

A basic mathematical model of the immune response

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Interaction of the immune system with a target population of, e.g., bacteria, viruses, antigens, or tumor cells must be considered as a dynamic process. We describe this process by a system of two ordinary differential equations. Although the model is strongly idealized it demonstrates how the combination of a few proposed nonlinear interaction rules between the immune system and its targets are able to generate a considerable variety of different kinds of immune responses, many of which are observed both experimentally and clinically. In particular, solutions of the model equations correspond to states described by immunologists as "virgin state," "immune state" and "state of tolerance." The model successfully replicates the so-called primary and secondary response. Moreover, it predicts the existence of a threshold level for the amount of pathogen germs or of transplanted tumor cells below which the host is able to eliminate the infectious organism or to reject the tumor graft. We also find a long time coexistence of targets and immune competent cells including damped and undamped oscillations of both. Plausibly the model explains that if the number of transformed cells or pathogens exceeds definable values (poor antigenicity, high reproduction rate) the immune system fails to keep the disease under control. On the other hand, the model predicts apparently paradoxical situations including an increased chance of target survival despite enhanced immune activity or therapeutically achieved target reduction. A further obviously paradoxical behavior consists of a positive effect for the patient up to a complete cure by adding an additional target challenge where the benefit of the additional targets depends strongly on the time point and on their amount. Under periodically pulsed stimulation the model may show a chaotic time behavior of both target growth and immune response. © 1995 American Institute of Physics.

I. INTRODUCTION, THE MODEL

Like the nervous system the immune system has a very high degree of complexity, even if its connection to the nervous system¹ is not taken into account. Therefore it is impossible to develop a nearly completely realistic mathematical model for every situation of host defense. Increasingly complicated mathematical models have been developed, for a few examples see Refs. 2–9. However, despite their complexity there is still incomplete understanding of the mechanisms of how the immune system really works, even though there is an enormous amount of "isolated" data.² In high-dimensional models often problems arise with parameter estimations^{4,5,8} and lack of insight into the model itself.

The model presented here follows a different strategy. It demonstrates that a considerable plurality of immunological phenomena can be the result of very few and simple basic interactive mechanisms. This approach is motivated by the modern theory of nonlinear dynamical systems¹⁰ implying that the behavior of a system may be far richer than its internal structure from which this behavior results. To find an interactive structure as simple as possible is a contribution to the question of how complex the immune system at least has to be in order to produce its observed responses.

We consider the relationship between the target and the immune system as a feedback loop. Figure 1 outlines the

mechanisms assumed to be essential for the immune–target interaction. The target may be any biological material such as bacteria, viruses or immunogenic tumor cells susceptible to an immune response. The temporal change of the target population size T is determined by the difference between their reproduction and their elimination. It is assumed that the reproduction rate is proportional to the target size. The elimination of the targets as the result of the interaction with specific immune components (effectors E) is considered to be proportional to the contact rate between the targets and the effectors.

Thus, the temporal change of the target population is described by the differential equation

$$\frac{dT}{dt} = rT - kTE$$

with non-negative rate constants r and k .

We define the immune competence E as the elimination capacity of the immune system with respect to that special target. E may be measured, e.g., by the concentration of certain immune cells, like cytotoxic T-cells, natural killer cells, or by the concentration of certain antibodies.

The immune competence E is supposed to be constituted by three different factors:

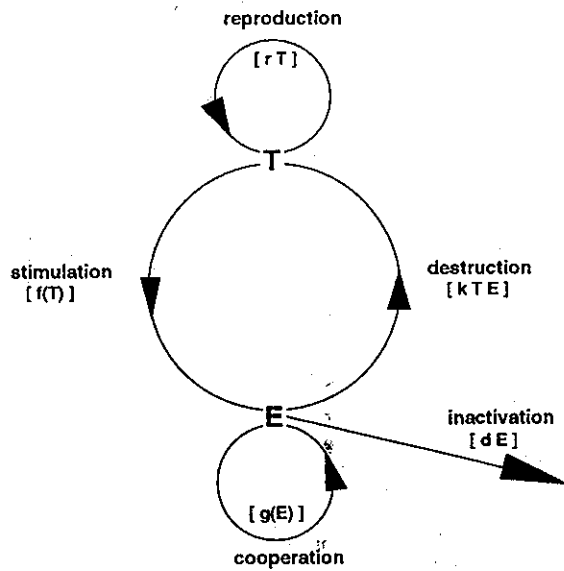


FIG. 1. Scheme of the essential mechanisms of interaction between a target population T and the effectiveness E of the immune system against this target. For details see text.

- (1) The targets trigger processes in the immune system leading to competence against them. For example, in the presence of targets nonspecific precursor cells, or not yet activated T-cells are transformed into specific helper cells, cytotoxic T-cells or plasma cells producing specific antibodies. The velocity of this stimulation is described by a function $f(T)$ which for specificity is given by

$$f(T) = p \frac{T^u}{m^v + T^v} \quad (T \geq 0) \quad (1)$$

with positive constants p , m , u and v , $u \leq v$. Depending on the parameters u and v there exist three different shapes of the stimulation function $f(T)$ as illustrated by Figs. 2(a)–2(c). All these functions are bounded accounting for the fact that the precursor population is limited. The sigmoid increase in the case $u > 1$ emphasizes that a small amount of targets may be more or less ignored by the immune system. This effect is known as low-zone unresponsiveness. The high-zone unresponsiveness,

$u < v$, is characterized by a decrease of immune response stimulation under high target burden. The parameter p represents the precursor pool size.

- (2) The immune reaction is additionally strengthened by autocatalytic and/or cooperative reinforcement of immune activation processes. This means, for example, that competent immune effector cells are able to proliferate and/or to stimulate themselves or precursor cells for increased proliferation or differentiation. The resulting increase rate of immune competence is modeled by the function

$$g(E) = s \frac{E^n}{c^n + E^n} \quad (2)$$

whose graph qualitatively looks like Fig. 2(a) ($n=1$) or Fig. 2(b) ($n>1$). The sigmoid shape takes into account that a critical number of immune cells may be necessary in order to realize the cooperative and autocatalytic effect.

- (3) Finally a term $-d \cdot E$ represents the finite lifetime of the immune competent cells or agents, with a positive death rate constant d .

A summary of the mathematical model for the interaction of the immune system and the target is given by the following system of two ordinary differential equations:

$$\frac{dT}{dt} = rT - kTE, \quad (3)$$

$$\frac{dE}{dt} = f(T) + g(E) - dE. \quad (4)$$

The system contains three nonlinear terms, TE , $f(T)$ and $g(T)$. It will be shown in the subsequent discussion that the interaction of these three factors is essential for the large variety of different types of behavior the model is admitting.

There is already a considerable number of low dimensional models (not more than three equations) in the literature. We point to the list¹¹⁻²¹ which is not claimed to be complete. These models are more or less related to the model presented here.

The essential feature of our model is the cooperation of the nonlinearities which has a great number of dramatic effects, in fact, observed in real immune responses. Most of the

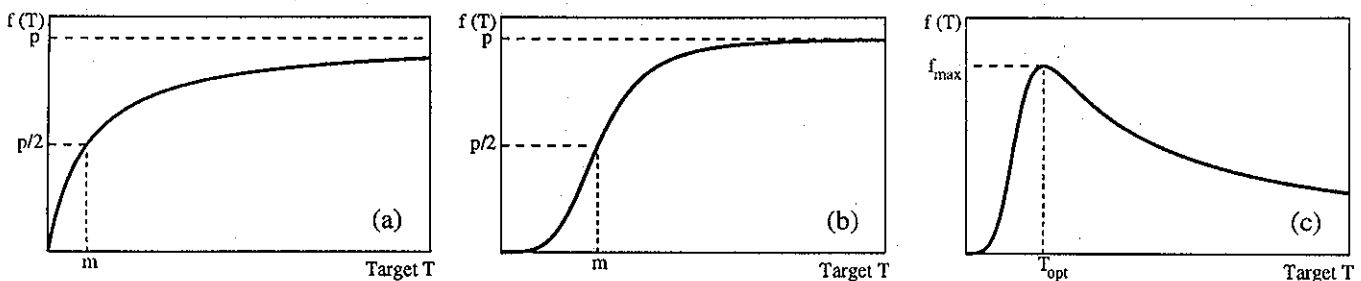


FIG. 2. Graph of the stimulation function $f(T)$ for three different sets of parameters: (a) $u=v=1$; (b) $u=v>1$; (c) $1<u<v$

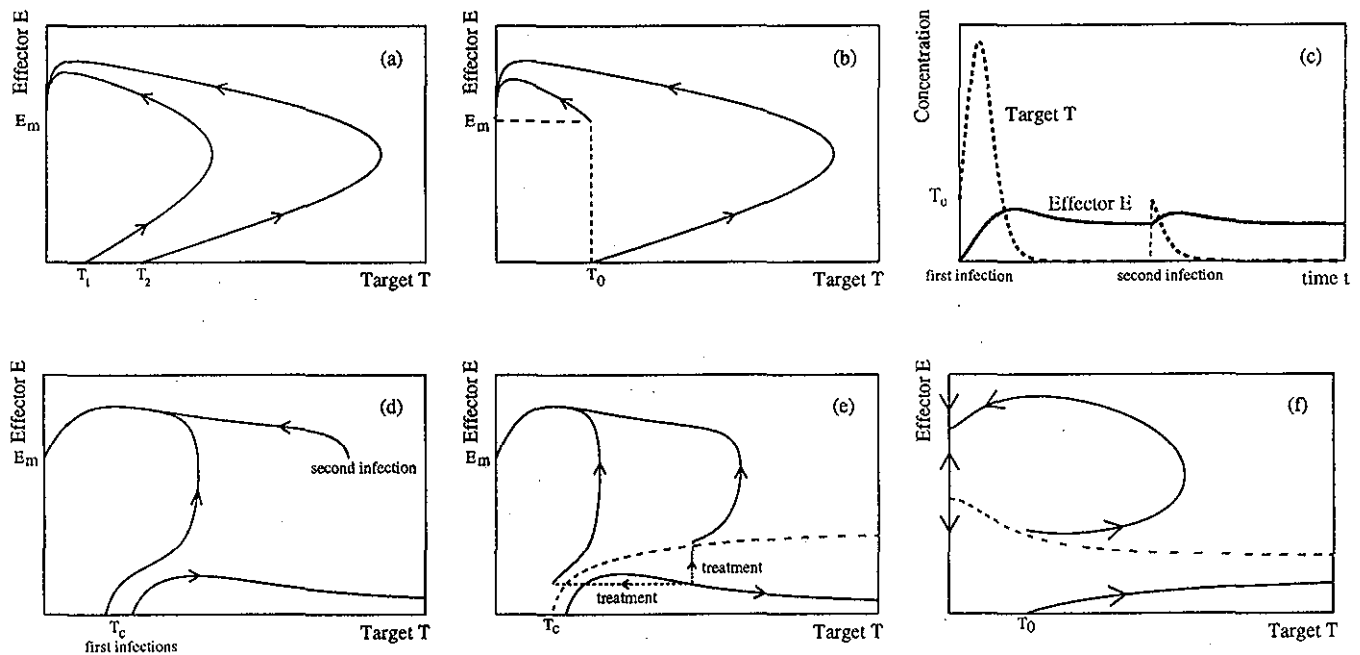


FIG. 3. Figures show numerical solutions of the model equations (3) and (4). (a) Trajectories in the phase plane corresponding to two differently strong infections. (b) Primary and secondary response represented in the phase plane and (c) in the time domain. (d) Essential increase of immune defense efficiency in a secondary response leading to a rejection of a much higher infectious dose than during a primary response. (e) Therapeutic interventions, indicated by dotted lines. (f) Example that any primary infection may be lethal despite the existence of an immune state. Values of parameters for the computation of the trajectories: $r, k, p, s = 2.3, 2, 1, 2.5$ [(a), (b), (c)]; $0.15, 0.1, 0.7, 2$ [(d), (e)]; $1.2, 1, 0.28, 2$ (f); $u, v, n = 1, 1, 1$ [(a), (b), (c)]; $1, 2, 3$ [(d), (e)]; $2, 2, 3$, (f).

models in the literature are less nonlinear, and thus are not able to produce this richness of behavior. Of course, there is overlap with the model of this paper, and some of them have special properties which ours is missing. It remains a future task to establish a reasonable relationship between the low-dimensional models contained in the literature.

II. RESULTS OF ANALYTICAL INVESTIGATIONS OF THE MODEL

The time courses of the immune competence E and of the targets T are determined as the solutions of the differential equation system (3) and (4). Of course, each of the solutions depends on an initial condition $T(0), E(0)$. Though there is no analytic expression for the solutions $T(t), E(t)$, $t \geq 0$, one of the advantages of the model is that a nearly complete phase plane analysis can be carried out, and thus a nearly complete overview of the qualitative behavior of the model is possible. Without giving details here of this analysis, in the following we shall use mainly phase portraits in the T - E plane to illustrate and to characterize the different types of behavior that may happen depending on the values of the constant parameters.

Note that by linear rescaling of E, T and t , it can be achieved that $m = c = d = 1$, so the model contains just seven independent parameters.

Figure 3(a) shows two trajectories $[T(t), E(t)]_{t \geq 0}$ in the phase plane solving the system of differential equations. They start from initial conditions $(T_1, 0)$ and, respectively, $(T_2, 0)$ corresponding to two infections of different strength, $T_1 < T_2$. No specialized immune effectors are present at the

time of infection, $t=0, E(0)=0$. In response to the targets the concentration and/or the activity of immune competent cells starts to increase. Moving along the trajectories the system finally converges towards the so-called immune state $(0, E_m)$, where no targets but only "memory cells" exist.

In case of a second infection the initial condition is (T_0, E_m) , $T_0 > 0$, and the immune system will respond faster. This is illustrated by Fig. 3(b) showing a primary and a secondary response with the same amount of infectious particles T_0 . The temporal relationship between first and second infection is illustrated more pronouncedly in the time domain, see Fig. 3(c). In reality the secondary response can be so strong and fast, that a reinfection is often not recognized as for instance in the case of rubella (German measles). This type of behavior of the model occurs if the parameters satisfy the conditions

$$n = u = v = 1; \quad s > 1 \quad \text{and} \quad r/k < s - 1$$

(note that there may be still other regimes in parameter space where the same type of behavior occurs). This can be proved by discussing the vector field in the T - E plane defined by the right hand side of the differential equations, in particular by discussing the direction of flow in those areas of the phase plane which are separated by the nullclines $dT/dt=0$ and $dE/dt=0$. This analysis reveals that under the above conditions on the parameters the system has exactly two steady states (T and E constant), namely $(0, 0)$ and $(0, E_m)$, $E_m = s - 1$. The first one turns out to be repelling, the second one is globally attractive in the domain $T \geq 0, E > 0$.

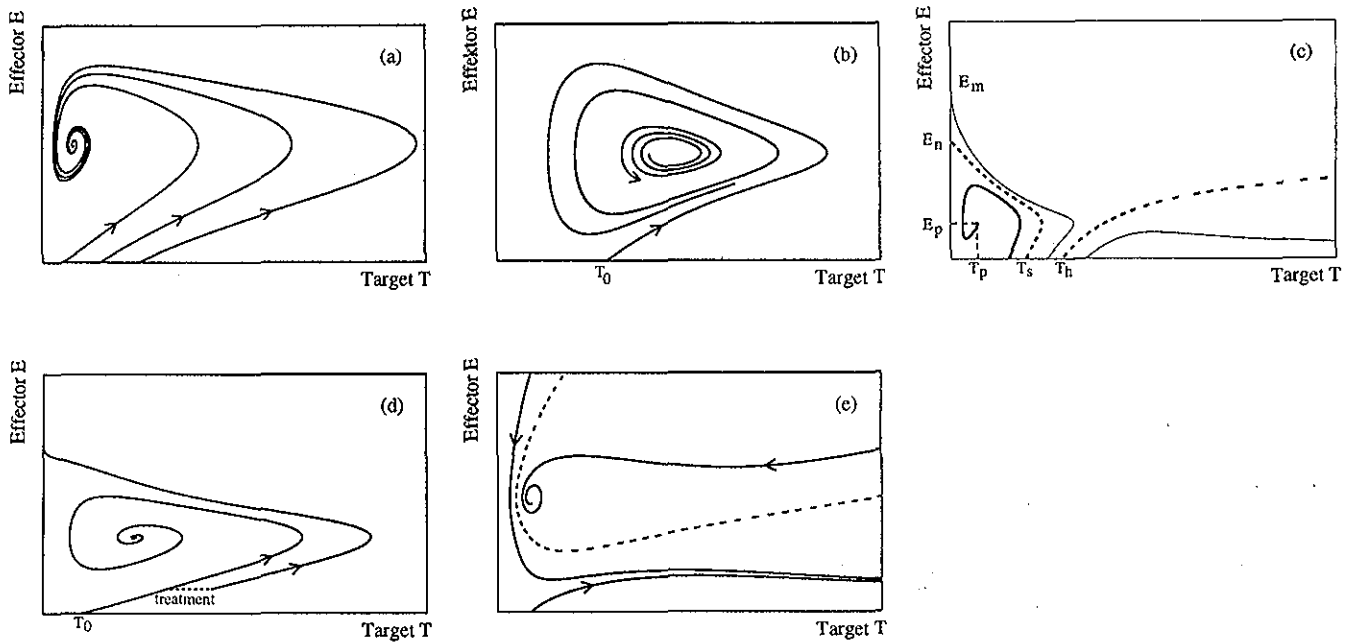


FIG. 4. Chronic coexistence of targets and effectors (a) in a steady state and (b) in a limit cycle. (c) Dose dependent outcome of an infection. (d) Paradox behaviors: a benefit effect from target increase, and (e) a target reduction or immune improvement may be lethal. Parameter values for (a)–(e), respectively: $r=4.5, 0.5, 0.3, 2.7, 0.6$; $k=3, 1, 1, 4.5, 0.5$; $p=3, 0.35, 0.7, 1, 0.7$; $s=0.5, 1.75, 2, 1.5, 1.6$; $u=2, 4, 1, 2, 1$; $v=2, 4, 2, 2, 2$; $n=1, 3, 3, 9, 3$.

Under other conditions on the parameters it may happen that the steady state $(0, E_m)$ is only locally attractive, for instance if

Condition (C):

$$n > 1; u < v; s > s_1; \max f(T) > f_1;$$

$$0 < E_1 < r/k < E_m$$

and r and k are sufficiently small. Here $s_1 = n/r \sqrt{(n-1)^{n-1}}$, $f_1 = z(E_1)$ where E_1 is the local maximum of the function $z(E) = E - g(E)$. The constant E_m is the largest solution of $E^n - sE^{n-1} + 1 = 0$.

In case of condition (C) there exists a threshold $T_c > 0$, such that whenever the infection dose $T_0 > T_c$ the solution satisfies $T(t) \rightarrow \infty, E(t) \rightarrow 0$ as $t \rightarrow \infty$, i.e., no immune state will be reached and the disease is lethal, see Fig. 3(d). Closer analysis shows that there is a separatrix [dashed curve in Fig. 3(e)] limiting the domain of attraction (“attraction basin”) of the immune state $(0, E_m)$. From the last two figures one can observe that with a second infection a higher infection dose can be tolerated than with the first one, a behavior which is well known for instance from cholera.

Beyond reproducing such facts the discussion of the model gives a deeper look on the prognosis and may lead to the discovery of strategies on how to interfere with the immune system or the pathogen target in order to cure the patient or at least to keep the disease under control.

An example can be concluded from Fig. 3(e). Assume the infection dose satisfies $T_0 > T_c$, i.e., without treatment the disease would be lethal. A treatment should aim at bringing the system on the other side of the separatrix into the domain of attraction of the immune state. This can be

achieved either by improving the immune competence (vertical dotted line) or by target reduction (horizontal dotted line), e.g., by antibiotics therapy, or by a combination of these two strategies.

The model also reproduces the behavior found with infections by smallpox. Here a primary infection ($E_0 = 0, T_0 > 0$) is generally lethal. However, by vaccination or by a previous infection with cowpox (a virus which is much less virulent than smallpox) an immune state $E_m > 0$ can be achieved. In fact, competent immune effectors generated against cowpox are also able to recognize and eliminate smallpox infected cells at least up to a certain degree. This situation is represented by our model if condition (C) is satisfied and r and k are sufficiently large. For an illustration see Fig. 3(f) where again the boundary of the attraction basin of the immune state is indicated by a dashed curve.

Such a basin where the immune system can eliminate the targets does not always exist, for example if the “pathogenicity constant” r/k exceeds a certain value E^* [denoting the supremum of the E -components of all points on the nullcline $0 = f(T) + g(E) - E$]. In this case, the target population always grows to infinity and no immunity is achieved.

Another situation where a complete target elimination cannot be reached arises if

$$n = 1, u = v, s < 1 \text{ and } 0 < r/k < E^*.$$

Under this condition a steady state $(T_p, E_p), E_p = r/k$, exists where both components are positive as illustrated in Fig. 4(a). Targets and immune competent cells coexist in an equilibrium, representing a more or less dangerous chronic disease. Hepatitis B and Salmonella are examples of this type.

The coexistence state is globally attractive for all initial conditions different from $(0,0)$. The movement into the positive steady state may be either oscillatory [Fig. 4(a)], e.g., if

$$0 < g'(r/k) < 1 - \sqrt{4kT_p f'(T_p)}$$

or monotone if

$$1 - \sqrt{4kT_p f'(T_p)} < g'(r/k) < 1.$$

A different type of coexistence is represented by a limit cycle [Fig. 4(b)] where target size and immune competence permanently oscillate around an unstable steady state. Such a limit cycle occurs for instance if

$$n > 1; u = v; s_0 < s < s_1; p > f_1; E_1 < r/k < E_2.$$

In addition to the constants defined with (C) the value of s_0 is given by

$$s_0 = 4n/\sqrt{(n-1)^{(n-1)} + (n+1)^{(n+1)}}$$

and E_2 denotes the local minimum of the function $z(E) = E - g(E)$. Herpes simplex and malaria are examples of diseases which may show a periodic or nearly periodic time course.

Oscillatory dynamics of the immune response has not yet found the attention it deserves. There is apparently a variety of autoimmune diseases, like multiple sclerosis and recurrent inflammations in various organs (e.g., gastrointestinal tract), which show more or less regular sequences of outbreaks. The model clearly shows this oscillatory behavior, which would occur even under much more general conditions on the parameter constants, if the model equations (3) and (4) would be modified more realistically by including time delay effects. Such a time delay model could be, e.g.,

$$\frac{dT}{dt} = rT(t-\tau) - kT(t)E(t),$$

$$\frac{dE}{dt} = f(T(t-\delta)) + g(E(t-\Delta)) - dE(t).$$

The positive delay constants τ , δ , Δ take into account times necessary for molecule production, proliferation, differentiation of cells, transport, etc. It is well known from the theory of differential-delay equations that time delays strongly support oscillatory behavior in these systems. However, we do not go into any analysis of this delay model. Instead, we continue with system (3) and (4).

There are even situations with five steady states: $(0,0)$ saddle, $(T_1, r/k)$ asymptotically stable, $(T_2, r/k)$ unstable, $(0, E_n)$ saddle, and $(0, E_m)$ asymptotically stable, see Fig. 4(c), where the unstable state is not specially marked (E_n is the smallest positive solution of $E^n - sE^{n-1} + 1 = 0$, E_m the largest one). Parameters are as in condition (C), however $0 < r/k < E_1$ and r and k sufficiently small. Then the development of a disease strongly depends on the dose of infection. There are two thresholds, T_s and T_h . A small target dose, $T_0 < T_s$, leads to permanent coexistence of targets and immune competent cells. However, a medium infectious dose, $T_s < T_0 < T_h$ generates an optimal immune response with elimination of the infectious germs, while a high infectious dose, $T_0 > T_h$, cannot be controlled by the immune

system. When the immune system has achieved a memory state $(0, E_m)$ a secondary infection will generally lead to that state.

The model also predicts the apparently paradox situation that instead of reducing the target burden, the opposite treatment, an increase in the number of targets, can be of benefit for the patient. As illustrated in Fig. 4(d), by this treatment the immune system escapes the state of coexistence leading again to the elimination of the pathogens and to the creation of an immune state. This case of the model, occurring for example if

$$n > 1; u = v; s > s_1; p > f_1; r/k < E_1$$

gives a rationale for active vaccination under certain conditions.

To be more accurate, an active vaccination operates generally with living but inactivated cells which are not able to reproduce themselves, i.e., $r = 0$ for these cells, or $r < 0$ because of degradation. A modification of the model takes this into account by distinguishing between active (T) and inactivated (T_i) targets:

$$\frac{dT}{dt} = rT - kTE, \quad (5)$$

$$\frac{dE}{dt} = f(T + T_i) + g(E) - E, \quad (6)$$

$$\frac{dT_i}{dt} = -d_i T_i - kT_i E. \quad (7)$$

Another paradoxical situation is predicted by the model [Fig. 4(e)] in the case that

$$n = 1; u < v; s - 1 < r/k < E^*.$$

Here an attempt to cure a patient from the chronic disease by immune stimulation or target reduction could lead to death after a short time of benefit. This situation occurs if the separatrix is crossed during the treatment.

III. CHAOTIC BEHAVIOR

Real time series data of the immune state of patients often look rather irregular. Figure 5(a) shows an empirical example of the number of phenotypically identified natural killer cells ($CD 16^+$, $CD 56^+$) versus total tumor size during the course of a metastatic disease (Fibrosarcoma). The number of peripheral blood derived NK cells was determined once every four or five weeks over a period of 475 days. The tumor load was evaluated on the basis of the diameters of several individual lesions registered on x-ray pictures. Both, the number of NK cells and tumor volume exhibit during this period a seemingly "chaotic" behavior: they fluctuate irregularly and apparently unpredictably. Sometimes the tumor even reduces its volume.

The model presented here is not able to produce any kind of chaotic behavior, since it is only two-dimensional. However, we can show that chaos can be induced if at least one of the parameters instead of being constant changes periodically. In this way we obtained the data of Fig. 5(b), where the tumor production rate r has been assumed to

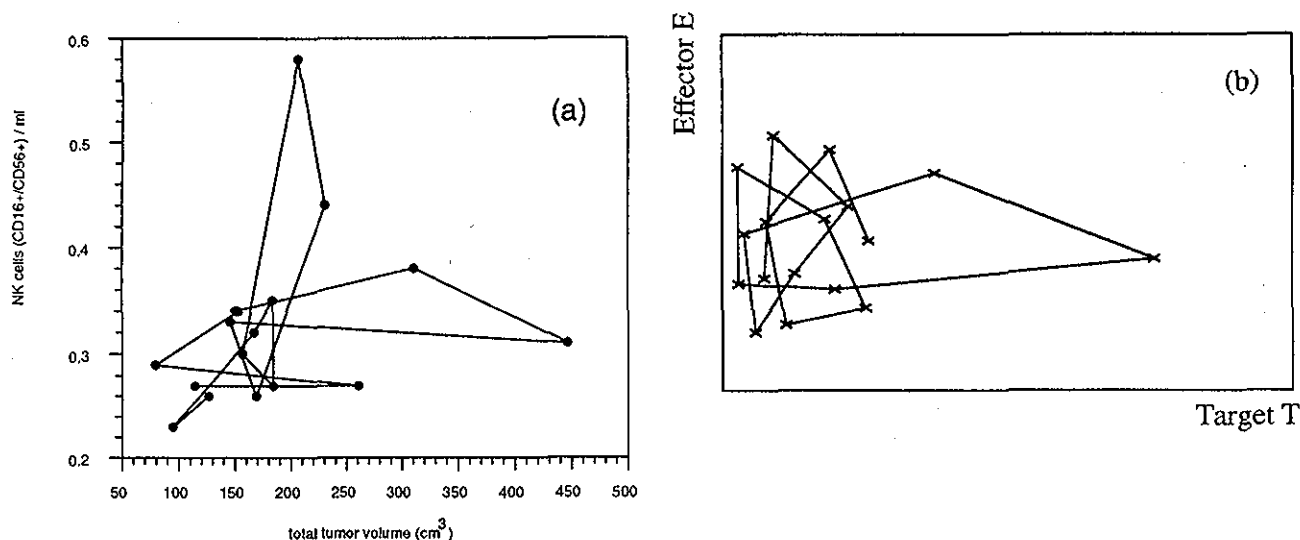


FIG. 5. (a) The NK cell and tumor relationship of a patient suffering from fibrosarcoma. (b) Calculations from the model based on the assumption of sinusoidally changing tumor reproduction rate. Chosen values are $r=0.7$, $k=1$, $p=0.5$, $s=1.4$, $u=v=1$, $n=3$, $\omega=0.97$, $A=0.7$; only points of the trajectory separated by 25 time units are plotted.

change sinusoidally and temporally equidistant samples have been taken from the trajectory. Hereby we demonstrate that even a chaotic behavior of the immune system can possibly be generated by a very small number of simple, fully deterministic conditions. Moreover, this model shows that uncorrelated data [like in Fig. 5(a)] do not necessarily exclude a strong connection between the measured quantities.

Of course, by these very few remarks on "chaotic behavior" we neither claim that the empirical data truly exhibit what is called "deterministic chaos" (which probably cannot be shown) nor do we suggest that our low dimensional model explains in any detail those irregular data.

IV. CONCLUSION

Here we stop this introductory discussion of the model. There are still more types of dynamic behavior occurring in other domains of the parameters.

In our opinion, there are at least two advantages of this rather simple and idealistic model which neglects many details. First of all, it shows clearly that the combination of a few mechanisms and interaction rules, as described by the right hand sides of our differential equations (3) and (4), can lead to a large variety of qualitatively different types of immune reactions corresponding to the large variety of phenomena in different diseases or even within a single disease. Second, the well developed techniques of phase plane analysis allow a nearly complete analytical discussion of the two-dimensional model, a goal that generally cannot be reached with high-dimensional systems. Of course, we do not claim, that more complicated models with more variables, for reviews see Refs. 22–27, become superfluous or even lose their significance by this approach. An introductory presentation of our model was given in Ref. 28.

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