Superspreading in the COVID-19 Epidemic Due to the Autointerference of Viruses

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Superspreading in the COVID-19 Epidemic Due to the Autointerference of Viruses

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It has been shown that autointerference of viruses limiting their replication leads to the emergence of a new stable asymptomatic state of the infected organism. This state gives viruses the ability to superspread and make a main contribution to the epidemic. We assume this to be responsible for the superspreading in the COVID-19 epidemic.

I. INTRODUCTION

The COVID-19 epidemic has a number of features that distinguish it from previous influenza epidemics. One of them is a significant number of *superspreaders* - asymptomatic carriers of viruses. These carriers feel healthy and, unlike the sick, have complete freedom of movement. Therefore, they make a large, if not decisive, contribution to the spread of viruses. Asymptomatic states are typical for many other viruses (for example, herpes), but until now they have never led to the development of epidemics. According to available data, 20% of those infected with the COVID-19 virus are responsible for 80% of cases of infection [1].

Overall, this creates a picture of the COVID-19 epidemic in which some people are spreading the virus while others are sick. Formally, this is manifested in the presence of two components of the epidemic - asymptomatic and symptomatic. On this basis, in our previous works, a two-component model was developed [2-4], describing the course of the COVID-19 epidemic. It is based on the very fact of the existence of an asymptomatic state of the infected, freely spreading the virus. However, in works [2-4] the nature of such a state was not considered in any way.

In this article, we analyse the possible reason for the existence and stability of an equilibrium asymptomatic state with a constant level of infection. This is the state of the *superspreader*. We show that both the very existence and the stability of this state can be due to the autointerference of viruses.

The phenomenon of autointerference of a virus of one species, which is a special case of the interference of several species, is well known [5]. This event causes protection or reduced virus replication in hosts inoculated with large virus doses, which in smaller quantities induce disease and high replication rates. This phenomenon was described first by Pasteur on the rabies virus in rabbits but has also been reported for other virus-host systems such as Influenza B in chick embryos, and yellow fever, dengue, and Rift Valley fever in mice [6].

We assume that autointerference restricts the replication of the COVID-19 virus and thereby protects the infected organism from its pathogenic effects. This allows to stabilize the number of viruses at a level that is safe for the body, but sufficient for their further spread. It is this state of the infected that we believe is responsible for the *superspreading*.

Since in our work we are talking about the possibility of the spread of viruses by asymptomatic carriers, we limit the consideration to only asymptomatic states. In such conditions, the primary nonspecific immunity plays the main role, and the body responds elastically to infection. This means that after the elimination of viruses, specific antibodies are not formed, and the body returns to its original state. This process is fundamentally different from a symptomatic disease or vaccination, when adaptive immunity is activated, specific antibodies are formed, and there is no return to the initial state.

II. EQUILIBRIUM OF NON-INTERACTING VIRUSES

In this section, we consider the dynamics of infection in the simplest case of a small number of non-interacting viruses, investigate the possibility of the existence and stability of an asymptomatic infected state, and draw a conclusion about the possible properties of the body's immune response to the virus.

To investigate the stability of the virus system in the human body, let us consider the change in the number of viruses over time t. It obeys a differential equation of the general form

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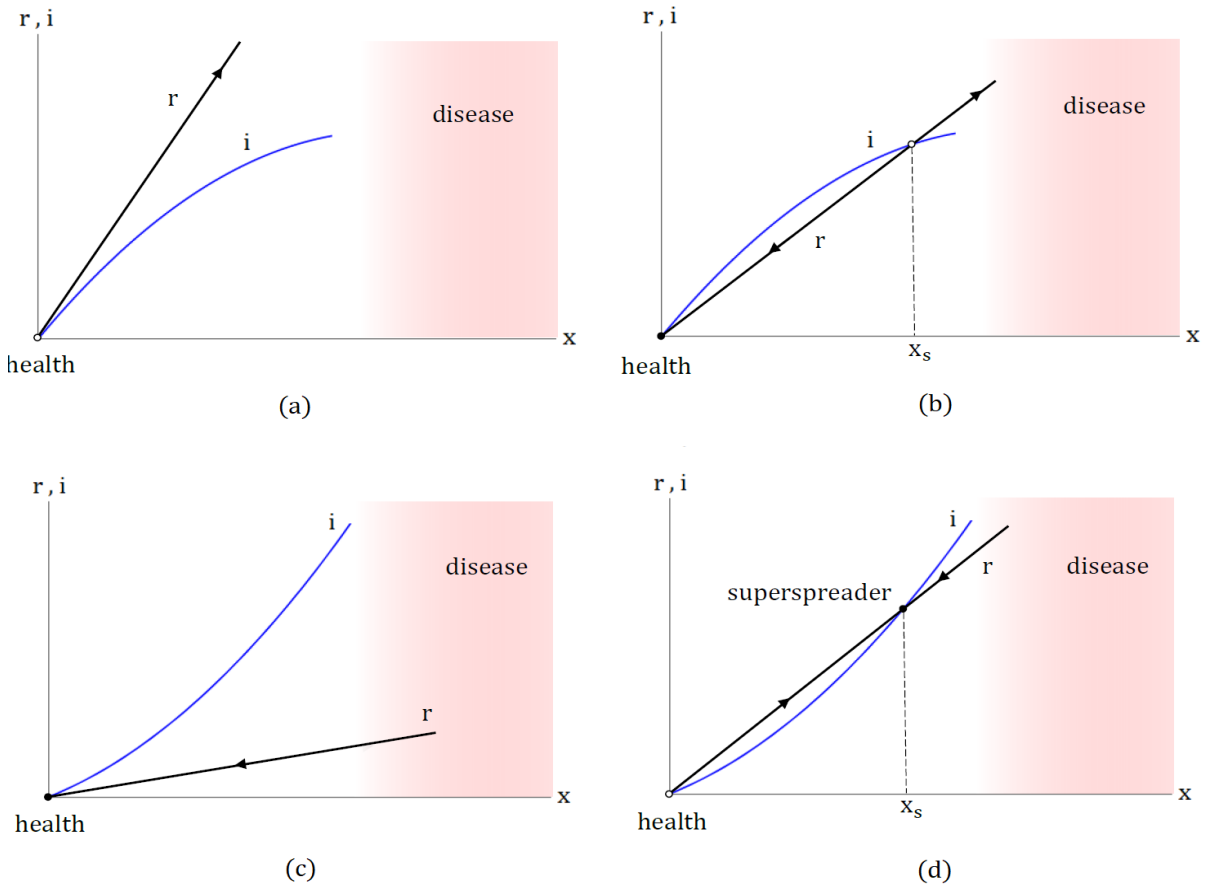

FIG. 1. Equilibrium states of the system of non-interacting viruses described by the differential equation (1). Here x is the number of viruses, $r(x) = kx$ is the replication rate of non-interacting viruses, and $i(x)$ is the rate of their elimination under the influence of nonspecific immunity.

$$\frac{dx}{dt} = r(x) - i(x). \tag{1}$$

Here x is the number of viruses, $r(x)$ is the rate of natural replication of viruses in the cells of the body, $i(x)$ is the rate of their elimination under the influence of immunity. We will consider the evolution of the number of viruses in an asymptomatic state, when this number is small enough not to disrupt the normal functioning of cells.

In the case of non-interacting viruses considered here, when their replication occurs independently, the replication function $r(x)$ is linear: $r(x) = kx$, where $k = \text{const}$ is a constant factor. The function of the immune response $i(x)$ is not known in advance. It depends on the individual characteristics and the general condition of the body. In what follows, we will discuss its possible properties.

We restrict the analysis of variants to two possible forms of the immune function $i(x)$ - *convex* and *concave*. More complex dependences $i(x)$ seem to us unlikely and are not considered. The equilibrium state of the system of viruses is the value x at which the right-hand side of equation (1) vanishes, i.e.,

$$r(x) = i(x). \tag{2}$$

The number of roots of this equation and the stability of the corresponding equilibrium states depend on the curvature of the immunity function i(x), as well as on the linear factor k of the replication function $r(x) = kx$. In this case, 4 possibilities arise, shown in Fig.1.

If the function $i(x)$ is *convex* and the replication factor k is large enough, $k > i'(0)$, then the only equilibrium state $x = 0$ is unstable. This case is shown in Fig. 1(a). This means that nonspecific immunity is not able to stop the replication of viruses, and the body inevitably goes into a state of illness. After that, symptoms appear, and specific immunity comes into play. This process is outside the scope of our analysis, limited only to asymptomatic states.

If the function $i(x)$ is *convex* and the replication factor k is not large enough, $k < i'(0)$, then the equilibrium state $x = 0$ becomes locally stable. This corresponds to a return of the body to its original state, free from viruses, without the appearance of any symptoms. This case is shown in Fig.1(b). Another equilibrium state $x = x_s$,

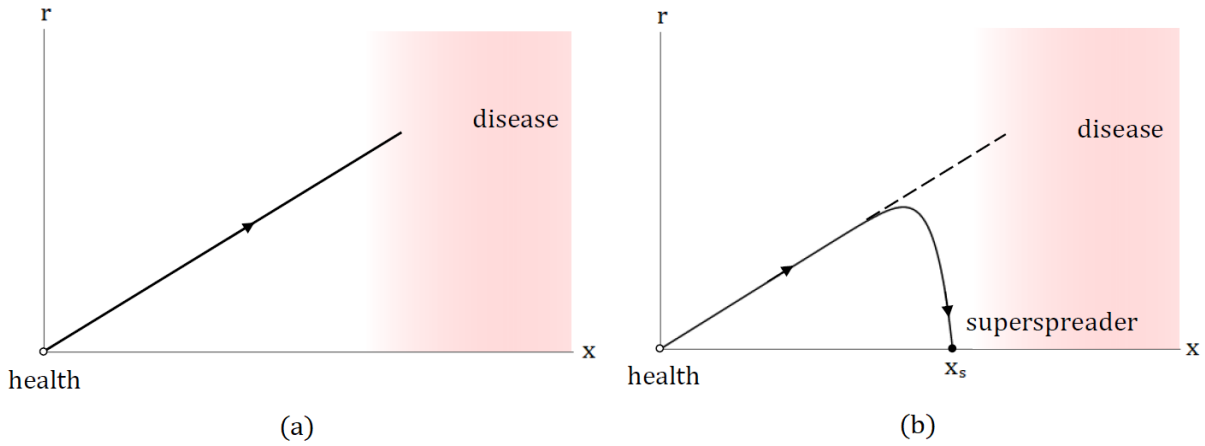

FIG. 2. Replication function $r(x)$ for a system of non-interacting viruses (a) and in the presence of interaction between viruses (b).

corresponding to an asymptomatic carrier of the virus, is unstable. If the value of x exceeds the critical value x_s, then instead of returning to the virus-free state $x = 0$, the number of viruses increases and the transition to the state of illness occurs.

If the function $i(x)$ is *concave* and the replication factor k is not large enough, $k < i'(0)$, then the only equilibrium state $x = 0$ is absolutely stable. This state corresponds to a return of the body to its original state, free from viruses, without the appearance of any symptoms. This case is shown in Fig.1(c).

Finally, if the function $i(x)$ is *concave* and the replication factor k is large enough, $k > i'(0)$, then the virus-free state $x = 0$ becomes unstable. Instead, as shown in Fig.1(d), a new stable state $x = x_s$ appears. In this state, a person is an asymptomatic carrier of the virus, i.e., *superspreader*. Can this combination of factors be realized?

A necessary condition for this is the *concave* function $i(x)$ shown in Fig.1(c,d). With this form of dependence $i(x)$, the organism after infection always remains asymptomatic. It is either the virus-free state $x = 0$ or an asymptomatic carrier state $x = x_s$. However, the absence of a transition to the symptomatic state of the disease is **contrary to experience** - infected people, although not always, get sick. Consequently, the immune function $i(x)$ is **not** *concave*, but *convex*, or has a more complex form.

Hence it follows that of the four considered possibilities, only the first two, presented in Fig.1(a,b), are realized. That is why, in the absence of interaction between viruses, only the virus-free state $x = 0$ can be stable. It occurs either directly, without a transition to the symptomatic phase of the disease (b), or after the transition to the symptomatic phase and switching on the specific immunity (a, b).

Therefore, **without considering the interaction of viruses**, the *superspreder* state $x = x_s$, although it can exist, cannot be stable.

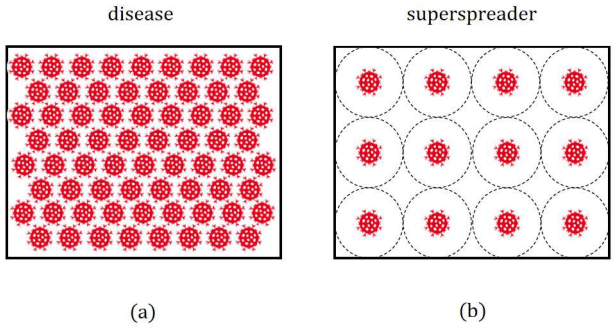

FIG. 3. The result of the replication of non-interacting viruses in the body is symptomatic disease (a). The result of the replication of interacting viruses is an asymptomatic state - *superspreader* (b).

III. REPLICATION OF INTERACTING VIRUSES

Since there is no stable *superspreader* state in the system of non-interacting viruses, it is logical to consider the interaction between viruses from this point of view.

It is known that under certain conditions, the interaction between viruses can slow down or even stop their replication. In such a system, the replication function $r(x)$ becomes nonlinear and can vanish at a certain concentration of viruses $x = x_s$, as shown in Fig. 2.

Essentially, Fig.2 shows the progress of viral replication in the absence of any immune response. It follows from this that the interaction of viruses by itself can stabilize the infected state.

In immunology, this phenomenon is called **viral autointerference**. It is important that, due to autointerference, the replication function $r(x)$ can go to zero even before the onset of symptoms of the disease. This leads to the possibility of the existence of a stable asymp-

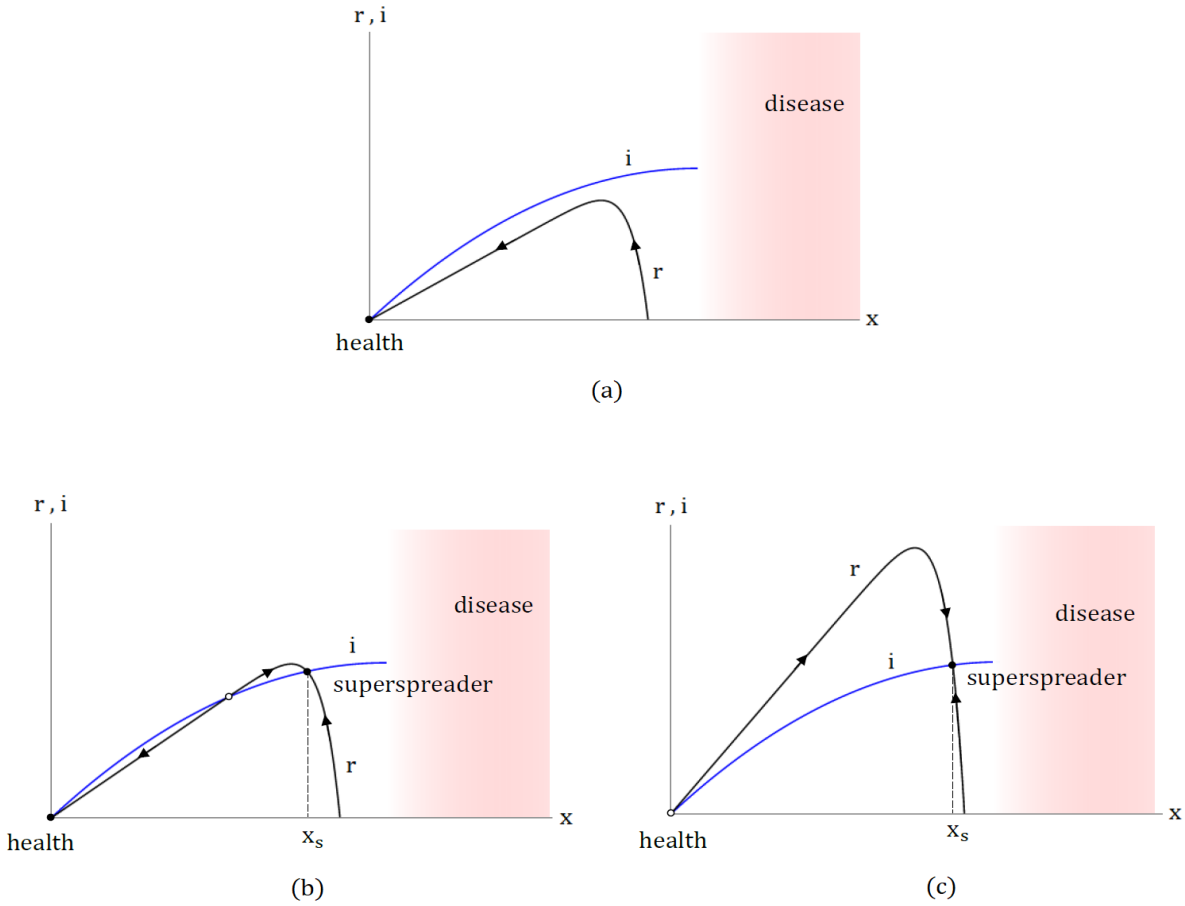

FIG. 4. Equilibrium states of the system of interacting viruses depending on the relationship between the nonlinear function of replication $r(x)$ and the function of immunity $i(x)$.

tomatic state in the infected, i.e., stable state of the *superspreader*. Fig.3 schematically shows the result of replication of non-interacting (a) and interacting (b) viruses.

In the absence of the interaction (case (a)), viruses replicate until they begin to affect the normal functioning of the organism. This is manifested in symptoms indicating the onset of the disease.

If there is interaction (case (b)), the replication occurs until the interaction of the viruses themselves stops the process. In Fig.3(b), for each of the viruses, the interaction area is conditionally shown, which determines the maximum concentration of viruses $x = x_s$. The larger the radius of this area, the lower the equilibrium concentration of viruses x_s.

Thus, the autointerference of viruses can stabilize the asymptomatic state of the carrier of the infection - the *superspreader* state. However, for this to happen, such a state must at least exist. Does it always exist? To answer this question, it is necessary to return to considering the immune response, determined by the immune function $i(x)$.

IV. EQUILIBRIUM OF INTERACTING VIRUSES

In this section, we consider the possible equilibrium states of the system of interacting viruses, taking into account the action of immunity.

The interaction of viruses leads to a non-linear replication function $r(x)$, shown in Fig.2(b). This function has a maximum and vanishes at some value of x. We will assume that this vanishing occurs at sufficiently small values of x, even in the asymptomatic region. Otherwise, the stage of symptomatic disease sets in, and specific immunity enters action. This leads to irreversible generation of antibodies and the original equation (1) becomes inapplicable.

As already shown in the second section, the immune response is described by the *convex* immune function $i(x)$. Taking this into account, the combined action of the autointerference and immunity leads to three possible variants corresponding to three different levels of replication $r(x)$ of interacting viruses. They are shown in Fig. 4.

In the case of sufficiently slow replication, when $r(x) < i(x)$ for any nonzero value of x (Fig.4(a)), the only equi-

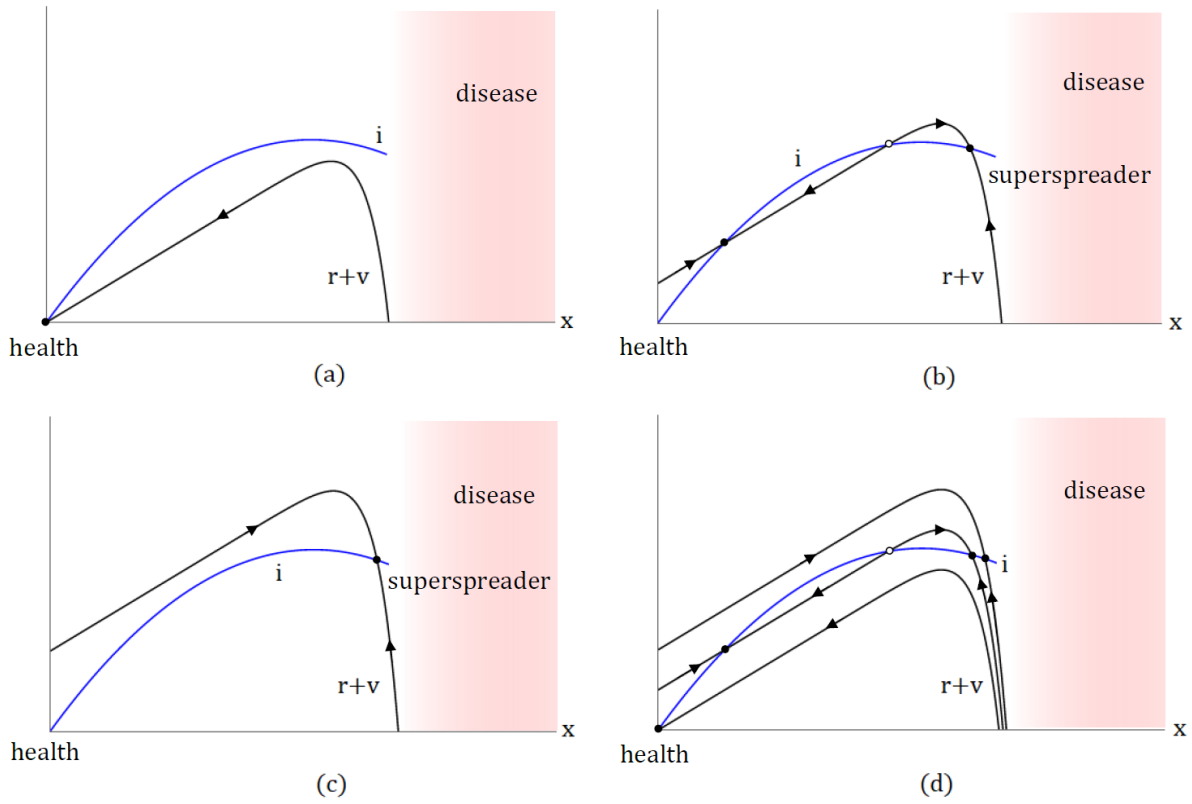

FIG. 5. Evolution of the equilibrium state of a system of interacting viruses with an increase in viral load v.

librium state is $x = 0$. This is the virus-free state.

With an increase in the size of the value of the replication function $r(x)$, along with this equilibrium state, two more appear, shown in Fig.4(b). The first one is unstable and the second one is stable. It is this that corresponds to the stable asymptomatic *superspreader* state. Thus, in this case, two states are locally stable: the virus-free state $x = 0$ and the *superspreader* state $x = x_s$.

A further increase in the values of the replication function $r(x)$ leads to the fact that the virus-free state $x = 0$ loses its stability, and the only stable state is the state of the superspreader $x = x_s$. This case is shown in Fig.4(c).

In none of the options is there a transition to the symptomatic state of the disease.

Thus, the autointerference of viruses should lead to two effects:

1) protection of the body from the transition to the state of symptomatic disease;

2) appearance of a stable asymptomatic state of the *superspreader*.

As can be seen from Fig.4, the first effect (the protection) manifests itself regardless of the level of replication $r(x)$, while the second (the appearance of the *superspreads*) requires a sufficiently high level of replication. The *superspreader* state is always stable if it exists.

V. EFFECT OF VIRAL LOAD

During an epidemic, both the body as a whole and its individual cells are under the influence of an external viral load. If the influx of viruses per unit of time is equal to v, then this value becomes an additional term on the right side of the original equation (1) for the dynamics of the number of viruses:

$$\frac{dx}{dt} = r(x) - i(x) + v. \tag{3}$$

In the presence of the viral load, the equilibrium state of the system of interacting viruses corresponds to the vanishing of the right side of this equation:

$$r(x) + v = i(x). \tag{4}$$

This can lead to the emergence of an equilibrium state of the *superspreader*, even if it was not in the absence of viral load, at $v = 0$. This evolution of the equilibrium state of a system of interacting viruses with an increase in the viral load v is shown in Fig. 5.

Suppose that in the initial position (a), which corresponds to the absence of an influx of viruses, $v = 0$, the only equilibrium state is the virus-free state $x = 0$. Then, with the appearance and growth of the viral load $v > 0$, a

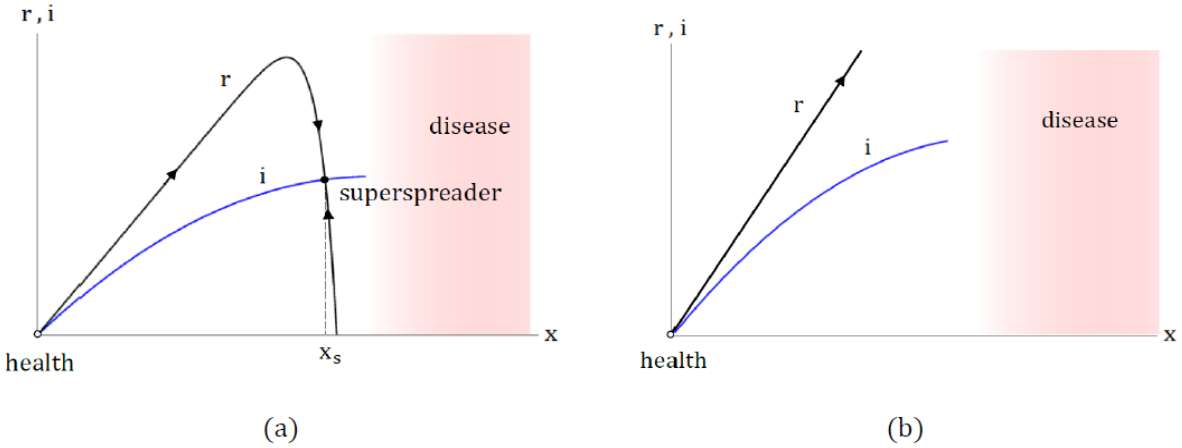

FIG. 6. Two options for the development of infection: with the participation (a) and without the participation (b) of the autointerference.

new equilibrium state of the *superspreader* (b) appears in the system, which, with a further increase in v becomes the only equilibrium state (c). The whole process in the same coordinate system is shown in Fig.5(d).

In an epidemic, the influence of the viral load should lead to a domino effect: if some of the members of the population become the *superspreaders*, then this leads to an increase in the viral load on the rest, which makes some of them also *superspreaders*, etc.

VI. DISCUSSION

Thus, taking into account the autointerference of viruses at a sufficiently high level of their replication inevitably leads to the appearance of the *superspreaders*. They are protected from the pathogenic effect of the virus by the autointerference factor of viruses, which limits their concentration in the body by the limiting value $x = x_s$. At the same time, this value is sufficient for the further spread of viruses.

This finding is consistent with the overall picture of the COVID-19 epidemic, but leaves two questions open:

1) **Under what conditions and how does an infection lead to a transition to a state of symptomatic disease?** Consideration based on equation (1) cannot answer this question, since this equation describes only asymptomatic states.

2) **How long can an infected person remain in a super-spreader state and what happens to him after that?** Based on the analysis carried out on the basis of equation (1), the state of the *superspreader* is always stable and therefore the infected person can stay in it indefinitely. This contradicts the experience of monitoring the condition of asymptomatic infected, which shows that the infection eventually clears up. Apparently, Eq.(1) with given functions of replication $r(x)$ and immune response $i(x)$ by itself is still insufficient for a correct answer to this question.

In view of the fundamental importance of these two issues, they deserve a separate discussion.

1) **Under what conditions and how does an infection still lead to a transition to a state of symptomatic disease?**

Since the autointerference of viruses makes the asymptomatic state of the *superspreader* the only possible equilibrium state of viruses in the body, it should be understood why in some cases this does not work.

As can be seen from Fig.6(a), the equilibrium concentration x_s is limited by the point of intersection of the graph of the function $r = r(x)$ with the x-axis. And if this point is in the asymptomatic area, then the corresponding state of the *superspreader* is obviously asymptomatic. The influence of the immunity function $i(x)$ can shift this point only in the asymptomatic direction of lower values of x, but cannot transfer it to the symptomatic area of larger values of x.

At the same time, in a certain part of cases, the transition to the symptomatic area always occurs. The reason for this may be that it is in this part of the cases that the autointerference mechanism does not turn on, and the unhindered multiplication of viruses occurs, as shown in Fig.6(b). In this case, a symptomatic disease occurs, leading to the activation of the adaptive immunity and the formation of specific antibodies.

In our previously constructed two-component model [2-4] of the COVID-19 epidemic, infection leads to a transition to a symptomatic state only with a certain fixed probability $p \in [0, 1]$. Comparison with the pandemic data shows that this value is a small parameter, and its value does not exceed 10^{-3}. In accordance with the previously said, this may mean that, with a probability of p, the autointerference of viruses is not turned on and their replication occurs independently of each other. This results in a linear function $r(x)$ and a transition to the stage of symptomatic disease, as shown in Fig.6(b).

We do not know why the autointerference of viruses in these cases may not be activated. Apparently, this issue

should become the object of virological research.

2) **How long can infected persons remain in the superspreader state and what happens to them after that?**

Since the state of the *superspreader* is a stable solution to equation (1), the infected person can stay in it indefinitely, which contradicts the experience of monitoring the state of asymptomatic infected. The reason for the exit of an infected person from the *superspreader* state can only be a change in the type of immune function $i(x)$. There are two possible reasons for this change.

a) In the course of a decrease in the level of the epidemic, the viral load v decreases and, in accordance with equation (3) and Fig.5, the equilibrium state of the superspreader $x = x_s$ disappears. After that, the only stable state is the virus-free state $x = 0$. It is into this state that the *superspreader* state goes.

b) The very immune function $i(x)$ in response to the presence of the virus in the body gradually increases. This also leads to the disappearance of the equilibrium state of the *superspreader*, as shown in Fig.4(a), and to the transition to the only stable virus-free state $x = 0$.

Therefore, in both scenarios, the result of the disappearance of the *superspreader* state is a transition to the virus-free state $x = 0$.

We provide an explanation of the super-spreading phenomenon based on the putative autointerference of COVID-19 viruses. However, **is it necessary to involve the autointerference of viruses in explaining this phenomenon?** As already mentioned in section 2 and shown in Fig.1(d), the state of the *superspreader* exists and can be stable for some special (*concave*) form of the immune function $i(x)$. However, in this case, it remains unclear why the *superspreader* state is atypical for other infections against which the same immune function $i(x)$ acts. This indirectly indicates that the existence of the *superspreaders* is not due to the specificity of the immune function $i(x)$, but to the virus-dependent replication function $r(x)$. Since the properties of this function are regulated precisely by the autointerference of viruses, this justifies the involvement of autointerference in explaining the phenomenon of the *superspreading*.

Note, further, that all conclusions based on equation (1) rely on the independence of the replication function $r(x)$, related to the properties of the virus, and the immune function $i(x)$, related to the immune state of the organism. In cases close to the average norm, this is apparently justified, but with strong deviations from it towards a decrease in immunity, such a separation may already be impossible. Then, instead of separate functions $r(x)$ and $i(x)$, one should immediately consider a single function $f(x) = r(x) - i(x)$. However, the contribution of such states to the epidemic is relatively small, and therefore they remained beyond the scope of this work.

CONCLUSIONS

Thus, we have shown that the autointerference of viruses can be precisely the factor that ensures the existence and stability of the *superspreader* state.

At the same time, the very existence of autointerference in coronaviruses is not an established fact of virology. It seems important and timely to investigate this factor and its influence on the course of COVID-19 infection.

In this sense, a comparative analysis of the autointerference of various strains, and first the Chinese strain of coronavirus, would be productive. The reason for this interest is that it is in China that the epidemic incidence of COVID-19 is abnormally low. This indirectly indicates a high degree of stability of the autointerference factor in the Chinese strain. It is the stable protective effect of the autointerference of the viruses of the Chinese strain that could explain the negligible symptomatic incidence of COVID-19 in China.

Studies of this kind could justify the zero pathogenicity of the Chinese strain and the possibility of its widespread use as a universal vaccine. We have already pointed out this possibility in [2,4].

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Figures

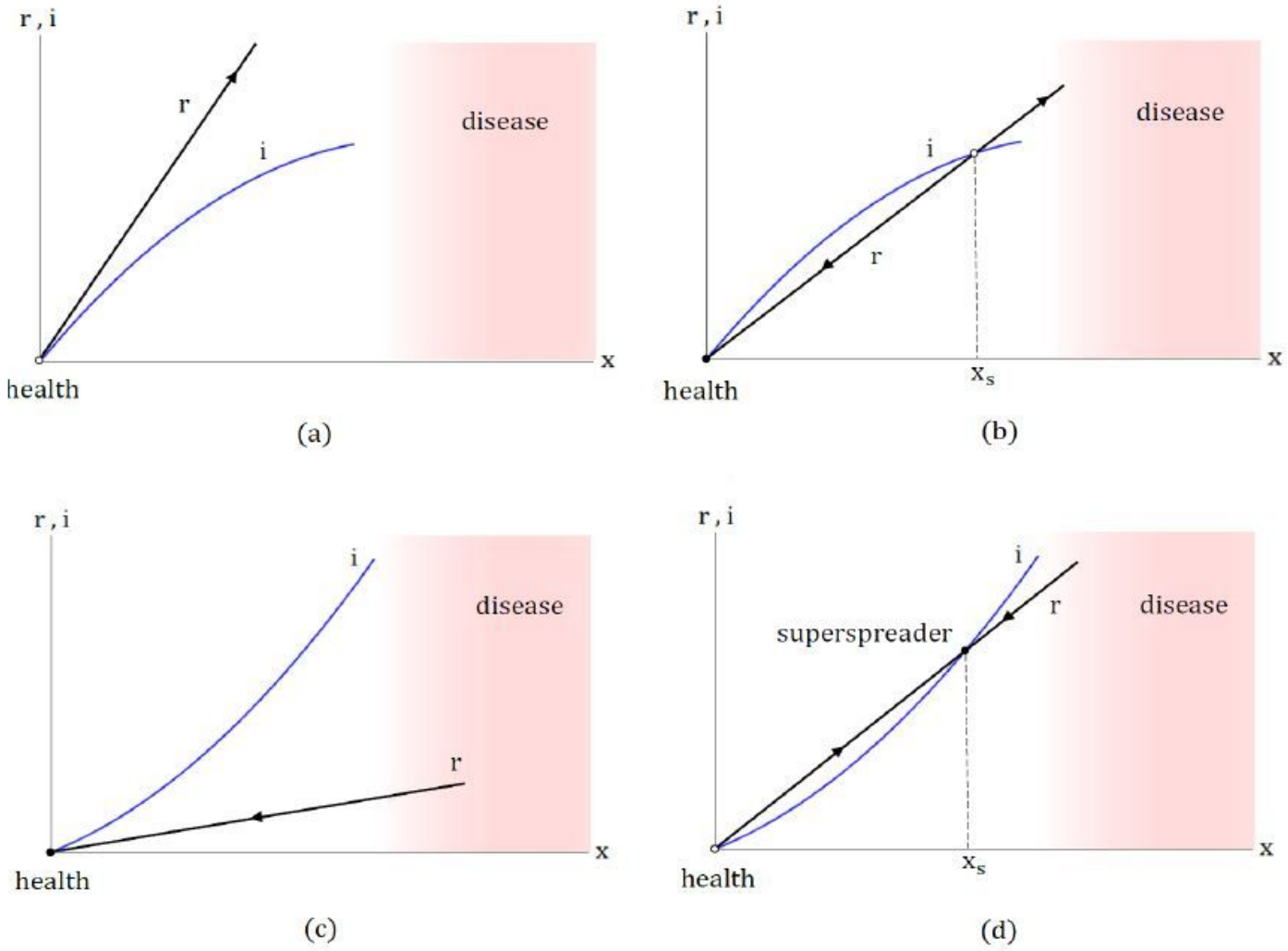

Figure 1

Equilibrium states of the system of non-interacting viruses described by the differential equation (1). Here x is the number of viruses, r(x) = kx is the replication rate of non-interacting viruses, and i(x) is the rate of their elimination under the influence of nonspecific immunity.

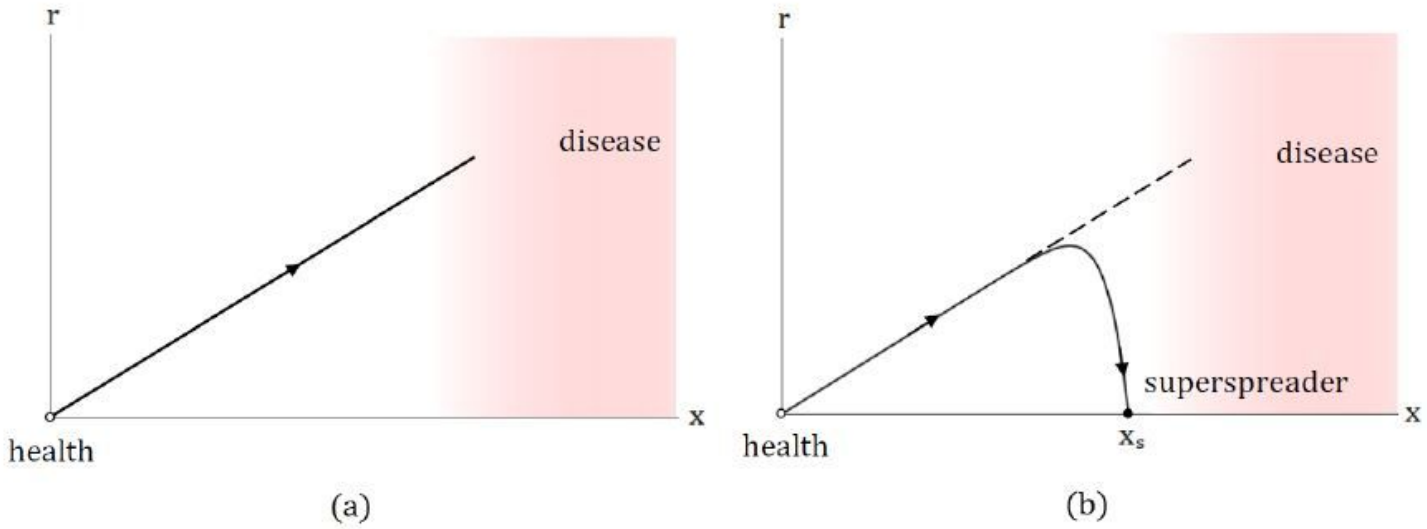

Figure 2

Replication function r(x) for a system of non-interacting viruses (a) and in the presence of interaction between viruses (b).

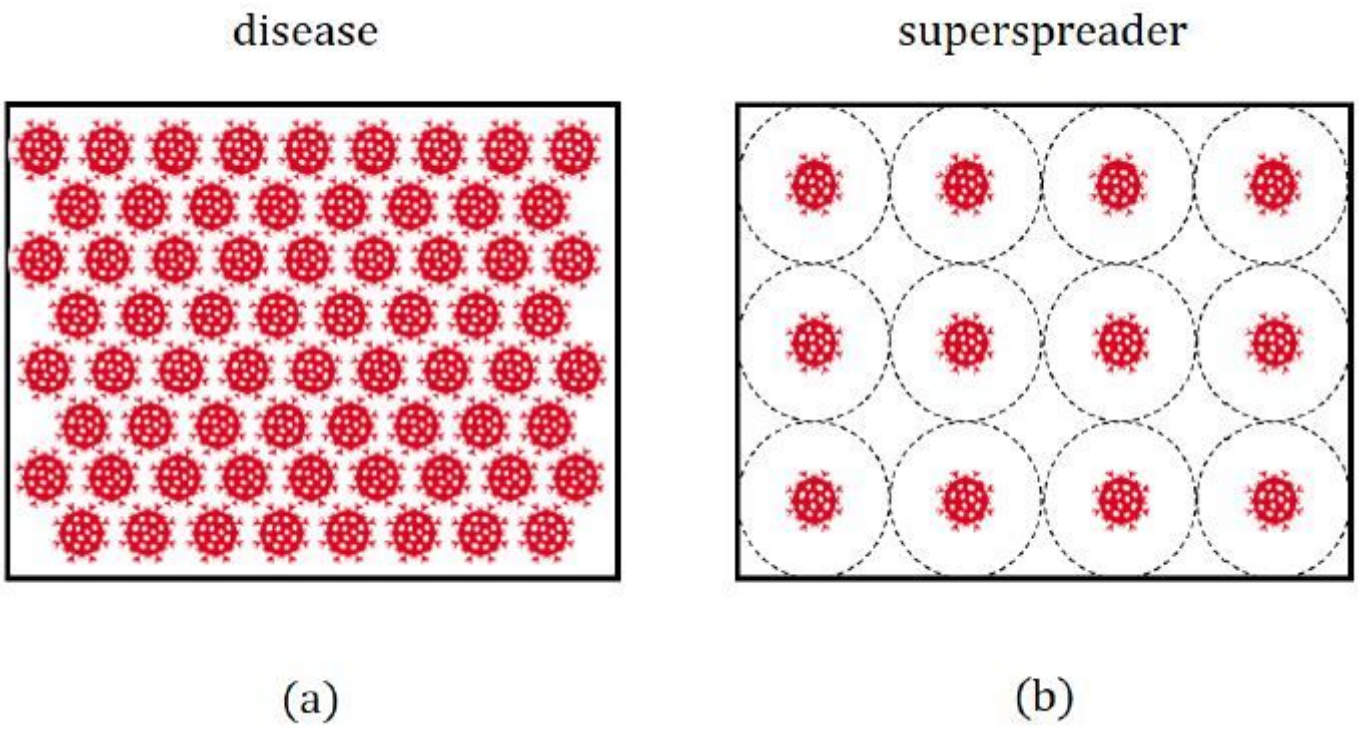

Figure 3

The result of the replication of non-interacting viruses in the body is symptomatic disease (a). The result of the replication of interacting viruses is an asymptomatic state - superspreader (b).

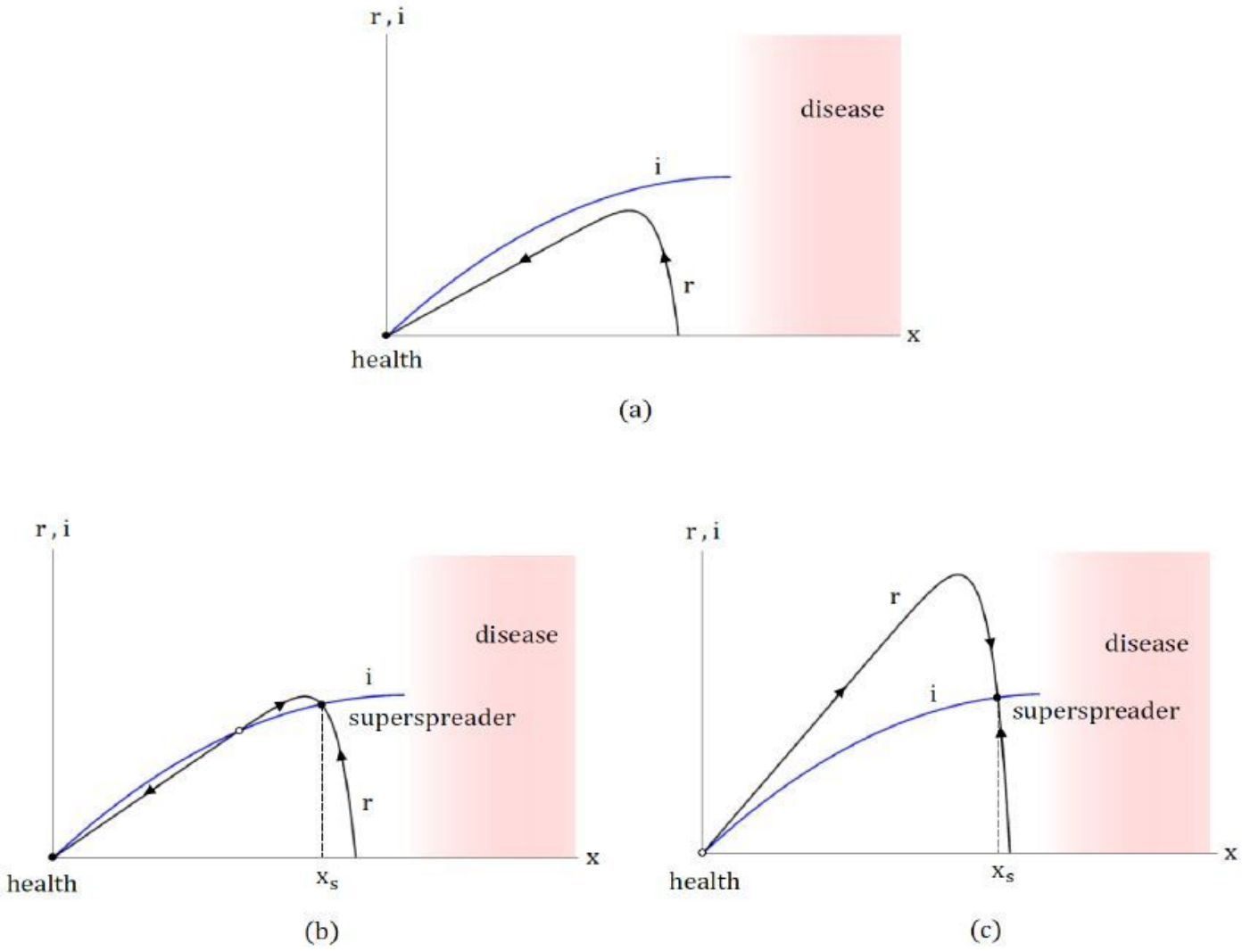

Figure 4

Equilibrium states of the system of interacting viruses depending on the relationship between the nonlinear function of replication r(x) and the function of immunity i(x).

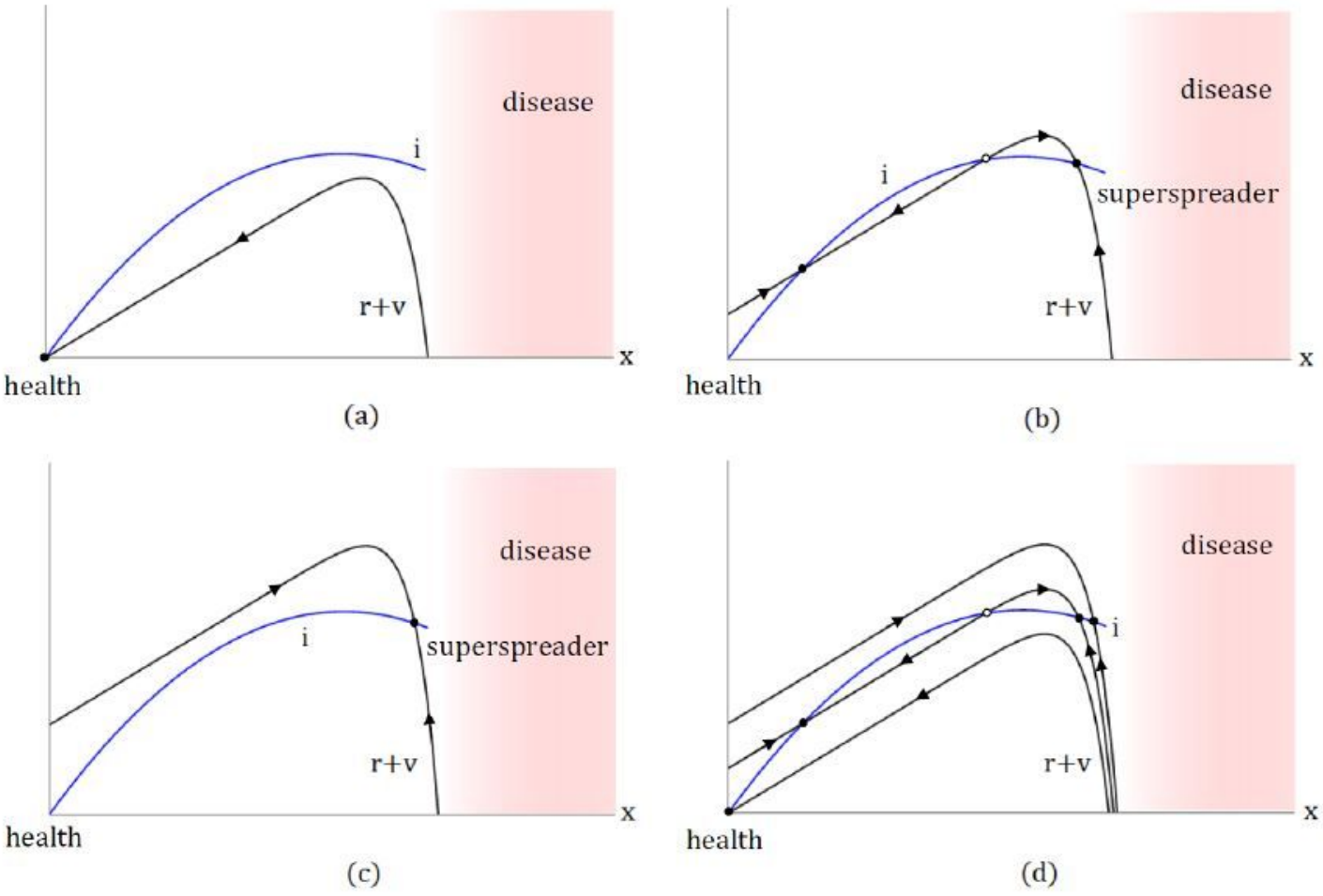

Figure 5

Evolution of the equilibrium state of a system of interacting viruses with an increase in viral load v.

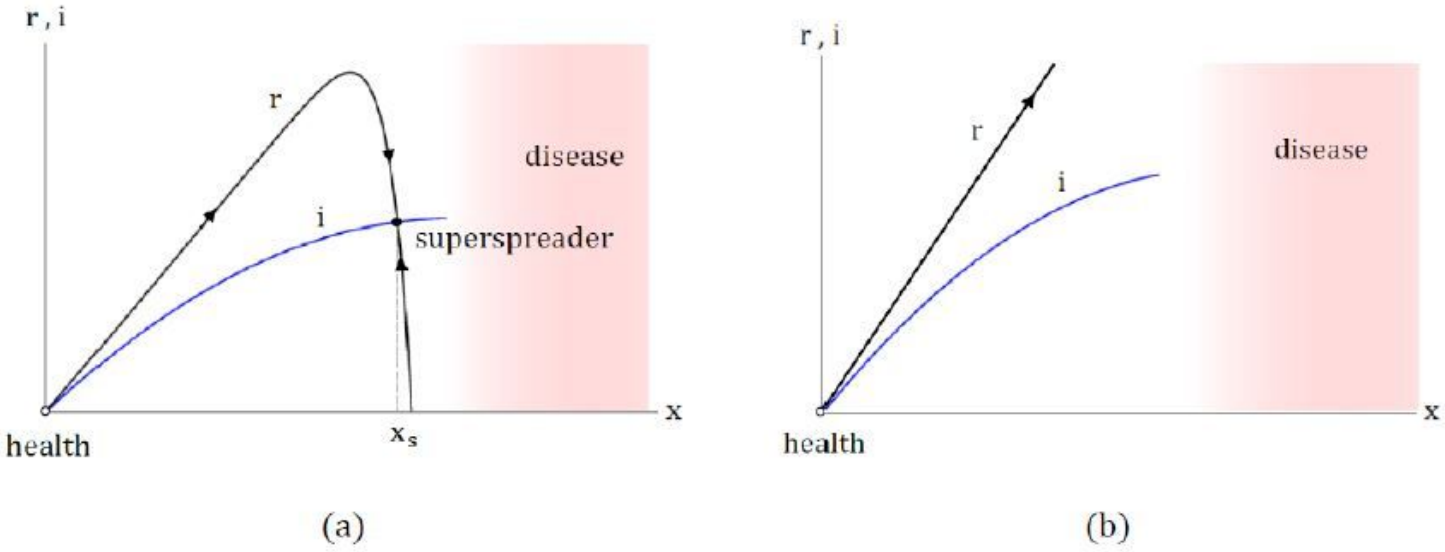

Figure 6

Two options for the development of infection: with the participation (a) and without the participation (b) of the autointerference.