

Mathematical modeling of the biomedical processes

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Preface

Currently, high requirements are imposed on the modern biology and medicine. The total amount of scientific information on the structure of a biological object or any disease increases every year and one person and even a group of people cannot accurately assess the importance of the available material. That's when mathematics comes to rescue and helps to structure the available materials. For example, statistical data allows for making forecasts and revealing problematic areas which require new ways and methods for their solution. As regards the detailed study of biomass processes, their experimental study is limited, and the mathematical simulation (modeling) is the most effective tool for their study. The use of the mathematic models allows for making the biological phenomena analysis more accurate. These models may be either purely statistical or dynamic. Honeycomb models and plant leaf position models belong to the first type while the population growth processes or those of epidemic advance belong to the second type. This tool development basically implies: 1) building a self-contained dynamic model of the process describing the biological environment patterns based on the ordinary difference equations system; 2) building a self-contained mechanical and mathematical models of the process describing the biological environment patterns based on the continuum mechanics partial differential equations system. It is well known that the above specified equations are basically solved using numerical methods due to their complexity and diversity. The degree of the mathematical methods elaboration in a scientific discipline serves as an objective characteristic of the depth of the studied subject knowledge.

The study book consists of 3(three) chapters describing mathematical methods for simulation some population dynamics models, those of infectious diseases as well as circulatory dynamics models. This educational aid's structure was made in such a way that allows for biomedical problems simulation using the mathematics and practically not requiring deep understanding of the process but requiring understanding the mathematical methods' principles.

The first chapter describes the basic mathematical methods of biomedical processes. The possibility of creating a mathematical basis for the field of taxonomy, as the science of classification, including theory, methods and applications is considered. The basic concepts of dynamical systems, methods of studying dynamical systems are considered also, some information is given on numerical methods for solving partial differential equations.

The second chapter are presented the population models and the characteristic

relationships are described. Also in this chapter are described the models of infectious diseases, provides a qualitative analysis of the simplest model of the disease, the possible forms of the dynamics of the disease and their classification are shown.

In the third chapter the spatial-heterogeneous models are presented and some hemodynamic problems are considered. The structure of this study book is designed to introduce students this vast field of science by choosing models and tasks from biomedicine, reflecting the diversity of existing mathematical approaches, subordinating the material to a certain logical sequence.

Chapter 1

Mathematical methods in biomedicine

The first chapter considers possibility of development of a mathematical basis for the field of taxonomy as a science of classification including theory, methods and applications; mathematical methods sphere of application is of special interest. This chapter also gives definition of some fundamental terms such as systematics, classification, taxon, describes the basic principles of classification, the formation of the very taxons and also describes the ways of similarity quantification.

1.1 Numerical Taxonomy

One of the main problems of biology is to include an organism in an appropriate systematic group once it has been named. Systematics means a scientific research of organisms diversity including not only description of these organisms and their referring to certain groups but also an explanation of such grouping. Classification is referring organisms to certain groups based on certain criteria, such, for example, as: morphological similarity or origin similarity. Taxonomy is determined as a science of classification including theory, rules, methods and applications. Taxon is any taxonomy group resulting from application of a certain classification method. Organisms may be grouped into one taxon based on: 1) significant phenetic similarity; 2) presence of signs suggesting a common origin, or 3) a real kinship. There are *monothetic* and *polythetic* groups, i.e. the groups of similar or different sets of features.

1.1.1 Numerical Taxonomy Principles

The main unit used in the taxonomy study is called the *operational taxonomic unit* or OTU. The below specified various methods of similarity calculation apply to any operational taxonomic units be they individual organisms or any abstract class of units.

In addition to monothetic and polytheistic, there is also the simplest case of classification - dichotomous classification based on the presence or absence of one feature or another; in this particular case, the presence can be designated by 1, and the absence can be expressed through 0. The main stages, of which consists the taxon formation

procedure using the mathematical methods, are as follows:

Stage 1	The number of t operational taxonomic units subject to classification is selected and for every of such OTU the sufficiently large number of n corresponding characteristic features is studied and coded. It is usually recommended that the number n would be within the range of 50 to 100 or more. If the number n is too small, the final taxon structure may be too sensitive to the random choice of features and the statistical accuracy of similarity coefficient may be too low. The input data may be expressed in the form of the $n \times t$ matrix.
Stage 2	All OTUs are compared with each other to determine the degree of similarity based on the corresponding set n of numerically coded features. The resultant set of measured <i>similarity coefficients</i> may be expressed in the form of $t \times t$ matrix. This matrix is, of course, symmetrical and, therefore, it is necessary to calculate and record only half of its elements below or above the main diagonal.
Stage 3	Based on the calculated similarity coefficients matrix, all OTUs may be subdivided into the corresponding groups. Very often, there may be several of such groups. Within any such group, taxonomic units are much more similar than the units belonging to different groups. In many cases, combining several groups into higher rank groups may result in a hierarchic structure. The complete scheme of such taxonomic "tree" is later represented in the form of a dendrogram (tree diagram).
Stage 4	Classification correctness verification by means of an experimental assessment of the process forecasting.

Therefore, the taxonomic analysis method presented here has a clear logical basis.

There are three main ways of the quantitative expression of similarity, namely: quantitative expression through association coefficients, correlation coefficients and distance indicators.

1.1.2 Similarity Assessment. Association Coefficient

Many various association coefficients are used in biology, ecology, zoology, psychology, etc. Nevertheless, all those coefficients are based on comparison of two sets of features for any certain pair of operational taxonomic units.

Let us consider j -th and k -th taxonomic units as an example. Let us suppose that the number of features available for both OTUs is n_{11} , and the number of "missing"

features is n_{00} ; let us express the total number of features available for the first and missing in the second taxonomic unit through n_{10} and the reverse combination as n_{01} .

Table 2. Comparison of two taxonomic units' characteristic features.

		0	1	Summ
k-th O.T.E	0	n_{00}	n_{01}	n_{0*}
j-th O.T.E	1	n_{10}	n_{11}	n_{*0}
	Summ	n_{*0}	n_{*1}	n

It is a common practice to write the number of matching and mismatching pairs of characteristic features designated correspondingly as m and u , where

$$m = n_{00} + n_{11}, \quad u = n_{01} + n_{10}, \quad m + u = n.$$

Therefore, there are m of features that are matching for both OTUs and mismatching u features. The simplest association coefficient is just a relative number of matching features.

$$S_1 = \frac{m}{n},$$

This correlation has the following properties: $S_1 \rightarrow 1$ at $m \rightarrow n$, i.e. $u \rightarrow 0$, $S_1 \rightarrow 0$ at $m \rightarrow 0$. Therefore, complete matching is expressed by 1 and complete mismatching by 0.

Save for coincidences by the absence of features, coefficient usage is more preferable.

$$S_2 = \frac{n_{11}}{n_{11} + u},$$

Same as above, complete matching $u \rightarrow 0$ and $S_2 \rightarrow 1$, while complete mismatching is $n_{11} \rightarrow 0$, $S_2 \rightarrow 0$.

1.1.3 Correlation Coefficient. Distance Factor

Correlation coefficients are used for measurement of the degree of correlation between two features and they are applied to the continuous variables. Let us suppose that all elements of the main matrix $n \times t$ are continuous variables. Then, for j -th taxonomic unit we will have n measurements designated as x_{ij} , $i = 1, \dots, n$. Let's suppose that the average value of the taxonomic units is equal to \bar{x}_j . Likewise, for the k -th taxonomic units there are measurements x_{ik} , $i = 1, \dots, n$ for average values \bar{x}_k . The correlation coefficient of the mixed moments between these two groups of measurements is equal.

$$r_{jk} = \frac{\sum_{i=1}^n (x_{ij} - \bar{x}_j)(x_{ik} - \bar{x}_k)}{[\sum_{i=1}^n (x_{ij} - \bar{x}_j)^2 \sum_{i=1}^n (x_{ik} - \bar{x}_k)^2]^{1/2}}$$

This coefficient varies from -1 in the event of complete negative correlation to +1 in the event of complete positive correlation.

Distance Factor

The use of some "distance" parameter is another way of determining the degree of similarity of two taxonomic units. Let us suppose that there are totally three features (i.e. $n = 3$) and changes revealed that those features are designated by the following values x_{1j} , x_{2j} , x_{3j} for j -th OTU and x_{1k} , x_{2k} and x_{3k} for k -th OTU. Then, these two taxonomic units may be univocally shown in the three-dimensional space by dots (x_{1j}, x_{2j}, x_{3j}) and (x_{1k}, x_{2k}, x_{3k}) , distance between which Δ_{jk} is determined by the expression

$$\Delta_{jk}^2 = (x_{1j} - x_{1k})^2 + (x_{2j} - x_{2k})^2 + (x_{3j} - x_{3k})^2$$

Generalized expression of distance between the j -th and k -th taxonomic units in the event of n features is as follows:

$$\Delta_{jk}^2 = \sum_{i=1}^n (x_{ij} - x_{ik})^2.$$

Distance Δ_{jk} between two dots is equal to zero if the values of x_{ij} and x_{ik} for all i (i.e. for every feature) match precisely. Any difference leads to increase of this value and, therefore, it is quite sensible to consider this distance as a difference indicator.

Another method is to normalize the data on the matrix rows, as it was described when considering the correlation coefficients. If normalized changes are used, z_{ij} than the above distance calculation formula shall be replaced with the following formula.

$$\Delta_{jk}^2 = \sum_{i=1}^n (z_{ij} - z_{ik})^2.$$

Value Δ_{jk} depends not only on the very results of changes z_{ij} , but also on the number of compared features n . In one case only, when the comparisons of all pairs of taxonomic units are based on one and the same value of n , this is of no significant importance. To simplify comparison in the events when different n values are used, it is better to calculate the mean square value for distance

$$d_{jk}^2 = \frac{\Delta_{jk}^2}{n}.$$

In terms of numerical taxonomy, taxonomic distance parameters are the simplest and the most convenient.

1.1.4 Analysis Methods in the Numerical Taxonomy

Described below are several simple methods of hierarchical analysis, namely: the most distant neighbours method or full connection method, the nearest neighbour method or single connection method and the weighted pair-wise average. One of the methods is the method of the most distant neighbour or full connection.

Let us suppose that it is necessary to classify the given set of objects by the nearest neighbour method. The distance between two classes is determined as the distance between the nearest representatives of the classes. For this purpose, a matrix of distances between the objects is calculated. At each step of the distance matrix, the minimum value is determined corresponding to the distance between two of the closest objects. The found objects are combined into one new object. This procedure is repeated until all the considered objects are combined. Let us suppose that the following distance matrix is given:

	1	2	3	4
1	0	2.06	4.03	6.32
2	2.06	0	4.12	2.25
3	4.03	4.12	0	3.50
4	6.32	2.25	3.50	0

Step 1 In accordance with the classification criteria, combination happens between the objects the distance between the nearest representatives thereof is least of: 1 and 2, 3 and 4. The distance of combination is 2.06. It is necessary to carry out recalculation of the distance matrix with due account for the new object:

	1,2	3	4
1,2	0	4.12	6.32
3	4.12	0	3.50
4	6.32	3.50	0

Step 2 The given step's objects are as follows: (1,2), 3, 4. In accordance with the new distance matrix, 3 and 4 are the closest objects. Distance of combination - 3.5. It is necessary to carry out recalculation of the distance matrix with due account for the new object:

	1,2	3,4
1,2	0	6.32
3,4	6.32	0

Step 3 The given step's objects are as follows: (1,2), and (3, 4). Distance between them is equal to 6.32; this distance between the 1st and 4th objects. Hierarchy formation is completed. The results of classification by the nearest neighbour method are given in the form of a tree diagram:

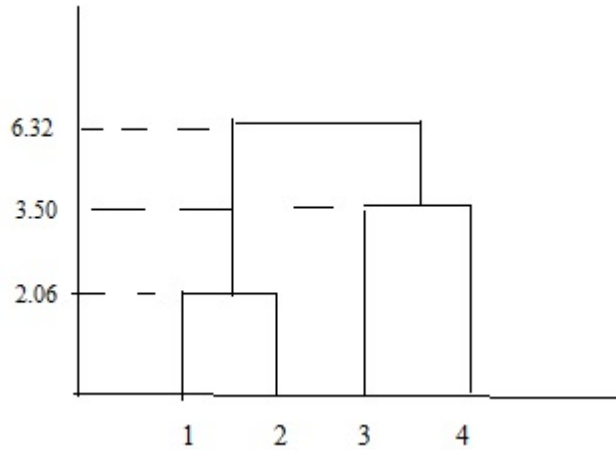


Figure 1.1.1

When the nearest neighbour method is used, special attention shall be paid to selection of measure of distance between the objects. Based on such measure, the initial distance matrix is formed that determines the whole further classification process.

The Nearest Neighbour Method or Single Connection Method

The given method of hierarchical analysis differs from the previous one by determining the distance between the classes, i.e. distance between two classes is determined as the distance between the nearest representatives thereof. Let us suppose that it is necessary to classify the given set of objects by the nearest neighbour method. The distance between two classes is determined as distance between the nearest representatives of the classes. A matrix of distance between the objects is calculated. At each step of the distance matrix the minimum value is determined corresponding to the distance between two of the closest objects. The found objects are combined into one new object. This procedure is repeated until all the considered objects are combined. Let us suppose that the following distance matrix is given:

	1	2	3	4
1	0	2.06	4.03	6.32
2	2.06	0	2.5	4.12
3	4.03	2.5	0	2.24
4	6.32	4.12	2.24	0

Step 1. In accordance with the classification criteria, combination happens between the objects the distance between the nearest representatives thereof is least of: 1 and 2, 3 and 4. The distance of combination is 2.06. It is necessary to carry out recalculation of the distance matrix with due account for:

	1,2	3	4
1,2	0	2.5	4.12
3	2.5	0	2.24
4	4.12	2.24	0

Step 2. The given step's objects are as follows: (1,2), 3, 4. In accordance with the new distance matrix, 3 and 4 are the closest objects. Distance of combination - 2.24. It is necessary to carry out recalculation of the distance matrix with due account for the new object:

	1,2	3,4
1,2	0	2.5
3,4	2.5	0

Step 3. The given step's objects are as follows: (1,2), and (3, 4). Distance between them is equal to 2.50; this is the distance between the 2nd and 3rd objects. Hierarchy formation is completed. The results of classification by the nearest neighbour method are given in the form of a tree diagram:

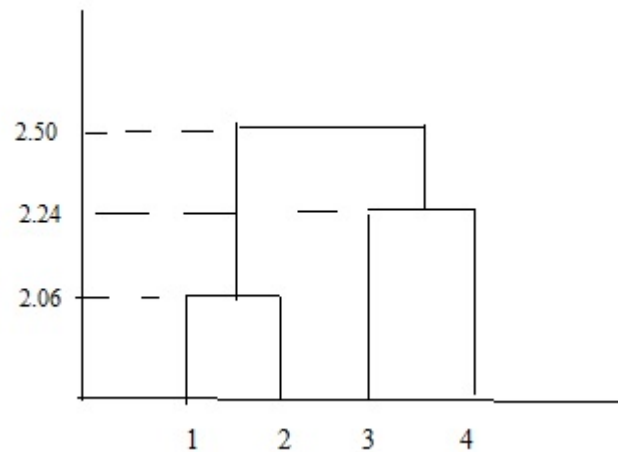


Figure 1.1.2

(1) have continuous first-order partial derivatives in x_1, x_2, \dots, x_n . Then it follows from the theory of differential equations that for any $t = t_0$ and any point $M_0(x_{01}, x_{02}, \dots, x_{0n})$ the only solution of the system (1.1) exists, passing through the point M_0 at the time $t = t_0$. We consider the equation (first-order system) $\dot{x} = x$ and its general solution $x = Ce^t$.

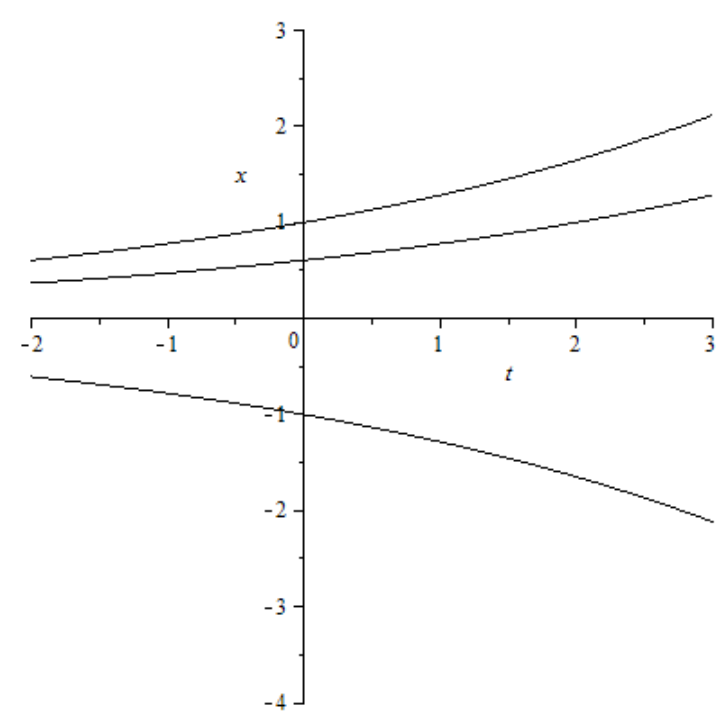


Figure 1.2

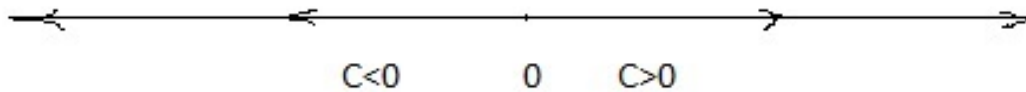


Figure 1.3

The Fig. 1.2 shows the integral curves of this equation. The phase trajectories are the projections of the integral curves onto the line (Figure 1.3).

Thus, the integral curves give complete information about the solutions of the system, and the phase trajectories carry less information. It can be seen from Fig. 1.2

that the velocity of change of x increases with increasing of t , this is not visible in the phase trajectory. However, it is easier to study phase trajectories (without knowledge of integral curves). To obtain integral curves, it is necessary to solve a system of differential equations, which is often impossible; moreover, if a solution is obtained for the system, it is so tedious, that the study of its properties becomes a complex problem.

We consider the following properties of phase trajectories:

Property 1. If $x = \phi(t)$ is a solution of the system (1.2), then for any real number c , $x = \phi(t + C)$ there is also a solution of the system (1.2).

Property 2. Two phase trajectories of the system (1.2) either do not have common points, or coincide. Thus, the phase space of the system (1.2) consists of disjoint phase trajectories, i.e. through each point one and only one phase trajectory goes through.

Definition: The point $a = (a_1, a_2, \dots, a_n)$ is called the equilibrium position of the system (2), if $f(a) = 0$. In other words, a - is the solution of the system $f(x) = 0$.

For example, for a system

$$\begin{cases} \dot{x} = y, \\ \dot{y} = -x \end{cases}$$

$(0; 0)$ - is the only equilibrium position.

$$\text{The system } \begin{cases} \dot{x} = x(x - y), \\ \dot{y} = x^2 - 3y + 2 \end{cases}$$

has three equilibrium positions: $(1;1)$, $(2;2)$, $(0;2/3)$.

Property 3. If a is the equilibrium position of system (1.2), then $x = a$ is the solution of system (1.2), and the point $x = a$ is its phase trajectory.

Property 4. Every phase trajectory of system (1.2) has one of three types:

- smooth curve without self-intersections,
- closed smooth curve,
- point.

The solution of the system (1.2) passing through the point $x_0 = (x_{01}, x_{02}, \dots, x_{0n})$ will be denoted as $x = x(t, x_0)$, $(x_0 = x(0, x))$

Property 5. $x(t_1 + t_2, x_0) = x(t_2, x(t_1, x_0))$ - is a group property . That is, if the movement begins along the phase trajectory from the point x_0 and goes along t on $t_1 + t_2$, then it appears at the same point as moving from the point $x(t_1, x_0)$ on t_2 .

The qualitative theory of differential equations deals with the study of the properties of a dynamical system without solving it. Figure 1.4 shows curves that can not be phase trajectories.

The investigation of a dynamical system consists of studying of phase trajectories with different behaviors - the phase portrait of a dynamic system or individual trajectory properties.

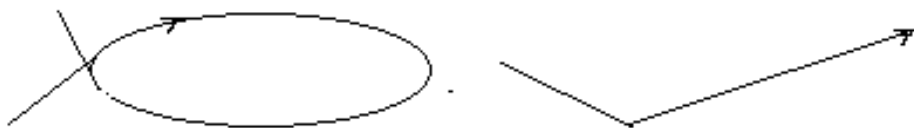


Figure 1.4

1.2.2 One-dimensional linear systems. Stability of the equilibrium position of one-dimensional systems

We consider the one-dimensional system:

$$\dot{x} = f(x) \tag{1.3}$$

where $x \in R^1$, $f(x)$ – numeric function.

The phase space here is a straight line. It is clear that if $f(x) > 0$ at some interval, then $\dot{x} > 0$, with time the coordinate x grows and the depicting point moves along the phase line to the right, if $f(x) < 0$, then - to the left. If $f(x) = 0$, then x is the position of equilibrium.

Example. To represent the phase portrait of the equation

$$\dot{x} = x(x - 1)(x + 2)^3(x - 3)^2$$

We find the positions of equilibrium and use the method of intervals to determine the signs of the right-hand side of the equation (Figure 1.5): After this, we represent the

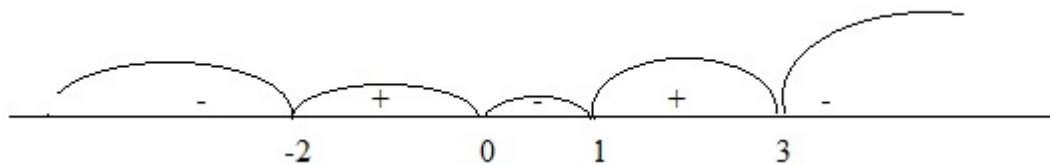


Figure 1.5

phase portrait (Figure 1.6). From this figure it is clear that there exists a neighborhood of the point O as such that for any initial point x_0 from this neighborhood

$$\lim_{x \rightarrow \infty} x(t, x_0) = 0,$$

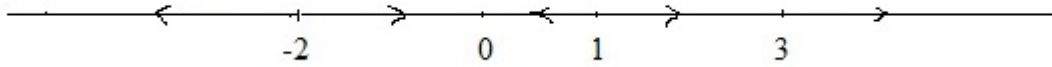


Figure 1.6

i.e., the depicting point, having started the motion "near" to $x = 0$, tends to this equilibrium position with the passage of time. This equilibrium position is called *asymptotically stable*. The equilibrium positions $x = -2$, $x = 1$, $x = 3$ are called unstable.

stability of state equilibrium can be defined as follows: if, for a sufficiently small deviation from the equilibrium position, the system never goes far from a singular point, then the singular point will be a *stable equilibrium state*, which corresponds to a *stable regime* of the system functioning.

A mathematical definition of the stability of the equilibrium state of the equation $dx/dt = f(x)$ is as follows:

The state of equilibrium *is stable by Lyapunov*, given an arbitrarily small positive number ϵ , one can always find such δ , that

$$|x(t) - \bar{x}| < \epsilon \text{ для } t_0 < t < +\infty$$

если

$$|x(t_0) - \bar{x}| < \delta \tag{1.4}$$

In other words, for a *stable* equilibrium state the following statement is true: if at a time the deviation from the equilibrium state is small ($|x(t_0) - \bar{x}| < \delta$), then at any subsequent time $t > t_0$ the deviation of the solution of the system from the state of equilibrium will also be small: $|x(t) - \bar{x}| < \epsilon$.

In other words: steady state is called *stable* if small deviations do not lead the system too far from the vicinity of this steady state.

A steady state is called asymptotically stable if small deviations from it decrease with the time. A steady state is called unstable if small deviations increase with the time.

1.2.3 Two-dimensional linear systems. The equilibrium position and the stability of two-dimensional linear systems

We consider phase portraits of two-dimensional systems:

$$\begin{cases} \dot{x} = f_1(x, y) \\ \dot{y} = f_2(x, y). \end{cases}$$

We begin our study with linear systems:

$$\begin{cases} \dot{x} = ax + by \\ \dot{y} = cx + dy \end{cases} \quad (1.5)$$

where a, b, c, d — real numbers.

We first consider the degenerate case $ad - bc = 0$. We divide the second equation of system (1.5) by the first

$$\frac{\dot{y}}{\dot{x}} = \frac{dy}{dx} : \frac{dx}{dt} = \frac{dy}{dx} \approx \frac{cx + dy}{ax + by}.$$

The right-hand side of the equation is shortened, then:

$$\frac{dy}{dx} = k.$$

Where from $y = kx + m$, where k, m are real numbers. The phase trajectories (1.5) are located on parallel lines $y = kx + m$, and all points of the line $ax + by = 0$ are the equilibrium positions of the system (1.5).

In the case when the system (1.5) has the form

$$\begin{cases} \dot{x} = 0 \\ \dot{y} = cx + dy \end{cases}$$

it is necessary to divide the first equation by the second:

$$\frac{dx}{dy} = 0$$

In case, if

$$\begin{cases} \dot{x} = 0 \\ \dot{y} = 0 \end{cases}$$

all points of phase plane are equilibrium state.

Now, it is $ad - bc \neq 0$. In this case, the system if equilibrium

$$\begin{cases} ax + by = 0 \\ cx + dy = 0 \end{cases}$$

Has the only solution $(0;0)$, therefore, (1.5) has the only equilibrium state $(0;0)$.

We make linear transformation in (1.5)

$$\begin{cases} u = Ax + By \\ v = Ex + Fy \end{cases} \quad (1.6)$$

Where A, B, E, F are real numbers, $AF - BE \neq 0$. We can choose the coefficient's A, B, E, F as such to allow the new system to have the appearance

$$\begin{cases} \dot{u} = \lambda_1 u, \\ \dot{v} = \lambda_2 v. \end{cases} \quad (1.7)$$

$$\begin{cases} \dot{u} = A\dot{x} + B\dot{y} \\ \dot{v} = E\dot{x} + F\dot{y} \end{cases}$$

$$\begin{cases} \dot{u} = A(ax + by) + B(cx + dy) = \lambda_1 u = \lambda_1(Ax + By) \\ \dot{v} = E(ax + by) + F(cx + dy) = \lambda_2 v = \lambda_2(Ex + Fy) \end{cases}$$

$$\begin{cases} A(ax + by) + B(cx + dy) = \lambda_1(Ax + By) \\ E(ax + by) + F(cx + dy) = \lambda_2(Ex + Fy). \end{cases}$$

Equating the coefficients under x and y , we have

$$\begin{cases} Aa + Bc = \lambda_1 A, \\ Ab + Bd = \lambda_1 B, \\ Ea + Fc = \lambda_2 E, \\ Eb + Fd = \lambda_2 F, \end{cases}$$

that is,

$$\begin{cases} (a - \lambda_1)A + cB = 0, \\ bA + (d - \lambda_1)B = 0, \\ (a - \lambda_2)E + cF = 0, \\ bE + (d - \lambda_2)F = 0. \end{cases}$$

These systems have non-zero solutions if λ_1 и λ_2 are the solutions of equation

$$\begin{vmatrix} a - \lambda & c \\ b & d - \lambda \end{vmatrix} = \begin{vmatrix} a - \lambda & b \\ c & d - \lambda \end{vmatrix} = 0 \quad (1.8)$$

or, revealing the determinant, we get:

$$\lambda^2 - (a + d)\lambda + ad - bc = 0.$$

Equation (1.8) is called the characteristic equation of the system (1.5), and λ_1, λ_2 are called *characteristic numbers*.

Let us consider various cases.

1. λ_1 и λ_2 действительные и $\lambda_2 > \lambda_1 > 0$. Solving each equation of the system (1.7) separately, we obtain

$$u = C_1 e^{\lambda_1 t}, v = C_2 e^{\lambda_2 t} \quad (1.9)$$

то есть при $C_1 \neq 0$.

$$v = C_2 e^{\lambda_2 t} = |C_1|^{-\frac{\lambda_2}{\lambda_1}} C_2 |C_1 e^{\lambda_1 t}|^{\frac{\lambda_2}{\lambda_1}} = |C_1|^{-\frac{\lambda_2}{\lambda_1}} C_2 |u|^{\frac{\lambda_2}{\lambda_1}} = C_3 |u|^{\frac{\lambda_2}{\lambda_1}}. \quad (1.10)$$

As $\frac{\lambda_2}{\lambda_1} > 1$, then the phase trajectories of the system (1.7) have the form shown in Fig. 1.7.

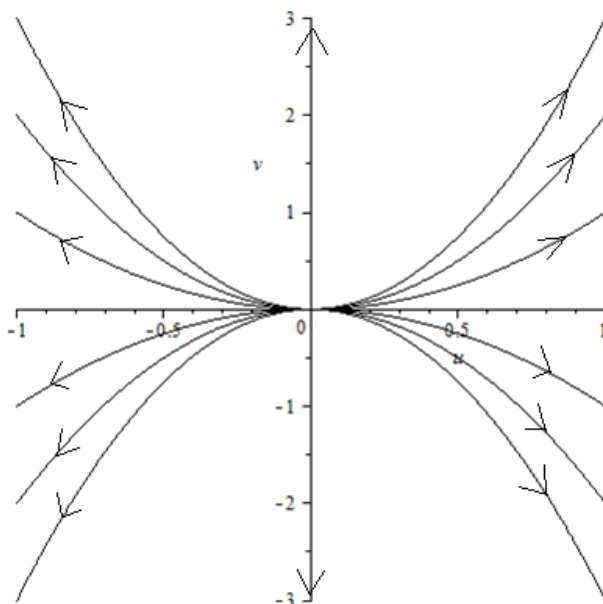


Figure 1.7

When $C_1 = 0$ and $C_2 = 0$ it follows from (1.9) that on the lines $u = 0$ and $v = 0$ the phase trajectories are also located. As $\lambda_1 > 0$ and $\lambda_2 > 0$, then from (1.9) we obtain

$$\lim_{t \rightarrow \infty} u = \infty, \quad \lim_{t \rightarrow \infty} v = \infty,$$

that is, the arrows are directed from the point $(0; 0)$. This equilibrium position is called an *unstable node*.

If $\lambda_1 > \lambda_2 > 0$ then $0 < \frac{\lambda_2}{\lambda_1} < 1$ and the phase portrait is shown in Fig. 1.8.

2. λ_1 and λ_2 are real, and $\lambda_2 < \lambda_1 < 0$. As $\frac{\lambda_2}{\lambda_1} > 1$ then the phase trajectories of the system (1.7) have the same form as in Fig. 1.7. But it follows from (1.9) that

$$\lim_{t \rightarrow \infty} u = 0, \quad \lim_{t \rightarrow \infty} v = 0.$$

The equilibrium position in this case is called a *stable node*.

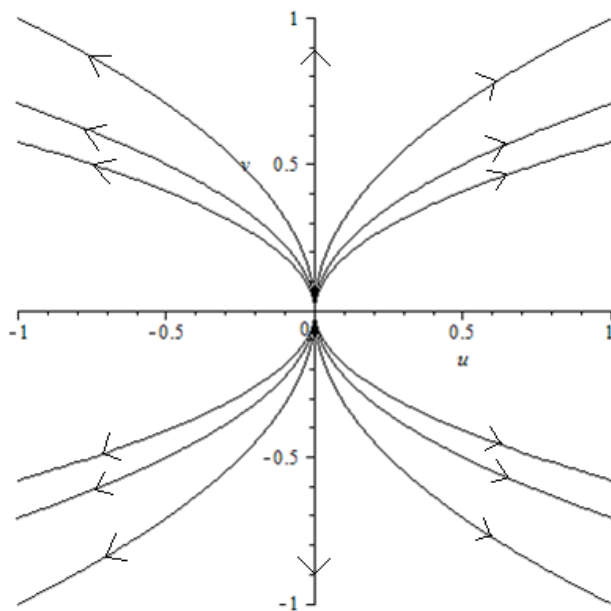


Figure 1.8

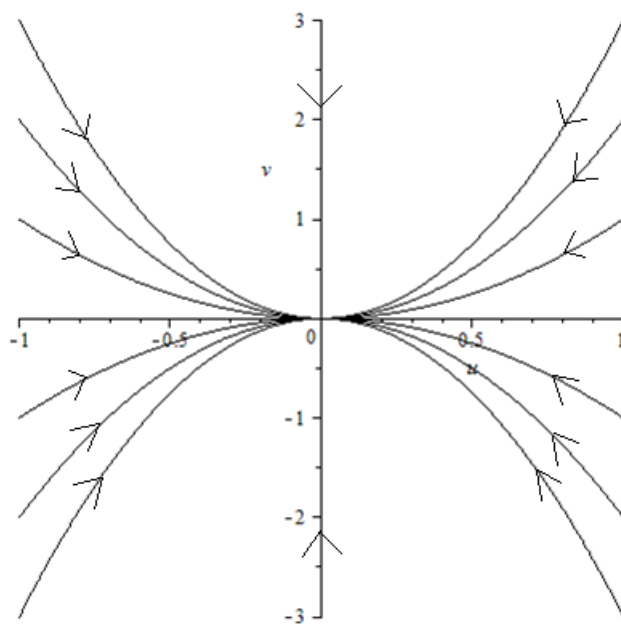


Figure 1.9

If $\lambda_1 < \lambda_2 < 0$ then the phase trajectories have the same form as in Fig. 1.8, but the depicting points move along them to the origin of coordinates. Then the phase

portrait is shown in Fig. 1.9.

3. λ_1 and λ_2 are real, and $\lambda_1 = \lambda_2 = \lambda$. If the system (1.5) has the form

$$\begin{cases} \dot{x} = \lambda x, \\ \dot{y} = \lambda y, \end{cases} \quad (1.11)$$

then $x = C_1 e^{\lambda t}$, $y = C_2 e^{\lambda t}$ or $y = \frac{C_2}{C_1} x = C_3 x$ - lines moving through the origin of coordinates. The point (0;0) is a dicritical node that is stable at $\lambda < 0$ (Figure 1.10) and unstable for $\lambda > 0$ (Figure 1.11).

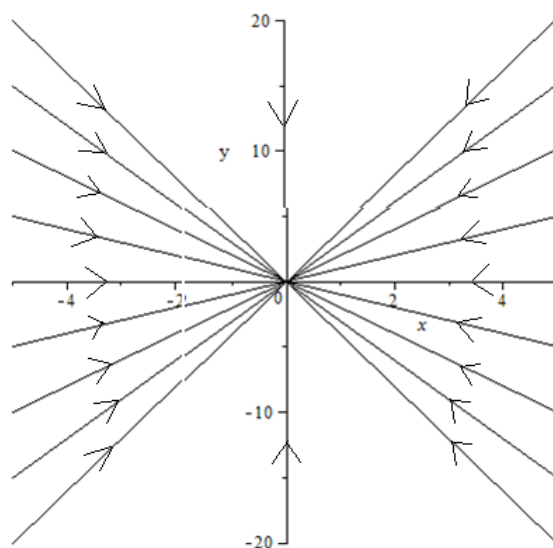


Figure 1.10

Now we give the location of the phase trajectories of the system (1.5) with $\lambda < 0$ (Fig. 1.12) and $\lambda > 0$ (Fig. 1.13). The equilibrium position in this case is called a *degenerate node* (respectively, stable and unstable).

4. λ_1 or λ_2 are real and of different signs. In (1.10) $\frac{\lambda_2}{\lambda_1} < 0$, and, besides, it follows from (1.9) that when $\lambda_1 > 0$, $\lambda_2 < 0$, $C_1 \neq 0$.

$$\lim_{t \rightarrow \infty} u = \infty, \quad \lim_{t \rightarrow \infty} v = 0,$$

and at $\lambda_1 < 0$, $\lambda_2 > 0$, $C_2 \neq 0$,

$$\lim_{t \rightarrow \infty} u = 0, \quad \lim_{t \rightarrow \infty} v = \infty.$$

The equilibrium position is called the *saddle*.

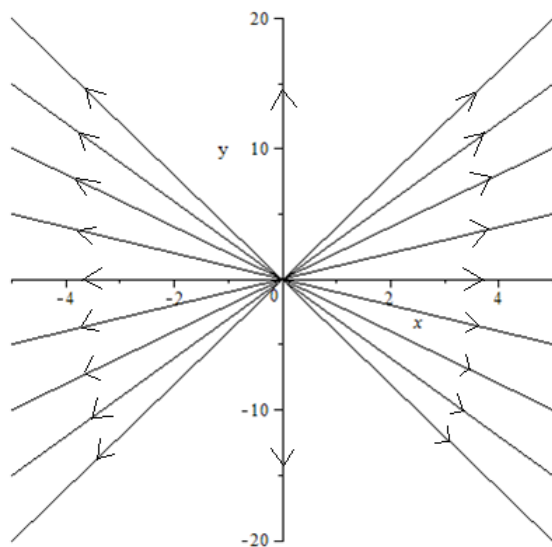


Figure 1.11

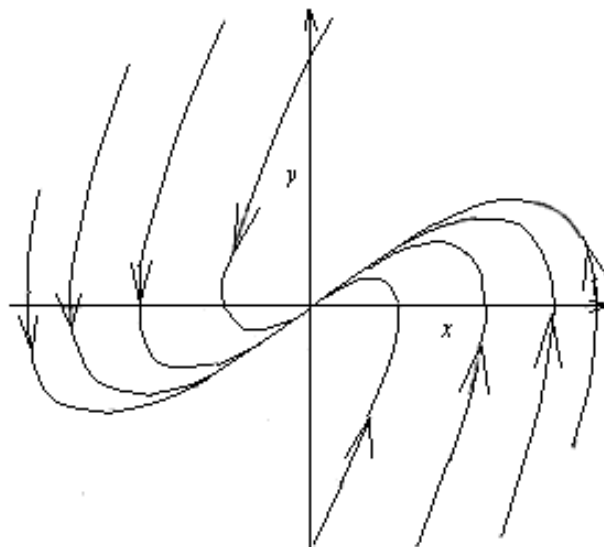


Figure 1.12

5. $\lambda_1 = p + iq, \lambda_2 = p - iq, p \neq 0, q \neq 0$. It can be proved that the system (1.5) can be lead to the following form by special linear transformations:

$$\begin{cases} \dot{u} = pu + qv, \\ \dot{v} = -qu + pv \end{cases} \quad (1.12)$$

Passing here to the polar coordinates

$$u = \rho \cos(\theta), \quad v = \rho \sin(\theta),$$

we have:

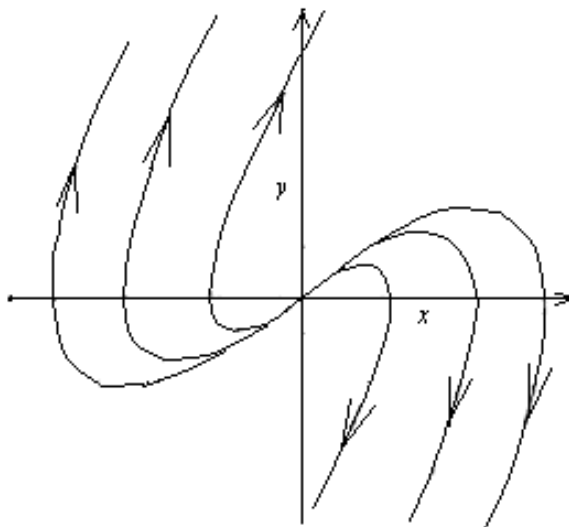


Figure 1.13

$$\begin{cases} \frac{d\rho}{dt}\cos\theta - \rho\sin\theta\frac{d\theta}{dt} = p\rho\cos\theta + q\rho\sin\theta \\ \frac{d\rho}{dt}\sin\theta + \rho\cos\theta\frac{d\theta}{dt} = -q\rho\cos\theta + p\rho\sin\theta \end{cases}$$

Multiplying the first equation of this system by $\cos\theta$, and the second by $\sin\theta$, and adding the resulting equations, we obtain

$$\frac{d\rho}{dt} = p\rho. \quad (1.13)$$

We find more

$$\frac{d\theta}{dt} = \dot{\theta} = \left(\arctan \frac{v}{u}\right)^* = \frac{1}{1 + \left(\frac{v}{u}\right)^2} \frac{\dot{v}u - v\dot{u}}{u^2} = \frac{u^2}{u^2 + v^2} * \frac{(-qu + pv)u - v(pu + qv)}{u^2} = -q.$$

It follows from (1.13) that if $p > 0$, then the depicting point moves away from the origin of coordinates with increasing of time, if $p < 0$, then approaching. In this case, it moves clockwise in a spiral ($\bar{\theta} < 0$) or counterclockwise ($\bar{\theta} > 0$) depending on the sign of q .

Summarizing the above, we obtain that if the real parts p of the λ_1, λ_2 are positive, the phase trajectories of the system (1.12) have the form shown in Fig. 1.16 or in Fig. 1.17. The equilibrium position "0" is called in this case *an unstable focus*.

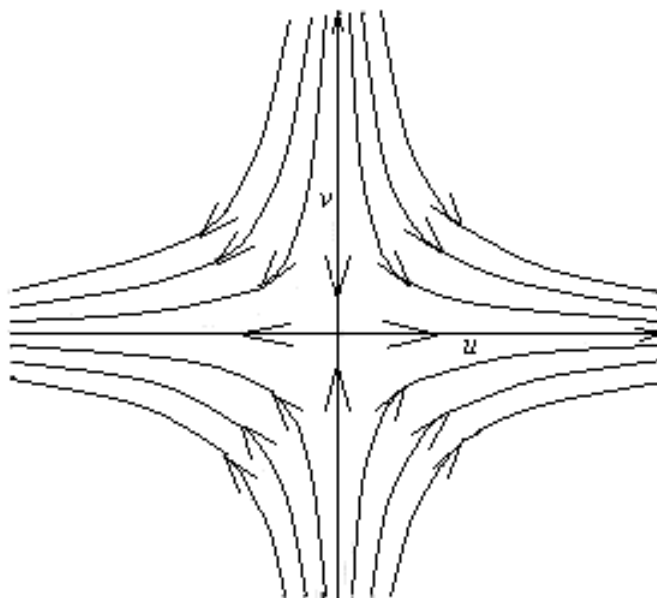


Figure 1.14

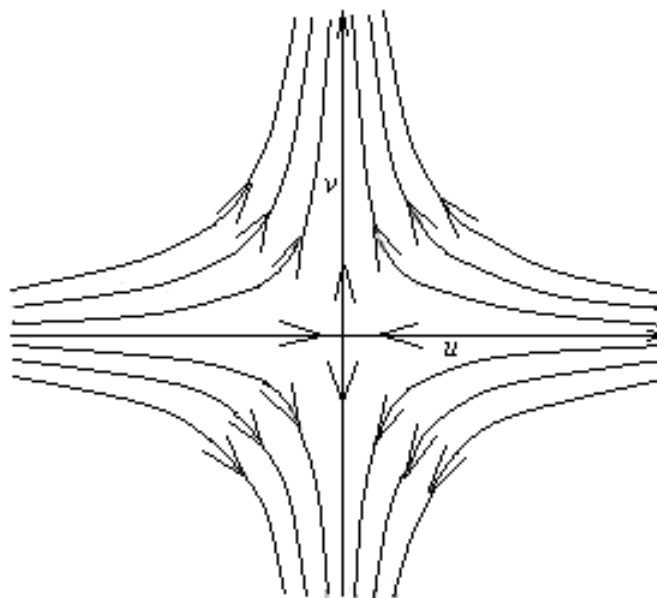


Figure 1.15

For the case $p < 0$ the phase trajectories are shown in Fig. 1.18 and in Fig. 1.19. The equilibrium position 0 in this case is a *stable focus*.

6. $\lambda_1 = iq, \lambda_2 = iq, q > 0$. BIn this case (1.13) gives $\rho = C_1$ that is, phase trajectories are circles with the center at the origin of coordinates (Fig. 1.20 or Fig. 1.21). The equilibrium position is called the *center*. Note that if we return to the variables x

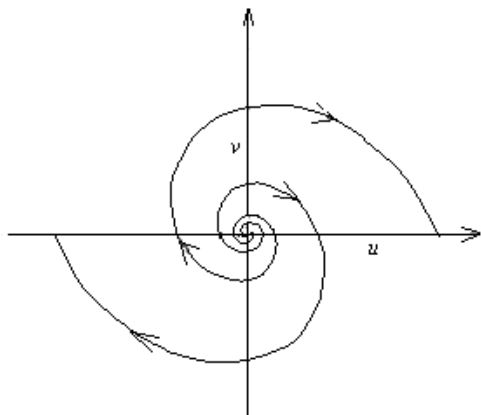


Figure 1.16

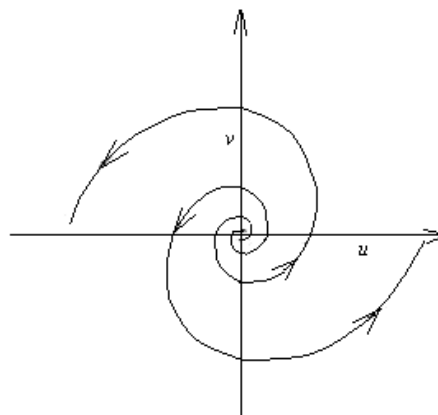


Figure 1.17

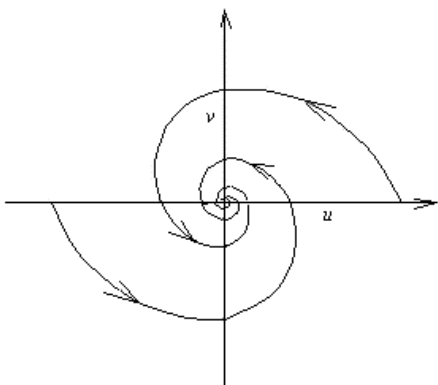


Figure 1.18

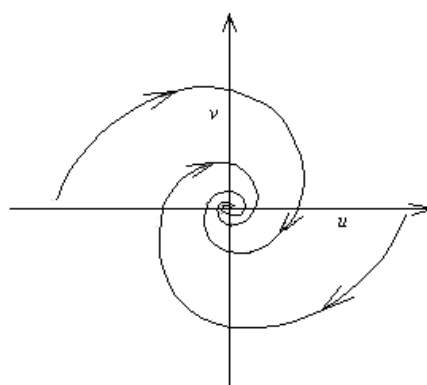


Figure 1.19

and y , that is, to the system (1.5), then the phase portraits will differ from the phase portraits of the systems (1.7) and (1.12) by rotation and stretching.

7. One or both of the characteristic numbers is equal to zero. Substituting in (1.8) $\lambda = 0$ we obtain $ad - bc = 0$, and this case was considered at the beginning of the section.

It is seen that in the case of a node and a saddle, there are four trajectories, each representing a half-line, lying on two straight lines $y = k_1x$ and $y = k_2x$.

If the equilibrium position is a node, then the remaining trajectories touch one of these lines at the origin of coordinates. For phase trajectories in the vicinity of the saddle these lines are asymptotes (and are called *separatrices of the saddle*).

Let us consider the behavior of the phase trajectories of the system

$$\begin{cases} \dot{x} = -3y, \\ \dot{y} = 2x - y. \end{cases} \quad (1.14)$$

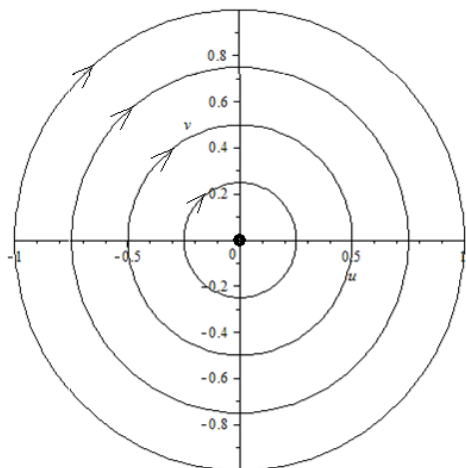


Figure 1.20

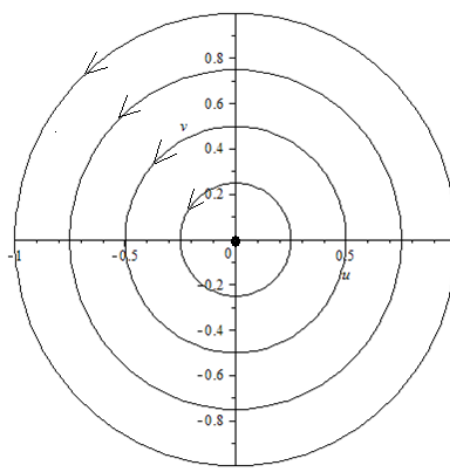


Figure 1.21

The characteristic equation for (1.14)

$$\begin{vmatrix} -\lambda & -3 \\ 2 & -1 - \lambda \end{vmatrix} = 0$$

where, $\lambda_1 = -\frac{1}{2} - \frac{\sqrt{23}}{2}$, $\lambda_2 = -\frac{1}{2} + \frac{\sqrt{23}}{2}i$, - roots of the equation of equilibrium, (0;0) - is a stable focus.

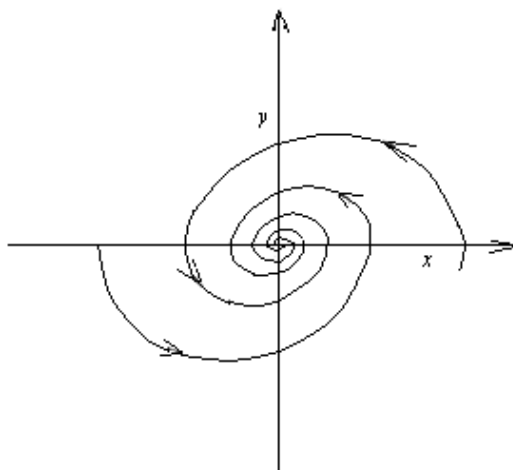


Figure 1.22

Example.

Consider the search for stationary states given by second-order nonlinear differential equations:

$$\begin{cases} \frac{dx}{dt} = x - 9xy - x^2 \\ \frac{dy}{dt} = 3xy - 4y - 2y^2 \end{cases} \quad (1.15)$$

Linearize the system (1.15) with the following substitution:

$$\begin{cases} x = \bar{x} + \xi \\ y = \bar{y} + \eta \end{cases}$$

$$\begin{cases} \frac{d\xi}{dt} = \bar{x} + \xi - 9(\bar{x} + \xi)(\bar{y} + \eta) - (\bar{x} + \xi)^2 \\ \frac{d\eta}{dt} = 3(\bar{x} + \xi)(\bar{y} + \eta) - 4(\bar{y} + \eta) - 2(\bar{y} + \eta)^2 \end{cases}$$

$$\begin{cases} \frac{d\xi}{dt} = \bar{x} + \xi - 9(\bar{x}\bar{y} + \bar{x}\eta + \xi\bar{y} + \xi\eta) - \bar{x}^2 - 2\bar{x}\xi - \xi^2 \\ \frac{d\eta}{dt} = 3(\bar{x}\bar{y} + \bar{x}\eta + \xi\bar{y} + \xi\eta) - 4\bar{y} - 4\eta - 2\bar{y}^2 - 4\bar{y}\eta - 2\eta^2 \end{cases}$$

$$\begin{cases} \frac{d\xi}{dt} = \bar{x} - 9\bar{x}\bar{y} - \bar{x}^2 + \xi(1 - 9\bar{y} - 2\bar{x}) - 9\bar{x}\eta - \xi^2 - 9\xi\eta \\ \frac{d\eta}{dt} = 3\bar{x}\bar{y} - 4\bar{y} - 2\bar{y}^2 + 3\xi\bar{y} + \eta(3\bar{x} - 4 - 4\bar{y}) - 2\eta^2 + 3\xi\eta \end{cases}$$

$$\bar{x} - 9\bar{x}\bar{y} - \bar{x}^2 = 0; \quad \bar{x}\bar{y} - 4\bar{y} - 2\bar{y}^2 = 0;$$

$$P'_x(\bar{x}, \bar{y}) = a = 1 - 9\bar{y} - 2\bar{x}; \quad P'_y(\bar{x}, \bar{y}) = b = -9\bar{x};$$

$$Q'_x(\bar{x}, \bar{y}) = c = 3\bar{y}; \quad Q'_y(\bar{x}, \bar{y}) = d = 3\bar{x} - 4 - 4\bar{y};$$

We cut off the nonlinear part.

$$\begin{cases} \frac{d\xi}{dt} = a\xi + b\eta \\ \frac{d\eta}{dt} = c\xi + d\eta \end{cases} \quad (1.16)$$

Let us find four singular points. To this end, we equate system (1.15) to zero:

$$\begin{cases} x - 9xy - x^2 = 0 \\ 3xy - 4y - 2y^2 = 0 \end{cases}$$

$$\begin{cases} x(1 - 9y - x) = 0 \\ y(3x - 4 - 2y) = 0 \end{cases}$$

$$1. \quad x_1 = 0, \quad y_1 = 0; \quad 2. \quad x_2 = 0, \quad y_2 = -2; \quad 3. \quad x_3 = 1, \quad y_3 = 0;$$

$$4. \quad \begin{cases} 1 - 9y - x = 0 \\ 3x - 4 - 2y = 0 \end{cases}$$

$$\begin{cases} x = 1 - 9y \\ 3 - 27y - 4 - 2y = 0 \\ -29y = 1 \end{cases}$$

$$x_4 = \frac{38}{29}, \quad y_4 = -\frac{1}{29};$$

We consider the system (1.16) at each of the four singular points. For the first point $(0, 0)$ we obtain the following coefficients:

$$a = 1 - 9\bar{y} - 2\bar{x} = 1;$$

$$b = -9\bar{x} = 0;$$

$$c = 3\bar{y} = 0; \quad d = 3\bar{x} - 4 - 4\bar{y} = 4;$$

$$\begin{cases} \frac{d\xi}{dt} = \xi \\ \frac{d\eta}{dt} = -4\eta \end{cases}$$

$$D = (a + d)^2 - 4(ad - bc) = 9 + 16 = 25$$

$$\lambda_{1,2} = \frac{(a + d) \pm \sqrt{D}}{2} = \frac{-3 \pm 5}{2} = 1; \quad -4.$$

Horizontal isocline: $\frac{d\xi}{dt} = 0, \quad \xi = 0.$

Vertical isocline: $\frac{d\eta}{dt} = 0, \quad \eta = 0.$

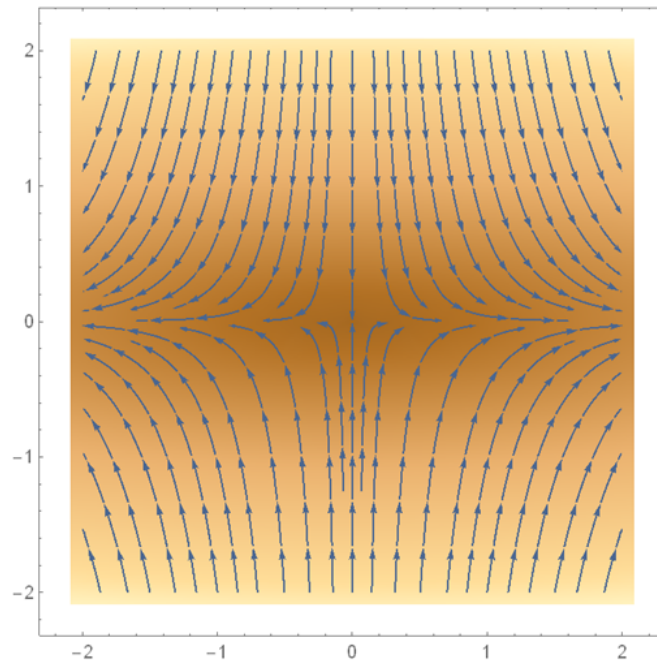


Figure 1.23 – Phase portrait is saddle

Consider the second stationary point: $(0, -2)$

$$\begin{aligned} a &= 1 - 9\bar{y} - 2\bar{x} = 19; & b &= -9\bar{x} = 0; \\ c &= 3\bar{y} = -6; & d &= 3\bar{x} - 4 - 4\bar{y} = 4; \end{aligned}$$

$$\begin{cases} \frac{d\xi}{dt} = 19\xi \\ \frac{d\eta}{dt} = -6\xi + 4\eta \end{cases}$$

$$D = (a + d)^2 - 4(ad - bc) = 23^2 - 4 * 76 = 225$$

$$\lambda_{1,2} = \frac{(a + d) \pm \sqrt{D}}{2} = \frac{23 \pm 15}{2} = 19; \quad 8.$$

Phase portrait is unstable node.

Horizontal isocline:

$$\frac{d\xi}{dt} = 0, \quad \xi = 0.$$

Vertical isocline:

$$\frac{d\eta}{dt} = 0, \quad \eta = \frac{3}{2}\xi.$$

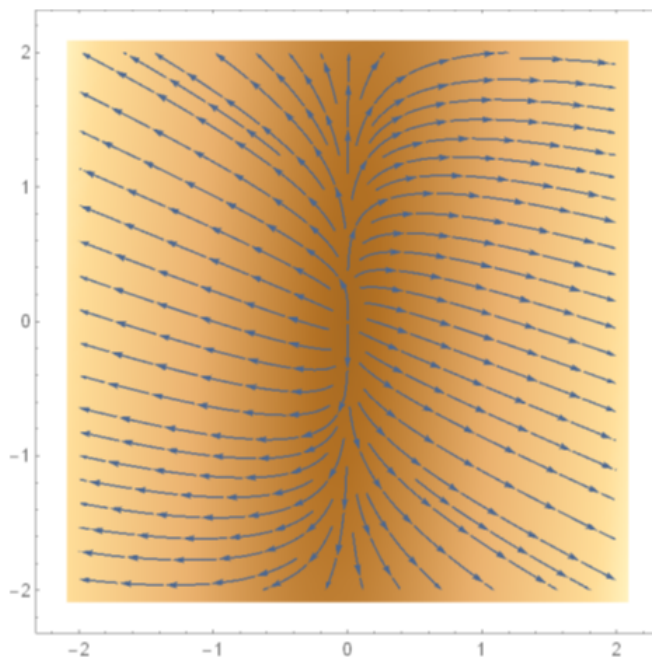


Figure 1.24 – Phase portrait is unstable node

Consider the third stationary point: $(1,0)$:

$$a = 1 - 9\bar{y} - 2\bar{x} = -1; \quad b = -9\bar{x} = -9;$$

$$c = 3\bar{y} = 0; \quad d = 3\bar{x} - 4 - 4\bar{y} = -1;$$

$$\begin{cases} \frac{d\xi}{dt} = -\xi - 9\eta \\ \frac{d\eta}{dt} = -\eta \end{cases}$$

$$D = (a + d)^2 - 4(ad - bc) = 4 - 4 = 0$$

$$\lambda_{1,2} = \frac{(a + d) \pm \sqrt{D}}{2} = \frac{-2}{2} = -1; \quad -1.$$

The phase portrait is a stable node. Horizontal isocline:

$$\frac{d\xi}{dt} = 0, \quad \eta = -\frac{1}{9}\xi.$$

Vertical isocline:

$$\frac{d\eta}{dt} = 0, \quad \eta = 0.$$

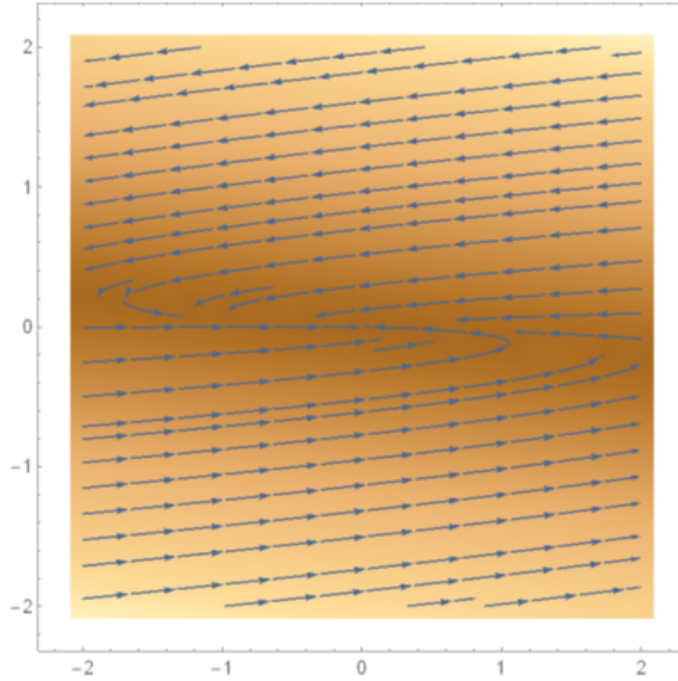


Figure 1.25 – Phase portrait is a stable degenerate node

Fourth stationary point - $\left(\frac{38}{29}, -\frac{1}{29}\right)$

$$a = 1 - 9\bar{y} - 2\bar{x} = -\frac{38}{29}; \quad b = -9\bar{x} = -\frac{342}{29};$$

$$c = 3\bar{y} = -\frac{3}{29}; \quad d = 3\bar{x} - 4 - 4\bar{y} = \frac{2}{29};$$

$$\begin{cases} \frac{d\xi}{dt} = -\frac{38}{29}\xi - \frac{342}{29}\eta \\ \frac{d\eta}{dt} = -\frac{3}{29}\xi + \frac{2}{29}\eta \end{cases}$$

$$D = (a + d)^2 - 4(ad - bc) = \frac{5704}{841}$$

$$\lambda_{1,2} = \frac{(a + d) \pm \sqrt{D}}{2} = \frac{-1.24 \pm 2.6}{2} = 0.68; \quad -1.92.$$

Phase portrait is saddle. Horizontal isocline:

$$\frac{d\xi}{dt} = 0, \quad \eta = -\frac{38}{342}\xi.$$

Vertical isocline:

$$\frac{d\eta}{dt} = 0, \quad \eta = \frac{3}{2}\xi.$$

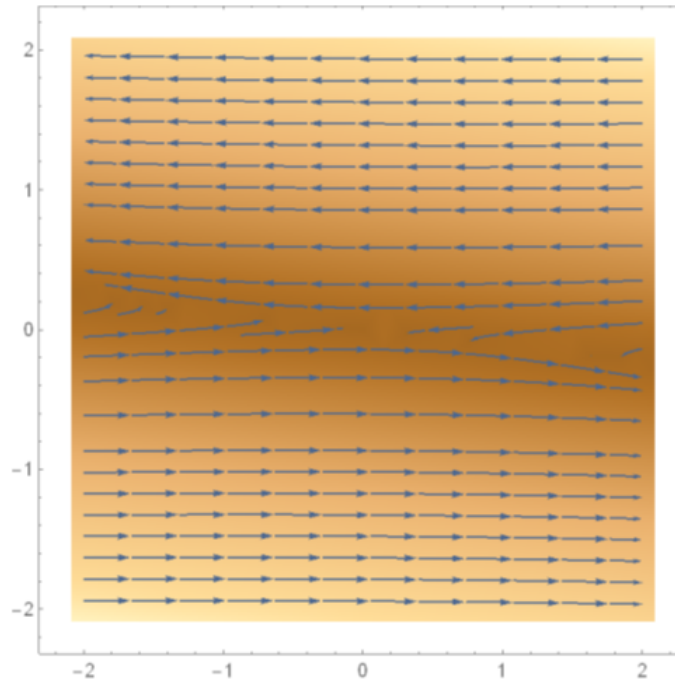


Figure 1.26 – phase portrait for the fourth stationary point is saddle

1.3 Some information on numerical methods for solution of the partial differential equations

In this part of the chapter we give some basic information on numerical methods for solution of the partial differential equations.

1.3.1 Finite-difference approximation of derivatives

We consider the function $p(x, y, z, t)$ of three spatial coordinates and time, the values of which are determined at the points of the space-time grid, separated by equal intervals (steps) along the corresponding directions. Dimensionless coordinates are entered:

$$i = \frac{x}{\delta x}, \quad j = \frac{y}{\delta y}, \quad k = \frac{z}{\delta z}, \quad t = \frac{T}{\delta t},$$

where, $\delta x, \delta y$ – are steps on horizontal coordinates, δz -is a vertical coordinate step, δt –is a time step. The value of a function $p(x, y, z, t)$ at the point x_i, y_j, z_k, t^n will be denoted as p_{ijk}^n , that is $p_{ijk}^n = p(x_i, y_j, z_k, t^n)$.

There are a number of ways to replace derivatives of functions by approximate finite difference relations. The choice of a suitable method for the difference approximation of the derivatives is determined by the specific features of the particular problem being solved. We consider two of them, the function of one of the coordinates, for example

x . Approximate values of the derivatives can be written in the form:

$$\left(\frac{\partial p}{\partial x}\right)_i \approx (\delta_x^1 p)_i = \frac{1}{\delta x}(p_{i+1} - p_i) \quad (1.17)$$

$$\left(\frac{\partial^2 p}{\partial x^2}\right)_i \approx (\delta_x^2 p)_i = \frac{1}{2\delta x}(p_{i+1} - 2p_i + p_{i-1}) \quad (1.18)$$

The first method of approximation of derivatives is called a two-point (one-sided difference upwind), the second method is a three-point approximation (centered difference). There are other more precise finite difference relations. Approximate values of derivatives of higher orders can be obtained using approximate expressions for first-order derivatives. Below is the finite difference approximation for the second derivative:

$$\left(\frac{\partial^2 p}{\partial x^2}\right)_i \approx (\delta_{xx} p)_i = \frac{1}{(\delta x)^2}(p_{i+1} - 2p_i + p_{i-1}). \quad (1.19)$$

The above relations can easily be extended to the case of a function of several variables, for example, for the Laplace operator the following finite difference approximation is obtained:

$$\begin{aligned} (\Delta p)_{ij} &= \frac{\partial^2 p}{\partial x^2} + \frac{\partial^2 p}{\partial y^2} \approx (\delta_{xx} p_{ij}) + (\delta_{yy} p_{ij}) = \\ &= \frac{1}{(\delta x)^2}(p_{i+1,j} - 2p_{i,j} + p_{i-1,j}) + \left(\frac{1}{(\delta y)^2}(p_{i,j+1} - 2p_{i,j} + p_{i,j-1})\right) \end{aligned}$$

1.3.2 Estimation of the accuracy of finite-difference approximation of derivatives

In solving this problem, an important step is to estimate the accuracy of the finite difference approximation of the derivatives. For this purpose, the difference between the approximate and exact values of the derivatives at the point i is introduced:

$$\varepsilon = \delta_x p - \frac{\partial p}{\partial x} \quad (1.20)$$

The use of the expansion of the Taylor series

$$p(x + \delta x) = p(x) + \frac{\partial p}{\partial x} \delta x + \frac{1}{2!} \frac{\partial^2 p}{\partial x^2} (\delta x)^2 + \frac{1}{3!} \frac{\partial^3 p}{\partial x^3} (\delta x)^3 + \dots$$

leads to the relations:

$$p_{i+1} = p_i + \left(\frac{\partial p}{\partial x}\right)_i \delta x + \frac{1}{2!} \left(\frac{\partial^2 p}{\partial x^2}\right)_i (\delta x)^2 + \frac{1}{3!} \left(\frac{\partial^3 p}{\partial x^3}\right)_i (\delta x)^3 + \dots$$

$$p_{i-1} = p_i + \left(\frac{\partial p}{\partial x}\right)_i (-\delta x) + \frac{1}{2!} \left(\frac{\partial^2 p}{\partial x^2}\right)_i (-\delta x)^2 + \frac{1}{3!} \left(\frac{\partial^3 p}{\partial x^3}\right)_i (-\delta x)^3 + \dots$$

substitution of the obtained expression in (1.20) leads:

$$\varepsilon_1 = (\delta_x^1)p - \frac{\partial p}{\partial x} = \frac{1}{2!} \left(\frac{\partial^2 p}{\partial x^2}\right)_i (\delta x)^2 + \frac{1}{3!} \left(\frac{\partial^3 p}{\partial x^3}\right)_i (\delta x)^3 + \dots = O(\delta x)$$

$$\varepsilon_2 = (\delta_x^2)p - \frac{\partial p}{\partial x} = \frac{1}{2 * 3!} \left(\frac{\partial^3 p}{\partial x^3}\right)_i (\delta x)^3 + \dots = O((\delta x)^2)$$

Considering the differences, one can see that the leading term of the series expressing the difference ε has a multiplier in the first case δx , in the second - $(\delta x)^2$. Since the grid spacing is small, we can say that these series have in the first case the first order of accuracy, in the second - the second, and is denoted by symbols $O(\delta x)$, $O((\delta x)^2)$.

1.3.3 Implicit and Explicit schemes

To solve the partial differential equations problems, the difference approximation of differential equations containing time derivatives is of particular interest. Here we consider two schemes: explicit and implicit. For simplicity, the simplest linear differential equation is considered:

$$\frac{\partial v}{\partial t} + c \frac{\partial v}{\partial y} = 0 \quad (1.21)$$

where c – constant.

When the desired variables can be expressed in terms of known parameters, such schemes are **explicit**. A finite-difference analogue of equation (1.21) can be written in the form:

$$\left(\frac{\partial v}{\partial t}\right)_j^n + c \left(\frac{\partial v}{\partial y}\right)_j^n = 0$$

The use of (1.18) for the derivative with respect to the spatial coordinate, and to the time derivative of (1.17), leads to the following two types of finite difference equations:

$$v_j^{n+1} - v_j^n + \frac{\alpha}{2} (v_{j+1}^n - v_{j-1}^n) = 0 \quad (1.22)$$

$$v_j^{n+1} - v_j^{n-1} + \alpha (v_{j+1}^n - v_{j-1}^n) = 0 \quad (1.23)$$

где $\alpha = c \frac{\delta t}{\delta y}$.

Assuming that the values v function at a given and preceding time, that is under $n, n - 1$ are known, using any of the expressions (1.22), (1.23) it is possible to express values at a future time, that is, a value v_j^{n+1} through known functions explicitly:

$$v_j^{n+1} = v_j^n - \frac{\alpha}{2}(v_{j+1}^n - v_{j-1}^n)$$

$$v_j^{n+1} = v_j^{n-1} - \alpha(v_{j+1}^n - v_{j-1}^n) = 0.$$

If the time derivatives and other terms of the differential equation are attributed to different points in time the implicit schemes are obtained. In this case, the unknown variables are not expressed explicitly. For example, if the time derivative is attributed to the moment in time n , and the other terms of the equation to the moment of time $n + 1$,

$$\left(\frac{\partial v}{\partial t}\right)_j^n + \alpha\left(\frac{\partial v}{\partial y}\right)_j^{n+1} = 0$$

then applying the second order of approximation of the derivatives one can obtain the following finite difference equation:

$$v_j^{n+1} - v_j^{n-1} + \alpha(v_{j+1}^n - v_{j-1}^n) = 0 \quad (1.24)$$

If the time derivative is attributed to the moment of time n the other terms of the equation can be expressed in terms of the function values at different time, including moment $n + 1$

$$\left(\frac{\partial v}{\partial t}\right)_j^n = \frac{1}{2}\left[\left(\frac{\partial v}{\partial y}\right)_j^{n+1} + \left(\frac{\partial v}{\partial y}\right)_j^{n-1}\right] \quad (1.25)$$

and applying to the derivatives of t and $n + 1$ the second way of approximating the derivatives, can be obtained:

$$v_j^{n+1} - v_j^{n-1} + \frac{\alpha}{2}(v_{j+1}^{n+1} - v_{j-1}^{n+1} + v_{j+1}^{n-1} - v_{j-1}^{n-1}) = 0 \quad (1.26)$$

The relations (1.24) and (1.26) give a connection between the future value of the function at the moment of time $n + 1$ and the value of the function at the previous moment of time. The function at the point $(j, n + 1)$ can not be expressed through the other functions explicitly, that is why similarly finite difference schemes are called implicit. Since the implicit schemes do not allow one to calculate the required variables, in practice these relationships are represented in the form of difference equations that can be solved by specially constructed methods (iterative). The choice of the scheme for approximation the equations is determined by the features of the problem being solved.

1.3.4 Estimation of the Stability of Finite-Difference Schemes

When solving finite-difference equations, it is necessary to repeatedly perform similar computational procedures. If you do not take special measures, then if you repeat the same calculations repeatedly, the small errors in the initial data or in the process of calculation may increase and distort the decision. This phenomena is called computational instability. We consider it using the equation (1.21) as an example. We first obtain an exact solution of the equation under the condition that at the initial time the function $v(y)$ has the form:

$$v(y) = Ae^{imy},$$

where A – wave amplitude, $m = 2\pi/L$ – wave number, L – wavelength, $i = \sqrt{-1}$.

In accordance with the form of the initial condition, we find the solution of (1.21) in the form:

$$v(y, t) = Ae^{i(my-\sigma t)},$$

where $\sigma = 2\pi/T$ – circular frequency, T – period. Velocity $c = \sigma/m$ – wave velocity. It is easy to see that

$$\frac{\partial v}{\partial t} = -i\sigma Ae^{i(my-\sigma t)}, \quad \frac{\partial v}{\partial y} = -imAe^{i(my-\sigma t)},$$

Substituting these expressions into equation (1.19), we obtain

$$iAe^{i(my-\sigma t)}[-\sigma + cm] = 0.$$

where from $\sigma = cm$, means

$$v(y, t) = Ae^{im(y-ct)}.$$

The resulting solution reflects the movement of the wave without changing the amplitude of the wave, which means the stability of the solution. If we go over to the corresponding finite-difference equations and represent the required function at the initial time in the form:

$$v_j^0 = Ae^{imj\delta y},$$

and the solution of the finite-difference equations will be search in an analogous form:

$$v_j^n = Ae^{i(mj\delta y - \sigma n\delta t)},$$

then it is easy to verify that

$$v_j^{n-1} = Ae^{i(mj\delta y - \sigma(n-1)\delta t)} = v_j^n e^{i\sigma\delta t},$$

$$v_{j+1}^n = v_j^n e^{im\delta y},$$

$$v_{j-1}^n = v_j^n e^{-im\delta y},$$

$$\begin{aligned}v_{j+1}^{n+1} &= v_j^n e^{j(m\delta y - \sigma\delta t)}, \\v_{j-1}^{n+1} &= v_j^n e^{i(-m\delta y - \sigma\delta t)}.\end{aligned}$$

We consider now an explicit scheme upwind differences, i.e. scheme (1.17). Substituting the expressions just obtained in (1.20), we arrive at the equation

$$v_j^n e^{-i\sigma\delta t} - v_j^n + \frac{\alpha}{2}(v_j^n e^{im\delta y} - v_j^n e^{-im\delta y}) = 0$$

or

$$v_j^n m[e^{-i\sigma\delta t} - 1 + \frac{\alpha}{2}(e^{im\delta y} - e^{-im\delta y})] = 0.$$

As $v_j^n \neq 0$, then it follows that

$$e^{-i\sigma\delta t} - 1 + \frac{\alpha}{2}(e^{im\delta y} - e^{-im\delta y}) = 0$$

We will take into account that according to Euler's formula $e^{iz} - e^{-iz} = 2i\sin z$, suppose that $\sigma = \sigma_r + i\sigma_i$, where σ_r и σ_i - are real and imaginary parts σ , and note that

$$e^{-i\sigma\delta t} = e^{-i(\sigma_r + i\sigma_i)\delta t} = e^{-i\sigma_r\delta t} e^{\sigma_i\delta t} e^{i\sigma_i\delta t} [\cos(\sigma_r\delta t) - i\sin(\sigma_r\delta t)]$$

Then we obtain

$$e^{\sigma_i\delta t} [\cos(\sigma_r\delta t) - i\sin(\sigma_r\delta t)] - 1 + i\alpha\sin(m\delta y) = 0$$

Separating the real and imaginary parts, we find:

$$e^{\sigma_i\delta t} \cos(\sigma_r\delta t) = 1$$

$$e^{\sigma_i\delta t} \sin(\sigma_r\delta t) = \alpha\sin(m\delta y)$$

Raising both sides of the equalities into squares and adding them, we find

$$e^{2\sigma_i\delta t} = 1 + \alpha^2 \sin^2(m\delta y)$$

Since, the right-hand side of this equation is always greater than one, then $e^{2\sigma_i\delta t} > 1$, which means,

$$2\sigma_i\delta t > 0$$

. Hence, always $\sigma_i > 0$. We now analyze the resulting solution

$$v_j^n = A e^{i(mj\delta y - \sigma n\delta t)} = A e^{i[mj\delta y - (\sigma_r + i\sigma_i)n\delta t]} = A e^{\sigma_i n\delta t} e^{i(mj\delta y - \sigma_r n\delta t)}$$

It can be seen that the first multiplier for the amplitude A at $\sigma_i > 0$ will increase with increasing of time, which means the amplitude of the initial wave will increase. The increase in amplitude will be the stronger, the larger the time step. At an infinitely small step with respect to the time the amplitude will not increase. Hence it can be concluded that an explicit scheme with one-sided upwind difference has computational instability.

Questions:

1. Describe the main groups of numerical taxonomy.
2. What are the main principles of numerical taxonomy?
3. Uncover the differences between the simply-connected method and the "full link" method.
4. Provide a definition of the dynamic system, give examples.
5. What is the depicting point of a dynamic system?
6. Explain, what the phase trajectory is, name the basic properties of the phase trajectories.
7. Explain the stability of the equilibrium position of one-dimensional systems.
8. What is the asymptotically stable equilibrium position of dynamical systems?
9. Provide a definition of stability by Lyapunov.
10. Explain what the characteristic equation of the dynamic system is?
11. Explain what the characteristic numbers of the dynamic system are?
12. Determine the conditions and describe the equilibrium position - an unstable node.
13. Determine the conditions and describe the equilibrium position - a stable node.
14. Determine the conditions and describe the equilibrium position - saddle.
15. Determine the conditions and describe the equilibrium position — a steady focus.
16. Determine the conditions and describe the position - centre.
17. Estimate the accuracy of finite-difference approximation of the second derivative $\frac{\partial^2 p}{\partial x^2}$ using the central difference (II method of representing of the first derivative).
18. Investigate the stability scheme with a central difference (1.24).
19. Investigate on stability an implicit scheme for approximation of equation (1.22).

Exercises:

1. Build a similarity matrix by statistical data.
2. Determine the taxonomic groups using the method of the most remote neighbors and build a dendrogram for the following matrix of characteristics:

1	0	3.06	20.3	7.52	5.03
2	3.06	0	7.50	8.24	3.45
3	20.3	7.50	0	2.25	3.65
4	7.52	8.24	2.25	0	4.81
5	5.03	3.45	3.65	4.81	0

1	0	2.06	40.3	6.32	2.08
2	2.06	0	3.50	4.12	5.43
3	4.03	3.50	0	2.25	3.65
4	6.32	4.12	2.25	0	4.81
5	2.08	5.43	3.65	4.81	0

3. Build an algorithm to determine taxonomic groups using the "medium link" method.

4. Draw the phase portraits of the following equations:

(a) $\dot{x} = 2x - x^2$

(b) $\dot{u} = (u - 1)(u^2 - 4)$

(c) $\dot{p} = p^2 + 1$

(d) $\dot{x} = 0$

(e) $\dot{x} = x^5(x - 1)^8(x + 2)^9(3 - x)^8$

(f) $\dot{v} = \sin v.$

(g) $\dot{x} = 9x - x^2$

(h) $\dot{u} = (u - 2)(u^2 - 9)$

(i) $\dot{p} = p^2 + 4$

(j) $\dot{x} = x^2(x - 1)^3(x + 2)^9(3 - x)^7$

(k) $\dot{v} = \cos v.$

5. Research the behavior of the phase trajectories of the following systems:

(a)
$$\begin{cases} \dot{x} = 5x - y, \\ \dot{y} = 3x + y. \end{cases}$$

(b)
$$\begin{cases} \dot{x} = -2x + y, \\ \dot{y} = x - 2y. \end{cases}$$

$$(c) \begin{cases} \dot{x} = y, \\ \dot{y} = 3x - y. \end{cases}$$

$$(d) \begin{cases} \dot{x} = x - y, \\ \dot{y} = x + y. \end{cases}$$

$$(e) \begin{cases} \dot{x} = 10x - 100y, \\ \dot{y} = x + 10y. \end{cases}$$

$$(f) \begin{cases} \dot{x} = x - 2y, \\ \dot{y} = x - y. \end{cases}$$

$$(g) \begin{cases} \dot{x} = 7x - 2y, \\ \dot{y} = x - 1.01y. \end{cases}$$

$$(h) \begin{cases} \dot{x} = y, \\ \dot{y} = 3x - y. \end{cases}$$

$$(i) \begin{cases} \dot{x} = x - y, \\ \dot{y} = x + y. \end{cases}$$

$$(j) \begin{cases} \dot{x} = 5x - 50y, \\ \dot{y} = x + 10y. \end{cases}$$

$$(k) \begin{cases} \dot{x} = 3x - 2y, \\ \dot{y} = x - 3y. \end{cases}$$

$$(l) \begin{cases} \dot{x} = 7x - 2y, \\ \dot{y} = x - 1.01y. \end{cases}$$

$$(m) \begin{cases} \dot{x} = 3x - y, \\ \dot{y} = 5x + y. \end{cases}$$

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Chapter 2

Mathematical modeling of the biomedical processes

2.1 Population and its characteristic relationships

Ecology is a science that explores the structure and functioning of a population, community, ecosystem in space and time, in natural and human conditions. A population is usually understood as the aggregate of a certain *number* of individuals. Many biological studies deal with such problems as the development and evolution of species, competition between species, the influence of environmental factors, the spread of epidemics, etc. None of these studies can be absolutely accurate if it does not begin with the construction of some acceptable mathematical model of the population in question.

Relationships in populations are intraspecific interactions. By the nature of these interactions, populations of different species are extremely diverse. In populations, there are all types of connections inherent in living organisms, but the most common are mutually beneficial and competitive relationships.

The population size is the total number of individuals in a given territory or in a given volume. *Population density* is the number of individuals per unit area or volume, for example, 150 pines per 1 hectare, or 0.5 grams of cyclops per water. They characterize the population density of these species. There are three types of population dynamics of numbers:

- 1) stable; 2) changeable; 3) explosive.

Types of population dynamics of numbers regulate their number and adapt to changing environmental conditions by updating and replacing individuals. Individuals appear in the population through birth and immigration, but disappear as a result of death and emigration.

One of the simplest models of population growth belongs to T. Malthus, who at the end of the 18th century. noted that populations tend to increase exponentially. In nature, the number of most living creatures can indeed increase in geometric progression, but the growth of populations is constrained by factors such as the struggle for existence, disease, natural death and destruction by predators. Usually, if the popula-

tion begins to develop in an environment with a sufficient amount of food and with a relatively small number of predators, then initially its population grows very quickly. Over time, food reserves are depleted, overpopulation leads to conditions less favorable for survival, fertility is reduced and mortality increases. Under certain conditions, an equilibrium state is reached and the population size becomes more or less constant. Obviously, it is very important to know the exact ratio between the population size at different times and the rates of reproduction and death.

2.1.1 The Malthusian growth model

The Malthusian model of population growth is a classic model of unlimited growth. Let $N(t)$ be the number of individuals in a population at time t , and let b and d be the average per capita birth rate and death rate, respectively. In a short time Δt , the number of births in the population is $b\Delta tN$, and the number of deaths is $d\Delta tN$. An equation for N at time $t + \Delta t$ is then determined to be:

$$N(t + \Delta t) = N(t) + b\Delta tN(t) - d\Delta tN(t),$$

which can be rewritten as:

$$(N(t + \Delta t) - N(t))/\Delta t = (b - d)N(t),$$

and as $\Delta t \rightarrow 0$,

$$\frac{dN}{dt} = (b - d)N. \quad (2.1)$$

With an initial population size of N_0 , and with $r = b - d$ positive, the solution for $N = N(t)$ grows exponentially: $N(t) = N_0e^{rt}$.

2.1.2 The Logistic equation

In accordance with the exponential law, an isolated population would develop under conditions of unlimited resources. As it was said above, in nature such conditions are extremely rare. It is assumed that the environment has an internal capacity of K , and populations exceeding this size increase mortality. To model population growth with an environmental carrying capacity K , we look for a nonlinear equation of the form

$$\frac{dN}{dt} = rNF(N),$$

where $F(N)$ provides a model for environmental regulation. This function must satisfy the following conditions:

1. $F(N) = 1$ (the population grows exponentially with growth rate r when N is small),
2. $F(N) = 0$ (the population stops growing at the carrying capacity),
3. $F(N) < 0$ при $N > K$ (the population decays when it is larger than the carrying capacity).

The simplest function $F(N)$ satisfying these conditions is linear and given by

$$F(N) = 1 - N/K$$

The resulting model is the well-known logistic equation

$$\frac{dN}{dt} = rN(1 - N/K). \quad (2.2)$$

This equation describes many biological processes.

In the logistic equation (2.2), the fixed points are $N^* = 0, K$. A sketch of $F(N) = rN(1 - N/K)$ versus N , with $r, K > 0$ in Fig. 2.1 immediately shows that $N^* = 0$ is an unstable fixed point and $N^* = K$ is a stable fixed point.

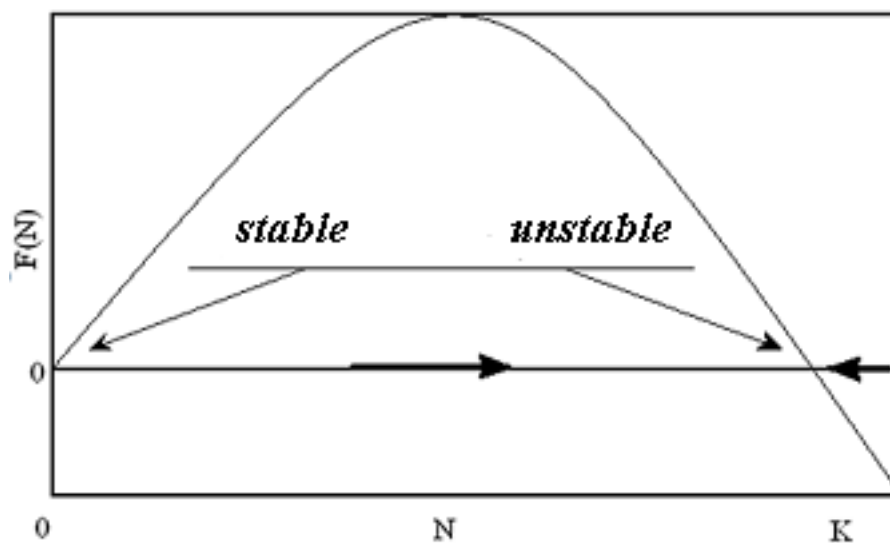


Figure 2.1

Applying the analytical approach and calculating the derivative of the function $F'(N) = r(1 - 2N/K)$, we find that $F'(0) = r > 0$ and $F'(K) = -r < 0$. Again we conclude that $N^* = 0$ is unstable and $N^* = K$ is stable.

We represent the analytical solution of the logistic equation. We begin by nondimensionalizing time and population size: $\tau = t/t^*$, $\eta = N/N^*$, therefore, the logistic equation (2.2) becomes:

$$\frac{d\eta}{d\tau} = r t_* \eta (1 - N_* \eta / K),$$

which assumes the simplest form with the choices $t_* = 1/r$ and $N_* = K$. Therefore, our dimensionless variables are $\tau = rt$, $\eta = N/K$, and the logistic equation, in dimensionless form, becomes

$$\frac{d\eta}{d\tau} = \eta(1 - \eta), \quad (2.3)$$

with the dimensionless initial condition $\eta(0) = \eta_0 = N_0/K$, where N_0 is the initial population size. Note that the dimensionless logistic equation (2.3) has no free parameters, while the dimensional form of the equation (2.2) contains r and K . Reduction in the number of free parameters (here, two: r and K) by the number of independent units (here, also two: time and population size) is a general feature of nondimensionalization.

Solving the dimensionless logistic equation (2.3) can proceed by separating the variables. Separating and integrating from $\tau = 0$ to τ and $\eta = 0$ to η yields

$$\int_{\eta_0}^{\eta} \frac{d\eta}{\eta(1-\eta)} = \int_0^{\tau} d\tau.$$

The integral on the left-hand-side can be performed using the method of partial fractions. Returning to dimensional variables, we finally have:

$$N(t) = \frac{N_0}{N_0/K + (1 - N_0/K)e^{-rt}}.$$

The conclusion of the Malthusian growth model implicitly assumed a large population size. Usually smaller populations exhibit stochastic effects, and this can greatly complicate the simulation.

2.1.3 A stochastic model of population growth

The population models we examined were deterministic. However, there are two aspects in which the deterministic model can not serve as an accurate reflection of real ecological systems. First, it does not take into account the probabilistic nature of the processes of reproduction and death; secondly, does not take into account the random oscillations occurring in the medium with time and lead to random fluctuations of the model parameters. Taking these factors into account leads to a significant complication of the mathematical apparatus. Therefore, usually researchers try to build deterministic models, confining themselves to mentioning the possible consequences of accounting stochastics. If the deterministic model indicates a stable equilibrium, the stochastic model predicts a long-term survival. If a deterministic model predicts periodic declines in the number of one or more species, the stochastic model will give some positive probability of extinction of these species. Finally, if the deterministic model does not reveal equilibrium or the equilibrium is unstable, the stochastic model predicts a high probability of extinction.

The size of the population N is now considered to be a discrete random variable. We define the time-dependent probability mass function $p_N(t)$ of N to be the probability that the population is of size N at time t . Since N must take on one of the values from zero to infinity, we have

$$\sum_{N=0}^{\infty} p_N(t) = 1$$

for all $t \geq 0$. Again, let b be the average per capita birth rate. Suppose that for $\Delta t \rightarrow 0$ the probability that a person gives birth for a time Δt is given by $b\Delta t$. For example, if the average per capita birthrate is one offspring every 365-day year, then the probability that a given individual gives birth on a given day is $1/365$. Furthermore, we will suppose that at $t = 0$, the population size is known to be N_0 , so that $p_{N_0}(0) = 1$, with all other p_N 's at $t = 0$ equal to zero.

We can determine a system of differential equations for the probability mass function $p_N(t)$ as follows. For a population to be of size $N > 0$ at a time $t + \Delta t$, either it was of size $N - 1$ at time t and one birth occurred, or it was of size N at time t and there were no births; that is

$$p_N(t + \Delta t) = p_{N-1}(t)b(N-1)\Delta t + p_N(t)(1 - bN\Delta t) \quad (2.4)$$

Subtracting $p_N(t)$ from both sides, dividing by Δt and taking the limit $\Delta t \rightarrow 0$, we obtain ordinary differential equations,

$$\frac{dp_N}{dt} = b[(N-1)p_{N-1} - Np_N], \quad N = 1, 2, \dots \quad (2.5)$$

где, $p_0(t) = p_0(0)$.

We first review how to solve a first-order linear differential equation of the form

$$\frac{dy}{dt} + ay = g(t), \quad y(0) = y_0 \quad (2.6)$$

where $y = y(t)$ and a is constant. First, we look for an integrating factor μ such that

$$\frac{d}{dt}(\mu y) = \mu\left(\frac{dy}{dt} + ay\right).$$

Differentiating the left-hand-side and multiplying out the right-hand-side results in μ :

$$y\frac{d\mu}{dt} + \mu\frac{dy}{dt} = \mu\frac{dy}{dt} + \mu ay,$$

which leads to the following equation:

$$\frac{d\mu}{dt} = \mu a$$

We may integrate this equation with an arbitrary initial condition, so for simplicity we take $\mu(0) = 1$. Therefore, $\mu(t) = e^{at}$. Hence,

$$\frac{d(e^{at}y)}{dt} = e^{at}g(t)$$

Integrating this equation from 0 to t yields, we get

$$e^{at}y(t) - y(0) = \int_0^t e^{as}g(s)ds$$

Therefore, the solution is

$$y(t) = e^{-at}(y(0) + \int_0^t e^{as}g(s)ds) \quad (2.7)$$

Equations (2.5) are equations (2.6) with:

$$a = bN \text{ и } g(t) = b(N - 1)P_{N-1}$$

With the population size known to be N_0 at $t = 0$, the initial conditions can be written succinctly as $p_N(0) = \delta_{N,N_0}$, where δ_{ij} is the Kronecker delta, defined as

$$\delta_{i,j} = \begin{cases} 0, & \text{if } i \neq j \\ 1, & \text{if } i = j \end{cases}$$

Thus, formally integrating (2.5) and using (2.7) we obtain the solution in the following form:

$$p_N(t) = e^{-bNt}[\delta_{N,N_0} + b(N - 1) \int_0^t e^{bNs} p_{N-1}(s) ds].$$

2.2 Models of interaction of two types

2.2.1 Competition between the two species

Suppose that two species compete for the same resources. To build a model, we can start with logistic equations for both species. Different species would have different growth rates and different carrying capacities. If we let N_1 and N_2 be the number of individuals of species 1 and species 2, then

$$\begin{aligned} \frac{dN_1}{dt} &= r_1 N_1 (1 - N_1/K_1), \\ \frac{dN_2}{dt} &= r_2 N_2 (1 - N_2/K_2), \end{aligned} \quad (2.8)$$

These are uncoupled equations so that asymptotically $N_1 \rightarrow K_1$ и $N_2 \rightarrow K_2$.

How do we model the competition between species? If N_1 is much smaller than K_1 , and N_2 much smaller than K_2 , then resources are plentiful and populations grow exponentially with growth rates r_1 and r_2 . If species one and two compete, then the growth of species one reduces resources available to species two, and vice-versa. Since we do not know the impact species one and two have on each other, we introduce two additional parameters to model the competition. A reasonable modification that couples the two logistic equations is

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1 + a_{12}N_2}{K_1}\right),$$

$$\frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{a_{21} N_1 + N_2}{K_2} \right) \quad (2.9)$$

where a_{12} and a_{21} are dimensionless parameters that model the consumption of species one's resources by species two, and vice-versa. For example, suppose that both species eat exactly the same food, but species two consumes twice as much as species one. Since one individual of species two consumes the equivalent of two individuals of species one, the correct model is $a_{12} = 2$ and $a_{21} = 1/2$. Another example supposes that species one and two occupy the same niche, consume resources at the same rate, but may have different growth rates and carrying capacities. Can the species coexist, or does one species eventually drive the other to extinction? It is possible to answer this question without actually solving the differential equations. With $a_{12} = a_{21} = 1$ as appropriate for this example, the coupled logistic equations (2.9) become

$$\begin{aligned} \frac{dN_1}{dt} &= r_1 N_1 \left(1 - \frac{N_1 + N_2}{K_1} \right), \\ \frac{dN_2}{dt} &= r_2 N_2 \left(1 - \frac{N_1 + N_2}{K_2} \right) \end{aligned} \quad (2.10)$$

We assume that $K_1 > K_2$. The only fixed points other than the trivial one $(N_1, N_2) = (0, 0)$ are $(N_1, N_2) = (K_1, 0)$ and $(N_1, N_2) = (0, K_2)$. Stability can be computed analytically by a two-dimensional Taylor series expansion, but here a simpler argument can suffice. We first consider $(N_1, N_2) = (K_1, \varepsilon)$, with ε small. Since $K_1 > K_2$, observe from (2.10) that $N_2 < 0$ so that species two goes extinct. Therefore $(N_1, N_2) = (K_1, 0)$ is a stable fixed point. We have thus found that, within our coupled logistic model, species that occupy the same niche and consume resources at the same rate cannot coexist and that the species with the largest carrying capacity will survive and drive the other species to extinction. This is the so-called principle of competitive exclusion, also called K -selection since the species with the largest carrying capacity wins. In fact, ecologists also talk about r -selection; that is, the species with the largest growth rate wins. Our coupled logistic model does not model r -selection, demonstrating the potential limitations of a too simple mathematical model. For some values of a_{12} and a_{21} , our model admits a stable equilibrium solution where two species coexist. The stable coexistence of two species within our model is possible only if $a_{12}K_2 < K_1$ and $a_{21}K_1 < K_2$. The stable coexistence of two species in our model is possible.

2.2.2 The predator-prey model

Lotka and Volterra proposed in the 1920s a mathematical model for the population dynamics of a predator and prey, and these Lotka-Volterra predator-prey equations have since become an iconic model of mathematical biology. To develop these equations, suppose that a predator population feeds on a prey population, that the number of prey

grow exponentially in the absence of predators (there is unlimited food available to the prey), and that the number of predators decay exponentially in the absence of prey (predators must eat prey or starve). Contact between predators and prey increases the number of predators and decreases the number of prey. Let $U(t)$ and $V(t)$ be the number of prey and predators at time t . To develop a coupled differential equation model, we consider population sizes at time $t + \Delta t$. Exponential growth of prey in the absence of predators and exponential decay of predators in the absence of prey can be modeled by the usual linear terms. The coupling between prey and predator must be modeled with two additional parameters. We write the population sizes at time $t + \Delta t$ as

$$\begin{aligned}U(t + \Delta t) &= U(t) + \alpha\Delta tU(t) - \gamma\Delta tU(t)V(t), \\V(t + \Delta t) &= V(t) + \epsilon\gamma\Delta tU(t)V(t) - \beta\Delta tV(t).\end{aligned}$$

The parameters α and β are the average per capita birthrate of the prey and the death rate of the predators, in the absence of the other species. The parameter γ is the fraction of prey caught per predator per unit time; the total number of prey caught by predators during time Δt is $\gamma\Delta tUV$. The prey eaten is then converted into newborn predators (view this as a conversion of biomass), with conversion factor ϵ , so that the number of predators during time Δt increases by $\epsilon\gamma\Delta tUV$.

Converting these equations into differential equations by letting $\Delta t \rightarrow 0$, we obtain the well-known Lotka-Volterra predator-prey equations:

$$\begin{aligned}\frac{dU}{dt} &= \alpha U - \gamma UV, \\ \frac{dV}{dt} &= \epsilon\gamma UV - \beta V.\end{aligned}\tag{2.11}$$

We now reconsider the Lotka-Volterra equations (2.11). Fixed point solutions are found by solving

$$\dot{U} = \dot{V} = 0.$$

Solutions are

$$(U_*, V_*) = (0, 0) \text{ or } (U_*, V_*) = \left(\frac{\beta}{\epsilon\gamma}, \frac{\alpha}{\gamma}\right).$$

The first fixed point $(0, 0)$ is unstable since the prey population grows exponentially if it is initially small. To determine the stability of the second fixed point, we write the Lotka-Volterra equation in the form:

$$\begin{aligned}\frac{dU}{dt} &= F(U, V) \\ \frac{dV}{dt} &= G(U, V),\end{aligned}$$

where

$$F(U, V) = \alpha U - \gamma UV, \quad G(U, V) = \epsilon \gamma UV - \beta V.$$

The partial derivatives are then computed to be:

$$\begin{aligned} F_U &= \alpha - \gamma V, & F_V &= -\gamma U \\ G_U &= \epsilon \gamma V, & G_V &= \epsilon \gamma U - \beta. \end{aligned}$$

The Jacobian at the fixed point $(U_*, V_*) = \left(\frac{\beta}{\epsilon \gamma}, \frac{\alpha}{\gamma} \right)$ is:

$$J_* = \begin{pmatrix} 0 & -\beta/\epsilon \\ \epsilon \alpha & 0 \end{pmatrix}.$$

Characteristic variables are determined from the equation:

$$\det(J_* - \lambda I) = \begin{vmatrix} -\lambda & -\beta/\epsilon \\ \epsilon \alpha & -\lambda \end{vmatrix} = \lambda^2 - \alpha \beta = 0.$$

has the solutions $\lambda_{\pm} = \pm i \sqrt{\alpha \beta}$, which are pure imaginary.

When the eigenvalues of the two-by-two Jacobian are pure imaginary, the fixed point is called a center and the perturbation neither grows nor decays, but oscillates. Here, the angular frequency of oscillation is $\omega = \sqrt{\alpha \beta}$, and the period of the oscillation is $2\pi/\omega$.

The Lotka-Volterra equations has four free parameters α , β , γ and ϵ . Theorem predicts that nondimensionalizing the equations can reduce the number of free parameters by three to a manageable single dimensionless grouping of parameters. We choose to nondimensionalize time using the angular frequency of oscillation and the number of prey and predators using their fixed point values.

We introduce dimensionless variables in the form:

$$\bar{t} = \sqrt{\alpha \beta} \epsilon, \quad \bar{U} = U/U_* = \epsilon \gamma \beta U, \quad \bar{V} = V/V_* = \gamma \alpha V. \quad (2.12)$$

Substitution of (2.12) into the Lotka-Volterra equations (2.11) results in the dimensionless equations:

$$\begin{aligned} \frac{d\bar{U}}{d\bar{t}} &= r(\bar{U} - \bar{U}\bar{V}), \\ \frac{d\bar{V}}{d\bar{t}} &= \frac{1}{r}(\bar{U}\bar{V} - \bar{V}), \end{aligned} \quad (2.13)$$

With single dimensionless grouping $r = \sqrt{\frac{\alpha}{\beta}}$. Specification of r together with initial conditions completely determines the solution. It should be noted here that the long-time solution of the Lotka-Volterra equations depends on the initial conditions. This asymptotic dependence on the initial conditions is usually considered a flaw of the model.

2.2.3 Generalized Models of Two Types Interaction

As it was mentioned above, the large number of models describing interaction of types was developed the right parts of which represented the functions of the interacting populations. The task of developing the common criteria allowing for determining the functions that can describe the particular pattern of the behavior of the temporary population size, including stable fluctuations was dealt with. The best know of these models were developed by Kolmogorov and Rosenzweig.

A.N. Kolmogorov considered the generalized model of biological species interaction of "Predator-Prey" or "Parasite-Carrier" type. The model is a system of two equations of general type.

$$\begin{aligned}\frac{dx}{dt} &= k_1(x)x - L(x)y \\ \frac{dy}{dt} &= k_2(x)y\end{aligned}\tag{2.14}$$

The model is based on the following assumptions:

Assumption 1	Predators do not interact with each other, i.e. the coefficient of predators reproduction k_2 and the number of its preys L , consumed by one predator in a unit of time does not depend on y .
Assumption 2	Increase in the number of preys in the presence of predators is equal to the increase in the absence of predators minus the number of preys consumed by the predators. Functions $k_1(x)$, $k_2(x)$, $L(x)$ are continuous and are determined on the positive semi-axis $x, y \geq 0$.
Assumption 3	$dk_1/dx < 0$. This means that the preys reproduction coefficient in the absence of predators decreases monotonously with increase in the number of preys reflecting the restricted nature of food and other resources.
Assumption 4	$dk_2/dx > 0$, $k_2(0) < 0 < k_2(\infty)$. With the increase in the number of preys, the coefficient of predators reproduction decreases monotonically with an increase in the number of preys, transferring from the negative values (when there is nothing to eat) to the positive ones.
Assumption 5	Number of preys consumed by one predator per a unit of time is $L(x) > 0$ at $N > 0$; $L(0) = 0$.

Time independent solutions (two or three) have the following coordinates:

$$(1). \quad \bar{x} = 0; \quad \bar{y} = 0.$$

Central point of coordinates irrespective of parameters' values is in the form of saddle.

$$(2). \quad \bar{x} = A, \bar{y} = 0. \quad (2.15)$$

The value of A is determined from the following equation: $k_1(A) = 0$. Стационарное решение (2.15) седло, если $B < A$, B определяется из уравнения:

$$k_2(B) = 0.$$

Time-independent solution (2.15) - saddle, if $B < A$, the value of B is determined by the following equation:

$$k_2(B) = 0.$$

Point (2.15) moves in the positive values area (positive square) if $B > A$. This is a stable node. The last case is that of death of a predator and survival of a prey.

$$(3). \quad \bar{x} = B, \quad \bar{y} = C. \quad (2.16)$$

The value of C is determined from the following equation:

$$k_2(B) = 0; \quad k_1(B)B - L(B)C = 0.$$

Point (2.16) - a node, stability of which depends on the sign of the value σ

$$\sigma^2 = -k_1(B)k_1(B)B + L(B)C.$$

Если $\sigma > 0$, the point is stable, if $\sigma < 0$ the point is unstable and there may be boundary cycles around it.

2.2.4 Microbial Population Simulation

Microbiological populations represent a really blood experimental object for verification of concepts, results of both ecological and evolutionary theories. For the most part microorganisms are one-celled organisms; they have the high surface to volume ratio and therefore, high intensity of exchange with environment, high rate of reproduction and large increase in biomass. There is another factor, which is relative homogeneity of the microorganisms culture within the propagator volume. This allows for neglecting spatial effects. In microbiology, empirical treatment to model building is widely used. There is limited growth of microorganisms in the natural continuous-flow systems and in the most common type of continuous propagators - chemostats, where the culture diluting rate or flow rate is set. Chemostat theory was first developed by Mono (1950) and Herbert (1956) and has been improved since then. The modern models take into account structural inhomogeneity of biomass, age inhomogeneity of culture and other details of cultivation. Subject to continuous mixing, the whole volume of the propagator may be considered as homogeneous, concentration of supporting medium and

cells at every point of propagator is considered to be the same and the behaviour of those concentrations in time may be described using the system of ordinary differential equations:

$$\begin{aligned}\frac{dx}{dt} &= \mu(S)x - Dx \\ \frac{dy}{dt} &= DS_0 - \alpha\mu(S)x - DS \\ \mu(S) &= \frac{\mu_m S}{K_m - S}\end{aligned}\tag{2.17}$$

The variables and the description of the reduced system of equations (2.17) are given below:

S	– supporting medium concentration
x	– cells content in propagator
S_0	– content of supporting medium put into the propagator
D	– velocity of culture dilution
α^{-1}	– «economic coefficient», indicating the part of consumed supporting medium used for biomass increase
$\mu(S)$	– increase in biomass through supporting medium
$D(x)$	– biomass outflow from the propagator
$\alpha\mu(S)x$	– amount of supporting medium consumed by the culture cells
DS	– unused supporting medium outflow from the propagator
DS_0	– supporting medium inflow into the propagator

Velocity of biomass growth is assumed to be depending on the supporting medium concentration in accordance with the Mono formula (third equation 2.17). Where: K_M - Michaelis constant is one of the most important values for the enzymatic reactions that are determined experimentally having sense and dimensionality of the supporting medium content at which the reaction velocity is equal to half the maximum μ_m - maximum growth velocity. The considered model is simplified and requires additional information for description of real processes. For example, at the large concentrations, supporting medium may have an inhibiting action and the rate formula shall be as follows:

$$\mu(S) = \frac{\mu_m S}{K_m + S + AS^2}.\tag{2.18}$$

Stationary modes study.

Let us enter sizeless concentration, time and velocity of flow

$$x' = \alpha x / K_S, \quad y = S / K_S, \quad y_0 = S_0 / K_S, \quad t' = t \mu_\alpha, \quad D' = D / \mu_\alpha$$

With new variables (let us leave out prime marks of the new variables), the system is as follows:

$$\begin{aligned}\frac{dx}{dt} &= \mu(y)x - Dx \\ \frac{dy}{dt} &= -\mu(y)x + D(y_0 - y) \\ \mu(y) &= \frac{y}{1+y}\end{aligned}\tag{2.19}$$

Let us calculate the steady-state concentration for biomass and substrate. Let us make the right parts of the equation equal to zero:

$$\begin{aligned}\left(\frac{\bar{y}}{1+\bar{y}} - D\right)\bar{x} &= 0 \\ -\frac{\bar{y}}{1+\bar{y}}\bar{x} + D(y_0 - \bar{y}) &= 0\end{aligned}\tag{2.20}$$

The algebraic equation system (2.20) has two solutions; correspondingly, the differential equations system (2.19) has two stationary states:

$$\bar{x}_1 = 0, \quad \bar{y}_1 = y_0,\tag{2.21}$$

$$\bar{x}_2 = y_0 - \frac{D}{1-D}, \quad \bar{y}_2 = \frac{D}{1-D},\tag{2.22}$$

Dimensionless concentration of cells x has sense only at the value of $x > 0$ and the dimensionless concentration of substrate y is limited with the value $y_0 = S_0/K$ - inflowing substrate medium concentration. Zero steady-state value of biomass (2.22) has sense only when dimensionless rate of flow D is below the certain value.

$$D \leq \frac{y_0}{1+y_0} = D_0\tag{2.23}$$

Boundary value of the flow rate is called a washout rate. In the dimensional form its value is:

$$D_\alpha = \frac{\mu_\alpha y_0}{K_S + y_0}\tag{2.24}$$

At the flow rate exceeding D_b , biomass increase cannot compensate its outflow and the culture is completely washed out from the propagator.

Let us determine the nature of stability of steady-state conditions of the system using the system linearization method in the neighbourhood of the steady-state condition.

Characteristic determinant of the system (2.19) is as follows:

$$\begin{vmatrix} \mu(\bar{y}) - D - \lambda & \frac{\bar{x}}{(1+\bar{y})^2} \\ -\mu(\bar{y}) & \frac{\bar{x}}{(1+\bar{y})^2} - D - \lambda \end{vmatrix}\tag{2.25}$$

Let us explore the nature of the washout mode stability - special point with the coordinates (2.21). In this case

$$\mu(y_0) = \frac{y_0}{1 + y_0} = D_\alpha \quad (2.26)$$

then, the characteristic determinant takes the form of

$$\begin{vmatrix} D_\alpha - D - \lambda & 0 \\ -D_\alpha & -D - \lambda \end{vmatrix} = 0 \quad (2.27)$$

The root of characteristic equation (2.27)

$$\begin{aligned} \lambda_1 &= -D \\ \lambda_2 &= D_\alpha - D \end{aligned} \quad (2.28)$$

are real and have various signs at $D < D_B$, which means the dilution rate below the washout rate. Thereat, the $(0, y_0)$ point is unstable - saddle.

If $D > D_B$ - both roots are negative and special point (2.21) is the stable node. This mode is called a washout mode. Supporting medium concentration in the propagator is equal; thereat, the inflowing substrate concentration S_0 and the biomass concentration is equal to zero. If an inoculant is placed in the propagator, microorganisms will be washed out therefrom before reproduction.

For the second special point with (2.22) coordinates, characteristic equation roots are equal to:

$$\begin{aligned} \lambda_1 &= -D \\ \lambda_2 &= -(D_\alpha - D)(1 + y_0)(1 - D). \end{aligned} \quad (2.29)$$

this equilibrium condition, which is not the zero one in terms of biomass, exists in the positive quadrant of the phase plane only at the dilution rate value $D < D_B$. Since

$$D_\alpha = \frac{y_0}{1 + y_0} \leq 1$$

all three multipliers used in the expression for λ_2 in (2.29) are positive. Correspondingly, $\lambda_2 < 0$ and the (2.22) point is the stable node. This is the working state of the flow-through propagator.

2.3 Modeling of infectious diseases

Infectious diseases at the present stage of human development continue to be a serious threat, which people have to reckon with in carrying out their activities in various fields. In emergency situations, knowledge of the dynamics of the risk of an infectious disease will allow timely implementation of a set of measures to protect the population, including preventive and curative nature. Along with this, the formulation of experiments in this area is practically impossible and the mathematical modeling of processes and phenomena taking place at the same time comes to the fore, the basis of which will be statistical information on morbidity. Along with this, the formulation of experiments in this area is practically impossible and the mathematical modeling of processes and phenomena taking place at the same time comes to the fore, the basis of which will be statistical information on morbidity. A qualitative prognosis of the spread of the disease is achievable only on the basis of adequate mathematical models. This chapter presents the most basic mathematical models of infectious disease and epidemics, such as *SI* and *SIR*. These models form the basis for more detailed and expanded models currently used by the world health organizations, both to predict the future spread of the disease, and to develop strategies for containment and eradication of diseases. Also in the chapter are the mathematical models in immunology developed by Marchuk. In some literature, the term "infectious disease" is understood as the relationship established between members of the biocenosis, one of which (antigen) due to the mechanisms of pathogenicity is able to exist in another, and this other (organism) by means of the immunity system is able to counteract the pathogenic action. One of the main ways to protect against infectious diseases is the system of immunity, the main function of which is to maintain the genetic permanence of the internal environment of the human body and ensure the normal functioning of all its systems.

2.3.1 Модель SI

The simplest model of an infectious disease categorizes people as either susceptible or infective (*S* (susceptible) and *I* (infective)). One can imagine that susceptible people are healthy and infective people are sick. A susceptible person can become infective by contact with an infective. Here, and in all subsequent models, we assume that the population under study is well mixed so that every person has equal probability of coming into contact with every other person. We derive the governing differential equation for the *SI* model by considering the number of people that become infective during time Δt .

Let $\beta\Delta t$ - be the probability that a random infective person infects a random susceptible person during time Δt . Then with *S* susceptible and *I* infective people, the expected number of newly infected people in the total population during time Δt is $\beta\Delta tSI$. Thus,

$$I(t + \Delta t) = I(t) + \beta \Delta t S(t) I(t),$$

and in the limit $\Delta t \rightarrow 0$,

$$\frac{dI}{dt} = \beta SI \quad (2.30)$$

We now assume a constant population size N , neglecting births and deaths, so that $S + I = N$. We can eliminate S from (2.30) and rewrite the equation as:

$$\frac{dI}{dt} = \beta NI(1 - I/N),$$

which can be recognized as a logistic equation, with growth rate βN and carrying capacity N . Therefore $I \rightarrow N$ as $t \rightarrow \infty$, and the entire population will become infective.

The SI model may be extended to the SIS model, where an infective can recover and become susceptible again. We assume that the probability that an infective recovers during time Δt , is given by $\gamma \Delta t$. Then the total number of infective people that recover during time Δt , is given by $I \times \gamma \Delta t$, and:

$$I(t + \Delta t) = I(t) + \beta \Delta t S(t) I(t) - \gamma \Delta t I(t)$$

or as $\Delta t \rightarrow 0$,

$$\frac{dI}{dt} = \beta SI - \gamma I \quad (2.31)$$

Using $S + I = N$, S we eliminate from (2.31) and define the basic reproductive ratio as:

$$R_0 = \beta N / \gamma$$

Equation (2.31) may then be rewritten as

$$\frac{dI}{dt} = \gamma (R_0 - 1) I (1 - I/N (1 - 1/R_0)),$$

which is again a logistic equation, but now with growth rate $\gamma (R_0 - 1)$ and carrying capacity $N (1 - 1/R_0)$. The disease will disappear if the growth rate is negative, that is, $R_0 < 1$, and it will become endemic if the growth rate is positive, that is, $R_0 > 1$. For an endemic disease with $R_0 > 1$ the number of infected people approaches the carrying capacity: $t \rightarrow \infty$.

We can give a biological interpretation to the basic reproductive ratio R_0 . Let $l(t)$ be the probability that an individual initially infected at $t = 0$, is still infective at time t . Since the probability of being infective at time $t + \Delta t$ is equal to the probability of being infective at time t multiplied by the probability of not recovering during time Δt , we have:

$$l(t + \Delta t) = l(t)(1 - \gamma\Delta t).$$

or as $\Delta t \rightarrow 0$,

$$\frac{dl}{dt} = -\gamma l.$$

With initial condition $l(0) = 1$, the decision is write in the form:

$$l(t) = e^{-\gamma t}$$

Now, the expected number of secondary infections produced by a single primary infective over the time period $(t, t + \Delta t)$, is given by the probability that the primary infective is still infectious at time t multiplied by the expected number of secondary infections produced by a single infective during time Δt ; that is, $l(t) \times S(t) \beta \Delta t$. We assume that the total number of secondary infections from a single infective individual is small relative to the population size N . Therefore, the expected number of secondary infectives produced by a single primary infective introduced into a completely susceptible population is:

$$\int_0^{\infty} \beta l(t) S(t) dt \approx \beta N \int_0^{\infty} l(t) dt = \beta N \int_0^{\infty} e^{-\gamma t} dt = \frac{\beta N}{\gamma} R_0,$$

where we have approximated $S(t) \approx N$ during the time period in which the infective remains infectious. If a single infected individual introduced into a completely susceptible population produces more than one secondary infection before recovering, then $R_0 > 1$, and the disease becomes endemic.

The spread of infectious diseases is a complex process with a multitude of interacting factors. The key role of mathematical epidemiology is to create patterns of pathogen distribution. These models serve as a mathematical basis for understanding the complex dynamics of the spread of the disease. In the next section, the classical *SIR* model will be described and investigated.

2.3.2 SIR Model of the epidemic

The *SIR* model, first published by Kermack and McKendrick in 1927, is undoubtedly the most famous mathematical model for the spread of an infectious disease. Here, people are characterized into three classes: susceptible S , infective I and removed R . Removed individuals are no longer susceptible nor infective for whatever reason; for example, they have recovered from the disease and are now immune, or they have been vaccinated, or they have been isolated from the rest of the population, or perhaps they have died from the disease. As in the *SIS* model, we assume that infectives leave the I class with constant rate γ , but in the *SIR* model they move directly into the R class. The corresponding coupled differential equations are:

$$\begin{aligned}\frac{dS}{dt} &= -\beta SI, \\ \frac{dI}{dt} &= -\beta SI - \gamma I, \\ \frac{dR}{dt} &= \gamma I,\end{aligned}$$

with the constant population constraint $S + I + R = N$. For convenience, we nondimensionalize this equation using N for population size and γ - for time; that is, let:

$$\bar{S} = \frac{S}{N}, \quad \bar{I} = \frac{I}{N}, \quad \bar{R} = \frac{R}{N}, \quad \bar{t} = \gamma t,$$

and define the dimensionless basic reproductive ratio as:

$$R_0 = \beta N \gamma \tag{2.32}$$

The dimensionless SIR equations are then given by:

$$\begin{aligned}\frac{d\bar{S}}{d\bar{t}} &= -R_0 \bar{S} \bar{I}, \\ \frac{d\bar{I}}{d\bar{t}} &= R_0 \bar{S} \bar{I} - \bar{I}, \\ \frac{d\bar{R}}{d\bar{t}} &= \bar{I},\end{aligned} \tag{2.33}$$

with dimensionless constraint $\bar{S} + \bar{I} + \bar{R} = 1$.

Let $(\hat{S}_*, \hat{I}_*, \hat{R}_*)$ be the fixed points of (2.33). Setting $d\hat{S}/d\hat{t} = d\hat{I}/d\hat{t} = d\hat{R}/d\hat{t} = 0$, we immediately observe from the equation for $d\hat{R}/d\hat{t}$ that $\hat{I} = 0$. Since with $\hat{I} = 0$, we have $\hat{R} = 1 - \hat{S}$, and all stationary points are given as $(\hat{S}_*, \hat{I}_*, \hat{R}_*) = (\hat{S}_*, 0, 1 - \hat{S}_*)$.

We will use the SIR model to address two fundamental questions: First- under what condition does an epidemic occur? Second - if an epidemic occurs, what fraction of a well-mixed population gets sick?

An epidemic occurs when a small number of infectives introduced into a susceptible population results in an increasing number of infectives. Let us determine the stability of a stationary point-the epidemic. The linear stability problem may be solved by considering only the equation for $d\hat{I}/d\hat{t}$ from (2.33). With $\hat{I} \ll 1$ and $\hat{S} = \hat{S}_*$ we have

$$\frac{d\hat{I}}{d\hat{t}} = (R_0 \hat{S}_* - 1) \hat{I},$$

that an epidemic occurs if $R_0\hat{S}_0 - 1 > 0$. With the basic reproductive ratio given by (2.32) and $\hat{S}_0 = S_0/N$, where S_0 is the number of initial susceptible individuals, an epidemic occurs if:

$$R_0\hat{S}_0 = \frac{\beta S_0}{\gamma} > 1$$

An epidemic occurs if an infective individual introduced into a population of S_0 susceptible individuals infects on average more than one other person.

We now address the second question: If an epidemic occurs, what fraction of the population gets sick? For simplicity, we assume that the entire initial population is susceptible to the disease, so that $\hat{S}_0 = 1$. We expect the solution of the governing equations (2.33) to approach a fixed point asymptotically in time (so that the final number of infectives will be zero), and we define this fixed point to be $(\hat{S}, \hat{I}, \hat{R}) = (1 - \hat{R}_\infty, 0, \hat{R}_\infty)$ with \hat{R}_∞ - equal to the fraction of the population that gets sick. To compute \hat{R}_∞ it is simpler to work with a transformed version of (2.33). By the chain rule, $d\hat{S}/d\hat{t} = (d\hat{S}/d\hat{R})(d\hat{R}/d\hat{t})$, so that

$$\frac{d\hat{S}}{d\hat{R}} = \frac{d\hat{S}/d\hat{t}}{d\hat{R}/d\hat{t}} = -R_0\hat{S},$$

Separating and integrating from the initial to final conditions:

$$\int_1^{\hat{I}-\hat{R}_\infty} \frac{d\hat{S}}{\hat{S}} = -R_0 \int_0^{\hat{R}_\infty} d\hat{R},$$

which upon integration and simplification, results in the following transcendental equation for \hat{R}_∞ :

$$1 - \hat{R}_\infty - e^{-R_0\hat{R}_\infty} = 0,$$

an equation that can be solved numerically using Newton's method. We have:

$$F(\hat{R}_\infty) = 1 - \hat{R}_\infty - e^{-R_0\hat{R}_\infty},$$

$$F'(\hat{R}_\infty) = -1 + R_0 e^{-R_0\hat{R}_\infty};$$

for fixed R_0 and a suitable initial condition for $R_\infty^{(0)}$ the solution will be determined as follows:

$$\hat{R}_\infty^{n+1} = \hat{R}_\infty^n - \frac{F(\hat{R}_\infty^{(n)})}{F'(\hat{R}_\infty^{(n)})}.$$

2.3.3 The Simplest Mathematical Model of Infectious Disease

This section describes immune response system proposed by Marchuk. It is believed that predecessors of immunocomponent cells (lymphocytes and leucocytes) are produced in the bone marrow same as the predecessors of blood cells. Let's designate these cells as S . Once in thymus gland, one part of such cells initiates development of a clone T - lymphocytes that further proliferate and differentiate in T_h helper lymphocytes, T_e effector (killer) lymphocytes and T_c suppressing lymphocytes (Fig. 2.3.1). The other part of the bone marrow cells produces predecessors B of lymphocytes that further transform into B lymphocytes. A part of stem cells remaining in the bone marrow develop into mature macrophages and the other types of peripheral blood leucocytes (Figure 2.3.2).

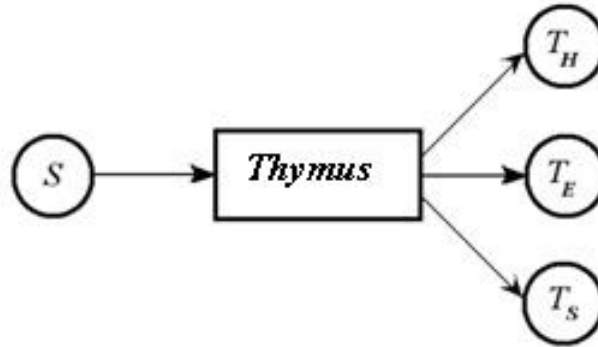


Figure 2.3.1

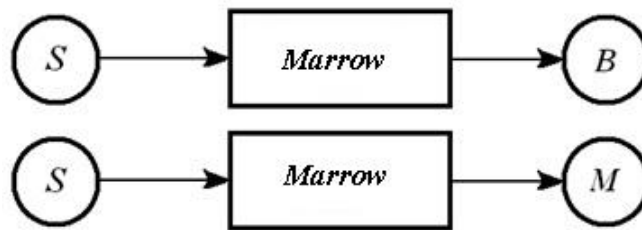


Figure 2.3.2

Each of populations T of lymphocytes performs its own function in the immune process. Thus, T_h helper lymphocytes interact with specific antigen and contributes to transformation of B cells in plasma cells. Effector lymphocytes are T_e basically responsible for genetic purity of its organism's cells. They destroy the degenerated cells with changed genetic structure due to mutation or damage by antigen. T_c - suppressors maintain the level of insusceptibility to organism's own antigens and to various antigens dwelling in organism. Suppressors also play an important part in immune response regulation. B -lymphocytes and macrophages are differentiated by different functions.

In the healthy organism, plasmatic cell are being continuously formed. These plasmatic cells produce Ig immunoglobulins capable of binding and neutralizing antigens. Bacterial or viral disease presupposes a period of latent development of a disease, when the antigens penetrated into the body reproduce without any pronounced reaction on the part of the immune system. During this period, the immune system is tuned to reaction of a specific antigen neutralization. Its essence consists in the following: The antibody response process is the joint activity of the following thee types of cells: macrophage, B - lymphocytes; T - lymphocyte; Macrophage is the main cell supplying antigen. Antigen V having met with macrophages M is consumed by them, processed and after that macrophages form a group of antigen determinants on its surface. This situation is depicted by the figure 2.3.3. Macrophages supply this group B - lymphocytes resulting in binding the antigen determinants V with the surface of B lymphocytes (figure 2.3.4).

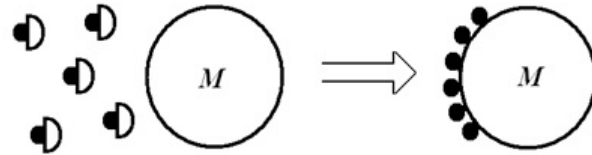


Figure 2.3.3

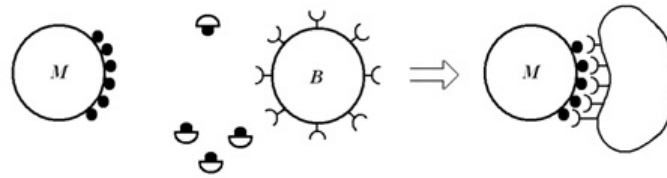


Figure 2.3.4

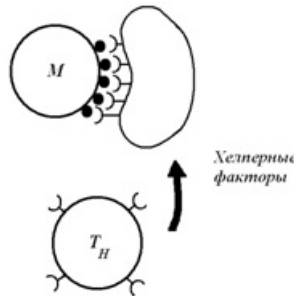


Figure 2.3.5

In the presence T_h of an assistant activated by the antigen, stimulation of B lymphocyte is triggered that, in turn, begins to divide and differentiate toward plasmatic cells

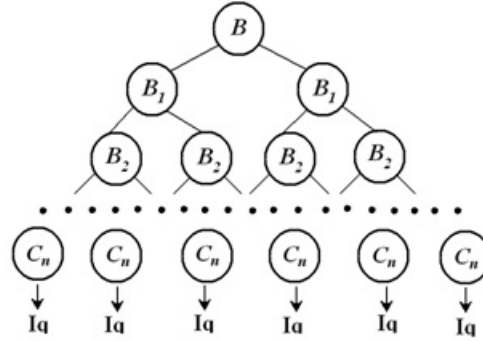


Figure 2.3.6

(fig.2.3.5). This cascade process of plasmatic cells clone formation lasts from several hours to several days (figure 2.3.6).

Therefore, in order to include B - lymphocytes in the antibody response process, a set of signals is required and this set is formed by surface receptor binding with antigen with participation of T_h helper. The above specified immunity process was called as humoral; nevertheless, cell immunity ensured with the help of T_e lymphocytes that destroy degenerative cells alien for the organism are of importance.

The existing mathematical models allow the following classification of immune response to antigen: subclinical form, acute form with recovery, acute form with lethal outcome, chronic form.

Building the Simplest Disease Model

The simplest mathematical model of infectious disease describing immunity system will be built based on the relation of the balance for each of the components of the immune response. There will be no difference between the cellular and humoral immunities involved in antigen control in constructing the simplest model. This model implies that the organism has sufficient resource of macrophages utilizing the immune response products as well as other non-specific factors necessary for normal functioning of immune system. The following three components are considered in the model: antigen, antibody and plasmatic cell. Either pathogenic bacteria or viruses act in this model as antigens. When there is a disease, the degree of lesion of an organ exposed to the antigen attack is of considerable importance since ultimately it results in decreased activity of immune system. Mathematical models shall reflect this.

The following are the main factors of and infectious disease: $V(t)$ - *it content of pathogenic reproducing antigens*, $F(t)$ - *it content of antibodies*. *Antibodies* shall mean immune system's medium neutralizing the antigens (immunoglobulins, cell receptors), $C(t)$ - *it content of plasma cells*, $m(t)$ - *it relative characteristic feature of an affected organ*.

An equation describing the change in the number of antigens in the organism is as follows:

$$dV = \beta V dt - \gamma F V dt, \quad (2.34)$$

Where the first term in the left part describes increase in the antigen number dV over the time interval dt due to reproduction. It is pro rata to V some number β that is called the *antigen reproduction coefficient*, $\gamma FV dt$ describes the number of antigens neutralized by the antibodies F over the time period dt , γ - coefficient connected with probability of antigen neutralizing by antibodies. Division of (2.34) by dt results in the equation

$$\frac{dV}{dt} = (\beta - \gamma F) V. \quad (2.35)$$

Using the simplest hypothesis of plasmatic cells' cascade population formation we arrive at the equation that describes plasmatic cells increase over the normal level C^* which is the constant level of plasmatic cells content in a healthy organism:

$$d(C - C^*) = dC = Q(t - \tau) dt, \quad (2.36)$$

$$Q(t) = \alpha FV. \quad (2.37)$$

The more complete equation will look like that:

$$dC = \alpha F(t - \tau) V(t - \tau) dt - \mu_c (C - C^*) dt. \quad (2.38)$$

The first term in the right part (2.38) describes generation of plasmatic cells, τ - time over which the plasmatic cells cascade is formed, α - coefficient taking into account probability of antigen-antibody encounter, cascade reaction triggering and the number of newly formed cells. The second term in this formula describes reduction of the plasmatic cells number due to ageing, μ_c - coefficient equal to the value reciprocal to the time of their life. Division of (2.38) by dt results in the following equation

$$\frac{dC}{dt} = \alpha F(t - \tau) V(t - \tau) - \mu_c (C - C^*). \quad (2.39)$$

Equation for the balance of the antibodies reacting with antigen is derived from the following formula:

$$dF = \rho C dt - \eta \gamma FV dt - \mu_f F dt. \quad (2.40)$$

Where $\rho C dt$ describes antibodies generation by plasmatic cells over a certain period of time dt , ρ - stands for the rate of antibodies generation by one plasmatic cell, the term $\eta \gamma FV dt$ stands for decrease in the number of antibodies over the dt period of time due to binding to antigens. (η is number of antibodies required for neutralization of one antigen). The third term $\mu_f F dt$ describes decrease in the number of antibodies due to ageing, where μ_f is a coefficient reciprocally proportional to the antibody decomposition time. By division of (2.40) by dt we arrive at the following equation:

$$\frac{dF}{dt} = \rho C - (\mu_f + \eta \gamma V) F. \quad (2.41)$$

The hypothesis that such organs production capacity depends on the extent of a target organ lesion leads to consideration of an equation for relative characteristic of the target organ lesion. Let us introduce the m value through the formula

$$m = 1 - \frac{M'}{M}. \quad (2.42)$$

This will be a relative characteristic feature of the target organ lesion where M is a characteristic parameter of a healthy organ (mass or area) and M' is a characteristic feature of a healthy part of the lesion affected organ. For the healthy organ this parameter is, quite naturally, equal to zero while for the affected organ its value is equal to 1 (one). The forth equation is introduced for this characteristic feature

$$\frac{dm}{dt} = \sigma V - \mu_m m. \quad (2.43)$$

The first term in the right part of (2.43) characterizes the degree of the target organ lesion. It is assumed that over the period dt of time increase in the relative parameter of the affected organ is pro rata to the number of antigens that is described by the term σV , where σ - is a certain constant value, which is specific for each particular disease. Decrease in this characteristic parameter happens due to the restorative activity of an organism. This term depends on the m value with the proportionality coefficient μ_m characterizing the reciprocal value of the restoration period of e times.

In the given mode, the factor of the vital organs lesion factor may be taken into account in equation (2.39) by replacing the coefficient α with the $\alpha \xi(m)$ product.

Therefore, we arrive at the following system of non-linear ordinary differential equation:

$$\begin{aligned} \frac{dV}{dt} &= (\beta - \gamma F) V, \\ \frac{dC}{dt} &= \xi(m) \alpha V(t - \tau) F(t - \tau) - \mu_c (C - C^*), \\ \frac{dF}{dt} &= \rho C - (\mu_f + \eta \gamma V) F, \\ \frac{dm}{dt} &= \sigma V - \mu_m m. \end{aligned} \quad (2.44)$$

Let us add the initial data to the equation system (2.44) at $t = t_0$. Usually, input conditions for the lag equations are set within the range of $[t_0 - \tau, t_0]$. Nevertheless, in the biological sense of the described processes, there were no viruses in the organism before the moment of contamination t^0 : $V(t) \equiv 0$ at $t < t^0$, and, therefore, the initial condition can be set at the t^0 point. Later on, when the initial conditions for

the equations of this type are considered, their setting at this point will mean that $V(t) \equiv 0$ at $t < t^0$. Therefore,

$$\begin{aligned} V(t_0) &= V_0, \quad C(t_0) = C_0, \\ F(t_0) &= F_0, \quad m(t_0) = m_0. \end{aligned} \tag{2.45}$$

So, let us call the equation system (2.44) with the initial data (2.45) as the *simplest mathematical model of a disease*.

Let us use $t_0 = 0$ as the initial moment in the (2.44) system of equations and let us suppose that the initial conditions remain positive (non-negative) and all parameters of the model are constant and positive values.

Qualitative Analysis of the Simplest Disease Model

General Results. The equation system (2.44) along with the initial data (2.45) describes the dynamics of infection development at the background of immune response. All constant values of the equation system are positive at $t = t_0 = 0$.

$$V_0 \geq 0, \quad C_0 \geq 0, \quad F_0 \geq 0, \quad m_0 \geq 0. \tag{2.46}$$

Solution of (2.44) problem, (2.45) exists and solely at all $t \geq 0$.

Steady-state Solutions. Let us equate all right parts to zero in order to arrive at steady-state solutions in the equation system (2.44):

$$\begin{aligned} (\beta - \gamma F) V &= 0, \\ \xi(m) \alpha V F - \mu_c (C - C^*) &= 0, \\ \rho C - (\mu_f + \eta \gamma V) F &= 0, \\ \sigma V - \mu_m m &= 0. \end{aligned} \tag{2.47}$$

Here $V(t - \tau) = V = \text{const}$, $F(t - \tau) = F = \text{const}$, value C^* is connected with F^* by the relation

$$C^* = \mu_f F^* / \rho,$$

where C^* and F^* are the values C and F for the healthy organism at $V = 0$. One of the steady-state solutions is as follows:

$$V = 0, C = C^*, F = F^* = \rho C^* / \mu_f, m = 0, \quad (2.48)$$

that describes the healthy organism condition. For analysis of this condition stability, let us consider small perturbations of unknown functions from the equilibrium condition (2.48) by assuming that

$$V = V', C = C^* + C', F = F^* + F', m = m'. \quad (2.49)$$

Let us put this expression in the equation system (2.44) and, considering the V' , C' , F' and m' values as small, let us discard the second order values:

$$\begin{aligned} \frac{dV'}{dt} - (\beta - \gamma F^*) V' &= 0, \\ \frac{dC'}{dt} + \mu_c C' &= \alpha F^* V' (t - \tau), \\ \frac{dF'}{dt} + \mu_f F' &= \rho C' - \eta \gamma F^* V', \\ \frac{dm'}{dt} + \mu_m m' &= \sigma V'. \end{aligned} \quad (2.50)$$

Let us solve this equation system at the following initial data:

$$V' = V_1, C' = C_1, F' = F_1, m' = m_1 \text{ at } t = 0. \quad (2.51)$$

Solution of the first equation (2.50) at $V' = V_1$, $t = 0$, is as follows:

$$V' = V_1 e^{(\beta - \gamma F^*)t}. \quad (2.52)$$

solution (2.52) tends toward zero with time subject to the condition

$$\beta < \gamma F^*. \quad (2.53)$$

With due account for this condition, the solution will take the following form:

$$V' = V_1 e^{-(\gamma F^* - \beta)t} = V_1 e^{-\beta_1 t}, \quad (2.54)$$

where $\beta_1 = \gamma F^* - \beta > 0$.

Since V' is different from zero only at $t > 0$, then, within the range of $[-\tau, 0)$; $V' = 0$, and, correspondingly, for all $t < \tau$; $V'(t - \tau) = 0$. This means solution of the second of equations (2.50) at $t < \tau$ that will be as follows:

$$C' = C_1 e^{-\mu_c t} \quad (2.55)$$

At $t \geq \tau$ with due account for the initial condition $C'(\tau) = C_1 e^{-\mu_c \tau}$ derived from (2.44) and that in accordance with (2.54), $V'(t - \tau) = V_1 e^{-\beta_1(t - \tau)}$, solution for $C'(t)$ is as follows:

in the event of $\beta_1 \neq \mu_c$:

$$C'(t) = C_1 e^{-\mu_c t} + \frac{\alpha F^*}{\mu_c - \beta_1} V_1 [e^{\beta_1(t - \tau)} - e^{-\mu_c(t - \tau)}]; \quad (2.56)$$

in the event of $\beta_1 = \mu_c$:

$$C'(t) = C_1 e^{-\mu_c t} + \alpha F^* V_1 (t - \tau) e^{-\beta_1(t - \tau)}. \quad (2.57)$$

General solution of the third equation is as follows:

$$F(t) = e^{-\mu_f t} \left[\int \rho C'(s) e^{\mu_f s} ds - \int \eta \gamma F^* V'(s) e^{\mu_f s} ds + A \right], \quad (2.58)$$

where constant A is determined through the corresponding initial condition. Here $F'(t) \rightarrow 0$ at $t \rightarrow \infty$, if $\beta_1 > 0$. The same is true for the solution of the fourth equation from (2.50), that has the structure similar to (2.56), (2.57):

a) in the event of $\beta_1 \neq \mu_m$:

$$m'(t) = \varepsilon_4 e^{-\mu_m t} + \frac{\sigma}{\mu_m - \beta_1} \varepsilon_1 (e^{-\beta_1 t} - e^{-\mu_m t});$$

б) in the event of $\beta_1 = \mu_m$:

$$m'(t) = \varepsilon_4 e^{-\mu_m t} + \sigma \varepsilon_1 t e^{-\beta_1 t}.$$

Therefore, all small disturbances of steady-state solution (2.48) at $\beta < \gamma F^*$ tends toward zero with time meaning an asymptotical stability of the given solution.

Possible Forms of Disease Dynamics and Their Classification

Analysis of disease model (2.44) allows to consider the qualitative pattern of the $V(t)$ solution - concentration of antigens at one set of coefficients or another. Let us consider two extreme cases that, in essence, are the boundaries for the solution $V(t)$. Let us assume that an organism does not produce antigens of the given specificity, i.e.: $F(t) = F^0 = 0$ for all $t \geq 0$ è $\rho \equiv 0$. In this particular case, equation for $V(t)$ will be as follows:

$$\frac{dV}{dt} = \beta V.$$

Solution of this equation is through the formula

$$V(t) = V^0 e^{\beta t},$$

where V_0 is an initial concentration of antigens (contamination dose) at the moment of time $t = 0$. As regards dynamics of an organ lesion, it can be described by the following equation:

$$\frac{dm}{dt} + \mu_m m = \sigma V^0 e^{\beta t},$$

solution of which subject to the condition of $m = 0$ at $t = 0$ shall be as follows:

$$m = \frac{\sigma V^0}{\beta + \mu_m} (e^{\beta t} - e^{-\mu_m t}).$$

It is not too difficult to see that in the absence of restorative processes in the affected organ, i.e. at $\mu_m = 0$,

$$m = \frac{\sigma V^0}{\beta} (e^{\beta t} - 1)$$

and with all $t \geq 0$

$$V = V^0 e^{\beta t}, \quad F = 0, \quad m = \frac{\sigma V^0}{\beta} (e^{\beta t} - 1). \quad (2.59)$$

This solution corresponds to the course of disease with lethal outcome because of the absence of any factors compensating the growth of antigens. The considered case is the extreme one. As a matter of practice, these events are quite rare. Nevertheless, sometimes the response of an immune system to antigen activity turns out to be so weak that the ideal case described herein is a good approximation. This situation, for example, occurs with some people of senior age immune system of which does not react properly to the antigen action or with the people with the secondary or congenital immunodeficiency.

The second extreme event occurs in the conditions of high-grade immune response (sensitivity) when the level of the antibodies present in an organism that are specific to the given antigen turns out to be sufficient to destroy all antigens presenting in the organism without triggering antibody production process. In this particular case, equation for $V(t)$ will be as follows:

$$\frac{dV}{dt} = (\beta - \gamma F) V,$$

Where $\beta \ll \gamma F$. Assuming the contamination dose V^0 to be small, the F value may be considered as a constant value determined by the normal level of F^* antibodies. Then, the above specified equation will be as follows:

$$\frac{dV}{dt} = (\beta - \gamma F^*) V,$$

and its solution will be as follows

$$V = V^0 e^{-(\gamma F^* - \beta)t}.$$

This means that antigen population in the organism will be decreasing exponentially. In the extreme case $\beta = 0$ we'll arrive at

$$V = V^0 e^{-\gamma F^* t}.$$

So, we have arrived at the two extreme solutions corresponding to the lethal outcome and high immunobarrier. At the set values of model coefficients and the initial conditions, correspondingly, all the values of various dynamics of disease will be within the shaded area shown on the figure 2.3.7.

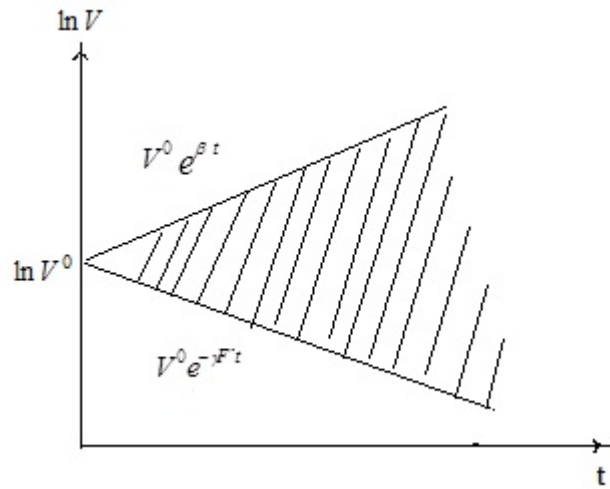


Figure 2.3.7

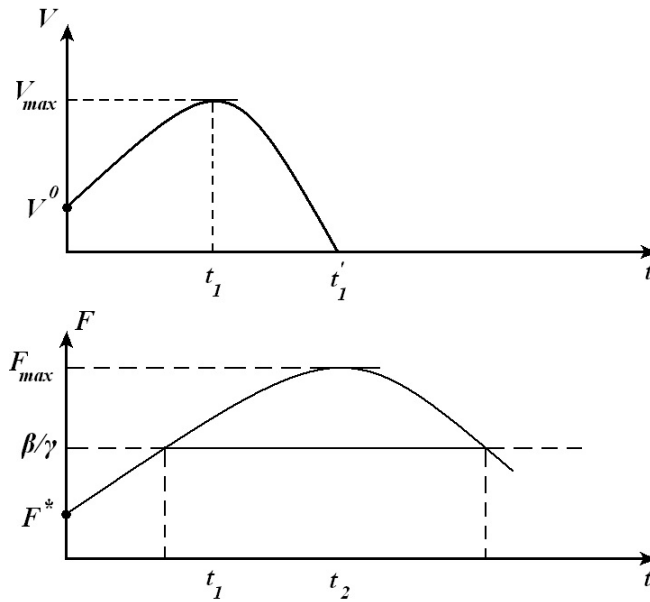


Figure 2.3.8

Let us consider less trivial cases of disease dynamics. Let us assume that contamination of a healthy organism with an initial dose of antigens V^0 happens at $t = 0$ and the condition $\beta > \gamma F^*$ becomes true. Then the initial conditions of (2.44) model will be as follows:

$$V(0) = V^0, \quad C(0) = C^*, \quad F(0) = F^*, \quad m(0) = 0.$$

Antigen content at $t > 0$ begins to grow since $dV/dt > 0$ is around the point $t = 0$ due to $\beta > \gamma F^*$. At the moment of time $t > t_1$ $V(t)$ reaches its maximum, i.e. $V(t_1) = V_{max}$, wherein $F(t_1) = \beta/\gamma$. At $t > t_1$, in the context of the model, $F(t)$ exceeds the level of β/γ and $V(t)$ reduces while $F(t) > \beta/\gamma$ is true, since $dV/dt < 0$.

The situation is possible when $F(t) > \beta/\gamma$ is true over the quite an extensive time period (t_1, t_2) and $V(t)$ over this period of time drops to the small values (practically to zero). This situation is shown on the figure 2.3.8. Solution of this type may be called as an *acute form of disease*.

If the time interval (t_1, t_2) is quite narrow, then, in the point $t = t_2$, $F(t_2) = \beta/\gamma$, and $V(t)$ reaches its minimum V_{min} , before dropping to the small values, and at $t > t_2$ $V(t)$ it begins to grow again since $dV/dt > 0$ at $t = t_1 + \varepsilon$ due to $F(t) < \beta/\gamma$, where ε is a small value. Further on, the quality of the process does not change and local maximums are interchanged with local minimums $V(t)$ (Fig. 2.3.9). Solution of this type represents *chronic form of disease*.

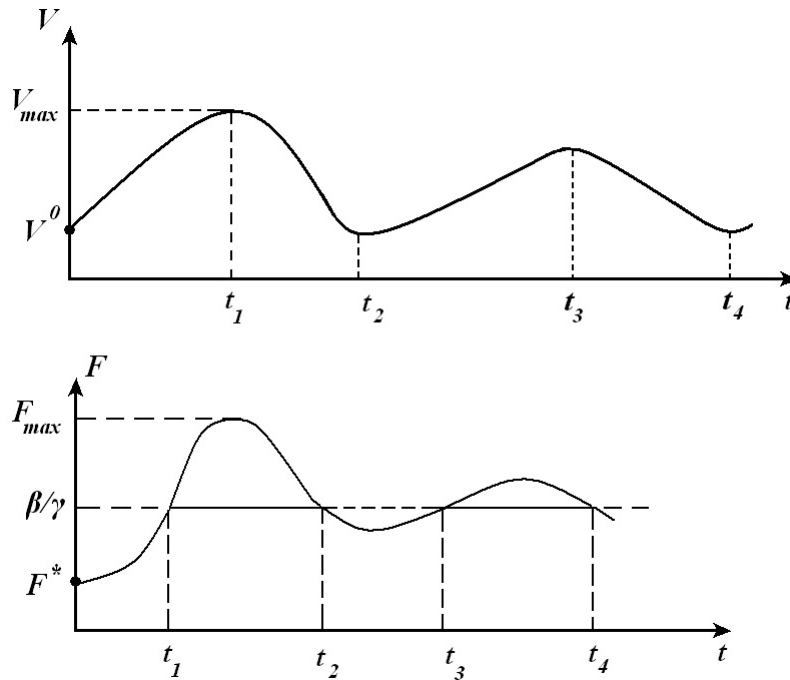


Figure 2.3.9

Therefore, relation between $\Delta t = t'_1 - t_1$ and $\Delta T = t_2 - t_1$ intervals determines the

outcome of a disease. If $\Delta T > \Delta t$, it means an acute form of disease (fig. 2.3.8). If $\Delta T = \Delta t$, it means a chronic form of disease (fig. 2.3.9). The higher is the maximum number of produced antibodies F_{max} , the higher is the $\Delta T = t_2 - t_1$, and, correspondingly, the lower is the probability of a chronic form occurrence.

Therefore, an outcome of a disease depends on whether or not the antigen derivative dV/dt may become negative and the duration of time it retains its sign. It is obvious that $dV/dt < 0$ if $V(t) > 0$ and $F(t) > \beta/\gamma$. In the suggested model, $V(t) \geq 0$, at that, equality to zero is possible only in the event of $V^0 = 0$. Thus, it was supposed that there is contamination of an organism, i.e. $V^0 > 0$, so, the true inequation $F(t) > \beta/\gamma$ is the necessary and sufficient condition for negativity of dV/dt . If the immunobarrier is not cleared ($V^0 < V$), the following cases are possible:

Case 1	$dV/dt < 0$ over the infinitely large period of time. Solution of this type is called a <i>subclinical form of disease</i> . In the event of $\beta > \gamma F^*$ $dV/dt > 0$ at t close to zero, $V(t)$ increases. Let us assume that $V(t)$ reaches maximum at the point of $t = t_1$ and after that point it decreases.
Case 2	$dV/dt < 0$ over the quite an extensive period of time (t_1, t_2) . This represents an <i>acute form of disease</i> (see figure 2.3.8).
Case 3	$dV/dt < 0$ over a small period of time (t_1, t_2) . This represents a <i>chronic form of disease</i> (see figure 2.3.9). If the points t_1 do not exist, then, the fourth case happens.
Case 4	$dV/dt > 0$ over the infinitely large period of time. This corresponds to the <i>lethal outcome</i> .

Thus, the modelling allowed us to identify four types of solutions that can be interpreted as a form of disease progression. The subclinical form is expressed by a steady output of antigens from the body, since in this case the antigens cannot overcome the immunological barrier. The acute form is characterized by a rapid increase in the concentration of antigens, a pronounced immune response and a sharp decline in the number of pathogens of the disease to values close to zero, which is understood as recovery. The chronic form is characterized by the presence in the body of a non-zero population of antigens with a sluggish dynamics. This form is associated with insufficiently effective stimulation of the immune system. The lethal outcome is associated with severe damage to the body, which is no longer able to ensure the normal functioning of the body.

2.3.4 Immunogenetic Description of Antivirus Immune Response Model

In modern medicine, the term is understood as the totality of physiological and pathological processes arising and developing in the body when pathogenic microorganisms or viruses are introduced into it that cause a violation of the constancy of

its internal environment and physiological functions. One of the main ways to protect the body from living bodies and substances bearing the signs of genetic foreignness is the immune system. The essence of the reaction of the immune system to the appearance of genetically foreign material (antigen), including pathogens, is the production of specific antibodies and killer cells capable of neutralizing and destroying antigens.

Immune response to the intrinsic pathogens of viral infections includes both types of immune response - humoral with the production of antibodies by the B -system of lymphocytes and cellular with accumulation of cytotoxic T -lymphocytes-effectors. The main type of immune response ensuring protection of the organism is the cellular one. Cytolytic T lymphocyte-effectors accumulated as the result of immune response detect the viral infected cells and destroys them acting as killers (assassins) of its own organism's cells. Therefore, antiviral immune response of cellular type is of autoimmune nature. This is the only way to clean the organism of viruses if, of course, intracellular protective mechanisms (interferon, enzymes, controlling the nucleic acid replication) of the viral infected cells won't be able to deal with this reproduction themselves.

Antivirus Immune Response Model Formulation

Formulation of the equations describing the development of the cellular type antiviral immune response is based on the following assumptions:

Assumption 1	Macrophages M representing the antigens of virus V , which we will designate as M_V , stimulate Ta -helper lymphocytes, which we will designate as H_E , and Te -effector lymphocytes, which we designate as E , accumulated effectors (E) kill virus-infected cells C_V sensitive to the given tissue virus (C).
Assumption 2	It is assumed that quantity of macrophags M in the organism is sufficient for M_V to be developed in the quantity pro rata the number of viruses.
Assumption 3	Stimulation of T -helpers (HE) depends on the extent of previous quantity of the given specificity and also of the number of M_V .
Assumption 4	It is assumed that H_E stimulated by M_V are divided, i.e. their number will increase. Subject to the sufficient number of M_V , $H_{E\text{RESULTING}}$ from division are stimulated again. After interaction with the E cells, helper-cell (H_E) completes its life cycle.
Assumption 5	It was assumed that under the effect of two signals - from M_V and H_E , the E cell gives rise to the clone of effector cells (E) with killing effect on C_V . As a result of the above, the number of newly occurring $4E$ cells depends on the preceding number of E cells of the given specificity in organism and on the number of M_V and that of stimulated H_E .

Assumption 6	Over a certain period of time, infected cells perform their normal functions. They die either because of the development of irreversible viral damage, or in the elimination of C_V cells by T -effectors (E). Therefore, the affected mass of the virus-sensitive tissue consists of the number of cells killed by the virus and the number of cells killed by the effector lymphocytes.
Assumption 7	Macrophages stimulate the helper lymphocyte (H_B) and B -cells.
Assumption 8	Stimulation of helper-lymphocytes (HB) depends on the extent of the value of the previous clone of the given specificity and also on the number of M_V .
Assumption 9	It is assumed that H_B is included similarly to H_E and is also characterized by monogamy with respect to B cells.
Assumption 10	Under the effect of two signals - from M_V and H_E , the B cell gives rise to the clone of plasmatic cells P similar to E cell.
Assumption 11	The produced antibodies are bound and eliminated only by extracellular viral particles released from the cells infected by virus after its destruction. The number of such viruses is pro rata the number of infected cells killed by virus and the number of cells killed by effector lymphocytes.
Assumption 12	Let us assume that all viruses in this model are "free", i.e. they are freely circulating outside cells in hemolymph and blood plasm and that all intracell processes are described through viruses replication coefficient with plasma penetration.

When describing a system of equations, the balance ratios are recorded for a time point t on an interval Δt that is so small that various processes of interaction between viruses and the immune system can be considered additive. All the quantitative characteristics of the various components in the final balance relations, which for $\Delta t \rightarrow 0$ take the form of differential equations, are normalized to a unit of time.

In accordance with the above specified facts and assumptions on dynamics of antiviral immune response, let us single out the following variable models:

Variable table.

$V_f(t)$	-number of viruses freely circulating in organism
$M_V(t)$	-the number of macrophages stimulated (by antigens)
$H_E(t)$	-the number of T -lymphocyte-helpers of cellular immunity
$H_B(t)$	- the number of T -lymphocyte-helpers of humoral immunity
$E(t)$	-the number of T -effector (killer) cells
$B(t)$	-the number of B -lymphocytes
$P(t)$	-the number of plasmatic cells
$E(t)$	-the number of antibodies
$C_V(t)$	-the number of the target organ's cells infected with viruses
$m(t)$	- non-functional part of the virus infected target organ

In describing the system of equations, balance ratios are written for the instant t within the interval Δt , which is so small that the various processes of viruses and the immune system interaction that happens within it can be considered as an additive one. All quantitative characteristics of various components in the final balance ratios that assume the form of a differential equation at $\Delta t \rightarrow 0$ are normalized per a unit of time. Let us write the balance equation to determine the number of free viruses:

$$\frac{dV_f}{dt} = \gamma_{CV} + nb_{CE}C_V - \gamma_{VF}FV_{Ef} - \gamma_{VM}MV_f - \gamma_{VC}(C^* - C_V - m)V_f \quad (2.60)$$

In the left part of (2.60) equation, the dV_f/dt characterizes the rate of change in the population of viruses in organism; the first term in the right part takes into account an increase in virus population per a unit of time in the course of their replication in infected cells C_V . ν coefficient depends on the virus replication rate. This model implies that the new viruses occurring in the virus infected cells penetrate the blood plasm and become "free". It is those free viruses that stimulate M cells M_V , transfer them in and afterwards are destroyed by antibodies.

The second term describes plasma penetration by viruses from the virus infected cells C_V being destroyed by E effector lymphocytes.

The third and fourth terms in (2.60) describe decrease in the number of free viruses due to interaction of M macrophages with F antibodies. The last term of the equation (3.29) describes reduction of V_f population through penetration by free viruses into healthy cells and their infection; at that, finiteness of the number of the target organ available for infection is taken into account. The values γ_{VM} , γ_{VF} , γ_{VC} are the constants characterizing the values of time of V_f viruses interaction with macrophages, antibodies and healthy cells correspondingly.

The balance equation for the number of macrophages connected with viruses (stimulated macrophages) is as follows: M_V

$$\frac{dM_V}{dt} = \gamma_{MV}V_fM - \alpha_M M_V \quad (2.61)$$

The first term on the right (2.61) describes the increase the number of macrophages bound with viruses per a unit of time. Here, same as in the equation (2.60), M is the

number of all macrophages in the organism that is considered to be known determined by the homeostasis. Coefficient γ_{MV} is a reciprocal value of time of interaction between viruses and M . The second term in equation (2.61) takes into account decrease in the population M_V cells through the natural processing or ageing. Coefficient α_M is equal to the reciprocal value of an average time of life M_V of cells in organism.

Let us further consider the equation of the balance of the helper lymphocytes number, H_E - cells ensuring proliferation of E -cells:

$$\frac{dH_E}{dt} = b_H^{(E)} P_H^{(E)} \left(t - \tau_H^{(E)} \right) - b_H^{(E)} M_V H_E - b_H^{(H_E)} M_V H_E E + \alpha_H^E (H_E^* - H_E) \quad (2.62)$$

$$P_H^{(E)}(t) = \rho_H^{(E)} M_V(t) H_E(t).$$

The first term on the right (?? describes an increase in the number of T -helper lymphocytes through their division under the effect of contact with the stimulated macrophage M_V . It takes into account delay in the process of occurrence of new H_E - cells after their interaction with stimulated macrophage M_V through τ_H^E . Coefficient b_H^E is the reciprocal value of an average time of interaction of H_E - cell with M_V . The second term describes reduction in the number of H_E cells that are divided after contact with the virus stimulated macrophages. The third term in (2.62) describes reduction of H_E -cells in their interaction with E effector lymphocytes resulting in increase in the number of effectors. Coefficient $b_H^{(H_E)}$ takes into account the double interaction time and $\rho_H^{(E)}$ describes the number of the newly formed cells. The last member in equation (2.62) takes into account maintenance of homeostasis of H_E cells equal to H_E^* in the absence of immune response of organism and cells destruction due to ageing. Coefficient α_H^E is equal to the reciprocal value of an average time of life H_E -cells. Members $b_H^{(E)} M_V H_E$ and $b_H^{(H_E)} M_V H_E E$ in equation (2.61) are absent since we assumed that after interaction of M_V with H_E and E stimulated macrophage does not die but continues to perform its functions.

Let us write the equation for T -helper lymphocytes ensuring proliferation of B -cells H_B :

$$\frac{dH_B}{dt} = b_H^{(B)} \rho_H^{(B)} M_V(t) \left(t - \tau_H^{(B)} \right) - b_H^{(B)} M_V H_B - b_H^{(H_B)} M_V H_B B + \alpha_H^B (H_B^* - H_B) \quad (2.63)$$

Here, the first term on the right is connected with proliferation of H_B -cells where the delay in occurrence of new cells after the initial contact with H_B -cell with virus-stimulated macrophage is taken into account. The second term describes reduction in the number of H_B -cells for the following division. The third term on the right describes reduction of H_B -cells as a result of interaction with M_V and B -cells. The last term in equation describes homeostasis (homeostasis-self-regulation, ability of an open system to maintain continuity of its internal state by means of coordinated reaction

aimed at maintenance of dynamic equilibrium). Constant $\rho_H^{(E)}$ describes the number of cells resulting from division.

Balance equation of effectors E will be as follows:

$$\frac{dE}{dt} = b_P^{(E)} P_E(t - \tau_E) - b_P^{(E)} M_V H_E E - b_{EC} C_V E + \alpha_E (E^* - E) \quad (2.64)$$

The first term on the right takes into account increase in the number of new effectors occurring per a unit of time over the period of time τ_E due to stimulated effectors division where $b_P^{(E)}$ is a coefficient taking into account the rate of cells stimulation. The second term describes decrease in the number of cells through the process of division. The third term in equation (2.64) takes into account decrease in population of E effector lymphocytes through destruction of virus-infected cells. Here, b_{EC} is the coefficient equal to the reciprocal value of an average time of interaction of effectors with C_V cells. The last term describes homeostasis of E cells.

Let us now write an equation for the balance of E effector-lymphocytes stimulated by the double interaction: on the one part - by stimulated macrophage M_V and on the other part - T -helper lymphocyte H_E :

$$P_E(t) = C M_V(t) H_E(t) E(t)$$

This relationship reflects the fact that the number of stimulated effectors is pro rata the production of probability of double interaction of E with M_V and H_E . Here, ρ_E - coefficient taking into account the number of cells resulting from proliferation.

Balance equation for B -cells is as follows:

$$\frac{dB}{dt} = b_P^{(B)} \rho_B M_V(t - \tau_B) H_B(t - \tau_B) B(t - \tau_B) - b_P^{(B)} M_V H_B B + \alpha_H^B (B^* - B) \quad (2.65)$$

The first two terms on the right describe, correspondingly, proliferation (increase) of B -cells and their consumption for the following proliferation, where ρ_B is the number of B cells resulting from division of cells. The last term (2.65) describes homeostasis.

Let us now write a balance equation for plasmatic cells. Let P be a content of plasmatic cells. Then the dynamic will be described by the following equation:

$$\frac{dP}{dt} = b_P^{(P)} \rho_P M_V(t - \tau_P) H_B(t - \tau_P) B(t - \tau_P) + \alpha_P (P^* - P) \quad (2.66)$$

The first term on the right describes the rate of formation and maturing of plasmatic cells from the stimulated B -cells with due account for delay. The last term in the (2.66) equation takes into account decrease in the number of the P cells due to ageing and also maintenance of homeostasis in the absence of antigen stimulation.

Let us further write an equation for F antibodies:

$$\frac{dF}{dt} = \rho_F P - \gamma_{FV} V_f F - \alpha_F F. \quad (2.67)$$

The first term of this equation on the right describes formation of antibodies by the clone of P plasmatic cells, and ρ_F stands for production of antibodies.

The second term describes consumption of antibodies for elimination of viruses; the last - reduction of the number of antibodies due to the natural ageing.

Let us pass over to description of the virus-infected cells balance equation C_V :

$$\frac{dC_V}{dt} = \sigma V_f (C^* - C_V - m) - b_{CE} C_V E - b_m C_V \quad (2.68)$$

This equation describes both infection of healthy cells C by "free" virus making them C_V and decrease in the number of infected cells due to elimination of such cells by effectors and destruction by viruses.

Finally, let us write an equation for non-functioning part of an organ affected by virus.

$$\frac{dm}{dt} = b_{CE} C_V E + b_m C_V - \alpha_m m \quad (2.69)$$

In this equation, the first term in its right part takes into account the effect of virus-infected cells elimination by effectors and the second term takes into account an irreversible damage of cells C_V by viruses resulting in inactivation of such cells. The last term describes restoration of damaged cells by means of tissue regeneration. b_{CE} , b_m , α_m - the corresponding coefficients.

Let us combine the above equations into a system and call it a mathematical model of antiviral immune response:

$$\frac{dV_f}{dt} = \gamma_{CV} + nb_{CE} C_V - \gamma_{VF} F V_{Ef} - \gamma_{VM} M V_f - \gamma_{VC} (C^* - C_V - m) V_f$$

$$\frac{dM_V}{dt} = \gamma_{MV} V_f M - \alpha_M M_V$$

$$\frac{dH_E}{dt} = b_H^{(E)} P_H^{(E)} (t - \tau_H^{(E)}) - b_H^{(E)} M_V H_E - b_H^{(H_E)} M_V H_E E + \alpha_H^E (H_E^* - H_E)$$

$$\frac{dH_B}{dt} = b_H^{(B)} \rho_H^{(E)} M_V (t) (t - \tau_H^{(B)}) - b_H^{(B)} M_V H_B - b_P^{(H_B)} M_V H_B B + \alpha_H^B (H_B^* - H_B)$$

$$\begin{aligned}
\frac{dE}{dt} &= b_P^{(E)} P_E (t - \tau_E) - b_P^{(E)} M_V H_E E - b_{EC} C_V E + \alpha_E (E^* - E) \\
\frac{dB}{dt} &= b_P^{(B)} P_B M_V (t - \tau^{(B)}) H_B (t - \tau^{(B)}) B (t - \tau^{(B)}) - b_P^{(B)} M_V H_B B + \alpha_H^B (B^* - B) \\
\frac{dP}{dt} &= b_P^{(P)} \rho_P M_V (t - \tau_P) H_B (t - \tau_P) H_B (t - \tau_P) B (t - \tau_P) + \alpha_P (P^* - P) \\
\frac{dF}{dt} &= \rho_F P - \gamma_{FV} V_f F - \alpha_F F \\
\frac{dC_V}{dt} &= \sigma V_f (C^* - C_V - m) - b_{CE} C_V E - b_m C_V \\
\frac{dm}{dt} &= b_{CE} C_V E + b_m C_V - \alpha_m m
\end{aligned} \tag{2.70}$$

The initial data shall be added to this equation system. If an organism is not infected by a virus, than the corresponding solution will be:

$$\begin{aligned}
V_f &= 0, \quad M_V = 0, \quad H_E = H_E^*, \quad H_B = H_B^*, \quad E = E^*, \\
B &= B^*, \quad P = P^*, \quad F = \frac{\rho_F P^*}{\alpha_F}, \quad C_V = 0, \quad m = 0.
\end{aligned} \tag{2.71}$$

The following situation is of interest: infection of a healthy organism with a low number of free viruses V_f^0 . In this context, let us assume that prior to the moment of infection t^0 , i.e. at $t < t^0$ the system is in the steady state (2.71) and at the moment $t = t^0$ an organism gets infected with a low dosage $V_f^0(t^0) = V_f^0$. All the other components at the moment $t = t^0$ remain their steady-state values. Since the model is autonomous, we can assume that $t^0 = 0$ without loss of generality.

Let us suppose that all coefficients included in the equation system of the model (2.70) are not negative; let us consider the initial conditions for the system (2.70) of the general type:

$$\begin{aligned}
V_f(0) &= V_f^0, \quad M_V(0) = M_V^0, \quad H_E(0) = H_E^0, \quad H_B(0) = H_B^0, \\
E(0) &= E^0, \quad B(0) = B^0, \quad P(0) = P^0, \quad F(0) = F^0, \\
C_V(0) &= C_V^0, \quad m(0) = m_0,
\end{aligned}$$

$$M_V(t) H_E(t) = \varphi_1(t), \tau_H^{(E)} \leq t < 0,$$

$$M_V(t) H_B(t) = \varphi_2(t), \tau_H^{(B)} \leq t < 0,$$

$$M_V(t) H_E(t) E(t) = \varphi_3(t), \tau_E \leq t < 0,$$

where $\phi(t)$, — are the continuous functions.

The formulated mathematical model of antiviral immune response will further be used for the purpose of computer-aided simulation exercise. It should be mentioned that in mathematical simulation special attention shall be paid to correct selection of differential equation coefficients phenomenologically reflecting various characteristics of immune response.

Mathematical modeling of the immune response in the infectious diseases is intensively developing, as a result of which new models are created, new immunological hypotheses are formulated, and knowledge about the mechanisms of the development of the disease and the possibilities of influencing its outcome is accumulated. Each solved problem gives the rise to a new circle of questions, often interesting for representatives of related fields of biological sciences. The following areas of future research are highlighted: construction and study of mathematical models of diseases and processes of the immune protection; justification and study of the general principles that determine the structure and the functioning of the immune system; building models of the relationship between the immune system and other protective and regulatory systems of the body; building models that take into account the mechanisms of the influence of the environmental factors on the function of the immune system. The use of the mathematical modeling of the immune response contributes the development of the mathematical methods, leads to the formulation of new problems, which in turn leads to the receipt of new theoretical results in the immunology.

Question:

1. Describe the mathematical model of limited and unlimited growth of the population.
2. Explain the difference in constructing continuous and discrete models of population growth.
3. Point out the main differences between Kolmogorov's model of interaction of two species of populations from Volterra models.
4. What are the main assumptions of the generalized model of interaction of biological species?
5. Describe the Mono Model, open the essence of the hemostat.
6. Derive the system of dimensionless equations to describe the behavior of the concentrates in the cultivator.

7. Describe the simplest mathematical model of an infectious.
8. Make an assessment of the stability of the equilibrium state of the system.
9. Describe the extreme cases of disease outcome in the mathematical model of an infectious disease based on the basic parameters.
10. Substantiate the assumption made in construction of an infectious disease mathematical model.
11. Describe the chronic form of disease in the mathematical model of an infectious disease based on the basic parameters analysis.
12. Describe the possible disease outcomes in the mathematical model of an infectious disease based on the basic parameters behaviour.
13. Describe the basic preconditions for construction of a mathematical model of cellular immunity.
14. Describe the basic preconditions for construction of a mathematical model of humoral immunity.

Exercises:

1. Relationships such as predator-prey or parasite-host can be described by a system of equations:

$$\begin{cases} \frac{dx}{dt} = x(6 - 3y - 0.5x) \\ \frac{dy}{dt} = y(5 + 0.8x - y) \end{cases}$$

Find the coordinates of the singular points. Determine the type of each of the determined stationary states.

2. The competition between two populations can be described by a system of equations:

$$\begin{cases} \frac{dx}{dt} = x(4 - y - 5x) \\ \frac{dy}{dt} = y(1 - 0.5x - 3y) \end{cases}$$

Find the coordinates of the singular points. Determine the type of each of the found states.

3. Solve the simplest disease model equations for the case $\beta < \gamma F^*$ (subclinical form of disease) and single out situations with effective or normal response ($\alpha\rho > \mu_c\eta\gamma$) and with weak response or immunodeficiency ($\alpha\rho < \mu_c\eta\gamma$).
 - (a) Show that an effective (normal) immune response is capable of preventing development of infection or quick suppression of its development. In the latter case, the course of disease resembles an acute form with recovery;

- (b) Show that in the event of a weak immune response, excess by an antigen of an immunobarrier ($V^0 > V^*$) will ultimately result in death of an organism.
4. Acute form of disease. Solve the simplest model of disease as the source of an acute form of disease with recovery of an organism with normal immune system. In this particular case, $\beta > \gamma F^*$ and, correspondingly, there is no immunobarrier to the disease agents.
 5. Hypertoxic form of disease. Provide a numerical solution for the case of immune response delay due to the immunodeficiency for the large values of delay $\tau_d > \tau$, where τ is a normal duration of the clone formation process and τ_d is increased duration. So, we have a mathematical model with a set of parameters characterized by a large value τ_d as compared with τ , describing the hypertoxic form of a disease.
 6. Chronic form of disease. Provide a numerical solution for the model of chronic form of disease depending on the contamination dosage of $V(0)$ (a), antigen replication rate β ($\beta_1 < \beta_2 < \beta_3$) (б)
 7. To propose a numerical solution of the equations of the simplest model of the disease in the case of $\beta < \gamma F^*$ (subclinical form of the disease), and distinguish situations with an effective, or "normal", answer ($\alpha\rho < \mu_c\eta\gamma$) and with a weak response, or "immunodeficiency" ($\alpha\rho > \mu_c\eta\gamma$).
 - (a) To show that an Effective (normal) immune response is able to prevent the development of the infection or even quickly stop it's spreading. In the latter case, the course of the disease resembles an acute form with recovery.
 - (b) To show that the excess of the immunological barrier by the antigen ($V_0 > V^*$) with the weak immune response, ultimately leads to the death of the organism.
 8. Acute form of the disease. Provide a solution to the simplest model of the disease, such as the occurrence of an acute form of the disease with recovery in the case of an organism with a normal immune system. In this case, $\beta < \gamma F^*$, and, therefore, there is no immunological barrier to pathogens.
 9. Hypertoxic form of the disease. Proposing a numerical solution for the case of the delayed immune response, due to the presence of immunodeficiencies, is implemented with large values of the delay $\tau d > \tau$, где τ is the normal duration of the cloning process, and τd is increased. So, we have a mathematical model, with a set of parameters characterized by a larger value of τd compared to τ , describing the hypertoxic form of the disease.
 10. Chronic disease. To present a numerical solution of the model in the chronic form of the disease depending on the dose of infection with $V(0)$ (a), reproduction rate of the antigen β ($\beta_1 < \beta_2 < \beta_3$) (b)

Project 1. Effect of the temperature response of an organism on disease dynamics.

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Chapter 3

Spatially Inhomogeneous Models

Mathematical models of populations considered herein above take into account only the process of reproduction (birth rate) and mortality. These models are called point or lumped models. Those are the models where the course of processes at all points of space is similar. Nevertheless, biological processes same as all natural processes in general happen in space and in time and are heterogeneous.

While previously the evolution of the system in time was described by the systems of ordinary differential equations, in this particular case of spatially-inhomogeneous systems evolution over time will be described by the partial differential equations. At that, "reaction-diffusion" type equations are very often used as a simulation tool. It is well-known that in the linear physical system, the transfer-diffusion processes result in leveling of concentrations of substances for the whole volume. Nevertheless, all biological systems are unbalanced and the processes that run in them are irreversible processes. That is exactly what allows the living systems to use the substance and energy flows for building and maintaining a structural and functional orderliness. Correspondingly, the mathematical models of biological systems shall largely be the non-linear models. Same as in the case with the point systems, some information on the non-linear system behaviour, in particular, on properties of its steady-state solutions, may be obtained by study of linearized system. One of the possible ways of spatially inhomogeneous systems description is to subdivide the whole system into small cells (spatial "grid"). Thereat, the whole system may be characterized by a large but finite set of numbers - concentration of substances in those cells. This approach is used for numerical solution of problems; it is convenient for calculations.

This chapter also considers certain problems of hemodynamics, blood circulation through the vessels, occurring due to difference of hydrostatic pressure at various sites of blood-vascular system. Incompressible liquid flow equations are the initial ones for the model. Various methods of natural experiments are used for forecasting the stenosis occurrence in blood. Nevertheless, mathematical methods of calculation of hemodynamic parameters in the area of thrombosis is of greater interest. Using the numerical methods of the input equations solution make it possible to calculate the ba-

sic hemodynamic parameters of blood circulation and stenosis development forecasting as a result of thrombosis.

3.1 Reaction-Diffusion Type Equation. Wave Solution

One of the simplest types of reaction-diffusion equation is the following equation

$$\frac{\partial u}{\partial t} = ku(1 - u) + D \frac{\partial^2 u}{\partial x^2} \quad (3.1)$$

where k , D are positive constants. Here, the scalar function $u(x, t)$ satisfies the set initial and boundary conditions. Equation (3.1) was suggested by Fisher as a stochastic model of gene dynamics in population that has selective advantage. A.N. Kolmogorov etc. is the more general type of equation for the given class of problems:

$$\frac{\partial u}{\partial t} = F(u) + D \frac{\partial^2 u}{\partial x^2},$$

where $F(u)$ is the scalar function of u variable.

Let us consider the conclusion made through equation (3.1) based on the considered particle flow movement. Let us suppose that a flow of particles is moving along the x axis. Let us express particle density through $u(x, t)$, i.e. the number of particles per a unit of length at the moment of time t at the point with x coordinate. Let's use $\Phi(x, t)$ to express the flow, i.e. the number of particles running through the point with x coordinate per a unit of time at the moment t . If no particles are formed (or disappear) within the interval $[x, x + \Delta x]$, the number of particles located within the span of the given interval $[x, x + \Delta x]$ over the time Δt can be calculated by the following formula:

$$N = - \int_x^{x+\Delta x} u(x, t) dx + \int_x^{x+\Delta x} u(x, t + \Delta t) dx = \int_x^{x+\Delta x} (u(x, t + \Delta t) - u(x, t)) dx. \quad (3.2)$$

The first part of this formula represents the number of particles that located within the span of the interval $[x, x + \Delta x]$ at the moment of time t , while the second part - the number of particles within the span of the interval at the moment of time $t + \Delta t$. The very same number of particles may be expressed as is specified below using the flow function $\Phi(x, t)$:

$$N = - \int_t^{t+\Delta t} \Phi(x + \Delta x, t) dt + \int_t^{t+\Delta t} \Phi(x, t) dt = - \int_t^{t+\Delta t} (\Phi(x + \Delta x, t) - \Phi(x, t)) dt. \quad (3.3)$$

Here, the first expression at the right part represents the number of particles that moved beyond the boundaries of the interval over the time Δt at the point x .

Integrand part in (3.2) and (3.3) can be correspondingly represented as

$$\frac{\partial u}{\partial t}(x, \tau)\Delta\tau \text{ и } \frac{\partial\Phi}{\partial x}(\xi, t)\Delta x, \text{ where } \tau \in [t, t + \Delta t] \text{ и } \xi \in [x, x + \Delta x].$$

At Δx and Δt tending toward zero, we arrive at the equation that expresses the flow conservation law:

$$\frac{\partial u(x, t)}{\partial t} + \frac{\partial\Phi(x, t)}{\partial x} = 0 \quad (3.4)$$

If there is a source of origin (or disappearance) of particles within the span of an interval $[x, x + \Delta x]$ depending on the flow density characterized by the function $F(u(x, t))$, the following expression shall be added to take into account the particles balance:

$$\int_t^{t+\Delta t} \int_x^{x+\Delta x} F(u(x, t)) dx dt.$$

Thereat, the law of conservation (3.4) will assume the form of

$$\frac{\partial u(x, t)}{\partial t} + \frac{\partial\Phi(x, t)}{\partial x} = F(u)$$

Let's suppose that there is the Fick's law between the flow function and density.

$$\Phi(x, t) = -c(u) \frac{\partial u}{\partial x}, \quad (3.5)$$

where $c(u)$ is some non-negative function. Then the equation (3.5) will assume the form:

$$\frac{\partial u}{\partial t} = F(u) + \frac{\partial}{\partial x} \left(c(u) \frac{\partial u}{\partial x} \right). \quad (3.6)$$

In the particular case, when $c(u) = D = const$ and $F(u) = ku(1 - u)$, Fisher-Kolmogorov equation (3.1) follows from (3.6). The type of the function $c(u)$ depends on specific conditions. Thus, for example, if $c(u) = u$, then we arrive at the following equation:

$$\frac{\partial u}{\partial t} = F(u) + \frac{\partial}{\partial x} \left(u \frac{\partial u}{\partial x} \right).$$

In this particular case the diffusion coefficient is pro rata the population density.

All the above arguments are generalized for multidimensional case $x \in R^n$ too. In this particular case, the flow equation will assume the following form:

$$\frac{\partial u(x, t)}{\partial t} + \operatorname{div}(\Phi(x, t)) = F(u),$$

Here, $\operatorname{div}(\Phi(x, t)) = \sum_{i=1}^n \frac{\partial \Phi_i(x, t)}{\partial x_i}$, $\Phi(x, t) = (\Phi_1(x, t), \Phi_2(x, t), \dots, \Phi_n(x, t))$ – is the flow vector.

Stability of Spatially Homogenous Steady-State Solutions

Let us assume that the following system is set in the restricted area $\Omega \subset R^n$:

$$u_t = f(u) + D\Delta u. \quad (3.7)$$

Here, $u(x, t) = (u_1(x, t), \dots, u_n(x, t))$, $x \in \Omega$, $t \in (0, \infty)$, $f(u)$ – is the vector-function determining the reaction of components $u_i(x, t)$.

$F(u) = (f_1(u), \dots, f_n(u))$, $D = (d_{ij})_{i,j=1\dots n}$ – matrix of diffusion, elements of which are constant non-negative values. At the moment $t = 0$, the initial conditions (Koshi data) were set:

$$u(x, 0) = \varphi(x) = (\varphi_1(x), \dots, \varphi_n(x)). \quad (3.8)$$

In the event of a closed system at the boundary G of area Ω , Neuman's conditions are true

$$\frac{\partial u}{\partial n} \Big|_{x \in \Gamma} = 0 \leftrightarrow \frac{\partial u_i}{\partial n} \Big|_{x \in \Gamma} = 0, \quad i = 1, \dots, n, \quad (3.9)$$

where n – an external normal to the G boundary.

The (3.7)-(3.9) problem is called the initial boundary value problem for the system of semi-linear equations of the parabolic type.

Definition 1 Vector functions $\nu(x)$, being the solutions to the problem

$$f(\nu) + D\Delta \nu = 0, \quad \frac{\partial \nu}{\partial n} \Big|_{x \in \Gamma} = 0, \quad (3.10)$$

are called the equilibrium positions of the dynamic system (3.7).

Definition 2 Equilibrium positions $\nu(x)$ of the dynamic system (3.7) is called stable if for arbitrarily small $\varepsilon > 0$ there is such a $\delta > 0$ that for any solutions of the system (7) $\tilde{u}(x, t)$ with initial conditions $\tilde{\varphi}(x)$ such that $\|\nu(x) - \tilde{\varphi}(x)\|_{H^1(\Omega)} < \delta$ is true $\|\nu(x) - \tilde{u}(x, t)\|_{H^1(\Omega)} < \varepsilon$ for all $t > 0$. If, additionally, the condition $\tilde{u}(x, t) \rightarrow \nu(x)$ is true in $H^1(\Omega)$ at $t \rightarrow \infty$, the equilibrium position $\nu(x)$ is called asymptotically stable.

Let us mention here that solution $\tilde{u}(x, t)$ to the system (3.7) with initial data $\tilde{\varphi}(x)$ should satisfy the boundary condition (3.9).

Study of equilibrium positions stability may be carried out using the theorem being analogous to the Lyapunov's theorem on stability at the first approximation for the finite-dimensional systems.

Let us suppose that $\nu(x)$ is the system (3.7) equilibrium position. If $\nu(x) \neq const$, than let us call this equilibrium position as *spatially inhomogeneous*. Let us consider the Jacobian matrix of the system (3.7) calculated in the equilibrium position,

$$A(x) = \left(\frac{\partial f}{\partial u} \right) \Big|_{u=\nu(x)}$$

and the corresponding boundary problem for the own values:

$$A(x)z(x) + D\Delta z(x) = \lambda z(x), \quad \frac{\partial z}{\partial m} \Big|_{x \in \Gamma} = 0, \quad z \in H^1(\Omega). \quad (3.11)$$

If $Re \lambda < 0$ for all own tasks, then the spatially inhomogeneous equilibrium position is asymptotically stable. Due to non-linear nature of function $f(u)$, the problem (3.10) to determine the spatially inhomogeneous equilibrium position of the system (3.7) is no simpler than the initial problem and allows for analytical solution in exceptional cases only. Above we have considered the space-time types of the behavior of the system, which can be described with the help of the concept of random displacement of individuals in a space similar to the Brownian motion of particle-diffusion. Such a representation is transferred from static physics.

3.2 Models of the reaction-diffusion-advection type

For real living systems, along with random displacement, there is a directional movement that can be determined by external forces, for example, by air or water currents, or by the action of some positive or negative stimulus (taxis). A directional component of population distribution is called advection. In view of this component, the spread of population density $P(x, t)$, where x is the spatial coordinate, t - time is described by the equation:

$$\frac{\partial P}{\partial t} = F(P) - \text{div}(vP) + \delta \Delta P. \quad (3.12)$$

Here, $F(P)$ is the term describing the local birth-death processes, $\delta \Delta P$ - random migrations (diffusion), the advective term $\text{div}(vP)$ describes the directed population density flux with velocity v . If the population is in a moving environment (air, water), the individuals naturally move along with this environment. In the general case, the rate is not constant and is determined by both the motion of the environment and

the taxis processes—the intrinsic motion of the individuals of the population in the direction of the positive stimulus or in the direction opposite to the negative stimulus. As a rule, the assumption of the proportionality of the velocity of directional motion to the gradient of the chemical stimulus is used. The movement of the predator population towards the gradient of the spatial distribution of the population of the victim is called trophotaxis (praytaxis). Most models suggest that the victims move randomly, and predators are capable of both random movements (diffusion) and directed movement (advection). The corresponding equations take the form:

$$\begin{aligned}\frac{\partial N}{\partial t} &= F(N, P) + \delta_N \Delta N, \\ \frac{\partial P}{\partial t} &= G(N, P) - \operatorname{div}(vP) + \delta_P \Delta P, \\ v &= \psi \nabla N\end{aligned}\tag{3.13}$$

Here N , P are the densities of prey and predator populations, respectively, $F(N, P)$, $G(N, P)$ are the species interaction functions, δ_N , δ_P are the diffusion coefficients; v - the advective velocity of the predator's own displacement at each point of space is proportional to the density gradient of the victim population. The study of autonomous models of the type (3.13) showed that the occurrence of inhomogeneous space-time regimes in them is due to the presence in local systems of periodic regimes associated with the substantial nonlinearity of trophic functions or the nonlinear dependence of the taxis flux on population density. This means that the characteristic time of formation of spatially inhomogeneous structures is comparable with the characteristic time of the birth-death processes. Meanwhile, often the aggregation of predators in places of accumulation of victims is a behavioral reaction that occurs at much faster times than the processes of reproduction and death. The description of trophotaxis by advective accelerations in the simulation of reaction-diffusion-taxis systems uses the assumption that taxis is determined not by speed, but by advective acceleration. Thus, the inertia of displacement is taken into account, which is ignored in taxis models of the form (3.11), assuming an instant adaptation of the taxis speed to the stimulus gradient. This means that not speed, but acceleration of displacement of predator density is determined by the density gradient of the victims. The analogy with mechanics is clear: not speed, but acceleration of body displacement is proportional to the acting force. Observations of schooled animals show that the change in their speed of movement depends on the magnitude of the stimulus gradient. Vegetable insects change their speed of movement (accelerated) depending on the quality and proximity of the stern spot. Schoolfish change direction depending on the difference between the current and preferred temperature. The dependence of the acceleration of motion on the stimulus gradient formed the basis for models describing the behavior of individual individuals. Let the advective acceleration at each point of space be proportional to the gradient of the distribution density of the victims:

$$\frac{\partial v}{\partial t} = k \nabla N, \quad (3.14)$$

$k > 0$, In population models with advective acceleration, it is assumed that in the flock of predators, the magnitude and direction of the velocities of individual individuals are equalized. This effect is described by the term "velocity diffusion". The equation for changing the speed (advective acceleration) takes the form:

$$\frac{\partial v}{\partial t} = k \frac{\partial N}{\partial x} + \delta_v \frac{\partial^2 N}{\partial x^2}, \quad (3.15)$$

where $N(x, t)$ is the density of the population at the point x at time t ; $v(x, t)$ - instantaneous velocity of displacement of predator density; k is the taxis coefficient, which characterizes the sensitivity of the predator to the heterogeneity of the distribution of the victims; δ_v is the diffusion coefficient of the velocity.

The predator-prey model with advective acceleration in dimensionless variables has the form:

$$\begin{aligned} \frac{\partial N}{\partial t} &= N(1 - N) - \frac{aN P}{1 + ahN} + \delta_N \frac{\partial^2 N}{\partial x^2}, \\ \frac{\partial P}{\partial t} &= \frac{aN P}{1 + ahN} - mP - \frac{\partial(Pv)}{\partial x} + \delta_p \frac{\partial^2 P}{\partial x^2}, \\ \frac{\partial v}{\partial t} &= k \frac{\partial N}{\partial x} + \delta_v \frac{\partial^2 v}{\partial x^2}. \end{aligned} \quad (3.16)$$

The problem was solved for impenetrable boundaries - zero flows on the borders:

$$v|_{x=0,L} = \frac{\partial N}{\partial x}|_{x=0,L} = \frac{\partial P}{\partial x}|_{x=0,L} = 0 \quad (3.17)$$

The model has spatially homogeneous solutions corresponding to the stationary states of the local system (3.16). There are three of them: zero for both species, corresponding to system degradation, zero for predators, and corresponding to non-zero numbers of both populations:

$$\bar{N}, \bar{P}, \bar{v} = \left(\frac{m}{a(1 - mh)}, \frac{a(1 - mh) - m}{a^2(1 - mh)^2}, 0 \right). \quad (3.18)$$

The spatially homogeneous regime (3.18) is stable to small perturbations, the victim search efficiency coefficient, is contained in the interval:

$$\frac{m}{1 - mh} < a < \frac{1 + mh}{h(1 - mh)}. \quad (3.19)$$

The analysis of the model (3.16) shows how the search activity of a predator, expressed in a nonzero value of the taxis coefficient k , causes the appearance of spatially inhomogeneous structures from the initially stable homogeneous periodic regime and the periodic mode C_0 . With growth of k , a homogeneous stationary state loses its stability, and in its neighborhood a periodic regime is inhomogeneous in space, which

becomes more complicated with a further increase in the taxis coefficient k , undergoes a cascade of period doubling, and subsequently becomes aperiodic. Variations in the average numbers of a predator and prey in a spatially inhomogeneous regime are much less than in a homogeneous regime for a fairly wide range of k . The trophotaxis model with advective acceleration (3.16) has properties that allow the paradox of biological control to be resolved.

At large values of the parameter a - the efficiency factor of predation - the oscillations of the numbers of both species with a large amplitude are established. The number of victims periodically reaches values close to the values of the capacity of the medium. This fact is the reason for the paradox of biocontrol, which consists in the fact that the traditional models of population dynamics are not able to describe both the stationary (Lagrange-stable) dynamics of the predator-driver system and the low pest population. The spatial model (3.16) satisfies the requirements for models of biological control. In the case of high predator voracity and in the absence of directional taxis (there are only random movements of individuals-diffusion), there is a low number of victims in the model, but an unstable stationary regime and a stable uniform periodic C_0 regime with a high amplitude. For sufficiently high values of the taxis coefficient k , the oscillatory mode of C_0 becomes unstable, and a stable inhomogeneous dynamic structure in which the amplitude of fluctuations of the population-averaged populations of populations is much smaller than the amplitude of a spatially uniform periodic regime C_0 . Thus, the predator-prey system stabilizes at a low population size of the victim.

3.3 Modeling of blood flow dynamics in vessels with stenosis

Recently, there has been an increase in interest in hemodynamic problems - the study of the properties of the movement of blood in blood vessels, especially in conditions of narrowing of the vessel. The dynamics of blood flow in blood vessels with thrombi is one of the urgent problems of hemodynamics. To predict the occurrence of stenosis in the blood, various methods of field experiments are used. However, the most interesting are the mathematical methods for calculating hemodynamic parameters in the region of thrombus formation. We note that in the mechanics of continuous media the flow of a fluid with nontrivial rheological properties in vessels of a given geometry has been studied repeatedly, including the flow of blood. The most widely known among specialists was Poiseuille's classical paper on the flow of blood in a cylindrical vessel, which to this day has not lost its significance. In this section, the formulation of the problem of the movement of blood in vessels with stenosis, the basic equations and the method for their solution are considered. The problem is considered in a two-dimensional formulation, the blood flow is considered to be an incompressible fluid. As a section of the vessel, a channel of length L and height H , the entire region D , is adopted.

The system of Navier-Stokes equations supplemented by the continuity equation is the initial one. The calculated region is shown in Fig. 4.1, where an atherosclerotic plaque with the size D_0 (stenosis region) is shown.

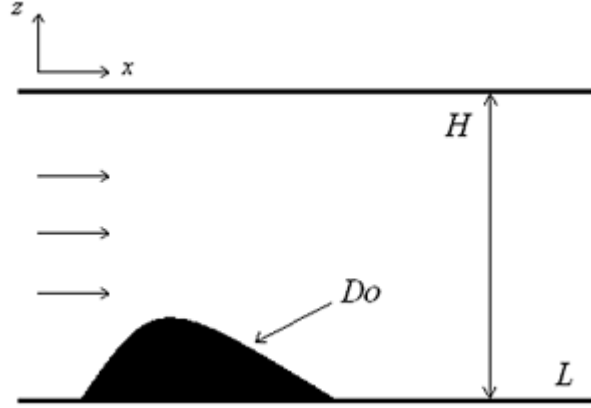


Figure 3.1

The system of initial equations can be written in dimensionless form:

$$\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + w \frac{\partial u}{\partial z} = -\frac{\partial p}{\partial x} + \frac{1}{Re} \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial z^2} \right), \quad (3.20)$$

$$\frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + w \frac{\partial w}{\partial z} = -\frac{\partial p}{\partial z} + \frac{1}{Re} \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial z^2} \right), \quad (3.21)$$

$$\frac{\partial u}{\partial x} + \frac{\partial w}{\partial z} = 0. \quad (3.22)$$

where, $Re = \frac{UL}{\nu}$ – is Reynolds number. As initial data, the initial velocity and pressure fields are given. The initial velocity profile is defined as follows:

$$u(0, x, z) = u_H \cdot \left(\frac{z}{H} \right)^{1/2}, \quad w(0, x, z) = 0, \quad 0 \leq x \leq L, \quad 0 \leq z \leq H.$$

Hydrostatic pressure is assumed for the initial distribution. The considered excess pressure P will be zero, that is $P(0, x, z) = 0$, $0 \leq x \leq L$, $0 \leq z \leq H$.

The boundary conditions:

In the input that is, when $x = 0$, the values of velocity, pressure, and temperature coincide with the initial conditions:

$$u(t, 0, z) = u(0, 0, z), \quad w(t, 0, z) = 0, \quad t > 0, \quad x = 0, \quad 0 \leq z \leq H,$$

$$p(t, 0, z) = p(0, 0, z) = 0, \quad t > 0, \quad x = 0, \quad 0 \leq z \leq H.$$

At the output, that is, when $x = L$ the following conditions are used: $\frac{\partial f}{\partial x} = 0$, $f = (u, w, p)$, $x = L$,

On the lower and upper boundary, that is, when $z = 0$, and $z = H$, the wall condition is specified:

$$\begin{aligned} u(t, x, 0) = 0, \quad w(t, x, 0) = 0, \quad t > 0, \quad z = 0, \quad 0 \leq x \leq L, \\ p(t, x, 0) = 0, \quad t > 0, \quad z = 0, \quad 0 \leq x \leq L. \end{aligned}$$

To satisfy the boundary conditions on the stenosis, we apply the method of fictitious domains described in Vabishevich's work in the extended domain $D_* \cup D$. Then the problem with stenosis for the system of equations (3.20) - (3.22) can be formulated as follows:

$$\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + w \frac{\partial u}{\partial z} = -\frac{\partial p}{\partial x} + \frac{1}{Re} \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial z^2} \right) - S \cdot (u - u_0), \quad (3.23)$$

$$\frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + w \frac{\partial w}{\partial z} = -\frac{\partial p}{\partial z} + \frac{1}{Re} \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial z^2} \right) - S \cdot (w - w_0), \quad (3.24)$$

где $S(x, z) = \begin{cases} 0, & (x, z) \in D \\ \varepsilon^{-2}, & (x, z) \in D_0 \end{cases}$, ε - is small parameter, u_0, w_0, T_0 - are the values of the components of velocity and temperature at the lower boundary.

Method of Solution

For solution of the formulated problem numerically, the splitting method described by Belotserkovsky is applied. Here, to approximate the convective terms, upwind schemes is used which leads to an increase in the stability of the computational algorithm for higher Reynolds and Peclet numbers. Let at some instant of time $t_n = n\Delta t$ (Δt is time step, n - number of steps) known velocity fields $V = (u, w)$, pressure p . Then the definition of unknown functions at time $t_{n+1} = (n+1)\Delta t$ represented in the form of a three-step splitting scheme.

At the first step, intermediate velocities are determined by equations

$$\frac{\tilde{u} - u}{\Delta t} = -u \frac{\partial u}{\partial x} - w \frac{\partial u}{\partial z} + \frac{1}{Re} \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial z^2} \right) - S \cdot (u - u_0), \quad (3.25)$$

$$\frac{\tilde{w} - w}{\Delta t} = -u \frac{\partial w}{\partial x} - w \frac{\partial w}{\partial z} + \frac{1}{Re} \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial z^2} \right) - S \cdot (w - w_0) \quad (3.26)$$

In the second step, the pressure field calculated from the Poisson equation is calculated from the intermediate velocity values from first step:

$$\frac{\partial^2 p}{\partial x^2} + \frac{\partial^2 p}{\partial z^2} = \frac{1}{\Delta t} \left(\frac{\partial \tilde{u}}{\partial x} + \frac{\partial \tilde{w}}{\partial z} \right) \quad (3.27)$$

At the third step, the final (on the time layer $n + 1$) velocity values are determined by equations

$$\frac{u - \tilde{u}}{\Delta t} = \frac{\partial p}{\partial x} \quad (3.28)$$

$$\frac{w - \tilde{w}}{\Delta t} = \frac{\partial p}{\partial z} \quad (3.29)$$

The algorithm of the method is as follows:

1 step. According to the velocity field known from the initial data, the intermediate velocity field from equations (3.25), (3.26) is found. This determines the right-hand side of equation (3.27).

2 step. After this, the Poisson equation (3.27) is solved in order to determine the pressure.

3 step. Later, the velocity field is corrected on the current time layer using equations (3.28), (3.29).

When calculating the parameters at the 1st step, the time advance is carried out in time with the stability condition by limit on the maximum time step:

$$0, 25(|u| + |w|)^2 \Delta t Re \leq 1 \text{ и } \Delta t / (Re \Delta x^2) \leq 0, 25$$

In determining the stability of a numerical method, the von Neumann method was used, in which the solution of the equations is represented by a Fourier series with a finite number of terms and the stability is determined by the fact that each oscillation decays.

3.4 Mathematical Simulation of the Process of Blood Clot Formation in the Blood Circulation

Normal functioning of the blood coagulation system ensures maintaining liquid flowing state of blood. Ability to ensure fast local reaction of organism in response to local violation of normal conditions of flow is the particular feature of blood coagulation system. In the real blood vessels, blood coagulation is activated by the factors active at the place of damage. These factors trigger a series of biochemical reactions resulting in formation of a thrombin. Some components of an inhibition system such as protein C, are the enzymes activated directly by thrombin. Occurrence of a large number of thrombins in the blood plasma triggers the reaction blocking its own production. Fibrinous clots (thrombus) formed in blood are spatially localized mass. By the present moment a number of mathematical models describing the cinematics of triggering the

key metabolites of the blood coagulation system has been developed.

Assumptions in the hemodynamic modeling

The vascular system is a complex network of branching vessels, spanning the length of the scale from meters to microns. The main features of the normal arterial system include compatible arterial walls, complex branching or tortuous arteries, as well as the regeneration of non-Newtonian blood. On the largest scale cases, simulation of the vasculature is similar to an alternating current circuit, where inductance and resistance (total resistance of electrical equipment to alternating current) are inertial and frictional (viscous) pulsating blood losses. Capacity is the correspondence of the walls of blood vessels, which act similarly through alternating local storage and release of the blood down the vessel. This last feature largely determines the phenomena of wave propagation - attenuation, dispersion, reflection, which can be used to derive the functional state of the vascular network from macroscopic measurements of pressure and flow. To assess vascular resistance, diameters and lengths of vessels are required, but otherwise the specific forms and connections of the vessel are largely insignificant, except perhaps when its effects are modeled using the imposition of correction factors or the resistance inconsistencies. The blood may be modeled as the Newtonian fluid, possibly with an adjustment to the apparent viscosity based on the size of the vessels included in the scheme. On the smallest scale, in arterioles and capillaries, where the diameters of the blood vessels approach the diameters of the red blood cells, the blood can no longer be considered as a homogeneous fluid with constant viscosity. As will be discussed below, on this scale one should no longer think of the blood as a continuum; however, simple models were developed that incorporated the effect of this discreteness on apparent viscosity. Individual arteries, usually branches, bends, sacs and constrictions, which became the cause or the effect of focal vascular diseases such as atherosclerosis and aneurysms, are considered. Due to the heart pulsation, it is often possible to neglect the pulsating (non-stationary) flow effects, waiting for the dynamics of the flow with low amplitude. Decades of research have emphasized an important role of the vascular geometry, leading to the emergence of distinct and surprisingly complex fluid mechanics in these vessels. As a result, the three-dimensional nature of the artery shape is crucial to consider. Such models are usually considered in isolation from the rest of the vascular network, or at least these effects are included in the input and output boundary conditions. Hard walls and Newtonian rheology are almost always accepted, although the relevance of these assumptions remains the subject of ongoing debate.

Rheology and Turbulence

It is generally accepted that the blood flow in the large arteries is laminar under normal physiological conditions, with the possible exception of the distal heart valves and the ascending aorta. It is also widely believed that turbulence occurs only in severe pathological conditions, especially after severe narrowing or stenosis, although

there is some evidence that mild stenosis can cause turbulence. Until recently, CFD studies have focused almost exclusively on nominally turbulent flows through idealized stenoses, for which the detailed experimental data are available. The so-called two-equilibrium turbulence models can be satisfactory for modeling stable turbulent flows, but tend to be excessively dissipative for transient, relaminarizing flows experienced under physiological conditions. More recent studies have focused on modeling methods with large eddies (LES) and even direct numerical simulation (DNS), the latter essentially being solved by the Navier – Stokes equations, resolved to the expected smallest length scales (i.e. Kolmogorov) eddies, where there is viscous dissipation. Regardless of CFD methodology, discussions about the nature of physiological “turbulence” are continuing, namely: is it a random and uncorrelated flow exhibiting a classical energy cascade in the strict mechanical sense, or is it in some cases just an unstable flow characterized by phenomena of vortex formation on frequencies significantly higher than the heart rate. It is believed that the turbulence caused by external compression of the artery causes the so-called Korotkoff sounds used to measure blood pressure. Noise (“bruits”) can also be detected by a stethoscope located above a stenotic surface vessel, such as the carotid artery, or by intracranial aneurysms, which may also have turbulent flow. Based on the question of whether these pathological flow conditions are turbulent, transient, or simply unstable, an important question arises about the physical scale of flow structures. The assumption that blood can be modeled as a homogeneous fluid is based on the assumption that arterial length scales (mm) are orders of magnitude larger than RBC length scales (mkm).

Blood coagulation mechanism

Blood coagulation is a well-known process after a wound and leading to cessation of bleeding (hemostasis). This goal is achieved by sealing the lesion with a clot (or thrombus). Before we turn to the mathematical models of the process, it is necessary to describe the concept of this incredibly complex biological process, as well as bleeding disorders, which arise as a result of the lack or dysfunction of some of the many elements that play a large role in it. Here been described the modern model of the blood coagulation process, avoiding the complexities of the chemistry of many proteins involved in the formation of a blood clot (as well as describing their complex structure), focusing on an illustration of their action, presenting a general sketch of the phenomenon. The circulatory system is equipped with incredibly complex chemical and mechanical processes, ready to repair the damage that may occur in the blood vessels, sealing them with a clot (or thrombus). The clot is a gel-like structure consisting of a polymer (fibrin) network, capturing various blood components. The components, necessary for the formation of a clot, are either present in the blood or are in the endothelium of the blood vessels, namely in the outer membrane, in the main part of the vessel (sheath) and in the innermost thin membrane. In fact, those that are contained in the walls of the blood vessels become available immediately after a lesion of a thin membrane, even in the presence of a tiny internal lesion. It is important to note that under normal conditions they do not come into contact with blood. The coagulation mechanism is

set in motion when it is really necessary, not acting under normal conditions, and at the same time, the coagulation process stops before it closes the vessel, allowing the blood to flow normally. Indeed, after the hemostasis process is complete, the thrombus will be gradually removed by another process known as fibrinolysis. To be more precise, it is wrong to treat these processes consistently. Hemostasis and fibrinolysis are both active, whether the blood clots grow or retreat as a result of an imbalance between these two processes. In addition to the physiological process of hemostasis after injury, it is well known that unwanted coagulation can occur due to a temporary decrease in the blood flow or stagnation (or sometimes in places of flow stagnation, usually accompanying abnormal vortices), which leads to the deep vein thrombosis, a disease caused by bone injury. for example during implant prosthetics. The classic coagulation cascade consists of an internal, external and common path. Over the past few decades, the understanding of the coagulation cascade is changing and constantly improving. The coagulation cascade consists of a) an initiation phase, b) an amplification phase, and c) a propagation phase. The initiation phase begins with exposure to tissue factor (TF), which is present in the subendothelial cells with the blood flow during vascular injury. TF binds to factor VIIa (FVIIa) and cleaves FIX and FX to form FIXa and FXa, respectively. The index "a" indicates that the blood factors are in an activated state, and the prefix "F" means a factor. FXa will then help convert FII to FIIa (thrombin). This is followed by the amplification phase, in which FIIa plays a central role, as shown in Figure 3.2.

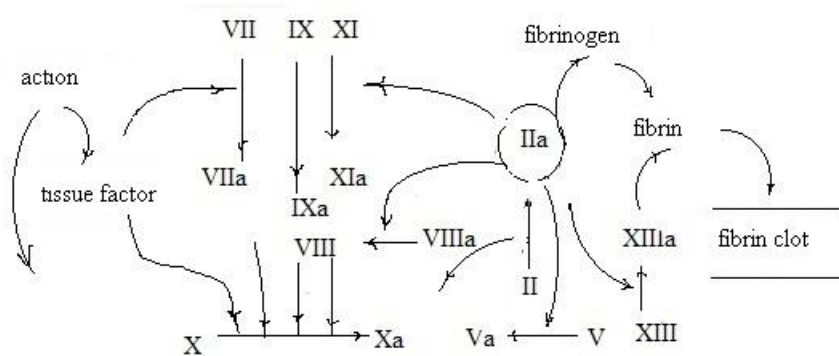


Figure 3.2

FIIa converts FV to FVa, FXI to FXIa and FVIII to FVIIIa. These parallel processes accelerate the production of FIIa and are therefore called the amplification phase. In the propagation phase, FXIa also converts FIX to FIXa, which, together with FVIIa, catalyzes the formation of FXa. Finally, FXIIIa catalyzes the formation of a cross-linked fibrin network.

Modern computational methods for the blood clot modeling

This section classifies various computational methods used for the hemostasis and

the thrombosis based on a spatial scales and a time scales.

Method - Level System

The method — a system of levels — is modeling the blood flow and coagulation on a larger scale; many mathematical relationships are used to reproduce experimental results. They are usually modeled using the CDR equations, and constants are estimated empirically from experiments. The advantage of these types of models with less complexity allows you to simulate the qualitative behavior of events associated with the blood coagulation. At the same time, due to the assumptions have made, the smallest details of the processes are lost. A simple example of this type of method is the modeling of fibrin coagulation using simple ordinary differential equations (ODE). The blood coagulation factors are modeled as time dependent concentrations, and chemical reactions are modeled using simple ODUs. Finally, the clotting time of fibrin from fibrinogen in the presence of thrombin is modeled and compared with experiments. An elegant way to simulate the kinetics of the enzymatic reaction and related products is the Michaelis-Menten kinetics, which relates the reaction rate to the substrate concentration. This method allows you to determine the formation of an enzymatic product using a simple relationship, such as $E + S \xrightarrow{k_f, k_r} ES \xrightarrow{k_c} E + P$, where (E) binds to the substrate (S) to form a complex (ES) which ultimately re-releases the product (P). They react with the direct velocity k_f , the opposite velocity k_r and the catalytic velocity k_c , they are collectively called reaction rate constants or simply rate constants. These equations can be written as a system of nonlinear ODUs, which determine the rate of change of reagents. Using this technique, it is possible to simulate the formation of the blood clot, where the blood factors, involved in the coagulation cascade, are modeled as the Michaelis-Menten system of equations.

Then, based on physiologically observed concentrations and rate constants, the reaction kinetics is been simulated. One of the drawbacks of these methods is the dependence on empirical models and experimental values of the rate constants, which makes the method susceptible to irregular kinetics. To take advantage of this method, it is necessary to carefully check the rate constants with experimental results. A system of reaction kinetics levels can be combined with spatial information to make it more realistic. In one of these studies, scientists combine the NS equations and the CDR equations to study the formation and division of the blood clot.

Continuous methods

While the methods of the level system may indicate the rate at which clotting or disintegration occurs in a particular hemostatic process, they are not sufficient in explaining coagulation and disintegration in terms of the physical length and the geometry scales. This becomes important when studying the blood clots in the complex geometries and with various mechanical and environmental factors. In its simplest form, the blood is modeled as the incompressible Newtonian fluid flowing between two parallel flat plates. This will lead to the Poiseuille flow, and the velocity across the flow section will be parabolic. The complexity of the models depends on the level of the

detail of the blood components under consideration. The basic model is a combination of the NS equations for flow dynamics and the CDR equations for the space-time evolution of concentration types. Most of the available continuous models suggest that the blood vessels are like rigid walls and the blood components are massless particles. This makes it possible to model equations only by directly solving the NS and the CDR equations, neglecting the inverse effect of particles on the flow velocity. Until now, the modeling of thrombus formation was considered as an increase in the concentration of platelets, fibrin or other blood components.

Methods of Discrete Particles

Due to its versatile ability to simulate liquids both at nano and microscales, the DPD (Dissipative Particle Dynamics) method drew the attention of researchers to the blood flow modeling. Platelets are usually modeled as particles or balls and fibrin in the form of polymer chains connected to each other by harmonic springs. When only platelets are considered for modeling, the DPD system is only freely distributed balls interacting with each other. Boundary conditions of pressure or velocity are often applied to the system through the external forces. These external forces can be determined by solving the simple Poiseuille flow or by connecting with the NS-equations.

Multiscale methods

In multiscale methods, two or more computational methods are combined with each other on different lengths or time scales, which differ from hybrid methods, which combine two or more methods on the same scales. A typical scenario of the multiscale modeling is the modeling of biochemical reactions of the blood factors using the MD modeling, their spatial and temporal concentrations through the CDR equations and the blood flow using the NS equations. Thus, it is possible to capture the macroscopic behavior of the clot formation without losing the nanoscale characteristics.

Simulation of the clot mechanics

Here are the models that are used to study the mechanical properties of the fibrin or the blood clot. The study of structure and mechanism of the blood clot is of great importance, since it can predict physiological or pathological conditions in which it can break off and lead to embolism or other conditions. The trend of numerical simulation over the years shows that simpler models, such as the single-component continuum models, are becoming redundant and are increasingly being replaced by the discrete particle methods, such as the DPD, and with a new method called multi-scale modeling. Continuous model level methods are still suitable for predicting the behavior of the upper level, based on the empirical data, which limits their use of the NS equations in combination with the CDR equations and the study of the blood flow dynamics. Bilateral communication of the NS equations with the CDRs or other methods is superior to unilateral communication in many aspects, such as an accurate distribution of the blood flow, the blood clot deformation due to a high shear flow, etc. The DPD is a

powerful fluid modeling method that currently finds place in many biological models. The basic requirements for the use of the DPD in simulating the blood flow are put forward by many authors and are constantly being improved. One of the advantages of the DPD is that it allows you to simulate many of the complex blood components, such as red blood cells, platelets and plasma as simple beads. These properties make the DPD a better choice than the boundary element methods, the discrete element method, etc. One of the biggest problems is modeling the blood as the non-Newtonian fluid, where the DPD shows some perspectives. However, care must be taken when introducing additional potentials into the DPD to simulate polymer chains, solid walls, dynamic bonding and fracture, etc. Since the DPD was originally designed for fluids with three basic soft interactive forces. Any modification to them will change the dynamics, and the parameters must be confirmed with experimental values. The multiscale blood clot models can effectively imitate blood clotting dynamics, biochemical reactions, concentration factors, etc. The model will have cascade sub-models that can serve as independent models for predicting several specific characteristics, such as fibrinogen-thrombin cleavage. A good multiscale model will have characteristics of the blood volume behavior modeling, such as diffusion, viscosity, etc., the mechanical properties of a thrombus under the shear flow, and dynamic properties to simulate the rupture of a thrombus are taken into account on the basis of molecular mechanics. With the development of more accurate models for the blood components, it will be promising to develop and model the realistic blood clot formation. The multiscale models of erythrocytes can predict the behavior of erythrocytes in the plasma flow, models of fibrin can mimic the atomic level to mesoscale properties. These achievements at different scales will allow developing new accurate multiscale models for predicting the process of the blood coagulation and its mechanics.

Mathematical Model

liquid form is considered to be incompressible and having the permanent viscosity; all biochemical processes of the key metabolites controlling the blood coagulation are taken into account. Mechanisms of reaction ensuring production of anticoagulating agents have not been studied sufficiently well; therefore, the given section presents a simplified mathematical model describing kinetics of production and diffusion over the space of two factors only: coagulation factor - thrombin and the factor preventing coagulation. The mathematical model boils down to transient equations of viscous incompressible liquid flow supplemented with the members of the convective transport of metabolites.

$$\operatorname{div}V = 0 \tag{3.30}$$

$$\frac{\partial V}{\partial t} + (V\nabla)V = -\nabla p + \mu\Delta V \tag{3.31}$$

$$\frac{\partial \theta}{\partial t} = D_1\Delta\theta - \operatorname{div}(V\theta) + \frac{\alpha\theta^2}{\theta + \theta_0} - \gamma\theta\phi - \chi_1\theta, \tag{3.32}$$

$$\frac{\partial \phi}{\partial t} = D_2 \Delta \phi - \operatorname{div}(V \phi) + \beta \theta \left(1 + \frac{\phi^2}{\phi_0^2}\right) - \chi_2 \phi, \quad (3.33)$$

$$\frac{\partial \psi}{\partial t} = k \theta \quad (3.34)$$

where V is velocity vector, p is pressure, θ is clot activator (thrombin) concentration, $\chi_1 = \alpha_* \bar{\chi}_1$, $\chi_2 = \alpha_* \bar{\chi}_2$, $b = \frac{\beta \theta_0}{\phi_0 \alpha_*}$, $c = \frac{\phi_0}{\varepsilon}$, ϕ is inhibitor content.

Thrombin catalyzes the reaction of the fibrin predecessor - fibrinogen turning into fibrin-monomer, content of which is expressed through ϕ , which, in turn, is polymerized subject to the condition of $\phi > \phi^c$ producing a clot.

Numerical Solution Algorithm

The purpose of numerical solution of unsteady-state equation for viscous incompressible liquid, the method of splitting into physical parameters, described in detail in the clause 3.3, is applied. For the purpose of parietal thrombus accounting, the method of immersed boundary is used, which means that an artificial force f , discrete in time is introduced in the impulse equation. This artificial force is applied only on the surface of an obstacle and within a body. The points of load application coincide with the points of velocity components determining. When a load application point coincides with a virtual boundary, an artificial force is applied in such a way so that the boundary condition of sticking would be fulfilled. Parameters of a cell containing a virtual boundary may not satisfy the mass conservation equation. Therefore, the source/sink of mass q , is introduced for this cell. Taking into account an artificial force $f_i = (f_u, f_v)$ and q , after the nondimensionalization procedure, the system (3.30)-(3.34) will be rewritten with the following set of inherent scales: concentration θ_0 and ϕ_0 , linear size L and the inherent velocity scale V in the form of

$$\operatorname{div} V - q = 0 \quad (3.35)$$

$$\frac{\partial V}{\partial t} + (V \nabla) V = -\nabla p + \frac{1}{Re} \Delta V + f_i \quad (3.36)$$

$$\frac{\partial \theta}{\partial t} = \frac{1}{Pe} \Delta \theta - \operatorname{div}(\theta V) + \frac{1}{M} \left(\frac{\theta(\theta - \bar{\chi}_1)}{\theta + 1} - \bar{\gamma} \theta \phi \right) \quad (3.37)$$

$$\frac{\partial \phi}{\partial t} = \frac{1}{Pe} \Delta \phi - \operatorname{div}(\phi V) + \frac{1}{M} (b \theta (1 - \varepsilon \phi) (1 + \phi^2) - \chi_2 \phi) \quad (3.38)$$

где $M = \frac{V}{\alpha_* L}$, $Pe = \frac{LV}{D}$, $b = \frac{\beta \theta_0}{\phi_0 \alpha_*}$, $c = \frac{\phi_0}{\varepsilon}$.

Boundary conditions for the Navier-Stokes equations were assumed as follows: the sticking conditions were assumed for the vessel walls and clot surface. The pressure values were set for the left and right boundaries of the considered area. It was assumed

that the vertical components at the input were equal to zero and the output boundary conditions were free. Initial concentration at the vessel lesion site was set as the boundary condition for the metabolite - thrombin.

For solution of equations describing the dynamics of distribution of blood coagulation system's main metabolites the second order spatial variables approximation implicit scheme was used.

Certain Numerical Results and Their Analysis.

Concentration wave of the activator, which has a speed $V_* = \sqrt{D_1(\alpha\chi_1)}$ in non-convective conditions, forms a polymerizing clot that blocks the bloodstream having velocity of V . As noted in the work of Ataluikhanov at al. arrest of hemorrhage as a result of thrombus growth is possible when these velocities are commensurable. Counteraction to the coagulation autowave may be characterized by dimensionless parameter $Gu = V/V_* = V/\sqrt{D_1(\alpha\chi_1)}$.

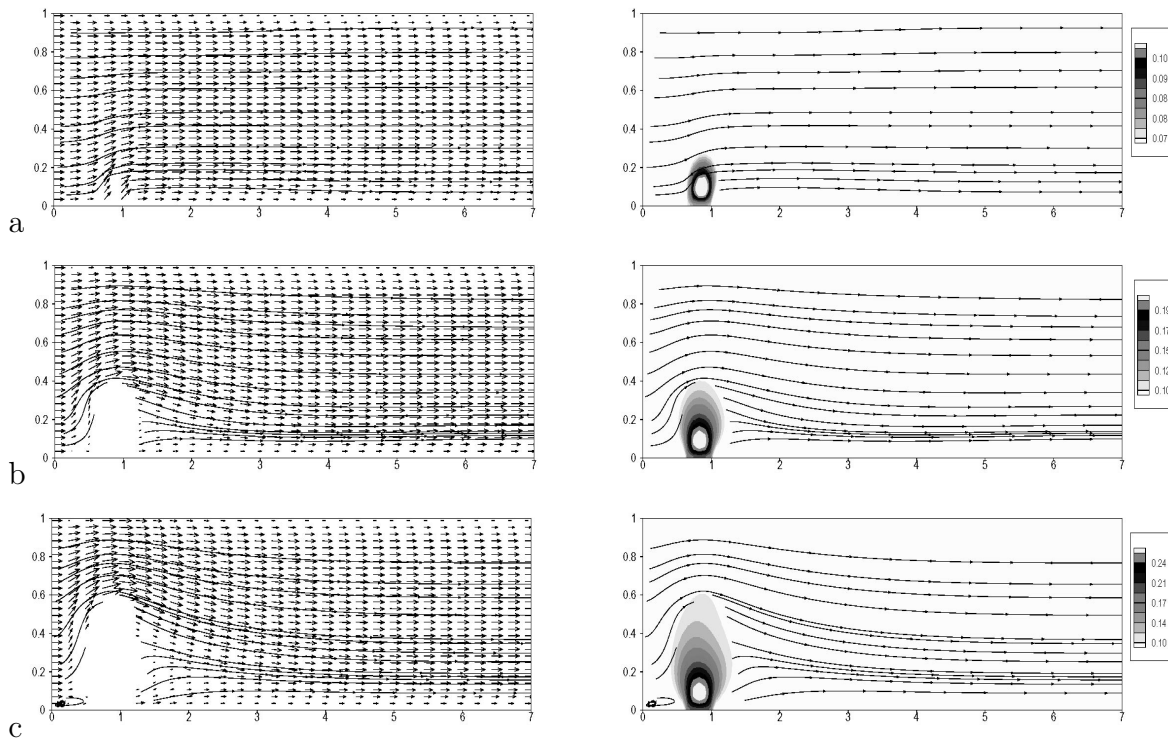


Figure 3.3 – thrombus formation at Re=0.01, Pe=10, Gu=1.7.

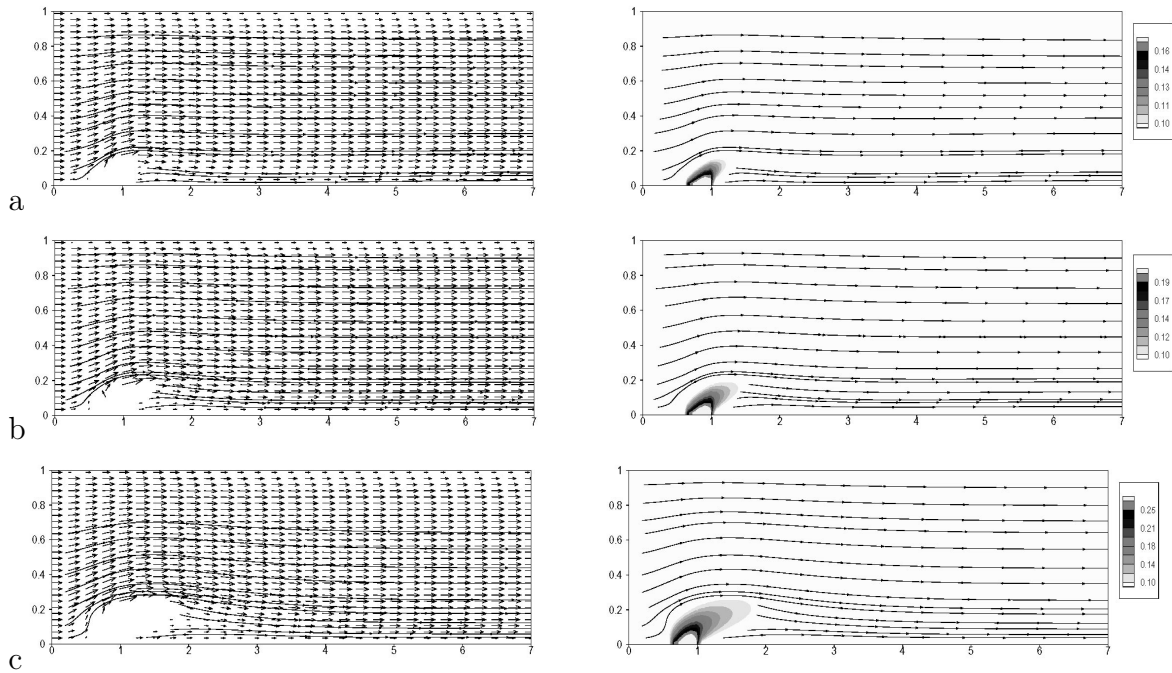


Figure 3.4 – thrombus formation at $Re=2$, $Pe=10$, $Gu=1.7$.

Figure 3.3 shows the numerical results for the following parameters: $Re = 0.01$, $Pe = 10$, $Gu = 1.7$ at different points in time. The initiation of blood coagulation due to a local increase in the concentration of the activator is accompanied by the formation of a thrombus, which displaces blood flow from the area adjacent to the injury site. In the event of low blood flow velocities, the primary wave (the initial perturbation wave is assumed) of activation of clotting is extinguished by the inhibitor wave and the growth of the thrombus stops. The thrombus covers up to one-third of the transverse vessel size. As it can be inferred from the flow line pictures, blood flow is driven out of the area adjacent to the injury site. Localized blood clot formation is determined by interaction of an activator and inhibitor with each other and also with the hydrodynamic flow.

Increasing the value of the Reynolds number leads to the demolition of a blood clot in the direction of flow, the blood clot takes an asymmetrical shape as it did in the first case (Fig. 3.4). Stopping of the hemorrhage resulting from a thrombus growth is possible when these velocities are commensurable. Flow counteraction to the coagulation autowave may be characterized by the dimensionless parameter Gu . The experimental results were obtained where change in the Gu value resulted in an intensive convective clot transfer. The anticlotting wave prevents further growth of thrombosis, blood flow driving out becomes more intensive and further numerical experiments revealed that blood clot detachment does not happen under these conditions. (рис 3.5).

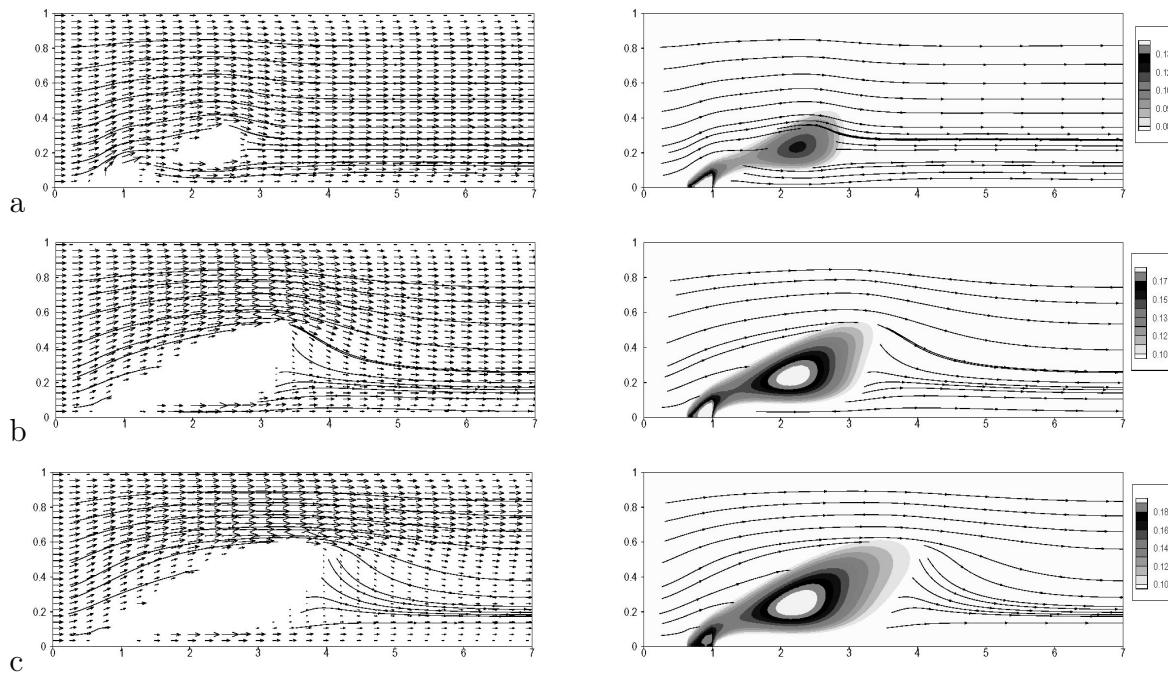


Figure 3.5 – thrombus formation at $\text{Re}=2$, $\text{Pe}=10$, $\text{Gu}=2.7$ at times $t=100$ (a), $t=400$ (b), $t=500$ (c).

Questions and exercises.

1. Using the dedimensionalization procedure, derive the equation (3.23) and (2.24).
2. Using the equation (3.20)-(3.22), derive the Poisson's equation for pressure (3.27).
3. Describe the second order spatial variables approximation implicit scheme for solution of equations describing the dynamics of distribution of blood coagulation system's main metabolites.
4. Using the von Neumann's method, show that if central differences are used to approximate the derivatives with respect to space, then the explicit first-order method of solving the one-dimensional wave equation is unstable.

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