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Modeling and simulations of CoViD-19 molecular mechanism induced by cytokines storm during SARS-CoV2 infection

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ABSTRACT

It is highly desired to explore the interventions of COVID-19 for early treatment strategies. Such interventions are still under consideration. A model is benchmarked research and comprises target cells, virus infected cells, immune cells, pro-inflammatory cytokines, and, anti-inflammatory cytokine. The interaction of the drug with the inflammatory sub-system is analyzed with the aid of kinetic modeling. The impact of drug therapy on the immune cells is modelled and the computational framework is verified with the aid of numerical simulations. The work includes a significant hypothesis that quantifies the complex dynamics of the infection, by relating it to the effect of the inflammatory syndrome generated by IL-6. In this paper we use the cancer immunoediting process: a dynamic process initiated by cancer cells in response to immune surveillance of the immune system that it can be conceptualized by an alternating movement that balances immune protection with immune evasion. The mechanisms of resistance to immunotherapy seem to broadly overlap with those used by cancers as they undergo immunoediting to evade detection by the immune system. In this process the immune system can both constrain and promote tumour development, which proceeds through three phases termed: (i) Elimination, (ii) Equilibrium, and, (iii) Escape [1]. We can also apply these concepts to viral infection, which, although it is not exactly "immunoediting", has many points in common and helps to understand how it expands into an "untreated" host and can help in understanding the SARS-CoV2 virus infection and treatment model.

1. Introduction

Subsequent to infection, an inflammatory process is generated in the tissue affected by the infection itself; this process is characterized by the presence of leukocytes and plasma proteins. This inflammatory response occurs after elements of the immune system such as macrophages, dendritic cells and natural killer (NK) cells are activated, thanks to appropriate molecular signals: pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).

The proinflammatory cytokines, activated by the PAMP or DAMP signaling pathways, are central in the realization of the inflammatory process itself; these molecules are well represented by IL-1, IL-6, IL-8, IL-12, IFN-γ, IL-18 and TNF and their action is manifested in the control of inflammatory foci through specific responses. TNF also has the ability to activate a cascade of anti-inflammatory cytokines that block the ongoing inflammation process and, in most cases, this process is resolved. An overproduction of proinflammatory cytokines, however, can give rise to what is called a "cytokine storm" which can have a harmful effect on the body through the production of a syndrome called "SIRS" (Systemic Inflammatory Response Syndrome) which leads to hypotension, pulmonary thrombosis, pulmonary edema and haemorrhage, and if not treated with appropriate therapy, it can lead to death.

1.1. SARS-CoV2

The reproductive rate (R_0) for SARS-CoV2 is estimated to be 2.5 (with range 1.8–3.6) compared with 2.0–3.0 for SARS-CoV and the 1918 influenza pandemic, 0.9 for MERS-CoV, and 1.5 for the 2009 influenza pandemic [2]. The latter infected around 8000 people in 2002, causing 800 deaths, while SARS-CoV2 currently infected 47,362,304 people, causing 1,211,986 deaths (https://covid19.who.int/ access at

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october 05, 2020 11.50 am). SARS-CoV2 therefore shows a high diffusion capacity compared to SARS-CoV.

There are many similarities of SARS-CoV2 with the SARS-CoV virus; a model by Xu et al. [3] found that the S proteins of SARS-CoV2 and SARS-CoV have identical threedimensional structures in the receptor-binding domain (RBD) that maintains van der Waals forces. SARS-CoV S protein has a strong binding affinity to human ACE2, based studies and crystal structure analysis [4]. SARS-CoV-2 and SARS-CoV S proteins share 76.5% identity in aminoacid sequences and the SARS-CoV2 and SARS-CoV S proteins have a high degree of homology.

The S protein/ACE2 binding in SARS-CoV2 induces conformational changes in aminoacids that generate salt bridges, increase van der waals interactions and, by this action, facilitate binding with ACE2 with much greater affinity than SARS-CoV [5].

1.2. Immune response

Immune cells work as a sort of careful surveillance in a healthy body. In most viral infections, the immune system has the ability to oppose the viral particle, at certain times of the infection (before entering the cell or leaving it, after replication), and to infected cells (in the production of proteins or in that of the viral assembly).

The reason is the expression of antigens of the infection in the membrane, that activate the immune response. As the body gets infected, the infected cells secrete proinflammatory cytokines which in turn activate the immune cells to differentiate in Th17 cells from CD4+ naÃ¯ve T lymphocytes differentiation of cytotoxic TCD8+ cells (CTL), differentiation in Th1 cells, resolution of the inflammatory state, repair of lung tissue, promotion of phagocytic activity of macrophages, prevents apoptosis induced by viral infection in lung epithelial cells, and regulates the expression of IgG isotypes [6].

Therefore, during this research we focus on the concentration of immune cells and will develop an equation based on the interaction/responses of immune cells to virus and pro inflammatory cytokines.

1.3. Pro-inflammatory cytokines

In SARS-CoV2, the action of IL-6 and IL-1 cytokines is of central interest, since elevated interleukin-6 (IL-6) dose is strongly associated with the need for mechanical ventilation in CoViD-19 patients. Also, the risk of respiratory failure for patients with high IL-6 levels is higher compared to patients with lower IL-6 levels [7]. Another fact is that in case of CoViD-19, suppression of proinflammatory IL-1 family members showed some therapeutic effect [8].

2. The anti-inflammatory cytokines

The anti-inflammatory cytokines do their job in both a healthy as well as in an infected body. When there is an onset of viral infection, these cytokines work in balance with pro-inflammatory cytokines. The action of the anti-inflammatory cytokines which tends to regulate the action of the inflammatory ones (in our case precisely of IL-6) is directed to the same cells that produce IL-6, which, through an inhibition mechanism, slow down (or production ceases altogether). Evidently, in the case of the "IL-6 storm", the action of these anti-inflammatory cytokines is insufficient.

The blockade of IL-6R receptors through monoclonal antibody has proven to be optimal to manage complications and avoid potentially fatal situations. Hence, there are cells that overexpress IL-6 which in turn triggers a chronic inflammatory event that feeds on itself as cells such as macrophages and fibroblasts continue to secrete IL-6, without undergoing negative regulation processes by anti-inflammatory cytokines.

2.1. Drug therapy in CoViD-19

The drugs available to control the pro-inflammatory cytokines are listed as:

- Inhibitor of Janus kinases (i.e., Ruxolitinib)
- Monoclonal antibody (i.e., Tocilizumab)

In this research, we simulate the impact of Tocilizumab. Tocilizumab is a humanized anti-IL-6 monoclonal antibody that is used against rheumatoid arthritis, juvenile idiopathic arthritis, and against cytokine release syndromes often induced by anti-cancer immune therapy conducted with T-CAR cells. During its action, Tocilizumab binds to both the soluble and membrane receptors of IL-6. The mechanisms of action and uses of Tocilizumab are different. Although not licensed for sepsis, Tocilizumab has been shown to have some effect on mouse models, suggesting modulation of the pathway associated with IL-6. The same drug has not previously been used for viruses such as SARS-CoV and MERS-CoV. The use in the case of SARS-CoV2 infection emerged after analysis conducted by some scholars who highlighted lymphopenia and a high presence of reactive protein C (CRP) in the case of CoViD-19 syndrome [9]; a multicenter study of 150 cases in Wuhan (China) confirms the low number of lymphocytes and the strong inflammation triggered by the syndrome [10]; the use of corticosteroids is not recommended in combination with Tocilizumab as it can exacerbate the symptoms related to CoViD-19 [11]. Cytokine storm syndrom Mehta et al. [12] has been identified in a group of CoViD-19 patients and data from 41 Wuhan patients in intensive care unit (ICU) indicated high levels of cytokines such as IL- 2, IL-7, IL-10, GCSF and others while IL-6 was not detected in high concentration; further data, however, indicates a high concentration of ferritin and a high presence of IL-6 as an indication of disease fatality. The China National Health Commission, in its revision to treatment for CoViD-19, seventh version (China's National Health Commission treatment guidelines 7th version, 2020), included Tocilizumab as therapy for SARS-CoV2 infected patients with serious lung damage and high levels of IL-6. There is still not much evidence on the effects of Tocilizumab in application to therapy for CoViD-19 and an evaluation of the concentration of cytokines present is recommended before administration of the drug [12]. In Table 1 below, a brief description of the evidence supporting Tocilizumab in the case of CoViD-19 is reported.

It was observed recently during a clinical study that when the drug was administered intermittently, the results were more convincing. We therefore propose that the use of tocilizumab of 8 mg/kg per day is recommended by Xu et al. [13], therapeutic scheme: 20 mg/mL vials.

2.2. Hypothesis

- Development of a model of IL-6 inflammatory syndrome in SARS-CoV2 and its quantification.
- Creation and application of a modeling computational framework for target cells (host), infected cells, immune cells, pro-inflammatory and anti-inflammatory cytokines.
- Analysis of cytokines related to viral load.
- Creation of a mathematical inflammatory subsystem, where the role of anti-inflammatory cytokines will not be considered.
- Creation of a "connection model" with the therapeutic use of a monoclonal antibody (tocilizumab) and analysis of the hypothesis of intermittent therapy as the best therapeutic value: the drug controlled the disease onset by delaying the cycle and changing its period.
- Analysis of the parallelism of the computational development of the "three Es" hypothesis in the development of cancer also applied to viral infection: quantitative analysis of the system and verification of the cells population.

3. Mathematical model

Different computational models based on the molecular mechanism of the said problems, are available in the literature [14–17]. During this research, we developed a model comprising target cells (X), virus infected cells (Y), immune cells (Z), pro-inflammatory cytokines C, and, anti-inflammatory cytokine A.

3.1. Host cells

$$\frac{dX}{dt} = rX\left(1-\frac{X}{K}\right) - \frac{\beta XY}{1+qZ} \tag{1}$$

where $rX(1-\frac{X}{K})$ is the logistic growth, $\frac{\beta XY}{1+qZ}$ is the infection rate and inhibition by immune response, r is the growth factor and K is the carrying capacity.

3.2. Infected cells by virus

$$\frac{dY}{dt} = \frac{\beta XY}{1+qZ} - \rho YZ - \phi yY \tag{2}$$

where $\frac{\beta XY}{1+qZ}$ is infected cells proliferation, ρYZ is inhibition by immune response and ϕyY is the death rate.

3.3. Immune-cells

$$\frac{dZ}{dt} = \rho Y_{(t)}Z_{(t)} + \frac{\delta ZC^2}{1+q_2U} - \phi_Z Z \tag{3}$$

3.4. Pro-inflammatory cytokines

$$\frac{dC}{dt} = \mu Y_{(t)}Z_{(t)} + \left(\frac{1}{\alpha_5^2+A^2}\right)\left(\frac{\alpha_2^3C^2}{\alpha_3^2+C^2}\right) - I_2C\left(\frac{U}{K_q+U}\right) - \phi_C C \tag{4}$$

3.5. Anti-inflammatory cytokines

$$\frac{dA}{dt} = \left(\frac{\alpha_4 ZC^2}{\alpha_3^2+C^2}\right) - \phi_A A \tag{5}$$

3.6. Drug

The equation for drug is:

$$\frac{dU}{dt} = h_2 e^{h_1 t} - h_3 U \tag{6}$$

In Eq. (2), the term ρYZ represents the loss of infected cells caused by the immune cells. The fraction $\frac{\beta XY}{1+qZ}$ is the proliferation of infected cells through interactions with targeted cells. This proliferation is inhibited by immune cells (Z).

In Eq. (3), the term $\frac{\delta ZC^2}{1+q_2U}$ represents the increase in immune cells due to pro-inflammatory cytokines. Tocilizumab is inhibiting pro-inflammatory cytokines to increase immune cells rapidly [18,19].

In Eq. (4), the term $\mu Y_{(t)}Z_{(t)}$ represents the release of pro-inflammatory cytokines C, when a cell (a particular line of cells) interacts with infected cells, there is a release of cytokines. Anti-inflammatory cytokines $\left(\frac{1}{\alpha_5^2+A^2}\right)$ interact with pro-inflammatory cytokines $\left(\frac{\alpha_2^3C^2}{\alpha_3^2+C^2}\right)$ and inhibit them in a two-variable model for the interactions between pro-inflammatory and anti-inflammatory cytokines, following a model that illustrates a range of possible behaviors, such as bistability and oscillations [20]. The term $I_2C\left(\frac{U}{K_q+U}\right)$ captures the effect of the drug on pro-inflammatory cytokines [21].

In Eq. (5), the anti-inflammatory cytokines act on modulating immune response and create a negative regulation circuits to the cascade of inflammatory cytokines that act locally or systemically; they are produced by monocyte-macrophages. They inhibit the immune inflammatory response.

In Eq. (6), we have used a single compartment model to calculate the concentration of drug in plasma. Administration of drug through intravenous infusion and its concentration in plasma can be easily calculated with exponential function [22,23]. In this equation, h_2 represents the absorption rate of the drug while h_3 is representing the clearance rate. The

Table 1
List of parameters selected for the sensitivity analysis.

Variable	Description	Unit
X	Host cells	cells
Y	Infected cells with virus in it	cells
Z	Immune Cells	cells
C	Pro-inflammatory cytokines	$\frac{pg}{ml}$
A	Pro-inflammatory cytokines	$\frac{pg}{ml}$
U	tocilizumab (drug)	$\frac{pg}{ml}$
Coefficients	Description	Units
r	growth rate	$\frac{1}{minute}$
K	carrying capacity	cells
β	replication rate of virus	$\frac{1}{minutes\times cells}$
ϕ_Y, ϕ_Z	death rates of infected & immune cells	$\frac{1}{minutes}$
ϱ	immune cell activation rate	$\frac{1}{minutes\times cells}$
μ	viral induced inflammatory	$\frac{\frac{pg}{ml}}{minutes\times cells^2}$
K_1, K_2	cytokine production rate half saturation constant of Â immune cells production	cells
q	saturation constant for inflammatory cytokine induced immune cells recruitment	$\frac{1}{cells}$
α_2	magnitude of additional pro-inflammatory cytokine production	$\frac{\frac{pg}{ml}}{minutes}$
α_3	pro-inflammatory cytokine concentration at which anti-inflammatory production is half maximal	$\frac{pg}{ml}$
α_4	magnitude of anti-inflammatory cytokine production	$\frac{\frac{pg}{ml}}{minutes\times cells}$
α_5	anti-inflammatory cytokine concentration	$\frac{pg}{ml}$
ϕ_C	death rate of pro-inflammatory cytokines	$\frac{1}{minutes}$
ϕ_A	death rate of anti-inflammatory cytokines	$\frac{1}{minutes}$
l_1	drug efficiency at cellular level	$\frac{cells\times ml}{minutes\times pg}$
l_2	drug efficiency at molecular level	$\frac{1}{minutes}$
h_3	per capita decay rate of the drug	$\frac{1}{minutes}$

drug inhibits pro-inflammatory cytokines to activate immune cells rapidly. This action is modelled as $\frac{\delta ZC^2}{1+q_2U}$ and the effect of drug on pro-inflammatory cytokines is modelled as $I_2C\left(\frac{U}{K_q+U}\right)$. Here, l_2 represents maximum drug interaction with pro-inflammatory cytokines while K is quasi-steady-state constant [21].

Now, we will nondimensionalize the system in a manner similar to [24], furthermore, we will reduce the system to inflammatory subsystem, where the role of anti-inflammatory cytokines will not be considered [25]. Here x, y, z, c and u are the dimensionless variables presenting the concentration of target cells, infected cells (viral load), immune cells, and, pro-inflammatory cytokines, with time scaled as well by r (details of nondimensionalization are provided in [26]. The equation for target cells is given as:

$$\frac{dx}{dt} = x\left(\hat{r}_1(1-x) - \frac{\hat{b}y}{1+q_1z}\right) \tag{7}$$

equation for viral load is given as:

$$\frac{dy}{dt} = y\left(\frac{bx}{1+q_1z} - k_1z - \hat{d}_y\right) \tag{8}$$

equation for immune cells is given as:

$$\frac{dz}{dt} = z\left(\hat{k}_2y + \frac{\hat{k}_cC^2}{1+q_2u} - \hat{d}_z\right) \tag{9}$$

equation for pro-inflammatory cytokines is given as:

$$\frac{dc}{dt} = \hat{k}_2yz - d_cc + \frac{\hat{I}_2cu}{K_q+u} \tag{10}$$

equation for drug is given as:

$$\frac{du}{dt} = \hat{h}_2\widehat{e^{h_1t}} - \hat{h}_3u \tag{11}$$

To describe dimensionless parameter, we use hat on it, however, in the rest of paper we do not use hat for convenience.

4. Computational analysis

4.1. Sensitivity analysis

Sensitivity analysis is a tool that helps build confidence in the model by studying uncertainty of the parameters. Here, we perform sensitivity analysis in order to check influence of parameters on the designed model. The parameters selected for sensitivity analysis are given in Table 1.

4.2. Stability analysis

If there is no viral load (*i.e*, $y = 0$) and no treatment term, then the above subsystem can be reduced to:

$$\frac{dz}{dt} = z(k_cc^2 - d_z) \tag{12}$$

$$\frac{dc}{dt} = -d_cc \tag{13}$$

For equilibrium point, we put $\frac{dz}{dt} = \frac{dc}{dt} = 0$. Now from Eqs. (12) and (13)

$$z(k_cc^2 - d_z) = 0$$

$$-d_cc = 0$$

Thus $(z_0, c_0) = 0, 0$ is an equilibrium point.

If $d_z > 0$ and $d_c > 0$, then the equilibrium point $(z_0, c_0) = 0, 0$ is locally asymptotically stable. The proof of this theorem is straightforward by defining Jacobian matrix at $(z_0, c_0) = 0, 0$ and using Lyapunov stability criterion. To analyze the regions, where the system will give convergent results, we have obtained the nulclines.

5. Graphical analysis

The aim of this section is to delibtrate the role of associatede key parameters arising in the model configuration as shown in in Fig. 1.

5.1. Cytokine sensitivity k_c

These results are obtained from the analysis of nondimensional inflammatory subsystem (Eq. (7)–(11)). We can see that the parameter k_c i.e., the cytokine sensitivity parameter, plays an important role. From Fig. 2, we can see that without drug, when the cytokine sensitivty parameter was increased, the infection load increased. For the dynamics with the infusion of drug, we can see that the infection load was much controlled.

5.2. Interaction parameter β

We have conducted numerical experiments for three increasing values of β, these results are presented in Fig. 3. Fig. 4 presents the dynamics for k_1 (immune cells activation rate) fixed to be 0.1. Without drug, the cytokine IL-6 release was higher, with increasing values of β, whereas with drug, it was controlled. On the other hand, when similar numerical experiments were repeated for k_1=0.05 (immune cells activation rate), we can see different results. The infection is more periodic and there is damping relative to time.

6. The 3Es of Immunoediting

The 3Es of immunoediting are defined as:

6.1. Immunoediting in oncology

We have known for some time that the immune system and malignant cells often coexist in a dynamic equilibrium, and the complex interaction between growing tumour and immune system can determine the course of the disease. Tumors must develop the ability to evade the immune system to proliferate and metastasize. Immune surveillance theory suggests that the immune system is proactively able to eliminate abnormal cells and prevent cancer formation in the

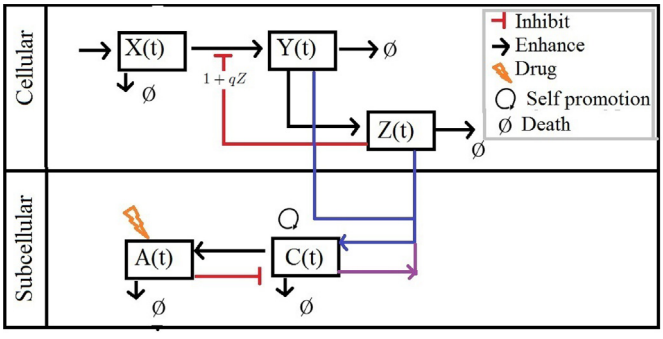

Fig. 1. Schematic of the model.

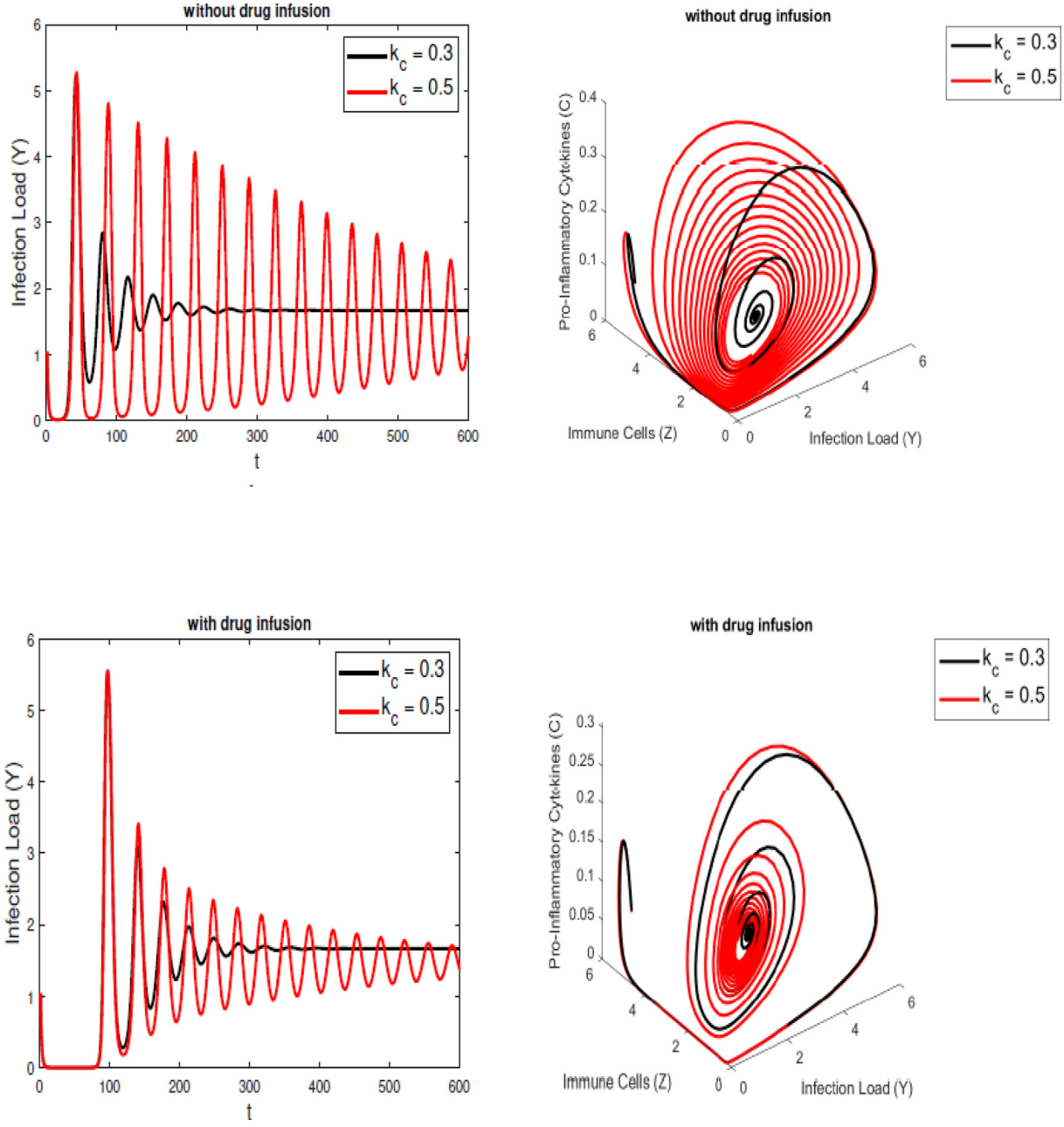

Fig. 2. Left panel, phase space portraits, right panel, dynamics of cytokines relative to the cytokine sensitivity parameter k_c.

body. Studies have shown that patients with impaired or suppressed immune function are exposed to an increased risk of developing cancer. In addition, although controversial, the use of immunosuppressive agents has been associated with an increased incidence of some cancers. Clearly the adaptive immune response is able to control the growth of some tumors, as evidenced by the observation that the presence of tumour infiltrating lymphocytes (TIL) is often associated with a greater survival. However, the system immunity is made less effective with tumour growth. The cancer immunoediting process is a dynamic process initiated by cancer cells in response to immune surveillance of the immune system; it can be conceptualized by an alternating movement that balances immune protection with immune evasion. The mechanisms of resistance to immunotherapy seem to broadly overlap with those used by cancers as they undergo immunoediting to evade detection by the immune system. A central principle of cancer immunoediting is that T-cell recognition of tumour antigens drives the immunological elimination or sculpting of a developing cancer. Cancer immunoediting is the process whereby the immune system can both constrain and promote tumour development, which proceeds through three phases termed: (i) Elimination, (ii) Equilibrium, and, (iii) Escape [1]. Throughout these phases, tumour immunogenicity is edited, and immunosuppressive mechanisms that enable disease progression are acquired. In the first phase, Elimination, transformed cells are destroyed by a competent immune system. Sporadic tumour cells that manage to survive immune destruction may then enter an Equilibrium phase where editing occurs. The third phase, Escape, represents the final phase of the process, where immunologically sculpted tumors begin to grow progressively, become clinically apparent and establish an immunosuppressive tumour microenvironment.

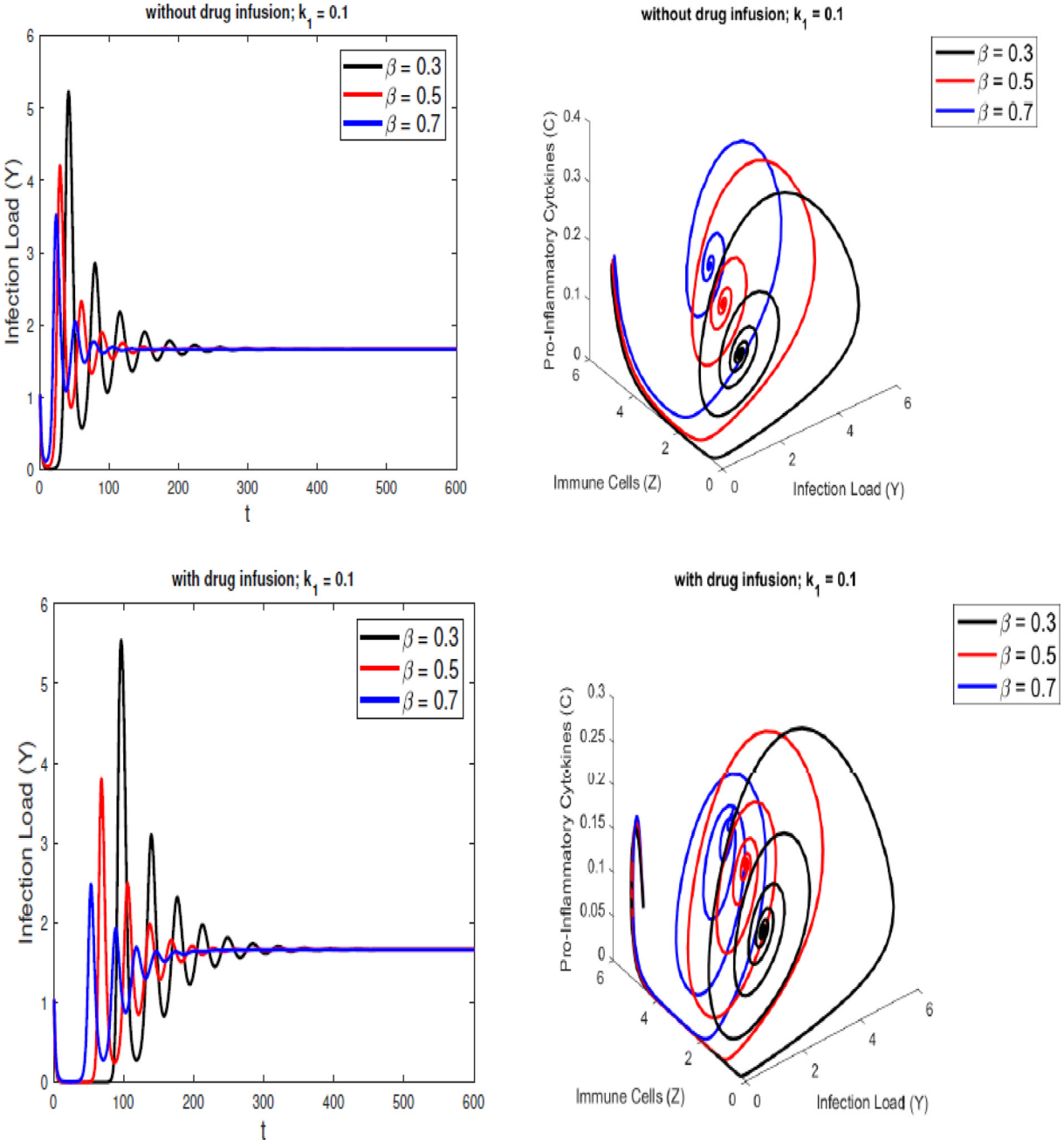

Fig. 3. Left panel, phase space portraits, right panel, dynamics of infection load relative to the interaction rate, for $k_1 = 0{:}1$.

6.2. Immunoediting in virology

We can also apply these concepts to viral infection, which, although it is not exactly "immunoediting", has many points in common and helps to understand how it expands into an "untreated" host. Immunoediting in untreated viral infections involves the equilibrium between CD8+ T cell (CTL) responses and viral agent, followed by the eventual escape of viral infected cells from CD8+ T cell killing in the majority of individuals. Infected cells, in the absence of appropriate antiviral treatment, are thought to persist and evade the immune response by hiding in a non-immunogenic quiescent state; infected cells that do not undergo this transition are largely eliminated. The variations imposed by cancer immunoediting serves as the basis for an evolutionary process known as clonal selection, which leads to the escape of tumors that have been immunoedited; for viral infection a similar variation leads to the examination of a sort of viral "reservoir" which, through its expression/latency, affects CTL functionality.

6.3. Immunoediting of SARS-2

There's a role of intrinsic immunoediting in the viral reservoir persistence [27] that passes through a balance between the persistence of the viral load and adaptation to the response of the CTL cells up to an increasingly ineffective response of the latter. This event leads to strengthening of the viral infectious capacity and due to the lack of immune response produces a deficiency of infection control. In the case of SARS-CoV2, all this passes through a strong induction of an inflammatory regimen operated by cytokines such as IL-6 and IL-1, which lead to an inflammatory syndrome that contributes to a lack of control of the infection. Furthermore it leads

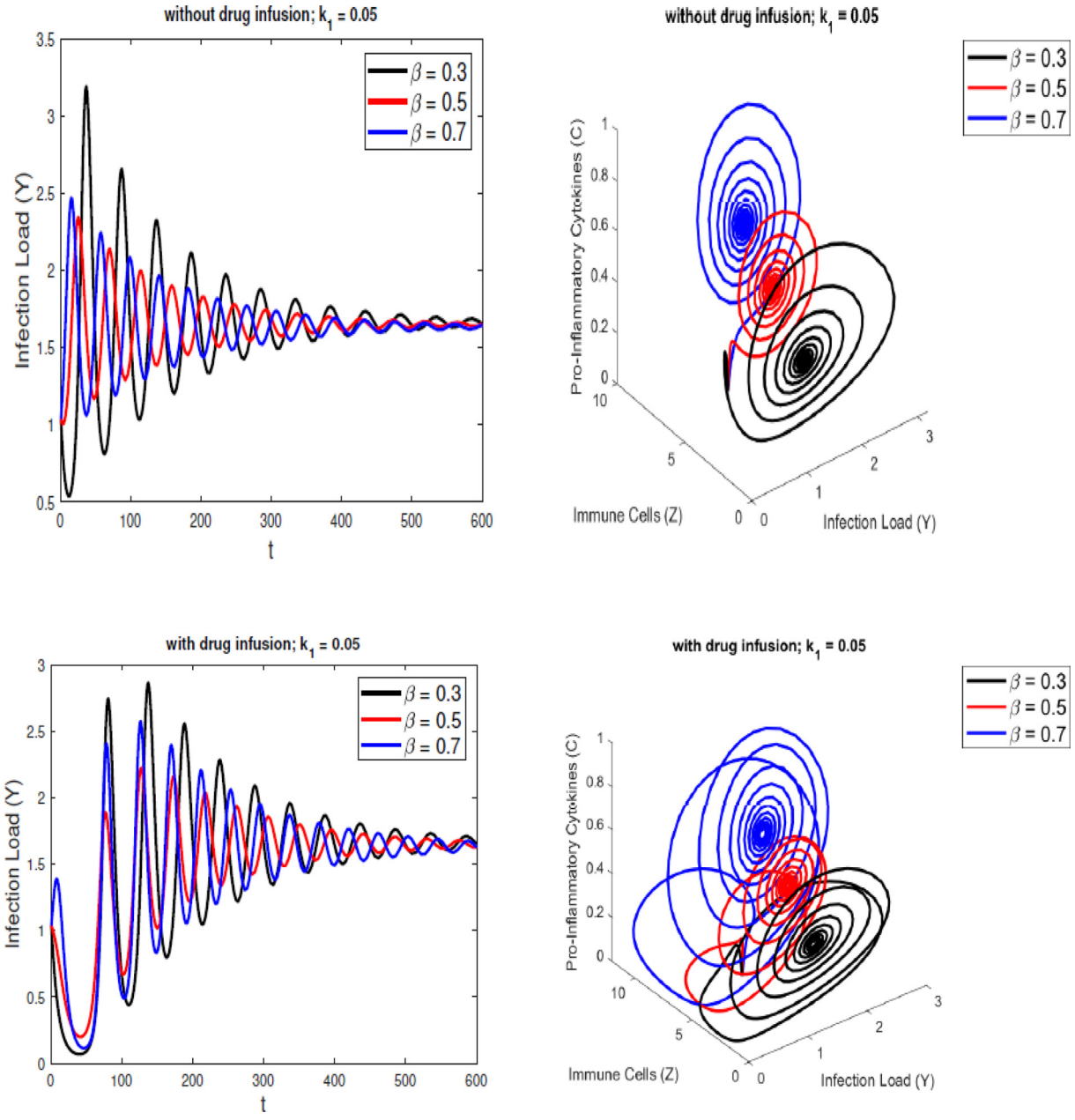

Fig. 4. Left panel, phase space portraits, right panel, dynamics of infection load relative to the interaction rate, for $k_1 = 0{:}05$.

to the viral escape, relative to a high viral reservoir, due to the strong infectious capacity of this virus [27].

We therefore propose an analysis based on the three immunoediting phases.

During this research, based on the results provided in the literature, the graphical interpretation of equilibrium, escape, and, elimination of the infection are presented in Figs. 5, 6 and 7 respectively. The analysis was based on the key parameters listed in Table 1.

6.3.1. Elimination

1. Infection of several CD4 + T cells and seeding of genetic variability (resulting virion factories).
2. Rise of CTL and natural killer (NK) cells responses which fight against the infected cells and eliminate many of them.

These dynamics for elimination are depicted in Fig. 5. The graphical analysis of two variables y (infection load) and z (immune cells) are plotted for specific values of b (replication rate of virus) and k_1 (immune cells activation). These values are obtained from bifurcation analysis, the details are provided in the appendix.

6.3.2. Equilibrium

1. Persistence of a population of SARS-2 infected cells.
2. Establishment of a viral set point representing an equilibrium between viral infection and adaptation to CTL response.
3. IL-6 inflammatory action.
4. Reduction in CTL response.

The dynamics are depicted in Fig. 6.

6.3.3. Escape

1. Inability of CTL cells to control infection.
2. Immune exhaustion.
3. Viral escape.
4. Progression to lungs failure.

The dynamics are depicted in Fig. 7.

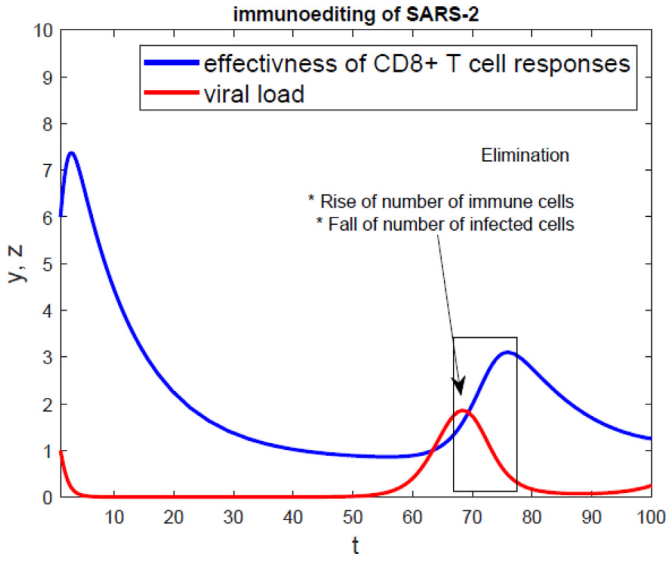

Fig. 5. Numerical simulations of the elimination process.

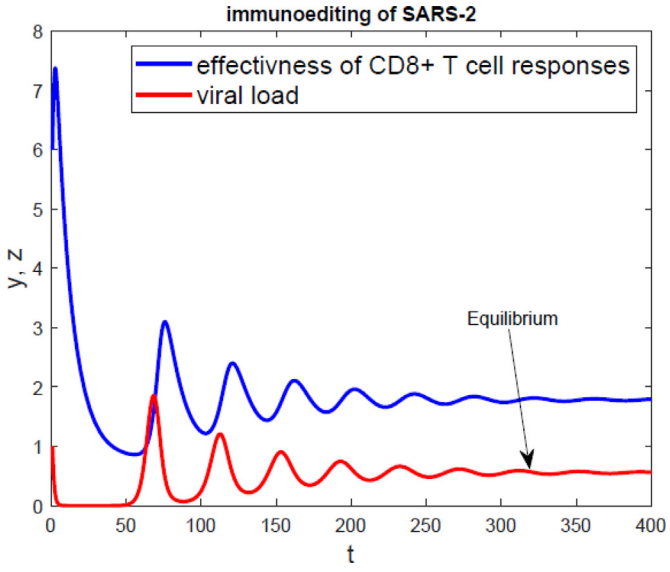

Fig. 6. The case of equilibrium.

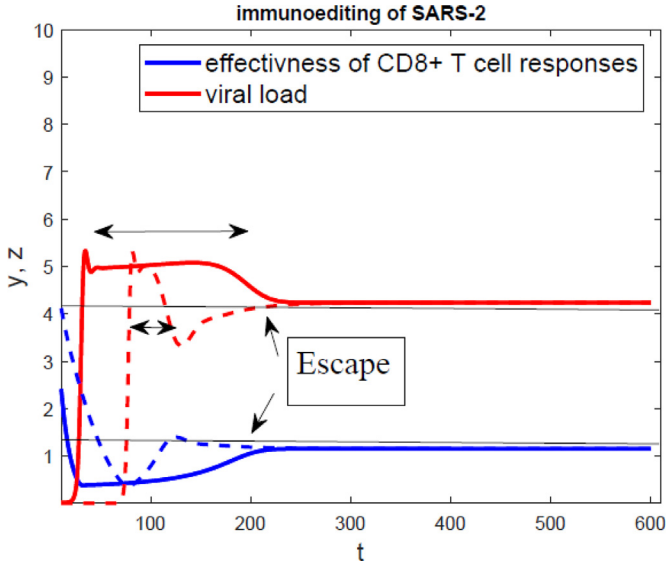

Fig. 7. Escape.

7. Conclusions

The pandemic generated by the SARS-CoV2 virus is currently causing several problems including many deaths and difficulties in health systems around the world. The creation of a vaccine is certainly desirable at the moment [28], but the need to understand both the SARS-CoV2 infection system and a possible therapy that can reduce the symptoms imposed by CoViD-19 is fundamental to reduce the heavy pathological damage and the load that every health system must bear, although containment measures such as "lockdowns" have managed to contain the spread of the infection and the various epidemiological conditions have entailed different choices, country by country, and often not uniformly (targeted lockdowns), reporting a reduction in infections [29].

The computation analysis carried out in this paper focuses on the inflammatory syndrome triggered by SARS-CoV2 infection and analyzes, through a sensitivity analysis, the parameters that trigger the CoViD-19 symptomatology and, thanks to an analogy conducted with the immunoediting related to cancer, quantitatively and qualitatively illustrates the interactions between the signal molecules of the immune system (cytokines) and the infectious characteristics, indicating the efficiency of a possible therapy that includes the use of monoclonal antibodies such as tocilizumab. Based on the results obtained from the nonlinear model, we conclude the following:

- The cytokines are sensitive to the viral load. The parameters controlling the cytokine sensitivity was helpful to drive this conclusion. The concentration of cytokine expression was affected by two important factors, k_c and drug dose. With drug infusion, the function was inhibited.
- The interaction rate matters a lot in the disease onset. The time delay is visible during the numerical analysis for different values of interaction rates.
- The drug controlled the disease onset by delaying the cycle and changing its period.
- TCZ does not overactive the immune cells except to induce, initially and temporarily, an increase in the level of IL-6 only to then begin to act by lowering the levels of IL-6 itself and this is integrated into the proinflammatory cytokines equation of the model. In fact, if the therapy is Â abruptly stopped in the initial phase, there is a sort of "disease flare" according to a theory called "bathtube theory". TCZ has a very low antigenicity which also entails little propensity to an autoimmune reactions therefore, also in this sense it does not activate (or very poorly active) the cells of the immune system.
- For reduced value of k_2, we achieved the escape dynamics.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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