DIFFERENTIAL STOCHASTIC APPROACH TO HOMEOSTASIS

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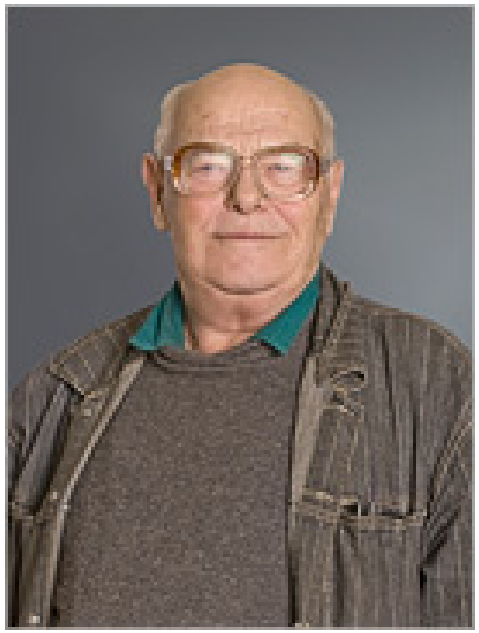
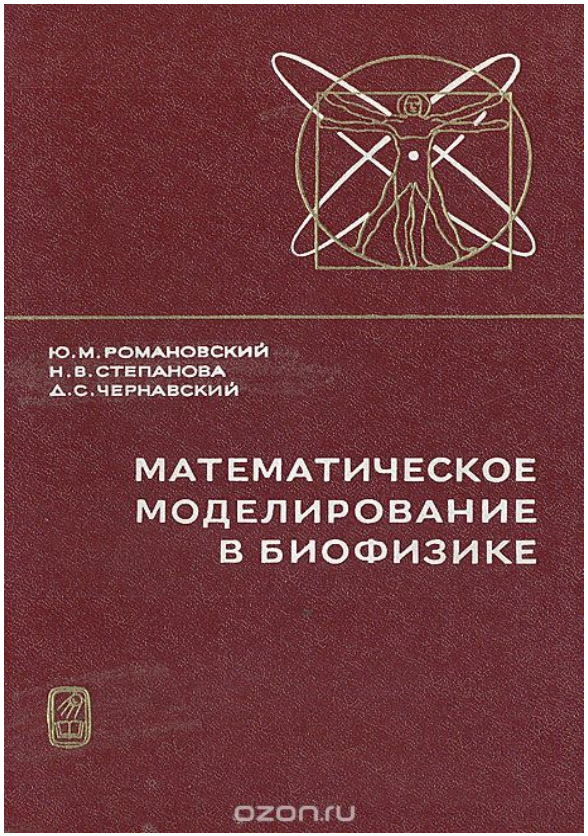
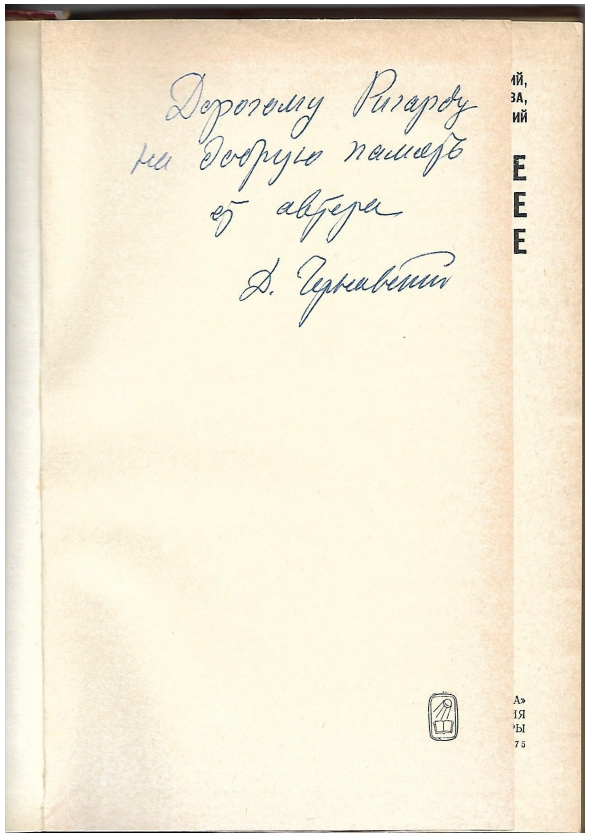
This lecture is dedicated to the memory of Dmitry Sergeyevich Chernavsky, who passed away in Moscow on June 19, 2016, at the age of 90.

Dmitry Sergeyevich Chernavsky, 24/02/1926 – 19/06/2016**.**



As early as in 1976 Professor Chernavsky was my first mentor in biomathematics. We have spent together three months in Utrecht, where he was invited by Theo Ruijgrook, and I was a visiting research felow invited by Martinus Veltman.





The book on Mathematical Modelling in Biophysics, by Yu.M. Romanovsky, N.V. Stepanova and D.S. Chernavsky, with Dmitry Sergeyevich's dedication, 1976.

- **Dmitry Sergeyevich Chernavski was not only an outstanding scientist, but also an exceptional man of wisdom and heart. He is duly regarded as one of the founding fathers of Russian school of mathematical biology and of entirely new domain of *synergetics*, with many successful followers and collaborators.**

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- But he also extended his hand to fellow scientists whenever they needed help; he served as messenger to Andrei Sakharov during his exile in Gorkiy town.
- In 2004 he won the highest prize ever awarded in Russia, for his contribution to the TV contest devoted to scientific discoveries. He divided the prize among the 192 competitors (including himself), giving 5000 euros to everyone.

Introduction

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- **In this lecture we present a few applications of differential analysis of dynamical changes and evolutionary trends in biological systems.**
- **First-order non-linear differential systems can successfully describe dynamics of interacting populations belonging to various species, but also the evolution of total numbers of living cells, antigens and antibodies.**
- **As usual with very big numbers, a continuous limit is proposed, consisting in replacing the actual numbers by relative probabilities of finding a specific item, a living organism or a specific cell.**

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- **The Lotka-Volterra type equations represent one of the best tools of modelling the variations in population density of coexisting biological species.**
- **In this tutorial lecture we shall sketch a brief history of mathematical modelling of biological systems, then give examples of applications of Lotka-Volterra type equations to population dynamics, immunology and homeostasis.**

- **The simplest paradigm of population dynamics can be represented by the symbolic differential equation:**

$$\frac{\Delta N}{\Delta t} \simeq [\text{birth rate}] - [\text{mortality rate}] + [\text{migration}] \quad (1)$$

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- The birth and mortality rates' definition is obvious; the "migration" term can be positive or negative, depending on the situation: it takes into account the difference between the incoming and the outcaming flux of members of considered population.

- **The first equation describing the population growth (without migration term) was proposed by Leonhard Euler as early as in 1748:**

$$P_{n+1} = (1 + x)\, P_n = (1 + x)^n\, P_O. \tag{2}$$

where x is the *relative growth rate* per unit of time (usually a year).

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- **The continuous limit**

$$\lim_{n\to\infty} \left(1 + \frac{x}{n}\right)^n = e^x.$$

defines the exponential function, introduced by Euler.

Later on **(1798) Thomas Malthus** gave the continuous version of Euler's equation:

$$\frac{dN}{dt} = b\,N - d\,N, \tag{3}$$

whose solution is

$$N(t) = N_0\; e^{(b-d)(t-t_0)}, \quad \text{where} \;\; N_0 = N(t_0). \tag{4}$$

$b > d$ leads to exponential growth, $b < d$ leads to exponential extinction, and only strict equality $b - d = 0$ ensures the stability (solution in form of a constant).

- In real life the resources are not infinite; when they come to exhaustion, the death rate of the species which needs them for sustaining its life becomes higher than the birth rate, and instead of growing, population starts to diminish until the resources become again sufficient.

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- Pierre-François Verhulst (1838, 1845) proposed the following modification of Malthus' law:

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right), \tag{5}$$

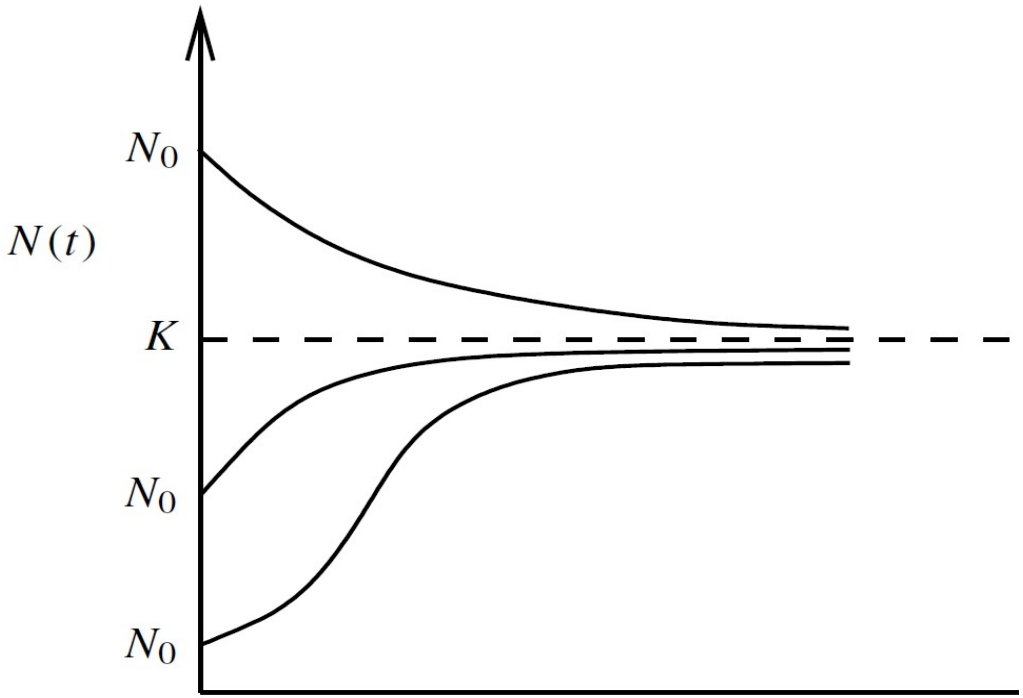
where K is the maximal population size compatible with maintaining renewable resources at a constant level.

The solution is:

$$N(t) = \frac{N_0 K \; e^{r(t-t_0)}}{K + N_0 \left(e^{r(t-t_0)} - 1\right)}. \tag{6}$$

and tends asymptotically to the limit value K, the maximal population able to survive on finite resources.

Graphical representation is shown in the Figure on the next slide.



Example of population evolution in Verhulst's model

- **Benjamin Gompertz added an extra hypothesis to Verhulst's model, with mortality rate exponentially growing when the resources do not suffice to sustain the species:**

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- **which is a limiting case of a more general equation (Birch, 1999):**

$$\frac{dN}{dt} = rN\left(1 - \left(\frac{N}{K}\right)^{\frac{1}{\nu}}\right). \tag{8}$$

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- $$\frac{dN}{dt} = rN\left(1-\frac{N}{K}\right)\left(\frac{N}{K_0}-1\right). \tag{9}$$

  where K_0 is the threshold population under which extinction becomes inevitable.

- **In some cases retardation effects must be taken into account:**

$$\frac{dN}{dt} = f\left(N(t), N(t-\tau)\right). \tag{10}$$

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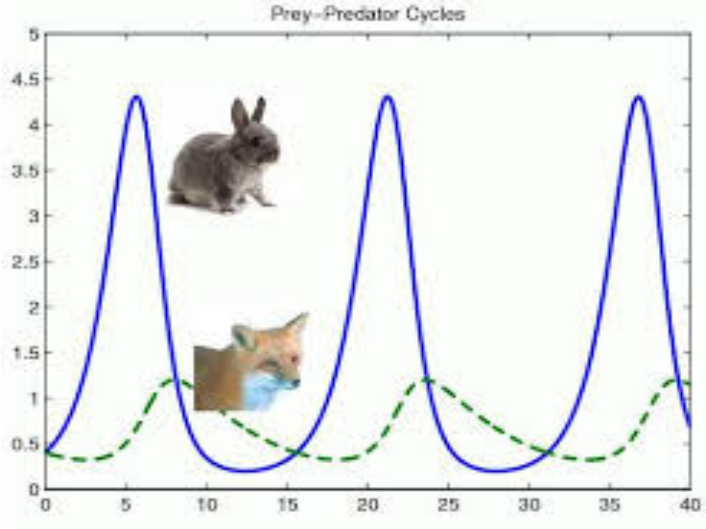
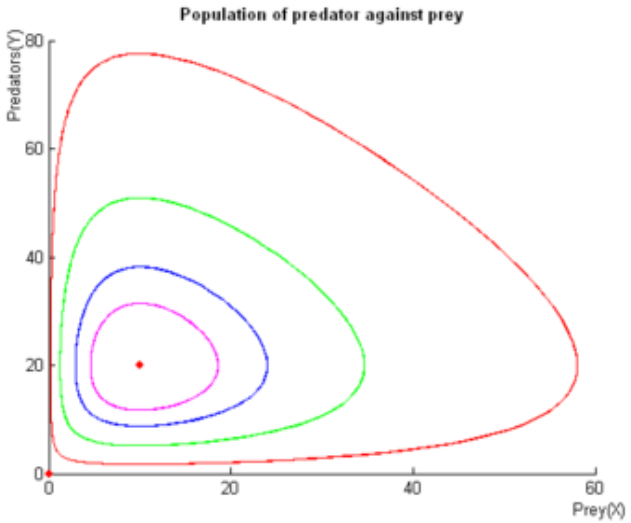
- This type of equation is used for the description of systems with periodic bursts of one of the populations, e.g. periodic illnesses like malaria, with the three-day cycle of parasite population in blood.

In 1931 Vito Volterra, (1860-1940), formulated and studied a general model based on quadratic differential equation, which since then bears his name along with Alfred J. Lotka, (1880-1949).





Typical time evolution of total numbers of prey (green) and predator (blue). On the right, the phase portrait of the system

The Lotka-Volterra equations

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- **The simplest model is given by two species only, the prey x and the predator y. The evolution of their (relative) numbers can be described as follows:**

The Lotka-Volterra equations

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- **which leads to the following differential system:**

$$\frac{dx}{dt} = Ax - Bxy, \qquad \frac{dy}{dt} = -Cy + Dxy.$$

The Lotka-Volterra systems have been used for description of a countless number of processes, not only in biology, but also in chemistry, solid state physics, microbiology and virology.
The most general Lotka-Volterra system, with m interacting and competing species takes on the following form:

$$\frac{dN_i}{dt} = N_i \left(b_i + \Sigma_{j=1}^{m} a_{ij} N_j\right). \tag{11}$$

A non-trivial equilibrium point $(\bar{N}_1, \bar{N}_2, ..., \bar{N}_m)$ is the solution of the system of m algebraic equations

$$b_i + \Sigma_{j=1}^{m} a_{ij} N_j = 0, \quad i = 1, 2, ..., m. \tag{12}$$

- **The predator-prey model has been extended independently by Lotka and Volterra already in the early thirties. The generalized version describes two or more coexisting species competing for food (or prey).**

$$\frac{dN_i}{dt} = r_i N_i \left(1 - \frac{N_i}{K_i} - \Sigma_{j=1}^{m} \alpha_{ij} \frac{N_j}{K_i}\right) \tag{13}$$

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- Here N_i is the population density of i-th species, r_i is the growth rate of i-th species when the numbers N_i are relatively *low*; K_i denote the carrying capacity of i-th species, and α_{ij} is the linear reduction of the i-th species due to the negative influence of the j-th species.

- **The model with two competing species was checked experimentally in early seventies M.E. Gilpin and F.J. Ayala, PNAS, 70 (12), pp. 3590-3593 (1973) on two different populations of Drosophila flies evolving in a closed environment with limited resources: *Drosophila Willistoni* and *Drosophila pseudoobscura*.**

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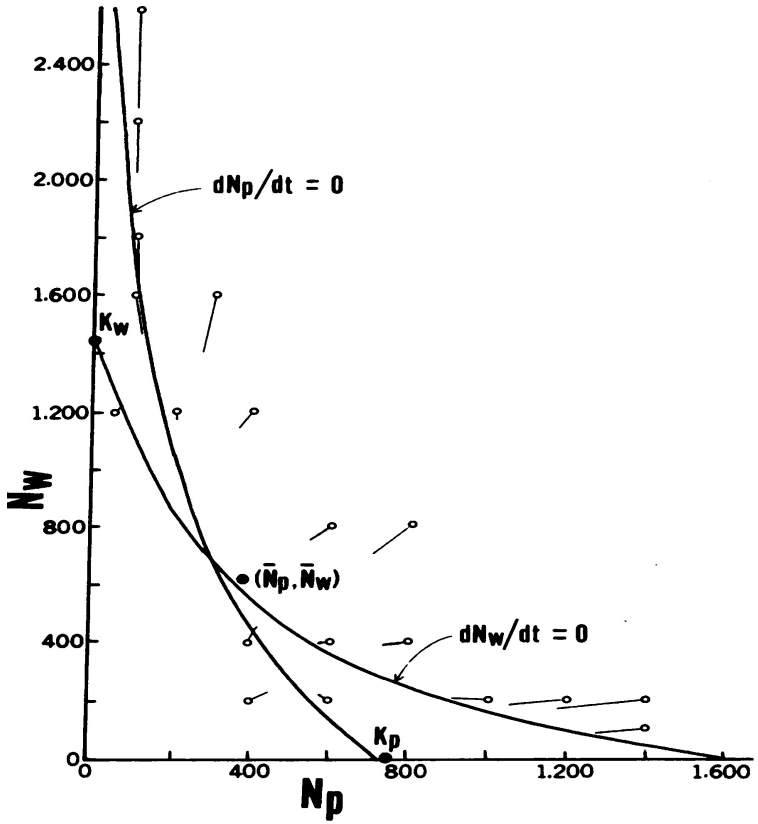
- The experimental results are visualized in the figure 23 in the form of vectors representing time derivatives

$$\left[\frac{dN_P}{dt}, \frac{dN_W}{dt}\right].$$

In many places those vectors are not horizontal close to the isoclines; which is far from being satisfactory.



The phase portrait of Lotka-Volterra system with two competing species. The isoclines, $dN_W/dt = 0$ and $dN_P/dt = 0$ separate regions with positive and negative growth for N_W and N_P.

In their 1973 paper Gilpin and Ayala proposed two alternative modifications of the classical Lotka-Volterra system, which in the two-component case introduce only one extra parameter to the model.

$$(A) \quad \frac{dN_i}{dt} = r_i N_i \left(1 - \left(\frac{N_i}{K_i}\right)^{\theta_i} - \Sigma_{j=1}^{m} \alpha_{ij} \frac{N_i}{K_i}\right). \qquad (14)$$

$$(B) \quad \frac{dN_i}{dt} = r_i N_i \left(1 - \frac{N_i}{K_i} - \Sigma_{j=1}^{m} \alpha_{ij} \frac{N_i}{K_i} - \beta_i \frac{N_i^2}{K_i}\right). \qquad (15)$$

Both models reduce to the classical model when $\theta_i = 1$ in the model (A), or when $\beta_i = 0$ in the model (B)

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- The non-vanishing parameter β in the model **(B)** supposes the existence of a social cooperation, which seems to be absent in the case of *Drosophila*. On the other hand, introducing the extra parameter θ_i in the **(A)** model gives the possibility to break the symmetry imposed in its absence in the two competeng species model, where the stability is achieved at equal numbers $\bar{N}_i = \frac{K}{2},\ i = 1, 2.$

In human populations interaction between two competing groups or communities can be described by **Lotka-Volterra system** with extra term corresponding to an incoming (or outcoming) population flux. A yearly balance of two populations whose initial numbers at the time t_1 are N_1 and N_2, after a year $(t \to t + \Delta t)$ changes by:

$$\Delta N_1 = \Delta s_1 + \alpha_1 N_1 + \beta_1 \ N_1 N_2,$$

$$\Delta N_2 = \Delta s_2 + \alpha_2 N_1 + \beta_2 \ N_1 N_2,$$

The coefficients β take into account the phenomenon of *conversion*, when the encounter with individuals of the second species transforms the members of one population into members of the other one. The increments Δs_1 and Δs_1 take into account the incoming or outcoming populations of both kinds.

- **Continous limit gives the following differential system:**

$$\frac{dN_1}{dt} = s_1 + N_1\left(\alpha_1 + \beta_1 N_2\right),$$

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- **It is easy to see that even when initially one has $N_1/N_2 \leq 0.05$ (less than five per cent), but if $s_1 \leq 0$ and $s_2 > 0$, and if at the same time $\beta_1 < 0$ while $\beta_2 > 0$, in a finite time (and usually more rapidly that one can imagine) the population 2 will become dominant, and finally will replace the population 1 .**

  Examples abound, also in recent history.

- **The problem of stability of solutions is very important. Levontin (1969) and May (1974) noted that Lotka-Volterra systems whose interaction matrix a_{ij} is *antisymmetric* are structurally unstable. In a paper published in 1977 B.S. Goh analyzed global stability of general Lotka-Volterra systems.**

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- **By definition, the equilibrium is feasible if $\bar{N}_i > 0$ for all $i = 1, 2, ..., m$. However, even if such an equilibrium is stable, it does not mean that stability will be observed in the more or less remote vicinity.**

- **An example of local stability combined with global instability: Let N_1 be the total predator number, N_2 the total number of prey.**

$$\frac{dN_1}{dt} = N_1 \ (-11 + N_1 + N_2)$$

$$\frac{dN_2}{dt} = N_2 \ (5.6 - 0.6N_1 - 0.5N_2) \qquad (16)$$

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- **We find easily the non-trivial stationary solution:**

$$\bar{N}_1 = 1, \quad \bar{N}_2 = 10. \tag{17}$$

In order to check the stability of this solution against small perturbations one should find the eigenvalues of the following matrix:

$$\bar{N}_i a_{ij}$$

(no summation over i). In the example cited here we have

$$a_{ij} = \begin{pmatrix} 1 & 1 \\ -0.6 & -0.5 \end{pmatrix},$$

so that

$$\bar{N}_i a_{ij} = \begin{pmatrix} 1 & 1 \\ -6 & -5 \end{pmatrix}$$

- **The eigenvalues are**

$$-2 \pm \sqrt{3}.$$

Both are negative, therefore the point $1, 10$ **is stable. However, the initial conditions**

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- **This example provides a plausible description of how a pest population which feeds on a plant species and whose population density is normally at low level, could sustain a population explosion when a burst of good weather shifts initial conditions.**

Graphical analysis of two species competition have given rise to a general expectation that in all Lotka-Volterra models of competition, *local stability* implies *global stability* in the feasible region. However, the following example puts an end to this illusion.

$$\frac{dN_1}{dt} = N_1\left(2 - 0.8N_1 - 0.7N_2 - 0.5N_3\right),$$

$$\frac{dN_2}{dt} = N_2\left(2.1 - 0.2N_1 - 0.9N_2 - N_3\right),$$

$$\frac{dN_3}{dt} = N_3\left(1.5 - N_1 - 0.3N_2 - 0.2N_3\right),$$

The non-trivial equilibrium solution is found at

$$\left(\bar{N}_1, \bar{N}_2, \bar{N}_3\right) = (1, 1, 1).$$

- **The above stationary solution**

$$\left(\bar{N}_1, \bar{N}_2, \bar{N}_3\right) = (1, 1, 1).$$

is stable because the eigenvalues of the matrix $(\bar{N}_i\ a_{ij}$ **are approximatively**

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- **However, a computer simulation shows that starting from the initial state**

$$(\bar{N}_1, \bar{N}_2, \bar{N}_3) = (0.5, 1, 2).$$

the solution tends rapidly to a totally different situation, with

$$(\bar{N}_1, \bar{N}_2, \bar{N}_3) = (0, 0, 7.5).$$

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- **A theorem by B.S. Goh (1977) sheds more light on the conditions under which *global stability* in Lotka-Volterra systems can be achieved. It states what follows:**
- **If the non-trivial equilibrium$(\bar{N}_1, \bar{N}_2, ...\bar{N}_m)$ of the Lotka-Volterra system**

$$\frac{d\vec{N}}{dt} = \vec{b} + A\vec{N}$$

is feasible, and if there exists a constant positive diagonal matrix C such that $CA + A^T C$ is *negative definite*, then the system is globally stable in the feasible region.

Recently (2014) Nick Britton discussed a generalization of the Lotka-Volterra model of competing species to the case including sources with constant flux:

$$\frac{dN_i}{dt} = s_i + N_i \left(b_i + \Sigma_{j=1}^{m} a_{ij} N_j \right), \tag{18}$$

which reduces to the standard Lotka-Volterra system for $s_i = 0, \quad i = 1, 2, ..., m.$

Britton generalized Goh's theorem for the case when $s_i \geq 0$**.**

In both cases the proof uses *Lyapunov's function*. The matrix C being equal to

$$C = \mathrm{diag}(c_1, c_2, ..., c_m),$$

Lyapunov's function is given by

$$V = \Sigma_{i=1}^{m}\, c_i \left[N_i - \bar{N}_i - \bar{N}_i \ln \frac{N_i}{\bar{N}_i} \right]. \qquad (19)$$

For large values of $\frac{N_i}{\bar{N}_i}$, the Lyapunov function is proportional to the energy of the species stored in its biomass.

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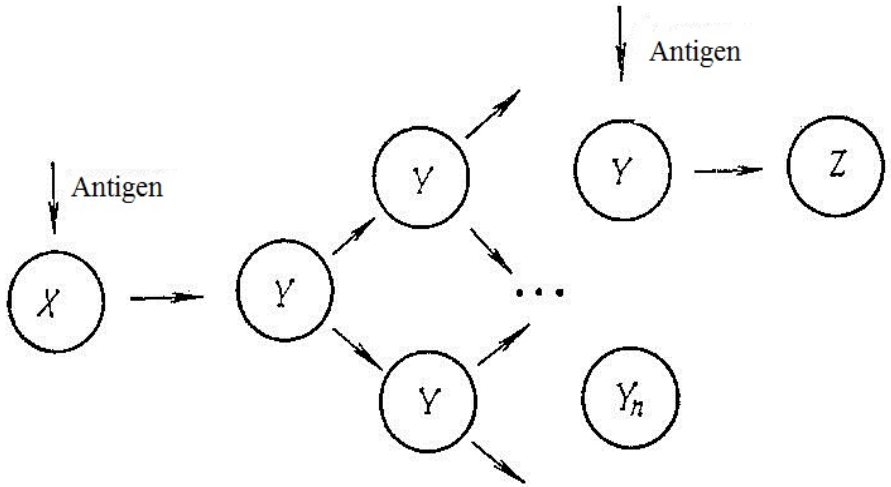
- Immunity reaction of living creatures, when it is successful, leads to a dynamical equilibrium that describes stationary state of organisms defending themselves against external agressions: bacteria, viruses, parasites, appearing in mathematical model under a common name *antigens* or *pathogens*.
- In organisms able to fight the intruder ("antigen") by producing antibodies, i.e. proteins able to neutralize the antigen of a given type, cells can be divided into three categories, which we shall denote by corresponding symbols X, Y and Z.



Transformations of cells under antigen's influence: after first encounter, "precursor calls" X transform into antibody producing cells Y; after second encounter, the Y cells are transformed into Z cells, more intensely productive, but not proliferating.

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  - The cells X are "precursors"; they circulate in organism's lymphatic system, and after some time, if they do not encounter antigen, die and are removed.

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- - The Y cells transform themselves into Z cells after a second contact with antigen. The Z cells produce antibodies more massively, but cannot divide anymore, because they are deprived of nucleus.

Here is the set of dynamical equations regulating the numbers of cells of the three types, X, Y and Z:

$$\frac{dX}{dt} = \nu - k_x\, X - \alpha_x\, XG;$$

$$\frac{dY}{dt} = \alpha_x\, XG + f(G)\, Y - \alpha_y\, YG - k_y\, Y;$$

$$\frac{dZ}{dt} = \alpha_y\, YG - k_z\, Z;$$

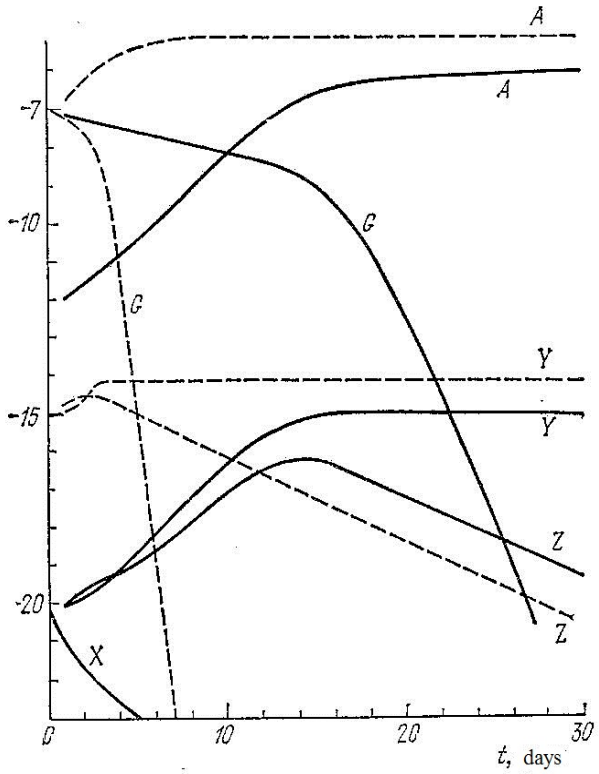
here $f(G) = \frac{mG}{K+G}$, where $\frac{1}{m}$ is the average time of reproduction of cells of Y type when the antigen supply becomes very high.

In order to close the system we have to add two extra equations for variations of antigens and antibodies:

$$\frac{dG}{dt} = \beta_0\ G - k_g\ G - l_g\ (AG)^n;$$

$$\frac{dA}{dt} = h_y\ Y + h_z\ Z - k_a\ A - l_a\ (AG)^n.$$

In most cases it is enough to assume that $n = 1$.



The response of the organism attacked by pathogens. Continuous lines: first reaction, Hatched lines: second reaction, with acquired immunity.

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- Homeostasis is the property of a system within an organism in which a variable, such as the concentration of a substance in solution, is actively regulated to remain very nearly constant.
- Examples of homeostasis include the regulation of body temperature or the concentrations of various ions, as well as that of glucose in the blood plasma, despite changes in the environment. Each of these variables is controlled by a separate regulator or homeostatic mechanism, which, together, maintain life.

The model of homeostasis presented here is due to V.I. Yukalov, D. Sornette, E.P. Yukalova, J-Y. Henry and J.P. Cobb,

arXiv : 0907.4628v1 [physics.bio-ph] (2009)

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It extends the previous model so as to include the numbers of immune cells of two types, naturally immune and with acquired immunity, infected cells, and dead cells.

Non-linear equations governing cell population.

- **A living organism can be regarded upon as a self-consistent system of cells subjected to an external pathogen flux.**

Non-linear equations governing cell population.

- **A living organism can be regarded upon as a self-consistent system of cells subjected to an external pathogen flux.**
- **Let us introduce *five* types of cells:**
  - **The healthy cells,**
  - **The ill cells,**
  - **Innate immune cells,**
  - **Specific immune cells,**
  - **Pathogens.**

- **Their respective numbers will be denoted by**

$$N_1,\ N_2,\ N_3,\ N_4\ N_5.$$

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- **The evolution equations should take into account the natural *life rate* of each species, the *interaction intensity* which defines the influence one of the species exerts on another one, and finally the *influx rate*, which here concerns mostly the pathogen cells invading the organism from the exterior.**

- **The general form of the evolution system is as follows:**

$$\frac{dN_i}{dt} = R_i N_i + \sum_j R_{ij} N_i N_j + F_i.$$

Here t **is time,** R_i **is the** *life rate*, R_{ij} **the** *interaction intensity* **and** F_i **the** *influx*.

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- **The quantities** R_i **and** R_{ij} **are treated as parameters, whether the influx** F_i **contains the** *external influx* **as well as the** *internal* **one, coming from cells in the organism itself. The latter part of the influx is usually a function of** N_j **with** $j \neq i$.

- In order to avoid inconsistency, we should assume that the influx terms cannot be more than quadratic functions of the N_i, as were the interaction terms. Also, if there is a non-zero term R_{ij}, then there should be, as a reaction to it, the conjugate term R_{ji}, although in general $R_{ij} \neq R_{ji}$.

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- Let us consider the living organism as a collection of N_1 healthy cells, N_2 ill cells, N_3 innate immune cells, N_4 specific immune celles, and N_5 pathogens.

1) *Healthy cells* **are characterized by a natural reproduction rate** $R_1 = A_1$**. The carrying capacity is limited, due to the finite size of the organism, by the negative coefficient** $R_{11} = -A_{11}$**,** $A_{11} > 0$**. We suppose that ill cells do not interact with the healthy ones, hence** $R_{12} = 0$**.**

2) *Ill cells* **have their natural reproduction rate** $R_2 = -A_2$**, with** $A_2 > 0$**. They can also exhibit unnatural proliferation when** $A_2 <$**, which happens when there is a cancer developing. Healthy cells do not usually interact with ill cells, therefore we shall set** $R_{12} = 0$**. Ill cells are usually of one or two orders of magnitude less numerous than the healthy ones, hence we shall set** $R_{22} = 0$**. Ill cells are killed and eliminated by immune cells, therefore we shall set** $R_{23} = -A_{23}$ **and** $R_{24} = -A_{24}$**, with** $A_{23} > 0$ **and** $A_{24} > 0$**.**

The degradation of ill cells is increased under the influence of pathogens, as the latter catalyze the immune system, therefore $R_{25} = -A_{25}$.
Finally, the number of ill cells rises as the pathogen infect the healthy cells, so we set $F_2 = A_{51} N_5 N_1$.

- **3)** *Innate immune cells* **die by apoptosis, like the healthy cells, with a rate** $R_3 = -A_3$**. They can be promoted by healthy cells, so** $R_{31} = A_{31}$**, or activated by ill cells, so** $R_{32} = A_{32}$**. The carrying capacity of immune cells is much larger than that of healthy cells, so we may set** $R_{33} = 0$**.**

- 3) *Innate immune cells* die by apoptosis, like the healthy cells, with a rate $R_3 = -A_3$. They can be promoted by healthy cells, so $R_{31} = A_{31}$, or activated by ill cells, so $R_{32} = A_{32}$. The carrying capacity of immune cells is much larger than that of healthy cells, so we may set $R_{33} = 0$.
- Innate immune cells are activated by specific immune cells, therefore $R_{34} = A_{34}$, and by the pathogens as well, so $R_{35} = A_{35}$. There is no external flux from the outside of the organism, so that $F_3 = 0$.

4) *Specific immune cells* also have a finite lifetime, characterized by their apoptosis rate $R_4 = -A_4$. They can be promoted by healthy cells, so we set $R_{41} = A_{41}$, or activated by ill cells, $R_{42} = A_{42}$. Innate immune cells inhibit an excessive amount of specific immune cells, therefore $R_{43} = -A_{43}$. As in the case of innate immune cells, there is no carrying capacity limitation, so $R_{44} = 0$. Pathogens activate specific immune cells, hence $R_{45} = A_{45}$. And there is no external flux, so $F_4 = 0$.

5) *Pathogens* **are characterized by a natural decay rate** $R_5 = -A_5$. **Their number does not depend on the number of healthy cells, so** $R_{51} = 0$. **Pathogens proliferate by lysis of ill cells, therefore** $R_{52} = A_{52}$. **They are killed and eliminated by innate as well as by the specific immune cells, so we have** $R_{53} = -A_{53}$.

The number of pathogens can be of an order or of several orders larger than the number of that of the healthy cells. Therefore there is practically no carrying capacity limitation for them, i.e. we can set $R_{55} = 0$.

Contrary to all other cells, the external flux is not zero, so $F_5 = F$. **Here we suppose that the exterior pathogen flux is constant.**

Taking into account all these assumtions leads to the following differential system:

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

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

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

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

$$\frac{dN_5}{dt} = A_5\,N_5 - A_{52}\,N_5 N_2 - A_{53}\,N_5 N_3 - A_{54}\,N_5 N_4 + F\,.$$

The numbers in the above equations are very great, so we should turn to relative concentrations, or probabilities of encounter of a given cell state among all cells. Usually the number of healthy cells is about $N_1 \simeq 10^{13}$, and the number of pathogens can be even greater, close to $N_5 \simeq 10^{14}$. It is natural to introduce the reduced variables:

$$x_i = \frac{N_i}{N}, \quad i = 1, 2, 3, 4, 5.$$

The sum of the x_i is not necessarily normalized to 1, but are of the same order of magnitude.

It is also necessary to determine a time scale characteristic of the system, and representing a typical duration of the homeostasis processes. Let us call this typical scale τ. Then we can define dimensionless decay rates

$$\alpha_i = A_i \tau;$$

and the dimensionless interaction parameters

$$\alpha_{ij} = A_{ij} N \tau.$$

and finally, the dimensionless pathogen influx:

$$\varphi = \frac{\tau}{N} F.$$

$$\frac{dx_k}{d\tau} = f_k$$

$$f_1 = \alpha_1 x_1 - \alpha_{11} x_1^2 - \alpha_{13} x_1 x_3 - \alpha_{14} x_1 x_4 - \alpha_{15} x_1 x_5$$

$$f_2 = \alpha_2 x_2 - \alpha_{23} x_2 x_3 - \alpha_{24} x_2 x_4 - \alpha_{25} x_2 x_5 + \alpha_{51} x_5 x_1$$

$$f_3 = \alpha_3 x_3 + \alpha_{31} x_3 x_1 + \alpha_{32} x_3 x_2 + \alpha_{34} x_3 x_4 - \alpha_{35} x_3 x_5$$

$$f_4 = \alpha_4 x_4 + \alpha_{41} x_4 x_1 + \alpha_{42} x_4 x_2 - \alpha_{43} x_4 x_3 + \alpha_{45} x_4 x_5$$

$$f_5 = \alpha_5 x_5 + \alpha_{52} x_5 x_2 - \alpha_{53} x_5 x_3 - \alpha_{54} x_5 x_4 + \varphi$$

Simplifying assumptions

- **In order to make this model operational, we must make some simplifying assumptions. First of all, we shall take for the normalizing constant N the capacity number of healthy cells,**

$$N = \frac{A_1}{A_{11}}$$

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- **The characteristic temporal scale τ can be identified with the characteristic time of healthy cells' reproduction,**

$$\tau = \frac{1}{A_1}$$

With this choice of scaling parameters we have

$$\alpha_1 = 1, \quad \alpha_{11} = 1.$$

Ill cells can either exhibit a natural decay, when $\alpha_2 > 0$, or they can show a pathological proliferation, when $alpha_2 < 0$. Let us introduce the parameter β such that

$$\beta = \frac{1 - \alpha_2}{2}, \quad \alpha_2 = 1 - 2\beta.$$

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

- **Next simplifying (but still quite realistic) assumptions are:**
  1) The innate and specific immune cells have the same apoptosis rate,

$$\alpha_3 = \alpha_4 = \alpha,$$

  and let us set also $\alpha_5 = 1$

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  1) The innate and specific immune cells have the same apoptosis rate,

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  and let us set also $\alpha_5 = 1$
- **2) Let also all interactions between healthy and immune cells be of the same strength:**

$$\alpha_{13} = \alpha_{31} = \alpha_{14} = \alpha_{41} = b$$

- **When $b = 0$, immune cells do not attack healthy cells, so there is no autoimmune deseases. Conversely, for $b > 0$, autoimmune disorders become possible. We shall also assume that all other processes, except those identified with b.**

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$$\alpha_{ij} = 1, \text{ except for } \alpha_{ij} = b$$

- **We are left now with only four parameters:**

$$\beta \; b \; \alpha, \text{ and } \varphi$$

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

1) *No chronic pathology and no autoimmune disorder*:

$$\beta = 0, \quad b = 0.$$

) *No chronic pathology, but presence of an autoimmune disorder*:

$$\beta = 0, \quad b = 1.$$

3) *Chronic pathology but no autoimmune disorder*:

$$\beta = 1, \ b = 0$$

4) *Chronic pathology and autoimmune disorder*:

$$\beta = 1, \ b = 1$$

We can also define four stationary states characterized by two "essential" variables, defined as follows:

$$x := x_1 + x_2,$$

the sum of the healthy and ill cells;

$$y = x_3 + x_4,$$

the sum representing the fraction of all immune cells, innate and specific alike.
For any given values of the parameters β and b, four stationary states characterized by the *fixed points* x^* and y^*:

A: Alive state: $x > 0,\ y > 0,$
when there are both self-immune cells and the specific immune cells;
B: Boundary state: $x > 0,\ y = 0.$
when there are self-immune cells, but not innate immune cells;
C: Critical state: $x = 0,\ y > 0.$
when only immune cells can survive,
D: Dead state: $x = 0,\ y = 0.$
when there are neither self-cells nor specific imumune cells.

- We can display the character of the stable points of the non-linear system on the plane parametrized by the remaining two free parameters, α and φ the first characterizing the common apoptosis rate of innate and specific immune cells, and the second defining the (dimensionless) pathogen flow.

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- The four possibilities are found inside the domains labeled with letters **A**, **B** **C** and **D**, and represented in the following Figures.

The phase portrait 1.

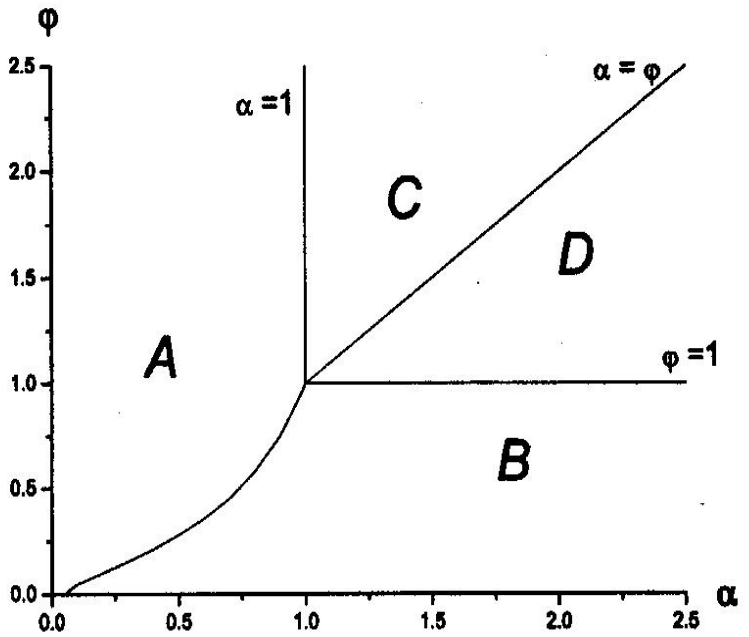

Figure: The phase portrait of the $\alpha - \varphi$ plane, with $\beta = 0$ and $b = 0$. No chronic pathology and no autoimmune disorder present.

The phase portrait 2.

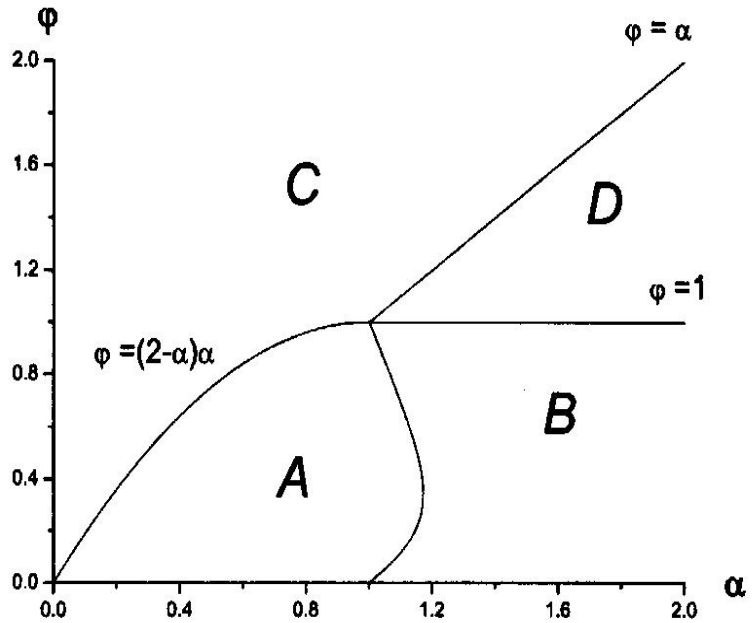

Figure: The phase portrait of the $\alpha - \varphi$ plane, with $\beta = 0$ and $b = 1$. Without chronic pathology, but with autoimmune disorder.

The phase portrait 3.

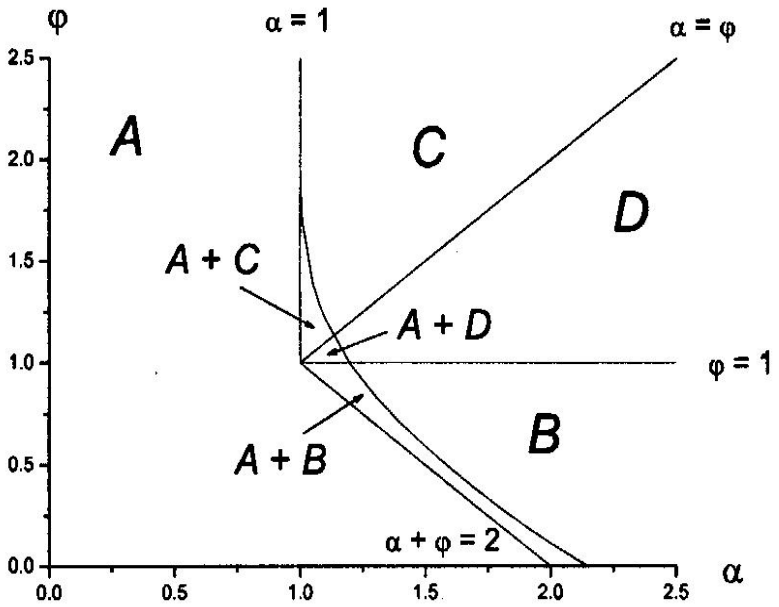

Figure: The phase portrait of the $\alpha - \varphi$ plane, with $\beta = 1$ and $b = 0$. Chronic pathology present, but no autoimmune disorder.

The phase portrait 4.

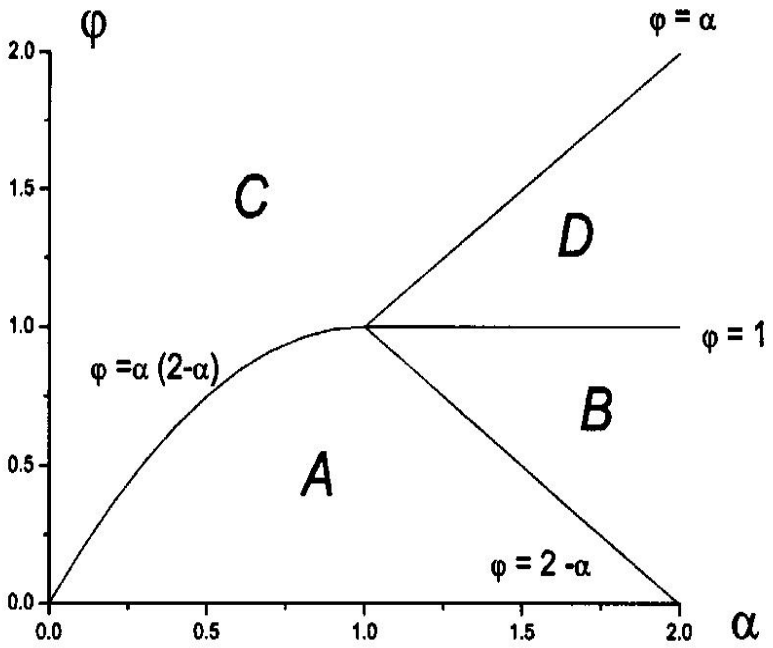

Figure: The phase portrait of the $\alpha - \varphi$ plane for $\beta = 1$ and $b = 1$. Both chronic pathology and immune disorder are present.