

MATHEMATICAL MODELS IN BIOPHYSICS

Riznichenko Galina Yur'evna

Biological faculty of the Lomonosov Moscow State University, Leninskie gori, Moscow, 119992, Russia

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Summary

Mathematical models represent a language for formalizing the knowledge on living 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, quasi-stochastic regimes, traveling 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 models of growth, interaction between the species, lotic cultures of the microorganisms, genetic trigger, intracellular calcium oscillations, glycolysis, nerve conductivity, and DNA untwisting. The detailing and identification of these models from experimental data allows the description of real processes in living systems, the examination of their mechanisms, and makes these models heuristic. The models of primary processes of the photosynthesis are a good example. Using 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 and on the laws of their interaction. The imitation models are constructed for all the levels of the organization of live systems, from the sub-cellular 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 living systems that are difficult to formalize.

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 sub-cellular 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 of the processes in living systems poses 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 the 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 compounds 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 quasi-stochastic 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 *Pattern Formulation and Neural Models*)

The next hierarchical level, **cellular biophysics**, is represented by the models describing processes in biological membranes, sub-cellular organelles (chloroplasts, mitochondria), and by the models of the nerve pulse propagation. Since the 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, belongs 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, and existence of spatial nonhomogeneity). Such an approach is historically 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.

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 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 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 a 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 *Population Models*).

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 or building blocks) 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 analogous 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: Auto-catalysis

The rate of growth is proportional to the population numbers, no matter this is 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:

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

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 Populations" (1798). According to (1), if the proportionality coefficient $R = r = \text{const}$ (as Malthus assumed), then the numbers grow exponentially and without limits:

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

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

period of 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 struggle 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 algae 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.

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Biographical Sketch

Galina Yu. Riznichenko is Professor in the Department of Biophysics and Head of the Department of Informatics, Biological Faculty, Moscow State University giving general courses on mathematical modeling in biology and some special courses in mathematical modeling in biology and environmental

sciences for graduate students and different groups of special education. She is an author of more than 100 papers and several textbooks and monographs on mathematical modeling in Biology and biophysics.

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