Dynamic analysis of a parasite population model

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We study the dynamics of a model that describes the competitive interaction between an invading species (a parasite) and its antibodies in an living being. This model was recently used to examine the dynamical competition between Tripanosoma cruzi and its antibodies during the acute phase of Chagas' disease. Depending on the antibody properties, the model yields three types of outcomes, corresponding, respectively, to healing, chronic disease, and host death. Here, we study the dynamics of the parasite-antibody interaction with the help of simulations, obtaining phase trajectories and phase diagrams for the system. We show that, under certain conditions, the size of the parasite inoculation can be crucial for the infection outcome and that a retardation in the stimulated production of an antibody species may result in the parasite gaining a definitive advantage. We also find a criterion for the relative sizes of the parameters that are required if parasite-generated decoys are indeed to help the invasion. Decoys may also induce a qualitatively different outcome: a limit cycle for the antibody-parasite population phase trajectories.

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I. INTRODUCTION

In a recent review, Perelson and Weisbuch described how scientists trained in physics and mathematics can actively contribute to the field of theoretical immunology [1]. Immunologists have had great success in understanding many of the molecules and cells of the immune system, but they fail to answer questions about the behavior of large collections of cells and molecules. They remark that dynamics is an area well appreciated by physicists but one in which little work is being done in immunology. Because of difficulties in collecting data from one animal at many time points, dynamic experiments are rarely done. It is therefore difficult to understand why the immune system operates sometimes in a steady state, or oscillates, or is chaotic. One goal of modeling in immunology is to deduce microscopic properties of the system from the properties of their elementary components and of their interactions, as it is done in statistical mechanics. Indeed, the contribution to the analysis of the interaction between the immune system and pathogen agents has recently found a place in the physics literature [1–5].

In this context we have developed a model for the competitive interaction between an invading species and its antibodies, which is directly applicable to Chagas' disease [6]. This is a widespread endemic disease in many Latin-American countries, with a total exposed population estimated at 60 million. It is caused by the parasite *Trypanosoma cruzi* and transmitted by a bloodsucking bug of the subfamily Triatominae by blood transfusion. Survivors of the acute phase of the disease have a positive serology for *T. cruzi;* the disease enters into a latent phase in which there are no clinical signs related to the infection. Parasite invasion is associated with strong antibody and cellular responses and severe heart disorders [7]. Parasite-specific antibodies have been shown to control the infection in experimental models [8–10]. Attempts to improve the condition of affected populations have motivated efforts to determine the molecular mechanisms involved in the parasite-host interaction, and searches for trypanocidal drugs and cardiac restoration procedures.

The model developed in Ref. [5] facilitates the identification and quantitative assessment of the relevant parameters involved in the parasitic infection and the generation of the immune response. Although at first sight it has some features in common with the Lotka-Volterra predator-prey model [11] and with epidemic models [12], it is actually much closer to the models for the immune reaction to viral infections [13]. While in a predator-prey model, the immediate result of the prey destruction is a strengthening of the predator population, in the parasite invasion model the interaction between parasites and antibodies results in the simultaneous removal of both species. As we shall see, the corresponding change of sign in a coupling term prevents the existence of closed plane phase trajectories and leads to very different outcomes.

The model provides a good description of experimental data for the Chagas disease [14]. In addition, we will see that it can describe some important properties of parasite-antibody systems, such as the presence of time delays in antibody activation and the action of parasite-generated decoys, which may modify the efficiency of the immune system.

The effect of time delays on population models has been carefully studied [11]. In immunology, delays have been shown to have drastic effects. For instance, Buric and coworkers have described how a delay in the immune response can introduce chaotic behavior into the Mayer model [15]. We will show that, although in most cases time delays have no effect after a short transient, the outcome of the parasite invasion can be sometimes switched from host death to survival by a suitable shortening of the delay.

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T. cruzi may shed segments that act as decoys for the antibodies [16,17]. Decoys can affect the efficiency of the immune system and may change the infection outcome. We will investigate the conditions that must be satisfied by the model parameters if the decoys are indeed to favor the parasite invasion; this will be revealed by shifts of the boundaries between the parameter regions corresponding to host death, host healing, and chronic disease.

The main purpose of this paper is to present an analysis of the dynamic properties of the model. We will examine in detail the properties of the time-dependent solutions, including the effect of delays and of the introduction of decoys.

The rest of this paper is organized as follows: In Sec. II we review the model, whose steady-state solutions are discussed in Sec. III, where we also present phase diagrams describing the infection outcome for the single antibody problem in terms of the parasite- and antibody-generation rates. The dynamic properties, including the effects of time delays on antibody activation, are analyzed in Sec. IV, whereas the influence of decoys is examined in Sec. V. The paper ends with a short discussion of possible model generalizations.

II. THE MODEL

To model the parasitemia evolution we adopt as a paradigm Chagas' disease. In this disease, parasite introduction usually stimulates population increases in several antibody species [14]. If we consider that N antibody species interact with the parasite population $n(t)$, the evolution of $n(t)$ is described by

$$\dot{n}(t)=\kappa n(t)-n(t)\sum_{i=1}^{N}\alpha_i a_i(t), \tag{1}$$

where the first term represents the asexual reproduction of the parasites and the second term represents their interactions with the antibodies. The coefficient κ controls the parasite reproduction rate, a_i is the population of the ith antibody species, and α_i defines the likelihood of antibody-parasite removal upon an encounter.

Assuming that the direct interaction between antibody species is negligible, the equation for the evolution of the population of the ith antibody species can be written as follows:

$$\dot{a}_i(t)=\gamma_i n(t)-\alpha_i a_i(t)n(t)-(1/\tau)[a_i(t)-a_{i0}], \tag{2}$$

where the coefficient γ_i controls the induced antibody creation. The initial condition $a_i(0)=a_{i0}$ corresponds to each species having its equilibrium population in the absence of infection and τ represents the intrinsic antibody lifetime.

III. STEADY-STATE PROPERTIES

By setting the time derivatives in Eqs. (1) and (2) equal to zero and adding the N algebraic equations resulting from Eqs. (2), we obtain a set of equations defining the steady-state populations,

$$n_s\left(\kappa-\sum_{i=1}^{N}\alpha_i a_{is}\right)=0 \tag{3}$$

and

$$n_s\sum_{i=1}^{N}\gamma_i-\kappa n_s-\sum_{i=1}^{N}\left(\frac{a_{is}-a_{i0}}{\tau_i}\right)=0, \tag{4}$$

where the subscript s labels the steady state. Hence the two possibilities for the steady-state parasite population are $n_s=0$ and

$$n_s=\left(\sum_{i=1}^{N}\gamma_i-\kappa\right)^{-1}\sum_{i=1}^{N}\left(\frac{a_{is}-a_{i0}}{\tau_i}\right). \tag{5}$$

If the initial antibody population is very low, we may take $a_{i0}=0$. In such a case the condition for a finite final parasite population is

$$\sum_{i=1}^{N}\gamma_i>\kappa. \tag{6}$$

The analysis of the solutions is greatly facilitated if we first consider the outcomes for a single antibody species [6]. If we analyze the asymptotic ($t\to\infty$) regime, we then find three different cases.

(I) Chronic disease: If $\gamma>\kappa>\alpha a_0$ (or $a_0<a_s$), i.e., for strong induced antibody formation and low removal efficiency, the system reaches a long-time steady state described by

$$n_s=\frac{\kappa-\alpha a_0}{\alpha\tau(\gamma-\kappa)},\quad a_s=\frac{\kappa}{\alpha}. \tag{7}$$

The stability of the steady-state solutions was proved using the Routh-Hurwitz criterion [11].

(II) Healing: If $\gamma>\kappa$ and $\alpha a_0>\kappa$, corresponding to strong induced antibody formation and high removal efficiency, the antibody number goes back asymptotically to its initial value a_0, while the parasite number goes to zero, i.e., the system returns to the initial conditions.

(III) Host death: If $\gamma<\kappa$, i.e., for weak induced antibody formation, the antibodies, regardless of their efficiency, are not created fast enough so as to control the infection.

A special case deserves separate consideration. If $\alpha a_0>\kappa$ and the initial inoculation is small, $n_0<n_s$, a highly efficient, even if slowly reproducing, antibody population can dispose off the invaders, leading to a return to the initial conditions, i.e., to healing. This is remarkable, because it indicates that the infection outcome may depend on the inoculation size. The existence of this subcase, which we label IIIb, can be explained by the following lemma.

Lemma. If $\gamma<\kappa<\alpha a_0$, the inequality $n_0>n_s$ is a necessary condition for host death.

Proof. For simplicity, we take α to be a constant. Under the specified conditions, the parasite population must initially decrease. However, host death implies that it must grow at long times, so that it has to go through a minimum

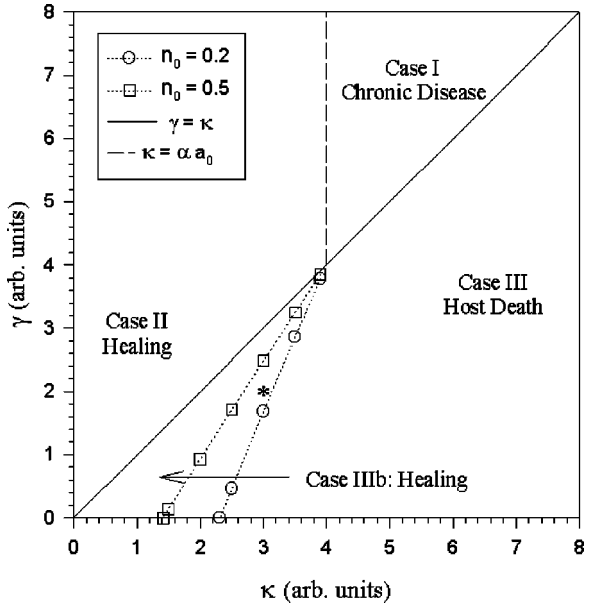

FIG. 1. Phase diagram describing the outcome of the parasite infection in terms of the parasite (κ) and antibody (γ) generation rates. The location of the boundary between cases III and IIIb depends on the size n_0 of the original infective population. The asterisk corresponds to the point in the phase diagram analyzed in Fig. 3. Here, we chose $a_0=\tau=0.1$ and $\alpha=40$.

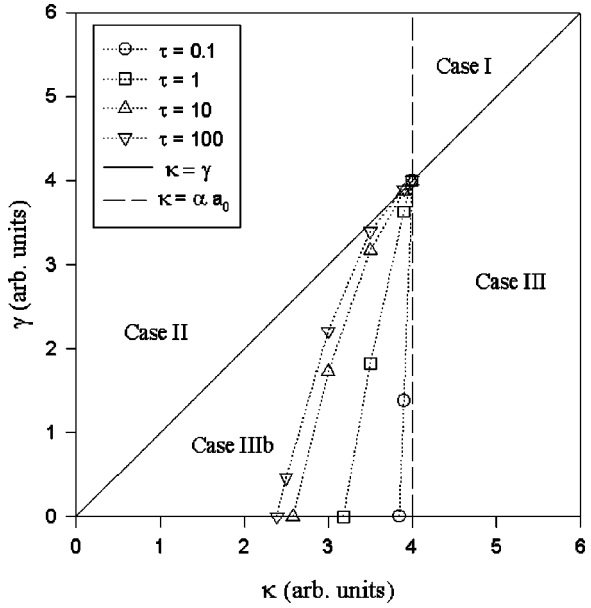

FIG. 2. Dependence of the location of the boundary between regions III and IIIb on the intrinsic antibody lifetime τ for the values detailed in the figure. The shape of this boundary obeys Eq. (9).

$n(t_{\min})$ at some intermediate time $t_{\min}$. The extremum condition $\dot{n}(t_{\min})=0$ implies that $a(t_{\min})=\kappa/\alpha$. The extremum is a minimum if

$$0<\left.\frac{\partial^2 n}{\partial t^2}\right|_{t_{\min}} = \kappa\dot{n}-\alpha n(t_{\min})\dot{a}-\alpha a(t_{\min})\dot{n}$$

$$=-\alpha n(t_{\min})\dot{a}(t_{\min}), \tag{8}$$

i.e., if $\dot{a}(t_{\min})<0$. By using Eq. (2), we see that this condition is equivalent to demanding $n(t_{\min})>n_s$. Hence, if $n_0 \gtrless n_s$, the parasite population will decrease and eventually disappear, resulting in host healing.

In the special case $a_0=0$, a steady state with a finite n_s occurs when $\gamma>\kappa$. Otherwise the infection cannot be controlled, whatever the antibodies' avidity α.

From the preceding discussion we see that the outcome of the parasitic invasion does not depend on the size of the invading population, except for the emergence of case IIIb. We can therefore construct a phase diagram in the plane defined by the growth rates γ and κ. This is done in Fig. 1, where the boundary between the domains corresponding to cases III and IIIb was found numerically for two different initial parasite populations.

An analysis similar to the one used to prove the lemma shows that the boundary between the regions corresponding to cases III and IIIb is described by the equation

$$\gamma=\left[1+\frac{1}{\alpha\tau n(t_{\min})}\right]\kappa-\frac{a_0}{\tau n(t_{\min})}. \tag{9}$$

Of course, this equation does not imply a linear relation between γ and κ because $n(t_{\min})$ is a function of κ. This is seen in Fig. 2, where we plot the boundary for several values of the antibody intrinsic lifetime τ. According to these results, for an invading force of fixed size, a shortening of the antibody lifetime favors healing. This apparently surprising behavior can be explained as follows: For short-lifetime antibodies, the immune system of a parasite-free host generates antibodies at a high rate to maintain a constant population. Therefore, the antibody creation induced by the parasite invasion represents a minor deviation from the steady state. In the opposite case, i.e. for large values of τ, the antibody production reacts slowly to a decrease in a, and the parasite population can grow without control. In particular, for ''immortal'' antibodies, i.e., for those that can be removed only by interaction with parasites, the boundary between regions III and IIIb coincides with the $\gamma=\kappa$ line: in this case the only relevant criterion for infection control is whether $\gamma>\kappa$ or not.

The properties of the parasite population corresponding to a particular point in the phase diagram are shown in Fig. 3. If the initial parasite population is smaller than n_s, the humoral system controls the infection and the parasite population decreases monotonically. If $n_0>n_s$, the parasite population initially decreases, reaching a minimum at a time $t_{\min}$, which is a sharply decreasing function of n_0 [see Fig. 3(a)]. From Fig. 3(b), we see that the difference between the initial population and that at the minimum $n(t_{\min})$ is substantial only if n_0 is close to n_s.

IV. DYNAMICS

A. General properties

The dynamic properties of predator-prey models are well known [11,18]. In Volterra's model, for example, the con-

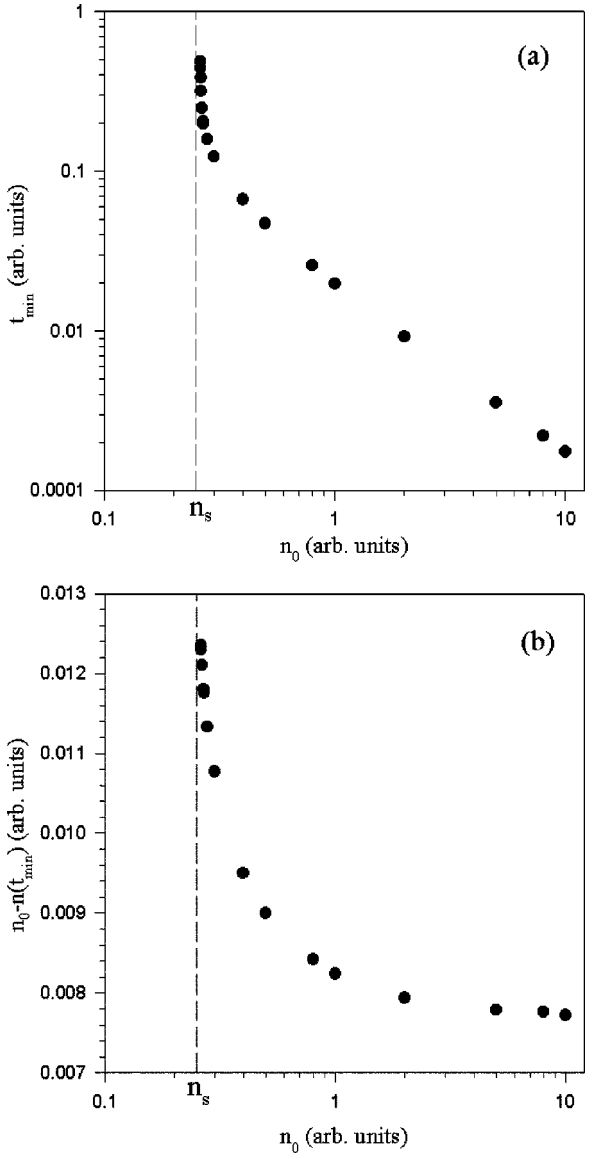

FIG. 3. Influence of inoculation size on the properties of the parasite population corresponding to the point $\kappa=3$, $\gamma=2$ of the phase diagram in Fig. 1. (a) Time at which the parasite population reaches a minimum (infection onset occurs at $t=0$). (b) Difference between initial and minimum parasite populations. For $t>t_{\min}$ the parasite population grows monotonically. If $n_0<n_s=0.25$, the parasite population is annihilated.

stant of motion and the ensuing closed orbits arise because the interaction terms have opposite signs in the equations for the predator and the prey: the immediate result of the predator-prey interaction is that the predator population increases while the prey population decreases [19]. As remarked in the Introduction, no closed orbits occur in our parasite invasion model. There is no constant of motion because the populations of *both* species are reduced by the interaction.

Time-dependent solutions to Eqs. (1) and (2) are easy to obtain numerically using a standard Euler method. A particularly informative way of presenting these solutions is to construct phase portraits: once $a(t)$ and $n(t)$ are calculated for any given parameter set, we assign to each value of the time a point in the (a,n) plane. By joining these points we then draw a trajectory describing the system evolution for each set of initial conditions. Phase portraits can also be built automatically by using mathematical software such as MATHEMATICA or MAPLE. We can draw some general conclusions about the dynamics of our model by looking at the phase portraits presented in Fig. 4.

In case I, the phase trajectories in the plane (a,n) [see Fig. 4(a)] exhibit closed loops ending at a fixed point corresponding to the steady state. This means that both populations oscillate as functions of time, which can be understood as follows: because of the strong growth rate and low avidity of the antibodies, both $n(t)$ and $a(t)$ grow sharply at short times. As a result, there is a rapid increase in the negative parasite-antibody encounter term, which induces a decrease in both populations. The nonlinearity of the coupling term generates an interesting phenomenon: the simultaneous decrease in the antibody and parasite populations eventually causes the right-hand side of Eq. (1) to become positive. Consequently, the parasite population starts increasing again, which triggers an upturn in the antibody population. We can see from Eq. (1), for $N=1$, that the *T. cruzi* population has either a maximum or a minimum at all times t_j such that the equation

$$\kappa-\alpha a(t_j)=0 \tag{10}$$

is satisfied.

In case II, because of the high creation rate and strong efficiency of the antibodies, the parasite population goes down to zero at long times. Although the parasite number always decays monotonically, the antibody number exhibits two different intermediate-time behaviors, depending on the value of α: for $\alpha>\gamma/a_0$, $a(t)$ goes through a minimum at intermediate times, whereas for $\alpha<\gamma/a_0$ the antibody population initially grows, passing through a maximum, before reaching the final state [see Fig. 4(b)]. An increase in the initial number of parasites has no qualitative effects beyond a short-time transient.

In case III the parasite population grows monotonically at long times due to fast replication while the antibody number goes to a finite constant. A large value of n requires that $\gamma=\alpha a$; therefore, the asymptotic value of the antibody number is

$$a_s=a(t=\infty)=\frac{\gamma}{\alpha}. \tag{11}$$

The long-time antibody population is now determined by the avidity and the rate of antibody creation and not by the rate of parasite creation, as in case I. The parasite population grows exponentially,

$$n(t\to\infty)\sim\exp[(\kappa-\gamma)t]. \tag{12}$$

Since $\dot{n}(t=0)<0$, $n(t)$ must have an intermediate-time minimum before going to its asymptotic value. This is observed in Fig. 4(c), which also shows that the initial condition $a_0>\kappa/\alpha$, $n_0<n_s$ leads to case IIIb (healing).

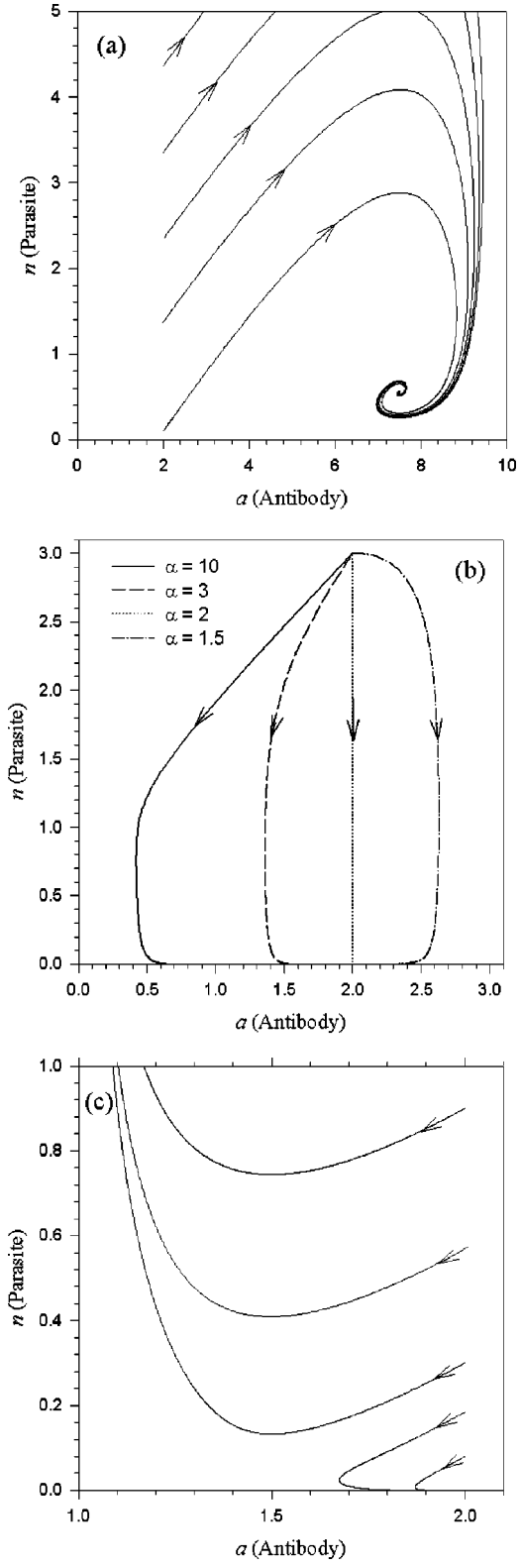

FIG. 4. Typical phase portraits for the antibody-parasite populations. In all cases, $\tau=10$ and $\kappa=3$. (a) Case I, $\alpha=0.4$ and $\gamma=4$. There is an oscillatory convergence towards $(a_s,n_s)=(7.5,0.55)$ (chronic disease). (b) Case II, $\alpha=2$ and $\gamma=4$. Convergence towards (0,2) (healing). (c) Case III, $\alpha=2$ and $\gamma=2$. Evolution towards $(1,\infty)$ (death). However, if $a_0>\kappa/\alpha=1.5$ and $n_0<n_s$, we are in case IIIb (healing).

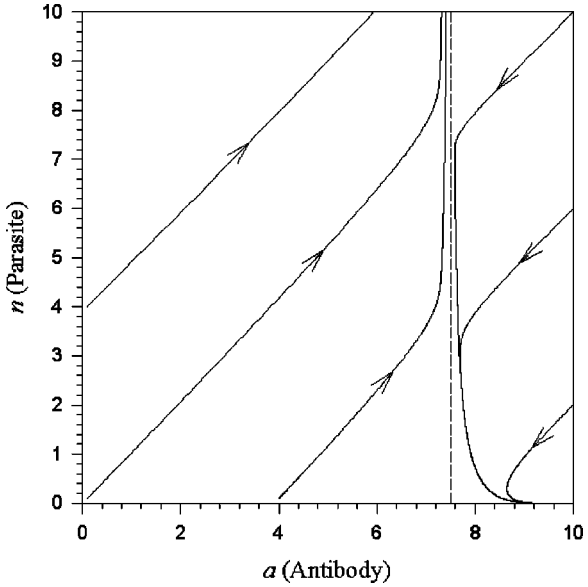

FIG. 5. Borderline case $\gamma=\kappa=3$. Phase portrait for $\alpha=0.4$ and $\tau=10$. If $\kappa>a_0\alpha$ the phase trajectories converge towards $(\kappa/\alpha,\infty)$, whereas if $\kappa<a_0\alpha$ they have their attractor at (a_0,∞).

Next, we consider the borderline case $\gamma=\kappa$. By setting $a(t)=\kappa/\alpha+R(t)$, we see that Eqs. (1) and (2) can be rewritten as

$$\dot{n}(t)=-\alpha R(t)n(t), \tag{13}$$

and

$$\dot{a}(t)=(1/\tau)[a_0-\kappa/\alpha-R(t)]-\alpha R(t)n(t), \tag{14}$$

respectively. At very short times, $\dot{a}(t)\approx\dot{n}(t)=-(\alpha a_0-\kappa)n_0$. Both populations vary linearly, with the same slope. The antibody number tends towards κ/α. Under the condition $\alpha\tau n\gg 1$, Eqs. (13) and (14) are approximately solved by writing $R(t)=\Delta/n(t)$, with $\Delta=(1/\alpha\tau)(a_0-\kappa/\alpha)$. In this regime, $a(t)\simeq\kappa/\alpha$ and $\dot{n}(t)\simeq(\kappa/\alpha-a_0)/\tau$. If $\kappa<a_0\alpha$ (at the frontier of case II), $n(t)$ decreases linearly until $\alpha\tau n\approx 1$ and the approximation above breaks down. Then $a(t)$ grows again towards its asymptotic value a_0 while the parasite population $n(t)$ decreases exponentially, as $\exp[-(\kappa-a_0\alpha)t]$. If $\kappa>a_0\alpha$ (at the frontier of case I above), $n(t)$ grows and the condition $\alpha\tau n\gg 1$ is always satisfied. Consequently, the parasite population will continue to grow linearly while the antibody population will tend to κ/α.

Figure 5 exhibits the two completely different outcomes of the borderline $\gamma=\kappa$ problem. The curves on the left (small a_0) correspond to the frontier between cases I and III, while those on the right correspond to the frontier between cases II and III. In agreement with the discussion above, at short times, phase trajectories are parallel straight lines of unit slope, for parasite and antibody numbers both depend linearly on time. At later times, all $a_0<\kappa/\alpha$ trajectories turn sharply up: while $a(t)$ goes to κ/α, $n(t)$ grows linearly with slope $(\kappa/\alpha-a_0)/\tau$. For $a_0>\kappa/\alpha$, i.e., at the frontier between cases II and III, $a(t)$ approaches κ/α at intermediate

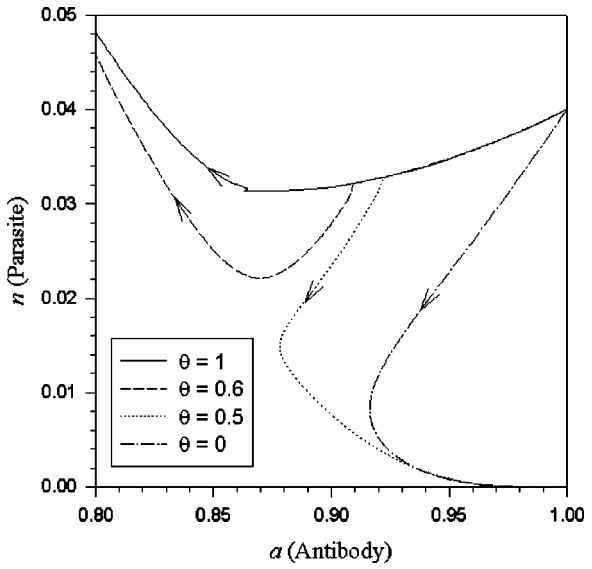

FIG. 6. Phase trajectories for the indicated time delays. For small delays, they converge to the attractor $(a_0,0)$ (healing), while for long delays they converge to $(0,\infty)$ (death). Here $a_0=1$, $n_0=0.04$, $\alpha=4.6$, $\tau=1/0.12$, $\kappa=4$, and $\gamma=3$.

times, while $n(t)$ decreases linearly. Finally, when n is so small that the condition $\alpha\tau n \gg 1$ is no longer satisfied, $a(t)$ approaches its asymptotic value (a_0) while $n(t)$ decays exponentially to zero.

B. Delays

Next, we consider the effects of a retardation in the immune system reaction to the invasion (as it occurs in the Chagas infection [6]). The retardation can be taken into account by introducing a time delay [11,20] θ_i in the term representing antibody generation in Eq. (2), which now reads

$$\dot{a}_i(t)=\gamma_i n(t-\theta_i)-\alpha_i a_i(t) n(t)-(1/\tau)[a_i(t)-a_{i0}]. \tag{15}$$

The equation for the parasite evolution remains unchanged.

It was recently shown that the introduction of a time delay in the immune response model of Mayer yields chaotic behavior [15]. This situation does not occur in our model; in most cases the time delay merely introduces a transient stage in which the parasites reproduce freely. After a time θ_i the system behaves as if it had started with an initial parasite population $n(\theta_i)$. The absence of delay-induced drastic changes is not surprising, since we have already seen that the different outcomes of the parasite-antibody competition model do not depend on the initial parasite population, but only on the constant model parameters, which remain unchanged with the introduction of the delay. If $\gamma<\kappa<\alpha a_0$, however, the parasite can use the delay to gain a definitive advantage, because the location of the phase boundary between cases III and IIIb does depend on n_0. By effectively increasing the parasite population at the time the antibodies are activated, the delay can induce a switch from case IIIb (survival) to case III (death). This is exemplified in Fig. 6 where phase portraits for a single antibody species are plotted. The phase trajectories undergo a sudden change in slope at the time the antibody molecules become efficient. For short-time delays, the trajectories converge towards the "healing" attractor $(a_0,0)$, whereas for long delays the trajectories tend to $(0,\infty)$ (patient death).

In principle, antibody production and parasite growth could depend on the availability of some essential nutrients. If this were the case, we should introduce a new variable $v(t)$, the amount of available critical nutrient, whose time variation would depend on the parasite number and on the antibody generation rate γ. The antibody generation rate would itself depend on the instantaneous value of v and perhaps even on its history. A long delay would tend to impair the immune system through a decrease in γ.

C. Oscillations

The oscillations appearing in case I deserve some further consideration. Simulations show that after an initial sharp decay, the time difference between successive extrema in $a(t)$ stabilizes due to the gentleness of the $n(t)$ oscillations, which provide a smooth feedback to the antibody number. We can analyze this behavior through a linearization of the evolution equations about a_s and n_s, writing

$$n(t)=n_s+N(t) \quad \text{with} \quad |N(t)| \ll n_s,$$

$$a(t)=a_s+A(t) \quad \text{with} \quad |A(t)| \ll a_s.$$

The system of Eqs. (1) and (2) becomes, to first order

$$\dot{N}=-\alpha n_s A, \tag{16}$$

$$\dot{A}=(\gamma-\kappa)N-\left(\frac{1}{\tau}+\alpha n_s\right)A. \tag{17}$$

We now define the parameters

$$T=\frac{2\tau(\gamma-\kappa)}{\gamma-\alpha a_0}, \tag{18}$$

$$\omega^2=\frac{\kappa-\alpha a_0}{\tau}-\left(\frac{\gamma-\alpha a_0}{2\tau(\gamma-\kappa)}\right)^2. \tag{19}$$

If $\omega^2<0$, the pair of Eqs. (16) and (17) has solutions that tend exponentially to their asymptotic values. More interesting is the $\omega^2>0$ case, corresponding to large κ values, for which we obtain the solutions

$$A(t)=e^{-t/T}A_0\cos(\omega t-\varphi), \tag{20}$$

$$N(t)=-\frac{\alpha n_s T e^{-t/T}}{1+(\omega T)^2}A_0[\cos(\omega t-\varphi)-\omega T\sin(\omega t-\varphi)], \tag{21}$$

where A_0 and φ are constants that depend on the initial populations. The parameter T is the characteristic time required to reach the stationary population.

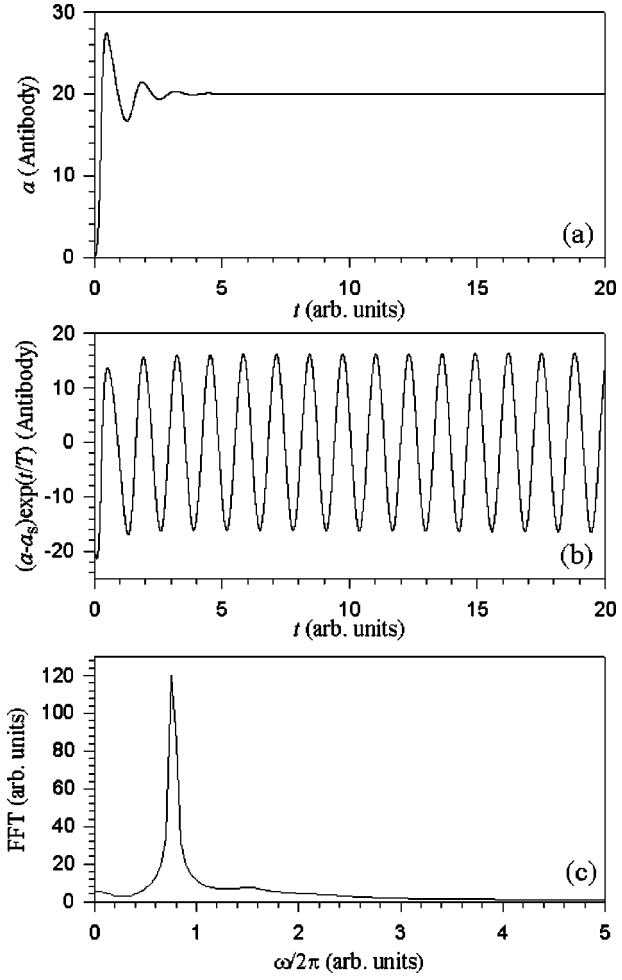

FIG. 7. Evolution of the antibody population. (a) Its full time dependence. (b) Regular oscillations exhibited once the exponential decay is extracted. (c) Fourier spectrum of the antibody population. The parameter values are, $a_0=0.01$, $n_0=0.1$, $\alpha=1$, $\tau=0.8$, $\kappa=20$, and $\gamma=40$.

This behavior is exemplified in Fig. 7. The regularity of the sinusoidal oscillations in the antibody number becomes evident when the exponential factor is extracted [see Fig. 7(b)]. This stabilized oscillatory behavior can be studied by using the fast Fourier transform. The resulting spectrum, shown in Fig. 7(c), has a unique peak corresponding precisely to the frequency predicted by Eq. (19).

V. DECOYS: AN EFFECTIVE SELF-DEFENSE MECHANISM?

Competition is a common occurrence in biological systems, be it at the molecular [21] or the macroscopic [11] levels. It is often the case that an additional species modifies the action of a predator against a specific prey. This competitor species may reduce [22] or increase [23] the probability of extinction of the prey. Of special interest to us is the case when the ''competitor species'' is an invader-generated decoy that confounds the immune system. Decoy generation may be a necessary by-product of the invader activity, or it may be part of a self-defense mechanism. It has been observed in the *T. cruzi* problem [16], where the parasite plays the role of the invading species. The effect of these decoys on the antibody and parasite populations can be quite complex, because they not only incapacitate antibody molecules, but they may also induce an extra activation of the antibody generating cells. This activation could, in principle, work in two different ways: (i) decoys stimulate the production of antibodies harmless to the invader, and then weaken the immune response by decreasing the amount of available specific antigen (since antibody-producing cells have a limited amount of amino acids to build them, an increase in the diversity must lower the specific antigen population); (ii) decoys stimulate the production of specific antigens (this would occur if the immune system cannot distinguish between a segment shed by the invader and the invading organism itself). The first case could be accounted for by suitably reducing the antibody generation rate. In the second case, it is not possible to ascertain *a priori* the outcome of the decoy action. We will find the condition that the parameters must satisfy in order to ensure that the decoys operate as an effective self-defense mechanism for the invaders.

In case (i) the effect of decoy action is quite straightforward (to decrease γ); for this reason, we will analyze only case (ii) in depth. When decoys are introduced in our model, the parasite evolution equation is not modified, but we have to add a new equation for the decoy population $d(t)$. In the single antibody problem we have

$$\dot{d}(t)=\kappa_d n(t)-\alpha_d a(t)d(t), \tag{22}$$

where κ_d is the decoy production rate and α_d defines the likelihood of antibody-decoy removal upon an encounter. Because of the presence of the decoys the antibody equation acquires an extra term

$$\dot{a}(t)=(1/\tau)[a_0-a(t)]+[\gamma-\alpha a(t)]n(t) +[\gamma_d-\alpha_d a(t)]d(t), \tag{23}$$

where the coefficient γ_d controls the decoy-induced antibody production. Following the same procedure as in Sec. III we find the steady-state populations in the chronic case to be

$$a_s=\frac{\kappa}{\alpha}, \tag{24}$$

$$d_s=\frac{(\kappa_d/\tau)(\kappa-a_0\alpha)}{(\gamma-\kappa)\alpha_d\kappa+(\gamma_d\alpha-\kappa\alpha_d)\kappa_d}, \tag{25}$$

and

$$n_s=\frac{\alpha_d}{\alpha}\frac{\kappa}{\kappa_d}d_s=\frac{\alpha_d(\kappa/\alpha\tau)(\kappa-a_0\alpha)}{(\gamma-\kappa)\alpha_d\kappa+(\gamma_d\alpha-\kappa\alpha_d)\kappa_d}. \tag{26}$$

The introduction of the decoys modifies the conditions leading to the different evolution cases mentioned in Sec. III. Again, the stability of the steady-state solutions was proved using the Routh-Hurwitz criterion [11]. This criterion indicates that case III (host death) occurs if

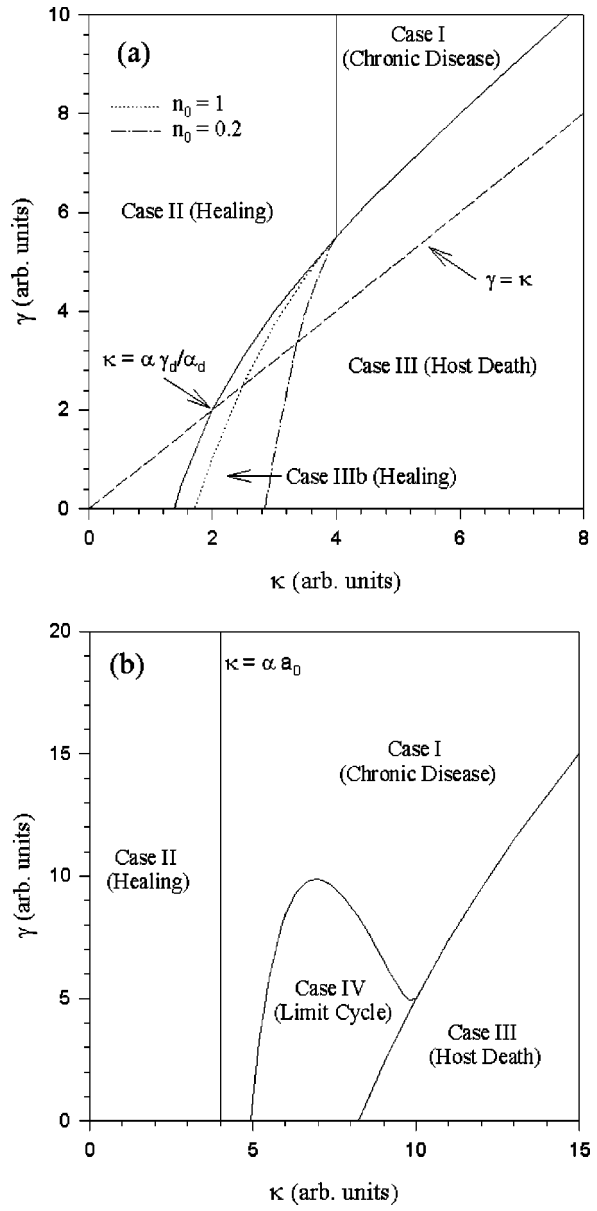

FIG. 8. Phase diagram for the problem with decoys for two sets of parameters: (a) $a_0=4$, $d(t=0)=0$, $\alpha=\alpha_d=1$, $\tau=10$, $\kappa_d=3$, and $\gamma_d=2$. The $\gamma=\kappa$ line corresponds to the phase separation in the absence of decoys. The separatrix between cases I and III tends asymptotically to $\gamma=\kappa+\kappa_d$. The location of the separatrix between cases III and IIIb depends on the initial parasite population n_0. (b) Same parameters, except that $\alpha_d=0.2$, $\kappa_d=10$, and $\gamma_d=3$.

$$\gamma<\kappa+\kappa_d-\frac{\alpha\gamma_d\kappa_d}{\alpha_d\kappa}, \tag{27}$$

otherwise, we are in case I (chronic disease), provided that $\kappa>\alpha a_0$.

The corresponding phase diagram is presented in Fig. 8(a). For high values of κ the boundary between regions III and I or II (healing) is shifted by the presence of decoys towards higher values of γ, favoring the parasite invasion. For small values of κ, however, the border bends down and the decoy production favors healing. From condition (27), it is clear that for

$$\kappa<\frac{\kappa_d}{2}\left(\sqrt{1+\frac{4\alpha\gamma_d}{\alpha_d\kappa_d}}-1\right), \tag{28}$$

the parasite population will disappear even if $\gamma=0$ (no parasite-induced antibody creation). The reason is that, under these conditions, decoy generation favors antibody production without substantially neutralizing the antibody population. By comparing the steady-state values, it is easy to see that decoy emission benefits the parasite if the condition

$$\kappa>\frac{\alpha}{\alpha_d}\gamma_d \tag{29}$$

is fulfilled. If, in fact, the invader releases decoys to take advantage of the immune system, it must have evolved in such a way that this inequality is satisfied. Otherwise the invasion would not be favored. Although it may be argued that calling the object a ''decoy'' would be a misnomer if inequality (29) is not satisfied, we keep the name for the sake of descriptive unity.

A further complication arises in the analysis of the frontier region between cases II and III. As in the no decoy problem, numerical analysis indicates that, if the parasite inoculation is small, region IIIb (healing) appears between II and III.

The Routh-Hurwitz analysis yields a second condition, which takes the form of a very complex inequality. For a set of parameters defined by this inequality, no stable state can be reached. Interestingly, numerical work shows that, for these parameters, which embody what we call case IV, a population limit cycle emerges. The phase diagram for a set of parameters exhibiting region IV is shown in Fig. 8(b). Region IV always appears inside region I, abutting the $\gamma=0$ line and/or region III.

A combination of the second Routh-Hurwitz condition and inequality (27) determines the following necessary condition for the existence of case IV,

$$\kappa_d>\frac{\alpha_d^2a_0^2+\sqrt{\alpha_d^4a_0^4+4\alpha\alpha_d\gamma_da_0^2(\gamma_d-\alpha_da_0)}}{2(\gamma_d-\alpha_da_0)}. \tag{30}$$

In Fig. 9 we present a typical phase portrait for this case. We can see that, independently of the initial conditions, the system trajectories always end in a limit cycle.

VI. DISCUSSION

We have extended the analysis of our model for the interaction between parasites and antibodies during the acute phase of Chagas' disease [6]. The dynamics of the parasite and antibody populations has been studied in detail, including the influence of the size of the parasite inoculation and of delays in the activation of the immune system. The influence of parasite-generated decoys has been also investigated, and we have obtained a simple criterion that enables us to determine whether the parasite is indeed benefited by decoy emis-

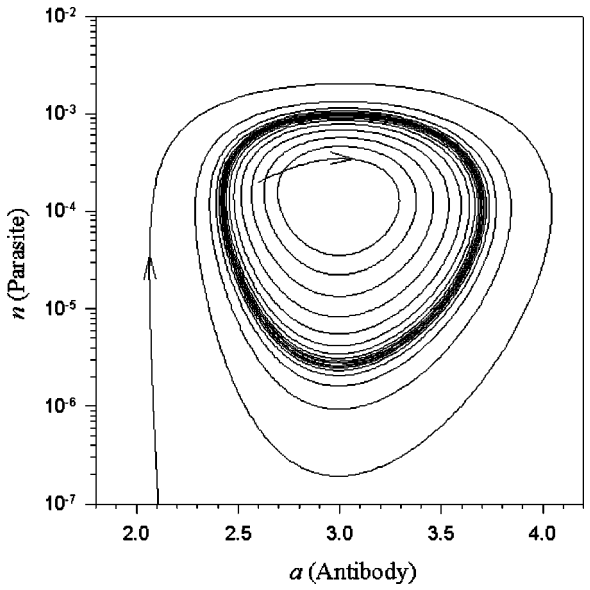

FIG. 9. Phase portrait for antibody and parasite population for a case IV system. Note the convergence towards a limit cycle. Here we took $a_0=2$, $d(t=0)=0$, $\alpha=1$, $\alpha_d=0.1$, $\tau=10$, $\kappa=3$, $\kappa_d=1000$, $\gamma=5$, and $\gamma_d=0.5$.

sion. The presence of decoys can substantially alter the population phase diagram. Under certain conditions, a qualitatively new type of outcome (a limit cycle) is possible. This limit cycle would imply nondecaying oscillations in the parasite and antibody populations.

A topic that has not been discussed here, but that deserves further study, is the influence of preceding infections, which could impair the response to a new one, with a different pathogen, or to vaccination. There is ample evidence that this is the case for various infections [24–26]. Another problem that could be modeled is the influence of decoys introduced artificially to combat disease [27].

The model presented here is particularly suitable to quantitatively investigate the effects of elements that modify the competitive process between an invading agent and the immune system. In this paper, we have discussed the effects of delays and of the introduction of decoys. Another element that deserves to be examined is the effect of noise. Noise has been shown to have substantial influence on predator-prey systems [28] and on epidemic models [29]. The interplay between delays and stochasticity is also a subject of current interest [30]. We are now starting an examination of the effects of noise on the parasite-antibodies system.

Our model could be also applied in the fields of chemotherapy and vaccination as a tool to help with the design of usually expensive and time-consuming *in vivo* experiments, by performing fast *in machina* simulations. The development of a successful vaccine against *T. cruzi* is a complex endeavor [31] and, by incorporating the action of chemotherapy, mathematical modeling could yield valuable predictions.

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