Lipschitz's condition.

Theorem 2. *Solutions of the system of equations (16) exists and will remains in* R_+^4. *Furthermore, the solutions of the model are positive.*

Proof. From the given system, we conclude the following:

$$\begin{aligned}
&{}^C D_t^\alpha A|_{A=0} \geq 0,\\
&{}^C D_t^\alpha I|_{I=0} \geq 0,\\
&{}^C D_t^\alpha C|_{C=0} \geq 0\\
&{}^C D_t^\alpha B|_{B=0} \geq 0.
\end{aligned} \tag{15}$$

We thus conclude that the model's solution remains in R_+^4 and $\sum$ is the feasible region with $\Omega \geq 0$.

Inflammatory sub-model analysis

The system is given as:

$$\begin{aligned}
{}^C D_t^\alpha A &= 1 - A + \frac{\kappa I}{1+\beta I},\\
{}^C D_t^\alpha I &= AB + \gamma\left(\frac{\eta A}{1+I} - 1\right) I,\\
{}^C D_t^\alpha B &= \mu(\epsilon - A)B,
\end{aligned} \tag{16}$$

The initial conditions are $(A(0), I(0), B(0)) \geq 0$.

Equilibrium points

The sub model has following equilibrium points which are obtained by letting equations of the model equal to zero

$${}^c D_t^\alpha A = {}^c D_t^\alpha I = {}^c D_t^\alpha B = 0. \tag{17}$$

the model a unique infection free equilibrium point. The infection free equilibrium point (A_0, I_0, B_0) is

$$E_0 = (1, 0, 0), \tag{18}$$

Both biologically and computationally, we can admit that there is always the infection-free equilibrium point that is not affected by any parametric value. In other words, the meaning of its existence is independent of the parametric values in analysis. In the absence of bacteria, two equilibrium points relative to the inflammatory process are computationally obtained; one is referred to as the "low inflammatory balance point" and the other is the "high inflammatory balance point" which are as follows:

$$E^- = (A^-, 0, I^-) \tag{19}$$

where:

$$A^- = \frac{\beta\eta + \beta + \eta\kappa - 1 - \rho}{2\beta\eta},$$
$$I^- = \frac{\beta\eta - \beta + \eta\kappa - 1 - \rho}{2\beta}. \tag{20}$$
$$\rho = \sqrt{(\beta(\eta-1) + \eta\kappa - 1)^2 + 4\beta(\eta - 1)}.$$

The high inflamed equilibrium point is only exists if $\eta > 1$

$$E^+ = (A^+, 0, I^+) \tag{21}$$

where:

$$A^+ = \frac{\beta\eta + \beta + \eta\kappa - 1 + \rho}{2\beta\eta},$$
$$I^+ = \frac{\beta(\eta-1) + \eta\kappa - 1 + \rho}{2\beta}. \tag{22}$$

The inflamed equilibrium point only exist if and only if η and κ greater then zero. The chronically infected or endemic equilibrium point $E^* = (A^*, B^*, I^*)$ is defined as

$$A^* = \epsilon,$$
$$B^* = \gamma(\epsilon - 1)\left(\frac{1}{\epsilon(\beta - \beta\epsilon + \kappa)} - \frac{\eta}{\beta + \beta\epsilon + \kappa + \epsilon - 1}\right), \tag{23}$$
$$I^* = \frac{\epsilon - 1}{\beta + \kappa - \beta\epsilon},$$

whose existence is depends on the basic reproduction number.

The "threshold quantity" is base reproduction number for fractional order computational dynamical system and is obtained by applying the next generation method. Basic reproduction number R_0 is a very important biological variable biologically since it is able to determine the global dynamics of the analysis of a model and to describe the analytical consequences and, as seen, it is essential for the determination and existence of the endemic equilibrium point. R0 is defined as:

$$R_0 = \frac{(\gamma - \gamma\eta)(\mu + \mu(\epsilon - 1))}{\gamma\mu - \gamma\eta\mu}. \tag{24}$$

Stability analysis

Theorem 3. *Suppose that x_1 and x_2 be positive integers such that $\gcd(x_1, x_2) = 1$. Suppose that $\theta = \frac{x_1}{x_2}$, then the equilibrium point of model (16) is asymptotically stable with $|\arg(\lambda)| > \frac{\pi}{2x_2}$*

The Jacobian matrix at infection free equilibrium point is

$$J_0 = \begin{pmatrix} -1 & \kappa & 0 \\ 0 & \gamma(\eta - 1) & 1 \\ 0 & 0 & (\epsilon - 1)\mu \end{pmatrix} \tag{25}$$

by expansion we get

$$(\lambda^{x_1} + \gamma_1)(\lambda^{x_1} + \Delta_2)(\lambda^{x_1} + \Delta_3) \tag{26}$$

where the coefficients are

$$\Delta_1 = -1,$$
$$\Delta_2 = \gamma(\eta - 1), \tag{27}$$
$$\Delta_3 = \mu(\epsilon - 1).$$

Arguments of roots $\lambda^{x_1} + \Delta_1 = 0$ are

$$arg(\lambda_i) = \frac{\pi}{x_1} + \frac{2\pi}{x_1} i > \frac{\pi}{x_2} > \frac{\pi}{2x_2}, i = 0, 1, 2, \ldots (p_1 - 1). \tag{28}$$

In the same pattern argument of root $\lambda^{x_1} + \Delta_2 = 0$ and $\lambda^{x_1} + \Delta_3 = 0$ and also greater than $\frac{\pi}{2x_2}$. Furthermore, if basic reproduction number $R_0 < 0$ and conditions holds for all polynomial (26), then system of equations at infection free equilibrium point is stable. But in case if the basic reproduction number $R_1 > 1$, then according to Descartes signs rule, there exists at least one root that gives positive root in other words which satisfied $|\arg(\lambda)| < \frac{\pi}{2x_2}$.

Hence, the endemic equilibrium point is asymptotically stable for $R_0 < 1$, otherwise it is unstable.

Thus the polynomial analysis, therefore, tends to show a positive evolution of the model subject to a stable infection free equilibrium point. Through the analysis of the Jacobian matrix at equilibrium point of infection free, the computation of the value of R_0 is concluded, in this case, to further define the development conditions of the model.

Theorem 4. *For the arbitrary fractional order α in interval (0,1], and $R_0 < 1$, the infection free equilibrium point of dynamical model (16) always globally asymptotically stable, otherwise it is unstable.*

Proof. According to the definition of Lyapunov function

$$P(t) = P_1(t)(A - A_0 - A_0 \ln\frac{A}{A_0}) + P_2(t)(B - B_0 - B_0 \ln\frac{B}{B_0}) + P_3(t)(I - I_0 - I_0 \ln\frac{I}{I_0}). \tag{29}$$

Where P_i as $i = 1 : 3$ are positive constants. The time derivative of above Eq. (29) we have

$$\begin{aligned} {}^C D_t^\alpha P &= P_1(\frac{A - A_0}{A})\,{}^C D_t^\alpha A + P_2\,{}^C D_t^\alpha B + P_3\,{}^C D_t^\alpha I \\ &= P_1(\frac{A - A_0}{A})[1 - A + \frac{\kappa I}{1 + \beta I}] \\ &+ P_2[AB + \gamma\left(\frac{\eta A}{1 + I} - 1\right) I] + P_3[\mu(\epsilon - A)B]. \end{aligned} \tag{30}$$

With the help of arithmetical geometrical inequality we have

$$\begin{aligned} (\frac{A - A_0}{A})[1 - A + \frac{\kappa I}{1 + \beta I}] &\le 0, \\ [AB + \gamma\left(\frac{\eta A}{1 + I} - 1\right) I] &\le 0, \\ [\mu(\epsilon - A)B] &\le 0. \end{aligned} \tag{31}$$

Hence for $R_0 < 1$ ${}^C D_t^\alpha P$ is negative. Therefore, model (16) is globally asymptotically stable at infection free equilibrium point E_0.

Stability at endemic equilibrium point

The Jacobian matrix at endemic equilibrium point is

$$J^* = \begin{pmatrix} -1 & \frac{\kappa}{(\beta I + 1)^2} & 0 \\ B + \frac{\gamma\eta I}{1+I} & \gamma\left(\frac{\eta A}{(1+I)^2} - 1\right) & A \\ -\mu B & 0 & \mu(\epsilon - A) \end{pmatrix}. \tag{32}$$

For $R_1 > 1$ stability of endemic equilibrium point has been explained in the previous theorem 3.

Theorem 5. *If the basic reproduction number $R_0 > 1$, the endemic equilibrium point is globally asymptotically stable.*

Proof. Suppose the Lyapunov function

$$Q(t) = (A - A^* - A^* \ln\frac{A}{A^*}) + (I - I^* - I^* \ln\frac{I}{I^*}) + (B - B^* - B^* \ln\frac{B}{B^*}). \tag{33}$$

By theorem 3, derivative along endemic equilibrium point is

$${}^C D_t^\alpha Q = (1 - \frac{A^*}{A})\,{}^C D_t^\alpha A + (1 - \frac{I^*}{I})\,{}^C D_t^\alpha I + (1 - \frac{B^*}{B})\,{}^C D_t^\alpha B. \tag{34}$$

Where:

$$\begin{aligned} (1 - \frac{A^*}{A})\,{}^C D_t^\alpha A &= (1 - \frac{A^*}{A})[1 - A + \frac{\kappa I}{1 + \beta I}], \\ (1 - \frac{I^*}{I})\,{}^C D_t^\alpha I &= (1 - \frac{I^*}{I})[\mu(\epsilon - A)B], \\ (1 - \frac{B^*}{B})\,{}^C D_t^\alpha B &= (1 - \frac{B^*}{B})[AB + \gamma\left(\frac{\eta A}{1 + I} - 1\right) I] \end{aligned} \tag{35}$$

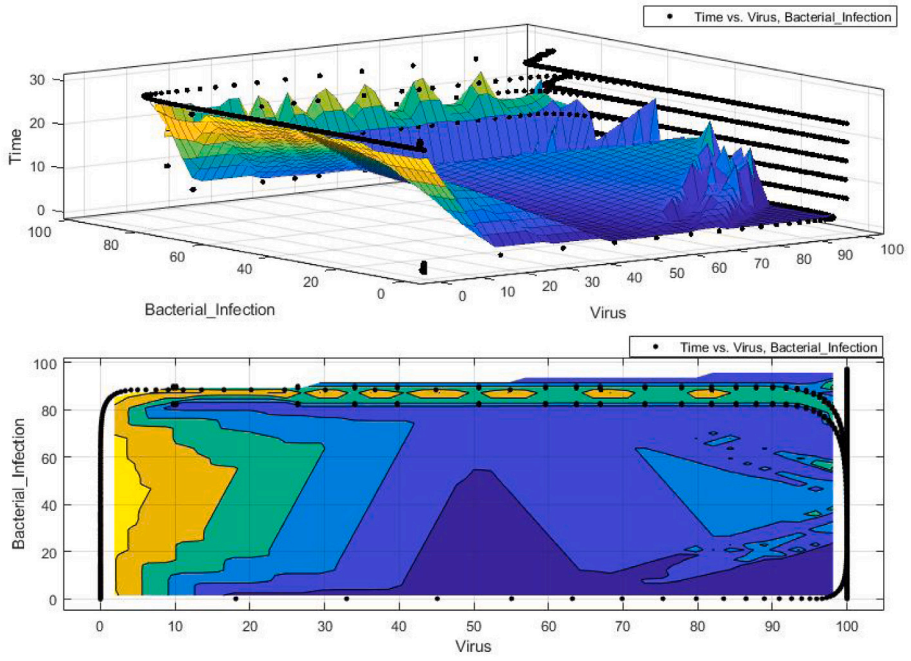

Fig. 2. Linkage of Bacteria Infection to the Viral Infection over the period of time, (top: 3D plot, bottom: contour plot.

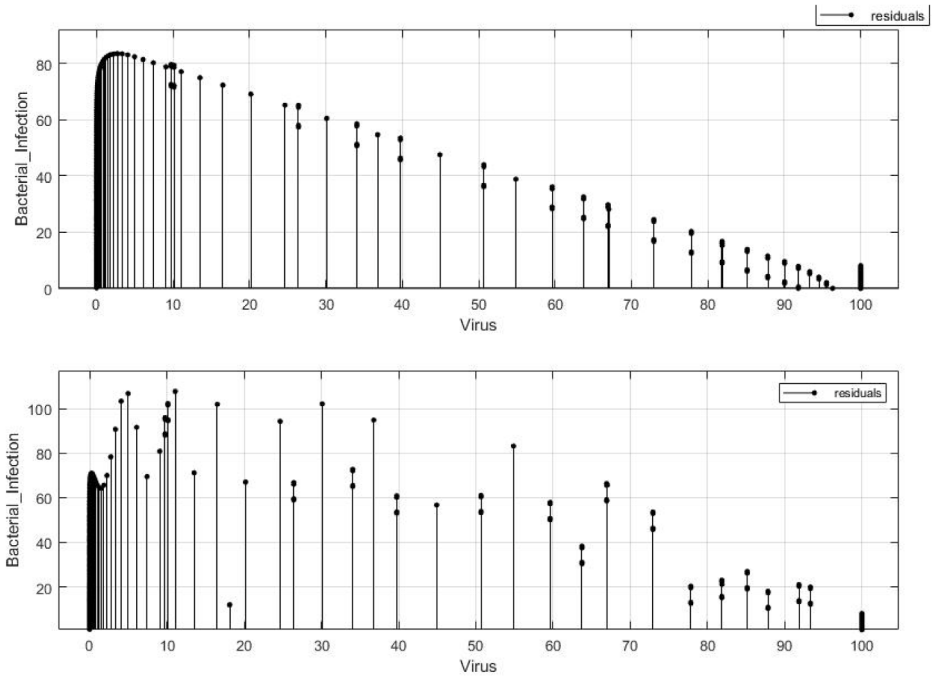

Fig. 3. The residual graphs for two different fractional orders (top $\alpha = 1$, bottom $\alpha = 0.9$).

By simplifying we have

$$
\begin{aligned}
{}^{C}D_t^{\alpha}Q = (1-\frac{A^*}{A})[1-A+\frac{\kappa I}{1+\beta I}] + (1-\frac{I^*}{I})[\mu(\epsilon-A)B] \\
+ (1-\frac{B^*}{B})[AB+\gamma\left(\frac{\eta A}{1+I}-1\right)I].
\end{aligned} \tag{36}
$$

By arithmetical geometrical inequality

$$
\begin{aligned}
(1-\frac{A^*}{A})[1-A+\frac{\kappa I}{1+\beta I}] \le 0, \\
(1-\frac{I^*}{I})[\mu(\epsilon-A)B] \le 0, \\
(1-\frac{B^*}{B})[AB+\gamma\left(\frac{\eta A}{1+I}-1\right)I] \le 0.
\end{aligned} \tag{37}
$$

Hence ${}^{C}D_{t}^{\alpha}Q \leq 0$, therefore by theorem 3 model (40) at endemic equilibrium point is locally asymptotically stable.

Piecewise derivative

All the differential equations and integral equations have numerous impacts.

Definition. Assume that we have two continuous functions X and Y such that X is not a constant increasing function and differentiable function Y, then piecewise derivative over $[0,T]$ interval

$$
\begin{aligned}
{}_{0}^{PG}DX(t) &= \begin{cases} \dfrac{dX}{dt} & if \quad 0 \le t \le t_1 \\ D_Y X(t) & if \quad t_1 \le t \le T \end{cases} \\
&= \begin{cases} \lim_{h\to 0} \dfrac{X(t+h)-X(t)}{h} & if \quad 0 \le t \le t_1 \\ \lim_{h\to 0} \dfrac{X(t+h)-X(t)}{Y(t+h)-Y(t)} & if \quad t_1 \le t \le T \end{cases}
\end{aligned} \tag{38}
$$

classic derivative ${}_{0}^{PG}DX(t)$ on $0 \le t \le t_1$ and global derivative on $t_1 \le t \le T$

Definition. Consider two continuous functions X and Y which are non-constant differentiable increasing function. Piecewise integral of function X with respect to function Y define here

$$
\begin{aligned}
{}_{0}^{PG}I_t X(t) &= \begin{cases} \int_0^t X(\tau)d\tau & if \quad 0 \le t \le t_1 \\ \int_{t_1}^t X(\tau)dY(\tau)d\tau & if \quad t_1 \le t \le T \end{cases} \\
{}_{0}^{PG}I_t X(t) &= \begin{cases} \int_0^t X(\tau)d\tau & if \quad 0 \le t \le t_1 \\ \int_{t_1}^t X(\tau)Y'(\tau)d\tau & if \quad t_1 \le t \le T \end{cases}
\end{aligned} \tag{39}
$$

classical integral ${}_{0}^{PG}I_t X(t)$ on interval $0 \le t \le t_1$ and global integral on $t_1 \le t \le T$.

For numerical scheme of model (16), following is supposed

$$
\begin{aligned}
&{}^{C}D_{t}^{\alpha}A = 1 + a\kappa I - A, \\
&{}^{C}D_{t}^{\alpha}I = AB + \gamma\,(b\eta A - 1)\,I, \\
&{}^{C}D_{t}^{\alpha}C = \sigma AI - \psi C, \\
&{}^{C}D_{t}^{\alpha}B = \mu(\epsilon - I)B.
\end{aligned} \tag{40}
$$

Where

$$
\begin{aligned}
a &= \frac{1}{1+\beta I}, \\
b &= \frac{1}{(1+I)(C+1)}.
\end{aligned} \tag{41}
$$

Applying the piece-wise derivative, we obtained

$$
\begin{aligned}
A(t) &= \begin{cases} A(0) + \int_0^{t_1}(1 + a\kappa I - A)d\tau \\ A(t_1) + \int_{t_1}^{t}(1 + a\kappa I - A)h'(\tau)d\tau \end{cases} \\
I(t) &= \begin{cases} I(0) + \int_0^{t_1}(AB + \gamma\,(b\eta A - 1)\,I)d\tau \\ I(t_1) + \int_{t_1}^{t}(AB + \gamma\,(b\eta A - 1)\,I)h'(\tau)d\tau \end{cases} \\
C(t) &= \begin{cases} C(0) + \int_0^{t_1}(\sigma AI - \psi C)d\tau \\ C(t_1) + \int_{t_1}^{t}(\sigma AI - \psi C)h'(\tau)d\tau \end{cases} \\
B(t) &= \begin{cases} B(0) + \int_0^{t_1}(\mu(\epsilon - I)B)d\tau \\ B(t_1) + \int_{t_1}^{t}(\mu(\epsilon - I)B)h'(\tau)d\tau. \end{cases}
\end{aligned} \tag{42}
$$

At $t = t_{n+1}$ we can write

$$
\begin{aligned}
A(t_{n+1}) &= \begin{cases} A(0) + \int_0^{t_1}(1 + a\kappa I - A)d\tau \\ A(t_1) + \int_{t_1}^{t_{n+1}}(1 + a\kappa I - A)h'(\tau)d\tau \end{cases} \\
I(t_{n+1}) &= \begin{cases} I(0) + \int_0^{t_1}(AB + \gamma\,(b\eta A - 1)\,I)d\tau \\ I(t_1) + \int_{t_1}^{t_{n+1}}(AB + \gamma\,(b\eta A - 1)\,I)h'(\tau)d\tau \end{cases} \\
C(t_{n+1}) &= \begin{cases} C(0) + \int_0^{t_1}(\sigma AI - \psi C)d\tau \\ C(t_1) + \int_{t_1}^{t_{n+1}}(\sigma AI - \psi C)h'(\tau)d\tau \end{cases} \\
B(t_{n+1}) &= \begin{cases} B(0) + \int_0^{t_1}(\mu(\epsilon - I)B)d\tau \\ B(t_1) + \int_{t_1}^{t_{n+1}}(\mu(\epsilon - I)B)h'(\tau)d\tau. \end{cases}
\end{aligned} \tag{43}
$$

Substituting with the formula of Newton polynomial interpolation,

$$
\begin{aligned}
A(t_{n+1}) &= \begin{cases} A(0) + \sum_{k=2}^{i} \begin{cases} \frac{5}{12}(1 + a\kappa I_{k-2} - A_{k-2})\Delta t \\ -\frac{4}{3}(1 + a\kappa I_{k-1} - A_{k-1})\Delta t \\ +\frac{23}{12}(1 + a\kappa I_k - A_k)\Delta t \end{cases} \\ A(t_1) + \sum_{k=i+3}^{n} \begin{cases} \frac{5}{12}(1 + a\kappa I_{k-2} - A_{k-2}) \\ \times (h(t_{k-1}) - h(t_{k-2})) \\ -\frac{4}{3}(1 + a\kappa I_{k-1} - A_{k-1}) \\ \times (h(t_k) - h(t_{k-1})) \\ +\frac{23}{12}(1 + a\kappa I_k - A_k) \\ \times (h(t_{k+1}) - h(t_k)) \end{cases} \end{cases} \\
I(t_{n+1}) &= \begin{cases} I(0) + \sum_{k=2}^{i} \begin{cases} \frac{5}{12}(A_{k-2}B_{k-2} + \gamma\left(b\eta A_{k-2} - 1\right)I_{k-2})\Delta t \\ -\frac{4}{3}(A_{k-1}B_{k-1} + \gamma\left(b\eta A_{k-1} - 1\right)I_{k-1})\Delta t \\ +\frac{23}{12}(A_k B_k + \gamma\left(b\eta A_k - 1\right)I_k)\Delta t \end{cases} \\ I(t_1) + \sum_{k=i+3}^{n} \begin{cases} \frac{5}{12}(\rho + aX_{k-2} + bY_{k-2} + cZ_{k-2} \\ -\beta X_{k-2}Y_{k-2}) \\ \times (h(t_{k-1}) - h(t_{k-2})) \\ -\frac{4}{3}(A_{k-1}B_{k-1} + \gamma\left(b\eta A_{k-1} - 1\right)I_{k-1}) \\ \times (h(t_k) - h(t_{k-1})) \\ +\frac{23}{12}(A_k B_k + \gamma\left(b\eta A_k - 1\right)I_k) \\ \times (h(t_{k+1}) - h(t_k)) \end{cases} \end{cases} \\
C(t_{n+1}) &= \begin{cases} C(0) + \sum_{k=2}^{i} \begin{cases} \frac{5}{12}(\sigma A_{k-2}I_{k-2} - \psi C_{k-2})\Delta t \\ -\frac{4}{3}(\sigma A_{k-1}I_{k-1} - \psi C_{k-1})\Delta t \\ +\frac{23}{12}(\sigma A_k I_k - \psi C_k)\Delta t \end{cases} \\ C(t_1) + \sum_{k=i+3}^{n} \begin{cases} \frac{5}{12}(\sigma A_{k-2}I_{k-2} - \psi C_{k-2})(h(t_{k-1}) \\ -h(t_{k-2})) \\ -\frac{4}{3}(\sigma A_{k-1}I_{k-1} - \psi C_{k-1})(h(t_k) - h(t_{k-1})) \\ +\frac{23}{12}(\sigma A_k I_k - \psi C_k)(h(t_{k+1}) - h(t_k)) \end{cases} \end{cases} \\
B(t_{n+1}) &= \begin{cases} B(0) + \sum_{k=2}^{i} \begin{cases} \frac{5}{12}(\mu(\epsilon - I_{k-2})B_{k-2})\Delta t \\ -\frac{4}{3}(\mu(\epsilon - I_{k-1})B_{k-1})\Delta t \\ +\frac{23}{12}(\mu(\epsilon - I_k)B_k)\Delta t \end{cases} \\ B(t_1) + \sum_{k=i+3}^{n} \begin{cases} \frac{5}{12}(\mu(\epsilon - I_{k-2})B_{k-2})(h(t_{k-1}) - h(t_{k-2})) \\ -\frac{4}{3}(\mu(\epsilon - I_{k-1})B_{k-1})(h(t_k) - h(t_{k-1})) \\ +\frac{23}{12}(\mu(\epsilon - I_k)B_k)(h(t_{k+1}) - h(t_k)) \end{cases} \end{cases}
\end{aligned} \tag{44}
$$

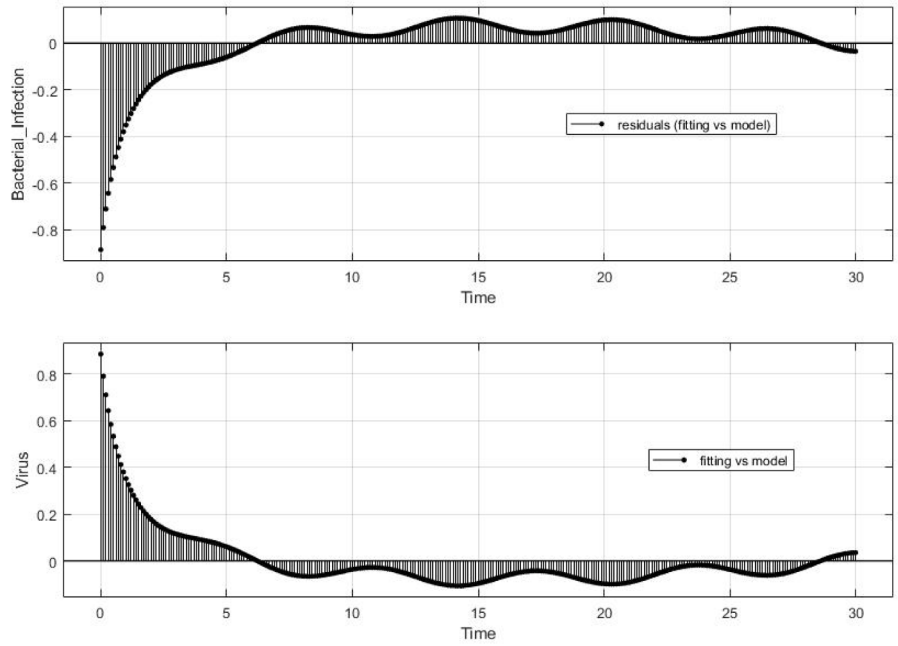

Fig. 4. The residual graphs for Bacterial infection onset and viral infection relative to time (note that the negative values of the residuals indicate the difference between the fitted and the modeled values, the virus and bacterial infection count was always taken to be positive).

Results and discussion

In the condition of bacterial super-infection in the condition of COVID-19, the analysis of anti-inflammatory cytokines is very important to understand its action against long-term inflammation resulting from the super-infection itself. Inspired from the noteworthy findings of Herald [25], for the proposed model analysis, it is assumed that the action of the anti-inflammatory cytokines may reduce the parameters relating to the equilibrium values of inflammation. In the sub-model relating to the inflammatory state, the hypothesis admits that the state of health always exists, regardless of the values of the parameters reported. The existence of three other equilibrium states in this sub-model is linked to the values of its parameters; for both computationally quantified "inflamed states", the very existence of such quantification depends on the values of κ and η. This is a fundamental point on which the development of the proposed model is based. Hypothetically, a very strong anti-inflammatory response could alter the parameters, perhaps attenuating the value of the macrophages sensitivity *kappa* thanks to the recruitment of other innate immunity effectors and allowing greater bacterial colonization. The complete model shows four computationally relevant states of equilibrium: the healthy state (absence of infection), the chronically inflamed state, the chronically infected state and the remission state of inflammation with a decrease in the bacterial population and bacterial sensitivity ϵ (fundamental state on which the hypothesis to develop the model is based). The increase in anti-inflammatory cytokines alters the conditions that lead to chronic inflammation by shifting the R0 threshold; a higher value of κ may be required, which implies a more marked action of macrophages in response to the signals of inflammatory cytokines, for the activation threshold to be achieved. The model, therefore, highlights how anti-inflammatory cytokines may not eliminate inflammation in the situation in which macrophages are highly sensitive and stimulable to pro-inflammatory signals, even if they tend to reduce the level of inflammation itself.

Figs. 2–4 depicts the numerical simulations, based on the modeling approach, the parametric values, based on the limited literature available on the novel topic, the intervals derived for the dynamical analysis in the previous section and the MCMC analysis for the parametric analysis [21,22,26–28,28–36].

It is obvious from the graphical interpretation that the linkage between the bacterial infection, with the COVID-19 viral infection is more stronger after the incubation period.

The proposed and hypothesized model describes an inflammatory response of macrophages that, although not specific for the respiratory system, can occur with high probability in COVID-19 concomitant super-infection; the present model can be adapted for analysis of macrophages-mediated inflammation in a tissue with a resident macrophages population. This model, therefore, can easily be a reference for the examination of super-infection in the respiratory tract even if there are up to some limits that may be subject to the further definition in subsequent works. The model assumes that there is an activation of the macrophages population always present while it is not considered that there are, within this population, two different states: one of rest and another activated. This situation also provides for the existence of a sort of "double phenotype" to be considered, namely the differentiation from monocyte to macrophages: this element can influence the inflammatory response [37]. Finally, the model could be made more specific by examining in depth the cytokines involved in the inflammation process under consideration. Cytokines have a redundant and pleiotropic action [38,39], while in the present computational analysis, for the sake of simplification, they have been considered proinflammatory and anti-inflammatory cytokines in a generic sense, producing the respective variables (inflammatory and anti-inflammatory) to illustrate a general picture of the process. This model, therefore, in addition to representing a good starting point for an analysis of the pathological event of bacterial super-infection in the condition of the COVID-19 syndrome, is also a basis on which to further expand and in-depth further computational processes also referable to other pathologies related to bacterial infections.

Conclusions

The results of the model show that a bacterial superinfection concomitant with a viral infection such as SARS-CoV2, can lead to chronic inflammation regardless of the presence of anti-inflammatory cytokines;

in fact, the self-induction cycle of pro-inflammatory cytokines can induce long-term inflammation even after the elimination of a secondary bacterial infection. Therefore, anti-inflammatory cytokines do not prevent long-term inflammation, but only reduce the level of this inflammation and increase the activation threshold. Therefore, it is assumed that when there is a correct anti-inflammatory effect of the cytokines, a pathogenic bacterial agent, even if not highly aggressive, will not be able to stimulate the event of chronic inflammation. If the macrophage population becomes more sensitive to the action of inflammatory cytokines (which can also occur through the progression of the disease), it is observed that a minimal pathogenic action initiated by bacteria may cause long-term inflammation. Therefore, if the biological mechanisms with which the anti-inflammatory cytokines act are compromised, the minimal action of the pathogens may be strongly amplified, thus boosting the chronicity of the inflammatory process.

CRediT authorship contribution statement

Zhenhua Yu: Conception of the manuscript, Computational modeling, Programming and literature review. **Ayesha Sohail:** Numerical analysis. **Robia Arif:** Conception of the manuscript, Dynamical analysis. **Alessandro Nutini:** Data analysis, Biological inference, Literature review. **Taher A. Nofal:** Conception of the manuscript, Numerical analysis. **Sümeyye Tunc:** Conception of the manuscript, Biological inference.

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.

Data availability

No data was used for the research described in the article.

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