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Mathematical Modeling and Aging: Research Program

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Abstract—Problems of mathematical modeling are considered in connection with the study of aging and longevity. The research directions are presented, which are expected to gain most from the application of mathematical modeling to solving the problem of the radical human life extension.

Keywords: aging, mathematical modeling, scientific research, life extension

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INTRODUCTION

In recent years, rapid progress has been made in mathematical modeling as a new method for studying various processes in nature, living systems, and society. This can be attributed to the general progress in science as the model description requires formal clarity and unambiguity. As early as 1975, it was noted that "now any theoretical...idea is usually formalized as a mathematical model. This can be attributed to the more stringent requirements on the accuracy and clarity of statements made" [40].

Models are used in biology because they are capable of substantiation and subject to the experimental validation of hypotheses, based on experimental data, on the internal mechanisms underlying the functioning of biosystems. Biological systems have gradually become one of the most attractive objects for modeling because their structure changes in time and space and they are open to energy and information flows and implement various control processes [7, 15, 31, 39, 40]. An important direction in this field is now the modeling of aging processes and longevity. The first publications devoted to this problem appeared as early as the 1960s, and now extensive investigations in this direction are underway, relating to the emergence of new technologies for acting on living organisms at all levels, from organelles to populations. However, despite the efforts of some organizations and individual researchers, the significance of modeling for gerontology is not yet completely understood in Russia.

The aim of this paper is to present a comprehensive program of scientific research in the field of mathematical modeling of aging and longevity, which could help in formulating goals and identifying the most significant and promising research directions reflecting the wide scope of advanced theories and concepts of aging.

Studies of a possible radical increase in the human lifespan, estimating the extent to which human lifespan depends on genetics, lifestyle, and environment, are the main subjects of gerontological research. Along with the increase in average human lifespan, the possibility of extending a "healthy" lifespan should be explored. In addition, it would be of great importance to substantiate the efficiency of various methods for the human life extension tested on laboratory animals.

1. MATHEMATICAL MODELING OF FUNDAMENTAL AGING MECHANISMS

The most important research direction in gerontology is analysis of the fundamental mechanisms underlying aging and mortality. All biological systems including organisms are subject to aging. However, the root causes, paths, and fundamental mechanisms of these processes are mostly far from clear [1, 2, 7, 47, 56].

Regulation and control processes in an organism differ. Where has regulation is mostly implemented at the physiological level, control is achieved at the systemic level, integrating this activity (nervous, immune, and humoral systems). The phenomenon of aging is assumed to result from efficiency loss in systems at both levels, i.e., the level of physiological systems and the highest control level. The human conscience can also be interpreted as an integrating system. Analysis of regulation and control processes as the basis of bodily aging primarily involves development of the concept and mathematical models explaining the phenomenon of aging as a result of regulation and control in complex biological systems. In particular, modeling must clarify the significance of resource distribution between preservation and repair systems of the body for aging and longevity.

Of no less importance is the field of modeling dealing with analysis of the body's preservation systems from the viewpoint of development and aging preven-

tion. Preservation systems (primarily, systems significantly reducing the oxidative vulnerability of an organism) prevent damage at the cellular level and thereby result in prevention of aging. Modeling of these processes will help to understand the role of such systems in the development of aging and in the emergence of the phenomenon of human longevity [21, 31]. This also involves the aging processes of the immune system [42, 43,104].

The second most important problem is the analysis of the role played by the brain (including conscience) in controlling the process of human aging. The role of the brain in the aging processes is insufficiently clear and has been touched upon only in studies by some foreign researchers. In modeling the aging processes, primary attention is on the aging of certain specific components of the brain system. At the same time, the effect conscience has on the aging process has been virtually neglected, although the organization of the mode of living and lifestyle is one of its main functions.

And finally, modeling of the regulatory and protective integrating systems of the body is of no less importance. Analysis and mathematical modeling of the mechanism underlying the functioning of these systems will help to clarify their role in the development of the aging processes and to estimate their efficiency for the potential attainment of longevity [2, 51]. In particular, such an analysis must take into account the existing correlations between bodily parameters, susceptibility to disease, presence of congenital vulnerability, etc.

Mathematical Modeling of Theories of Aging

A significant element in mathematical modeling of aging processes is comprehensive analysis of existing and newly proposed theories of aging. All of the classic theories of aging have much in common even though they differ in their postulation of the causes and emphasize certain specific aspects of aging. Mathematical modeling gives grounds for comparing different theories, making it possible to determine their general postulates and test the consistency of such theories with modern data on aging and longevity [23, 51, 88, 118]. In validating the theories on aging both, data on animal lifespans can be used (the aging characteristics of laboratory and wild populations of *Drosophila*, i.e., *D. melanogaster* and fruit flies Medfly and Mexfly, the life duration of nematode worms *C. elegans*, etc.) and data on human lifespan. These include historical data on different countries [14] and the results of modern research on the lifespan in various cultures, (e.g., the Paraguayan *Ache* tribe [72] or the Canadian sect of Hutterites). In addition, we can use the results of research on the human lifespan in various social and environmental conditions and for different behavior patterns. The first group can include, for example, conditions in different regions of the Russian Federation, and the second group can include the characteristics of aging and lifespan for sedentary and active life styles.

Validation of classical aging theories and their consistency with modern experimental data from developed mathematical models must first of all include the mortality model developed by Gompertz [67]. This should be followed by consideration of the programmed aging theory (Weismann, 1899 [115]), Rate of Life theory (Pearl, 1928 [100], Sohal, 1986 [108]), and theory of mutation accumulation (Medawar, 1952 [81]). We will analyze the oxidative damage theory (Harman, 1998 [69]; Emanuel, 1958 [50]) and the theory of antagonistic pleiotropy (Williams, 1957 [85]). In addition, we will consider the threshold theory (Smith, 1963 [61, 80]), the disposable soma theory (Kirkwood, 1998 [76]), and, finally, mitochondrial and thermodynamic [8] theories of aging.

As far as new theories are concerned, we plan to carry out mathematical modeling of the telomere theory of aging and study the model for the analysis of the redusome aging theory [36].

Evolutionary Aspects of Aging

If evolution is based on optimality principles, aging appears to be a natural phenomenon resulting from evolution. Mathematical modeling makes it possible to check this statement and establish a relation between evolutionary optimality and individual aging. In this context, the following research directions should be considered:

(1) *mathematical substantiation of the predetermination of aging as the optimal evolutionary strategy*; such an analysis must include Kirkwood's approach of insufficient resource invested in self-maintenance [76] and Khalyavkin's theory [48] on the possibility of preventing aging of organisms in special conditions;

(2) *mathematical modeling of artificial selection processes aimed at life extension*; the optimality estimate must develop from the natural selection processes in different conditions [32, 87] and the optimality hypothesis must be tested under the artificial selection [35];

(3) *interrelation of evolution and human conscience*; it appears important to consider conscience as a product of evolution and to analyze it as an evolutionary mechanism. The formalization of the considered concepts will require a mathematical description of various hypotheses connecting man's evolution and human conscience, the development of which will be included in the program.

Aging and Optimality of Biological Systems

According to the principles of evolutionary optimality, evolution results in the emergence of optimal systems. In analyzing biosystems, however, one should also allow for the existing limitations of the evolutionary process. In particular, Rashevsky's concepts must

be taken into account (1960s, [37]) about the optimal design of organisms, which had been preceded by the ideas of their minimum and optimal design. Within the concept of optimality of biosystems, the transition of control functions should be analyzed from the gene to an entire organism [38]. It is this transition that seems to trigger aging in organisms.

This section includes the following research directions:

mathematical modeling of the evolutionarily optimal strategies of development, reproduction, and survival [32, 87, 99,111];

modeling of individual patterns for the implementation of optimal evolution strategies (in particular, egg-laying patterns of fruit flies [30, 87]);

modeling the emergence of long-lived individuals resulting from the individual specifics of resource distribution [41, 87];

modeling of individual and population mechanisms of reproductive and postreproductive behavior from the viewpoint of lifespan optimality.

Modeling of Normal and Pathological Aging

Modern society is characterized by statistically significant and constant extension in human lifespan for economically developed countries, increasing at a rate of about two years and half a decade [93]. The general senescence of a population brings about the term "natural death from old age" [66]. Death is really the ultimate consequence of normal aging. Various diseases modulate this process, leading to premature death. In modeling pathological aging, special attention should be paid to genetic anomalies.

Within this section, the following problems must be considered: modeling of the modulating processes of "allostatic load" on the aging progress and on lifespan [53]; modeling of changes in the properties and accumulation of oxidized proteins with age and the effect of this accumulation on the physical state of the human body [12, 96].

In addition, it is also possible to model the aging of a "healthy" organism, modeling of senescence morbidity, and the role of age-related and chronic diseases in reducing the lifespan from the life expectancy level. Special attention should be paid to modeling of the mechanisms of progeria and Alzheimer's disease.

Mathematical Models of Mechanisms Underlying the Aging of Physiological Systems

In different sections of the program, aging of an organism's physiological systems is considered from different viewpoints. In some cases, a detailed description of the system (structure) itself is given, and other sections are concerned with its behavior (function). This section deals with the structural processes of aging. Thus, the respiratory system is considered an aging anatomical structure, and its mathematical modeling must include the processes of cellular aging of tracheae, bronchi, etc. Other physiological systems are treated in a similar way. This implies that such models must primarily be different variants of compartmental models [28].

There are numerous models nowadays describing the functioning of physiological systems in a stationary mode (operating in "fast" time). At the same time, there are almost no models on the behavior of these systems in "slow" time (aging processes) [89].

The purpose of such modeling is both a proper analysis of aging of the considered systems and the obtaining of a basis for constructing models of them within the concept of natural technologies. It would be feasible to model the aging processes of the nervous system and the brain, aging of regulatory and energy systems of the body, and to simulate the processes of cell division and growth, as well as of morphogenesis. The modeling of subcellular transport processes is also possible (membrane penetration of proteins, facilitated transport, active transport) as well as modeling of cellular processes in aging.

We plan to develop mathematical models for aging of bone marrow and the hematopoietic system, aging of the cardiovascular system, and aging of the reproductive and hormonal systems of the body. This can ultimately result in a virtual model of an aging organism (model of nematode worms *C. elegans*, model of the fruit fly, and model of a human body).

Modeling Bodily Response to the Environment and Its Effect on Aging

The bodily response to external stimuli reflects the adaptive capacity of an organism. If aging is assumed to be a process of decline in the homeostatic capacity to maintain life [34, 88], the modeling of these responses elucidates aging mechanisms. This section of the program includes the following directions:

modeling of cryogenic action on a cell and the entire body;

modeling of physiological adaptation [94, 95];

modeling of the effect of weak exposure of living organisms and age-related changes in their adaptive abilities. A comparative analysis of aging characteristics in the changing conditions must be performed.

2. MATHEMATICAL MODELING OF AGING PROCESSES WITHIN THE CONCEPT OF THE NATURAL TECHNOLOGIES OF AN ORGANISM

The systemic biological basis for mathematical modeling of aging processes is the concept of natural technologies of an organism proposed by the Academician Ugolev in 1987 [46]. Within this concept, an

organism is interpreted as a system implementing various technological chains aimed at life maintenance. Technology is understood as the combination of methods and instruments for the purpose of attaining the desired result, a technique for converting "the available to the necessary." In biological systems, technology is the set of mechanisms and ways in which substance, energy, and information are transformed, resulting in an integrated organismal system.

Development of a Concept Explaining Aging as a Reduction in Functionality of Natural Technological Systems

One of the most plausible theories of aging in the modern biological science is the theory of oxidative damage [50, 69]. According to it, aging of an organism results from the accumulation of damaged proteins.

The concept discussed in this section is aimed at developing an alternative viewpoint: Instead of considering the accumulation of damaged substances in the body, it is proposed to directly estimate how such accumulation impairs the efficiency of physiological systems [30, 34].

The creation of respective mathematical models is projected, in which the direct output quantity will be an indicator describing the functioning efficiency of different physiological systems. We plan develop structural models of natural technologies in aggregate and to define the optimal dimensionality for a system of natural technologies for modeled aging. In addition, a concept will be developed for integrating role played by energy homeostasis of an organism, as well as the concept of natural death from senescence, and, finally, a model of the cellular processes within the aggregate of natural technologies for modeling the rates of the decline in the efficiency indicators describing the functioning of individual physiological systems [24, 27].

Modeling of Particular Systems of an Organism as Essential Elements of the System of Natural Technologies

In this section, physiological systems must be treated as generalized means of transport and excretion of different substances to and from an organism and the system of the highest level (including the conscience) must be interpreted as the instrument of obtaining and use of information about the external world. Aging under such an approach is modeled as the decline in the efficiency of such mechanisms in practically every system of an organism (gastrointestinal tract, pulmonary system, kidneys, liver, bone marrow as a hematopoietic system, blood circulation, immune and hormonal systems, central and peripheral nervous systems, and highest control mechanisms, i.e., brain and conscience [27, 56]).

Modeling of Integrating Links in the System of Natural Technologies of an Organism

Usually, by integrating systems of an organism, physiological systems are understood as integrating the set of "lower-level" systems into a unified whole. These are assumed to include the nervous and humoral systems, and sometimes the lymphatic and circulatory systems. In our understanding, the main integrator in the system of natural technologies must be the system supplying energy to the body. Energy homeostasis makes it possible not only to integrate physiological systems but also to model the termination of life-sustaining activity. The first variants of the model of natural technologies have been recently developed with the system of oxygen homeostasis [25].

The program includes modeling of the homeostasis bloc as the central element integrating the processes of natural technologies. In addition, the interdisciplinary aging–homeostasis and homeostasis–aging interfaces should be modeled [25, 26]. Such interfaces support the interaction between different models in the system of natural technologies, which employ terms of different scientific disciplines. On the one hand, they must model the effect produced by the aging of separate physiological systems on the process of maintaining the energy homeostasis of an organism, and, on the other hand, they have to reflect how the reduction in the energy resource affects the functioning of different physiological systems. Finally, it is also possible to model the homeostasis as an age-related process of the decline in the homeostatic ability of an organism.

Scenario of Modeling of Aging Processes and Occurrence of Death within the Concept of an Organism's Natural Technologies

In modeling aging processes, a prominent place is held by a scenario approach [16], enabling the multivariate case study of aging processes including the occurrence of death. The efficiency of every organismal function can decrease with age according to various laws implementing different scenarios of aging.

Generally speaking, the scenario here is a kind of estimate of possible aging of a system. It correlates, on the one hand, the change in the external conditions and, on the other hand, the changes in the system's intrinsic variables. The scenario approach within the concept of natural technologies can be applied to forecasting the behavior of the body system and to determining life expectancy depending on particular environmental, social, and economic conditions. In addition, this approach can be used in studying the efficiency of decisions made concerning environmental changes and their comparison, as well as for selecting and working out optimal decisions on environmental control.

The possible directions of the investigations include life expectancy forecasts for various scenarios

of changes in environmental conditions in regions of Russia and forecasting life extension in Russia's regions depending on different managerial decisions. In addition, the modeling results can be tested from the available data on aging and human lifespan for various regions [19].

3. MATHEMATICAL MODELING OF LIFESPAN

There are two types of mathematical models, i.e., system models and data models [65]. System models are those modeling the structure of a system and the processes in it. Correspondingly, the previous sections considered the models for the aging of biological systems where the significant role belonged to the structure of the system, the processes and the mechanisms of its aging.

The data models operate the data themselves without considering the structure and the process of the systems functioning. The models of the lifespan are data models and mostly deal with the age of death. Such models either ignore the causes and manifestation of aging processes or treat them as the matters of secondary importance. For example, in the classic Gompertz model mortality is only differentiated by causes but not by the mechanisms leading to it.

Analysis and Development of Existing Mathematical Lifespan Models

Numerous lifespan models developed up to should be scrutinized to identify the key principles required for modeling of aging. The identified characteristics will be taken into account in developing new mathematical aging and lifespan models [2, 119],

Of interest will be to consider the mathematical modeling of the existing phenomenon of species-specific lifespan and to develop the classical lifespan models with allowance for population heterogeneity. In particular, this holds for the approach of Piantanelli [102] and the homeostatic approach of Novoseltsev [24, 34].

Development of Approaches and Mathematical Models for Forecasting the Lifespan of Experimental Animals and Human Life Expectancy

Despite the social and economic importance of human life expectancy, attempts to address this issue have not yet produced any significant results [70]. This problem was posed, in particular, in connection with clinical (postsurgical) aspects, but no adequate mathematical models have been developed in this field either [112]. Therefore, methods for solving this problem are still being sought using experimental animals (worms, fruit flies, and rodents) [59, 83, 97].

Such methods are based on mathematical models using correlations existing between various indicators (predictors) and lifespan [29, 92].

For animals, it seems feasible to elaborate mathematical models for predicting the lifespan of fruit flies [90], fruit flies Medfly, Mexfly, rodents; at the same time, for humans the genetic determinants of lifespan must be determined, as well as the role of the environment and the quality of medical service.

Modeling of Action on an Organism Aimed at Life Extension

This section of the program is of practical interest because the core of the life extension problem is connected both with the search for various longevity determinants and assessment of assessing effects of pharmaceutical, physical, chemical, and electrical nature of life extension [1]. The complexity of the problem is that the gerontological effect on humans can be directly determined only after a rather long time (several decades). Various impacts on an organism must be modeled in determining the positive response of an organism to a particular action with the purpose of optimizing the produced effect.

The program includes analysis and modeling of carolic restriction and dietary restrictions [68, 109], analysis of the role that reproduction restrictions can play in human life extension and in increasing the lifespan of laboratory animals [58, 68], and analysis and modeling of the effect from geroprotectors (melatonin, peptides, etc. [1]).

Special attention should be paid to modeling of the results of the subcellular effect on lifespan (Skulachev ion [49]). The cryogenic effect on lifespan, as well as the effect of stress and hormesis and the relations between hormetic effects and lifespan, can be modeled.

It is necessary to mathematize the analysis of the relations between resistance to stresses and lifespan for model animals and people [52]. Such phenomena as the effects of cold, radiation, and other types of mild exposure on the human body, should also be analyzed. In addition, the effects of brain stimulation (electric, electromagnetic, etc.) can be modeled with the purpose of the life extension. Such studies are mainly carried out in other countries [84, 106].

An important role will be played by research and mathematical modeling of the effect that lifestyle in various ethnical and religious cultures has on lifespan. Of special significance is the modeling of genetic modifications and their role in life extension [63, 64, 110].

Mathematical Models Describing Healthy Lifespan

Much attention in gerontology is paid to active lifespan (as distinguished from lifespan in general). This is connected with the desired objective of health preservation up to the maximum possible age. Success

in this area involves positive social results and, at the same time, the economic advantages of the increasing proportion of the able-bodied population in the aging society.

In order to simulate active lifespan, multistage demographic models can be used, as well as Markovian, semi-Markovian, and fuzzy models, [62, 79]. Such models study various levels of health loss, i.e., from full health to death. The models differ in the characteristic patterns of transfer between states and in the principles of an individual's being referred to a particular state.

For animals, this is associated with the development and analysis of models with incapacitation. The experimentally observed specifics of the behavior of flies remaining majority of their older life in temporal immobility (supine behavior) enable the construction of a mathematical model for their active lifespan [98, 104, 107].

The development of age-related bioindicators (both behavioral and physiological) will make it possible to parametrize the aging process and single out the stages corresponding to the human incapacitation process. Mathematical models for the human biological age [3, 5,11, 74, 75] should be analyzed.

In addition, special attention should be focused on modeling of age-related diseases. Here, conditions are implied that develop in older age due to the decline in the ability of the human body to respond effectively to external action, i.e., infections, and chronic diseases.

The modeling of the incapacitation processes is an important part of the program. By disability is meant a man's chronic inability to perform regular actions necessary for everyday life [54, 55, 60, 78]. The occurrence of this phenomenon in different age and social groups must be investigated as well as the dynamic changes in its incidence and the relation of disability and mortality to genetic and socioeconomic factors.

Finally, mathematical models of disability are considered. By disability is meant the medically recognized fact of loss of health caused by disease. The incidence of disability in different age groups is modeled as well as the dynamic changes in its occurrence in age groups and the relation between disability and mortality.

Analysis and Modeling of the Changes in Human Lifespan in Historical Perspective

In a historical perspective, average human life expectancy is increasing. Mathematical modeling makes it possible to evaluate the role of different factors in this process. We plan to simulate the change in human lifespan based on paleodemographic data and to calculate life tables and distribution in the death age of primitive man [73].

It would be feasible to model and analyze the phenomenon of the dramatic increase in human lifespan from ancient times to present day.

4. MATHEMATICAL MODELING AND ANALYSIS OF AGING PROCESSES AND HEALTH LOSS AT THE LEVEL OF DIFFERENT GROUPS AND POPULATIONS

Aging, lifespan, and changes in the state of health are subject to numerous uncontrolled factors and are described as random processes, which can only be studied at a mass scale, or in the investigation of groups or populations of individuals. Therefore, it is significant to take into account the specificity of the collected statistical data and populations.

Analytical Methods Taking into Account the Specificity of Data Collection and Its Organization

The development of mathematical models for changes in the indicators of health, morbidity, and mortality of a population is based on longitudinal and latitudinal data (including cohort analysis of data obtained from time samples) [22].

Data Analysis of Population Genetics

The purpose of this section is mathematical modeling to find the genetic determinants of healthy longevity. From the modern viewpoint, human longevity and state of health are inherited characteristics. Data on the lifespan and health state of twins show that the approximately 25% of lifespan is determined genetically [71], in about 50% of cases lifespan is determined by vulnerability to mortality from all causes [116], and the degree of genetic determinism of capacity for ages above 75 ranges from 10 to 45% [21]. The study of longevity and state of health of relatives enables the identification of genetic characteristics associated with healthy longevity [114, 117]. Mathematical modeling serves as a tool that makes it possible to associate and combine genetic and demographic data.

Mathematical Modeling and Analysis of the Relation between Chronic Morbidity and Human Aging and Mortality

The purpose of research in this section is studying and modeling the relation between the level of chronic disability and mortality in older age groups. In order to understand the relation between health and longevity, the influence of adaptation mechanisms on lifespan must be investigated. Assuming that the human body, in addition to the reproductive function, can allocate resources either on health maintenance or on life preservation, the significance of these types of resource consumption for healthy life extension must be quantitatively estimated by mathematical modeling.

In addition, the influence of concomitant morbidity on mortality should be modeled. This will provide deeper understanding of the mechanisms underlying human health loss and, consequently, help to identify directions for improving the human state in old age. The preliminary estimates of cause-specific mortality based on US data prompt the conclusion that the incidence of autoimmune diseases reduces cancer mortality [82]. This can point to stimulation of bodily defenses in conditions of chronic disease and show ways to develop both anticancer therapy and antiaging therapy, understood as treatment for health preservation of senior citizens.

5. DEVELOPMENT OF METHODS FOR EXTENDING THE RESULTS ON LIFE EXTENSION OBTAINED FOR MODEL ANIMALS TO HUMANS

This extension can be implemented at various levels, i.e., genetic, subcellular, cellular, systemic, the level of external actions on an organism, and the evolutionary level.

At the genetic level, it is necessary to simulate the impact of expression of the genes common to humans and animals on life extension and to analyze the role played by evolutionally conservative genes.

At the subcellular level, it is feasible to simulate the processes of protein repair and degradation. In modeling, proteomics can be used, i.e., the large-scale study of proteins, particularly their interactions in living organisms including the human body. Scientists engaged in proteomics investigate the "production" of proteins, their decomposition, and protein substitution in the body.

At the cellular level, regenerative reactions are modeled that protect animal and human organisms from damage, as well as the reactions of consumption, generation, and accumulation of energy at the cellular level in order to explain the differences in life duration for various animal species and humans.

At the systemic level, human and animal homeostasis and homeostenosis should be modeled.

The development of mathematical models describing the result of external impact on the lifespan of laboratory animals in terms of adaptation and energy reallocation between the vital functions of an organism and the reaction norm is a task of the program at the level of external actions. Finally, investigations at this level include modeling of the influence exerted on lifespan by exposure of an organism (animal and human) to events and impacts at various stages of ontogenesis, and mathematical modeling of health loss fundamentals common to animals and men.

At the level of evolutionary mechanisms, research must primarily focus on mathematical modeling (and estimation) of limitations to changes in life duration for various animal species and human lifespan.

6. DEVELOPMENT OF METHODOLOGY FOR MODELING OF AGING PROCESSES, HEALTH LOSS, AND MORTALITY

Efficient analysis and development of mathematical models required for implementing the program call for the invention of new and improvement in existing methods of mathematical modeling [4, 33, 39, 45]. Such methods are currently based on apparatus of control science, informatics, and mathematical statistics. Among mathematical modeling methods, universal techniques can be singled out suitable for analyzing objects of random nature. These include statistical modeling, modeling allowing for uncertainty of input data, methods for model identification from imperfect data, and the synergetics methods [17,18].

In addition, there are methods allowing for the specifics of the systems with aging (methods of reliability theory, interdisciplinary modeling, homeostatic models, and balance models). The program includes the work covering both types of models.

We plan to consider energy balance models (Penna [101], Pletcher and Neuhauser [103], and their development), models of reliability theory (models developed by Kol'tover [9, 12, 13], Gavrilov and Gavrilov [6], and Nikulin [86]), an approach to modeling aging based on energy homeostasis. In addition, it would be feasible to consider Monte Carlo methods as applied to oxygen homeostatic models, as well as to analyze population models of aging, synergistic RDA models (the approach developed by Malinetskii [17, 18]), and interdisciplinary modeling (Novoseltsev's approach [34, 91]).

A separate analysis should be performed on heterogeneity problems (the approach developed by Yashin and Mikhalskii [20, 113, 119]).

The specific character of the data on aging and longevity consists in the absence of preliminary information on the structure of the process, the impossibility of its comprehensive observation, and the relatively small number of long-living subjects. We plan to overcome these difficulties by employing state-of-the-art methods for data analysis in uncertainty conditions, allowing for partial observability of aging processes and health loss, and developing formal stochastic models of aging [5, 44, 120]. The requirements must be formulated to the scope and quality of information necessary for identifying mathematical models of aging and experimental evaluation of the obtained models' accuracy based on modeled data

CONCLUSIONS

Mathematical modeling has become one of the most powerful instruments in science in general and in biological sciences in particular. The study of laws and patterns regulating the aging of different organisms and the search for approaches to extending healthy human life is becoming a priority research direction,

not only bringing together various biological and medical disciplines, but also making use of a wide range of mathematical methods, in particular, mathematical modeling. Although such research is actively under way in many directions, there is still no comprehensive concept of mathematical modeling for aging processes and attaining longevity as an important scientific branch of mathematical modeling.

In summary, it must be noted that one and the same phenomenon can be described by numerous models depending on the objectives set by their creators. Therefore, a certain skepticism is typical of biology as far as mathematical models are concerned. "Mathematicians, physicists, and specialists in the field of population genetics can weave sophisticated nets of mathematical theories, which seem fully devoid of empirical value" [105]. At the same time, one can quote the well-known maxim of the champion of mathematical modeling, G. Box, "All the models are wrong but some of them are useful" [57], proving that mathematical models, even though abstract, make it possible to gain specific knowledge. The last statement is also supported by the stable trend to subject biological hypotheses to a rigorous mathematical analysis. Note in this connection that all the best known experimental groups of biologists prefer to establish direct contacts with teams of mathematicians [58, 77, 99].

In this paper, the authors attempted to present their understanding of the development program for mathematical modeling in gerontology as a field of science. Its implementation will help to solve many general biological problems as well as social ones concerning the extension of healthy human life to attain healthy longevity. In addition to the development of the modeling methodology itself, addressing the issues included in the program will call for research of computer bases, which will have to extend beyond its scope. Separately, problems must be considered related to organization of works in the field of aging and longevity modeling.

The overall progress in biological science and improvement in the country's general life conditions play an important role in implementing the main objectives set by the program. The development of the infrastructure, the propagation of a healthy lifestyle, promotion of the environmental well-being of territories, and other benefits of civilization must take their due place in the continuing process of constant life extension in developed countries. It is increasingly evident that the achievements of modern civilization act as protection mechanisms, promoting the increase in human lifespan. Humanity "would have found it extremely difficult to survive in natural conditions without the protection provided by the mechanisms of civilization" [10].

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