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STABLE STATES OF BIOLOGICAL ORGANISMS

V.I. Yukalov
Department of Management, Technology and Economics,
Swiss Federal Institute of Technology, CH-8032 Zürich, Switzerland
Bogolubov Laboratory of Theoretical Physics,
Joint Institute for Nuclear Research, Dubna 141980, Russia
e-mail:yukalov@theor.jinr.ru
D. Sornette
Department of Management, Technology and Economics,
Swiss Federal Institute of Technology, CH-8032 Zürich, Switzerland
E.P. Yukalova
Department of Management, Technology and Economics,
Swiss Federal Institute of Technology, CH-8032 Zürich, Switzerland
Department of Computational Physics, Laboratory of Information Technologies,
Joint Institute for Nuclear Research, Dubna 141980, Russia
J.-Y. Henry
Institut de Médecine et Sciences Humaines,
10 route de Bremblens, CH-1026 Echandens, Switzerland
J.P. Cobb
Cellular Injury and Adaptation Laboratory,
Washington University, St. Louis, USA

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Abstract

A novel model of biological organisms is advanced, treating an organism as a self-consistent system subject to a pathogen flux. The principal novelty of the model is that it describes not some parts, but a biological organism as a whole. The organism is modeled by a five-dimensional dynamical system. The organism homeostasis is described by the evolution equations for five interacting components: healthy cells, ill cells, innate immune cells, specific immune cells, and pathogens. The stability analysis demonstrates that, in a wide domain of the parameter space, the system exhibits robust structural stability. There always exist four stable stationary solutions characterizing four qualitatively differing states of the organism: alive state, boundary state, critical state, and dead state.

1 Introduction

Biological organisms are among the most complex systems, requiring for their mathematical description rather elaborate equations [1–3]. Such equations are, as a rule, nonlinear, because of which they can possess different solutions, depending on the system parameters. The solutions of nonlinear equations are known to be very sensitive to the values of the control parameters. Sometimes, a slight variation of a parameter results in a discontinuous change of the system behavior, which is manifested in the qualitative change of its phase portrait. Such abrupt transformations of the phase diagram demonstrate the structural instability of the related dynamical system and are also called catastrophes [4]. In many cases, these catastrophes describe a real morphogenesis occurring in complex systems under the variation of the parameters. However, structural instability may also happen as an artifact, simply because a real complex system has not been correctly modelled by a dynamical system. It is therefore extremely important to carefully take into account the basic features of the real system, when modelling it by mathematical equations. Even a small term can essentially influence the behavior of a nonlinear dynamical system [5]. This especially concerns the terms reflecting fundamental symmetries of the complex system.

In the present paper, we consider such a very complicated biological system as an organism consisting of five components, healthy cells, ill cells, two types of immune cells, innate and specific, and pathogens. Our aim is twofold. First, we formulate the dynamical system describing the homeostasis of an organism as a whole, paying attention to the necessity that the action-counteraction exchange symmetry be preserved. The principal point in our description is the treatment not of some parts of an organism, but the study of the latter as a self-consistent system. Second, we perform the stability analysis and demonstrate that the system exhibits a remarkable structural stability: in a very wide range of parameters, there always exist only four stable stationary solutions characterizing four organism states: alive state, boundary state, critical state, and dead state. Such a structural stability found in the proposed dynamical system provides an important validation step for the model [6], as it captures one of the most important characteristics of biological organisms, that of adapting robustly to different conditions.

2 Construction of evolution equations

Let us consider biological species, enumerated with the index $i = 1, 2, \ldots$, the number of agents of the i-th type being N_i. Evolution equations can be represented either by differential or difference equations. Keeping in mind a very large number of interacting agents and the interaction times short as compared to the observation time, we employ here a picture with continuous time. The general structure of the dynamical system, describing the evolution of the species, can be represented as a set of differential equations

$$\frac{dN_i}{dt} = R_i N_i \; + \; \sum_i R_{ij} N_i N_j \; + \; F_i \; , \tag{1}$$

where t is time, R_i is a life rate, R_{ij} is an interaction intensity, and F_i is an influx. The quantities R_i and R_{ij} are treated as parameters. The influx F_i describes an input that is external with respect to the i-type species. That is, F_i may include a flux that is external for the organism as a whole and also it may describe a flux from other species. Generally, F_i can be a function of N_j, with $j \neq i$, such that

$$\frac{\partial F_i}{\partial N_i} = 0 \; . \tag{2}$$

To be self-consistent, the set of equations (1) has to satisfy two major requirements. First of all, the various processes included in the consideration must be of the same order of nonlinearity. This means that, since the interaction term in Eq. (1) is of second order, the fluxes F_i have also to be not higher than of second order with respect to N_j, with $j \neq i$.

Another important requirement is the existence of the *action-counteraction symmetry*. This means that, if in Eqs. (1) there occurs a term $R_{ij} N_i N_j$ then, these equations have to contain the exchange term $R_{ji} N_j N_i$. That is, if there is an action, there should exist a counteraction, which can be schematically formulated as the symmetry

$$R_{ij} N_i N_j \; \leftrightarrow \; R_{ji} N_j N_i \; . \tag{3}$$

Note that $R_{ij} \neq R_{ji}$ in general.

To specify a biological system, we consider an organism consisting of N_1 healthy cells, N_2 ill cells, N_3 innate immune cells, N_4 specific immune cells, and N_5 pathogens. The organism homeostasis is characterized by the processes and reactions between the cells and pathogens. A detailed medical description of these processes and reactions is given in Ref. [7]. Here, we shall list them only in brief, specifying the parameters R_j and R_{ij}, with taking account of the typical signs of these parameters.

(i) *Healthy cells* are characterized by a natural reproduction rate $R_1 \equiv A_1$. Since the body volume is limited, the carrying capacity limitation is governed by $R_{11} \equiv -A_{11}$. Ill cells do not interact directly with healthy cells, which implies that $R_{12} = 0$. Healthy cells can be occasionally attacked by innate as well as specific immune cells, hence $R_{13} \equiv -A_{13}$ and $R_{14} \equiv -A_{14}$, which causes autoimmune diseases. Pathogens infect healthy cells, thus $R_{15} \equiv -A_{15}$. We treat an organism as a self-organizing system, which means that healthy cells can be reproduced inside the organism, but are not supplied from exterior, that is, $F_1 = 0$.

(ii) *Ill cells* have either a natural death rate $R_2 \equiv -A_2$, when $A_2 > 0$, or can exhibit an unnatural proliferation, when $A_2 < 0$, which happens under certain diseases, such as cancer. Healthy cells do not directly interact with ill cells, so $R_{21} = 0$. The carrying capacity limitation for ill cells, while it may exist, is considered to be much larger than that for healthy cells, which allows us to set $R_{22} = 0$. Ill cells are killed and eliminated by immune cells, hence $R_{23} \equiv -A_{23}$ and $R_{24} \equiv -A_{24}$. The degradation of ill cells is increased under the influence of pathogens as the latter catalyze the immune system, hence $R_{25} \equiv -A_{25}$. The number of ill cells rises as a result of pathogens infecting healthy cells, which gives $F_2 = A_{51} N_5 N_1$.

(iii) *Innate immune cells* die by apoptosis, with a rate $R_3 \equiv -A_3$. They can be promoted by healthy cells, so $R_{31} \equiv A_{31}$. And they are activated by ill cells, $R_{32} \equiv A_{32}$. The carrying capacity of immune cells is much larger than that of healthy cells, which makes it admissible to set $R_{33} = 0$. Innate immune cells are activated by specific immune cells, hence $R_{34} \equiv A_{34}$. And they are activated by pathogens, $R_{35} \equiv A_{35}$. There is no external flux from outside of the organism, that is $F_3 = 0$.

(iv) *Specific immune cells* also have a finite lifetime, characterized by an apoptosis rate $R_4 \equiv -A_4$. They are promoted by healthy cells, $R_{41} \equiv A_{41}$, and are activated by ill cells, $R_{42} \equiv A_{42}$. Innate immune cells inhibit an excessive amount of specific immune cells, $R_{43} \equiv -A_{43}$. Similarly to innate cells, for specific immune cells, the carrying capacity limitation can be ignored, so that $R_{44} = 0$. Pathogens activate specific immune cells, hence $R_{45} \equiv A_{45}$. And there is no external flux, $F_4 = 0$.

(v) *Pathogens* are characterized by a natural decay rate $R_5 \equiv -A_5$. Their number does not depend on the number of healthy cells, $R_{51} = 0$. Pathogens proliferate by the lysis of ill cells, $R_{52} \equiv A_{52}$. They are killed and eliminated by innate, as well as specific immune cells, hence $R_{53} \equiv -A_{53}$ and $R_{54} \equiv -A_{54}$. The number of pathogens can be an order of or several orders larger than that of healthy cells. Therefore, there is practically no carrying capacity limitation for them, that is, it is safe to set $R_{55} = 0$. Contrary to all other organism cells, pathogens are supplied from the external surrounding, therefore $F_5 = F$ is not zero, but is to be treated as a parameter characterizing the environment in which the organism lives. In this letter, we only focus on a constant pathogen flux.

Taking into consideration the described processes transforms Eq. (1) to the set of five evolution equations

$$\frac{dN_1}{dt} = A_1 N_1 - A_{11} N_1^2 - A_{13} N_1 N_3 - A_{14} N_1 N_4 - A_{15} N_1 N_5 \; ,$$

$$\frac{dN_2}{dt} = -A_2 N_2 - A_{23} N_2 N_3 - A_{24} N_2 N_4 - A_{25} N_2 N_5 + A_{51} N_5 N_1 \; ,$$

$$\frac{dN_3}{dt} = -A_3 N_3 + A_{31} N_3 N_1 + A_{32} N_3 N_2 + A_{34} N_3 N_4 + A_{35} N_3 N_5 \; ,$$

$$\frac{dN_4}{dt} = -A_4 N_4 + A_{41} N_4 N_1 + A_{42} N_4 N_2 - A_{43} N_4 N_3 + A_{45} N_4 N_5 \; ,$$

$$\frac{dN_5}{dt} = -A_5 N_5 + A_{52} N_5 N_2 - A_{53} N_5 N_3 - A_{54} N_5 N_4 + F \; . \qquad (4)$$

Using explicitly Eqs. (4) is not convenient, since the numbers of cells are extremely large. For instance, the number of healthy cells is $N_1 \sim 10^{13}$, and the number of pathogens can be as large as

$N_5 \sim 10^{14}$ or more. Therefore, to be practical, Eqs. (4) are to be normalized by introducing a normalization constant N and defining the cell fractions

$$x_i \equiv \frac{N_i}{N} \qquad (i = 1, 2, 3, 4, 5) \; . \tag{5}$$

Note that the cell fractions do not sum up to 1, since N is arbitrary (but is introduced so that we deal with quantities of order 1).

Also, it is necessary to determine a time scale characterizing a typical duration of the homeostasis processes. We thus introduce a typical time scale τ. Then we define the dimensionless decays rates

$$\alpha_i \equiv A_i \tau \tag{6}$$

and the dimensionless interaction parameters

$$a_{ij} \equiv A_{ij} N \tau \; . \tag{7}$$

In addition, we define the dimensionless pathogen influx

$$\varphi \equiv \frac{\tau}{N} \, F \; . \tag{8}$$

Making use of the dimensionless quantities, and measuring time in units of τ, we reduce Eqs. (4) to the dynamical system

$$\frac{dx_i}{d\tau} = f_i \qquad (i = 1, 2, 3, 4, 5) \; , \tag{9}$$

with the right-hand sides

$$\begin{aligned}
f_1 &= \alpha_1 x_1 - a_{11} x_1^2 - a_{13} x_1 x_3 - a_{14} x_1 x_4 - a_{15} x_1 x_5 \; , \\
f_2 &= -\alpha_2 x_2 - a_{23} x_2 x_3 - a_{24} x_2 x_4 - a_{25} x_2 x_5 + a_{51} x_5 x_1 \; , \\
f_3 &= -\alpha_3 x_3 + a_{31} x_3 x_1 + a_{32} x_3 x_2 + a_{34} x_3 x_4 + a_{35} x_3 x_5 \; , \\
f_4 &= -\alpha_4 x_4 + a_{41} x_4 x_1 + a_{42} x_4 x_2 - a_{43} x_4 x_3 + a_{45} x_4 x_5 \; , \\
f_5 &= -\alpha_5 x_5 + a_{52} x_5 x_2 - a_{53} x_5 x_3 - a_{54} x_5 x_4 + \varphi \; .
\end{aligned} \tag{10}$$

Equations (9) and (10) are the basic equations describing the organism homeostasis.

3 Structural stability analysis

The dynamical system, given by Eqs. (9) and (10), contains 25 parameters α_j and a_{ij}, which appears to be an insuperable obstacle for studying its properties. The situation can be simplified by choosing appropriate scaling parameters N and τ. Thus, for the normalization constant N, we can take the capacity number of healthy cells

$$N = \frac{A_1}{A_{11}} \; . \tag{11}$$

As the temporal scale τ, it is reasonable to choose the characteristic time of healthy-cell reproduction

$$\tau = \frac{1}{A_1} \; . \tag{12}$$

With these scaling parameters, we have

$$\alpha_1 = 1 \; , \qquad a_{11} = 1 \; . \tag{13}$$

These values characterize the typical rates and interactions involved in the homeostasis of the organism.

As is noted above, ill cells can either exhibit a natural decay, when $\alpha_2 > 0$, or can show a pathological proliferation, when $\alpha_2 < 0$. It is convenient to use the notation

$$\beta \equiv \frac{1 - \alpha_2}{2} \; , \qquad \alpha_2 = 1 - 2\beta \; . \tag{14}$$

The value $\beta = 0$ corresponds to $\alpha_2 = 1 > 0$, while $\beta = 1$ corresponds to $\alpha_2 = -1 < 0$.

We may assume that the innate and specific immune cells enjoy the same apoptosis rate

$$\alpha \equiv \alpha_3 = \alpha_4 \; . \tag{15}$$

And let us set $\alpha_5 = 1$. We denote the parameters, associated with the interactions between immune and healthy cells as

$$b \equiv a_{13} = a_{31} = a_{14} = a_{41} \; . \tag{16}$$

When $b = 0$, immune cells do not attack healthy cells, hence there are no autoimmune diseases. Conversely, for $b > 0$, autoimmune disorders become possible. We also may assume that all other processes, except those related to Eq. (16), are characterized by the intensities being comparable to a_{11} (equal to 1 according to Eq. (13)). That is, we can put

$$a_{ij} = 1 \qquad (a_{ij} \neq b) \; . \tag{17}$$

In this way, we are left with four parameters, α, β, b, and φ.

The values of the parameters β and b control the occurrence of a chronic pathology or of an autoimmune disorder. Varying these parameters, we can reach four limiting cases.

(i) *No chronic pathology and no autoimmune disorder*:

$$\beta = 0 \; , \qquad b = 0 \; . \tag{18}$$

(ii) *No chronic pathology with autoimmune disorder*:

$$\beta = 0 \; , \qquad b = 1 \; . \tag{19}$$

(iii) *Chronic pathology but no autoimmune disorder*:

$$\beta = 1 \; , \qquad b = 0 \; . \tag{20}$$

(iv) *Chronic pathology and autoimmune disorder*:

$$\beta = 1 \; , \qquad b = 1 \; . \tag{21}$$

We can change the parameters β and b in the range between these limiting cases, thus, considering a variety of different organisms. For each fixed pair of β and b, we vary the parameters α and φ in a wide range, finding all admissible fixed points of the dynamical system. In the standard way, we accomplish the Lyapunov stability analysis and select the stable fixed points. In order to present the results of our analysis in the most illuminating form, it is useful to define the sum of the healthy-cell fraction and of the ill-cell fraction,

$$x \equiv x_1 + x_2 \; . \tag{22}$$

Also, we introduce the summary fraction of all immune cells

$$y \equiv x_3 + x_4 \; . \tag{23}$$

The main, and to some extent surprising, conclusion of the stability analysis for the dynamical system (9) is its remarkable structural stability. Varying the parameters β and b between the qualitatively different cases (18) to (21) always results, for any given β and b, in four stationary organism states characterized by the fixed-point values x^* and y^*.

A. Alive state:

$$x^* > 0 \; , \qquad y^* > 0 \; , \tag{24}$$

when there are both self-cells and immune cells.

B. Boundary state:

$$x^* > 0 \; , \qquad y^* = 0 \; , \tag{25}$$

when there are self-cells, but no immune cells.

C. Critical state:

$$x^* = 0 \; , \qquad y^* > 0 \; , \tag{26}$$

when only immune cells survive.

D. Dead state:

$$x^* = 0 \; , \qquad y^* = 0 \; , \tag{27}$$

when there are neither self-cells nor immune cells.

All these states are always present in the phase diagram on the $\alpha-\varphi$ plane. The boundaries between the states, of course, are different for different β and b, but all four states do remain stable.

The exact domains of stability for each of the states (24) to (27), as well as the values of all stationary fractions x_j^*, have been found numerically and, in some cases, analytically. Here, we illustrate the

results by the phase portraits corresponding to the limiting cases (18) to (21).

The case (18) of no chronic pathology and no autoimmune disorder is represented in the phase portrait of Fig 1. The case (19) of no chronic pathology but with autoimmune disorder is shown in Fig 2. In Fig. 3, the case (20) is demonstrated, when there is chronic pathology but there is no autoimmune disorder. And Fig. 4 illustrates the case (21), when there exist both chronic pathology as well as autoimmune disorder. As is seen, the boundaries between the states move when varying the system parameters, but all four states (24) to (27) are always present. The case (20) differs from other cases by the presence of a narrow region of bistable states. In this region, there exist large fluctuations of the coexisting states [8,9]. The dead state (27) is always located in the same part of the phase diagram.

We have also studied the case, when the pathogen influx randomly fluctuates around its mean value (8). In that case, the cell fractions also fluctuate in time. Then the picture, presented here, corresponds to the behavior of guiding centers that are defined by the averaging method [10].

Concluding, we have constructed a dynamical system describing the homeostasis of an organism as a whole. The organism is composed of five types of components: healthy cells, ill cells, innate and specific immune cells, and pathogens. A principal novelty in formulating the model is that we consider not some parts of an organism, but treat it as a total self-consistent system subject to the influence of pathogens. Another important point in constructing the evolution equations is that we take into account the action-counteraction symmetry (3). By varying the system parameters in a very wide range, we have shown that the dynamical system (9) enjoys a remarkable structural stability, always exhibiting four stable stationary states. These results remain valid if we include in the dynamical system (9) nonzero values of the carrying capacity limitations for ill cells and immune cells. We have also accomplished direct numerical solution of Eqs. (9) and (10), confirming the structural stability of the dynamical system.

Our basic aim here has been to present the new model of a biological organism and to accomplish a detailed stability analysis making it possible to find numerically the typical phase portraits. An important result of the present paper is the remarkable structural stability

of the studied biological system. The found four stable states characterize all basic states of an organism: alive relatively healthy state, boundary ill state, critically ill state, and the dead state.

We do not overload this paper by discussing various admissible medical interpretations and applications. This analysis will be the topic of separate publications.

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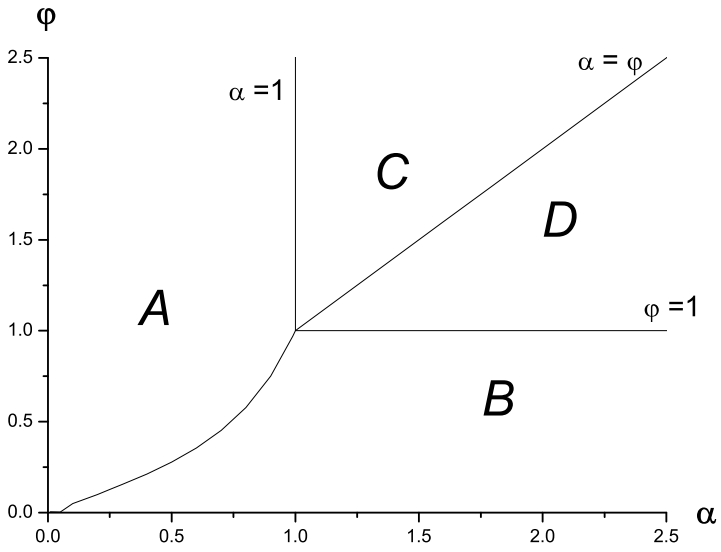

Figure 1: Phase portrait on the $\alpha - \varphi$ plane for the case (18) of no chronic pathology ($\beta = 0$) and no autoimmune disorder ($b = 0$), showing the stability domains of the stationary states (24) to (27).

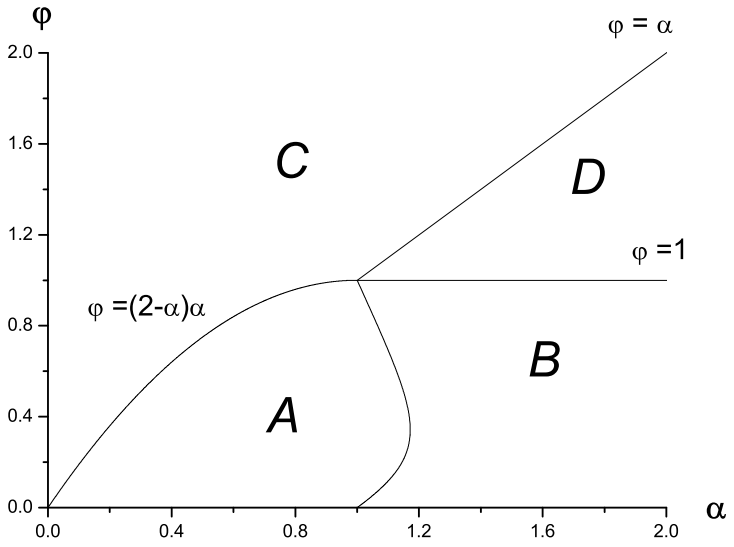

Figure 2: Phase portrait for the case (19) of no chronic pathology ($\beta = 0$) but with autoimmune disorder ($b = 1$), demonstrating the stability regions of the stationary states (24) to (27).

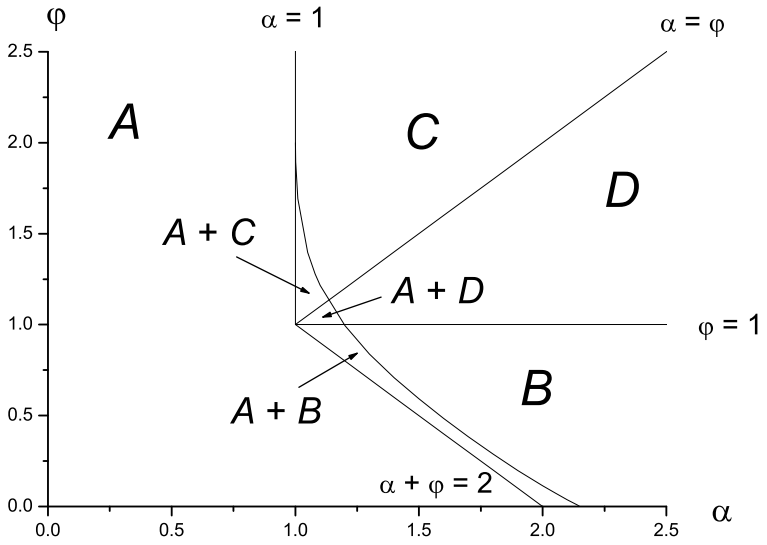

Figure 3: Phase portrait for the case (20), when there exists chronic pathology ($\beta = 1$) but there is no autoimmune disorder ($b = 0$). The peculiarity here is in the occurrence of bistable states.

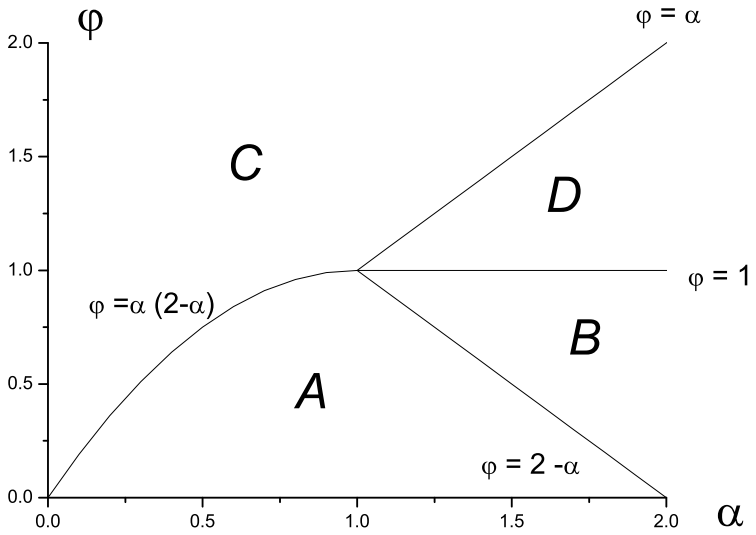

Figure 4: Phase portrait for the case (21), when both chronic pathology ($\beta = 1$) and autoimmune disorder ($b = 1$) are present. The classification of the stationary states is the same as in Eqs. (24) to (27).

Comment

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Comment on STABLE STATES OF BIOLOGICAL ORGANISMS

Richard Kerner
Laboratoire de Physique Théorique de la Matière Condensée,
Université Pierre-et-Marie-Curie - CNRS UMR 7600
Tour 22, 4-ème étage, Boîte 121,
4, Place Jussieu, 75005 Paris, France

This article deals with a mathematical model considering any living organism as a dynamical system ruled by certain number of parameters. Of course, the utmost complexity of biological organisms makes it impossible to take into account all the influences, be they external or internal, that tend to modify its state and which may also have a retarded effect. One of the critical remarks that could be formulated from the very beginning is that the authors do not take into account this aspect of living oganisms, which would lead to differential equations with retarded parameters, applied to the study of living organisms and the equilibrium between species since the famous Volterra model.

But the critical remarks of this kind are often sterile and lead nowhere - after all, no model, especially trying to describe this extremely complex realm, can pretend to take into account all the essential parameters ruling system's behavior. The authors choose *five*

parameters characterizing the state of a multicelluler organism subjected to a *constant* (which, by the way, represents a serious limitation of the model they present) influx of pathogen cells from the surrounding medium. The cells are divided into four groups, the *healthy cells*, the *innate immune cells*, the *specific immune cells* and the *ill cells*. The numbers of cells of each kind are the dynamical parameters of the organism, ruled by kinetics described by the differential system (4).

This dynamical system is then analyzed with traditional methods, revealing *four* singular solutions whose stability can be tested by linearization and the subsequent analysis of their Lyapunov exponents.

The paper is interesting, concise and well written. The argument is clear and quite convincing; nevertheless, many questions remain open, e.g. the stability of the entire picture in phase space under the addition of extra dimension (a new parameter taken into account). But this will be perhaps the subject of next publications by the same authors.

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