Strong Correlations in a Biological System as a Cause of Sustained Epidemic Waves: Implications for Understanding the COVID-19 Pandemic

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We consider an epidemic in a strongly correlated biological system, where the influence of the environment on the individual state and immune response of the infected is decisive. This leads to the 3D Lotka-Volterra system and explains the existence of sustained epidemic waves that are absent in the conventional SIRS model. Taking the biological correlations into account turns the population into a single organism, as a result of which the course of the epidemic reproduces all phases of an individual's infection. We argue that strong correlation effects are critical in shaping the COVID-19 epidemic, which is adequately described by the 3D Lotka-Volterra equations.

I. MOTIVATION AND INTRODUCTION

The current COVID-19 pandemic has several features that distinguish it from previous epidemics. One of them is the presence of pronounced non-seasonal epidemic waves. This phenomenon requires study and explanation for two reasons. First, it is necessary to correctly predict the course of the epidemic in order to make a reasonable allocation of medical resources. Secondly, the course of the epidemic itself provides important information about its structure, and, consequently, about the possible ways of effective response. In the present work, we propose a potential mechanism for the emergence of self-consistent epidemic waves and substantiate the applicability of this mechanism to the current COVID-19 epidemic.

The problem of the origin of epidemic waves was studied long before the outbreak of the COVID-19 epidemic [1, 2]. Many infections do not create long-term immunity and therefore, due to re-infection, they can be cyclically repeated. However, this does not necessarily lead to a cyclical course of the epidemic, as is known from the examples of several infectious diseases [3, 4]. In order for the individual cyclical nature of the disease to manifest itself in the form of epidemic waves, it is necessary to have some factor that synchronizes the course of this disease in many people. For some epidemics, seasonal changes in the weather and the level of immunity are an acceptable reason for this synchronization [5]. The epidemic waves of COVID-19, however, are not seasonal and therefore cannot be explained in this way. Apparently, this means that the periodicity of the epidemic process in this case is due not to external factors, but to the internal mechanism of the epidemic itself. And this implies correlations between individual members of the biological population.

Thus, the pronounced epidemic waves of COVID-19 suggest a strong correlation between the course of infection in an individual and the course of the epidemic in the entire population. In this paper, we present a model that looks at such correlations and, on its basis, explains the emergence of sustained epidemic waves. We do not take into account the effects of targeted vaccination or virus mutations that significantly change its biological properties. These factors are external to the model and can also initiate the appearance of epidemic waves. They are outside the scope of our work.

The paper is organized as follows. The second part presents the basic principle of the 2-component model of the COVID-19 epidemic proposed in our previous work [6]. This consists in the separate accounting of symptomatic and asymptomatic infected. In the next, third section, the spread of infection in the asymptomatic sector of the epidemic is considered within the framework of the standard SIRS model, which ignores the biological correlations. In the fourth section, we consider the biological correlations by replacing the parameters of the SIRS model with its variables. This transforms it into a symmetric 3D Lotka-Volterra model. In the fifth part, a generalization of this model to the asymmetric case is considered, which has the same degree of generality as the original SIRS model, and at the same time takes the correlations into account. In the final part, we summarize and list the questions that remain open.

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II. SYMPTOMATIC AND ASYMPTOMATIC COMPONENTS OF THE COVID-19 EPIDEMIC

In recent works [6–9], we have developed a 2-component model of the COVID-19 epidemic, which is based on dividing all infected people into 2 groups - asymptomatic infectious agents and symptomatic patients. The main idea of this model is that some people spread the infection and others get sick. This is what distinguishes the COVID-19 epidemic from previous epidemics, when the proportion of asymptomatic carriers was small, and they did not have a decisive impact on the epidemic process. The model explains the persistent plateau in the COVID-19 pandemic that emerged after the first epidemic peak. Comparison with epidemic data showed that asymptomatic carriers dominate, and the resulting symptomatic morbidity is only a small observable part of the pandemic iceberg. At the same time, asymptomatically infected people make up its main and unobservable part.

The 2-component model of the epidemic assumes that the infection is mainly spread by asymptomatic carriers. The corresponding formal parameter is the probability p that a person becomes ill after infection. In this case, they lose mobility, and with it the ability to further spread the infection. Consequently, this first group of infected give a small contribution to the spread. With a probability $(1-p)$, a person carry the infection asymptomatically and all this time continue to spread the infection. Consequently, it is this second group of infected people that makes the main contribution to the spread. Comparison of the results of the model [6] with the data of the COVID-19 epidemic leads to a value of $p \sim 10^{-3}$, which justifies the dominant role of asymptomatically infected people in the spread of infection. In [6], arguments are given in favour of the fact that long-term immunity is acquired only by those who have had a symptomatic infection. Asymptomatically infected people acquire only short-term immunity. Therefore, in what follows, they can be re-infected and with the same probability p to get sick. Thus, the virus circulates in the population and after a while the endemic equilibrium number of asymptomatic infected is established. And this is the reason for the incidence plateau.

III. ASYMPTOMATIC RE-INFECTION WITHOUT CORRELATIONS: SIRS SYSTEM

In [6] it was shown that in the zero approximation in the small parameter $p \ll 1$, the asymptomatic sector of the 2-component model is completely autonomous. It describes the invisible asymptomatic circulation of the virus, in which the vast majority of the population is involved. Since asymptomatic infection does not create long-term immunity, the asymptomatic sector of the epidemic can be naturally described by the equations of the conventional SIRS model [1, 2]:

$$\begin{cases} \frac{dS}{dt} = \sigma R - IS \\ \frac{dI}{dt} = IS - \omega I \\ \frac{dR}{dt} = \omega I - \sigma R \end{cases} \tag{1}$$

Here S, I and R - respectively, the proportion of susceptible, **asymptomatic** infected and temporarily immunized. The constants ω and σ mean the rate of virus elimination and the rate of deactivation of the immunity. The spread rate of the virus is taken as a unit. The **symptomatic** daily incidence J is expressed through the solution of the system (1) as follows:

$$J = pIS. \tag{2}$$

This relation expresses the simple fact that in each act of infection (term IS), the probability of symptomatic infection is p.

Due to identity

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0 \tag{3}$$

equations (1) preserve the norm

$$S + I + R = 1 \tag{4}$$

which corresponds to the adopted zero approximation in the small parameter p. Considering the symptomatic incidence in the next approximations makes this amount less than one, since those who have been ill acquire permanent immunity and leave the epidemic process.

When the epidemic condition $\omega < 1$ is fulfilled, the system of equations (1) has two equilibrium points: one unstable node $(1, 0, 0)$ and one stable focus

$$\left(\omega, \frac{1-\omega}{\sigma+\omega}\sigma, \frac{1-\omega}{\sigma+\omega}\omega\right). \tag{5}$$

This is shown schematically in Fig. 1.

Thus, epidemic waves in the SIRS system exist in a certain range of parameters, but they quickly fade out and turn into a plateau over time. In accordance with expression (2), the plateau corresponds to a constant incidence rate

$$J = p\sigma\omega\frac{1-\omega}{\sigma+\omega}. \tag{6}$$

In the range of values of the parameters $\sigma \ll \omega \ll 1$ of interest to us, the steady-state incidence rate is $J = p\sigma$.

This plateau following from the SIRS system (1) is consistent with the time-averaged course of the pandemic, obtained after summing the data around the world. However, it is in odds with the sustained waves of incidence observed in most countries. This indicates the inadequacy of the SIRS equations to describe the dynamics of

FIG. 1. Phase portrait and epidemic dependence of the symptomatic daily incidence $J(t) = pI(t)S(t)$ in the standard SIRS system.

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the epidemic. What factors should enter the model to reproduce the sustained epidemic waves?

In order for such waves to exist and be maintained, synchronization of all three stages of the epidemic process is necessary: 1) infection, 2) activation of the short-term immunity and elimination of the infection, and 3) deactivation of the short immunity. Due to the pair term IS in equations (1), the SIRS system provides synchronization of individual infection processes. However, this system describes two other stages, the elimination of infection and the loss of immunity in each infected person, as separate and uncorrelated processes. This is evident from the fact that the corresponding terms ωI and σR in the equations (1) are only linear and do not imply any environmental influence.

This approach, which ignores the possible influence of the environment on the human's organism, is justified if the person is symptomatically ill. In this case the patient is isolated, which neutralizes the effects of the environment.

On the other hand, this is not the case for asymptomatic infected. They do not become isolated and remain under the constant influence of the environment. In such conditions, there should be a significant influence of the environment on the individual immune response. Therefore, it is in the asymptomatic sector of the epidemic that correlations with the biological environment must be important and decisive.

IV. ASYMPTOMATIC RE-INFECTION WITH CORRELATIONS: SYMMETRIC 3D LOTKA-VOLTERRA SYSTEM

To take into account such correlations, in the linear terms ωI and σR of the system of equations (1), the fixed parameters of the system ω and σ should be replaced by some functions of the dynamic variables of the model describing the current state of the entire population. We can take R and S as such variables. Initially, we will choose these functions as follows:

$$\omega \to \omega(R,S) = R, \quad \sigma \to \sigma(R,S) = S. \tag{7}$$

The implication of these assumptions is that the immunized environment (R) stimulates the immune response and leads to accelerated elimination of the virus (with rate $\omega = R$). This can be explained by the fact that the immunized environment releases a small number of viruses in weakened and damaged state, which stimulates a person's immune response, and then is quickly eliminated from his body.

On the other hand, an unimmunized and virus-free environment (S) negatively affects the temporary immunity of the individual and leads to a more rapid loss of this immunity (with rate $\sigma = S$). The reason for this is that in the environment of healthy, unimmunized people, temporary immunity is not supported by the persistent influx of viruses from the environment and therefore is quickly lost.

In other words, the population behaves like a single organism and in each individual case moderates both the activation of the individual immune response and its deactivation.

After replacing (7) in equations (1), they acquire the symmetric form

$$\begin{cases} \frac{dS}{dt} = SR - IS \\ \frac{dI}{dt} = IS - IR \\ \frac{dR}{dt} = IR - SR \end{cases} \tag{8}$$

This is the 3-dimensional Lotka-Volterra system [10]. It has 4 stationary points: 3 saddles $A(1,0,0), B(0,1,0), C(0,0,1)$ and one centre $O(1/3,1/3,1/3)$. Like the original system of equations (1), it ensures the conservation of the norm. Moreover, by virtue of the identity

$$\frac{1}{S}\frac{dS}{dt} + \frac{1}{I}\frac{dI}{dt} + \frac{1}{R}\frac{dR}{dt} = 0 \tag{9}$$

system of equations (8) has one more integral of motion

$$w = SIR = const. \tag{10}$$

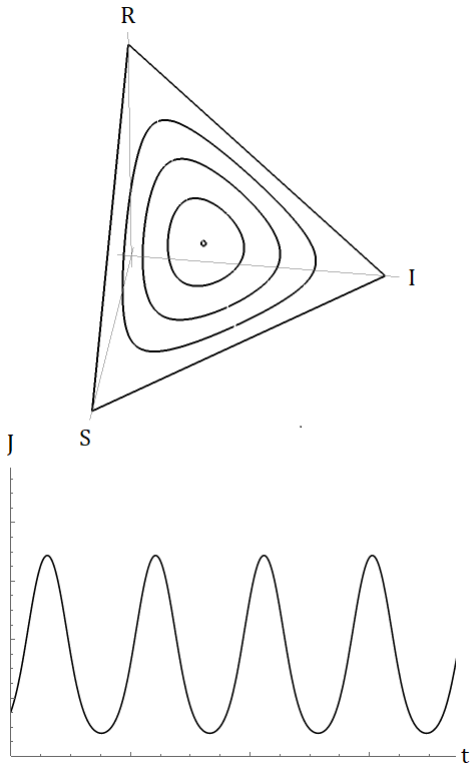

FIG. 2. Phase portrait and epidemic dependence of the symptomatic daily incidence $J(t) = pI(t)S(t)$ in the symmetric 3D Lotka-Volterra system.

Due to this integral, all phase trajectories of the system are sections of hyperboloids (10) by the plane $S+I+R = 1$ and are closed. Therefore, all its solutions are periodic and describe sustained oscillations (Fig. 2).

A linear analysis of system (8) in the vicinity of the stationary point O leads to the community matrix

$$\mathbb{A} = \begin{Vmatrix} 0 & -1 & 1 \\ 1 & 0 & -1 \\ -1 & 1 & 0 \end{Vmatrix} \tag{11}$$

having eigenvalues 0 and $\pm i\sqrt{3}$. This gives the period of small amplitude epidemic waves

$$T = \frac{2\pi}{\sqrt{3}}. \tag{12}$$

Such waves are analogous to those arising in the predator-prey system and described by the classical 2D Lotka-Volterra system [11]. This example shows that taking correlations into account makes epidemic waves in a population persistent.

V. THE GENERAL CASE: ASYMMETRIC 3D LOTKA-VOLTERRA SYSTEM

The 3D symmetric Lotka-Volterra system considered in the previous section is nothing more than a convenient illustration of a way to account for strong biological correlations. It has no free parameters.

Next, we will consider its generalization to a more realistic asymmetric case which, like the original SIRS system, has 3 free parameters. This is an asymmetric 3D Lotka-Volterra system (a member of the so-called ABC family [10]), represented by following equations

$$\begin{cases} \frac{dS}{dt} = bSR - cIS \\ \frac{dI}{dt} = cIS - aIR \\ \frac{dR}{dt} = aIR - bSR \end{cases} \tag{13}$$

with 3 free positive parameters a, b and c. Comparison of equations (13) with equations (1) enables to relate the factors of the asymmetric 3D Lotka-Volterra system with those of the original SIRS system:

$$aR \leftrightarrow \omega, \tag{14}$$

$$bS \leftrightarrow \sigma, \tag{15}$$

$$cI \leftrightarrow I. \tag{16}$$

Considering the constraints $0 \leq R, S \leq 1$, this makes it possible to make clear the meaning of the parameters a, b, c. Constants a and b are the maximum (amplitude) values of the rate of virus elimination and the rate of deactivation of immunity. Such maximums are achieved in the most favourable phases of the epidemic for these two processes - respectively, at $R = 1$ and $S = 1$. The third constant c coincides with the constant speed of the spread of the virus, which is taken as unity in the system of equations (1).

The asymmetric system (13), like the symmetric system (8), keeps unchanged normalization (4). As in the symmetric case, the asymmetric Lotka-Volterra system has an additional first integral which directly generalizes its previous symmetric form (10):

$$w = S^a I^b R^c = const. \tag{17}$$

It coincides with the symmetric expression (10) for $a = b = c = 1$. This generalization changes the symmetry and shape of the phase trajectories shown in Fig. 2 but does not affect the topology of the phase portrait, see Fig. 3.

The centre of the phase trajectories in the asymmetric case moves to a new position

$$\left(\frac{a}{a+b+c}, \frac{b}{a+b+c}, \frac{c}{a+b+c} \right). \tag{18}$$

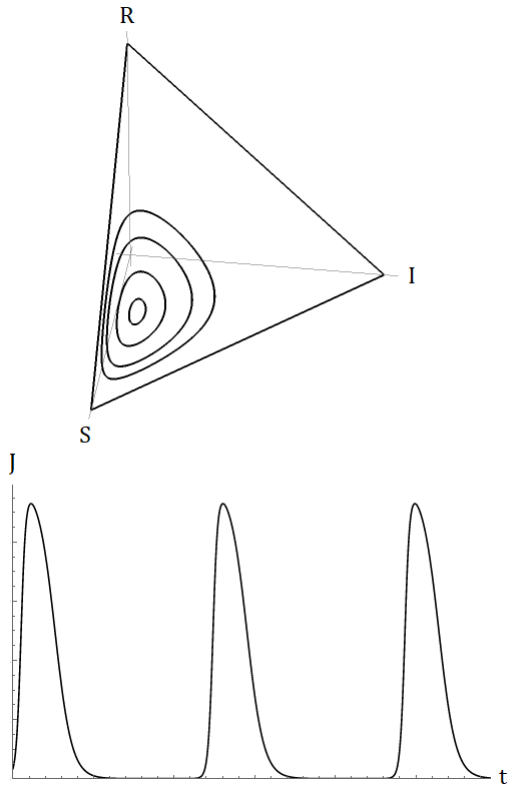

FIG. 3. Phase portrait and epidemic dependence of the symptomatic daily incidence $J(t) = pI(t)S(t)$ in the asymmetric 3D Lotka-Volterra system.

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Oscillations in the vicinity of this equilibrium point is determined by the linearized community matrix, which now has the form

$$\mathbb{A} = \begin{Vmatrix} 0 & -c & b \\ c & 0 & -a \\ -b & a & 0 \end{Vmatrix}. \tag{19}$$

Its eigenvalues, 0 and $\pm i\sqrt{a^2+b^2+c^2}$, give the period of small-amplitude epidemic waves

$$T = \frac{2\pi}{\sqrt{a^2+b^2+c^2}}. \tag{20}$$

It should be noted that with an increase in the amplitude of the epidemic waves, they becomes nonlinear, and their period T increases, tending to infinity as the phase trajectory approaches the boundary of the triangular simplex. In this sense, relation (20) gives only the minimum value of the period when their amplitude is small.

The daily rate of new symptomatic cases at the epidemic plateau according to general use (2) is

$$J = p\frac{ab}{(a+b+c)^2}. \tag{21}$$

This replaces the former daily incidence formula (6), obtained from the initial SIRS system (1) without taking correlations into account.

A distinctive feature of the 3D Lotka-Volterra system, which includes strong correlations, is precisely the sustained epidemic waves in the vicinity of the plateau, which quickly relax in the SIRS system.

If the system is close to the point of endemic equilibrium (18), then the amplitude tends to zero and the same epidemic plateau is observed as at the equilibrium point (5) of the conventional SIRS system. In other words, considering strong correlations affects only dynamics of the epidemic, leaving its statics unchanged. Since correlations do not affect the statics of the epidemic, it is appropriate to apply the correspondence principle and require that the equilibrium point (5) in the SIRS system (1) that ignores correlations coincide with the equilibrium point (18) in the Lotka-Volterra system (13) that takes the correlations into account. Together with the obvious relation (16), this fixes the values of all three free parameters a, b, c:

$$a = \frac{\sigma+\omega}{1-\omega}, \tag{22}$$

$$b = \frac{\sigma}{\omega}, \tag{23}$$

$$c = 1. \tag{24}$$

For such values of the parameters a, b, c, the equilibrium point (18) and the incidence rate at the plateau (21), when correlations are taken into account, coincide with the equilibrium point (5) and the equilibrium incidence rate (6) in the conventional SIRS model. Thus, the static parameters of the SIRS equations (1), which ignore the correlations and correctly describe only statics of the epidemic, uniquely determine all three parameters of the 3D asymmetric Lotka-Volterra equations (13), which take into account correlations and correctly describe both statics and dynamics of the epidemic.

This completes the transition from the conventional SIRS model, which ignores correlations and describes damped epidemic waves shown in Fig.1, to the asymmetric 3D Lotka-Volterra model that explicitly accounts for them and describes sustained epidemic waves shown in Fig.3.

VI. CONCLUSIONS AND OPEN QUESTIONS

The fundamental difference between the initial SIRS equations (1) and the 3D Lotka-Volterra equations (13) is that in the first case, all parameters of the infected organism during an epidemic remain unchanged, while in the second they are modulated by the general state of the population. It is this influence that is a strong correlating factor in the biological system. This factor ensures the synchronization of the epidemic at all 3 stages of individual interaction with the virus (infection, activation of

immunity/elimination of the virus, deactivation of immunity) and, as a consequence, the emergence of persistent epidemic waves.

Since in these 3 processes the cyclical course of the epidemic in the population mimics the cyclical course of the infection in asymptomatically infected people, it can be said that strong biological correlations transform the population into a single organism.

An important prerequisite for this is, apparently, the asymptomatic nature of the course of the infection in the vast majority of infected. These asymptomatic infected have almost no individual motivation to eliminate the virus and act under the systemic dictates of the biological population. In accordance with the estimates of our work [6], this is precisely the situation, which takes place during the current COVID-19 pandemic. And this is the main reason to assume that strong biological correlations are causing the observed persistent epidemic waves.

It should be noted that the very idea of strong biological correlations is relative: we are talking not so much about the strength of correlations, but about the weakness of the individual immune response in case of asymptomatic infection. **The uniqueness of the COVID-19 epidemic is that an infection that is insensible for most humans is nevertheless sensible for the humanity as a whole**. Therefore, the response to it is controlled not at the level of individual immunity, but at the level of the entire biological population. And the importance of the biological correlations is dictated by the very logic of the COVID-19 epidemic process.

Thus, biological correlations may be the very mechanism that stabilizes the waves of the COVID-19 epidemic and explains the lack of their attenuation.

Along with this, several questions remained beyond the scope and require further research.

1. We are not aware of any specific mechanism of the influence of the environment on the immune system of the infected, other than the infection itself. So far, the only source of information about this kind of impact is only the epidemic waves themselves and their characteristics. Therefore, such mechanisms should be identified and become the subject of appropriate research.

2. There is an alternative approach to explaining persistent epidemic waves, based on a fundamental and sharp limitation of the duration of the incubation period and the duration of the action of immunity [12]. This factor acts in the same direction as correlations, and apparently can be considered together with them.

3. The above analysis considers the systemic response of the population to the epidemic but does not consider the mutations of viruses that also form the system. It is known that during the COVID-19 epidemic, mutations of the virus are observed, which make a noticeable contribution to the variations in incidence and apparently, also initiate epidemic waves.

4. Finally, the correlation mechanism of stabilization of epidemic waves is quite general and can be the basis for considering an epidemic of any nature which does not lead to long-term immunity.

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[1] R.M.Anderson and H.M.May, Infectious Diseases of Humans: Dynamics and Control, Oxford University Press (1991).
[2] J.D.Murray, Mathematical Biology, Springer (1993).
[3] N.C.Grassly, C.Fraser and G.P.Garnett, Nature **433**, 417 (2005).
[4] B.Grenfell and O.Bjørnstad, Nature **433**, 366 (2005).
[5] G.Abramson and V.M.Kenkre, Phys.Rev. **E66**, 011912 (2002).
[6] J.Dimaschko, V.Shlyakhover and M.Iabluchanskyi, Why did the COVID-19 epidemic stop in China and does not stop in the rest of the world? (Application of the Two-Component Model), SciMed. J. **3**, 88 (2021).
[7] J.Dimaschko, Superspreading as a regular factor of the COVID-19 pandemic: I. A two-component model, medrxiv.org/content/10.1101/2020.06.29.20138008v5 (2020).
[8] J.Dimaschko, Superspreading as a regular factor of the COVID-19 pandemic: II. Quarantine measures and the second wave, medrxiv.org/content/10.1101/2020.08.14.20174557v2 (2020).
[9] J.Dimaschko and V.Shlyakhover, Superspreading as a Regular Factor of the COVID-19 Pandemic: III. Stopping the Epidemic with and without Vaccination, 10th Webinar COVID-19: Forecast and Prediction, February 19th - 20th, https://www.youtube.com/watch?v=tPyg7NjIxmY (2021).
[10] R.S.Maier, The integration of three-dimensional Lotka–Volterra systems, Proc. R. Soc. A **469**, 20120693 (2013).
[11] V.Volterra, Fluctuations in the Abundance of a Species considered Mathematically, Nature **118**, 558 (1926).
[12] S.Gonçalves, G.Abramson, and M.F.C.Gomes, Oscillations in SIRS model with distributed delays, Eur. Phys. J. **B81**, 363 (2011).