# MATHEMATICAL MODELS IN BIOPHYSICS

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**Key words**: Biological systems, Biochemical reactions, Interaction of species, Age structure, Glycolysis, Cell regulation, Cell cycles, Oscillations, Metabolism control, Mathematical modeling, Molecular dynamics, Morphogenesis, Nerve conductivity, Selection, Population dynamics, Spatio-temporal organization, Trigger systems, Photosynthesis

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## Glossary

**Biological structure:** A holistic system of the components performing a certain function in alive systems. Biological systems include complex systems of the various levels of organization: biological macromolecules, subcellular organelles cells, organs, organisms, and populations.

**Age structure:** The distribution of the number of species in a population with respect to ages. A discrete and continuous representations of the age structure are employed.

**Biochemical kinetics:** The branch of science examining the temporal behavior of the components of chemical reactions, their transformations, and interactions.

**Kinetic models:** The models describing the behavior of the system's components in time. Concentrations of the system's components are usually the variables in these models. Most often, the ordinary differential equations are an apparatus of kinetic models, as well as the delayed equations, partial differential equations, and finite-difference equations.

**Theory of metabolism control:** The branch biochemical kinetics examining complex networks of metabolic processes and the sensitivity of their individual stages to the changes in exterior and interior parameters of the system.

**Logistic growth:** The population growth law described by a curve that has a lag period, and a limit value determined by the capacity of the population ecological niche.

**Cellular cycle:** The sequence of phases passed by a cell from the preceding to next fission. In continuously proliferating cells, it consists of the interphase (the growth period) and mitosis (the fission period).

**Models of the interaction between the species:** Mathematical models governed by differential or finite-difference equations describing the spatio-temporal changes in the population number of species in their mutual interaction ( predation, symbiosis, competition, etc.).

**Molecular dynamics:** The branch of physical and mathematical modeling of the behavior of biological macromolecules (polypeptides, polynucleotides, proteins) that simulates the concerted motion of the atoms, which compose a molecule, in space and time.

**Morphogenesis:** The formation of forms: the appearance of new forms and structures in the course of individual and historical development of organisms. Models of the morphogenesis describe the spatio-temporal evolution; classical models use the partial differential equations as a tool.

**Nerve conductivity:** The capability of the nerve cells (neurons) of the excitation and of the transmission of the excitation to other nerve cells, muscular and other tissues.

**Population dynamics:** The branch of mathematical modeling that describes the processes of growth and development of individual populations and the interaction between different populations. Quantity and density of populations are the variables in these models.

**Population:** relatively isolated group of species of the same kind. In mathematical description, both homogeneous populations and structured with respect to age, gender, etc. are considered.

**Lotic cultures of microorganisms:** A technique for cultivating the microorganisms in which a substrate comes in continuously and a mixture of the substrate and biomass is continuously removed. This method is widely used in biotechnology. Models of continuous cultivating are classical objects in mathematical biology and are also applicable to the natural systems open with respect to matter.

**Stationary regime:** A regime of the functioning of a system which settles in time and whose characteristics then remain unchanged. In the models, this corresponds to the concept of an attractor.

**Trigger models:** nonlinear models (as a rule, the systems of differential equations) with two or several stable stationary states.

**Growth equation:** differential or finite-difference equation describing the change in quantity (density) of a population in time.

**Phase pattern:** graphical image of a system in the phase plane (or in a multidimensional space); the values of variables are marked on the coordinate axes. In such a representation, the behavior of variables in time for every initial point is described by a phase trajectory. A set of such phase trajectories for arbitrary initial conditions represents a phase pattern.

**Summary**

Mathematical models represent a language for formalizing the knowledge on live systems obtained in theoretical biophysics. Basic models represented by one or two equations allowing a qualitative examination, make it possible to describe principal regularities of biological processes: growth restrictions, presence of several stable stationary states, oscillations, quasistochastic regimes, travelling pulses and waves, and the structures inhomogeneous in space. The nonlinearity of these models is their most important property: it reflects mathematically the openness of biological systems and their state beyond thermodynamic equilibrium. This type of models includes the models of growth, interaction between the species, lotic cultures of the microorganisms, genetic trigger, intracellular calcium oscillations, glycolysis, nerve conductivity, and DNA untwisting. The detalization and identification of these models from experimental data allows the description of real processes in live systems, the examination of their mechanisms, and makes these models heuristic. The models of primary processes of the photosynthesis are a good example. Using the computers, the imitation models develop vigorously, describing the behavior of a complex system on the basis of the knowledge on its elements and on the regularities of their interaction. On the level of biological macromolecules, these are the models of molecular dynamics, based on the characteristics of individual atoms an don the laws of their interaction. The imitation models are constructed for all the levels of the organization of live systems, from the subcellular organelles to the biogeocenoses. The development prospects for mathematical models in biology rest on the use of information technologies. The latter allow the integration of knowledge both in the form of mathematical objects and in the form of visual images, which presents a notion on complex laws of the functioning of the regulation laws in alive systems that are difficult to be formalized.

## 1. Introduction

Biophysics represents a science on fundamental laws underlying the structure, functioning, and development of living systems. Along with experimental methods, it actively uses mathematical models for describing the processes in living systems of various organization level, starting with biomacromolecules and then at the cellular and subcellular level, at the level of organs, organisms, populations and communities, biogeocenoses, and finally, at the level of the biosphere as a whole . The mathematization degree in this or another field of biophysics depends on the level of experimental cognition of the objects and on the facilities of mathematical formalization of the processes under examination.

All living systems are far from thermodynamic equilibrium. They are the systems open to the fluxes of matter and energy and have complex inhomogeneous structure and hierarchic system for controlling the processes both in the interior environment and changing conditions of the exterior environment. Therefore, mathematical formalization of the concepts on the processes in living systems represents considerable difficulties. Unlike physics, in which mathematics is a natural language, these are **mathematical models** in biology and biophysics, as they are referred to, because of the individuality of biological phenomena. The term «**model»** emphasizes here, that some qualitative and quantitative characteristics of the process in a living system are abstracted, idealized, and described mathematically, rather than the system itself.

In describing processes in biomacromolecules, the approaches of physics, quantum mechanics, and thermodynamics are often employed. The complexities here are associated with unique structure of biomacromolecules (proteins, lipids, polynucleotides) containing many thousands of atoms. Mathematical modeling of intramolecular interactions between atoms and structural fragments of such molecules and of their

interactions with water environment and low-molecular compound is only possible by using powerful computer facilities (methods of molecular dynamics).

The second large class of models is represented by the **models of biochemical reactions,** including enzyme reactions. These are well developed and analytically examined reactions of enzyme catalysis (Michaelis–Menten, Higgins, Reich, Sel'kov) and other local models governed by ordinary differential equations. Analytical and numerical examination of these models allowed the conditions for the emergence of qualitatively new regimes to be formulated: multi steady-state, self-oscillating, and quasistochastic in the chains of metabolic reactions. This class also includes the models of processes in active mediums, whose local elements represent biochemical reactions with regard to the processes of spatial transfer (the «reaction–diffusion» models; for details, see 6.3.6.3)

The next hierarchical level, **cellular biophysics**, is represented by the models describing processes in biological membranes, subcellular organelles (chloroplasts, mitochondria), and by the models of the nerve pulse propagation. Starting with 1990s, the theory of metabolic control is actively developed, whose goal is the examination and search for maximally controllable stages in complex metabolic cycles of intracellular reactions.

Finally, **mathematical biophysics of complex systems,** which historically has appeared before the others, includes the models associated with system mechanisms that determine the behavior of complex systems. These are the models of population dynamics, which became an original «mathematical polygon» of all mathematical biology and biophysics. The basic models of population dynamics are the basis of models in cellular biology, microbiology, immunity, theory of epidemics, mathematical genetics, theory of evolution, and other directions of mathematical biology. Imitation modeling of multicomponent biological systems, aimed at the prognosis of their behavior and at the search of optimal control, belong to another direction in modeling complex biological systems. These are the models of haematogenesis, models of the digestive tract and models of other life support systems in organism, models of morphogenesis, and also models of the production process in plants, models of aquatic and terrestrial ecosystems and, finally global models.

**2. Specificity of mathematical modeling of living systems**

Despite the diversity of living systems, they all possess the following specific features that must be taken into account in constructing the models.

1. *Complex systems.* All biological systems are complex, multicomponent, spatially structured, and their elements possess individuality. Two approaches are feasible in modeling such systems. The first one is aggregated and phenomenological. According to this approach, the determining system characteristics are singled out (for example, the total number of classes) and qualitative properties of the behavior of these quantities in time are considered (stability of a stationary state, presence of oscillations, existence of spatial nonhomogeneity). Such an approach is historical the most ancient and is inherent in the dynamic theory of populations. Another approach implies the detailed consideration of the system's elements and their interactions, the construction of an imitation model, whose parameters have clear physical and biological sense. Such a model does not permit an analytical examination but, if the fragments of a system are sufficiently examined experimentally, can yield a quantitative forecast of the system's behavior under various exterior impacts.

2. *Proliferating systems* (*capable of self-reproduction*). This most important feature of living systems determines their ability to reprocess inorganic and organic matter for the biosynthesis of biological

macromolecules, cells, and organisms. In phenomenological models, this property is expressed by the autocatalytic terms in equations, which determines the possibility of growth (exponential under unlimited conditions), of the instability of a stationary state in local systems (the necessary condition for the appearance of oscillatory and quasistochastic regimes), and of the instability of homogeneous stationary state in spatially distributed systems (the condition of spatially inhomogeneous distributions and autowave regimes). An important role in the development of complex spatio–temporal regimes belongs to the processes of interaction between the components (biochemical reactions) and to the transfer processes both chaotic (diffusion) and associated with the direction of exterior forces (gravity, electromagnetic fields) or with adaptive functions of living organisms (for example, the motion of cytoplasm in cells under the action of microphylaments).

3. *Open systems,* steadily passing through themselves the flows of matter and energy. Biological systems are far from thermodynamic equilibrium and, therefore, are described by **nonlinear equations**. The linear Onzager relations that relate the forces and flows are valid only near the thermodynamic equilibrium.

4. Biological objects possess a complex multilevel **regulation system**. In biochemical kinetics, this is expressed by the presence of feedback loops, both positive and negative, in systems. In equations of local interactions, the feedbacks are described by nonlinear equations; their character determines the possibility of the appearance and properties of complex kinetic regimes, including oscillatory and quasistochastic ones. Such types of nonlinearity, in describing the spatial distribution and transfer processes, stipulate the patterns of stationary structures (spots of various forms, periodic dissipative structures) and types of the autowave behavior (moving fronts, traveling waves, leading centers, spiral waves, etc.).

5. Living systems have a **complex spatial structure**. A living cell and the organelles in it have membranes, and any living organism contains enormous number of membranes, whose total area reaches tens of hectares. It is natural that the medium inside living systems cannot be regarded as a homogeneous one. The emergence of such a spatial structure and the laws of its formation represent one of the problems in theoretical biology. Mathematical theory of morphogenesis is one of approaches to the solution of this problem (for details, see 6.3.6.3).

The membranes not only single out various reaction volumes of living cells, but also separate the biotic and abiotic (medium). They play a key role in the metabolism selectively, passing through themselves the flows of inorganic ions and organic molecules. In the membranes of chloroplasts, the primary photosynthesis processes occur: the accumulation of the light energy in the form of the energy of highly energetic chemical compounds; they are used for the synthesis of organic matter and in other intracellular processes. The key stages of the breathing process are concentrated in the membranes of mitochondria, the membranes of nerve cells determine their capability to the nerve conductivity. Mathematical models of the processes in biological membranes comprise a significant portion of mathematical biophysics. Existing models are mostly presented by the systems of differential equations. However, it is obvious that continuous models cannot describe in detail the processes that occur in such individual and structured systems as living systems. As computational, graphical, and intellectual facilities of computers develop, the imitation models, based on the discrete mathematics, play ever increasing role in mathematical biophysics.

6. *Imitation models* of concrete complex living systems, as a rule, take into account all available information about given object. The imitation models are employed to describe the objects of different organization levels of live matter: from biomacromolecules to biogeocenoses. In the latter case, the models must include the blocks describing both living and «inert» components (see 6.3.6.2). Models of **molecular dynamics** are a classic example of imitation models, in which the coordinates and impulses of all atoms that compose a biomacromolecule and the laws of their interactions are prescribed. A pattern of «life» of a system, simulated

by computer allows one to follow the manifestation of physical laws in the functioning of the simplest biological objects – biomacromolecules and their environment. Similar models, in which the elements (bricks) are not atoms but groups of atoms, are employed in modern technique of the computer construction of biotechnological catalysts and therapeutics that act on certain active groups of membranes of microorganisms and viruses or perform some other directed actions.

The imitation models were created for describing the physiological processes that occur in vitally important organs: nerve tissue, heart, brain, digestive tract, and blood vessels These models are used to simulate the «scenarios» of processes that occur normally and in various pathologies, to examine the influence of various exterior impacts to these processes, including the therapeutics. The imitation models are widely used for describing the production process in plants and are applied to the development of optimal regime of growing plants aimed at obtaining the maximal harvest or the ripening of fruits uniformly distributed in time. Such projects are especially important for expansive and energy consuming greenhouse farming.

### 3. Basic models in mathematical biophysics

In mathematical biophysics, as in any science, simple models exist that are liable to analytic examination and possess properties that allow a whole spectrum of natural phenomena to be described. Such models are called basic. In physics, harmonic oscillator (a ball, material point, on a spring without friction) is a basic model. First, the essence of processes is examined in detail mathematically with the use of a basic model and then, by analogy, the phenomena are comprehended that occur in much more complex real systems. For example, the relaxation of conformation states of a macromolecule is considered similarly to an oscillator in viscous medium.

Despite enormous diversity of living systems, one can single out some of their inherent most important properties: growth, self-restriction of growth, ability to switching, i.e., the existence of two or more stationary regimes, self-oscillating regimes (biorhythms), spatial nonhomogeneity, and quasistochasticity. All these properties can be demonstrated on comparatively simple nonlinear dynamic models, which play the role of basic models in mathematical biology.

#### 3.1. Unlimited growth. Exponential growth. Self-catalysis (Auto-catalysis)

The rate of growth is proportional to the population numbers, no matter is this a hare population or a population of cells; this is one of fundamental assumptions underlying all models of growth. For many one-cell organisms or for the cells contained in cellular tissues, the proliferation means simple division, that is, doubling the number of cells for a certain time interval called the characteristic division time. The proliferation of plants and animals, whose organization is complex, follows more complex laws; however, in the simplest model, one may assume that the proliferation rate of a species is proportional to the numbers of this species.

This is written mathematically with the use of a differential equation linear with respect to a variable $x$ characterizing the numbers (concentration) of individuals in population:

$$\frac{dx}{dt} = R\ x \qquad (1)$$

Here, $R$ can be, in general case, a function of both the numbers and time or depend on other exterior and interior parameters.

The law (1) was formulated by Thomas Robert Malthus (1766--1834) in his book "On the Growth of Population" (1798). According to (1), if the proportionality coefficient $R=r=\text{const}$ (as Malthus assumed), then the numbers grow exponentially and without limits:

$$x = x_0 e^{rt}; \qquad x_0 = x(t=0). \tag{2}$$

For most populations, the limiting factors exist, and the growth of population terminates due to a variety of reasons. Human population is the only exception: during the whole historical time, it increases even faster than exponentially. The investigations performed by Malthus exerted a great influence both on economists and biologists, in particular, Charles Darwin analyzes the Malthus theory in his diaries in detail. Darwin understands the straggle for existence in real living nature as one of the causes for breaking the Malthus law.

The law of exponential growth is valid at a certain growth stage for the cell populations in a tissue, for alga or bacteria in a culture. In models, the mathematical expression that describes the increase in the rate of change of a quantity is referred to as autocatalytic term (the catalysis means a modification of the reaction rate, usually the acceleration, with the help of substances that do not participate in the reaction), and the **autocatalysis** means the "self-acceleration" of a reaction.

### 3.2. Bounded growth. The Verhulst equation.

The Verhulst model (1848) is a basic model that describes the limited growth:

$$\frac{dx}{dt} = rx\left(1 - \frac{x}{K}\right) \tag{3}$$

The parameter $K$ is called the "population capacity" and expressed in the units of numbers (concentration); it is of system character that is, determined by a number of different factors. Among the latter, these are the limitation to the amount of substrate for the microorganisms, space available for a cell population in a tissue, the food base, or the refuge for superior animals. Diagrams of the dependence of the right-hand side of Eq. (3) on the numbers $x$ and on the population numbers in time are presented in Figs. 1a, 1b.

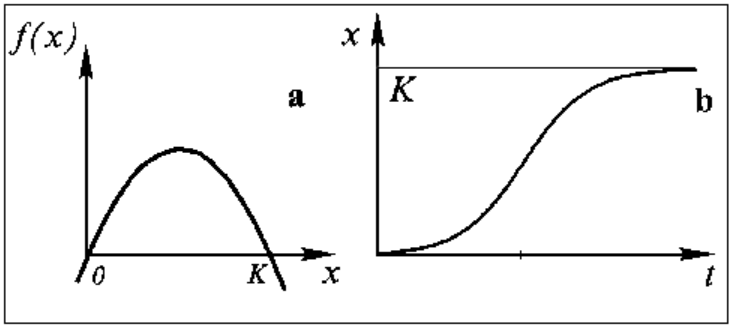


Fig. 1: Bounded growth: (a) dependence of the growth rate on the numbers; (b) dependence of the numbers on time for the logistic equation.

The examination of a discrete analogue of Eq. (3) in the second half of the 20th century has revealed its quite new and wonderful properties. Consider the population numbers at sequential moments, which corresponds to

a real procedure of counting the species (or cells) in a population. The dependence of the numbers at a time step numbered $n+1$ on the numbers at the preceding step $n$ can be written as

$$x_{n+1} = r x_n (1 - x_n) \qquad (4)$$

The behavior of the variable $x_n$ in time as dependent on the parameter $r$ can be characterized not only by unbounded growth, as it was in the continuous model (3), but also be oscillating or quasistochastic, as it is shown in Fig. 2 on the left. The parameter of own growth rate $r$ increases in the downward direction. The curves representing the dependence of the numbers at a given moment ($t+1$) on the numbers at preceding moment $t$ are depicted in Fig. 2 on the left; This rate increases at small numbers and, at higher numbers, decreases and then vanishes. Dynamic type of the population growth curve depends on the growth rate at small numbers, i.e., is determined by the derivative (by the tangent of inclination angle of this curve) at zero that is determined by the coefficient $r$. For small $r$ ($r < 3$), the population number tends to a stable equilibrium. When the diagram on the left becomes steeper, the stable equilibrium passes into stable cycles. As the numbers increase, the cycle length increases, and the values of numbers repeat in 2, 4, 8, ... $2^n$ generations. At the value $r > 2.570$, the chaotization of solutions happens. At $r$ sufficiently large, the population dynamics demonstrates chaotic spikes (outbursts of the insect numbers). Equations of this type describe the numbers dynamics of seasonally proliferating insects with not overlapping generations.

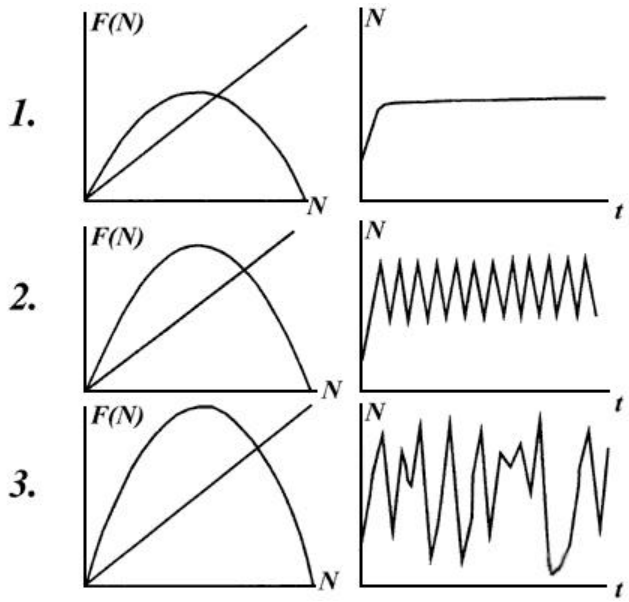


Fig. 2: (a) dependence of the numbers at subsequent step on the numbers at preceding step and (b) behavior of the numbers at different values of the parameter $r$ for the discrete model of logistic growth (3): (1) bounded growth; (2) oscillations; (3) chaos.

The discrete description proved to be instrumental for the systems of most different nature. The representation of dynamic behavior of a system at a plane in the coordinates $[x_t, x_{t+T}]$ allows one to determine if the observed system is oscillatory or quasistochastic. For example, such representation of the cardiogram data made it possible to establish that normal systoles of human heart are of irregular character, while in the period of breast-pang fits or in a preinfarct state, the systolic rhythm becomes strictly regular. Such a **«rigid»** regime "aggravation?" is a protective reaction of organism in a stress situation and points to the danger to the life of system.

### 3.3. Constraints with respect to a substrate. The models of Monod and Michaelis–Menten

Shortage of food is one of the limits for growth (in microbiological language, **substrate limitation)**. It is well known from biological studies that, under the conditions of the limit by substrate, the growth rate increases proportionally to the substrate concentration, and in the abundance of substrate, arrives at a constant value determined by genetic capabilities of population. For a certain period the population numbers increase exponentially, until the growth rates starts being limited by some other factors. The dependence of the growth rate $R$ in formula (1) on the substrate can be presented in the form

$$R(S) = \frac{m_0 S}{K_S + S} \tag{5}$$

Here, $\hat{E}_S$ is a constant equal to the substrate concentration, at which the growth rate is equal to the half of maximal; $m_0$ is the maximal growth rate equal to $r$ in (2). Eq. (5) was written for the first time by outstanding French biochemist Jacques Monod (1912--1976). In collaboration with Francoise Jacob, he developed a concept on the role of transport ribonuclein acid (messenger) – mRNA- in the proliferation apparatus of a cell. As a development of the concepts on gene complexes, which they have called the operons, Jacob and Monod postulated the existence of a gene class that regulates the functioning of other genes by affecting the synthesis of RNA. This mechanism came to be completely for bacteria, and both scholars (and also Andre L'vov) were awarded by Nobel prize in 1965. Jacques Monod was also a philosopher of science and an exceptional writer. In his famous book "Chance and Necessity" (1971), (Monod) speaks out his thoughts on random origin of the life on earth and on the evolution, and also on the role of man and his responsibility for the processes that occur on the earth.

The Monod model (5) coincides in form with the Michaelis--Menten equation (1913) that describes a dependence of the fermentative reaction rate on the substrate concentration under the condition when the total number of enzyme molecules is constant and much smaller than the number of substrate molecules:

$$m(S) = \frac{m_0 S}{K_M + S} \tag{6}$$

Here, $\hat{E}_i$ - is the Michaels constant, one of most important quantity in enzyme reactions, determined experimentally and having the sense and dimension of the substrate concentration, at which the reaction rate is a half of maximal. The Michaels--Menten law is derived on the basis of chemical kinetics equations and describes the formation rate of a product according to the scheme:

$$E+S \hat{U} [ES] \hat{U} E+P.$$

The Michaels--Menten formula (6) reflects deeper regularities in the kinetics of enzyme reactions that, in turn, determine the vital activity and growth of microorganisms described by empirical formula (5); this determines the similarity of Eqs. (5) and (6).

### 3.4. Competition. Selection

Biological systems interacts with each other at all levels, be it the interaction of macromolecules in the process of biochemical reactions or the interaction of species in populations. The interaction can occur in structures, then a system can be characterized by a certain set of states, which happens at the level of subcellular, cellular,

and organism structures. Kinetics of the processes in structures is described in mathematical models, as a rule, by the systems of equations for probabilities of the states of complexes.

In the case, when the interaction occurs at random, its intensity is determined by the concentration of interacting components and by their motility, the generalized diffusion. These are the concepts that are conventional in the basic models of the species interaction. The monograph by Vito Volterra "Mathematical Theory of the Struggle for Existence" (1931), in which mathematical models of the species interaction were considered, became a classical book. In this book, properties of biological objects and their interactions are postulated in a mathematical form and then examined as mathematical objects.

Vito Volterra (1860--1940) acquired the worldwide popularity with his works in the field of integral equations and functional analysis. Beside pure mathematics, he was interested in the application of mathematical methods to biology, physics, and social sciences. For the years in Italian Air Forces, he was seriously engaged in the research on military engineering and technology (problems in ballistics, bombing, and echo sounding). This personality combined the talent of scientist and the temperament of an active politician, principal opponent of fascism. He was the only Italian senator who voted against the passage of power to Mussolini. When, in the years of fascist dictatorship in Italy, Volterra had worked in France, Mussolini, who wanted to attract the world-wide famous scholar to his side, proposed him various high positions in fascist Italy, always received a decisive refusal. The antifascist position made Volterra to reject the chair of the Rome University and the membership in Italian academic societies.

Volterra got seriously interested in the dynamics of populations starting with 1925, after the discussions with a young zoologist Umberto D'Ankona, future husband of his daughter, Louisa. D'Ankona, examining the statistics of fish markets in Adriatic, has established a curious fact: when in the years of the First World War (and immediately after) the fishing intensity dropped sharply, the relative portion of predator fish in a catch had increased. This effect was predicted by the model "predator--victim" proposed by Volterra.

Volterra assumed, by analogy with statistical physics, that the interaction intensity is proportional to the probability of meeting (collision probability for molecules), that is, to the product of concentrations. These and some other assumptions (see 6.3.6.2), made it possible to construct a mathematical theory of the interaction between populations of the same trophic level (competition, symbiosis) or different trophic levels (predator-pray, parasite--host).

The simplest of these models, the model of selection on the basis of competitive relations, works in considering competitive interactions of any nature: biochemical compounds of various types of optical activity, competing cells, species, and populations. Its modifications are applied when describing the competition in economy. Let us to consider two absolutely identical species with the same proliferation rate that are antagonists, that is, when meeting, they suppress each other. A model of their interaction can be written as (Chernavskii, 1984)

$$\begin{aligned} \frac{dx}{dt} &= ax - bxy \\ \frac{dy}{dt} &= ay - bxy \end{aligned} \qquad (7)$$

According to this model, symmetric state of the existence of both species is unstable: one of interacting species inevitably dies out, while another proliferates infinitely. The introduction of a limit in substrate (type 5) (eq.5) or a system factor (type 2) (eq.2) allows the construction of models, in which one of species survives and attains

certain stable numbers. They describe the Gause –competition principle well known in experimental ecology, according to which only one species survives in every ecological niche.

In the case, when the species possess different own growth velocities, the coefficients in autocatalytic terms are different, and the system's phase pattern becomes nonsymmetrical. At various relations of parameters in such a system two possibilities exist: the survival of one of two species and extinction of another (if mutual suppression is more intense than the self-regulation of the numbers) and the coexistence of both species (when mutual suppression is less then the self-limitation of the number of each species).

### 3.5. The Jacob and Monod trigger system

The Jacob—Monod model of alternative synthesis of two ferments, presented in Fig. 3a, is one more classic bistable system. A gene-regulator of each scheme synthesizes an inactive repressor. This repressor, combining with the product of opposite system of the enzyme synthesis, forms an active complex. The active complex, reversibly reacting with a portion of the structural gene, the operon, blocks the synthesis of mRNA. Thus, the product of the second system $P_2$ is a corepressor of the first system, while $P_1$ is a corepressor of the second system. One, two, and more molecules can participate in the corepression process. Obviously, at such a character of the interaction, the second system will be blocked by intense activity of the first system and vice versa. Models of such system were proposed and thoroughly examined by B.C.Goodwin and D.S.Chernavskii. After corresponding simplifications, the equations describing the synthesis of the products $P_1$ and $P_2$ take the form:

$$\frac{dP_1}{dt} = \frac{A_1}{B_1 + P_2^m} - q_1 P_1, \qquad \frac{dP_2}{dt} = \frac{A_2}{B_2 + P_1^m} - q_2 P_2. \tag{8}$$

Here, $P_1$ and $P_2$ are the products concentrations, $A_1$, $A_2$, $B_1$ and $B_2$ are expressed through the parameters of their systems. The power index $m$ shows, how many molecules of the active repressor (compounds of molecules of the product with molecules of inactive repressor that is assumed to be in abundance) combine with the operon to block the synthesis of mRNA. A phase pattern of the system (trajectories of a system under different initial conditions on the coordinate plane, where parameters of the system are marked on the axes) at $m = 2$ and certain relations between the remaining parameters is shown in Fig. 3b. It is if a trigger character, like the phase pattern of the system of two competing species. The similarity suggest that the competition of species, enzymes, and states underlies the ability of a system to switching. The possibility of a trigger to switch from one stationary state to another is an important aspect in the models of cellular cycle, differentiation, and in other models. A system can be «thrown» over the separatrix in two ways: by adding a sufficient amount of the substance that was minimal in the initial state, or parametrically, having changed the character of the phase pattern so that the initial state of the system becomes unstable (the transition through the saddle–node bifurcation) and the system acquires only one stable steady state that was separated by a separatrix from the initial state. This is the regulation type that is proposed in the models of the cellular cycle. Moreover, the change of the system's parameters can be conditioned by genetic program, for example, in the case of cellular cycle, occur in the process of the cell's growth.

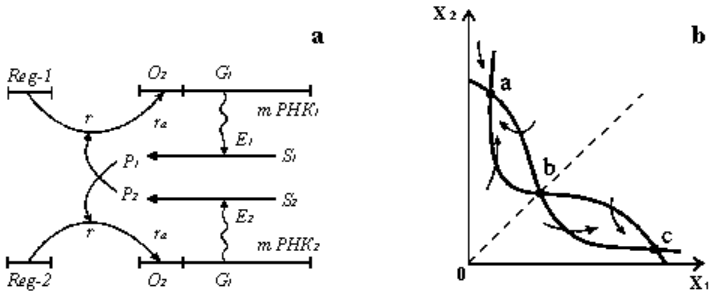


Fig. 3. (a) Jacob–Monod scheme for the synthesis of two enzymes; (b) phase pattern of a trigger system. .

### 3.6. Classic Lotka–Volterra models

The simplest nonlinear models of the interaction between chemical substances in the Lotka equations and between species in the Volterra models made it possible, for the first time, to understand that selfoscillations are possible in an energetically rich system due to specificity of the interaction between its components. Lotka considered his equation in 1925 in the book «Elements of Physicochemical Biology»; it describes a system of the following chemical reactions:

**À þ X þ Y þ B þ**

In some volume, the substance A is in abundance. Molecules of A turn convert into molecules of X (the zero level reaction) at a constant rate (the constant $k_0$). The substance X can convert into the substance Y, and the rate of this reaction is the higher, the higher the concentration of the substance Y (the second order reaction). This is shown by reverse arrow over the symbol Y in the scheme. In turn, molecules of Y decompose irreversibly and, as a result, the substance B forms (the first order reaction). The system of equations describing this reaction has the form:

$$\begin{aligned} \frac{dx}{dt} &= k_0 - k_1 xy, \\ \frac{dy}{dt} &= k_1 xy - k_2 y \\ \frac{dB}{dt} &= k_2 y \end{aligned} \qquad (9)$$

Here, $x$, $y$, and $B$ are concentrations of chemical components. The first two equations of the system are independent of $B$, therefore, they can be considered separately. In this system, at certain values of the parameters, damped oscillations are possible.

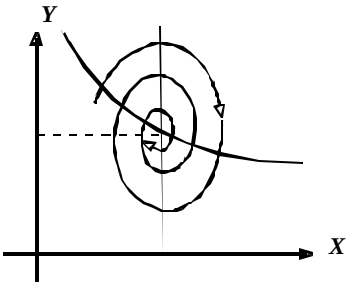


Fig. 4.: The Lotka model of chemical reactions. Phase pattern of a system for the parameter values corresponding to damped oscillations.

Classic Volterra equation describing the predator–prey interaction of species is a basic model of continuous oscillations. As in the models of competition (8), the interaction between species is described according to the principles of chemical kinetics: the decrement rate of the pray numbers ($x$) and the gain in the predator numbers ($y$) is believed to be proportional to their product

$$\begin{aligned} \frac{dx}{dt} &= ax - bxy \\ \frac{dy}{dt} &= cxy - dy \end{aligned} \qquad (10)$$

A phase pattern of this system is presented in Fig. 5. The numbers of preys ($x$) and predators ($y$) are marked on the axes. It is seen that the numbers of predators and victims preys oscillate in antiphase. The simplest Volterra model (10) has an essential drawback: oscillation parameters of its variables vary with fluctuations of parameters and variables of the system (nonrobust system).

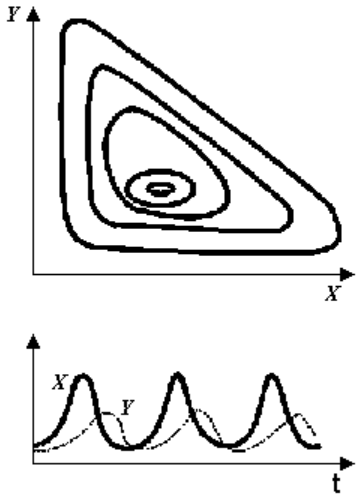


Fig. 5.: Volterra model predator–prey describing continuous oscillations of the numbers. (a) the phase pattern; (b) the dependence of the numbers of predators and preys on time.

### 3.7. Models of the interaction between species

In the middle of the 20th century, the interest to ecology and fast development of computing facilities, which made it possible to solve and examine the systems of nonlinear equations, stimulated the development of

population dynamics. This direction is dedicated to the search for general criteria to establish, what models can describe those or another features in the behavior of interacting populations and, in particular, stable oscillations.

These studies developed in two directions. The representatives of the first direction, describing the functions of model systems, prescribe only qualitative properties of these functions, such as positiveness, monotonicity, and the relation larger–smaller (Kolmogorov, 1972; Rosenzweig, 1969; Pielou, 1969; Mac'Atrur, 1971; Nisbet and Gurney, 1982).

Kolmogorov's work (1935, revised in 1972) can serve as an example. He considered a generalized model of the interaction between biological species, the scheme predator–prey or parasite–host. The model is presented by a system of two equations of general type:

$$\frac{dx}{dt} = k_1(x)\,x - L(x)\,y, \qquad \frac{dy}{dt} = k_2(x)\,y. \tag{11}$$

The following assumption are made in this model:

(1) Predators do not interact with each other, i.e., the proliferation coefficient of predators $k_2$ and the number of preys $L$ consumed by one predator at a unit of time are independent of $y$.

(2) The increment of the number of preys in the presence of predators is equal to the increment in the absence of predators minus the number of preys consumed by predators. The functions $k_1(x)$, $k_2(x)$ *and* $L(x)$ are continuous and defined on the positive semiaxes $x,y \geq 0$.

(3) $dk_1/dx<0$. This means that the proliferation coefficient of preys in the absence of predators monotonously decreases with the increase in the numbers of preys, which reflects the limitation of food and other resources.

(4) $dk_2/dx<0$, $k_2(0)<0<k_2(\infty)$. With the growth of the prey, numbers, the proliferation coefficient of predators decreases monotonously with increasing numbers of preys, passing from negative values (when there is nothing to eat) to positive values.

(5) The number of preys, consumed by one predator at a unit of time $L(x)>0$ for $N>0$; $L(0)=0$

An analysis of model (11) and its special cases, for example, the Rozenzweig model (1965, 1969), lead to the conclusion that regular oscillations in the system take place if the numbers of predators is limited by the presence of preys. If the numbers of preys, is limited by the presence of resources they need, or the numbers of predators are bounded not by the quantity of preys, but by some other factor, this leads to damped oscillations. Damped oscillations also happen in the presence of a refuges for prays, which makes them inaccessible for predators.

In the framework of the second direction, various modifications of the Volterra model were sequentially considered, obtained by including various additional factors into the original system (Yevlev, 1955; MacArthur, 1971; Giplin, 1973; Poluektov, 1980; Shafer, 1984; Dunban, 1984; Bazykin, 1985; Malchow and Medvinskii, 1995, 1998).

A modification of the Volterra model with regard to substrate limitations in the Monod form (Eq. (5) and a description of the self-limitation of the numbers (as in Eq. (2)) lead to the model examined by A.D.Bazykin in his book «Biophysics of Interacting Populations» (1985).

$$\frac{dx}{dt} = Ax - \frac{Bxy}{1+px} - Ex^2,$$
$$\frac{dy}{dt} = -Cy + \frac{Dxy}{1+px} - My^2 \quad , \tag{12}$$

System (12) combines properties of the basic equations (1), (2), (5), and (10). At small numbers and in the absence predators, the prays ($x$) will proliferate by exponential law (1); the predators ($y$) in the absence of prays will die out also by exponent. If there are many species of this or another kind, then, according to the basic model (2), the Verhulst system factor works (the term $-Ex^2$ in the first equation and the term $-My^2$ in the second one). Intensity of the interaction between species is assumed proportional to a product of their numbers (as in model (10)) and described in the Monod (form model 5); the species-pray plays the role of substrate, and the species-predator plays the role of microorganisms. Parametric space of model (12) is divided into a number of domains with different character of the phase pattern. This model allows the description of complex types of behavior of interacting species: the presence of two stable steady states, dumped oscillations of the numbers, auto-oscillations, etc. Theoretical analysis of models of the interaction between species can be found in the book «Biophysics of Interacting Populations» by A.D.Bazykin and also in the books by Svirezhev and Logout, 1978, by Zaslavskii and Poluektov, 1988, and in others..

Computing facilities made it possible to apply the results obtained with the models (11), (12) to concrete populations, in particular, to the problems of optimal fishery (hunting, etc) and to the development of biological methods of the struggle with insect-pest. The development of criteria for the nearness of a system to dangerous boundaries, after which the system ceases to exists or passes into a qualitatively another state. In so doing, character of the dynamics of a population changes dramatically, for example, the population passes from monotonous growth to sharp oscillations of its numbers or simply dies out. Such boundaries are referred to as **bifurcational** ones. An analysis of model properties shows that very slow restoration of the numbers after the impact of an unfavorable factor is one of indicators of the nearness to a dangerous boundary. A change in a form of the oscillations of predator and pray numbers is also an indicator of danger. If nearly harmonic oscillations become relaxational, that is, characteristic times of the changes in numbers start growing more and more different with the amplitude increasing in time, this can result in the loss of the system's stability or in the extinction of one or both species.

### 3.8. Models of the enzyme catalysis

Enzymes are highly specialized catalysts accelerating the rate of biochemical reactions by hundred thousand and million times. Any enzymatic transformation starts with the fixation of substrate molecules by an active center of enzyme and completes by breaking these fixations. For the first time, the hypothesis on the formation of a liable substrate–enzyme complex was suggested by Brown and Anry in 1902. Trying to qualitatively explain the phenomenon of the saturation of amialase reactions by substrates, Anry in 1904 has suggested that the reaction of the enzyme substrate complex formation is in the state of equilibrium and derived the equation of initial reaction rate

$$m(S) = \frac{m_0 S}{K_M + S}$$

Michaelis and Monod in 1914 and later Briggs and Holane in 1925 have arrived at a similar equation assuming quasi-stationary character of the enzyme–substrate complex formation reaction. In 1943, Chance has experimentally confirmed the formation of such a complex by a spectrophotometric method and traced the changes in its concentration in the course of the reaction catalyzed by the enzyme peroxidase. In 1930, Holdane has extended theoretical concepts on the enzyme–substrate complex to the case of two-substrate and reversible reactions and postulated the existence of different enzyme –substrate, enzyme–product, and enzyme–inhibitor intermediate complexes. At presence, a great number of such complexes have been examined.

The inclusion of an inhibitor to the system, in particular, in the case when the substrate molecules play the role of an inhibitor and form both active and inactive complexes with the substrate, lead to more complex and nonlinear expression for the rate of reaction:

$$v = \frac{k\ s}{K_m + s + s^2 / K_s}$$

Such type of nonlinearity entails important properties of enzyme systems: manifoldness of steady states, oscillatory character of the changes in variables, and quasi-stochastic regimens. An analysis of kinetic features of various schemes of enzyme reactions with the help of representations in a phase plane and in a parametric space is presented in detail in (Ivanitsky et al, 1978, Murray, 1993)

### 3.9. Model of a continuous microorganism culture

Microbiological populations are a good experimental object for verifying ideas and results of both ecological and evolutionary ideas. Microorganisms are mostly one-cellular organisms; they possess a high surface–volume ratio and, therefore, high intensity of the exchange with environment, high proliferation rates, and large mass increments. Usually, the apparatus of ordinary differential equations is used for mathematical description of microbial populations. As for microbiological systems, such a description is much better justified than as related to the land and water highest organisms. In laboratory investigations, *in vitro*, more than $10^{10}$ individuals are usually treated. In a large industrial fermentor, about $10^{16}$–$10^{17}$ yeast-cells can live simultaneously. A deviation of the numbers from average values caused by random factors is proportional to $1/\sqrt{N}$, where $N$ is the population numbers. Thus, for numerous populations, one may construct a model in terms of average numbers or concentrations. Relative homogeneity of a microorganism culture in the cultivator's volume is another factor that allows the spatial effects to be disregarded.

In microbiology, an empirical approach to the construction of models is commonly used. Of all the factors that affect the growth of a cell, a limiting one is usually chosen, and then a dependence of the growth rate on its concentration is found empirically. Generally, the cell concentration kinetics in a homogeneous culture is described by the equation

$$\frac{dx}{dt} = x(m - v) \tag{13}$$

Here, $x$ is the cell concentration in a cultivator, and $\mu$ is a function describing the proliferation of a population. It may depend on the cell concentration $x$, substrate concentration (denoted usually by $S$), temperature, pH of a medium, and on other factors; $\nu$ is the rate of elution

To support a culture in the region of unlimited growth, external regulators are required. In the case of growth limited by an external factor, for example, by the shortage of substrate, steady working regime of cultivator is attained by self-regulation. This takes place in natural lotic systems and in the most frequently used type of continuous cultivators, hemostate, in which the dilution rate for a culture or the flow velocity is prescribed. Monod (1950) and Herbert (1956) were the first in developing the hemostate theory, which is continuously refined since then. In modern models, structural nonhomogeneity of biomass, age-related nonhomogeneity, and other details of cultivating are taken into account.

Under the condition of continuous mixing, it is possible to assume that the total cultivator volume is uniformly filled, and that the concentrations of a substrate and cells are the same at every point of cultivator. Then, the behavior of these concentrations in time can be described by the system of ordinary differential equations:

$$\begin{aligned} &(a)\quad \frac{dx}{dt} = \mu(S)x - Dx, \\ &(b)\quad \frac{dS}{dt} = DS_0 - \alpha\,\mu(S)x - DS, \\ &(c)\quad \mu(S) = \frac{\mu_m S}{K_m + S} \end{aligned} \tag{14}$$

Here, $S$ is the substrate concentration; $x$ is the cell concentration in a cultivator; $S_0$ is the concentration of a substrate loaded into cultivator; $D$ is the flow (delusion) velocity of a culture; and $\alpha$ is an «economical coefficient» indicating what portion of consumed substrate is spent to the biomass increment. The meanings of other terms in the right-hand sides of equations are as follows: $\mu(S)x$ is the biomass increment at the account of consumed substrate; $-Dx$ is the outflow of biomass from cultivator; $-\alpha\mu(S)x$ is the amount of substrate consumed by the culture cells; $DS_0$ is the inflow of substrate into cultivator; and $-DS$ is the outflow of unutilized substrate from cultivator. The growth rate of biomass is assumed to be dependent only on the substrate concentration according to the Monod formula (5).

The model considered is simplified and, to describe real processes, requires some complements. For example, at high concentrations, the substrate can exert an inhibiting action, and then the formula for the growth rate should be written as

$$\mu(S) = \frac{\mu_m S}{K_m + S + AS^2} \tag{15}$$

In a system with such dependence of the growth rate on the substrate, trigger regimes are possible, i.e., the presence of two stable steady states and the dependence of steady substrate and biomass concentrations on the initial conditions (on the volume of yeast and on the initial biomass concentration).

The growth rate of biomass can also be influenced by the concentration of metabolism products in the medium that surround a cell. Then, two equations that describe the dynamics of the biomass concentration in the continuous cultivation process must be supplemented by the third equation describing the dynamics of metabolism products concentration

$$\mu(S) = \frac{\mu_m S}{(K_m + S) + (K_P + P)} \tag{16}$$

Formula (16) is well known as the Monod–Jerusalemskii formula.

In biotechnology, for calculating the optimal cultivation regimes, the formulas are applied that take into account other peculiarities of the metabolism of the microorganisms themselves, and also of the conditions of their cultivation.

### 3.10. Age structure of populations

The homogeneity of cells in a microbe population is always relative. The age structure plays an important role in the growth processes in microbe populations. Only the cells of a certain age (or certain size) are capable of dividing, i.e., of increasing their numbers. The age heterogeneity of a population can be a cause of complex nonmonotone dynamics of its numbers.

The simplest two-age model of a cell population was proposed by N.V.Stepanova (1985). The population is divided into two groups of cells: the young and old ones. The cells of the first group grow intensively, but have not reached physiological maturity and are incapable of dividing. The members of the second group are capable of dividing, and the fission process can be delayed with the help of inhibitors. Equations for the numbers of young ($N_1$) and old ($N_2$) cells have the form

$$\begin{aligned} \frac{dN_1}{dt} &= \frac{2}{T_2} N_2 - \frac{1}{T_1} N_1 - D N_1, \\ \frac{dN_2}{dt} &= \frac{1}{T_1} N_1 - \frac{1}{T_2} N_2 - D N_2 \end{aligned} \qquad (17)$$

Here, $T_1$ is the average maturation time of a young cell; $T_2$ is the average reproduction period of an old cell; and $D$ is the flow velocity. The multiplier 2 in the first equation reflects the fact that an old cell divides into two young ones. An assumption that the old cells can secret an inhibitor allows the description of oscillatory regimes in the system.

#### 3.10.1. The Leslie matrices

A specification of the population age structure leads to a class of *matrix models*, first proposed by Leslie (1945, 1948). It is assumed that a population contains $n$ age groups and those with the numbers $k$, $k+1$, …, $k+p$ procreate offspring. The proliferation occurs at certain moments $t_1$, $t_2$, , $t_n$. Then, at an initial moment $t_0$, the population is characterized by the column vector

$$X(t_0) = \begin{vmatrix} x_1(t_0) \\ x_2(t_0) \\ \\ x_n(t_0) \end{vmatrix} \qquad (18)$$

The vector $X(t_1)$ that characterizes the population at the next moment, for example, in the year, is related with the vector $X(t_0)$ by the passage matrix $L$ as follows:

$$X(t_1) = \begin{Vmatrix} x_1(t_1) \\ x_2(t_2) \\ \\ x_n(t_n) \end{Vmatrix} = \begin{Vmatrix} \sum_{i=k}^{k+p} a_i x_i(t_0) \\ b_1 x_1(t_0) \\ \\ b_{n-1} x_{n-1}(t_0) \end{Vmatrix}. \tag{19}$$

Let us explain the meaning of the vector on the right-hand side. The offspring that has appeared for a unit of time from all reproductive groups joins the group 1. It means that the first component of the vector is**:**

$$x_1(t_1) = \sum_{i=k}^{k+p} a_i x_i(t_0) = a_k x_k(t_0) + a_{k+1} x_{k+1}(t_0) + \ldots + a_{k+p} x_{k+p}(t_0). \tag{20}$$

The second component is obtained with regard to the passage of individuals, which were in the first group at the moment $t_0$, into the second group and with regard to possible death of a part of these individuals:

$$b_1 x_1(t_0),\ 0 < b_n < 1.$$

The third group and all remaining components are obtained similarly. All individuals, which were in the last age group at the moment $t_0$, die out at the moment $t_1$. Therefore, the last component of the vector $X(t_1)$ is composed only of the individuals that have passed from the preceding the group:

$$x_n(t) = b_{n-1} x_{n-1}(t),\ 0 < b_n < 1.$$

The coefficients $\alpha$ and $\beta$ are the birthrate and survival rate, respectively. They were constant in the Leslie models; in more complex models, they can be represented by more complex functions depending on time, substrate concentration, and population size.

The vector $X(t_1)$ is obtained by multiplying the vector $X(t_0)$ by the matrix $L$:

$$X(t_1) = LX(t_0) \tag{21}$$

this matrix has the form

$$L = \begin{Vmatrix} 0 & 0 & 0 & a_k & a_{k=1} & a_{k=p} & 0 & 0 \\ b_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ & & & & & & & \\ 0 & 0 & & & & & 0 & 0 \\ 0 & 0 & & & & & b_{n-1} & 0 \end{Vmatrix} \tag{22}$$

The diagonal consist of zeros, the survival coefficients $b$ are below diagonal elements, and the terms that characterize the number of individuals born in corresponding groups are in the first raw. All remaining elements of the matrix are equal to zero. Thus, if the structure of the matrix $L$ and the initial population state (the column vector $X(t_0)$) are known, it is possible to forecast the state of the population at an arbitrary moment:

$$X(t_k) = LX(t_{k-1}) = L^k X(t_0) \tag{23}$$

The leading eigenvalue of the matrix $L$ yields the rate, at which a population proliferates, when its age structure becomes stable.

### 3.10.2. Continuous models of the age structure

Continuous models deal with a continuous function of the age distribution of organisms rather than with the numbers of individual groups. An equation for the distribution function density was suggested by MacCendrick in 1926, «rediscovered» by von Ferster in 1959 and wears the name of the latter. The equation represents a differential form of the conservation law for the numbers of individuals. There are two independent variables in this equation: $t$, the time, and $\tau$, the age which is counted from the moment of birth; $n(t,\tau)d\tau$ is the number of individuals whose age is in the interval $[\tau,,\tau+d\tau]$. The total number of the individuals of all ages at a moment $t$ is determined by the integral $N(t) = \int_0^\infty n(t,\tau)d\tau$. The Forster equation has the form

$$\frac{\partial n(t,\tau)}{\partial t} + \frac{\partial n(t,\tau)}{\partial \tau} = -[D(t) + w(t,\tau)n(t,\tau)] \tag{24}$$

with the initial condition $n(0,\tau)=g(\tau)$

There is the derivative $dn/d\tau$ on the left-hand side of Eq. (24), moreover, it is taken into account that $d\tau/dt=1$; the terms on the right-hand side describe the processes that lead to the change in the number of the cells of certain age. The decrement of cells can be induced by various causes, such as the mortality and migration; for a lotic culture, all these causes can be disregarded as compared to the flow of cells through cultivator. The flow velocity $D(t)$ is independent of the age of cells, but can depend on time. The term $-w(t,\tau)u(t,\tau)$ describes the decrement of cells form a given age interval during the fission into the daughter cells at a rate of $w$. The increment of the numbers resulting from the proliferation occurs in the zero age and is a part of the boundary condition at $\tau=0$:

$$n(t,0) = k\int_0^\infty n(t,\tau')W(t,\tau')d\tau' \tag{25}$$

Here, $k$ is the offspring numbers in a single proliferation act, $W(t,\tau')d\tau'$ is the probability of the proliferation of a parent in the age interval $[\tau',\tau'+d\tau']$ that is equal to the specific proliferation rate

$$W(t,\tau)d\tau = w(t,\tau)d\tau, \quad w = W\frac{d\tau}{dt} = W \tag{26}$$

If the parents remain in population after the proliferation (yeast), then $W(t,\tau)$ is the density of unconditional probability of a fission at the age $\tau$ (the fission age distribution function). If the cells drop out of their age group after the fission (algae, bacteria), then $W(t,\tau)$ is the density of conditional probability of fission at the age $\tau$ if the cell has reached this age without fission.

There are models that describe the distribution of cells with respect to sizes and masses. They are easier to correlate with experimental data, since there are experimental methods for determining the sizes of cells. The methods of micromeasurements are actively developed that also allow the other parameters of individual cells (for example, photosynthetic activity, chlorophyll content in algae, intracellular pH, etc.) to be measured. The methods of lotic microfluorimetry are applied ever wider, which makes it possible to register spectral characteristics of hundreds and thousands of microorganisms and construct corresponding distributions of the indicators of individuals. Information about the evolution of these distributions presents new possibilities for estimating the state of microorganism populations, for example, the state of the plankton populations in seas, of the microorganisms in soil, and of the blood cells.

**4. Oscillations and rhythms in biological systems**

Periodic change in various characteristics is typical of biological systems. The period of these variations can be related to periodic changes in the life conditions on the earth, such as the seasons of the year and the alternation of day and night. However, many periodic processes have a frequency not related explicitly to the external geo-space cycles. These are the so-called "biological clocks" of various nature: the oscillations of biomacromolecules, biochemical oscillations, rhythms of breathing, cordial contractions, periodic changes in body temperature, and up to population waves. Regular periodic change in the quantities represents one of the types of stationary (time-independent) regimes of a system's behavior. The regimes that become settled with time and then remain unchanged are called the attracting ones or the *attractors*. If oscillations in a system have constant period and amplitude, settle independently of initial conditions and are supported due to properties of the system itself rather than because of periodic forcing, then such a system is called the *self-oscillating system.* In the phase plane, the attracting regime of self-oscillations has a closed isolated phase trajectory, the *limit cycle*. Continuous oscillations in such systems are stable, since deviations from a stationary oscillatory regime are damping. Class of self-oscillatory systems includes the oscillations in metabolic systems, periodic photosynthesis processes, variations of the calcium concentration in a cell, oscillations in a cordial muscle, and variations in the numbers of animals in populations and communities.

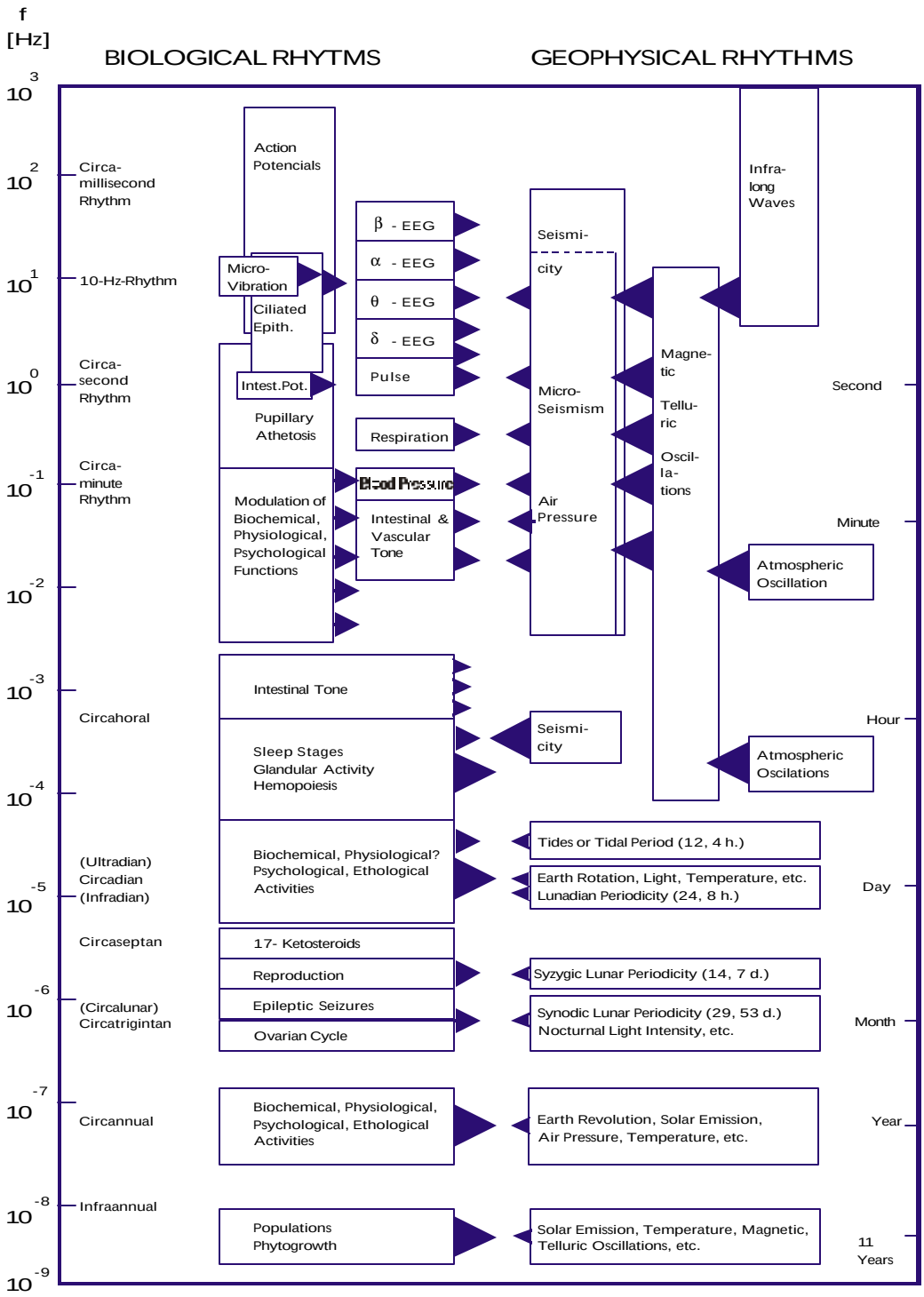


Fig. 6. Biological and geophysical rhythms in nature.

### 4.1. Oscillations in Glycolysis

The **glycolysis** is a classic example of an oscillatory biochemical reaction. In the glycolytic process, the glucose and other sugars decompose, moreover, the compounds containing six molecules of carbon turn into

tricarbon acids that include three carbon molecules. Due to the excess of free energy in the glycolysis process, two ATP molecules form per one molecule of the six-carbon sugar. The main role in the generation of observed concentration oscillations of the reaction components fructose-6 phosphate, fructose -1, 6 phosphate, and restored NAD, (nicotine-aminadenin-dinucleotide) belongs to the key enzyme of the glycolytic path, phosphofructokinase (PPK). A simplified scheme of reactions is represented in Fig. 7

$$\begin{array}{ccccc} & & \textit{Activation} & & \\ & & \downarrow & & \\ [\mathrm{Gl}] & \rightarrow & \mathrm{F6P} & \rightarrow & \mathrm{FP_2} \rightarrow \\ & & (\boldsymbol{x}) & & (\boldsymbol{y}) \end{array}$$

Fig. 7. Simplified scheme of the glycolysis reactions.

In scheme in Fig 7, [Gl] is the glucose, F6P is the fructose-6-phosphate**,** substrate of the key reaction, and ($FP_2$) – fructosebiphosphate is a product of this reaction, which is a substrate in the next stage. The both reactions are catalyzed with enzymes. In dimensionless coordinates, the system of equations that governs the reactions can be written as

$$\begin{aligned} \frac{dx}{dt} &= k - c\,\frac{x}{(K_{mx}+x)}\frac{y}{(K_{my}+y)} \\ \frac{dy}{dt} &= c\,\frac{x}{(K_{mx}+x)}\frac{y}{(K_{my}+y)} - q\,\frac{y}{(K'_{my}+y)} \end{aligned} \qquad (27)$$

Here, the dependencies of reaction rates on the variables are written in the Michalis-Menten (Monod) form, as in Eq. (6). The kinetics of the changes in variables and the phase patterns of the system at various values of parameters are presented in Fig. 8. Oscillatory reactions in the glycolysis system were first predicted with a mathematical model (Higgis, 1964) and only after that registered experimentally in a laboratory with the help of the method of differential spectrophotometry (B.Chance).

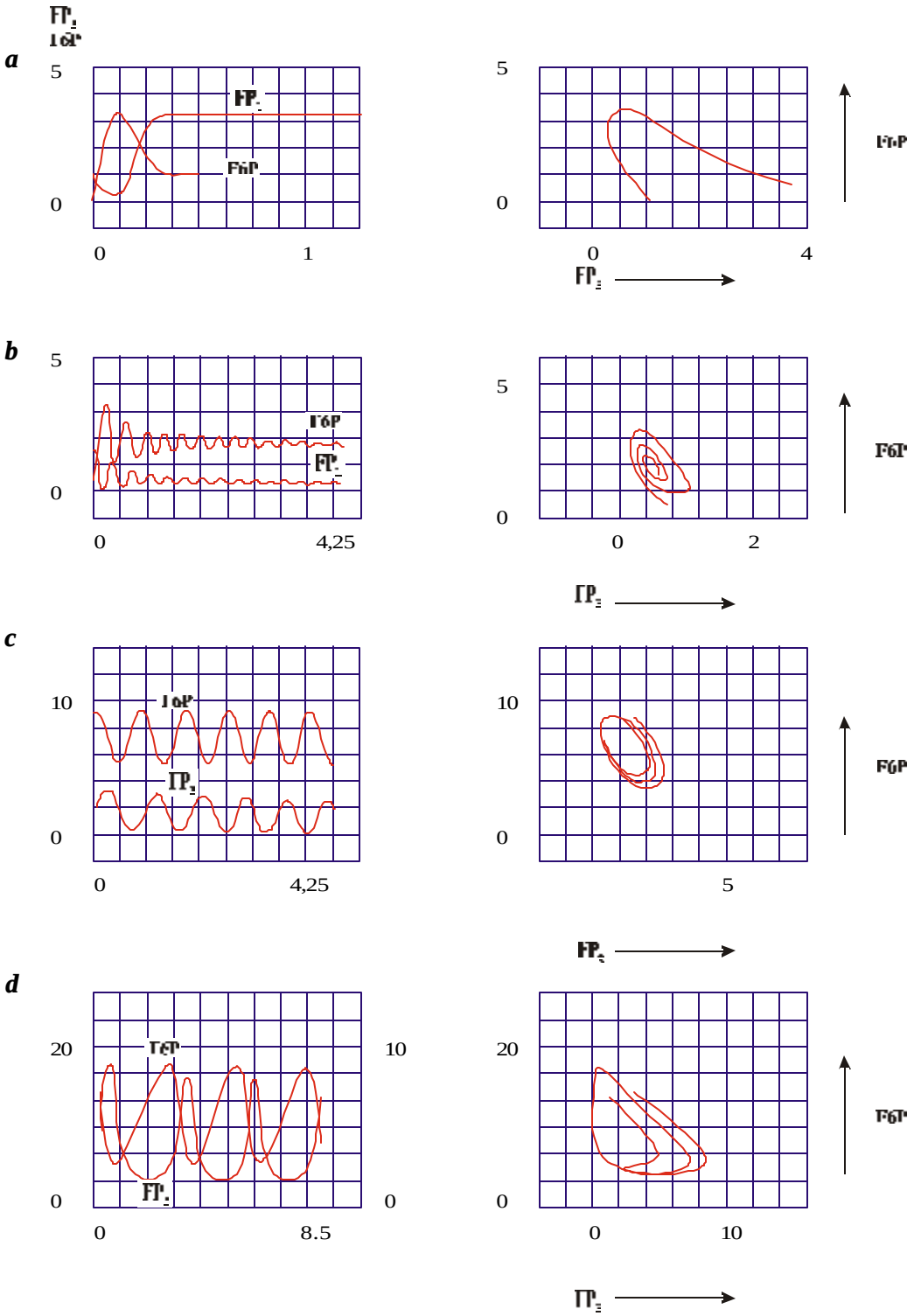


Fig. 8. Glycolysis model. Kinetics of the concentration variations: fructose-6-phosphate (x), fructosebiphosphate (y) (on the left) and a phase pattern of the system (on the right); (a) oscillationless process; (b) damping oscillations; (c) quasiharmonic oscillations; (d) relaxation oscillations.

### 4.2. Intracellular calcium oscillations

In many types of living cells, the oscillations of intracellular calcium concentration are observed; their period can vary in the range from 0.5 to 10 min. The simplest scheme of the processes that lead to the enzyme-conditioned calcium concentration oscillations is presented in Fig. 9. For the first time, these oscillations have been observed by End with co-authors (1970) on the of skeletal muscle cells, by Fabiato (1975) on the cells of sarcoplasmatic reticulum of an ox heart, and later by many other researchers.

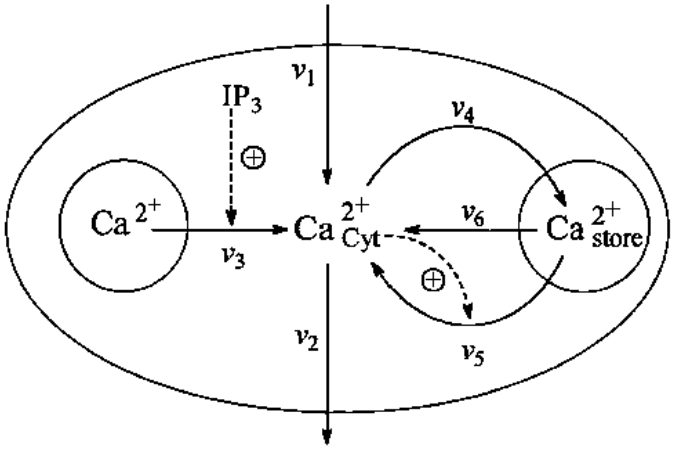


Fig. 9. Scheme of the processes, leading to intracellular oscillations of calcium concentration (Dupont, Goldbeter, 1983). Here, $IP_3$ is a receptor stimulating the oscillations.

A scheme and a model of these processes were proposed and described by Dupont and Goldbeter (1989, 1994). The following processes are considered: the inflow and outflow of calcium through a plasmatic membrane (velocity constants $v_1$ and $v_2$, respectively); the enzyme-activated release of calcium from the pool (velocity $v_3$); the active transport of cytosolic calcium into the pool ($v_4$); the release of calcium from the pool activated by the cytosolic calcium ($v_5$); free drain of calcium from the pool into the cytosol ($v_6$). A reduced model consists of two differential equations

$$\begin{aligned} \frac{dS_1}{dt} &= v_1 - v_2 + v_3 - v_4 + v_5 + v_6 \\ \frac{dS_2}{dt} &= v_4 - v_5 - v_6 \end{aligned} \qquad (28)$$

Here, $S_1$ is the calcium concentration in the cytosol; $S_2$ is the calcium concentration in the enzyme-sensitive pool. The expressions for velocities were proposed for the first time by Simogyi and Stuckin (1991):

$$v_2 = k_2 S_1; \quad v_4 = k_4 S_1; \; v_5 = \frac{k_5 S_2 S_1^{nH}}{K_{0..5}^{nH} + S_1^{nH}}; \quad v_6 = k_6 S_2 \qquad (29)$$

The model predicts the oscillations of the calcium concentration in time that are close to experimental (Fig. 10).

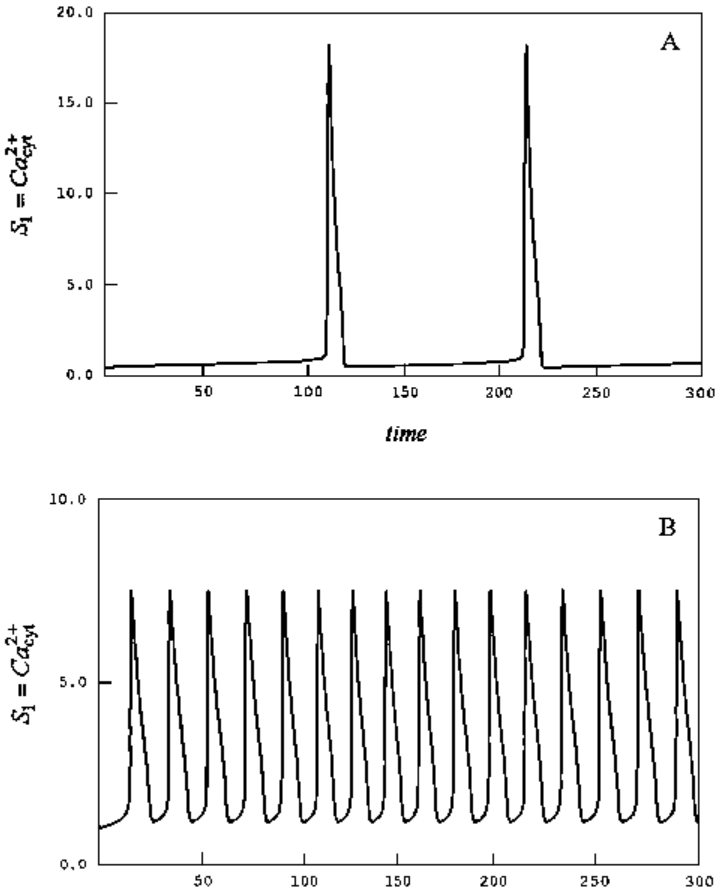


Fig. 10. Model of intracellular calcium concentration oscillations. The kinetics of calcium concentration for different values of parameters (Dupont, Goldbeter, 1983).

### 4.3. Cellular cycles

A cell duplicates its contents and divides into two cells in its life cycle. In an organism of a mammal, to support its life, millions new cells are produced every second. Perturbations in the cell proliferation are manifested as oncological diseases. This is why modeling of the cellular division regulation mechanisms attracts great interest.

Cellular cycle consists of two phases: the Mitosis (M-phase) includes the division of preliminarily duplicated nuclear material and the division of the cell itself, the cytokinesis, and takes about one hour. The interphase takes much longer: this period between two mitoses includes the growth stage $G_1$, the DNA replication phase (S), and the preparation phase $G_2$ for the division. The cell cycle is regulated by genes and by proteins-enzymes of two major classes. Cyclin-dependent protein-kinases (Cdk) induce a sequence of processes by phosphorilating individual proteins. The cyclines that are synthesized and decomposed in each new division cycle, become linked to the Cdk molecules and control their ability to the phosphorilation without cyclin the Cdk are not active. The number of these molecules-regulators is different in the cells of different types. In the division of a yeast cell, one Cdk and nine cylcines play the main role; they form new nine different cycline-Cdk complexes. In mammals, whose organization is much more complex, six Cdk and more than a dozen of cyclines have been examined. The exit of a cell from the $G_1$ and $G_2$ phases is controlled by the promoter-factor of the S-phase (SPF) and by the promoter-factor (MPF), which are the geterodimers. There exists a

special control point of the cellular cycle (Start), at which the growth terminates ($G_1$-phase) and the synthesis of DNA starts.

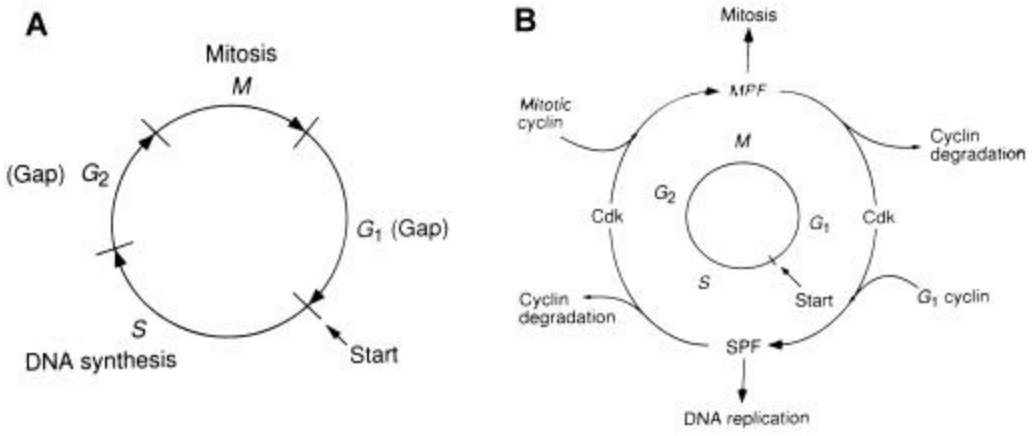


Fig. 11. Scheme of cellular cycle.

A simple model of this process was proposed by Tyson (1995). The existence of a transcription factor SBF is postulated, which can be in active $S_a$ and in passive $S_i$ forms. It passes into the active form under the action of the cycline Cln (N) and Start-kinase (Cdc28-Cln3) and becomes inactivated by another substance (E). The cycline is produced by the activation of SBF and degenerates. The SBF is activated by Cln and the start-kinase and inactivated by the phosphatase. A dimensionless model of these processes has the form

$$\frac{dn}{dt} = \frac{s}{k_s + s} - n,$$
$$\frac{ds}{dt} = (a + l\,n)\frac{1-s}{k_i + 1 - s} - m\frac{s}{k_a + s} \qquad (30)$$

The model has one or three stationary solutions (two stable solutions) depending on the values of parameters and describes a switch of the system from the $G_1$-phase into the S-phase as the parameter $\alpha$ increases (in the process of cellular growth).

The addition of two equations of similar type allows the description of a switch from the $G_2$-phase into the mitosis phase M. A complete model that takes into account other regulation enzymes in the phosphorelated and dephosphorelated form contains nine nonlinear equations (Novak, Tyson, 1993) and describes agreeably the division kinetics of the oocytes *Xenopus*. This model is applicable to the description of the division of other cells, with the parameters properly chosen. A great number of works was dedicated to the attempts of modeling a periodic impact on the cellular cycle aimed at the optimization of the parameters of x-ray, radio, and chemotherapy in treating the cells of oncological tumors.

In modern literature on mathematical biology, thousands of self-oscillating systems on various levels of living nature are considered. No doubts, the self-oscillatory character of these processes is an evolutionary invention of nature and their functional role has a number of aspects. Firstly, the oscillations make it possible to divide

processes in time, when several different reactions occur at the same time in the same compartment of a cell, organizing the periods of high and low activity of individual metabolites. Secondly, characteristics of the oscillations, their amplitude and phase, carry certain information and can play a regulatory role in the cascades of processes that occur on the levels of a cell and of a living organism. Finally, the oscillatory (potentially or really) systems serve as local elements of distributed active media capable of a spatial-temporal self-organization, including the morphogenesis processes.

Intracellular oscillations determine endogenous biological rhythms (biological clocks) inherent to all living systems. These are the rhythms that determine the periodicity of cellular division and control the time of birth and death of living organisms. The models of oscillatory systems of type (27)--(30) are used in the enzyme catalysis, theory of immunity, theory of trans-membrane ion transport, microbiology, and biotechnology.

## 5. Space–time self-organization of biological systems

All biological systems – biological macromolecules, cells, tissues, and biocenosis – are active distributed systems. The transformation of substances and energy in these systems occurs in individual elementary volumes related to each other by the substance transportation, diffusive or directed under the action of external forces or with the help of special adaptation mechanisms inherent to living organisms. Every elementary volume is a system open with respect to mass and substance that is far from thermodynamic equilibrium, moreover, the energy-carrying substances or other energy sources are distributed in space and connected between themselves by the fluxes of substance and energy. In such systems, the so-called autowave processes are possible: the propagation of pulses and excitation waves, the formation of stationary spatially inhomogeneous distributions of substances, and other self-organization phenomena (for details, see 6.3.6.3). Processes in excitable membranes of the nerve fibres, such as the nerve pulses, waves in the nerve networks of brain, and the excitation waves in muscles, are the most thoroughly examined. The waves of electric potentials propagate in the fibres of cordial muscle. Pathological states here in the form of arrhythmia and fibrillation are determined by the appearance of autonomous sources of waves, the reverberators. Other types of autowave processes manifest themselves in the morphogenesis processes in the tissue differentiation. Genetic systems of the protein biosynthesis are local reaction elements of such systems, and the transport processes are performed by the systems of active transmembrane transport. In some communities (collective amoebas), the cellular interaction is performed by secreting the substances-attractants (cyclic AMP). Mutual movement of the cells to a source of signals and their aggregation are of a wave character. Autowave processes are also in the basis of the motions in the walls of blood vessel channels, peristalsis of other sections of gastrointestinal tract, mechanical displacements of the cells on a plane surface, and other processes.

### 5.1. Life waves

The drive for growth and proliferation leads to the propagation is space, occupation of new habitat, and expansion of living organisms. The life propagates as a flame over a steppe during a steppe fire. This metaphor reflects the fact that the fire propagation (in a one-dimensional case, the propagation of a flame in a Bickford fuse) and the propagation of a species are described by the same model. The famous combustion model was independently proposed by Fisher (1937) and by Russian mathematicians Petrovskii, Kolmogorov, and Piskunov (1937), namely in a biological statement as the propagation model of a dominating species in space. The all three authors of this study are the outstanding Russian mathematicians. Academician Ivan Petrovskii (1901–1973) is the author of fundamental studies in the theory of differential equations, algebra, geometry, mathematical physics; he was the rector of Lomonosov Moscow State University (1951–1973). Andrey Kolmogorov headed Russian mathematical school in the probability theory and theory of functions, he is the author of fundamental works in mathematical logic, topology, theory of differential equations, theory of

information; he was an organizer of school and university mathematical education, and has written a number of studies based on biological statements.

Consider a statement of the problem on the propagation of a species in an active, i.e., rich of energy (food) medium. Let the propagation of a species at any point of the straight line $r>0$ is described by the function $f(x) = x(1-x)$. At an initial moment, the all domain on the left of zero is occupied by a species $x$ whose concentration is close to unity. On the right of zero, the territory is empty. At a moment $t = 0$, the species starts propagating (diffusing) to the right at a constant diffusion $D$. This process is described by the equation

$$\frac{\partial x}{\partial t} = f(x) + D\,\frac{\partial^2 x}{\partial r^2} \qquad (31)$$

In such a system, for $t>0$, a concentration wave starts propagating into the domain $r > 0$, which is a result of two processes: random motion of individuals (diffusion of particles) and the proliferation described by the function $f(x)$. With time, the wave front moves to the right and its form approaches a definite limit form. Propagation velocity of the wave is determined by a diffusion coefficient and by a form of the function $f(x)$; for the function $f(x)$ that vanishes at $x = 0$ and at $x = 1$ and is positive at intermediate points, the velocity is expressed by the simple formula: $l = 2\sqrt{Df'(0)}$.

An analysis of spatial translocations in the model predator–pray (10) shows that, in such a system, in the case of unlimited space, the waves of «escape and pursuit» start propagating (Chow and Tam, 1976). In a limited space, stationary spatially inhomogeneous structures (dissipative structures) settle, or the autowaves, depending on the system's parameters.

### 5.2. Autowaves and dissipative structures

Nonlinear interaction of the components in a system combined with transport processes leads to complex spatial and temporal behavior regimes of the system's components. The first model of such kind of interaction was examined by Turing in his work «Chemical Basis of Morphogenesis». Alan M. Turing (1912–1954), English mathematician and logician, became famed for his studies in computer logic and the theory of automation. In 1952, he published the first part of an investigation dedicated to mathematical theory of the structure formation in an initially homogeneous system where chemical reactions occur simultaneously, including autocatalytic processes accompanied by the energy consumption, and passive processes of transport–diffusion. The Turing work became classic, and its ideas are in the basis of modern theory of nonlinear systems, theory of self-organization, and synergetics. Consider the system of equations:

$$\begin{aligned} \frac{\partial x}{\partial t} &= P(x,y) + D_x\,\frac{\partial^2 x}{\partial r^2} \\ \frac{\partial y}{\partial t} &= Q(x,y) + D_y\,\frac{\partial^2 y}{\partial r^2}. \end{aligned} \qquad (32)$$

Equations of such a type are called the «*reaction–diffusion*» equations (see 6.3.6.3). In linear systems, the diffusion is a process that leads to the equalization of concentrations over the whole reaction volume. However, in the case of nonlinear interaction between the variables $x$ and $y$, the instability of homogeneous stationary state can arise, and complex spatio-time regimes form like the **autowaves** or *dissipative structures*. They are represented by stationary in time and inhomogeneous in space concentration distributions, maintained on the account of the dissipation of system's energy. The appearance of structures in

such systems is stipulated by the difference in the diffusion coefficients of reagents, namely, by the presence of a short-range «activator» with a small diffusion coefficient and of a long-range «inhibitor» with a large diffusion coefficient.

### 5.3. The basic model «Brusselator»

Such regimes in a two-component system were examined in detail on the basic model **«brusselator»** (Prigogine and Lefever, 1968), named after the Brussels scientific school headed by I.R.Prigogine, in which these investigations were carried out most intensively. Il'ya Prigogine (born in Moscow, 1917) worked in Belgium for all his life. From 1962, he is the director of International Solvey Institute for Physical Chemistry, and from 1967, the director of the Center of Statistical Mechanics and Thermodynamics of the Texas University, USA. In 1977, he won the Nobel Prize for his works on nonlinear thermodynamics, in particular, on the theory of dissipative structures. Prigogine is the author and co-author of the whole series of books: «Thermodynamic Theory of Structure, Stability, and Fluctuations», «Order out of Chaos», «Time Arrow», and others. In these books, he develops mathematical, physico-chemical, biological, and philosophical ideas of the theory of self-organization in nonlinear systems, examines the causes and regularities of the birth of «order **out of** chaos» in the energy-rich systems open for the fluxes of matter and energy, which are far from thermodynamic equilibrium, under the action of random fluctuations.

The classic «brusselator» model has the form

$$\begin{aligned} \frac{\partial x}{\partial t} &= A + X^2 Y - (B+1)\,X + \frac{\partial^2 x}{\partial r^2} \\ \frac{\partial y}{\partial t} &= BX - X^2 Y + \frac{\partial^2 y}{\partial r^2} \end{aligned} \qquad (33)$$

and describes a hypothetical scheme of chemical reactions:

$$\begin{array}{llll} A \Leftrightarrow X, & & 2X+Y \Leftrightarrow 3X, \\ B+X \Leftrightarrow Y+C, & & X \Leftrightarrow R \end{array}$$

The so-called three-molecule reaction, the conversion of two molecules $x$ and one molecule $y$ into $x$, is a key stage. Such a reaction is possible in the processes with participating enzymes with two catalytic centers.
The specification of the models of type (32-33) made it possible to describe the propagation of waves in a cordial muscle, formation of the plankton patches in the ocean (Malchow, Medvinskii) etc.

### 5.4. Models of morphogenesis

The nonlinearity of a reaction combined with the diffusion of substance provides for the possibility of spatio-time regimes, including the formation of spatial structures in an initially homogeneous system, the *morphogenesis*.

Models of the formation of the structures, stationary in time and inhomogeneous in space, the *«pattern formation»*, including models of the skin coloration of animals, are described in detail in the monographs J.D.Murray, «Lectures on Nonlinear Differential Equations», Oxford, 1977 and J.D.Murray, «Mathematical Biology», Springer, 1993. The coloration of the «leopard skin» type could appear in the reaction–diffusion system, in which the local interaction is described by the mechanisms similar to the Jacob and Monod

mechanisms (the Chernavskii model). A model describing the cell differentiation in hydra is also widely known (Gierer, Mainhardt, 1972). A local dimensionless model has the form

$$\frac{du}{dt} = a - bu + \frac{u^2}{v(1+Ku^2)} = f(u,v),$$
$$\frac{dv}{dt} = u^2 - v = g(u,v) \qquad (34)$$

where $a$, $b$, and $K$ are constants. The model describes an autocatalytic production of the activator $u$ by the term $u^2/[v(1+K u^2)]$ with respect to the saturation up to the quantity $1/(Kv)$ for large $u$. The inhibitor $v$ is being activated with increasing $u$ according to the second equation, but inhibits the production of the activator.

In Murray's works, for describing the skin coloration in animals, a model was used, whose local version, proposed by Thomas in 1976, possesses similar properties:

$$\frac{\partial u}{\partial t} = \gamma f(u,v) + \nabla^2 u, \quad \frac{\partial v}{\partial t} = \gamma g(u,v) + d\nabla^2 v,$$
$$f(u,v) = a - u - h(u,v), \quad g(u,v) = \alpha(b - v) - h(u,v), \qquad (35)$$
$$h(u,v) = \frac{\rho u v}{1 + u + Ku^2}$$

Here, $a$, $b$, $\alpha$ and $\rho$ are positive parameters. The relation of diffusion coefficients $d$ is larger than unity, which is the condition of diffusion instability. The factor $\gamma$ determines the size of a domain in periodic coloration.

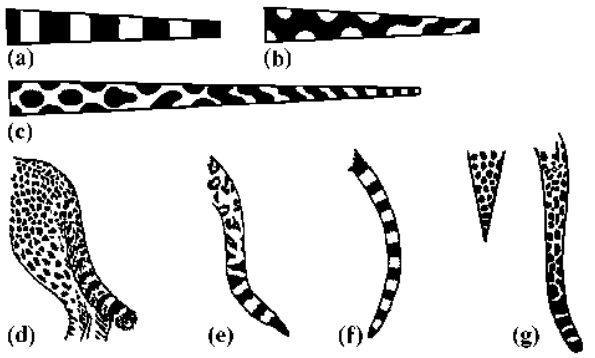


Fig. 12. Examples of the modeling results (a)–(c) and of the natural coloration of a jaguar's tail (d)–(f) (J.D.Murray, «Mathematical Biology», Springer, 1993).

More realistic models that take into account the mechanochemical interactions, are examined in the works by L.V.Belousov and B.N.Belintsev (B.N.Belintsev, Physical Bases of Biological Intermutation, Moscow, 1991).

**5.5. The Belousov–Zhabotinskii reaction**

Spatio-time regimes predicted by the models *reaction-diffusion* can be observed using chemical models. The most famous among them is the reaction described in 1958 by Russian chemist Belousov: the oxidation of citric acid by the potassium bromate catalyzed by the ion pair $Ñå^{4+}$– $Ñå^{3+}$. The examination of this reaction was continued by Zhabotinskii (1964) who has shown that, instead of cerium, manganese and iron can be used as a catalyst, and, instead of citric acid, a number of organic compounds can be used as a deoxidizer. These compounds have a methylene group or form it in the oxidation. The malonic and brominemalonic acids are such compounds. Usually, the reactions are carried out at 25C in a sulphate mixture of potassium bromate, malonic and brominemalonic acids and cerium sulphate. Hundreds of studies are dedicated to the Belousov–Zhabotinskii reaction, since it presents a possibility to observe the features of complex self-organization processes in a simple chemical system and allows the various types of control including different illumination regimes (Muller, Zykov, 1998). A simplified scheme of this reaction is presented in Fig 13.

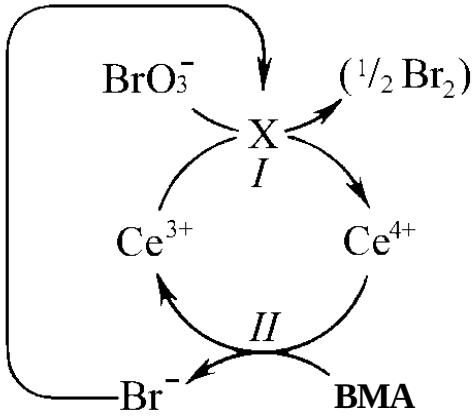


Fig. 13. Scheme of the Belousov–Zhabotinskii reaction.

In the case of thorough mixing, the variations in the solution coloration are observed in a certain range of initial concentration, induced by the variations of the $Ñå^{4+}$ concentration. The oscillations of $Ñå^{4+}$ are of relaxation character, their period is clearly divided into two parts: the $T_1$ phase of increase and the $T_2$ phase of decline.

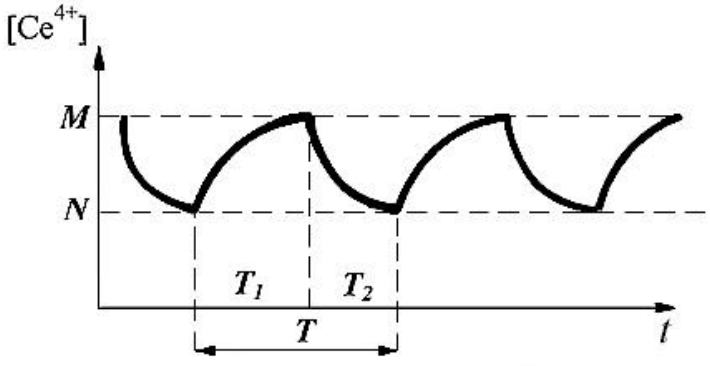


Fig. 14. Oscillations in the Zhabotinskii model (Zhabotinskii, 1974).

From the chemical standpoint, the reaction mechanism is very complex and contains the tens of intermediate stages. Here are the main stages:

(1) the oxidation of the trivalent cerium by the bromate:

$$Ce^{3+} \xrightarrow{BrO_3} Ce^{4+}$$

(2) the deoxidation of the quadrivalent cerium by the malonic acid:

$$Ce^{4+} \xrightarrow{\text{ÌÊ}} Ce^{3+}$$

Products of the bromate reduction, formed at Stage 1, produce the bromine-derivative MA. Brommalonic acids obtained are destroyed with yielding $Br^-$. The bromide is a strong inhibitor of the reaction. Here is a scheme of this reaction:

$$A \xrightarrow{k_1} Y \xrightarrow{k_3} X \xrightarrow{k_4} Z \xrightarrow{k_5} P$$

The notation: $x$ – the cerium ion concentration; $y$ – autocatalisator concentration, $z$ – the bromide concentration.

Taking into account the hierarchy of the reaction rate constants and introducing dimensionless variables, we transform the kinetic equations into the system of two equations for the cerium ion concentrations and one equation for the autocatalyst x:

$$\begin{aligned} \frac{dy}{dt} &= l_1 y(c-x) - l_2 yz + l_5, \\ \frac{dx}{dt} &= l_1 y(c-x) - l_3 x, \\ \frac{dz}{dt} &= l_3 x + l_6 (l_7 y - l_8)^2 x - l_4 z \end{aligned} \qquad (36)$$

Taking into account the hierarchy of the reaction rate constants, one can replace the differential equation for z by an algebraic equation and, introducing dimensionless variables, pass to the system of two equations:

$$\begin{aligned} \frac{dx}{dt} &= y(1-x) - \delta x, \\ \varepsilon \frac{dy}{dt} &= y\{1 - x[1 + \alpha + (y-\alpha)^2]\} + \varepsilon \end{aligned} \qquad (37)$$

In the world literature, the model «oregonator», proposed by Field, Koros and Noyes (1972) is most widely employed. As a local element, the model

$$\begin{aligned} e\frac{dx}{dt} &= qy - xy + x(1-x) \\ d\frac{dy}{dt} &= -qy - xy + 2fz \\ \frac{dz}{dt} &= x - z \end{aligned} \qquad (38)$$

is most frequently used. Here small parameters $\varepsilon$, and $\delta$ reflect a corresponding hierarchy of the times of processes, and $x$ corresponds to the dimensionless concentration of $HBrO_2$, $y$ - $Br^-$, $z$ - $Ce^{4+}$.

To study the spatio-time structures, the model describing the spatio-time dynamics of $HBrO_2$ (the $u$ variable) and that of the catalyst $Ce^{4+}$ (the variable $v$) is frequently used:

$$\begin{aligned} \frac{\partial u}{\partial t} &= \Delta u + \frac{1}{e}\left(u - u^2 - fv\frac{u-q}{u+q}\right) \\ \frac{\partial v}{\partial t} &= u - v \end{aligned} \qquad (39)$$

Results obtained in examining the Belousov–Zhabotinskii reaction in experiments and in modeling are widely used for describing and interpreting the processes in active media of the most diverse biological nature.

### 5.6. Theory of nerve conductivity

Cells of different organs can be divided into two types: excitable cells of the nerve tissues, heart, cells of smooth and skeleton muscles and nonexcitable cells, such as the epithelium cells and photoreceptors. After an impact of electric current, the excitable cells relax immediately to their initial state. In excitable cells, a sequence of processes occurs that depends on a value of the current pulse passing through the membrane. If a pulse exceeds a threshold value, a single nerve pulse appears on the excitable membrane of the nerve tissue, the so-called action potential that lasts about 1 ms and propagates along a nerve tissue at a speed from 1 to 100 m/s, preserving constant amplitude and form.

Modern concepts on the generation of a nerve pulse are based on the studies by A.Hodgkin, A.Haxley, and B.Katz, performed on giant squid tissues (1952) and honored by the Nobel Prize. The propagation mechanism of an electric pulse along a membrane axon (width of about 50–70 A) is associated with the fact that the permitivity of a membrane depends on existing currents and voltages and is different for different ions. The sodium (Na and Ka) ply the major role in this process. Calcium ions also play an important role in regulating the processes. The first model of the propagation of an electric pulse along the axon of giant squid was proposed by Hodgkin and Haxley (1952); at present, it is still the basic model for describing such phenomena. In this model, positively directed current (I) from the interior to the exterior side of the axon membrane is considered. The current I(x) consists of the flows of ions through the membrane and of the current induced by a change in the transmembrane potential on the membrane that possesses the capacitance C. Here is the general equation for the current changes:

$$I(t) = C\frac{dV}{dt} + I_i \tag{40}$$

Here, $C$ is the membrane capacity, $I_i$ is the contribution of currents due to the transmembrane transport of ions. On the basis of experimental data, Hodgkin and Huxley have written the following equation for $I_i$ :

$$I_i = I_{Na} + I_K + I_L = g_{Na} m^3 h (V - V_{Na}) + g_{NK} m^4 (V - V_{Ka}) + g_{NL} (V - V_{la}) \tag{41}$$

where $V$ is the potential, $I_{Na}$, $I_{Ka}$, $I_L$ are, respectively, sodium and calcium currents and the «leakage» current conditioned by the flows of other ions through the membrane; $g$ are the membrane capacities for corresponding ions. The quantities $m$, $n$, and $h$ are the variables varying from 0 to 1, for which the following empirically obtained equations are valid:

$$\begin{aligned}
\frac{dm}{dt} &= \alpha_m(V)(1-m) - \beta_m(V)m \\
\frac{dn}{dt} &= \alpha_n(V)(1-n) - \beta_n(V)n \\
\frac{dh}{dt} &= \alpha_h(V)(1-m) - \beta_h(V)m
\end{aligned} \tag{42}$$

Qualitatively, $\alpha_n$, and $\alpha_m$ represent the functions similar to *(1+tanhV)/2*, and $\alpha_h$ is a function like *(1-tanhV)/2*.

If the current pulse $I_a(t)$ is applied to a membrane, then Eq. (40) takes the form

$$C\frac{dV}{dt} = g_{Na} m^3 h (V - V_{Na}) + g_{NK} m^4 (V - V_{Ka}) + g_{NL} (V - V_{la}) + I_a \tag{43}$$

Equations (40)–(43) compose a system of four equations known as the Hodgkin–Huxley system. Being computed, it reproduces agreeably the phenomena of the passing of current through a squid axon membrane observed experimentally. The system has a stable stationary solution in the absence of exterior currents, but when the pulse applied exceeds a threshold value, demonstrates a regular periodic excitation of the membrane.

The model can be simplified with respect to the temporal hierarchy of the variables $m$, $n$, and $h$. The sodium currents (the value $m$) are much faster than the calcium ones (the value $n$); therefore, according to the Tikhonov theorem, the differential equations for the sodium component can be replaced by geometrical equations (dm/dt=0). If one assumes that the leakage currents are even slower ($h=h_0$ = const), then the model is reduced to the system of two equations in two variables:

$$\begin{aligned}
&\frac{dv}{dt} = f(v) - w + I_a, \quad \frac{dw}{dt} = bv - \gamma w, \\
&f(v) = v(a - v)(v - 1)
\end{aligned} \tag{44}$$

where $0 < a < 1$, $b$ and $\gamma$ are positive constants, $v$ plays the role of potential, and $w$ characterizes nonlinear conductivity properties of a membrane for all types of ions. The Fitz–Hugh–Nagumo model (1961, 1962) is well examined analytically and frequently used as a local element for describing the wave propagation in active biological media, such as a cordial muscle (Fig. 16) or a cerebric tissue

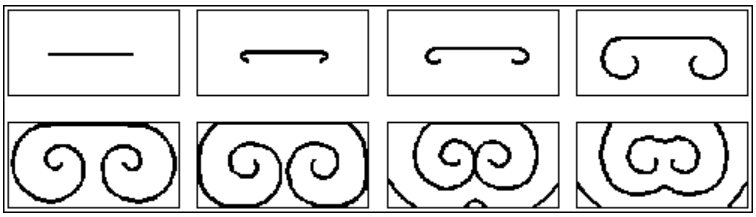

Fig. 15. Evolution of a spiral wave in the Fitz–Hugh–Nagumo model (Tsejikama, 1989).

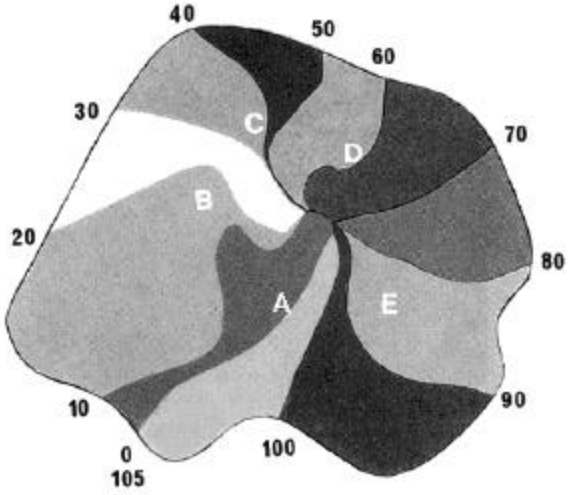


Fig. 16. Spiral waves of the potential propagation in a rabbit hart (the experiment by Bonke and Shopman, 1977).

**6. Physico-mathematical models of biomacromolecules**

Functional properties of proteins, as well as their enzyme activity, are determined by their capability of conformational transformations. Internal motions of atoms and atom groups in globular proteins occur with characteristic times about $10^{-13}$–$10^{-15}$ s and with amplitudes about 0.02 nm. Significant changes in the conformation, for example, opening a «pocket» of the reaction center for the formation of the enzyme-substrate complex, require collective coordinated motions with characteristic times by many orders longer and with amplitudes of an order of tens of Angstroms. Only in the end of the 20$^{th}$ century, powerful computer facilities made it possible to follow, by the method of molecular dynamics, how the physical interactions of individual atoms are realized in the form of macroscopic conformation motions.

The model of a molecular system of N atoms is represented by N material points, whose motion is described by classic Newton equations:

$$m_i \frac{d^2 r}{dt^2} = F_i \quad (i = 1, \ldots, N)$$

Initial coordinates and velocities of particles are prescribed with regard to the data of X-ray spectroscopy and nuclear magnetic resonance. Conformation energy of a molecule is determined by the aggregate atom-atom interactions and can be approximated by the potential function

$$U(r_1, \ldots, r_n) = \frac{1}{2}\sum k_b (b - b_0)^2 + \frac{1}{2}\sum k_\Theta (\Theta - \Theta_0)^2 + \frac{1}{2}\sum k_j [1 + \cos(nj - d0] + \sum (\frac{A}{r^{12}} - \frac{B}{r^6} + \frac{q_1 q_2}{D_r}) + \sum (\frac{A'}{r^{12}} - \frac{C'}{r^{10}})$$

(45)

The summation is performed over all valent bonds, valent angles, dihedral (torsion) angles, pair of particles without valent bonds, and over the pair of particles that form a hydrogen bond. The constants in formulas depend on a type of the bond and the types of particles, b is the length of valent bond, $\Theta$ is the valent angle, $\varphi$ is the dihedral angle, r is a distance between the particles. The force acting to the *i*-th particle is calculated from the expression for the potential energy:

$$F_i = -\frac{\partial U(r_1, \ldots r_N)}{\partial r_i}$$

Potential (45) contains the terms corresponding to different physical components of atomic interaction: deformation energy of valent bonds, deformation energy of valent and dihedral angles, and the energy of Van der Waals and electrostatic interactions. Parameters of the atom-atom interactions are determined empirically from the conditions of maximal consistency between the spectral, thermodynamic, and structural characteristics of low-molecular components of biological macromolecules calculated from the potential and measured experimentally. The trajectories obtained for individual atoms are analyzed by the method of correlation functions and with the help of the charts of free conformation energy of molecules. These charts represent the surfaces of the realization probability distributions of different energy conformations and their cross-sections. For the correlating degrees of freedom, as a rule, extended narrow areas are observed, along which the collective transformation of conformation occurs. For noncorrelating variables, there is a set of unlinked sharp local minima. The transition between the latter involves the traverse of a high potential barrier. Otherwise, there are vast areas of relatively free motion. Structure of the hypersurfaces of the potential energy levels for the systems with conformation degrees of freedom cardinally differs from similar hypersurfaces of rigid molecular systems, for example, in crystals, where they are of regular character.

### 6.1. Molecular dynamics

The first numerical experiments with a protein molecule, the inhibitor of the tripsine of pancreatic gland, were carried out by the method of molecular dynamics by J.A.MacKemon and colleagues in 1957. The molecule consists of 58 amino acid residua and contains 454 heavy atoms. The structure also includes four internal water molecules localized in the accordance with crystallographic data. It proved to be possible to reproduce the main element of the protein secondary structure: an antiparallel convoluted $\beta$-structure, and also a short $\alpha$-spiral segment.

In recent years, the calculations of molecular dynamics of mioglobine, lisocime, calbindine, and retinal-bonding protein were performed; the transport of an electron in the protein complexes such as ferrocytochrome C – ferrocytochrome B5 and ferrocytochrome C-**peroxidase** in a water environment was also modeled. As a result of modeling, spatial structure of these complexes was predicted. In the calculations, considerable lability of the region of protein-protein contact was observed, including the displacement of an aromatic protein group into the contact region for the times about 1 ps. The results of molecular dynamics corroborate the role of fluctuations in the electron-conformation interactions that accompany the processes of electron transport, migration and transformation of energy, and enzyme catalysis.

### 6.2. Models of the DNA motility

In modeling the functional motions of the DNA, it proved to be fruitful to search for a mechanical analogue, that is, for a model system well examined in mechanics with a similar set of structural elements, motions, and interactions. There exist hundreds of various models that describe motions of the DNA: continual and discrete, spiral and disregarding the spiral structure, imitating the motion of every or almost every atom of a fragment and imitating only he major subunits, homogeneous models and the models taking into account the existence of a sequence of bases.

Models of an elastic bar of a circular cross-section (Level 1 in the figure) are the simplest ones. A discrete analogue is represented by a chain of linked disks (or beads), whereas every disk corresponds to one or several nucleotide pairs. The dynamics of elastics bar is characterized by three types of internal motions: longitudinal displacements, rotational or torsion motions, and transverse displacements. Usual plane waves are the solutions of a system of equations, and the spectrum of the DNA oscillations consists only of three acoustic branches: longitudinal, transverse, and flexural.

Models of the second level take into account that the DNA molecule consists of two polynucleotide chains, and it can be modeled by two elastic bars weakly interaction between them and convoluted into a double spiral. A discrete analogue of such a model represents two chains of disks linked by longitudinal and transverse springs, and the stiffness of longitudinal springs is much stronger than that of transverse ones. The spectrum of torsion oscillations calculated by such (linear) model consists of two branches: acoustic and optical.

The third hierarchic level accounts for the fact that each of the chains consists of three subunits: sugars, phosphates, and bases. The fourth level is represented by the lattice models of the DNA and describes the motion of atoms that compose a lattice cell (Powell, 1987). Problems of this kind prove to be solvable in a linear (harmonic) approximation, yielding complex DNA spectra that contain a multitude of branches. Models of the fifth level simulate structure and motions of the DNA with a maximum accuracy (the models of molecular dynamics).

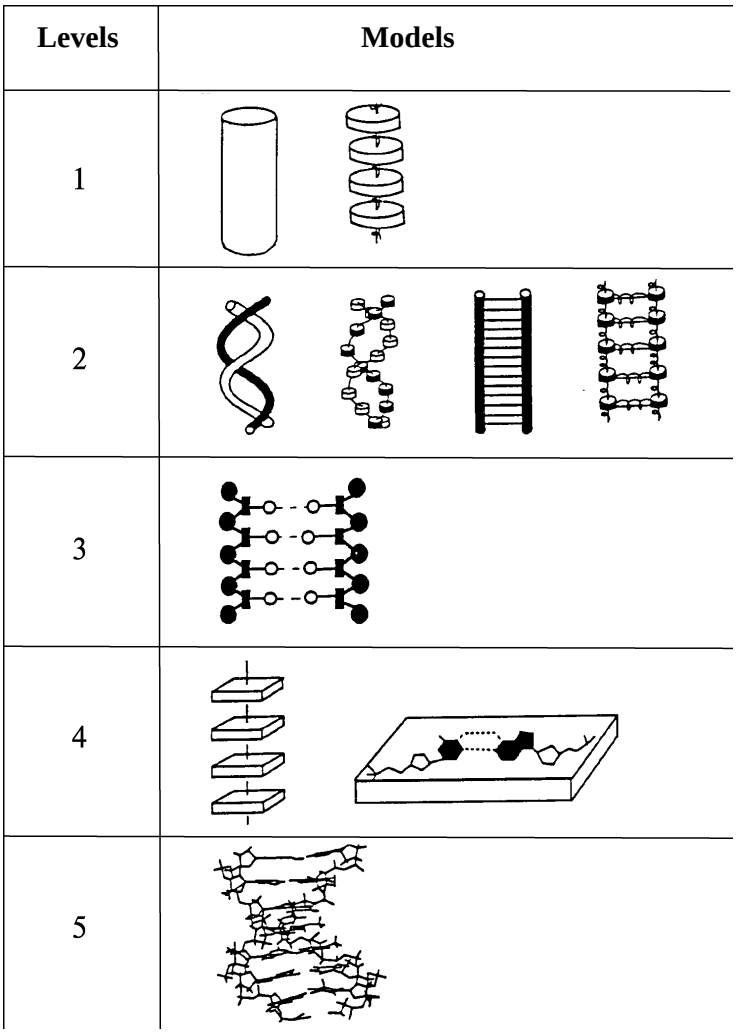


Fig. 17. Levels of the modeling of DNA motiliy.

Englander, Kallenbach, Heeger, and Krumhansl, 1980, carried out a pioneering research in examining the internal dynamics of the DNA. The method of hydrogen-tritium exchange was used to show a principal possibility of the formation of open states in the DNA defined as motile local regions (from one to several pairs of bases long), inside which the hydrogen bonds are torn. The formation of such open states is related to considerable angular deviations of the bases from an equilibrium state. Mathematically, this process was described with the use of the Hamiltonian formalism widely applied in theoretical and mathematical physics. In modeling the internal DNA motility, the authors did not limit themselves to modeling small deviations from an equilibrium state (harmonic or linear approximation), but considered the motions of large amplitude (nonharmonic or nonlinear approximation). It was shown that nonlinear wave solutions of the Gordon sine-equation

$$j_{tt} - j_{zz} + \sin j = 0 \tag{46}$$

are the mathematical images that can imitate the open DNA states. Here, the function $j(z,t)$ describes angular deviations of the bases from the equilibrium states.

A modification of the Englander model (Yakushevich, 1998) describes the processes of rotational motions of the bases around the sugar-phosphate chains characteristic of large amplitudes. These motions lead to the rupture of hydrogen bonds and to the formation of open states. In describing the dynamic properties, an analogy between the DNA molecule and a chain of linked pendulums is used. The bases associated with sugars play the role of rotating pendulums in the DNA, the sugar-phosphate chain plays the role of a horizontal chain, and the role of the external gravitational field is played by the field induced by the second thread of the DNA that weakly interacts with the first one through the hydrogen bonds between the bases. Dynamics of the chain is well examined and described by a set of $n$ nonlinear equations. For the $n$-th pendulum, the equation has the form

$$I \frac{d^2 \varphi_n}{dt^2} = K(\varphi_{n+1} - 2\varphi_n + \varphi_{n-1}) - mgh \sin \varphi_n \quad , \tag{47}$$

where $\varphi_n$ is the angular deviation of the $n$-th pendulum from an equilibrium state; $I$ is the second moment of the pendulum; $K$ is the stiffness coefficient; $m$ and $h$ are the pendulum's mass and length, respectively; ad $g$ is the gravitation constant. In passing to a continual approximation, one may write the equation for the dynamics of rotational oscillations of the DNA bases:

$$I_0 \varphi_{tt} - K_0 \varphi_{zz} + V_0 \sin \varphi = 0 \, , \tag{48}$$

where $I_0$ is the second moment of a basis, $K_0$ is the stiffness coefficient of a sugar-phosphate chain, and $V_0 \sin \varphi$ is a force acting between the bases inside the pairs.

This equation of the type sine-Gordon has a solution of the type «kink»:

$$\varphi(z,t) = 4 arctg\{\exp(\gamma x / \delta)\}. \tag{49}$$

Here, $\gamma = [1 - Iv^2 / K_0 a^2]^{-1/2}$; $x = z - vt$; $v$ is the velocity of a nonlinear wave (kink) propagation; $\delta = (K_0 a^2 / V_0)^{1/2}$; and $a$ is a distance between the nearest pairs of bases along the chain. A qualitative pattern corresponding to this solution is presented in Fig. 18.

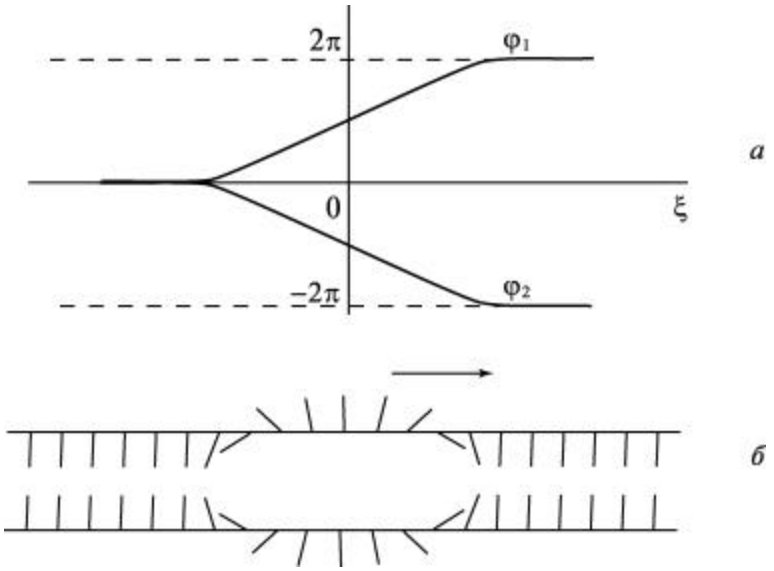

Fig. 18. The DNA untwisting scheme.

Two sugar-phosphate chains are depicted by two long lines, while the bases are marked by a multitude of short lines. The kink corresponds to a local region with torn pairs of bases. Solution (49) describes a local deformation (the opening of the pairs of bases) moving along the DNA molecule at a speed $v$. In the propagation process of a wave, the acceleration can be observed due to constant pumping of energy and the deceleration because of the effects of internal friction. The irregularities of the DNA are taken into account in the form of blocks with dominating content of the G-C-pairs on the background of remaining part of molecule that generally contains the A-T-pairs. This allows the estimation of the minimum value of nonlinear wave velocity that is necessary to surmount a barrier of G-C blocks and to continue the motion. The model considered allows a qualitative explanation of the long-range interaction effects in the DNA molecule and the propagation of conformation waves through the regulator regions, which is especially important for the regulation of the DNA activity. The nonlinear conformation waves moving along the DNA can also play a role in the coordination of the work of several genes.

## 7. Modeling of complex biological systems

Achievements of modern biology revealed numerous facts on the structure and regulation types of many intracellular systems. Schemes of processes are composed, chemical structure and, in most cases, molecular structures of the components of processes are examined, including the bio-regulators. This made it possible to construct mathematical computer models that allow the formalization of the knowledge on complex biological objects. The degree of specification of models can be different depending on the goal of modeling and on the completeness degree of the examination of objects. If the modeling is aimed at the control, for example, an efficiency increase in the output of a biotechnological process is desired, then it is often sufficient to consider individual blocks as components and examine stationary states of a system. For practical purposes of biotechnology and pharmacology rather complex metabolic nets are considered. They are modeled by «constructors», that is, programs that write automatically differential equations according to prescribed scheme of processes and expressions for the rates of individual reactions. In investigation such complex systems, the theory of metabolic control has deserved a good reputation.

If an object is thoroughly examined, mathematical models become an effective method of fundamental research. By solving inverse problems, they allow the estimation of kinetic and physical parameters of a holistic system, which is impossible in experiment without fractionating a system. In complex biological systems, the latter leads to the modification of the functional activity.

### 7.1. Metabolic control analysis.

Developed for estimating the state of complex metabolic nets, the theory of the control of metabolism is a specially designed mathematical apparatus for examining the regular properties of polyenzyme metabolic systems in which metabolic intermediates are not only the participants of the stages of a chemical transformation, but also the regulators of individual enzymes. The major results in the modern theory of Metabolic Control Analysis were obtained by English (H. Kacser and J.A. Burms) and German (R. Heinrich and T.A. Rappoport) researchers. Substantial contribution to the development of mathematical basis of this theory was made by Russian scientists B.N. Kholodenko and O.V. Dyomin.

The regulator features of metabolic systems manifest in their ability to consistently vary the values of flows and the concentrations of substances in changing conditions of environment so that a stationary state with minimal deviations from a concentration norm of the key metabolites be maintained in a cell. In earlier works, it was assumed that the decisive role in controlling a system belongs to a single link (for example, they introduced a notion of a regulating enzyme subject to the effector impact, the «bottle neck», the enzyme with low catalytic activity limiting the substance flow along the metabolic channel, etc.).

The further specification of the concepts on the functioning of metabolic nets has shown that the regulator properties are inherent in a metabolic system as a whole and appear due to the interaction and correlated functioning of all the links of a system.

In the framework of the theory of the Metabolic Control Analysis, the description of the regulation in a metabolic system is performed in the language of special quantitative characteristics, system and local indicators of the regulation. The main system indicators, the control coefficients, characterize the contributions of individual enzymes and also of external parameters to the control of system variables, that is, stationary metabolic flows and concentrations.

The control coefficient of an enzyme $E_i$ with respect to flux J is determined by the expression

$$\check{N}_i^J = \frac{\partial \ln|J|}{\partial \ln E_i}. \qquad (50)$$

The control coefficient of an enzyme $E_i$ with respect to a metabolite $x_k$ is represented as

$$\check{N}_i^k = \frac{\partial \ln x_k}{\partial \ln E_i}$$

Local indicators (elasticity coefficients) describe the kinetic properties of individual functional links of a system, the enzyme reactions. The elasticity coefficient of an enzyme $E_i$ with respect to a metabolite $x_k$ describes a response of the rate of the $i$–th reaction $v_i$ to the change in the concentration of the given metabolite:

$$e_k^i = \frac{\partial \ln|v_i|}{\partial \ln x_k} \qquad (51)$$

Since its rise, the theory of metabolic control analysis is directly related to experimental investigations devoted to the measurements of quantitative indicators of the regulation in various metabolic systems.

### 7.2. Mathematical models of primary photosynthetic processes

At present, the system of primary photosynthetic processes is one of the most thoroughly experimentally examined biological systems. This determines a possibility of constructing successful mathematical models of a system as a whole and of its fragments. The contents and structure of the components of the photosynthetic apparatus are determined by biochemical and genetic methods and by the methods of the X-ray analysis.

The system of primary processes possesses one more extremely important feature that distinguishes it form other biological systems. This system is being «switched on» by the light, and it can be tested as an electronic device by the delta-shaped (laser flash) or rectangular (switching on a constant light) impulses. Therefore, spectrophotometrical methods prove to be extremely efficient here (differential and impulse spectrophotometry in the absorption bands of individual molecules, participants of the primary reactions, fluorometry, the methods of electronic paramagnetic and nuclear magnetic resonance, etc.). It is also important that it is possible to separately single out fragments of photosynthetic reaction centers of the photosystems 1 and 2 from a photosynthesizing organelle, the chloroplast, and bacterial reaction centers from chromotophore of photosynthesizing bacteria, by biochemical methods. The fragments of photosystems singled out preserve the ability to the absorption of the light and to the light-induced division of the charges. It is possible, by chemically modifying the composition of such fragments and by changing the regime of the illumination, the redox conditions, and the pH of a medium, to observe the relaxation processes by spectral methods and make conclusions on kinetic characteristics of the system, first of all, such as the constant rates of the electron transfer on individual steps of the photosynthetic electron-transport chain. Namely due to these features, the system of primary photosynthesis processes proved to be a favored object for mathematical modeling.

There is an important problem in mathematical modeling: the identification of the system's parameters, that is, the estimation of the constant rate of individual reactions from experimental curves that reflect the change in time of the concentration of this or another component. It is often possible to experimentally register the change of only one or several components (for example, the EPR-signal of a photoactive pigment of photosystem I or fluorescence intensity of photosystem II) and, with mathematical model, identify the rate constants for the electron transfer processes in the photoreaction center or in other parts of the chain. It is well known from the mathematical theory of identification that an unambiguous estimation is possible only for linear systems with completely observed vector of states. Naturally, this condition is not fulfilled in real systems. However, using additional experimental data, such an estimate can be performed for relatively simple systems, for example, for isolated photoreaction centers. In a holistic, non-fragmented system, such as the chloroplast of green plants or the chromatophore of bacteria, which include the whole aggregate of the components of photosynthetic apparatus, the registered kinetic curves are, as a rule, of complex character, since they reflect the interconnection of numerous processes. The information on kinetic parameters of a system can be derived from such curves only with the help of mathematical models. In so doing, a problem arises, how to conjugate the knowledge and concepts on individual stages of photosynthesis processes, examined separately by the methods of different sciences, into a united scheme.

The primary photosynthetic processes include the absorption of a quantum of light, the migration of energy in a light-harvesting complex, consisting of the molecules of chlorophyll and carotinoides, the charge separation in photoreaction centers, the electron transfer and coupled translocation of protons and other ions through the thylakoid membrane, and the formation of the transmembrane electrochemical potential that is necessary for the functioning of the ATP-synthase. As a result of primary photosynthesis processes, the macroergic ATP

(adenosine-triphosphate) compounds from the ADP (adenosine-diphosphate) and inorganic phosphate as well as the reduced NADP (nicotine-amide-dinucleotide–phosphate) are produced that are necessary for the work of the Calvin cycle of $CO_2$ fixation. The scheme of the processes in the thylakoid membrane is schematically shown in Fig. 19.

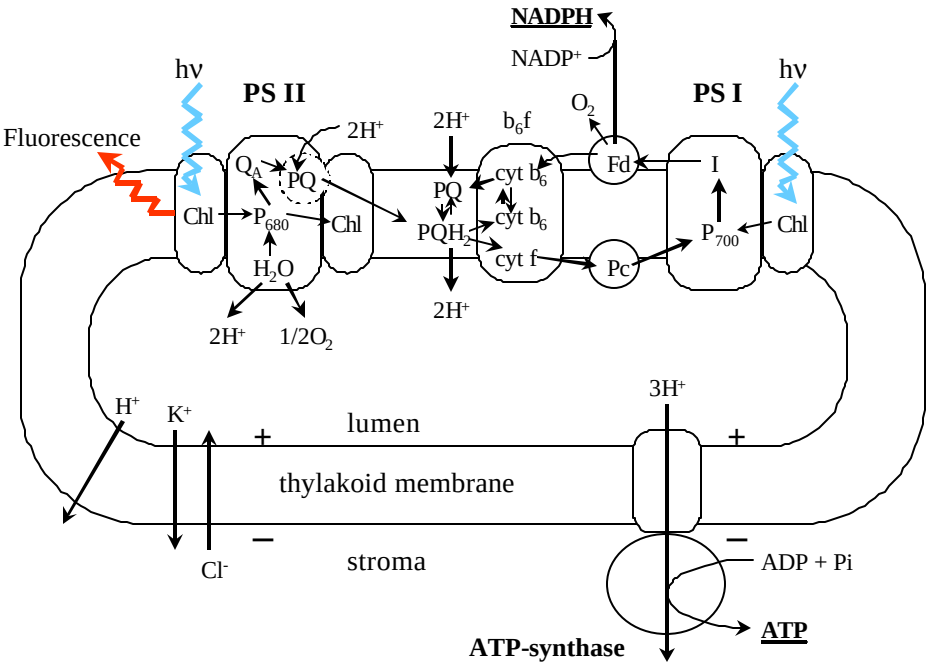


Fig. 19. Scheme of the processes in a chloroplast.

In the first models of the photosynthetic electron transport (in 1960–1970s), the reaction of transport from a molecule-donor to molecule-acceptor was described by the mass action law, assuming that the reaction rate is proportional to the composition of the reagent concentrations (bimolecular reactions). However, as is seen from Fig. 19, the transport processes occur here in fixed carrier complexes rather than by the way of random collisions. At present, not only chemical composition is deciphered, but also the coordinates of individual molecular groups participating in the electron transport. It is possible to indicate an «electronic path», that is, the path of an electron from one atom to another within the same molecule.

The specification degree of the description of processes is determined by the goals of modeling. Usually, each molecule is considered as a carrier, which can be in one of the states: neutral (oxidized), without an electron, and reduced (neutral) with an electron. Various conformation states are also possible, as well as protonated and deprotonated states, etc.

In the general case, when a complex consists of n carriers, states of the complex $\left[C_1 C_2 \ldots . C_n\right]$ are determined as an ordered aggregate of the states of the carriers $C_i$ that compose the complex

The transitions between the states are described by equations linear with respect to the probabilities of the states:

$$\frac{dp_i}{dt} = \sum_{j=1}^{l} (p_j k_{ij} - p_j k_{ij}), \text{ with the initial conditions } p_i(0) = b,\ i = 1, \ldots l$$

or in the vector form

$$\frac{dP}{dt} = K^T P, \quad P(0) = B$$

The probability to find a carrier in a certain state L is a sum of probabilities of the complex's states in which the carrier is represented in the given state

$$P(D) = \sum_{S_q \in L} p(S_q, t)$$

The more accurate are the concepts on the processes that occur in a complex, the more detailed scheme can be composed and the larger number of equations is required to describe the transitions between the states. Thus, the transitions between the states of the photosystem 2 complex are presented in Fig. 20. Due to large differences between the rate constants in individual links of the chain (fast processes are marked by the dashed arrows) and with regard to the temporal hierarchy, the system can be reduced, and the differential equations for fast variables can be replaced by algebraic ones.

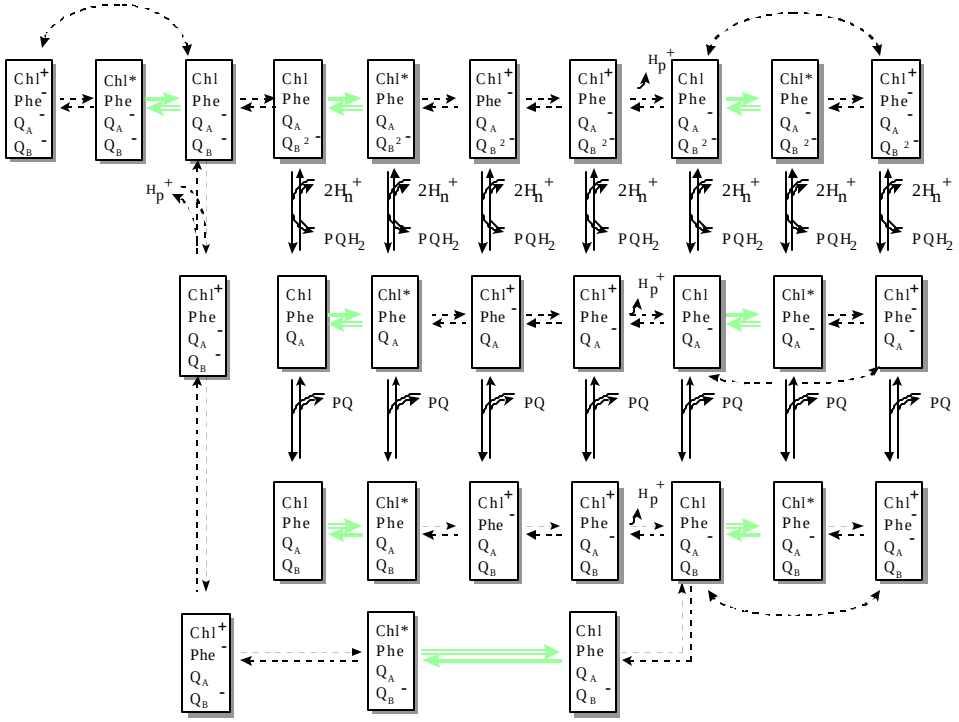


Fig. 20. Scheme of the transitions between the states in photosystem 2 of the higher plants.

The cytochrome complex and the photosystem 1 complex are also characterized by a set of large number of states. The model that describes, in addition, the interaction between the complexes, ion fluxes, and the work of ATP-synthase contains the tens of equations and hundreds of parameters, and many of them are well known from literature. However, these parameters were estimated for different objects and under different conditions. Most often, they are being estimated in experiments on separated fragments; where the reaction rate coefficients can differ from those in the whole chloroplasts. Therefore, when using in a model, the parameters, as a rule, require a refinement.

The results of detailed mathematical modeling and parameter identification for individual photosynthesizing complexes, included in the complicated system of interacting components and the results of reduced models allow the conclusion that the regulator properties of a system are different at different levels of the system organization. At the level of photosynthetic reaction centers, the control is stiff. A quantum of light starts a strict sequence of processes, and its absorption leads to the redistribution of the charges and conformation changes directed at the fastest carrying out of an electron outside the photosynthetic pair. The photosynthetic reaction centers themselves are «standardized» for a large degree: their organization is similar to PS1, PS2, and bacterial centers. The identification of mathematical models based on experimental data confirms that the parameters change rather a little when the external conditions, such as pH, the redox potential, viscosity of a medium, etc., vary. Kinetic patterns of the processes that occur in these centers are, as a rule, of the simple relaxation character.

At the level of the interaction between the systems, the regulation is of more «flexible» character. Here, the diffusion stages substantially depend on pH, the redox conditions, and viscosity, which allow the regulation of these stages at the cellular and organism levels when the external conditions vary and in the process of growth. The kinetic patterns are more complicated and they can contain a number of maxima, which is manifested in characteristic forms of the fluorescence induction curves in the minute temporal range.

The accumulation of knowledge on structure and composition of the photosynthesis apparatus and details of its organization, on one hand, and the development of computer technology on the other hand, the mathematical modeling becomes ever more instrumental in the translation of the data of spectral measurements into the language of kinetic parameters and, further, with the help of computer visualization, into the language of structural changes of the photosynthesis apparatus.

**8. Conclusions**

Mathematical biophysics is a very rapidly developing field at the junction of applied mathematics, physics, and experimental and theoretical biology. The qualitative modeling continuous developing, passing from the examination of models of two-component local systems in ordinary differential equations and mappings and partial differential equations of the reaction-diffusion type to more complicated mathematical objects: delayed equations, equations with random terms, and to the models of higher dimension. The imitation modeling develops especially fast and allows the computer simulation of the behavior of complex biological systems on the basis of the concepts on the properties and interaction of their elements. The integration of various types of knowledge on the system and visualization of these concepts in the form of computer models with all advantages of the visual thinking into the cognition process is a qualitatively new stage of mathematical modeling in biophysics.

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