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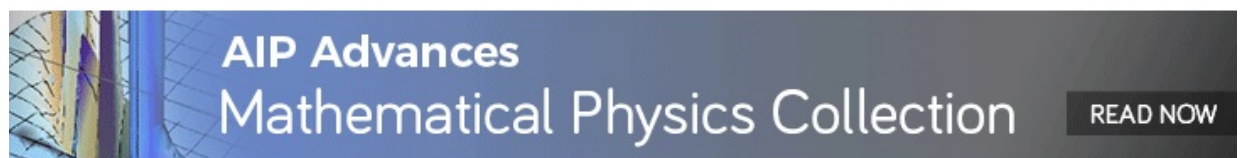
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ABSTRACT

Using nonlinear mathematical models and experimental data from laboratory and clinical studies, we have designed new combination therapies against COVID-19.

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Currently, there are no approved treatments for the SARS-CoV-2 infection. Moreover, scientists do not know any treatment that would consistently cure COVID-19 patients. This paper is an argument for combination therapies against COVID-19. We investigate a nonlinear dynamical system that describes the SARS-CoV-2 dynamics under the influence of immunological activity and therapy. Using the nonlinear mathematical model and experimental data from laboratory and clinical studies, we have designed new combination therapies against COVID-19. The therapies are based on antivirals in combination with other therapeutic approaches. The general therapeutic plan is as follows: Gene therapy and/or antivirals plus immunotherapy and anti-inflammatory drugs and/or drugs that control cytokine storms plus cytotoxic therapies. We believe that these new therapies can improve patient outcomes.

I. INTRODUCTION

Emerging viral diseases have caused significant global devastating pandemics, epidemics, and outbreaks (Smallpox, HIV,

Polio, 1918 influenza, SARS-CoV, MERS-CoV, Ebola, and SARS-CoV-2).

Currently, there are no approved treatments for any human coronavirus infection. Moreover, scientists do not know any treatment that would consistently cure COVID-19 patients. The world is facing a general catastrophe as people see the reality of alarming rises in infections, a building economic crisis, a shortage of ventilators, the lack of coronavirus testing, and many other disasters. The governments are desperate to find a solution. In some cases, they are even promoting unproven “remedies.” We need a treatment that is 95% effective in order to safely open the countries and save the world from an economic catastrophe.

There is a wealth of literature dedicated to mathematical modeling of the virus-immune system interaction. See, for example, Ref. 1. There are many treatments in development. However, most of them have drawbacks.²

This paper is an argument for combination therapies against COVID-19. We have shown before that combination therapies can be better than monotherapies. For instance, for some cancer tumors, the immunotherapies do not work at all.³⁻⁵ We have proposed to use a combination of therapies that could eradicate the cancer

completely.³⁻⁵ In the present paper, we will design new therapies based on antiviral agents in combination with other therapeutic approaches. These new therapies should improve patient outcomes.

II. GROWTH MODELS

There are several famous equations that have been used to describe cell population growth: exponential, Gompertz, logistic, and power-law equations.⁹

In Ref. 7, a biophysical justification for Gompertz's equation was presented.

The deduction is based on the concept of entropy. The entropy definition used in Ref. 7 is the well-known Boltzmann–Gibbs extensive entropy. González and Rondón have used the new non-extensive entropy⁸⁻¹⁰ in the derivation of a new very general growth model.⁶

The exponential, logistic, Gompertz, and power laws are particular cases of the new equation. The new model has the potential to describe all the known and future experimental data.⁶

Boltzmann–Gibbs statistics satisfactorily describes nature if the microscopic interactions are short-range and the effective microscopic memory is short-ranged, and the boundary conditions are nonfractal.

There is a large series of recently found natural systems that present anomalies that violate the standard Boltzmann–Gibbs method.

A non-extensive thermostatistics, which contains Boltzmann–Gibbs as a particular case, was proposed in a series of papers.⁸⁻¹¹

Nowadays, scientists have produced a large number of successful applications of the new theory. These are mostly phenomena in complex systems.

The mentioned thermodynamic theory contains the non-extensive entropy,

$$S_q = k \frac{1 - \sum_{i=1}^w p_i^q}{q - 1}, \tag{1}$$

where k is a positive constant, w is the total number of possibilities of the system, $\sum_{i=1}^w p_i = 1$, $q \in \mathbb{R}$. This expression recovers the Boltzmann–Gibbs entropy,

$S_1 = -k \sum_{i=1}^w p_i \ln p_i$, in the limit $q \rightarrow 1$. Parameter q characterizes the degree of non-extensivity of the system.

This can be seen in the following rule:

$$S_q(A + B)/k = [S_q(A)/k] + [S_q(B)/k] + (1 - q) [S_q(A)/k] [S_q(B)/k], \tag{2}$$

where A and B are two independent systems in the sense that $P_{i,j}(A + B) = P_i(A)P_j(B)$. We could say that parameter $(1 - q)$ characterizes the complexity of the system.

The case $1 - q \geq 0$ implies that the system is resilient. In our case, this means that the virus infection is resilient.

For example, this condition indicates that the virus infection will lead to a drug-resistant disease. In particular, this disease can become resistant to the attack of the immune system and conventional therapy.

The new generalized equation for population growth is as follows:

$$\frac{dX}{dt} = \frac{kX_\infty}{q - 1} \left[1 - \left(\frac{X}{X_\infty} \right)^q - \left(1 - \frac{X}{X_\infty} \right)^q \right], \tag{3}$$

where $X(t)$ is the growing population, k is certain free parameter, and X_∞ is the asymptotic value of $X(t)$ when $t \rightarrow \infty$.

We have already remarked that this is a very general model that contains the most known growth models.⁵

Now, we will show that this model is universal in the sense discussed in Refs. 12 and 13 and includes many other classes of models as particular cases.¹⁴

For early stages of the infection, (3) can be written in the following form:¹⁴

$$\frac{dX}{dt} = \alpha_q \left(\frac{X}{M_\infty} \right)^q \left[1 - \left(\frac{X}{M_\infty} \right)^{1-q} \right], \tag{3a}$$

where $\alpha_q = \frac{kqM_\infty}{1-q}$, $M_\infty = q^{\frac{1}{q-1}} X_\infty$.

An analytical solution to Eq. (3a) can be expressed as

$$\left(\frac{X}{M_\infty} \right)^{1-q} = 1 - \left[1 - \left(\frac{X_0}{M_\infty} \right)^{1-q} \right] e^{-qkt}, \tag{3b}$$

where X_0 is the initial condition so that $X(t = 0) = X_0$.

We can re-write solution (3b) as

$$r(\tau) = 1 - e^{-q\tau}, \tag{3c}$$

where $r = \left(\frac{X}{M_\infty} \right)^{1-q}$ and $\tau = kt - \ln(1 - r_0)^{1/q}$.

This calculation shows that our model represents a universal growth law.¹²⁻¹⁴

So even this general class of growth laws are a particular case of Eq. (3).

III. THE MODEL

In the present paper, we will investigate the following dynamical system:

$$\frac{dX}{dt} = \frac{kX_\infty}{q - 1} \left[1 - \left(\frac{X}{X_\infty} \right)^q - \left(1 - \frac{X}{X_\infty} \right)^q \right] - bXY - c_1(t)X, \tag{4}$$

$$\frac{dY}{dt} = d(X - eX^2)Y - fY + V - c_2(t)Y, \tag{5}$$

where X denotes the virus population and Y denotes the population of lymphocytes. Equation (4) describes the reproduction of the virus. The virus is killed when it meets agents of the immune system (term $-bXY$).

The reproduction of the agents of the immune system is described by the term $d(X - eX^2)Y$, where initially the presence of the virus stimulates the reproduction of $Y(t)$. When virus load is very large, the person is so sick that the reproduction of $Y(t)$ is inhibited. The term $-fY$ corresponds to the natural death of lymphocytes. The term V represents an external flow of lymphocytes.

The term $-c_1(t)X$ stands for virus-killing process due to different therapies. The term $-c_2(t)Y$ shows that therapies can also affect other normal cells (including the immune system).

Systems (4) and (5) are inspired by models of the immune system developed in Refs. 15 and 16. However, instead of the exponential growth assumed in Ref. 15 and 16, we are using our growth model given in Eq. (3).

IV. INVESTIGATION OF THE MODEL

First, we will consider the case where $q > 1$, $X_\infty e \gg 1$, $c_1(t) = 0$, $c_2(t) = 0$.

Let us define $a = \frac{qk}{q-1}$. The dynamical systems (4) and (5) can have, in principle, four fixed points

$$P_I = (X_1, Y_1) = \left(0, \frac{V}{f}\right), \tag{6}$$

$$P_{II} = (X_2, Y_2), \tag{7}$$

where $\frac{1}{2e} < X_2 < X_\infty$, $Y_2 = \frac{a}{b}$,

$$P_{III} = (X_3, Y_3), \tag{8}$$

where $0 < X_3 < \frac{1}{2e}$, $Y_3 = \frac{a}{b}$,

$$P_{IV} = (X_4, Y_4), \tag{9}$$

where $X_4 = X_\infty$.

The conditions for the existence of points P_{II} and P_{III} are the following inequalities:

$$\frac{1}{4e^2} - h > 0, \tag{10}$$

$$h > 0, \tag{11}$$

where $h = \left(\frac{f^a}{b} - V\right) \frac{b}{ead}$.

The eigenvalues of the Jacobian matrix corresponding to the fixed point P_I are

$$\lambda_1^{(I)} = a - \frac{bV}{f}, \tag{12}$$

$$\lambda_2^{(I)} = -f. \tag{13}$$

If $af < Vb$, the fixed point P_I is a stable node and the fixed point P_{II} is a saddle (see Figs. 1 and 2). If $af > Vb$ and $h - \frac{1}{4e^2} < 0$, then the four fixed points exist and are non-negative. Both fixed points P_I and P_{II} are now saddles. Between these two points, there is the point P_{III} , which is stable (see Figs. 3 and 4).

If $af > Vb$ and $h - \frac{1}{4e^2} > 0$, then there are only two fixed points: point P_I that is now unstable and point P_{IV} that is stable. As a result, most trajectories tend to point P_{IV} (with maximum virus population). This is not a very favorable situation for the patient (see Fig. 5).

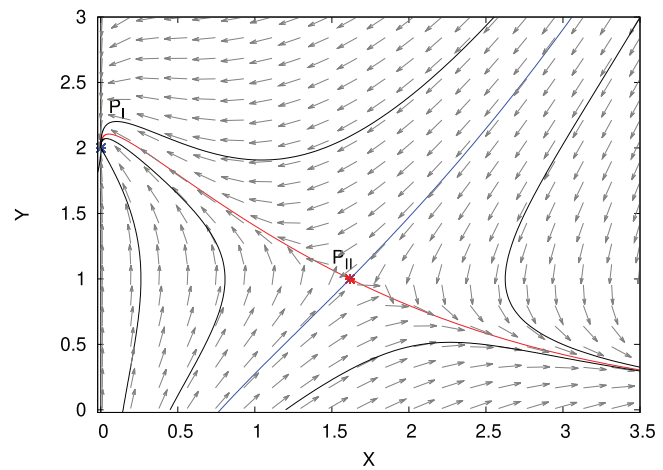


FIG. 1. Phase space representation of the dynamics of the dynamical systems (4) and (5). The meaning of the axes is as follows: X is the virus population and Y is the population of lymphocytes. The curves on the plane (X, Y) are constructed using solutions to Eqs. (4) and (5): $X(t)$ and $Y(t)$, for different initial conditions. In this case, the fixed point P_I is a stable node, the point P_{II} is a saddle, and the point P_{IV} (where $X \approx X_\infty$) is a stable node (not shown). The blue line is the stable manifold of the saddle point P_{II} . And the red line is the unstable manifold of the mentioned saddle point. The blue line is a global separatrix of the dynamics. All the initial conditions that are on the "left" of the blue line will lead to a phase trajectory that tends to the point P_I (where $X = 0$). All the initial conditions that are on the "right" of the separatrix will lead to a phase trajectory that tends to the point P_{IV} (where $X \approx X_\infty$). This picture occurs when $q > 1$, $bV > af$.

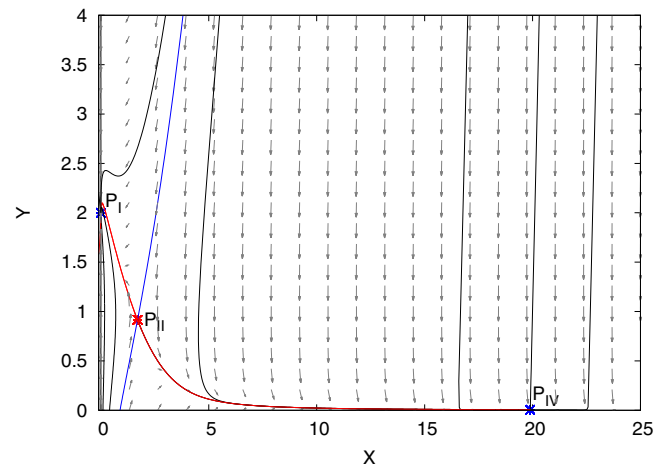


FIG. 2. Phase space representation of the dynamics of the dynamical systems (4) and (5). The phase trajectories on the plane (X, Y) are created using solutions to (4) and (5): $X(t)$ and $Y(t)$. This situation is topologically equivalent to that shown in Fig. 1. However, now we are showing the fixed point P_{IV} , where $X \approx X_\infty$.

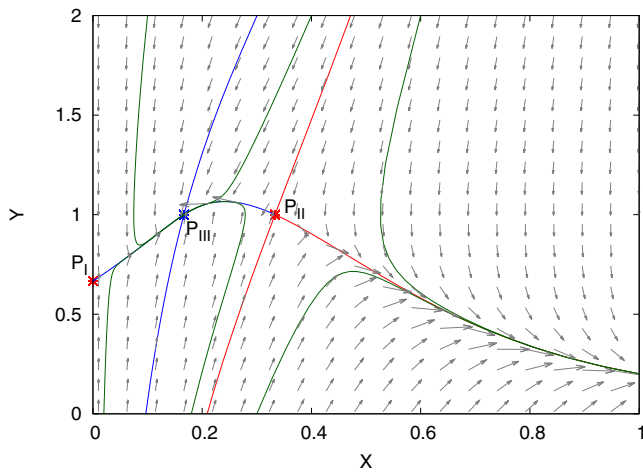


FIG. 3. Phase space representation of the dynamics of systems (4) and (5). The phase trajectories are constructed using solutions to Eqs. (4) and (5). As in Figs. 1 and 2, the axis X represents the virus population and the axis Y represents the population of lymphocytes. In this case, the fixed point P_I is unstable and the fixed point P_{III} is still a saddle. Now, there is a new fixed point P_{III} that is a stable node (for which $X > 0$). In this figure, the separatrix is represented with a red line. All the phase trajectories that are on the “left” of the separatrix are approaching the fixed point P_{III} (where $X > 0$). All the phase trajectories that are on the “right” of the separatrix are approaching the fixed point P_{IV} , where $X \approx X_\infty$ (not shown). Note that there are trajectories for which $X(t)$ is monotonically increasing from a small value until it reaches a maximum (point P_{III}). Conditions $bV < af$ and $h - \frac{1}{4e^2} < 0$ are satisfied.

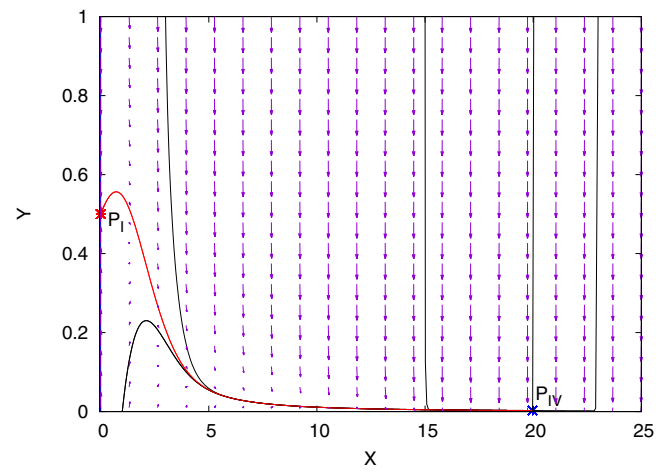


FIG. 5. Phase space representation of the dynamical systems (4) and (5), created with solutions to Eqs. (4) and (5) for different initial conditions. Here, X is the virus population and Y is the population of lymphocytes. In this case, the fixed points P_I and P_{III} disappear. Point P_I is unstable. The separatrix does not exist anymore. All phase trajectories tend to the point P_{IV} , where $X \approx X_\infty$. Conditions $af > bV$ and $h - \frac{1}{4e^2} > 0$ are satisfied.

In the neighborhood of point P_{II} , the separatrix of the saddle can be approximated by the straight line

$$Y = - \left(\frac{\lambda_2^{(II)}}{bX_2} \right) X + \frac{a + \lambda_2^{(II)}}{b}. \tag{14}$$

Any point corresponding to initial conditions of the Cauchy problem on the right of the separatrix leads to a dynamics where the trajectory approaches the point of maximum virus load (point P_{IV}).

On the other hand, if the initial conditions correspond to a point located on the left of the separatrix, the system will evolve to a stable fixed point.

Using (14), we can calculate the threshold or critical virus population that would lead to a dynamics approaching point P_{IV} ,

$$X_{crit} = \left(1 + \frac{a}{\lambda_2^{(II)}} \right) X_2. \tag{15}$$

When X_∞ is small, the outcome can be very favorable.

For instance, when

$$X_\infty < \frac{11}{6e} + \frac{2f}{3d}, \tag{16}$$

all the phase trajectories tend to the fixed point $P_I(X = 0)$.

We can also apply the isocline method in order to further investigate the system. A careful analysis of the behavior of the phase trajectories allows us to conclude that the condition

$$d > 4ef \tag{17}$$

is favorable for the patient. This is a sufficient condition to avoid an uncontrollable rise of the virus population leading to the point P_{IV} .

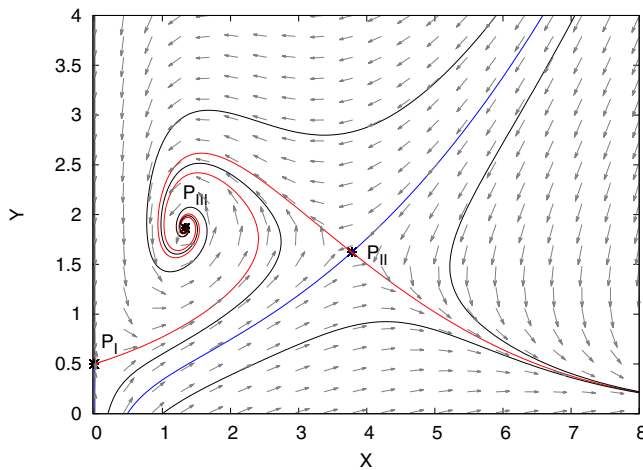


FIG. 4. Phase space representation of the dynamical systems (4) and (5), created using solutions to Eqs. (4) and (5). The meaning of the axes is as follows: X is the virus population and Y is the population of lymphocytes. This big picture of the dynamics is similar to that shown in Fig. 3. However, here the fixed point P_{III} is a stable focus.

In many cases, it is convenient to re-write the systems (4) and (5) as one equation where the only unknown is $\mathbf{X}(t)$,

$$\frac{d^2X}{dt^2} + [f - d(X - eX^2)] \frac{dX}{dt} - \frac{1}{X} \left(\frac{dX}{dt} \right)^2 = -\frac{dU(X)}{dX}. \quad (18)$$

In general, it is useful to discuss the dynamics of virus population as a general equation of the following type:

$$\frac{d^2X}{dt^2} + F_{dis} \left(X, \frac{dX}{dt} \right) = -\frac{dU}{dX}. \quad (19)$$

See Ref. 17 for a simple explanation. Equation (19) is equivalent to Newton’s equation for a “fictitious” particle moving in the potential $U(X)$ under the action of nonlinear damping.

The potential $U(X)$ can have minima and maxima. So, we can conceive the situation where the “fictitious” particle is trapped inside a potential well. The particle needs to jump over a barrier for the virus population to continue increasing. Studying the relative heights of the barriers, we get the condition

$$9e(Vb - af) + 2ad > 0, \quad (20)$$

when this condition is satisfied, the “right” barrier of the potential well is higher than the “left” barrier. This case is more favorable for the patient.

A careful analysis shows that the condition

$$2d > 9ef \quad (21)$$

is very favorable for the patient.

The general meaning of conditions (17), (20), and (21) is that the comparison between the values of d and the product ef can decide the outcome.

Let us analyze now the case $q \leq 1$. When

$$q \leq 1, \quad (22a)$$

the point P_I will be always unstable. This means that it is almost impossible to reduce the virus population to zero. This finding will play a very important part in the design of new therapies. Let us discuss time-dependent therapy against COVID-19.

Let us consider the dynamical systems (4) and (5) with time-dependent therapy

$$\mathbf{c}_1(t) \text{ and } \mathbf{c}_2(t) = \epsilon \mathbf{c}_1(t), \text{ where } \epsilon < 1.$$

Using ideas from Ref. 6, we can obtain the following result. If $q < 1$, it is very difficult to cure the virus disease. If we have a target decay for the virus population $\mathbf{X}(t)$, then $\mathbf{c}_1(t)$ must behave as

$$c_1(t) = \left[\frac{kX_\infty^{1-q}}{1-q} \right] \left(\frac{1}{X(t)^{1-q}} \right). \quad (22b)$$

For instance, if we require the virus population to be reduced following a power law, say, $\mathbf{X}(t) \approx \alpha/t^\gamma$, then the therapy must behave as $\mathbf{c}_1(t) = t^{\gamma(1-q)}$. The exponent gamma represents the rate of decay of the virus population.

We have designed therapies using the following late-intensification schedules:

$$c_1(t) = c_0 \ln(e + \delta t) \quad (22c)$$

and

$$c_1(t) = c_0 [1 + \delta t]^{\gamma(1-q)}, \quad (22d)$$

where $\mathbf{c}(t) = \mathbf{c}_0$ is a well-known constant-dose treatment taken by a patient for several days (see Ref. 4). Our logarithmic late-intensification schedule has been very successful (see Ref. 5 and references quoted there in). The traditional therapy is changed only slightly.

However, the results are spectacular.

V. MONOTHERAPIES

When $q > 1$, the parameters of the system and the initial conditions play an important role in the outcome. The virus–host interaction is decisive. There are situations where the immune system by itself can reduce the virus population to zero. Under other circumstances, the virus population will increase to numbers that can threaten the patient’s survival. If we apply conventional antiviral therapies with $\mathbf{c}(t) = \mathbf{c}_0$ in systems (4) and (5) (where \mathbf{c}_0 is a constant), for $q > 1$, the cure can be accelerated.⁶

If $q \leq 1$, then for any value of \mathbf{c}_0 , the virus population is never reduced to zero. The fixed point P_I is always unstable.

The medical significance of this result can be expressed employing this statement: when $q \leq 1$, the disease is resistant to the immune response and the action of conventional therapy.

VI. COMBINATION THERAPIES

Our analysis shows that for $q \leq 1$, the virus can develop resistance both against the attack of the immune system and all conventional monotherapies with constant doses of the medication. All this investigation leads to combination therapies.

First, we have to use therapies that change the parameters in such a way that fixed point P_I becomes asymptotically stable (a stable node). Then, we need to apply therapies that will help the phase trajectory to go to the point P_I . The condition $q > 1$ should be completed with the stability of fixed point P_I ,

$$bV > \frac{qkf}{q-1}, \quad (22e)$$

and complemented with condition (17).

This means that immunotherapy is also very important for the development of antiviral therapies.

This work can guide physicians to rationally design new drugs or a combination of already existing drugs for the development of antiviral therapies.

Condition (22e) shows that the killing ability of the immune system and the external flow of lymphocytes should be stronger than the virus replication and the natural death of immune system agents.

Additionally, condition (17) says that the reproduction of the lymphocytes should be stronger than the inhibition of the immune system due to the general health weaknesses created by the disease.

The perfect strategy is to use a therapy that can change q so that the fixed P_I can be, in principle, stable. Of course, this does not guarantee that the point P_I is stable.

The condition $q > 1$ is a necessary condition for the stability of point P_I . However, it is not a sufficient condition.

Later, we need another therapy that will change the other parameters (see Sec. III) so that the fixed point P_I is actually asymptotically stable. This step is probably satisfied with an immunotherapy.

Finally, we need a treatment $c(t)$ that definitely kills the virus, leading the phase trajectory to the fixed point. The ideal candidate for the first task could be a gene-targeted therapy. On the other hand, we believe there are antivirals that can be utilized in order to accomplish this goal.

VII. SOME BIOPHYSICAL ANALYSIS

Drug repurposing for SARS-CoV-2 is very important for our world. It can represent an effective drug discovery strategy from the existing drugs. It could shorten the time and reduce the cost compared to *de novo* drug discovery.⁴⁴

Phylogenetic analysis of 15 HCoV whole genomes reveals that SARS-CoV-2 shares the highest nucleotide sequence identity with SARS-CoV.⁴⁴

A molecular docking study has been published by Abdo Elfiky.⁴¹

The results show the effectiveness of ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir as potent drugs against SARS-CoV-2 since they tightly bind to its RdRp. Additional findings suggest guanosine derivative (IDX-184), Sofosbuvir, and YAK as top seeds for antiviral treatments with high potential to fight SARS-CoV-2 strain specifically.

VIII. REAL EXPERIMENTS AND CLINICAL STUDIES

We have reviewed the medical literature on COVID-19 treatments. There is experimental evidence supporting combination therapies.^{18–54} However, medical practice has been concentrated mostly on monotherapies.^{18–54}

Even when combination therapies have been used, in many cases, the combinations have not been optimized. We believe we can improve the treatment outcomes using our results.

Combination of antivirals is the most common therapeutic set.^{18–54} In many cases, the used antivirals were previously developed for other viruses (e.g., SARS, MERS, Ebola, Flu, and HIV).^{18–54}

We present a summary of the studies about COVID-19 treatments.

Therapy 1: Lopinavir + Ritonavir (Antivirals against HIV) + Oseltamivir (Flu) Lopinavir/Vitanovir are approved protease inhibitors for HIV.

Results: There is some scientific evidence that this combination can work.^{18,52,53}

Inconsistent results in some completed clinical trials.

Therapy 2: Antiflu arbidol + Anti-HIV antiviral darunavir.

Results: There is some scientific evidence that these combinations can help.^{18,52}

Therapy 3: Lopinavir/ritonavir + ribavirin.

This is an anti-HIV therapy used in SARS.

Results: There is some scientific evidence that this combination could work.¹⁹

Therapy 4: Remdesivir + lopinavir/ritonavir + interferon beta.

Remdesivir interferes with virus RNA polymerases to inhibit virus replication and was used for the Ebola virus outbreak.

Results: The combination is being tested for MERS. There is some scientific evidence that this combination could work for other coronaviruses.¹⁹

Therapy 5: Cloroquine, hydroxychloroquine.

This is an antimalarial drug.

Results: Inconsistent results in completed clinical trials^{2,21,22,26,27,36} and in Ref. 39.

Therapy 6: Hydrochloroquine + antibiotic azithromycin.

Results: Didier Raoult and co-workers published results of a completed clinical trial that “proved” efficacy.²¹ However, nowadays, this therapy is considered controversial.

Therapy 7: Convalescent plasma.

Convalescent plasma from cured patients provides protective antibodies against SARS-CoV-2.

Results: Proven efficacy.^{24,28–33,53}

Therapy 8: “Natural killer” cell therapy.

Natural killer cell therapy can elicit rapid and robust effects against viral infections through direct cytotoxicity and immunomodulatory capability.⁵³

Results: Being tested in clinical trials^{31,53} and Ref. 38.

Therapy 9: EIDD-2801.

This is an antiviral.

EIDD-2801 is incorporated during RNA synthesis and then drives mutagenesis, thus inhibiting viral replication.⁵³

Results: Being tested in clinical trials.^{37,38,53}

Therapy 10: Remdesivir.

This is an antiviral that interferes with virus RNA polymerases to inhibit virus replication.

Results: Approved by FDA. Inconsistent and conflicting results in completed clinical trials.^{40,46–48,53,54} This is a promising drug.

Therapy 11: Ivermectin.

Results: Leon Caly *et al.*⁴⁵ have observed that the FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. The authors have shown that this drug actually “kills” the virus within 48 h. This drug is being used extensively and massively in some countries (e.g., South America), in some cases, as a national policy. However, there are no completed clinical trials.

Therapy 12: Human monoclonal antibodies.

Results: Wang *et al.* have found a human monoclonal antibody (47D11) that neutralizes SARS-CoV-2.⁵⁰ Being tested in clinical trials.

Therapy 13: Mesenchymal stem cells. This is a cell therapy. MSCs have regenerative and immunomodulatory properties and protect lungs against ARDS.

MSC therapy can inhibit the over activation of the immune system and promote repair improving the microenvironment. They regulate inflammatory response and promote tissue repair and regeneration.⁵¹ Results: Proven efficacy in completed clinical trials.⁵³

Therapy 14: Lopinavir/ritonavir + ribavirin + interferon beta-1b1.

Results: Fan-Ngai Hung *et al.* have published positive and promising results of a clinical trial.⁴⁸

IX. NEW COMBINATION THERAPIES

We have estimated the parameters of the model [Eqs. (4) and (5)] using published data from the dynamics of different kinds of biological populations.^{18–69}

These data include sets of virus population and cell populations.

In all the cases, the growth of the studied populations represents the most relevant behavior of the disease.

Some examples are the virus population and the neoplastic cell population. Normally, these are the only published data.

The value of the virus population density is provided by the viral load = number of copies/ml.

Actually, what we usually know is \log_{10} (number of copies/ml), or \log_{10} (number of copies/1000 cells).

Sometimes, the parameters are estimated using best-fit solution functions.

In other cases, approximate values of the parameters are obtained from some characteristics of the dynamics like the slope of the tangent line to the graphed function, the fixed points, the stability conditions, and the eigenvalues of the Jacobian matrix.

Often, data about the immune behavior are not explicitly available. So, we use a version of the model that consists of one nonlinear differential equation only for $X(t)$.

However, that equation contains the parameters that characterize the immune system. Thus, these parameters can be estimated, too.

We have observed several patterns in the virus dynamics.^{18–69}

First pattern: The viral load increases rapidly and reaches a peak. Then, the viral load declines due to the action of a strong immune system. The final viral load cannot be detected. We assume it is zero (see Fig. 1).

Second pattern: The viral load increases rapidly and reaches the peak, followed by a plateau. The plateau can be short or long. After the plateau, the viral load declines to zero. (In this case, the dynamics reaches a fixed point. Then, the parameters of the immune system change (e.g., b , V .) Then, the fixed point P_I is stable again.

Third pattern: The viral load increases rapidly and reaches a peak, followed by a plateau with a large value of the virus load. The plateau never ends. The patient dies. The viral load never declines (Figure 5).

Fourth pattern: The viral load increases rapidly and reaches a peak. Then, the viral load declines. The decline is followed by a long plateau. The value of the virus load is much smaller than the peak. However, it is far from zero (see Fig. 3).

These behaviors can also occur under the action of therapy.^{18–69}

Let us introduce the units of the variables and parameters.

Define the variable $X(t) = \log_{10}$ (number of copies/ml).

$[X(t)] = uv$. Thus, $X = 1 uv$ if (the number of copies)/ml = 10. Here, uv stands for unit of viral load, where X is given in units of \log_{10} (number of copies/ml).

$Y(t)$ is the number of lymphocytes/ml, $[Y(t)] = 1 nc$, where $1 nc = 1$ lymphocyte/mL, $[a] = 1/\text{day}$, $[f] = 1/\text{day}$, $[b] = 1/(\text{nc})\text{day}$, $[V] = \text{nc}/\text{day}$, $[d] = 1/(\text{uv})\text{day}$, $[a] = 1/uv$, q is dimensionless.

Let us discuss some particular examples of real virus population growth.

Example 1 (Patient 14 in Ref. 56): $X_\infty = 8 uv$, $k = 0.04$ (1/day), $q = 2$, $(a - Vb/f) = -0.71$ (1/day), $(d - 4ef) = 0.6$ [1/(uv)day].

In this case, the immune system is so strong that it is able to eradicate the virus by itself. Virus load is approaching zero after 10 days.

Example 2 (Patient 7 in Ref. 56): $X_\infty = 8.5 uv$, $q = 2$, $k = 0.05$ (1/day), $e = 0.1$ (1/uv), $b = 0.028$ (1/(nc) day), $f = 0.251$ (1/day), $V = 0.002$ ((nc)/day), $a = 0.1$ (1/day), $d = 0.119$ (1/(uv) day).

In this case, the viral load will reach the maximum. Then, the virus load will decline. But, it will not approach zero. The value of $X(t)$ will be approximately constant for a long time.

In the dynamical system, this is a stable fixed point. The real data show a long plateau where $2uv < X < 3uv$. The known data do not show an end to this plateau.

Example 3 (Patient 1 in Ref. 65): $X_\infty = 7.9 uv^*$, here X is given in units of \log_{10} (number of copies/1000 cells), $q = 0.9$, $k = 0.1$ (1/day), $f - Vb/a = 0.25$ (1/day), $d - 4ef = 0.2$ [1/(uv) day],

$(1/2e) - \sqrt{(1/4e^2) - h} = 4.2 uv^*$. Initially, the viral load increases and reaches the maximum, followed by a plateau. Both the model and the real data agree with this.

Later this patient was treated with remdesivir. Now we re-estimate the parameters

$X_\infty = 7.3 uv^*$, here X is given in units of \log_{10} (number of copies/1000 cells), $q = 2$, $k = 0.01$ (1/day), $a - Vb/f = -4.2$ (1/day), $d - 4ef = 0.3$ [1/(uv) day].

Now both the model and the real data show that the viral load will approach zero!

The antiviral changed parameters q and $(a - Vb/f)$.

The cases of patients 2, 4, and 5 from Ref. 65 are very similar to Example 1.

The immune system is able to eradicate the virus without external therapy.

Example 4 (Patient 3 from Ref. 65): $X_\infty = 7.8 uv^*$, $q = 0.82$, $k = 0.04$ (1/day), $f - Vb/a = 0.46$ (1/day), $d - 4ef = -0.46$ [1/(uv) day].

The viral load reaches a maximum, followed by a plateau. This is an 80 years old man with a very depressed immune system (he had thyroid cancer).

This patient was sick with COVID-19 for 24 days. He was medicated with remdesivir starting on day 16.

The viral load decreased slightly. However, the immune system was too weak.

The viral load never reduced to zero. The patient died on day 24. This patient probably needed a combination therapy containing antivirals, immunotherapy, and a virus-killing medication.

Example 5 (Patient DF from Ref. 69): $X_\infty = 8.4 uv$, $q = 0.6$, $k = 0.02$ (1/day), $b = 0.024$ [1/(nc)day], $d = 0.0001$ [1/(uv)day], $f = 0.2$ (1/day), $e = 0.02$ [1/(uv)], $V = 0.0002$ [(nc)/day].

The viral load increases until it reaches the maximum. The immune system is so weak that we can consider that it is not working at all.



FIG. 6. General therapeutic plan.

The viral load will never decrease. The patient died on day 18.

Example 6 (The case of the patient reported in Ref. 60):
 $X_\infty = 9.5$ uv, $q = 1.8$, $k = 0.01$ (1/day), $a - Vb/f = -0.35$ (1/day)
 $d - 4ef = 0.5$ [1/(uv)day].

The viral load increases very fast and the peak is very high. Common sense would have led physicians to consider this case as critical.

However, this patient was treated with a combination therapy.

According to the estimated parameters, we believe the treatment changed parameter q .

The immune system was working well. The viral load is eradicated. This is seen in the dynamics of the model and in the real clinical data.

We have investigated all the data published in Refs. 18–69.

For instance, in Ref. 69, the authors studied 52 patients. The cases are very similar to the examples and patterns that we have described here. They found mild, severe, critical, and deadly cases.

In general, considering all the literature^{18–69} here are interesting points that must be remarked.

Some older patients with rapid evolution toward critical disease with multiple organ failure presented a long sustained persistence of SARS-CoV-2.

This persistent high viral load is explained by the ability of the SARS-CoV-2 to evade the immune response.⁶⁵

SARS-CoV-2 might be able to inhibit immune system signaling pathways, resulting in a malfunctioning of the immune system.

In most critical patients, the blood viral load was never eliminated.⁶⁹

This can be explained with the stable fixed points of our model.

The results of our investigation of the model, the virus kinetics research, and the data from lab experiments and clinical studies^{18–69} lead us to the following strategy to cure COVID-19:

A combination of antivirals can change the virus reproduction capabilities (parameter k) and drug resistance (parameter q). This can make the fixed point P_I stable.

A combination of immunotherapies can boost the immune system (parameters b, d, V).

The agents of the immune system can reduce the virus load (see Figs. 1–4).

A virus-killing therapy.

Even if the point P_I is stable and the immune system is working, it is possible that the virus dynamics is not riding a phase trajectory

that is approaching the fixed point P_I , where $X = 0$. For instance, if the initial condition is on the “right” of the separatrix of the saddle point P_{II} , then $X(t)$ is not approaching the point $X = 0$.

A virus-killing therapy can change the position of the initial point (X_0, Y_0) , in such a way that this point will be on the “left” of the separatrix (see Fig. 1).

Now there is always a phase trajectory that will drive the viral load, $X(t)$, to the point where $X(t) = 0$. The particular medications that will be used in every combination are selected from the set of drugs already tested in clinical trials.

The ideas discussed in the first six sections of the paper lead to the conclusion that we need a combination therapy that contains at least some of the following features:

- A combination of drugs that impair somehow the biophysics of the virus replication, infection, and/or treatment resistance.
- A combination of drugs that enhance the immune system ability to provide enough agents and their capability to fight the virus + anti-inflammatory drugs.
- A cell-killing therapy.

Our paper is not only about mathematical models. We have critically reviewed all the published data about possible medical treatments against COVID-19.

We have used a method that we have developed called Complex Systems Investigation to analyze the data.

Complex Systems Investigation contains ideas from Nonlinear Dynamical Systems, Inverse Problems, and Experimental Design Mathematics. Our results show that a successful treatment should be a combination of therapies as that shown in Fig. 6.

This is just a useful therapeutic plan. We will see later that the role of a cytotoxic therapy sometimes can be played by an immunotherapy or an antiviral. Figure 6 shows a very general plan.

Now, we will present several concrete combination therapies. There are certain observations¹⁸ that support the existence of synergism between remdesivir and monoclonal antibodies. Considering the fact that our investigation leads to a combination of antivirals, immunotherapy, and virus-killing medications, the mentioned synergism help us build the treatment shown in Fig. 12.

The simplest of our designed therapies is shown in Fig. 7, and Figs. 8–15 show different alternative treatments.

Baricitinib is an important anti-inflammatory drug. It also has anti-viral effects.⁵⁵

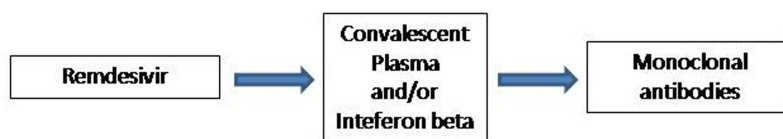


FIG. 7. One of the simplest therapies: Remdesivir plus immunotherapy plus monoclonal antibodies.

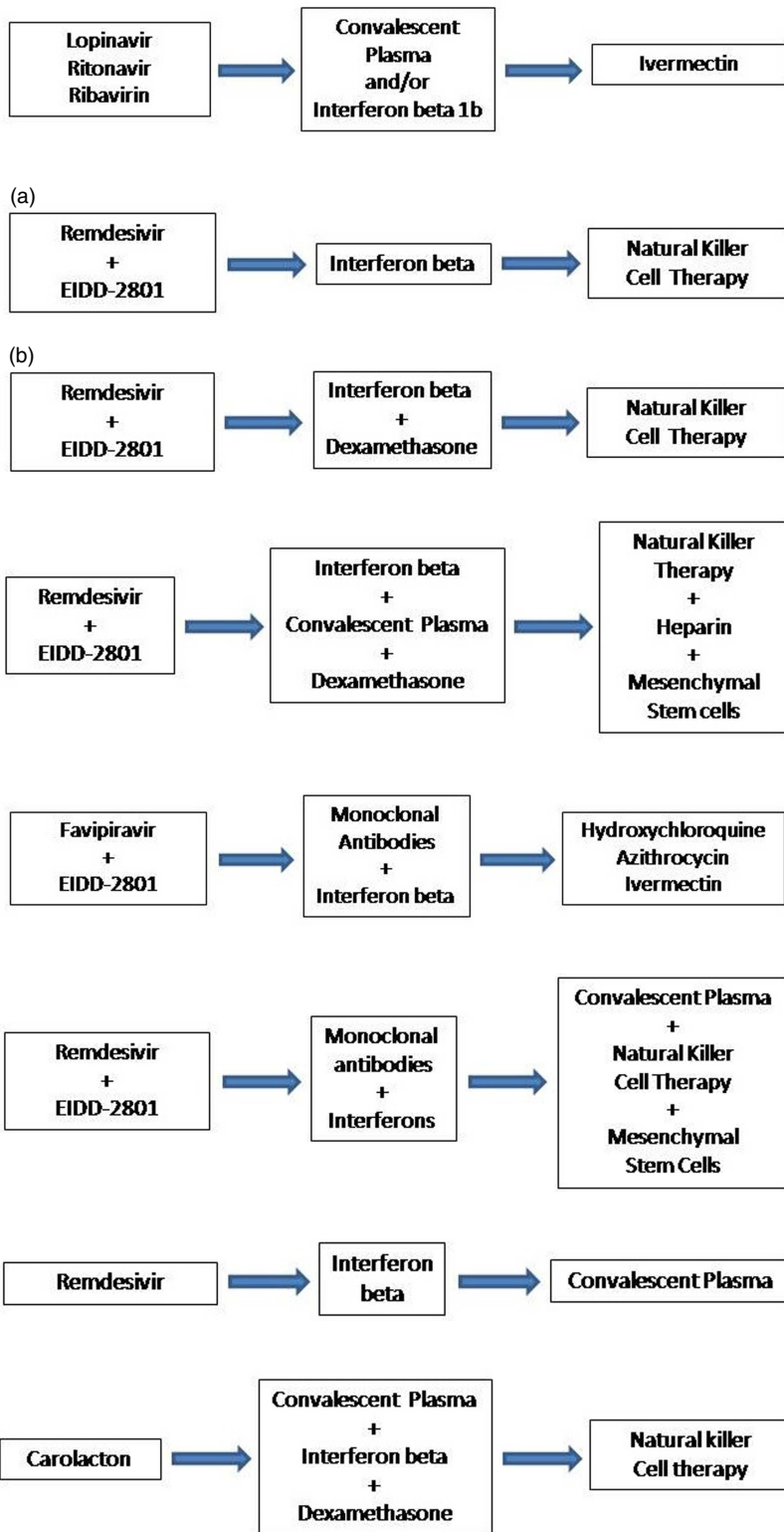


FIG. 8. Anti-HIV cocktail plus immunotherapy plus ivermectin.

FIG. 9. (a) Antiviral combination plus interferon beta plus natural killer cell therapy. (b) Antiviral combination plus Interferon beta plus Natural Killer Cell Therapy plus Anti-inflammatory drug.

FIG. 10. Powerful combination therapy that should kill the virus and save lives. The treatment includes a cocktail of antivirals: Remdesivir plus EIDD-2801, immunotherapy, natural killer cell therapy, mesenchymal stem cells, a corticosteroid, and an anti-coagulant.

FIG. 11. This is a combination of antivirals, an immune system booster, monoclonal antibodies, azithromycin, and the controversial hydroxychloroquine.

FIG. 12. This therapy contains a combination of antivirals, monoclonal antibodies, an immune system booster, convalescent plasma, Natural Killer Cell Therapy, and an immune system modulator. This is a powerful combination.

FIG. 13. This is a next-door therapy. Any hospital should be able to provide this treatment, which could save patients' lives.

FIG. 14. This could be a perfect realization of the General Therapeutic Plan (see Fig. 6): Gene therapy → immunotherapy + an anti-inflammatory drug → cytotoxic therapy.

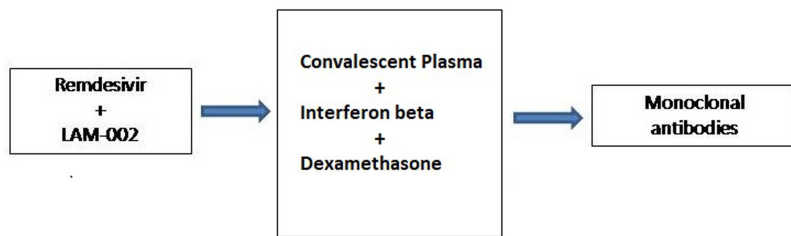


FIG. 15. The combination remdesivir plus LAM-002 should cripple the virus, the immunotherapies should kill the virus, and dexamethasone should relieve the inflammation and avoid the cytokine storms. The whole combination should control the immune system disorders, allergic reactions, and the breathing problems. This therapy should save lives and help patients recover faster.

A commonly used steroid, dexamethasone, can control the cytokine storms and can reduce the risk of death.

Consider all the calculations presented together with the previous examples. We have done a similar research work with all the experimental data available in Refs. 18–69.

Sometimes, the data are very fragmented. In some cases, we only know the input, the medications, and the output.

For instance, consider a patient with the following estimated parameters before therapy:

$\mathbf{X}_\infty = 9.3 \text{ uv}$, $\mathbf{q} = 0.97$, $\mathbf{k} = 0.04 \text{ (1/day)}$, $\mathbf{b} = 0.01 \text{ [1/(nc)day]}$, $\mathbf{d} = 0.0005 \text{ [1/(uv)day]}$, $\mathbf{e} = 0.03 \text{ [1/(uv)]}$, $\mathbf{V} = 0.0001 \text{ [(nc)/day]}$, $\mathbf{X}_0 = 4 \text{ uv}$.

Evidently, the patient has a bad prognosis. There is no way that this viral load will decrease under natural circumstances. We will apply the therapy shown in Fig. 10.

Our result is as follows:

The first round (antiviral combination: remdesivir + EIDD-2801) will produce the parameters: $\mathbf{q} = 1.9$, $\mathbf{k} = 0.01 \text{ (1/day)}$. These are the only parameters that can be changed with the given antivirals.

After the immunotherapy (convalescent plasma + interferon beta), we get

$(\mathbf{a} - \mathbf{Vb}/\mathbf{f}) = -0.82 \text{ (1/day)}$ and $\mathbf{d} - 4\mathbf{ef} = 0.71 \text{ [1/(uv)day]}$.

Additionally, the virus-killing medication (Natural Killer Cell Therapy) will reduce the “initial” viral load to the value $\mathbf{X}_{02} < 1.4\mathbf{uv} < \mathbf{X}_{\text{crit}}$. Now, there is a phase trajectory that can carry the viral kinetics to the stable fixed point \mathbf{P}_1 with the value $\mathbf{X} = 0$ (see Fig. 1).

We can cure this patient with a fulminant COVID-19 infection! We believe these results can explain the clinical outcomes observed in Refs. 27–30.

Regeneron pharmaceuticals has developed monoclonal antibodies to treat MERS. This company is already working on similar antibodies that might work against SARS-CoV-2.

Lopinavir/ritonavir + arbidol improved pulmonary computed tomography images.⁵⁵

Interferons + Natural killer cells are promising. Interferons can enhance natural killer cells cytotoxicity. Mesenchymal stem cells will act against inflammatory factors (cytokine storms).

MTHFV1 is a gene indispensable for viral replication in bat and human cells.

Carolacton is a MTHFV1 inhibitor. It is a natural bacteria-derived product.⁵⁵

This is a good candidate for the first round in the combination therapy (see Fig. 14).

A candidate for natural killer cell therapy is CYNK-001.³⁷

The most powerful therapy is shown in Fig. 10. Probably, this therapy should be used in the most severe critical fulminant cases.

On the other hand, Fig. 13 shows the next-door therapy. In principle, all elements should be available right now in every American city.

X. DISCUSSION

Remdesivir is considered the most promising drug for COVID-19 and MERS.

However, the clinical trials have produced conflicting results. Sometimes, the results are encouraging; sometimes, there are no significant benefits at all. Sometimes, the people are still dying even taking remdesivir.

Our response to this paradox is that remdesivir will work as part of a combination therapy. Our result is that the idea of using remdesivir and some immunotherapies in combination would have profoundly excellent prospects (see Figs. 6–15).

We have tried to construct the combinations using drugs that have shown proven efficacy in completed clinical trials and/or laboratory experiments.⁵⁵

Parameter \mathbf{q} is related to the nature and structure of the virus. It is responsible for the virus explosive reproduction. Furthermore, when $1 - \mathbf{q} \geq 0$, the virus can develop drug resistance and the ability to escape the immune system attack. Fortunately, some antivirals can change parameter \mathbf{q} .

For instance, the drug EIDD-2801 interferes with a key mechanism that allows the SARS-CoV-2 virus to reproduce in high numbers and cause infections.

EIDD-2801 is incorporated during RNA synthesis and then drives mutagenesis, thus inhibiting viral replication. So, this antiviral changes the nature of the virus.

The action of EIDD-2801 and remdesivir is different. Remdesivir shuts down viral replication by inhibiting a key enzyme, the RNA polymerase.

Both remdesivir and EIDD-2801 can change parameter \mathbf{q} . Antivirals keep the virus from functioning and/or reproducing. If we combine them, we can increase the probability that they will do the job of changing the biophysics of the virus. Then, we can add immunotherapies to eradicate the virus.

These two antivirals are much more potent if given early. In general, this is the case for most antivirals.

Some physicians can have concerns because, for them, it is not clear whether several combinations of medications and the high doses of the drugs in question could cause side effects.

Our research leads to the following solution to these problems: the addition of new drugs to the therapy and the total increase of

doses can be administered using late-intensification schedules (e.g., logarithmic or power-law therapies⁴⁻⁶).

Our stable fixed point with a small but finite virus population explains the following mystery: why a lot of patients who recovered from Coronavirus have retested positive.⁷

The existence of a finite minimum of the virus load in order to start an infection [Eq. (15)] explains that there is a threshold value for a person exposure to sick people so that the person becomes infected. Our findings can also inform vaccine development. A vaccine works by training the immune system to recognize and combat viruses.

Some precedents. Therapy of HIV is complicated by the fact that the HIV genome is incorporated into the host cell genome and can remain there in a dormant state for prolonged periods until it is reactivated. Some scientists believe that it is not possible to actually eradicate the virus completely.

Our research shows that this is a very striking example where $q \leq 1$. Following our ideas, it is possible that HIV can be completely eradicated. AZT was the first antiviral agent used for the treatment of HIV and was introduced in 1987. However, it became clear that mono therapy with AZT did not provide durable efficiency and hardly made any dent in the mortality rate.

Later, different studies showed that combination therapy with two nucleotide analogs was better than monotherapy with only one.

After several experimental breakthroughs, a combination therapy known as HAART (highly active antiretroviral therapy) using two or three agents became available. By combining drugs that are synergistic, non-cross-resistant, and no overlapping toxicity, it may be possible to reduce toxicity, improve efficacy, and prevent resistance from arising.

All the antiviral drugs and therapeutic methods now known were discovered by random search in the laboratory.

We believe that using mathematical biophysics it is possible to create a rational approach for the discovery of new antiviral compounds and the design of the optimal combination therapy.

XI. CONCLUSIONS

We would like to remark the following points about our research results:

- We have developed a mathematical model to describe the SARS-CoV-2 viral dynamics. The model is a nonlinear dynamical system.
- We have investigated the dynamical system theoretically and numerically.
- We have found conditions for the stability of the fixed point that corresponds to the complete eradication of the virus.
- We identified the separatrix that separates the initial conditions that lead to the maximum value of the viral load from the initial conditions that lead to a limited growth of the virus population.
- We have studied the global dynamics of the dynamical system. We can predict the evolution of any initial condition.
- The fixed point $\mathbf{X} = \mathbf{0}$ is stable when

$$q > 1, \quad (23)$$

$$Vb > af. \quad (24)$$

- If the following conditions are satisfied:

$$af > Vb, \quad (25)$$

$$h - \frac{1}{4e^2} > 0, \quad (26)$$

then the separatrix does not exist and there are no restrictions to the growth of the viral load. This is a terrible situation.

- Furthermore, condition $q \leq 1$ means that the virus cannot be eradicated by the immune response or using any conventional monotherapy.
- Let us discuss the biological meaning of the following conditions:

$$Vb > af, \quad (27)$$

$$d > 4ef, \quad (28)$$

$$q > 1. \quad (29)$$

In the real-life scenario, conditions (27)–(29) mean that the immune system is working well and the virus infection is not drug resistant. The combination therapy must be able to generate conditions (27)–(29).

- Our study provides explanations to several phenomena that have been observed during the experimental studies of SARS-CoV-2 virus.
- We have critically reviewed the experimental and clinical literature about COVID-19.
- Using the results from the investigation of the model and experimental data from laboratory and clinical studies, we have designed new combination therapies against COVID-19.

Beigel *et al.*⁵⁵ have published a paper in The New England Journal of Medicine with the information about the NIAID-supported study titled “Remdesivir for the treatment of COVID-19.”

NIAID director has said that remdesivir will become the standard care of COVID-19. The drug shortened the course of illness from an average of 15 days to about 11 days and did not cause an excess of side effects. However, there is high mortality despite the use of the drug. According to the study, it is clear that the medication is not a cure and it is not sufficient to help patients.

Our take is that remdesivir alone is not enough. Many other treatments, given as monotherapies, have failed to provide the promised results.

Our conclusion is that we need new scientifically designed combination therapies.

Using mathematical models and experimental data from laboratory and clinical studies, we have been able to design new therapies, which, we expect, will cure the patients (see Figs. 6–15).

The new therapies also should be validated in double-blind, placebo-controlled trials with a large number of patients.

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DATA AVAILABILITY

The data that support the findings of this study are available within the article.

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